Neonatal nonpolio enterovirus and parechovirus infections

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**Abstract**

Nonpolio enteroviruses and parechoviruses are frequent causes of neonatal infection. Clinical manifestations of infection range from asymptomatic infection to mild infection without sequelae to septic shock with multiorgan failure. Neonates with clinically apparent infection typically have mothers and/or other contacts with recent symptoms consistent with a viral illness. Severe neonatal infection with nonpolio enterovirus or parechovirus cannot be differentiated clinically from serious bacterial infection. The preferred method for diagnosing neonatal nonpolio enterovirus or parechovirus infection is PCR as it is rapid, sensitive, specific, and commercially available for the detection of virus from various clinical specimens. Investigational agents such as the capsid inhibitors pleconaril and pocapavir show promise for treatment of neonatal enterovirus infections, and other investigational agents are being developed. This review focuses on the epidemiology, diagnosis, and treatment of neonatal nonpolio enterovirus and parechovirus infections.

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**Etiology and epidemiology of neonatal nonpolio enterovirus and parechovirus infections**

Enteroviruses and parechoviruses are small, non-enveloped, single-stranded RNA viruses in the Picornaviridae family (which also includes rhinoviruses and hepatoviruses).<sup>1,2</sup> There are 12 species within the Enterovirus genus;<sup>3</sup> human enteroviruses (HEV) are organized into four different enterovirus species, A through D, based on molecular serotyping.<sup>1,2</sup> Traditionally, human enteroviruses are categorized into polioviruses and nonpolio enteroviruses (coxsackieviruses, echoviruses, and numbered enteroviruses). Human enteroviruses are further subtyped into over 70 subtypes: polioviruses (types 1–3), coxsackieviruses (types A1–14, A16–17, A19–22, A23, B1–6), echoviruses (types 1–9, 11–21, 24–27, 29–33), and enteroviruses (types A71, A76, A89, A90, A91, A114, A119, B69, B73–75, B77–88, B93, B97, B98, B100, B101, B106, B107, C95, C96, C99, C102, C104, C105, C109, C113, C116–118).<sup>1</sup>

Molecular studies have also identified 16 human parechovirus (HPeV) types in the Parechovirus genus (species Parechovirus A).<sup>1,3,5</sup> Parechoviruses were initially classified as echovirus 22 and 23 within the Enterovirus genus when isolated during a summer diarrhea outbreak in children in Ohio in 1956, but were renamed HPeV genotypes 1 and 2 in

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1999 based on differences compared with other picornaviruses using newly available molecular techniques, as well as other biological properties. Although nonpolio enteroviruses and parechoviruses belong to different genera, the epidemiology and clinical characteristics of neonatal infection with these viruses is remarkably similar.

Nonpolio enteroviruses and parechoviruses are distributed throughout the world and worldwide serologic surveys have demonstrated neutralizing antibodies for various HEV and HPeV types. In tropical climates HEVs and HPeVs circulate and cause infection year-round. In temperate climates, HEVs and HPeVs primarily cause infection in the summer and fall. The predominant circulating types of HEVs and HPeVs vary over time and location and epidemic and pandemic outbreaks occur. Between May and August 2016 an outbreak of HPeV infections causing sepsis was noted in neonates and infants in Leicester, United Kingdom.

The National Enterovirus Surveillance System (NESS) is a passive detection system that collects data on HEV and HPeV infections in the United States. Between 2009 and 2013, NESS found that the most common HEV type causing infection was CV-A6 followed by E11, E18, CV-A9, and CV-B4 and the most common HPeV type causing infection was HPeV3, followed by HPeV1. CV-A6 was thought to be the predominant type of HEV infection detected during this time period due to a 2011-2012 outbreak of severe hand, foot, and mouth disease. Of 1763 specimens in which the age of the patient was known, 39% were from children less than one year of age. Between 2009 and 2013 the proportion of positive tests increased in March through June and decreased in November or December of most years.

Enteroviruses and parechoviruses are primarily transmitted by the fecal-oral and respiratory routes. Children are the most vulnerable to infection with enteroviruses and parechoviruses given their immunologic susceptibility and their often suspect hygiene habits. Nosocomial transmission and outbreaks of HEVs and HPeVs have been documented in pediatric settings including many nursery and neonatal intensive care units. Perinatal transmission of enteroviruses and parechoviruses is also well documented. In utero transmission of nonpolio enterovirus occurs, but is less common than intra- or postpartum acquisition. The chief modes of perinatal transmission are by intrapartum exposure to maternal blood and/or genital secretions, as well as the fecal-oral and respiratory routes after delivery.

Some studies have suggested that the transmission of nonpolio enteroviruses by breastfeeding may be possible. Coxackievirus B3 was detected in the breast milk of two symptomatic breastfeeding mothers who had newborns that developed hepatitis and meningitis due to Coxackievirus B3 at least 7 days of age evoking the possibility that Coxackievirus B3 was transmitted via breast milk. Ascending infection with nonpolio enteroviruses and parechoviruses also likely occurs.

The majority of neonates with clinically apparent nonpolio HEV infection have mothers with symptoms consistent with a viral illness (fever, abdominal pain, and URI symptoms) shortly before or after delivery. Similar symptoms are also often present in other family members. In addition, neonates with clinically apparent nonpolio HEV infection generally are full term and have uncomplicated postnatal courses before disease onset. Both parechoviruses and enteroviruses can survive on environmental surfaces for several days allowing for transmission by fomites. While the incubation period for parechoviruses has not been defined, the incubation period for nonpolio enterovirus infections is 3-6 days except for acute hemorrhagic conjunctivitis which has an incubation period of 24-72 hours. HPeV and HEV shedding can occur for 1-3 weeks after infection from the upper respiratory tract and for less than 2 weeks to several months in the stool contributing to the dissemination of infection.

Enterovirus infections are fairly common in pregnant women and in neonates. Forty-two percent of 1794 pregnant women who participated in a serological study, conducted over 10 years, were found to be infected with enteroviruses. The incidence of neonatal nonpolio enterovirus infection was investigated in Rochester, New York in 1981 by obtaining weekly culture specimens in 586 infants until one month of age. The incidence of acquisition of nonpolio enterovirus infection in the first month of life was 12.8% and lack of breastfeeding and lower socioeconomic status were associated with an increased risk of infection. A 13-month Finnish population-based prospective survey of infants less than 29 days of age with suspected systemic infection found that 4% of the 137 patients evaluated had enterovirus infection.

Studies of the general incidence of neonatal parechovirus are lacking. A recent 4-year study from Spain looking at the molecular epidemiology of enterovirus and parechovirus infection analyzed 3688 clinical samples (CSF, sera, throat swabs, stool, vesicular swabs, or biopsies) from neonates less than 28 days of age admitted to hospitals with symptoms compatible with enterovirus infection. Twenty percent of the neonatal clinical specimens were RT-PCR positive for enterovirus. Twenty-three EV types were identified in the neonatal specimens with the most predominant types being echovirus (E) 5, E11, and coxsackievirus (CV) B4. A subgroup of 1873 enterovirus negative clinical samples (CSF and sera) across multiple age groups (newborn to >65 years of age) were screened for HPeV by RT-PCR. Two percent of the specimens were positive and of those 70% were neonatal specimens. HPeV 3 was the predominant type noted to cause disease. Of note, HPeV types 1 and 3 are most often associated with infection in humans.

The major risk factor for symptomatic neonatal enterovirus infection is the absence, or low titer, of maternal neutralizing antibody to the infecting enterovirus serotype. Maternal evidence of a recent viral illness, prematurity, the onset of infection in the neonate within the first few days of life, and infection with echovirus 11 or coxsackieviruses B2–5 are well-documented risk factors for the development of severe neonatal nonpolio enterovirus infection. Infection with parechovirus 3 is a risk factor for the development of severe neonatal parechovirus infection. Recognized risk factors for symptomatic neonatal enterovirus infection in nursery outbreaks include: prematurity, lower birthweight, being a twin, nasogastric intubation or feeding, oropharyngeal instrumentation, need for intensive care, close proximity to the index patient, and/or care by the same nurse during the same shift as index patient.
A recent retrospective analysis found no significant associations between causative enterovirus genotypes and clinical phenotypes of severe enterovirus infection in 30 hospitalized children in England between 2012 and 2013; 74% of the causative HEV strains were able to be genotyped and 12 HEV types were detected. However, multiple other studies have documented an association between severe clinical infection and coxsackieviruses B2–5, echoviruses 5, 6, 11, 16, and 19, and parechovirus 3.1,16

Mortality rates for nonpolio enteroviruses and parechoviruses are related to the clinical infection phenotype and range from 0% to 83%.1,16,26,27 Mortality is highest in neonates with severe hepatitis, myocarditis, and those with both hepatitis and myocarditis.16,26 Infants infected with echovirus 11 nosocomially have been noted to have lower mortality and milder disease than infants infected vertically.26 Outcomes for survivors of nonpolio enterovirus myocarditis and hepatitis are encouraging with minimal long-term sequelae.1,16

Long-term sequelae for neonates with nonpolio enterovirus CNS infection appears to vary with some studies reporting no neurologic damage and others reporting decreased intelligence compared to control groups, language and speech dysfunction, motor dysfunction, seizures, defects in vision, and/or microcephaly.1,16 Little is known about the long-term sequelae of neonates with parechovirus. In an analysis of 11 infants (aged 1–90 days) with symptomatic parechovirus infection 4 (36%) had evidence of long-term sequel; neurodevelopmental delay in 3 infants with meningoencephalitis and the need for liver transplantation in 1 infant with hepatic failure.27

Clinical manifestations of neonatal nonpolio enterovirus and parechovirus infections

Fetal death and congenital anomalies

Infection with nonpolio enteroviruses during pregnancy is common.16 However, there is little evidence to suggest that maternal infection during pregnancy is associated with fetal death and/or congenital anomalies. A Swedish study evaluated 80 women who miscarried before 13 weeks of gestation; 42% had IgM antibody to coxsackieviruses B versus 18% of controls.26 There are no studies suggesting infection with numbered enteroviruses or echoviruses during pregnancy is a cause of spontaneous abortion.1 There are case reports of stillbirth related to maternal and/or fetal infection with coxsackieviruses, echoviruses, and enterovirus 71.129–31 Cases of congenital anomalies such as urogenital anomalies, gastrointestinal tract anomalies, cardiovascular defects, pulmonary hypoplasia, have also been described after maternal and/or fetal infection with nonpolio enteroviruses during pregnancy.1,11,16 To date no fetal deaths or congenital anomalies have been associated with human parechovirus infection.

Asymptomatic infection

The majority of neonates with nonpolio enterovirus infection have no apparent signs or symptoms of infection. This was clearly documented in a neonatal nonpolio enterovirus incidence study where 79% of children who acquired nonpolio enteroviruses in the first month of life were asymptomatic.19 HPeV are commonly detected in the stool of asymptomatic infants implying that HPeV infection is for the most part subclinical.32 Although frequent neonatal HPeV asymptomatic infection is presumed, it has not been specifically addressed.

Mild infection

Neonates with nonpolio enterovirus disease for the most part have mild, self-limited, localized infection.16,17,33 Nonspecific signs and symptoms of mild infection include fever, rash, irritability, and/or poor feeding.1,16,17,33 Gastrointestinal symptoms (diarrhea and emesis) and respiratory symptoms (cough, wheezing, rhinorrhea, tachypnea, and herpangina) may be observed.1,16,17 Mild infection may include aseptic meningitis with an elevated cerebrospinal fluid (CSF) leukocyte count and a normal or increased CSF protein concentration.1,16,17 Fever typically resolves in 2–4 days and other symptoms, on average, resolve after 7 days.1,16 In an investigation of 338 neonates with proven nonpolio HEV infection, 26% were classified as having benign disease, defined as pneumonia, other respiratory illness, nonspecific febrile illness, exanthematous illness, or gastrointestinal illness, and 47% were diagnosed with aseptic meningitis, for a total of 73% with mild infection.33 On occasion, a biphasic pattern of nonpolio HEV infection occurs among neonates with mild disease who develop severe infection after a short period of recovery.16

Given the epidemiologic and clinical similarities between nonpolio HEVs and HPeVs the proportion of neonates with mild infection due to HPeV is likely comparable to that for nonpolio HEV. In a series of 3 cases of neonatal infection with HPeV 3 all three neonates had self-limited, mild disease with fever, tachypnea, and rash.34 One neonate had otitis media, and another had conjunctivitis.34 Fever resolved within 5 days in all 3 neonates.34 In a Spanish multicenter prospective study of 84 neonates hospitalized with fever without source, clinical sepsis, and/or meningitis/encephalitis, 38% were PCR positive for nonpolio HEV from serum or CSF.35 The 52 specimens negative for nonpolio HEV were tested for HPeV and 9 neonates (11%) were PCR positive for HPeV from serum or CSF.35 Of these 9 neonates, 67% were characterized as having fever without source.35 The average duration of fever of all 9 neonates with HPeV was 1.3 days ± 1.1 days.35

Severe infection

Severe infection with nonpolio HEV is less common than asymptomatic or mild infection but has a far greater mortality rate.1,16 Abzug et al.17 studied 29 neonates with proven nonpolio HEV infection in the first 2 weeks of life and found that 17% had severe multisystem disease. In an investigation of 338 neonates with proven nonpolio HEV infection 27% were classified as having severe disease.33 Given the similarities between nonpolio HEVs and HPeVs it is not surprising that in one study, 22% of 9 neonates with clinically apparent HPeV infection were characterized as having clinical sepsis.35
As previously mentioned, echovirus 11, coxsackieviruses B2–5, and parechovirus 3 are the most recognized causes of severe neonatal infection.1,16

Severe neonatal infection with nonpolio HEV or HPeV cannot be reliably differentiated clinically from each other, nor from serious bacterial infection, or disseminated and central nervous system neonatal Herpes Simplex Virus infection. Therefore, nonpolio HEV or HPeV must be considered in the differential diagnosis of any neonate with presumed sepsis. The differential diagnosis for severe neonatal infection with nonpolio HEV or HPeV also includes noninfectious etiologies such as congenital heart disease and various metabolic disorders. These neonates may exhibit one or more of the following signs and symptoms: fever or hypothermia, anorexia, lethargy, abdominal distention, rash, hypotonia, diarrhea, emesis, seizures, hypotension, jaundice, apnea, or hepatomegaly.1,16

Severe neonatal infection with nonpolio HEV or HPeV may manifest as sepsis, encephalitis or meningoencephalitis, myocarditis, pneumonia, and/or hepatitis.1,16

Hepatitis due to nonpolio HEV or HPeV may be necrotic or fulminant.1,4,5,16,32 Thrombocytopenia, elevated transaminases, hyperbilirubinemia, disseminated intravascular coagulation, and/or liver failure may occur.1,4,5,16,32 Myocarditis often progresses rapidly and may present with the following cardiac findings: cardiomegaly, arrhythmias, congestive heart failure, and/or myocardial infarction.1,16 Pericarditis is much less commonly seen with neonatal disease as compared to enterovirus cardiac disease in children and adults.1 Pneumonia as the primary indicator of nonpolio HEV or HPeV infection is less common but can be rapidly progressive and lead to prolonged illness.1,16

Encephalitis or meningoencephalitis is commonly seen in neonates with presumed sepsis due to nonpolio HEV or HPeV.1,4,5,16,32 Profound lethargy, seizures, decreased consciousness, hypertonicity, and/or focal neurologic abnormalities may develop swiftly after initial symptoms of fever, poor feeding, and/or listlessness.1,16,32 Sporadic severe manifestations of neonatal nonpolio HEV and HPeV infection include necrotizing enterocolitis and hemorrhagic lymphohistiocytosis.1,16,32

Nonpolio HEVs have also been implicated as a cause of acute flaccid paralysis in children (most commonly enterovirus 71) and may be associated with acute flaccid myelitis.3 However, only 2 case reports of neonatal acute flaccid paralysis (one each due to coxsackievirus B2 and enterovirus 71) have been detailed in the medical literature.1 Although HPeV infection is recognized as a cause of acute flaccid paralysis, no cases of acute flaccid paralysis have been reported with neonatal HPeV infection.52

The peripheral leukocyte count is typically normal or mildly elevated in neonates with either neonatal nonpolio enterovirus or parechovirus infection.17,35,36 Evaluation of cerebrospinal fluid (CSF) may reveal a normal white blood cell count or pleocytosis.17,25,27,35,36 CSF protein is usually normal to slightly elevated and CSF glucose is typically in the normal range.17,25,27,35,36 CSF pleocytosis and elevated CSF protein appear to occur more commonly in neonatal HEV infection than HPeV infection.5,25,27,35,36 In an early comparison of severe neonatal parechovirus and nonpolio enterovirus infection 6 of 15 (40%) neonates with HEV infection who had evaluation of their CSF had pleocytosis while 1 of 8 (13%) neonates with HPeV meningoencephalitis had CSF pleocytosis.27 In addition, CSF protein was significantly higher in the neonates with HEV infection.27 Similarly, in a more recent Spanish multicenter prospective comparison of 32 neonates with clinically apparent HEV infection and 9 neonates with clinically apparent HPeV infection the neonates with HEV infection had a statistically significantly higher CSF WBC and protein than the neonates with HPeV infection (250 cells/mm³ and 104 mg/dl versus 5.7 cells/mm³ and 49 mg/dl, respectively).35 CSF glucose levels were normal in both groups.35 In some neonates with meningitis or meningoencephalitis due to nonpolio enterovirus the CSF WBC may be >1000 cells/mm³ akin to values seen with neonatal bacterial meningitis.1,16,27 In spite of a viral etiology, an early neutrophil predominance is commonly seen in the CSF with nonpolio enterovirus neonatal meningitis.17

Hepatic involvement is common in neonatal nonpolio enterovirus or parechovirus infection and transaminases and bilirubin are often elevated.1,4,5,16,25 In the setting of hepatic disease, platelet count, coagulation tests, and ammonia should be monitored closely. Chest radiography should be obtained if respiratory or cardiovascular symptoms are noted. An echocardiogram is necessary, to evaluate for a possible pericardial effusion and to assess myocardial function, if pericarditis or myocarditis is suspected.

The majority of nonpolio enteroviruses and human parechoviruses can be isolated from tissue culture in 3 to <10 days using specific tissue culture cell lines.1,4,5,16 Traditionally, stool/rectum specimens have had the highest yield in neonatal HEV infection, with CSF and nasopharyngeal/throat specimens having slightly poorer yields and serum and urine specimens having the lowest yields.35,36 However, given the expense and expertise needed for isolation from tissue culture, the need for careful specimen collection and handling, and the advent of rapid diagnostic methods for diagnosing HEVs and HPeVs, viral tissue culture is now rarely used to diagnose clinical infection.

Although serologic techniques (enzyme immunoassay, neutralization assays, etc.) and antigen detection methods (immunofluorescence, ELISA, etc.) are available to diagnose HEVs and HPeVs, the sensitivity of these methods is limited.1,16 In addition, most serologic assays require the collection of acute and convalescent neonatal serum, to demonstrate a rise in antibody titer, which is impractical.1,16

The preferred method for diagnosing neonatal nonpolio enterovirus or parechovirus infection is reverse transcriptase-polymerase chain reaction (PCR).1,4,5,16 Separate PCR assays that are rapid, sensitive, and specific are available

**Diagnosis of neonatal nonpolio enterovirus and parechovirus infections**

Although the definitive diagnosis of neonatal nonpolio enterovirus or parechovirus infection cannot be made clinically, the diagnosis may be suspected based on seasonality, exposure history (contacts with recent symptoms consistent with a viral illness), and clinical symptoms (meningitis, myocarditis, and hepatitis).
commercially for the detection of HEVs and HPeVs from a variety of clinical specimens. Standard EV RT-PCR assays will not detect HPeV and both must be ordered separately by the clinician considering these diagnoses. PCR is more sensitive and rapid (and equally as specific) than tissue culture for the detection of HEVs and HPeVs from CSF. PCR is also more sensitive and rapid than tissue culture for the detection of HEVs and HPeVs from blood and urine in neonates. A limitation of PCR testing is that the serotype of the infecting strain is not known. As severe neonatal HEV or HPeV infection cannot be differentiated clinically from severe bacterial infection or disseminated or central nervous system neonatal herpes simplex virus infection the rapid diagnosis of HEV or HPeV infection can potentially lead to fewer interventions and decreased antibiotic and/or antiviral exposure. We suggest that PCR testing for both nonpolio enteroviruses and parechovirus be obtained from clinically indicated sites for all neonates with suspected sepsis, since disease due to enterovirus and parechovirus cannot be distinguished clinically.

**Treatment of neonatal nonpolio enterovirus and parechovirus infections**

There are no currently FDA-approved therapies available for enterovirus infections in any age group. However, the two categories of treatment that are considered most frequently are passive immunotherapy with intravenous immune (IVIG), which may provide neutralizing antibody for clearance of virus, as well as experimental antiviral therapies that inhibit enterovirus replication.

**Immune globulin**

IVIG has been utilized in many centers for treatment of neonates with severe enterovirus and parechovirus sepsis, although its use is predominantly based on anecdotal experience rather than randomized controlled clinical trials. The rationale for its use as reported in case reports, as well as one small randomized trial, are its relative safety, the fact that neutralizing antibody titers against the most commonly circulating enteroviruses are present in most IVIG products, the correlation of severe disease with lack of neutralizing antibody, and experience with its use in hypogammaglobulinemic patients with severe enterovirus disease. In the only existing randomized trial in neonates, administration of IVIG at a dose of 750 mg/kg was associated with modest boosts of serum neutralizing antibody titers to viral isolates of patients, subtle clinical benefits, and faster cessation of viremia and viruria in patients who received a high titer (≥1:800) of neutralizing antibody to their own viral isolates.

**Investigational antiviral agents**

The class of investigational drugs known as capsid inhibitors has shown activity in vitro and in vivo against enteroviruses. Using crystallography to resolve viral structure, these drugs were engineered specifically to enter, wedge, and block a key hydrophobic binding “canyon” on the viral surface, preventing viruses from docking and binding onto target host cell receptors. Capsid inhibitors prevent viral attachment, uncoating of viral nucleic acid, and thus inhibit viral replication.

The first of this class of investigational drugs, pleconaril, has broad and potent activity against enteroviruses, excellent oral bioavailability, and is well tolerated. Pleconaril has been utilized in clinical trials including children and adults with enterovirus meningitis, and in adults with upper respiratory tract infections caused by picornaviruses (rhinoviruses or enteroviruses), as well as showing promise for the treatment of neonatal enterovirus infections, with demonstrated efficacy and safety. Several case reports using pleconaril for treatment of neonatal enterovirus sepsis have reported safety and potential efficacy. The largest pleconaril treatment trial in the neonatal population to date was a randomized, double-blind, placebo-controlled trial of pleconaril for the treatment of neonates with enterovirus sepsis. The National Institute of Allergy and Infectious Disease Collaborative Antiviral Study Group of the US National Institutes of Health evaluated the safety and efficacy of 7 days of oral pleconaril treatment compared to placebo in 61 infants with presumed enterovirus sepsis (hepatitis, coagulopathy, and/or myocarditis) with onset prior to 15 days of life, 43 of whom had confirmed enterovirus infection. Of note, a similar percentage of subjects in both treatment groups (36% pleconaril group and 34% placebo group) also received IVIG therapy. Virologic (opharynx, rectum, urine, and serum), clinical, pharmacokinetic, and safety measures were evaluated. Although both groups had clearance of enterovirus oropharyngeal culture positivity at 5 days, the subjects in the treatment group became culture negative from all anatomic sites combined faster than the placebo group (median 4 versus 7 days, P = 0.08), and fewer subjects in the treatment group remained polymerase chain reaction (PCR)-positive from the oropharynx (23% versus 58%, P = 0.02; median, 14.0 days). By intent to treat, mortality was lower in the pleconaril treatment group (23% versus 44% mortality; P = 0.02). However, among enterovirus-confirmed subjects, there was only a trend for improved mortality in the treatment group compared to placebo group (23% versus 42%, P = 0.26). Adverse event profiles were similar in the treatment and placebo groups, and no deaths were attributed to study treatment. As stated by the authors, these findings support the safety of pleconaril in this cohort of very ill newborns.

Pocapavir (V-073), a more recently developed capsid inhibitor, has also been demonstrated to have potent activity against enteroviruses in vitro and in vivo, is clinically being evaluated as an anti-poliovirus drug for use in global eradication efforts, and has variable activity against nonpolio enteroviruses. In a randomized, blinded, placebo-controlled study of 144 adults challenged with monovalent oral poliovirus type 1 vaccine (mOPV1) and subsequent treatment with pocapavir or placebo, safety and efficacy were documented, with significant acceleration of stool viral clearance of live poliovirus in the treatment group. The first reported use of pocapavir for treatment of severe neonatal enterovirus sepsis due to Coxsackievirus B3 was in a preterm infant with severe enterovirus sepsis including hepatic necrosis and coagulopathy syndrome. The infant began treatment at 18
days of age with pocapavir at a dose of 20 mg/kg/day; a dosage that has been shown to be safe and well tolerated in adults, and is 20–25 times below the no adverse effect levels in preclinical toxicology studies. The drug was suspended in high-lipid content formula and administered via nasogastric tube once daily for 10 days. No significant adverse drug-related events were observed, and the child recovered with minimal sequelae. An additional case utilizing pocapavir for treatment of twins with neonatal enterovirus sepsis has also been reported with similar outcomes. The manufacturer of pocapavir (ViroDefense, Inc, Chevy Chase, MD; mscolloett@aol.com) may be contacted on a case-by-case basis for consideration of experimental administration of pocapavir via an FDA emergency IND program.

There is great potential for discovery and development of other novel antiviral agents with activity against human picornaviruses including rhinoviruses and enteroviruses using high throughput screening of existing compounds. For instance, recently, a group of novel small molecule inhibitors against human rhinovirus replication (hRV) were identified using this methodology that have potent and selective antiviral activities against both hRV-A and hRV-B. Existing, currently licensed compounds of other classes have also been screened for possible enterovirus antiviral activity. For instance, the widely used agent fluoxetine was recently discovered to have antiviral activity against enterovirus D68 in vitro and has been utilized in the setting of treatment of acute flaccid myelitis in humans, although it has not yet been used in the setting of neonatal enterovirus/parechovirus sepsis. The potential for monoclonal antibodies with antienterovirus activity is being explored, predominantly with focus on anti-poliovirus activity due to current emphasis on global poliovirus eradication efforts, but the expansion of their use to nonpoliovirus infections is another potential future application.

Very recently, a novel early-stage inhibitor of Coxackievirus B3 (CVB3) replication, 4-dimethylamino benzoic acid (4EDMAB) was discovered, which has a targeted mechanism that is different from that of known capsid binders. Molecular modeling suggests that the compound binds to a small cavity in the viral VP1 capsid, which is different from the hydrophobic pocket in the canyon where bind to a small cavity in the viral VP1 capsid, which is distinguishable from capsid due to bacterial and herpes simplex virus infection in this age group. Testing using separate and specific RT-PCR for both enteroviruses as well as parechoviruses should be considered in tandem for this patient population. Treatment is currently investigational, but has included IVIG, as well as viral capsid inhibitors pleconaril and pocapavir, with evidence for safety as well as potential efficacy in the neonatal age group. Additional agents with antiviral activity are in the preclinical discovery phase, but are sorely needed.

Disclosures

Nada Harik and Roberta DeBiasi have no conflicts of interest to report.

References


