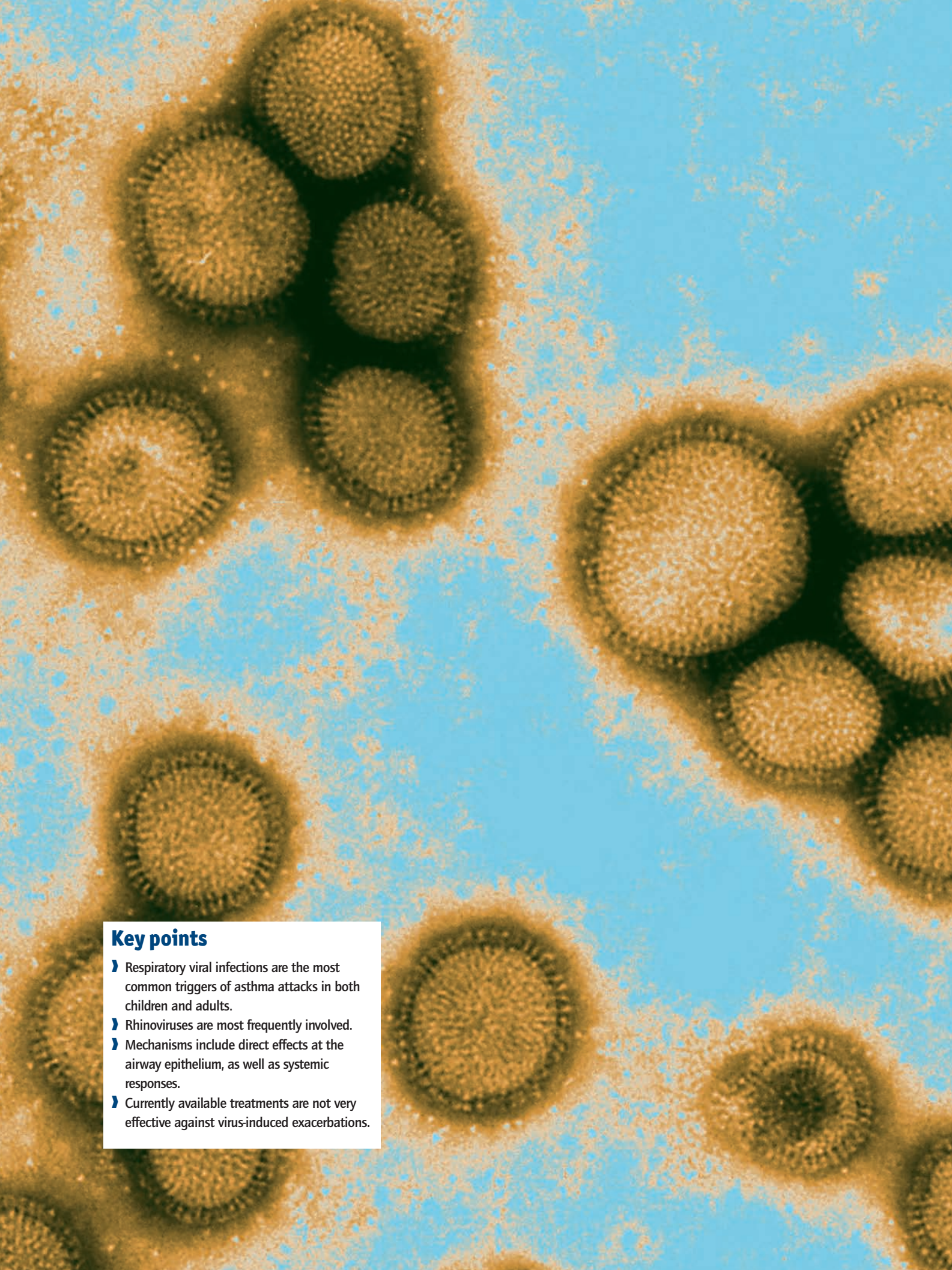

Key points

- Respiratory viral infections are the most common triggers of asthma attacks in both children and adults.
- Rhinoviruses are most frequently involved.
- Mechanisms include direct effects at the airway epithelium, as well as systemic responses.
- Currently available treatments are not very effective against virus-induced exacerbations.

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Viruses and asthma exacerbations

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Educational aims

- To emphasise that respiratory viruses are major triggers of acute asthma exacerbations in both children and adults.
- To describe the current understanding of underlying mechanisms.
- To discuss possibilities for intervention.

Summary

Acute exacerbations of asthma are the major cause of morbidity and mortality of the disease, and one of the most difficult outcomes to prevent and treat. Respiratory viral infections cause >80% of asthma exacerbations in children and >50% in adults. In recent years, an increasing number of studies have investigated the mechanisms underlying asthma exacerbations; however, our understanding is still incomplete. Promising new data suggest the possibility for novel prevention and/or therapeutic strategies. This review aims to increase understanding of the epidemiology, mechanisms and potential treatments for virus-induced asthma exacerbations.

All patients with asthma are at risk of having exacerbations. Exacerbations are a major cause of morbidity and mortality, and are associated with high costs, including time lost at school and work, primary care consultations and hospital admission. Such risk is only partially affected by the optimisation of treatment with inhaled glucocorticosteroids and long-acting β_2-agonists, suggesting that the pathogenesis of asthma exacerbations and that of persistent asthma are likely to be different.

Triggers of asthma exacerbations

The observation that common colds in asthmatic individuals very frequently lead to acute asthma exacerbations has been consistently observed in clinical practice. Viral identification was first achieved >30 years ago using culture and serology. However, these methods have low sensitivity, especially for rhinoviruses (RV) and corona viruses, thus underestimating the impact of viral infection on acute wheezing.

This problem was solved with the development of molecular diagnostic tools, such as PCR (figure 1). At present, these methods are mostly available for research purposes, but are steadily becoming more widely used and standardised.

The use of PCR-based techniques and prospective study designs were critical for the accurate description of the role of viral infections in asthma exacerbations. In the mid-1990s, the proportion of exacerbations associated with an upper respiratory tract viral infection was 85% in children and 44% in adults [1, 2]. More recent studies have confirmed and provided more information about these data. In children visiting the emergency

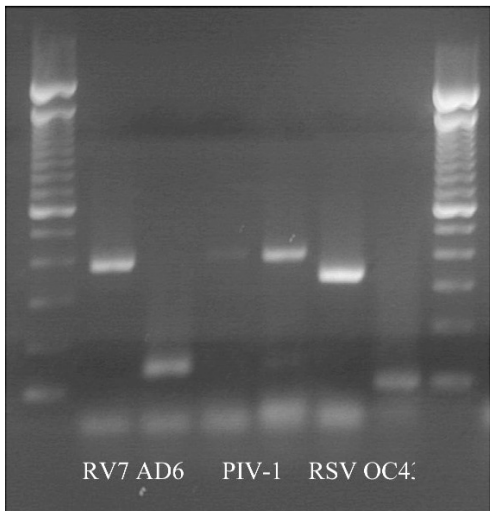

Figure 1
Amplicons from PCR for RV, adenovirus (AD), parainfluenza (PIV)-1, RSV and corona (OC) performed on a nasal lavage sampled from an infant hospitalised for acute bronchiolitis.

room for an asthma exacerbation, respiratory viruses were detected in 82% of infants and 83% of older children [3]. A similar detection rate (82%) was found in children hospitalised with severe exacerbations [4]. In inner-city asthmatic adults, virus was detected in 44% of followed-up subjects and up to 55% of subjects presenting to the emergency department [5]. However, in a more recent study, where PCR was applied for all common respiratory viruses, the detection rate reached 76% [6].

Therefore, it was confirmed that respiratory viruses are very common triggers of asthma attacks, and are present in the vast majority of instances.

Agents involved in acute episodes of wheeze

The most commonly involved viruses are RVs, respiratory syncytial virus (RSV), influenza and parainfluenza viruses, corona viruses, enterovirus and adenovirus (figure 2).

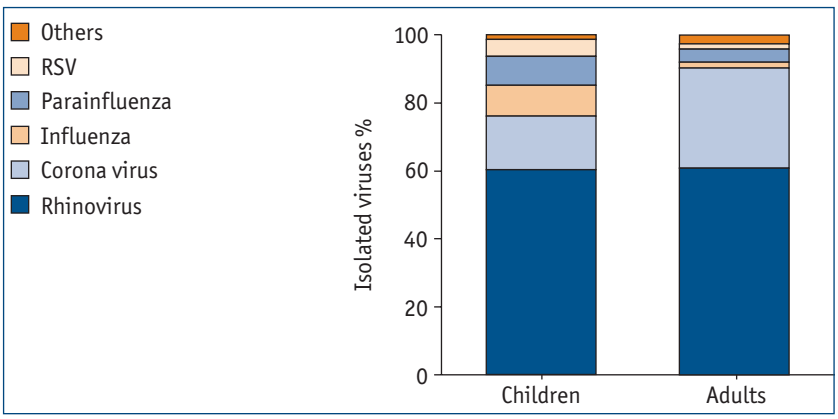

Figure 2
Viral agents implicated in acute asthma exacerbations in school children and adults, as a percentage of total isolated viruses. Rhinovirus and corona viruses represent 80–90% of cases. Adapted with permission from [7].

RSV is the most commonly identified agent in acute bronchiolitis in infancy, which is frequently indistinguishable from the first acute exacerbation of asthma [8]. Later on in life, RSV usually produces only non-complicated upper airways infections, but serious RSV infections can become a problem in the elderly. It is still unclear whether RSV may be a direct cause of asthma, or if it affects only genetically predisposed subjects.

RV is the most dominant virus, probably at all ages and certainly after infancy, representing up to two thirds of upper respiratory infections. They are also associated with ~50% of all asthma exacerbations in studies of asthmatic children [9].

RVs are small RNA viruses belonging to the family Picornaviridae, which also includes enteroviruses, cardioviruses and apthoviruses. There are >100 serotypes. They are non-enveloped viruses with an icosahedral (20-sided) shape and they are ~25 nm in diameter. They are divided into two different types: major (90%), which bind to intercellular adhesion molecule (ICAM)-1; and minor (10%), which bind to the low-density lipoprotein receptor [10].

Influenza and parainfluenza viruses affect all age groups, and they represent an important pathogen during winter [11]. Corona viruses are frequent agents in common colds, as well as adenoviruses. *Mycoplasma* and *Chlamydia pneumoniae* are also among the agents isolated in both colds and asthma exacerbations, although the relative proportion varies considerably between studies.

In the last few years, new respiratory viruses have been identified that are potential asthma exacerbation precipitants. Human metapneumovirus (hMPV) was detected in up to 7% of adults hospitalised for an acute asthma exacerbation [12]. hMPV is a recently discovered paramyxovirus that has been classified in the genus *Metapneumovirus* and the subfamily Pneumovirinae. The epidemiological profile and clinical manifestations of hMPV infection are similar to RSV, as hMPV was detected in up to 16% of infants hospitalised for acute bronchiolitis in a previous study [13].

Torqueteno virus (TTV), a single-stranded circular DNA virus, was originally identified in 1997 and classified in a new genus, *Anellovirus*. A recent study detected an increased amount in children with mild-to-moderate asthma in comparison with healthy controls, with a correlation between nasal TTV load and airway resistance [14].

Mechanisms of virus-induced acute asthma exacerbations

Respiratory viruses may induce asthma exacerbations though direct effects on their main target, *i.e.* the airway epithelium, as well as *via* a systemic immune reaction. Additional mechanisms, such as neural reflexes or physiological disturbances (mouth breathing, reduced mucociliary clearance), have been proposed but not yet adequately studied.

Epithelial effects

Viral replication in the bronchial epithelium

Most respiratory viruses are able to replicate in both the upper and lower respiratory epithelium, thus inducing cytotoxicity. The ability of RVs to infect and replicate in the lower airway has been questioned in the past, based on temperature preferences. It was shown, however, that RVs are able to replicate at a lower airway temperature [15] and to infect human bronchial epithelial cells [16]. Replication characteristics are not different from those reported for nasal and tracheal epithelium, suggesting that the whole respiratory tree may be equally susceptible to RV. Using human volunteers who were subjected to an experimental RV upper respiratory infection, the current authors were able to detect both genomic and replicative strand viral RNA using *in situ* hybridisation in the bronchial biopsies of 50% of infected subjects [16], indicating that RVs not only reach and enter the bronchial epithelium after upper airway infection but also replicate in it (figure 3). These results were confirmed in a recent study using multiple mucosal biopsy samples and cell brushings, and immunohistochemistry with specific monoclonal antibodies against RV16, which demonstrated a patchy distribution of infected cells [17].

Viral infection induces epithelial inflammation

When a virus reaches and infects the bronchial epithelium, it may upregulate the expression of a range of pro-inflammatory mediators (table 1). The pro-inflammatory cytokine interleukin (IL)-1β was detected in nasal secretions of experimentally infected volunteers. IL-8, a key mediator in neutrophil-mediated acute inflammation, was also detected in naturally occurring infections correlating with neutrophilia in blood and nasal samples in children with virally precipitated asthma or experimental infection [18].

Epithelial neutrophil-activating peptide (ENAP)-78, which also induces neutrophil migration, was found to be elevated in nasal samples from RV-infected subjects [19]. Other RV-induced mediators include eotaxin and RANTES (regulated on activation, T-cell expressed and secreted), potent eosinophil chemoattractants, and IL-16 and monocyte chemoattractant protein (MCP)-1 chemoattractants for CD4 T-lymphocytes and natural killer cells, respectively.

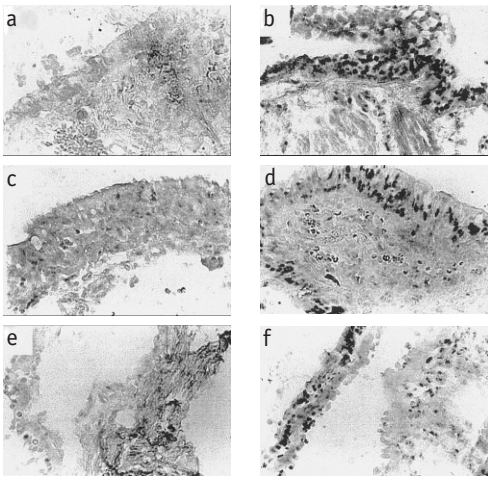

Figure 3
In situ hybridisation for rhinovirus RV16 in sections of human bronchial biopsy samples. Negative bronchial biopsy samples taken before infection from subjects (a, c and e) are compared with RV16-positive biopsy samples from the respective subjects obtained during experimental RV16 infection (b, d and f). The hybridisation signal for RV16 is visible in the cells (black) and is localised mainly on epithelium. Adapted with permission from [16].

Table 1 Mediators released from epithelial cells after RV infection

Pro-inflammatory mediator release	*RV serotype*	*Bronchial epithelial cells used*
ENAP-78	*39*	*BEAS-2B*
Eotaxin	*1b, 16*	*BEAS-2B*
Eotaxin-2	*1b, 16*	*BEAS-2B*
FGF-2	*1b, 16*	*BEAS-2B*
G-CSF	*39*	*BEAS-2B*
GM-CSF	*2, 14, 16, 39, 49*	*BEAS-2B*
GRO-a	*39*	*BEAS-2B*
IL-1β	*39*	*BEAS-2B*
IL-6	*1A, 2, 7, 14, 16, 39*	*BEAS-2B*
IL-8/CXCL8	*1b, 2, 7, 9, 14, 16, 3*	*BEAS-2B*
	9, 49	*MRC-5*
IL-11	*14*	*A549, MRC-5*
IL-16	*2, 7*	*HBEC*
MIP-1	*1b, 16*	*BEAS-2B*
RANTES	*1b, 2, 7, 16, 49*	*BEAS-2B, HBEC, A549*
FGF-2	*1b*	*BEAS-2B*
VEGF	*1b*	*BEAS-2B, HBEC*

G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; GRO: growth-related oncogene; MIP: macrophage inflammatory protein.

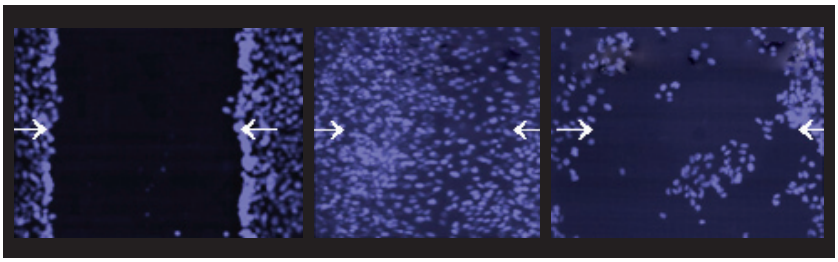

Figure 4
BEAS-2B cells were mechanically damaged following RV, with or without infection. Cells were stained with the DNA dye DAPI, and taken at baseline and after 24 hours. There is defective healing in RV-infected cells. Adapted with permission from [24].

Interestingly, it has recently been shown that RV infection may stimulate the epithelial production of fibroproliferative and angiogenic factors, such as fibroblast growth factor (FGF)-2 and vascular endothelial growth factor (VEGF) [20], suggesting a pathway that may contribute to the structural changes (remodelling) seen in asthma.

Parainfluenza viruses also induce epithelial inflammation, leading to epithelial damage and influx of inflammatory cells. They can also cause bronchial hyperresponsiveness and bronchial fibrosis through the induction of transforming growth factor-β, possibly contributing to the pathological structural changes in asthma [21].

Influenza viruses infect airway epithelial cells, leading to enhanced inflammation, cell death, as well as the release of pro-inflammatory mediators and chemokines RANTES, MCP-1 and IL-8 [22].

RV is also able to induce the upregulation of ICAM-1, its own receptor [23]. ICAM-1 plays a major role in leukocyte recruitment and allergic inflammation, as well as vascular cell adhesion molecule (VCAM), which is also induced.

Most of the above mediators, including IL-8, IL-6, CXCL10, ICAM-1 and VCAM, are transcriptionally regulated by nuclear factor (NF)-κB.

RV induces cytotoxicity and apoptosis in bronchial epithelium

It has been generally accepted that RVs do not induce cytotoxicity *in vitro* or *in vivo*. However, two recent studies that were designed to assess the ability of RVs to infect primary human bronchial epithelial cells have unexpectedly observed RV-associated cytotoxicity [16]. Further investigating this phenomenon in an *in vitro* BEAS-2B cell line system, it was shown that RVs can become cytotoxic, depending upon serotype, dose and especially confluence of the cultured epithelium [24], suggesting that RVs can adopt this property in a damaged epithelium. Furthermore, RV may delay wound healing (figure 4), possibly through a defect in the proliferative capacity of epithelial cells. Another recent study has also shown that RV14 can induce epithelial cell death *via* mitochondrial pathway-induced apoptosis [25].

Apoptosis is an essential physiological mechanism used by the epithelium as self-defence against virally infected cells. This mechanism seems to be defective in bronchial epithelial cells from asthmatic individuals; when infected with RV, the cells displayed profoundly impaired apoptosis mediated through interferon (IFN)-β, resulting in increased virus replication [26]. It has also been proposed that infection with *C. pneumoniae* may inhibit epithelial cell apoptosis, thus enhancing infected cell and pathogen survival [27]. Although this article is focused on viral infection, increasing evidence suggests a role for atypical bacterial (*C. pneumoniae* and *M. pneumoniae*) in both chronic-stable and acute exacerbations of asthma [28].

Systemic effects

In a simplified model, asthma is characterised by a T-helper cell (Th)1/Th2 imbalance, with a Th2 preponderance. IFN-γ is the central cytokine in type I, as opposed to IL-4 and IL-5 in type II responses. It seems contradictory that a viral infection, which is mainly IFN inducing, may exacerbate a Th2 disease. However, it appears that Th1/Th2 cytokine imbalance affects the way a host responds to viral infection. An inverse correlation between RV persistence after experimental infection, as well as symptom score, and the ratio IFN-γ/IL-5 levels in nasal secretions has been reported [18]. When peripheral blood mononuclear cells (PBMCs) from normal or atopic asthmatic subjects were exposed to RVs, time- and dose-dependent increases of IFN-γ, IL-12 and IL-10 were observed in both groups [29]. IL-4 was induced only in the asthmatic group, which produced significantly lower levels of IFN-γ and IL-12, and higher levels of IL-10. Until recently, it was not certain whether RVs can actually reach the bloodstream. However, it has recently been shown that RV viraemia occurs frequently after a cold, although it only lasts for a short period of time and is more frequent in cases where an acute asthma exacerbation occurs [30].

During RV experimental infection, an increase in submucosal lymphocytes and eosinophils has been observed; in the case of

asthmatic subjects, only the latter persisted into convalescence [31]. When PBMCs from normal and atopic asthmatic individuals are exposed to RV, there are no differences in T- or B-cell proportions, whereas CD14+ monocytes are reduced [32]. An increase in cell activation (CD25+ upregulation) and induction of the costimulatory machinery are observed. B7-1 (CD80) was upregulated on monocytes and B7-2 (CD86) on B-cells, and this was suboptimal in the asthmatic population. Interestingly, these costimulatory molecules were downregulated in the peripheral blood of atopic asthmatic children during an acute exacerbation, a finding that has been attributed to possible migration of activated cells in the lung [33].

Viral infection induces long-lasting airway hyperresponsiveness

Airway hyperresponsiveness (AHR) is associated with the pathogenesis of asthma. Several studies have shown increased AHR after respiratory infections. Human experimental infections with RV increased AHR to non-specific stimuli for up to 4 weeks after a viral infection in allergic subjects [34]. More recently, a cohort of children with post-viral asthma was prospectively followed-up and AHR was assessed at regular intervals after a cold. The majority of documented infections were due to RV (82%). The duration of post-viral AHR is actually much longer, ~7 weeks when no subsequent cold occurs, but because of recurrent colds it frequently continues for several months. Atopic subjects had an increased number of colds and, therefore, significantly prolonged duration of AHR [35].

Synergy between viral infections and other environmental factors

Epidemiological studies suggest a synergy between viral infections and other environmental factors in the induction of exacerbations.

GREEN *et al*. [36] have reported that the risk of admission to hospital with acute asthma in adults was clearly increased with the combination of sensitisation and current exposure to high levels of sensitising allergens and the presence of a viral infection. In human experimental RV infection models, it has been shown that there is an augmentation of allergen-induced effects after viral infection [37]. When the current authors exposed bronchial epithelial cells to RV and Der p I (the major allergen of house dust mite), a synergistic effect in the induction of IL-8 and ICAM-1 was observed. However, other studies have failed to demonstrate synergy [38], possibly due to differences in exposure characteristics.

Exposure to NO_2 in the week before the start of a respiratory viral infection has been associated with an increased severity of asthma exacerbation [39]. *In vitro*, epithelial cells exposed to RV and NO_2 resulted in a synergistic increase in both IL-8 release and ICAM-1 expression [40].

Antiviral strategies for the prevention and treatment of virus-induced asthma exacerbations

Whether a window of opportunity exists from the occurrence of a viral upper respiratory infection until the development of an acute asthma exacerbation, during which an antiviral strategy may be effective, is not known. Alternatively, it cannot be predicted whether immunisation against one or more of the viruses involved will be able to reduce virus-associated asthma episodes or just shift the problem to different strains. In order to answer the above questions, reliable antiviral tools are required. Unfortunately, the only virus for which there is reliable prevention (and an effective vaccine) is influenza. Of course, the effectiveness of the vaccine varies every year and does not apply to pandemic strains. Conversely, RVs represent the majority of virus-induced asthma exacerbations cases, for which the treatment options remain unsatisfactory. RV has >100 serotypes, making it impossible to develop an effective vaccine. Vaccines for other respiratory viruses are either in development, are not sought after or are impractical.

A variety of antiviral agents against RVs have been studied. Additional antiviral/anti-inflammatory strategies against the common cold have been suggested with varying but usually little success (table 2) [41].

Antiviral strategies include the regularly used, but with small therapeutic value, ascorbic acid, zinc and echinacea. Local IFN-α therapy

Educational questions

1. Which of the following causes the highest proportion of asthma exacerbations:
   a) Allergen exposure.
   b) Viral infections.
   c) Pollutants.
   d) Stress.
2. Put into sequence the events that take place in the airways, leading from exposure to virus to an acute asthma attack.
   a) Mediator production.
   b) Epithelial infection.
   c) Oedema and bronchoconstriction.
   d) Cellular infiltration.
   e) Virus replication.
3. Which of the following treatments have been shown to have a moderate benefit in preventing virus-induced asthma exacerbations (true or false)?
   a) Ascorbic acid.
   b) Macrolide antibiotics.
   c) Corticosteroids.

has been abandoned due to frequent nasal side-effects. Macrolide antibiotics, bafilomycin A1 and erythromycin have been shown to inhibit ICAM-1 epithelial expression, and hypotheses about their potential as anti-inflammatory agents have yet to be definitively proved [42], as clinical proof is missing or negative.

During the last few years, anti-rhinoviral compounds such as plecoranil (Schering-Plough Corporation, Kenilworth, NJ, USA), which act by preventing the uncoating of picornaviruses [43], the RV 3C protease inhibitor ruprintrivir (Agouron Pharmaceuticals Inc., San Diego, CA, USA) [44] and soluble ICAM-1 (tremacarna/BIRR; Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA) [45] have shown promising results in early-stage clinical trials, but have not yet reached the bedside.

Therefore, strategies for virus-induced asthma and related exacerbations are, in principal, anti-inflammatory, following strategies against persistent asthma. Glucocorticoids (GCs) are effective *in vitro* [46]; however, they show poor efficacy in models of human experimental infection [47]. In almost all major clinical studies, no virological identification during exacerbations has been performed. Therefore, it is not possible to conclude whether the benefit observed with GCs during exacerbations also includes virus-induced ones. This is also the case for GCs in combination with long-acting β_2-agonists (LABAs), which are superior to GCs alone in reducing the frequency of asthma exacerbations [48]. However, a recent study demonstrated that *in vitro* treatment with GCs/LABA was able to suppress the production of pro-inflammatory mediators in RV-infected bronchial epithelial cells in a synergistic or additive manner [49]. These data suggest the need for focused clinical studies looking into the combined effect of GCs/LABA in virus-induced asthma exacerbations.

Finally, there is evidence that leukotriene receptor antagonists may be effective in virus-induced asthma. BISGAARD *et al*. [50] used montelukast in the prevention of virus-induced asthma exacerbations in 2–5-year-old children taking part in a 12-month, multicentre, double-blind, parallel-group study. Children receiving montelukast had a 32% reduction in asthma exacerbations, a delayed time to first exacerbation and less use of inhaled GCs.

In conclusion, there are promising strategies for either specific antiviral or anti-inflammatory prevention/treatment of virus-induced asthma exacerbations. However, more focused clinical studies are needed in order to bring any of these approaches closer to clinical practice.

Table 2 ***Proposed therapies against virus-induced asthma exacerbations***

Vitamin C
Zinc gluconate lozenges
VLDL receptor fragments
Soluble ICAM derivatives
RV 3C protease inhibitors
Pleconaril
IFN-α_2
IFN-β
Inhaled GC therapy
GCs in combination with β_2-agonists
Bafilomycin A1
Erytromycin
Inhibitors of NF-κB signalling

VLDL: very low-density lipoprotein; GC: glucocorticoid.

Suggested further reading

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Suggested answers

1. b
2. b, e, a, d, c
3

a) False.
b) False.
c) True.

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