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Repeat Lumbar Punctures in Infants with Meningitis in the Neonatal Intensive Care Unit

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Abstract

Objective—The purpose of this study is to examine the results of repeat lumbar puncture in infants with initial positive cerebrospinal fluid (CSF) cultures in order to determine the clinical characteristics and outcomes of infants with repeat positive cultures.

Study Design—Cohort study of infants with an initial positive CSF culture undergoing repeat lumbar puncture between 1997 and 2004 at 150 neonatal intensive care units managed by the Pediatrix Medical group. We compared the clinical outcomes of infants with repeat positive cultures and infants with repeat negative cultures.

Result—We identified 118 infants with repeat CSF cultures. Of these, 26 infants had repeat positive cultures. A higher proportion with repeat positive cultures died compared to those with repeat negative cultures, 6/23 (26%) vs. 6/81 (7%), respectively (p=0.02).

Conclusion—Among infants with a positive CSF culture, a repeat positive CSF culture is common. The presence of a second positive culture is associated with increased mortality.

Keywords

neonate; newborn; cerebrospinal fluid; infection; mortality

INTRODUCTION

Meningitis in the young infant is a life-threatening disease with high rates of mortality and morbidity.[1, 2, 3, 4] Lumbar puncture (LP) and culture of the cerebrospinal fluid (CSF) are essential to the diagnosis and treatment of bacterial or fungal meningitis. For infants with an initial positive CSF culture, clinicians often perform one or more follow-up LPs to assess for treatment effect by CSF sterilization. Although post-treatment LP is sometimes performed as a "test of cure," examination of CSF after completion of antimicrobial therapy has been found to be of little value in children > 1 month of age.[5]

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CONFLICT OF INTEREST STATEMENT
The authors report no conflicts of interest.

A repeat LP during the course of therapy, however, may provide reassurance of effective therapy in patients with particularly virulent or resistant organisms, in patients with worsening clinical status, or in infants, in whom subtle changes in clinical status may be difficult to discern.[6, 7] Published guidelines from the American Academy of Pediatrics Task Force on Diagnosis and Management of Meningitis recommend repeat CSF examination in children when there is no clinical evidence of improvement 24–72 hours after initial positive CSF cultures.[8] Others have recommended that all infants with bacterial meningitis should undergo repeat LP at 48 hours after initiation of therapy.[9] The purpose of this study was to examine the results of repeat LP in infants in the neonatal intensive care unit (NICU) with initial positive CSF cultures in order to determine: 1) demographic characteristics and organisms associated with repeat positive CSF cultures; 2) clinical outcomes in infants with and without repeat positive cultures; 3) utility of CSF parameters (white blood cell (WBC) count, protein, glucose) for predicting infection clearance.

MATERIALS AND METHODS

We evaluated the LP results from all infants discharged from one of 150 NICUs managed by the Pediatrix Medical Group from 1997 to 2004. The data were obtained from an electronic medical record as described previously.[10, 11] Briefly, the primary care provider enters the data prospectively in order to generate clinical progress notes for the medical record, and the data are sent to a common database following discharge. We excluded LP data from infants with no positive CSF cultures, CSF cultures positive for viral pathogens or bacteria that are often considered contaminants (including coagulase-negative *Staphylococcus*), CSF shunts or reservoirs, an adjusted age > 44 weeks at the time of first positive CSF culture, or only a single LP. The first LP resulting in a positive CSF culture was considered to be the first LP for each subject. If the second LP was performed > 30 days following the first LP, the subject was considered to only have a single LP and was excluded from analysis. Two patients had a second infection with a different organism, and one patient had an infection with the same organism after >30 days. Only the culture data for the first infection identified for each infant was included. The CSF parameter data were checked independently by three individuals for accuracy.

We compared the demographic characteristics of infants who had a repeat positive CSF culture and infants who had repeat negative CSF cultures using the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. In order to estimate the optimal time to repeat an LP, we calculated the proportion of positive CSF cultures and stratified by the number of LPs performed previously and the number of days since the original LP. We also fit a logistic regression model using the CSF culture result (positive/negative) as the dependent variable and the number of days since the original LP as the independent variable.

In order to illustrate the length of time required for clearance of infection, we calculated Kaplan-Meier survival curves with the failure event defined as the first negative CSF culture after which there were no more positive CSF cultures for that patient. We divided the pathogenic organisms into three groups (Gram-positive bacteria, Gram-negative bacteria, and *Candida*) and compared the equality of the survival functions for each group of organisms using the Wilcoxon (Breslow) test. Time required to clear infection was calculated as the number of days between the initial positive culture and the first negative culture following the last positive culture.

We conducted a separate Kaplan-Meier analysis to illustrate the time required to normalize CSF parameters. Normal CSF parameters for premature infants (< 37 weeks gestational age) were defined as a WBC count < 26/mm^3, glucose > 23 mg/dL, and protein < 151 mg/dL.[12]

Normal CSF parameters for term infants (≥ 37 weeks gestational age) were defined as a WBC count < 22/mm^3, glucose > 37 mg/dL, and protein < 89 mg/dL.[12]

Finally, we compared mortality across the organism groups and between patients with repeat positive cultures and no repeat positive cultures using Fisher's exact tests. Reported p-values are two-tailed, and p-values < 0.05 were considered statistically significant. We conducted the analysis with STATA 10 (College Station, TX). The Duke University Institutional Review Board provided permission to conduct this investigation.

RESULTS

Of the 14,018 infants with LP data, 118 (0.8%) met the inclusion criteria; two LPs were performed in 65 infants, three LPs were performed in 19 infants, and ≥4 LPs were performed in 34 infants. The median birth weight, gestational age at birth, and day of life of lumbar puncture were 1448 g [interquartile range; 879–2912], 31 weeks [27–37], and 17 days [4, 28], respectively. Of the 118 infants, 26 (22%) had at least 1 repeat positive culture. There was no difference in gestational age, post-menstrual age, birth weight, sex, or race between infants with repeat positive cultures and those with repeat negative cultures. Infants with repeat positive cultures were older at time of first LP than infants with repeat negative cultures, postnatal age 27 days vs. 14 days (p=0.001).

Pathogens isolated from CSF included 51/118 (43%) Gram-positive bacteria, 53/118 (45%) Gram-negative bacteria, and 14/118 (12%) *Candida* species (Table 1). There was no difference in the proportion of organisms classified into each of these groups between infants with repeat positive cultures and infants with repeat negative cultures (p=0.74). The most commonly identified pathogens were Group B *Streptococcus* and *Escherichia coli*.

Of a total of 319 repeat CSF cultures, 41 (13%) were positive. Most (34/41, 83%) of the repeat positive CSF cultures occurred within the first 7 days after the first LP (Table 2). The likelihood of a repeat positive CSF culture decreased as the number of days between the first positive and repeat LP increased (odds ratio [OR]; 0.88 [0.83–0.94], p<0.001). Only five patients had repeat positive cultures after the first 7 days; for 3/5 (60%) of these patients, a repeat positive culture after 7 days represented the first repeat positive culture, although one of these patients had no interim negative cultures.

Among infants with positive cultures, the median time to clear infection was 4 [2–7] days (Figure 1A), and the time to clear infection did not differ among organism groups: 3 [2–6] days for Gram-positive organisms, 5 [2–8] days for Gram-negative organisms, and 3 [2–6] days for *Candida* (p=0.16). Of the 118 patients, 1 (1%) patient died and 4 (3%) patients were discharged or transferred prior to documentation of negative CSF cultures.

We also examined the time required to normalize CSF protein, glucose, and WBC count (Figure 1B-D). Of the 84 infants who cleared the infection and had a value recorded for CSF protein at the time of last positive LP, 71 (85%) had an abnormal initial value, and only 8/71 (11%) normalized this parameter. Of the 82 infants who cleared the infection and had a value recorded for CSF glucose at the time of last positive LP, 44 (54%) had an abnormal initial value, and 16/44 (36%) normalized this parameter. Of the 91 infants who cleared the infection and had a value recorded for CSF WBC count at the time of last positive LP, 72 (79%) had an abnormal initial value, and only 13/72 (18%) normalized this parameter. Only 37/75 (49%) infants who cleared the infection and had values for CSF protein, glucose, and WBC count at the time of last positive culture were in the abnormal range for all parameters. Of the 67/75 (89%) infants who cleared the infection and had abnormal values of at least one parameter at the time of last positive culture, 3/67 (4%) eventually normalized all 3 CSF parameters. There was no significant difference in the survivor functions for any of the

individual CSF parameters between infants with repeat positive cultures and infants with repeat negative cultures.

Of the 118 infants with a repeat LP, 104 infants had available mortality data. Of these, 12/104 (12%) died prior to discharge. Death occurred in 2/44 (4%) of infants with Gram-positive infections, 4/46 (9%) of infants with Gram-negative infections, and 6/13 (46%) of infants with *Candida* infections (p=0.001). A significantly higher proportion of infants with repeat positive cultures died compared to infants with repeat negative cultures, 6/23 (26%) vs. 6/81 (7%), respectively (p=0.02).

Of the 14,018 infants with LP data, 103 infants had an initial positive CSF culture but no repeat LP. Ninety of these infants had available mortality data. Of these, 11/90 (12%) died, which was not statistically different from the mortality of infants who received repeat CSF examination but had repeat negative cultures6/81 (7%), (p=0.32). For 10 of the 11 infants without repeat LP for which date of death was known, death occurred >7 days after the positive culture in 6/10 (60%) and >3 days after the positive culture in 8/10 (80%). The distribution of organisms for infants with no repeat LP was significantly different from that for infants with a repeat LP (p=0.004); infants with no repeat LP were less likely to have Gram-negative infections (26/103 [25%] vs. 53/118 [45%]) and more likely to have Gram-positive infections (67/103 [65%] vs. 51/118 [43%]), while the proportion of fungal infections between the groups was similar (10/103 [10%] vs. 14/118 [12%]). There was no difference in gestational age (p=0.55), birth weight (p=0.81), or postnatal age (p=0.05) between infants with and without repeat LPs.

DISCUSSION

We found that among infants with a positive CSF culture, infants with a positive repeat CSF culture were more likely to die compared to infants with a repeat negative culture, and there was no difference in demographic characteristics or organisms between the two groups. These data would suggest that any benefit to repeat CSF examination might be for optimization of therapy. Among infants who had no repeat culture performed, the mortality was similar to those infants with a repeat negative culture. This most likely represents confounding by indication,[13, 14] which might explain the relationship between repeat LP and a higher incidence of positive cultures. The decision to perform a repeat LP was based on the clinician's perception that it was indicated. Alternatively, a repeat LP may be a marker for a sicker appearing infant. However, lack of a repeat culture does not rule out persistent infection. Infants with > 4 LPs likely reflected post-infection hydrocephalus.

Some organizations recommend repeat CSF examination in all infants with bacterial meningitis.[9] However, many clinicians do not routinely repeat LPs in this population, and nearly half of infants with culture-proven bacterial meningitis in our study did not receive a repeat LP, higher than previously reported.[15] Although our study did not demonstrate clear benefit to repeat LP in infants with meningitis, there are several theoretical advantages to this practice. In unstable infants a repeat LP may allow clinicians to determine if the current antimicrobial therapy is effective. In infants with meningitis due to Gram-negative bacilli, a repeat LP may be particularly useful because duration of therapy is determined by time required for CSF sterilization.[16] Repeat CSF examination might also be important due the growing impact of Gram-negative bacilli resistant to standard antimicrobial therapy as well as new strains of methicillin-resistant *Staphylococcus aureus*.[17, 18, 19] In addition, the CSF penetration of some antifungals is unreliable, which results in increased risk for persistent infection.[20] Neonatal invasive fungal infection is associated with a high prevalence of death and neurodevelopmental impairment. Infants who do not receive repeat CSF examination

might be at higher risk for death or poorer long term outcomes if delayed clearance is not identified and therapy is not adjusted accordingly.

We aimed to identify infants who are at the highest risk of repeat positive culture. Infants with greater postnatal age were at significantly higher risk of repeat positive cultures. This finding should be interpreted with caution, however, because we did not correct for data on type and timing of antimicrobial therapy. It is possible that older infants had a less severe clinical presentation, were treated less aggressively, and were therefore more likely to have repeat positive CSF cultures. There was no obvious discernible pattern that readily identified infants who were more likely to have a repeat positive culture from those who had a repeat negative culture.

We attempted to estimate the most appropriate time to perform an LP. We found that the majority of repeat positive cultures occurred within the first 7 days after the first LP. Thus, this time period appears to offer the highest yield for repeat positive culture. However, the majority (3/5; 60%) of the patients who had repeat positive cultures after the first 7 days did not have evidence of a repeat positive culture within the first 7 days. Because many infants never had a repeat LP performed, and because the repeat LP was performed as prescribed by the clinical attending (and not by study procedure, e.g. every 48–72 hours until negative), it is difficult for us to recommend the optimum time for a repeat LP.

Clinicians often rely on CSF parameters such as protein, glucose, and WBC count for the diagnosis of meningitis and monitoring the response to treatment. However, CSF parameters have been shown to be unreliable for determining the presence of meningitis in infants[10, 21, 22] and predicting treatment failure in end-of-treatment CSF examination in children.[5] Our data are consistent with these observations, as many infants who cleared their CSF infection never normalized their CSF protein, glucose, and WBC count. Thus, we have no data to suggest that the recommendations determining the length of therapy should be modified based on CSF parameters.

The strengths of this study include the large sample size and a focus on the neonatal population admitted to the NICU. This study is limited by lack of antimicrobial therapy information and the clinician reasoning for repeating LPs. If more infants in the group with repeat positive cultures received their LP due to worsening clinical status, then this could partially explain the increased mortality in this group.

Meningitis remains a significant cause of mortality and morbidity in the neonatal population. We found that repeat LPs often revealed persistence of infection even after 7 days following the initial diagnosis, and repeat positive CSF cultures in infants with meningitis are associated with increased mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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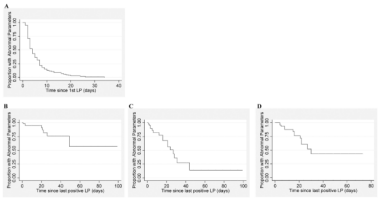

Figure 1.
Kaplan-Meier curves. (A) Time required to clear infection in infants with an initial positive CSF culture. Time required to normalize (B) CSF protein; (C) CSF glucose; (D) CSF WBC count.

Table 1

Organisms

	Positive repeat culture – N (%)	**Negative repeat cultures – N (%)**
Total	26 (100%)	92 (100%)
Gram-positive	10 (39%)	41 (45%)
Group B *Streptococcus*	3 (12%)	17 (18%)
Staphylococcus aureus	2 (8%)	12 (13%)
Enterococcus spp.	5 (19%)	5 (5%)
Gram positive cocci – unspeciated	0 (0%)	4 (4%)
Streptococcus pneumoniae	0 (0%)	2 (2%)
Listeria monocytogenes	0 (0%)	1 (1%)
Gram-negative	12 (46%)	41 (45%)
Escherichia coli	2 (8%)	20 (22%)
Enterobacter spp.	5 (19%)	5 (5%)
Pseudomonas spp.	2 (8%)	4 (4%)
Serratia spp.	1 (4%)	4 (4%)
Klebsiella spp.	1 (4%)	2 (2%)
Acinetobacter spp.	0 (0%)	2 (2%)
Citrobacter spp.	0 (0%)	1 (1%)
Gram-negative bacilli – unspeciated	0 (0%)	1 (1%)
Haemophilus influenzae	1 (4%)	0 (0%)
Neisseria meningitidis	0 (0%)	1 (1%)
Salmonella spp.	0 (0%)	1 (1%)
Candida	4 (15%)	10 (11%)

Table 2

Proportion of positive CSF cultures stratified by LP number and the number of days after the first LP

Days after 1st LP	2nd LP (N, %)	3rd LP (N, %)	4th LP (N, %)	5th LP (N, %)	6th LP (N, %)	>6th LP (N, %)	Total (N, %)
0–3	19/78, 24%	4/7, 57%	1/1, 100%	0/0, 0%	0/0, 0%	0/0, 0%	24/86, 28%
4–7	2/30, 7%	4/15, 27%	2/7, 29%	1/4, 25%	1/2, 50%	0/1, 0%	10/59, 17%
8–14	1/6, 17%	1/14, 7%	1/8, 13%	1/4, 25%	0/4, 0%	0/8, 0%	4/44, 9%
15–21	0/3, 0%	0/9, 0%	1/9, 11%	0/5, 0%	0/2, 0%	0/12, 0%	1/40, 3%
22–28	0/1, 0%	0/4, 0%	0/5, 0%	1/5, 20%	0/3, 0%	0/13, 0%	1/31, 3%
>28	0/0, 0%	0/4, 0%	0/4, 0%	0/7, 0%	0/7, 0%	1/37, 3%	1/59, 2%