Brief Communication

The value of latex particle agglutination test for rapid detection of bacterial antigens in the cerebrospinal fluid

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Acute bacterial meningitis remains a very important disease worldwide, and it could be associated with serious sequelae and poor prognosis particularly in cases of delayed diagnosis and improper management. The 3 most common bacterial pathogens, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* account for more than 80% of cases. However, the incidence of bacterial meninigitis declined dramatically as a result of the universal pneumococcal conjugate and *Haemophilus influenzae* type b (Hib) vaccinations. The laboratory diagnosis of bacterial meningitis rests on cerebrospinal fluid (CSF) examination. Typically, a CSF glucose concentration decreased to less than 40 mg/dL with a CSF-to-blood glucose ratio less than 0.31, and a CSF protein concentration elevated to more than 220 mg/dL were found to be significant indicators of acute bacterial meningitis. The CSF lactate concentrations elevated to more than 35 mg/dL have also been suggested as a diagnostic predictor of acute bacterial meningitis, however, results are generally nonspecific. In untreated bacterial meningitis, the CSF white blood cell count is usually elevated to more than 2000/mm^3 with neutrophils predominating. Gram stain and bacteriological culture should be performed on all CSF specimens even if the white blood cell count is normal. Gram stain permits rapid and accurate identification of the causative microorganisms in 60-90% of patients with bacterial meningitis and has a specificity of nearly 100%.[1] The clinical utility of the Gram stain depends on the bacterial pathogen and its concentration in CSF. The probability of positive Gram stain and culture may decrease in patients who have received prior antimicrobial therapy,[2] and this will consequently complicate management as negative cultures do not exclude the possibility of bacterial infection. The concentrations of C-reactive protein (CRP) in serum or CSF, and serum procalcitonin are elevated in patients with acute bacterial meningitis. In patients with meningitis in whom the CSF Gram stain is negative and analysis of other parameters is inconclusive, serum concentrations of CRP or procalcitonin that are normal or below the limit of detection have a high negative predictive value in the diagnosis of bacterial meninigitis, so patients with a presumptive diagnosis of viral meningitis can be carefully observed without initiation of antimicrobial therapy.[3] Latex particle agglutination (LPA) tests are rapid antigen-antibody assays used to screen body fluids for bacterial surface antigens. Specifically, these tests detect polysaccharide capsular constituents of common pathogenic bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis, Escherichia coli*, and *Streptococcus agalactiae* (β-hemolytic streptococci group B). The use of LPA has been suggested for the etiologic microbiology diagnosis of pretreated bacterial meningitis, however, this approach has been recently challenged.[4]

This study was approved by the Research Ethics Committee of the Royal Medical Services, Amman, Jordan, and conducted at King Hussein Medical Centre (KHMC), Amman, Jordan, a tertiary referral hospital, between 1st February and 31st December 2005 to evaluate the accuracy and clinical usefulness of LPA. The results of LPA were studied in comparison with isolation of viable organisms in CSF or blood cultures. A true positive was defined if CSF or blood cultures yielded organisms of the same type as the positive LPA. False negative was defined as any negative LPA with positive relevant cultures. False positive was defined as any positive LPA test with negative cultures without clinical or Gram stain, or both, evidence of infection. The sensitivity, specificity, and predictive values were calculated using standard statistical formulas. In KHMC, LPA was ordered and performed routinely on CSF specimens using Wellcogen Bacterial Antigen Kit (Remel Europe Ltd, Kent, UK) throughout the study period. These kits detect *Streptococcus agalactiae*, *Haemophilus influenzae type b*, *Streptococcus pneumoniae*, *Neisseria meningitidis* serotypes ABCYW135, and *Escherichia coli* serotype K1 antigens. The LPA was not performed on CSF collected from patients who underwent recent neurosurgical procedures or whom had ventriculoperitoneal shunts as coagulase-negative Staphylococci, the most common bacterial cause of meningitis in this group of patients, grow readily in culture and are not detected by LPA. Clinical and laboratory data were collected for all patients who had their CSF tested by LPA. Bacterial meninigitis was defined as being present if either CSF culture were positive for a bacterial pathogen, or in the presence of CSF pleocytosis (>7 cells/mm^3 regardless of the number of CSF red blood cells) and a positive blood culture for a bacterial pathogen. Aseptic meningitis was defined as CSF pleocytosis with negative bacterial cultures. Patients with negative cultures who had received antibiotics within the 72 hours before lumbar puncture were considered to have pretreated culture-negative meninigitis.

Out of 1140 CSF examined in this study, 22 (1.9%) pathogenic organisms were isolated in pure cultures: 15 *Streptococcus pneumoniae* (68.2%), 4 *Haemophilus*

Table 1 - Results of LPA and CSF/blood cultures.

Results	Positive LPA	Negative LPA	Total
Positive CSF/blood culture	4	18	**22**
Negative CSF/blood culture	14	1104	**1118**
Total	**18**	**1131**	**1140**

LPA - latex particle agglutination test, CSF - cerebrospinal fluid

influenzae (18.2%), 2 *Streptococcus agalactiae* (9.1%), and one *Neisseria meningitidis* (4.5%). Out of the 22 patients with bacterial meninigitis: 17 (77.3%) had positive CSF cultures alone, 3 (13.6%) had positive blood cultures alone, and 2 (9.1%) had both positive CSF and blood cultures. Four LPA were true positives, 1104 true negatives, 14 false positives, and 18 false negatives (**Table 1**). The sensitivity was 18%, and the specificity was 98.7%. The positive predictive value was 22%, and the negative predictive value was 97.6%. Out of the 1140 patients who had LPA performed on the CSF, 1002 (88%) had no pleocytosis and all of these had negative latex studies. Of the 138 patients with CSF pleocytosis, 22 (16%) patients had bacterial meninigitis, 79 (57%) had aseptic meninigitis, and 37 (27%) had pretreated culture-negative meninigitis. None of the pretreated culture-negative meningitis had a positive LPA.

The study showed that LPA had poor sensitivity to be used as a screening method for acute bacterial meningitis. The LPA did not identify a single bacterial pathogen not identified by CSF, blood culture, or both and Gram stain. Therefore, LPA should never be substituted for culture and Gram stain, and if only a small amount of CSF is received, culture and Gram stain should always have priority over LPA. The LPA was described as a low-yield procedure in patients whose CSF specimens have normal laboratory parameters. It was shown in a large 10-year retrospective study that the likelihood to identify the pathogen in culture-negative meningitis by LPA alone is very rare.[5] It must be emphasized that a negative LPA does not rule out infection caused by a specific meningeal pathogen in patients with presumed bacterial meningitis and a negative CSF Gram stain. Accurate LPA results have no demonstrable clinical impact and a positive LPA does not affect clinical therapy or hospital course.[4] Despite negative LPA, nearly all patients with clinically-suspected meninigitis were treated with 7 days or more of intravenous antibiotics. Therefore, the appropriate antibiotic therapy and duration of treatment must be determined according to the clinical findings and other laboratory parameters rather than LPA results. The cost implications of LPA tests have been previously highlighted.[4] The initial cost of LPA is further magnified by numerous repeats ordered when initial results, either positive or negative, disagree with clinical impressions. False positive LPA are associated with additional indirect costs of ordering unnecessary laboratory tests, prolonged hospitalization, and unnecessary antibiotic treatment. The potential discomfort to the patient and the family should also be considered. False negative LPA may be of clinical concern particularly when screening for a severe, life threatening illness such as meningitis. The LPA has been previously described as a prime example of inefficiency in clinical microbiologic testing. The LPA has no place in modern diagnostic medical microbiology and its continued use should be seriously questioned in an era when cost containment and clinical efficiency are becoming increasingly important.

In conclusion, the results of this study echo previous findings, and a decision has been made to completely abandon the use of LPA in our institution.

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References

1. Sáez-Llorens X, McCracken GH Jr. Bacterial meningitis in children. ***Lancet*** 2003; 361: 2139-2148.
2. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. ***Pediatrics*** 2001; 108: 1169-1174.
3. Nathan BR, Scheld WM. The potential roles of C-reactive protein and procalcitonin concentrations in the serum and cerebrospinal fluid in the diagnosis of bacterial meningitis. ***Curr Clin Trop Infect Dis*** 2002; 22: 155-165.
4. Hayden RT, Frenkel LD. More laboratory testing: greater cost but not necessarily better. ***Pediatr Infect Dis J*** 2000; 19: 290-292.
5. Nigrovic LE, Kuppermann N, McAdam AJ, Malley R. Cerebrospinal latex agglutination fails to contribute to the microbiologic diagnosis of pretreated children with meninigitis. ***Paediatr Infect Dis J*** 2004; 23: 786-788.