

COXSACKIEVIRUS AND ECHOVIRUS DISEASE IN THE NEWBORN INFANT



Mohammed ELkhwad MD
Neonatal Division
MHMC CWRU



Enteroviruses

- **Enteroviruses** are a large group of viral agents that inhabit the intestinal tract and are responsible for significant and frequent human illnesses that produce protean clinical manifestations.



ETIOLOGY.

Enteroviruses are RNA viruses belonging to the Picornaviridae family. The original enteroviral subgroups--

- Coxsackieviruses,
 - Echoviruses,
 - Polioviruses
- were differentiated by their effects in tissue culture and animals



Enteroviruses

- Polioviruses: Types 1-3
- Coxsackieviruses A: Types A1-A24 (A23 has been reclassified as echovirus 9)
- Coxsackieviruses B: Types B1-B6
- Echoviruses: Types 1-33 (echovirus 10 has been reclassified as Rhinovirus 1)
- Echovirus 28 has been reclassified as Rhinovirus 1A)
- Types 68-72



PATHOGENESIS.

- The neuropathy of poliomyelitis and other paralytic diseases caused by nonpolio **enteroviruses** is due to direct cellular destruction.
- Secondary damage may be due to immunologic mechanisms.



Epidemiology

- Although most neonatal enteroviral infections are acquired directly from the mother, some infections are transmitted nosocomially.



Epidemiology

- Introduction of infection into the nursery has been traced to an infected mother or to ill hospital personnel.
- Infant-to-infant spread within nurseries probably occurs via the hands of personnel engaged in mouth care, gavage feeding, and other activities requiring close direct contact.



Epidemiology

- Because most neonatal **enterovirus** infections are sporadic rather than nosocomial, the incidence and severity of neonatal enteroviral infection generally reflect the occurrence of enteroviral disease in the community.



Pathophysiology

- Most **newborns** with life-threatening **enterovirus** disease are infected via vertical transmission from the infected mother in the perinatal period.
- Approximately 60 to 70% of women who bear infected infants have a febrile illness during the last week of pregnancy.



Pathophysiology

- Ample experimental evidence indicates that the fetus is relatively protected by the placenta during maternal infection, but the **newborn** has a high risk of infection, perhaps as a result of exposure to either virus-positive cervical secretions or viremic maternal blood.



Pathophysiology

- Although most vertically transmitted **enterovirus** infections are probably acquired during delivery, some infants are infected before delivery as evidenced by the recovery of virus from cord blood and the development of disease within the first 2 days of life



Pathophysiology

- Once a **newborn** infant is infected, it is presumed that **enteroviruses** spread systemically via the blood stream. Tropism for and replication within specific organs of the neonatal host appear to depend on both virus and host factors.



Pathophysiology

- Both premature and term human infants respond adequately to **enterovirus** infection with humoral neutralizing antibody.
- However, macrophage function, which does not sufficiently mature until several weeks of age in the human neonate, is necessary to limit initial enteroviral replication.



Pathophysiology

- The outcome of neonatal infection is also strongly influenced by the presence or absence of passively acquired maternal antibody specific for the infecting **enterovirus** serotype



Pathophysiology

- Thus, the timing of maternal infection in relation to the development of maternal IgG antibody and delivery of the infant may be the most critical factor in determining the outcome of neonatal **enterovirus** infection.



Clinical Manifestations

- Symptoms develop in most neonates with generalized coxsackievirus and echovirus disease between 3 and 7 days of life.
- A small number have signs of illness in the delivery room or within the first 1 to 2 days of life



Clinical Manifestations

- conversely, the onset of fatal infection has been documented in infants as old as 3 months.
- Male infants and premature infants are overrepresented among infants with serious illness.



Clinical Manifestations

- Early symptoms are generally mild and nonspecific and include
 - listlessness
 - anorexia
 - transient respiratory distress.



Clinical Manifestations

- Fever may or may not be present.



Clinical Manifestations

- Generalized **enterovirus** disease in the **newborn** most often occurs in one of two characteristic clinical syndromes
 - myocarditis
 - fulminant hepatitis.



Myocarditis

- Signs of neonatal myocarditis include
 - rapid onset of heart failure,
 - respiratory distress,
 - tachycardia often exceeding 200 beats per minute,
 - cardiomegaly, systolic murmurs, and electrocardiographic evidence of myocardial injury and arrhythmias.



Myocarditis

- systolic murmurs,
- electrocardiographic evidence of myocardial injury and arrhythmias



Myocarditis

- Cyanosis and circulatory collapse rapidly develop in severely affected infants



Myocarditis

- Fatal cases are often accompanied by disseminated viral infection involving other organs
 - CNS
 - liver
 - pancreas
 - adrenal gland.



Myocarditis

- Most affected neonates are lethargic, but seizures, a bulging fontanelle, and CSF pleocytosis indicate the presence of meningoencephalitis.



Myocarditis

- Mortality is less than 50%.
- Death usually occurs within 1 week of onset.



Myocarditis

- Myocardial function rapidly improves in surviving infants after defervescence, generally by 1 week, although in a few infants convalescence is prolonged for several weeks.



Myocarditis

- . Infants dying of myocarditis have
 - enlarged dilated hearts
 - extensive myonecrosis
 - a variable degree of cardiac inflammation.



Hepatitis

- The initial symptoms of severe neonatal hepatitis syndrome are
 - lethargy
 - poor feeding
 - increasing jaundice.
 - These nonspecific symptoms may initiate an evaluation and therapy for bacterial sepsis.



Hepatitis

- However, within 1 to 2 days, the jaundice progresses and ecchymoses, bleeding from puncture sites, and signs of metabolic acidosis develop.



Hepatitis

- From this stage, most infected infants rapidly progress downhill with uncontrollable hemorrhage, hepatic failure, acute renal



Hepatitis

- Hepatic transaminases rise rapidly to extremely high levels.
- Thrombocytopenia is generally profound;
- markedly prolonged prothrombin times and partial thromboplastin times are indicative of profound hepatic failure



Hepatitis

- More than half of infants with severe neonatal echovirus hepatitis die within days after the onset of symptoms despite therapy with blood products and intensive supportive care.



Hepatitis

- Some ultimately fatal cases survive for 2 to 3 weeks with supportive care.



Hepatitis

- Postmortem findings include
- massive hepatic necrosis and
- extensive hemorrhage into the cerebral ventricles,
 - pericardial sac,
 - renal medullae, and interstitial spaces of many solid organs.



Hepatitis

- The long-term prognosis for surviving infants is not well known, although hepatic fibrosis and chronic hepatic insufficiency develop in some early in life.



Pneumonia

- Several cases of **enterovirus** pneumonia occurring in the first few days of life have been reported, all of them fatal and caused by echovirus types 6, 9, and 11 and group A coxsackievirus type 3



Diagnosis and Differential Diagnosis

- The diagnosis of neonatal coxsackievirus and echovirus infection is most rapidly made by
 - detection of viral RNA by PCR
 - isolation of virus in cell culture.



Diagnosis and Differential Diagnosis

- Virus is usually present in the infected neonate in high titer, so recovery is relatively rapid from:
 - oropharyngeal secretions,
 - feces,
 - urine



Diagnosis and Differential Diagnosis

- virus may also be recovered from
 - blood
 - CSF
 - ascitic fluid
 - multiple tissues obtained at biopsy or autopsy.



Diagnosis and Differential Diagnosis

- Because infected infants make humoral antibody to the virus, the diagnosis can also be made by serologic means when a specific **enterovirus** serotype is suspected.



Management

- Management of neonatal enteroviral disease is supportive.
- Infants in congestive heart failure require judicious fluid management and administration of inotropic agents and diuretics.



Management

- The profuse bleeding and coagulopathy that result from hepatic failure necessitate frequent replacement therapy with
 - packed red blood cells
 - platelets,
 - fresh frozen plasma.



Management

- Vitamin K should be administered intravenously in pharmacologic doses.
- Large doses of IGIV, which have been reported to improve outcome



Management

- Pleconaril, an orally administered experimental antipicornavirus drug, is undergoing evaluation in infants with serious enteroviral infections.



References:

- 1) Nishikii Y, Nakatomi A, Doi T, Oka S, Moriuchi H. Favorable outcome in a case of perinatal enterovirus 71 infection. *Pediatr Infect Dis J*. 2002 Sep;21(9):886-7.
- 2) Murugan SJ, Gnanapragasam J, Vettukattil J. Acute myocardial infarction in the neonatal period. *Cardiol Young*. 2002 Jul;12(4):411-3.
- 3) Abzug MJ, Levin MJ, Rotbart HA: Profile of enterovirus disease in the first two weeks of life. *Pediatr Infect Dis J* 1993 Oct; 12(10): 820-4
- 4) Cherry J: Enteroviruses. In: Remington J, Klein J. (eds): *Infectious Diseases of the Fetus and Newborn Infant*. 4th ed. Philadelphia, Pa: WB Saunders Co; 1995: 404-446
- 5) Cherry J: Enteroviruses: Coxsackieviruses, Echoviruses and Polioviruses. In: Feigin R, Cherry J, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia, Pa: WB Saunders Co; 1998: 1787-1839.
- 6) Dagan R: Nonpolio enteroviruses and the febrile young infant: epidemiologic, clinical and diagnostic aspects. *Pediatr Infect Dis J* 1996 Jan; 15(1): 67-71.
- 7) Joki-Korpela P, Hyypia T: Diagnosis and epidemiology of echovirus 22 infections. *Clin Infect Dis* 1998 Jul; 27(1): 129-36.



Questions

- What are enterovirus and main types?
- Describe the Epidemiology of enteroviruses for Neonates
- What are the clinical signs and symptoms of these viral infection?
- How can a diagnosis be made and what work-up indicated?
- What are the signs and symptoms of viral Myocarditis and hepatitis?
- What are the management Options for neonatal Enteroviral infection?