Review article

A REVIEW ON HUMAN METAPNEUMOVIRUS AND HUMAN BOCAVIRUS ASSOCIATED WITH ACUTE RESPIRATORY TRACT INFECTIONS

Abstract

Acute respiratory tract infections (ARTIs) are among the most significant causes of morbidity and mortality among young children in developing countries. Human metapneumovirus (hMPV) and human bocavirus (HBoV) infections are uncommon, especially among rural children. Acute respiratory infections are infectious and can also spread from one person to another, and the disease is quite widespread. It is hazardous for children, older adults, and people with immune system disorders. According to the World Health Organization (WHO), acute respiratory infections are estimated at 2.6 million deaths in children annually worldwide [1]. Based on published literature, only a few studies have identified ARTIs or shown the importance of early diagnosis and treatment of ARTIs. This review article aims to comprehensively describe the aetiology, epidemiology, clinical features, diagnostic methods, and treatment in managing hMPV and HBoV.

Keywords: communicable diseases, emerging, human metapneumovirus, human bocavirus, acute respiratory tract infections.

Introduction

There is a significant prevalence of ARTIs of viral and bacterial origin, such as the common cold, pharyngitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, and bronchopneumonia. These ARTIs are associated with high mortality rates and high economic costs [2]. ARTIs are infections of body parts involved in breathing, such as the sinuses, throat, airways or lungs. Viral pathogens are the most common cause of respiratory disease in children. The causative agents include rhinoviruses, respiratory syncytial virus, influenza virus, parainfluenza virus, hMPV, HBoV, measles, mumps, adenovirus, and coronaviruses [3, 4]. HBoV and hMPV are two important viruses for children with ARTIs. HBoV was initially identified in the airway of children with high rates of mixed infection with other viral pathogens. Detecting the virus in the stool has raised questions about the proper role of HBoV as a cause of respiratory diseases [5]. The hMPV has been established as a common cause of upper and lower respiratory

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tract infections in children, compared second only to the respiratory syncytial virus as a cause of bronchiolitis in infants. These viruses are also important causes of ARTI in the elderly and immunocompromised patients. The hMPV belongs to the Paramyxoviridae family and has a negative-sense single-stranded RNA genome, which includes eight genes coding for nine different proteins [6]. HBoV belongs to the Parvoviridae family and has single-stranded DNA [7]. The hMPV and HBoV are now considered critical viral pathogens that cause undiagnosed LRTI and URTI in children less than five years of age. Diagnostic tools have been developed for the clinician, and effective treatment and prevention strategies are being investigated. This review focuses on epidemiology, pathogenesis, clinical features, and diagnostic techniques for HBoV and hMPV.

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Acute Respiratory Tract Infection

ARTIs include infections in any area of the respiratory tract, including paranasal sinuses, the middle ear, and the pleural cavity lasting less than 30 days [8]. Respiratory infections can be bacterial or viral in origin, the latter being more common and

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are mostly limited to the upper respiratory tract. ARTIs can be classified as upper respiratory tract infections (URIs) or lower respiratory tract infections (LRIs) based on the organs affected. Based on the clinical severity, ARTIs can be classified into mild, moderate, and severe types [9]. Children are especially at risk because of their constant contact with other kids who could be virus carriers. Children often do not wash their hands regularly, rub their eyes, and put their fingers in their mouths, resulting in the spread of viruses. People with heart diseases or other lung problems are more likely to contract an acute respiratory infection. Anyone whose immune system might be weakened by another disease is at risk. Smokers are also at high risk and have more trouble recovering from it [10].

URI can be defined as an acute febrile illness with cough, coryza, sore throat, or hoarseness, which are very common in the community and are one of the primary reasons for hospitalization, particularly during the winter and wet season. The frequency of URI can be six to eight episodes per year and even more in children attending daycare centres and schools. Most of these URIs are mild, self-limiting, and not often life-

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threatening. URI in infants can cause lethargy and poor feeding. It can also lead to clinical conditions like acute otitis media, asthma exacerbations, and LRI, such as bronchitis, bronchiolitis, and pneumonia [11].

LRI is an acute illness (present for 21 days or less), usually with cough as the primary symptom, and secondarily sputum production, dyspnoea, wheezing or chest discomfort/pain with no other complications (e.g., sinusitis or asthma). Tachypnea, fever, cough, hypoxia, bronchitis, bronchiolitis, and pneumonia are the clinical symptoms of LRI. Chest radiograph changes include infiltrated hyperinflation and peribronchial cuffing. LRI, particularly pneumonia, causes the most severe illnesses and deaths in ARTIs. The disease's severity is very high in children under five years of age and the immunocompromised [12].

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Prevalence of ARTIs

Globally, ARTIs (predominantly pneumonia) have a 20% of mortality among children <5 years old. If neonatal pneumonia is also considered, the mortality increases to 35–40% among under-five children, accounting for 2.04 million deaths/per year.

Southeast Asia has the highest incidence of ARI, followed by the sub-Saharan African countries; they contribute to more than 80% of the total global cases [13]. Multiple social and environmental factors affect the morbidity and mortality of ARI in childhood. Factors include poverty, poor nutrition, poor housing conditions, indoor air pollution (including parental smoking), poor ventilation, overcrowding, industrialization, sociocultural values, overuse and misuse of antibiotics, lack of basic health services, and lack of awareness [14]. It is also important to note that a quarter of ARI deaths in children are attributable to passive smoking. The National Family Health Survey, conducted in 2019–2020, reported a 2.4% prevalence of ARI in the preceding two weeks in the urban areas and a 3.8% in the rural areas in Maharashtra state. In the Indian slum areas, ARI constitutes more than two-thirds of all childhood illnesses [15]. Globally, in 2010, nearly 2, 65,000 hospital deaths of young children were attributed to ARI, 99% of which were reported in developing countries. In urban slum areas, ARI constitutes over two-thirds of all childhood illnesses. In India, 14.3% of the deaths among infants and 15.9% among children between 1 and 5 years of age are due to ARTIs, and most of

these deaths are preventable. Because of the high morbidity and mortality rates associated with ARTIs, their control continues as a major challenge to the healthcare system [16].

Aetiology of ARTIs

A wide range of microorganisms, including bacteria, viruses, fungi, and protozoa, can cause respiratory tract infections, the standard being bacteria and viruses. Viruses are responsible for most upper respiratory tract infections, while bacterial infections can be primary or secondary to measles, influenza, or RSV infections [17]. The common bacteria known to cause acute respiratory tract infections are *Streptococcus pneumoniae, Haemophilus influenzae* (type B), *Streptococcus pyogenes* and *Staphylococcus aureus.* Other pathogens are *Mycoplasma pneumoniae and Chlamydia pneumoniae* which causes atypical pneumonia [18]. ARTIs in viruses are a significant cause of morbidity and mortality. The primary viral etiological agents of ARTIs in all age groups include respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses (PIV), adenoviruses, human rhinovirus (hRV), hMPV, HBoV, coronaviruses and picornaviruses [19, 20]. Among these, RSV, hMPV, hRV and PIV predominate as the cause of ARTIs in

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children under five years of age and have a seasonal occurrence with or without co-infection [21].

Diagnosis of viral respiratory tract infections

The differentiation of the etiological agent for respiratory tract infection based on clinical conditions is practically impossible. Rapid and precise diagnosis of the etiological agent is essential in treating and controlling the spread of viral respiratory infections [22]. Laboratory diagnosis can significantly improve care based on the appropriate diagnostic method chosen by the health care personnel in performing the test. There are various methods for detecting respiratory tract infections: rapid antigen testing, immunofluorescence tests for antibody detection, conventional and rapid cell culture methods, and molecular-based nucleic acid amplification assays [23]. The various specimen types for detecting respiratory viruses include nasopharyngeal aspirates, nasopharyngeal washes, nasopharyngeal swabs and oropharyngeal swabs in viral transport media. Sputum, endotracheal aspirates, and bronchioalveolar lavages are collected in tubes. The sensitivity of each method depends on factors such as sample type, time of

sample collection, the onset of the symptoms, patient age, antigen target, and the properties of the virus [24, 25]. Immunocompromised patients shed low titters of the virus over an extended period, making it difficult to detect it by nonmolecular methods. Hence nucleic acid amplification by molecular-based methods has become more popular for identifying respiratory viruses as they are rapid and most sensitive assays [26, 27]. The various methods for identifying respiratory viruses have their advantages and drawbacks.

The traditional tube culture method is advantageous for growing a wide variety of viruses, including novel or unknown viruses, but it takes days and often weeks to provide results. Over the years, modified cell culture methods such as the centrifugation-enhanced shell-vial method have reduced the turnaround time from 10 days to 24 hours [28]. Shell-vial culture using combination cell lines allows simultaneous detection of multiple respiratory viruses and, as compared to conventional culture, has similar sensitivity for parainfluenza 1-3 (87% vs 83%) and

influenza A/B (78% vs 75%) and significantly higher sensitivity for RSV (73% vs 42%) [29].

Rapid immunoassays (RIAs) can deliver test results in less than 30 minutes and are usually performed in the point of care testing (POCT), thus allowing the test results to be incorporated into the clinical decision-making algorithm. In the pediatric population, commercially available immunoassays have demonstrated high sensitivity (93%) for the detection of RSV, and a systematic review of published studies has further revealed that the sensitivity of RSV RIAs is relatively higher for children (81%) than adults (29%). The higher sensitivity can be attributed to the fact that pediatric patients often shed higher titers of respiratory viruses for a longer time than adults [30, 31].

Pathogen-specific antibodies typically appear about two weeks after the initial infection and can be detected by serological tests. Serological tests can successfully identify antibodies to most respiratory pathogens such as RSV, adenovirus, influenza A and B, parainfluenza 1-3 virus, etc., and can detect mixed infections from hospitalized children suffering from acute respiratory

infections, except infants for whom an antibody response is usually undetected [32]. However, it has been reported that serological assays are significantly less sensitive for the detection of parainfluenza virus and adenovirus when compared to molecular methods, such as RT-PCR [33]. RT-PCR can detect 40% more specimens from pediatric patients that were positive for at least one respiratory virus than were detected by fluorescent antibody assay (FA). FA testing, in addition to RT-PCR, is useful for epidemiological studies as it increases the probability of identifying acute viral infections and has been used to accurately assess respiratory viruses other than influenza in children [34, 35, 36].

HUMAN METAPNEUMOVIRUS

Discovery and classification of hMPV

The hMPV was initially isolated in the Netherlands from 28 nasopharyngeal aspirates (NPA) collected from children younger than five years of age presenting with respiratory tract infections over 20 years [37, 38]. The virus replicated very

slowly in tertiary monkey kidney cells, and the cytopathic effect produced was similar to that of RSV. Electron microscopy of the supernatant from the infected cells showed the presence of paramyxovirus-like pleomorphic particles with a diameter of 150 to 600nm with short projections of 13 to 17 nm length was observed. The nucleocapsid was not visible as in the case of other Paramyxoviruses like RSV and parainfluenza. It was inactivated by chloroform and did not agglutinate erythrocytes. Reverse transcriptase reaction using primers specific to other respiratory viruses did not produce positive results. The genomic pattern and morphological features classified it under the *Paramyxoviridae*, subfamily Pneumovirinae, and genus Metapneumovirus [39, 40].

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Genotypes of hMPV

The genomic organization of hMPV is similar to RSV; however, hMPV lacks the non-structural genes NS1 and NS2, and the hMPV antisense RNA genome contains eight open reading frames in slightly different gene order than RSV (viz. 3'-N-P-M-F-M2-SH-G-L-5') [41]. The hMPV is genetically similar to the avian metapneumoviruses A, B, and, in particular, type C.

Phylogenetic analysis of hMPV has demonstrated the existence of two main genetic lineages termed subtype A and B containing within them the subgroups A1/A2 and B1/B2 respectively. Genotyping based on sequences of the F and G genes showed that subtype B was associated with increased cough duration and general respiratory systems compared to hMPV-A [42]. The hMPV infects airway epithelial cells in the nose and lungs. In addition to interacting with heparan sulfate and other glycosaminoglycans, hMPV attaches to the target cell via its glycoprotein (G) protein. The hMPV fusion (F) protein encodes an RGD (Arg-Gly-Asp) motif that engages RGD-binding integrins as cellular receptors [43, 44, and 45] and then mediates fusion of the cell membrane and viral envelope in a pH-independent fashion, likely within endosomes.

Prevalence of hMPV

The hMPV is more commonly found in the pediatric population, predominately in children less than two years of age with an average age of 22 months. Approximately 90 to 100% of children are infected by hMPV by the age of 5 to 10 years old,

according to seroprevalence studies [46]. About 5 to 10% of pediatric hospitalizations result from hMPV causing acute lower respiratory tract infections. On average, children under six months of age with hMPV infection were three times as likely to be hospitalized compared to children between the ages of 6 months to 5 years [47, 48]. Re-infection may occur due to different viral genotypes or insufficient immunity from the initial infection. Although adults typically only experience mild flu-like symptoms, complications can be seen in the elderly, immunocompromised, or those individuals with chronic lung diseases [49, 50].

Clinical manifestations of hMPV

The hMPV infects the cells of the respiratory tract, including the mouth, nose, and throat, when it enters the body. Whenever these cells are infected, the immune system reacts and causes symptoms like pain, low-grade fever, cough, runny nose, headache, and sore throat. In some people, the disease can affect the bronchi or main airways. The spread of this virus can cause coughing and wheezing. Children under one year can experience decreased fever and weight loss [51, 52]. There is a possibility

that hMPV can cause severe illness requiring hospitalization in certain patient populations. These include immunocompromised patients and those with preexisting cardiac or respiratory conditions. These patients are more susceptible to developing acute respiratory failure requiring high-flow oxygen support, with some patients even deteriorating enough to require mechanical ventilation. Patients need to be admitted to the intensive care unit for close monitoring [53].

Diagnosis of hMPV

The diagnosis of hMPV infection can be approached using techniques like cell culture, nucleic acid amplification tests, antigen detection and serological methods. The hMPV replicates poorly in conventional cell cultures and reveals mild cytopathic effects [54]. Also, the technique is laborious and expensive and requires special procedures like trypsin addition. The various cell lines in which hMPV can be cultivated are tertiary monkey kidney cells, Vero cells, LLC-MK2-cells, BEAS-2B cells, A549

cells, and HepG2 [55]. The cytopathic effects are seen in tertiary monkey kidney, LLC-MK2 and Vero cell lines but only after 10 to 21 days of incubation. The shell vial culture technique, which includes centrifugation, short incubation and fluorescent staining, is a rapid method for identifying hMPV [56]. Direct immunofluorescence assay is a rapid method for identifying hMPV in which labelled antibodies are used to identify hMPV antigens in respiratory specimens. ELISA and microarray methods are also used but are not available commercially. Reverse transcriptase PCR assays amplifying the viral RNA is the most widely used and sensitive method employed to identify hMPV. Various regions viz F, N, G, L, and M are commonly used as targets. The F and N genes are considered more specific and conserved, suitable for identifying hMPV [57, 58].

Treatment for hMPV

No specific FDA-approved antiviral therapy is currently available for hMPV infection. Routine treatment includes symptomatic care, with respiratory support when required [59]. The primary mainstays of treatment are supportive measures. Anti-pyretic medications such as acetaminophen and ibuprofen

are given to those patients with fever. Intravenous fluid hydration is indicated if the patient appears dehydrated and cannot tolerate oral hydration [60]. Additionally, patients with hMPV may require supplemental oxygen support such as high flow nasal cannula or even mechanical ventilation in severe cases causing acute respiratory failure, especially in patients with preexisting respiratory or cardiac illness and those with immunocompromised. Most patients do undergo a full recovery. However, every patient with hMPV should be placed on droplet precautions to limit and prevent spread. There is no current vaccine available for hMPV [61, 62]. However, various vaccines against different structures of hMPV have been tested on non-human primates and rodents that appear promising. Still, none have been tested on human volunteers.

Prevention of hMPV

Control measures used for other respiratory illnesses should be emphasized: covering the mouth and nose with a tissue when coughing or sneezing, or coughing or sneezing into the upper sleeve rather than the hands, prompt disposal of used tissues and proper hand washing. Wash their hands often with soap and

water for at least 20 seconds. Avoid touching eyes, nose, or mouth with unwashed hands. Avoid close contact with people who are sick [63].

HUMAN BOCAVIRUS

Discovery and classification of HBoV

HBoV was discovered in Sweden in 2005 from the pooled cell-free filtrates of the NPA from children with ARTIs by molecular screening methods. HBoV belongs to the family Parvoviridae, subfamily parvovirinae and genus Bocavirus. The name Bocavirus was derived from the combination of the terms bovine parvovirus (BPV) and canine minute virus (CMV) and was based on the sequence similarities and genomic organization of these two close relatives [64]. The parvoviruses associated with human infections are parvovirus B19 (B19V), within the genus Erythroparvovirus, the apathogenic adeno-associated virus, belonging to the genus Dependoparvovirus, and the recently discovered parvoviruses 4 (PARV4) and 5 (PARV5), affiliated with the new genus Tetraparvovirus [65, 66]. The latter has not yet been associated with any clinical

significance; based on similarity, however, it has been allocated to the new genus Hokovirus [67, 68].

Genotypes of HBoV

The genus Bocavirus consists of bovine parvovirus (BPV), canine minute virus (CMV) and HBoV [69]. At present, there are four subtypes of HBoV (1 to 4) have been identified. HBoV 1 is the common subtype found in respiratory specimens, whereas the other three are commonly identified in gastrointestinal specimens. HBoV genotypes belong to Parvoviridae, subfamily Parvovirinae, and genus Bocavirus and cause infection in vertebrates exclusively [70, 71]. Parvoviridae also comprises the subfamily Densovirinae, which infects arthropods and shares no sequence homology with the other subfamily. The current classification of the International Committee on Taxonomy of Viruses database recognizes eight genera of the subfamily Parvovirinae: Amdoparvovirus, Aveparvovirus, Bocaparvovirus, Copiparvovirus, Dependoparvovirus, Erythroparvovirus, Protoparvovirus and Tetraparvovirus [72, 73].

Etiology of HBoV

The exact mode of transmission of HBoV infection is unknown. HBoV1 is presumed to be transmitted through inhalation of aerosols contaminated by the virus, similar to the mode of transmission of other parvoviruses. HBoV has been detected in urine and faeces and is also known to cause viraemia in the active stage of replication in the host. Nosocomial acquirement of HBoV infection has also been reported [74].

The pathogenesis of HBoV needs to be better established due to the need for standardized in vitro culture methods and animal models. There are studies across the world which suggest that HBoV is a respiratory pathogen. It is known to cause lower respiratory tract infection, and the symptoms associated are acute wheezing, bronchiolitis, fever and pneumonia. The occurrence of HBoV infection in immunocompromised (transplant) individuals has also been established [75]. HBoV DNA has been detected in the serum of patients with acute primary and severe infections [76]. Several studies indicate the

role of HBoV (especially subtypes 2, 3 and 4) as a gastrointestinal pathogen [77]. HBoV was also identified from urine specimens. The pathogenicity of HBoV can be assumed to be analogous to that of minute virus of canines (MVC). The virus enters the body through the respiratory tract, multiplies, and enters the bloodstream and, finally, the gastrointestinal tract through blood or ingestion. Viral shedding occurs either by coughing or defecation [78]. Reports suggest latent infection or the persistence of HBoV in patients. There is a high rate of co-infection of HBoV with other viruses [79, 80].

Prevalence of HBoV

In three studies, HBoV was detected via PCR in respiratory secretions from 1 of 126 (0.8%), [19] 3 of 202 (1.5%), [20], and 3.1% [21] of adults with respiratory tract infection [81, 82, 83]. Five cases were included in a case study of five adults with bocavirus-associated pneumonia [84]. Another series included one hospitalized and four outpatient cases of bocavirus-associated pneumonia in adults. The first report of HBoV and adenovirus co-infection in immunosuppressed and nonimmunosuppressed children in Mexico was published in

[85]. [84] Serologic responses to HBoV infection have also been documented. A 2008 study by Lindner found an immunoglobulin G (IgG) response in 280 of 299 (94%) adults, while immunoglobulin M (IgM) results were positive in 2 of 299 cases (1%) [85].

Clinical manifestations of HBoV

The clinical manifestations of HBoV infections are indistinguishable from that of other respiratory pathogens [86]. The common respiratory symptoms in HBoV-infected individuals are wheezing, respiratory distress, fever, cough, rhinorrhea, bronchiolitis and pneumonia. HBoV 1 has been identified in the NPA and middle ear fluid in children with acute otitis media [87]. Several studies have detected HBoV in stool samples of children with an acute gastrointestinal disorder, but its pathogenicity is uncertain [88, 89]. The risk factors associated with HBoV infection are similar to those for other respiratory viruses like congenital heart diseases, asthma, chronic obstructive pulmonary disease, immunosuppression, maternal smoking, premature birth, and winter birth. Daycare

centres and sewage or river water drinking may also be a factor for HBoV infection [90].

Diagnosis of HBoV

Currently, there needs to be an adequate culture method developed for the identification of HBoV. Hence the identification of the virus is commonly carried out from NPAs using conventional and real-time PCR assays, mostly targeting the NS1, NP1 and VP1/2 genes [91]. Other molecular methods are also used for detecting HBoV [92]. Real-time PCR is more sensitive, specific and time-saving when compared to conventional PCR assay methods. A wide range of commercial multiplex assay methods is also available to detect HBoV [93]. The EIA of IgG avidity has been developed to diagnose primary HBoV infection and immune activation accurately [94]. Antibodies against HBoV in serum can be detected using ELISA methods with virus-like particles (VLPs) of VP1 and VP2 [95, 96]. Immunofluorescence assays for detecting IgG antibodies and assays based on biomarkers are encouraging methods for identifying HBoV infections [97, 98, 99]. Initial screening of clinical samples (respiratory or stool) followed by the

subsequent serum sample will help in the accurate diagnosis of HBoV infection as the virus will be present in the blood during the active infective stage.

Treatment of HBoV

No specific in vivo or in vitro antiviral therapy or prevention by immunization is available for HBoV. There are only supportive measures present. The transmission of the virus through contaminated aerosols should be prevented using standard precautions [100, 101].

Prevention of HBoV

The preventive and infection control measures for HBoV1 are the same as for other respiratory viruses [102]. As these viruses infect the respiratory tract, the viruses are disseminated into the air by coughing. Although the major mode of transmission of respiratory viruses is through large droplets, transmission through contact and infectious respiratory aerosols of various sizes may also occur [103]. However, adequate hand hygiene, medical masks and gloves, and isolation precautions are general infection control measures for all respiratory viral infections.

Conclusion

ARTIs contribute to significant morbidity and mortality in children and adults worldwide. Over the last two decades, novel viral infections have dramatically emerged. A cautious thought of clinical features, diagnosis and epidemiology survey is necessary to direct the clinicians in decision-making on diagnosis and treatment. This review can help to understand the clinical presentations, diagnostic methods, available treatments and prevention of ARTIs.

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