A Polymerase Chain Reaction-based Epidemiologic Investigation of the Incidence of Nonpolio Enteroviral Infections in Febrile and Afebrile Infants 90 Days and Younger

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ABSTRACT. Objective. Enteroviruses are important pathogens in infants, but their true contribution to febrile illness in infants ≤90 days old is unknown. The purpose of this study was to use the polymerase chain reaction (PCR) for diagnosis of enteroviral (EV) infection in febrile and afebrile infants ≤90 days of age to improve the understanding of the epidemiology of EV infection in this population.

Methods. Patients included all unimmunized, febrile infants ≤90 days of age admitted to Primary Children’s Medical Center (Salt Lake City, UT) for sepsis evaluation from December 1996 to December 1997. Blood, urine, cerebrospinal fluid, and throat swabs were tested for enteroviruses using a PCR assay (Roche Molecular Systems, Branchburg, NJ). Alternate PCR assays separated polio and nonpolio enteroviruses. Results of bacterial cultures, outcome, and hospital charges were obtained. Blood from afebrile, control infants ≤90 days old was tested for enteroviruses.

Results. A total of 345 febrile infants were enrolled; 89 (25.8%) were positive for enterovirus. The incidence of EV infection ranged from 3.2% in January to 50% in August and October. Five EV-positive, febrile infants (5.6%) had concomitant urinary tract infections, and 1 (1.1%) had concomitant bacteremia. Infants with confirmed EV infection were significantly less likely to have bacterial infection than those who were EV-negative. All infants infected with an enterovirus recovered. Average length of stay was 3 days, average charges were nearly $4500. Eighty-six afebrile control infants were enrolled; 6 (6.9%) were positive for enterovirus; 3 had received oral polio vaccine.

Conclusions. Nonpolio EV infections commonly cause fever in infants ≤90 days of age. Rates of EV positivity are low in afebrile, unimmunized infants. The use of PCR to identify febrile infants with nonpolio EV infections may decrease length of hospital stay, unnecessary antibiotic administration, and charges. Pediatrics 1999;103(3). URL: http://www.pediatrics.org/cgi/content/full/103/3/527; enterovirus, PCR, febrile infants, bacterial infection, poliovirus.

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AMPLIGICOR Enteroviral PCR kits were contributed by Roche Molecular Systems (Branchburg, NJ).

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ABBREVIATIONS. SBI, serious bacterial infection; PCR, polymerase chain reaction; EV, enteroviral; RNA, ribonucleic acid; PCMC, Primary Children’s Medical Center; CSF, cerebrospinal fluid; OPV, oral polio vaccine; WBC, white blood cell count; EDTA, edetic acid; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus; CNS, central nervous system; LOS, length of stay; UTI, urinary tract infection.

The management of fever in infants, especially those ≤90 days of age, is controversial. Approximately 10% of fevers in this age group are a result of bacterial infections; 90% are assumed to be the result of a viral infection. A published practice guideline recommends extensive laboratory investigation and antibiotic administration for most febrile infants ≤90 days of age. Hospitalization is recommended for all infants <28 days and for infants between 28 and 90 days who do not meet the low-risk clinical and laboratory criteria for serious bacterial infection (SBI). These guidelines, which provide early diagnosis and treatment for infants with life-threatening bacterial infections, also result in unnecessary treatment for ~90% of febrile infants. Physicians often disregard practice guidelines, with one study reporting <10% adherence to the published recommendations for the management of a hypothetical 60-day-old infant with fever and symptoms of a viral illness.

None of the existing algorithms for the evaluation of febrile infants incorporates testing for viral infections. However, the increasing availability of viral diagnostic methods that use antigen detection or the polymerase chain reaction (PCR) allows the rapid identification of specific viral pathogens in febrile and afebrile infants. This information may be valuable in developing new, less invasive strategies for the management of febrile infants.

Nonpolio enteroviruses may be a significant cause of fever and hospitalization in infants ≤3 months of age. Most admissions for sepsis evaluations occur from July through October, corresponding to the recognized peak of reported enteroviral (EV) disease. In addition, nonpolio enteroviruses have been detected in infants at low risk for SBI twice as often as those determined to be at high risk.

Cell culture-based detection of enteroviruses is of limited practical use because of slow turnaround time (3.7 to 8.2 days) and limited sensitivity. PCR for EV ribonucleic acid (RNA) detection appears to be highly sensitive. In several studies that com-
Viral cultures are not performed routinely on infants undergoing an evaluation for sepsis and were not required for enrollment in this study. Results of viral cultures specifically ordered on individual patients by attending physicians were collected.

**PCR Assay**

**Enteroviruses**

Enterovirus was detected using a formatted reverse transcription-PCR assay (AMPLICOR EV PCR kit, Roche Molecular Systems, Branchburg, NJ) as described previously. The primers are directed at the 5' noncoding region, which is highly conserved among all known human enteroviruses. An optical density reading of >0.350 was considered positive. The assay required ~5 hours to complete. Any EV RNA remaining after PCR analysis was frozen at -70°C.

**Polioviruses**

After identification of an enterovirus by the AMPLICOR EV kit, all positive specimens identified during the 1997 nonpeak EV season (January 1 to June 1; n = 17) and all positive control specimens (n = 6) were tested retrospectively in an effort to differentiate polio from nonpolio enteroviruses. Two independent PCR methods were investigated and optimized against known positives for all three polioviruses, coxsackie A 16, coxsackie B 2 and 3, echovirus 6, and enterovirus 70 isolates. Multiplex PCR was performed using the general EV primers and the specific polio primers described.

The PCR reactions were performed using residual AMPLICOR RNA that had been stored at -70°C for 6 to 12 months after original EV detection. Specimens from febrile patients included nine blood, seven CSF, and one urine samples; specimens from control patients all were blood samples. Original specimen volumes had been exhausted, preventing reextraction of EV RNA.

**Archival Samples**

To determine the sensitivity and specificity of the AMPLICOR EV PCR assay, archival specimens known to be positive for enteroviruses by culture were tested. Specimens included blood, urine, CSF, throat swabs, stool, and other tissues frozen at -70°C for 1 to 12 years. Negative controls included stock cultures of cytomegalovirus, herpes simplex (HSV), Orthopoxviruses (RVS), rhinovirus, and varicella zoster virus (VZV).

**Statistical Analysis**

Prophet (National Center for Research Resources and the National Institute of Health), a data storage and statistical analysis package, was used for data entry, sorting, and statistical analysis. The t test was used for analysis of continuous variables and χ² test or Fisher's exact test for analysis of dichotomous variables. A P value <.05 was set as the level of significance.

## RESULTS

### Fiebrile Infants

**PCR Analysis**

A total of 345 febrile infants were enrolled. Their demographic and clinical characteristics are shown in Table 1. Fourteen febrile infants were excluded from the study because they had received OPV. Specimens available for PCR analysis totaled 965 (Table 2). All febrile infants had at least one specimen for PCR analysis; 323 patients (94%) had two or more specimens for analysis, and 238 (69%) had three or more.

A total of 89 infants (25.8%) were diagnosed with EV infections; 88 (98.9%) of these infants had a positive EV PCR assay from one or more specimens. One infant (1.1%) had a positive CSF EV culture and negative PCR results from blood, urine, and throat; no CSF PCR was performed.

The types of specimens available for analysis from
all febrile infants are shown in Table 2. Forty-four infants (49.4%) had two or more specimens positive for enterovirus, and 17 (19.3%) had three or more positive specimens. Eighty infants (91%) were diagnosed with an EV infection based on a positive result from a normally sterile site such as blood, urine, or CSF. Eight infants (9.0%) had an enterovirus identified from a throat swab specimen only.

For the 80 infants with a positive PCR assay from a sterile site, a positive blood PCR identified 55 (69%), a positive CSF PCR identified 62 (77.5%), and the combination of either a positive blood or positive CSF PCR identified 77 (96%) of these infants.

Of the 55 infants who had a positive EV PCR from blood, 50 (91%) had CSF available for PCR analysis. Forty (80%) had a positive CSF PCR assay. Three additional infants with a positive blood PCR had CSF pleocytosis, but a negative CSF PCR assay. Overall, 86% of viremic infants had evidence of central nervous system (CNS) infection, but only 38% had CSF pleocytosis.

Thirty-two infants (40%) with positive PCR results from blood, urine, or CSF also had throat swab specimens available for PCR analysis; 13 (40.6%) were positive for enterovirus. Of the patients with enterovirus detected in the throat only, 2 had CSF pleocytosis, 1 had a negative CSF PCR, and 1 did not have CSF available for PCR analysis.

### TABLE 3. Comparison of EV Culture Results With EV PCR Results in 13 Patients With CSF Pleocytosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>EV Culture</th>
<th>EV PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stool, negative</td>
<td>Blood and CSF, negative</td>
</tr>
<tr>
<td>2</td>
<td>Stool, negative</td>
<td>Blood, urine, and CSF, negative</td>
</tr>
<tr>
<td>3</td>
<td>Stool, negative</td>
<td>Blood, urine, and CSF, negative</td>
</tr>
<tr>
<td>4</td>
<td>Stool and nasopharynx, negative</td>
<td>Blood, urine, and CSF, negative</td>
</tr>
<tr>
<td>5</td>
<td>Stool, eye, and throat, negative</td>
<td>Blood, urine, and CSF, negative</td>
</tr>
<tr>
<td>6</td>
<td>CSF, negative</td>
<td>Blood, positive, CSF and urine, negative</td>
</tr>
<tr>
<td>7</td>
<td>CSF, negative</td>
<td>Blood, CSF, and throat, positive</td>
</tr>
<tr>
<td>8</td>
<td>Stool and throat, negative</td>
<td>Blood and CSF, positive</td>
</tr>
<tr>
<td>9</td>
<td>Stool and throat, negative</td>
<td>Blood and CSF, positive</td>
</tr>
<tr>
<td>10</td>
<td>Stool, positive</td>
<td>CSF, positive</td>
</tr>
<tr>
<td>11</td>
<td>CSF, positive</td>
<td>Blood, urine, and throat, negative</td>
</tr>
<tr>
<td>12</td>
<td>CSF, positive</td>
<td>CSF, positive</td>
</tr>
<tr>
<td>13</td>
<td>CSF and throat, positive</td>
<td>Blood and CSF, positive</td>
</tr>
</tbody>
</table>

Viral Culture
Thirteen infants (3.7%) had EV cultures ordered by their attending physician (Table 3). All had CSF pleocytosis. Four infants (30.7%) had a positive EV culture, whereas 8 (61.5%) had a positive PCR.

Demographic and Clinical Variables
EV infections were diagnosed during every month of the year except May 1997. The seasonal distribution of EV infections is shown in Fig 1. Two peaks of EV infection were identified; the expected summer/fall peak from June through November 1997, and a second spring peak in February and March 1997.

Febrile infants with EV infection did not differ from those without EV infection with respect to age, gestational age, temperature, duration of symptoms, or ill contacts (Table 1). Infants with EV infection were more likely to have CSF pleocytosis (54.4% vs 22.5%; \( P < .0001 \)), with significantly higher average CSF WBC counts than those who were EV-negative (191 vs 24; \( P < .0005 \)).

Infants with EV infections had an average length of stay (LOS) of 3 days, with hospital charges of $4476, which did not differ significantly from those without EV infection (Table 1). Infants with EV infection and CSF pleocytosis had the highest average LOS, 3.4 days, with charges of $5048. A single EV-positive patient was excluded from calculations of LOS and charges because co-morbidities requiring
surgical treatment resulted in an LOS of 7 weeks with charges >$100,000.

Eighty-seven EV-positive infants (97.7%) were cared for by general pediatricians or family physicians. Two EV-positive infants (2.3%) required treatment in the pediatric intensive care unit, primarily for co-morbid conditions (bacteremia, 1; congenital heart disease, 1). None of the EV-positive infants had evidence of severe EV disease such as myocarditis or necrotizing hepatitis. All infants with EV infection were discharged from the hospital in good condition. In the non-EV-infected infants, there was one death secondary to disseminated infection with *Aspergillus* sp in an infant with chronic granulomatous disease.

**Concomitant Bacterial Infections**

Table 4 lists the final diagnosis for all febrile infants. Six EV-positive infants (6.7%) had concomitant bacterial infections. Five of the infants (5.6%) had urinary tract infections (UTI), and 1 (1.1%) had bacteremia with *Campylobacter jejuni*. Four infants (80%) with UTI had abnormal urinalysis (>10 WBC, positive leukocyte esterase and nitrite), and one of these had a congenital urogenital abnormality. No EV-positive infant who fulfilled the Rochester low-risk criteria had SBI.

Thirty-eight EV-negative infants (14.8%) had evidence of bacterial infection, including 19 with UTI, 5 with bacteremia, 4 with cellulitis, 3 with omphalitis, 3 with pneumonia, 2 with dacryocystitis, and 1 with meningitis. One infant with fungemia also was included in the SBI group. The incidence of blood stream infections in the EV-negative group was 2.3% and the incidence of CNS infection was 0.4%. When compared with the EV-positive group, there was a significant difference in the overall incidence of SBI (*P* < .048), but not in the incidence of blood stream infections or bacterial meningitis.

Of the 256 non-EV-infected infants, alternative viral diagnoses were made for 31 infants (RSV, 27; rotavirus, 2; HSV-1; and varicella, 1). None of these infants had concomitant SBI. When these infants were excluded from analysis along with those who were diagnosed with EV infection, there were 225 infants for which no viral infection was confirmed. The incidence of SBI was 16.8% in these infants compared with an incidence of 5% in the infants with confirmed viral infection (*P* = .0016). The incidence of blood stream or CNS infections was 3.1% in the nonviral group compared with 0.8% in the group with confirmed viral infection (*P* = .18, NS).

**Control Infants**

Eighty-six control infants were enrolled (Table 5; 66 (77%) from outpatient surgery during the months of July through November 1997. Twenty (23%) were admitted for a sepsis evaluation secondary to a nonfebrile indication such as lethargy or poor feeding. These 20 infants were admitted during the months of January through August 1997 (3 during July through

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 86)</th>
<th>EV PCR, Positive (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical patient</td>
<td>66 (77%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Age</td>
<td>54.1 d</td>
<td>74.5 d</td>
</tr>
<tr>
<td>Immunized</td>
<td>25 (29%)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

**TABLE 5.** Control Infants
Fever.25,26 EV infections were detected in most likely had primary EV infection, which resulted was as high as 50%. During the summer and fall, the incidence 1997 were found to be infected with a nonpolio en-

infants admitted to PCMC for suspected sepsis in clinicians' perception of the utility of viral culture.

terovirus. The positive and negative control samples produced an amplicon of the predicted size for po-

EV-positive control infants were significantly older than were EV-positive febrile infants (74.5 days vs 30.8 days; \( P = .026 \)). Twenty-six control infants (30%) were neonates; however, there were no asym-

tomatic EV infections noted in this group.

Assay for Polioviruses

When assayed using two different methods, none of the 23 off-season or control EV-positive samples produced an amplicon of the predicted size for po-

liovirus. The positive and negative control samples for each reaction produced amplicon corresponding to predicted base-pair sizes for all methods.

Archival Data

PCR analysis of 382 archival specimens revealed an overall sensitivity of the AMPLICOR assay of 94%. The specificity was 100%.

DISCUSSION

Nonpolio enteroviruses are one of the most common causes of fever leading to hospitalization in infants \( \leq 90 \) days of age. Greater than 25% of febrile infants admitted to PCMC for suspected sepsis in 1997 were found to be infected with a nonpolio en-

terovirus. During the summer and fall, the incidence was as high as 50%.

EV-positive infants averaged 30 days of age and most likely had primary EV infection, which resulted in fever.25,26 EV infections were detected in 5% of afebrile, unimmunized control infants. No asym-

tomatic EV infections were detected in afebrile neo-

nates. No infections with polioviruses were detected in either off-season study patients or control infants. Concerns regarding asymptomatic viremia secondary to OPV administration is likely to become less important in the future, because the majority of US pediatricians have adopted a sequential schedule for polio immunization with inactivated polio vaccine given during early infancy.27,28

EV PCR improves diagnostic capability significantly.16-20 Although EV culture is readily available in our institution, it was ordered for only 3.7% of the febrile infants enrolled in this study, which reflects clinicians' perception of the utility of viral culture.

The EV PCR assay had excellent sensitivity and specificity as demonstrated by performance with ar-

chival data and results were comparable with other published reports.19-20 In febrile patients who had both types of testing, PCR was twice as sensitive as EV culture. Additionally, a prospective study was conducted concurrently in our laboratory during the 1997 EV season, in which positive PCR results were corroborated by clinical data. Results of 463 CSF specimens submitted for EV culture revealed that PCR had a sensitivity of 97.4% compared with 53.4% by culture for the detection of EV meningitis.29 We are confident that PCR is a reliable and sensitive method of EV detection.

PCR of both blood and CSF was the most sensitive for the diagnosis of EV infection. The utility of whole blood in diagnosing EV infection in infants both with and without meningitis was encouraging. Nearly 70% of EV-positive infants had a positive PCR from blood. EV PCR of blood, in combination with CSF EV PCR, is important in establishing the diagnosis of EV infection. In this study, the CSF PCR assay did not identify 4 cases of presumed EV meningitis. All four infants had CSF pleocytosis; 3 had a positive blood PCR and 1 had a positive throat PCR. The addition of the urine and throat swab PCR did not improve our ability to diagnose EV infection significantly.

Availability of EV PCR will enhance the recognition of infants with EV infection and will expand the current understanding of the epidemiology and con-

sequences of EV infections in this age group. For example, EV infections were detected throughout the year, not only in the expected summer/fall. In addi-

tion, no gender differences in the incidence of EV infection were noted in this study. Previous reports, especially those documenting severe disease, have shown a male predominance.30,31 Although nonspe-

cific febrile illnesses are widely assumed to be the most common presentation of EV infection, they make up only 9% of reported cases of EV infection in infants.30,32 This study confirms that nonspecific febrile illnesses are common but underdiagnosed. Without the use of PCR, \( >95% \) of the EV infections identified in this study would have remainedundiagnosed.

Seventy-five percent of EV-positive infants had evidence of CNS involvement and almost 90% with a positive blood PCR had either a positive CSF PCR or CSF pleocytosis. This is in contrast to published re-

ports, based on culture data, that describe an inverse relationship between viremia and meningitis and may reflect the differences in methodology.33,34 The finding that the vast majority of infants had evidence of CNS infection may be explained by the EV serotypes that predominated in our community in 1997, primarily echoviruses 6 and 30. Alternatively, it may reflect the actual incidence of CNS invasion in young infants by all EV serotypes that, before the availability of PCR, was unrecognized because of the lack of CSF pleocytosis and the lack of sensitivity of viral culture.

Limited studies on the long-term neurodevelop-

mental outcome of infants after EV meningitis have been performed, with conflicting reports.35-38 Several
PCR results, combined with the knowledge that con-
clinically important. The rapid availability of EV
febrile infant, especially one with CSF pleocytosis, is
of identifying a specific virus in a febrile infant.
will depend on understanding the clinical relevance
possible in the future. The utility of this technology
rapid diagnosis of multiple viral infections will be
integrated chip-based capillary electrophoresis, the
produce CNS involvement and which infants, if any,
may be at risk for neurodevelopmental delay.
EV-positive infants were significantly less likely to
have SBI than were EV-negative infants; however, all
together in the hospital until their CSF
懔 derive CNS involvement and which infants, if any,
been confirmed to be negative at 72
The use of viral culture
well documented to change patient management
nearly 50% of patients with aseptic meningitis.
The more rapid technique of PCR has the potential to
influence patient care to a much greater extent. Other
reports have postulated a reduction of 1.2 days for
LOS and between 17% and 35% for hospital charges
in nearly 50% of patients with aseptic meningitis.
The more rapid technique of PCR has the potential to
influence patient care to a much greater extent. Other
reports have postulated a reduction of 1.2 days for
LOS and between 17% and 35% for hospital charges
with the use of EV PCR for febrile infants with CSF
pleocytosis.
Rapid viral testing in algorithms for the evaluation
of febrile infants for suspected sepsis should be con-
sidered. Eliminating infants with confirmed viral in-
fecions from the pool of all febrile infants, as shown in
this study, increases significantly the probability of
identifying a bacterial infection in the remaining
infants. New approaches have been proposed for
febrile infants with RSV infection who are known to
be at low risk for concomitant SBI. With improve-
m ents in nucleic acid detection methods, including
integrated chip-based capillary electrophoresis, the
rapid diagnosis of multiple viral infections will be
possible in the future. The utility of this technology
will depend on understanding the clinical relevance of
identifying a specific virus in a febrile infant.
The identification of a nonpolio enterovirus in a
febrile infant, especially one with CSF pleocytosis, is
clinically important. The rapid availability of EV
PCR results, combined with the knowledge that con-
comitant SBI is rare in febrile, EV-positive infants,
could decrease length of hospitalization, antibiotic
administration, and the associated iatrogenic mor-
bidity of the sepsis evaluation significantly.

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