CORRECTION OF CEREBROSPINAL FLUID PROTEIN IN INFANTS WITH TRAUMATIC LUMBAR PUNCTURES

Todd W. Lyons, Boston Childrens Hospital
Andrea T. Cruz, Baylor College of Medicine
Stephen B. Freedman, University of Calgary
Joseph L. Arms, Childrens Minnesota
Paul L. Aronson, Yale School of Medicine
Alesia Fleming, Emory University
Dina M. Kulik, Hospital for Sick Children
Prashant Mahajan, University of Michigan
Rakesh D. Mistry, Childrens Hospital Colorado
Christopher M. Pruitt, University of Alabama Birmingham

Only first 10 authors above; see publication for full author list.

Journal Title: Pediatric Infectious Disease Journal
Volume: Volume 36, Number 10
Publisher: Lippincott, Williams & Wilkins | 2017-10-01, Pages 1006-+
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1097/INF.0000000000001634
Permanent URL: https://pid.emory.edu/ark:/25593/tdpqm

Final published version: http://dx.doi.org/10.1097/INF.0000000000001634

Copyright information:
© 2017 Wolters Kluwer Health, Inc. All rights reserved.

Accessed February 13, 2020 12:32 PM EST
Correction of Cerebrospinal Fluid Protein in Infants with Traumatic Lumbar Punctures

Todd W. Lyons, MD1, Andrea T. Cruz, MD, MPH2, Stephen B. Freedman, MDCM, MSci3, Joseph L. Arms, MD4, Paul L. Aronson, MD5, Alesia H. Fleming, MD, MPH6, Dina M. Kulik, MD7, Prashant Mahajan, MD, MBA, MPH8, Rakesh D. Mistry, MD, MS9, Christopher M. Pruitt, MD10, Amy D. Thompson, MD11, and Lise Nigrovic, MD, MPH1 for the Herpes Simplex Virus Study Group of the Pediatric Emergency Medicine Collaborative Research Committee (PEMRC)

1Division of Emergency Medicine, Boston Children’s Hospital, Boston, MA
2Sections of Pediatric Emergency Medicine and Pediatric Infectious Diseases, Baylor College of Medicine, Houston, TX
3Sections of Pediatric Emergency Medicine and Gastroenterology, Alberta Children’s Hospital, Alberta Children’s Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
4Department of Pediatrics, Children’s Hospitals and Clinics of Minnesota, Minneapolis, MN
5Departments of Pediatrics and Emergency Medicine, Yale School of Medicine, New Haven, CT
6Department of Pediatrics, Emory University School of Medicine, Atlanta, GA
7Division of Pediatric Emergency Medicine, Hospital for Sick Children, Toronto, Ontario, Canada
8Department of Emergency Medicine and Pediatrics, University of Michigan, Ann Arbor, MI
9Section of Pediatric Emergency Medicine, Children’s Hospital Colorado, Aurora, CO
10Division of Pediatric Emergency Medicine, University of Alabama at Birmingham, Birmingham, AL

Corresponding Author and Reprint Requests To: Todd W. Lyons, Division of Emergency Medicine, Boston Children’s Hospital, 300 Longwood Avenue, Boston, MA 02115. Todd.Lyons@childrens.harvard.edu. Phone: (617) 355-6624, Fax (617) 730-0876.

Acknowledgement Affiliations: 1Alpert Medical School of Brown University, Providence, RI, 2Northwestern University Feinberg School of Medicine, Chicago, IL, 3University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 5University of Texas Southwestern Medical Center, Dallas, TX, 6Washington University School of Medicine, St. Louis, MO, 7University of Washington School of Medicine, Seattle, WA, 8University of Alberta Faculty of Medicine and Dentistry, Edmonton, AB, 9University of California-San Diego School of Medicine, San Diego, CA, 10University of Michigan Medical School, Ann Arbor, MI, 11University of California-Davis School of Medicine, Sacramento, CA, 12St. Louis University School of Medicine, St. Louis, MO, 13University of Minnesota Masonic Children’s Hospital, Minneapolis, MN

Conflicts of Interest: None of the authors have any conflicts of interest to report.

Author Contributions: Dr. Lyons conceptualized and designed the study, acquired, analyzed, and interpreted the data and drafted the initial manuscript. Drs. Cruz and Freedman conceptualized and designed the parent study, oversaw data acquisition and analysis, and aided with drafting the manuscript. Drs. Arms, Aronson, Fleming, Kulik, Mahajan, Mistry, Pruitt and Thompson acquired and interpreted data. Dr. Nigrovic conceptualized and designed the study, conceptualized and designed the parent study, oversaw data acquisition, analyzed and interpreted the data, and drafted the initial manuscript. All authors critically revised the manuscript for intellectual content and approved the final manuscript as submitted.
Abstract

In our multi-center cohort of infants ≤60 days of age, we identified 2,646 infants with a traumatic lumbar puncture of which 31 (1.2%) had bacterial meningitis. For every 1,000 cerebrospinal fluid (CSF) red blood cells per mm$^3$, cerebrospinal (CSF) protein increased 1.1 mg/dL [95% confidence interval (CI) 1.0–1.2 mg/dL].

Keywords

bacterial meningitis; cerebrospinal fluid; protein; infants

BACKGROUND

Febrile infants ≤60 days old who present to the emergency department (ED) are frequently evaluated for bacterial meningitis with a lumbar puncture (LP). Because cerebrospinal fluid (CSF) culture results require at least 24 hours to reliably exclude bacterial growth, clinicians combine immediately available clinical and laboratory factors, including CSF protein, to assess risk of bacterial meningitis. An elevated CSF protein has been associated with a higher risk of bacterial meningitis in children and may lead to empiric bacterial meningitis coverage. However, up to one-third of LPs in infants will be traumatic, increasing both CSF red blood cell (RBC) count and CSF protein, and limiting clinicians’ ability to utilize CSF protein values in assessing an infant’s risk of bacterial meningitis. Prior single-center studies have shown that the presence of RBCs in the CSF raises the CSF protein between 1.1–1.9 mg/dL for every additional 1,000 CSF RBCs. The ability of CSF protein corrected for CSF RBCs to discriminate between infants with and without bacterial meningitis has not been examined.

We assembled a large, multi-center cohort of infants ≤60 days of age with traumatic LPs. We examined the relationship between CSF protein and CSF RBCs and assessed the ability of corrected and uncorrected CSF protein to identify infants with bacterial meningitis.

MATERIALS AND METHODS

We performed a planned secondary analysis of a retrospective cohort study of infants who presented to the ED of one of the 23 participating centers in the Pediatric Emergency Medicine Clinical Research Committee (PEM CRC) herpes simplex virus (HSV) study (details of study protocol previously described). We limited our analysis to 20 sites which contributed CSF cell counts and protein. The study was approved by each of the participating institutional review boards.

We included infants ≤60 days old presenting to a participating ED between January 1, 2005 and December 31, 2013 who had a CSF culture obtained within 24 hours of ED presentation and who had available CSF cell counts and chemistries. We limited our analysis to those with a traumatic LP defined as a CSF RBC ≥10,000 cells/mm$^3$, a level of peripheral blood
contamination of the CSF which makes the interpretation of CSF protein challenging. Infants with CSF RBCs $\geq 1,000,000$ cells/mm$^3$ were excluded, as we could not confirm the presence of CSF in these samples. Infants could be included more than once if they had more than one eligible ED encounter.

Site investigators abstracted the following data elements from the electronic medical record: patient demographics, laboratory results (complete blood count, CSF cell counts and protein) and microbiologic results [blood, urine and CSF cultures, and viral testing (HSV and enteroviral PCR testing) when performed].

Our primary outcome was bacterial meningitis; defined as the growth of a bacterial pathogen in CSF culture. We classified the following pathogens as contaminants: coagulase-negative staphylococci, Viridans streptococci, Propionibacterium acnes and Corynebacterium species.

First, we explored the relationship between CSF protein and CSF RBCs using regression with CSF protein the as the dependent variable and CSF RBCs as the independent variable. We decided a priori to assess the relationship as linear, based on prior evaluations, and to enhance clinical applicability, as non-linear relationships are difficult to apply.

Second, we calculated corrected CSF protein as: Corrected CSF protein = CSF protein – (CSF RBC x Correction Factor), where the correction factor was determined using the beta-coefficient from our regression. A normal CSF protein value was defined as $\leq 115$ mg/dL for infants 0–28 days of age and CSF protein $\leq 89$ mg/dL for infants 29–60 days of age.

We calculated the following test characteristics for the corrected and uncorrected CSF protein as a predictor of bacterial meningitis: sensitivity, specificity, negative predictive value (NPV) positive predictive value (PPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR). Finally, we calculated the area under the curve (AUC) from the receiver operating characteristic (ROC) curves for both corrected and uncorrected CSF protein.

The analyses and figure for this paper were generated using SAS software version 9.4 (SAS Institute Inc. Cary, NC, USA 2015).

RESULTS

We identified 23,618 LPs, of which 19,819 (83.9%) had both CSF RBC counts and CSF protein available for analyses. Of these, 2,659 (13.4%) were traumatic. We excluded 13 (0.5%) LPs with a CSF RBCs $> 1,000,000$ cells/mm$^3$, yielding a final sample of 2,646 LPs (13.4% of eligible LPs). Median patient age was 25 days [Interquartile Range (IQR) 13–39 days) and 1442 (54.5%) were male. Thirty-one infants (1.2%, 95%CI 0.8–1.6%) had bacterial meningitis.

CSF protein increased 1.1 mg/dL (95% CI 1.0–1.2 mg/dL) for every 1,000 increase in the CSF RBC count (Figure 1A). Using the 1.1 mg/dL correction factor, we found no difference between corrected and uncorrected CSF protein with regard to sensitivity, NPV, PPV, negative likelihood ratio or positive likelihood ratio for detection of bacterial meningitis.
(Figure 1B). However, the specificity of corrected CSF protein was higher than the uncorrected CSF protein. While corrected CSF protein had slightly higher AUC for its ROC curve for detection of bacterial meningitis compared to uncorrected CSF protein, discriminatory ability was low for both.

Of the 31 infants with bacterial meningitis, 4 infants (12.9%, 95% CI 5.3–29.0%) had normal corrected CSF protein but an elevated uncorrected CSF protein. All four of these misclassified infants were ≤28 days of age and were hospitalized on empiric antibiotics awaiting bacterial culture results. CSF cultures of these infants grew the following pathogenic organisms: *Staphylococcus aureus* (2), *Moraxella* species (1) and *Escherichia coli* (1).

1,006 (38.0%) infants had HSV PCR testing of the CSF performed and 4/1006 (0.4%) were positive. Among these 4 infants, uncorrected CSF protein was elevated in two infants and corrected CSF protein was elevated in only one infant. 473 (17.9%) infants had enteroviral PCR testing performed and 66/473 (14.0%) were positive. Among these 66 infants, uncorrected CSF protein was elevated in 48 infants and corrected CSF protein was elevated in 32 infants.

**DISCUSSION**

In our large, multi-center cohort of infants with traumatic LPs, CSF protein increased 1.1 mg/dL for every increase of 1000 CSF RBCs per mm$^3$. Corrected CSF protein had a similar sensitivity but higher specificity when compared to uncorrected CSF protein. However, both corrected and uncorrected CSF protein alone had low discriminatory ability to identify infants with bacterial meningitis.

Previous studies have evaluated the relationship between CSF protein and CSF RBCs in CSF. Our results are similar to a previous examination of 1,354 children of all ages, which found a CSF protein to CSF RBC ratio of 1.1 mg/dL per 1,000 CSF RBCs (95% CI 0.9–1.1 mg/dL). Our results differed from another investigation of 1,241 infants ≤56 days of age which found a ratio of 1.9 mg/dL per 1,000 CSF RBCs (95% CI 1.7–2.1 mg/dL). Both studies examined this relationship in all CSF samples obtained, regardless of CSF RBC counts. In fact, the majority of children in both studies had non-traumatic LPs, where the CSF protein may not require correction.

Our findings add to the current understanding of the optimal interpretation of CSF protein in a young infant with traumatic LPs. First, our large, multi-center population increases the generalizability of our findings. Second, our analysis was limited to infants with traumatic LPs, thus our results are applicable to a very large population for which CSF protein correction may be clinically indicated. Our study compared the predictive ability of corrected vs. uncorrected CSF protein to determine the risk of bacterial meningitis. We found that neither corrected nor uncorrected CSF protein has adequate discriminative ability to be used alone for bacterial meningitis risk stratification. Therefore, clinicians should interpret CSF protein in combination with other clinical and laboratory values when assessing an individual infant’s risk of bacterial meningitis. If clinicians incorporate CSF
protein into this evaluation, corrected CSF protein offers higher specificity and slightly higher overall discriminatory ability compared to uncorrected CSF protein. However, this must be weighed against the risk of misclassifying a few additional infants with bacterial meningitis as having a normal corrected CSF protein.

Our study has limitations. First, despite a large sample of infants, bacterial meningitis was rare, and we may be underpowered to detect small difference in sensitivity of CSF protein. Second, we did not have data on clinical appearance, which may limit generalizability of our results. Third, not all infants underwent testing for HSV and enteroviral CSF infections. Therefore, we were unable to test characteristics of either uncorrected or corrected CSF protein for either enteroviral or HSV infection. Finally, as some study infants may have received antibiotic pretreatment before diagnostic lumbar puncture rendering the CSF culture falsely negative, we may have misclassified infants as not having bacterial meningitis. However, antibiotic pretreatment in young infants is exceedingly rare (0.1%). Therefore, we would caution against application of our results to infants with antibiotic pretreatment prior to LP.

Acknowledgments

Funding: The network data center managed by Baylor College of Medicine was supported by the Section of Emergency Medicine, American Academy of Pediatrics (AAP) and Baylor College of Medicine. Dr. Lyons was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (National Institutes of Health) T32 Training Grant (5T32HD040128-12). Dr. Freedman is supported by the Alberta Children’s Hospital Foundation Professorship in Child Health and Wellness. Paul L. Aronson is supported by CTSA grant number KL2 TR001862 from the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH).

We would like to acknowledge the significant contributions made by other site investigators: Aris C. Garro MD MPH,1 Suzanne M. Schmidt MD,2 Fran Balamuth MD PhD,3 Samir S. Shah MD MSCE,4 Joanna E. Thomson MD MPH,5 Pamela J. Okada MD,5 David Schnadower MD MPH,6 Neil G. Uspal MD,7 Sarah J. Curtis MD MSc,8 Paul T. Ishimine MD,9 Stuart A. Bradin DO,10 Kendra L. Grether-Jones MD,11 Aaron S. Miller MD MSPH,12 Jeffrey Louie MD13

Abbreviations

- **AUC**: Area under curve
- **CSF**: cerebrospinal fluid
- **CI**: confidence interval
- **ED**: emergency department
- **HSV**: herpes simplex virus
- **LP**: lumbar puncture
- **-LR**: negative likelihood ratio
- **NPV**: negative predictive value
- **PEMCRC**: Pediatric Emergency Medicine Collaborative Research Committee
- **+LR**: positive likelihood ratio
PPV  positive predictive value  
ROC  receiver operating characteristic  
RBC  red blood cell  

References  
Figure 1.
A. Plot of cerebrospinal fluid protein versus cerebrospinal fluid red blood cells in infants ≤ 60 days with a traumatic lumbar puncture. B. Test characteristics of uncorrected and corrected cerebrospinal fluid protein for the detection of bacterial meningitis in infants ≤ 60 days with a traumatic lumbar puncture

Abbreviations: mg=milligram, dL=deciliter, mm3 = cubic millimeter, PPV=positive predictive value, NPV=negative predictive value, +LR=positive likelihood ratio, -LR=negative likelihood ratio, AUC=area under curve for receiver operating characteristics curve

1Slope of regression line = 0.0011 (mg/dL)/(cells/mm3)
2Significantly different compared to uncorrected CSF protein at p < 0.001
3Significantly different compared to uncorrected CSF protein at p = 0.00