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Enteroviruses in the Early 21st Century: New Manifestations and Challenges

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Abstract

Purpose of review—Enteroviruses cause a wide variety of diseases with neurologic, respiratory, skin, and gastrointestinal findings. The purpose of this review is to clarify changes in the classification of enteroviruses, provide information about recent disease outbreaks, and to summarize progress toward treatment and prevention of these infections.

Recent findings—Enteroviruses are now classified into 4 distinct species. New variants of Coxsackievirus B1, Enterovirus-A71, and Enterovirus-D68 (EV-D68) have emerged as causes of recent outbreaks in the United States and other countries, including more severe disease manifestations than previously described. EV-D68 now commonly circulates in the United States, and has been linked to severe respiratory disease and associated with acute flaccid myelitis. Overcoming enormous political and logistical challenges, fewer than 100 cases of polio have been reported in 2015, and the initiation of “endgame” strategies appears imminent. Unfortunately treatment for enterovirus infections remains supportive, although the recently completed pleconaril trial in newborns suggests that antiviral therapy may reduce mortality in neonatal disease.

Summary—Clinicians should be aware of the respiratory and neurological manifestations associated with EV-D68 and the potential for severe disease seen with other recently described enterovirus variants. Healthcare professionals should recognize the utility of rapid diagnostic methods and progress toward prevention and treatment of enterovirus infections.

Keywords

enterovirus EV D68; poliovirus eradication; hand foot and mouth disease; enterovirus treatment; pleconaril

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Introduction

Enteroviruses usually cause mild infections but also cause encephalitis, myocarditis, poliomyelitis, acute heart failure and sepsis. Disease activity is typically seasonal, and infections occur in the summer and early fall in temperate parts of the world. Enteroviruses are subject to significant change over time due to errors introduced during genome replication. Recombination between enteroviruses is also common, further promoting genetic diversity. This genetic plasticity allows for widespread epidemics and sporadic outbreaks to occur. In this article we will review recent changes in the classification and epidemiology of enteroviruses and describe clinical manifestations of emerging strains of members of all 4 species of enterovirus that infect humans. We will also outline progress toward the elimination of polio, and prevention and treatment options for other enteroviruses, and highlight research priorities.

Current Taxonomy

Enteroviruses are members of the picornavirus family, a collection of small non-enveloped viruses with a small and relatively simple message sense genome. Serologically distinct enteroviruses were originally distributed into four groups based on their different effects in tissue culture and patterns of disease in experimentally infected animals: polioviruses (causal agents of poliomyelitis in humans and non-human primates), coxsackie A viruses (associated with herpangina, human central nervous system disease, and flaccid paralysis in suckling mice), coxsackie B viruses (human central nervous system and cardiac disease, spastic paralysis in mice), and the echoviruses (nonpathogenic in mice, and not initially linked to human disease).

Enteroviruses are now assigned sequential numbers and grouped based on genetic and phenotypic similarity. To date, more than 110 genetically distinct enteroviruses that infect humans and non-human primates have been identified and placed into 4 species (Table 1). The EV-A group includes Coxsackievirus A6 (CV A6), coxsackievirus A16 (CVA16), Enterovirus A71 (EV-A71) and 22 other serotypes. CVA16 and EV-A71 are the most common causes of hand foot and mouth disease (HFMD), especially in Southeast Asia. EV-B is the largest enterovirus species, consists of 63 viruses including coxsackievirus B1-B6, 7 of the original echoviruses, and 50 other serotypes. EV-C includes the three polioviruses and 20 other serotypes, including EV-C105, which has been linked to recent pediatric cases of acute flaccid myelitis. EV-D includes EV-D68, EV-D70, EV-D94, EV-D111, and EV-D120. EV-D68, originally identified in 1962, caused recent outbreaks of severe respiratory disease and possible neurologic disease.

Recent Outbreaks

Epidemic Hand Foot and Mouth Disease (HFMD)

Hand foot and mouth disease (HFMD) was originally identified as a specific manifestation of enterovirus infections in 1956. [1,2] HFMD is caused by many enteroviruses, but most often by several members of the EV-A species: coxsackieviruses A6 and A16 and enterovirus 71 (EV-A71). Outbreaks of EV-A71 HFMD have been frequently reported since

1969, but a series of EV-A71 epidemics in the Asia-Pacific region (Australia, Japan, Malaysia, Taiwan, Vietnam, and China) between 1997 and 2010 have raised particular concern about the potential emergence of EV-A71 as a worldwide health threat. [3–5] In the largest of these, thousands of Taiwanese infants and children in 1998 developed the characteristic hand-foot-and mouth disease seen with EV-A71 (and CV-A16) in which small fluid-filled lesions appear on the hands, feet, and buttocks, and in the mouth. [6–8] Brain stem encephalitis and non-cardiogenic pulmonary edema were commonly encountered in these recent outbreaks, and were associated with a high mortality rate. [4,6,7,9] Neurologic and neuropsychiatric sequelae appear to be common in children who survive EV-A71 central nervous system infection. [3,10] HFMD outbreaks represent a perennial threat in China, resulting in an estimated 7.2 million cases between 2008 and 2012. [11] EV-A71 was responsible for about 80% of approximately 82,000 severe cases and 93% of the 2457 deaths during this period. [11]

By contrast, recent outbreaks of severe HFMD in the United States were caused by CVA6, mirroring similar outbreaks in Finland and other countries. [12,13] These cases occurred in late fall and winter of 2011–2012. Hospitalization occurred in 19% of total cases and 24% of cases were seen in adults. In some infants and children with CVA6 infections, impetiginous and remarkably large bullous lesions were seen, leading to the descriptive title of “eczema coxsackium”. [14] Onychomadesis (loss of fingernails and toenails) occurred in some individuals. The average severity of illness, identification of CVA6, and seasonality each were unusual for HFMD in the United States. [13,14]

Coxsackievirus B1 myocarditis in newborns

A recent outbreak of coxsackievirus B1 (CVB1) (a member of the EV-B species) also demonstrated the epidemic potential of enteroviruses. In mid-2007, cases of severe neonatal disease due to CVB1 were recognized nearly simultaneously in Chicago, IL, Los Angeles, CA, and Kotzebue, AK. Three deaths occurred among 21 confirmed cases (14%). [15] Additional cases were identified in 22 other states over the next 18 months [16,17], and CVB1, not previously associated with infant mortality, transiently became the predominant enterovirus serotype identified in the United States. [18] Reports of CVB1 disease to CDC’s National Enterovirus Surveillance System (NESS) have waned since 2009, but it remained among the most commonly circulating enteroviruses between 2009 and 2013. [19]

Poliomyelitis eradication – progress and perils

Significant progress has been made in the global effort to interrupt poliovirus transmission and eradicate polio. Wild poliovirus type 2 (WPV2) circulation has not been detected since 1999, and no cases of paralysis caused by wild poliovirus 3 (WPV3) have been identified since 2012. Moreover, no cases of polio have occurred in India since 2011 and the country is now considered polio free. [20] These successes reaffirm the technical possibility of eradication of polio, but challenges remain in Pakistan, Afghanistan, and Nigeria. [21] Of these, Nigeria appears to be closest to fully interrupting poliovirus circulation and elimination of polio, but events there have demonstrated the fragile nature of progress. In 2000, rumors that the vaccine could produce sterility led to a prolonged ban on immunization by the Sharia council of Nigeria. [21] Over the 16 month period of

interruption caused by this ban, polio cases rose from less than 50 in 2000 to more than 250 in 2003, and poliovirus was exported to 25 other countries that had previously been declared polio free. [21] Fortunately, these setbacks were reversed, and no cases of paralysis due to wild poliovirus have been identified in Nigeria since July, 2014.

Efforts to eliminate poliovirus circulation continue in Afghanistan and Pakistan, but progress has been delayed by factors that have made vaccination unavailable for approximately 5–25% of children in the region. In Afghanistan, these barriers include limited healthcare, poverty, and religious restrictions on interactions between caregivers and vaccinators, and threats of violence. Mirroring attacks on vaccinators in Nigeria in 2013, threats and killings of vaccinators have also occurred in both Pakistan and Afghanistan. [22]

Oral poliovirus vaccine (OPV) has been an essential tool in the effort to eliminate polio, but its use is not risk free. Vaccine associated paralytic poliomyelitis (VAPP) may occur after OPV administration, and cases have been reported since 1960. These events are rare, and more likely to occur after the first dose or in persons with a primary immunodeficiency. Paralysis may also occur with infection with vaccine derived polioviruses (VDPV); these are OPV-like isolates, which are distinguished from vaccine strains by genetic analysis of VP1 capsid encoding sequences. By definition, circulating VDPV (cVDPV) differ from the OPV strains by >0.6% (PV2) or >1% (PV1 and PV3); these changes indicate persistent replication after administration of OPV. [23] In Afghanistan, the first case of disease caused by cVDPV was reported in 2009–2010, and 11 cases were reported in 2012. These cases had a median age of 18 months, and vaccination history of 2 OPV doses, suggesting inadequate vaccination may propagate the risk of spreading WPV from OPV [22] Better adherence to vaccination schedules and increased vaccination campaigns with complete penetration into at risk populations are crucial. Strategies to decrease poliomyelitis in Afghanistan include identifying high-risk areas, and focusing special efforts on these areas. [22] Transit vaccination teams at border crossings into Pakistan and Iran have been successful in vaccinating >1 million children per year. [22] These efforts may be bearing fruit, as no cases of paralysis caused by cVDPV have been reported in Afghanistan or Pakistan between January and October of 2015.

The existence of circulating cVDPV has shaped plans for the polio eradication “end game”. In 2015, 15 cases of polio have been caused by cVDPV, and 51 by WPV1. A shift from use of trivalent oral poliovirus vaccine in favor of more bivalent OPV (types 1 and 3), phased introduction of inactivated poliovirus vaccine (IPV), and prompt efforts to extinguish cVDPV outbreaks are key elements of plan to eradicate polio. Accurate and consistent environmental surveillance to detect ongoing circulation of poliovirus will be essential in these efforts. [24]

Emerging Enteroviruses and associations with Acute Flaccid Myelitis

Evaluation of recent causes of acute flaccid myelitis

EV-C enterovirus diseases include emerging strains EV-C105, C109, and C116, which have been detected throughout the world. EV-C105 was first reported in the Democratic Republic of Congo in late 2010 from a fecal sample of a patient with acute flaccid paralysis. It was

initially misclassified as EV-C109, but was reclassified in 2012 as EV-C105. [25] EV-C105 was also reported in New Zealand in a man with respiratory symptoms including cough and wheezing [26]. Five circulating EV-C105 strains were compared from Europe and Africa in 2015. This comparison showed EV-C105 was closely related to EV-C109 and EV-C118, but that the strains circulating in Africa were distinct from the strains circulating in Europe. [27] Tracking other non-polio enterovirus causes of acute flaccid myelitis, including EV-C105, remains an important step in poliovirus elimination. [28,29]

Enterovirus D68 respiratory and neurologic disease

Enterovirus D68 (EV-D68) was first isolated in 1962 [30] from children with respiratory illness, but had limited circulation in the United States for the next 4 decades, with only 26 reports to the NESS between 1970 and 2005.[31] EV-D68 has been increasingly reported worldwide since 2004, with reports from Thailand, the Netherlands, New Zealand, Kenya, and a cluster of 120 patients in Japan in 2010. [32] In the United States between 4.3 % of specimens sent to NESS between 2009 and 2013 were positive for EV-D68. [19] Between 2013–2014, EV-D68 was detected in 1% of nasopharyngeal swabs performed in a surveillance study of children hospitalized with severe respiratory illness in the Philippines, 7 of 20 (35) of those with EV-D68 infection developed wheezing. [33] Moreover, EV-D68 viruses detected after October 2013 represented a distinct genetic sub-lineage compared to EV-D68 collected between 2011 and 2013. [33]

During the summer of 2014, EV-D68 was detected in every U.S. state, excluding Alaska. [34] Beginning with reports from Kansas City, MO, in 2014 EV-D68 was linked to clusters of severe respiratory illness. Symptoms often included shortness of breath, wheezing, and respiratory failure requiring mechanical ventilation. EV-D68 caused more severe disease in patients with history of asthma and reactive airway disease. Less than 50% of patients were febrile, and it is possible that milder cases of respiratory illness caused by EV-D68 were being underreported [35]. Co-detection of other pathogens was rare. These outbreaks were eventually detected due to the striking severity of disease. More outpatient surveillance data is needed to determine the full spectrum of disease of EV-D68, which may include a majority of patients with more mild disease.

EV-D68 was also detected in respiratory specimens of a few patients with acute flaccid myelitis, and in some patients with aseptic meningitis or encephalitis. EV-D68 has been reported in at least 2 patients with enterovirus-associated encephalitis, suggestive of neurotropism. There was an outbreak of enterovirus D68 respiratory illness in Colorado, described as a defined cluster of acute flaccid myelitis and cranial nerve dysfunction in a small population of patients. EV-D68 was isolated from the respiratory tract of 5 of 11 patients in this outbreak, [36] but causality was not clearly demonstrated. The virus has not yet been detected in the spinal fluid of any patients with acute flaccid myelitis. Additional investigation is needed to determine if there is a direct link between EV-D68 infection and AFM, including the possibility that the virus is a trigger of immunologic grey matter injury. [34]

Treatment of enteroviruses: recent progress

Treatment of enteroviruses is supportive, focusing on the management of the most severe physiological derangements. For example, in 2014 approximately 51% of patients with EV-D68 infections at one center required ventilator assistance (non-invasive or mechanical ventilation). [35] In cases of neonatal sepsis and meningitis, administration of IGIV or hyper immune plasma has been used, based on case reports and small clinical studies suggesting amelioration of disease. However, high concentrations of antibody to neutralize the specific virus found in the infected individual are needed to alter the disease course. [37,38] After the 2014 outbreak of EV-D68 commercial IGIV lots were tested for levels of antibody to D68 and were shown to have high titers of neutralizing. [39] Passive immunization with IGIV could be attempted in EV-D68 disease as an adjunct to supportive care.

The enterovirus outbreaks described above highlight the ongoing, unmet need for antiviral medications with activity against enteroviruses. Further impetus for the development of anti-enteroviral medications comes from the threat represented by the cVDPVs and the persistent replication of OPV strains in immunocompromised hosts. [40]

A variety of molecules have been identified that bind to enterovirus capsids or that interfere with viral proteins involved in enterovirus replication; several of these have made it into clinical trials. Pleconaril is a viral capsid inhibitor with broad antiviral activity against enteroviruses and rhinoviruses. It binds to the viral capsid and prevents attachment, uncoating, and subsequent release of intracellular viral RNA. Pleconaril has modest antiviral activity in the treatment of common colds due to rhinoviruses and enteroviruses, but was not granted FDA approval due to concerns about drug-drug interactions, evolution of drug resistance, and other concerns. [41] However, the results of a lengthy double-blind, placebo-controlled trial of pleconaril for the treatment of neonates with enterovirus sepsis were recently published. [42] In intent to treat analysis, deaths were less common in pleconaril treated infants than placebo recipients (10/43 (23%) versus 8/18 (44%), $p = 0.02$), but the differences in mortality rates of children with proven enterovirus infection were not significantly different (7/31 (23%) versus 5/12 (42%), $p=0.26$). [42] The small study size of the study, low serum concentrations of pleconaril in the first 24 hours of treatment, and other factors make it difficult to assess the therapeutic potential of pleconaril in neonates. The authors called for additional studies based on evidence of viral suppression and other statistical signals suggesting drug efficacy. [42]

Other capsid-binding agents exist including pirodavir and vapendavir, and these exhibit activity against EV-A71 and poliovirus strains. [43] However, clinical experience with these is very limited, and none had significant antiviral activity against the strains of EV-D68 that circulated in 2014. [44] Other novel specific inhibitors of enterovirus have been identified. However, progress towards clinical studies has been impeded due to limited antiviral activity, poor bioavailability, intrinsic resistance by some circulating strains, and pharmacoeconomic considerations. [38]

Repurposing of existing medications would facilitate the development of antiviral therapy for enteroviruses. For example, the antimalarial drug mefloquine, the antidepressant

fluoxetine, and the diuretic amiloride all exhibit in vitro activity against one or more enteroviruses.[38] Similarly, fluoxetine was found to inhibit EV-B and EV-D enteroviruses, including EV--D68, and group B coxsackieviruses. [44–46] Unfortunately, achievable serum concentrations of fluoxetine and its active metabolite norfluoxetine are lower than inhibitory thresholds likely to be required to treat systemic disease [45]; CSF concentrations are higher and hypothetically therapeutic. [47] Similarly, mefloquine exhibits little activity at achievable concentrations. At present, specific antiviral therapy for enteroviruses remains beyond the horizon.

Vaccine Development

Based on prior experience with poliovirus it is assumed that an effective vaccine could play an important role in reducing the disease burden associated with enteroviruses. There has been ongoing research in this area, with significant study of vaccines for EV-A71. Immunization of pregnant mice with virus like particles (VLPs) demonstrated protection of neonatal mice challenged with EV-A71. [48]. A live attenuated strain of EV-A71 was derived from the prototype strain BrCr, and inoculation of monkeys led to production of antibodies that demonstrated cross reactivity with many enterovirus strains. However in this study it also led to neurologic symptoms and was found to enter the spinal cord. [49,50] More recently, large scale clinical trials of an inactivated alum-adjuvant vaccine. [51] This vaccine was 95.1% effective in preventing HFMD in recipients of 2 doses. High levels of neutralizing antibodies were demonstrated and no vaccine-attributable adverse events were reported during the study. [51] More follow up is needed to determine long term protection.

Conclusion

Recent outbreaks have highlighted the public health impact of enteroviruses; recurrences of known pathogens and the evolution of additional new variants should be anticipated. Continued surveillance of circulating strains is essential, and clinicians should utilize rapid molecular diagnostic methods to recognize enteroviral disease. The morbidity and mortality associated with recent enterovirus outbreaks demonstrates the urgent need for antiviral therapies for enteroviruses. Research to develop vaccines and antiviral agents should be prioritized.

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Key Points

- Recent outbreaks of EV-A71 demonstrate the magnitude and significant morbidity associated with enteroviruses, and emphasize the need for vaccine development.
- EV D68 has previously caused respiratory disease but recently has been isolated in several epidemics causing severe disease in children, and has been suspected of causing neurologic disease in some cases, but the link is unclear.
- There has been significant progress in the effort to eradicate polio, but challenges remain in areas where the political climate impairs vaccination efforts.
- Treatments for enterovirus are mainly supportive, but antivirals are currently being investigated.

Table 1

Enteroviruses: Current Taxonomy and Associated Diseases in Recent Outbreaks

Enterovirus Species	Types	Recent Outbreaks
A	Coxsackievirus 1–8, 10, 12, 14, 16 Enterovirus A71, A76, A89, A90, A114, A119, A120, A121	Severe Hand-Foot – and Mouth Disease due to CVA6, CVA16, and A71 in many countries
B	Coxsackie B 1–6, A9, Echovirus 1–7, 9,11–21, 24–27, 29–33 Enterovirus B 69, 73–75, 77–88, 93, 97, 98, 100, 101, 106 and 107	Neonatal sepsis due to CVB1
C	Coxsackie virus A1, 11, 13, 17, 19, 20, 21, 22, 24, Enterovirus C 95, 96, 99, 102, 104, 105, 109, 113, 116–118 Poliovirus 1–3	Small outbreaks of cVDPV and paralytic disease to newer EV-C viruses
D	EVD68 D70, D94, D111	Worldwide reports of EVD68 respiratory diseases. Association with acute flaccid myelitis