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Enteroviral Infections in Infants

Srijan Singh[1], **Sushant Satish Mane**[2], **Gangajal Kasniya**[3], **Sofia Cartaya**[4], **Mohd Mujibur Rahman**[5], **Akhil Maheshwari**[6], **Mario Motta**[7], **Pradeep Dudeja**[8]

[1]Department of Pediatrics, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India

[2]Department of Pediatrics, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India

[3]Department of Pediatrics, Cohen Children's Medical Center, New Hyde Park, New York, United States of America

[4]Department of Pediatrics, University of South Florida, Tampa, Florida, United States of America

[5]Department of Neonatology, Institute of Child and Mother Health, Dhaka, Bangladesh

[6]Global Newborn Society, Clarksville, Maryland, United States of America

[7]Neonatologia e Terapia Intensiva Neonatale ASST Spedali Civili di Brescia, Italy

[8]Department of Gastroenterology, University of Illinois at Chicago, Illinois, United States of America

Abstract

Enteroviruses (EVs) are major pathogens in young infants. These viruses were traditionally classified into the following four subgenera: polio, coxsackie A and B, and echoviruses. Now that poliomyelitis seems to be controlled in most parts of the world, coxsackie and echoviruses are gaining more attention because (i) the structural and pathophysiological similarities and (ii) the consequent possibilities in translational medicine. Enteroviruses are transmitted mainly by oral and fecal–oral routes; the clinical manifestations include a viral prodrome including fever, feeding intolerance, and lethargy, which may be followed by exanthema; aseptic meningitis and encephalitis; pleurodynia; myopericarditis; and multi-system organ failure. Laboratory diagnosis is largely based on reverse transcriptase–polymerase chain reaction, cell culture, and serology. Prevention and treatment can be achieved using vaccination, and administration of immunoglobulins and antiviral drugs. In this article, we have reviewed the properties of these viruses, their clinical manifestations, and currently available methods of detection, treatment, and prognosis.

Corresponding Author: Srijan Singh, Department of Pediatrics, Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India, Phone: +91 9953537342, srijanstar89@gmail.com.

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INTRODUCTION

Enteroviruses belong to the Picornaviridae family of viruses.[1] In infants, these pathogens can cause varied clinical manifestations, including hand, foot, and mouth disease; respiratory illness; myocarditis; meningitis; and sepsis; and even lethal multi-system organ failure. These viruses are transmitted primarily from one person to another.[2]

Enteroviruses were identified as a distinct class of viruses in 1957.[3] These pathogens were named based on their natural enteric habitat.[3] Many serotypes were identified based upon neutralization with specific antisera and with polymerase chain reactions,[4] and were initially classified into the following four subgenera:[2] (a) Polioviruses (serotypes 1–3); (b) Coxsackieviruses (CVs) group A (CV-A; serotypes 1–22 and 24); (c) CV-B; serotypes 1–6); and (d) echoviruses (serotypes 1–9, 11–21, 24–27, and 29–33). Newer classifications divide EVs into four species, A-D, based on the regions of the viral RNA that encode for the VP1 capsid protein.[5] Serotypes added after 1970 are simply named as EVs with a species designation (such as EV-D68) (Table 1).[6] New serotypes are being continuously added and the number now exceeds more than 100.[7,8] Now that poliomyelitis seems to be better controlled, the CVs and the echoviruses are receiving more attention.

Virology

Enteroviruses are small (approximately 27 nm), non-enveloped virions with an icosahedral capsid with 60 subunits, each formed from four proteins (from VP1 to VP4).[9] Each virion has a linear, single-stranded, positive-sense RNA genome of about 7.5 kB (Fig. 1).[10] We have developed a standardized 16-component table to describe viral pathogens. Detailed information is available for some of these components in EVs (Table 2).

Intracellular Replication

Enteroviruses replication is initiated by attachment to cell membrane receptors which determine host cell susceptibility.[11] Penetration and uncoating of the virions lead to the release of RNA into the cell cytoplasm and synthesis of negative-strand RNA begins within 30 minutes.[12] The newly formed positive-strand RNAs serve as a message for translation and are incorporated into newly formed virions. Complete virions can be seen by electron microscopy within hours.[13]

Coxsackieviruses and echoviruses are non-enveloped virions with an icosahedral capsid structure containing linear single-stranded RNA (Fig. 1).[10] As described above, group A has 23 serotypes (1–22 and 24). Coxsackieviruses-B are usually classified into 6 serotypes (1–6), namely, the CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, and CV-B6.[14]

Epidemiology

Seasonal and Demographic Distribution

Enteroviruses infections occur throughout the year in warmer regions. This differs from the temperate climates, where the incidence is higher in summer and fall.[15] Infants are most susceptible, particularly males.[16] The incubation periods for enterovirus infections vary with different clinical syndromes.[17]

Transmission

Transmission of EVs occurs mainly by oral and fecal–oral routes.[13] It is enhanced by poor sanitary conditions, contaminated water, food, and fomites.[18] Flies appear to be a significant vector in situations of poor sanitation and heavy human infection.[19] Swimming pools are a major channel of spread during summer.[20] Respiratory route is an important mode of transmission for some serotypes, including CV A21 and EV-D68.[21] Moreover, EV-D70 is shed with tears and spreads *via* fingers and fomites.[22] There is a high incidence of secondary infection in household contacts, especially in infants.[23]

Furthermore, CV-B affects infants of both genders with equal incidence. Compared to older children and adults, neonates and young infants may be affected more frequently and with higher severity of the disease.[24] Also, CV-B4 has higher mortality than other serotypes. Moreover, CV-B virus is the major cause of viral myocarditis, especially in neonates and younger children.[1,25] The prevalence of echovirus excretion in the community resembles the general population. Most transmission is vertical, from the mother to her fetus/newborn.[26]

Pathophysiology

These virions penetrate the cell surface, get uncoated, and the viral genome functions as mRNA for the viral polyprotein (Fig. 2). The polyprotein has three domains, from P1 to P3, which are cleaved into three to four proteins each. Domain P1 is liberated from the polyprotein by 2A protein and gets split into three proteins, VP0, VP1, and VP3, by 3C protease. Protein VP0 is processed further into smaller proteins, VP4 and VP2. They form eight-stranded antiparallel β-sheets. The amino acids in the loops that connect the β-strands and the N-terminal and C-terminal sequences that extend from the β-barrel domain of VP1, VP2, and VP3 give the EVs their distinct antigenicity.[27]

The coxsackie–adenovirus receptor (CAR) and the decay-accelerating factor (DAF) are receptors involved in the pathogenesis of coxsackie B virus infections.[27] Interaction of CV-B with CAR and DAF leads to the pathogenesis of various clinical manifestations, especially acute and chronic myocarditis. The CAR is expressed in the intercalated discs in the heart. DAF is expressed mostly in epithelial and endothelial cells. Interaction of cardiotropic CV-B with DAF and CAR enhances viral entry into myocardial cells and is responsible for myocarditis.[28] Pathogenesis of CNS infections may involve hematogenous spread or axonal transport. Also, CV-B is subdivided into the following two DAF-binding phenotypes: The CV-B that does not bind to DAF (CV-B2, 4, and 6) and the CV-B that binds to DAF and requires CAR for infection.

Echoviruses bind to integrin $\alpha_v\beta_3$ (vitronectin receptor; serotypes 1, 9),[29] integrin $\alpha_2\beta_1$ (serotypes 1 and 8), and the human neonatal Fc receptor (FcRn; binds serotypes 5–7, 9, 11, 13, and 30).[30] Moreover, FcRn is a pan-echovirus receptor; it is expressed in the placenta, intestinal epithelium, hepatocytes, and cerebral endothelial cells. This pattern of expression is consistent with the organ sites targeted by echoviruses, as the primary entry site of infection is the intestinal, and secondary sites of infection include the liver and brain.[31]

Host Factors

Neonates are predisposed to infections with CV-B and certain serotypes of echovirus (such as 11). Vertical transmission is more common than postnatal transmission. Infection is more frequent in seasonal community outbreaks of CV-B disease. Neonates are predisposed to severe infections with EVs, but the involved mechanisms are still not known.[32] The relative functional inability of neonatal macrophages and dysregulated cytokine/chemokine responses have been implicated.[33]

Passively acquired antibodies from mothers seem to be protective against serious disease and death.[34] Infants with transplacental acquired antibodies have relatively asymptomatic infections. The timing of the mother's infection determines the outcome of neonatal CV-B infection. Maternal infections beginning more than 5–7 days before delivery allow transplacental passage of specific immunoglobulin G (IgG) antibodies and prevents severe neonatal disease. Infants with maternal infections in the immediate peripartum period have a relatively poor prognosis. The clinical expression of neonatal CV-B disease depends on the timing of maternal infection, age, and passively acquired maternal antibodies.

Clinical Manifestations

These viruses can cause a range of clinical manifestations including fever, lethargy, myalgia, ileus, and diarrhea; exanthemata; aseptic meningitis and encephalitis; pleurodynia; and myopericarditis.

Hand, Foot, and Mouth Disease (HFMD)

The HFMD is a common illness in children characterized by fever, vesicles on the buccal mucosa and tongue, and tender cutaneous lesions on the hands, feet, buttocks, and genitalia (Flowchart 1).[35] Moreover, EV-A71 is the most frequently seen causative organism and can be associated with encephalitis, pulmonary edema and heart failure.[36,37] An atypical presentation of HFMD characterized by vesiculobullous lesions is caused by CV-A6.[38,39] Echovirus serotypes 3 and 33 have also been isolated.[40,41]

Herpangina

The CVs are a major cause of herpangina, a vesicular enanthem of the in the oral cavity.[42] Echoviruses can also rarely be the causative agents. It affects infants only when they have reached the age of 3 years or more of age and is more common in summers.[43] Sore throat, fever, and odynophagia are the predominant symptoms.

Maculopapular Eruptions

Generalized maculopapular eruptions are seen with EV infections.[44,45] The “Boston exanthem” is a febrile 24–36-hour prodrome followed by the appearance of small, non-pruritic, pink maculopapular eruptions on the face and upper chest.[46] Petechial and purpuric rashes have been associated with echoviruses 9 and 25 and CV-A9 infections.[44,47,48]

Urticaria-like Eruptions

Cutaneous manifestations of CV A9 and some echoviruses can range from *urticarial*, scarlatiniform, vesicular, pustular, and/or petechial lesions.[49]

Central Nervous System Infections

Acute CNS infection occurs at all ages. Aseptic meningitis is the most common CNS manifestation. Polioviruses, EV-D68, and EV-A71 target motor nuclei within the brainstem and spinal cord, causing acute paresis of cranial and spinal nerves. The CV-A2 and echovirus 9 have also been identified.[50,51]

Myocarditis

The CV-B types 2, 3, 4, and 5 are the most common causes of neonatal myocarditis.[5,50,52,53] Onset of symptoms is generally before day 10 of life. It has a biphasic presentation. Non-specific signs and symptoms of lethargy, poor feeding, or mild respiratory distress precede the onset of myocarditis by 2–5 days.[54] These infants continue to have respiratory distress, tachycardia, jaundice, and diarrhea. There may also be temperature instability, tachycardia, arrhythmias, hepatomegaly, and poor perfusion. The EKGs show low voltage and other electrophysiologic abnormalities. Echocardiographic studies indicate poor left ventricular or biventricular function.

Infants with CV-B myocarditis may have concomitant meningoencephalitis, pneumonia, hepatitis, pancreatitis, and adrenalitis. Mortality among infants with myocarditis alone is around 30–50% and is higher in cases with multisystem involvement. Meningoencephalitis may manifest with altered sensorium, seizures, flaccid paralysis, and coma.

Echovirus infections have been associated with neonatal hepatitis. Congenital infections with echovirus 11, 21, and 30 can cause fulminant neonatal hepatitis, which can be lethal.[55,56] Echovirus 6 has been associated with fever, respiratory distress, sepsis-like syndrome, acute respiratory and renal failure, and disseminated intravascular coagulopathy. Autopsy studies have shown jaundice, anasarca, massive hepatic necrosis, adrenal hemorrhagic necrosis, renal medullary hemorrhage, hemorrhagic non-inflammatory pneumonia, and severe encephalomalacia.[56]

The histopathology of neonatal EV infections typically shows diffuse or scattered lesions with perivascular infiltration, consisting of mononuclear cells and polymorphonuclear leukocytes in the cerebrum, cerebellum, pons, medulla, and spinal cord.

Undifferentiated Fever and Aseptic Meningitis

Viral meningitis is most common in infants less than 1 year of age.[15,16] More than 90% of viral meningitis in infants is due to species B EVs (group B CVs and most echoviruses).

Neonates infected with CV-B are at risk for a severe systemic illness especially meningitis or meningoencephalitis.[53] Infection due to CV-B is a cause of 53–63% of the cases of fever without focus in infants less than 3 months of age.[57,58] The CV-B serotypes 2, 4, and 5 are most commonly identified in these infants. Infants may present with irritability, lethargy, poor feeding, vomiting, diarrhea, exanthems,and respiratory distress.[59] A sepsis screen can help rule out bacterial infection. The cerebrospinal fluid (CSF) study reveals aseptic meningitis in almost half of the infants with enterovirus infection.[60]

The CSF typically shows monocytic pleocytosis (100–1000 cells/mm^3) with normal or decreased glucose and slightly increased protein levels. Most infants recover within 2–10 days without complications. Also, 10% of infants may progress to develop seizures, obtundation, or raised intracranial pressure. The short-term prognosis of enterovirus meningitis is good. It is not associated with long-term neurodevelopmental deficits in most patients.[2]

Overall, about 5% of all cases of acute encephalitis are caused by EVs.[61] The CV serotypes A9, B2, and B5, and echovirus serotypes 6 and 9 are frequently associated with encephalitis.

Respiratory Tract Diseases

Many CV-B infections are accompanied by respiratory distress and non-specific radiological signs.[62] Echovirus 6 and CV-A serotypes 4, 6, 9, and 10 are other causative agents.[56]

Ocular infections

Acute hemorrhagic conjunctivitis is a highly contagious but self-limited ocular infection. A CV-A24 variant is responsible for outbreaks.[63] Transmission is by eye discharge, fingers,and fomites. Symptoms peak in 2–3 days and it resolves within 10 days without complication.

Hepatitis

Echoviruses, particularly serotypes 5–7, 9, 11, 14, 19–21, and 30 may cause severe hepatitis with foci of hepatic necrosis.[64] Upper respiratory infection, general signs of sepsis-like illness, meningitis, gastroenteritis, aseptic meningitis, gastroenteritis, meningoencephalitis, and fatal interstitial pneumonia may be seen. No association was found between maternal echovirus serotype 9 infection and congenital malformations.[65,66] Echoviral infections can cause considerable mortality in epidemics.

Cloud Baby

Echovirus 20 has been associated with Staphylococcal colonization and dissemination in nurseries. Eichenwald and associates identified this phenomenon and named these infants as “cloud babies.” Active staphylococcal dissemination occurred only during the time that echovirus 20 was recovered from the nasopharynx; hence, viral–bacterial synergism was postulated as a mechanism.

Diagnosis

Most EV cause self-limited illnesses and are diagnosed based on clinical manifestations. A laboratory diagnosis is required when the identification of the causative organism has management implications as in central nervous system infections, myopericarditis, and in neonates and immunocompromised patients. Laboratory diagnosis is also required in disease outbreaks.

Lab Diagnosis

Reverse Transcriptase–Polymerase Chain Reaction

Detection of virus in the blood, CSF, pericardial fluid, lacrimal fluid, urine, respiratory secretions, or tissue by reverse transcriptase polymerase chain reaction (RT-PCR) is diagnostic of infection.[67-70] A positive RT-PCR test from stool may represent the carrier state. In CSF, RT-PCR is more rapid and sensitive than cell culture.

Viral Isolation (Cell Culture)

For serotype identification, specimens should be sent to a reference laboratory where an isolate can be amplified in cell culture and identified at the serotype level with special PCR primers or genomic sequencing.[67-69]

Cell culture is expensive and culture in multiple cell lines is required for optimal sensitivity. Recovery of an isolate in cell culture helps in its typing for clinical and epidemiologic purposes. The characteristic enterovirus cytopathic effect (CPE) requires 2–6 days to develop in primary cell culture.[70,71] Indirect immunofluorescence may be used to confirm the virus causing the CPE.[71]

Serology

Serology is not generally used for the diagnosis of acute enteroviral illnesses except when infection with a specific serotype is suspected. The diagnosis of acute infection can be made retrospectively with a 4-fold or greater increase in antibody titers between acute and convalescent specimens separated by a minimum of 4 weeks. Serum IgM antibodies to the CV-B can often be detected early in the course of illness.[72,73] Type-specific immunoassays that measure the antibody response against the more common enterovirus serotypes are of limited utility due to cross-reactivity and standardization issues.

Management

The management of CVB disease in the newborn is predominantly supportive care (Flowchart 2). The severity of disease and poor prognosis have generated interest in immunoglobulins (Ig) for the treatment of neonatal enterovirus infections.

Antiviral Therapy for Severe Cases

Most enteroviral infections are self-limited and do not require specific therapy. Exceptions are fulminant neonatal infection, severe myocarditis, chronic infection, and disseminated infections in B cell-immunodeficient patients and hematologic malignancies.

Antiviral Drugs

Antiviral drugs against EVs have limited availability. There are a few available options:

- Capsid inhibitors are drugs that inhibit viral attachment and uncoating. They have been shown to have activity against EVs. Pocapavir is an orally administered drug under development to treat chronic enterovirus infections, although resistance was quick to develop.[74] It is available only for poliovirus infections in B cell-deficient patients.
- Pleconaril, an orally administered capsid inhibitor, has been tested clinically against enterovirus and rhinovirus infections but is not currently available for systemic administration.[75]

Intravenous (Ig)

There is no clear evidence of benefit. It may be used in life-threatening enteroviral infections but is not recommended for routine use.[76] A retrospective study showed that intravenous immune globulin (IVIG) increases survival.[76] However, a randomized controlled trial at a dose of 750 mg/kg found no clinical benefit.[77] There is also no convincing evidence of benefit in acute myocarditis. There is anecdotal, not convincing, evidence for the use of IVIG and maternal plasma transfusions in echovirus infections.[78,79]

Prevention

General Measures

Simple hygienic measures, such as hand washing, are important to prevent the spread of infection.[80] Alcohol-based hand sanitizers may not be optimally effective for EVs.[81] In hospitalized patients, standard precautions are indicated to control outbreaks.[82] In outbreak settings, standard contact and droplet precautions for suspect cases in healthcare settings have been recommended.

Vaccines

Three inactivated enterovirus A71 vaccines have been tested in China for use in pediatric patients.[83-85] In a multi-center RCT in children aged from 2 to 71 months who received the B4 genotype-based enterovirus A71 vaccine, the vaccine efficacy was found to be 96.8%.[86]

Pregnant Women

Neonatal CV-B infections are acquired in the peripartum period either from the mother or nosocomial sources. The risk of maternal infection late in gestation can be avoided by hand washing, especially after changing diapers and after close contact with objects contaminated by feces, urine, or respiratory secretions. Strict enforcement of recommended infection control practices for health care workers is warranted to reduce transmission in newborn nurseries. If feasible, the delivery may be delayed till 5-10 days after symptoms onset to allow the transplacental transfer of maternal IgG antibodies to improve outcomes.

Future Directions

We need specific antivirals and vaccines targeting coxsackie virus infections in neonates. There is also a need for well-controlled trials to evaluate IVIG as a preventive measure against nosocomial transmission of EVs.

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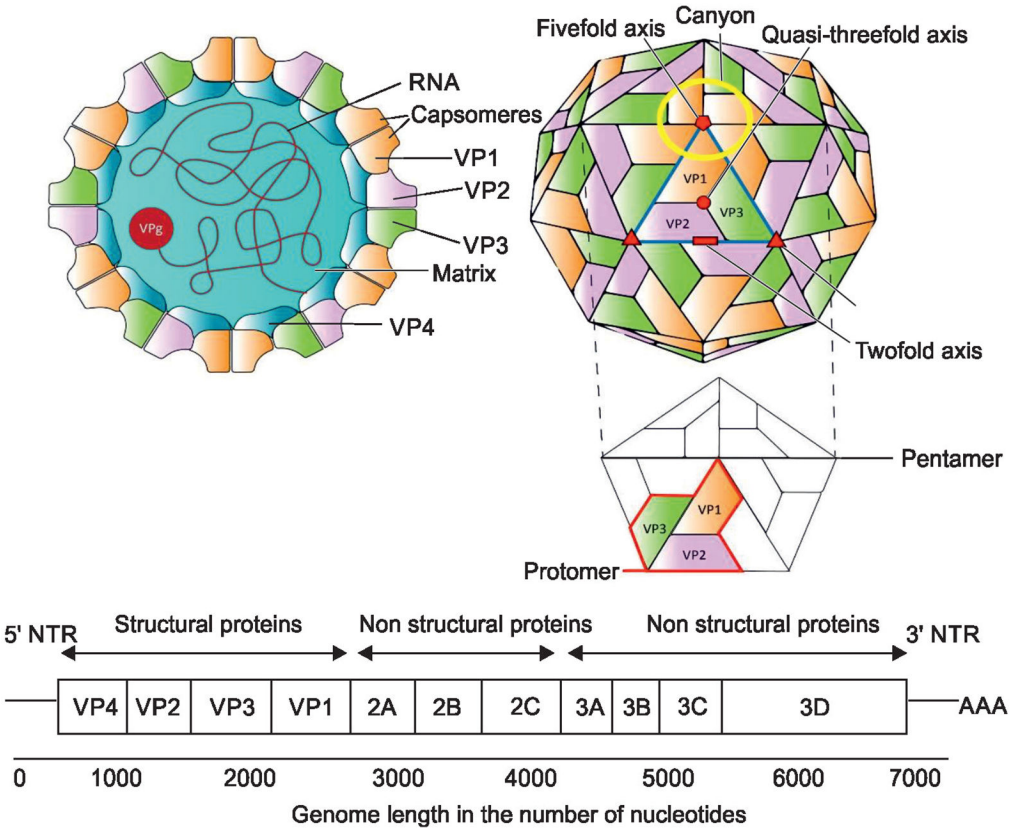


Fig. 1:

Schematic diagram showing the structure of EVs. Left-side of the schematic panel shows a cross-section with the location of the RNA, capsomeres, the matrix, and the viral proteins (VPs); Right-side of the schematic panel shows the surface with the location of structural and non-structural VPs on the surface of viral particles

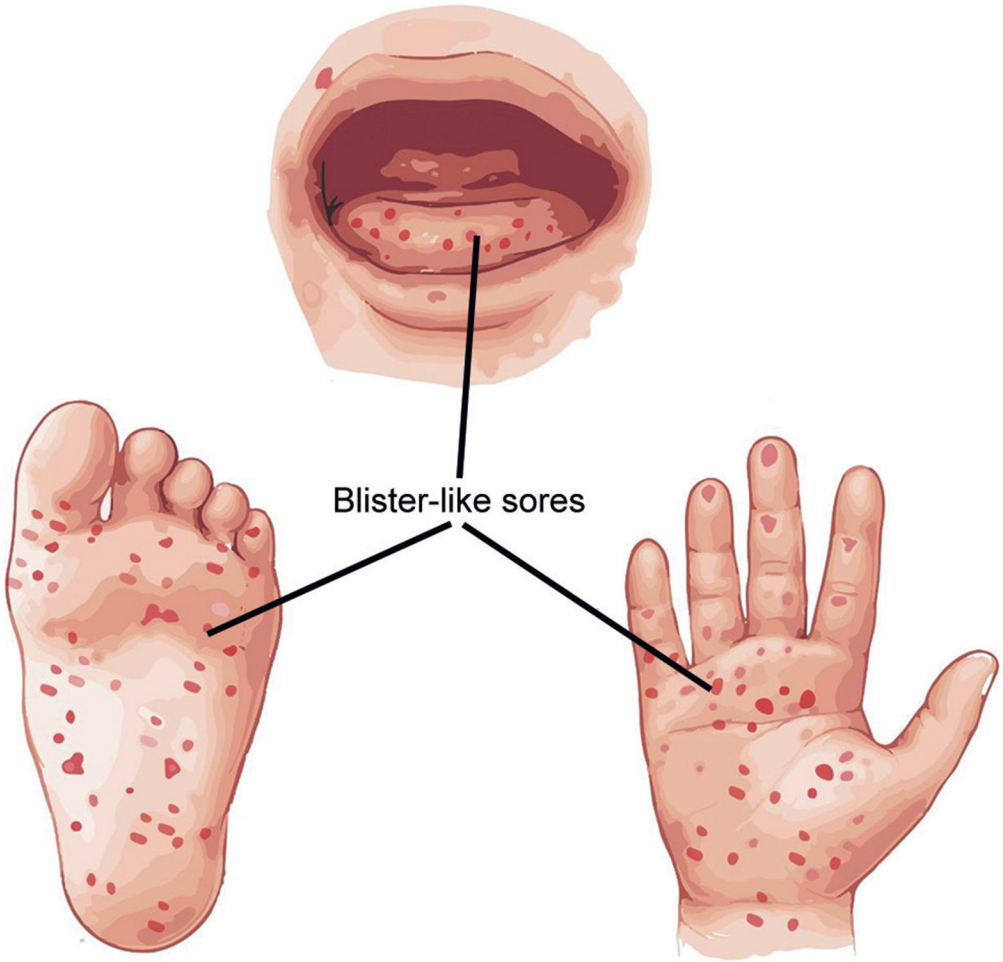
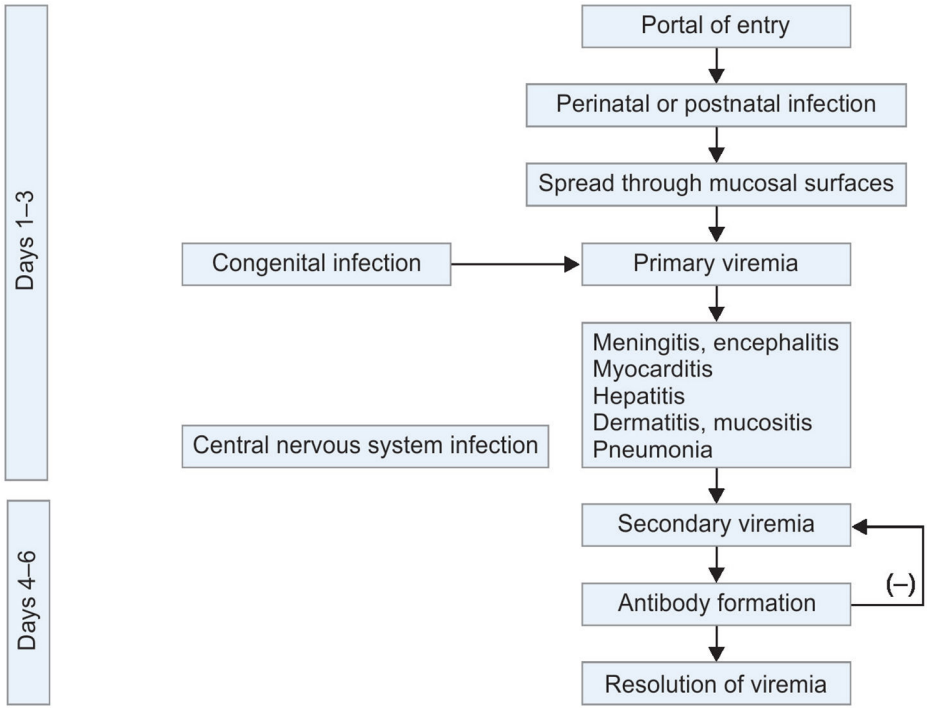
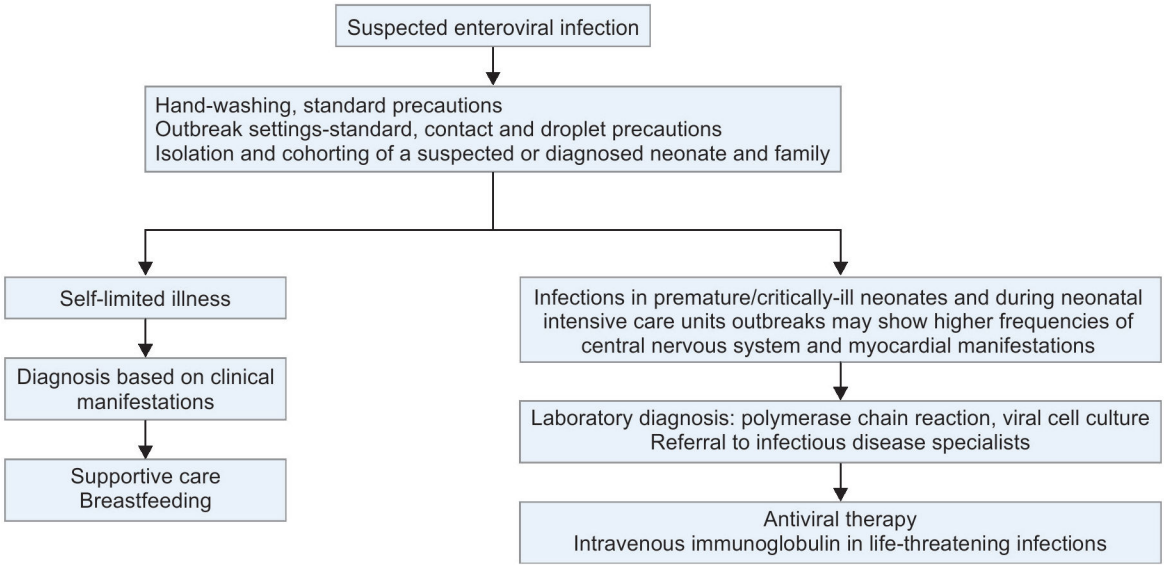


Fig. 2:
An artist's recall of vesico–bullous (blister-like) sores in hand, foot, and mouth disease.



Flowchart 1:
Temporal evolution of enterovirus infections before and after birth



Flowchart 2:
Algorithm for management of a neonate with suspected enteroviral infection

Table 1:

Genomic classification of EVs

Species designation	Types
Human enterovirus A (HEV-A)	CV A2–8, A10, A12, A14, and A16 EV A71, A76, A89, A90, A91, A114, and A119
Human enterovirus B (HEV-B)	CV A9 CV B1–6 Echovirus 1–9, 11–21, 24–27, and 29–33 Enterovirus 69, B73–B75, B77–B78, B93, B97, B98, B100, B101, B106, and B107
Human enterovirus C (HEV-C)	Poliovirus 1–3 CV A1, A11, A13, A17, A19–22, and A24 Enterovirus C95, C96, C99, C102, C104, C105, C109, C113, C116–118
Human enterovirus D (HEV-D)	Enterovirus D68, D70, D94, and D111

Table 2:

List of major structural components of EVs have been listed (we have used a standardized table developed to describe viral pathogens)

Structure	Available information
Lipid envelope	EVs are small, spherical viruses made up of an RNA genome surrounded by a protein shell.These viruses lack a "membrane."[87]
Glycoproteins	Proteins such as A9 and 3A are important; interact with host secretory carrier membrane protein 3 and participate in viral replication.[87]
Receptor-binding motifs	The arginine–glycine–aspartic acid (RGD) motif found in the VP1 capsid protein of CV-A9 has a role in cell entry. This motif binds integrins to promote entry into the cells.[88]
Envelope protein E	Either not expressed or relevance unclear in fetal/infantile disease.
Membrane protein	Either not expressed or relevance unclear in fetal/infantile disease.
MHC or HLA Proteins	Either not expressed or relevance unclear in fetal/infantile disease.
Spike protein	Either not expressed or relevance unclear in fetal/infantile disease.
Surface tubules	Lipid droplets (LDs) are transported to lysosomes by autophagy. Lipases are recruited to the LD surface for sequential hydrolysis of TGs stored within LDs. After enterovirus infection, TGs within LDs transformed into fatty acids.[89]
Palisade layer	Either not expressed or relevance unclear in fetal/infantile disease.
Viral tegument	Either not expressed or relevance unclear in fetal/infantile disease.
Lateral bodies	Either not expressed or relevance unclear in fetal/infantile disease.
Capsid	EVs are small (approximately 27 nm), non-enveloped virions with an icosahedral capsid with 60 subunits, each formed from four proteins (VP1 to VP4).[9]
Capsomeres	Viral polyprotein domains (from P1 to P3) are cleaved into 3–4 domains each; P1 is liberated from the polyprotein by 2A protein. Amino acids in the loops that extend from the β-barrel domain of VP1, VP2, and VP3 give the EVs their distinct antigenicity.
Core membrane	Either not expressed or relevance unclear in fetal/infantile disease.[9]
Protein core	Details on genome-associated polyprotein are described below.
Core fibrils	Either not expressed or relevance unclear in fetal/infantile disease.
Matrix	Virions penetrating the cell surface get uncoated and the viral genome functions as mRNA for the viral polyprotein.[90]
Enzymes	Details scant. Alter the expression of host enzymes.[91]
RNA elements	Enteroviral 3' non-translated regions (3'NTR) are comprised of two (X and Y) hairpin structures.[92]
Nucleus	Either not expressed or relevance unclear in fetal/infantile disease.
Nucleosome	Either not expressed or relevance unclear in fetal/infantile disease.
DNA	No DNA genome exists
RNA	The enteroviral genome (7.5-8 kb) is flanked by a 5'-UTR that is composed of an RNA cloverleaf structure and an internal ribosomal entry site (IRES).[5,9]
Genome-associated polyprotein	A single polyprotein is cleaved by the host and viral protease into 4 capsid VP proteins and 7 non-structural proteins. The capsid protein VP1 varies and confers antigenic properties.[93]
RNA polymerase	The RNA-dependent RNA polymerase (RdRP), known as 3D protein, functions as a replica for viral RNA synthesis in infected cells.[94]

Structure	Available information
Reverse transcriptase	Either not expressed or relevance unclear in fetal/infantile disease.
Head	Either not expressed or relevance unclear in fetal/infantile disease.
Base plate	Either not expressed or relevance unclear in fetal/infantile disease.
Integrase	Either not expressed or relevance unclear in fetal/infantile disease.
Tail	Either not expressed or relevance unclear in fetal/infantile disease.
Tail fiber	Either not expressed or relevance unclear in fetal/infantile disease.
Neck	Either not expressed or relevance unclear in fetal/infantile disease.

HLA, human leukocyte antigens; MHC, major histocompatibility complex; TGs, triglycerides