Role of Empiric Parenteral Antibiotics Prior to Lumbar Puncture
in Suspected Bacterial Meningitis: State of the Art

David A. Talan, Jerome R. Hoffman, Thomas T. Yoshikawa, and Gary D. Overturf

The performance of lumbar puncture (LP) in patients with suspected meningitis is often delayed if, for example, the clinical presentation suggests a need for prior computed tomographic (CT) scan or if patients are initially examined at settings with limited clinical facilities. The role of empiric parenteral antibiotic therapy prior to LP under these circumstances has not been critically analyzed. Review of the literature suggests that in cases of bacterial meningitis (1) the existing data are inadequate to assess the effect of a short delay of therapy on mortality and morbidity; (2) a short period of antibiotic therapy prior to LP does not change cerebrospinal fluid (CSF) white blood cell count, protein, or glucose; (3) the yield of CSF gram stain and culture may be somewhat reduced by a short period of antibiotic therapy, but these tests often remain positive; and (4) adjunctive tests, including blood cultures and CSF antigen tests, can often independently identify the bacterial meningopathogen. The available evidence suggests that if bacterial meningitis is suspected and LP must be delayed, intravenous antibiotics are warranted before CSF is obtained.

Bacterial meningitis is a life-threatening but potentially treatable disease. Therefore, it is of critical importance to establish rapidly the etiologic diagnosis and institute effective antibiotic therapy. In uncomplicated cases, this can be accomplished in a relatively short time by performing a lumbar puncture (LP) and analyzing the CSF for cell count and bacteria by gram stain. However, circumstances often arise in which an LP cannot be performed immediately. LP has been associated with serious complications and death in patients with elevated intracranial pressure [1-5]. Thus, in patients with signs associated with increased intracranial pressure, such as papilledema or focal neurologic deficits, it may be necessary to defer an LP until a computed tomographic (CT) scan can be obtained. A recent series suggested that the “frequent” practice of obtaining a CT scan prior to LP contributed to a significant delay in the treatment of bacterial meningitis [6]. Patients are commonly seen first in an outpatient setting in which there may be inadequate facilities for acute care or inadequate technical or laboratory capabilities to permit an LP to be done. The time involved in transferring a patient to an appropriate facility delays the definitive evaluation by LP. In situations such as these, the clinician must decide whether to treat immediately with empiric parenteral antibiotics or wait to initiate treatment until CSF can be obtained for analysis and culture.

Because bacterial meningitis is rapidly progressive and potentially fatal, it has been proposed that, if the diagnosis is suspected and the LP will be delayed, intravenous antibiotic therapy should be instituted immediately without obtaining CSF for microbiologic studies. McGee and Kaiser [7] state that “the first consideration in a patient with the acute presentation of meningitis is therapy, not specific diagnosis.” However, a basic caveat of traditional infectious disease practice is that adequate cultures should be obtained prior to the initiation of antibiotic treatment so that the etiologic pathogen(s) can be isolated and appropriate treatment begun. Should the specific bacterial etiology be obscured by prior antibiotic therapy, causing sterilization of CSF cultures, the patient may be committed unnecessarily to a course of expensive and potentially toxic therapy. In
addition to the risk and cost of unnecessary treatment of nonbacterial meningitis, there is the chance that therapy may not be efficacious because of the presence of organisms such as penicillin- or chloramphenicol-resistant pneumococci [8] or ampicillin- or chloramphenicol-resistant *Haemophilus influenzae* [9, 10].

Therefore, in cases in which there must be a delay in obtaining CSF, the decision to initiate treatment prior to an LP in order to maximize therapeutic efficacy comes at the possible expense of a decreased diagnostic accuracy. The benefits — or potential detriment — of such an approach have not been critically analyzed. To better understand this problem we addressed three questions: Does a delay in administering antibiotics affect mortality and/or morbidity? Does administration of antibiotics prior to an LP obscure the diagnosis of bacterial meningitis? Are there other methods of diagnosing bacterial meningitis if the CSF is made sterile by antibiotics?

**Effect of Delay in Administration of Antibiotics on Mortality and/or Morbidity**

Bacterial meningitis is a potentially rapidly fatal disease for which the only form of effective treatment is specific antimicrobial therapy. Thus, it seems reasonable to assume that a delay of even a few hours in the administration of antibiotics could have an adverse effect on prognosis. Nevertheless, to answer this question definitively, a clinical study would be required in which patients with suspected bacterial meningitis were randomized to receive antibiotics either immediately or only after some defined period of delay. For obvious ethical reasons such a study cannot be done. Therefore, there are no existing studies that directly examine the effect of any delay of antibiotics on the prognosis of bacterial meningitis. Only indirect information relevant to this question is available. Several studies have compared the mortality and morbidity of patients with bacterial meningitis who present to the hospital after a variable duration of symptoms [11–27]. It is important to note that these studies examine the effect on prognosis of a potential delay of therapy of 1–2 days, whereas circumstances that preclude immediate evaluation of suspected meningitis by LP at most require several hours.

Table 1 summarizes studies in which mortality was evaluated in patients with various etiologies of bacterial meningitis in relation to the duration of symptoms prior to presentation to the hospital. Most studies did not demonstrate a statistically significant relation between mortality and duration of symptoms [11–16]. In the study by Olsson et al. [17] of 43 patients with pneumococcal meningitis, there was

**Table 1. Bacterial meningitis: duration of illness vs. mortality.**

<table>
<thead>
<tr>
<th>Years of study [reference]</th>
<th>No. of patients</th>
<th>Organism</th>
<th>Overall</th>
<th>Duration of illness (days)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950–1960 [17]</td>
<td>43</td>
<td>PN</td>
<td>65</td>
<td>&gt;2</td>
<td>NS</td>
</tr>
<tr>
<td>1950–1960 [18]</td>
<td>107</td>
<td>All</td>
<td>40</td>
<td>&lt;1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>1953–1971 [19]</td>
<td>468</td>
<td>HI</td>
<td>8</td>
<td>&gt;1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>1971–1976 [20]</td>
<td>207</td>
<td>PN</td>
<td>45</td>
<td>&gt;1</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

**NOTE.** All = *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and other bacteria; PN = *S. pneumoniae*; HI = *H. influenzae*.

* P value determined by χ² test. NS = not significant (i.e., P > .05).
a mortality of 57% in patients who presented with <2 days of symptoms compared with 80% in patients with >2 days of symptoms. However, this association did not reach statistical significance ($\chi^2, P > .05$). This study was remarkable for an unusually high overall mortality. However, this may have been because of the inclusion of an older population with exclusively pneumococcal meningitis, since both advanced age and a pneumococcal etiology are associated with a poorer prognosis [11]. Also, 72% of the patients had a major coexisting illness. The authors concluded that “delay in seeking treatment appears to be primarily responsible for the higher mortality in this group of patients.”

In contrast to the report by Olsson et al. [17] the studies by Carpenter and Petersdorf [18], Davis et al. [19], and Baird et al. [20] yielded opposing results; that is, patients with a shorter duration of symptoms suffered a significantly greater mortality. Carpenter and Petersdorf [18] studied 107 children and adults with various etiologies of meningitis, including Streptococcus pneumoniae, Neisseria meningitidis, and H. influenzae. Seventeen (47%) of 36 patients who were admitted within the first 24 hours of their illness subsequently died. On the other hand, patients who were hospitalized 1–7 days after the onset of symptoms had a mortality of only 23% (16 of 71 cases, $P < .05$). The authors speculated that this difference in mortality was secondary to the phenomenon of patients with more severe infections seeking earlier hospitalization.

Davis et al. [19] studied 468 children with H. influenzae meningitis. Death occurred in 24 (11%) of 220 children whose duration of symptoms prior to admission was <1 day. This mortality was at least twice (5%, 12 of 248) the death rate in children whose duration of symptoms prior to admission was >1 day ($P < .05$). In this study, prior treatment with antibiotics also was associated with a significantly lower mortality. These investigators suggest that there might be at least two clinical forms of H. influenzae meningitis. One form is “hyperacute” and characterized by a short-course, fulminant illness with a rapid progression of clinical signs and symptoms. This syndrome is similar to that of severe meningococcal meningitis. The other form of H. influenzae meningitis is a milder illness, with a more gradual onset of symptoms, that is less likely to be recognized as meningitis by a physician on the first visit and has a lower mortality. The possibility that prior antibiotic therapy ameliorated the severity of the illness and subsequently delayed presentation to the hospital was not mentioned.

Thus, a direct correlation or association between duration of symptoms and mortality for bacterial meningitis has not been demonstrated consistently. To a great extent this is due to the inherent limitations involved in analyzing an outcome—namely mortality—that may be affected by multiple additional variables such as patient age, associated underlying illnesses, etiology and virulence of the infecting organism, and prior antibiotic therapy. In order to be interpreted, these variables must be identified and studied for their independent importance by multifactorial analysis. The duration of illness may also be difficult to ascertain. In retrospective studies such as these, it is often difficult to determine accurately the duration of symptoms by reviewing hospital records. Also, it is impossible to determine when symptoms of meningitis—as opposed to the prodromal infection—begin.

Several other retrospective studies with similar limitations have attempted to evaluate the effect of the duration of symptoms prior to treatment on morbidity rather than mortality. Bohr et al. [13] studied the association between the duration of symptoms before treatment—specifically, hemiplegia, gait ataxia, intellectual dysfunction, epileptic fits, serious hearing deficits, and vestibular dysfunction—and subsequent morbidity in 875 patients with bacterial meningitis. There was a positive correlation between the duration of symptoms before treatment and the rate of sequelae at discharge. These investigators also studied late neurologic sequelae in 164 patients with pneumococcal meningitis [14]. Patients who had symptoms for >48 hours prior to admission had a greater incidence of severe sequelae than did patients who had symptoms for <48 hours. Herson et al. [21] found that of 73 children with H. influenzae meningitis, those with symptoms of >3 days' duration were more likely to have died or had severe morbidity (defined as blindness, hydrocephalus, institutionalization, microcephaly, quadraplegia, severe retardation, or uncontrolled seizures).

Several investigators have studied retrospectively the relation between the development of sensorineural hearing loss and the duration of symptoms prior to treatment. Nadol [22] studied the development of sensorineural hearing loss in 210 patients with various bacterial etiologies of meningitis who were followed only during the acute and recuperative phases of the illness. While the average duration of symp-
toms was 32 hours in survivors without hearing loss, it was 47 hours in those with hearing loss (either partial or complete) \( P < .05 \). Richner et al. [23] recalled children for audiometric testing who had suffered \( H. influenzae \) meningitis several years earlier. He found that while only 2\% of patients whose \( H. influenzae \) meningitis had been treated within 48 hours had evidence of sensorineural hearing loss, 86\% of those who had had symptoms for $> 48 \text{ hours}$ had demonstrable hearing loss \( P < .05 \).

In contrast to the above data, Dodge et al. [24] reported a prospective evaluation of sensorineural hearing loss in 185 children with bacterial meningitis and found that only 10.3\% had persistent bilateral or unilateral hearing loss. This was not correlated with the duration of illness. Kaplan et al. [25] recently evaluated these data and those of another prospective series with regard to neurologic sequelae and the prior administration of oral antibiotics in children with meningitis caused by \( H. influenzae \). Children who were pretreated were more likely to have paresis and sensorineural hearing loss at follow-up; the duration of illness prior to admission was significantly longer for pretreated than for untreated children. While the investigators found no significant association between duration of illness prior to admission and deafness (data evaluated by multiple logistic regression analysis), children who were ill for $> 1 \text{ day}$ prior to admission had a greater relative risk of developing severe sensorineural hearing loss than did children ill for $< 1 \text{ day}$.

Although a delay in definitive antibiotic therapy would seem logically to contribute to a poor outcome, the existing literature has not resolved this issue. Nevertheless, it is a reasonable concern that even a short delay of antibiotic therapy may be deleterious, particularly for the subpopulation with hyperacute bacterial meningitis. It is clear that mortality and morbidity are not consistently predicted by the duration of symptoms prior to presentation, and it may be difficult clinically to identify a high risk population. However, if there were no risk of obscuring the diagnosis and preventing identification of the bacterial etiology of meningitis, the immediate institution of antibiotics, prior to (delayed) LP, would appear to optimize a desirable therapeutic outcome.

**Effect of Administration of Antibiotics Prior to Lumbar Puncture on the Diagnosis of Bacterial Meningitis**

The traditional methods of diagnosing bacterial meningitis include an analysis of CSF cell count, protein, glucose, gram stain, and culture. To what extent are the results of these tests affected by intravenous administration of antibiotics several hours before an LP is performed? While no published study directly addresses this question, the answer can be extrapolated from data from two sources: clinical investigations that have compared the results of traditional CSF tests in meningitis patients who either did or did not receive antibiotics in prior outpatient treatment, and studies in which CSF has been analyzed serially during the administration of therapeutic antibiotics.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Organism</th>
<th>Positive smear</th>
<th>Positive culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>19*</td>
<td>HI</td>
<td>Treated (%)</td>
<td>Untreated (%)</td>
</tr>
<tr>
<td>25†</td>
<td>HI</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>28‡</td>
<td>All</td>
<td>41</td>
<td>69§</td>
</tr>
<tr>
<td>29‡</td>
<td>All</td>
<td>35</td>
<td>53§</td>
</tr>
<tr>
<td>30‡</td>
<td>All</td>
<td>68</td>
<td>73</td>
</tr>
<tr>
<td>31‡</td>
<td>All</td>
<td>68</td>
<td>84§</td>
</tr>
<tr>
<td>32‰</td>
<td>All</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** HI = *Hemophilus influenzae*; All = *H. influenzae, Streptococcus pneumoniae, Neisseria meningitidis*, and other bacteria.

* Includes only cases with positive CSF cultures.
† Includes only cases with positive blood or CSF cultures, positive CIE or LA, or positive gram stain.
‡ Includes only cases "typical" of bacterial meningitis (i.e., increased CSF white blood cell count, increased protein, decreased glucose).
§ \( P < .05 \).
†† Includes all cases of meningitis with CSF white blood cell count $> 10/\text{mm}^3$. 

Table 2. Effect of prior outpatient antibiotic treatment on cerebrospinal gram-stain smears and cultures.
The term *partially treated meningitis* has been applied to those patients with bacterial meningitis who have received some form of antibiotic therapy (usually oral) prior to a diagnostic LP; several investigators have studied the effect of partial treatment on CSF parameters in such patients [19, 25, 28–32]. Studies of this nature are somewhat difficult to evaluate because of differing criteria used to define bacterial meningitis. Because CSF culture is the gold standard for the diagnosis of bacterial meningitis, any attempt to study the effect of prior antibiotics on the yield of CSF cultures must also evaluate those patients who have negative CSF cultures. Thus, some investigations included patients with negative CSF culture but in whom CSF protein, glucose, white blood cell count, and differential are “typical” or “consistent” with bacterial meningitis; others have included all patients with >10 white blood cells/mm³ in the CSF. This is problematic because a variable number of cases of nonbacterial meningitis will be included depending upon the stringency of definition.

With an appreciation of the confounding methodologic problems in these studies, it is still possible to draw some conclusions. Table 2 summarizes studies that have analyzed the effect of prior outpatient antibiotic therapy on CSF gram-stained smears and cultures. The studies by Harter [28], Dalton and Allison [29], Winkelstein [30], and Jarvis and Saxena [31] defined meningitis by a positive culture (CSF or blood) or smear or negative cultures and smear but “typical” CSF parameters consistent with bacterial meningitis. Criteria for typical CSF parameters varied but in general included an elevated white blood cell count with a predominance of polymorphonuclear cells, elevated CSF protein, and decreased CSF glucose. Converse et al. [32] defined meningitis by a CSF white blood cell count of >10 cell/mm³. Davis et al. [19] included only cases of bacterial meningitis with positive CSF cultures, while Kaplan et al. [25] included only cases with positive blood or CSF cultures, positive counterimmunoelectrophoresis (CIE) or latex agglutination (LA), or positive gram stain.

In general, partial (oral antibiotic) treatment resulted in a decrease in the number of positive CSF cultures of 4%–33%, and a decrease in CSF gram stains of 7%–41%. It is important to note that antibiotic treatment can also alter the accuracy of the gram-stain results; dead or injured gram-positive organisms may appear to be gram-negative [33]. These studies did not consistently reveal that the identification of a specific bacterial agent of meningitis was more difficult than that of any other specific bacteria following antibiotic therapy. In the patients with positive CSF cultures, the CSF cell counts, protein, and glucose were similar in patients with or without partial treatment. Because of the methodologic problems described above, it is difficult to draw conclusions regarding the effect of prior treatment on CSF parameters in culture-negative patients.

From these data it can be assumed that if prior administration of oral antibiotics decreases the yield of CSF gram stains and culture, then the administration of intravenous antibiotics prior to LP would have a similar effect. Experimental studies using rabbit meningitis models suggest that CSF cultures would remain positive following treatment with β-lactam antibiotics for 8–12 hours [34].

Several studies in humans have also reported the continued positivity of CSF cultures in some patients relatively early after the initiation of antibiotic therapy [35–48]. Wilson and Haftalin [33] studied 62 children with *H. influenzae* meningitis who had repeat LP performed 26 hours (mean) after initiation of intravenous ampicillin therapy. Fourteen (23%) of 62 children continued to have positive CSF cultures that could not be attributed to antibiotic resistance. Ten of these 14 positive isolates could only be grown on Levinthal medium and not on standard chocolate agar medium. These children had a poorer clinical outcome with a higher frequency of neurologic sequelae. Feldman [36] studied 27 children with culture-positive bacterial meningitis caused by *H. influenzae* (19 cases, one of which was a relapse), group B streptococci (five cases), *S. pneumoniae* (three cases), and *N. meningitidis* (one case). Patients had initial LP followed by a repeat LP 24 hours after initiation of intravenous ampicillin or penicillin, alone or in combination with chloramphenicol. Persistent positive CSF cultures (using standard microbiologic methods) were present in four (18%) of 22 patients. Three isolates were *H. influenzae* and one was group B streptococci. The author examined CSF bacteria concentration and found that patients with persistent positive cultures had high initial bacterial concentrations. These patients also had organisms with high (“resistant”) MICs to ampicillin and penicillin but not to chloramphenicol when a correspondingly large inoculum was used for in vitro susceptibility testing. Despite this, antibiotic therapy was eventually effective. Overturf et al. [37] reported that, de-
spite good antibiotic susceptibility and a favorable clinical outcome, nine (38%) of 24 patients with *H. influenzae* meningitis treated with carbenicillin and one (6%) of 17 patients treated with ampicillin had positive CSF cultures on standard culture media after 12–24 hours of therapy. After 2–3 days of therapy, however, all CSF cultures were sterile. Barson et al. [38] reported on 50 children with bacterial meningitis due to *H. influenzae* (42 cases), *S. pneumoniae* (four cases), *N. meningitidis* (three cases), and *Streptococcus agalactiae* (1 case), who had LP repeated 10.5–18 hours after starting treatment. Eight (33%) of 24 children treated with ceftriaxone and eight (40%) of 20 children treated with ampicillin and chloramphenicol had persistently positive cultures. In all except one case the persistent pathogen was *H. influenzae*. Repeat CSF cultures were more likely to be positive in cases with initial CSF bacterial colony counts of $\geq 10^7$ cfu/mL. In a series in which LP was repeated earliest, specimens were obtained 4–12 hours after the initiation of therapy [39]. Del Rio et al. studied 78 cases of bacterial meningitis caused by *H. influenzae* (54 cases), *S. pneumoniae* (nine cases), and *N. meningitidis* (nine cases). Nine (43%) of 21 patients treated with ceftriaxone and 11 (58%) of 19 patients treated with ampicillin or chloramphenicol had persistent positive CSF cultures at 4–12 hours. In all patients except one, the persistent pathogen was *H. influenzae*. There was no significant difference between CSF bacterial concentration or susceptibility in those CSF specimens in which cultures remained positive and those in which they did not; clinical outcome was similar, despite the presence or absence of positive cultures.

These studies demonstrate that intravenous antibiotics will significantly decrease the frequency of positive cultures after initiation of therapy. However, even after 24 hours, as many as 38% may have positive cultures. As antibiotic killing of bacteria proceeds at a rate of $\sim 1.0$ log/hour [34] one would predict that if LP were performed after only 1–2 hours of intravenous antibiotics, it would be possible to obtain positive CSF cultures in the majority of patients. A study to address this question directly would be feasible if, in patients with presumed bacterial meningitis, CSF were sampled for culture at serial hours after parenteral antibiotics are initiated.

Because CSF white blood cell count, protein, and glucose will not be affected to a significant degree, administration of antibiotics prior to LP will not usually obscure the physician’s initial impression of bacterial meningitis. Nevertheless, since the yield of CSF culture and gram stain may be reduced, if these tests are relied upon alone, it might be impossible to make a definitive diagnosis of bacterial meningitis and identify the specific bacterial pathogen.

**Alternative Diagnostic Methods If CSF Is Made Sterile by Antibiotics**

At present three tests other than CSF culture and gram stain are available to establish the specific bacterial etiology in cases of meningitis. These are blood cultures, CSF counterimmunoelectrophoresis (CIE), and CSF latex agglutination (LA) and coagglutination (CoLA). Blood cultures can be obtained easily prior to the initiation of antibiotic therapy, even when LP must be delayed. In $\sim 50\%$ of cases of bacterial meningitis, blood cultures are positive for the etiologic agent (see table 3) [11, 12, 15, 17, 19, 31, 49, 50]. The yield of positive cultures depends to a great extent on the specific bacterial pathogen and its tendency to disseminate via the blood stream. Some cases of bacterial meningitis may occur as a result of local extension and thus are associated with negative blood cultures. Swartz and Dodge [49] reported positive blood cultures in 79% of cases of *H. influenzae* meningitis, 56% of cases of *S. pneumoniae* meningitis, 33% of cases of *N. meningitidis* meningitis, 29% of cases of beta-hemolytic streptococcal meningitis, and only 17% of cases of *Staphylococcus aureus* meningitis. On the other hand, Finland and Barnes [50] noted positive blood cultures in 63%–86% of cases of bacterial meningitis caused by these organisms. Thus, in patients with clinical and other laboratory findings suggestive of menin-

**Table 3. Frequency of positive blood cultures in cases of bacterial meningitis.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Organism</th>
<th>No. of cases with positive blood cultures/ no. of cases with bacterial meningitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>All</td>
<td>72/242 (30)</td>
</tr>
<tr>
<td>12</td>
<td>PN</td>
<td>22/40 (55)</td>
</tr>
<tr>
<td>15</td>
<td>All</td>
<td>60/133 (45)</td>
</tr>
<tr>
<td>17</td>
<td>PN</td>
<td>23/43 (53)</td>
</tr>
<tr>
<td>19</td>
<td>HI</td>
<td>152/349 (44)</td>
</tr>
<tr>
<td>31</td>
<td>All</td>
<td>52/105 (50)</td>
</tr>
<tr>
<td>49</td>
<td>All</td>
<td>79/153 (52)</td>
</tr>
<tr>
<td>50</td>
<td>All</td>
<td>289/371 (78)</td>
</tr>
</tbody>
</table>

NOTE. All = *Hemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and other bacteria; PN = *S. pneumoniae*; HI = *H. influenzae*.
Bacterial meningitis to whom antibiotics are administered after blood samples are obtained for culture but before an LP is performed, the presence of bacteremia will establish a presumptive diagnosis of bacterial meningitis.

CIE, LA, and CoLA are laboratory tests that can identify CSF antigens of the commonest bacterial meningopathogens—i.e., *H. influenzae*, *S. pneumoniae*, and *N. meningitidis*. Currently, prepared antisera against these organisms have an acceptable sensitivity and specificity. In various studies CIE is capable of detecting antigen in 50%–90% of patients with meningococcal meningitis, 50%–100% of patients with pneumococcal meningitis, and 77%–90% of patients with *H. influenzae* type b meningitis, [51–61]. Nonspecific reactions are rare. Gram stain is similarly sensitive but may be difficult to interpret after antibiotic therapy is initiated. Recent reports suggest that LA and CoLA are much more sensitive than CIE with similar specificity [51, 54, 62–64]. CIE, LA, and CoLA can be particularly useful in patients with meningitis in whom antibiotics have been administered (either orally or parenterally) before a diagnostic LP is performed. Bacterial antigens may persist in the CSF for several days after antibiotic therapy. Bortolussi et al. [51] reported that, on repeat lumbar puncture, all patients with initially positive LA had a persistently positive test from 1 to 6 days after the initiation of intravenous antibiotic therapy for various etiologies of bacterial meningitis. This has been confirmed by other authors [54, 64]. Thus, the yield from CIE, LA, and CoLA would be essentially unaffected if antibiotics were administered several hours prior to obtaining spinal fluid.

CIE, LA, and CoLA have limitations that must be considered. While a positive test using these techniques is very helpful, a negative test does not necessarily exclude the diagnosis of bacterial meningitis. Currently there is no consistently reliable antiserum to detect the polysaccharide of *N. meningitidis* serogroup B, a serogroup that is responsible for ~50% of meningococcal meningitis in the United States. Pneumococcal serotypes 7 and 14 are also not reliably detected. Because *S. pneumoniae* and *N. meningitidis* account for the vast majority of adult bacterial meningitis, CIE, LA, and CoLA are much less reliable in adults than in children in whom *H. influenzae* is the commonest pathogen. CIE, LA, and CoLA assays are not useful in diagnosing gram-negative bacillary, staphylococcal, and listerial meningitis. These organisms are more commonly isolated from immunocompromised hosts with meningitis, those patients with meningitis associated with endocarditis, or those patients developing meningitis following surgery; therefore, in such patients, CIE, LA, and CoLA should not be relied upon to establish a diagnosis. Most importantly, although CIE, LA, and CoLA may identify the bacterial pathogen, they do not provide direct information about the antibiotic susceptibility of the organism.

Other tests that may be helpful but that are less available include the enzyme-linked immunosorbent assay (ELISA) for capsular antigen and the limulus lysate assay for endotoxin. ELISA has compared well to CIE and LA for the detection of *H. influenzae* type b and pneumococcal antigen [65, 66]. The limulus lysate assay detects endotoxin from gram-negative bacillary organisms (e.g., *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) as well as *H. influenzae* and *N. meningitidis* [67, 68]. Most reports indicate that the test is rapid and reliable. However, in one study by McCracken and Sarff [69], the limulus test failed to diagnose culture-positive gram-negative bacterial meningitis in 31% of the cases in neonates.

Discussion

The performance of LP in patients with suspected meningitis may be delayed when clinical situations dictate a need for prior CT scan. The risks of LP and the indications for CT scanning prior to LP have been debated. There have been several reports of acute neurologic deterioration immediately following LP in patients with increased intracranial pressure or intracranial mass lesions. Duffy [1] followed for one year 30 patients with raised intracranial pressure who had neurologic deterioration during or following LP. These patients were subsequently found to have intracranial mass lesions or infarction. Thirteen of these patients had loss of consciousness during or immediately after LP; the neurologic status of the others deteriorated to various degrees over the next 12 hours. The same author noted neurologic deterioration following LP in seven of 55 patients with subarachnoid hemorrhage [2]. All six patients who were subsequently investigated had evidence of herniation confirmed by necropsy or CT scan. Garfield, who described one of the largest series of brain abscess cases, demonstrated that in 140 patients in whom LP was performed, 41 had “significant deterioration in the level of consciousness” during the
48 hours following the procedure [3]. Carey et al. [4] reported eight of 62 patients with brain abscess who died within 36 hours following LP.

Other studies, however, suggest that even in the presence of papilledema the risk of herniation after LP is small. Korein et al. [5] reported possible complications following LP in seven of 59 patients with raised intracranial pressure without papilledema and in one of 70 patients with papilledema (85% of whom also had increased intracranial pressure). These data and a review of 348 additional cases from the literature revealed possible complications in only 1.2% of patients with papilledema on whom LP was performed. Thus, it is clear that rapid and severe neurologic deterioration has been associated with the performance of LP; because of the close temporal relation, these reports strongly suggest that LP was the cause of the deterioration. The frequency with which these complications occur in various settings, however, cannot be easily assessed.

Because of reports such as these, it has been recommended that LP not be performed in the presence of signs of increased intracranial pressure or intracranial mass lesions. With the advent of CT scanning, these contraindications for LP have become indications for CT scan prior to LP. The exact role of CT scan prior to LP is particularly germane with regard to the evaluation of patients with suspected meningitis because the findings of fever, headache, and stiff neck are features also common to the diagnoses of intracranial abscess (including subdural empyema) and subarachnoid hemorrhage. However, which clinical signs should preclude LP is not completely clear.

In the series reported by Duffy [1] of the 30 patients whose neurologic status deteriorated after LP, five were subsequently diagnosed with cerebral abscess that was treated initially as meningitis. These five deteriorated after repeat LP. While all of the other 25 patients had either papilledema or other evidence of an intracranial space-occupying lesion, in only one of the five with suspected meningitis and actual brain abscess were focal neurologic signs reported; none of the five apparently had papilledema. In Duffy’s series of patients with subarachnoid hemorrhage, five of the seven who worsened after LP were initially grade 2 — defined as moderate-to-severe headache, nuchal rigidity, and no neurologic deficit other than cranial nerve palsies [2]. There was no mention of the presence or absence of papilledema in these patients. These observations led Duffy to suggest that LP not be performed when there is a history of progressive headaches associated with changes in mental status and the presence of focal neurologic signs or papilledema. He expressed caution about the use of LP when a syndrome suggestive of cerebral abscess was present — such as an ear, nose, or sinus infection — followed by signs of meningitis. He also suggested that CT scan be the initial investigation prior to LP in all cases of suspected subarachnoid hemorrhage.

Garfield [3] noted that convulsions, hemispheric signs, or papilledema were present in 68% of his series of 200 patients with brain abscess, compared with 30% of his series of 50 patients with nontuberculous bacterial meningitis. Based on this finding he stated that, in the presence of these signs, LP is contraindicated. A current neurology textbook by Adams and Victor [70] states that “in patients with suspected (raised) intracranial pressure, LP should be preceded by CT scan whenever possible.” McGee and Kaiser [7] state that LP is contraindicated in the presence of papilledema or focal findings (except ophthalmoplegia) until a CT scan has excluded the possibility of a mass lesion.

Although general guidelines can be given, the exact indications for CT scan prior to LP in a given patient suspected of meningitis are not clear. Moreover, the available data indicate that overt clinical signs are not always manifest when intracranial hypertension or mass lesions exist. Focal neurologic findings have been noted in 15%-30% of patients with proven bacterial meningitis [71], although the percentage of patients with suspected meningitis who have these findings may be less. Because of these uncertainties, the ready availability of CT scans, and the present medicolegal climate, the CT scan is often employed and, perhaps, overutilized prior to LP in the evaluation of patients with suspected meningitis. It is our opinion that the CT scanning is particularly overutilized in the pediatric population, in which the likelihood of brain abscess and subarachnoid hemorrhage is very small relative to the frequency of meningitis. Further studies are needed to determine the value or detriment of CT scan performed prior to LP in cases of suspected meningitis.

Another situation that may result in delay of LP is the initial evaluation of a patient at a setting where LP cannot be performed. Even at our urban centers, patients are frequently referred to us with suspected meningitis in whom LP has not been performed. Patients are seen at offices, clinics, and urgent care
centers that may not have the LP equipment available, may not have the time or the laboratory facilities to initiate a septic workup, or may not have the capability to manage an acutely ill patient. Furthermore, the urgency for rapid transport of the patient to an acute-care facility may preclude further diagnostic evaluation, i.e., LP. It is our opinion that in severely ill patients, obtaining CSF is of low priority compared with initiating treatment and ensuring that patients are expeditiously moved to an acute-care hospital.

In situations such as these in which LP is delayed and bacterial meningitis is suspected, the clinician must decide whether or not to treat immediately with empiric parenteral antibiotics. While no study currently exists that directly addresses the potential advantages or disadvantages of giving immediate antibiotic therapy prior to LP, and while the indirect data regarding this issue are inconclusive, it would be reasonable to assume that a delay of therapy may be deleterious. Moreover, direct and indirect evidence currently available suggests that immediate antibiotic therapy shortly before LP is unlikely to seriously hamper the clinician's ability to diagnose the specific etiology of bacterial meningitis. By combining the results of preantibiotic blood cultures, subsequent CSF cultures, and CSF, CIE, LA, or CoLA, it should be possible to make an etiologic diagnosis in the large majority of patients with bacterial meningitis, despite a short period of prior antibiotic therapy.

With regard to epidemiologic considerations, it is important to note that ~75% of all cases of bacterial meningitis occur in children less than 10 years of age, and approximately two-thirds of these cases are due to H. influenzae. Compared to other meningopathogens, H. influenzae appears to be easier to grow from early postantibiotic CSF cultures, is more frequently cultured from blood, and is identified with greater sensitivity by CSF, CIE, LA, and CoLA. Thus, particularly in the pediatric population—in which most cases of suspected bacterial meningitis occur—it is extremely unlikely that a single dose of parenteral antibiotic would prevent the identification of the offending bacteria. In other populations, such as neonates, adults, and immunocompromised patients, the sensitivity of blood cultures and immunologic tests for meningopathogens that commonly infect these groups is less secure; thus, there is a greater justification for obtaining CSF either before antibiotics are given or at least within 1–2 hours of initiating therapy.

The necessity to establish a specific etiologic bacterial diagnosis is diminished because of the improved broad-spectrum coverage of new antibiotics, such as the third-generation cephalosporins. Yet, bacterial identification and antibiotic-sensitivity testing remain desirable because of the emergence of antibiotic resistance among common meningopathogens—such as ampicillin- or chloramphenicol-resistant H. influenzae and penicillin- or chloramphenicol-resistant pneumococci [8–10]—and the increasing number of immunocompromised and postsurgical patients who develop meningitis with unusual bacteria such as Listeria monocytogenes and gram-negative organisms. In cases in which LP is delayed, the bacterial pathogen and its antibiotic susceptibility can usually be established, even after antibiotics are administered, by blood cultures and subsequent CSF cultures. In cases in which cultures are sterile, CIE or LA may identify the bacterial pathogen, but the antibiotic sensitivity of the organism will not be known. In this situation, treatment can be based upon the known epidemiology of bacterial meningitis. Only rarely will both cultures and immunologic tests not reveal the causative bacteria and mandate continued empiric broad-spectrum antibiotic coverage. Appropriate empiric antimicrobial regimens and appropriate dosages have been recommended previously [71]. Initiation of a combined regimen of chloramphenicol and ampicillin in children less than 5 years of age and a regimen of ampicillin or penicillin G alone in older children and adults is sufficient for disease suspected to be caused by community-acquired meningopathogens. Alternatively, a single initial dose of a number of third-generation cephalosporins (cefotaxime, ceftriaxone, ceftriaxone) could be utilized for these patients. Initial empiric therapy must be sufficiently broadened to include coverage for community-acquired meningopathogens, staphylococci, L. monocytogenes, and gram-negative organisms (including Pseudomonas aeruginosa) in immunosuppressed hosts or in patients recovering from neurosurgical procedures (e.g., a regimen of vancomycin and a third-generation cephalosporin).

**Conclusion**

Should empiric parenteral antibiotics be adminis-
tered prior to LP, the risk of obscuring the diagnosis of bacterial meningitis is small, as is the risk that the patient would receive inadequate antibiotic treatment. Evidence found in this review supports the recommendation that, if bacterial meningitis is suspected and LP will be delayed, intravenous antibiotics should be given immediately after blood samples are drawn for culture. Further research needs to be done to determine the conditions that lead to delays in the evaluation of patients with suspected bacterial meningitis, the role of CT scanning in the initial evaluation of these patients, and the effects of early therapy on the ability to identify bacterial meningopathogens.

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