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# The common cold and asthma

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## Introduction

This review focuses on how a viral infection and disease of the upper airways can influence asthma, a disease of the lower airways. We will, therefore, discuss "the common cold", which is caused predominantly by rhinovirus (RV) and coronavirus, and we will not deal with a general airway infection ("flu"), caused by influenza-, parainfluenza- and adenovirus, because these viruses may trigger asthma predominantly by a direct infection of bronchial cells.

The common cold is, as indicated by the name, a very frequent disease. In otherwise healthy persons it is a trivial disorder, although it causes considerable morbidity, absence from school and work, and complications such as bacterial otitis media and sinusitis. Common cold viruses frequently trigger acute exacerbations of asthma and of chronic obstructive lung disease. In patients with chronic lung diseases a common cold often has serious consequences, resulting in considerable morbidity and increased mortality.

Obviously, the common cold is a key disease in this supplement on "The nose and paranasal sinuses in asthma". Considering the paramount importance of a viral airway infection for asthma morbidity it is surprising that relatively few studies have investigated the nature of the link between a common cold/an RV infection and asthma.

Below we will give an overview of the published literature on the common cold and asthma but we will also refer to recent review articles by Holgate (1), Johnston (2) and Busse (3). These scientists have initiated most of the recent work on the link between the common cold and asthma. We shall begin, however, with a description of the pathophysiology of the common cold/RV infection, its transmission and its treatment, because knowledge of these issues is of importance for a full understanding of the link between common

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cold and asthma, and possibly for future attempts of preventing cold-induced asthma exacerbations.

## Rhinovirus colds and naturally acquired colds

### Virology

In textbooks and review articles RV is described as being responsible for 50–60% of acute viral upper respiratory illnesses, and coronavirus for about 10–20%, while influenza virus, parainfluenza virus, adenovirus and respiratory syncytial virus (RSV) account for a minor proportion of common colds (4). A recent study, using the sensitive reverse transcription polymerase chain reaction (RT-PCR) technique, however, has shown RV to be relatively more important and have identified this virus in 80% of adults with cold symptoms during the autumn (5).

RV is one of the most well-described viruses on the molecular level (4). It is a nonenveloped, 30-nanometer RNA particle (picornavirus). The surface of the virus has deep canyons, containing the ligand for the RV receptor on the epithelial cells, which is intercellular adhesion molecule-1 (ICAM-1) (5) (see later).

RV has more than 100 immunotypes. Infection with each type provides immunity, but vaccination is not realistic due to the considerable antigen diversity (4).

### Transmission of rhinovirus

Introduction of RV into the eye or the nose is a highly efficient way of initiating an experimental infection. By contrast, inoculation of RV into the mouth or exposure to infected volunteers, for example by prolonged kissing, is an inefficient method of initiating infection (6).

Children are the major reservoir for RV. Young children experience about eight colds a year, while adults have one to two colds (7). In addition, children easily acquire a runny nose as they have the same number of mucous glands as adults, but a smaller mucosal area and therefore a lower mucociliary transport capacity. Consequently, transmission occurs readily in families with young children (6, 8), especially when they attend kindergartens. Such children are “toxic”.

During colds, nasal secretions containing RV, contaminate the fingers and the environment of the infected person. RV retains infectivity for up to 3 days, for example, on plastic surfaces (6).

Attempts to transmit RV infection by experimental exposure have shown that a 15-s hand-to-hand contact between a virus-infected and an antibody-negative person followed by touching the eye or the nostril, is a very efficient way to transmit RV (9).

The hand contact–self inoculation model has been used to test virucidal hand treatment (10), environmental disinfectants (11) and virucidal nasal tissues (12). The findings in these studies support the finger-to-eye and finger-to-nose inoculation routes of cold transmission, and they indicate that stopping virus transmission may be one way to reduce the number of cold-induced asthma exacerbations.

### Initial infection of cells, shedding and spread of rhinovirus

As mentioned above, the portal of entry for RV can be either the eye or the nose, where the virus can be placed by a finger during eye rubbing and nose picking, respectively. The relative importance of these two sites of entry, in different age groups, is unknown. Is it an open question whether the lower airways can be infected by RV and if so, whether it is by direct inhalation or by spread of infectious secretions from the nose (13) (see later).

When virus is placed in the nostril it comes into direct contact with skin or with squamous epithelium in the mucous membrane. It does not seem to be possible for a finger to reach the ciliated epithelium, which can transport the virus to the adenoid area, where infection appears to be initiated (see later). One can speculate, however, that a few virus particles, placed in the nostril, are carried to the ciliated epithelium by the sniffing of nasal secretions, running to the nostrils. Cold air induces glandular hypersecretion by a cholinergic reflex (14), which may explain why it is commonly believed that exposure to cold air predisposes to the development of an infectious common cold, or in other words why “a cold is called a cold”.

When RV is placed in the eye it will pass through the nasolacrimal duct to the nasal cavity, apparently without infecting the epithelial cells in the conjunctiva, which is difficult to understand because the receptor for RV, ICAM-1 can be upregulated in conjunctival cells (see later). In a study of the spread of RV, we inoculated virus in conjunctiva on one side. Virus could then be detected in brush biopsy samples from the nasopharyngeal mucosa earlier, more frequently, and for longer (up to 3 weeks) than in samples from the nasal cavities (15). The more frequent detection of virus in the nasopharynx than in the nose may be simply because the nasopharynx is the endpoint of the mucociliary

clearance from the nasal passages. On the other hand, RV replication has been demonstrated by *in situ* hybridization in surface cells, probably M cells, in the lymphoepithelium of the adenoids (16). This indicates that the adenoid may hold a key position regarding initial RV infection.

RV replication occurs, in ciliated and in nonciliated columnar epithelial cells, in the nasopharynx and in the nasal passages, and the newly formed viruses are shed into respiratory secretions (17, 18). However, the number of infected epithelial cells seems to be low. Turner and colleagues (18), utilizing immunohistochemical staining of sloughed epithelial cells from patients with experimental RV-induced colds, found that less than 2% of the cells were positive for RV antigen. By *in situ* hybridization, Bardin and coworkers (19) found RV replication in a few cells in nasal biopsies from only half the patients with RV-induced colds. Arruda and coworkers (16, 17) examined multiple nasal scrape biopsies from volunteers with colds and demonstrated RV replication in only a few cells, providing further evidence for virus infection in a limited number of epithelial cells. In two studies, Winther and coworkers (15, 20) took several brush biopsies and found virus growth in only a part of the biopsies, showing that the RV infection of the nasal lining is not universal but "spotty".

#### ICAM-1 is the major receptor for rhinovirus

It is of considerable interest that the receptor for 90% of the RV types is ICAM-1 (21). Conjunctival cells and columnar epithelial cells in the nose do not constitutively express ICAM-1 but they do so when they are antigen-stimulated, for example by allergen exposure of IgE-sensitized individuals (22). One could therefore speculate that antigen-stimulated persons are particularly susceptible to RV infections. However, it is an important counterargument that almost all normal seronegative volunteers can be infected by an experimental inoculation of RV (4). It is our hypothesis that ICAM-1 receptors in the nasopharynx hold a key position in the initial contact between virus and host cells, as cells with constitutively high ICAM-1 expression have been demonstrated on the surface of the normal adenoid (23).

As in the nose, ICAM-1 is not constitutively expressed by surface epithelial cells in the bronchi, but it is upregulated in symptomatic asthma (24). In theory, this could make asthmatic bronchial airways more sensitive than normal airways to direct infection with RV.

#### Viral cytopathologic effect

The effect of cold viruses on nasal epithelial cells has been studied *in vitro* by Winther and coworkers (25). Experimental infection with RV and with coronavirus does not result in visual damage to the epithelial cells. The cilia continue to beat on the nasal tissue fragments (26) and the nasal epithelial cell monolayer remains confluent (27). Thus, RV has no or a negligible cytopathologic effect on ciliated cells.

In contrast, infection of nasal cultures with influenza- and adenovirus results in a complete destruction of the epithelial cells within a few days (25, 26). Infection with RSV has an intermediate position (27).

One can speculate that there are two explanations of the differences between a common cold (symptoms predominantly from the upper airways) and a flu (symptoms from the entire airways). *Hypothesis 1*: a cold is caused by viruses, infecting only the upper airways, while a flu is due to a virus infection of the entire airways. *Hypothesis 2*: a common cold is caused by viruses having no or little cytopathologic effect, while a flu is due to viruses which damage the epithelial lining. Probably the last hypothesis is most likely.

#### Cellular inflammatory changes

The first study of nasal histology in naturally occurring colds dated from 1930. In this work, substantial separation and sloughing of the nasal epithelium was reported (28). Based largely on this study, it was assumed for more than 50 years that the cold viruses damage the nasal epithelial lining, directly causing the cold symptoms, and also impairing mucociliary clearance, resulting in a secondary bacterial infection with neutrophilia and purulent secretions.

It was not until 1984 that a subsequent study was published using light and scanning electron microscopy (29). This study showed a largely intact and continuous epithelial surface. There was accumulation of neutrophils in spite of the absence of a concomitant bacterial infection (30). Based on these observations, we hypothesized that the virus infection of the epithelial cells causes the neutrophilia and the cold symptoms indirectly by the release of a series of inflammatory cytokines and mediators, predominantly from the epithelial cells. This hypothesis is supported by the *in vitro* studies, mentioned above, which show that RV does not cause any gross damage of the epithelial cells (25).

### Ciliated epithelial cells

Nasal biopsies from patients with naturally acquired colds (29, 31) have shown an intact and continuous epithelium by light and by scanning electron microscopy. Considering the dynamics of airway epithelium, showing closure of cell defects within minutes after trauma (32), these findings do not exclude an increased turnover rate and shedding of epithelial cells during a RV cold. In fact, in a study of naturally acquired colds, Pedersen and coworkers (33) found a reduced number of ciliated cells in nasal scrape biopsies during and for some weeks after a naturally occurring cold. It is possible that this study was undertaken during a period with an epidemic of influenza-, parainfluenza or adenovirus infection. This study of naturally acquired colds ("wild colds") needs confirmation with the use of modern diagnostic tests for establishing the virus etiology, because the results differ strikingly from the *in vitro* studies showing no or very little cytopathologic effect of RV and coronavirus on ciliated cells. However, also some early studies of nasal smears from patients with naturally acquired colds have shown shedded ciliated cells with signs of damage ("cilio-cytophthoria") (34).

The apparent contradiction between the findings of viable epithelial cells in *in vitro* studies of RV infection and the reduced mucociliary clearance in *in vivo* studies of naturally acquired colds may be explained by a transmission electron microscopic study by Afzelius (35). Among hundreds of nasal biopsies he found a single biopsy with infection of the columnar cells with a virus (coronavirus?). The infected cells looked viable without destruction, but the cilia were retracted from the surface into the cytoplasm.

### Neutrophils

In our first study of naturally acquired colds, the number of neutrophil leukocytes was clearly increased in the surface epithelium and in the lamina propria very early during the disease (day 2) (29).

In experimental RV infection the results are less obvious. While one study showed a slightly increased number of neutrophils in nasal biopsies on days 1 and 2 of infection (36), another study (37) failed to show any change in the number of neutrophils on day 4 of the illness.

Infiltration of neutrophils into (and through) the nasal mucosa seems to be an early and transient event. Within 24 h of RV inoculation Naclerio and coworkers (38) found an increase of neutrophils in nasal washes obtained every 4 h around the clock, and the number had already begun to decrease by day 3. An increased number of neutrophils was found by Levandowsky and coworkers (39) in nasal washes

from patients with experimental RV colds on day 4 after virus inoculation.

It is important to include sham-inoculation in these type of studies because a biopsy procedure in itself can induce neutrophilia, probably by perturbation of epithelial cells and subsequent release of IL-8 (36).

Experimental RV infection is associated not only with an increase in neutrophils in the nose but also in the blood (40, 41).

### Mast cells and eosinophils

Studies have shown no changes in the number of mast cells and eosinophils in the nasal epithelium and lamina propria during a cold (29, 37). This suggests that these cells are not involved in the pathogenesis of a common cold. However, it cannot be excluded that an RV common cold enhances allergen-induced degranulation of basophils and mast cells, as interferon released by peripheral blood cells, incubated with virus, promotes basophil histamine release (3). In addition, antihistamines have an effect on common cold symptoms (see later).

### Lymphocytes

The lymphocytes in lamina propria of the nasal mucous membrane have been examined by immunohistochemistry in two studies of RV colds (37, 42). No changes in the total number of the cells or in the lymphocyte subsets ( $CD3^+$ ,  $CD4^+$ ,  $CD8^+$ ,  $CD22^+$ ) were detected.

Therefore, any change in the number of circulating lymphocytes does not seem to be caused by a changed recruitment of lymphocytes to the upper airways. Possibly, the finding may reflect lymphocyte homing to the lower airways during a cold (see later).

The published data on the number of circulating lymphocytes in experimental RV infection are conflicting. In three studies (39–41), the numbers of T cells was reduced early during the infection. Winther and coworkers (42), on the other hand, did not find any change in  $CD3^+$ ,  $CD4^+$ ,  $CD8^+$ ,  $CD22^+$  (B cells) and  $CD57^+$  (natural killer cells). Skoner and coworkers (43) found an increased number of both total lymphocytes, and of the  $CD4^+$  and  $CD8^+$  subsets.

Interestingly, a recent study by Vianna and coworkers (44) has shown a decreased peripheral blood T-cell response to phytohemagglutinin and a reduced cytokine formation during a common cold (clinical diagnosis). One can speculate that this reduced T-cell activity may be part of the explanation why common colds induce complications such as acute otitis media, sinusitis, activation of herpes,

exacerbations of asthma and chronic obstructive lung disease.

### Proinflammatory cytokines and inflammatory mediators

RV primarily infect the nasal epithelial cells and this triggers the synthesis and release of cytokines and mediators, causing a cascade of inflammatory reactions which are assumed to be responsible for the cold symptoms (45, 46).

#### Cytokines

The cytokines, which function as neutrophil chemoattractants and activators, are of particular interest since the number of neutrophils in nasal lavage fluid is increased and the number of neutrophils correlates with symptoms in experimental RV colds (38). In this respect, IL-8 is of the greatest importance, as it is a strong chemoattractant for neutrophils and it also activates the cells.

*In vitro* studies of cell cultures have shown that an RV infection induces IL-8 production in both epithelial cells (47, 48) and in fibroblasts (49). *In vivo* studies of naturally acquired colds (50, 51) and of experimental RV colds (52) have shown an increased level of IL-8 in nasal lavage fluid.

Also, infection with RSV induces significant IL-8 production in epithelial cells both in the nose (51) and in the bronchi (52).

Viral infections stimulate the release of other cytokines (IL-1 $\beta$ , IL-6, tumor necrosis factor- $\alpha$ , interferon- $\gamma$ ) into nasal secretions (50, 51, 53–59) but their role in the pathogenesis of the common cold is not clear. Interferon- $\gamma$  probably plays an important role in terminating the virus infection. IL-6 may be important in stimulating T lymphocytes (60). It has been shown that IL-6 and IL-8 are generated following virus-induced activation of the transcription factor NF- $\kappa$ B (56).

One study of nasal lavage fluid has shown a different cytokine profile in experimental colds (interferon- $\gamma$  and IL-1 $\beta$ ) and in allergic rhinitis (GM-CSF and IL-1 $\beta$ ) (61). Further studies are needed to characterize the cytokine/chemokine profile of RV-induced infection.

#### Kinins

Kinin levels are increased in nasal lavage fluid from patients with experimental (38) and with natural RV colds (62). The concentration of kinins peaks at the same time as the symptoms.

Intranasal challenge with bradykinin in normal subjects produces rhinorrhea, nasal obstruction and a sore throat (63). As these symptoms imitate common cold symptoms, it provides suggestive evidence that kinins might contribute to

the symptomatology of viral colds. However, a possible causal role for kinins in the development of cold symptoms cannot be established until it is possible to block their action by specific drugs.

#### Histamine

There is no histologic evidence of mast cell degranulation during a common cold (29), and the level of histamine in nasal lavage fluid is not increased during an experimental RV infection (64–66).

The usefulness of H<sub>1</sub> antihistamines for the treatment of common cold has been the subject of controversy (67). However, there are now three double-blind, placebo-controlled and randomized studies with adequate statistical power which show a beneficial effect of antihistamines on cold symptoms (68–70). The findings of a significant effect on sneezing, less effect on rhinorrhea and no effect on blockage speak in favor of an H<sub>1</sub> receptor blockage being the mode of action, because this is the same symptom profile seen in the treatment of allergic rhinitis.

#### Leukotrienes

Sulfido-leukotrienes, sprayed into the nose, induce vascular changes (71) and they also act as secretagogues (72). It is possible that drugs that inhibit the synthesis of leukotrienes and drugs that block the leukotriene receptor might have some beneficial effect on nasal blockage and mucus hypersecretion in colds. This hypothesis can now be tested as leukotriene receptor antagonists are commercially available.

#### Prostaglandins

Intranasal challenge with prostaglandin D<sub>2</sub> and with prostaglandin F<sub>2 $\alpha$</sub>  results in sneezing and coughing (73). The role played by prostaglandins in the common cold can be judged by the clinical effect of NSAIDs. These drugs seem to have some beneficial effect on coughing (74) and on sneezing, but not on blockage, and there seems to be a negative effect on rhinorrhea (75).

### Nasal hyperresponsiveness

Several reports have shown that a common cold may increase the nonspecific bronchial responsiveness in asthma (see later). The possibility that a viral infection of the nose also produces nasal hyperresponsiveness, however, has not received much attention.

Grønberg and colleagues (76) performed nasal challenges with histamine and methacholine during and after a

naturally acquired cold. Both the sneezing and the secretory response to histamine were significantly increased but only during the first 3 days of the disease, while the secretory response to methacholine was increased for 9 days. In a study of experimental RV infection Doyle and coworkers (77) also found an increased nasal responsiveness to histamine challenge for sneezing and rhinorrhea but not for blockage. While the mean number of histamine-induced sneezes increased from 4.5 to 10.5 in nonallergic volunteers, the increase in allergic rhinitis patients (studied outside the pollen season) was from 10.0 to 19.5.

Greiff and coworkers (78) measured histamine-induced mucosal exudation of plasma before and during a coronavirus infection. The concentration of plasma components in nasal lavage fluid was significantly increased during the infection, indicating the existence of an exudative hyperresponsiveness. These authors also studied the permeability of the mucous membrane from the lumen to the tissue. In contrast to common belief, the permeability, measured as the ability to absorb  $^{51}\text{Cr-EDTA}$ , was not increased during the viral infection.

#### **Involvement of the paranasal sinuses**

A study of naturally acquired viral rhinitis using CT scan imaging showed somewhat surprisingly extensive abnormalities in the paranasal sinuses in 87% of patients in the 3–5 days after onset of nasal symptoms (79). The abnormalities resolved spontaneously without antibiotics within 3 weeks.

The CT abnormalities, which consisted of opacities in the ostiomeatal complex and paranasal sinuses, may have been due either to accumulation of mucus, to mucosal congestion/edema, or to both. The presence of air bubbles in the opacities indicates an accumulation of mucus. It is difficult to explain the occurrence of air bubbles without assuming that the secretion is blown into the sinuses from the nasal cavity. If such a mechanism is at work for introducing secretions into the sinus cavities, viruses and bacteria may follow the same route. Recent experimental data support this hypothesis.

#### **Treatment of the common cold**

Therapy of a common cold has three purposes: 1) to reduce symptoms; 2) to decrease viral shedding and spread of the infection; and 3) to prevent complications, i.e. bacterial sinusitis and otitis media, and exacerbations of asthma and of chronic obstructive lung disease.

#### **Interferon- $\alpha$**

Interferon- $\alpha$  has antiviral activity against RV. Prophylactic intranasal administration, beginning when one family member developed cold symptoms, reduced the risk of acquiring a cold by 80% among other family members (80). When used in the initial phase of a cold, intranasal interferon- $\alpha$  decreased RV shedding but it had little effect on alleviating the symptoms (81). The reason for the limited symptomatic response to interferon- $\alpha$ , in spite of the antiviral effect, may be because the viral infection already had triggered the inflammatory cascade, responsible for the cold symptoms.

#### **Corticosteroids**

A series of cytokines are upregulated in the common cold, and the important IL-8 is generated followed virus-induced activation of NF- $\kappa\text{B}$  (56). Corticosteroids interact with this transcription factor and can, in theory, be expected to have an anti-inflammatory effect and to be useful for symptomatic treatment of the common cold. However, in practice corticosteroids are only marginally effective on cold symptoms. In one study intranasal corticosteroid treatment, begun prior to RV inoculation, showed trends towards fewer symptoms during the first 2 days, but this was followed by a normal progression of manifestations of the common cold (82). In another study, a high dose of intranasal corticosteroid had no clinically recognizable effects on the symptoms of a naturally acquired cold, but it produced prolonged shedding of viable RV (83). Oral prednisone (60 mg daily) did not improve cold symptoms in volunteers with experimental induced RV colds but it did produce increased viral shedding (83).

It is difficult to explain why corticosteroids have no or little symptomatic effect in the common cold (a cytokine-driven neutrophil-dominated inflammatory disease), while these drugs have a marked effect in allergic rhinitis (a cytokine-driven eosinophil-dominated inflammatory disease), considering that NF- $\kappa\text{B}$  seems to be a pathway for drug activity in both diseases.

#### **Vasoconstrictors**

$\alpha$ -adrenoceptor agonists reduce the severity of a common cold illness significantly (86, 87), showing that vasodilatation, and not edema formation, is the major cause of nasal blockage. Intranasal application has a definitely better therapeutic index than oral administration, but a nasal spray should only be used for 1–2 weeks due to the risk of rhinitis medicamentosa.

### Anticholinergics

Intranasal ipratropium bromide is effective in stopping watery nasal discharge in the initial phase of a cold by blocking the cholinergic innervation of the submucosal glands (88). This is clear evidence that the rhinorrhea in common cold is a glandular product and not plasma exudation. Ipratropium bromide has no effect on viscous mucopurulent secretions (88).

### Antihistamines and NSAIDs

Described above.

### Combined therapy

Probably the most effective treatment of common cold consists of a combination of antiviral and antimediator drugs, as proposed by Gwaltney (87). In a study of volunteers with experimentally induced RV infection combined treatment with intranasal interferon- $\alpha$ , intranasal ipratropium bromide and oral naproxen significantly reduced the viral titer and the overall cold symptoms (87). A fortune is still awaiting the inventor of an effective treatment for the common cold.

## Common cold viruses as triggers of asthma exacerbations

### Magnitude of the problem

Clinical experience has indicated that a viral airway infection precedes the large majority of acute episodes of wheeziness in infants and children, and that it is also an important cause of exacerbations of asthma in adults (90).

The study of the association between viral airway infections and wheezy episodes/exacerbations of asthma has been hampered by the lack of sensitive diagnostic tests for virus infection (91). Recently, the very sensitive PCR and RT-PCR technique have been used in two studies.

Johnston and coworkers (92) studied 108, 9–11-year-old children with asthma. In more than 80% of the episodes with wheezing and reduced peak flow, PCR on respiratory secretions was positive for virus, and this was picornavirus, i.e. RV, in two-thirds of the cases. Thus, this study showed that at least 80% of reported exacerbations of asthma in school children are associated with an upper airway infection, caused mainly by RV.

Nicholson and coworkers (93) studied the role of a common cold in exacerbations of asthma in 138 adults in a longitudinal study. The patients reported clinical colds in

80% of episodes with asthma symptoms. A virus was identified in 57% of subjects with symptomatic colds, and in these cases RV was found in 64% and coronavirus in 30%. Thus, at least half the asthma exacerbations were associated with a virus infection, predominantly with RV. The authors conclude that acute airway infections may be as commonly linked to exacerbations of asthma in adults as in children.

In conclusion recent studies, using the highly sensitive PCR technique, have indicated that a viral airway infection, especially with RV, is an important precipitator of asthma episodes, even more important than believed earlier.

### Lower airways in naturally acquired colds

While studies have shown convincingly that colds can increase asthma severity, there is little information on the direct effect of a naturally acquired cold virus infection on the immunopathology of the lower airways.

Trigg and coworkers (94) studied whether naturally acquired colds increase lower airway inflammation in nonasthmatic subjects. Twenty subjects (12 normal persons and eight atopics and four of these rhinitics) had a bronchoscopy before and during a cold. A viral infection was diagnosed in eight of the subjects (six normal and two atopics). In bronchial biopsies, during colds, eosinophils and CD8<sup>+</sup> T cells increased significantly, and neutrophils increased in bronchial washings.

The authors conclude that lower airway inflammation is present in subjects with a cold, and that many subjects with symptoms, traditionally thought to indicate upper airway infection, have evidence of lower airway inflammation. However, the atopic subjects in this study had more activated eosinophils and less positive virological tests than the nonatopic controls, which raises a question about the validity of the study. Symptoms of a virus cold and of allergic rhinitis are similar, and allergic subjects may have reported symptoms of allergic inflammation as “a cold”.

### Lower airways in experimental rhinovirus infection

A number of studies have dealt with experimental RV infection, lower airway inflammation, and bronchial responsiveness. In these studies virus inoculation has been performed using standard methods. The inoculum is dripped or sprayed into the nasal cavity which makes bronchial deposition of the virus unlikely. RV 16 (39, 40, 94–96) and RV 39 (97) have been used.

#### Enhanced bronchial inflammation

Bronchoscopy studies during an experimental RV infection have shown an increase in mucosal CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> cells (41), in epithelial eosinophils (41), and in the concentration of ECP in induced sputum (97). Interestingly, the epithelial eosinophil numbers were elevated for a prolonged period in asthmatic volunteers (41), and there seems to be a positive correlation between the concentration of sputum-ECP and the change in bronchial responsiveness (PC<sub>20</sub> histamine) (99). While these results indicate that a viral infection can activate eosinophils *in vivo*, RV has little effect on eosinophil activation *in vitro* (100).

Based on these studies it has been hypothesized that an immunologic response, involving T cells and eosinophils, may be responsible for the virus-induced increase in airway responsiveness in asthmatics (41), described below.

Also the concentration of IL-6 and IL-8 in induced sputum is increased during an experimental RV infection (97).

It is difficult to explain why RV, which primarily infect the upper airways and cause rhinitis symptoms, induce a T-cell/eosinophil inflammation in the bronchi but not in the nose.

#### Increased bronchial response to antigen

Busse and colleagues (101–103) performed segmental bronchial provocation with allergen during bronchoscopy in volunteers with and without an experimental RV infection. During the viral infection there was an increased symptom response to the allergen challenge (both early and late response), an increased level of histamine and protein and an increased number of eosinophils in bronchoalveolar lavage fluid. The authors conclude that these data show an increase in inflammatory response during the RV infection, which indicates that RV upregulates the inflammatory response to allergen, and this may be due to an increased generation of cytokines. The findings imply that viral infections and allergies may have synergistic effects on lower airway inflammation that increases the likelihood of wheezing.

#### Increased bronchial response to histamine and methacholine

Asthma symptoms are closely associated with bronchial hyperresponsiveness, making measurement of PC<sub>20</sub> or PD<sub>20</sub> to inhaled histamine or methacholine useful parameters for studying the link between common cold and asthma.

#### Normal subjects

Skoner et al. (98) and Gern et al. (96) did not find any change in nonspecific bronchial responsiveness during an experimental RV infection in normal volunteers.

#### Allergic rhinitis

Lemanske and colleagues (95) studied 10 ragweed-allergic subjects outside the pollen season. An RV infection resulted in a significantly increased bronchial responsiveness to histamine. Gern and coworkers (96) obtained a similar result in 18 subjects with a positive skin test to ragweed, cat or housedust mite but without rhinitis symptoms. In contrast Skoner et al. (98), in a large study of 46 subjects with seasonal allergic rhinitis, studied outside the pollen season, were unable to find any significant change in bronchial responsiveness during a RV infection. Thus, the results are conflicting, and this is probably due to differences in the selection of patient populations (mild or severe rhinitis).

#### Allergic asthma

While Halperin and coworkers (104) found increased responsiveness to histamine in only four out of 22 asthma subjects after experimental RV infection, three other studies of asthma patients have all shown a significant reduction in PC<sub>20</sub> or PD<sub>20</sub> to inhaled histamine or methacholine (40, 41, 97). The increase in bronchial responsiveness in these studies has been modest, which may be due to the selection of patients. For safety reasons, only patients with mild asthma have been studied.

Understandably, asthma patients who increase their bronchial sensitivity to nonspecific stimuli also do so to a specific challenge with allergen, especially demonstrated by an increased late-phase responsiveness (95).

#### Mechanisms by which viruses precipitate asthma

A number of mechanisms have been proposed to explain how a common cold can induce asthma, but so far no explanation is satisfactory. In principle, a common cold can induce asthma exacerbations in two different ways: 1) directly by a virus infection of the lower airways, and 2) indirectly by an infection, limited to the upper airway, which by immunological and neurogenic mechanisms induces lower airway inflammation, hyperresponsiveness and asthma symptoms.



### Does rhinovirus infect the lower airways?

Clearly, this is an important question for the understanding of the link between a common cold and asthma. Most evidence, so far, has been equivocal on the question (4). It has been difficult to determine whether virus growth occurs in the bronchi because of the problem of obtaining lower airway specimens that are not contaminated with nasopharyngeal secretions during sampling (104).

Gern and coworkers (105) used RT-PCR to identify RV in bronchoalveolar lavage cells from volunteers inoculated intranasally with RV. The RT-PCR was positive in eight of eight inoculated volunteers, and negative in the controls. Although these results suggest that RV can infect the lower airways, it is necessary to remember that RT-PCR is an extremely sensitive test and that contamination from the upper airways cannot completely be excluded. The final proof will be to show RV infection of bronchial epithelial cells by *in situ* hybridization as was done for nasal epithelial cells by Arruda and coworkers (17). A recent study of *in situ* hybridization has shown rhinovirus signals in five of 10 bronchial biopsies, strongly suggesting that rhinoviruses do replicate in the lower airways (Sebastian L. Johnston, personal communication).

### Direct effect of lower airway infection on asthma

Theories have been advanced, placing the bronchial epithelial cell in a central position. However, there are major problems with most of the hypotheses, described below. First, it is doubtful whether bronchial epithelial cells are infected by RV. Secondly, considering the minor cytopathic effect of RV on the epithelial lining in the nose and on epithelial cells *in vitro*, it seems highly unlikely that there are any marked structural and functional changes in the bronchial epithelium.

#### Cytokines

Epithelial cells are able to secrete a broad array of cytokines, as discussed earlier. *In vitro* studies indicate that RV induces secretion of IL-1, IL-6, IL-8, IL-11, RANTES and GM-CSF from epithelial cells (105). IL-11 is secreted in large amounts and may have a direct effect on bronchial hyperresponsiveness (106). Respiratory viruses have the ability to induce the release of cytokines also from other cell types. Balfour-Lynn and coworkers (107) reported that tumor necrosis factor- $\alpha$ , a proinflammatory cytokine, produced primarily by mononuclear phagocytes, was detectable in nasopharyngeal secretions in over three-quarters of infants with wheezing illness.

#### Mediators

Epithelial cells also produce biochemical mediators, such as products of 15-lipoxygenase activity (15-HETEs and leukotriene B<sub>4</sub>) which can directly contract bronchial smooth muscles (108).

#### Bronchodilator factor

It has been reported that the epithelium is a source of a regulator protein (endogenous bronchodilator factor) with a protective role that maintains bronchial patency. Also it has been speculated that epithelial damage may reduce the synthesis of this protein resulting in bronchoconstriction (109).

#### Neurogenic inflammation

Based on rodent studies, it has been hypothesized that epithelial damage, by loss of neutral endopeptidase and reduced breakdown of neuropeptides such as substance P, results in the development of neurogenic inflammation. However, neurogenic inflammation has not been described in humans.

#### Vagal reflex

It seems reasonable to assume that disruption of the surface epithelium may induce airway hyperresponsiveness by exposing sensory nerve endings to irritants and inflammatory mediators, so the afferent fibers cause increased vagal activity leading to enhanced bronchoconstriction.

#### Antigen absorption

It has long been believed that epithelial stripping aids penetration of antigens into the mucous membrane, but Greiff and coworkers (78) have now shown clearly that mucosal absorption of macromolecules is not increased during an infection with coronavirus.

### Indirect effect of upper airway infection on asthma

In theory, an indirect effect from an infection, limited to the upper airways, could be mediated by the following mechanisms: 1) impaired nasal physiology; 2) a nasobronchial reflex; 3) aspiration of infectious secretions; and 4) absorption of cytokines and mediators, causing recruitment and activation of immune cells, which may have an effect not only in the nose but also in the lower airways and in other parts of the body.

Emphatically, we find the last possibility most likely. A systemic effect of an RV cold on host defense factors is supported by the observation that a common cold not only induces an exacerbation of asthma, but can also reactivate a

herpes infection on the lip. It has been described above that a common cold can reduce the T-cell response and cytokine formation (44).

Whether RV induces bronchoconstriction by direct infection or as an indirect consequence of upper airway infection, it can be hypothesized that it is the inflammatory response to the cold virus that is responsible for triggering virus-induced exacerbation of asthma and not a direct cytopathologic effect on bronchial cells, and this is similar to the hypothesis advanced earlier for the nasal cold symptoms.

As described earlier, other viruses (influenza-, parainfluenza- and adenovirus), having a pronounced cytopathologic effect, may induce asthma symptoms by other mechanisms.

## Does allergy predispose to common cold?

### Increased frequency

As mentioned earlier, allergen exposure upregulates the expression of ICAM-1 on the surface of the airway epithelium (22), and one can therefore speculate that allergen-exposed allergic patients may have an increased susceptibility to RV infections. However, there are no data in support of this hypothesis, and it is not common clinical experience that allergic patients have more colds than normal persons. As it can be difficult to distinguish between an attack of allergic rhinitis and a viral infection, modern and sensitive diagnostic tests (PCR and RT-PCR) are necessary in studies of the frequency of RV infections in atopic and nonatopic individuals.

### Increased severity

It can also be speculated that allergic rhinitis, associated with upregulation of ICAM-1 and with the presence of inflammatory cells in the surface epithelium, leads to more cold symptoms during a virus infection because it is amplified by ongoing inflammation.

Some support for this hypothesis comes from a study by Bardin and coworkers (19), who inoculated 11 normal volunteers (five atopic and six asthmatic patients) with RV. The authors concluded that the results "suggest heightened susceptibility to the detrimental effects of a cold in the atopic/asthmatic patients".

Hinriksdottir (110) studied 64 patients with allergic rhinitis and 23 nonallergic individuals who recorded symptoms of upper airway infections for 1 year. There was no

difference between the two groups concerning the number of upper airway infections or the duration of the disease. Doyle and coworkers (77) found that experimentally induced RV colds are clinically similar in normal and allergic subjects.

In summary, the above studies indicate that allergic rhinitis cannot be considered to increase the frequency or the severity of upper respiratory infections.

## Prevention and treatment of common cold-induced asthma

### Reduced transmission

When mothers, exposed to a child with a fresh cold at home, regularly dipped their fingers in 2% aqueous iodine, the number of new colds was reduced by 67% (6). Another study of the hand-contact route of cold transmission was performed under natural conditions in asthmatic children (111). One group of children was trained to avoid self-inoculatory (finger/nose) behavior and they were then compared with untrained controls. Following the training period, the groups were followed for several months during which time the trained group had significantly less self-inoculatory behavior, fewer viral respiratory infections and fewer attacks of asthma.

These data indicate that patients with asthma may be able to reduce the number of colds and of acute exacerbations. Washing hands after an infectious contact can be recommended, as well as avoiding finger-to-eye and finger-to-nose contact. Alternatively, right-handed asthmatics could touch their eyes and nose only with the left hand, adapting the practice of using a "clean hand" for this purpose and a "dirty hand" for contact with the surroundings.

It is possible that an asthmatic mother having a small child may, in the future, be able to reduce the number of asthma exacerbations by use of an antiviral hand lotion or an intranasal interferon- $\alpha$  spray, when the child get cold symptoms. Finally, kindergartens are not suitable places for patients with severe asthma, children and adults.

### Corticosteroids

It is general practice, recommended in international consensus reports (112), to treat severe exacerbations of asthma with corticosteroids. A rationale for doing this is a reduced sensitivity of T cells to corticosteroid treatment during a common cold, recently shown by Vianna and coworkers (44).

Most, but not all, placebo-controlled trials have shown a beneficial effect of corticosteroids in acute severe asthma (113). Although airway infections, including common colds, are known to be important causes of asthma exacerbations, there does not seem to be any placebo-controlled study on the use of corticosteroids in this specific situation. A Medline search of published articles (1 June 1998) gave the following number of publications: asthma 51972; asthma and corticosteroids 1956; asthma and common cold 89; asthma and common cold and corticosteroids 3.

In an open study of preschool children who suffered from repeated asthma attacks, related to upper airway infections, Brunette and coworkers (114) found that a short burst of oral prednisone (1 mg/kg), given as soon as the first symptoms of an infection appeared, resulted in a significant decrease in the number of wheezing days and visits to the emergency room.

Recently, Doull and coworkers (115) performed a double-blind study of the prophylactic effect of inhaled beclomethasone dipropionate (400 µg/day) on wheezing episodes associated with viral infection in 104 children aged 7–9 years. Although there was a significant increase in FEV<sub>1</sub> and in methacholine PD<sub>20</sub> the authors conclude that the treatment offered no clinically significant benefit on the wheezing episodes.

## Conclusions

Studies of the link between the common cold and asthma are few and our knowledge is remarkably insufficient, considering the important clinical significance of this issue. It is clear that RV causes little damage to epithelial cells in the nose, and it is not definitely proven that the viruses infect the lower airways. It remains to be established, therefore, whether a RV infection causes wheezing by a direct infection of the lower airways or by alternate mechanisms through which upper airway infections can cause changes in lower airway function. It is hypothesized that virus-induced generation of cytokines, mainly by epithelial cells, amplifies the T-cell-driven eosinophil inflammation in asthma, but it is unclear how the virus-induced inflammation, characterized by a Th<sub>1</sub>-type cytokine response, enhances inflammation in asthma, characterized by a Th<sub>2</sub>-type cytokine response. Furthermore, it is not in accordance with an important role played by cytokines in the production of cold symptoms that corticosteroids have no or little effect on the nasal symptoms of a cold. Clinical experience shows that corticosteroids have a beneficial effect on cold-induced asthma exacerbations, but placebo-controlled studies have not been performed. Finally, intervention studies are needed to show whether attempts of stopping virus transmission to asthma patients can reduce their number of colds and of asthma exacerbations.

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