Enteroviruses & Parechoviruses rashes and beyond

Alison M Kesson

Head, Infectious Diseases and Microbiology

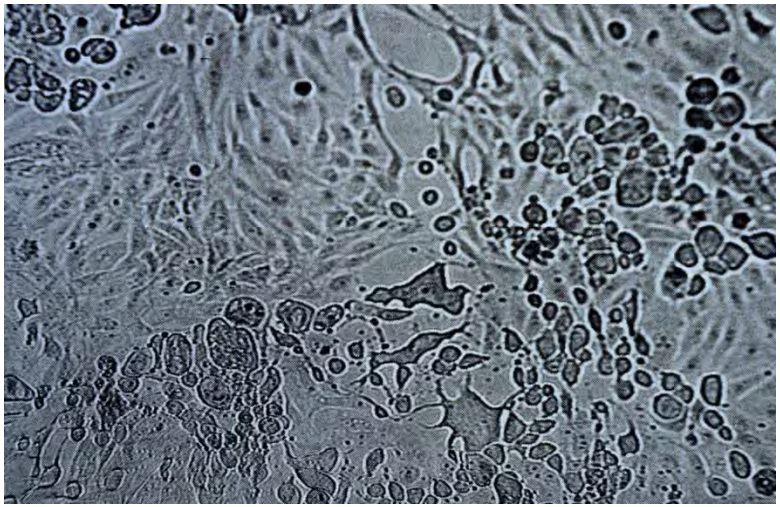
Enteroviruses

Enteroviruses

- Human enteroviruses (EV) are members of the *Enterovirus* genus and family of *Picornaviridae.*
- As a single-stranded +sense RNA molecule, the picornaviruses have a complex 5′-non-coding region that facilitates ribosomal entry and translation of a single polypeptide protein.
- Cleavage of this poly-protein releases both enzymatic and structural proteins.

Enteroviruses

- Stable against lipid solvents, detergents, 70% ethanol and propanol.
- Readily inactivated at 42^{o}C, UV and drying
- Cytolytic in cell culture with rounding, shrinking, nuclear pyknosis, refractility and cell degeneration.



Enterovirus Classification

- Originally classified into four groups:
  - polioviruses,
  - coxsackie A,
  - coxsackie B, and
  - echoviruses.
- Based on the
  - physical structure
  - the tissue cultures in which they would grow
  - their pathogenesis in humans and experimental animals.

Enterovirus Classification

- Enterovirus genus has five species of human enteroviruses: human enteroviruses A, B, C, and D.
- Polioviruses are now in human enterovirus C
- Viruses within a species can recombine to produce viable hybrids

Cluster	Members
A	CAV serotypes and Enterovirus 71
B	CAV-9, CBV serotypes 1-6, echoviruses, Enterovirus 69
C1	Polioviruses 1-3
C2	CAV serotypes
D	Enteroviruses 68 and 70

Enterovirus Classification

- Enterovirus species have
  - Greater than 70% amino acid identity in viral capsid P1 coding regions and non-structural proteins 2C aand 3CD
  - Limited range of natural hosts and host receptors
  - Genome GC content varying by less than 2.5%
  - Share compatability in proteolytic processing, replication, encapsidation and genetic recombination

Enteroviruses

- Most infections asymptomatic
- Often mild non-specific disease
- Serious illness especially infants and immunocompromised especially with low IgG
- Disease caused by cytopathic effects on tissue or host immune response.
- Echo virus 22 and 23 now parechoviruses 1 and 2.

Pathogenesis

- Incubation time for enteroviruses is 2-35 days with average 7-14 days
- Primary site of infection is epithelial cells of respiratory or GI tracts and lymphoid follicles of small intestine
- Replicate at primary site with viraemia leading to secondary site of tissue infection.
- Dissemination – exanthems, myalgias or multi-organ disease in neonates.

Asymptomatic infection

- Most enterovirus infections are asymptomatic, there are estimates of 10–15 million symptomatic infections per year in the United States, suggesting that most humans are infected at least once a year.
- Most clinical association made from studies of outbreaks.
- Link of EV infection with disease made with caution
- Inapparent infections and prolonged shedding in faeces are common.
- Inferred link between disease and EV if virus isolated from sterile site corresponding to clinical symptoms

Clinical Syndromes

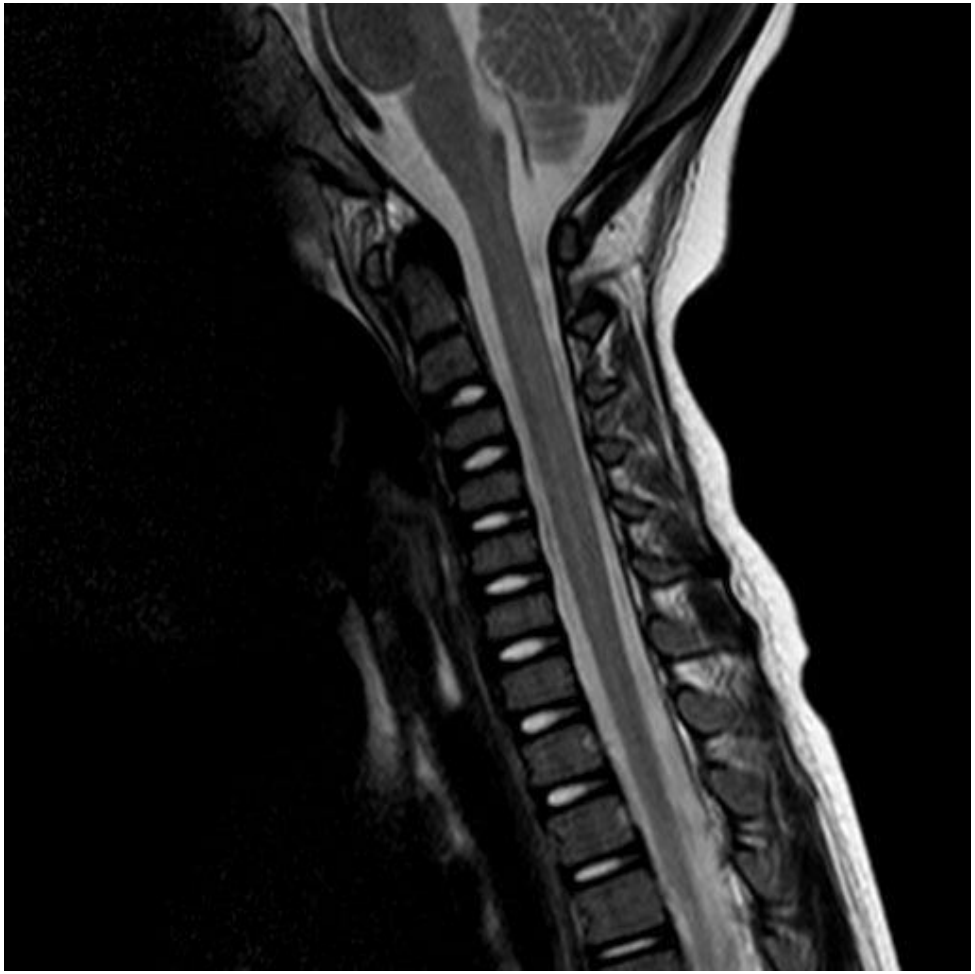
- **CNS** - meningitis, encephalitis, flaccid paralysis
- **Respiratory** - URTI, pharyngitis, bronchitis, bronchiolitis, pneumonitis
- **Exanthems** - HFMD, herpangina
- **Cardiac** - myocarditis, pericarditis
- **GIT** – vomiting, diarrhoea, hepatitis, pancreatitis, diabetes
- **GUT** – nephritis, orchitis, epididymitis
- **Other** - pleurodynia, acute haemorrhagic conjunctivitis, neonatal disseminated disease, chronic infection in hypogammaglobulinaemia.

Acute Flaccid Paralysis

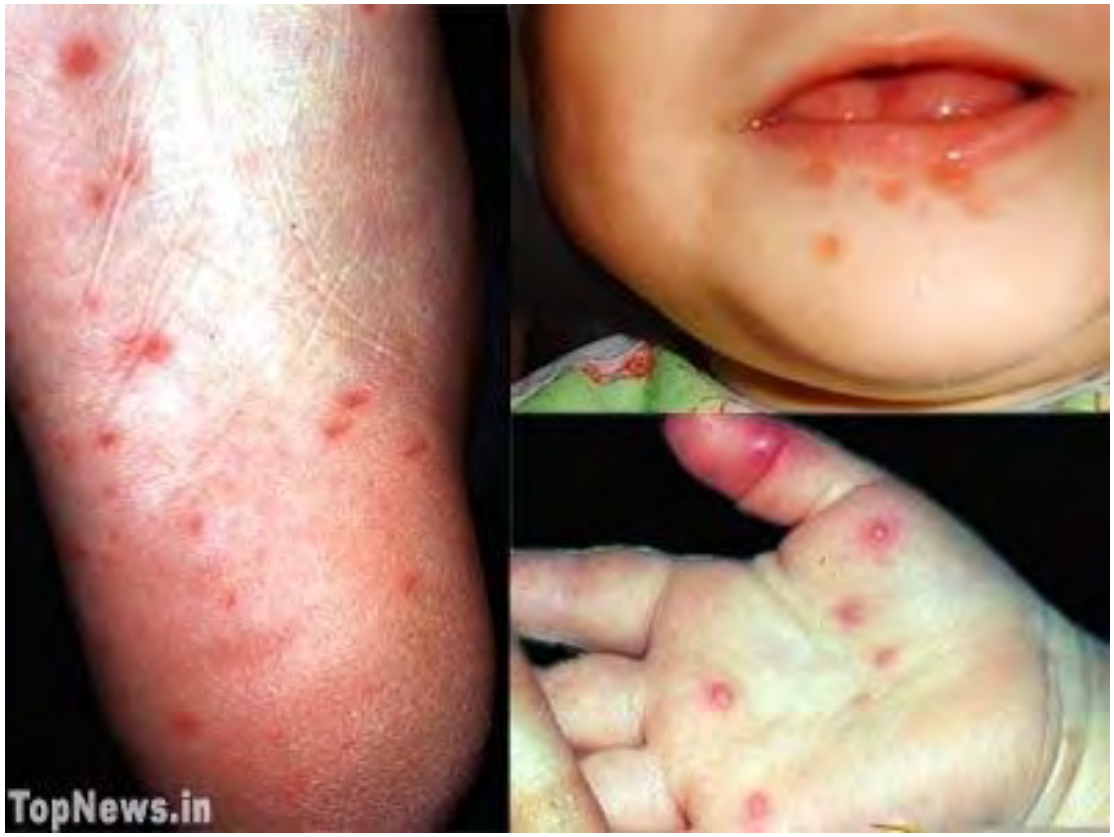
- Inflammatory damage to anterior horn cells of the spinal cord resulting in acute-onset lower motor neuron paralysis (or paresis) of one or more muscles
- Polioviruses 1, 2,3, EV71, EV 70 Echo, others .
- Variable severity – majority asymptomatic
- Onset of fever and myalgia up to 7 days followed by sudden onset of weakness progressing for 4 days and typically asymmetric.

Acute Flaccid Paralysis

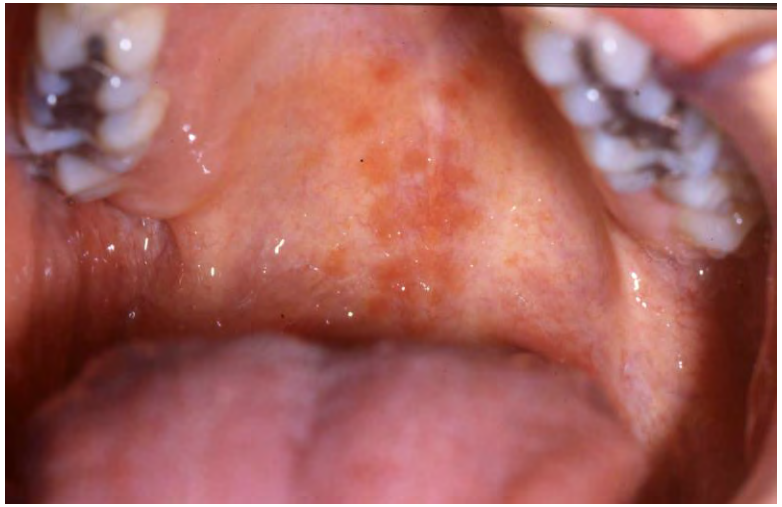
- Higher cerebral functions not altered unless hypoxia
- CSF – lymphocytic pleocytosis and protein elevation
- Defect in motor horns of spinal cord on MRI
- Most recover but 70% have residual motor weakness
- Loss of motor neurons – denervation atrophy of muscles.
- Delayed progression of neuromuscular symptoms may occur 20 years or longer – not related to virus replication – deterioration of nerves involved in re-innervation during original recovery

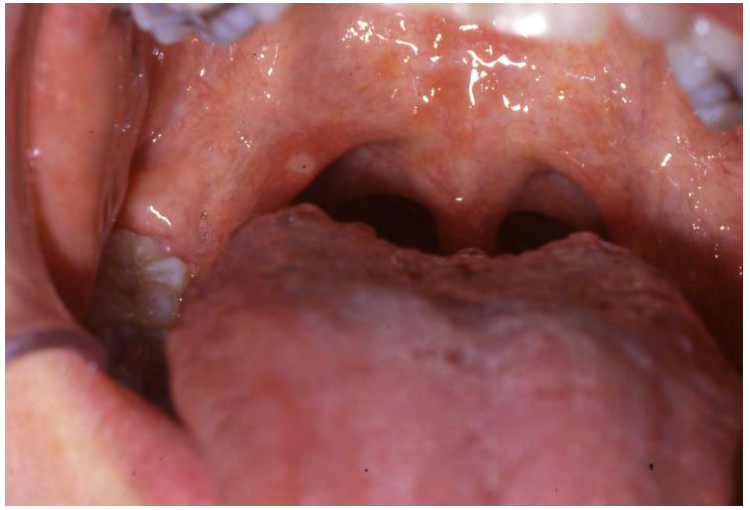


Hand Foot and Mouth Disease

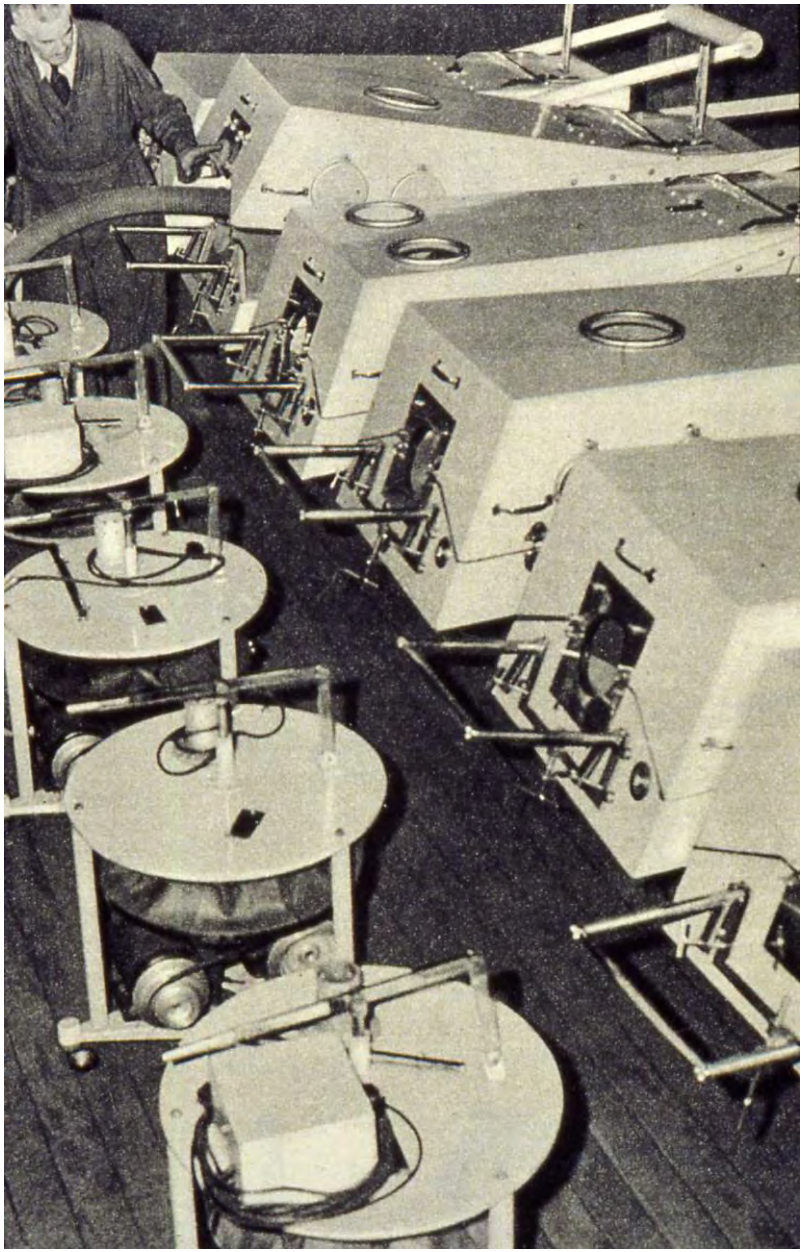


Enanthem

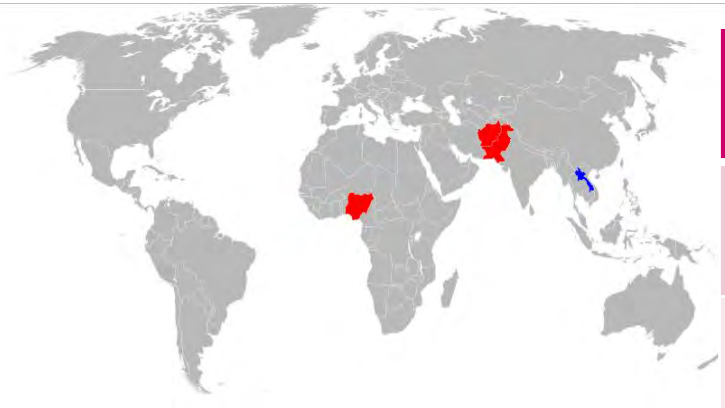




Iron lungs used to support polio patients



Polio 10 Jan 16 (WHO)



By Tobus - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=46924836

Country	WPV	VDPV	Trans mission	Types
Pakistan	20	1	endemic	WPV1 VDPV2
Afghanistan	13	0	endemic	WPV1
Nigeria	4	1	endemic	WPV1 VDPV2
Laos	0	3	VDPV	VDPV1

Laboratory Diagnosis

- EV infections usually common, non-invasive and prolonged.
- Detected EV may not be cause of illness – issue of probabilities
- Recognised clinical syndrome – probably causation
- EV in diseased tissue of fluid (CSF) – evidence of invasion and therefore causation.

Parechoviruses

Parechoviruses

- Human parechoviruses (HPeVs) are members of the *Picornaviridae*
- Human parechoviruses 1 and 2 (HPeVs) were initially classified as echoviruses 22 and 23 but were later classified into their own genus based upon their distinct biological and genomic sequence characteristics (sharing less that 30% amino acid identity with other Picornaviruses) and a unique capsid structure consisting of 3 rather than 4 capsid proteins

-

Parechoviruses

- HPeVs occur worldwide, comprising up to 17 genotypes.
- 17 types have been described on the basis of the phylogenetic analyses of the VP1 encoding region, the majority of published reports - HPeV types 1-8.
- Infections with human parechoviruses (HPeVs) are associated with a wide range of clinical presentations in children, ranging from mild or asymptomatic infections to severe sepsis-like presentations or meningoencephalitis

Parechoviruses

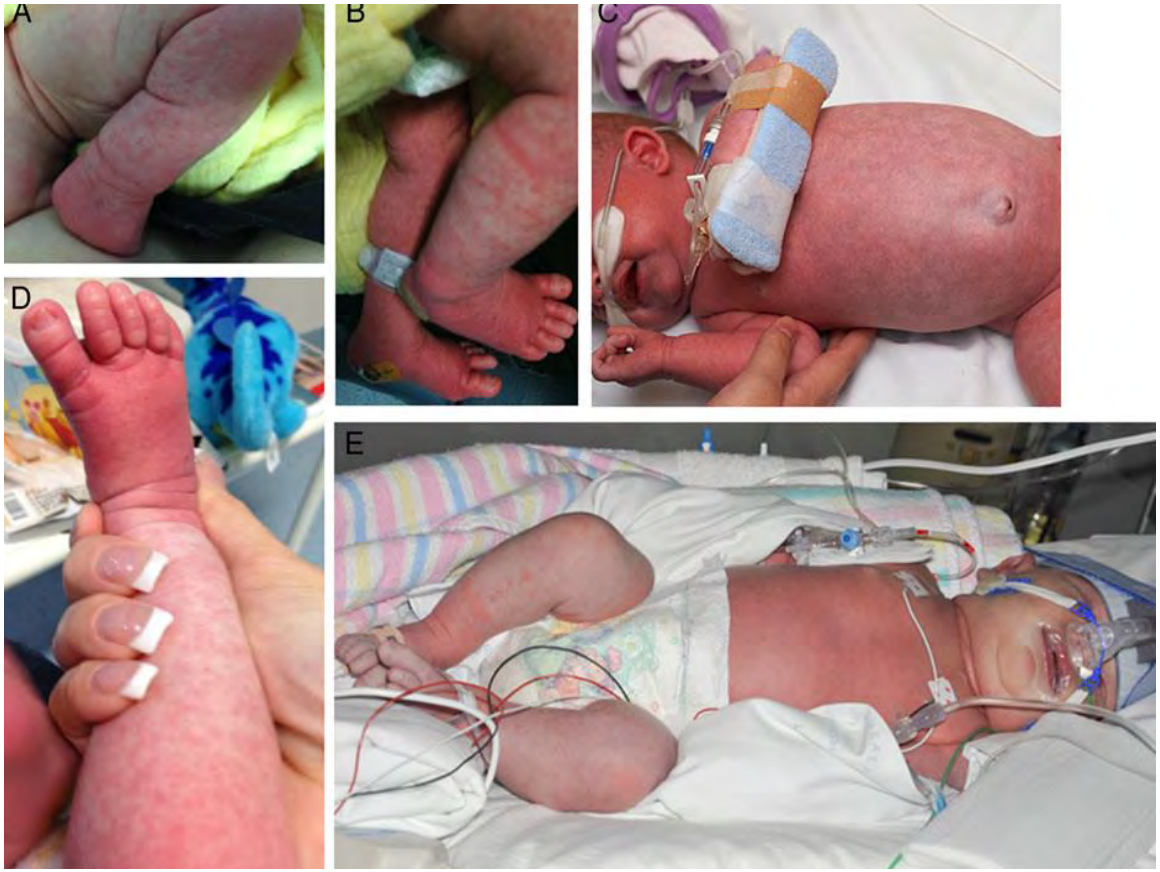
- Echoviruses were first isolated in 1951 and received their name because they were **E**nteric isolates that mediated a **C**ytopathic effect mostly in **H**uman cells but were not associated with a human disease ("**O**rphans").
- Molecular sequencing demonstrated that echovirus 22 and 23 were genetically distinct from other enteroviruses and thus reclassified into a new genus Parechovirus, of which there are now 17 strains.
- Serologic studies have shown that HPeV infections are ubiquitous, with seroconversion usually occurring the first year of life.

Clinical Significance

- HPeV1, HPeV2 and HPeV4-8 mainly cause
  - mild gastrointestinal or respiratory illness;
  - occasionally more serious diseases reported:
    - myocarditis,
    - encephalitis,
    - pneumonia,
    - meningitis,
    - flaccid paralysis,
    - Reye syndrome
    - fatal neonatal infection.

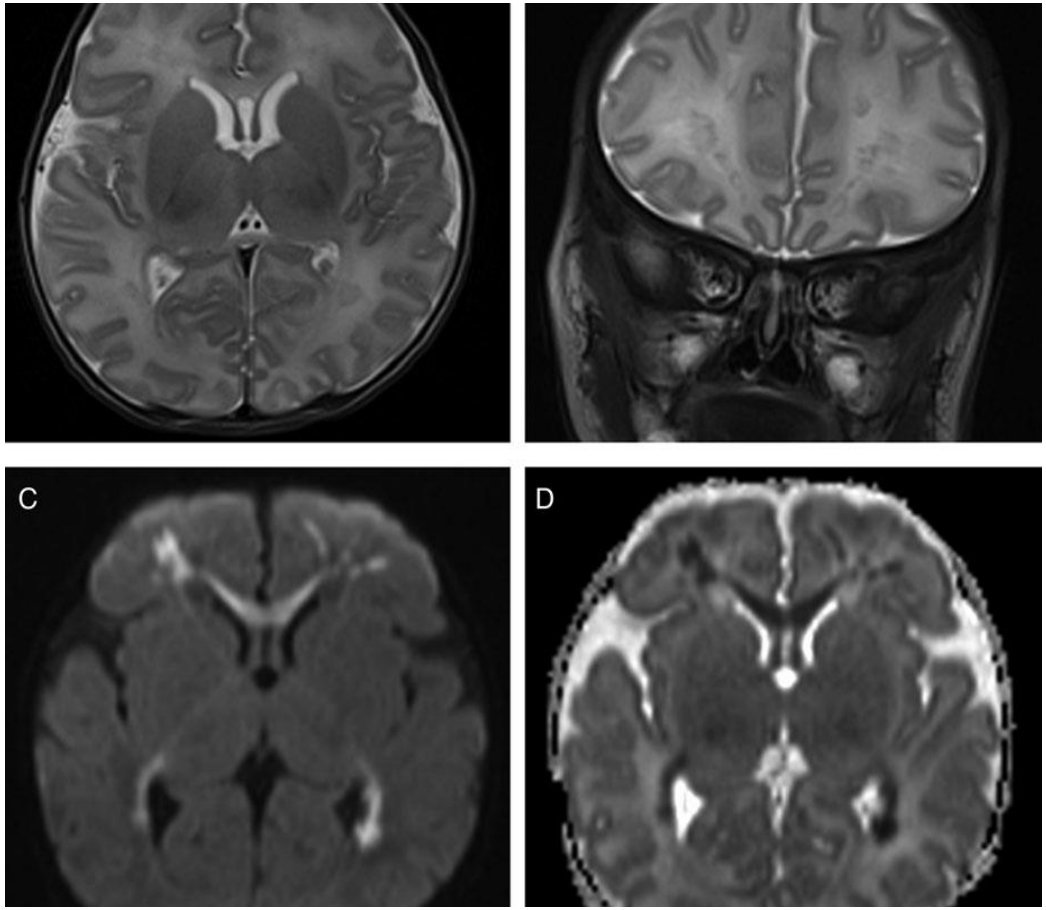
Clinical Significance

- HPeV3 causes severe illness in young infants, including sepsis like illness and conditions involving CNS
- HPeV3 is the most common single cause of aseptic meningitis / meningoencephalitis in infants less than 90 days in North America, usually with biannual summer-fall seasonality.
- HPeV3 CNS infections usually lack cerebrospinal fluid pleocytosis



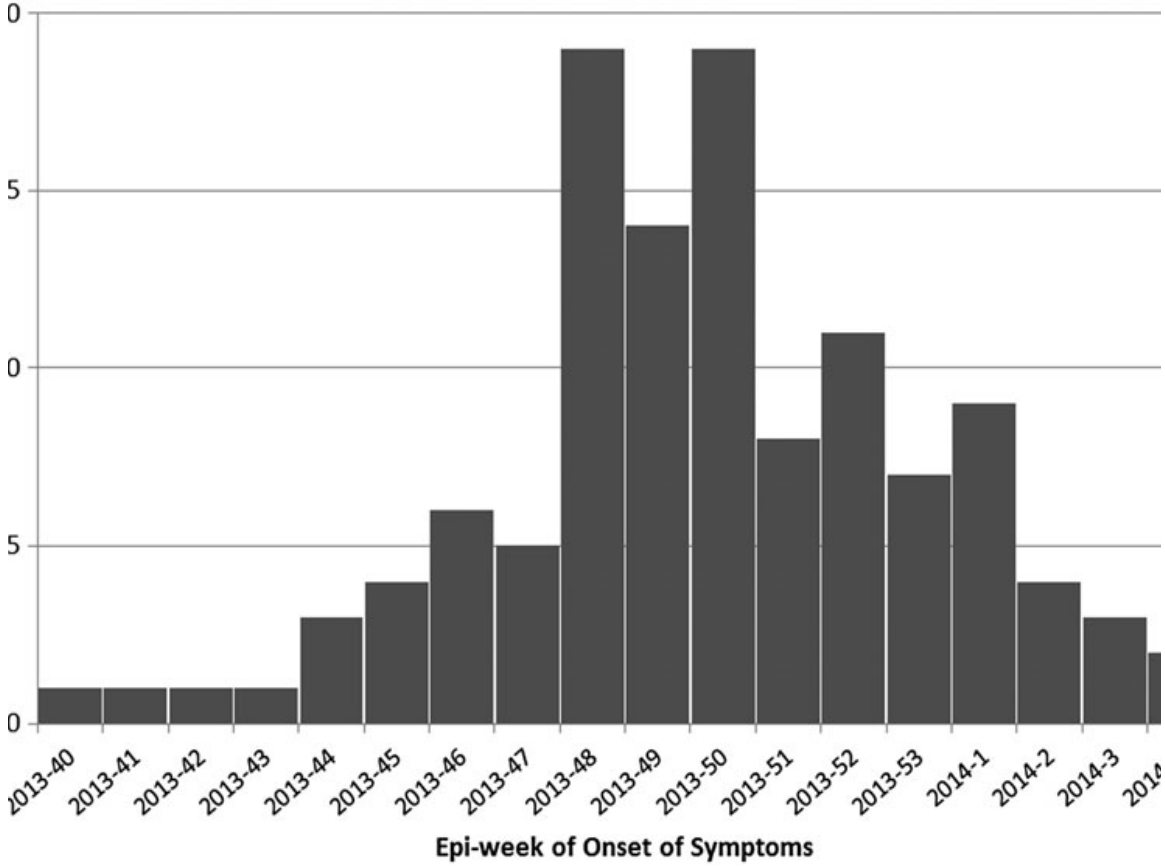
Khatami (2015) CID 60, 228

A, B and D: three images from the same infant showing edema and redness of the hands and feet. This infant was suspected to have possible neonatal Kawasaki disease, or congenital hemophagocytic lymphohistiocytosis. C, infant with generalized erythematous rash, mottling of skin, and abdominal distension. This infant required additional high flow oxygen administration. E, infant with generalized oedema, erythrodermic rash to the trunk, and poor perfusion (delayed capillary refill time). This infant required continuous positive airway pressure support.



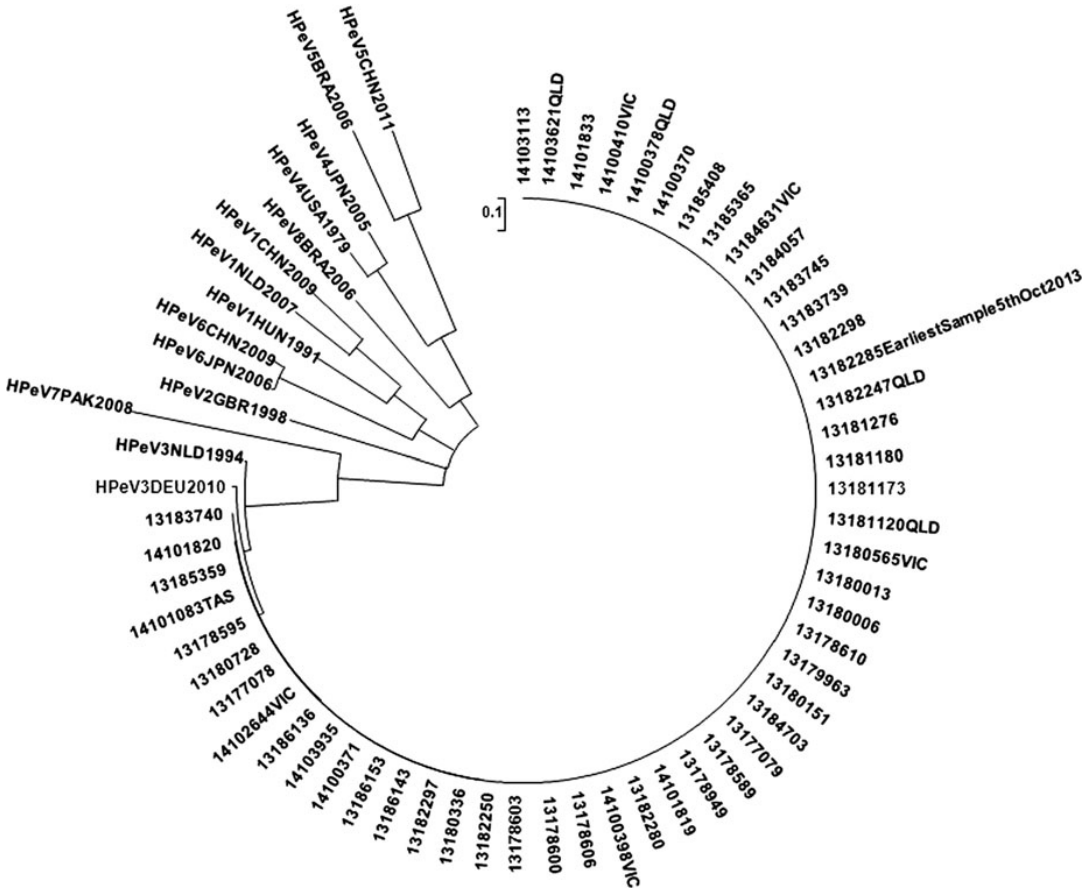
Khatami (2015) CID 60, 228

Brain magnetic resonance imaging of an infant with human parechovirus infection. Top row (A and B): T2-weighted images demonstrating multiple areas of hypo-intensity in the frontal cortex white matter and genu of the corpus callosum, with mild surrounding oedema and hyper-intensity. Bottom row: diffusion weighted image (C) and apparent diffusion coefficient map (D) demonstrating patchy areas of diffusion restriction, most marked in the periventricular white matter and genu of the corpus callosum.



Khatami (2015) CID 60, 228

Number of confirmed human parechovirus cases admitted to 5 hospitals in New South Wales each week between October 2013 and January 2014.



Khatami(2015) CID 60, 228

Phylogenetic tree demonstrating all human parechovirus type 3 isolates genotyped during the Australian epidemic, October 2013–January 2014, at the Victorian Infectious Diseases Reference Laboratory, including 41 isolates from New South Wales (1 adult) and 10 isolates from other states. Reference strains from various countries and years are included for comparison.

Diagnostic tests

- The most sensitive method for detecting EVs and HPeV is polymerase chain reaction (PCR) assays on stools, respiratory swabs, blood and cerebrospinal fluid
- Diagnostic assays are not routinely available and the involvement of EVs and particularly HPeV is therefore substantially underestimated

Therapy EVs and HPeVs

- Supportive
- No antiviral medication is available
- The use of monoclonal antibodies is still being evaluated
- No vaccine available

Thank you

Questions?