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.

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, ethylenediaminetetraacetic 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.12 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.3 A published practice guideline recommends extensive laboratory investigation and antibiotic administration for most febrile infants ≤90 days of age.4 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).4 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.5

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.6–8 Most admissions for sepsis evaluations occur from July through October, corresponding to the recognized peak of reported enteroviral (EV) disease.6 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.9

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.10 PCR for EV ribonucleic acid (RNA) detection appears to be highly sensitive.10–15 In several studies that com-
pare PCR with EV culture directly, PCR consistently is the more sensitive diagnostic technique.\textsuperscript{16–20} Recently, EV PCR has been combined with a colorimetric detection system that yields results in 4 to 6 hours.\textsuperscript{10} The potential of this rapid diagnostic method to impact the clinical management of febrile infants prompted an investigation to better describe the epidemiology of nonpolio enteroviruses in febrile and afebrile infants ≈90 days of age.

METHODS

Patient Enrollment

All infants admitted to Primary Children's Medical Center (PCMC), a 232-bed, tertiary-care children's hospital in Salt Lake City, UT, for a sepsis evaluation between December 1996 and December 1997 were eligible for enrollment. Infants included in the study were ≥90 days of age; had been discharged from the hospital after birth; had a history of or a documented temperature ≥38°C; and had undergone a complete sepsis evaluation including cultures of blood, urine, and cerebrospinal fluid (CSF). Infants who had received oral polio vaccine (OPV) were excluded because these infants may have had a positive EV PCR secondary to vaccine virus.

Demographic and clinical information for febrile infants was obtained by chart abstraction and recorded on a prepared data collection form. Data abstracted for febrile infants included date of birth; gestation; gender; date of admission; date of discharge; hospital charges; temperature; duration of illness; ill contacts; CSF profile; results of blood, urine, and CSF cultures; results of viral cultures; results of other viral diagnostic testing; discharge diagnosis; and clinical outcome. CSF pleocytosis was defined as ≥22 white blood cells (WBC) in infants <4 weeks, ≥15 WBC in infants 4 to 8 weeks, and ≥7 WBC in infants >8 weeks.\textsuperscript{12,13} SBI was defined as bacteremia, bacterial meningitis, urinary tract infection (>100 000 colony-forming units per milliliter of a single organism), soft tissue or bone infection, bacterial pneumonia, or bacterial enteritis.

To determine the incidence of EV infection in asymptomatic infants, in 1997 control infants were recruited from the outpatient surgery department from July to November, the recognized peak of EV circulation. Infants enrolled were ≥90 days of age, afebrile, undergoing elective surgery, and had a preoperative complete blood count. Infants immunized with OPV were not excluded because at the time of their enrollment, an assay that would distinguish between polio and nonpolio enteroviruses was available in the laboratory. In addition, infants enrolled as suspected sepsis cases, but who were afebrile, also were included as controls.

Demographic and clinical information for the surgical control infants was obtained from the surgical log and included date of birth, age, gender, date of surgery, and surgical procedure.

PCR results were not available to clinicians and were not used in patient management decisions. This study was approved by the institutional review boards of both the University of Utah and the PCMC.

Specimen Collection

For febrile infants, specimens of blood, urine, or CSF that remained after routine tests were completed were used for the EV PCR assay. In the event that insufficient specimen was available for both bacterial culture and PCR, only bacterial culture was performed.

Specimens consisted of whole blood in an edetic acid collection tube and urine and CSF in polypropylene collection tubes. All urine specimens were collected by sterile catheterization technique. From July through October, 1997, throat swab specimens were obtained from patients using sterile Dacron swabs and were placed in M4 viral transport media (Micro Test, Inc, Liburn, GA). Whole blood was stored at room temperature, and CSF, urine, and throat swabs were refrigerated at 4°C. For control infants, specimens consisted of whole blood in edetic acid collection tubes stored at room temperature. Specimens were recovered from the laboratory within 48 hours and frozen at −20°C until the PCR assay was performed. The PCR assay was performed on all specimens within 30 days of collection.

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 (AMPLIGOR EV PCR kit, Roche Molecular Systems, Branchburg, NJ) as described previously.\textsuperscript{10} 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.\textsuperscript{23,24} Multiplex PCR was performed using the general EV primers and the specific polio primers described.\textsuperscript{23,24}

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), Orf, respiratory syncytial (RSV), 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

Febrile 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 a 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.

**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

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**TABLE 1. Demographic and Clinical Information for All Febrile Infants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>EV-Positive (n = 89)</th>
<th>EV-Negative (n = 256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.8 d (SD = 16.4 d)</td>
<td>28.2 d (SD = 19.4 d)</td>
</tr>
<tr>
<td>Range, 3–65 d</td>
<td></td>
<td>Range, 1–85 d</td>
</tr>
<tr>
<td>Gender</td>
<td>43 (48.3%) Male</td>
<td>134 (52.3%) Male</td>
</tr>
<tr>
<td>LOS</td>
<td>3 d</td>
<td>2.8 d</td>
</tr>
<tr>
<td>Charges</td>
<td>$4476</td>
<td>$4387</td>
</tr>
<tr>
<td>Temperature</td>
<td>38.75°C (range, 38°C–41.1°C)</td>
<td>38.62°C (range, 38°C–40.8°C)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>2.1 d</td>
<td>1.8 d</td>
</tr>
<tr>
<td>Ill contacts</td>
<td>44 (49.4%)</td>
<td>111 (43.3%)</td>
</tr>
<tr>
<td>CSF WBC</td>
<td>191*</td>
<td>24</td>
</tr>
<tr>
<td>CSF protein</td>
<td>105</td>
<td>89</td>
</tr>
<tr>
<td>CSF glucose</td>
<td>45</td>
<td>47</td>
</tr>
</tbody>
</table>

* \( P = .0005 \).

**TABLE 2. Results of PCR Testing for Febrile Infants**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>PCR-positive/Total Tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>55/328 (16.7)</td>
</tr>
<tr>
<td>Blood, July–November 1997</td>
<td>41/143 (28.7)</td>
</tr>
<tr>
<td>CSF</td>
<td>62/313 (19.8)</td>
</tr>
<tr>
<td>CSF, July–November 1997</td>
<td>46/137 (33.6)</td>
</tr>
<tr>
<td>Urine</td>
<td>20/252 (7.9)</td>
</tr>
<tr>
<td>Throat</td>
<td>21/272 (29.1)</td>
</tr>
<tr>
<td>CSF, July–November 1997</td>
<td></td>
</tr>
</tbody>
</table>

**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, urine, and CSF, 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>
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 ($P \leq .048$), 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 group 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 August 1997) and had a congenital urogenital abnormality. No EV-positive infant who fulfilled the Rochester low-risk criteria had SBI.

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Six control infants (6.9%), all from the surgical group, tested positive for enteroviruses by PCR of whole blood. Twelve percent of immunized control infants were EV-positive compared with 4.9% of unimmunized control infants.

Although most control infants were selected during the peak of EV season, significantly fewer were EV-positive than febrile infants enrolled throughout the year (6.9% vs 25.8%; \(P = .0002\)). For control infants enrolled between July and November, 8.6% (6/69) had a positive PCR of whole blood compared with 28.7% of febrile infants enrolled during the same time period \( (P = .001)\). Control infants enrolled between the months of July and November were significantly less likely to be EV-positive than were febrile infants during the same period (8.6% of control infants vs 42.5% of febrile infants; \(P = .0001\)).

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 asymptomatic 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 poliovirus. 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 ≤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 enterovirus. 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 asymptomatic EV infections were detected in afebrile neonates. 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 archival data and results were comparable with other published reports.\(^{15-20}\) 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 465 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 consequences of EV infections in this age group. For example, EV infections were detected throughout the year, not only in the expected summer/fall. In addition, 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 nonspecific 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 remained undiagnosed.

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 reports, 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 neurodevelopmental outcome of infants after EV meningitis have been performed, with conflicting reports.\(^{35-38}\) Several
authors have documented language delays in infants who have had EV meningitis before 3 months of age.36,38 PCR diagnosis followed by molecular typing could clarify which serotypes are most likely to produce CNS involvement and which infants, if any, may be at risk for neurodevelopmental delay.39

EV-positive infants were significantly less likely to have SBI than were EV-negative infants; however, all enterovirus-infected infants were hospitalized and received broad-spectrum intravenous antibiotics, most for a minimum of 48 hours. The use of EV PCR is not meant to replace the current evaluation for sepsis, but to act as a diagnostic adjunct in determining which infants are at lowest risk for SBI. Five of the 6 infants with concomitant SBI were recognized at the time of presentation, either by clinical (shock, respiratory failure, 1) or laboratory findings (abnormal urinalysis, 4). Widespread use of rapid EV testing in febrile infants could decrease significantly length of hospitalization and unnecessary antibiotic administration in infants who are nontoxic-appearing and who have a normal urinalysis result.

EV-positive patients with CSF pleocytosis had the longest hospital stays and highest charges of any infants admitted for suspected sepsis. Presumably, these infants remained in the hospital until their CSF bacterial cultures were confirmed to be negative at 72 hours. These infants would potentially benefit the most from rapid diagnosis. The use of viral culture has been documented to change patient management in nearly 50% of patients with aseptic meningitis.40 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.41,42

Rapid viral testing in algorithms for the evaluation of febrile infants for suspected sepsis should be considered. Eliminating infants with confirmed viral infections 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.43–45 With improvements in nucleic acid detection methods, including integrated chip-based capillary electrophoresis, the rapid diagnosis of multiple viral infections will be possible in the future.46 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 concomitant SBI is rare in febrile, EV-positive infants, could decrease length of hospitalization, antibiotic administration, and the associated iatrogenic morbidity of the sepsis evaluation significantly.47

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REFERENCES

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

Carrie L. Byington, E. William Taggart, Karen C. Carroll and David R. Hillyard

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