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Human metaneumovirus(HPMV): A Comprehensive Review of Etiology,Pathogenesis, and Current Treatment Statergies.

Akanksha, Ashish Patial
Student
Gautam college of pharmacy, Bahra university

Abstract:Acute respiratory infections are frequently caused by the human metapneumovirus (HMPV), especially in young children, elderly people, and immunocompromised individuals. Nearly every child will have contracted HMPV by the time they are five years old. HMPV has been around for at least 65 years and is closely related to avian metapneumovirus subtype C. However, immunity is incomplete, and re-infections occur throughout adult life. Symptoms are similar to those of other respiratory viral infections, ranging from mild (cough, rhinorrhea, and fever) to more severe (bronchiolitis and pneumonia). The preferred method for diagnosis is reverse transcription-polymerase chain reaction as HMPV is difficult to culture. Although there have been many advances made in the past 16 years since its discovery, there are still no US Food and Drug Administration-approved antivirals or There are vaccinations to treat HMPV. Models of non-human primates and small animals have been developed for the investigation of HMPV. In addition to the animal models of HMPV pathogenesis and host immune response, this review will concentrate on the epidemiology, transmission, and clinical symptoms in humans.
Keywords: viral pneumonia, acute respiratory illness, and human metapneumovirus.

Etiology:

In 2016, the lipid-enveloped, single-stranded, negative-sense, non-segmented RNA virus known as human metapneumovirus was reclassified from the Paramyxovirdae family to the Pneumoviridae family and the Metapneumovirus genus. Infectious respiratory droplets spread it. Severe HMPV infection has been linked to immunocompromised status, early birth, and underlying chronic heart, lung, or neurological conditions.

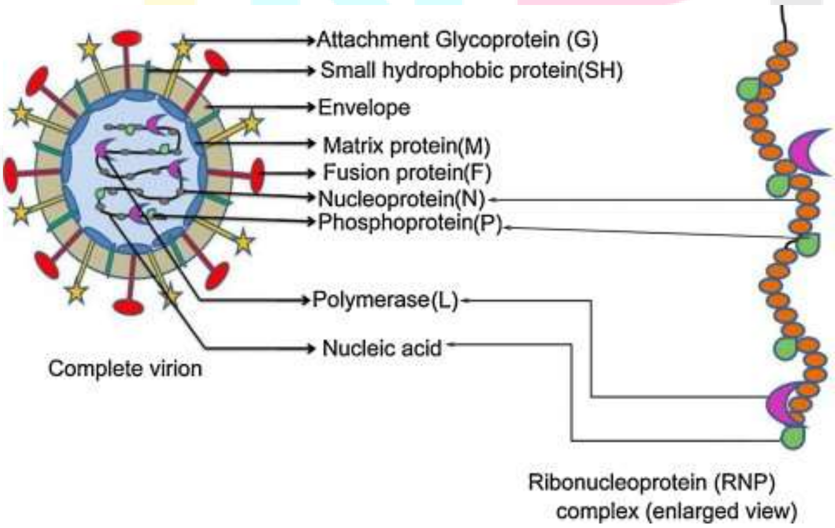
Introduction:

The respiratory virus known as Human Metapneumovirus (HMPV), which belongs to the Pneumoviridae family, can cause everything from minor colds to serious lung infections including pneumonia and bronchiolitis. HMPV is a major cause of respiratory disorders globally, especially in the winter and spring, although being less well-known than the flu or Respiratory Syncytial Virus (RSV). The virus is extremely dangerous, especially for susceptible groups like small children, the elderly, expectant mothers, and people with compromised immune systems. It's critical to spread awareness and take preventative measures because this virus might cause serious problems for them. Groups at High Risk for HMPV in Young Children: Serious respiratory diseases like pneumonia and bronchiolitis are particularly dangerous for infants and toddlers. Pregnant Women: Respiratory problems brought on by HMPV during pregnancy may pose a health risk to the mother and the unborn child.

Immunocompromised People: People who have compromised immune systems, whether as a result of illnesses or therapies like chemotherapy, are more likely to suffer from severe symptoms.

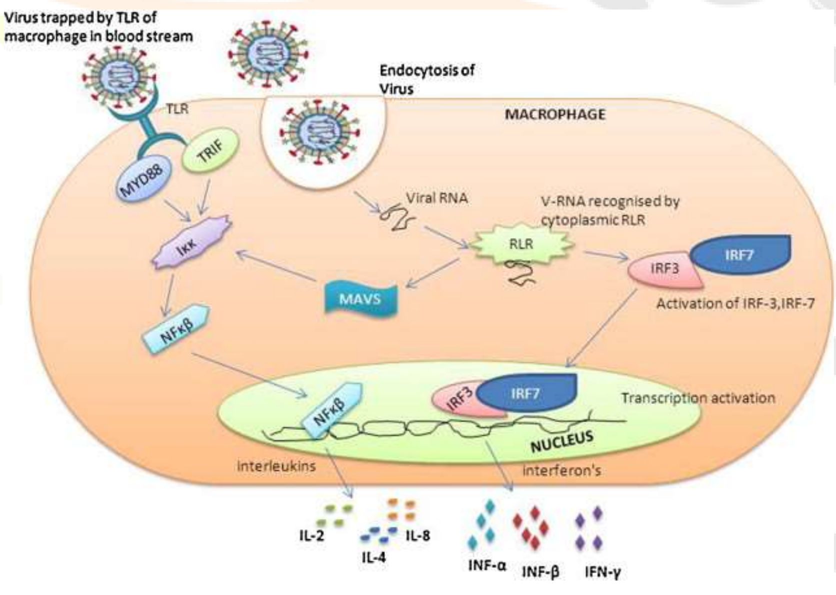
Molecular virology:

The hMPV virion ranges in size from 150 nm to 600 nm and is pleomorphic.5. hMPV's genomic orientation is similar to that of other Paramyxoviridae family members (Figure 1). The avian pneumovirus (aMPV), especially type C, and hMPV share a very similar genomic organization. With the exception of a few variations in gene order and the lack of the non-structural genes from the hMPV genome, the genomes of hMPV and hRSV are very similar (Figure 2). It has been determined that the two non-structural proteins (NS1 and NS2) of hRSV are strong multifunctional antagonists of the interferon (IFN) signaling pathways. The difference in the degree of host innate immune response seen during hRSV and hMPV infections may be due to the absence of these proteins.Eight genes that code for nine proteins make up the negative-sense single-stranded RNA that makes up the hMPV genome. From 3' to 5' end, the genes in the genome are arranged as follows: N–P–M–F–M2–SH–G–L. These proteins are the following: the viral polymerase (L protein), the small hydrophobic glycoprotein (SH protein), the attachment glycoprotein (G protein), the phosphoprotein (P protein), the matrix protein (M protein), the fusion glycoprotein (F protein), the putative transcription factor (M2-1 protein), and the RNA synthesis regulatory factor (M2-2 protein). M protein envelops the RNA core, which is encased in a lipid envelope. The three surface glycoproteins (F, SH, and G) are present in this envelope as spikes that range in size from 13 to 17 nm. The core nucleic acids form a nucleocapsid with a diameter of 17 nm and are linked to the P, N, L, M2-1, and M2-2 proteins. hMPV binds and fuses to cell surface heparan sulphate receptors with the aid of the G and F proteins. The viral nucleocapsid replicates after entering the host cell's cytoplasm following the fusion process. Together with the viral P, N, L, and M2 proteins, the freshly created viral genome assembles and travels in the direction of the host cell membrane. The F, SH, and G proteins are now visible on the membrane's outer side when the virion sprouts out of the cell.During virus replication, the P protein stabilizes the L protein, enabling the creation of the virus ribonucleoprotein (RNP) complex. Through its interactions with the RNP complex, the M protein is essential for virus assembly and budding. The viral genome is encapsulated by the N protein, which shields it from nuclease activity. By lowering the host's innate immunity, the M2-2 protein contributes significantly to virulence in addition to controlling viral transcription and replication.Similar to other Paramyxoviridae family members, hMPV uses particular ways to impede the host's innate immune system. By controlling pattern recognition receptors, including toll-like receptors, retinoic acid-inducible gene-like receptors, and other signaling molecules, the virus counteracts cellular reactions.Infection decreases antigen-specific T cell activation and disrupts dendritic cell function.



Pathogenesis:

A limited and delayed immune response, as well as delayed cytotoxic T-lymphocyte activity and poor viral clearance after primary infection, may be the cause of persistent hMPV infection.By infecting dendritic cells, hMPV prevents superantigen-induced T cell activation. As a result, long-term immunity generation is hindered and the proliferation of antigen-specific CD4+ T cells is limited.Cytokine responses are known to be modulated by respiratory viruses. The cytokines interleukin (IL)-12, tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, IL-8, and IL-10 are less effectively induced by hMPV than by RSV and influenza.71 In BALB/c mice and cotton rats, hMPV infection causes pulmonary inflammatory changes and raises the levels of interleukins (IL-2, IL-8, IL-4), interferon (IFN-α), macrophage inflammatory protein 1α, and monocyte chemotactic proteins in the lungs and bronchoalveolar lavage fluid. Perivascular and peribronchiolar infiltration and inflammation are further consequences of these alterations. Immunological and histological studies reveal the development of intra-alveolar foamy and hemosiderin-loaded macrophages, smudge cells, alveolar damage, and hyaline membrane disease.Cellular signaling that is dependent on toll-like receptors is known to be induced by hMPV infection. It is uncertain, therefore, how toll-like receptor-mediated signaling works to protect the host from pulmonary hMPV infection and pathogenesis. . According to a recent study, following intranasal infection with hMPV, MyD88-deficient mice exhibited considerably lower levels of pulmonary inflammation and related illness in comparison to wild-type C57BL/6 mice.Figure 4 depicts the molecular processes involved in the pathophysiology of hMPV. There is currently insufficient data to establish if hMPV can induce a systemic infection or if it only infects the respiratory system. A study that found hMPV in middle ear fluid and another that found hMPV RNA in the brain tissue of a patient who died of encephalitis provide some indication that the latter is feasible, but more research is required.



Molecular processes involved in the etiology of hMPV infection. Nuclear factor kappa beta (NFκβ) is activated when a virus attaches to the toll-like receptors (TLR) of macrophages and/or dendritic cells, activating multiple immune system adaptor molecules (TRIF and MYD88). The cytoplasmic RIG1-like receptor (RLR) detects the RNA of the internalized virus and activates NFκβ by activating the transcription activators interferon regulatory factors 3 and 7 (IRF-3 and IRF-7) and mitochondrial antiviral signaling protein (MAVS). Lastly, a number of interleukins and interferons are produced in response to NFκβ and IRFs.

Symptoms:

The following symptoms are frequently linked to HMPV: cough, fever, congestion of the nose, and dyspnea. Clinical signs of an HMPV infection are similar to those of other viruses that cause upper and lower respiratory infections, and they can develop into bronchitis or pneumonia. The median length of

sickness varies based on severity but is comparable to other viral respiratory infections. The anticipated incubation time is 3 to 6 days.

Transmission:

Transmission of HMPV from an infected individual to others can occur through:

Personal contact

- *Droplets from coughing and sneezing*
- *Touching a surface with HMPV on it and then*
- *Touching your mouth, nose, or eyes before washing your hands.*
  HMPV is thought to spread through direct or close contact with infected individuals or objects (fomites).Symptoms and disease presentation of HMPV are similar to those of other respiratory viruses causing both upper and lower respiratory tract infections.Symptoms can include cough, rhinorrhea, sore throat, and fever as well as lower respiratory tract symptoms such as wheezing, difficulty breathing, and hypoxia.The clinical diagnoses most commonly associated with HMPV are bronchiolitis and pneumonia.

Diagnosis:

hMPV has been grown and isolated using a variety of cell lines, including Vero cells, 75 HEp-2 cells, Hep G2 cells, 76 293 cells,29 and LLC-MK2 cells5. The most effective cell l:ines for hMPV development were a human Chang conjunctiva cell line (clone 1-5C4) and a feline kidney CRFK cell line, according to a recent study that used 19 distinct cell lines to cultivate hMPV.hMPV grows slowly in cell culture, and its late cytopathic effects range from minor syncytium development to cell rounding and separation from the culture matrix. Because of this, cell culture techniques are frequently combined with the use of anti-hMPV antibodies in direct fluorescence or ELISA-based assays to detect the hMPV antigen. When compared to real-time RT-PCR detection of hMPV, the sensitivity and specificity of cell culture detection techniques were determined to be 68% and 99%, respectively.78 Cell culture is rarely used to diagnose hMPV infection these days; instead, molecular techniques like RT-PCR and/or real-time RT-PCR are more frequently employed. In order to provide a tool that can detect a more comprehensive panel of respiratory viruses, two research have designed and assessed multiplex PCR assays.Now that multiplex RT-PCR (mRT-PCR) has been developed, a more sensitive and quick test for hMPV detection can be created.

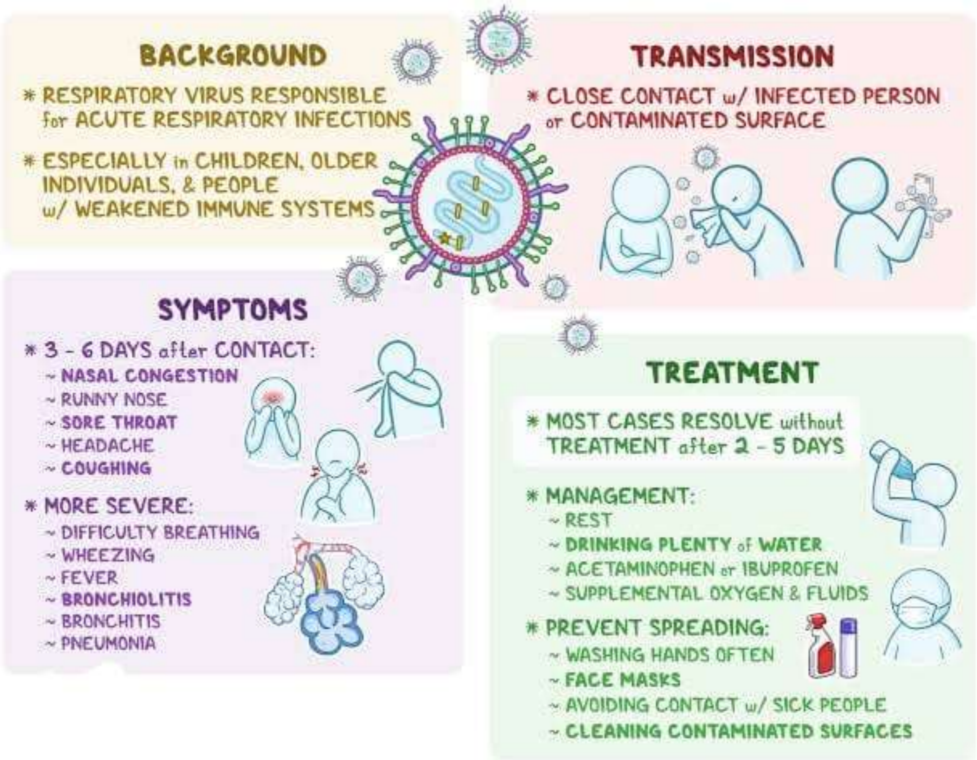
mRT-PCR methods have a sensitivity and specificity of 100% and 96%, respectively, compared to 54.6% and 100% for rRT-PCR.81 Another advantage of mRT-PCR is the ability to detect co-infections, even with very low viral loads that are undetectable via cell culture or immunostaining.

However, routine diagnostic RT-PCR for hMPV detection is still not possible in many clinical laboratories. The first line of diagnosis for hMPV infections is a mix of direct fluorescent antibody techniques and immunofluorescence assays, with RT-PCR performed on the negative samples for a

quick and precise diagnosis.For the quick diagnosis of hMPV in clinical labs, the availability of shell vial centrifugation culture and hMPV monoclonal antibodies will be very helpful in the future.

Treatment and control strategies:

The majority of hMPV infection therapies now on the market are supportive. However, several studies have suggested that ribavirin, immunoglobulin, fusion inhibitors, and tiny interfering ribonucleic acids could be used to treat and manage hMPV infection. Numerous hMPV vaccination candidates have been tested in non-human primate and rodent models. None have been tested on human volunteers yet, despite their encouraging results. When tested in mice, a heat-inactivated viral vaccination against hMPV increased lung illness, suggesting potential issues.



Conclusions:

In terms of morbidity and mortality, human metapneumovirus, or hMPV, is a relatively new virus1 that seems to be just as harmful as hRSV. Understanding the pathophysiology of hMPV and the molecular limitations causing severe disease is crucial for both treating infections and creating an effective vaccine against this significant respiratory virus. Recent research has provided some insight into the pathophysiology of hMPV and enabled us to assess live vaccination candidates through the use of reverse genetics platforms and animal models for hMPV infection. Clinical trials must now be started in order to assess the various hMPV infection therapy options.

Results :

191 (4.0%) of the 4730 examined specimens were positive for hMPV, and 62.8% of those 191 were found to be genotype A. Every year, hospitalized patients had a greater positive rate of hMPV than outpatients. The majority of children who tested positive for hMPV were less than five. The respiratory syncytial virus (RSV) and parainfluenza virus 3 overlapped or followed the peak of hMPV activity, which primarily happened in late spring. Lower respiratory tract infections accounted for 68.6% of hMPV-infected individuals, of which 79.4% required hospitalization. In children, upper respiratory tract infections were detected in 31.4% of cases. It was discovered that other respiratory viruses coexisted with hMPV in 9.4% of the positive samples.

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