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CHAPTER 6

Exacerbations of chronic respiratory diseases

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6.1 INTRODUCTION

Human rhinovirus (RV) infection has emerged as an important trigger for exacerbations of chronic respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and interstitial lung disease (ILD) including idiopathic pulmonary fibrosis (IPF). Epidemiological studies have played a central part in understanding the association of RV and other respiratory viruses in exacerbations of chronic respiratory diseases. This chapter offers a summary of the epidemiological literature that has linked RV infection with acute exacerbations, and Table 6.1 refers to the key references establishing the importance of RV infection in exacerbations of chronic respiratory diseases. Through a range of postulated mechanisms, RV infection elicits a complex host response that in part, may actually contribute to disease pathology and perpetuate symptoms rather than prevent virus infection and the associated symptoms. Whether or not RV infection directly triggers these events that add to, synergize with, or change the nature of the host response that drive disease, or whether the underlying disease makes certain individuals susceptible to RV infection is a pertinent question in the field. This chapter includes an in-depth commentary on the reasons why RV is the most common viral pathogen associated with exacerbations of these diseases; including the impact of current and emerging treatments on the outcome of RV infections and disease progression. Finally we explore the potential for new therapeutic opportunities to better manage chronic respiratory diseases whilst minimizing the acute and chronic disease promoting effects of RV infections.
6.2 EXACERBATIONS OF ASTHMA

Asthma is a chronic disease of the conducting airways characterized by airway hyperreactivity that causes reversible airway smooth muscle (ASM) mediated bronchoconstriction. Another defining feature of asthma is airway inflammation that perpetuates airway hyperreactivity as well as mucus production, which together with airway inflammation cause airway narrowing, airway obstruction, and resistance to airflow and symptoms. Asthma has been linked to numerous stimuli including airway infections, various allergens, exposure to airborne pollutants, exercise, stress, and nervous provocation. The key feature of asthma is decreased lung function, measured as spontaneous changes in peak expiratory flow (PEF) or a decrease in forced expiratory volume in 1 second following provocation. Symptoms include nocturnal awakenings, dyspnea, wheeze, and tightening of the chest. The immediate effects of asthma are generally reversible by a short-acting \( \beta_2 \)-agonist. Asthma is now considered a heterogeneous, complex disease and can present as a chronic, stable disease of different

### Table 6.1 Key epidemiological evidence supporting the role of rhinovirus (RV) and other respiratory viruses as exacerbators of chronic respiratory diseases.

| Reference     | Disease          | Insights                                                                                                                                 |
|---------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Johnston ¹    | AE/Wheeze        | Highlighted the importance of viruses, particularly RV to be associated with 85% of AE and wheeze events in children                     |
| Corne²        | AE               | Showed that while having the same frequency of RV infections, asthmatics had more severe and longer duration of symptoms versus nonasthmatics |
| Johnston ³    | AE               | Identified viruses, particularly RV as vectors for the September asthma epidemic in the Northern Hemisphere                               |
| Bonnelykke⁴   | AE/Wheeze        | Demonstrated a link between CDHR3 variants and recurrent AE or wheeze in children                                                      |
| Seemungal⁵    | COPD-E           | Demonstrated association of RV with COPD-E and disease severity                                                                        |
| Papi⁶         | COPD-E           | Showed that RV was the most readily virus detected in COPD-E versus stable COPD                                                        |
| Bafadhel⁷     | COPD-E           | Showed that RV associated COPD-E were associated with certain biomarkers such as serum CXCL10                                          |
| Collinson⁸    | CF-E             | Showed an association between picornaviruses, CF disease severity, and bacterial infections in CF-E                                      |
| Wootton⁹      | IPF-E            | Showed that viruses, including RV, were associated with IPF-E and not stable disease                                                   |

AE, Asthma exacerbations; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; CDHR3, cadherin-related family member 3; CF, cystic fibrosis.

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### 6.2 EXACERBATIONS OF ASTHMA

Asthma is a chronic disease of the conducting airways characterized by airway hyperreactivity that causes reversible airway smooth muscle (ASM) mediated bronchoconstriction. Another defining feature of asthma is airway inflammation that perpetuates airway hyperreactivity as well as mucus production, which together with airway inflammation cause airway narrowing, airway obstruction, and resistance to airflow and symptoms. Asthma has been linked to numerous stimuli including airway infections, various allergens, exposure to airborne pollutants, exercise, stress, and nervous provocation. The key feature of asthma is decreased lung function, measured as spontaneous changes in peak expiratory flow (PEF) or a decrease in forced expiratory volume in 1 second following provocation. Symptoms include nocturnal awakenings, dyspnea, wheeze, and tightening of the chest. The immediate effects of asthma are generally reversible by a short-acting \( \beta_2 \)-agonist. Asthma is now considered a heterogeneous, complex disease and can present as a chronic, stable disease of different
severity, including mild, moderate, or severe. Responses to treatments, such as glucocorticosteroids (GCs) and bronchodilators, may also vary, and be categorized as well, partial, or poorly controlled. The most common endophenotype is Th2/type 2 associated or allergic asthma, which is defined by a physician’s diagnosis of asthma often associated with high serum Immunoglobulin E (IgE) levels, positive skin prick tests to aeroallergens, and/or confirmed diagnosis of an atopic disorder such as allergic rhinitis. Evidence of interleukin (IL)-5, IL-4, or IL-13 driven inflammation, or increased levels of eosinophils in blood or lower airway samples, or high levels of FeNO may also confirm Th2 or type-2 associated asthma. Other asthma endophenotypes may exist, including adult-onset asthma; steroid resistant, poorly steroid responsive, or neutrophilic asthma; fixed airflow limitation asthma; or more simply termed type 2 low asthma. However, these are not as well defined by genetic analysis or biomarkers as allergic asthma.\textsuperscript{11,12} Currently, the exact nature or existence of these subgroups is vigorously debated.\textsuperscript{13,14} Erroneous diagnosis, effects of treatments, and other confounders have led to a lack of consensus. The identification of correct asthma endophenotypes and implementation of precise medicine approaches represents an important ongoing challenge to the field.

Asthma exacerbations (AE) are defined when a stable individual with asthma suddenly becomes uncontrolled, experiences increased symptoms resulting in General practitioner (GP) consultation or hospitalization, and additional treatment including oral GCs. In the United States, there are approximately 1.6 M emergency room visits associated with asthma each year,\textsuperscript{15,16} and approximately 5\% of asthmatic individuals have at least one AE per year.\textsuperscript{17} AE may have multiple predictors; however recent AE history is the strongest predictor for a future AE event. In children, the number of allergic sensitization triggers and race are other important predictors.\textsuperscript{18} AE are more common in individuals with poor lung function, or who are classified as having severe or difficult to treat asthma, which may comprise up to 15\% of all asthmatics.\textsuperscript{18,19} AE may be life threatening, and results in significant morbidity worldwide including school/study absenteeism and sick leave. Recent economic studies have shown that individuals suffering from AE have increased both total healthcare and asthma specific healthcare costs, when compared with individuals who do not experience AE.\textsuperscript{20} In unadjusted total costs, individuals that experience AE may accrue costs of >$9000 USD per year, compared with approximately $5000 USD per year for individuals who do not.
AE are triggered by many factors; however respiratory virus infections are the most common, associated with up to 85% of AE in both adults and children.\textsuperscript{21–23} Historically, detection methods for viruses in respiratory clinical samples such as nasal secretions and throat swabs relied on in vitro cell culture based methods. This approach had limitations not least of which was the inability to propagate many clinically important viruses—including a significant number (approximately 40% based on current classification) of RVs we now know to belong to the RV-C species. In the mid-1980s nucleic acid based molecular methods become the method of choice, and in recent years, next generation sequencing\textsuperscript{24} and DNA and protein based virus-chip methods\textsuperscript{25,26} have become available with the added advantage of potentially discriminating different viruses of the same kind.

Viruses often detected in respiratory samples obtained during AE include respiratory syncytial viruses (RSVs), influenza viruses, adenoviruses, human RVs, coronaviruses, parainfluenza viruses (PIV), as well as the more recently identified metapneumoviruses and bocaviruses; however these are less common.\textsuperscript{22,27–29} Among these respiratory viruses, RVs are the most common viruses detected and typically account for between 29% and 55% of virus-induced AE (Fig. 6.1) although this number can be as high as 87%.\textsuperscript{22} Differences in detection rate involve volunteer demographics including age, geography, and method of detection.\textsuperscript{22} Of the different RV genotypes, RV-A and RV-C are more commonly associated

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure_6.1.png}
\caption{Association of different respiratory viruses and atypical bacteria in asthma by age expressed as a %. RV accounts for approximately 33\% in children under 2 years of age, 55\% in older children 6–17 years of age, and 29\% of adults. Data are median % values and have been reproduced from published review articles.\textsuperscript{22,23} RV, Rhinovirus.}
\end{figure}
with AE than RV-B. The RV-C group\textsuperscript{30,31} shows unique sequences at the ICAM-1 and LDL receptor binding sites, initially suggesting they have a unique receptor,\textsuperscript{32} which has since been identified as cadherin-related family member 3.\textsuperscript{33} RV-C may contain a group of viruses that are associated with more severe AE events requiring hospitalization,\textsuperscript{34} although how this occurs is unknown.\textsuperscript{31} Epidemiological studies have shown that in the Northern Hemisphere, RV infections result in a marked increase in emergency room admissions due to AEs.\textsuperscript{35} In fact this “asthma epidemic” has been shown to coincide with Labor Day in Canada,\textsuperscript{3} the third week of September, approximately 2 weeks after children return to school, highlighting the important role school age children have as vectors of RV induced AEs.

While the strong association of RV infection and AE events from epidemiological studies investigating virus detection rates in hospitalized cases of AEs do not definitely prove RV causes AE, or infer mechanisms, they have been very important in highlighting the important connection between viral infections and asthma. More recently, human experimental infection models of RV-A in asthmatics\textsuperscript{36–38} and mouse models of allergen exposure with RV infection\textsuperscript{39–41} have also been established that thus definitively show the ability of RV infection to contribute to lower airway inflammation, and induce changes in lung function consistent with the symptomology observed in naturally occurring AEs.

6.3 EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is progressive respiratory condition caused by exposure to cigarette smoke and in some parts of the world, biomass fuel burning. It is characterized by chronic inflammation of the small airways, accelerated loss of lung function and/or emphysematous disease associated with airflow limitation. It is a significant source of morbidity and in terms of mortality worldwide, COPD is currently the third leading cause of noncommunicable death.\textsuperscript{42} The exact prevalence of COPD is difficult to accurately assess, indeed numbers varying between 200 and 600 million are still referenced. However, the recent update of the Global Burden of Disease has led to an agreed number of 328 million people having COPD worldwide, which includes 168 million men and 160 million women.\textsuperscript{43}

The exact threshold for the duration/intensity of cigarette smoking that will result in COPD varies between individuals. In the absence of a
predisposing factor (e.g., genetic, environmental, or occupational), smoking less than 10–15 pack-years of cigarettes is unlikely to result in COPD. Alternatively, the single best predictor for airflow obstruction is a history of more than 40 pack-years of smoking [positive likelihood ratio, 12 (95% CI, 2.7–50)]. As is the case with most chronic lung conditions, the disease course includes chronic respiratory symptoms such as wheeze and breathlessness, punctuated by periods of increased symptomatology, known as acute exacerbations. Acute exacerbations (COPD-E) are significant events in COPD, as they accelerate disease progression, impair quality of life, and are the predominant cause of mortality. Additionally, they often necessitate unscheduled healthcare visits, treatment costs, and hospitalizations, which account for $18 billion in direct costs annually in the United States alone.

Preventing COPD-E is a major unmet therapeutic goal. A crucial step toward this goal is the recognition that acute exacerbations are most commonly due to respiratory virus infection, specifically RV. It follows that the host immune response to virus infection may be impaired, and that a better understanding of how the immune response differs in COPD compared with smokers or healthy individuals has the potential to lead to the development of new therapies.

Historically, the main cause of COPD-E was considered to be bacterial infections and this belief is reflected in the continued extensive use of antibiotics in COPD exacerbations, despite weak evidence of their efficacy. Earlier studies using diagnostic techniques such as culture detected viral infections in a minority of COPD exacerbations, resulting in the focus on bacteria. However, some RVs are difficult to culture in standard assays, and serology is not practical due to the presence of more than 100 serotyped strains and ~60 nonserotyped strains. Therefore, without polymerase chain reaction (PCR), these viruses cannot be easily identified. As a result, early studies using other diagnostic methods underestimated the prevalence of viruses being detected in 22%–64% of COPD exacerbations with RVs the most prevalent.

As in asthma, ultimate proof of causation between RV infection and the induction COPD-E comes from a human model of experimental RV infection in COPD. RV are identified in community treated mild exacerbations, in hospitalized patients, and in very severe exacerbations requiring intensive care. Virus infection rates during acute exacerbations are unlikely to represent chronic infection or seasonal carriage, as viral PCRs are rarely positive when patients are sampled prior to or
after an exacerbation,\textsuperscript{5,6,60} or in time-matched controls.\textsuperscript{51,54,56,59} Whilst these studies support a causal relationship, they cannot exclude secondary causation (e.g., bacterial coinfection or air pollution). The novel experimental infection studies using RV in COPD subjects shows clear increases in lower respiratory tract symptoms following inoculation, along with airflow obstruction, and systemic and airway inflammation mimicking a COPD-E observed during naturally occurring infection. Indeed, in experimental infection studies, in over 90% of RV infected COPD subjects, COPD exacerbation criteria were met, suggesting that the virus detection frequencies reported in naturally occurring exacerbations (22\%-64\%) are actually a gross underestimate of the true frequency of viruses as precipitants of exacerbations. In the experimental infection model, RV RNA was present in the upper respiratory tract prior to progressing to the lower airway and causing COPD exacerbation onset, thereby excluding secondary causation.\textsuperscript{64,65,70} Moreover these studies demonstrated a temporal relationship between viral replication in the airways, symptoms, and exacerbation onset, and viral clearance and exacerbation resolution. The virus load also correlated with markers of inflammation, and oxidative and nitrosative stress in the airways.\textsuperscript{64,70} Therefore these studies have provided compelling evidence to the field that RV infection is directly linked to COPD-E.

### 6.4 EXACERBATIONS OF CYSTIC FIBROSIS

CF is a common Mendelian autosomal recessive genetic disorder that affects more than 70,000 individuals worldwide.\textsuperscript{71} More than 2000 culpable gene variants have been identified. The most common, and widely studied, is the Phe508del, which is predominantly found in populations with northern European heritage;\textsuperscript{72,73} whilst individuals with CF from other regions have a wider range of mutations with the Phe508del mutation being much less prevalent.

The mutation of this gene leads to defective function of the CF transmembrane conductance regulator (CFTR) protein. Pulmonary involvement is the most prominent manifestation of the disease due to tenacious mucus secretion, decreased mucociliary clearance, resulting in inflammation and recurrent infection.

Respiratory infections are the leading cause of acute exacerbations resulting in morbidity, decline in lung function, and hospitalizations. The predominant cause of infectious complications in CF is considered
bacterial infection, with *Pseudomonas aeruginosa* the most common organism cultured. The role of a dysfunctional CFTR protein plays a key role in deficient innate immunity to *P. aeruginosa* infection due to resultant increased innate inflammation owing to disruptions in lipid metabolism, enhanced interactions of *P. aeruginosa* with epithelial cells, or a direct role for the CFTR in bacterial clearance subsequent to CFTR-mediated epithelial cell ingestion. There is relatively little published work on the role of RV infections in CF exacerbations (CF-E), but recent studies suggest that viral infections have a significant impact. Thus the role of respiratory viruses is likely to have been significantly underestimated in the past. For example, prior to the utilization of modern PCR techniques, studies relying on serology, culture, and immunofluorescence implicated a viral cause in 10%–28% of exacerbations in CF patients. However, PCR studies have increased this detection rate to 46% of exacerbating patients, compared with only 18% of patients in stable condition. RV has been specifically identified in 13%–58% of CF patients with acute respiratory illness and was associated with worse respiratory symptoms, airway function deterioration, and greater incidence of secondary bacterial infection, compared with matched uninfected patients. A number of different viral species have been detected in CF patients, with the most common being RVs, influenza viruses, and RSVs. Interestingly, the rates of viral infections in children with CF is not elevated in comparison to healthy children but importantly the severity of clinical illness associated with infection is demonstrably greater. As is the case in other airways diseases, viral infections are associated with decline in lung function and more severe clinical illness in CF, indicating that they contribute to disease progression demonstrating the need for further research in this field.

### 6.5 Exacerbations of Interstitial Lung Disease

The field of ILD includes a plethora of different, individual conditions that exhibit varying expected prognoses and disease courses. The most common ILD is IPF. IPF affects approximately 3 million people worldwide, with incidence increasing dramatically with age, it has a reported median survival of approximately 3 years from the time of diagnosis. Age is the strongest demographic risk factor for IPF, suggesting that “accelerated” lung aging is a driving force for its development. The pathogenesis of IPF development is an area of much debate. A sequence of three pathophysiologic stages has been described (see Table 6.2).
However, it is important to clarify that not all individuals in the predisposition stage will go on to exhibit clinically detectable disease. Similarly, not all patients with IPF develop all stages in a sequential order before established disease is detected.

As in asthma, COPD, and CF, the disease course of IPF commonly exhibit stable periods punctuated by acute exacerbations in symptoms, associated with a stepwise decline in lung function. A proportion of these episodes may be the result of sequelae from infection that cannot be detected due to late presentation and limited microbiological detection methods, but studies of naturally occurring exacerbations have concluded that viruses only account for a small number of these events.

Epidemiological evidence of infective etiology in IPF exacerbations (IPF-E) originates from work demonstrating that IPF-E was significantly more common in the winter and spring months and in patients who are taking immunosuppressive medications. IPF increases the risk of pulmonary infections fourfold, although it is unclear how many of these are viral. Moreover, community acquired pneumonia (both viral and bacterial) is associated with a higher mortality in ILD than otherwise healthy controls.

The importance of viral infection in the disease progression of ILD is again indirectly supported by small trials of antiviral therapy. Two cases described by Tang et al. were positive for EBV on PCR of sputum samples, treated with valacyclovir, and went on to exhibit stabilization in at
least one of the two cases. A 14-day trial of ganciclovir in patients with severe IPF and positive EBV serology brought about improvements in 64% (9/14) patients in terms of three of FVC, shuttle walk test, DTPA scan, and steroid dose. The small sample size, lack of a control group, and open-label design make it difficult to draw conclusions from this study. The optimal duration of therapy is also unclear, as 6/9 patients who responded and 3/5 patients who did not respond died within 12 months. Further studies are necessary to establish the true burden and consequences of RV, particularly given the paucity of effective treatments for IPF.

Chronic subclinical viral infection has been implicated in the pathogenesis of some ILDs, for example with the viruses EBV, CMV, HHV7 and HHV8, and hepatitis C. The hypothesis is that chronic and/or recurrent viral infection induces alveolar endothelial cell injury, in turn triggering the release of proinflammatory mediators, which bring about the increased disease pathology.

### 6.6 Characteristics of Rhinovirus that May Promote Exacerbations of Chronic Respiratory Diseases

As RV is linked to exacerbation pathogenesis, a key question is therefore what properties of RV might contribute to disease mechanisms. Certainly the “commonness” and ease of transmission of the common cold virus; the fact there are any number of 160+ antigenically distinct viruses circulating at any one time is important. Furthermore, other factors that contribute to the predominance of RV in exacerbation of chronic respiratory diseases can be broadly described as follows: the ability of RV to (1) induce inflammation, nervous provocation, airway remodeling or repair processes, and airway mucus production; (2) synergize or add to ongoing, established inflammation (e.g., allergic or type-2 mediated immune pathways in asthma); (3) promote or contribute to secondary bacterial infections by degrading antimicrobial defenses (epithelial junctional proteins and airway barrier integrity and antimicrobial peptides); and (4) expose impaired or aberrant host antiviral innate immunity that is either intrinsic or caused by treatment regimes. It is likely that RV meets one or more of these criteria in a manner that makes it qualitatively different from other respiratory viruses. In the case of asthma, RV, or certain subtypes of RV, have been referred to as “asthmagenic viruses” due to their ability to be
Table 6.3 Summary of characteristics of rhinovirus (RV) infection that may explain the high frequency of RV infection in exacerbations of chronic respiratory diseases.

| Disease | Characteristic | Induce inflammation and repair, provoke nerves | Interact with ongoing inflammation | Promote secondary bacterial infections | Benefit from treatment |
|---------|---------------|-----------------------------------------------|----------------------------------|---------------------------------------|-----------------------|
| AE      |               | $X^{a,b,c,d}$                                  | $X^{e,f}$                        | $X^{g}$                               | $X^{h}$               |
| COPD-E  |               | $X^{a}$                                       | $X^{e}$                          | $X^{g}$                               | $X^{h}$               |
| CF-E    |               | $X^{a}$                                       | $X^{e}$                          | $X^{g}$                               |                        |
| IPF-E   |               | $X^{a}$                                       | $X^{e}$                          | $X^{g}$                               | $X^{h}$               |

$X_a$: Induce a broad range of inflammatory cytokines and chemokines including tumour necrosis factor (TNF), IL-1β, CXCL10, CCL5, granulocyte-macrophage colony-stimulating factor (GM-CSF), etc.

$X_b$: Induce Th2 mediated allergic inflammation including proTh2 cytokines IL-33, IL-25, TSLP.

$X_c$: Induce FGF, VEGF, collagen, perlecan, promoting remodeling and fibrosis.

$X_d$: Evoke airway hyperresponsiveness or induce TRPV1 and TRPA1 receptors.

$X_e$: Work in an additive manner with existing Th2 mediated inflammation enhancing IL-4 and IL-13 responses.

$X_f$: Enhancing airway eosinophilia.

$X_g$: Promote secondary bacterial infections, including proteobacteria including *Haemophilus influenzae* and *Moraxella catarrhalis* or *Pseudomonas aeruginosa* in CF.

$X_h$: RV infections may be affected by the actions of GCs and β2 agonists, which reduce antiviral immunity.

Associated with AE more readily than other respiratory viruses. In one recent study, RV was described as exacerbating existing asthma, while the effects of influenza infection, which in terms of symptoms were quite different and more systemic, were described as asthma-augmented influenza infection, supporting the idea that the nature of RV infection may be distinct from other respiratory viruses. In this section, the characteristics of RV infection that may explain its predominance in exacerbations of chronic respiratory diseases will be given due attention. Table 6.3 offers a summary.

1. *Induction of inflammation, nervous provocation, airway remodeling or repair processes, and airway mucus production.* A key feature of RV and other respiratory viruses in promoting exacerbations is their ability to induce either lung inflammation, nervous provocation, or in the case of asthma and IPF, lung injury, repair, or remodeling. Many of the innate receptors that recognize RV, including Toll-like receptors (TLRs),
RIG-I like helicases, and nucleotide-binding oligomerization domain (NOD)-like receptors, activate the NF-κB family of transcription factors, which induce over 100 proinflammatory and host response genes. RV, RSV, and influenza induce a range of proinflammatory cytokines, chemokines, growth factors, and adhesion molecules and mucins, thus contributing to lung inflammation.

The ability to promote lung inflammation is important in diseases where lung inflammation is key, and includes asthma, CF, and COPD. Mucins cause mucous plugging of the airway while cytokines facilitate cellular chemotaxis, activation, and proliferation of immune cells in the infected airway. RV can increase airway hyperresponsiveness by increasing 5-lipoxygenase and the cyclooxygenase pathway enzyme COX-2. While not as well characterized as asthma, inflammation is relevant in COPD, with a surprisingly low number of in vitro studies comparing the responses of cells from COPD patients to viral infection with those from healthy controls.

Similarly the few available studies examining naturally occurring virus-induced COPD exacerbations have demonstrated a role for inflammatory cells such as neutrophils and eosinophils and proinflammatory mediators such as CXCL8/IL-8, CXCL-10/IP-10, and CCL-5/RANTES. Experimental RV infection studies in COPD have indicated that RV induces airway neutrophilic inflammation and innate inflammatory mediators such as IL-1β, GM-CSF, CXCL8/IL-8, and TNF. These, and other in vitro studies, indicate an enhanced inflammatory response to virus infection in COPD subjects and this may be one mechanism whereby viruses induce exacerbations. The role of neutrophils is incompletely understood. While having the ability to damage tissues and contribute to airway inflammation, they undoubtedly have important roles in antibacterial defense, may produce type I IFNs, and in mouse models, may have antiviral properties. Of interest, a recent Phase 2a clinical trial of AZD5069, an inhibitor of the neutrophil chemokine receptor CXCR2, failed to affect severe AE rate, lung function of asthma control questionnaire (ACQ) score. The mechanisms of viral-induced CF-E and increased clinical illness are not well characterized with inconsistent results from published studies. Whilst some groups have demonstrated increased production of proinflammatory cytokines and chemokines by airway epithelial cells obtained from CF patients compared with healthy controls, others have failed to
detect any differences. \cite{110,111} It is unclear what leads to these contrasting observations.

RV infection has been shown to damage and compromise the integrity of the airway; through infecting airway epithelial cells and directly causing cell death \cite{112} and/or epithelial cell shedding. \cite{113,114} They can also affect epithelial permeability leading to increased airway inflammation and creating opportunities for increased secondary infections, \cite{115} allergen uptake, \cite{116} or exposure to environmental pollutants or irritants; all of which may trigger exacerbations of chronic respiratory diseases. In terms of nervous provocation, RV has recently been shown to upregulate the transient receptor potential (TRP) channel family members TRPA1 and TRPV1 in neuroblastoma cells \cite{117} and may be important in the cough response \cite{65} and sensitivity to methacholine \cite{118} observed during infection.

RV can also induce mediators required for airway repair, which results in airway scarring or remodeling. These processes include angiogenesis, increased ASM proliferation and hypertrophy, and thicker basement membranes owing to collagen and fibronectin deposition as well as the generation of new lymphatic vessels that ultimately result in thicker airway walls and reduced lung function; the importance of these process is obvious in asthma. Whether or not RV infection directly initiates this process is unclear; however, RV can induce some of these proangiogenic mediators including fibroblast growth factor and vascular endothelial growth factor, \cite{119,120,121} required for fibrosis in IPF, and the structural proteins perlecan and collagen \cite{122} the building blocks of airway remodeling.

2. *Viruses synergize or add to ongoing, established inflammation.* Evidence for this property is greatest for RV infections in asthma, where a synergy between viral infections and allergen sensitization and exposure was first realized through epidemiological studies \cite{123,124} and additional evidence for this interaction has been gained in both human challenge \cite{36,37} and mouse models of RV. \cite{39,40,125,127} In individuals with asthma, RV infection of the bronchial epithelium also likely has additive and synergistic effects on allergen sensitization and challenge as the epithelial derived pro-Th2 factors IL-33, IL-25, and thymic stromal lymphopoietin, which activate Th2 cells, DCs, and type 2 innate lymphoid cells, are induced readily by RV infection. \cite{37,126,128} This now allows a direct link to how respiratory virus infection of the airway epithelium can augment existing Th2 pathways in asthma.
Whether or not increased RV disease burden in asthma is simply a result of a type 2 skewed environment or whether RV contributes to type 2 inflammation is a wider debate that is often discussed in asthma onset.\textsuperscript{23,129} Concerning AE, RV is perhaps most easily understood as a direct contributor to established type 2 inflammation as discussed above, the results of which tip the fine balance between stable asthma and increased symptoms leading to AE. A study of cohabiting asthma and nonasthmatic pairs in the 1990s found that while the frequency of RV infection was not different between asthmatics and healthy volunteers, asthmatics had a more severe and longer duration of lower airway symptoms,\textsuperscript{2} consistent with the concept that individuals with asthma may not be prone to greater number of RV infections, but deal with the infection in a fundamentally different manner from non-asthmatic individuals. Further studies using RV experimental challenge generally show that asthmatics and nonasthmatics have equal rates of successful infection,\textsuperscript{36,37} while asthmatics generate greater lower airway symptom scores, which increase with decreased asthma control.\textsuperscript{130} How underlying type 2 immunity and allergic inflammation may influence the course of RV infection is another matter, and will be discussed in detail below.

3. \textit{To promote or contribute to secondary bacterial infections by degrading antimicrobial defenses}. The ability to promote secondary bacterial infection is most relevant for AE, or wheeze in children, COPD-E, and CF-E. As RV can disrupt the integrity of the airway epithelium, and reduce antibacterial cytokine responses\textsuperscript{131} and degrade antimicrobial peptides,\textsuperscript{132} this may promote secondary bacterial infection including enhanced dispersal,\textsuperscript{115} further infiltration and colonization of bacterial species that may already be present at low level. In AE in children, RV can increase \textit{Moraxella} abundance.\textsuperscript{133,134} In CF, exacerbations associated with a respiratory viral infection are associated with increased bacterial load,\textsuperscript{135} although not all studies report this association.\textsuperscript{136}

Viral and bacterial infections are common in COPD-E but when the role of dual virus–bacterial was previously considered studies appeared to indicate that it does not play a prominent role in COPD-E with low detection rates ranging from 6.5\%\textsuperscript{62} up to only 27\%.\textsuperscript{6,63,67} However, Papi et al. did observe that exacerbations with dual infection are more severe.\textsuperscript{6} Then, in a study of experimental RV infection, secondary bacterial infections were detected in 60\% of COPD patients
with confirmed RV infection, and increases in proteobacterial DNA sequences, including the potentially pathogenic *Haemophilus influenzae* have been reported. Crucially viruses and bacteria were detected at separate time points with a pattern of virus infection occurring first and bacterial infection later. The implications were that studies of naturally occurring exacerbations that collect samples at a single time point are underestimating the true incidence of dual infection, and are likely missing secondary infections. This was confirmed in a more recent study of naturally occurring exacerbations in which patients were sampled at two time points during an exacerbation. When RV was initially detected but bacteria were absent, 73% had a bacteria detected when sampled again at day 14.

There is also evidence that dual virus—bacterial infection contributes to COPD-E severity. In those COPD patients with *H. influenzae* detected at exacerbation, the presence of a symptomatic cold was associated with higher bacterial loads, and in hospitalized patients with COPD-E, dual virus—bacterial infection correlated with impaired lung function and longer hospital stay. During experimental RV infection, coinfection was associated with prolonged lower respiratory symptoms. In summary, the role of dual virus—bacterial infections in COPD exacerbations is likely to have been overlooked and may be an important factor contributing to the severity of COPD exacerbations.

4. *To expose impaired or aberrant host antiviral innate immunity that is either intrinsic or caused by treatment regimes.* One example is that the above chronic respiratory diseases are associated in some way with impaired antiviral immunity. A striking example is the effects of type 2 mediated allergic inflammation in allergic asthma on the antiviral Interferon (IFN) response. Deficient type I and type III IFNs have been associated with upregulated type 2 pathways that involve the presence of IgE, skin prick test (SPTs), or eosinophilic inflammation, and it is believed this may be the root cause of impaired antiviral immunity, potentially resulting in higher virus loads, and ultimately increased symptoms and worse lung function.

Several studies have observed impaired IFN in cells derived from people with asthma. Not all studies have observed this and differences could be accounted for by different culture methods, virus stocks, asthma severity, or unappreciated subtle differences in the asthma endophenotypes of the donors. In support of these ex vivo findings, virus load is higher in individuals with atopic asthma compared with nonasthmatics.
following experimental RV challenge; and recently, bronchial epithelial IFN-α/β staining by immunohistochemistry was impaired in individuals with atopic asthma, and was inversely related to increased clinical symptoms and increased virus load following experimental RV challenge.

Mechanisms associated with impaired IFN include the crosslinking of IgE on DCs derived from people with asthma prevents virus-induced IFN-α production; BECs derived from people with asthma have been shown to have higher expression levels of suppressor of cytokine signaling-1, which when nuclear, prevents virus-induced IFN-β and IFN-λ production. Macrophages may recognize respiratory viruses via TLR7, and TLR7 expression is deficient in macrophages, and bronchial tissue from people with asthma and may explain why their cells are also impaired in IFN production during viral infection.

Other than direct, cell culture based studies where IFN transcripts or protein are measured following ex vivo virus infection, an alternative method of perceiving impaired IFN in individuals with asthma is to use large transcriptomic studies. These studies have the advantages of often incorporating more donors than possible with culture based studies. A recent study investigated the gene expression patterns of bronchial brushings. Genes strongly correlating with FeNO levels were used to identify clinically important clusters of asthma phenotypes. Although type I and III IFNs and their downstream genes did not form an identifiable cluster, a group of individuals with high Nos2 expression and genes associated with type 2 immunity were also found to have low expression levels of genes related to innate immunity and antimicrobial defense. The fact that the samples were taken during stable asthma (not at exacerbation) likely explains the lack of type I and III IFN and related genes found to be associated with any cluster of asthma phenotypes.

If the idea that type 2 inflammation may be related to impaired IFN is correct, then the association of increased severity of RV infection in AE could be explained by the type 2-dominated inflammatory environment providing a susceptibility factor for RV infection. In epidemiological studies of respiratory virus infections, the exact endophenotype of asthma is seldom studied, and there is no detailed data on IFN expression. Therefore, this idea remains a compelling hypothesis. In support, a recent study of over 300 children from a birth cohort study found that cluster analysis of ex vivo responses in peripheral blood mononuclear cell (PBMCs) at age 11 to different viruses and TLR ligands were related to asthma at ages through to age 16. One cluster, defined by very low type
IFN induction and high proinflammatory cytokine induction, had the strongest relationship with asthma risk, frequency of AE, and unscheduled visits to primary health services associated with asthma. While impaired IFN in asthma is a controversial topic, and may be present in a yet to be properly classified endophenotype of type 2 asthma, this phenomenon does bring about new avenues for therapy, including IFN therapy for asthma, as discussed below.

Impaired production of IFNs may increase susceptibility to virus infection in COPD. In the experimental RV infection studies in COPD, virus load was higher in the COPD subjects compared with non-COPD subjects. This suggests that the mechanisms controlling viral replication are defective in COPD as all subjects were inoculated with the same intranasal virus dose. Despite this, it remains unclear whether production of IFN is impaired in all COPD patients. Ex vivo RV stimulated macrophages from COPD subjects produce less IFN compared with non–COPD subjects; however, not all studies have supported this observation, with similar and even increased IFN production reported in cells obtained from COPD subjects. A recent study also observed impaired IFN-β induction in response to influenza virus infection. The failure to robustly induce IFN-β transcription was thought due to a lack of protein kinase R expression and lack of formation of the IFN-β enhanceosome at the IFN-β promoter.

The presence of RV during CF exacerbations may also be attributed to impaired antiviral immunity. One possibility is the CF epithelium is intrinsically proinflammatory or alternatively antiviral innate immune responses in CF cells are inherently deficient. Zheng et al. support the premise that impaired innate host defense causes susceptibility to viral infections in patients with CF highlighting increased replication following PIV infection of cultured airway epithelial cells from CF donors with correction by subsequent administration of IFN-α. Although IFN responses were not impaired, there was reduced induction of nitric oxide synthase 2 (NOS2) in CF airway epithelial cells. NOS2 is important as it is required for production of nitric oxide (NO), which is a known antiviral mediator. Therefore, impaired NO synthesis may be one mechanism of impaired antiviral host responses in CF. Holtzman et al. hypothesized “hypersusceptibility” to virus infection, via defective IFN pathways, is a unifying pathway in asthma, COPD, and now CF. The overriding hypothesis is that chronic airway inflammation, regardless of origin, interferes with innate immunity causing a suboptimal or blunted antiviral response that
leads to an imbalanced host response reinforcing the preexisting predominant inflammatory phenotype.

Viral exacerbations of IPF may also be a result of impaired antiviral immunity. A study of familial IPF has identified one way in which antiviral immunity can be affected in ILD. Genetic studies in six affected families identified a gene (ELMOD2). Further work has demonstrated that ELMOD2 is involved in type I and III IFN induction in response to TLR3 activation, an important part of the innate immune response to viruses including RV.

### 6.7 RHINOVIRUS—TREATMENT INTERACTIONS IN CHRONIC RESPIRATORY DISEASES

Medications used to treat patients with chronic respiratory diseases affect immunity and airway function and therefore have the potential to modify the response to RV and affect disease outcomes. Associations between RV infection and current therapy use may broadly be divided into two main groups; firstly RV or other respiratory viruses may benefit from the direct action of the therapy, for example through suppressing important host responses that have direct antiviral effects. Another is as a confounder; that is, therapy use may promote or coincide with some unknown risk or susceptibility factor (e.g., antibiotics). Surprisingly, little attention has been paid to the detrimental effects current treatments for chronic respiratory diseases may have on antiviral host responses. Each treatment and the effects they may have on immunity relevant to viral or bacterial infection in chronic respiratory diseases are discussed below.

**GCs, β₂ agonists, and leukotriene receptor antagonists** are examples of immunomodulatory or antiinflammatory medication widely used to treat chronic respiratory diseases, particularly asthma and COPD. As asthma is a chronic disease often requiring daily treatment with a range of immunomodulatory or immunosuppressive agents, such as GCs, this idea seems plausible. Hypogammaglobulinemia has been associated with GC use in asthmatics, although whether this contributes to increases in infection is not clear. GCs, β₂ agonists, and PDE4 inhibitors can have potent suppressive effects on IFNs as seen in tissue culture experiments, and recently Singanayagam et al. showed that in a mouse model, the GC fluticasone propionate could suppress IFN induction and antibacterial immunity, leading to increased virus-induced mucin expression and RV replication.
In IPF, the degree to which IPF-E is due to an impaired immune response arising from the ILD itself, as opposed to the immunosuppressive/antifibrotic treatments that many of these patients are given (e.g., GCs), is difficult to differentiate and research into the ILDs is further complicated by the heterogeneity of disorders, the short time frame available for treatment (3–5 years), and relatively imprecise diagnostic criteria.

Antibiotics may act as a confounder, and may be associated with respiratory infections. The hygiene hypothesis states that the increasing incidence of allergic diseases in the Western world is based on higher standards of personal cleanliness and has thus reduced the opportunity for cross infection of microorganisms. Here antibiotics may alter the microbiome, and thus immune maturation and development. Current international guidelines do not support the use of antibiotics for asthma, yet antibiotics are often prescribed as a general treatment for lower respiratory tract infections (LRTIs), and asthma despite evidence for a bacterial or viral etiology. Antibiotic exposure in the uterus has been associated with an increased risk of asthma in cohort analyses, and this association is more than tripled if antibiotics were used to treat respiratory infections rather than antibiotics used for either urinary tract or skin infections. Early antibiotic use is also believed to increase asthma risk by 2–3 fold in 7–8 year olds. Here antibiotics may drive changes in the microbiome, deplete potentially protective microorganisms including *Prevotella* spp., or contribute to airway dysbiosis as seen in the gut and affect immune development. The fact that this could alter immune responses to viral infections and thus predispose to AE rates seems plausible. In mice, long-term treatment with antibiotics negatively impacts on immunity to influenza.

In a recent large cohort study, a significantly higher risk of physician-confirmed wheezing after antibiotic prescription and a twofold increase in severe wheeze or AE after antibiotic prescription was also observed. In children who wheezed, the risk of AE and admissions to hospital were also significantly increased in the 2 years after the first antibiotic prescription. Children who received antibiotics in infancy had significantly lower induction of cytokines from virus-infected PBMCs at age 11. The conclusion was that an increased susceptibility to viral infections is associated with both early life antibiotic prescription and asthma risk, although the authors could not exclude reverse causation, in that antibiotic use or asthma influence PBMC responses to viruses later in life. Clearly this is an area of emerging interest and further large clinical studies are required to
understand the interrelationships between RV and asthma and COPD treatments, and to determine whether certain treatments do benefit respiratory infections in asthma.

6.8 FUTURE DIRECTIONS FOR THERAPEUTIC APPROACHES

The predominance of RV infections in exacerbations of chronic respiratory diseases must therefore strengthen their claim as a direct target in these diseases. Unfortunately, the successful development of antivirals and vaccines for RV has been disappointing when compared with the development of successful antivirals for RSVs\textsuperscript{166,167} and vaccines for influenza.\textsuperscript{168} This next section will consider future directions of targeting RV directly, and will consider other therapy options available that may indirectly affect RV-induced host responses critical in exacerbations of chronic respiratory diseases.

Antivirals for RV, discussed elsewhere, have been seldom tested in individuals with chronic respiratory diseases. The 1990s and early 2000s saw a number of RV-specific antivirals tested in healthy volunteers; however none were considered efficacious enough to transcend the early clinical development pipeline.\textsuperscript{169,170} Recently, a series of compounds that act on host N-myristoyltransferases were shown to have antiviral effects on in vitro models of RV infection by blocking virus capsid assembly, although efficacy was only observed when compounds were given during, or within, 3 hours of infection.\textsuperscript{171} Challenges to the use of antivirals in chronic respiratory disease such as asthma and COPD are many, and have been discussed in a recent review article;\textsuperscript{169} they include dosing, treatment timing relevant to infection, relationships between virus load and symptom onset and duration, and use of existing therapies.

IFN-β has potent effects on RV in vitro and in vivo\textsuperscript{125,172} and IFN-β (SNG001) therapy was tested in asthma in 2014;\textsuperscript{173} however it did not significantly alter lung function or ACQ scores in a study of naturally occurring infections. In a subgroup analysis, asthmatics with more severe disease did experience improvements in ACQ and morning PEF compared with placebo, suggesting that a pan antiviral may be useful in treating AE in more severe patients. A confounding factor for IFN-β therapy acting as an antiviral is the fact that IFN-β may provide additional therapeutic benefit by downregulating type 2 pathways.\textsuperscript{150} This makes IFN therapy attractive as a therapy for AE, but complicates the interpretation of any positive effects; the fact that asthmatics may be defective in IFN
induction further makes IFN-therapy attractive, but may additionally complicate the interpretation of trials with IFNs. Additionally, IFN-inducing agents such as TLR9 agonists may also hold promise for AE by downregulating type 2 immunity via inducing IFNs. The converse may also be true of anti-Th2 cytokine therapy, which does show impressive reductions in AE rate; however it is unclear if they act by reducing ongoing type 2 inflammation alone, or by restoring a defective IFN-mediated antiviral response. Anti-IgE has been shown to affect AE rates in asthmatic children, and a recent study of 300 volunteers showed that AE rate during anti-IgE therapy was directly related to ex vivo levels of IFN-α produced from RV infected PBMCs.

These mechanisms may also be relevant in COPD, as COPD patients may exhibit increased eosinophil infiltration during COPD-E. Clearly, further careful research is needed in this area, and the use of anti-Th2 biologics and anti-IgE in established experimental RV challenge studies may also help discern their true mechanism of action and how asthmatics are benefiting.

Azithromycin, a macrolide antibiotic has shown promise in reducing rates of AE and COPD-E, and reducing the number of wheeze events and LRTIs in young children. The fact that some of these effects are observed in the absence of proven bacterial infection is intriguing, suggesting that azithromycin may have additional benefits and is not just a mere antibiotic. In one study, the effects were most obvious for volunteers with proven RV infection suggesting that RV may in some way be susceptible to azithromycin, although secondary bacterial infections that may have been a consequence of RV infection were not studied. Potential antiviral properties of azithromycin are supported by in vitro studies that show that azithromycin can boost RV-induced IFN responses, thus reducing viral load. The augmentation of IFN is specific, and virus-induced inflammatory mediators are not affected, although the mechanism remains to be properly elucidated, and the direct benefit of azithromycin on RV infection is yet to be proven in a clinical setting.

6.9 SUMMARY

Exacerbations of respiratory diseases represent a major unmet need in respiratory medicine. The past 20 years have undoubtedly put respiratory viral infections center stage as triggers for exacerbations, and their
perceived importance will only increase as diagnostic tests improve. Many challenges still remain in elucidating mechanisms of disease immunopathology, identifying at-risk populations, optimizing treatment, and identifying future therapeutic targets. For basic research, an important directive will be to continue to translate findings from in vitro or ex vivo culture systems and animal models, into human models. The different respiratory diseases are also at different stages in terms of addressing unmet therapeutic needs; a subpopulation of asthmatics experiencing AE will benefit from additional anti-type 2 cytokine therapy, while a better understanding of basic disease mechanisms is needed for other subgroups. These new disease modifying approaches are yet to be applied to COPD-E, and there are reasons for cautious optimism that COPD-E may benefit from approaches successfully applied to asthma. CF and the ILDs represent different challenges, more basic research is required to better understand the role of viruses, underlying mechanisms of disease and other triggers of exacerbations; these two diseases may also be candidate diseases for direct antiviral therapy.

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