Viral Infections of Humans: Epidemiology and Control, 6th edition, edited by Richard A. Kaslow, Lawrence R. Stanberry, and James W. Le Duc

1. Chapter Title

Rhinoviruses

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Words: 11228

Index terms: Common cold, contact transmission, droplet transmission, enterovirus, picornavirus, pneumonia, rhinovirus, wheezing illness.

3. Abstract

Rhinoviruses belong to a large group of RNA viruses that include 169 virus types classified in three species, A, B, and C in the *Picornaviridae* family and the *Enterovirus* genus. Rhinoviruses replicate in the nasopharynx and the resulting infections maybe asymptomatic or symptomatic with respiratory symptoms. Immunity is type-specific, which is why repeated infections caused by different rhinovirus types are common. Rhinovirus infections are extremely frequent. Typical epidemiological feature of rhinoviruses is that several virus types circulate at the same time. Peak season in the northern hemisphere is the fall, and a smaller peak is seen in the spring, but in general rhinoviruses are present year-around. The major transmission routes are droplet transmission and contact transmission directly via hands or indirectly via surfaces and fomites. The most frequent clinical manifestation of rhinovirus is the common cold. Rhinoviruses are also a major cause of lower respiratory tract infections, which often manifest as wheezing illnesses, in young children as bronchiolitis and in older children and adults as exacerbation of asthma. Rhinoviruses are an important cause of pneumonia and acute otitis media, alone or together with bacteria. The molecular detection of rhinoviruses typically involves reverse transcription quantitative polymerase chain reaction (RT-qPCR) followed by sequencing of partial capsid region to determine the virus type. No antiviral drugs or vaccines against rhinovirus are available. Hygiene precautions and avoidance of contacts are used in prevention.

4. Keywords

Common cold, enterovirus, picornavirus, rhinovirus, wheezing illness.

5. Introduction

The common cold caused by a rhinovirus is probably the most frequent acute infectious disease of humans globally. All people are familiar with the unpleasant, although mild, symptoms of the common cold. Since the vast majority of rhinovirus infections result in self-limiting upper respiratory tract illnesses, the role of rhinovirus as a severe disease-causing agent is easy to underrate in comparison to other viral pathogens. The notion of rhinovirus as harmless is, however, wrong; it is clearly one of the most important respiratory pathogens. It causes a high proportion of hospitalizations due to respiratory tract infections in children (mostly presenting as wheezing illnesses), severe pneumonia in immunosuppressed people and in older adults, and it associates with antibiotic use because of suspected or confirmed viral-bacterial co-infections. Global morbidity and mortality caused by rhinovirus is poorly characterized but can be assumed to be high. The laboratory diagnosis of rhinovirus infection is made by the reverse transcription quantitative polymerase chain reaction (RT-qPCR) method, but its availability varies globally. Unfortunately, the role of rhinovirus in disease pathogenesis is not easy to establish because rhinoviruses are frequently detected in healthy individuals. Specific prevention and treatment modalities are still lacking.

6. Historical Background

As methods for virus isolation in tissue culture were developed in the 1950s, several viruses causing respiratory tract infections in humans were identified. First isolations of rhinovirus from respiratory secretions of individuals with common cold were published by Pelon et al. in 1957 (1) and by Price in 1956 (2). Rhinovirus was soon found to be highly frequent in people with upper respiratory illnesses, and it was labeled as “the common cold virus”. During the first decades after its identification, epidemiologic research on rhinovirus infections was active and fruitful, despite

only the availability of laborious virus culture and serologic methods. Studies revealed the seasonal occurrence, transmission in households and communities, circulation of several serotypes at the same time, and clinical picture with mostly mild, upper respiratory tract manifestations (only examples of early work given as references here) (3–6). Subsequently, research interest in rhinovirus seemed to temporarily subside, and from the clinical point of view, it was simply considered a common virus, which caused mild infections, but was not very important from the hospital perspective. Renewed enthusiasm in rhinovirus emerged towards the end of the last century with the implementation of polymerase chain reaction (PCR) method in rhinovirus diagnostics and other methods that facilitated more detailed virologic research. After turn of the century, novel rhinoviruses now classified in *Rhinovirus C* species were identified (7,8). Further research has demonstrated that rhinovirus causes severe illnesses either alone or in synergy with bacteria, and it is a major causative agent of infectious diseases that result in hospitalizations, physician visits, antibiotic treatments, and work or school absences. Studies aiming at development of specific prevention or treatment for rhinovirus have not yet resulted in approval of any pharmaceuticals for clinical use.

7. Methodology of Epidemiologic Analysis

7.1. Sources of Data

Use of rhinovirus diagnostics in clinical practice has increased only recently. Specific diagnostics of rhinovirus is mostly done in hospitals in connection with a clinical virology laboratory, and there is a lot of variation in diagnostic practices between geographic areas. In most countries rhinoviruses are not included in the list of microbes that are reportable to national registries, which hampers epidemiologic surveillance. The major sources of data for rhinovirus epidemiology are cohort and cross-sectional studies, and surveillance reports from centers that have rhinovirus diagnostics.

These factors make the generalizability of the data somewhat uncertain. Laboratory methodological aspects have had an important effect on the relative lack of epidemiologic data for rhinoviruses, especially for earlier studies, as RT-qPCR is needed for the detection of rhinovirus and Sanger sequencing is needed for the determination of rhinovirus types.

Human challenge models, referring to experimentally infecting human volunteers under controlled conditions, have been used in studies of rhinovirus transmission and pathogenesis, and in studies of potential vaccines and antiviral drugs. Such models are readily applicable to rhinovirus research because the natural infection is mild (9). Although no drug against rhinovirus is available, the risk of complications of experimental infection by wild-type virus is low in otherwise healthy adults. Such models have been safely used even in volunteers with asthma or chronic obstructive pulmonary disease (COPD), to facilitate study of rhinovirus-induced exacerbation of these diseases (10,11).

7.2. Morbidity and Mortality

Accuracy of estimates of morbidity caused by rhinovirus has improved along with increased use of RT-qPCR method for detection of rhinovirus in severely ill patients. Data on hospitalizations caused by rhinovirus in children is fairly abundant, although timely nation-level data are usually not available. There is substantially less knowledge regarding the morbidity in adults and in outpatients. It has appeared that rhinovirus-specific diagnosis codes are not routinely used when causes of hospitalization are documented by using the International Classification of Diseases (ICD, currently 10th revision) codes, which hinders registry studies and surveillance. Furthermore, frequent detection of rhinovirus from healthy individuals makes it often difficult to ascertain the pathogenic role of this virus, which complicates the assessment of morbidity.

Detailed reports of rhinovirus-associated deaths in patients with lung transplantation or other immunosuppressive conditions and in elderly persons provide strong evidence that rhinovirus can cause mortality (12,13). However, there is a lack of knowledge regarding mortality related to rhinovirus infections in all parts of the world, and in particular in developing countries. This is mostly due to unavailability of virologic diagnostics and uncertainty regarding the role of rhinovirus in the pathogenesis of infection. As rhinovirus infections often cause respiratory distress (wheezing) and pave the way for bacterial superinfections, it can be assumed that substantial unrecognized mortality exists globally.

7.3. Environmental Surveys

As humans are the only host species for rhinoviruses, they are not found in the environment outside human habitation. By contrast, various surfaces and fomites, as well as air samples from living and working spaces and other environments are often positive for rhinovirus by sensitive methods. For example, rhinovirus has been detected in 20% of samples collected from surfaces of primary school desks (14), in 42% of samples collected from nurses' stations in geriatric nursing homes (15), and in various surface samples collected from the passenger area of an airport (16). Environmental surveys have provided interesting knowledge, but it is difficult to assess the role of virus findings from environmental samples in the transmission of rhinovirus. This is partly because RT-qPCR is typically used for rhinovirus detection instead of virus culture, and the presence of viable virus on environmental samples remains unclear.

7.4. Laboratory Methods in Epidemiologic Surveillance

Since rhinoviruses have traditionally not been regarded as significant pathogens as, for example, related enteroviruses (currently classified in the same genus; see section 8.1), there is only limited

systemic surveillance data. Instead, data on rhinovirus epidemiology is often derived from pediatric cohort studies or from case reports where a specific rhinovirus type has been linked to severe infections. Studies from diverse geographic regions have attempted to characterize the molecular epidemiology of rhinoviruses and to identify virus type-specific clinical features. Before molecular era, rhinovirus cultivation in HeLa cells, where virus-induced cytopathic effect is visible, was long considered the standard method for virus isolation and detection. However, the cultivation method is time-consuming (up to 14 days) and sometimes inconclusive; while rhinovirus A and B types were diagnosed by cultivation method in 1960s, cultivation of rhinovirus C types (discovered in 2006 by genetic analysis) has not been successful with the standard methods. There are only a few reports of successful cultivation of a few rhinovirus C types in non-conventional tissue models.

Lack of conserved antigenic regions has made measurement of antibody responses impractical in both clinical diagnostics and epidemiologic research. Consequently, there are no antigen detection methods available for rhinoviruses. Instead, sensitive RT-qPCR methods have been used for diagnosing rhinovirus for more than 15 years, and currently sensitivities at the level of 10-100 genome copies are easily obtained from clinical specimens. RT-qPCR uses conserved 5´-terminal sequence regions that are highly conserved between virus types. To distinguish rhinoviruses from related enteroviruses, entero- and rhinovirus-specific probes are used in routine diagnostics (17,18). Virus typing focuses on VP4/VP2 and VP1 regions (section 8.1), which are amplified by standard RT-PCR followed by Sanger-sequencing of the amplicon and subsequent phylogenetic analysis.

During recent years, introduction of rapid multiplex PCR panels has increased the practice of diagnosing rhinovirus as well as other respiratory viruses. However, some panels are not able to differentiate between rhinoviruses and related enteroviruses, and detected viruses are

usually not further studied at type level. Generally there is not routine use of broad multiplex respiratory virus panels for adults or children presenting to outpatient clinics or emergency departments with symptoms of respiratory tract infection because studies have not consistently shown beneficial impact such as a decrease in antibiotic prescribing (19,20).

8. Biological Characteristics

8.1 Classification of Rhinoviruses

Rhinoviruses form one of the largest group of viruses that infect humans. Since their discovery in 1956 until the 1987, they were classified into two rhinovirus serotypes, A and B, (genus *Rhinovirus*, family *Picornaviridae*) using a serological cross-neutralization assay. While this method is based on virus growth in HeLa cell cultures, molecular genotyping techniques, first applied to enteroviruses in 1999, provided a method for genetic typing of rhinoviruses. This approach facilitated the discovery of novel rhinoviruses in 2006, which were assigned to a new rhinovirus species C, Rhinovirus C (RV-C) (21,22). Consequently, the naming convention was changed from “serotype” to “genotype” or preferably “type” to represent rhinovirus variants that have been identified and classified by genetic comparisons. In accordance with genetic typing, names of rhinovirus species have been changed to remove references to host species names (approved by the International Committee on Taxonomy of Viruses [ICTV] Feb 2013). That is, rhinovirus species formerly called for example “Human rhinovirus A; HRV-A” is now “Rhinovirus A; RV-A”. Based on the genetic analyses, rhinoviruses were further assigned to genus *Enterovirus* within the family *Picornaviridae*. Despite close genetic similarities to enteroviruses, rhinoviruses have remarkably different phenotypic characteristics; they are acid labile, while enteroviruses are stable at low pH, and this apparently explains in large part their different tropism and pathogenicity. According to the latest release of ICTV (23) and ICTV Master Species list, there are 169 rhinovirus types assigned to the three

rhinovirus species (Rhinovirus A, Rhinovirus B, and Rhinovirus C) under the *Enterovirus* genus (https://www.picornaviridae.com/) (Table 1). Recommendations for the nomenclature of rhinoviruses have recently been introduced (24). Independent from phylogeny, different rhinovirus types have also been classified into “major” (intercellular adhesion molecule 1 [ICAM-1]) and “minor” (low-density lipoprotein receptor [LDLR]) receptor groups depending on their cellular receptor specificity. This characteristic feature is based on virus particle properties.

Current typing of clinical isolates and further taxonomical classification of novel rhinoviruses is based on capsid region sequences, VP4/VP2 and particularly VP1 (21). VP4/2 has been extensively used in epidemiological analyses for prediction of rhinovirus species and type because of its shorter length, greater sequence conservation, and the possibility of using the same set of primers for amplification of the types in all three species. While the majority of rhinovirus types group congruently between VP1 and VP4/VP2 (with 10% threshold), a threshold of 13% divergence in VP1 nucleotide sequences has been proposed for taxonomical type assignment. In the VP1 region, a rhinovirus type should have at least 13% (RV-A), 12% (RV-B), or 13% (RV-C) nucleotide divergence from all other rhinovirus types (21). Nevertheless, the use of the VP1 region for definition of new rhinovirus types should not discourage typing by using untranslated 5´-end and VP4/VP2 genomic regions, especially if the VP1 sequence is unavailable. In contrast to enteroviruses, rhinoviruses are not prone to recombine, and, therefore, VP1 typing can be used with confidence to define rhinovirus types in clinical specimens with respect to their pathogenic features.

8.2. Virus Structure and Genome Organization

Rhinoviruses were among the first viruses for which structures with atomic detail were determined. Since 1985, when the X-ray structure of rhinovirus B14 (RV-B14) was determined,

several high-resolution rhinovirus particle structures and virus variants showing receptor interactions have been resolved. Rhinovirus particles are small, spherical, and non-enveloped with a diameter of about 30 nm and a density close to 1.28 g/ml, which is less than in most picornaviruses. Viral capsid is composed of assembly of 12 pentamers, each with five protomers consisting of four different capsid proteins. These 60 copies of capsid proteins, VP1, VP2, VP3, and VP4, give the virion a symmetrical, icosahedral structure (Figure 1). VP1, VP2, and VP3 proteins are exposed and thus the major targets of the immune response, and they account for antigenic diversity, while the VP4 is localized on the internal surface of the capsid and interacts with the RNA genome. VP1 cores at five-fold axes of symmetry surround the deep surface depression, “canyon”, which serves as the cellular receptor binding site and immunogenic surface. The surface area of receptor binding in the canyon has been proposed to allow neutralization by antibodies, which block viral infectivity, but also immune evasion of rhinoviruses via mutations. The floor of the canyon within the VP1 harbours a small, hydrophobic pocket, which can uptake and bind antiviral drugs such as pleconaril. Pleconaril-like molecules occupy the hydrophobic pocket and displace the pocket factor, thereby increasing particle stability and preventing receptor binding and/or genome release (25).

The icosahedral capsid surrounds a densely packed, single-stranded, positive-sense RNA genome of 7079 (RV-C1) to 7233 (RV-B92) bases excluding the 3' poly(A) tail of variable length (Figure 2). Rhinoviral RNA functions similarly to a messenger RNA (mRNA) and is infectious in the cell interior. At the 5’ end of the genome there is a covalently linked VPg protein (3B gene product; genome-linked virus protein). Recent studies suggest that instead of possessing a role in virus replication, VPg has a role in encapsidation of newly synthesized viral RNAs into capsids (26). The 5’-terminal non-coding region (NCR) with an approximate length of 650 nt contains regulatory elements: cloverleaf structure, pyrimidine-rich tract, and internal ribosome entry site (IRES)

control virus replication, innate immunity, and translation, respectively. In the 3’ end of the viral genome there is a short, 50 nt, 3’NCR. It also has a secondary structure, a pseudoknot, that controls viral RNA synthesis. The genome ends with a poly-A tail, which is indispensable for infectivity. Within functional protein-encoding genes there is also a Cre element (cis-acting replication element), which interacts with VPg and resides in variable genes subject to rhinovirus species.

Between the 5´- and 3´-NCRs there is a single long open reading frame (ORF) controlled by IRES, which encodes a large precursor polyprotein of 2100 amino acids. Translated precursor polyprotein is divided in three regions, P1-3 and processed to form eleven individual viral proteins by virus-encoded proteinases. P1 encodes viral capsid proteins (VP1-4), while P2 and P3 encode functional proteins, of which 2Apro and 3Cpro are involved in protein processing, 2B, 2C, 3A, and 3Dpol in genome replication, and VPg in encapsidation.

8.3 Replicative Life Cycle

To complete a successful infectious cycle, cellular infection must proceed via several steps including cell attachment, internalization/entry, endocytosis, genome replication, particle assembly, and exit. Recognition of cell surface receptor(s) by virus particle determines the host range and tropism of cell and tissue infection and is the first step in the virus replicative cycle. The “major group” rhinovirus types utilize the cell surface receptor ICAM-1, while the “minor group” types attach to and enter cells via the LDLR. A few rhinovirus C types have been assigned to use cadherin-related family member 3 (CDHR3) as a receptor, but its role as a true rhinoviral receptor has not been fully demonstrated (27). Some of the major receptor group rhinoviruses seem to use heparan sulfate as an additional receptor, but this may also be due to adaptation to experimental cell cultures using high infectious doses of virus.

Virus binding to the cell surface receptor initiates a cascade of events leading to virus internalization apparently via a receptor-mediated endocytosis mechanism. Both clathrin-dependent and independent endocytic and macropinocytosis mechanisms are used depending on virus and experimental cell type. Viruses are transported to the cytosolic replication site in endosomal vesicles for viral RNA release instead of direct release of viral RNA into cell cytosol upon contact with the receptor. Virions undergo conformational changes triggered by interaction with ICAM-1 receptor and/or pH changes in endosomes. It is thought that the RNA genome crosses the endosome membrane into the cytosol through a pore formed by viral proteins or following membrane rupture. Genome replication occurs in cytosol in association with cytoplasmic membranes and lipids to yield a viral polyprotein that is processed into functional viral proteins (28). In experimental cell cultures, virus is released by cytolysis, rupture of cell membranes. However, it has been suggested that a portion of viruses is secreted non-lytically in phosphatidylserine lipid-enriched vesicles. This may be relevant in clinical infection since, in nature, the primary site of infection of rhinoviruses is ciliated airway epithelium, and it is presumed that virus is released non-lytically. Since receptor usage is highly dependent on cell type, virus strain, or even virus passage number (due to adaptation), the actual role of any of these molecules and mechanisms in clinical infection needs further study.

8.4. Animal Models and Virus/Vector Interactions

The host range of rhinoviruses is very limited; they are able to replicate only in cells of primate origin. Chimpanzees can be infected with rhinoviruses A and B, but although viral shedding has been detected, they develop only few or no signs or symptoms of illness. Consequently, humans are the only known natural hosts of rhinoviruses. As an exception, a lethal rhinovirus C infection has been described in a wild infant chimpanzee during an outbreak of respiratory illness in the

chimpanzee community (29). For pathogenicity studies a reliable small-animal model would be useful, but this is hampered by lack of known murine rhinoviruses, which would cause infection-related symptoms and disease similarly to human rhinoviruses. Such a limitation has partially been overcome by mouse-adapted human rhinoviral strains and transgenic mouse model expressing the human cellular receptor ICAM-1 (30). Several features of these models resemble infection in humans, including replication in the respiratory epithelium and induction of type I interferons, neutrophil chemokines, and neutrophilic airway inflammation. Rhinovirus infection in a mouse model increases inflammation in response to allergen exposure, suggesting that small-animal model could be informative for asthma-related studies. However, these models require the use of high doses of viruses, and virus titer declines in 12 to 24 hours limiting the ability to investigate viral replication, virus-induced inflammation, and airway dysfunction. Consequently, small-animal models have not attracted much attention in studies of rhinovirus-related pathogenicity. *In vitro* - reconstituted differentiated human airway epithelia models have been developed to substitute for lacking animal models (31). These tissues exhibit in vivo morphological and growth characteristics of the respiratory epithelium and allow a thorough analysis of some aspects of the pathogenesis of rhinovirus in humans. Importantly, such tissue systems allow parallel comparison of RV-A and RV-B types to RV-C types, which do not grow in standard cell cultures.

9. Descriptive Epidemiology

9.1. Incidence and Prevalence

Rhinovirus epidemiology is characterized by high incidence and prevalence particularly in children but also in adults, and by simultaneous circulation of several virus types. Prospective follow-up of healthy child or adult cohorts have documented 1 to 4 symptomatic rhinovirus infections per year in young children and 0.5 to 1 in adults (32–35). The principal clinical manifestation is usually an

upper respiratory tract infection (i.e., common cold), but occasionally a lower respiratory tract infection (bronchitis, bronchiolitis, or pneumonia) also develops. Since it is challenging to collect diagnostic specimens during all respiratory infections even in study settings, the upper estimates of above-cited incidence ranges probably hold true. By estimating the etiology of undiagnosed respiratory infections based on proportion of rhinovirus in diagnosed cases, an incidence of 3.5 cases per year in children younger than 2 years was determined (35).

Etiologic studies of common cold have revealed that rhinovirus causes 40% to 90% of cases in subjects of all ages, varying by the season and population studied (33,36,37). Several studies have reported rhinovirus as a highly frequent finding in children hospitalized with respiratory tract infections (see section 12.1.). In a population-based study, five hospitalizations per year per 1000 children less than 5 years of age was reported, and a history of wheezing or asthma was a risk factor (38). This figure is comparable to the number of annual hospitalizations caused by respiratory syncytial virus (RSV), which is usually considered the most important virus causing hospitalizations in this age group. Adult hospitalizations associated with rhinovirus have been less studied, but they also appear to be frequent. Annually, seven rhinovirus-associated emergency room visits and three hospitalizations per 1000 adults have been reported (39).

Rhinovirus is also prevalent in individuals who are apparently healthy. Asymptomatic rhinovirus infection has been reported in 11% to 47% of children and in 2% to 9% of adults by using PCR (40,41). Since mild respiratory symptoms are very common, classification of individuals as symptomatic or asymptomatic varies among studies depending on how detailed the interview of symptoms was and on stringency of criteria. Someone may feel not being ill even if she or he has mild rhinorrhea or other cold symptoms. This is particularly true for young children, who cannot report their symptoms. Nevertheless, truly asymptomatic rhinovirus infections do occur and they are not uncommon, and still, detection of rhinovirus clearly associates with the presence

of respiratory symptoms. In a daycare study, 18% of children without any clinical findings, 24% of children with few signs, and 41% of children with several clear signs of respiratory tract infection were positive for rhinovirus (42). In a birth cohort study, 32% of 1-year-old children had respiratory symptoms at the time of sampling, and 38% of them were positive for rhinovirus, compared to 8% of asymptomatic children (35). In a systematic review of case-control studies in adults aged ≥65 years, pooled odds ratio for rhinovirus detection was 7.1 in those with an acute respiratory infection compared with asymptomatic individuals, and virus-specific attributable fraction among the exposed was 86% (43).

9.2. Epidemic Behavior

Epidemic behavior of rhinovirus reflects the relatively high transmissibility, short incubation time, nonspecific clinical manifestations including asymptomatic infections, circulation of several rhinovirus types in the same population at the same time, and the lack of durable immunity to the virus. Mild and nonspecific clinical manifestations make it difficult to track rhinovirus epidemiology based on the clinical presentation. In epidemiologic studies, virus type-specific diagnostic methods are needed to truly document the transmission chains of rhinovirus.

Close contacts promote rhinovirus transmissions, and transmission between household members is frequent. Earlier studies using viral culture and serologic methods reported household transmission rates of 11% to 56% (3,5,44,45). In a follow-up of families by RT-qPCR and virus typing after rhinovirus infection in an index child, rates were higher, 100% for siblings and 50% for adults, but a considerable part of infections were asymptomatic and several rhinovirus types could be found in the same families (18). In this study, rhinovirus infections occurred also in follow-up of families with a rhinovirus-negative index child. These findings highlight the simultaneous circulation of several rhinovirus types and efficient transmission, as well as lack of

development of symptomatic infection in part of subjects, particularly adults, probably because of earlier immunity. Other studies utilizing repeated sampling, close follow-up, and rhinovirus typing in households or in child daycare or school settings have also documented rapid spread of specific rhinovirus types and repeated infections caused by other rhinovirus types (46–48).

9.3. Seasonality

High epidemic seasons for rhinovirus in the northern hemisphere are fall (September-November) and spring (peak in May) (4,49). However, rhinovirus infections occur year-around although at a lower intensity outside epidemic seasons. In the southern hemisphere there is more epidemiologic variability but seasonal patterns opposite to the north have been reported (50). Rhinovirus C types are frequently detected in the Latin America between April and July (51). In Australia the high epidemic season for rhinovirus is in February to March and another peak in around October, with continuous circulation at lower levels (52).

Reasons behind epidemic seasonality are unclear for rhinovirus as well as for other respiratory viruses. Iterative seasonal behavior of the human population has been postulated as an important factor. Summer vacations from school and workplaces and increased proportion of activities in outdoors compared to indoors decrease close contacts between individuals of all ages during the summer. Air humidity decreases during the winter in temperate climates, which may enhance passage of viruses in small droplets. These mechanisms do not explain the period of relatively low rhinovirus circulation in mid-winter, during the time of influenza and RSV epidemics. Interference between respiratory viruses has been suggested to be involved in this phenomenon. Antiviral state induced by the innate immune response and interferon production during a respiratory infection caused by influenza virus or other respiratory viruses could prevent contagion of rhinovirus. Such inhibitory effect has been demonstrated in children; those infected with RSV

are less likely to be positive for rhinovirus than RSV-negative children (53). In addition to these mechanisms, development and duration of type-specific immunity against rhinoviruses undoubtedly influences their seasonal epidemiology.

9.4. Other Environmental Characteristics

Rhinovirus is efficiently transmitted in crowded indoor spaces. Examples of such environments are childcare facilities, schools, institutional residences, and certain workplaces. Poor ventilation may facilitate the transmission. Any effects of atmospheric or environmental conditions such as high or low temperatures, humidity, pollens, or air pollutants are insufficiently characterized but they may have a role in transmission of rhinovirus.

9.5. Host Characteristics

Children of approximately 1 to 5 years of age are highly susceptible to rhinovirus. Major reasons for this are limited virus type-specific immunity and frequent close contacts with other children and adults at this age. Risk factors for viral respiratory tract infections in children include presence of siblings, exposure to tobacco smoke, male sex, low socioeconomic status, and lack of breast-feeding (54,55). However, these risk factors do not fully explain the fact why some children have much more frequent respiratory tract infections than others.

In adults 30-40 years of age, who are often parents of young children, the incidence of rhinovirus infections is higher compared to younger or older adults. At the age of 60-70 years contact of grandparents with their grandchildren may increase the risk of rhinovirus infection. Chronic conditions such as COPD, asthma, and bronchopulmonary dysplasia due to premature birth increase the risk of severe infection but no effect on the acquisition of rhinovirus has been reported.

Presence of certain gene variants can predispose individuals to severe manifestations of rhinovirus infection such as severe wheezing illness (see section 11.1.5.). Genetic susceptibility may also affect the risk of having recurrent rhinovirus infections. Children with an asthma-associated allele of the rhinovirus C receptor CDHR3 had more frequent respiratory tract infections caused by rhinovirus C than children with the major allele in two birth cohorts (56). Of the pattern recognition receptors, a common variant form in toll-like receptor (TLR) 8 was associated with an increased risk and another in TLR7 with a decreased risk of recurrent rhinovirus infections in a birth cohort study (57). Genetic variants in proteins of the immune system including mannose binding lectin, TLR2, interleukin (IL) 6, IL10, interferon-induced protein 44-like (IFI44l), and others have been reported to associate with recurrent respiratory tract infections or otitis media in children, but several of them probably affect susceptibility to virus-associated bacterial colonization and infection rather than susceptibility to rhinovirus infection (57–59).

10. Mechanisms and Routes of Transmission

10.1. Mechanisms

Rhinovirus is secreted in respiratory secretions. Mechanism of transmission is through the inoculation of virus onto the respiratory epithelium via the nose or conjunctiva of the eyes. The primary site of virus replication is the nasal and nasopharyngeal epithelium.

10.2. Routes

Rhinovirus is transmitted via air by droplets and by direct (often hand-to-hand) or indirect (via surfaces or fomites) contact. Studies conducted in the 1970s and 1980s emphasized the role of contact transmission and demonstrated that experimental rhinovirus infection was readily transmitted between volunteers by hand-to-hand contact (60). As people touch their nose or eyes

with their hands unnoticed, they directly or indirectly transmit the virus to other people's hands, who auto-inoculate themselves (61). Role of this mode of transmission is supported by the fact that, due to its non-enveloped structure, rhinovirus stays viable on various surfaces at least for several hours. Rhinovirus has been detected by culture from fingertips after touching surfaces contaminated by mucus from an infected patient 24 hours earlier, and by PCR after an interval of 48 hours (62).

Other experimental studies in volunteers have demonstrated that rhinovirus can be efficiently transmitted via air, under conditions of close distance (around a table) for a long duration (12 hours) among the subjects, which is compatible with droplet transmission (63). Transmission from long distances through air has not convincingly been documented, although rhinovirus genome can be detected in air specimens. Rhinovirus was detected by RT-PCR in air samples from hospital rooms of rhinovirus-positive patients (64). Rhinovirus RNA was only rarely detected in weekly air samples collected at a university campus, whereas influenza viruses were detected more frequently (65). Taken together, the current concept is that the predominant route of rhinovirus transmission is via air by respiratory droplets, and another route is direct or indirect contact transmission. It is clear that close and prolonged contacts increase transmission.

Incubation time of rhinovirus is short, 1 to 3 days, and virus secretion starts before onset of symptoms. Presymptomatic individuals are contagious, and those who do not develop any symptoms can have high viral loads and transmit the virus. However, there is evidence from household and community studies that children with symptoms have a major role as spreaders of rhinovirus (18,46,48). Symptoms of upper respiratory infection such as sneezing and coughing increase production of respiratory droplets and facilitate transmission.

A simulation study provided the basic reproductive number R_0 for rhinovirus as 2.7 in the fall season (September to December) and 2.6 in the spring (February through July) (66). The

rapid dynamics of rhinovirus transmission results in a large number of infections in close-connected groups such as families, children's daycare groups, schools, or workplaces before any intervention to prevent infections can be commenced. Interestingly, during strict non-pharmacologic preventive measures including societal lockdowns in many countries due to the coronavirus disease 2019 (covid-19) pandemic in 2020-2022, rhinoviruses remained the most prevalent of all respiratory viruses, while influenza and RSV outbreaks largely did not occur and other respiratory viruses were largely absent (67,68).

Nasopharyngeal rhinovirus load is highest at the beginning of symptoms and rapidly declines thereafter. Shedding time of viable rhinovirus is 1 to 2 weeks, assessed by virus culture after experimental infection in volunteers (69,70). Shedding of rhinovirus after natural infection has been evaluated by PCR. Some studies have reported high percentages of PCR positive subjects several weeks or months after the primary infection and concluded that the shedding time is long. This conclusion is uncertain and probably wrong due to lack of virus typing in those studies. It is well known that recurrent rhinovirus infections are highly frequent, and positive PCR after infection more likely represents new infection by a different virus type than prolonged virus shedding. Studies using virus sequencing or other methods that are able to differentiate between rhinovirus types have clearly demonstrated that the shedding time of rhinovirus is in general rather short, 1 to 2 weeks, similarly to other RNA viruses, and prolonged shedding is uncommon in immunocompetent subjects (71,72). Mean shedding time in one study was 10 days for children and 11 days for adults (72). In contrast, people with profound immunosuppression, such as hypogammaglobulinemia or lung transplantation, shed rhinovirus for long periods, even for months or more than a year (12,73). Persistence of the same virus type in such cases has been confirmed by sequencing.

Being acid-sensitive, rhinovirus is inactivated in the stomach and live virus is usually not passed in the feces. There are some exceptions to this rule, since the stomach of infants is not acidic, and some adults have neutral pH in the stomach due to medications or illnesses. In a screening study of stool samples collected for clinical diagnostics mostly from young children with diarrhea, 10% were positive for rhinovirus by RT-qPCR with viral loads comparative to enteroviruses (74). Nevertheless, fecal secretion is regarded as not important in the spread of rhinoviruses.

11. Pathogenesis and Immunity

11.1. Virus-host Interactions

11.1.1. Pathogenesis

Rhinovirus is primarily a respiratory tract pathogen introduced by droplets or contact to nasal mucosa. While experimental infection in human volunteers has demonstrated that rhinovirus can be detected throughout the upper respiratory tract, it is evident that the primary site of virus replication is nasal epithelium and posterior nasopharynx from which the virus can spread to other parts of the respiratory system for example by nose blowing (75). Incidentally, the first successful cultivation of a rhinovirus C type was reported in sinus mucosal organ culture (76), while conventional rhinovirus A and B types also grow on experimental cell lines such as HeLa and WI-38. In the lower airways, rhinoviruses have been detected in bronchial biopsies from volunteers with experimental infection. Contrary to many other respiratory viruses, rhinovirus is seldom associated with destruction of airway epithelial cells. Instead, pathogenesis and symptoms are related to immune responses that may result in airway obstruction and wheezing. Consequently, in nasal epithelial cells rhinovirus replication is linked to virus receptor tropism and limited expression of viral receptors, ICAM-1 or LDLR, which are upregulated by immune mediators and

thus have a positive effect on transmission of the virus within tissues (77,78). Rhinovirus C probably uses as its cellular receptor CDHR3 (79). Viremia has been detected at a low prevalence in children with rhinovirus pneumonia, and rarely also in association with asymptomatic infection (80). Despite of that, systemic dissemination of rhinovirus to other than respiratory organs is rare.

11.1.2. Co-infections with Other Viruses

Respiratory tract infections are increasingly diagnosed by multiplex PCR methods that can detect several viruses, and with some platforms, also bacteria simultaneously from a single specimen. Rhinovirus is often detected together with another respiratory virus, most frequently coronaviruses, parainfluenza viruses, influenza A and B viruses, RSV, and human bocavirus. In a study of military recruits with febrile respiratory infections, co-infection with human adenovirus and rhinovirus resulted in lower titers of rhinovirus compared to infections with rhinovirus alone suggesting some form of viral interference between these groups (81). Whether viral co-infections cause more severe symptoms than infections due to a single virus is a debated issue. In some studies, association with more severe clinical picture has been found, but in others there are no differences (82). The variable findings can be partly explained by study designs and virus-related differences in clinical manifestations. For example, if severity assessed by presence of high fever is compared between patients with rhinovirus only versus rhinovirus and influenza virus infection, patients with a double infection can be anticipated to have more severe symptoms, but in comparison of influenza only to influenza plus rhinovirus the clinical picture is similar. Although rhinovirus as a secondary agent would not increase the intensity of symptoms it may increase the duration of illness (53). Virus load determined based on Ct value by RT-qPCR has been suggested as a method to identify the virus that is causing the illness in case of two or more simultaneous

viruses, but there remains uncertainty in this approach due to dynamic changes in virus loads during the illness (83).

11.1.3. Synergism with Bacteria

Since early times, clinicians have observed that the common cold can sometimes lead to development of a severe pneumonia. Other, more frequent complications of rhinoviral upper respiratory infection include acute otitis media and sinusitis. Although all these clinical manifestations can be caused by rhinovirus only, they often are bacterial infections that arise during or after rhinovirus infection. Furthermore, blood-culture positive invasive pneumococcal disease in children has, at least in some geographical areas, similar seasonal epidemiology than rhinoviruses have, and a temporal association has been demonstrated in an ecological study (84).

Nasopharyngeal colonization by pathogenic bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenzae* is the first step in the development of bacterial respiratory infection, and it is increased during the common cold. A family study showed that rhinovirus infection facilitates the acquisition of *S. pneumoniae* from the community outside the household and increases transmission of pneumococcus between family members (85). Cluster analysis has suggested that severe rhinovirus infections may be associated with increased proportions of *Haemophilus*- or *Moraxella*-dominant microbiota profiles in the nasopharynx (86). Rhinovirus increases bacterial adherence in the respiratory epithelium by several mechanisms including disturbance of the function of ciliated cells and upregulation of receptors for bacterial adhesion, such as the platelet-activating factor receptor (87). In some instances, rhinovirus infection has been shown to disrupt the epithelial cell barrier and tight junction complex, predisposing to bacterial invasion (88). In addition, effects of rhinovirus infection on the innate immune responses of the host may increase susceptibility of the host to development of bacterial infection (89).

11.1.4. Mechanisms Linking Rhinovirus Wheezing to Development of Asthma

The susceptibility to rhinovirus infections appears to be linked to a predisposition to wheezing, since the prevalence of rhinovirus-induced wheezing has been as high as 50-80% during the first year of life in infants with recurrent moderate-to-severe respiratory illnesses from atopic families (90). Many studies have linked rhinovirus-induced wheezing in early life to other atopic characteristics such as allergen-specific sensitization, increased eosinophil counts both in blood and nasal mucus, or presence of atopic eczema, all of which have additive effects on asthma risk (91). Low interferon responses secondary to young age and allergic sensitization could increase susceptibility to viral infections (92). The interaction between rhinovirus-induced wheezing and atopy is likely to become stronger by increasing age in children, since the prevalence and intensity of respiratory allergy increases with age (93,94). *In vitro* studies have shown that a broken epithelial barrier favors rhinovirus replication in deeper cell layers and increases the number of its own receptor, ICAM-1, as well as enhances absorption of aeroallergens and bacterial pathogens (88,95). Rhinovirus infection promotes IL1β and IL6, which may contribute to breaking tolerance to allergens (96).

Genetic variants at the 17q21 locus increase not only risk of severe rhinovirus-induced wheezing episodes in early childhood but also subsequent asthma in children predisposed to wheezing during rhinovirus infections (97). While the mechanism for this effect is still unknown, it is notable that farm exposure also interacts with 17q21 variant-associated risk of asthma (98). Exposure to animal sheds may reduce genetically determined asthma risk by promoting the individual's capability of coping with early viral infections.

Repeated rhinovirus infections and allergen exposure may enhance the airway epithelial cell production of IL25 and IL33, which further promote T helper 2 -type airway

inflammation and remodeling (91). Repeated rhinovirus infections may also induce vascular endothelial growth factor, transforming growth factor β, and chemoattractants for airway smooth muscle cells and thereby further contribute to airway remodeling (99). These effects may be more pronounced during early life (100).

11.1.5. Risk Factors for Severe Infection

Compared to the high prevalence of rhinovirus infections, severe wheezing, exacerbations of asthma, and rhinoviral pneumonia are, after all, relatively uncommon. It is, therefore, likely that host and environmental factors are important risk factors. Immunocompromised conditions increase risk of severe infections, but already a small deviation in immune balance towards type 2 polarized characteristics and low interferon responses increases risk of severe manifestations of rhinovirus infection. In particular, rhinovirus infection in connection to exposure to aeroallergen, airway inflammation, and a broken epithelial barrier are likely to trigger asthma exacerbations and increase the risk of asthma.

Data on genetic risk factors for severe rhinovirus infections is scarce. Life-threatening infections caused by rhinovirus and other respiratory viruses have been described in association with a rare mutation in IFIH1, resulting in deficiency of the melanoma differentiation-associated gene 5 (MDA5) protein, which is essential in the interferon response to rhinovirus infection (101). Common variant forms in genes of innate immune factors such as TLR7, TLR8, IFI44L, and MBL associate with recurrent rhinovirus infections or development of bacterial complications but not clearly with severe rhinovirus infection (see section 9.5.). The strongest asthma locus discovered to date, 17q21, has been found to be associated with rhinovirus-induced wheezing during the early years of life as well as with markedly increased risk of subsequent asthma (97). Another interesting asthma gene with a putative role in rhinovirus-induced wheezing and exacerbation of

asthma is the CDHR3. Recently, experimental studies suggest that CDHR3 may function as a rhinovirus C receptor (79). The important role of CDHR3 was subsequently confirmed clinically in birth cohort studies where a variant form of gene for CDHR3 was specifically associated with rhinovirus C -induced respiratory illnesses (56). This is particularly interesting since RV-C as well as RV-A virus types cause more severe respiratory illnesses than RV-B types (102).

The microbiome has the potential to stimulate the developing immune system and act as a disease modifier (103). The respiratory microbiome may modulate the severity of acute respiratory infections independent of specific causative virus, while at the same time, rhinovirus may increase the severity of the infection independent of the bacteria (104). Antibiotic treatment during acute childhood wheezing has decreased the duration of the symptoms, thus pointing toward microbial effects (105). However, it should be noted that antibiotics are not recommended for rhinovirus infections in the absence of confirmed bacterial infection.

Dietary factors are known to affect risk of viral wheezing illnesses. Particularly, vitamin D levels as well as fish oil consumption have been inversely linked to risk of recurrent wheezing and susceptibility to infection in wheezing children (106,107).

11.2. Innate, Cellular, and Humoral Immunologic Mechanisms

Rhinovirus has a naked protein particle structure and its genome is composed of single-stranded RNA molecule. Consequently, different parts of the virus are recognized by different innate immunity receptors including TLRs, retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which trigger downstream signals, which are important for limiting viral replication (108). Thus, it is not surprising that rhinovirus, like many other viruses, has developed mechanisms to inhibit these antiviral responses by cleaving proteins such as RIG-I and IPS-1 (109,110). While the viral capsid is recognized by TLR2,

the viral genome is recognized by endosomal TLR7 and TLR8. Rhinovirus produces double-stranded RNA (dsRNA) as a replication intermediate, which results in the type I interferon response via MDA-5 and RIG-1 pathways. These events result in a cascade of immune mediator expression including interferon-α and interferon-β, RANTES, IP-10, IL6, IL8, and epithelial cell-derived neutrophil-activating peptide 78. The binding of NLRs activates caspase 1, which regulates the processing and release of IL18 (111,112).

Activation of T cells is important in achieving control of rhinovirus replication and clearance of infection. T cell-mediated immune response is rapid and correlates inversely with virus shedding and symptoms. T cell epitopes of rhinoviruses are not as strictly virus type-specific as B cell epitopes (113).

Rhinoviruses are important triggers of acute asthma attacks. Rhinovirus infection induces type 2 innate cytokines, including IL25 and IL33. These activate type 2 immunity through type 2 T helper cells and type 2 innate lymphoid cells that produce IL5 and IL13 (114). The activation of type 2 immunity opens tight junctions in the epithelial barrier causing it to leak (115,116). Consequently, these events lead to swelling of the airways, smooth muscle contraction, and mucus production, which in turn may produce asthma-like airway obstruction and wheezing. It is important to note, however, that rhinovirus does not appear to cause type 2 immunity, rather it thrives in it and thus seeks such environments in susceptible individuals.

Adaptive humoral immunity has a major role in the prevention and control of rhinovirus infection. Rhinovirus infection in a susceptible individual results in the development of virus type-specific neutralizing serum antibodies (IgG) and secretory antibodies (IgA) on the mucosal surfaces of the airways. Viral VP1 protein is the most immuno-dominant antigen, and IgG1 antibodies to it correlate with the severity of upper and lower respiratory tract symptoms. Unfortunately, the VP1 protein is also the most variable rhinovirus protein and hence cross-

reactions between virus types are not common. Type-specific immune responses do not protect against infection by other circulating rhinovirus types. Since there is little cross-neutralization among types, vaccine development is also challenging (see section 13.3.). Patients with primary hypogammaglobulinemia experience more frequent and severe rhinovirus infections despite the administration of replacement immunoglobulin therapy (73).

11.3. Immunologic Measurements

Serologic methods are not suitable for clinical diagnostics of rhinovirus infections, and they are not routinely used in epidemiologic surveillance. This is due to the ubiquitous nature of rhinoviruses, simultaneous circulation of several rhinovirus types, and lack of conserved antigenic regions. T cell responses have been measured only in research settings. As rhinovirus can often be detected in asymptomatic subjects, particularly children, there is interest in development of measures of the innate immune response for clinical use in order to demonstrate the pathogenic role of rhinovirus in patients. Symptomatic rhinovirus infections can be differentiated from asymptomatic infections by the gene expression response pattern (117). A more simplified assessment of the antiviral response can be done by measurement of one or few antiviral proteins or their mRNA. Myxovirus resistance protein A (MxA) is an interferon inducible protein with activity against a broad range of viruses. Its concentration in the blood has been studied as a biomarker of viral infection. Blood MxA level is increased in symptomatic but not in asymptomatic rhinovirus infections in children (118). Furthermore, mRNA for MxA or other antiviral factors can be measured in respiratory tract specimens, potentially at the same time with detection of viral RNA (119,120). These methods are not yet in diagnostic use, but combination of virus detection by RT-qPCR and demonstration of antiviral innate immune response is an interesting prospect as it would provide a better assessment of the pathogenic role of rhinovirus in the illness than RT-qPCR only.

12. Patterns of Host Response

12.1. Clinical Manifestations

Rhinovirus causes upper and lower respiratory tract infections, and a considerable portion of infections are asymptomatic. Rhinovirus A and C types are more prevalent in wheezing illnesses and pneumonia than rhinovirus B types, and all rhinoviruses cause the common cold (Table 2). RV-A types have been reported to cause more severe upper respiratory symptoms in adults compared to RV-B (121), and RV-A and RV-C types to cause more severe symptoms in children compared to RV-B (102).

12.1.1. Upper Respiratory Tract Infections and Bronchitis

The most frequent clinical manifestation in children and adults is the common cold. Symptoms include rhinorrhea and nasal congestion, cough, sore throat, tiredness, and headache. Fever is common in children but not in adults. The median duration of symptoms has been reported as 7 days in adults, 10 days in school-aged children, and 9 days in children younger than 2 years of age (35,122,123). Although usually a mild illness, the common cold is so frequent that it causes extensive effects on the society, seen as healthcare service use, over-the-counter medicine use, antibiotic prescriptions (either inappropriate or for treatment of bacterial complications), and absences from work, school, and daycare.

Acute otitis media in children almost always develops in connection with a viral upper respiratory tract infection. Rhinovirus-associated otitis media can be caused by the virus only, but typically it is a viral-bacterial infection involving pathogenic synergy between rhinovirus and bacteria such as *S. pneumoniae*, *H. influenzae,* or *M. catarrhalis*. Bacteria can be cultured from the majority of middle ear samples collected from children with acute otitis media, but also

rhinovirus can often be detected in middle ear secretion (124). Both viruses and bacteria travel to the middle ear space from the nasopharynx via the Eustachian tube, which normal function is disturbed during rhinovirus infection. Rhinovirus is not as strongly associated with otitis media as RSV or adenovirus (125). However, since rhinoviruses are more common in the population than other respiratory viruses, a major part of all otitis media cases in children develop during a rhinovirus infection (55,126).

Acute sinusitis is a common complication of rhinoviral respiratory tract infection. Viral-bacterial pathogenesis has been documented in sinusitis, particularly in older children and adults. Nevertheless, most cases of rhinovirus-associated sinusitis are self-limited illnesses and antibiotics are recommended only for severe or prolonged manifestations. Clinical approach to acute bronchitis developing in association with rhinovirus infection is similar; guidelines support avoiding antibiotics in individuals without COPD or other conditions that predispose to a complicated illness.

12.1.2. Pneumonia

Rhinovirus is an important causative agent of pneumonia. It has been detected in about 30% of children and in 9% of adults with a community-acquired pneumonia (127–129). In a prospective community based study, 60 of 96 rhinovirus infections in elderly people manifested as lower respiratory tract illnesses, and underlying conditions and smoking were identified as risk factors (130). Young age and preterm birth have been identified as risk factors for rhinovirus pneumonia in children (131).

Rhinovirus can cause severe pneumonia alone or together with other viruses or bacteria. In a prospective study of severe pneumonia in adults at the intensive care unit, rhinovirus was identified in 15 of 49 patients who needed mechanical ventilation, in most cases

together with bacteria (132). Eleven of the 15 rhinovirus-positive specimens were collected from the lower airways. Malcolm et al described a series of 20 patients with rhinovirus isolated by viral culture from bronchoalveolar lavage specimens (133). Patients had an age range of 2.5 to 86 years, they had underlying immunosuppressive medications or conditions such as organ transplantation, malignancy, or acquired immune deficiency syndrome (AIDS), and the course of their illness was severe with 25% mortality. Chronic rhinovirus infection of the lung has been documented in lung transplant patients, causing graft dysfunction and death (12). Long-term infection caused by single rhinovirus type has been confirmed in these cases by sequencing of PCR products from repeated lower respiratory tract specimens. Furthermore, there is strong evidence for rhinovirus as the causative agent of severe or even life-threatening pneumonia in children, mostly in those with underlying conditions or born prematurely, but occasionally in otherwise healthy children (80,134–137).

Despite the convincing evidence of the capability of rhinovirus to cause lower respiratory tract infections, there remains uncertainty about its causative role in pneumonia, alone or as a predisposing factor for bacterial pneumonia. This is largely due to collection of diagnostic samples from the upper airways, where rhinovirus is commonly detected also in healthy subjects. Healthy children have been reported to have a similar prevalence of rhinovirus in nasopharyngeal specimens as children with pneumonia, whereas in adults rhinoviruses are detected more often in association with pneumonia (138,139). A predisposing role for rhinovirus in the pathogenesis of bacterial pneumonia is supported by the known mechanisms of rhinovirus in promoting bacterial colonization and invasion.

12.1.3. Wheezing illnesses from Bronchiolitis to Asthma Exacerbation

Wheezing illnesses include bronchiolitis in infants, recurrent wheezing in young children, and exacerbation of asthma in adolescents and adults. Rhinovirus is highly prevalent in all these clinical manifestations (Figure 3). According to a broad definition of bronchiolitis, it is a virus infection of bronchioles and their surrounding tissue, and clinically, the first expiratory breathing difficulty of children aged less than 2 years (140). In fact, PCR diagnostics has reached a 100% virus detection rate in severe bronchiolitis (141). Rhinovirus is the second most common viral agent of bronchiolitis after RSV during infancy, but it starts to dominate virus detection after 12 months of age (93). RSV and rhinovirus are the most common coinfections, occurring in 10-40% of the severe cases (93,142). In children with recurrent wheezing and in the exacerbations of asthma, rhinovirus is the main trigger accounting for up to 80-90% of virus positive samples (91,93).

Of clinical characteristics of patients with dyspnea, rhinovirus is typically associated with wheezing and many atopic characteristics such as atopic eczema, aeroallergen sensitization, increased blood eosinophil count, and increased exhaled nitric oxide level (91,94,143).

12.1.4. Link between Rhinovirus-induced Wheezing and Asthma

The major viral cause of early wheezing, rhinovirus, is an important clinical marker for increased risk of subsequent asthma. In contrast to RSV bronchiolitis, atopy has been clearly associated with childhood asthma development after rhinovirus-induced early wheezing. High risk (atopic families) birth cohort studies from the United States and Australia have shown that young children suffering from rhinovirus-induced wheezing episodes are at high risk of school-age asthma (odds ratio for rhinovirus up to 9.8, vs. RSV 2.6) (91,144). The risk is especially high if children were sensitized during first 3 years of life (odds ratio up to 45) (94). Rhinovirus etiology of early wheezing appears to serve as an important clinical marker also at the more severe end of illness. A recent study on hospitalized children showed that rhinovirus-induced severe first wheezing episode at an age less

than 2 years was a risk factor (odds ratio 5.0) for atopic asthma at school-age along with early sensitization and eczema (odds ratios 12 and 4.8, respectively) while RSV was associated with neither atopic nor non-atopic asthma (145). These studies do not answer to the question whether bronchiolitis is the cause of lung injury that results in subsequent wheezing episodes and development of asthma or if there is an inherent predisposition to both acute bronchiolitis and later asthma, with bronchiolitis being an early marker of this predisposition. Nevertheless, the data suggests that atopic airways have an increased susceptibility for asthma development after rhinovirus-induced bronchiolitis.

12.1.5. Other Clinical Manifestations

Rhinovirus has a central role in the etiology of recurrent respiratory tract infections in children, albeit together with other viruses and bacteria. In a cohort study, 10% of children suffered from recurrent respiratory infections, of which 58% were caused by rhinovirus (55). Most of these children also have recurrent otitis media and many have wheezing illnesses or asthma, and rhinovirus infections closely associate also with these manifestations.

Neonatal rhinovirus infection can present with fever and nonspecific signs of a generalized infection, and result in hospitalization because of suspected sepsis. Respiratory symptoms usually emerge during a short follow-up. In addition to patients with lung transplant or hypogammaglobulinemia, other patients with primary or secondary immunodeficiency or chronic lung disease can have severe or prolonged respiratory tract infections caused by rhinovirus. The predisposing chronic conditions include cancer with immunosuppressive treatment, cystic fibrosis and other chronic lung diseases, and debilitating neurologic conditions.

Rhinovirus infections with infectious foci outside the respiratory tract are rare. Evidence for a rhinovirus-induced pericarditis has been provided in a case report (146). Central

nervous system infection has been anecdotally reported in association with rhinovirus infection, but causality remains unclear.

12.2. Diagnostic Approaches

Although typical clinical manifestations do exist, clinically rhinovirus infections are indistinguishable from respiratory infections caused by other viruses that also cause similar symptoms. Despite this, a syndromic diagnosis based on clinical and epidemiological findings without virologic confirmation is sufficient for clinical evaluation of the majority of patients with non-severe rhinovirus illnesses. Whenever a confirmed diagnosis of rhinovirus is needed, it is based on the detection of virus or its genome from appropriate clinical specimens. Since rhinovirus infection is, in most cases, limited to the upper respiratory airways, a nasal or nasopharyngeal swab is the most sensitive sample. Diagnosis of rhinovirus in clinical specimens is performed almost solely by molecular methods, and particularly by RT-qPCR, which exceeds the traditional virus isolation by tissue culture methods both in speed and sensitivity. For rhinovirus genome detection, the most sensitive assays rely on highly conserved sequence stretches in the 5' NCR of the genome. However, this region is conserved between both rhinovirus and enterovirus types, and therefore the result is often reported as "rhinovirus/enterovirus". There are numerous published in-house protocols guiding the set-up of sensitive and specific assays. In some in-house assays, rhinovirus is specifically differentiated from enterovirus by using sequence-specific probes, but such methods are not widely used. Commercial multiplex platforms are available for either detection of rhinovirus/enterovirus together or rhinovirus and enterovirus separately along with the detection of other major respiratory viruses.

Antigen detection assays are not in use for routine detection of rhinoviruses due to lack of specific detector antigens. Antibodies can be measured in both serum and nasal secretions

by neutralization, plaque reduction, and enzyme-linked immunosorbent assays (ELISAs) in research settings (147,148). However, similarly to antigen detection assays, the lack of a common antigen across the rhinovirus strains makes the detection of antibody responses impractical in clinical diagnostics. Furthermore, antibodies are not detectable until 1 to 3 weeks post-infection, which makes antibody measurement useful for certain epidemiological studies but not for diagnosing acute rhinovirus infections (149).

13. Control and Prevention

13.1. Physical Barriers and Hand Hygiene

Physical distancing prevents spread of rhinovirus and should be applied if feasible. For example, avoidance of large child groups in early childhood education is rational (but perhaps not feasible). Since hand contact is important in the transmission of rhinovirus, hand hygiene by washing hands with soap and water should be emphasized in prevention. Hand sanitization with alcohol-based rubs can also be used, but the efficacy on rhinovirus, which is a non-enveloped virus, is uncertain. In one study, thorough hand washing with soap and water efficiently removed rhinovirus from hands of volunteers, whereas ethanol-containing hand rub was ineffective (150). On the contrary, in another study, ethanol hand sanitizer was effective in removing rhinovirus from hands (151). In a randomized trial conducted among office employees, intervention by a campaign of intensified hand washing had only marginal effect in reducing occurrence of respiratory tract infections (152). In hospital settings, droplet precautions, together with contact precautions under circumstances of copious moist secretions and close contacts, are recommended for infection control in treatment of patients with rhinovirus infection (153). Universal use of surgical face masks in health care in contacts with all patients with symptoms of respiratory tract infection, and during the

covid-19 pandemic also with all other patients, is now widely applied and it may be beneficial in prevention of rhinovirus transmission between patients and personnel.

Use of face masks in public places has emerged as an important mitigation measure during the covid-19 pandemic. Post-pandemic practices of face masking by the public remain to be seen. Possibly masks will be used at least by persons with symptoms of common cold. To what extent this would prevent transmission of rhinovirus is currently not known.

13.2. Pharmaceuticals

13.2.1. Therapy

No antiviral agent has been authorized for treatment of rhinovirus infection. Intranasally administered interferon alpha-2b was studied both for treatment and prophylaxis of common cold in 1980s. However, it was not effective in treatment of naturally occurring common cold in a placebo-controlled trial, started within 48 hours from onset of symptoms (154). Later, other drug candidates with antiviral activity against rhinovirus have reached clinical studies, which have been conducted in the setting of an experimental or naturally occurring common cold. One of the drug candidates, tremacamra, acts as an inhibitor of attachment of the major group rhinoviruses to ICAM-1 receptor. Intranasally administered tremacamra showed a modest therapeutic effect on experimental rhinovirus infection in human volunteers if started early, but its efficacy was not high enough to encourage further development (155). Mechanisms of other antiviral candidates include inhibition of the interaction between the viral capsid protein and its cellular receptor, and inhibition of proteases. Extensive clinical studies were done with pleconaril, a capsid binding agent, which has antiviral activity against rhinovirus and other picornaviruses (156). Pleconaril was evaluated by the U.S. Food and Drug Administration as a treatment for common cold, but it failed because of interactions with oral contraceptives and other drugs, development of viral resistance,

and modest efficacy against rhinoviruses (157). However, there is still interest in its activity against enteroviral infections. Vapendavir is another capsid-binding agent that reached phase 2 trials for treatment of rhinovirus infections in adults with asthma or COPD (158). A limitation of capsid-binding agents is that several such compounds are not active against rhinovirus C types. Novel antiviral approaches in early phase of development include targeting the viral RNA (25). Symptomatic treatment of common cold includes acetaminophen or nonsteroidal anti-inflammatory drugs and possibly nasal ipratropium (159). In addition, there is evidence for effect of oral zinc lozenges for adults but not for children (160).

Rhinovirus induced exacerbation of asthma is treated according to current asthma guidelines, primarily with bronchodilators and severe episodes also with systemic corticosteroids. Regular inhaled corticosteroid or other asthma control medications are used to prevent acute episodes. Anti-inflammatory treatment targets the type 2 immunity and/or the inflammatory responses of the airways and thereby reduces the risk of severe rhinovirus infections (161). Two separate clinical trials suggest in post hoc and secondary outcome analyses that treating the first rhinovirus-induced wheeze episode with a 3-day course of prednisolone decreases the risk for recurrences and subsequent school-age asthma by 30% (162–165). Also, *in vitro* models showed that the corticosteroid, budesonide effectively suppressed proinflammatory and remodeling-associated mediators such as IL6 and vascular endothelial growth factor (VEGF) that are induced in rhinovirus infections (166). It has also been suggested that high-dose β_2-agonist and systemic corticosteroid treatments may have positive synergistic effects in severe rhinovirus-induced wheezing episodes (167). In agreement, fluticasone and salmeterol both reduce rhinovirus-induced VEGF production *in vitro* individually but they function synergistically when administered simultaneously (168).

13.2.2. Prophylaxis

Intranasal interferon alpha2 was found to be effective in reducing occurrence of rhinoviral colds when used continuously or whenever someone in the household developed symptoms of respiratory infection (169,170). However, it caused nasal irritation and did not advance to clinical use.

In the absence of specific antiviral drugs against rhinovirus, there have been attempts to prevent common cold using available nonspecific agents such as vitamins. A systematic review concluded that vitamin C is not effective in prevention of the common cold, with the exception of people under severe physical stress, such as long-distance runners, skiers, or soldiers, who might benefit from vitamin C supplementation (171). Vitamin D is needed in the immune defense, and vitamin D deficiency predisposes subjects to respiratory tract infections. However, an increased dose of vitamin D compared to the routinely recommended supplementation did not prevent respiratory infections in children followed from 2 weeks to 24 months of age (172). Probiotics may prevent respiratory tract infection, although there is inconsistency between studies. Prebiotics (galacto-oligosaccharide and polydextrose mixture) and a probiotic (*Lactobacillus rhamnosus* GG) prevented symptomatic viral (and also specifically rhinoviral) respiratory tract infections in preterm infants in a placebo-controlled randomized trial (173).

13.3. Vaccines

Despite the high burden of rhinovirus infections, which is characterized by common cold, lower respiratory tract infections, exacerbations of both asthma and COPD, and by association with development of asthma, no rhinovirus vaccine has been evaluated in clinical trials. Large number of rhinovirus types (currently 169) and antigenic heterogeneity within viral capsid proteins are

major barriers to effective vaccine development. Consequently, limited cross-reactivity of neutralizing antibodies requires multiple adjuvanted immunizations in a mouse model. Using viral antigen formulations up to 25-valent in mice and 50-valent in rhesus macaques, the rhinovirus vaccine immunogenicity was shown to be related to sufficient quantity of input virus type-specific antigen; such a vaccine would be expensive to manufacture (174). Rhinovirus vaccine studies have been summarized in a review (175).

13.4. Programmatic Approaches

Young children have a prominent role in spread of rhinoviruses in communities. Multifaceted approaches should be utilized in child daycare settings in order to diminish transmission of rhinovirus as well as other viruses. Precautions including instructions for hand washing, adequate cleaning of surfaces and toys, and teaching children to cover their nose and mouth with tissue when sneezing or coughing should be implemented and the policies should be formulated in written. Daycare facilities should have proper ventilation and enough space for different activities. Training of staff is important, and even more important factors are limitations on group sizes, avoidance of overcrowding, and having enough adult professionals in relation to the number of children in daycare. Above-mentioned and other infection control practices have been shown to be effective in daycare settings, but only to some extent (176). Age-appropriate behaviour of young children involving close contacts with other children and adults, ubiquitous nature of the numerous rhinovirus types, high viral loads at or just before the beginning of symptoms, and asymptomatic infections make it difficult to prevent the transmission of rhinovirus by programmatic approaches.

Hand hygiene, respiratory etiquette, and other standard precautions for infection control should be applied in schools and workplaces as well.

Individuals with respiratory symptoms transmit rhinovirus more efficiently than asymptomatic rhinovirus-positive subjects. In general, people with symptoms of an acute respiratory infection should stay at home instead of coming to daycare, school, or workplace. However, this practice has often not been followed in case of the common cold with mild symptoms. With emergence of the covid-19 pandemic, the importance of avoiding contacts during symptomatic respiratory tract infections has been highlighted, and at the same time, telecommuting has become available as a frequently used option for professionals in different occupations. It is advisable to stay at home with an upper respiratory tract infection, if possible. It is appropriate to return to daycare, school, or workplace when symptoms of common cold are decreasing, as the virus load rapidly decreases.

14. Unresolved Issues and Prospects

The biological mechanisms allowing the epidemiologic pattern of a high number of simultaneously circulating rhinovirus types in human populations are poorly understood. Development of immune response against rhinoviruses is not fully characterized and it remains unknown why viruses that differ from each other only by minor genetic and antigenic characters can re-infect the same individuals only after a short interval of few days or weeks. Factors behind the diversity of circulating rhinoviruses and limited natural immunity against them should be better understood in order to develop effective vaccines.

A treatment for common cold has been hoped for since the discovery of rhinovirus. Recognition of severe respiratory illnesses caused by rhinovirus in otherwise healthy and in immunocompromized individuals has indicated the need for effective antiviral drugs against rhinovirus. Despite setbacks regarding drugs that showed early promise, there are possibilities for

new prospects in rhinoviral drug development based on the detailed knowledge of the structural and functional characteristics of the virus.

A prerequisite for drug and vaccine development projects is the understanding of clinical effects of rhinovirus. A lot of progress has occurred in this field but there are still uncertainties regarding the role of rhinovirus in the pathogenesis of severe pneumonia and in development and exacerbation of chronic illnesses such as asthma. Global morbidity and mortality caused by rhinovirus is poorly known. Resolving these clinical and translational science questions is similarly important as the puzzling themes in virology and immunology of rhinovirus. Currently our abilities to act against this agent that causes enormous burden of disease are distinctly inadequate.

15. Cross-References (list of relevant chapters from Table of Contents on Meteor)

Relevant Websites:

https://talk.ictvonline.org/

http://www.picornaviridae.com/

http://www.picornastudygroup.com/

http://viperdb.scripps.edu

Figure Legends

Figure 1. Structure of rhinovirus A2 (RV-A2). From left to right: cryo-electron microscopy reconstruction of RV-A2, symmetry of icosahedral virus particle, and five-fold axis of symmetry representing three surface-exposed viral capsid proteins, VP1, VP2, and VP3. CryoEM image courtesy of Dr. Dieter Blaas.

Figure 2. Schematic presentation of rhinovirus RNA genome.

Figure 3. New diagnostic thinking concerning bronchiolitis and first wheezing episode (177).

16. References

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Table 1. Rhinovirus classification and receptors.

Genus	Species and receptor	Virus types*	Number of virus types
Enterovirus	*Rhinovirus A* - ICAM-1	A7-A13, A15-A16, A18-A22, A24, A27-A28, A32-A34, A36, A38-A41, A43, A45-A46, A50-A51, A53-A61, A63-A68, A71, A73-A82, A85, A88-A90, A94, A96, A100-A109	80
	Rhinovirus A - (V)LDLR	A1-A2, A23, A25, A29-A31, A44, A47, A49, A62	
	Rhinovirus B - (V)LDLR	B3-B6, B14, B17, B26-B27, B35, B37, B42, B48, B52, B69, B70, B72, B79, B83-B84, B86, B91-B93, B97, B99-B106	32
	Rhinovirus C - CDHR3	C1-C57	57

*According to www.picornaviridae.com and ICTV Master Species List (https://talk.ictvonline.org/).

Abbreviations: CDHR3, cadherin-related family member 3 receptor; ICAM-1, intracellular adhesion molecule 1 receptor; (V)LDLR, (very) low density lipoprotein receptor.

Table 2. Clinical manifestations, typical patient groups, and virus species in rhinovirus infections.

Manifestation	**Patient groups**	**Rhinovirus species**	**Comments**
Common cold	All ages	A, B, C	
Acute otitis media	Young children	A, B, C	Bacterial co-infections
Sinusitis	Adolescents and adults	A, B, C	Bacterial co-infections
Bronchitis	Adults	A, B, C	
Bronchiolitis	Infants	A, C	Predicts development of asthma
Wheezing illness	Young children	A, C	Predicts development of asthma
Asthma exacerbation	Older children, adolescents and adults	A, C	
Pneumonia	Children and older adults	A, C	Bacterial co-infections
Severe or prolonged respiratory illness	Immunocompromized individuals	A, B, C	High morbidity and mortality

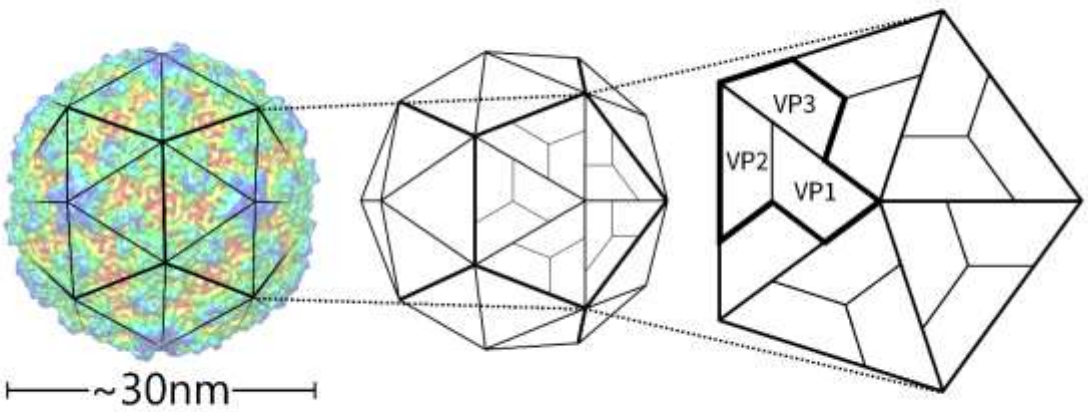

Figure 1.

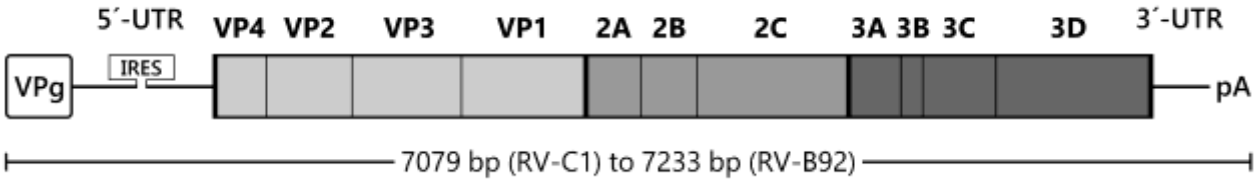
5´-UTR
VP4
VP2
VP3
VP1
2A
2B
2C
3A
3B
3C
3D
3´-UTR
VPg
IRES
pA
7079 bp (RV-C1) to 7233 bp (RV-B92)

Figure 2.

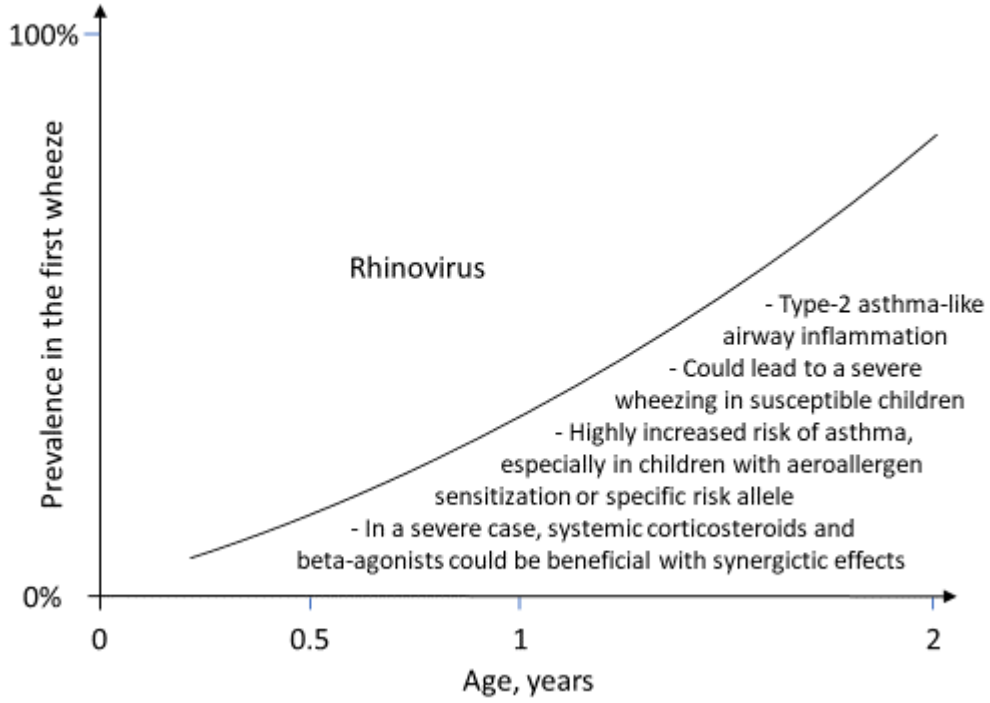
100%
Prevalence in the first wheeze
0%
Rhinovirus
- Type-2 asthma-like airway inflammation
- Could lead to a severe wheezing in susceptible children
- Highly increased risk of asthma, especially in children with aeroallergen sensitization or specific risk allele
- In a severe case, systemic corticosteroids and beta-agonists could be beneficial with synergictic effects
0
0.5
1
2
Age, years

Figure 3.