

# Neonatal Enterovirus Infections Reported to the National Enterovirus Surveillance System in the United States, 1983–2003

Nino Khetsuriani, MD, PhD, Ashley LaMonte, MPH, M. Steven Oberste, PhD,  
and Mark Pallansch, PhD

**Background:** Neonatal enterovirus (EV) infections lead to a wide range of clinical manifestations, from mild febrile illness to severe, sometimes fatal, sepsislike disease.

**Methods:** To determine the relationship of EV serotypes with the risk of neonatal infection and its fatal outcome, we analyzed data reported to the National Enterovirus Surveillance System (NESS) during 1983–2003.

**Results:** Of the 26,737 EV detections reported during this period, neonates accounted for 2544 (11.4% of those with known age). Serotypes most commonly isolated from neonates included echovirus (E) 11 (14.0% of EV with known serotype), coxsackievirus (CV) B2 (8.9%), CVB5 (7.5%), E6, E9 and CVB4 (6.8% each). CVB1–4, E11, and E25 were significantly more common, whereas CVA16, E4, E9, E21, E30, and human parechovirus 1 (formerly E22) were less common among neonates than among persons aged  $\geq 1$  month. Fatal outcome was noted for 3.3% of reports, with neonates at a higher risk of death than persons aged  $\geq 1$  month (11.5% versus 2.5%; odds ratio [OR] 5.1; 95% confidence interval [CI] = 3.3–7.8). Neonates infected with CVB4 were at a higher risk of death (OR 6.5; 95% CI = 2.4–17.7) than those infected with other EV.

**Conclusion:** EV are important neonatal pathogens associated with high risk of infection and death. Because of the limitations of the NESS (incomplete reporting, limited clinical data, bias towards more severe and younger cases), additional studies are needed to better evaluate the role of different EV in neonatal infections.

**Key Words:** enteroviruses, neonatal enterovirus infections, neonates

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Enteroviruses (EV) (family Picornaviridae, genus *Enterovirus*) are among the most common viruses infecting humans. *Enterovirus* includes 5 species of human EV (A, B, C, D, and polioviruses), with 68 currently recognized serotypes, traditionally classified as polioviruses, echoviruses, coxsackieviruses and numbered EV.<sup>1</sup> EV cause an estimated 10 to 15 million symptomatic infections in the United States each year. Diseases associated with EV infections range from minor undifferentiated febrile illness with or without rash (“summer cold”) and hand, foot, and mouth disease to more serious, sometimes fatal conditions, including aseptic meningitis, encephalitis, polioliike paralysis, myopericarditis and chronic EV infection of immunodeficient persons.<sup>2,3</sup>

Newborn infants, because of the immaturity of their immune response mechanisms, are considered to be at a higher risk of infection and serious clinical manifestations due to EV infections.<sup>2</sup> EV infections in neonates are common, especially during the summer and fall months,<sup>4–6</sup> and lead to a wide range of manifestations, from mild febrile illness to severe, potentially fatal sepsislike conditions with multiorgan failure, referred to as “neonatal enteroviral sepsis.”<sup>2,7,8</sup> Factors associated with the increased risk of neonatal EV infection include acquisition of infection transplacentally or from exposure to maternal secretions or blood during delivery, symptomatic EV illness in the mother around the time of delivery, and the lack of preexisting maternal antibodies to an infecting serotype.<sup>4,7,9–11</sup> Prenatal, intranatal, or early postnatal infection with clinical illness manifested in the first 2 weeks of life is associated with an increased risk of severe neonatal illness.<sup>8,9</sup>

Previous reports suggested that the risk of symptomatic neonatal EV illness varies by infecting serotype<sup>5</sup> and that group B coxsackieviruses (CVB) and echovirus (E) 11 are most commonly associated with neonatal enteroviral sepsis.<sup>9,10,12–14</sup> Of the 2 major clinical presentations of the neonatal enteroviral sepsis, the encephalomyocarditis syndrome (severe myocarditis, often accompanied by heart failure, and meningoencephalitis), is predominantly associated with CVB, whereas the hemorrhage-hepatitis syndrome (overwhelming hepatitis with hepatic failure and disseminated intravascular coagulation) is often associated with E11.<sup>9,12–14</sup> However, no previous studies have analyzed large numbers of surveillance reports for a large population over multiple years to address the relationship of specific EV serotypes with the occurrence and outcome of neonatal infections.

In this study, we describe the epidemiology of neonatal EV infections and analyze the relationship of individual serotypes with the risk of neonatal infection and its fatal

outcome using the data reported to the National Enterovirus Surveillance System (NESS) at the Centers for Disease Control and Prevention (CDC) during 1983–2003.

**METHODS**

NESS is the only nationwide, multiyear data source on circulating EV serotypes in the United States. The purpose of the system is to monitor temporal and geographic trends of EV infections across the United States. EV detections by serotype are reported by state public health laboratories and some private laboratories to CDC on a monthly basis. Limited demographic and clinical data are also collected. Because EV infections, with the exception of poliovirus infections, are not nationally notifiable conditions, reporting to NESS is voluntary, and the number of participating laboratories varies from one year to another.<sup>15,16</sup>

In this study, we analyzed the distribution of reported nonpolio EV detections by age group (neonates, defined as infants aged <1 month, versus those aged ≥1 month) by serotype, year, month, and outcome (fatal or not).  $\chi^2$  And Fisher exact test were used for comparisons and odds ratios (OR) and 95% confidence intervals (CI) were calculated. Poliovirus reports were excluded from the analysis. E22 and E23, which have been reclassified as human parechoviruses (HPeV) 1 and 2, respectively (members of genus *Parechovirus*, family Picornaviridae), were included because they share basic epidemiologic and clinical characteristics with nonpolio EV<sup>3,17</sup> and continue to be reported to NESS.<sup>15,16</sup>

**RESULTS**

Of the 26,737 nonpolio EV detections reported to NESS during 1983–2003, age was noted for 22,348 (83.6%). During the study period, neonates accounted for 2544 reports (11.4% of those with known age). EV serotype was specified in 24,607 (92.0%) instances and was recorded as unknown in 2130 (8.0%) reports. Simultaneous detection of 2 EV serotypes in specimens from the same patient was noted on 73 (0.3%) occasions. Age and specified EV serotype were available for 20,548 reports (76.9%).

EV most commonly detected in neonates included E11 (14.0% of 2356 reports with known serotypes), CVB2 (8.9%), CVB5 (7.5%), E9, E6, CVB4 (6.8% each), E30 (6.0%), CVB3 (5.9%), CVB1 (5.7%) and coxsackievirus A (CVA) 9 (4.9%) (Table 1). Together, these 10 most common serotypes accounted for 73.3% of all detections of EV of known serotype among neonates.

In the older age group, the 10 most common serotypes included E30 (12.0% of 18,239 reports with known serotypes), E9 (11.2%), E11 (10.6%), CVB5 (8.0%), E6 (6.1%), CVA9 (5.0%), E7 (4.9%), CVB2 (4.9%), E18 (4.1%) and CVB4 (3.6%) (Table 1). These viruses accounted for 70.4% of all detections of EV of known serotypes among persons aged ≥1 month.

Seasonal patterns of EV detection were similar in both age groups, with most of detections during June through October, but the summer-fall peak was slightly more prominent for persons aged ≥1 month. EV detected during June-

**TABLE 1.** Reported Enterovirus Serotypes by Age Group, NESS, 1983–2003

Serotype	Age <1 mo (n = 2356)			Age ≥1 mo (n = 18,239)			<1 mo vs. ≥1 mo, OR (95% CI)
	No.	%	Rank	No.	%	Rank	
<b>CVA9</b>	117	4.9	<b>10</b>	901	5.0	<b>6</b>	NS
<b>CVA10</b>	0	0		61	0.3	>10	<b>0 (0–0.6)</b>
<b>CVA16</b>	9	0.4	>10	200	1.1	>10	<b>0.4 (0.17–0.70)</b>
<b>CVB1</b>	135	5.7	<b>9</b>	465	2.6	>10	<b>2.3 (1.90–2.85)</b>
<b>CVB2</b>	211	8.9	<b>2</b>	896	4.9	<b>8</b>	<b>1.9 (1.62–2.24)</b>
<b>CVB3</b>	139	5.9	<b>8</b>	531	2.9	>10	<b>2.1 (1.71–2.55)</b>
<b>CVB4</b>	161	6.8	<b>4–5</b>	651	3.6	<b>10</b>	<b>2.0 (1.62–2.36)</b>
<b>CVB5</b>	176	7.5	<b>3</b>	1453	8.0	<b>4</b>	NS
E3	18	0.8	>10	131	0.7	>10	NS
<b>E4</b>	35	1.5	>10	540	3.0	>10	<b>0.5 (0.34–0.71)</b>
E5	40	1.7	>10	350	1.9	>10	NS
<b>E6</b>	160	6.8	<b>6</b>	1118	6.1	<b>5</b>	NS
<b>E7</b>	109	4.6	>10	900	4.9	<b>7</b>	NS
<b>E9</b>	161	6.8	<b>4–5</b>	2033	11.2	<b>2</b>	<b>0.6 (0.50–0.70)</b>
<b>E11</b>	331	14.0	<b>1</b>	1924	10.6	<b>3</b>	<b>1.4 (1.22–1.58)</b>
E13	35	1.5	>10	322	1.8	>10	NS
E14	28	1.2	>10	259	1.4	>10	NS
E16	34	1.4	>10	178	1.0	>10	NS
E17	22	0.9	>10	130	0.7	>10	NS
<b>E18</b>	78	3.3	>10	750	4.1	<b>9</b>	NS
E20	30	1.3	>10	245	1.3	>10	NS
<b>E21</b>	16	0.7	>10	256	1.4	>10	<b>0.5 (0.28–0.82)</b>
E24	19	0.8	>10	236	1.3	>10	NS
<b>E25</b>	47	2.0	>10	229	1.3	>10	<b>1.6 (1.15–2.23)</b>
<b>E30</b>	142	6.0	<b>7</b>	2189	12.0	<b>1</b>	<b>0.5 (0.39–0.56)</b>
E31	14	0.6	>10	100	0.5	>10	NS
EV71	16	0.7	>10	176	1.0	>10	NS
<b>HPeV1</b>	19	0.8	>10	422	2.3	>10	<b>0.3 (0.21–0.56)</b>

Not presented in the table are CVA1-8, CVA11-14, CVA17, CVA20-21, and CVA24, CVB6, E1-2, E12, E15, E19, E26-27, E29, E32-33, EV68, and HPeV2, each of which accounted for ≤0.5% of reports in both age groups. CVA19, CVA22, EV69, and EV70 have not been reported during the study period. EV with unknown serotype are excluded. Both serotypes from reports of mixed infections are included. Top 10 ranks and serotypes with significant findings are shown in bold font. NS, not significant.

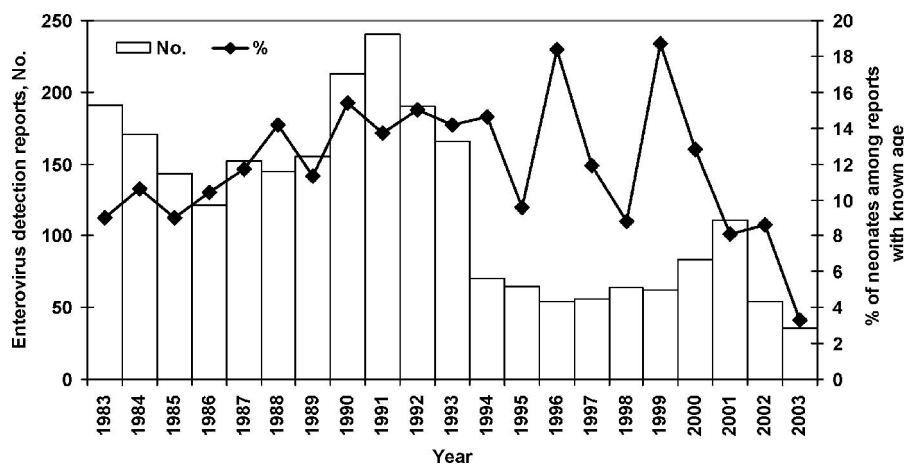


FIGURE 1. Temporal trends in enterovirus detections among neonates, NESS, 1983–2003.

October accounted for 79.3% of all reports among persons aged  $\geq 1$  month and for 71.6% among neonates (OR 1.2; 95% CI 1.03–1.3).

Comparison of the distribution of EV serotypes among neonates and persons aged  $\geq 1$  month showed that CVB1, CVB2, CVB3, CVB4, E11, and E25 were reported significantly more often among neonates, whereas CVA16, E4, E9, E21, E30, and HPeV1 were significantly more common among persons aged  $\geq 1$  month (Table 1).

The annual proportion of neonates among all reports varied widely from year to year (range, 3.3%–18.7%), with greater variability after the mid-1990s (Fig. 1). Higher proportions were noted during 1990–1994 (between 13.7% and 15.4%) and in 1996 (18.4%) and 1999 (18.7%); lower proportions, in 1995 (9.6%), 1998 (8.8%) and 2003 (3.3%).

Outcome information was not reported after 1998 and was recorded for 3937 (17.8% of all reports before 1999) cases. Age, outcome, and serotype were recorded in 3224 reports during 1983–1998. Fatal outcome was noted in 131 reports (3.3% of all 3937 reports with known outcome) and was significantly more common among neonates (11.5%) than among those aged  $\geq 1$  month (2.5%; OR 5.1; 95% CI 3.3–7.8). Independent of age, those infected with CVB4 (OR 3.3; 95% CI 1.7–6.4) and HPeV1 (OR 3.7; 95% CI 1.7–7.6) were at a significantly higher risk, whereas those infected with E9 were at significantly lower risk (OR 0.1; 95% CI 0.–0.4) of death compared with those infected with other serotypes.

When stratified by age group (Table 2), CVB4 was associated with significantly higher risk of fatal outcome than other EV for neonates (OR 6.5; 95% CI 2.4–17.7), but not for those aged  $\geq 1$  month (OR 0.9; 95% CI 0.1–3.8). HPeV1 was associated with significantly higher risk of death than other serotypes for persons aged  $\geq 1$  month (OR 4.6; 95% CI 2.0–10.5), but not for neonates (OR 1.9; 95% CI 0.04–19.7). E9 had significantly lower risk of death than other EV for those aged  $\geq 1$  month (OR 0; 95% CI 0–0.5; Fisher exact test,  $P < 0.05$ ), but not for neonates (OR 0.3; 95% CI 0.02–2.5; Fisher exact test,  $P > 0.05$ ). There were no significant differences in the risk of fatal outcome for other serotypes in either age group.

TABLE 2. Fatal Outcome of Enterovirus Infection by Serotype for the Neonates and Persons Aged  $\geq 1$  mo, 1983–1998

Serotype	Age <1 mo			Age $\geq 1$ mo		
	Died, n	Total, n	% Fatal	Died, n	Total, n	% Fatal
CVA9	2	32	6.3	3	265	1.1
CVA16	0	1	0	1	69	1.4
CVB1	0	18	0	0	82	0
CVB2	3	34	11.1	5	196	2.6
CVB3	3	16	18.8	4	102	3.9
<b>CVB4*</b>	10	25	40.0	2	88	2.2
CVB5	0	28	0	4	254	1.6
E4	0	3	0	1	57	1.8
E5	0	9	0	2	58	3.4
E6	3	16	18.8	6	146	4.1
E7	2	15	13.3	2	166	1.2
<b>E9*</b>	1	22	4.5	0	326	0
E11	8	42	19.0	10	311	3.2
E14	0	1	0	3	49	6.1
E17	0	1	0	0	27	0
E18	0	1	0	1	44	2.3
E20	1	6	16.7	1	73	1.4
E21	0	3	0	1	30	3.3
E24	0	2	0	1	46	2.2
E25	0	4	0	1	31	3.2
E30	1	5	20.0	8	283	2.8
<b>HPeV1*</b>	1	5	20.0	8	81	9.9

The analysis is limited to the subset of 3224 records with known serotype, age, and outcome (295 records of neonates, of which 35 died, and 2929 records of persons aged  $\geq 1$  mo, of which 74 died). The following serotypes were reported in  $\leq 15$  instances for both age groups: CVA2-4, CVA7, CVA10, CVA13-14, CVA21, CVB6, E1-3, E12-13, E15-16, E19, E27, E29, E31, E33, EV68, EV71, HPeV2. None of them was significantly associated with the risk of fatal outcome in either age group. Other serotypes were not reported for either age group. Serotypes with statistically significant associations are shown in bold font.

\*Statistically significant results: CVB4, age <1 mo: odds ratio (OR) 6.5; 95% confidence intervals (CIs) = 2.4–17.7;  $P$  value, Fisher exact test,  $<0.001$ . E9, age  $\geq 1$  mo: OR 0; 95% CI = 0–0.5;  $P$  value, Fisher exact test,  $<0.05$ . HPeV1, age  $\geq 1$  mo: OR 4.6; 95% CI = 2.0–10.5;  $P$  value, Fisher exact test,  $<0.001$ .

## DISCUSSION

The present analysis of the EV surveillance data in the United States confirmed the high risk of EV infections in neonates. The risk of the fatal outcome of EV infections was significantly higher for neonates compared with persons aged

≥1 month, and the relative risk of infection and death varied by infecting serotype.

Reports of neonatal infections clearly accounted for a disproportionately high percentage (11.5%) of reported EV detections in the United States during the study period, demonstrating the increased risk of EV infection. For comparison, the annual birth cohort in the United States during this time was approximately 1.5% of total population.<sup>18</sup> The analysis by serotype confirmed previously noted positive associations of E11 and CVB with neonatal infections<sup>9,10,12–14</sup> and documented several previously unrecorded associations. Thus, a relatively uncommon virus, E25, was positively associated with neonatal infections, whereas CVA16, E4, E9, E21, E30, and HPeV1 infected neonates significantly less frequently than older persons.

The increased risk of the fatal outcome of EV infections for neonates found in this study is consistent with previous clinical observations.<sup>9,14,19</sup> Of the EV previously associated with severe neonatal infections, all 5 common CVBs (CVB1–5) and E11 had the increased risk of neonatal infection. However, only CVB4, with a very high (40.0%) case fatality reported to NESS, had significantly increased risk of death compared with other EV serotypes. It is possible that associations of some other EV with the risk of neonatal death may have been missed due to relatively small number of reports with known outcome. For example, case fatality among neonates infected with E6, E11, E20, E30, CVB3, and HPeV1 was substantial (between 16.7% and 20%), and the proportion of fatal outcomes associated with E9 was only 4.5% but was not significantly different compared with neonates infected with other EV serotypes.

The use of multiyear national EV surveillance data to estimate the relative risks of EV infection and its fatal outcome by serotype and age group allowed identification of significant associations, which may have implications from both clinical and public health standpoints. However, NESS is not a population-based surveillance system. The absolute risks and rates of infection cannot be estimated according to these data, and the estimates of relative risks are subject to potential selection biases. Neonatal reports, especially fatal cases, could be over-represented due to the potential testing bias toward younger and more severe cases,<sup>5,10,20</sup> which is difficult to measure. The substantial difference in the proportion of neonates between the NESS data and general United States population partly results from the selection bias but partly reflects truly increased risk of fatal outcome of enterovirus infection for neonates. Also, the overall case fatality for aseptic meningitis, the syndrome primarily associated with EV, was only 0.4% in the study of national viral meningitis hospitalization rates in the United States during 1988–1999,<sup>21</sup> compared with 11.5% for neonates and 2.5% for all other ages combined, in our study. This suggests that although the testing bias toward more severe cases may be more prominent for neonates, it is likely present across all age groups, somewhat limiting its potential overall impact on our results.

The lack of clear-cut correlation between the proportion of neonatal EV reports and the serotypes prevailing nationwide in a given year is not surprising, considering the large number of EV serotypes that commonly cocirculate and the opposite direction of their associations with neonatal infec-

tion. Nevertheless, in some years, remarkably high or low proportions of neonates could be explained by the predominance of serotypes associated with higher or lower risk of neonatal infections. For example, low proportions of neonates were observed during the years when E9 and E30, associated with lower risk of neonatal infections, accounted for exceptionally high proportion of reported EV (1995, E30, 45% of all detected EV; 1998, E30, 46%; 2003, E9 and E30 together, 67% of all EV reports). High proportions of neonates were noted for 1992 and 1999, when E11, associated with increased risk of neonatal infection, was the most common serotype (25% and 39% of all reports, respectively).<sup>15,16,22,23</sup> The slightly less pronounced seasonality of EV detections observed for neonates could be due, at least in part, to testing bias. Because of the potential severity of illness in this age group and the need for differentiating from bacterial infections, neonates may be more likely to be tested for EV even when presenting outside the typical season of high EV activity.

The identified differences by serotype in the risk of infection and its outcome underscore the importance of serotype-based EV diagnostics. Viral culture followed by neutralization test with intersecting pools of standard antisera has been a gold standard for EV identification for many years. However, it is being increasingly replaced by molecular-based methods.<sup>1,6,24–27</sup> EV RT-PCR assay is becoming more common in routine clinical practice for diagnostic purposes but does not allow serotype differentiation.<sup>24,25,28</sup> Molecular serotyping methods for detecting individual EV serotypes, including VP1 gene sequence-based typing and serotype-specific PCR assays for certain EV, have been developed<sup>28–34</sup> and could be useful for public health surveillance and, in certain circumstances, for clinical diagnostic purposes. Because of the differences in predominant clinical manifestations and outcomes associated with different EV serotypes,<sup>1,2</sup> as well as their differential sensitivity to antipicornavirus medications currently under development,<sup>35,36</sup> serotype-based EV surveillance in the United States will need to be maintained and improved.

The present study demonstrated that EV are important neonatal pathogens associated with high risk of infection and death. However, because of the limitations of the NESS,<sup>15</sup> which, apart from the above-discussed testing bias, include incomplete reporting and limited clinical and outcome information, additional studies are needed to better evaluate the role of individual EV in neonatal infections and to obtain population-based estimates of the risk of EV infection.

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