A Study to Develop Clinical Prediction Rules for the Use of Lumbar Puncture in Community Acquired Acute Bacterial Meningitis in the Emergency Department

Douglas McLachlan

A. Study Purpose and Rationale (Lay Abstract)

Bacterial meningitis may be defined as an inflammatory response to bacterial infection of the pia-arachnoid and the cerebrospinal fluid of the subarachnoid space. Although the precise epidemiology of bacterial meningitis is unavailable, the incidence is thought to be between 3 and 5 per 100,000 people per year in the United States (1). This disease is rapidly fatal within days and has a mortality rate of 25% despite medical interventions (2). ABM is considered a medical emergency and requires rapid diagnosis and treatment. Unfortunately, this illness is difficult to diagnose accurately, and usually requires an invasive procedure called a lumbar puncture (also known as a spinal tap), which is rarely diagnostic and whose findings still must be corroborated with the history, physical exam and other laboratory tests in order to be maximally useful (3).

The purpose of this study is to examine the clinical judgment physicians use in their decision to perform lumbar puncture through the use of a clinical prediction rule to substantiate when lumbar puncture is needed. This retrospective study of 250 patients will then be tested on a second set of 250 patients to validate the prediction rule.

B. Literature Review

Despite the severity of acute bacterial meningitis, this disease has been poorly characterized until recently. Most large series of the clinical presentation of ABM in the past have included both children and adults, with children accounting for 45 to 87% of cases (2). Results have rarely been reported according to age group in these studies. Thus, much of our understanding of the presentation of bacterial meningitis in adults, has been extrapolated from data mixed with children. Table one presents a chart of the known sensitivity and specificity of criteria used to diagnose ABM in adults, (2, 3, 4). History alone has poor sensitivity. The classic trial physical exam findings are nearly 100% sensitive. Overall specificity of clinical data in low or unknown.

HISTORY	SENSITIVITY	SPECIFICITY
Headache	50%	NS
Neck stiffness	28%	NS
(Both HA and stiff neck)	88%	NS
PHYSICAL EXAM	**SENSITIVITY**	**SPECIFICITY**
Fever	95%	45%
Neck Stiffness	88%	NS
Altered Mental Status	70%	67%
(At least one above Exam Finding)	99-100%	NS
Kernig Sign	97% (contested 9%)	NS (100%)
Kerig's and Brudzinski's signs	50%	NS
Focal Neurologic Signs	28%	60% (Jolt accentuation of HA)
Seizures	10-30%	NS
LABORATORY DATA	**SENSITIVITY**	**SPECIFICITY**
CSF Gram Stain	60-90%	NS
CSF Culture	70-85%	NS

NS=Not Stated

a. Complications of LP

Rt is clear that lumbar puncture is a critical, but not conclusive, step in the evaluation of ABM. Though a relatively safe procedure, minor and major complications can occur even when good techniques are applied. Some include backache (25%), severe radicular pain (15%), and paraparesis (1.5%). Severe complications occurred in 6.7% of patients receiving anticoagulants following the procedure and in none who did not receive anticoagulants (3). Risks of introducing a CSF infection via lumbar puncture have usually been attributed to contaminated instruments or poor technique. The most severe complication, tonsillar herniation resulting in death less than 48 hours after LP, is largely prevented by performed a CT scan before LP in patients at risk for having a new cranial lesion (3). In summary, although LP is a relatively safe procedure, it can have significant sequella.

b. Potential Sociological Factors involved in a Physicians Decision Threshold to Perform LP

Critical race theorists may argue that the legacy of the Tuskeegee Experiment leaves a stigma surrounding LP that the medical community must confront. Given the disproportionate numbers of people of color with incident and prevalent HIV/AIDS, and the higher need of LP among this immunocompromised community, it can be argued that race may play a role in a physician's threshold to perform LP. This study continued for nearly 40 years requiring serial lumbar puncture to document the natural history of the disease and CNS manifestations.

From a feminist perspective, the medical community has a long history of excessive interventions on patients' bodies. For as a physician may view the body as textbook, the patient may see it in more personal terms. A re-negotiation of the doctor-patient contract has driven searches for less invasive procedures. Most notably movements away from bilateral mastectomy for stage one breast cancer, decreasing rates of hysterectomy and vaginal delivery after cesearian section. Finding an objective means to inform a physician's threshold to perform LP may minimize many forms of bias.

c. Clinical Prediction Rules (CPR's)

Clinical experience provides an intuitive sense of which findings on history, physical examination and investigation are critical in making an accurate diagnosis or an accurate assessment of our patients' condition. While often extraordinarily accurate, this intuition may sometimes be misleading. A clinical decision rule can be defined as a clinical tool that quantifies the individual contributions that various components of the history, physical exam, and basic laboratory results make toward the diagnosis, prognosis or likely response to treatment (5). CPR's are most likely to be useful in situations where decision making is complex, the clinical stakes are high, or when there are opportunities for cost savings. This study will develop decision rules for the use of lumbar puncture in the evaluation of bacterial meningitis.

C. OBJECTIVE/HYPOTHESIS

Twenty-three standardized clinical variables will be assessed to develop a clinical prediction rule to use lumbar puncture in the diagnosis of acute bacterial meningitis with 100% sensitivity and maximal specificity.

D. METHODS

a. Study Design

The prediction rule will be derived from a retrospective database of all CSF fluid collected at the New York Presbyterian Hospital microbiology department from January lst 1993 to December 31, 2003. Among the CSF fluid results included in this study, half will be randomly assigned for the derivation stage of the study. The remainder will be used as a validation step to test how well the CPR predicts

bacterial meningitis. A chart review will be required to verify the clinical picture, history, physical exam findings and demographic variables known at the time of presentation.

b. Inclusion/Exclusion criteria

To be included in the derivation cohort, patients must be at least 18 years of age, and have a principle indication for LP of meningitis. Only those with acute illness (less than seven days of symptoms and a definite or probable bacterial cause will be included. CSF samples obtained for reasons other than meningitis will be excluded including for the diagnosis of subarachnoid hemorrhage, treatment of pseudotumor cerebri, normal pressure hydrocephalus, evaluation of CNS vasculitis, multiple sclerosis, Guillain-Barre Syndrome, spinal anesthesia or intrathecal chemotherapy (3). Patients initially treated at other hospitals but were transferred to this hospital for further therapy are excluded. Patients with a recent previous hospitalization less than seven days prior to admission are excluded. Patients with presumed nosocomial meningitis with symptoms that began more than 48 hours after admission will be excluded. All patients with HIV and a known CD4 count >= 100 will be included in the derivation cohort (6).

c. Outcome Definitions

The diagnosis of bacterial meningitis will be based on A: a compatible clinical picture and one of the following: a positive cerebrospinal fluid culture, or confirmation at autopsy. The diagnosis of ABM will also be presumed B: in the setting of negative CSF with either a positive CSF antigen test or quellung test, or a positive blood culture identification of gram-negative diplococci on CSF gram stain or sputum or throat cultures positive for Neisseria meningitidis in patients with a petechial or purpuric rash and a fulminant course. Lastly C: "culture-negative" bacterial meningitis will be included in the analysis if the clinical picture is consistent with pleocytosis of at least 100 neutrophils per cubic millimeter despite negative blood and cerebrospinal fluid cultures CSF gram stain but positive for organisms other than gramnegative diplococci, or not available (2).

d. Variable Selection

Candidate predictor variables will consist of three demographic characteristics (age >=60 / <60yo, sex and race African-AmericanALatino/White/Other), six historical variables (headache, neck stiffness, headache and neck stiffness, nausea/vomiting, rash, season of presentation), ten physical exam findings (fever, stiff neck, altered mental status, classic triad of fever/stiff neck/altered mental status, Kernig's sign, Brudzinski's sign, focal neurological signs, seizures.) Six predisposing factors will also be included (altered immune state/HIV, diabetes mellitus, alcoholism, CSF leak and prior neurosurgery, and hepatic cirrhosis.) These variables were selected because they are the most widely studied for diagnosis, prognosis and mortality.

e. Data Analysis

Frequency tables will be made to assess how commonly each candidate predictor variable is present in the study population and for the purpose of comparison to previously published work. Clinical variables will be assessed separately for association with bacterial meningitis by univariate analysis including a chisquared test for nominal data and an unparied t test for continuous data (9). Those variables found to be strongly associated with ABM ($P < 0.05$) will be analyzed by multivariate analysis. Inter-observer agreement of physical exam findings will be assessed using kappa, however, as this is an retrospective study, physicians were not blinded to each other's results.

Recursive partitioning will be used to identify models of the best combination of predictor variables for ABM. The primary objective of this model building will be to develop a rule that is 100% sensitive for detecting ABM while achieving the maximum possible specificity. Recursive partitioning analysis successively divides the patients into subpopulations and results in I or more strata that include only patients with ABM (8). We aim for the simplest model with maximal predictive power.

f. Power Calculations

Power calculations are rarely a part of this methodology. By definition, a clinical prediction rule has 100% sensitivity to identify the outcome of interest. The goal for CPR's are to draw robust conclusions which can be generalized beyond the study population. Thus, the goal is to validate study findings in other populations to guarantee generalizability. Previously published derivation studies included study populations as small as 150-200 subjects (7, 8, 9). We expect nearly 1000 CSF fluid samples exist in our cohort over the last ten years. Assuming 50% of these would result in bacterial meningitis, we would need 240 cases to be 98% confident that we would obtain no false positives. This number is adequate given the number of predictive variables that will be assessed.

g. Validation Design

In the validation stage of the study, the classification performance of the decision rules for identifying clinically bacterial meningitis will be assessed by calculating likelihood ratios with 95% confidence intervals. Two by two punnett squares will also be used to calculate the negative and positive predictive values. Given the binary predictive nature of the decision rules, no attempt was made to construct receiver operating characteristic curves.

h. Miscellaneous

Because this is a retrospective study, no procedures have been done solely for research purposes. There are no study drugs, medical devices, or questionnaires used. Confidentiality of study data will be preserved given that only people who have successfully completed the HIPAA course will review charts. Furthermore, the study will use unique identifiers to encode patient data rather than names. Hospital unit numbers will be used to correlate WebCis data to the chart review.

E. REFERENCES

1.) Harrisons Principles of Internal Medicine. 15'h ed. Anthony Fauci. 2001, McMillin. Pp2419-2424.

2.) Acute Bacterial Meningitis in Adults: a review of 493 episodes. NIL Durand, SB Calderwood, DJ Weber, et al. NEJM January 7, 1993; Vol 328(l), pp2l-28.

3.) Lumbar puncture: technique, indications, contraindications and complications. KS Johnson, DJ Sexton. UpToDate; www.utdol.com; 2004.

4.) Clinical Presentations, Diagnosis and prognostic factors of bacterial meningitis. SL Kaplan. Infectious Disease Clinics of North America. September 1999; Vol 13, No.3. pp579-594.

5.) Users' Guides to the Medical Literature. XXII: how to use articles about clinical decision rules. TG McGinn, GH Guyatt, PC Wyer, et al. JAMA July 5, 2000; Vol 284, No. 1; pp79-84.

6.) Cox, GM, Perfect, JR. Cryptococcus neoformans var neoformans and gattii and Trichosporon species. Topley and Wilson's Microbiology and Microbial Infections (9th Ed), Edward, LA (Ed), Arnold Press, London 1997.

7.) Decision Rules for the Use of Radiography in Acute Ankle Injuries. Refinement and Prospective Validation. IG Stiell, GH Greenberg, RD McKnight et al. JAMA March 3,1993 Vol 269, No.0 p1127-1132.

8.) Clinical Prediction Rules. A review and suggested modification of methodological standards. A Laupacis, N Sekar, IG Stiell. JAMA February 12, 1997; Vol277, No. 6 p489-494.

9.) A Study to Develop Clinical Decision Rules for the Use of Radiography in Acute Ankle Injuries. IG Stiell, GH Greenberg, RD McKnight, et al., Annals of Emergency Medicine, April 1992; Vol 21 No. 4. pp384-390.