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Review Article

Human Metapneumovirus Infections: a Comprehensive Review of Diagnosis and Management

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Abstract

Respiratory tract infections are one of the most common illnesses experienced worldwide. Around 3 to 20% of these infections are caused by Human metapneumovirus. The spectrum of clinical manifestation can range from a mild upper respiratory tract infection to a severe illness resulting in acute respiratory distress syndrome that may require ventilator support in the ICU. Risk factors of progression to severe illness include young age (< 5 years), older than 65 years, chronic cardio-respiratory co-morbidity, and immunosuppression. There is no evidence to suggest specific treatment other than supportive care. Ribavirin and immunoglobulins have been employed in some patients as a last resort. Vaccine development for human metapneumovirus is currently under research.

Keywords: Human metapneumovirus, Acute hypoxic respiratory failure, upper respiratory tract infection, bronchiolitis, acute respiratory distress syndrome, pneumonia.

Introduction

Respiratory tract infections are one of the most common illnesses that occur worldwide [1]. These can range from mild rhinitis to severe hypoxic respiratory failure secondary to pneumonia. In fact, respiratory tract infection is the leading cause of death in children younger than 5 years of age worldwide and the third leading cause of death in adults [2]. The human respiratory syncytial, influenza, parainfluenza, coronavirus, and rhinovirus cause most respiratory tract infections [3]. It is believed that many unknown pathogens may be circulating, and the current diagnostic methods have limited ability to detect them. In 2001, a novel agent was discovered in nasopharyngeal aspirates of children and infants hospitalized for respiratory tract infections in the Netherlands and was called Human metapneumovirus (HMPV) [4,5]. This review discusses epidemiology, clinical manifestations, diagnostic methods, and treatment of Human metapneumovirus infections.

Epidemiology

Human metapneumovirus can cause upper and lower respiratory tract infections and affect all age groups. It has been isolated as a cause of respiratory infection in every continent [4]. Serological studies reveal the presence of HMPV antibodies in samples obtained in 1958, suggesting the existence of this virus at least for the past 66 years [5]. Human metapneumovirus is responsible for about 15% of respiratory illnesses in children with an estimated annual hospitalization rate of about 0.1% and contribute to 3% of respiratory illnesses in adults [6,7]. HMPV is the second leading cause of bronchiolitis in infants and is responsible for 10% of hospitalizations in children. 70% of the hospitalized children required respiratory support, with 5% of them eventually requiring mechanical ventilator [6].

Maternally derived antibodies seem to be protective during the first 6 months of age. Following this, children experience higher rates of infection during the first 5 years of age, and most of these infections are symptomatic. Although most young adults are seropositive with good neutralizing titers of antibodies, presenting with mild to no symptoms, older adults (> 65 years) and other individuals with respiratory co-morbidity remain susceptible to infections and can succumb to severe illness [7,8].

HMPV has been attributed to be responsible for 9% of adult respiratory infections in hematological malignancies and 6% in lung transplant recipients [9]. Mortality due to HMPV in hematopoietic stem cell transplant recipients can vary from 10-

80%, and the presence of neutropenia could play a significant role in poor outcomes [9,10].

Typically, HMPV infections cause outbreaks of respiratory infections, especially during late winter and early spring (December to February) in temperate regions [4]. Whether a seasonal predisposition occurs in a tropical or subtropical climate is unclear, as an outbreak has been reported in late spring and summer in a subtropical region [11,12].

In 2018, it has been estimated to have affected 14.2 million children under the age of five worldwide. One study isolated HMPV in approximately 10% of patients (13% of children, 4% of adults) hospitalized secondary to respiratory infections. Of these cases, half of them had another co-pathogen. Some data suggest an attack rate of more than 34% among residents of long-term facilities, causing severe pneumonia, making it one of the nosocomial pathogens [12]. Of note, it has also been isolated in asymptomatic individuals, accounting for a possibility of latent infections responsible for transmission [13].

The Virus

Human Metapneumovirus (HMPV) is an enveloped, nonsegmental negative-sense single-stranded RNA virus belonging to the Pneumoviridae family of the genus Metapneumovirus. The genomic composition is similar to respiratory syncytial virus (RSV), except that HMPV lacks NS1 (nonstructural) and NS2 genes and harbors different gene orders in their opening reading frame. For this reason, this has been classified under Metapneumovirus (meta refers to a specific sequence), whereas RSV is classified as Orthopneumovirus. Partial cross-immunity may occur between RSV and HMPV. Based on phylogenetic study, it is subtyped into two groups, A and B (sub-grouped as A1/A2a, A2b, B1/B2). The envelope of HMPV contains three glycoproteins, which include the F (fusion), G (glycoprotein for attachment), and SH (short-hydrophobic) proteins [14]. See (Figure-1). Multiple genotypes may exist during the same outbreak, and similar strains may be isolated in different locations with different time stamps, suggesting the possible role of viral circulation [15]. Subtype B is thought to be associated with more prolonged and more severe respiratory illness with wheezing more frequently than sub-type A, although this has been debated, as one study suggested that genotype A is more pathogenic than sub-type B. Genotype A may predominantly cause pneumonia resulting in hypoxia. In contrast, genotype B is more often associated with bronchiolitis [16,17]. As most adults are sero-positive by the age of 12, it occurs as an epidemic outbreak rather than pandemic as the sero-positivity seems to be protective [6]. Point mutations and antigenic drift occur in HMPV, but these may not be responsible for most re-infections, however theoretically, when they do occur, these may result in pandemic [14].

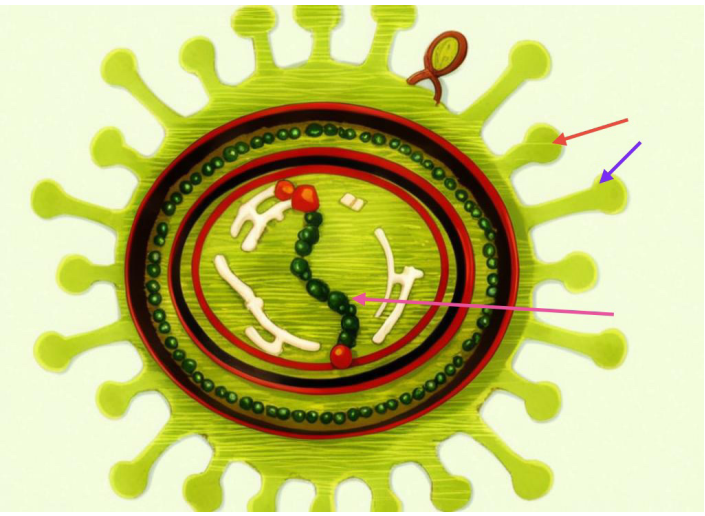

Figure 1: Schematic illustration of Human Metapneumovirus. Blue arrow: G protein that interacts with the integrin receptor of respiratory epithelial cells. Red arrow: F protein that promotes the fusion of virus envelop with the host cell membrane. Pink arrow: negative sense single stranded RNA. Credit: Joanna Kristeva/ Original Artwork 2025.

Pathogenesis

The G protein of HMPV interacts with the integrin Alpha-V-beta-1 receptor of respiratory epithelial cells [18]. Subsequently, the F protein promotes the fusion of the virus envelope with the host cell membrane, releasing viral ribonucleoprotein into the cytoplasm. Infected cells can also form syncytium, like that caused by the human syncytial virus. Nucleocapsids are formed after transcription and are incorporated into virions that bud from the cell membrane for continued infection and transmission via airborne droplets [19]. The infected cells evoke an inflammatory response, as evidenced by perivascular and peri bronchial cellular infiltration, responsible for respiratory symptoms, including mucus hyperproduction and bronchial hyper-responsiveness, similar to other respiratory viral pathogens. Other pathological findings include the presence of intra-alveolar foamy and hemosiderin macrophages, epithelial cell degeneration, detached ciliary tufts, and rounded red cytoplasmic inclusions [20,21].

Transmission occurs via close contamination with secretions and fomites; hence, droplet precautions are recommended, including physical separation of at least 6 feet. The incubation period is between four to nine days, followed by peak viral shedding, which persists for approximately an additional week. The person remains infectious from day 2 to day 14, although the virus may persist in the lungs for several weeks. It is unlikely that HMPV infects

other organ systems and very rarely may result in encephalitis, as the virus prefers to target predominantly ciliated epithelial cells. Clinical manifestations typically occur 1-2 days after peak shedding [22, 23].

High Viral load (VL > 1000 copies/ml) has been demonstrated to be independently associated with severe illness requiring hospitalization for a longer duration [24,25]. Immunocompromised individuals are believed to lack the ability to control viral replication and hence result in severe illness.

Clinical features

Most HMPV infections present with upper respiratory tract symptoms in adults; it can cause severe lower respiratory illness in young children (< 5 years of age, especially if prematurity), anatomical lung disease such as trachea-laryngomalacia, neuro-muscular disorder, older adults (> 65 years of age mainly when associated with frailty), chronic cardio-respiratory co-morbidity (such as COPD, Asthma, cancer) and immunocompromised individuals [7, 26, 27].

Clinical features are similar to other respiratory viral illnesses, and signs and symptoms alone cannot differentiate HMPV infections from other respiratory pathogens. HMPV can cause upper and lower respiratory tract infections, including rhinitis, pharyngitis, conjunctivitis, otitis media, bronchiolitis, and pneumonia [28]. Most adults have around a week of self-limiting upper respiratory viral illness (rhino-pharyngo-laryngitis) with symptoms of cough (90%), rhinitis with nasal congestion, rhinorrhea (70%), hoarseness (50-67%). Fever is rare in adults (< 4%), while pyrexia is common in children (50-80%) [29,30].

Children under the age of five (especially prematurity), older adults > 65 years (with frailty), and immunocompromised individuals are at high risk of developing severe illnesses involving the lower respiratory tract, often responsible for hospitalization. The severe illness may present as bronchiolitis or pneumonia, that may progress to acute respiratory distress syndrome. In these cases, the upper respiratory symptoms last up to 48 hours, followed by bronchiolitis, which may evolve into pneumonia. The presence of wheezing and tachypnea in a suspected respiratory infection is a clinical clue for bronchiolitis [31]. Typical radiographic features for viral bronchiolitis include peri-bronchial cuffing and hyperinflation [32]. Shortness of breath, tachypnea, fever, and hypoxia suggest pneumonia, with radiographic infiltrates confirming the diagnosis. Recurrent infections are typically mild except in immunocompromised individuals who may suffer from severe illness during reinfection. Immunocompromised individuals include patients infected with human immunodeficiency virus (HIV), patients with cancer, and organ transplant recipients with immunosuppressive therapies [33].

During the acute phase of the illness, the inflammatory reaction in the upper airway may partially or fully collapse the eustachian tubes, resulting in acute otitis media. The literature suggests that HMPV may be responsible for primary or secondary otitis media in about 6-30% of cases in children [34].

Other manifestations in children during illness may include apnea spells with cyanosis, febrile seizure, diarrhea, rash, and abnormal liver function tests. Some case reports exist to suggest HMPV is responsible for encephalitis and sepsis syndrome [35,36].

Many young adults remain asymptomatic or may experience mild rhinitis or flu-like illness. Patients with chronic airway disease (e.g., asthma, COPD, reactive airway disease, bronchiectasis) can have prolonged cough and wheezing for up to several weeks, and some have exacerbation of their underlying disease [37]. During the peak season, 6-12 % of COPD exacerbations have been attributed to HMPV, with a probable case fatality rate of at least 9.4% among institutionalized older adults [38]. Pregnant women are also considered at high risk for severe disease associated with HMPV infection [39].

It is believed that HMPV may be responsible for some cases of Asthma in the long term [4]. In the case of lung transplant recipients, HMPV infection can lead to chronic allograft dysfunction [40].

Diagnosis

RT-PCR (Reverse transcriptase-polymerase chain reaction) on respiratory secretions is the most sensitive method for diagnosing HMPV. It is available as part of a multiplex PCR panel (The BioFire Film Array Respiratory Panel). A multiplex respiratory panel is preferable, as it can also detect co-infection with other pathogens [41]. A multiplex RT-PCR has higher sensitivity than a real time RT-PCR [42].

Direct immunofluorescence (DFA) or Enzyme-linked immunosorbent assay (ELISA) are other rapid methods to detect the virus on respiratory secretions but lack the sensitivity of PCR. DFA has a sensitivity of only 38% compared to PCR. Direct fluorescent antibody testing can be done on nasopharyngeal aspirates with a turnaround time of approximately three hours [43].

Viral cultures are falling out of favor as they are less sensitive (68% compared to PCR) and cumbersome. Many cell lines have been used for the growth and isolation of HMPV. These include Vero cells, Hep-2 cells, Hep G2 cells and LLC-MK2 cells. HMPV exhibits slow growth rate and delayed cytopathic effect decreasing the sensitivity of detection. However, viral cultures can be made efficient by using monoclonal antibodies either using DFA or ELISA for rapid detection [44].

Serology is discouraged for making a diagnosis of acute infection, as HMPV antibodies when detected by enzyme-linked immuno-

sorbent assay or neutralizing antibodies, are universally present by the age of 5 to 12. However, serology is extremely useful for epidemiological and research purposes. If a diagnosis of acute infection needs to be made by serology, a four-fold increase of titer in serial samples or seroconversion is considered a definitive serological diagnosis [8].

Peri-hilar opacities associated with hyperinflation strongly suggest bronchiolitis, whereas ground glass opacities or consolidation suggest pneumonia. See (figure-2). Pleural effusion or pneumothorax is relatively uncommon [45]. It is often recommended to obtain a computer tomography of the chest for immunocompromised individuals. Immunocompromised individuals include HIV, organ transplant, HSCT, lymphopenia, neutropenia, corticosteroid > 30 mg/day, malignancy and those who are receiving immunosuppressive therapies. These individuals when present with pneumonia, having a low threshold for bronchoscopy, bronchial washing or broncho-alveolar lavage improves outcomes. Furthermore, as co-infections are very common in this population, a mere isolation of an infectious agent in upper respiratory samples does not always co-relate with the pathogen responsible for pneumonia [46].

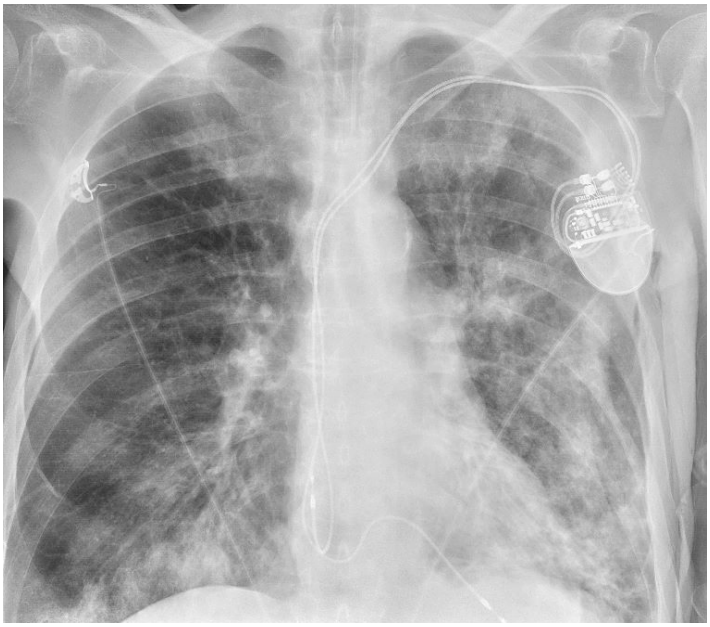

Figure 2: This is the chest x ray of a 72-year-old male patient with significant cardio-respiratory co-morbidity admitted for hypoxia and acute exacerbation of chronic obstructive pulmonary disease (COPD). The CXR demonstrates multifocal opacities in a pattern suggestive of broncho-pneumonia. His respiratory viral panel was positive for human metapneumovirus. He was discharged on day 5 of admission and required intravenous steroids for the treatment of COPD exacerbation. Courtesy of Ramakanth Pata, MD.

Due to seasonal distribution, it should be remembered that there is always a potential for co-infection. Fifty percent of the time, HMPV is a co-pathogen with RSV, Pseudomonas, or invasive fungal infections; hence, further diagnostic evaluation should be considered if co-infection is suspected [47]. It is currently believed that a co-infection of HMPV and RSV may cause more severe bronchiolitis in children [31]. Whether this applies to other age groups is unclear.

If the clinical picture suggests encephalitis in a patient with HMPV infection, magnetic resonance imaging of the brain (MRI) should be considered which may show multifocal cortical and subcortical lesions. In some case studies, the virus has been also been isolated from PCR of cerebrospinal fluid [35].

It is also worth noting that lymphopenia and elevated monocytes are present in many viral infections, including HMPV [48].

Management

Infectious precautions for HMPV infections include handwashing, droplet and contact precautions. If cohorting is applied, HMPV patients should not be kept near RSV patients as co-infections tend to be severe. Patients likely shed the virus for many days to weeks; hence, close contact with an immunocompromised individual should be avoided during acute illness and early convalescence [49].

The management is mainly supportive. Standard guidelines apply for the management of bronchiolitis, such as bronchodilators, adequate hydration, and oxygen support. There is no robust data to support the efficacy of bronchodilators or inhaled steroids, but they are used empirically when a diagnosis of bronchiolitis is made [50]. In patients with pneumonia, Oxygen supplementation, adequate hydration and respiratory support including mechanical ventilation are provided as needed. Standard guidelines for acute respiratory distress syndrome should be employed such as lung protective strategy, prone positioning and titration of positive end-expiratory pressure [51].

Although ribavirin has shown in vitro activity against HMPV, its role in treating human infections remains unclear, and evidence is conflicting. Ribavirin is a guanosine triphosphate analog that limits viral transcription and possibly has an immunomodulatory role [52]. Similarly, non-specific polyclonal Immunoglobulins have conflicting evidence in managing HMPV infection [53, 24, 55, 56]. Mouse models support the therapeutic efficacy of the humanized monoclonal antibody (mAb 338) that was designed against the HMPV F protein [57].

Ribavirin +/- intravenous immunoglobulin has been proposed as a last resort option in severely ill patients who are severely immunocompromised (e.g.: malignancy or organ transplant recipients). This should be done as a part of a shared decision process if de-

sired, as the evidence is of low quality and conflicting, with some cases reporting worsened outcomes, while other reporting survival [54-56].

Several molecules and peptides that inhibit the fusion F protein are under development [58]. The pharmaceutical industry has been interested in developing exogenous small interfering RNA (siRNA) targeting HMPV N and P proteins and other viral genes [59].

Prevention

Currently, there is no vaccine available for preventing HMPV infection. Based on the animal models, a formalin-inactivated HMPV vaccine enhanced the Th2 response with subsequent pulmonary disease and hence was not considered for further trials. Potentially, a nano-emulsion-inactivated vaccine may be more protective rather than a formalin inactivated vaccine. Research is being done to configure a recombinant vaccine involving the F protein. G protein-based vaccines have been controversial due to their low immunogenicity profile. A recombinant live attenuated vaccine is also currently under development [60].

One study observed that nine-valent pneumococcal conjugate vaccines have decreased the prevalence of HMPV-associated severe illness and rates of hospitalization, especially in HIV-infected children [61]. This association may either represent HMPV as a co-pathogen causing bacterial pneumonia or possibly vaccine-related immunity against the virus suggesting cross reactivity.

Summary

Since its discovery in 2001, considerable progress has been made in understanding the epidemiology, pathogenesis, and clinical features of HMPV infection. HMPV is one of the etiological agents for respiratory illnesses that can vary from mild rhinitis to severe hypoxic respiratory failure. Risk factors for severe illness include children younger than 5 years, older adults > 65 years of age, patients with chronic cardio-pulmonary co-morbidity, and immunocompromised individuals. Clinical manifestations of severe infection associated with HMPV include either bronchiolitis, which presents with wheezing and tachypnea or can present as pneumonia that manifests as hypoxia with other signs of pneumonia. Treatment is mainly supportive and includes adequate hydration, oxygen supplementation, bronchodilators, and inhaled steroids as needed. Mechanical ventilation should be considered in accordance with clinical practice guidelines. Ribavirin and immunoglobulins may be considered a last resort, but the evidence is conflicting. Droplet precautions should be employed as a part of infection control. Research is ongoing to develop specific antiviral therapies and vaccines that are effective with high, long-lasting immunogenicity and minimal adverse effects.

Conflicts of interest

Both authors declare no conflicts of interest. No financial disclosures. No funding has been received for this project. All images were obtained after permission from relevant parties.

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