

Rhinoviruses as pathogens of the lower respiratory tract

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Rhinoviruses (RVs) are the most common upper respiratory pathogens, inducing the majority of common colds worldwide. RV-related morbidity, although significant cumulatively, has been considered trivial for the individual patient. However, recent strong epidemiological associations of RVs with asthma exacerbations, including severe episodes requiring hospitalization, indicate that RV infections can result in serious disease. Current evidence supports the possibility that RVs infect the lower airways, inducing a local inflammatory response. Such evidence suggests that the role of RVs in other lower respiratory diseases, such as pneumonia, bronchitis, bronchiolitis and cystic fibrosis, should be re-examined with polymerase chain reaction-based methodologies, which are considerably more sensitive than traditional, cell culture-based techniques. The mechanisms through which RVs induce lower airway disease are studied to understand the relative contributions of the epithelial, neurogenic and immune components in the antiviral response, and to permit the design and implementation of specific treatments.

Key Words: *Asthma; Chronic obstructive pulmonary disease; Common cold; Cystic fibrosis; Pneumonia; Rhinovirus*

Les rhinovirus, agents pathogènes des voies respiratoires inférieures

RÉSUMÉ : Les rhinovirus (RV) sont les principaux agents pathogènes des voies respiratoires supérieures, causant la plupart des rhumes dans le monde. La morbidité liée aux RV, même si elle est imposante collectivement, est plutôt bénigne individuellement. Toutefois, de fortes associations épidémiologiques récentes liant les RV à des crises d'asthme, parfois suffisamment sérieuses pour nécessiter l'hospitalisation, indiquent que les infections à RV peuvent entraîner de graves maladies. Aujourd'hui, des preuves étayent la possibilité que les RV infectent les voies respiratoires inférieures, provoquant une réaction inflammatoire locale. Ces preuves donnent à penser qu'il faudrait revoir le rôle des RV dans d'autres maladies des voies respiratoires inférieures, comme les pneumonies, les bronchites, les bronchiolites et la mucoviscidose, à l'aide de techniques fondées sur la réaction en chaîne de la polymérase, qui sont beaucoup plus sensibles que les techniques traditionnelles, fondées sur la culture des cellules. Les mécanismes par lesquels les RV entraînent une maladie des voies respiratoires inférieures font l'objet d'études pour que soit mis en évidence le rôle relatif des éléments épithéliaux, neurogènes et immunitaires dans la réaction antivirale et qu'on soit en mesure de concevoir et d'appliquer des traitements appropriés.

Rhinoviruses (RVs) are probably the most common pathogens of the respiratory tract. They were identified less than four decades ago; however, they are the major cause of the common cold, a disease with over 2000 years of re-

corded history that affects all human populations, and causes considerable morbidity and economic burden worldwide (1). Nevertheless, probably due to the benign nature of most RV colds, which appear to threaten seriously only the health of

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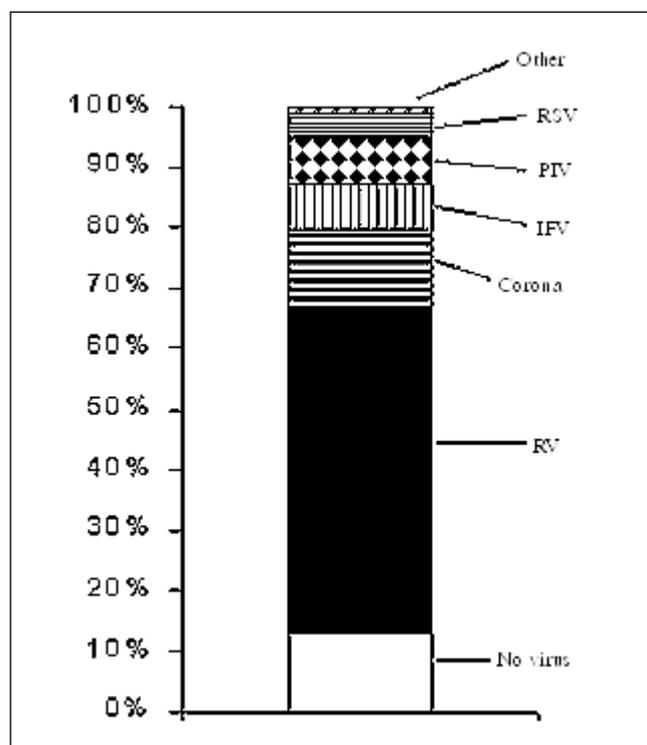


Figure 1) Detection rates of respiratory viruses in children aged nine to 11 years with exacerbations of asthma. Rhinoviruses (RV) predominate, followed by coronaviruses (Corona). Influenza (IFV), parainfluenza (PIV) and respiratory syncytial (RSV) viruses are also present. Viruses were absent in only 15% of exacerbations

immunocompromised populations, little attention has been paid to a common clinical observation, ie, the development of lower respiratory disease, most commonly asthma exacerbations, a few days after the cold. Several early studies have sought to establish objectively such an effect (2-5). It was only after the advent of polymerase chain reaction (PCR)-based detection methodologies that it was shown that the majority of asthma attacks in children (6) and a considerable percentage in adults (7) follow RV colds. Although it is still unclear how RVs compare with other respiratory viruses in their ability to induce asthma, their high prevalence probably makes them one of the most significant pathogens in this context.

These important epidemiological observations have raised considerable interest in the underlying mechanisms of virus-induced asthma exacerbations, the understanding of which may lead to new strategies for treatment. The possible implication of RVs in other lower respiratory illnesses, such as pneumonia, bronchiolitis and chronic obstructive pulmonary disease (COPD) must also be considered. Very recently, it was shown that RVs can directly infect the lungs and induce inflammatory responses in bronchial epithelial cells (8). The frequency of infection and the nature of the inflammatory response observed were similar to those of the upper respiratory tract, suggesting that RV infections may be one of the most important causes of lower, in addition to upper respiratory disease. The current paper briefly reviews the

clinical and epidemiological evidence linking RVs with lower respiratory disease, and presents the current evidence of the pathogenic mechanisms that may lead to lower respiratory disease.

CLINICAL AND EPIDEMIOLOGICAL EVIDENCE

RVs and asthma: A considerable number of epidemiological studies on the role of viruses in asthma exacerbations were performed during the 1970s and 1980s; more than 20 such studies included RVs among the investigated pathogens (9). Incidental studies attempted to isolate viruses in acute episodes of asthma, while prospective studies followed patients with asthma, and virus isolation was undertaken either during respiratory infections or on a regular basis. Several important conclusions were drawn from these early reports. First, while RVs were among the most prevalent microorganisms in the majority of cases, significant variability in their identification rates was observed among the studies. Furthermore, the overall virus identification rates seemed to correlate with the success or lack of success of RV isolation. The fluctuations were suggestive of a possible weakness in RV detection methodology. Second, it was shown that early sampling is critical to the successful isolation of viruses (4), and that identification rates tend to be higher in outpatients or patients from the general practice than in hospitalized patients, and higher in prospective studies than in incidental studies. Finally, only a few studies focused on adults, showing considerably lower overall and RV-specific identification rates than those rates obtained in children.

The advent of PCR-based methods for virus identification proved to be a key point in the understanding of asthma exacerbation pathogenesis. This was particularly true for RVs and coronaviruses, for which classical methods are technically demanding and of low sensitivity (10). Using both virus culture and PCR, two recent, prospectively designed studies have readdressed the problem, demonstrating that virus involvement in asthma exacerbations is much more frequent than previously believed, with RVs being the predominant pathogens. In a community-based study, 108 children aged nine to 11 years were followed for a year (6). The children were instructed to record upper and lower airway symptoms daily, according to a symptom list and symptom scale, which were provided. Peak expiratory flow measurements were obtained twice daily. Parents were advised to contact the investigators if there was a significant change in the recorded parameters or a subjective feeling that the child was developing a cold, in which case specimens for virological testing were promptly obtained. Virological analysis was extensive, using a combination of traditional methodologies such as culture, immunofluorescence and serology, and PCR for picornaviruses and coronaviruses. Several interesting findings were reported. First, viruses were associated with 80% to 85% of respiratory disease episodes (Figure 1). Virus detection rates fell within this narrow range for all different presentations of these episodes, whether exclusively upper respiratory, lower respiratory or a combination of the two, with or without wheezing, thus supporting a common cause and pathogenic mechanism for this

wide spectrum of clinical symptomatology. RVs accounted for approximately two-thirds of all identified viruses. Furthermore, the superiority of PCR was also clearly demonstrated because it was able to identify more than three times the number of RVs than culture alone.

A similarly designed study was performed by Nicholson et al (7) in which 138 asthmatic adults, aged 19 to 46 years, were followed for two years. Virus identification rates were lower, associated with 44% of asthma exacerbations. However, when subjective criteria were used, 80% of asthma exacerbations occurred with symptomatic colds, while 90% of colds were associated with symptoms of asthma. It is possible that the discrepancy between subjective symptomatology and objective virus detection may be attributed to a decreased virus shedding in adults (7), or perhaps to less intensive monitoring and later sampling than was the case in the study in children. These results also show that the majority of asthma attacks are associated with viral infections of the upper respiratory tract. In agreement with the pediatric study, RVs accounted for almost 65% of all identified pathogens, while RV PCR was more than twice as sensitive as virus culture.

Following the above studies, several questions about the clinical characteristics as well as the underlying mechanisms of the observed disorders have arisen. Because both of the above studies were community based, it was important to determine whether common colds could also lead to severe asthma requiring hospitalization. To answer that question, the data obtained from the Southampton pediatric cohort (6) were compared with hospitalizations for asthma in the area during the same time period (11). Strong correlations were found between the seasonal patterns of upper respiratory infections and hospital admissions for asthma (Figure 2). These included both pediatric, adult and combined admissions, even though they were stronger for the pediatric population. Interestingly, there was a close relationship between the peaks of both respiratory infections and hospital admissions, and the start of a new school term or half-term, establishing school attendance as the major factor determining pediatric, but not adult, admissions for asthma. It should be noted that the transmission of RVs is highly dependent upon congregation, especially among children, in contrast to other respiratory virus types, whose temporal variations are more strongly correlated with the season. Hence, it was not surprising that RVs were associated with all four peaks that were identified for hospital admissions.

This evidence underlines the importance of RVs as precipitants of lower respiratory disease, in both prevalence and severity. Nevertheless, significant gaps in the actual epidemiological characteristics of RVs require more extensive studies to be performed. Year-to-year variations are common among respiratory viruses, indicating that long term studies are required. Age-related differences are also large, especially in young children and infants. The optimization and automation of PCR-based techniques will be crucial in this process. Furthermore, the role of RVs in diseases such as bronchiolitis, COPD and pneumonia, while they are currently thought to be involved to a rather limited

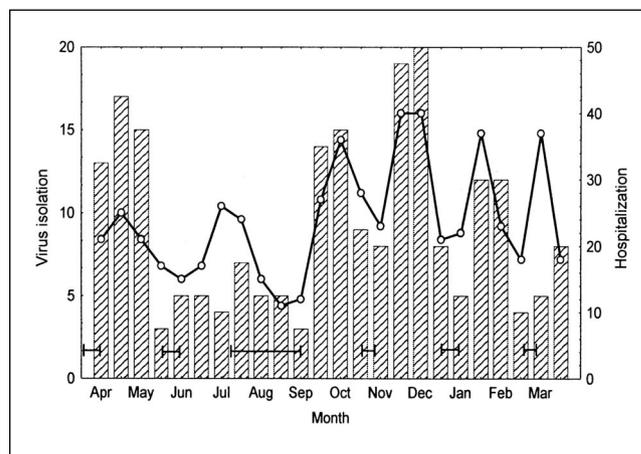


Figure 2) Time-trend of virus detection rates (bars) in comparison with asthma hospitalization rates (line) in the Southampton, United Kingdom area during the same year. A close association can be observed. Peaks of both parameters follow the return to school from vacation, which are shown as range bars at the bottom of the histogram bars

degree (12), has to be re-evaluated using such methodologies.

RV infections in specific populations: The ability of RVs to induce severe lower respiratory disease raises the possibility of a significant contribution of these agents in morbidity and mortality of immunocompromised populations. Unfortunately, only a small number of studies are available, most of which were performed before the advent of PCR. Nevertheless, the ability of RVs to cause severe disease and even death in such patients was recognized in these early studies. In a case report published in 1969 (13), a 61-year-old woman with myelomatosis, who was hospitalized for elective splenectomy, developed a cold and subsequently pneumonia, dying two days later. RV13 was isolated from lung tissue specimens obtained postmortem. In a recent study, RV pneumonia was associated with significant mortality in bone marrow transplantation recipients (14). Another study reviewed the records of hospitalized children, in which an RV had been isolated, during a two-year period (15). Twenty-three of 35 cases (66%) were from patients with severe underlying disease including malignancies, respiratory tract abnormalities and congenital heart lesions. Most children were admitted because of acute respiratory illness, and focal infiltrates were observed on 68% of available x-rays, while severe symptomatology including respiratory distress and lethargy was present in almost half of the patients.

Recently, the effects of RV infection were evaluated in children with cystic fibrosis (16) and bronchopulmonary dysplasia (17). In both cases, RV infection was associated with pulmonary function abnormalities and disease progression. While RV infections were equally as severe as those caused by other viruses of the upper respiratory tract, their prevalence has been considerably higher, accounting for almost half of the colds in children with cystic fibrosis and 20% of lower respiratory tract illnesses in infants with bronchopulmonary dysplasia.

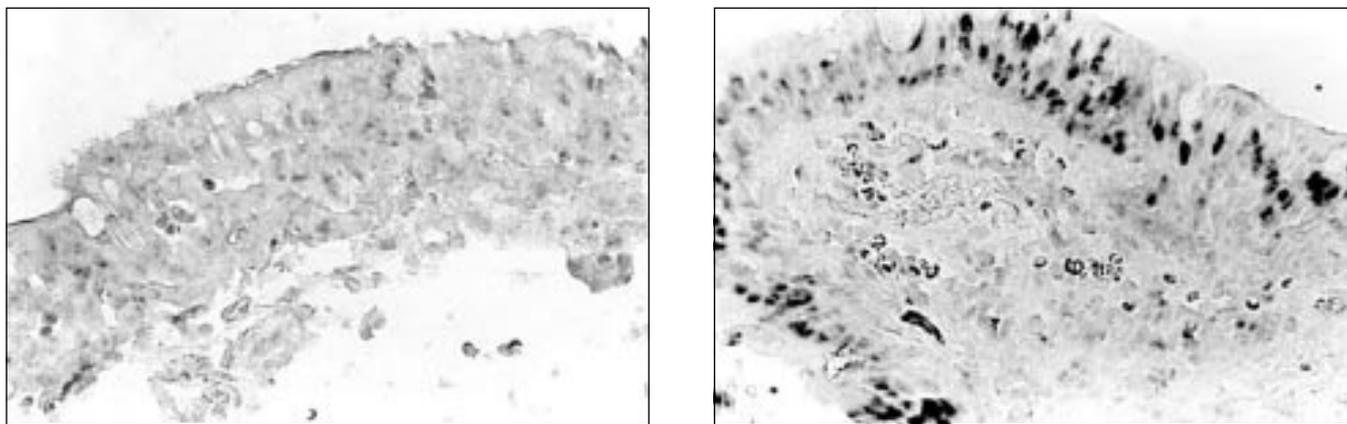


Figure 3 *In situ* hybridization for rhinovirus RNA in bronchial biopsies before (**left**) and after (**right**) an experimental rhinovirus infection. The strong positive signal of the latter sample, localized in the bronchial epithelium, confirms the presence of the virus in the lower airways

Equally as susceptible and prone to complications are the elderly. Although it is recognized that upper respiratory infections may have considerable implications in the aged, resulting in lower respiratory or systemic involvement that leads to hospitalization and even death, only one group has used PCR to evaluate RV prevalence in this age group in the community (18,19). In those studies, half of the identified viruses were RVs. Increased morbidity was documented, with the median duration of illness being double that in adults, and lower respiratory complications being present in 62% of RV infections, in contrast to 5% to 34% reported in people younger than 40 years of age. One death subsequent to RV infection was reported. However, mortality may be higher in different settings, such as in a long term care facility, where an RV outbreak resulted in 3% mortality as reported in one study (20).

From these studies, it can be concluded that although RVs do not seem to produce more severe disease or complications than other common cold viruses, they account for very significant lower respiratory morbidity and mortality by being the most prevalent respiratory pathogens after the first year of life.

MECHANISMS

RV infection in the lower airways: Crucial to the understanding of the pathogenesis of RV-induced lower respiratory disease is the debate over whether RV infection occurs in the lung, directly inducing local immunological and inflammatory responses, or whether the lower respiratory disease is a result of indirect mechanisms consequent upon infection of the upper airway alone. Although data supporting both hypotheses have been reported, current evidence seems to favour the former. The clinical studies that were mentioned above, linking RVs with lower airway syndromes, could not exclude either of the mechanisms; however, RV isolation from postmortem lung tissue specimens is certainly suggestive of lung infection (13). Furthermore, tracheobronchitis has been induced in volunteers with RV in small-particle aerosol (21). Nevertheless, these reports were not designed to assess whether the presence of RV in the lower

airways was part of the common cold's natural history or whether it could occur only under exceptional conditions. Horn et al (22) attempted to address this question by simultaneously isolating RVs in sputum, and nasal and throat swabs from children with wheezy bronchitis (22). Virus was recovered more often from sputum than from the nose or the throat, suggesting lower airway involvement. Further support for the direct infection hypothesis came from studies of experimental RV infections. In one such study (23), RV was isolated from lower airway secretions sampled by bronchoscopy. More recently, RV RNA was identified by PCR in bronchoalveolar lavage cells from experimentally infected volunteers (24). When the bronchoalveolar lavage fluid from the positive samples was examined, detection rates were lower, indicating that RV RNA was largely cell associated. The major criticism of these studies has been that it is impossible to exclude totally virus contamination from the upper airways during the sampling procedure, although the latter study took several precautions to minimize that possibility. Another frequent argument against RV infection of the lower airway is that RVs replicate optimally at the cooler temperature of the nasal cavities (33°C) rather than the warmer environment of the lung (37°C). However, it was recently shown that the higher temperature of the lower airways is not a preventive factor for RV replication and some strains may even prefer it (25). In a recent study by Papadopoulos et al (8), *in situ* hybridization was used to obtain conclusive evidence that RV productive infection occurs in the human lung. RV RNA was present in 50% of bronchial biopsies from normal and asthmatic patients after an experimentally induced upper respiratory infection (Figure 3). When hybridization probes complementary to the replicating strand of the virus were used, a positive signal was also obtained that was colocalized with the signals obtained with the genomic strand probes, showing that the virus was actively replicating. It should be noted that similar identification rates have been obtained in the past using the same method in nasal epithelium, where RV replication is not disputed. It is the authors' belief, therefore, that lower respiratory infection with RV is probably the norm rather than the exception dur-

ing a common cold, and that difficulties establishing this fact relate to difficulties with RV detection and with confident exclusion of contamination of the sample with virus derived from the upper respiratory tract.

Further evidence supporting RV replication in the lower respiratory tract comes from the recent demonstration that cultured primary epithelial cells from human bronchi were consistently infected after exposure to RVs (8). RV infection resulted in the production of several proinflammatory cytokines and chemokines from these cells including interleukin (IL)-6, IL-8, regulated-on-activation normal T-cell-expressed and -secreted beta-chemokine (RANTES) and IL-16, all of which have been implicated in the pathogenesis of asthma. Very similar results have also been presented recently from another group, confirming the ability of RVs to replicate in vitro in bronchial epithelium, inducing a significant cytokine response and, in some cases, cytotoxicity (26). Also, the authors of the present paper recently observed significant increases of eotaxin and eotaxin-2 after exposure of respiratory epithelial cell lines to RVs (NG Papadopoulos and SL Johnston, unpublished data).

The secretion of chemoattractants for eosinophils (chemokines) and lymphocytes (chemokines and IL-16) is probably one of the mechanisms inducing bronchial epithelial and subepithelial infiltration with these cells after experimental RV colds, which has been previously documented (27). In that study, the increased numbers of infiltrating eosinophils persisted into convalescence in patients with asthma. It is tempting to speculate that the epithelial response to RVs may be augmented in people with asthma but there is currently no evidence to address this question. However, there is compelling evidence suggesting that RVs are not confined to the upper airways, and that their pathogenicity in the lung is, at least partly, a result of infection and induction of local inflammatory responses.

Indirect mechanisms: Direct bronchial infection by RVs can by no means exclude the contribution of indirect mechanisms in the generation of RV-mediated lower airway disease. Neural pathways are able to aggravate asthma and are probably involved in airway pathophysiology induced by respiratory viral infections (28), but they have not been studied in detail with RVs. Ineffective metabolism of substance P, neurokinin-A and possibly other neuropeptides resulting from reduced activity of neutral endopeptidase 24-11 (NEP) has been documented in animal models of influenza (29) and parainfluenza (30) infections. However, it is possible that NEP inactivation is a result of extensive epithelial cytotoxicity and, therefore, would be less pronounced in RV infections. To date, no information is available on the effects of RV on NEP or tachykinins.

On the other hand, there is evidence that a systemic immune response to RV occurs after upper respiratory infections. Leukocyte numbers fall in peripheral blood during the cold, followed by recovery or even lymphocytosis within a week (31). Furthermore, peripheral blood mononuclear cells (PBMCs) are activated, as indicated by increased production of IL-2 and interferon-alpha (IFN- α) and enhanced natural

killer cell cytotoxicity after in vitro mitogen stimulation (32). Gern et al (33) have shown that RV16 enters monocytes and airway macrophages in vitro and activates these cells without active replication of the virus. Furthermore, RV16 produced a nonspecific activation of lymphocytes from allergic subjects through a monocyte-dependent mechanism (34). In general, cytokine responses to RVs have been shown to be T helper (Th)-1-like, with high amounts of IL-2 and IFN- α and no IL-4 production (35). It was, therefore, difficult to establish a connection between such a response and asthma, which is typically mediated by Th2 responses. However, recent evidence indicates that the exposure of PBMCs to RVs can also upregulate Th2-type cytokines including IL-4, IL-10 and IL-13. Furthermore, PBMCs from people with atopic asthma produce significantly less IFN- α and IL-12 but more IL-10 in response to RVs (NG Papadopoulos et al, unpublished data). Although the actual consequences of these abnormalities remain to be established, it is possible that reduced Th1 cytokines may result in delayed viral clearance, compatible with reports of increased susceptibility of patients with atopic asthma to RV infections, and a consequent augmentation of the inflammatory response in such patients. This hypothesis and the putative mechanisms involved clearly require further investigation.

CONCLUSIONS

The importance of RVs as mediators of serious illness of the lower airway is just beginning to be appreciated. As far as asthma is concerned, considerable effort has been devoted to the unraveling of the possible interactions of viruses and allergens. While there is considerable evidence showing that allergen or methacholine-induced bronchial hyperresponsiveness is augmented by experimental RV infection in allergic patients (36,37), we do not yet know the naturally occurring sequence of events leading to an asthma exacerbation, to what extent viruses or allergens induce such exacerbations alone or in combination, and, finally, the mechanisms underlying this possible interaction. Moreover, it seems that more epidemiological studies, using contemporary methodologies, will be necessary to evaluate the role of these viruses in COPD, cystic fibrosis and pneumonia.

Specific antirhinoviral treatments are still not available (38). This can be partly attributed to the belief that RVs can cause only trivial disease. Because the evidence for a significant RV-related morbidity is becoming compelling, it seems that these viruses may be an important target against which novel therapeutic strategies should be aimed.

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