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BRIEF REPORTS

Impact of In-Hospital Enteroviral Polymerase Chain Reaction Testing on the Clinical Management of Children With Meningitis

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BACKGROUND: Enteroviral meningitis is a common cause of meningitis in children which requires only supportive care.

OBJECTIVE: To evaluate the impact of implementing an in-hospital enteroviral polymerase chain reaction (EVPCR) testing protocol on the clinical management of children with meningitis.

DESIGN: Retrospective cohort study.

POPULATION: Children <19 years old with meningitis.

INTERVENTION: EVPCR testing differed by time period: send-out testing protocol from July 1, 2006–June 23, 2008 (pre-period) versus in-house testing protocol from June 24, 2008–June 30, 2010 (post-period).

MEASUREMENTS: Test turnaround time, test utilization, length of stay, and duration of parenteral antibiotics.

RESULTS: Of the 441 study patients, 216 (49%) presented during the post-period. Median age was 2.9 months (interquartile range, 1.5–96 months). Test turnaround time decreased with the in-house test (53 hours pre vs 13 hours post, $P < 0.001$), and test utilization increased (28% pre vs 62% post, $P < 0.001$). Among children with a positive EVPCR test, both length of stay (44 hours pre vs 28 hours post, $P = 0.005$) and duration of parenteral antibiotics (48 hours pre vs 36 hours post, $P = 0.04$) decreased in the post-period. No change in either of these outcomes was observed in children with meningitis and a negative EVPCR test.

CONCLUSION: In-house EVPCR testing reduced test turnaround time, increased test utilization, and reduced both length of stay and duration of parenteral antibiotics for children with a positive result. Clinicians caring for children with meningitis should have access to in-hospital EVPCR testing. *Journal of Hospital Medicine* 2012;7:517–520.

Non-polio enteroviruses are the most common cause of aseptic meningitis in children.[1] While bacterial meningitis requires parenteral antibiotics, aseptic meningitis requires only supportive care.[1] Enteroviral reverse transcription polymerase chain reaction (EVPCR) testing of the cerebrospinal fluid (CSF) allows the virus to be detected with high sensitivity and specificity.[2] Because children with a positive EVPCR test are at low risk of bacterial meningitis,[3] access to rapid EVPCR results has the potential to impact the clinical management of children with meningitis.[4,5] We studied the impact of implementing an in-hospital EVPCR testing protocol on the clinical management of children with meningitis in a single-center retrospective cohort.

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MATERIALS AND METHODS

Study Design and Population

We identified children, <19 years of age, with meningitis evaluated at a single tertiary care pediatric center between July 2006 and June 2010. We defined meningitis as a CSF white blood cell (WBC) count ≥10 cells/mm^3 corrected for the presence of CSF red blood cells (RBCs) (1 WBC for every 500 RBCs).[6] We excluded children with any of the following: critical illness (defined as hypotension or respiratory failure), purpura, recent neurosurgery, ventricular shunt, immunosuppression, focal bacterial infection requiring parenteral antibiotics, positive CSF Gram stain, or known Lyme disease. The Institutional Review Board approved this study with waiver of informed consent.

Data Collection and Case Definitions

We abstracted historical and physical examination findings, as well as laboratory and microbiologic results, from the medical record. We defined bacterial meningitis as the isolation of pathogenic bacteria from the CSF or blood cultures. Children who had received antibiotics within 72 hours of diagnostic lumbar puncture, with negative cultures, were considered to have pretreated culture-negative meningitis. Otherwise, children with negative bacterial cultures were classified as having aseptic meningitis.

EVPCR Testing

During the study pre-period (July 1, 2006 through June 23, 2008), EVPCR tests were flown once daily to a commercial laboratory (ARUP Laboratories, Salt Lake City, UT) where they were run in batches. During the post-period (June 24, 2008 through June 30, 2010), the study institution replaced the send-out test with an in-hospital EVPCR test (Gene Xpert EV Technology; Cepheid, Sunnyvale, CA)[7] that allows multiple specimens to be run simultaneously, multiple times daily (between 7:00 AM and 10:00 PM), with results available in as little as 2.5 hours. We defined turnaround time for the test from specimen obtainment to test result.

Outcome Measures

Our 2 primary outcomes were length of stay and duration of parenteral antibiotics. Length of stay was measured as time from emergency department arrival to discharge (emergency department or inpatient discharge). We defined the duration of parenteral antibiotics as time from the first to the last dose of parenteral antibiotics administered, plus the standard antibiotic dosing interval for that antibiotic. For children with Lyme meningitis, the duration of parenteral antibiotic coverage was defined a priori as 48 hours, the standard time to reliably exclude bacterial growth from culture.[8]

Statistical Methods

Primary outcomes were compared using univariate analyses in 6 patient groups: 1) all patients, and those with 2) a positive EVPCR test, 3) a negative EVPCR test, and a positive test who were 4) $\leq$90 days old, 5) $>$90 days old, and 6) presented during peak enteroviral season (June through October). We utilized Mann–Whitney tests for continuous variables and χ^2 tests for proportions. We compared the median turnaround time for EVPCR results and the percentage of tests returning prior to discharge between the pre- and post-periods. We performed interrupted time series spline analyses to assess for trends in our primary outcomes, independent of the change in EVPCR testing protocol. All analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Inc, Chicago, IL).[9]

RESULTS

Of the 593 children with meningitis, 152 (26%) were excluded for the reasons noted above. The 441 patients included in our analyses had the following final diagnoses: bacterial meningitis (1 patient with *Streptococcus pneumoniae*, 0.2%), pretreated culture-negative meningitis (42 patients, 10%), and aseptic meningitis (398 patients, 90%).

We compared patient populations and EVPCR testing characteristics between the pre- and post-study periods (Table 1). While CSF glucose differed between study periods, the difference was not felt to be clinically significant. However, during the post-period, more children presented during enteroviral season. Clinicians were more likely to order an EVPCR test for children with aseptic, than bacterial, meningitis (213/370 [58%] vs 0/1 [0%]).

TABLE 1. Comparison Between Study Patients Who Presented During the Pre- and Post-Periods

Characteristic	Pre-period (N = 225)	Post-period (N = 216)	*P* Value
Demographics			
Age (months)*	3 (2–106)	3 (1–88)	0.20
Male, n (%)	135 (60)	129 (60)	0.95
Historical features			
Duration of illness (days)*	2 (1–4)	2 (1–4)	0.20
Duration of fever (days)*	1 (1–2)	1 (1–2)	0.52
Antibiotic pretreatment, n (%)	29 (13)	13 (6.0)	0.015
Temperature at ED presentation* (°C)	37.6 (36.8–38.4)	37.8 (37.1–38.2)	0.51
Presentation June through October, n (%)	127 (56)	143 (66)	0.040
Laboratory results			
Peripheral WBC (cells/mm^3)*	10.4 (8.2–13.7)	10.4 (7.8–13.6)	0.67
Peripheral ANC (cells/mm^3)*	5.2 (3.1–7.4)	4.9 (2.6–8.2)	0.47
CSF WBC (cells/mm^3)*	55 (19–176)	62 (17–250)	0.66
CSF ANC (cells/mm^3)*	8 (0–45)	7 (1–41)	0.78
CSF glucose (mg/dL)*	57 (50–65)	54 (48–60)	0.01
CSF protein(mg/dL)*	50 (34–80)	48 (34–70)	0.73
Traumatic lumbar puncture (CSF RBC $\geq$500 cells/mm^3), n (%)	48 (21)	43 (20)	0.71
Patient management			
Admission to the hospital, n (%)	196 (87)	190 (88)	0.68
Parenteral antibiotics initiated, n (%)	206 (92)	200 (93)	0.80
Enteroviral PCR Testing			
Testing utilization, n (%)	62 (28)	133 (62)	<0.001
$\leq$90 days of age, n (%)†	18 (16)	57/114 (50)	<0.001
$>$90 days of age, n (%)‡	44 (39)	76/102 (75)	<0.001
Positive test result, n (%)	33 (53)	80 (60)	0.22
Test turnaround time, hours*	53 (46–67)	12 (6–17)	<0.001

Abbreviations: ANC, absolute neutrophil count; CSF, cerebrospinal fluid; ED, emergency department; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell. * Median (interquartile range). † Population: 227 children <90 days of age. ‡ Population: 214 children $\geq$90 days of age.

We evaluated the impact of the in-hospital EVPCR test on the length of stay and duration of parenteral antibiotics for the 6 predefined patient groups (Table 2). Length of stay could be determined for 432 (98%) of study patients, and duration of parenteral antibiotics for 365 (83%). We found a clinically important decrease in both length of stay and duration of parenteral antibiotics for children with a positive EVPCR test in the post-period. For every hour earlier the EVPCR results returned, length of stay was reduced by 0.3 hours (β = 0.3, 95% confidence interval [CI] 0.1–0.5), and parenteral antibiotics were reduced by 0.3 hours (β = 0.3, 95% CI 0.1–0.5). However, even in the post-period, the median length of time from a positive EVPCR test result to hospital discharge was 14 hours (interquartile range, 5–33 hours).

We observed no trend in length of stay in either testing period (β = −0.17, 95% CI −3.9 to 3.6 pre vs β = −1.64, 95% CI −6.3 to 3.0 post), with no change following the introduction of the faster EVPCR

TABLE 2. Univariate Comparison of Length of Stay and of Parenteral Antibiotics (in Hours) Between the Pre- and Post-Testing Periods

Patient Group	Pre-Period	Post-Period	*P* Value[1]
1) All study patients	N = 225	N = 216	
Length of stay*	49 (26–62)	47 (26–62)	0.09
Duration of parenteral antibiotics*	48 (24–64)	48 (24–60)	0.23
2) Children with a positive EVPCR test	N = 32	N = 80	
Length of stay*	44 (28–54)	28 (19–46)	0.005
Duration of parenteral antibiotics*	48 (30–72)	36 (24–49)	0.037
3) Children with a negative EVPCR test	N = 29	N = 53	
Length of stay*	61 (30–114)	59 (45–109)	0.67
Duration of parenteral antibiotics*	52 (47–84)	54 (48–70)	0.93
4) Children ≤90 days of age with positive EVPCR test	N = 9	N =39	
Length of stay*	66 (50–71)	37 (27–53)	0.003
Duration of parenteral antibiotics*	74 (69–94)	48 (36–60)	0.002
5) Children >90 days of age with positive EVPCR test	N = 23	N = 41	
Length of stay*	32 (27–50)	21 (4–30)	0.002
Duration of parenteral antibiotics*	38 (24–60)	24 (24–36)	0.009
6) Children with a positive EVPCR test who presented during peak enteroviral season	N = 29	N = 72	
Length of stay*	43 (28–53)	26 (17–38)	0.002
Duration of parenteral antibiotics*	46 (24–70)	36 (24–48)	0.05

Abbreviations: EVPCR, enteroviral polymerase chain reaction.
* Median (interquartile range).

protocol ($P = 0.52$). We observed an increase in duration of parenteral antibiotics in the pre-period ($\beta = 5.4$, 95% CI 0.3 to 10.6), with no trend in the post-period ($\beta = -1.7$, 95% CI −5.2 to 1.8), but the difference was not significant ($P = 0.08$).

DISCUSSION

The in-hospital EVPCR testing protocol reduced test turnaround time and increased testing. Children with a positive test had a shorter length of stay and duration of parenteral antibiotics. Decreasing the test turnaround time for EVPCR improved the care of children with enteroviral meningitis by reducing the length of unnecessary hospitalizations and parenteral antibiotics, with the potential for reducing the costs associated with these admissions.

Accurate identification of children with enteroviral meningitis, an often self-limited infection requiring supportive care, can reduce hospitalization and unnecessary antibiotics. Previously, a positive EVPCR test result has been associated with a reduction in length of stay and of parenteral antibiotics,[4,5,10–12] with a direct correlation between test turnaround time and length of stay.[12,13] Moreover, positive EVPCR test results that were available prior to hospital discharge resulted in shorter length of hospital stay and duration of parenteral antibiotics.[10]

Our study is the largest to investigate the impact of implementing an in-hospital EVPCR testing protocol, with the goal of making results available in a clinically useful time frame for all patients. Older EVPCR tests were typically performed in batches, or at centralized laboratories.[4,5,10–13] The in-hospital EVPCR test utilized is a simple testing platform, which can be run multiple times daily. While there were higher charges associated with increased testing in the post-period, these were more than offset by a reduced length of stay. Using study institution patient charges, we estimate that overall patient charges decreased approximately $80,000 in the post-period, compared to the pre-period (an average reduction of $375 per patient).

Many children were not discharged when a positive EVPCR test result became available. Some children with enteroviral meningitis will have persistent symptoms that require inpatient management. In addition, results that returned in the evening or nighttime were less likely to result in immediate hospital discharge. However, children with a positive EVPCR test are at very low risk for bacterial meningitis.[3] As clinicians' knowledge of, and comfort with, the EVPCR test increase, this technology has the potential to further decrease the costs of caring for children with enteroviral meningitis.[14]

Our study had several limitations. First, it was retrospective; however, primary outcomes were objective measures accurately recorded in the medical record for most patients. Second, our study was single-center, and findings may not be generalizable to other settings. Third, the management of children with meningitis may have been changing over the study period, independent of the in-hospital EVPCR test. However, among children with a negative test, we observed no change in either of our primary outcomes. Fourth, given the large number of physicians involved with testing and treatment decisions, we could not adjust for clustering at the physician level. Fifth, we corrected CSF WBC in the case of a traumatic lumbar puncture (LP). Although use of this correction might underestimate the true CSF WBC count,[6] the percentage of children with traumatic lumbar punctures was the same in both testing periods. Lastly, we evaluated the impact of a diagnostic test immediately after introduction into the clinical setting. As new medical technologies often take time to be adopted into clinical practice,[15] we would expect the impact to increase over time.

CONCLUSIONS

In-hospital EVPCR testing can improve the care of children with meningitis by reducing the length of unnecessary hospitalizations and parenteral antibiotics. Clinicians caring for children with meningitis should have access to in-hospital EVPCR testing.

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