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Rhinoviruses

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Introduction

Human rhinoviruses (HRV) are ubiquitous pathogens which are the leading cause of the common cold syndrome. Once considered mostly a nuisance, these viruses are now appreciated as the cause of medically significant illness and a substantial burden of disease. Although illness is typically mild and self-limited, lost time from work and school creates a considerable economic burden. Infection of the upper airways is the most common site of infection, although lower airways disease is also now well documented, as is the link between HRV infection and exacerbations of asthma. Unfortunately, effective specific antiviral treatments and vaccines remain elusive. In this article, the basic virology, pathogenesis of disease, epidemiology, clinical manifestation, and current methods of treatment and prevention will be reviewed.

Virology

HRV is a member of the *Enterovirus* genus within the *Picornaviridae* family. Since it was first identified in 1956, 101 serotypes

of rhinovirus have been cultured and distinguished by distinctions in neutralizing antibody. These 101 serotypes have been classified into two species, HRV-A and HRV-B, though in recent years sequencing technology has led to the identification of more than 60 genotypes of viruses which do not grow in culture and have been placed into a third species, HRV-C (Bochkov et al., 2015). The rhinoviruses are also classified on the basis of receptor specificity. The ‘major’ receptor group, which comprises ~90% of serotypes A and B, uses the intercellular adhesion molecule 1 (ICAM-1) as the receptor for infecting host cells (Staunton et al., 1989). Twelve HRV-A serotypes use an alternative site, the low-density lipoprotein receptor (LDLR), and the receptor for the HRV-C viruses is human cadherin-related family member 3 (Bochkov et al., 2015).

Rhinoviruses are small, nonenveloped viruses with a single strand of positive-sense RNA (Greenberg, 2003). Each virion is composed of 7.2 kb of genomic material packed in a 30-nm icosahedral protein shell known as a capsid (Royston and Tapparel, 2016; Figure 1(a)). The capsid is, in turn, comprised of 12 pentamers each with five protein subunits called protomers containing four viral proteins, VP1, VP2, VP3, and VP4.

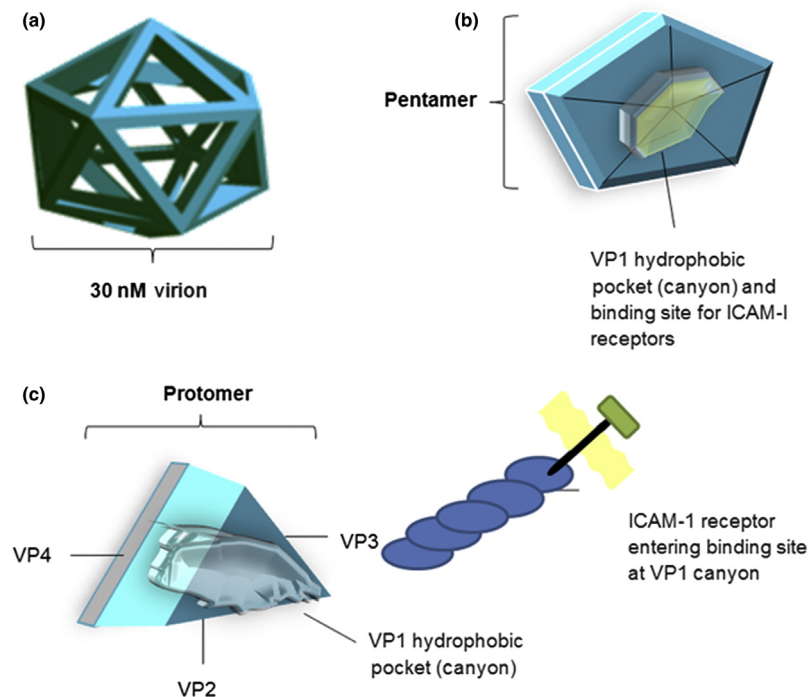


Figure 1 Structure and principle features of human rhinovirus (HRV). (a) A virion is composed of 7.2 kb of genomic material packed in a 30-nm icosahedral protein shell known as a capsid. (b) The capsid is comprised of 12 pentamers with a central shared depression or ‘canyon.’ (c) Protomers are protein subunits of the pentamer containing four viral proteins, VP1, VP2, VP3, and VP4. VP1 proteins form a hydrophobic pocket in the canyon region which serves as the binding site for intercellular adhesion molecule 1 (ICAM-1) receptors in host cells.

Each pentamer contains a central shared depression or 'canyon' in the five VP1 proteins of the protomer subunits, which serves as the binding site for ICAM-1 receptors in host cells (Figure 1(b) and 1(c)). Once attachment to the host cell is achieved, viral replication occurs in the host cell cytoplasm. Antibody neutralization occurs when IgG binds to the viral surface and obstructs access of the host-cell receptor to the viral attachment site at the base of the canyon (Turner, 2015). VP2 and VP3 are also found on the surface of the capsid and have antigenic sites important for the host immune response. VP4 is located on the internal side of the capsid and interacts with the viral genome. The genomic data that code for VP1 are somewhat conserved among the various subtypes of HRV, though variations in VP1, VP2, and VP3 account for antigenic diversity among serotypes and impede the development of effective vaccines and antiviral agents.

Transmission

For infection to occur HRV must reach the nasal mucosa of the susceptible individual. Transmission from infected to susceptible individuals most likely occurs when viral load is highest and secretions are plentiful and difficult to control. Under experimental conditions, a viral titer of 10^3 TCID₅₀ (tissue culture infective dose) was needed to transmit infection and most often occurred on the 2nd or 3rd day of a cold during peak symptoms (Turner, 2015). Epidemiologic evidence suggests that direct contact and self-inoculation account for the majority of HRV transmissions. Classic transmission studies of infected and susceptible subjects demonstrated that hand to hand or from hands to intermediary surfaces with recipient self-inoculation efficiently transmits HRV (Hendley et al., 1973). More recent experimental studies have shown that transmission of HRV is possible by small and large particle aerosols, but how frequently this occurs in natural settings is unclear.

Disease Pathogenesis

Once the virus reaches the nasal mucosa, attachment to the epithelial cells occurs via the ICAM-1 receptor in 90% of infections or by the LDLR receptor depending on the serotype (Pitkaranta and Hayden, 1998). HRV grows best at 33 °C in cell culture and primarily in the upper respiratory tract, although infection of the lower airways and sinuses, at higher body temperatures, is possible. Both ciliated and nonciliated epithelial cells can be infected, and as infection progresses, affected areas may be patchy (Figure 2). HRV infection is not cytopathic, and it is generally accepted that the majority of symptoms are due to the host inflammatory response. Infection is limited to the respiratory tract with only rare reports of invasive disease (Brownlee and Turner, 2008). Although HRV is rarely cultured from blood, HRV RNA has been detected in the plasma in ~10% of normal children with HRV infection and was more common in those with severe illness and asthma exacerbations. However, it is unclear if detection of viral RNA in plasma truly represents systemic infection.

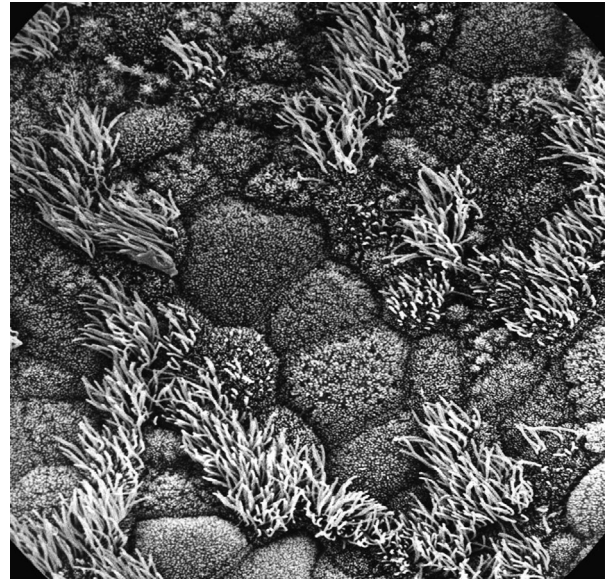


Figure 2 Nasal epithelial inflammation following human rhinovirus (HRV) infection. Scanning electron microscopy showing intact nasal epithelial surface with ciliated cells of a patient infected with the common cold 2 days after the onset of symptoms.

Once infection has been established, a complex interplay of neurogenic and host responses occurs. Early infection is characterized by a vigorous inflammatory response brought about by the elaboration of a variety of proinflammatory cytokines and chemokines, including interleukin (IL)-1B, IL-6, IL-8, and interferon-induced protein 10 (Pitkaranta and Hayden, 1998; Turner, 2015). The concentration of these inflammatory mediators correlates with the severity of symptoms and results in an influx of neutrophils, increased vascular permeability, swelling of the nasal mucosa, and leakage of serum into nasal secretions. The kinins, bradykinin, and lysyl bradykinin can also be found in the secretions of HRV-infected individuals, and their presence and concentrations also correlate with symptoms. Yet, treatment by blocking kinins has been ineffectual in alleviating symptoms raising questions as to the relevance of kinins in HRV disease pathogenesis. Moreover, despite the frequency of antihistamines in many cold treatments, there is no evidence of histamine release in HRV infection. This may be due to the fact that neurogenic reflexes also appear to play a role in disease pathogenesis, with parasympathetic nerves controlling the flow of secretions from the nasal seromucous glands. Finally, the importance of HRV infection and asthma exacerbations is now well recognized (Gern and Busse, 1999). The precise mechanism by which this occurs has yet to be fully investigated but appears to involve genetic predisposition and allergic airway factors measured by immunoglobulin E (IgE).

Immune Response and Protection

HRV-specific neutralizing antibody has been shown to be protective against infection and symptoms with homologous

viruses (Gwaltney et al., 1966). Infection results in the production of both serum IgG and nasal IgA beginning around 2 weeks after infection and results in long-lasting protection to the specific infecting HRV serotype. Resolution of symptoms and clearance of virus occur before the induction of nasal or serum antibodies, indicating a different mechanism for viral clearance. The inflammatory response produced during initial infection with HRV does not appear responsible for clearance of the virus. Although the inflammatory response correlates with symptoms, asymptomatic individuals with little or no inflammatory response can efficiently clear HRV infection. The mechanism by which HRV clearance occurs likely involves the cellular immune response. Both CD4 and CD8 cells can recognize heterologous HRV antigens and represent memory cells in persons with prior HRV infection (Kennedy et al., 2012; Steinke et al., 2015). These cells function as immune surveillance and are able to produce a rapid adaptive immune response.

Epidemiology

HRV have worldwide distribution and circulate throughout the year. In temperate climates, peaks of viral activity are seen in the late summer and fall as well as the late spring (Pitkaranta and Hayden, 1998). Although HRV activity is relatively low during the summer months, it remains the most common cause of the common cold throughout the year. Multiple serotypes can circulate simultaneously in the same geographic area, and no clear pattern of reappearance has been noted. Households and schools are the most common places for spread of HRV infection.

HRV affects persons of all ages with the highest incidence documented in young children. The incidence of HRV infection in children during the first 2 years of life was noted to be 0.7–2 infections per year in older studies using cell culture for viral detection (Brownlee and Turner, 2008). More recently, Winther et al. reported an average incidence of six picornavirus infections per year in a cohort of children aged 3 months to 15 years. Colds remain common among working adults averaging two per year with HRV accounting for 23–50% of illnesses and then appear to decline in frequency toward middle age (Gwaltney et al., 1966). Although the incidence of acute respiratory tract infection declines with age, HRV infection can be a problem for older adults. In studies of community-dwelling older adults HRV was identified in 24% of illnesses reported by 533 elderly persons followed for two winters in the United Kingdom (Nicholson et al., 1997). Additionally, HRV has been described as a cause of infection in older adults in day cares, long-term care facilities, and hospitalized with acute respiratory tract illnesses.

Asymptomatic HRV infection was recognized in the era of diagnosis by viral culture, but the widespread use of reverse transcription polymerase chain reaction (RT-PCR) for detection in recent studies demonstrates a high incidence of asymptomatic infection. Approximately 12–22% of asymptomatic subjects sampled are positive for HRV and approximately 20% of all HRV infections detected by RT-PCR are asymptomatic (Brownlee and Turner, 2008). These

findings make assessing the casualty of HRV with illness in epidemiologic studies challenging without the use of control subjects.

Clinical Illness

Upper Respiratory Infection

The most frequent clinical syndrome ascribed to HRV is the common cold, an aggravating but usually self-limited illness. Sir William Osler characterized the illness particularly well in the *Principles and Practice of Medicine* published in 1925: “the patient feels indisposed, perhaps chilly, has a slight headache, and sneezes frequently... At first the mucous membranes of the nose is swollen, “stuffed up,” and the patient has to breathe through the mouth. A thin, clear, irritating secretion flows, and makes the edges of the nostrils sore ... usually within 36 hours the nasal secretions become turbid and more profuse... and gradually, within 4–5 days, the symptoms resolve” (Gwaltney et al., 1967). In his studies, Gwaltney et al. (1967) had detailed the symptoms and time course of the typical HRV upper respiratory infection (URI). Rhinorrhea (65%) and sneezing (50%) were the most common complaints in the first 3 days. Scratchy or mild sore throat and headaches are also common in the first few days of illness. Fever is uncommon, although some patients complained of feverishness (15%) and chilly sensations (10%). Lower respiratory tract symptoms such as hoarseness and cough are less common occurring in one-fourth to one-third of cases although if present, symptoms tend to linger throughout the illness. When compared with other viral respiratory illnesses, significantly more sneezing occurred with HRV infections. The mean length of illness was 8.9 days with a range of 1–33 days.

URI Complications

Acute Otitis Media

Respiratory viral infection is felt to be a common predisposing factor for acute otitis media (AOM). Middle ear pressures have been shown to be abnormal in up to 75% of individuals with either experimentally induced or natural HRV infection (McBride et al., 1989). These abnormalities gradually abate over a 2-week period; however, swelling and obstruction of the Eustachian tube may lead to the development of AOM. A number of studies indicate that direct viral infection of the middle ear fluid is possible as HRV can be detected by viral culture (1–8%) and PCR (24%) of middle ear fluids in infected individuals. Thus, AOM may be due to virus, secondary bacterial infection, or coinfection (Greenberg, 2003).

Acute Sinusitis

Primary viral rhinosinusitis appears to be a common phenomenon during uncomplicated natural infection with HRV. Sinus abnormalities were observed on computed tomography (CT) scans in over 85% of adults with colds (Gwaltney et al., 1994). Most commonly affected were the maxillary (85%) and ethmoid sinuses (65%), though the sphenoid (39%) and

frontal sinuses (32%) could also be affected. HRV can often be detected by culture and RT-PCR in sinus brushings or aspirates from patients with viral rhinosinusitis, though the pathogenesis remains incompletely defined. The pressure created by nose blowing, sneezing, and coughing is felt to be an important factor in propelling HRV into the sinuses (Greenberg, 2003). Importantly, in most patients, the abnormalities found on CT scans resolve within 2 weeks without antibiotic treatment.

Lower Respiratory Tract Infections

Because HRV replicates most efficiently at 33 °C, for many years infection of the lower respiratory tract at higher body temperatures was felt to be unlikely. Recent studies have established HRV replication in the lower airways in natural and experimental infection. After experimental infection with HRV by inoculation of the upper respiratory tract, HRV was detected by *in situ* hybridization on bronchial biopsy during the peak of infection and 6–8 weeks later (Papadopoulos et al., 2000). Consistent with this observation, HRV infection has been linked to bronchiolitis, exacerbations of asthma and chronic obstructive pulmonary disease (COPD), and rarely pneumonia.

Asthma

HRV is an important trigger for asthma exacerbations in children and adults (Gern and Busse, 1999). The peak of asthma exacerbations in the fall coincides with the increase in HRV activity as well as the start of the school year and seasonal allergen exposures. Using RT-PCR in addition to standard testing, Johnson et al. demonstrated that over 80% of the asthma exacerbations in children aged 9–11 years were associated with viral infections of which HRV accounted for approximately two-thirds. In addition to epidemiologic links of HRV and asthma, HRV human challenge models have provided insights into the mechanisms by which HRV infection may worsen asthma (Greenberg, 2003; Papadopoulos et al., 2000). Intranasal and inhaled inoculations of HRV induced bronchoconstriction after methacholine challenge in subjects with mild to moderate asthma (Gern and Busse, 1999). The host immune response to infection induces proinflammatory mediators leading to a cascade of inflammation, activation of neural pathways to enhance airway hyperresponsiveness, and obstruction (Figure 3). In addition to asthma, HRV has been associated with ~40% of acute exacerbations of COPD (Greenberg, 2003). In longitudinal studies of

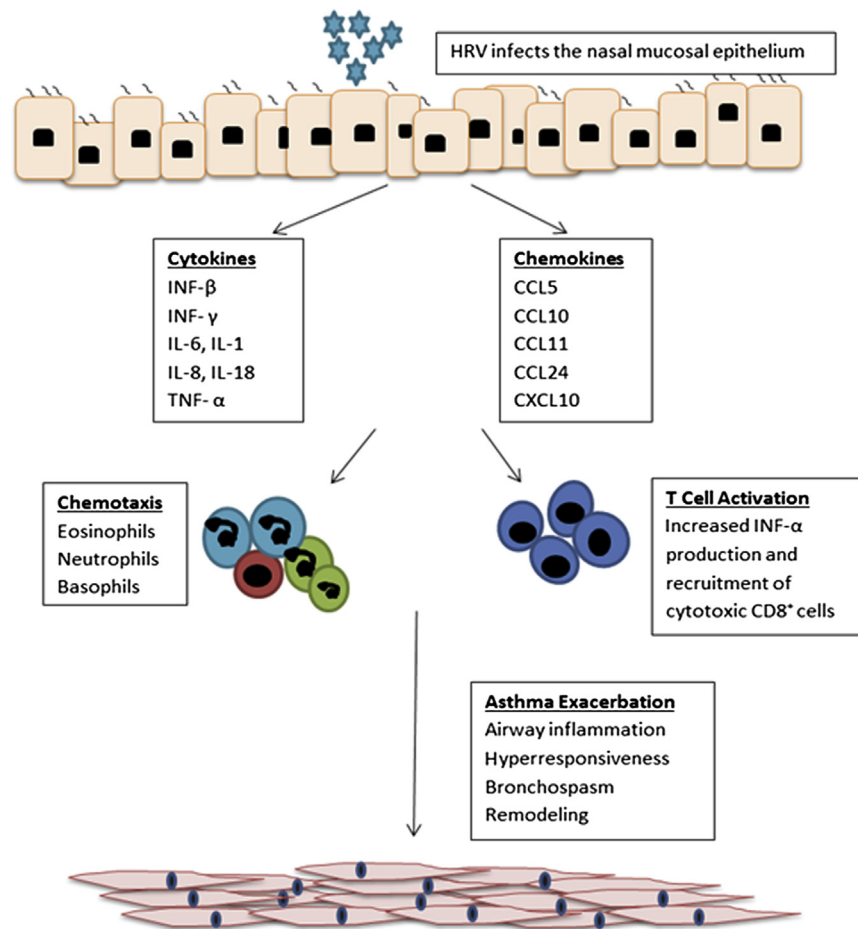


Figure 3 Mechanisms of inflammation and asthma exacerbation triggered by human rhinovirus (HRV) infection. The host immune response to infection induces proinflammatory mediators leading to a cascade of inflammation that triggers airway hyperresponsiveness and obstruction.

respiratory illness, HRV were the most commonly identified pathogens. For patients with moderate to severe COPD, viral infections frequently lead to emergency room visits (12%) and hospitalizations (19%).

Bronchiolitis and Pneumonia

The role of HRV as a cause of bronchitis or pneumonia in immunocompetent persons is unclear. A number of studies using either culture or RT-PCR have detected HRV in the upper airways in a small percentage of young children hospitalized with bronchiolitis or pneumonia (Brownlee and Turner, 2008). HRV was detected in 21% of children <3 years of age hospitalized with bronchiolitis but was the sole pathogen in only 2%. Similarly, 24% of children hospitalized with pneumonia had HRV found in secretions but over half had evidence of simultaneous bacterial infection. While there may be an association of HRV with these types of lower respiratory tract disease, the frequency of HRV in the general population makes assessing causality difficult.

The evidence of lower respiratory tract infections with HRV in immunocompromised patients is more convincing (Greenberg, 2003). In a study of 22 hospitalized immunocompromised patients, 32% developed fatal pneumonia. In six of seven total cases HRV was isolated from bronchiolar lavage fluid or endotracheal aspirates. Persistent HRV in the lower respiratory tract of lung transplant patients has also been documented (Brownlee and Turner, 2008; Ison et al., 2003).

Diagnosis

Although symptoms associated with 'the common cold' syndrome are often attributed to HRV disease, the clinical findings of rhinovirus infections are indistinguishable from those of other viral pathogens. A specific microbiologic diagnosis is most often made by detecting HRV in culture or with molecular assay and rarely using immunofluorescence or serotype-specific antibody assays. A variety of sample types from the upper airways have been used to confirm infection including nasal washes, nasopharyngeal swabs, and combined nose and throat swabs, though a few studies now convincingly report lower respiratory tract disease with virus detected in sputum and bronchoalveolar lavage samples from immunocompromised hosts (Ison et al., 2003; Papadopoulos et al., 2000). For most patients, the timing of collection also plays a role in where virus is detected, with the highest concentration of virus typically detected in nasal fluids in the first 2–7 days when symptoms also peak (Turner, 2015).

Viral Culture

Traditionally, viral culture has been used to identify HRV infection. Viral isolation is accomplished by inoculation of virus on human embryonic fibroblast cells, incubation at 33 °C, and demonstration of cytopathic effect in the cell monolayers. In clinical practice, however, this proves to be a time-consuming method of diagnosis, requiring several days for virus isolation and yielding results usually after the acute phase of infection.

Consequently, microbiologic confirmation is rarely sought using culture methods.

Molecular Assays

In contrast, the advent of new molecular techniques has led to a better understanding of the burden of disease associated with HRV infection with some studies demonstrating an increase in yield of three- to fivefold compared to standard virus culture (Pitkaranta and Hayden, 1998). While not necessarily widely used in practice, RT-PCR has become the standard diagnostic tool and proven to be efficient, sensitive, and specific for detecting rhinoviruses. Single-target HRV RT-PCR assays use primers that probe a conserved region of the HRV genome and are able to detect most serotypes (Pitkaranta and Hayden, 1998; Turner, 2015). However, HRV RT-PCR assays are currently only available commercially as part of multiplexed real-time PCR platforms for respiratory viruses such as the FilmArray Respiratory Panel (Biofire, Utah). This has resulted in some loss of sensitivity and specificity since most of these assays are unable to distinguish between HRV and other enteroviruses. However, one potential benefit of using RT-PCR in practice is the ability to identify low-level viremia and asymptomatic shedding which may be important for infection control purposes in hospital wards with immunocompromised patients.

Serological Assays

Rhinovirus antigen detection using ELISA assays has been attempted but requires serotype-specific antibody and is therefore only of use in research settings. A single immunoassay has been developed which utilizes antibody against a conserved protein, the 3C protease of rhinovirus, but is unfortunately too insensitive for diagnostic use (Turner, 2015). Similarly detection of serotype-specific neutralizing antibodies has been useful to diagnose natural HRV infections in family cohort and experimental virus challenge studies but is impractical for clinical use.

Treatment

Treatment of HRV infections is supportive. The use of over-the-counter therapies may reduce symptoms of the common cold syndrome but are not specific to HRV infections. These remedies include antihistamines and nonsteroidal anti-inflammatory drugs which may alleviate symptoms without shortening duration of viral shedding and are also associated with sedation. Other therapies reported to decrease symptoms, such as decongestants, saline nasal spray, expectorants, zinc sulfate lozenges, and high-dose vitamin C, have not been shown to be of significant benefit in randomized controlled trials (Turner, 2015).

Antiviral Agents

Currently, there are no antiviral drugs approved for clinical use in HRV infections although a few agents have been advanced to clinical trials and shown modest results in decreasing either symptom severity or viral activity.

Leukocyte interferon was the first agent tested for activity against rhinovirus infection and demonstrated efficacy in preventing infection but not as treatment. However, the development of leukocyte interferon for prophylaxis was impeded by its prohibitively high cost and association with nasal toxicity (Turner, 2015). Conversely, monoclonal antibody blockade of the ICAM-1 receptor, the site of cellular attachment for the majority of HRV-A and HRV-B serotypes, has also been studied and demonstrated a reduction in the severity of symptoms and viral shedding but failed to prevent infection in the rhinovirus challenge model (Greenberg, 2003). Moreover, with the discovery of HRV-C viruses, which utilize a different cellular receptor, interest in this approach has waned.

Rupintrivir

The HRV 3C protease cleaves the rhinovirus genome into individual structural and enzymatic components and is important to viral replication (Turner, 2015). It is highly conserved among rhinovirus serotypes and consequently a target for antiviral therapy. Rupintrivir is a 3C protease inhibitor which in experimental trial did not prevent rhinovirus infection but in clinical trial modestly reduced illness severity when treatment was initiated within 1 day of infection (Patick et al., 1999).

Pleconaril

Finally, the hydrophobic pocket formed by VP1 in the canyon region of the capsid, which facilitates attachment to the ICAM-1 receptors of host cells, has also been a target for drug development. Capsid-binding agents bind to the hydrophobic pocket and prevent viral attachment to the cellular receptor and therefore viral replication. Pleconaril is a capsid-binding agent with demonstrated antiviral activity against enteroviruses. In two large randomized, double-blind, placebo-controlled trials, patients with common cold symptoms were treated with pleconaril versus placebo within 24 h of symptom onset (Hayden et al., 2003; Greenberg, 2003). Compared to placebo, pleconaril treatment resulted in reduced illness duration by 1 day and an overall decrease in the severity of symptoms. However, it was found to induce cytochrome P-450 3A enzymes and therefore was not approved by the Food and Drug Administration due to the potential for severe drug-drug interactions (Greenberg, 2003). New formulations of this agent are currently being considered for clinical trial.

Prevention

Efforts to develop an effective vaccine for HRV infections have been unsuccessful to date, and strategies for preventing HRV infections are focused primarily on the interruption of transmission. Since transmission occurs from direct contact, standard precautions including appropriate handwashing practices are likely the most effective preventive tool. In high-risk patients such as patients who have undergone

recent stem cell transplantation, more stringent infection control practices including screening of symptomatic patients, early implementation of droplet and contact precautions, and restriction of visitors with upper respiratory tract symptoms have been shown to reduce rates of nosocomial infections (Ison et al., 2003). A number of handwashing agents have been assessed for their potential virucidal activity such as hand sanitizers containing 62% ethanol and treatments with acidic compounds (Turner et al., 2012; Turner, 2015). None have demonstrated efficacy for the prevention of infection and are likely to be as effective as the use of soap and water.

Vaccines

Shortly after the discovery of rhinoviruses, serum serotype-specific neutralizing antibody and nasal HRV-binding immunoglobulin IgA were shown to be protective against infection. Efforts to develop HRV vaccinations soon followed, and initial clinical trials in humans involved the use of formalin-inactivated single serotype HRV vaccines. Results of these trials demonstrated significant reduction in the rate of symptomatic colds (Glanville and Johnston, 2015). However, with the discovery of HRV antigenic diversity resulting in more than 100 different serotypes isolated, this approach was abandoned in favor of multivalent vaccines incorporating 10 serotypes which unfortunately failed to demonstrate significant cross-protection among HRV serotypes. Consequently HRV vaccine research was largely abandoned for more than 20 years.

Recent advances in the development of a mouse model for HRV infection have permitted exploration of alternative approaches to immunization including induction of T cell-mediated immunity. In one recent report, recombinant VP0 protein (VP4 + VP2 precursor), which appears to be highly conserved in HRV-A and HRV-B serotypes, was used as an immunogen in mice and shown to induce cross-serotype T cell recruitment and activation as well as neutralizing antibody production which resulted in accelerated clearance of virus *in vivo* (McLean, 2014). This approach suggests that cross-serotype protection is possible, and while it is unlikely that a single immunogen will generate protection against all HRV serotypes, VP0 may be a useful candidate for a broadly protective subunit vaccine.

Conclusion

HRV infect persons of all ages. Infections in children can occur two to seven times a year and continue through life resulting in two to five symptomatic illnesses per year in adults. While most illnesses are mild and self-limited, in at-risk populations HRV infections may result in severe illnesses. Consequently, though innocuously referred to as 'the common cold,' HRV infections constitute a significant burden with associated health care and economic costs. Further study is needed to understand the pathogenesis of disease and adaptive immune responses associated with HRV infections which may also provide new targets for antiviral agents and broadly cross-protective vaccines.

See also: Influenza; Pneumonia; Respiratory Infections, Acute; Respiratory Syncytial Virus; Viral Infections, an Overview with a Focus on Prevention of Transmission.

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