

Lack of Sensitivity of the Latex Agglutination Test to Detect Bacterial Antigen in the Cerebrospinal Fluid of Patients with Culture-Negative Meningitis

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For culture-negative meningitis, use of the latex agglutination test for detection of bacterial antigen in the CSF has a sensitivity of only 7%. Routine use of the latex agglutination test may not contribute to the management of suspected acute bacterial meningitis, since patients are treated on the basis of their clinical presentations and CSF findings.

Use of one of the tests that detect bacterial antigen in CSF is suggested for cases of suspected bacterial meningitis when Gram stain results are negative [1]. In the literature, the reported sensitivity of these tests ranges from 50% to 100% [2, 3]. In practice, we have rarely seen a positive CSF bacterial antigen test result when the results of Gram stain or culture are negative. In a careful review of the literature, we found that the stated sensitivity of 50%–100% that is associated with these bacterial antigen tests only holds true for gram- or culture-positive cases. With the exception of data from a few small studies, the sensitivity of bacterial antigen tests in culture-negative cases of meningitis is largely unknown. In this retrospective study, we evaluated the sensitivity of the latex agglutination test one of the available methods of CSF bacterial antigen detection, in cases of gram- and culture-negative meningitis.

This study was conducted at Coney Island Hospital, an acute-care teaching hospital located in Brooklyn, New York. It involved a multistep retrospective review of the medical records of both adult and pediatric patients. Before the patients' medical

charts were reviewed, a clinical definition of acute bacterial meningitis was formulated on the basis of published reports of the following CSF abnormalities that are independently associated with bacterial meningitis: glucose concentration, <34 mg/dL; CSF:blood glucose ratio, <0.23; protein concentration, >220 mg/dL; total leukocyte count, >2000 cells/ μ L; and total neutrophil count, >1180 cells/ μ L [4, 5]. Any patient who had ≥ 1 of these CSF abnormalities and a clinical presentation that was consistent with acute meningitis (e.g., fever, headache, and neck stiffness or altered mental status) was considered to have acute bacterial meningitis

In step 1, the results of a total of 945 lumbar punctures that were performed in our hospital during a 25-month period were reviewed. Any CSF specimen that had ≥ 1 of the aforementioned abnormalities was selected for this study. In step 2, specimens that had Gram stain or culture results that were positive for organisms for which there is no bacterial antigen detection test were excluded from further analysis. The remaining specimens were then evaluated for the results of the latex agglutination test. The laboratory in our hospital has used the Wellcogen Bacterial Antigen Kit (Murex Biotech) to detect *Streptococcus* group B; *Haemophilus influenzae* type b; *Streptococcus pneumoniae*; *Neisseria meningitidis* serogroups A, C, Y, and W135; and *Neisseria meningitidis* serogroup B/*Escherichia coli* serogroup K1 antigen in CSF. In step 3, the clinical presentations of these cases were verified, and cases were excluded if they were not consistent with acute meningitis. Finally, the sensitivity of the bacterial latex agglutination test was determined for gram- and culture-negative cases.

A total of 35 CSF specimens were found to have abnormal parameters. All of the patients from whom these specimens were obtained had clinical presentations that were consistent with acute meningitis. Five of the 35 specimens were excluded because the CSF yielded organisms that could not have been diagnosed by use of the latex agglutination test—namely, 1 specimen yielded *Listeria monocytogenes*, 3 yielded *Staphylococcus aureus*, and 1 yielded *Mycobacterium tuberculosis*. The abnormalities of the 30 remaining CSF specimens that were included in this study are summarized in table 1. Most of the patients from whom these specimens were obtained had received antibiotic(s) prior to undergoing lumbar puncture. For 27 of these patients, lumbar puncture was done on the day of admission to the hospital, and for the rest of the patients, it was done subsequently.

Results of the latex agglutination test were positive for 4 of the 30 specimens (overall sensitivity, 13.5%). Two of these test

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Table 1. CSF abnormalities of the 30 patients included in this study.

Parameter of the CSF specimen	No. of patients (n = 30)
Glucose concentration, <34 mg/dL	9
CSF:blood glucose ratio, <0.23	11
Protein concentration, >220 mg/dL	23
Total leukocyte count, >2000 cells/ μ L	4
Total neutrophil count, >1180 cells/ μ L	6

NOTE. A total of 11 patients had multiple CSF abnormalities.

results were positive for pneumococci; 1, for *Neisseria meningococci* serogroups A, C, Y, and W 135; and 1, for *Neisseria meningococci* serogroup B/E. *coli* serogroup K1. Two cultures of CSF specimens were positive for pneumococci. Both of these CSF specimens also had positive latex agglutination test results, resulting in a 100% sensitivity of this test in cases of culture-positive meningitis. Of the 28 patients with negative culture results, only 2 had positive latex agglutination test results (sensitivity, 7%). Both of these patients had multiple other CSF abnormalities. We did not evaluate the sensitivity of this test in patients with positive culture results who had less severe CSF abnormalities that did not fulfill our inclusion criteria.

For the bacterial antigen detection test to be acceptable in clinical practice, it should be highly sensitive in cases of suspected bacterial meningitis with negative Gram stain or culture results. If the Gram stain or culture results are positive, there is no need to know the result of an antigen test, since it will not change the management of the disease. Studies that have concluded that CSF bacterial antigen detection tests have a sensitivity of $\geq 50\%$ have included cases of meningitis that were all, or mostly all, CSF culture positive [3, 5, 6]. When the CSF bacterial antigen test was used for unselected CSF specimens (clinical presentation and other CSF abnormalities were not considered), this test had a poor sensitivity (<5%) [7, 8]. In one study of 43 CSF specimens with ≥ 2 abnormalities, only 3 specimens had a positive antigen test result [9]. All 3 specimens had CSF cultures or blood cultures that were positive for the same organism and thus did not contribute to the diagnosis.

There are only a few studies that have reported the sensitivity of this test in cases of culture-negative meningitis. In a small study of 16 pediatric patients with meningitis, the antigen test results were negative for all 10 culture-negative cases of meningitis, for a sensitivity of 0% [10]. In one study that used a counterimmunoelectrophoresis method, 4 (8%) of the 53 patients with cultures that were negative for meningitis tested positive for antigen [5]. This study included both pediatric and adult patients. In another study, the results of the CSF bacterial antigen detection test were positive for 5 (17%) of the 29 pediatric patients with negative culture results [7]. There is only

one study that has found a sensitivity of 25% (15 of 61 patients) for the bacterial antigen test in cases of culture-negative meningitis [11]. All of these 61 cases were found in children (median age, 8 months) who received antibiotics before lumbar puncture was performed. The sensitivity of this test may be slightly higher for pediatric patients.

The CSF criteria that we have used were found to be individual predictors of bacterial, rather than viral, meningitis with a specificity of 99% or better in 2 studies [4, 5]. Our study is the first to use these strict CSF criteria to evaluate the sensitivity of the latex agglutination test in the detection of bacterial antigen in CSF. Most other studies have used variable and less rigid CSF criteria to diagnose meningitis. However, our finding of a 7% sensitivity of the latex agglutination test in cases of culture-negative meningitis is consistent with the findings from other reports. Few studies have addressed the cost of this test. One study has estimated that the cost of each test is approximately \$100 [9], whereas another study has calculated the cost per test as \$240 [12]. Irrespective of the cost, a test that does not assist in the management of culture-negative meningitis may not be recommended for routine use.

A number of authors have suggested that the bacterial antigen detection test can be used in cases of gram- and culture-negative meningitis [7, 8]. On the basis of our findings and those of other investigators, we believe that this test is not useful in the treatment of such patients. If a patient has clinical features and CSF findings that are consistent with bacterial meningitis, then the patient must be treated with antibiotics. The infectious diseases literature that is commonly read and cited should state that the sensitivity of the CSF bacterial antigen detection test is 0–25% for patients whose cultures are negative for acute bacterial meningitis.

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