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Rhinovirus Infection in Children—a Narrative Review

Guwani Liyanage, M.D., Department of Paediatrics, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka

Abstract

First discovered in the 1950s, rhinoviruses (RVs) are linked to a broad spectrum of clinical syndromes, particularly in young children. RVs cause greater morbidity than previously recognized and impose substantial health care expenditure and missed days of work due to physician visits, hospitalization, and childcare. Our understanding of the genomic structure of RVs has increased with advances in molecular methods. RT-PCR is the most commonly used method for RV detection at present. Currently, treatment of RV infection is mostly supportive; there are no approved antiviral medications available yet. This review aims to provide the most current information on clinical syndromes, pathogenesis, host immunological responses, diagnostics, and therapeutic and preventive strategies related to RV infection in children.

Introduction

Rhinovirus (RV) is among the most frequent causative agents of upper respiratory tract infections in children and adults and is linked to a broad spectrum of clinical syndromes. Generally, by 2 years of age, approximately 90% of children have antibodies against RV [1]. The "common cold" is the colloquial term given for mild, self-limiting upper respiratory infections, and RV is the primary causative organism that is implicated, not only in children, but also in adults [2]. Importantly, though, RV is also responsible for rhinosinusitis, otitis media, and croup. Additionally, the past few decades have highlighted that RVs can also be associated with more significant clinical manifestations, including associations with wheezing, asthma, and community-acquired pneumonia (CAP) [3,4]. Some of these illnesses and presentations may require hospitalization, imposing substantial economic costs on health care systems throughout countries [5]. The development of a vaccine for RV has been a challenge, largely due to the issue of strain diversity, and as a result, an effective vaccine is not yet available [6].

This review highlights the most recent information on clinical syndromes, pathogenesis, host immunological response, diagnostics, and therapeutic and preventive strategies related to RV infection in children.

Epidemiology

RV circulates year round in tropical, subtropical, semiarid, and temperate regions. In temperate climates, RV peaks during the spring and autumn [7]. Conversely, influenza virus and respiratory syncytial virus (RSV) peak in the winter. In the tropical belt, although clear peaks are not noticeable, incidence is high during the rainy season. RVs commonly infect all age groups. Infants, young children, and the elderly have the highest rates of severe infection among hospitalized patients with RV infections [8,9]. RV is acquired mostly from the community, although nosocomial infections have been reported [10]. Transmission of RV occurs primarily through inhalation of respiratory droplets, although RV shedding in aerosols is not yet well understood. However, RV can also survive on surfaces and on undisturbed skin for several hours, so spread may

Corresponding author: Guwani Liyanage, M.B.B.S., M.D., Department of Paediatrics, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda 10250, Sri Lanka. Tel.: 0773593785. E-mail: guwani@sjp.ac.lk.

also occur through direct person-to-person contact or through contaminated surfaces or direct inoculation of the eye or nose mucosa with fingertips [11]. Non-enveloped viruses, such as RV, rotavirus, and adenovirus, are relatively resistant to alcohol-based hand sanitizers and disinfectants, limiting the effectiveness of these products for the viruses [12]. In a study comparing the effectiveness of handwashing with soap and water versus the use of alcohol-based hand sanitizers, the authors found that handwashing was sufficient to inactivate over 5 $\log_{10}$ norovirus particles. In contrast, the alcohol hand sanitizer was unable to inactivate the same virus [13].

Virus Characteristics

RV is a non-enveloped, positive-sense RNA virus that belongs to the family *Picornaviridae* and genus *Enterovirus*. According to the latest recommendations from the International Committee for Taxonomy of Viruses, members of the genus *Enterovirus* infectious to humans are split into two major groups: four species of enteroviruses (enterovirus A to enterovirus D) and three species of RV (rhinovirus A to rhinovirus C) [14]. Although enteroviruses and RVs are genetically related, they are highly heterogeneous in terms of disease manifestation and antigenic characteristics. Among the RVs, rhinovirus A and rhinovirus C are linked to more severe disease and asthma exacerbations than is rhinovirus B [15]. Rhinovirus C, which was identified more recently, is a major cause of RV-associated sequelae. Over 50% of RV infections in young infants are due to rhinovirus C, and it is the most frequently detected RV species during asthma exacerbations in children [15].

The RV capsid is composed of four proteins (VP1, VP2, VP3, and VP4), which encase the RNA genome. The first three capsid proteins are responsible for viral antigenic diversity, whereas VP4 is internalized, anchoring the RNA to the capsid [7]. Incredibly, approximately 170 distinct RV serotypes have been described to date [14]. Notably, infection with one RV serotype does not confer immunity to the other RV serotypes. Thus, an individual can get lifelong re-infections when exposed to different serotypes. However, some closely related serotypes that provide some cross-protection have been identified [7].

In general, RV is an upper respiratory tract pathogen, replicating well at temperatures of 33 to 35°C. This temperature preference may be one reason that RVs do not typically infect the lower respiratory tract, where lung tissue temperatures are around 37°C. However, there are many reports of RV isolated from lung aspirates, contradicting the previous belief that replication is reduced in temperatures above 37°C [16].

Pathogenesis

Direct effects of the virus on host tissue and the pro-inflammatory immune responses to infection (innate, humoral, and cellular) are the two main mechanisms responsible for RV pathogenesis. Unlike RSV and influenza virus, RV is seldom associated with cell destruction and cytopathology of the airway epithelium [17]. Instead, RV disrupts the epithelial barrier and leads to vascular leakage and excess mucus production, with some cytopathology [18]. Once infected, the innate immune responses that are initiated include induction of interferons and chemokines and recruitment of inflammatory cells (neutrophils and mononuclear cells) into the airway [17]. Products of neutrophil activation, such as elastase, can upregulate goblet cell secretion of mucus and are likely to be involved in obstructing the airways, leading to lower airway symptoms. The humoral immune responses are important in preventing RV infections; however, the exact mechanism is not known. Serotype-specific IgA detection on day 3 and IgG detection on days 7 and 8 post-infection have been demonstrated by experimental RV inoculation studies in humans [19]. Although IgA falls to an undetectable level by 3 to 6 months, IgG persist longer and may be detectable for life [19,20]. Impact of neutralizing antibody titers on the reduction in symptom severity and protection from infection by the same serotype were observed after experimental exposure of adult volunteers to RV [21]. However, patients with hypogammaglobulinemia are more susceptible to RV infection despite intravenous immunoglobulin treatment; thus, it is not clear whether secretary IgA has a more important role in mitigating RV infections [22].

In the absence of an effective humoral and innate immune response, T cells play the primary role in virus eradication. Upon infection, various chemokines, such as CXCL10, induce cytotoxic T-cell and helper T-cell responses. The type of stimulated T-cell response in a healthy individual is typically via the T helper type 1 (Th1) pathway, characterized by secretion of interferon gamma (IFN-γ). Interleukins (IL-4, IL-5, and IL-13) are secreted by T helper type 2 (Th2) immune reaction, which is believed to be associated with induction of asthma [23].

Many underlying mechanisms are postulated for the development of asthma following RV infection. It could be that RV infection induces various cellular factors that regulate host responses, airway inflammation, remodeling, and increase of pro-inflammatory cytokine and chemokine production [7]. Also, RV infection, in the presence of allergen exposure, promotes Th2 immune response, as described earlier. When RV infection is acquired in the first months of life, there is a greater tendency to induce Th2 immune response than Th1 reaction [24]. Further, genetic factors may further predispose some populations to RV-associated asthma, including the newly described CDHR3 gene (encoding cadherin-related family member 3), which is highly expressed in the airway epithelium in children with specific phenotypes of asthma [25]. Experimental expression of CDHR3 enables cells that are normally resistant to rhinovirus C infection to support both virus binding and replication [26].

Also, individuals with a diagnosis of asthma are predisposed to RV-induced asthma exacerbations. One proposed mechanism is damage of the epithelium following exposure to environmental allergens, which increase susceptibility to infection [23]. Disturbed airway epithelium may favor viral entry into deeper cell layers, where RV has been demonstrated to replicate more actively. Additionally, allergic sensitization and alterations in the airway microbiome influence the severity of the viral infection and the risk of asthma exacerbation [27]. Bronchial epithelial cells of

asthmatics are likely to have increased viral shedding, low IFN-γ, and increased cell destruction [23].

RVs may also increase host susceptibility to bacteria by multiple different mechanisms, demonstrated *in vitro* using lower and upper airway epithelial cells. For example, adhesion of *Streptococcus pneumoniae* to tracheal epithelial cells is enhanced by increasing platelet-activating factor receptors, while RV disruption of tight junctions facilitates transmigration of *Staphylococcus aureus* [28,29]. In addition, RVs impair immune responses of alveolar macrophages to bacterial products. RV-activated macrophages produce less tumor necrosis factor α and IL-8 than non-RV-activated macrophages when exposed to bacterial Toll-like receptor agonists, such as lipopolysaccharide and lipoteichoic acid of the bacterial cell wall [16].

Clinical Syndromes

Rhinovirus A is detected more frequently than rhinovirus C and rhinovirus B in respiratory illnesses [30]. Rhinovirus C is reported to be predominantly associated with asthma exacerbations and more serious respiratory illness in young children [31]. However, similar clinical presentations across species have been reported [9].

Upper respiratory tract infections

Generally, young children get six to eight "colds" per year, while older children will have fewer episodes [32]. RV is the most frequent cause of the common cold and is responsible for at least 50% of episodes in adults [2]. It is a self-limited infection in the immunocompetent host, characterized by rhinorrhoea, nasal congestion, cough, sore throat, headache, and low-grade fever. Symptoms may last for a period of 7 to 14 days. Although it is a relatively mild illness, parental anxiety is considerable, and many parents may ultimately visit a physician [5]. Thus, direct and indirect medical costs due to missed work and caring for an ill child are considerable [5].

The common cold may be associated with sinus involvement (viral rhinosinusitis), which in most cases resolves spontaneously. However, in some cases, it can progress to bacterial sinusitis and induce chronic rhinosinusitis with exacerbations [28].

RV is traditionally also associated with otitis media. In bacterial-viral confections of acute otitis media, detection of RV was associated with lower antibiotic response rates than co-infection with RSV, parainfluenza virus, influenza virus, or other viruses [33]. Although parainfluenza viruses are most commonly associated with croup, recent reports have cited RV as an increasingly frequent aetiological agent of the diseas,e as well [9].

Lower respiratory tract infections

There is substantial evidence for the association of RV infection with a variety of lower respiratory tract manifestations, including bronchiolitis and pneumonia. RSV is the most common cause of bronchiolitis during the first year of life; however, RV starts to dominate thereafter [34]. There is a high risk of subsequent development of asthma among children with severe bronchiolitis requiring hospitalization (Table 1).

RV is also responsible for lower respiratory tract infections in young infants and children with chronic diseases (e.g., cystic fibrosis and bronchiolitis obliterans) and malignancy [35]. Many studies have reported RV as a pathogen in CAP. A recent study by Gonapaladeniya et al. (unpublished) conducted among 149 Sri Lankan children between 3 months and 14 years of age with radiologically confirmed CAP isolated RV in nasopharyngeal secretions of 44 (29.5%) children. In 28 of them, RV was present concurrently with other viruses or bacterial pathogens. Louie et al. reported that RV was the only organism detected in half of thevchildren with lower respiratory tract infections admitted to an intensive care unit [36]. Nevertheless, confirming the role of RV in causation of CAP is a challenge. The well-known Etiology of Pneumonia in the Community (EPIC) study detected one or more viruses among 17% of control subjects compared to 22% of children with radiographically confirmed CAP at the same study site during the same period [4].

Rhinoviral infections and asthma

It is heavily debated whether viral infections cause asthma. In a longitudinal study, Kotaniemi-Syrjänen et al. reported that the likelihood of asthma in hospitalized children with RV-associated wheezing was four times higher than in children with wheezing episodes linked to other viral infections [37]. Several other studies have reported that severe acute bronchiolitis or early wheezing is linked to a greater risk of developing asthma later in childhood (Table 1). A family history of atopy, type of virus (rhinovirus A and C), pre-existing airway inflammation (Th2 polarized inflammation and airway remodeling), genetic predisposition to allergy, adverse

Table 1. Outcomes of rhinovirus infection in children

Authors, yr, country	Age at recruitment	Study design	Outcome, age (yr)	Virus risk factors [OR (CI)][a]	Prevalence of recurrent wheezing/ asthma (%)
Ruotsalainen et al. [3], 2013, Finland	1–23 mo	67 hospitalized children with bronchiolitis and 155 controls	Asthma, 16.5	7.3 (2.1–26)	28
Takeyama et al. [39], 2014, Japan	<3 yr	80 children with wheezing on admission and 136 controls	Recurrent wheezing, 4.2		81
Rubner et al. [40], 2017, United States	Birth to 3 yr	217 children	Asthma, 13	3.3 (1.5–7.1)	

[a] OR, odds ratio; CI, confidence interval.

environment (allergens, smoking, or pollution), and loss of personal microbial diversity increase the risk further [28]. Antibiotic use, urbanization, and increased hygiene are likely reasons for loss of microbial biodiversity.

It is estimated that 85 to 95% of exacerbations in children and 75 to 80% in adults with asthma are associated with viral infections [23]. In a study among 9- to 11-year-old children, 46 to 50% of asthma exacerbations were attributed to RV infection [38]. Peaks of exacerbations were seen when children returned to or started school, as the likelihood of getting respiratory infections increased [38].

Diagnosis

Respiratory specimen collection should be done as soon as possible in the course of illness, as the probability of detecting most viruses lessens significantly 72 hours after the onset of illness [41]. Nasopharyngeal swabs or aspirates are generally considered the specimens of choice for upper respiratory tract respiratory viruses, including RV, and are preferred over oropharyngeal swabs [7,42]. Tracheal aspirate or bronchoalveolar lavage fluid could be used to investigate lower respiratory tract infections.

There are four main ways that RV can be detected in a patient's samples: viral culture, serology, molecular assays (e.g., reverse transcriptase real-time polymerase chain reaction [RT-PCR]) and direct detection via an immunofluorescence assay. Viral culture to detect RV is time-consuming and laborious, thus limiting its usefulness in acute patient management. Additionally, viral culture is no longer routinely performed in most clinical laboratories, and it is generally less sensitive than molecular methods [43]. Finally, unlike rhinovirus A and rhinovirus B, rhinovirus C does not grow in conventional cell cultures and would be missed by this method [44].

Antibodies to RV in serum can be detected by immunofluorescence, enzyme-linked immunosorbent assay (ELISA), and complement fixation tests. The detection of antibodies as a diagnostic method for RV is severely limited and is not advisable for many reasons, most importantly, the delay in seroconversion of 1 to 3 weeks post-infection, the high rate of seroprevalence in the population, and the lack of appropriate cross-reactive antigens to cover a large number of serotypes [7,45]. Therefore, performing serology may be useful in epidemiological studies, but it is not recommended for diagnosis of an acute RV infection.

In contrast, molecular assays can accurately and rapidly detect RVs from respiratory specimens. In single-plex RV RT-PCR assays, a single gene target with high homology among RV species is amplified in a single reaction, whereas multiplex RT-PCR assays permit simultaneous amplification of multiple target sequences from many different respiratory pathogens in a single test. Importantly, RT-PCR assays do not differentiate between RVs from enteroviruses (EVs), as the 5′ untranslated region, common to and homologous in both RV and EV, is the most commonly used target region in RT-PCR assays due to its high sensitivity. As a result, given that commercial kits cannot differentiate between RV and EV, results are often reported as RV/EV [48]. RV may co-exist with other viruses and bacteria, particularly among immunocompromised children, making syndromic, multiplex respiratory RT-PCR assays beneficial in this population [7]. For otherwise healthy children, a more targeted diagnostic approach using a single-plex RV RT-PCR assay may be preferred.

While molecular assays are more sensitive than serology and viral culture, this sensitivity may also be a limitation as detection of RV, especially in the upper respiratory tract samples, may not always be attributable to disease causation [4]. For example, detection of RV in the nasopharynx could result from prolonged viral shedding after resolution of a previous symptomatic infection. Also collecting the respiratory samples during the incubation period before the onset of symptoms and/or with unrecognized symptoms due to an asymptomatic RV infection could make interpretation difficult [7]. Asymptomatic infections are not uncommon among children and adults [4,46].

Finally, rapid RV antigen detection kits using immunofluorescence have been developed; however, they are typically less sensitive than molecular assays, although some studies report a high level of specificity [47]. Due to the availability of molecular assays, however, antigen testing for RV is not widely used in the clinical setting.

Treatment

Several therapeutic interventions are suggested to prevent development of asthma following RV-induced wheezing. Use of a short course of systemic steroids in the initial wheezing episode induced by RV was shown to reduce recurrences of wheezing in children within the subsequent 12 months. Also, it significantly reduced the subsequent risk of asthma by 30% [27,49]. The likely mechanism of this is via targeting Th2 polarized immunity and/or virus-induced inflammation in the airways.

In treatment of exacerbation of asthma due to RV infections, there is increasing evidence that inhaled steroids, in combination with long-acting beta-agonists, shows superiority over use of steroids alone [50]. A combination of these has been shown to suppress several chemokines and remodeling-associated growth factors synergistically. In children with allergic asthma, omalizumab (anti-IgE) has been shown to reduce the duration of illness, viral shedding, and the risk of RV-associated infections [51]. Seasonal peaks in asthma exacerbations could be reduced by year-round treatment of at-risk populations with omalizumab. At present, there is no approved antiviral therapy for RV infections, however.

The large number of RV serotypes and their genetic diversity and error-prone RNA polymerase have been the major obstacles to antiviral and vaccine development [52]. There are a few antiviral agents, such as pleconaril, amantadine, and rimantadine, which have been tested for clinical efficacy. However, their clinical use is questionable due to adverse events and drug resistance [52]. The need to administer antivirals very early in the disease course and, in turn, difficulties associated with rapid diagnosis in some locations and high cost involved in the production of drugs are just a few of the other hindrances.

Prevention of RV Infections

Physical distancing, respiratory masks, and hand hygiene are useful for prevention of viral transmission. A recent systematic review of the factors associated with mitigating transmission of coronaviruses (e.g., severe acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus) reported that physical distancing of 6 feet or more and use of face masks (N95 respirators or surgical masks) has a protective effect [53]. Frequent and correct hand hygiene is also an effective measure [54]. Alcohol-based hand sanitizers have become a popular substitute for traditional handwashing with soap and water. However, they are ineffective against non-enveloped viruses, such as RV [13].

There are no licensed vaccines available as yet for RV. Due to many technical and logistical issues, developing a vaccine has been a daunting task. The presence of high and increasing numbers of viral strains with a lack of cross-protective immunity continues to be an obstacle to vaccine development [7]. A polyvalent vaccine could cover multiple serotypes to enhance the development of neutralizing antibodies. Although, theoretically, neutralizing antibodies secure immunity against RV, there is minimal cross-protection by serotype-specific neutralizing antibodies [15]. Therefore, inclusion of a range of antigens to secure adequate protection is a key challenge. Also, there is a lack of epidemiological data on the specific serotypes of rhinovirus A and rhinovirus C that should be given priority in vaccine preparations [15]. Another challenge is finding the exact model for experiments. Although mice and cotton rats are the models for vaccine trials, they do not resemble the RV pathogenesis of humans in some respects [55]. Despite all of these challenges, there have been recent advances in the development of an effective vaccine, and a vaccine may be feasible in the future.

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