

RHINOVIRUS - NOT JUST THE COMMON COLD!

Running title: Rhinovirus - Not just the common cold!

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Abstract

Rhinoviruses (RV) are ubiquitous respiratory tract pathogens. They affect both the upper and lower respiratory tract and cause colds but have also been associated with wheezing, asthma exacerbations and pneumonia. New blood transcription profiling techniques of the host immune response are becoming available to characterise the pathogenesis of RV in humans. This review will outline the clinical impact of RVs in children.

Key words: Rhinovirus, asthma, bronchiolitis, blood transcription profiling

Background

Rhinoviruses (RV) are small, approximately 30nm in diameter, viruses consisting of a simple viral capsid and a positive sense single strand of ribonucleic acid (RNA) with a genome approximately 7200kb in size. The capsid contains four proteins, VP1–VP4, arranged in 60 repeating protomeric units in an icosahedron. (1,2) RVs exhibit considerable genetic diversity.(1,2) They are classified in the order *Picornavirales*, family *Picornaviridae* and genus *Enterovirus*. Within the *Enterovirus* genus there are three RV species; A, B and C.(3) Within each of these species, isolates are subdivided into numeric genotypes that are primarily based on sequence comparisons of the VP1 protein or VP4/VP2 coding region.(4) There are over 100 RV genotypes. The genetic diversity of RVs is continuously changing and consequently the classification of RVs is regularly updated.(3) Within the RV-A species, for example, a discrete “clade D” has recently emerged which may in time be classified separately from RV-A.(4)

RVs enter via the upper respiratory tract and bind to respiratory epithelial cells via several receptors which are different depending on the RV species. RV-A and RV-B bind to the intercellular adhesion molecule 1 (ICAM-1) receptor and low-density lipoprotein receptor (LDLR) and RV-C binds to the newly identified cadherin-related family member 3 receptor (CDHR-3).(5–7) The attachment of RV to its receptor in susceptible patients elicits an innate immune response leading to airway inflammation and remodelling (Figure 1).

RVs are the most common cause of respiratory tract infection in infants and almost all infants develop at least one RV infection in the first year of life.(8) Prematurely born infants and older children with asthma are particularly at risk of developing severe RV infections.

Rhinovirus: A lower respiratory tract pathogen

Until relatively recently RVs were thought to only infect the upper respiratory tract and not result in lower respiratory tract infection (LRTI). Most RVs replicate best at 33-35°C and although the core lung temperature is 37°C, the airways are cooler.(9) The lower respiratory tract, therefore, provides the ideal environment for RVs to flourish. Using viral culture it has been shown that RVs replicate as well as, or better in lower respiratory tract cells compared with upper respiratory tract cells.(9) In addition, in an experimental model of RV infection of the upper airway in adults, RV has been subsequently recovered from the lower respiratory tract and the amount of RV detected in sputum was often higher than that detected in the upper airways.(9) RV can also be detected in the lower airways in children with tracheostomies where there is no risk of the results being affected by sample contamination from the upper airways.(10)

In vitro studies have demonstrated that bronchial epithelial cells are susceptible to RV infection. (11) Compared with the suprabasal fraction, basal cells in mature airway epithelium show increased ICAM-1 expression, RV viral capsid protein (VP2) staining and RV RNA copies per cell, demonstrating their susceptibility to infection by RVs. In addition, epithelial injury has been shown to allow greater RV replication, perhaps explaining the more severe disease seen in children with pre-existing lung disease such as asthma or bronchopulmonary dysplasia.(11,12)

Although the ICAM-1 receptor and LDLR on epithelial cells are well known targets for RV-A and RV-B,(13) the target for RV-C, CDHR3, has only recently been identified by gene expression analysis.^{6 14} Expression of eight genes, including those coding for CDHR3, which were common to the plasma membrane and receptor, were significantly higher in cells which were susceptible to RV-C versus those which were non-susceptible. A recent study(6) demonstrated a single nucleotide polymorphism, C529Y, in the gene coding for the CDHR3 protein was associated with increased expression of the CDHR3 protein resulting in increased RV-C binding to the epithelial cells and subsequent progeny yield. A Danish GWAS study identified CDHR3 as a susceptibility locus for asthma exacerbations. Children 2-6 years old with the AA genotype of the CDHR3 gene had an increased risk of severe asthma exacerbations compared with those with the GG genotype. Together these studies suggest RV-C acts via this receptor to cause asthma exacerbations in susceptible children.(7)

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Are RVs frequent aetiological agents of acute respiratory tract infections?

In the Childhood Origins of ASThma (COAST) high risk cohort (at least one atopic parent), RVs were detected in over 50% of children with respiratory tract infections (RTI) not requiring hospitalisation.(15) Another prospective study of 119 children in day care covering 115 child-years showed a mean of 4.1 RTIs in the first year and 1.2 in the second year. At least one virus was detected in 67% of RTI and co-infections were detected in 27% of RTIs.(16) RVs were the most common viruses detected. An analysis comparing asymptomatic virus detection versus the first subsequent illness in the same subject demonstrated that RVs were detected more commonly in children with RTIs (44% versus 20%) although the difference did not quite reach statistical significance ($P=0.06$). In 1052

hospitalised children, of whom 46% had a virus detected, 15% (i.e. one third of those with a detected virus) had RV.(17) After RSV (15.6%), RV was the most common virus detected. The RV hospitalisation rate was 2.2 per 1000 children less than five years old.

In hospitalised infants with bronchiolitis how does RV compare to RSV?

Studies have compared the demographic and clinical characteristics of infants hospitalised with RSV and RV bronchiolitis. Jartti et al(18) used multivariate analysis to show that RV bronchiolitis was associated with a significantly shorter hospital length of stay (LOS) than was RSV bronchiolitis in infants (median LOS 2 days versus 1 day). Children in the RV group were older, had a history of wheeze, a shorter duration of respiratory illness before hospitalization and a higher Respiratory Distress Severity Score than infants with RSV.(18) No infants with RV bronchiolitis required paediatric intensive care unit admission but 9% of those with RSV infection did. Midulla et al(19) found infants with RV bronchiolitis were older and had a lower clinical severity score at hospital admission and shorter hospital LOS than infants with RSV bronchiolitis. Another study showed infants with RV bronchiolitis were significantly less likely to have a hospital LOS more than three days compared with infants with RSV bronchiolitis (OR 0.36 [95% CI 0.20-0.63]), but infants with RSV and RV dual infections were significantly more likely to have a LOS more than three days (OR 1.33 [95% CI 1.02-1.73]).(20)

Why does it matter which virus is responsible for causing bronchiolitis?

At present the management of bronchiolitis does not differ irrespective of the viral aetiology. There are no active treatments and thus management is supportive. However, a randomised controlled trial (RCT) comparing a short course of oral prednisolone to placebo in infants 3-35 months old with a first hospitalisation due to viral induced wheeze demonstrated in children with RV infection that treatment with prednisolone was associated with reduced recurrent wheezing over one year follow up.(21) The same was not found in children with RSV infection (prednisolone did not affect the frequency of recurrent wheezing). In a subsequent study(22), of 79 children hospitalised due to a first episode of RV-induced wheezing, those with high RV viral loads (greater than 7000 copies/ml) and treated with prednisolone had a significantly longer time to recurrence of symptoms compared with those with a RV viral load less than 7000 copies/ml. It is possible that the acute management of different viral aetiologies of bronchiolitis impacts the chronic respiratory morbidity even if there is no impact on the course of the acute infection. Future studies of treatments for viral bronchiolitis should have longer term follow up to assess this possibility.

Do rhinoviruses play a role in pneumonia?

The Etiology of Pneumonia In the Community (EPIC) study(23) investigated 2638 children less than 18 years old hospitalised with pneumonia in the US. Eighty-nine per cent of children had radiographically confirmed pneumonia and 81% had a pathogen identified; 66% virus, 8% bacteria and 7% both. RVs were the second most commonly identified pathogen (27%) after RSV (28%). RV was more common in children younger than five years of age compared with those five years and older. For RV 49%, and RSV 48%, were single virus infections and in the other 51% and 52% respectively another pathogen was also identified. A

South African study found RVs to be detected just as frequently in children with WHO defined pneumonia, irrespective of severity, as in controls who did not develop pneumonia (35% versus 39%).(24) The controls may have had less severe respiratory tract infections.

Does RV viral load affect disease severity?

Several studies have attempted to address this question and have found conflicting results. An analysis of 694 infants with RV bronchiolitis found no association between RV viral load, as assessed by semi-quantitative [cycle threshold (Ct)] real-time reverse transcriptase polymerase chain reaction (RT-PCR) and hospital LOS.(25) In a Vietnamese study Ct values were not associated with disease severity in children with single RV infections.(26) However, in a Japanese study of children less than four years old, although overall there was no association between RV viral loads and disease severity, in children between 11 months and three years old, a higher RV viral load was associated with more severe disease.(27) In hospitalised Chinese children less than two years old a higher viral load was also associated with more severe disease in children with RV-A but not in children with RV-C.(28) In another study conducted in 50 children hospitalised with RV LRTIs, six children also had RV viraemia. The children with viraemia had significantly higher viral loads in nasopharyngeal samples, as measured by quantitative RT-PCR, and more severe disease as assessed by increased respiratory rate, lower oxygen saturations and increased need for supplemental oxygen and a higher white blood cell count and C-reactive protein.(29) These studies suggest the patient characteristics (e.g. age) and RV species may influence the impact of viral load on disease severity.

Why are asthmatic children particularly susceptible to RV infections?

A study investigating the role of maternal atopy on infant RV infections between 2004-2008 included 383 mother-infant dyads. One hundred and four infants had RV infections and 279 RSV infections. Infants of mothers with atopic asthma were more likely to have RV than RSV infection (OR 2.42 [95% CI 1.19-4.90]). In addition, infants of mothers with atopic asthma had more severe RV infections compared with those infants with mothers who were not atopic.(30) Although the mechanism behind this has not been fully elucidated it has been shown that atopic asthmatics have deficient type III interferon- λ responses to RV infection when compared with healthy controls.(31)

Prematurely born infants are also particularly susceptible to RV infections.(12) Those who develop RV LRTI, compared with those who do not, are more likely to develop chronic respiratory morbidity, including asthma symptoms, especially those who have had RV-C infection.(32,33)

Treatments and vaccines for rhinovirus infection

There are currently no licensed treatments or vaccines for RV infections although several are in development. Pleconaril, a viral capsid inhibitor, has been shown to reduce RV viral load in respiratory secretions and shorten the duration of respiratory symptoms in adults with RV respiratory tract infections.(34) However, it is not licensed for use in the UK or USA. Other medications that are under development for the treatment of RV infections include

rupintrivir, vapendavir, OC459 (a CRTH2 receptor antagonist) and soluble ICAM-1.(35–38) Due to an incomplete understanding of the immune response to RVs and the large number of genetically distinct RV strains, the search for a RV vaccine has so far proved elusive. Several RV vaccines, however, are currently in development.(39)

Can transcriptional profiling help the understanding of the pathogenesis of RV infections?

Blood transcriptional profiles can differentiate between various respiratory viral infections in children.(40) In a study including 137 hospitalised infants less than two years old with RSV, RV or influenza LRTIs blood transcription profiles classified infants correctly based on the causative pathogen with 95% accuracy (Figure 2).(41) A subsequent study from the same group was conducted to elucidate the significance of RV detection. Four groups of infants were compared: a) infants with RV infection requiring hospitalisation (“inpatients”), b) infants with symptomatic RV infection not requiring hospitalisation (‘outpatients’), c) RV positive asymptomatic healthy infants, and d) RV negative asymptomatic healthy controls. (42) Infants with symptomatic RV disease (whether or not they required hospitalisation) had similar blood transcriptional profiles which were significantly different to those of infants who had asymptomatic RV detection. Those infants with asymptomatic RV detection had blood transcriptional profiles similar to those of RV negative healthy controls (Figure 3). (42) This methodology can therefore be used to differentiate between infants with and without active RV infection. Assessing the genes that are up- and down-regulated in these different groups can also provide a picture of the immunopathological mechanisms behind RV infections, for example, genes related to interferon, neutrophil function and apoptosis were

over expressed in infants with symptomatic RV infection. (42) This has the potential to identify new targets for treatments or vaccines.

Can we measure disease activity/severity using new genomics assays?

Molecular distance to health (MDTH) scores measure the magnitude of transcriptional perturbation of individual patients compared with healthy controls. (42) Infants with symptomatic RV infection, whether inpatients or outpatients had significantly higher MDTH scores than healthy controls and infants with asymptomatic RV detection. Those infants with asymptomatic RV infections were not distinguishable (i.e. had similar MDTH scores) from healthy RV negative controls. (42) MDTH scores may also be able to differentiate between infants requiring inpatient and outpatient care as they are significantly correlated with clinical disease severity scores. (42)

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Conclusion

In summary, there is now sufficient evidence to state that RVs are major paediatric pathogens which affect both the upper and lower respiratory tracts and frequently cause wheezing, asthma exacerbations and pneumonia, as well as “common colds”. A defective immune response to RV infection involving interferon- λ may be one of the mechanisms behind exacerbations in asthmatic children. New blood transcription profiling techniques of the host immune response may help further characterise the pathogenesis and clinical disease of RV in humans and identify novel sites for treatment or vaccine development.

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Rhinovirus infections are associated with increased risk of recurrent wheezing --so toy both are right so will keep as it is.

Conflict of Interest

SBD, AM and OR have no conflicts of interest to declare.

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Figure captions

Figure 1 The pathogenesis of RV infection. Adapted from Saraya et al.(5)

Figure 2 Transcriptional profiles from children with influenza, RSV, and HRV LRTI. From Mejias et al.(41)

Figure 3 Transcriptional profiles from children with symptomatic and asymptomatic RV infection. From: Heinonen S, et al. Am J Respir Crit Care Med. 2016 Apr 1;193(7):772-82. Rhinovirus Detection in Symptomatic and Asymptomatic Children: Value of Host Transcriptome Analysis. (42) Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

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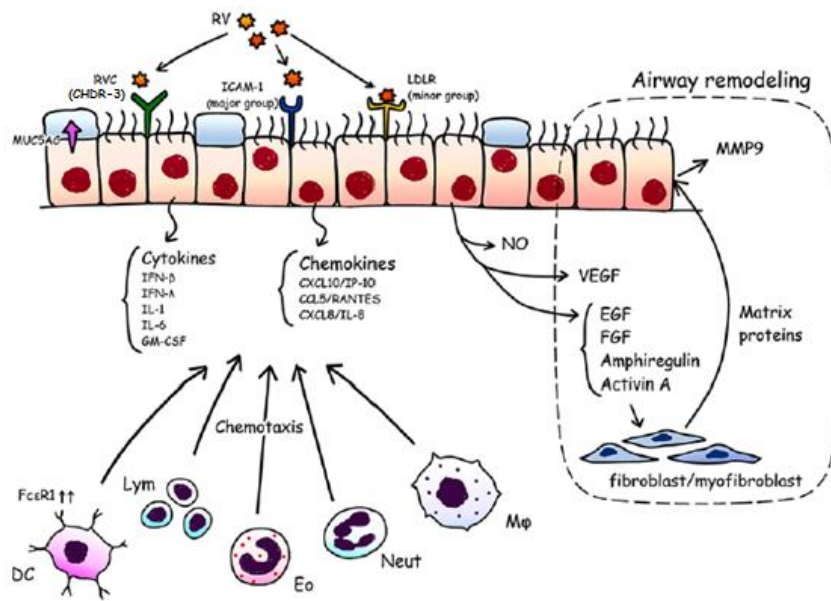


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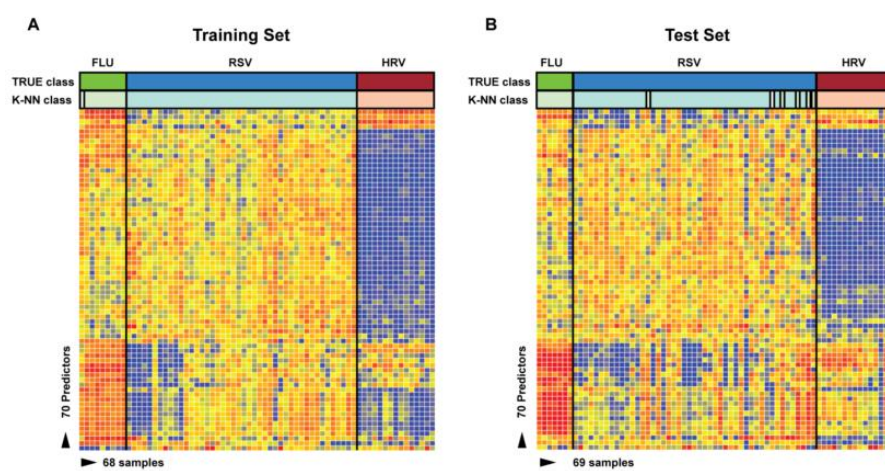


Figure 3 Transcriptional profiles from children with symptomatic and asymptomatic RV infection. From: Heinonen S, et al. Am J Respir Crit Care Med. 2016 Apr 1;193(7):772-82. Rhinovirus Detection in Symptomatic and Asymptomatic Children: Value of Host Transcriptome Analysis. (42) Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

