Journal of NeuroVirology, 11: 424–433, 2005

ISSN: 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280591002531

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Review

Enteroviruses as agents of emerging infectious diseases

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Although the enteroviruses as a group are ubiquitous and not normally considered as "emerging pathogens," the many different serotypes circulate at different frequencies in any given year and the prevalence of a given serotype may fluctuate wildly from year to year. As a result, several enterovirus serotypes have been associated with the emergence of specific diseases (for example, pandemic acute hemorrhagic conjunctivitis) and specific serotypes have emerged to cause outbreaks of major public health concern. Enterovirus 71 is a recognized cause of epidemic severe central nervous system disease in Southeast Asia. Acute hemorrhagic conjunctivitis was a newly described disease in the 1970s associated with emergence of enterovirus 70 and coxsackievirus A24 variant. In addition, the impending eradication of poliovirus and some of the challenges currently faced by the eradication program present the possibility that poliomyelitis could emerge in the posteradication era. These links between enterovirus infections and emerging diseases are reviewed. *Journal of NeuroVirology* (2005) **11,** 424–433.

Keywords: emerging infectous disease; enterovirus

Introduction

Enteroviruses are among the most common of human viruses, infecting an estimated 50 million people annually in the United States and possibly a billion or more annually worldwide (Morens and Pallansch, 1995; Pallansch and Roos, 2001). Most infections are inapparent, but enteroviruses may cause a wide spectrum of acute disease, including mild upper respiratory illness (common cold), febrile rash (hand, foot, and mouth disease and herpangina), aseptic meningitis, pleurodynia, encephalitis, acute flaccid paralysis (paralytic poliomyelitis), and neonatal sepsis-like disease. Although fewer than 1% all of infections cause significant symptomatic illness, enterovirus infections result in 30,000 to 50,000 hospitalizations per year in the United States, with aseptic meningitis cases accounting for the vast majority of the hospitalizations (Pallansch and Roos, 2001). In addition to these acute illnesses, enteroviruses have also been associated with severe chronic diseases, including myocarditis and dilated cardiomyopathy (Kearney *et al*, 2001; Kim *et al*, 2001; Martino *et al*, 1995; Zhang *et al*, 2000), type 1 diabetes mellitus (Hyoty and Taylor, 2002; Leinikki, 1998; Rewers and Atkinson, 1995), and neuromuscular diseases (Dalakas, 1995).

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General characteristics

Viral taxonomy

Of the 89 recognized enterovirus serotypes (King *et al*, 2000), 64 are known to infect humans (Pallansch and Roos, 2001) and additional serotypes have been characterized (Norder *et al*, 2003; Oberste *et al*, 2000a, 2001, 2004a). Most of the human enterovirus serotypes were discovered and described between 1947 and 1963 as a result of the application of cell culture and suckling mouse inoculation to the investigation of cases of paralytic poliomyelitis and other central nervous system diseases (Committee on Enteroviruses, 1962; Panel for Picornaviruses, 1963). The human enteroviruses

were originally classified on the basis of human disease (polioviruses), replication and pathogenesis in newborn mice (coxsackie A and B viruses), and growth in cell culture without causing disease in mice (echoviruses), but they have recently been reclassified, based largely on molecular properties. In the current classification scheme, the genus is divided into five species: (i) *Poliovirus* (PV; PV1 to PV3), (ii) *Human enterovirus A* (HEV-A; CVA2 to CVA8, CVA10, CVA12, CVA14, CVA16 and EV71), (iii) *Human enterovirus B* (HEV-B; CVA9, CVB1 to CVB6, E1 to E7, E9, E11 to E21, E24 to E27, E29 to E33 and EV69), (iv) *Human enterovirus C* (HEV-C; CVA1, CVA11, CVA13, CVA15, CVA17 to CVA22, and CVA24), and (v) *Human enterovirus D* (HEV-D; EV68 and EV70). Recent studies suggest that polioviruses should be reclassified as members of HEV-C (Brown *et al*, 2003). Several new serotypes (EV73-75 and EV77-78), all members of HEV-B, have been recently described (Norder *et al*, 2003; Oberste *et al*, 2000a, 2001, 2004a).

Genomic organization

The enterovirus genome is a single-stranded, positive-sense RNA of about 7.4 kb, with a 22-amino-acid virus-encoded protein (3B*VPg*) covalently linked to the 5′ end. The single open reading frame encodes a polyprotein of about 2200 amino acids that is processed to yield the four capsid proteins, 1A to 1D (VP4, VP2, VP3 and VP1, respectively); a protease, 2A*pro*, and proteins 2B and 2C; the 3B*VPg* precursor (3AB), the major viral protease (3C*pro*), and the RNA-dependent RNA polymerase (3D*pol*).

Receptor usage

Virus infection is dependent on the presence of specific receptors. Seven distinct receptors for different enteroviruses have been identified from human cells, the poliovirus receptor (PVR; CD155), three integrins ($\alpha_2\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_6$), decay-accelerating factor (DAF; CD55), the coxsackievirus-adenovirus receptor (CAR), and intracellular adhesion molecule 1 (ICAM-1) (Bergelson *et al*, 1992, 1994, 1997; Carson *et al*, 1997; Mendelsohn *et al*, 1989; Roivainen *et al*, 1994; Schneider-Schaulies, 2000; Shafren *et al*, 1997; Williams *et al*, 2004). Some enteroviruses are able to use more than one receptor and other unidentified receptors may also exist.

Pathogenesis

Enteroviruses are cytopathic, and much of the associated disease presumably results from tissue-specific cell destruction but some disease manifestations, enteroviral exanthems and myocarditis for example (Modlin, 1990; Pallansch and Roos, 2001; Woodruff, 1980), are thought to result from the host immune response to the infection. In most cases, however, the actual mechanisms of virus-induced disease have not been well characterized. Some insight into human myocarditis has been gained from recent studies using animal model systems (Gauntt, 1997; Kandolf, 1996; Kim *et al*, 2001; Klingel *et al*, 1996; Tracy *et al*, 2000). Typically, the primary site of infection is the epithelial cells of the respiratory or gastrointestinal tract, followed by a viremia that may lead to a secondary site of tissue infection. Secondary infection of the central nervous system results in aseptic meningitis or, rarely, encephalitis or paralysis. Other tissue-specific infection can result in pleurodynia or myocarditis. Disseminated infection can lead to exanthems, nonspecific myalgias, or severe multiple-organ disease in neonates.

Enterovirus infection elicits a strong humoral immune response. Often this response is heterotypic; that is, infection with one serotype induces an immune response that cross-reacts with other serotypes (Dorries and ter Meulen, 1983; Pattison, 1983). Young children develop a more homotypic response, whereas older children and adults develop a more heterotypic response. This age difference in the specificity of the antibody response to an enterovirus infection presumably reflects exposure to a greater number of serotypes with increasing age. The basis of this heterotypic response is not known, but it may reflect the presence of epitopes shared among multiple serotypes.

Enterovirus identification

The availability of sequence data for all members of the enterovirus genus has enabled differentiation of viruses based on the nucleic acid sequence encoding the VP1 capsid protein (Oberste *et al*, 1999d). Molecular identification can be performed using reverse transcriptase–polymerase chain reaction (RT-PCR) amplification products obtained from original clinical specimens (Casas *et al*, 2001; Palacios *et al*, 2002b) or virus isolates (Caro *et al*, 2001; Casas *et al*, 2001; Manzara *et al*, 2002; Norder *et al*, 2001; Oberste *et al*, 1999c, 2000b, 2003). Sequences surrounding the VP4-VP2 junction have also been used for molecular typing (Arola *et al*, 1996; Ishiko *et al*, 2002; Santti *et al*, 1999), but this region does not always provide a reliable identification (Casas *et al*, 2001). Sequences in various portions of the enterovirus coding region correlate with species, but only capsid sequence correlates with serotype, due to the high frequency of interserotypic recombination among cocirculating enteroviruses of the same species (e.g., within HEV-B) (Brown *et al*, 2003; Lindberg *et al*, 2003; Lukashev *et al*, 2003; Lukashev *et al*, 2004; Oberste *et al*, 2004a, 2004b). Several new serotypes, including EV73 (Norder *et al*, 2002; Oberste *et al*, 2001), EV74 (Oberste *et al*, 2000a, 2004a), EV75 (Oberste *et al*, 2004a), and EV77-78 (Norder *et al*, 2003), have been

detected and characterized using molecular typing systems and sequencing.

Epidemiology and molecular epidemiology

Enteroviruses are isolated in the highest titer and for the longest time in stool specimens but can also be isolated from respiratory secretions (Pallansch and Oberste, 2003). Therefore, both fecal-oral transmission and spread by contact with respiratory secretions (person-to-person, fomites, and possibly large particle aerosol) are considered the most important modes of transmission. The relative importance of the different modes probably varies with the virus and the environmental setting. In addition, enteroviruses that cause a vesicular exanthema can, presumably, be spread by direct or indirect contact with vesicular fluid which contains infectious virus (Pallansch, 2000). Exceptions to the usual modes of enterovirus transmission are the agents of acute hemorrhagic conjunctivitis, EV70 and CVA24 variants. These two viruses are seldom isolated from respiratory tract or stool specimens and are probably spread primarily by direct or indirect contact with eye secretions (Pallansch, 2000).

Many studies have examined the prevalence of antibodies to the enteroviruses in specific populations (Bell and McCartney, 1984; Danes and Jaresova, 1985; Lau, 1983; Manjunath *et al*, 1982; Margalith *et al*, 1986; Morag *et al*, 1984; Mukundan and John, 1983; Santhanam and Choudhury, 1984). Several important conclusions can be drawn from these serosurveys. First, the number of persons who have neutralizing antibody to any given enterovirus is large, indicating a high incidence of past infection. A high incidence of recent infection is also suggested by immunoglobulin M (IgM) surveys, which typically show 4–6% positivity. Second, infections with one serotype of enterovirus can boost the antibody titers to other enterovirus serotypes as measured by either IgM or neutralization. The pattern of the heterotypic response varies by serotype and among individuals. Third, the pattern of antibody prevalence by serotype varies by geographic location, by time, and by age. Thus prevalence data from different years and locations are not directly comparable. These three points must be considered when interpreting the findings of serologic studies of associations between enterovirus infection and disease.

An important concept in understanding the epidemiology of the enteroviruses is variation: by serotype, by time, by geographic location, and by disease. This concept is illustrated in surveillance studies of non-polio enterovirus infections (Centers for Disease Control and Prevention, 1997; Centers for Disease Control and Prevention, 2000; Moore, 1982; Morens and Pallansch, 1995; Morens *et al*, 1979; Strikas *et al*, 1986; Trallero *et al*, 2000; Yamashita *et al*, 1992). There are two major patterns of enterovirus prevalence: endemic and epidemic (Pallansch and Oberste, 2003). The epidemic pattern, as typified by echovirus 9 (E9), is characterized by sharp peaks in numbers of isolations followed by periods with few isolations. From 1970 to 2001, major epidemics of E9 occurred in the United States every 3 to 4 years, in 1971, 1975, 1978, 1981, 1984, 1988–1989, 1992, 1995, and 1998. Echovirus 30 (E30) also exhibits an epidemic pattern, but with much broader peaks, spanning 1978–1985, 1990–1993, and 1997–1998. By contrast, CVB3 was isolated in about the same numbers every year, with only one major peak (in 1980), typifying the endemic circulation pattern. Similar endemic and epidemic patterns are seen for other enteroviruses, but the biological basis for these patterns remains unknown.

The adoption of molecular techniques for characterization of enterovirus epidemiology extends this knowledge. Enterovirus nucleotide sequencing was first used as an epidemiologic tool to characterize the geographic distribution of wild polioviruses, using a 150-nucleotide sequence surrounding the VP1-2A junction (Rico-Hesse *et al*, 1987). These studies showed that polioviruses circulating in a given geographic region tended to be closely related genetically and distinct from those circulating in distant locales. Since then, the sequence window has been expanded to include the entire VP1 gene (~900 nucleotides) to provide higher resolution, and this region has been adopted as the standard for molecular epidemiologic investigations of both polioviruses and nonpolio enteroviruses (Kew and Pallansch, 2002).

The epidemic behavior of some enteroviruses is illustrated by E30 where prevailing lineages displace the less established lineages (Oberste *et al*, 1999b; Palacios *et al*, 2002a; Savolainen *et al*, 2001). E30 lineages do not seem to be geographically restricted as a given lineage may circulate in different regions of the world at the same time.

The sudden emergence of E13 as a prominent enterovirus worldwide in 2001 (Avellon *et al*, 2003; Mullins *et al*, 2004), and its subsequent disappearance, demonstrates the potential of enteroviruses to unpredictably circulate with considerable clinical disease, and underscores the continued need for enterovirus surveillance. Global circulation of enterovirus serotypes causing widespread clinical disease has been noted in the past, particularly with E9, E30, and EV70, and EV71 (Brown *et al*, 1999; Melnick, 1997; Oberste *et al*, 1999a).

The endemic behavior of other enteroviruses at the molecular level is exemplified by cocirculation of CVB4 strains belonging to different genetic lineages within one country (Mulders *et al*, 2000). CVB4 can circulate in a given area for many decades; viruses belonging to the same genotype were found in the Netherlands between 1965 and 1990. On several occasions genetically similar viruses were found to circulate in geographical regions that were far apart,

reflecting either previous epidemic spread or global persistence of the genotype.

Enterovirus 71

Enterovirus 71 (EV71) is one of two EV serotypes most often associated with large outbreaks of hand-foot-and-mouth disease (HFMD) and may also cause a variety of neurologic diseases, including aseptic meningitis, encephalitis, and poliomyelitis-like paralysis. EV71 has caused epidemics of severe neurologic disease in Australia, Europe, Asia, and the United States (Abubakar *et al*, 1998; Alexander *et al*, 1994; Blomberg *et al*, 1974; Chonmaitree *et al*, 1981; Chumakov *et al*, 1979; da Silva *et al*, 1996; Deibel *et al*, 1977; Gilbert *et al*, 1988; Ishimaru *et al*, 1980; Kennett *et al*, 1974; Komatsu *et al*, 1999; McMinn *et al*, 1999; Melnick, 1984; Nagy *et al*, 1982; Samuda *et al*, 1987; Schmidt *et al*, 1974; Shindarov *et al*, 1979). Most recently, EV71 was associated with fatal cases of brain-stem encephalitis during large HFMD outbreaks in Malaysia in 1997 (Cardosa *et al*, 2003; Chan *et al*, 2000) and in Taiwan in 1998 (Ho *et al*, 1999; Lin *et al*, 2003). Like poliovirus, EV71 displays an affinity for anterior horn cells (Chumakov *et al*, 1979) and it is the most common non-polio enterovirus associated with poliomyelitis-like paralysis (Melnick, 1984).

Three neurological syndromes were recognized as complications of EV71 infection in the Taiwanese epidemic: aseptic meningitis (3 patients), brain-stem encephalitis, or rhombencephalitis (37 patients), and acute flaccid paralysis (4 patients) (Huang *et al*, 1999). The severity of the rhomboencephalitis was graded from I to III: grade I disease was characterized by myoclonic jerks, tremor, and ataxia; grade II disease exhibited myoclonus and cranial nerve involvement; and grade III disease included extensive brain stem damage and acute cardiorespiratory failure. Pathological examination showed focal inflammation of the pontine tegmentum in grade I disease whereas widespread inflammation was seen in the central gray matter of the spinal cord and medulla oblongata in grade III disease. It is possible that the brain stem lesions resulted from direct invasion by EV71 (Chang *et al*, 1998; Lum *et al*, 1998). Interestingly, destruction of the respiratory and vasomotor centers in the lower brain stem appear to explain the neurogenic pulmonary edema and vasomotor collapse in patients with grade III disease (Lum *et al*, 1998). It should be noted that there is no histologic evidence for viral myocarditis in EV71 infection, arguing against a cardiogenic cause of the pulmonary edema (Yan *et al*, 2000).

EV71 usually accounts for less than 3% of the enteroviruses reported annually in the United States (Brown *et al*, 1999). However, a seroepidemiological study conducted in New York State in 1972 showed that EV71 infection is relatively common; 26% adults had detectable anti-EV71 antibodies in their serum (Deibel *et al*, 1977). Preliminary studies suggest that neutralizing antibodies against EV71 may have been present in the serum of approximately half of the adult population before and after the epidemic in Taiwan (Ho, 2000).

Given the nature of the pathogenicity of this serotype and the outbreaks of severe disease with which it has been associated, the molecular epidemiology of EV71 has been widely studied (Brown *et al*, 1999; Cardosa *et al*, 2003; Chu *et al*, 2001; Herrero *et al*, 2003; McMinn *et al*, 2001; Shimizu *et al*, 2004). The molecular epidemiological analysis of recent and previous EV71 isolates indicates that there are two major EV71 genogroups (B and C) cocirculating worldwide (the EV71 prototype strain, BrCr, is the only known example of genogroup A). Viruses of both genogroups B and C have been associated with both mild and severe disease so the viral factors influencing disease severity remain unknown.

Poliovirus

Since the start of the World Health Organization's Global Polio Eradication Initiative, the number of cases of acute flaccid paralysis (AFP) due to poliovirus has been reduced by over 99%, from over 350,000 in 1988 to 784 in 2003 and to 185 during January–April 2004. In 2003, endemic wild poliovirus circulation continues in only six countries (India, Pakistan, Afghanistan, Egypt, Nigeria, and Niger), but cases linked to reservoirs in Nigeria and Niger have been reported in several other West and Central African countries (Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Côte d'Ivoire, Ghana, and Togo), one Southern African country (Botswana), and one in the Middle East (Lebanon). In the first part of 2004, a total of 17 cases have been reported from six of these countries and one in Southern Africa (Botswana) (Centers for Disease Control and Prevention, 2004). The importation of wild poliovirus into these countries was largely attributable to continued high-level transmission in Nigeria and Niger coupled with declining and poor quality polio vaccine coverage in the affected countries. Elimination of remaining wild poliovirus reservoirs and maintaining adequate vaccine coverage in adjacent areas is critical to preventing poliovirus from re-emerging as a significant cause of AFP in areas from which wild poliovirus has been eliminated.

The last case of poliomyelitis in the Western Hemisphere associated with circulating indigenous wild poliovirus was reported in Peru in 1991 (Robbins and de Quadros, 1997). The only known wild poliovirus infections in the Americas after 1991 were imported cases (Drebot *et al*, 1997). Neither of these importations was associated with paralytic disease, and intensive surveillance found no evidence of spread of virus to the wider community. In countries using

oral poliovirus vaccine (OPV), type 1 vaccine virus is often isolated from the stools of patients with AFP (Andrus *et al*, 1995; de Quadros *et al*, 1997) and OPV-derived viruses may occasionally cause vaccine-associated paralytic poliomyelitis (VAPP), due to reversion of attenuating mutations in the vaccine strains. In 2000 to 2001, cases of AFP were reported from the Dominican Republic and Haiti; poliovirus type 1 was isolated from stool samples collected from the case patients (Kew *et al*, 2002). Sequence characterization of the two isolates showed that they were not related to any known wild polioviruses, but that they were closely related (>97% VP1 sequence identity) to the Sabin type 1 vaccine strain and to each other. The degree of VP1 sequence similarity to the OPV strain was significantly lower than is normally observed (>99.5%) with vaccine-related isolates from cases of AFP or VAPP and the sequence relationships between the two isolates suggested that they were derived from a recent common ancestor, as is typical of wild polioviruses isolated during an outbreak (Shulman *et al*, 2000). Taken together, the data suggested that vaccine-derived polioviruses (VDPVs), derived from a single OPV dose given in 1998 to 1999, had reverted to wild-virus virulence and transmissibility and circulated widely for 2 to 3 years, due to the extremely low rate of vaccine coverage (7% to 40%) (Kew *et al*, 2002). Evidence of circulating VDPVs has also been found in at least three other countries (Egypt, Philippines, and Madagascar), in addition to the Hispaniola outbreak, suggesting that the risk of VDPV-associated AFP outbreaks is high in areas with inadequate polio immunization (Centers for Disease Control and Prevention, 2001, 2002; Yang *et al*, 2003).

The events in Hispaniola challenge the long-held assumption that polio outbreaks could recur in nonendemic countries only by reintroduction of wild poliovirus. The risk of wild poliovirus importation into Hispaniola was thought to be low (because of minimal contact with polio-endemic areas) and steadily declining (because of the rapid progress toward polio eradication worldwide) (World Health Organization, 2001). A widening immunity gap developed after 1989 when wild poliovirus circulation ceased and the rates of OPV coverage fell. It is critically important to prevent the development of similar immunity gaps in other nonendemic countries, especially as awareness of polio as a serious public health threat wanes. The Hispaniola outbreak and the cases of wild poliovirus importation reaffirm the need to maintain high levels of polio vaccine coverage and sensitive polio surveillance in all countries until global eradication has been achieved and certified.

Enterovirus 70

EV70 was first isolated in 1971 as one of two enteroviruses associated with a newly described disease, pandemic acute hemorrhagic conjunctivitis (AHC) (Mirkovic *et al*, 1973). The AHC epidemic had begun in 1969 in Ghana and spread across Africa to India and the Far East, with small outbreaks in Europe. It subsided, only to reappear in India in 1979, with subsequent spread to South America and the Caribbean, with isolated cases in the southern United States. The other enteroviral agent of AHC is an antigenic variant of coxsackievirus A24 (Mirkovic *et al*, 1974). The origin of EV70 remains a mystery. It is most closely related genetically to EV68, a potential progenitor whose existence was known at the time of EV70's global emergence in the AHC pandemic of 1970; however, the relationship is not so close as to suggest a direct ancestral relationship. It has been hypothesized that EV70 may have emerged through an unknown mechanism from an animal reservoir (Yoshii *et al*, 1977). One can only speculate that additional members of HEV-D remain to be discovered, either in humans or in animals, and that one of these strains may be closely related to the direct progenitor of the original EV70 AHC strain.

Simian enteroviruses

Although it may be uncommon, picornaviruses appear to be capable of occasionally infecting a species other than the natural host(s). Antigenic and molecular comparisons have suggested that swine vesicular disease virus emerged in the past 50 years through infection of swine with the human pathogen, coxsackievirus B5, followed by subsequent adaptation and evolution of the virus in the new host (Brown *et al*, 1973; Graves, 1973; Zhang *et al*, 1993, 1999). Serologic studies have suggested that the simian picornaviruses may infrequently infect humans, particularly those with natural or occupational exposure to wild primates (Kalter and Heberling, 1971). There is no evidence that simian picornaviruses are capable of causing disease in humans, but a number of other primate viruses, including herpesvirus B, are closely related to human pathogens and have the potential to directly cause serious disease in humans (Gorbach *et al*, 1992). The increasing encroachment of human activity on wild primate habitats may increase the risk of virus infection in species other than the natural host.

EV70 and EV71, agents of acute hemorrhagic conjunctivitis and HFMD, respectively, appear to have emerged as human pathogens relatively recently, but their origins remain unknown. EV70 emerged in a region of the world that is inhabited by wild primate populations, but none of the simian enteroviruses were members of HEV-D, the group that includes EV70. Likewise, none of the simian viruses were closely related to EV71, but many clearly belong to HEV-A, of which EV71 is also a member. Further studies are needed to study the natural enteroviral flora of wild primates, as very few species have been sampled

to date, and to determine the potential for primate enteroviruses to infect and cause disease in humans.

Conclusions

Most emergent viruses are zoonotic, with natural animal reservoirs a more frequent source of new viruses than is the spontaneous evolution of a new entity. The most frequent factor in emergence is human behavior increasing the probability of transfer of viruses from their endogenous animal hosts to man. Rodents and arthropods are most commonly involved in direct transfer, and changes in agricultural practices or urban conditions that promote rodent or vector multiplication favor increased incidence of human disease. Other animals, especially primates, are important reservoirs for transfer by arthropods. However, enteroviruses are widely accepted as having only a human reservoir.

In addition to the human and nonhuman primate enteroviruses, there are also enteroviruses that infect cattle and swine (King *et al*, 2000). Although no systematic surveys have been conducted, it is likely that other mammalian species also harbor members of the Enterovirus genus. One or more of these unknown animal enteroviruses may develop the ability to infect and cause disease in humans.

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