Cost Analysis of Enteroviral Polymerase Chain Reaction in Infants With Fever and Cerebrospinal Fluid Pleocytosis

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Background: Infants with fever and cerebrospinal fluid (CSF) pleocytosis are routinely admitted to the hospital for parenteral antibiotic therapy for potential bacterial meningitis pending results of CSF culture. Published estimates suggest that 90% of all episodes of meningitis are caused by enterovirus. Enteroviral polymerase chain reaction (ePCR) has a sensitivity of 92% to 100% and a specificity of 97% to 100% in CSF.

Objective: To compare a management strategy using ePCR with current practice to determine potential savings by allowing earlier discharge.

Methods: Decision analysis comparing 2 strategies for the care of a retrospective cohort of infants with fever and CSF pleocytosis: standard practice vs ePCR testing of all CSF samples. Model assumptions include the following: (1) standard practice patients continue parenteral antibiotic therapy until CSF cultures are negative at 48 hours, (2) patients with positive ePCR results would be discharged after 24 hours, (3) patients with positive ePCR results have a negative CSF culture, and (4) costs are calculated from actual patient charges with a cost-to-charge ratio of 0.65.

Subjects: All infants aged 28 days to 12 months admitted to an urban teaching hospital with fever, CSF pleocytosis, and a negative CSF Gram stain from January 1996 through December 1997.

Outcome Measure: Total cost of hospitalization.

Results: A total of 126 infants were identified. One hundred twelve (89%) were discharged with a diagnosis of aseptic meningitis; 72% of these cases occurred during the peak enterovirus season (June to October). Three of 3 patients with positive CSF cultures had bacterial growth within 24 hours of admission. Mean length of stay for patients with aseptic meningitis was 2.3 days (SD, ±1.4 days). Total cost of hospital care for all 126 infants was $381,145. In our patient population, total patient costs would be reduced by the ePCR strategy if enterovirus accounts for more than 5.9% of all meningitis cases. Varying the sensitivity of the ePCR assay from 100% to 90% changes the “break-even” prevalence from 5.8% to 6.5%. Total cost savings of 10%, 20%, and 30% would occur at an enteroviral meningitis prevalence of 36.3%, 66.7%, and 97.1%, respectively.

Conclusions: Enteroxiral PCR analysis of CSF for infants admitted to the hospital with meningitis can result in cost savings when the prevalence of enteroviral meningitis exceeds 5.9%. Limiting use of ePCR to the enterovirus season would increase cost savings. A prospective study is needed to validate these results.


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VALUATION OF infants with high-grade fever and cerebrospinal fluid (CSF) pleocytosis includes broad-spectrum antibiotic therapy and hospital admission. In most cases, bacterial cultures remain negative and the infant is discharged with a diagnosis of aseptic meningitis. Nonpolio enteroviruses are the infectious agent in at least 66% and up to 90% of these cases, with peak incidence during the late summer and early fall in temperate climates. The most common enterovirus serotypes associated with aseptic meningitis are coxsackie B5; echoviruses 4, 6, 9, and 11; and the numbered enteroviruses. Beyond the immediate neonatal period (>28 days of life), enteroviral meningitis is associated with a benign clinical course. Current therapeutic interventions for central nervous system enteroviral infections are limited to supportive care, although new antiviral therapies are under development.

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The diagnosis of enteroviral infection has previously been made by viral culture of infected body fluid, which re-
PATIENTS AND METHODS

PATIENT SELECTION

We reviewed all Children’s Hospital, Boston, Mass, emergency department patient records from January 1, 1996, to December 31, 1997, using a computerized search tool to identify all infants aged 28 days to 12 months with fever (temperature ≥38°C) and CSF pleocytosis (white blood cell count ≥0.006 × 10⁹/L). A total of 166 infants were identified.

We limited our study population to patients in whom no source of fever could be immediately identified and in whom a positive ePCR would alter subsequent management. Forty patients were thus excluded. Ten infants were eliminated owing to definite bacterial meningitis with a CSF Gram stain showing organisms. Ten were excluded on the basis of the following diagnoses: urinary tract infection with more than 10 to 20 white blood cells per high-power field (7 patients), positive blood culture at admission (2 patients), and periorbital cellulitis (1 patient). Fifteen patients were excluded on the basis of having a recognizable viral syndrome that otherwise dictated their clinical management (9 patients with gastroenteritis were admitted due to dehydration and 6 patients with bronchiolitis were admitted due to respiratory distress/hypoxia). Finally, 5 patients were eliminated because of recent ventriculoperitoneal shunt placement, which is associated with an increased risk of central nervous system bacterial infection.16 We included infants with bloody spinal taps since CSF results were considered uninterpretable by the treating clinicians. We determined the discharge diagnoses for each patient by independently reviewing the medical record and the CSF culture results. We determined length of stay by calculating the number of days each patient was in the hospital at midnight. Approval for chart review was granted by the Children’s Hospital institutional review board (protocol 98-11-089).

Recently, microbiologic developments have allowed the application of reverse transcriptase polymerase chain reaction (PCR) technology to the diagnosis of enteroviral infections. Clinical testing of this new modality on CSF for the diagnosis of meningitis has been shown to be significantly more sensitive than culture.5 The enteroviral PCR (ePCR) assay uses a simple colorimetric detection technique with results available within 5 hours.5 Using either standardized specimens or specimens from patients with negative CSF viral cultures, but with enterovirus identified elsewhere (blood, throat, or stool), currently published ranges of CSF ePCR for sensitivity are 92% to 100% and for specificity are 97% to 100%.10,15

We propose that the clinical application of ePCR in the diagnosis of meningitis has potential cost savings in terms of shorter hospital stays and decreased antibiotic use. Several models of early discharge have already predicted significant reductions in hospital costs.14,15 This study models the universal application of ePCR to infants admitted to the hospital with meningitis to determine the prevalence of enteroviral infection needed to achieve cost savings.

COST ASSUMPTIONS

We determined actual hospitalization costs for each patient from hospital billing records based on 1996-1997 levels. Cost calculations used a standard cost-to-charge ratio of 0.65. An overnight hospital stay cost $637 per night, which included nursing services. Intravenous cefotaxime (dose of 200 mg/kg per day divided in 4 daily doses for a 6-kg child) cost $96 per day, which included drug preparation and administration. A level I attending physician cost $107 for the first day and $65 for subsequent days based on charges at a local private pediatric practice. Thus, the cost per hospital day after the first day was $798. The cost for the reverse transcriptase ePCR was estimated at $90 based on expected commercially available materials ($35) plus labor costs ($55) of running batched specimens. Creation of dedicated laboratory space within the treating facility was not included in our cost model.

DECISION ANALYSIS

A cost minimization strategy was used to compare standard care with universal ePCR testing. The model assumes the following: (1) standard practice consists of parenteral antibiotic therapy until CSF cultures are negative at 48 hours; (2) ePCR testing results are available within 24 hours of admission for all patients; (3) patients with positive ePCR are discharged after 24 hours; and (4) patients with positive ePCR results and negative CSF bacterial cultures at 24 hours will remain culture negative. Savings per patient included inpatient hospital bed, antibiotics, and inpatient attending fee costs. Cost savings were calculated over a 0% to 100% range in the prevalence of enteroviral meningitis in the study population. An ePCR sensitivity of 99% and a specificity of 97% were used. Sensitivity analysis was performed by varying ePCR sensitivity over a 90% to 100% range. Cost analysis was also performed by varying the percentage of patients discharged at 24 hours over a 30% to 100% range.

RESULTS

PATIENT SELECTION

Figure 1 depicts the applied decision analysis. A total of 126 infants aged 28 days to 12 months with fever, CSF pleocytosis, and no other emergency department diagnosis were admitted for meningitis treatment. The discharge diagnoses of these patients were aseptic meningitis (112 patients), bacterial meningitis (7 patients), and urinary tract infection (7 patients). Only 3 of the patients with bacterial meningitis had pathogens grow in their CSF cultures. All 3 organisms had grown by 24 hours. The other 4 patients had been pretreated with antibiotics, rendering the CSF culture uninterpretable to the treating clinician. Patients with a discharge diagno-
sis of aseptic meningitis had a mean length of stay of 2.3 days (SD, ±1.4 days).

**DECISION ANALYSIS**

The cost minimization strategy applied to the study patients is depicted in Figure 1. The total cost for the 126 study patients was $381,145, based on actual billing records. Testing with ePCR for all 126 study patients would have cost $11,340. A positive ePCR result would save 1.3 hospital days per patient by allowing hospital discharge at 24 hours. The savings of $1037 per patient was calculated using cost assumptions stated in the “Patients and Methods” section (1.3 × $798).

The break-even point was defined as the prevalence at which the charge for performing the ePCR assay was exactly equal to the hospitalization charges saved, as depicted in Figure 2. This equivalence occurred at an enteroviral prevalence of 5.9% among children with CSF pleocytosis. Total cost savings of 10%, 20%, and 30% would occur at an enteroviral meningitis prevalence of 36.3%, 66.7%, and 97.1%, respectively.

**SENSITIVITY ANALYSIS**

Cost savings depend on the actual sensitivity of the ePCR assay. If the actual sensitivity of the assay is 90%, well below published estimates, the break-even prevalence would be 6.5%. If the actual sensitivity is 100%, the break-even point occurs at a 5.8% prevalence.

If only 50% of the infants with positive ePCR results are actually discharged at 24 hours, the break-even points occur at a prevalence of 13.5% with a sensitivity of 90% and a prevalence of 12.1% with a sensitivity of 100%.

**SEASONAL SELECTION**

Figure 3 depicts the discharge diagnosis of study patients by month. Seventy-two percent of infants with aseptic meningitis each year are admitted to the hospital between June and October during the peak enteroviral season. The incidence of bacterial meningitis and urinary tract infection in the sample remains constant throughout the year.

**COMMENT**

Meningitis is a common pediatric infection that requires hospital admission and parenteral antibiotic therapy although the majority of cases are caused by viral rather than bacterial pathogens. Using our model assumptions, we found ePCR to be a cost-effective strategy in managing infants with fever and CSF pleocytosis. If the actual prevalence of enteroviral meningitis was above 5.9%, ePCR screening for admitted patients would result in over-
all cost savings by allowing earlier hospital discharge. Estimates of the prevalence of enteroviral meningitis in infants with CSF pleocytosis range from 66% to 90% depending on the season.\textsuperscript{1,3} Therefore, over the entire likely range of ePCR assay sensitivity from 100% to 90%.

Our diagnostic strategy has the following limitations. Only direct costs of hospitalization were used in this analysis. Indirect costs, such as parental missed workdays or additional expenses of child care, and benefits to the family of early discharge have not been included. Not all infants with documented enteroviral infections will be ready for discharge at 24 hours. Only patients who are clinically well would be able to be discharged early. Many infants will have associated poor oral intake, ongoing diarrheal or vomiting losses, high-grade fevers, or behavioral changes. These clinical criteria would potentially reduce the number of infants actually eligible for early discharge and in turn reduce calculated cost savings. However, even by altering the percentage of eligible patients who are actually discharged to as low as 50%, the break-even point still occurs at a relatively low prevalence (12.1%-13.5%) over the range of sensitivity from 100%-90% of enteroviral infection. Additional costs could occur if the infants discharged early returned to their primary care physician or emergency department for reevaluation.

A key assumption of our decision analysis is that patients with documented enteroviral disease do not have concomitant bacterial central nervous system infection. A false-positive ePCR result might allow a patient with true bacterial meningitis (who appears clinically well) to be discharged early. The probability of a false positive depends on the prevalence of true infection in the study population as well as the specificity of the ePCR test (at the published specificity of 97%, this probability is given by the following formula:

\[ (1 - \text{Specificity}) \times (1 - \text{Prevalence}) = 0.03 \times (1 - \text{Prevalence})].\]

The early discharge of an infant with bacterial meningitis would occur only in 2 distinct scenarios: (1) the infant had a false-positive ePCR result and a false-negative 24-hour CSF culture or (2) the infant had a true-positive ePCR result and a false-negative 24-hour CSF culture. Discharging a patient under either of these scenarios would certainly adversely affect outcome; however, we believe that the likelihood of either scenario occurring is quite low.

Scenario 1 represents the patient who has bacterial, but not viral, meningitis and whose CSF cultures were not positive at the time of potential discharge (24 hours). In our study population, only 2.3% of CSF cultures yielded bacteria and all organisms had been identified within 24 hours of inoculation. A review of the CSF cultures from our laboratory revealed that 73% of all positive CSF cultures had grown pathogens within 24 hours and that for the most common pathogens (\textit{Streptococcus pneumoniae}, \textit{Escherichia coli}, \textit{Neisseria meningitidis}, and streptococci group B), 42 (98%) of 43 CSF cultures were positive within 24 hours (A. B. Macone, PhD, Division of Laboratory Medicine, Children’s Hospital, Boston, unpublished data, January 1993 through December 1997). Scenario 1 clearly represents the minority of patients with bacterial meningitis. As a safeguard against poor outcomes from premature discharge of patients with bacterial meningitis, one could administer a dose of a long-acting cephalosporin prior to discharge pending final culture results.\textsuperscript{17} Our model, however, does not take into account the cost of the additional dose of antibiotics.

Scenario 2 represents the patient who has both viral and bacterial meningitis. In a recent study of 345 febrile infants younger than 90 days with identifiable enteroviral disease, none had bacterial meningitis.\textsuperscript{18} There is growing evidence that the risk of bacteremia may be decreased in the setting of other identifiable viral syndromes as well.\textsuperscript{19,20} Furthermore, as in the case of scenario 1, early discharge would occur only in patients with bacterial meningitis who appeared clinically well at 24 hours and had negative 24-hour CSF cultures.

It should be noted that our study does not take into account the possibility of deterioration of the test characteristics of ePCR testing in “real-world” use. Widespread ePCR testing would require very strict standards to ensure that contamination of samples does not occur. Any reduction in test characteristics of the ePCR would adversely affect our model outcomes.

To be truly cost-effective, regional testing centers for ePCR analysis would likely need to be established. Each pediatric inpatient facility will have only a small number of samples and results need to be available within 24 hours to be clinically relevant. By pooling samples, this number could be dramatically increased. This would reduce the costs of duplicating extensive quality control measures and decrease additional use of laboratory space and effort, which were not accounted for in our model. However, our model does not take into account the additional cost of transporting samples in a rapid fashion under controlled conditions.

During the peak enteroviral season, June to October in temperate climates, the number of available samples and the prevalence of enteroviral disease increases. Focusing testing to this season would allow greater economies of scale and more accurate test results. Testing with ePCR may provide an additional uncalculated benefit for infants who received antibiotic therapy before obtaining their CSF cultures. In our study population, 4 patients were treated for bacterial meningitis despite nega-
tive CSF cultures because they had received antibiotic pretreatment. Documented enterovirus infection has the potential to shorten both length of antibiotic therapy and hospital stay in these infants.

Polymerase chain reaction testing is becoming more readily available in the clinical setting. Our model supports the assumption that universal ePCR testing of infants admitted to the hospital with meningitis would save costs by allowing earlier discharge. This treatment strategy needs prospective validation in a clinical setting with measurement of both direct and indirect costs and benefits.

Accepted for publication March 3, 2000.

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REFERENCES