

# Lumbar Puncture in Pediatric Bacterial Meningitis: Defining the Time Interval for Recovery of Cerebrospinal Fluid Pathogens After Parenteral Antibiotic Pretreatment

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**ABSTRACT.** *Objective.* Despite the lack of evidence defining a time interval during which cerebrospinal fluid (CSF) culture yield will not be affected by previous antibiotic therapy, recent publications cite a "minimum window" of 2 to 3 hours for recovery of bacterial pathogens after parenteral antibiotic administration. We conducted a retrospective review of children with bacterial meningitis to describe the rate at which parenteral antibiotic pretreatment sterilizes CSF cultures.

*Methods.* The medical records of pediatric patients who were discharged from a tertiary children's hospital during a 5-year period with the final diagnosis of bacterial meningitis or suspected bacterial meningitis were reviewed. The decay in yield of CSF cultures over time was evaluated in patients with lumbar punctures (LP) delayed until after initiation of parenteral antibiotics and in patients with serial LPs before and after initiation of parenteral antibiotics.

*Results.* The pathogens that infected the 128 study patients were *Streptococcus pneumoniae* (49), *Neisseria meningitidis* (37), group B *Streptococcus* (21), *Haemophilus influenzae* (8), other organisms (11), and undetermined (3). Thirty-nine patients (30%) had first LPs after initiation of parenteral antibiotics, and 55 (43%) had serial LPs before and after initiation of parenteral antibiotics. After  $\geq 50$  mg/kg of a third-generation cephalosporin, 3 of 9 LPs in meningococcal meningitis were sterile within 1 hour, occurring as early as 15 minutes, and all were sterile by 2 hours. With pneumococcal disease, the first negative CSF culture occurred at 4.3 hours, with 5 of 7 cultures negative from 4 to 10 hours after initiation of parenteral antibiotics. Reduced susceptibility to  $\beta$ -lactam antibiotics occurred in 11 of 46 pneumococcal isolates. Group B streptococcal cultures were positive through the first 8 hours after parenteral antibiotics. Blood cultures were positive in 74% of cases without pretreatment and in 57% to 68% of cases with negative CSF cultures.

*Conclusions.* The temptation to initiate antimicrobial therapy may override the principle of obtaining adequate pretreatment culture material. The present study demon-

strates that CSF sterilization may occur more rapidly after initiation of parenteral antibiotics than previously suggested, with complete sterilization of meningococcus within 2 hours and the beginning of sterilization of pneumococcus by 4 hours into therapy. Lack of adequate culture material may result in inability to tailor therapy to antimicrobial susceptibility or in unnecessarily prolonged treatment if the clinical presentation and laboratory data cannot exclude the possibility of bacterial meningitis. *Pediatrics* 2001;108:1169–1174; *bacterial meningitis, spinal puncture, cerebrospinal fluid, diagnostic techniques and procedures, time factors, pneumococcal meningitis, microbial sensitivity test.*

ABBREVIATIONS. CSF, cerebrospinal fluid; LP, lumbar puncture; CSF WBC, cerebrospinal fluid leukocyte concentration; ED, emergency department; MIC, minimum inhibitory concentration; LPd, delayed LP group; LPP, prior LP group; LPP/p, LP pre- and postantibiotic group; CI, confidence interval; IQR, interquartile range; CT, computed tomography.

**B**y conservative estimate, culture-confirmed bacterial meningitis affects 5755 people in the United States each year, nearly half of whom are 18 years of age or younger.<sup>1</sup> Even with current antibiotic therapy, the mortality rate is 4% to 15%, depending on the infecting organism, with hearing loss in 2% to 28% and mental retardation in 2% to 17%.<sup>2</sup>

Ideally, the clinical suspicion of bacterial meningitis is supported by cerebrospinal fluid (CSF) indices consistent with bacterial infection and confirmed by the recovery of a bacterial pathogen. However, a clinical practice of initiating antimicrobial therapy before lumbar puncture (LP) may confound the culture result. Supporting this practice is the widely held belief that parenteral antibiotic therapy may be instituted early in suspected bacterial meningitis without compromising the yield of subsequent CSF cultures. At least 1 text and 1 review article published after the introduction of the *Haemophilus influenzae* type b conjugate vaccine suggest a "minimum" window of 2 to 3 hours.<sup>3,4</sup> However, no published data identify the duration of a time interval within which previous parenteral antibiotics will not affect CSF culture results. Our clinical observation suggested that pretreatment with parenteral antibiotics may impede the recovery of CSF pathogens more rapidly than suggested in the literature. Because of the absence of data to define this interval, we conducted a retrospective review of children with

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bacterial meningitis to determine the yield of CSF cultures obtained shortly after the initiation of parenteral antibiotic therapy.

## METHODS

The Institutional Review Board of Children's Hospital San Diego gave administrative approval for this study. The medical records of all patients who were discharged from Children's Hospital between January 1, 1992, and December 31, 1996, with the final diagnosis of bacterial meningitis or suspected bacterial meningitis were identified by a computerized search for the *International Classification of Diseases, Ninth Revision* codes for bacterial meningitis and meningococcal meningitis. Patients were included when they met any 1 of the following criteria: CSF culture positive for a known bacterial pathogen; positive CSF antigen study or Gram stain in conjunction with a CSF leukocyte concentration (WBC) of  $>10/\text{mm}^3$  ( $10 \times 10^6/\text{L}$ ); blood culture positive with CSF WBC of  $>100/\text{mm}^3$  ( $100 \times 10^6/\text{L}$ ); or, in the absence of bacterial isolate, CSF WBC of  $>4000/\text{mm}^3$  ( $4000 \times 10^6/\text{L}$ ). The last criterion was chosen because a CSF WBC of  $>4000/\text{mm}^3$  ( $4000 \times 10^6/\text{L}$ ) as a single criterion should exclude 93% to 98% of enteroviral disease.<sup>5</sup>

Exclusion criteria were positive CSF viral study in the absence of a known bacterial meningopathogen, neural tube defect, CSF shunt or catheter, penetrating cranial injury, neurosurgical procedure other than LP within the previous month, or a medical record that was unavailable or incomplete.

Each record was abstracted by a single investigator (P.S.) for demographic and historical data, microbiologic studies, referral pattern, chronologic data, and sequence of interventions. The majority of the records were reviewed by 1 of the 2 senior investigators, and all data sheets and accuracy of data entry were reviewed by a second investigator (J.T.K.). Times of parenteral antibiotic administration and of CSF collection were obtained from referring office and facility notes, emergency department (ED) and transport nursing and physician notes, laboratory reports, inpatient medication administration records, physician admission orders, and inpatient progress notes. The time interval of interest was from the initiation of parenteral antibiotic therapy until the collection of the first pretreated CSF sample or the first follow-up CSF sample in the case of serial LPs. The time of medication administration was defined by the start of infusion of the first dose of any parenteral antibiotic. When multiple chronologic entries existed concerning a single event, preference was given to the chart entry created by the individual who most closely witnessed it. Additional data included previous office or emergency visits, previous oral antibiotic treatment, results of blood cultures and antigen tests, and antibiotic susceptibilities of pneumococcal isolates. Non-susceptibility was defined as a minimum inhibitory concentration (MIC) for penicillin of  $\geq 0.1 \mu\text{g}/\text{mL}$  or a ceftriaxone/cefotaxime MIC of  $\geq 1.0 \mu\text{g}/\text{mL}$ .

Patients were assigned to the following groups: delayed LP (LPd) group when the first LP occurred after initiation of parenteral antibiotics, previous LP (LPp) when the only LP preceded parenteral antibiotics, and LP pre- and postantibiotic (LPp/p) group when LPs occurred before and after initiation of parenteral antibiotics. The primary outcome was the yield of pretreated CSF cultures in the LPd and LPp/p groups by organism and time from antibiotic administration. Descriptive statistics were performed using Microsoft Excel (Redmond, WA), version 2000.

## RESULTS

Of 165 cases, 37 were excluded because of ventriculoperitoneal shunts (14), postoperative infection (2), open neural tube defect with multiple pathogens (1), and incomplete or unavailable charts (7); 13 received antibiotic therapy for bacterial meningitis but did not meet the study definition, based on laboratory criteria (12) and presence of epidural abscess (1). The remaining 128 patients met study criteria by positive CSF culture (104); CSF pleocytosis with positive CSF Gram stain, alone (5) or in conjunction with positive antigen test (2); CSF pleocytosis with positive blood culture, alone (4) or in conjunction with a

positive CSF Gram stain (4), antigen test (3), or both (2); and by CSF indices alone (4). All patients who were included because of positive antigen test, Gram stain, or blood culture had CSF WBC of  $>200/\text{mm}^3$  ( $200 \times 10^6/\text{L}$ ). In no case was a CSF antigen test the sole determinant of inclusion or of pathogen identification. Of the 4 patients who met entry criteria by CSF indices alone, 1 orally pretreated patient had CSF WBC of  $9950/\text{mm}^3$  ( $9950 \times 10^6/\text{L}$ ), normal glucose and protein determinations, and negative Gram stain and culture. Another, pretreated with cephalexin for 5 days, had CSF WBC of  $4825/\text{mm}^3$  ( $4825 \times 10^6/\text{L}$ ), markedly elevated protein concentration, and group A streptococcal superinfection of varicella. One of the remaining 2 patients was parenterally pretreated, but both had CSF WBC of  $>8000/\text{mm}^3$  ( $8000 \times 10^6/\text{L}$ ), abnormal glucose or protein concentrations, and no positive microbiologic studies.

The patients ranged in age from 1 day to 16 years (median: 8 months). Slightly more than half (68 of 128) were girls. Fifty-five patients (43%) presented directly to the Children's Hospital ED, and the rest were transferred from other facilities or admitted directly from physicians' offices. Twenty-nine (41%) of 71 patients who were transferred from other facilities had received parenteral antibiotics before LP, compared with 10 (18%) patients who were admitted from the Children's Hospital ED (intergroup difference [ $\Delta$ ]:  $-23\%$ ; 95% confidence interval [CI]:  $-38\%$ ,  $-8\%$ ). Reasons for delayed LPs, determined for the latter group from the ED charts, included antibiotics given just before LP (3 cases, all with LP within the first 35 minutes), delay for computed tomography (CT; 1 case), misdiagnosis as retropharyngeal abscess (1), parenteral antibiotics administered by primary care physician (2), and unsuccessful LP attempts in neonates (3). Twenty-seven (21%) of the patients had been treated as outpatients before hospital admission; of these, 20 (74%) had received oral antibiotics. One additional child received antibiotics from her family's own supply. A total of 123 (96%) patients survived to discharge.

Final organisms were determined in 125 cases (98%) on the basis of CSF cultures, blood cultures, and antigen studies of CSF (Table 1), with *Streptococcus pneumoniae* (38%), *Neisseria meningitidis* (29%), and group B *Streptococcus* (16%) identified most often. Median patient ages varied by organism: *S pneumoniae*, 9 months (interquartile range [IQR]: 5 months, 19 months); *N meningitidis*, 31 months (IQR: 7 months, 58 months); and group B *Streptococcus*, 21 days (IQR: 9 days, 31 days). Initial CSF cultures were positive in 104 (81%). Because many patients were transferred from other facilities, microbiologic data from sources other than CSF were not available for all patients. However, results of initial blood cultures were available for 100 patients, 66 of which were positive, including 62 (74%) of 84 obtained before any antibiotics, 2 of 7 obtained after oral pretreatment, and 2 of 9 obtained after parenteral pretreatment. Of the 24 patients with negative initial LPs, blood culture results were available for 23, with 13 (57%) positive for the presumed pathogen. All 13

**TABLE 1.** Infecting Pathogens and Microbiologic Studies Identifying Organisms

Final Organism	n*	CSF Culture*	Blood Culture	CSF Antigen	Other Indirect
<i>S pneumoniae</i>	49	45	1	1†	Gram stain (2)
<i>N meningitidis</i>	37	27	6‡	1†	Gram stain (3)
<i>H influenzae</i> §	8	7	1	0	
<i>E coli</i>	4	3	1†	0	
Group B <i>Streptococcus</i>	21	18	3	0	
Other¶	7	5	1	0	Wound culture (1)
Undetermined	3	0	0	0	
Total	129	105	13	2	5

\* Totals exceed numbers of patients and positive cultures because of isolation of *S pneumoniae* and *H influenzae* in a single patient.

† Gram stains also positive.

‡ Additional positive tests: CSF antigen (2) and Gram stain (3).

§ *H influenzae* isolates: type b (5), type e (1), type f (1), not typed (1).

|| Additional positive tests: CSF antigen (1) and Gram stain plus CSF antigen (2).

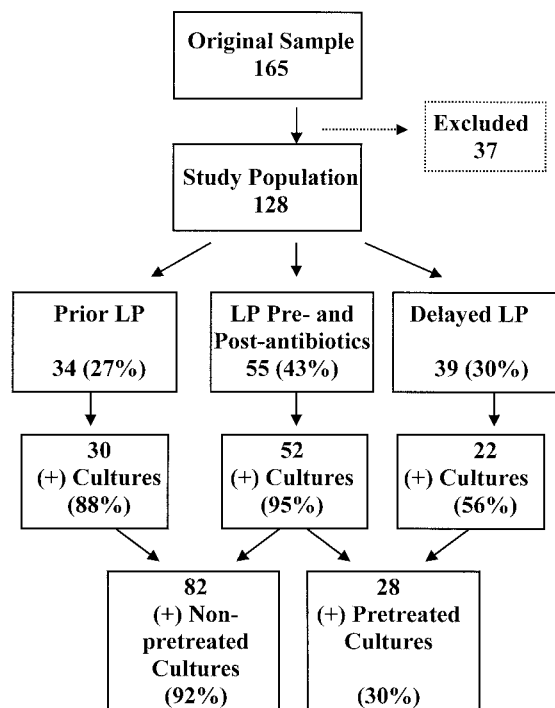
¶ *Acinetobacter lwoffii* (1), group A *Streptococcus* (2), group F *Streptococcus* (1), *K pneumoniae* (1), *L monocytogenes* (1), and *P mirabilis* (1).

positive blood cultures from the CSF culture-negative group occurred among the 19 with no known antibiotic treatment before blood sampling (68%). Among patients with positive initial CSF cultures, 53 of 77 known blood culture results were positive (69%), including 49 (75%) of 65 without any pretreatment and 2 each among 7 parenterally and 5 orally pretreated blood cultures. Despite the apparent differences in blood culture yields between groups with positive and negative CSF cultures, the 95% CIs for differences in proportions included 0.

Figure 1 demonstrates the composition of the study population by timing of LP and CSF yield. LPs were performed on 39 patients (30%) after initiation of parenteral antibiotics (LPd group), on 34 patients (27%) before parenteral antibiotics (LPp group), and on 55 patients (43%) both before and after initiation of parenteral antibiotics (LPp/p group). The combined LPp and LPp/p groups had 82 positive CSF

cultures (92%) obtained before parenteral antibiotic therapy, and the LPd group had 22 positive CSF cultures (56%;  $\Delta$ : -36%; 95% CI: -53%, -19%).

Antibiotic pretreatment in the LPd and LPp/p groups almost always included a third-generation cephalosporin (ceftriaxone, 72%; cefotaxime, 26%), with 98% of known doses at least 50 mg/kg or 1 g. Fifteen patients, all from the LPd group, underwent LPs within 1 hour of parenteral antibiotics with negative CSF cultures in 3 of 9 cases of meningococcal meningitis (Table 2). The earliest instances of sterilization of *N meningitidis* occurred within 15 and 20 minutes of initiation of infusion of ceftriaxone 175 mg/kg and 50 mg/kg, respectively. One CSF culture remained positive for *N meningitidis* after 75 mg/kg ceftriaxone intravenously, given in separate doses of 49 mg/kg and 26 mg/kg at 1.5 and 2.3 hours, respectively, before repeat LP. The remaining CSF cultures for *N meningitidis* were sterile (Fig 2). Culture-negative pneumococcal meningitis occurred as early as 4.3 hours after antibiotics. Five of the positive pretreated pneumococcal cultures occurred with organisms that were nonsusceptible to penicillin and/or ceftriaxone, including 1 obtained 48 hours after outpatient pretreatment with ceftriaxone and amoxicillin-clavulanic acid (MIC for penicillin 2.0  $\mu$ g/mL and



**Fig 1.** Study population by timing of LP and antibiotic administration.

**TABLE 2.** Sterility of CSF Cultures Over Time for the 3 Most Common Pathogens

Time Interval (Hour)	<i>N meningitidis</i>	<i>S pneumoniae</i>	GBS	Combined
0-1	3/9 (33)*	0/3 (0)†	0/3 (0)	3/15 (20)
1.1-2	—	0/3 (0)‡	—	0/3 (0)
2.1-3	3/4 (75)‡	0/3 (0)†	—	3/7 (43)
3.1-4	1/1 (100)	0/1 (0)	—	1/2 (50)
4.1-5	—	1/2 (50)†	—	1/2 (50)
5.1-6	2/2 (100)‡	2/2 (100)	0/1 (0)	4/5 (80)
6.1-24	3/3 (100)	3/5 (60)	0/1 (0)	6/9 (67)
24.1-48	2/2 (100)	7/8 (88)*†‡	2/2 (100)	11/12 (92)
48.1-72	3/3 (100)	4/4 (100)	1/2 (50)	8/9 (89)
72.1	2/2 (100)	7/7 (100)‡	6/6 (100)	15/15 (100)

Data presented as number sterile/evaluable cases (%). Table excludes LPp/p patients whose CSF cultures were sterile before parenteral antibiotics.

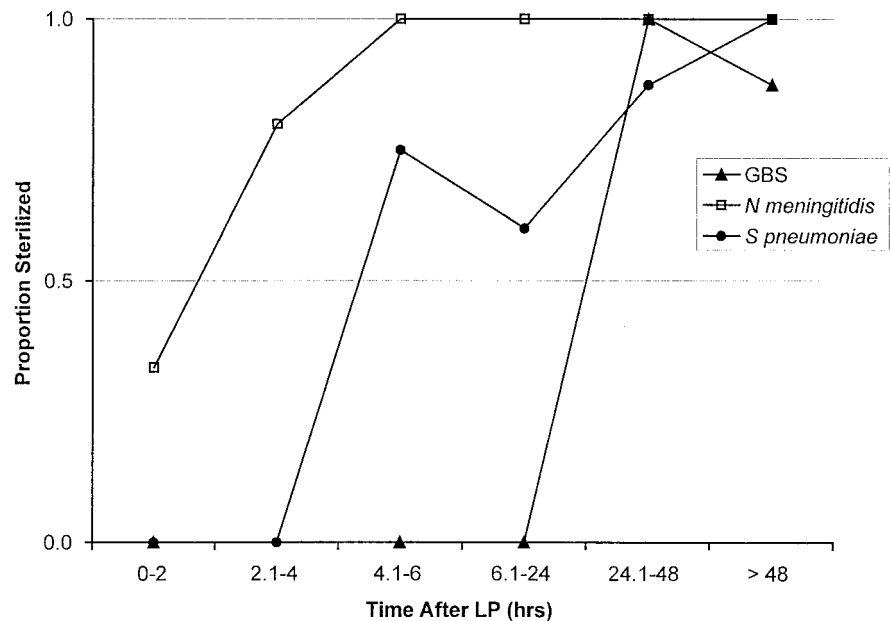
\* Includes 1 orally pretreated patient with positive CSF culture.

† Includes at least 1 nonsusceptible pneumococcal isolate.

‡ Includes 1 orally pretreated patient with sterile CSF culture.



Fig 2. CSF sterilization. Proportions of cultures for *S pneumoniae*, *N meningitidis*, and group B *Streptococcus* rendered sterile are graphed as a function of time since administration of parenteral antibiotics.



for ceftriaxone 1.0  $\mu\text{g}/\text{mL}$ ). Another isolate had penicillin and ceftriaxone MICs of 2.5 and 0.5  $\mu\text{g}/\text{mL}$ , respectively, and was positive at 1 hour 5 minutes and 43 hours after initiation of parenteral antibiotics. Between 4 and 10 hours after initiation of antibiotics, 5 of 7 cases of pneumococcal meningitis had negative CSF cultures (Fig 2). Early CSF cultures for group B streptococci obtained within 8 hours of parenteral antibiotics were positive. Delayed LPs for group B streptococci obtained from 33.5 hours after antibiotics were sterile with a single exception at 60 hours (Fig 2). Within the LPp/p group, no follow-up cultures were positive when obtained >3 hours after beginning parenteral antibiotic therapy specifically directed against meningitis.

Twenty-one patients had received oral antibiotics for courses of 1 to 21 days (median: 1 day; IQR: 1 day, 2 days) before LP. When orally pretreated, only 14 CSF cultures (67%) were positive, including 12 of 17 without parenteral pretreatment (LPp plus LPp/p, 71%) and 2 of 4 in the LPd group (50%). Without oral or parenteral pretreatment, 70 of the 72 patients (97%) in the combined LPp and LPp/p groups had positive cultures. Patients with no oral or parenteral pretreatment had significantly greater CSF culture yields than patients with any oral pretreatment ( $\Delta$ : 31%; 95% CI: 10%, 51%) and orally pretreated patients with no parenteral pretreatment ( $\Delta$ : 27%; 95% CI: 5%, 49%). However, the difference in culture yields decreased when parenterally pretreated patients were included in the comparison (67% vs 84%;  $\Delta$ : 17%; 95% CI: -4%, 39%). The 2 cases of CSF culture-negative meningitis with no known oral or parenteral pretreatment included *Escherichia coli* bacteremia with a traumatic, small-volume initial LP, and a large pleocytosis on subsequent LP; and presumed bacterial meningitis with no positive cultures and CSF WBC of 11 800/ $\text{mm}^3$  (11 800  $\times$  10<sup>6</sup>/L).

Of the 49 cases of pneumococcal meningitis, 3 pretreated patients lacked any positive cultures. Isolates in the remaining 46 included 11 (24%) nonsus-

ceptible to  $\beta$ -lactam antibiotics with penicillin MICs of  $\geq 0.1$   $\mu\text{g}/\text{mL}$  in 11 and ceftriaxone/cefotaxime MICs of  $\geq 1.0$   $\mu\text{g}/\text{mL}$  in 4 (9% of isolates).

#### DISCUSSION

In our study of antibiotic pretreatment in bacterial meningitis, negative CSF cultures occurred in 44% of initial LPs performed after parenteral antibiotics compared with only 8% of those performed before parenteral antibiotics and only 3% of those with neither oral nor parenteral pretreatment. Within 1 hour of parenteral antibiotics, 3 of 9 cases of meningococcal meningitis had sterile cultures. None remained positive >2 hours after receiving  $\geq 50$  mg/kg of a third-generation cephalosporin. After 4 hours from the initiation of antibiotics, CSF cultures were usually negative for *S pneumoniae*, although positive cultures persisted in the setting of decreased susceptibility to  $\beta$ -lactam antibiotics.

Although CSF culture is the standard for diagnosing bacterial meningitis, delay in LP may occur for several reasons. Hemodynamic instability and infection at the site of proposed puncture are recognized contraindications. Some clinicians may precede LP with CT for fear of precipitating cerebral herniation.<sup>6</sup> However, one review of the literature found herniation unlikely in pediatric bacterial meningitis in the absence of neurologic abnormality or coma.<sup>7</sup> One report described LP-related herniation despite normal CT findings (images not provided).<sup>8</sup> However, the clinical signs may have represented an early opportunity to institute treatment for intracranial hypertension. Febrile pediatric patients also may be treated with parenteral antibiotics and transferred to tertiary facilities without previous LP either because of a lack of technical expertise or because of an assumption that the yield of CSF cultures obtained several hours later will not be compromised. Despite the lack of evidence, a widely used text published in 1998 refers to a "minimum window of 2 to 3 hours ... when CSF cultures are not adversely affected"

and states that "in the pediatric population a single dose of antibiotic before transport is unlikely to prevent bacterial identification."<sup>3</sup>

The clinician may face additional pressures to administer parenteral antibiotics before definitive studies are performed. Although potential diagnostic delays are not conclusively associated with worsened outcome,<sup>9</sup> reported time intervals from presentation to antibiotics averaging 2 to 3 hours for pediatric bacterial meningitis<sup>10–12</sup> have prompted recommendations for changes in clinical management practices to shorten this interval.<sup>12,13</sup> "Expert" opinion on the expected time to antibiotics is widely divergent.<sup>11</sup> Therefore, physicians who are concerned about cerebral herniation or delays in therapy may elect to defer LP and may be falsely reassured that the bacterial pathogen and its antibiotic susceptibility can be determined at a later time. However, CSF culture recovered the pathogen in only 81% of our study patients and 92% even in the absence of parenteral antibiotic pretreatment. Furthermore, data that associate delayed sterilization with adverse outcomes also seem to implicate patient age, disease severity, and bacterial concentrations as causal factors.<sup>14,15</sup>

Previous antibiotic therapy is unlikely to alter the biochemical and cellular abnormalities of CSF sufficiently to prevent the recognition of bacterial meningitis,<sup>16,17</sup> but oral antibiotic pretreatment will decrease CSF bacterial concentrations and yields of Gram stain and culture.<sup>17,18</sup> Recovery of *H influenzae* is possible in 43% of CSF samples obtained 4 to 12 hours after 75 mg/kg ceftriaxone<sup>19</sup> and in 2% to 3% performed 18 to 36 hours after initiation of ceftriaxone,<sup>20</sup> cefotaxime,<sup>21</sup> and meropenem.<sup>21</sup> However, no data directly address shorter time intervals within which parenteral antibiotics will not impair CSF culture recovery.

CSF sterilization as a result of antibiotic pretreatment may result in unwarranted or unnecessarily prolonged treatment if the clinical presentation and other laboratory investigations cannot exclude the possibility of bacterial meningitis. Of the 12 cases with culture-negative pleocytosis that failed to meet our study criteria, at least 7 were pretreated patients who received  $\geq 7$  days of parenteral antibiotics for this reason, including 1 whose LP was completed within 5 minutes after antibiotics. Previous  $\beta$ -lactam administration is unlikely to prevent recognition of organisms with reduced susceptibility. However, pretreatment with multiple antibiotics that target resistant organisms may preclude the use of simpler and less toxic regimens, if cultures subsequently fail to yield a bacterial pathogen.

The increasing prevalence of nonsusceptible pneumococcal isolates in invasive infections<sup>22</sup> and meningitis<sup>23</sup> is a significant concern. During a 3-year period, reduced susceptibility to penicillin increased by 50% and that to ceftriaxone increased 3-fold (and by 9 times for meningitis).<sup>22,23</sup> Our study revealed nonsusceptibility to  $\beta$ -lactam antibiotics in 22% of all cases of pneumococcal meningitis. Antibiotic-resistant meningococci are not a significant problem in the United States, with intermediate resistance remaining stable at approximately 3% of isolates be-

tween 1991<sup>24</sup> and 1997.<sup>25</sup> However, reports of rapidly increasing penicillin resistance in Spain,<sup>26</sup> penicillinase production,<sup>27,28</sup> the acquisition of  $\beta$ -lactamase-encoding plasmids,<sup>28</sup> and high-level chloramphenicol resistance<sup>29</sup> predict that knowledge of antibiotic susceptibility will become increasingly important in guiding therapy for meningococcal disease.

Coant et al<sup>30</sup> reported positive blood cultures in up to 97% of patients with bacterial meningitis in the 2- to 24-month age range. However, these data pertain to a subset of patients with positive CSF cultures when *H influenzae* was the predominant pathogen. In our study, 74% of available blood cultures obtained before antibiotics were positive compared with only 57% when the CSF culture was negative. Similarly, Klugman et al<sup>21</sup> found positive blood cultures associated with 58% of positive CSF cultures. Although CSF antigen tests may identify bacterial pathogens in 87% of cases of partially treated meningitis,<sup>31</sup> the antibiotic sensitivity will remain unknown. Such tests did not contribute to the diagnosis in our patients, and their diagnostic utility has been questioned by others.<sup>32</sup> Other diagnostic modalities, such as the polymerase chain reaction assay, may prove useful for the identification of bacterial species and antimicrobial resistance.<sup>33</sup> However, the technique does not yet enjoy widespread acceptance, and its yield is adversely affected by previous antibiotic therapy.<sup>34</sup>

The limitations of this study include its dependence on the accuracy and completeness of the medical record for chronologic data and culture results. Even with complete chronologic data, it often is impossible to determine the rapidity of antibiotic infusion and whether the time documented represents the beginning or end of infusion. Such data also are subject to inaccuracy in the calibration of timepieces used in clinical settings<sup>35</sup> and in the documentation of time intervals by clinical personnel.<sup>36</sup> The strict study criteria may have excluded patients who had bacterial meningitis and minimal CSF changes<sup>37</sup> and who would have received a full course of parenteral antibiotic treatment on the basis of clinical judgment. However, we opted to miss possible cases of true sterilization to avoid inclusion of cases of nonbacterial meningitis. Because the intentions of the treating physicians were unknown, pretreated patients may have differed in disease severity or presentation. Patients who present with clinically and biochemically more severe disease and greater CSF bacterial burdens may have delayed sterilization.<sup>14,38,39</sup> Conversely, an atypical presentation with milder disease may be associated with more rapid sterilization. The study sample does not permit assessment of the role of reduced susceptibility in early CSF sterilization. The lack of uniformity in antibiotic choice, dosage, and route of administration poses some difficulty in interpretation, but it does reflect the range of therapies given as pretreatment in diverse clinical settings. A prospective study in humans would face the ethical barrier of delaying initial LPs in suspected bacterial meningitis or the practical difficulty of frequent CSF sampling after antibiotic administration. Consent would be problematic, and any sampling

method or device could alter antimicrobial efficacy and the resultant microbiologic data.

Recent published opinion suggests that antibiotic administration before LP is unlikely to hinder the recovery of a bacterial meningopathogen.<sup>3</sup> However, no previous publication directly supports this assumption. The present study demonstrates that CSF sterilization occurs more rapidly after initiation of parenteral antibiotics than previously suggested. We demonstrated that CSF cultures may be sterilized within 1 hour of parenteral antibiotic therapy for meningococcal meningitis and within 4 hours for pneumococcal meningitis. As the use of the pneumococcal conjugate vaccine increases, the proportion of children with meningococcal meningitis will increase, leading to substantial increases in the proportion of CSF cultures that are negative within 1 hour of antibiotic therapy. Therefore, if technically feasible, hemodynamically stable patients with suspected meningitis and no evidence of cerebral edema or herniation syndromes should undergo lumbar puncture before the administration of parenteral antibiotics.

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