Strategies to improve detection and management of human parechovirus infection in young infants

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Human parechovirus infections are the second most common cause of viral meningitis in children. These infections are most frequently seen in infants younger than 90 days. Clinical manifestations include encephalitis, meningitis, myocarditis, and sepsis, which can lead to serious neurodevelopmental sequelae in young infants. Molecular techniques, including PCR assays, are the preferred diagnostic methods and have contributed to an increase in reported cases, along with an increasing awareness of the causal role of human parechovirus in infant diseases. However, focused clinical and diagnostic investigations of human parechovirus in infants and the use of their results in management is varied, partly because of the scarcity of robust incidence data and spectrum of clinical presentations of the infection. In this Review, we outline clinical cohort and epidemiological studies that can be used to inform the evidence-based management of young infants with human parechovirus disease and identify key research priorities. An improved understanding of the pathogenesis and epidemiology of these infections is required to inform an evidence-based approach to diagnosis and treatment in the future.

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Introduction

Human parechoviruses (HPeVs) are small, non-enveloped RNA viruses in the Parechovirus genus within the Picornaviridae family.[1] Transmission occurs primarily via the faeco-oral or respiratory routes.[2] Most cases of HPeV infection occur in children and cause mild upper respiratory or gastrointestinal symptoms.[2] Less common, severe clinical manifestations of primary HPeV infection have been increasingly recognised, including encephalitis, meningitis, myocarditis, and sepsis.[3–7] Data suggest that infants with parechovirus encephalitis might have normal short-term outcomes but can develop long-term neurodevelopmental sequelae, such as gross motor impairment, communicative delay, cerebral palsy, and visual impairment,[8,9] which have been under-reported previously.

The extent to which molecular diagnostic methods for HPeV, such as PCR, are used varies greatly between hospitals and can be restricted to particular age ranges of patients, by presence of abnormal cerebrospinal fluid (CSF) measurements, or by the clinician's request; many hospital laboratories do not offer testing for HPeV. It is therefore likely that a substantial number, perhaps the majority, of HPeV infections are undiagnosed in acute, symptomatic presentations. Here we consider advances in the understanding of HPeV disease in infants to improve recognition of the full spectrum of HPeV infection, describe the clinical burden of disease, inform appropriate testing, and prioritise areas of future research.

Epidemiology of HPeV infections

The true overall burden of HPeV infections is not known. Studies have been broadly restricted to describing the incidence and burden of HPeV within specific, narrowly defined cohorts, such as single centres or during outbreaks.[10–14] It is difficult to make meaningful comparisons between cohort studies as the threshold to test, diagnostic techniques used, samples collected, populations analysed, and years studied all vary substantially. Thus, the type of robust longitudinal data that can help inform future studies of treatment and prevention are largely missing. To our knowledge there are no published data on the burden of HPeV disease in low-income and middle-income countries. Such data are required for identifying vulnerable populations, understanding why specific HPeV types are associated with severe disease, and quantifying the disease burden relative to other infectious causes of meningitis, encephalitis, and sepsis.

There are 19 known types of HPeV, but most cases of severe disease are in infants younger than 3 months and are caused by HPeV type 3 (HPeV3).[10,12,15,16–18] HPeV types 1, 4, and, 6 are associated with less severe disease than is HPeV3 and most frequently cause mild gastroenteritis in children younger than 2 years.[19–21] A longitudinal study that examined stool samples over 12 months in Norwegian children showed no association between acquiring HPeV1 infection and developing disease.[22] A case-control study in China showed no difference in HPeV1 viral loads between asymptomatic children and children admitted to hospital with gastroenteritis.[23] These findings suggest that HPeV1 isolated in the stool of infants with gastroenteritis might not always be the cause of disease.

Surveillance data from one region in the UK reported an increase in cases of HPeV during 2016 compared with previous years, despite using the same assay and clinical testing algorithm.[24] The National Enterovirus Surveillance Study (NESS) is a passive surveillance system that collects anonymous clinical and demographic data on enterovirus and HPeV from 17 laboratories across the USA.[25] During the period 2009–13, HPeV3 was the most commonly reported HPeV type and peaks of infections occurred in summer months in even-numbered years, as has been reported widely elsewhere.[4,11,22,26–28] This biennial cycle of infections is consistent with studies in Scotland and the Netherlands, which showed similar peaks of

HPeV3 infection in infants every 2 years,[2,29] the reasons for which remain unclear. A 4-year national laboratory surveillance study in Denmark analysed 6817 specimens collected from 4808 children with suspected enteroviral disease, who had fever and signs suggestive of meningoencephalitis, for which they attended hospital or primary care physicians.[20] In total, 202 (3%) specimens from 149 (3%) children were positive for HPeV. The overall median age of HPeV-infected infants was 39 days (IQR 21–71).

Between 2013 and 2014, 183 infants with HPeV3 disease were identified over a 4-month period in New South Wales, Australia,[15] highlighting the potential of HPeV to cause an epidemic, as well as the endemic disease previously described. Active enhanced surveillance mechanisms were developed after clinicians recognised clusters of cases. Methods of surveillance included clinicians identifying cases at three sentinel sites (active surveillance), laboratories reporting positive HPeV specimens from sentinel and regional laboratories to a central laboratory (passive surveillance), and emergency departments recording the number of febrile infants attending or admitted to the hospital (syndromic surveillance). Increased testing for HPeV at the earliest opportunity in febrile infants who were admitted to hospital ensured that the mean length of stay was reduced by 30% compared with before the outbreak, and thus, antimicrobials were discontinued earlier.

National surveillance of circulating HPeV through laboratory reporting of all positive samples to the national communicable diseases database is necessary to detect outbreaks, monitor novel circulating strains, inform current epidemiology, and potentially inform future treatment trials. If surveillance at a national level detected an outbreak, active enhanced surveillance (case finding by clinicians or laboratories at individual hospitals) should be performed to ensure early disease recognition.

Understanding disease patterns through host, viral, and environmental factors

Multiple cohort studies have shown that the prevalence of HPeV3-associated sepsis-like illnesses and CNS infections (encephalitis and meningitis) are highest in infants younger than 3 months.[5,12,15,16,30] The UK Childhood Meningitis and Encephalitis Study (UK-ChiMES) is the largest and most recent study to assess the cause of meningitis and encephalitis in children in the UK. An interim analysis from this study of more than 3000 infants and children younger than 16 years with suspected meningitis or encephalitis showed that enterovirus and HPeV were the commonest causes of viral meningitis in the paediatric population.[31]

HPeV3 infections are much less common than HPeV1 infections in women of child-bearing age and the general adult population, on the basis of blood and CSF microbiological sampling studies from Europe.[4,32,33] Seroprevalence studies have reported that antibodies against HPeV1 are present in approximately 30% of infants aged 1 year, 70% by age 2 years, and in 92–99% of adults.[33,34] By contrast, the seroprevalence of HPeV3 is low in children (<2·7% in infants younger than 3 months) and only increases to 10–13% by adulthood.[33] The absence of maternal antibodies that might limit the susceptibility and systemic spread of HPeV3 might potentially account for the high rates of severe disease observed in young infants. A study in Japan measured titres of neutralising antibody against HPeVs in 175 cord blood samples from neonates, and in serum samples from neonates and young infants with severe clinical manifestations related to HPeV3 infection.[35] Although systematically higher seroprevalence of HPeV3 of up to 60% was observed in the Japanese adult population than was previously observed in Finland and the Netherlands,[34–37] negative or low antibody titres (<1:16) were observed in all HPeV3-infected infants at disease onset, supporting the hypothesis that maternal antibodies might help protect young infants from developing HPeV disease.

It has been proposed that HPeV types might differ in their virulence.[38,39] There is some virological evidence for such a hypothesis; HPeV3 replicates more rapidly than HPeV1 in vitro in neuronal cells, and this tendency might equate to a neuropathogenic phenotype in vivo.[39] HPeV3 strains lack the arginine-glycine-glutamic acid sequence at the capsid protein that is used for virus entry and found in HPeV1. The use of an alternative entry receptor might thus modify the cellular tropism and neuropathogenicity of HPeV3.[38] A study of autopsies of two preterm infants with HPeV3 infection, who had significant periventricular white matter changes, showed that the infected cells were confined to the meninges and the smooth muscle of pulmonary vessels.[40] The authors suggested that in the absence of infected periventricular cells the encephalitic change seen could be due to vascular compromise. A study characterising innate immune responses in 11 infants with HPeV meningitis showed that most cytokines and chemokines remained in the control range because of early disruption of the interferon cascade.[41] The decreased immune response seen in infants with HPeV meningitis might account for the absence of CSF pleocytosis seen in infants with HPeV meningitis.

A nationwide cohort linkage registry study on birth and sibling relationships in Denmark between 2009, and 2012, showed an increase of nine times in the likelihood of a younger sibling (younger than 5 years) contracting HPeV3 infection (but not other types of HPeV infection) compared with first-born children.[42] The authors showed that the younger sibling was more likely to be affected by HPeV3 and non-HPeV3 infections if there was a smaller age gap between siblings. This study suggests that older siblings play an important role in transmission of HPeV to their younger siblings and appropriate precautions for infection control are needed to prevent and reduce the spread of the virus within households and in hospitals. Similar findings

were noted during an outbreak of HPeV3 in Japan.[43] This study included 43 young infants who were hospitalised with sepsis or sepsis-like illnesses, with HPeV3 detected in CSF. Clinical data and stool samples were collected from close relatives. In total, 22 (51%) of 43 of hospitalised infants had been in contact with family members who had symptoms indicative of viral infection (ie, fever, diarrhoea, and upper respiratory tract infection signs) and were positive for HPeV. Another case series describing an outbreak of HPeV in a neonatal intensive care unit in Kansas reported that 11 out of 23 infected neonates had a symptomatic household contact (with rash, gastrointestinal, or respiratory symptoms) in the week before the onset of symptoms.[44] These findings should emphasise the importance of preventive measures, including hand hygiene, in households with young infants to prevent the transmission of viral pathogens.[45,46]

In summary, HPeV3 disease is most commonly seen in infants younger than 3 months. This prevalence might result from host (eg, lack of maternal antibodies), viral (eg, HPeV3 being a particularly neuropathogenic type), and environmental factors (eg, presence of older siblings in the family). Understanding differences in HPeV1 and HPeV3 pathogenesis (ie, receptor usage for HPeV3, infectivity in endothelial vascular cells using 3D models) might be necessary to inform any future treatment studies.

Clinical manifestations and outcomes of HPeV disease

HPeV infection causes a wide spectrum of clinical manifestations, most commonly fever, irritability, poor feeding, tachycardia, and rash (table). Multiple studies have shown that HPeV3 can cause severe sepsis-like illness.[5,13,49,50–52] Fever, reduced feeding, neurological symptoms (irritability and seizures), and rash are the commonest clinical signs in children admitted to hospitalised. Although leucopenia with spiking fever has been proposed as a specific feature associated with HPeV infection,[10,53] there are no clinical features that clearly distinguish HPeV3 infection from other viral and bacterial causes of sepsis in young infants; hence, a low threshold is needed for the testing of blood and CSF samples for HPeV in unwell infants younger than 6 months. Previous studies also emphasise that the absence of CSF pleocytosis is a common feature in HPeV meningoencephalitis, so the presence of an increased white blood cell count in CSF should not be used as a criterion to identify whether HPeV testing should be done. HPeV rarely causes clinical disease in adults but has been associated with myalgia in a small observational study in Japan, acute flaccid paralysis in a series of six patients in Jamaica, and severe sepsis in an elderly Canadian woman.[54–56]

A maculopapular rash is a common sign of HPeV infection. Shoji and colleagues showed that most infants

	Khatami et al, Australia[10] (n=118)	Vergnano et al, UK[11] (n=50)	Wildenbeest et al, Netherlands[47] (n=138)	Sharp et al, USA[48] (n=66)	Selvarangan et al, USA[12] (n=58)
Demographics	Retrospective clinical cohort aged <12 months (median 39 days old) over 4 months in 2013, across five hospitals during an HPeV outbreak; 75% of infants were <60 days old; 55% were male; 25% were admitted to an ICU	Retrospective clinical cohort aged <12 months between 2008, and 2012, in three hospitals; 48% of infants were <30 days old; 56% were male; 50% were admitted to an ICU	Universal molecular study of stool samples collected between 2004, and 2008, in two hospitals; 43% of infants with HPeV1 and 69% with HPeV3 were <6 months old; 59% of infants with HPeV1 and 65% with HPeV3 were male; number of ICU admissions is unknown	Universal molecular study in CSF samples collected over 5 months in 2009, in one hospital; 100% of infants were <5 months old; 60% of infants were male; 12% of infants were admitted to an ICU	Universal molecular study in CSF samples between 2006, and 2008, in a tertiary centre; infants had a mean age of 6·6 weeks; 70% of infants were male; number of ICU admissions is unknown
Virus type (% of infants)	HPeV3 (100%)	Not tested	HPeV1 (81%), HPeV3 (19%)	HPeV3 (51 [77%] of 66 positive CSF specimens)	HPeV3 (52 [98%] of 53 positive CSF specimens)
Main clinical features at presentation (% of infants)	Tachycardia (98%); fever (94%); irritability (93%); tachypnoea (91%); poor feeding (70%); poor perfusion (55%); fever (94%)	Poor feeding (96%); fever (82%); appeared unwell (74%); irritability (64%); mottling (54%)	HPeV 1: gastrointestinal symptoms (97%); URTI 39%; HPeV3: gastrointestinal symptoms (80%); fever (53%); skin symptoms (37%); neurological symptoms (32%); fever 34%	Fever (91%); irritability (91%)	Irritability (98%); fever (95%); non-specific rash (59%)
Major laboratory measurements at presentation (% of infants)	Absent CSF pleocytosis* (96%); CRP <10 mg/dL (69%); APTT >50 s/ PT≥1·5 s (54%); white blood cell count <1×10⁹ cells per L (19%); platelets <150×10⁹ platelets per L (10%); AST/ALT >100 U/L (33%)	Absent CSF pleocytosis (95%); deranged clotting (95%, only 18 infants tested); CRP <10 mg/dL (80%); AST/ALT >100 U/L (45%)	Not measured	Absent CSF pleocytosis (98%)	Absent CSF pleiocytosis (88%)
Follow-up after discharge	Four infants showed gross motor delay at 6-month follow-up	One infant died, six (32%) of 19 showed developmental delay, and three showed identifiable neurological sequelae until age 18 months	Not measured	Not measured	Not measured

HPeV=human parechovirus. ICU=intensive care unit. URTI=upper respiratory tract infections. CSF=cerebrospinal fluid. CRP=C-reactive protein. APTT=activated partial thromboplastin time. AST=aspartate transaminase. ALT=alanine transaminase. *Defined as white blood cell count in CSF of >12 cells per μL in a neonate younger than 1 month.

Table: **Clinical and laboratory features of the five most recent and largest HPeV clinical cohort studies to date**

with HPeV3 sepsis-like syndrome[16] developed an erythematous palmar and plantar rash within 5 days after the onset of fever.[28] The rash was limited to the distal extremities and no other systemic rash was present. A small retrospective study of children with meningitis and encephalitis in Germany showed that in 12 young infants, HPeV was strongly associated with maculopapular rash and seizures (p<0·0001).[57] These data suggest that HPeV should be tested for in febrile infants with a maculopapular rash.

HPeV has been associated with myocarditis in case reports of infants aged 6 weeks, 5 months, and 14 months,[47,48] but there are no robust cohort data describing how common cardiac sequelae are in HPeV infection. Myocarditis should be considered a rare but serious event in acutely unwell infants.

Small studies have also shown that HPeV can cause white matter involvement of the brain,[58] which can lead to physical and learning disabilities, persisting in one child until age 7 years.[11,58] A Dutch group showed that white matter abnormalities occurred in nine out of ten children who presented with seizures and had HPeV meningoencephalitis (diagnosed on the basis of positive CSF PCR). Results of MRI scans showed subcortical white matter changes, which involved entire tracts of fibres.[58] Typical neurodevelopmental outcomes occurred in five children and severe sequelae in the other four (cerebral palsy, learning disability, epilepsy, and possible developmental abnormalities).

A prospective cohort study in Australia showed the importance of close follow-up in children with HPeV meningoencephalitis, even in those with good clinical short-term outcomes.[8] Seven of nine children with confirmed HPeV encephalitis had white matter diffusion restriction on MRI (three of whom had normal cranial ultrasound scans). Although only three children had any sequelae noted at the time of hospital discharge, by 12 months five of the children showed neurodevelopmental sequelae: three were severe (two with cerebral palsy and one with central visual impairment) and two had gross motor delay.

These are similar findings to other small sized cohort studies. Vergnano and colleagues reported that ten out of 12 young infants with meningoencephalitis had white matter changes and Khatami and colleagues reported similar results for four out of 11 young infants.[10,11] However, MRI was done in unwell infants who had clinical indications for neuroimaging. The extent of white matter damage in mild clinical cases is unknown, and it might be that some children will have neurological abnormalities, which might then lead to subtle deficits later. These data suggest that MRI should be carefully considered in patients with HPeV meningoencephalitis. Close follow-up after discharge for 24 months is warranted to test for neurodevelopmental sequelae. Long-term sequelae in infants with sepsis-like disease is not yet fully understood.[10]

It is still unknown how many infants die because of HPeV disease as clinical samples are not routinely taken and tested for HPeV.[59,60] The largest study to specifically assess the case fatality rate of HPeV reported that in approximately 18 (4%) of 426 specimens taken from autopsies, deaths were due to HPeV.[61] Most studies of deaths from HPeV are case reports of infants with severe white matter abnormalities and HPeV3 infection.[40,62] Histopathological findings from these case reports suggest that the virus disrupts blood vasculature through haemorrhage and thrombosis. Testing for HPeV should be done routinely when investigating infectious causes of infant mortality.

HPeV infection should be highly suspected in unwell febrile infants younger than 6 months. MRI to assess white matter involvement should be done in young infants with suspected encephalitis, who should be followed up until at least age 2 years. MRI should also be considered in infants with neurological signs (eg, irritability, lethargy, seizures). Infants with meningitis and no parenchymal involvement have been shown to have good clinical outcomes.[63,64]

Improving diagnosis of parechovirus infections

A single HPeV gene is divided into regions coding for structural proteins VP0, VP3, and VP1, which assemble to create the virus particle, and the replication-associated proteins such as the RNA polymerase (3D) and the protease (2C). Areas of the genome that are targeted by PCR include the 5-untranslated region (5′UTR) for virus detection and VP1 and VP3 for virus typing (figure).

There have been several advances in the development of PCR tools to improve sensitivity and speed of testing for HPeV.[65–70] PCR methods target the 5′UTR of HPeV, as this region is most conserved in sequence, whereas the more genetically variable structural coding regions are used for typing (VP3 and VP1, figure).[71,72] Most commercial and in-house assays are designed to simultaneously detect HPeV and enterovirus.[66,69,72,73] It is important that an assay has been shown to detect all HPeV types, with sensitivity approaching 400 copies per mL in CSF.[72] The detection of HPeV in CSF samples is regarded as diagnostic of disease, whereas, it is less clear whether detection of HPeV in stool samples is associated with clinical disease.[74,75] However, a Dutch group did a retrospective study investigating the correlation between positive PCR findings in stool samples and clinical symptoms.[47] The authors showed that a positive HPeV3 stool sample was associated with neurological symptoms and sepsis-like illness and that the virus was more commonly detected in infants younger than 6 months than in older children. The same group showed that HPeV shedding in the faeces occurred up to 6 months after onset of symptomatic infection.[76] Faecal viral loads could not be used to differentiate between severe or mild disease, nor between symptomatic or asymptomatic infection.

The uptake of RT-PCR assays to detect HPeV varies across UK laboratories. 22 out of 31 large paediatric

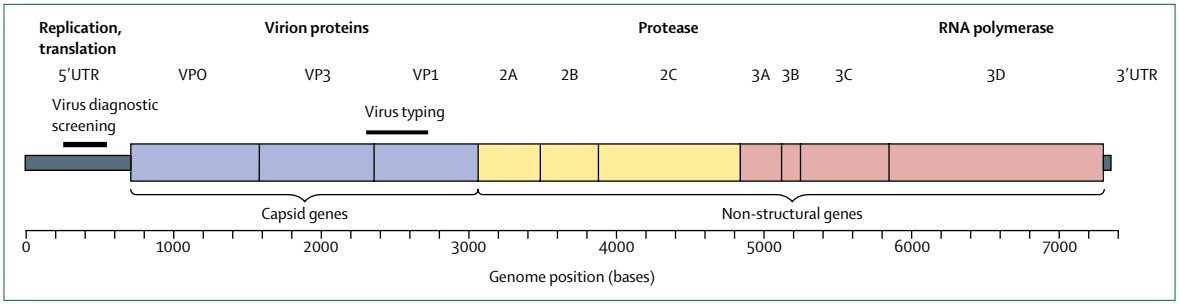

Figure: **Diagrammatic view of the parechovirus genome**
UTR=untranslated region.

centres in the UK taking part in the UK-ChiMES study varied in local practice regarding HPeV testing (Sadarangani M, unpublished). In total, nine (40%) of 22 centres had no standard process to test for HPeV and only tested samples on a case-by-case basis. Only six centres (27%) tested all CSF samples (regardless of white blood cell count in CSF). Five centres (22%) tested samples if requested by a clinician (highlighting the importance of awareness of the clinical signs associated with HPeV infections) and a further five centres tested if there was any evidence of CSF pleocytosis (despite the number of published studies showing the presence of severe HPeV infection in the absence of CSF pleocytosis (Sadarangani M, unpublished).

Increased use of PCR in HPeV testing has the potential to directly affect clinical care of individual patients. A study in France compared the effect of PCR in managing patients during two separate outbreaks of echovirus type 30 in 2000, and 2005, in a single tertiary unit.[77] In 2000, cell cultures that were inoculated with CSF samples gave a positive result in 10 days and a negative result in 14 days at the earliest. PCR was used during the 2005 outbreak, and reduced mean hospital length of stay from 5·4 days to 2·2 days, saving €322 000. The largest study to assess the effect of using PCR to detect enterovirus in CSF on length of hospital stay in infants younger than 90 days was done over six enteroviral seasons in a single tertiary US centre.[78] The authors showed that there was a decrease in length of stay of 1·5 days and a 33% reduction in antimicrobial use in children who test enterovirus positive in CSF compared with children who were enterovirus-negative on PCR. Even without targeted treatment for HPeV infections, early identification of infections in infants might have similar clinical and economic benefits, eg, stopping use of unnecessary antimicrobial drugs, minimising extensive investigations, and reducing the length of hospital stay. The costs of sensitive multiplex PCR assays continue to decline and results can be obtained within hours of receiving the sample in most diagnostic laboratories.[65,79,80] It should be emphasised that multiple studies highlight the fact that HPeV is routinely detected in CSF in the absence of pleocytosis.[8,13,28,66,81–83] CSF samples should therefore be routinely tested for HPeV in infants younger than 6 months (for whom the clinical burden is highest) during an acute illness, irrespective of CSF white blood cell count. Blood, stool, and respiratory samples should also be considered for testing in young infants to increase the diagnostic yield.

A positive diagnosis of HPeV infection would allow cessation of antibiotic therapy and might thereby facilitate early discharge from hospital.[84] Additionally, testing for HPeV using PCR in blood samples of infants who are being assessed for infection would increase the diagnostic yield, as higher viral loads are seen in serum than in CSF.[51] A gradual shift in laboratory testing from pathogen-specific (ie, requiring a clinician to suspect the presence of HPeV and request PCR) to syndromic (ie, submitting samples for multiplex meningo-encephalitis or sepsis panels, which include HPeV in a diagnostic array) will probably further improve detection. Increased testing of infant CSF and blood samples is required to clarify the disease epidemiology and the full range of clinical syndromes, and will enable improved targeted testing in the future.

Therapeutic interventions in development

The manufacture of antivirals against RNA viruses needs to consider the high mutation rate of these viruses.[85] There is no approved antiviral therapy for the treatment of HPeV disease and no phase 2 or phase 3 treatment trials are in progress. Pleconaril has been shown to inhibit the replication of some enterovirus types and rhinoviruses[86] by inhibiting the uncoating of viral RNA and progeny virions during enterovirus replication. However, structural studies suggest that the binding site is blocked in HPeV3.[87] These findings have been supported by a clinical report that suggests pleconaril has no effect on HPeV replication.[88]

Intravenous immunoglobulin has been shown to have some effectiveness in treating severe diseases, similar to its use in treating severe enterovirus infection in neonates, but data have been restricted to case reports and not controlled studies.[89,90] A report showed some success in using intravenous immunoglobulin to treat an infant with severe myocarditis caused by HPeV1 and dilated cardiomyopathy.[91] The infant had an increase in HPeV1 antibody titres after treatment with intravenous immunoglobulin, which correlated with an improvement

Search strategy and selection criteria

We searched PubMed for articles published from January, 1966, to September 2017, with the terms "human parechovirus", "parechovirus" and "prevalence", "seroprevalence", "incidence", "clinical features", "epidemiology", "diagnosis", or "treatment". We also searched reference lists of identified studies. The final choice of literature and references included were based on relevance to this topic. Only articles published in English were selected.

in clinical presentation. Karelehto and colleagues examined the titres of anti-HPeV3 antibodies in Dutch and Japanese intravenous immunoglobulin preparations and showed there was a decline in neutralisation efficiency in batches against clinical strains identified after 2005.[92] The authors suggested that the loss of neutralisation capacity might reflect the IgG obtained from adult plasma donors who had not been infected with HPeV3 strains identified after 2005.

A Finnish group have developed two monoclonal antibodies that act against HPeV1.[93] The antibodies prevent aggregation and inhibit RNA genome uncoating and replication in the cell. A state-of-the-art reconstructive design of the HPeV3 genome suggests that a highly ordered region of the virus might have a role as a treatment target for neutralising antibodies.[87] Antibody-based therapies are a potentially feasible option to treat HPeV, as the therapies have restricted sequences. However, to date, no HPeV3 monoclonal antibody has been developed, which could be used to help treat the commonest disease-causing type in young infants.

Conclusion

HPeVs are an increasingly recognised cause of morbidity in infants. This increase is probably due to the introduction of highly sensitive molecular techniques to detect viruses and changes in disease epidemiology (variations in virulence or incidence of the virus in susceptible populations), as shown by outbreaks in Australia and increased rates of disease in the UK. Routine hygiene measures should be reinforced by health-care workers to prevent transmission from adults and siblings to infants younger than 6 months. Clinicians should be aware of the potential causal role of HPeV3 in infant disease. In the assessment of a febrile infant, CSF, blood, respiratory, and stool samples should be submitted for HPeV testing. In turn, laboratories should routinely test for HPeV in CSF samples in infants younger than 6 months. These procedures will improve the diagnostic yield and the success rate of identification. Detecting HPeV in affected infants should be encouraged as part of good antimicrobial stewardship, minimising unnecessary investigations and potentially reducing length of hospital stay, thus being of clinical, economic, and public health use. Furthermore, Australian data have highlighted the importance of carefully following up affected infants with HPeV encephalitis to assess for neurodevelopmental sequelae and consider a brain MRI. There are no antiviral or vaccine candidates in the pipeline, partly because of the lack of longitudinal data informing such trials. Active enhanced surveillance is essential to monitor outbreaks and monitor long-term disease trends, as well as contribute towards the understanding of the clinical burden of HPeV infection. Future studies should seek to improve our understanding of pathogenicity (eg, which strains are responsible for causing outbreaks and severe disease), host immunity (eg, which infants are most likely to develop disease), and antiviral candidates.

Contributors

SK and MS conceptualised the paper and did the literature review and devised the table. SK wrote the first draft of the paper. PS and HH devised the figure. PS, HH, and AJP contributed to the literature review and provided scientific content to each section of the manuscript. All authors reviewed and approved the final version of the manuscript.

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