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

Abstract

One of the major causes of morbidity and mortality among young children in developing nations is acute respiratory tract infections (ARTIs). Additionally, it is contagious, widely prevalent, and contagious from person to person. It poses a risk to young children, the elderly, and those with immune system disorders. Acute respiratory infections are thought to cause 2.6 million child deaths annually worldwide, according to the World Health Organization (WHO) [1]. Infections in children with human metapneumovirus (hMPV) and human bocavirus (HBoV) are linked to a high prevalence of AIRTs. It has been determined that hMPV is the second-leading cause of infant bronchiolitis, after the respiratory syncytial virus, of upper and lower respiratory tract infections. Although HBoV was first discovered in children's airways, the high rates of detection of other viral pathogens and the discovery of HBoV in stool raise doubts about the virus's significance in respiratory tract infections. Only a few studies, according to the published literature, have identified ARTIs or demonstrated the significance of early diagnosis and treatment of ARTIs. This review article aims to provide a thorough explanation of

the aetiology, epidemiology, clinical characteristics, diagnostic approaches, and management of hMPV and HBoV.

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

Introduction

“Viral and bacterial ARTIs, including the common cold, pharyngitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, and bronchopneumonia, are very common. High mortality rates and high economic costs are linked to these ARTIs” [2]. ARTIs are infections of breathing-related body parts, such as the lungs, sinuses, throat, or airways. The most frequent cause of paediatric respiratory illness is viral pathogens. Rhinoviruses, respiratory syncytial viruses, influenza, parainfluenza, hMPV, HBoV, measles, mumps, adenoviruses, and coronaviruses are among the culprits [3, 4]. Two crucial viruses for children with ARTIs are hMPV and HBoV. Children with high rates of mixed infection with other viral pathogens had the airways where HBoV was first

discovered. Questions have been raised about the proper function of HBoV as a cause of respiratory diseases in light of the virus's detection in stool [5]. “Children's upper and lower respiratory tract infections have been linked to the human papillomavirus (hMPV), which is second only to the respiratory syncytial virus as a cause of bronchiolitis in young children. These viruses are significant contributors to ARTIs in elderly and immunosuppressed patients. The hMPV is a member of the Paramyxoviridae family and has an eight-gene negative-sense single-stranded RNA genome that codes for nine different proteins” [6]. HBoV has single-stranded DNA and is a member of the Parvoviridae family [7]. The undiagnosed lower respiratory tract infections (LRTIs) and upper respiratory tract infections (URTIs) in children under the age of five are now thought to be caused by the hMPV and HBoV, which are now regarded as critical viral pathogens. Effective diagnostic tools have been created for clinicians, and strategies for treatment and prevention are being researched. This review focuses on the pathogenesis, clinical characteristics, epidemiology, and diagnostic methods for HBoV and hMPV.

Acute Respiratory Tract Infection

Infections of the respiratory tract are many different types, such as pleuritis lasting less than 30 days, sinus infections, and rhinitis [8]. “Infections of the respiratory tract can be bacterial or viral in origin, with viral infections being more common and typically only affecting the upper respiratory tract. Depending on which organs are impacted, ARTIs can be divided into upper respiratory tract infections (URIs) or lower respiratory tract infections (LRIs). There are three categories of clinical severity for ARTIs: mild, moderate, and severe” [9]. “The constant contact that children have with other children who might be virus carriers puts them in particular danger. Children frequently rub their eyes, do not regularly wash their hands, and put their fingers in their mouths, all of which contribute to the spread of viruses. Acute respiratory infections are more common in people who have heart disease or other lung conditions. Anyone whose immune system may have been compromised by another illness is vulnerable. Smokers are more vulnerable and experience more difficulty in recovering” [10].

In the winter and wet seasons, URIs is a common cause of hospitalization due to cough, coryza, sore throat, or hoarseness, frequently associated with acute febrile illnesses. In children attending daycare facilities and schools, the number of URI episodes per year can range from six to eight, and they can even be more frequent [11]. The majority of these URIs are self-limited, mild, and rarely life-threatening. Infants with URIs may become lethargic and have trouble feeding. Additionally, it can result in clinical conditions such as acute otitis media, asthma flare-ups, and LRIs like bronchitis, bronchiolitis, and pneumonia [12].

"The most common symptom of an LRIs is cough, followed by dyspnea or wheezing, chest discomfort and pain (usually occurring within 21 days of the onset of the illness) (e.g., sinusitis or asthma). The clinical symptoms of LRIs include tachypnea, fever, cough, hypoxia, bronchitis, bronchiolitis, and pneumonia" [13]. Chest radiograph changes include infiltrated hyperinflation and peribronchial cuffing. LRIs, particularly

pneumonia, cause the most severe illnesses and deaths in ARTIs. In children under five years of age and immunocompromised individuals, the severity of the disease is very high [14].

Prevalence of ARTIs

20% of children under the age of five die from ARTIs (most commonly pneumonia). As a result of neonatal pneumonia, the mortality rate for children under the age of five rises to 35-40%, or 2.04 million deaths per year. The countries of sub-Saharan Africa have the second-highest incidence of ARIs, and together they account for more than 80% of all cases worldwide [15]. “The morbidity and mortality of ARI in children are affected by a variety of social and environmental factors. Poverty, poor nutrition, inadequate housing, indoor air pollution (including parental smoking), poor ventilation, overcrowding, industrialization, sociocultural values, excessive and inappropriate use of antibiotics, a lack of essential health services, and a lack of awareness are some of the contributing factors” [16]. “It's also crucial to remember that a quarter of

child ARI deaths can be linked to passive smoking. According to the National Family Health Survey, which was conducted in 2019–2020, the prevalence of ARIs in the two weeks prior was 2.4% in urban areas and 3.8% in rural areas of Maharashtra state. Over two-thirds of all paediatric illnesses are caused by ARIs in Indian slum areas" [17]. "Almost 2, 65,000 hospital deaths of young children were attributed to ARI globally in 2010, with 99% of these deaths being reported in developing nations. Over two-thirds of all paediatric illnesses occur in urban slum areas. In India, ARTIs account for 15.9% of deaths among children aged 1 to 5 and 14.3% of deaths among infants, the majority of which are preventable. Because of the high rates of morbidity and mortality linked to ARTIs, the healthcare system continues to face significant difficulties in controlling individuals" [18].

Aetiology of ARTIs

"Infections of the respiratory tract can be brought on by a variety of microorganisms, the most common of which are bacteria and viruses. Most upper respiratory tract infections are caused by viruses, whereas bacterial infections can be either

primary or secondary to infections with measles, influenza, or respiratory syncytial virus (RSV)" [19]. "Streptococcus pneumoniae, Haemophilus influenzae (type B), Streptococcus pyogenes, and Staphylococcus aureus are the most prevalent bacteria that have been linked to ARTIs. Chlamydia pneumoniae and Mycoplasma pneumoniae are additional pathogens that cause atypical pneumonia" [20]. "A significant cause of morbidity and mortality is ARTIs in viruses. Respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses (PIV), adenoviruses, human rhinovirus (hRV), hMPV, HBoV, coronaviruses, and picornaviruses are the main viral etiological agents of ARTIs in all age groups" [21, 22]. RSV, hMPV, hRV, and PIV are the most common among them and are seasonal illnesses that can occur with or without co-infection in children under the age of five [23].

Diagnosis of viral respiratory tract infections

It is practically impossible to distinguish the cause of a respiratory tract infection based on clinical circumstances. In order to treat and stop the spread of viral respiratory infections, a quick and accurate diagnosis of the etiological agent is crucial

[24]. Based on the appropriate diagnostic approach selected by the medical staff when performing the test, laboratory diagnosis can significantly improve care. There are numerous techniques for identifying respiratory tract infections, including molecular-based nucleic acid amplification assays, immunofluorescence tests for antibody detection, conventional and quick cell culture techniques, and rapid antigen testing [25]. Nasopharyngeal aspirates, nasopharyngeal washes, nasopharyngeal swabs, and oropharyngeal swabs in viral transport media are among the different specimen types used to identify respiratory viruses. Tubes are used to collect sputum, endotracheal aspirates, and bronchioalveolar lavages. Each method's sensitivity is influenced by various elements, including the type of sample, the moment the sample was taken, the onset of the patient's symptoms, their age, the antigen target, and the characteristics of the virus [26, 27]. Immunocompromised individuals shed low titers of the virus over a long period, making non-molecular methods of detection challenging. As a result, molecular-based methods for nucleic acid amplification have gained popularity because they are quick and highly sensitive assays for

identifying respiratory viruses [28, 29]. Each method for detecting respiratory viruses has benefits and disadvantages.

“Although it takes days and frequently weeks to see results, the traditional tube culture method is useful for growing a wide variety of viruses, including new or unidentified viruses. The turnaround time has been lowered from 10 days to 24 hours over time thanks to modified cell culture techniques like the centrifugation-enhanced shell-vial method” [30]. “In comparison to conventional culture, shell-vial culture using combination cell lines enables the simultaneous detection of multiple respiratory viruses. It has similar sensitivity for parainfluenza 1-3 (87% vs 83%) and influenza A/B (78% vs 75%) and noticeably higher sensitivity for RSV (73% vs 42%)” [31].

“Rapid immunoassays (RIAs), which are frequently used in point-of-care testing (POCT), can deliver test results in less than 30 minutes and allow the test results to be incorporated into the clinical decision-making algorithm. Commercially available immunoassays have shown high sensitivity (93%) for the detection of RSV in the paediatric population. Further research

has shown that the sensitivity of RSV RIAs is comparatively higher for children (81%) than for adults (29%), according to a systematic review of published studies. Because paediatric patients frequently shed higher titers of respiratory viruses for a longer period of time than adults, the higher sensitivity can be attributed to this" [32, 33].

Serological tests can identify pathogen-specific antibodies, which typically appear two weeks after the initial infection. The majority of respiratory pathogens, including RSV, adenovirus, influenza A and B, parainfluenza 1-3 virus, etc., can be successfully detected by serological tests. With the exception of infants, for whom an antibody response is typically undetectable, it can also identify mixed infections in hospitalised children with acute respiratory infections [34]. Serological assays, in contrast to molecular techniques like RT-PCR, have been found to be significantly less sensitive for the detection of parainfluenza virus and adenovirus [35]. Compared to fluorescent antibody assay, RT-PCR can identify 40% more samples from paediatric patients who tested positive for at least one respiratory virus (FA). In epidemiological studies, FA

testing is beneficial in addition to RT-PCR because it improves the likelihood of detecting acute viral infections and has been used to precisely assess respiratory viruses other than influenza in children [36, 37, 38].

HUMAN METAPNEUMOVIRUS

Discovery and classification of hMPV

The hMPV was first discovered in 28 nasopharyngeal aspirates (NPA) taken from kids under five who had respiratory tract infections over a 20-year period in the Netherlands [39, 40]. The virus produced a cytopathic effect similar to RSV and replicated very slowly in tertiary monkey kidney cells. The supernatant from the infected cells revealed by electron microscopy contained paramyxovirus-like pleomorphic particles with diameters ranging from 150 to 600 nm and short projections of 13 to 17 nm in length. Unlike with other Paramyxoviruses like RSV and parainfluenza, the nucleocapsid was not apparent. It did not agglutinate erythrocytes and was inactivated by chloroform. Other respiratory virus-specific primers used in a reverse transcriptase reaction failed to yield promising results. The morphological characteristics and genomic pattern placed it

in the Paramyxoviridae, Pneumovirinae subfamily, and Metapneumovirus genus [41, 42].

Genotypes of hMPV

“The genomic organisation of hMPV and RSV is similar, but hMPV lacks NS1 and NS2, and the antisense RNA genome of hMPV has eight open reading frames in a slightly different gene order than RSV (3'-N-P-M-F-M2-SH-G-L-5')” [43]. The avian metapneumoviruses A, B, and type C in particular are genetically related to the human metapneumovirus (hMPV). The two main genetic lineages of hMPV, designated subtypes A and B, with their respective subgroups A1/A2 and B1/B2 have been identified through phylogenetic analysis. When compared to hMPV-A, subtype B of the virus was associated with longer-lasting coughs and general respiratory systems, according to genotyping based on the F and G gene sequences [44]. In the nose and lungs, the hMPV infects cells that line the airways. The glycoprotein (G) protein of hMPV, in addition to interacting with heparan sulphate and other glycosaminoglycans, is what allows it to affix to the target cell. In order to mediate the fusion of the cell membrane and viral envelope in a pH-independent manner, most likely inside endosomes, the hMPV fusion (F)

protein encodes an RGD (Arg-Gly-Asp) motif that engages RGD-binding integrins as cellular receptors [45, 46, 47].

Prevalence of hMPV

The hMPV is more frequently detected in children, mostly in those under two years old, with an average age of 22 months. According to seroprevalence studies [48], by the ages of 5 to 10, 90 to 100% of children have contracted hMPV. Acute lower respiratory tract infections brought on by hMPV account for 5 to 10% of paediatric hospitalisations. In general, infants with hMPV infection were three times more likely to be hospitalised than infants between the ages of 6 months and 5 years [49, 50]. Different viral genotypes or insufficient immunity from the initial infection may cause re-infection. Although adults typically only have mild flu-like symptoms, older people, people with compromised immune systems, and people with chronic lung diseases may experience complications [51, 52].

Clinical manifestations of hMPV

When the hMPV enters the body, it infects the cells of the respiratory tract, including the mouth, nose, and throat. The immune system responds whenever these cells become infected

and produces symptoms like pain, low-grade fever, cough, runny nose, headache, and sore throat. The disease may impact some people's bronchi or major airways. Coughing and wheezing may be brought on by the virus's spread. Reduced fever and weight loss can occur in children under one year old [53, 54]. In some patient populations, it's possible that hMPV can lead to severe illness that necessitates hospitalisation. Patients with compromised immune systems and those who already have cardiac or respiratory conditions are among them. These patients are more likely to experience acute respiratory failure that necessitates high-flow oxygen support; in some cases, these patients may even deteriorate to the point where mechanical ventilation is necessary. Patients must be brought into the intensive care unit for constant observation [55].

Diagnosis of hMPV

Techniques like cell culture, nucleic acid amplification, antigen detection, and serological methods can be used to diagnose hMPV infection. In conventional cell cultures, the hMPV reproduces ineffectively and exhibits only mild cytopathic effects [56]. Additionally, the method costs a lot of money and

calls for unique steps like trypsin addition. Tertiary monkey kidney cells, Vero cells, LLC-MK2-cells, BEAS-2B cells, A549 cells, and HepG2 cells are among the various cell lines in which hMPV can be grown [57]. Tertiary monkey kidney, LLC-MK2, and Vero cell lines all exhibit cytopathic effects, but only after 10 to 21 days of incubation. A quick method for determining hMPV is the shell vial culture technique, which incorporates centrifugation, brief incubation, and fluorescent staining [58]. A quick method for identifying hMPV is the direct immunofluorescence assay, which uses labelled antibodies to find hMPV antigens in respiratory specimens. Microarray and ELISA techniques are also employed but are not offered commercially. The most popular and accurate method used to identify hMPV is reverse transcriptase PCR assays, which amplify the viral RNA. Targets commonly used include the regions F, N, G, L, and M. The F and N genes are thought to be more specific and conserved for identifying hMPV [59, 60].

Treatment for hMPV

There is currently no specific FDA-approved antiviral treatment for hMPV infection. Symptomatic care is a regular part of

treatment, and when necessary, respiratory support is provided [61]. Supportive measures are the mainstays of treatment. Patients with fever are given anti-pyretic drugs like acetaminophen and ibuprofen. If the patient appears dehydrated and is unable to tolerate oral hydration, intravenous fluid hydration is recommended [62]. In severe cases resulting in acute respiratory failure, patients with hMPV may also need additional oxygen support, such as a high flow nasal cannula or even mechanical ventilation. This is particularly true for patients with pre-existing respiratory or cardiac disease and those who are immuno-compromised. The majority of patients do recover completely. To limit and stop spread, every patient with hMPV should be put on droplet precautions. For hMPV, there is currently no vaccine available [63, 64]. However, a number of vaccines that have been tested on rodents and non-human primates against various hMPV structures seem promising. However, none have been examined on human test subjects.

Prevention of hMPV

Emphasis should be placed on the preventative measures used to treat other respiratory illnesses, including covering the mouth

and nose with a tissue when coughing or sneezing, or coughing or sneezing into the upper sleeve rather than the hands, promptly throwing away used tissues, and washing hands properly. They frequently wash their hands for at least 20 seconds with soap and water. Do not touch your mouth, nose, or eyes with unwashed hands. Avoid being in close proximity to sick people [65].

HUMAN BOCAVIRUS

Discovery and classification of HBoV

By using molecular screening techniques, HBoV was identified in Sweden in 2005 from the combined cell-free filtrates of the NPA from kids with ARTIs. HBoV is a member of the genus Bocavirus, family Parvoviridae, and subfamily Parvovirinae. Based on the sequence similarities and genomic organisation of these two close relatives, the name Bocavirus was created by combining the terms bovine parvovirus (BPV) and canine minute virus (CMV) [66]. Parvovirus B19 (B19V), a pathogenic adeno-associated virus, a member of the genus

Dependoparvovirus, and the recently identified parvoviruses 4 (PARV4) and 5 (PARV5), members of the new genus Tetraparvovirus, are the parvoviruses linked to human infections [67, 68]. Although the latter hasn't yet been linked to any clinical significance, the new genus Hokovirus has been assigned to it based on similarities [69, 70].

Genotypes of HBoV

Bovine parvovirus (BPV), canine minute virus (CMV), and HBoV are all members of the genus Bocavirus [71]. There are currently 1 to 4 different subtypes of the HBoV virus. While the other three are frequently found in gastrointestinal specimens, HBoV1 is the most frequent subtype found in respiratory specimens. Only vertebrates can contract HBoV genotypes, which are members of the family Parvoviridae, subfamily Parvovirinae, and genus Bocavirus [72, 73]. The subfamily Densovirinae, which infects arthropods and has no sequence homology with the other subfamily, is part of the Parvoviridae family. Eight genera of the subfamily Parvovirinae are recognised by the current classification of the International Committee on Taxonomy of Viruses database: Amdoparvovirus,

Aveparvovirus, Bocaparvovirus, Copiparvovirus, Dependoparvovirus, Erythroparvovirus, Protoparvovirus, and Tetraparvovirus [74, 75].

Prevalence of HBoV

In three studies, HBoV was found using PCR in the respiratory secretions of adults with respiratory tract infections in 1 of 126 (0.8%), 3 of 202 (1.5%), and 3.1% cases [76, 77, 78]. A case study of five adults with bocavirus-associated pneumonia included five cases [79]. Adults with bocavirus-associated pneumonia were the subjects of one hospitalised and four outpatient cases in another series. Serologic responses to HBoV infection have also been documented. The first report of HBoV and adenovirus co-infection in immune-suppressed and non-immuno-suppressed children in Mexico was published in. In a 2008 study by Lindner, 280 of 299 adults (or 94%) had an immunoglobulin G (IgG) response, while 2 of 299 cases (or 1% of the population) had an immunoglobulin M (IgM) response [80].

Clinical manifestations of HBoV

Clinical signs and symptoms of HBoV infections are similar to those caused by other respiratory pathogens [81]. Wheezing, respiratory distress, fever, cough, rhinorrhea, bronchiolitis, and pneumonia are common respiratory symptoms in HBoV-infected people. In children with acute otitis media, HBoV has been found in the NPA and middle ear fluid [82]. Although HBoV has been found in stool samples from kids with acute gastrointestinal disorders in several studies, its pathogenicity is unknown [83, 84]. Similar to other respiratory viruses, HBoV infection is at risk for congenital heart conditions, asthma, chronic obstructive pulmonary disease, immunosuppression, maternal smoking, preterm birth, and winter birth. Infection with the HBoV may also result from day-care facilities, drinking sewage or river water, or both [85].

Diagnosis of HBoV

Currently, a suitable culture method for HBoV identification needs to be developed. As a result, real-time PCR assays are frequently used to identify viruses from NPAs, typically

focusing on the NS1, NP1, and VP1/2 genes [86]. For the detection of HBoV, other molecular techniques are also employed [87]. Comparing real-time PCR to traditional PCR assay techniques, real-time PCR is more sensitive, specific, and time-saving. There are numerous commercial multiplex assay techniques that can be used to find HBoV [88]. To accurately identify primary HBoV infection and immune activation, the EIA of IgG avidity has been developed [89]. ELISA techniques can be used to find HBoV antibodies in serum using VLPs of VP1 and VP2 viruses [90, 91]. Detecting HBoV infections can be made possible by immunofluorescence assays that look for IgG antibodies and biomarker-based assays [92, 93, 94]. As the virus will be present in the blood during the active infective stage, initial screening of clinical samples (respiratory or stool) followed by a subsequent serum sample will aid in the accurate diagnosis of HBoV infection.

Treatment of HBoV

There are no specific in vivo or in vitro antiviral treatments or vaccinations that can prevent HBoV. Only encouraging measures are in place. Standard safety measures should be taken

to prevent the virus from being spread through contaminated aerosols [95, 96].

Prevention of HBoV

Similar to other respiratory viruses, HBoV1 prevention and infection control measures are necessary [97]. Coughing causes these viruses to spread into the air as they infect the respiratory tract. Although contact and infectious respiratory aerosols of various sizes can also spread respiratory viruses, large droplets are the primary means of transmission for most respiratory viruses [98]. But general infection control measures for all respiratory viral infections include good hand hygiene, medical masks and gloves, and isolation precautions.

Conclusion

In adults and children around the world, ARTIs significantly increase morbidity and mortality. Novel viral infections have suddenly become more prevalent over the past 20 years. Clinicians must be guided in their decision-making regarding

diagnosis and treatment by a careful consideration of clinical features, diagnosis, and epidemiology research. The clinical manifestations, diagnostic techniques, available treatments, and prevention of ARTIs can all be better understood with the aid of this review.

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