REVIEW ARTICLE

Impact of Enterovirus Testing on Resource Use in Febrile Young Infants: A Systematic Review

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A B S T R A C T

CONTEXT: Enterovirus infection commonly causes fever in infants aged 0 to 90 days and, without testing, is difficult to differentiate from serious bacterial infection.

OBJECTIVE: To determine the cost savings of routine enterovirus testing and identify subgroups of infants with greater potential impact from testing among infants 0 to 90 days old with fever.

DATA SOURCES: Studies were identified systematically from published and unpublished literature by using Embase, Medline, the Cochrane database, and conference proceedings.

STUDY SELECTION: Inclusion criteria were original studies, in any language, of enterovirus infection including the outcomes of interest in infants aged 0 to 90 days.

DATA EXTRACTION: Standardized instruments were used to appraise each study. The evidence quality was evaluated using Grading of Recommendations Assessment, Development, and Evaluation criteria. Two investigators independently searched the literature, screened and critically appraised the studies, extracted the data, and applied the Grading of Recommendations Assessment, Development, and Evaluation criteria.

RESULTS: Of the 257 unique studies identified and screened, 32 were completely reviewed and 8 were included. Routine enterovirus testing was associated with reduced hospital length of stay and cost savings during peak enterovirus season. Cerebrospinal fluid pleocytosis was a poor predictor of enterovirus meningitis. The studies were all observational and the evidence was of low quality.

CONCLUSIONS: Enterovirus polymerase chain reaction testing, independent of cerebrospinal fluid pleocytosis, can reduce length of stay and achieve cost savings, especially during times of high enterovirus prevalence. Additional study is needed to identify subgroups that may achieve greater cost savings from testing to additionally enhance the efficiency of testing.

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Infants in the first couple months of life often present to the emergency department with febrile illnesses. Given their young age, immature immune systems, and recent exposure to birth canal flora, most infants in this age group will undergo evaluation for serious bacterial illnesses (SBIs), including bacteremia, urinary tract infection, and meningitis. After initial evaluation, infants are typically hospitalized for empirical antibiotic therapy while awaiting bacterial culture results. Despite the focus on SBIs, fever in febrile young infants is more often viral than bacterial in etiology. Krober et al[1] identified viral pathogens 41% of the time as compared with 15% for bacterial pathogens in febrile infants <90 days of age. The most common viral pathogen isolated in this series of 182 febrile infants was enterovirus.[1]

Enterovirus is a common cause of fever occurring in 26% to 60% of cases of hospitalized young infants in various communities.[2,3] Young infants with enterovirus infection generally have a benign course with resolution of fever within 3 days.[2–4] However, the clinical symptoms and signs of enterovirus can be difficult to distinguish from SBIs at the time of presentation,[2,3] and many infants undergo SBI testing and hospitalization for this reason. The objective of this systematic review was to determine whether routine enterovirus testing for all infants 0 to 90 days of age presenting with fever could result in a reduction in resource use. The study also aimed to identify specific patient subgroups with the potential for the greatest benefit from enterovirus testing through reductions in resource use.

METHODS
Search Strategy and Study Selection
We performed a systematic review of the published and unpublished medical literature. Two independent investigators and an experienced medical librarian searched Medline, Embase, and the Cochrane database for studies related to enterovirus infection or testing. The initial search strategy included the search terms "neonate" AND "fever" AND "enterovirus" in the PubMed search engine, without filters or limits. We used a second strategy to identify

additional articles with the search terms of "enterovirus testing" AND "neonates" in PubMed. We also searched the related articles column in PubMed and the reference lists of articles to identify additional articles. We searched for unpublished studies in published abstracts from national conference proceedings in the previous 3 years, in trial registries, and from national experts. The last search was performed in December 2015.

Two investigators screened the title and abstract of potentially eligible studies independently to identify articles related to enterovirus infection and/or testing. The investigators then met to determine the studies eligible for inclusion and any disagreements were resolved through discussion and consensus. Studies were included if they involved infants 0 to 90 days old within the population and if the outcomes of our study questions were assessed in this population. The outcomes included resource use (defined as hospital length of stay [LOS], cost, or charges) and patient subgroups for optimal resource use. We sought to include only systematic reviews, randomized controlled trials, and prospective cohort studies, but included retrospective cohort studies if they were the only study type used to address any of our study questions. We excluded case reports and case series with <20 infants 0 to 90 days old when larger studies existed to evaluate the same outcomes, nonsystematic review articles, and any study deemed to have major methodological flaws that would compromise internal study validity.

Risk of Bias Assessment for Individual Studies
Two investigators independently critically appraised the articles using study design–specific Critical Appraisal Skills Program (CASP) tools.[5] The investigators used a CASP instrument for each study to assess the risk of bias by evaluating whether the study question was clearly defined, appropriately designed, methodologically valid, and had meaningful results and generalizable conclusions. The instrument also served as a template for extracting the key elements of each study for the systematic review.

Quality of Evidence
Two investigators independently used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[6] to evaluate the quality of evidence for each systematic review question. This system takes into account findings from multiple studies and grades the quality of evidence for each question as either high, moderate, low, or very low. The initial quality of evidence is high for results from randomized controlled trials and is low for results from observational studies. Ratings can be downgraded due to risk of bias, inconsistency, indirectness, imprecision, or publication bias. Ratings can be upgraded due to the presence of a large effect or a dose-response gradient or if attempts to control for confounding would not change the observed effect.

Analysis
Formal meta-analyses were not performed because the results were not suitable for combination due to study heterogeneity within study populations and variation in the reporting of outcomes. When confidence intervals (CIs) were not provided for individual studies by the authors, 95% CIs were calculated using the binomial CI calculator within Stata version 13 (Stata Corp, College Station, TX).

RESULTS
Our search identified 378 articles, of which 257 were from unique studies (Fig 1). Of the 32 studies that underwent full-text review, 7 were prospective cohort studies, 9 were retrospective cohort studies, 2 were retrospective cross-sectional studies, 5 were diagnostic studies, 1 was an economic evaluation, 1 was a case-control study, and 7 were case series. Twenty-four of these studies were excluded: 18 because they did not measure any of the outcomes of interest, 5 because they had <20 patients <60 days old with larger studies available to evaluate the same outcomes, and 1 because of the concern for biased methodology (Supplemental Table 5). The 1 study excluded due to major bias was excluded because of concern for selection bias.[4] Enterovirus polymerase chain reaction (PCR) testing of the cerebrospinal

| 276 studies identifed through database search |

| -0 studies identified by contacting experts -0 studies identified by manual national abstract review -102 studies identified by review of reference lists |

| 121 duplicates removed |

| 257 records screened |

| 225 studies excluded |

| 32 full text articles reviewed |

| 24 excluded: - 5 case series - 18 no outcomes of interest - 1 major bias |

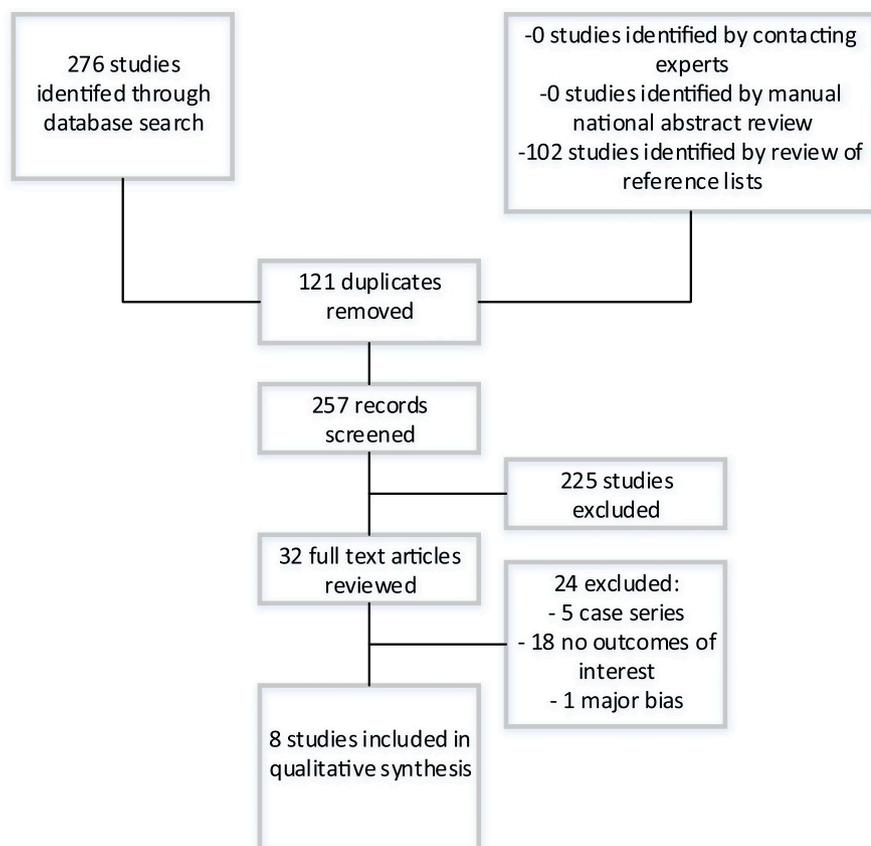| 8 studies included in qualitative synthesis |

FIGURE 1 Search strategy.

fluid (CSF) was performed on only ill-appearing infants or infants <15 days of age, which comprised 29% of the population.[4] The majority of the population was not tested.

After screening, assessment of eligibility, and full-text review, 8 studies were included in the systematic review (Fig 1, Table 1). The 8 studies included 1 prospective cohort study, 3 retrospective cohort studies, 2 diagnostic studies, 1 cross-sectional study, and 1 cost minimization analysis.

Primary Outcome: Resource Use

Of the 8 included studies, 4 included data pertaining to the impact of enterovirus PCR testing on hospital cost and LOS: 3 retrospective cohort studies[7–9] and 1 retrospective cost minimization study (Table 1).[10] The 3 retrospective cohort studies focused on the impact on hospital LOS whereas the cost minimization study identified the prevalence of enterovirus needed to achieve cost savings with

empirical testing (Table 2).[7,8,10] In Stellrecht et al,[7] the faster turnaround time for the PCR was correlated with a reduction in LOS by nearly half. This study, however, was limited by a small sample of infants <3 months of age ($n = 31$), missing laboratory data, and potential for selection bias because all patients with CSF were not tested for enterovirus.[7] Dewan et al[8] had similar findings, but with a much larger sample size and higher degree of precision. They found that the LOS was reduced by 15% to 45% (10–33 hours) for patients who had a positive enterovirus test.[8] Ramers et al[9] focused on a subgroup of neonates with pleocytosis and also found similar reductions in LOS (Table 2). In the cost minimization analysis, the investigators found that enterovirus PCR testing can lead to cost savings when the prevalence of enterovirus is >5.9% with the assumption of discharge after 24 hours of hospitalization and a negative CSF culture.[10] The greatest limitation of this study is that the

comparison of outcomes in the "standard" practice group as compared with enterovirus PCR testing of all samples was based on decision tree modeling with assumptions of the outcomes in each arm rather than observed patient outcomes. In addition, one of the assumptions of all patients being discharged by 24 hours if they tested positive for an enterovirus was based on a population of infants 28 days to 12 months old and may not be generalizable to infants <28 days old. The authors, however, report that if only 50% are discharged within 24 hours, cost savings could be achieved with an enterovirus prevalence of 13%.[10] Additional cost savings were seen as the prevalence was increased within their model. Overall, all 4 studies found reductions in LOS and potential cost savings with routine enterovirus testing; the magnitude of benefit was greater with faster turnaround times of enterovirus testing and with higher prevalences of enterovirus.[7,8,10]

Secondary Outcomes: Patient Subgroups

We found 5 studies that assessed whether enterovirus testing should be tailored to certain subgroups of young infants: 1 large prospective cohort study,[11] 3 retrospective cross-sectional studies,[12–14] and 1 retrospective cohort study.[7] In the prospective cohort study by Byington et al,[11] the investigators found that there was no difference in clinical characteristics, such as age, sex, duration of symptoms, and temperature, between enterovirus-positive and enterovirus-negative patients (Table 2). These patient characteristics were not evaluated further in other studies, but the frequency of pleocytosis in young infants with enterovirus infection was additionally assessed. Three retrospective studies assessed the frequency of CSF pleocytosis in young infants with enterovirus infection.[7,12,13] In these studies, infants <3 months of age with enterovirus infection had pleocytosis 44% to 90% of the time (Table 2).[7,12,13] Younger infants with enterovirus infection had a lower frequency of pleocytosis, especially in the first month of life.[12,13] Lower peripheral white blood cell count and lumbar puncture within 24 hours of onset of

TABLE 1 Summary of Study Characteristics

Study[a]	Study Design and Aim	Sample Size	Population	Type of EV Test	Prevalence of EV	Outcomes
Stellrecht et al[7]	Retrospective cohort; assess the clinical impact of EV PCR testing	$N = 1056$	Pediatric and adult patients with CSF EV PCR	CSF EV real-time PCR	20% ($n = 20/100$) in infants <1 mo old	Not clearly defined; LOS
Dewan et al[8]	Retrospective cohort; evaluate the impact of EV testing on LOS	$N = 1231$	Febrile infants <56 d old	CSF EV PCR	25% ($n = 308/1231$)	LOS
Ramers et al[9]	Retrospective cohort; to determine the impact of EV-PCR testing on diagnosis and clinical management of suspected aseptic meningitis cases	$N = 276$	Pediatric patients 0–16 y old with EV PCR sent	CSF EV PCR	49% ($n = 137/276$)	LOS, time from PCR result to discharge, intravenous antibiotic use, and use of ancillary tests. CSF pleocytosis also reported
Nigrovic et al[10]	Cost minimization analysis using a decision tree; assess whether empirical EV PCR testing as compared with usual practice would lead to cost savings and identify the prevalence of EV needed to result in cost savings	$N = 126$	Infants 28 d to 12 mo old with fever and CSF pleocytosis	CSF EV PCR	NA; prevalence was varied within the decision tree to assess which prevalence led to cost savings	Total cost for usual care group and total cost for empirical EV testing group. Cost was defined using a cost-to-charge ratio of 0.65 and included hospital bed, nursing services, physician fee, and antibiotic.
Byington et al[11]	Prospective cohort epidemiologic study; describe the epidemiology of EV infection through PCR testing of infants <90 d of age with and without fever	$N = 345$	Infants <90 d old with and without fever	Blood, urine, CSF, throat EV PCRs	26% ($n = 89/345$)	Characteristics of infants with and without EV infection
Yun et al[12]	Retrospective cross-sectional; describe characteristics of EV meningitis in absence of pleocytosis	$N = 390$	Children with +CSF EV PCR	CSF EV PCR	NA; only patients with EV included	CSF pleocytosis
Seiden et al[13]	Retrospective cross-sectional; to identify factors associated with CSF pleocytosis	$N = 154$	Infants <90 d old with +CSF EV PCR	CSF EV PCR	NA; only patients with EV included	CSF pleocytosis
Mulford et al[14]	Cross-sectional study of diagnostic test; to determine if pleocytosis and/or elevated protein levels were predictive of positive EV PCR.	$N = 728$	Pediatric and adult patients	CSF EV PCR	38.1% ($n = 277/728$); reference standard was CSF EV PCR	Test properties for pleocytosis and CSF protein to diagnose EV infection

EV, enterovirus. NA, not applicable.

[a] Studies are listed by order of citation in the text.

symptoms were associated with this lack of pleocytosis.[12] In addition, Mulford et al[14] showed that CSF pleocytosis has poor sensitivity for prediction of enterovirus infection in patients ≤2 months of age.

The study by Stellrecht et al[7] was limited by poor precision for the estimates of pleocytosis due to the small sample of infants <90 days of age (Table 2). Due to the retrospective nature of the 4 studies, there was a potential for selection bias because enterovirus testing was not performed on all infants with CSF available. Given the absence of pleocytosis in a large percentage of young infants and the poor sensitivity for pleocytosis to predict enterovirus infection, testing for enterovirus should not be restricted to infants with CSF pleocytosis. No

other patient characteristics have been identified to promote selective testing of patients.

Study and Evidence Quality

Risk of Bias of Individual Studies

The cohort studies included in this review had several limitations (Table 3). Precision of the outcomes for several studies was low due to small sample size,[7] and there was incomplete reporting of outcome data.[8] Two studies, Ramers et al[9] and Seiden et al,[13] had the potential for selection bias based on their population definitions. Ramers et al[9] only included patients who were tested for enterovirus, and the criteria for enterovirus testing was unclear in this retrospective study. Selection bias may have

also been present in Seiden et al[13] because lumbar puncture was not performed on every patient and the factors that influenced the decision to perform a lumbar puncture were unclear. We did not report the data for pleocytosis for 1 study because high age-based cutoff points were used, which could have biased the results toward an underestimation of the frequency of pleocytosis.[9] Cross-sectional studies and cohort studies with limited follow-up after hospitalization were marked as "not applicable" for the concern for attrition bias because longer follow-up was not needed to measure the outcomes of interest.

For the 1 diagnostic study included in this review, CIs were not reported for the test

TABLE 2 Summary of Key Study Results by Outcome

Study[a]	Resource Use	Subgroups/Pleocytosis
Stellrecht et al[7]	In infants <3 mo of age (n = 31), a positive correlation was found between decreased turnaround time and decreasing LOS (r^2, 0.92, P = .009).	16 of 31 were EV positive and, of those, only 44% (95% CI 19.8%–70.1%) had CSF pleocytosis.
Dewan et al[8]	The EV-positive infants had 26% shorter LOS compared with those infants that were not tested, with adjusted β coefficient, −0.305 (95% CI −0.457 to −0.153, P < .001).	NI
Ramers et al[9]	In a subgroup of 146 infants <1 mo old with pleocytosis, LOS (median 42.5 vs 71 h) and time from PCR result to discharge (median 7.2 vs 28 h) were shorter for EV-positive patients compared with EV-negative patients. Less had CT/MRI (10% vs 71%), radiographs (26% vs 80%), EEG (3% vs 27%), and median days IV antibiotics (2 vs 4 d) occurred for EV-positive patients compared with those with a negative test (P < .001 for all comparisons).	Pleocytosis reported for EV-positive infants <1 mo old and 1–2 mo of age. However, possible discrepancies were seen in the numbers in various parts of the manuscript.
Nigrovic et al[10]	EV PCR testing can lead to cost savings when the prevalence of EV is >13.5% with the assumption of discharge of 50% of infants with a positive PCR after 24 h of hospitalization.[b]	NI
Byington et al[11]	NI	No difference in age, sex, LOS, temperature, or duration of symptoms between EV-positive and EV-negative infants.
Yun et al[12]	NI	68%–77% of 22 infants <1 mo old did not have CSF pleocytosis.
Seiden et al[13]	NI	CSF pleocytosis present in 71% (n = 109/154) of patients and increased with age in 59%, 74%, and 90% of infants aged 0–28, 29–56, and 57–90 d, respectively (P = .007).
Mulford et al[14]	NI	For infants ≤2 mo of age: sensitivity of pleocytosis, 70% (95% CI, 59%–79%), specificity, 73% (95% CI, 63%–81%), PPV, 69% (95% CI, 58%–79%), NPV, 74% (95% CI, 64%–82%). Test properties for CSF protein were not reported for this age group.

CT, computed tomography; EV, enterovirus; IV, intravenous; NI, not included; NPV, negative predictive value; PPV, positive predictive value.

[a] Studies are listed by the order of citation in the text. For studies that included an older population, the results are reported for the subgroup of infants <90 days of age. The upper age limit of the subgroup reported varies by study.

[b] Results reported according to the decision tree assumption suitable for infants 0 to 90 days of age.

properties.[14] By calculating CIs from the raw data, we found that Mulford et al[14] had precise estimates for the test properties for pleocytosis when used to diagnose patients with enterovirus infection. Additionally, the study by Mulford et al[14] did not describe the disease severity of the population and, thus, spectrum bias cannot be excluded. Little information was provided to describe the study population aside from the age of the participants.

One economic analysis by Nigrovic et al[12] was included in this review. Overall, this study was limited because the comparison between the cost of empirical enterovirus testing versus "standard practice" was based on decision tree modeling with assumptions for the LOS in each arm. The enterovirus PCR testing group was assumed to be discharged at 24 hours and the standard therapy group was assumed to stay in the hospital for 48 hours before discharge. It is possible that LOS from actual patient observations, if measured, may have differed from these assumptions. Another major weakness of the study was the lack of measurement of effectiveness of the intervention, which was routine enterovirus testing. There is evidence that CSF enterovirus PCR has good sensitivity and specificity and that enterovirus PCR testing leads to shorter LOS. However, there is no evidence about the effectiveness of diagnosing bacterial meningitis and the decision tree includes the assumption that the CSF culture would be negative at 24 hours and remain negative. Given the small number of patients (N = 126), the investigators did not have a large enough sample to give precise estimates of bacterial meningitis in the population studied. It is also unclear whether all important costs were measured. The investigators evaluated cost savings for inpatient hospitalization, antibiotics, and inpatient attending fee. They did not measure any costs from the parent or societal perspectives.

Quality of Evidence

When assessing the quality of the body of evidence to determine whether enterovirus testing led to a reduction in resource use, the overall quality of the evidence was low (Table 4). The quality of the evidence was downgraded by 1 point due to concern for bias in Nigrovic et al[10] because there was a lack of evidence to show equal effectiveness in both arms for this cost minimization study. The quality of the evidence was upgraded by 1 point for dose response because Stellrecht et al[7] showed that a decrease in turnaround time for enterovirus PCR led to a shorter LOS and Ramers et al[9] showed a shorter time to discharge after the PCR result was available for neonates with pleocytosis and a positive test.

The evidence for testing in the absence of pleocytosis was of low quality (Table 4). The evidence was downgraded by 1 point because there could have been some selection bias involved in patient recruitment because all patients were not

TABLE 3 Risk of Bias of Individual Studies Using CASP Tools

	Focused Question	Recruitment of Population	Exposure	Outcome	Confounding	Follow-up	Precision	Fit With Other Evidence
Cohort studies								
Stellrecht et al[7]	/	/	+	/	/	NA	—	+
Dewan et al[8]	+	+	+	+	+	/	+	+
Ramers et al[9]	+	/	+	/	/	NA	/	+
Byington et al[11]	+	+	+	+	NA	+	/	+
Yun et al[12]	+	/	/	+	+	NA	+	+
Seiden et al[13]	+	/	+	+	+	NA	+	+
Diagnostic study	Focused question	Reference standard	Verification bias	Review bias	Defined disease status	Methods of test	Precision	Important outcomes
Mulford et al[14]	+	+	+	+	/	+	+	+
Economic evaluation	Focused question	Competing alternatives	Effectiveness of intervention	Effects of intervention	Measurement of costs	Discounting	Incremental analysis	Sensitivity analysis
Nigrovic et al[10]	+	+	—	—	/	NA	+	+

+, no concern for bias; —, concern for bias; /, cannot tell if bias present; NA, not applicable to the study.

tested for enterovirus. The evidence was upgraded by 1 point for large effect because a large percentage of infants <90 days with enterovirus meningitis had no pleocytosis.

DISCUSSION

In this systematic review of the literature, we found that empirical enterovirus testing can reduce hospital costs and LOS. No subgroups, including patients with pleocytosis, were identified to support a more selective approach for testing. Within the evidence, several factors were reported to affect the likelihood of cost savings through routine testing. The local prevalence and seasonality of enterovirus infection in the community determines the degree of potential cost savings.[10] The cost of the enterovirus PCR and the turnaround time of the enterovirus PCR test should also be considered.[7,10]

In addition to community prevalence and test characteristics, physicians must also be willing to discharge these young infants from the hospital sooner when enterovirus testing is positive. Shorter discharge times may be justified given the lower frequency of SBI in infants with enterovirus infection. Three prospective studies have reported the frequency of total SBI to be 1.6%, 6.6%, and 6.7% in infants that tested positive for enterovirus.[11,15,16] Of the infants with enterovirus infection and SBI, urinary tract infection was the most common, bacteremia occurred in ≤1% of the population, and none of the infants had concurrent bacterial meningitis.[11,15,16] Rittichier et al[16] found that all patients with bacteremia were <28 days old. Given previous studies that have reported that 91% of blood cultures will be positive by 24 hours if the patient has true bacteremia,[17] a 24 hour length of observation may be reasonable for a well-appearing neonate with enterovirus infection and even shorter observation times or discharge from the emergency department could be considered for well-appearing infants >28 days old.

These shorter observation times can increase cost savings and decrease hospital exposure for these young infants.

This systematic review has several limitations. The quality of the evidence to address the benefit of enterovirus testing was low given the observational nature of the studies included in this review. However, the findings of these studies appear to be consistent. Studies consistently report a shorter LOS for enterovirus-positive infants as compared with enterovirus-negative infants. The absence of pleocytosis in enterovirus-positive infants has also been consistently reported to occur more frequently in younger infants. Another limitation is that several studies included older infants and children within the population, and the subgroups reported had varying definitions for the upper age limit. Due to this limitation, quantitative analysis was not performed.

Additional studies are needed to evaluate the impact of empirical enterovirus testing

TABLE 4 Quality of the Body of Evidence for Each Outcome Using GRADE

Does Enteroviral Testing Reduce Resource Use?

Starting Level of Quality[a]	Downgrade					Upgrade			Final Level of Quality
	Bias	Inconsistent	Indirect	Imprecise	Publication Bias	Large Effect	Dose Response	Direction of Confounding	
2 plus ⊕⊕○○	−1	0	0	0	0	0	+1	0	2 plus ⊕⊕○○
Should EV Testing Be Performed in Absence of Pleocytosis?									
2 plus ⊕⊕○○	−1	0	0	0	0	+1	0	0	2 plus ⊕⊕○○

[a] Evidence quality is rated as high (4 plus, ⊕⊕⊕⊕), moderate (3 plus, ⊕⊕⊕○), low (2 plus, ⊕⊕○○), or very low (1 plus, ⊕○○○) using GRADE.

on specific subgroups of infants with and without pleocytosis. The majority of studies in this review reported the frequency of pleocytosis in young infants, but none of the studies directly compared LOS, antibiotic use, and ancillary testing in infants with and without pleocytosis. Ramers et al[9] reported great potential for cost savings in neonates with pleocytosis, but data on the potential for cost savings in neonates without pleocytosis were lacking. The age of the infant may also affect cost savings because many physicians manage neonates more conservatively than infants 1 to 2 months of age.

CONCLUSIONS

Routine enterovirus testing of febrile young infants 0 to 90 days of age has the potential to result in cost savings through a reduction in hospital LOS. Testing during times of higher enterovirus prevalence and with the use of a PCR test with faster turnaround time may yield higher cost savings. Additional studies are needed to evaluate the impact of enterovirus testing on resource use in specific subgroups of young infants based on age and pleocytosis.

REFERENCES

1. Krober MS, Bass JW, Powell JM, Smith FR, Seto DS. Bacterial and viral pathogens causing fever in infants less than 3 months old. *Am J Dis Child*. 1985;139(9):889–892

2. Abzug MJ. Presentation, diagnosis, and management of enterovirus infections in neonates. *Paediatr Drugs*. 2004;6(1):1–10

3. Abzug MJ, Rothart HA. Enterovirus infections of neonates and infants. *Semin Pediatr Infect Dis*. 1999;10(3): 169–176

4. Gomez B, Mintegi S, Rubio MC, Garcia D, Garcia S, Benito J. Clinical and analytical characteristics and short-term evolution of enteroviral meningitis in young infants presenting with fever without source. *Pediatr Emerg Care*. 2012;28(6): 518–523

5. Critical Appraisal Skills Programme (CASP). CASP checklists. Available at: www.casp-uk.net/#!casp-tools-checklists/c18f8. Accessed November 4, 2015

6. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454): 1490–1494

7. Stellrecht KA, Harding I, Woron AM, Lepow ML, Venezia RA. The impact of an enteroviral RT-PCR assay on the diagnosis of aseptic meningitis and patient management. *J Clin Virol*. 2002; 25(suppl 1):S19–S26

8. Dewan M, Zorc JJ, Hodinka RL, Shah SS. Cerebrospinal fluid enterovirus testing in infants 56 days or younger. *Arch Pediatr Adolesc Med*. 2010;164(9): 824–830

9. Ramers C, Billman G, Hartin M, Ho S, Sawyer MH. Impact of a diagnostic cerebrospinal fluid enterovirus polymerase chain reaction test on patient management. *JAMA*. 2000; 283(20):2680–2685

10. Nigrovic LE, Chiang VW. Cost analysis of enteroviral polymerase chain reaction in infants with fever and cerebrospinal fluid pleocytosis. *Arch Pediatr Adolesc Med*. 2000;154(8):817–821

11. Byington CL, Taggart EW, Carroll KC, Hillyard DR. A polymerase chain reaction-based epidemiologic investigation of the incidence of nonpolio enteroviral infections in febrile and afebrile infants 90 days and younger. *Pediatrics*. 1999;103(3). Available at: www.pediatrics.org/cgi/content/full/103/3/e27

12. Yun KW, Choi EH, Cheon DS, et al. Enteroviral meningitis without pleocytosis in children. *Arch Dis Child*. 2012;97(10):874–878

13. Seiden JA, Zorc JJ, Hodinka RL, Shah SS. Lack of cerebrospinal fluid pleocytosis in young infants with enterovirus infections of the central nervous system. *Pediatr Emerg Care*. 2010;26(2):77–81

14. Mulford WS, Buller RS, Arens MQ, Storch GA. Correlation of cerebrospinal fluid (CSF) cell counts and elevated CSF protein levels with enterovirus reverse transcription-PCR results in pediatric and adult patients. *J Clin Microbiol*. 2004;42(9):4199–4203

15. Martínez Planas A, Muñoz Almagro C, Luaces Cubells C, et al. Low prevalence of invasive bacterial infection in febrile infants under 3 months of age with enterovirus infection. *Clin Microbiol Infect*. 2012;18(9):856–861

16. Rittichier KR, Bryan PA, Bassett KE, et al. Diagnosis and outcomes of enterovirus infections in young infants. *Pediatr Infect Dis J*. 2005;24(6):546–550

17. Biondi EA, Mischler M, Jerardi KE, et al; Pediatric Research in Inpatient Settings (PRIS) Network. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr*. 2014;168(9): 844–849

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