Term Newborns Who Are at Risk for Sepsis: Are Lumbar Punctures Necessary?

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ABSTRACT. Objectives. To determine: (1) whether a lumbar puncture (LP) is indicated in asymptomatic full-term newborns delivered by mothers at risk of intrapartum sepsis; and (2) whether gentamicin improves bacterial coverage for such newborns when used with ampicillin.

Design. A retrospective chart review from 1987 through 1993 of all newborns with positive blood and/or cerebrospinal fluid cultures in the first 7 days of life.

Methods. Pregnant women were screened in the second trimester for group B streptococci and given ampicillin during labor if two or more risk factors were present: group B streptococci colonization, maternal fever or leukocytosis, rupture of membranes at more than 18 hours, foul-smelling amniotic fluid, and fetal tachycardia. After sepsis evaluation (LP, blood culture, white blood cell count, and differential), asymptomatic infants received ampicillin and gentamicin for 48 to 72 hours unless cultures grew pathogens.

Results. Of approximately 24,452 full-term births in 7 years, 7% (1712) had evaluations for symptoms of sepsis, and 14% (3423) were asymptomatic but had evaluations for maternal risk factors. There were 11 cases of meningitis, all involving symptomatic newborns; 10 of these 11 had positive blood cultures for the same organism. In asymptomatic infants, none of the 3423 had meningitis (95% confidence interval, 0 to 0.0008), although 35 grew contaminants. Of 73 pathogens isolated from blood or cerebrospinal fluid, 7 (9.5%) were resistant to ampicillin. Addition of gentamicin provided coverage for only 2 of these 7 pathogens. Of 5135 infants who received ampicillin and gentamicin, only 2 required gentamicin for improved coverage.

Conclusions. (1) LP is unnecessary in asymptomatic full-term newborns. (2) Empiric coverage for asymptomatic newborns with maternal risk factors need not include gentamicin at all hospitals, because it only improved the coverage of ampicillin alone from 90% to 93% of pathogens, but it exposed more than 5000 infants to the side effects of gentamicin. (3) The presence of leukopenia (<5000 white blood cells/mm³) is highly predictive of bacteremia. Pediatrics 1997;99(4). URL: http://www.pediatrics.org/cgi/content/full/99/4/e10; newborn, lumbar puncture, meningitis.

ABBREVIATIONS. GBS, group B streptococci; LP, lumbar puncture; CSF, cerebrospinal fluid; I:T, immature-to-total; WBC, white blood cell; CI, confidence interval; ROC, receiver operating characteristic.

Since the early 1970s, group B streptococci (GBS) have been the leading causes of infection in the immediate newborn period in the United States. The clinical impact of GBS sepsis has led to the development of different strategies to improve overall neonatal survival. In the absence of effective vaccination against GBS, intrapartum maternal chemoprophylaxis is the preferred method for preventing neonatal and maternal morbidity.2-4 Lumbar puncture (LP) is often performed immediately after delivery in asymptomatic newborns after chemoprophylaxis as part of a sepsis evaluation to diagnose bacterial meningitis. However, the studies evaluating the clinical usefulness of LP have been done primarily in preterm infants5-7 or in neonatal intensive care units with both full-term and preterm infants.8-10 It may not be appropriate to generalize the findings from high-risk populations to asymptomatic full-term infants cared for in general nurseries. In addition to the increased cost from unnecessary tests, one also runs the risk of a significant number of the cerebrospinal fluid (CSF) cultures being contaminants. Such contaminants result in a prolongation of the infant’s length of stay while awaiting the results of further diagnostic tests.

The three goals of this study were: (1) to determine whether the LP is useful in asymptomatic full-term newborns at risk of sepsis; (2) to see whether the neonatal white blood cell (WBC) count or immature-to-total (I:T) neutrophil ratio predicts bacteremia; and (3) to see whether the use of gentamicin in addition to ampicillin in asymptomatic infants is justified.

METHODS

Procedures

The medical records of all neonates with gestational ages of 37 weeks or more who had blood or CSF cultures positive for pathogens within the first 7 days of life at the MetroHealth Medical Center were evaluated retrospectively. The MetroHealth Medical Center is a level III regional referral center for newborns, but only those infants born in-house were evaluated during this review. Neonatal transports and outside deliveries were excluded. During the study period, 1987 through 1993, approximately 24,452 full-term newborns were admitted to the well infant nurseries. The number of sepsis evaluations is calculated from actual counts done for 2-week periods in 1993. Eight percent of infants did not
have a successful LP completed. For comparison, with 1987 through 1993 data the number of full-term newborns with GBS bacteremia and/or meningitis from 1980 through 1986 was also calculated from laboratory log books, but these charts were not reviewed except to confirm the diagnosis.

Infants with symptoms of sepsis (respiratory distress, poor vascular perfusion, temperature instability, bloody stools, lethargy, and recurrent hypoglycemia) had a sepsis evaluation performed. The evaluation consisted of an LP, blood culture, and a WBC count with differential. Symptomatic infants received 7- to 10-day courses of ampicillin and gentamicin intravenously.

Starting in 1987, all pregnant women presenting in the second trimester had cultures of the rectum and lower vagina taken for GBS. Because approximately 10% of all women at our hospital do not receive prenatal care, our hospital policy was established to allow intrapartum antibiotic treatment even if vaginal and rectal cultures had not been done. Ampicillin was given during labor if two or more risk factors for GBS sepsis were present. These risk factors were: (1) maternal colonization with GBS, (2) maternal fever, (3) prolonged rupture of fetal membranes at more than 18 hours, (4) foul-smelling amniotic fluids, (5) unexplained fetal tachycardia, and (6) elevated maternal WBC count. Immediately after delivery, the infant had a sepsis evaluation completed. The infant then received ampicillin and gentamicin intravenously for 48 to 72 hours; drugs were discontinued if blood and CSF cultures were negative for pathogens. For the purpose of assessing the usefulness of WBC counts and I:T neutrophil ratios, we used a combination of (1) which consisted of infants in whom contaminants grew in blood or CSF but who were not infected.

Definitions
Symptomatic infants were defined as those with respiratory distress, temperature instability or elevation, lethargy, poor perfusion, bloody stools, or unexplained recurrent hypoglycemia. Contaminants in the blood culture could not be vigorously eliminated, because duplicate blood cultures were not obtained. Because this was a retrospective review, we used the clinicians’ decisions to treat less than 7 days as evidence of a contaminant. All such infants did well after antibiotics were stopped. 28 of 31 contaminants were Staphylococcus epidermidis. In the CSF an organism was defined as a contaminant if either one of the following applied: (1) a second LP showed no pleocytosis, no bacterial growth, and normal chemistries, and antibiotics were stopped (5 cases); or (2) no second LP was done because the clinicians judged the organism a contaminant and stopped antibiotic therapy in less than 7 days (30 cases). Pleocytosis was defined as more than 32 WBCs/mm² in an LP with less than 1000 red blood cells/mm². Leukopenia was defined as fewer than 5000 WBCs/mm².

Laboratory Methods
Blood specimens were obtained by venipuncture, arterial puncture, or umbilical catheterization and inoculated into the blood culture system produced by Bactec (NRLA/7A, Becton Dickinson, Towson, MD). This consists of a set of two bottles with aerobic and anaerobic media. The amount of blood for culture was approximately 0.5 mL/bottle. The isolated microorganisms were identified by standard methods in the Department of Microbiology at the MetroHealth Medical Center.

CSF specimens were obtained and sent to the microbiology laboratory, where the specimens were plated on Trypticase soy agar with 5% sheep blood, MacConkey II agar, and chocolate II agar and also placed in thioglycolate broth. The specimens were incubated for 5 days at 37°C in a carbon dioxide incubator. Organisms were identified by standard laboratory methods.

Statistical Analysis
The data were analyzed with the Statistical Package for the Social Sciences (Chicago, IL) PC+ version 4.0. Interval variables were reported as the means ± SD. Dichotomous variables were analyzed by the χ² test with a Yates correction. Interval variables were analyzed with either the pooled or separate variance t test depending on the F ratio of the variances. All tests were two tailed. In addition, the 95% confidence intervals (CIs) are reported for proportions. The receiver operating characteristic (ROC) curve for determining the best cutoff value for an abnormal test result was graphed by plotting the sensitivity versus the false-positive rate (1 – specificity) for various values of the I:T neutrophil ratio.

RESULTS
To assess the appropriateness of LP in the first 7 days of life, we reviewed the medical records of full-term infants born from 1987 through 1993 with positive blood and/or CSF cultures (Fig 1). During this 7 year period there were an estimated 24,452 full-term infants born at our hospital. Approximately 7.2% of infants were symptomatic and had sepsis evaluations, and 14% were asymptomatic but received sepsis evaluations for maternal risk factors. We did not collect data on how many women met the criteria for antibiotic prophylaxis but were not treated appropriately. We do know that compliance with maternal prophylaxis was not perfect, because 10 cases of GBS bacteremia that we identified met the criteria for prophylaxis, but the mothers were not given any antibiotics before delivery (8 cases) or received them less than 2 hours before delivery (2 cases). One of these 10 infants died of GBS sepsis that may have been preventable. There were also four deaths that were not preventable; three were caused by organisms other than GBS, and one occurred in a GBS-colonized woman with no risk factors. Prophylaxis given 4 or more hours before delivery was remarkably effective. The only failure to prevent GBS bacteremia occurred in a woman given erythromycin (because of a penicillin allergy) more than 4 hours before delivery. Fig 1 shows that approximately 3423 asymptomatic women received prophylaxis before delivery (as well as many of the 1712 women who gave birth to symptomatic infants), yet only this one prophylactic failure occurred.

We did assess compliance with the postpartum evaluations of the infants. A review of 100 consecutive charts of infants born from October 1 through 16, 1994, was done to check compliance of the pediatric house staff with the protocol for sepsis evaluations. There were 10 symptomatic infants, and all were evaluated and received antibiotics pending culture, except for 1 who did not have an LP attempted and 2 who had unsuccessful LPs. There were 5 asymptomatic infants with two or more risk factors, and all
5 received complete sepsis evaluations. No unnecessary evaluations were done.

Of the 3423 asymptomatic infants, 17 (0.5%) had positive blood cultures, compared with 55 (3.2%) of 1712 symptomatic infants ($P < .001$). There were 72 positive blood cultures in 7 years (Table 1). Infants who had organisms isolated from the blood included 32 with GBS, 10 with *Escherichia coli*, 7 with *Streptococcus faecalis*, 6 with *Streptococcus pneumoniae*, (pneumococcus), 3 with *Bacteroides* sp, 1 with *Neisseria meningitidis*, 1 with *Haemophilus influenzae*, 2 with *Staphylococcus aureus*, 3 with *S epidermidis*, and 7 with *Streptococcus* sp. GBS accounted for half of the cases of sepsis despite the early recognition of risk factors and administration of antibiotic prophylaxis. For comparison, we identified all cases of full-term newborns with bacteremia and/or meningitis from the 7 years preceding institution of intrapartum prophylaxis (1980 through 1986). Table 2 shows that the rate of GBS infection per year was 2.3 per 1000 full-term births during the earlier period and 1.3 per 1000 in the latter period, which was a 43% decline ($P = .018$, $\chi^2$ test).

CSF specimens were obtained before initiation of postnatal antibiotic therapy in 21% of all full-term births (Fig 1). None of the specimens taken in asymptomatic infants yielded pathogens. Of the 1712 symptomatic infants, 11 infants had CSF cultures positive for pathogens (Table 3). GBS accounts for more than half of the pathogens isolated from CSF. Table 1 shows that *E coli* was commonly isolated from blood, yet it was not isolated from the CSF. No Gram-negative enteric organism caused meningitis in more than 24 000 deliveries. Ten of 11 infants had the same pathogens in the blood as in the CSF. No asymptomatic infant had meningitis, of 3423 evaluated by LP. The upper 95th percentile for this confidence limit is 0.0008, which means that, at most, 8 of 10 000 LPs in asymptomatic infants would yield pathogens.

We next examined the sensitivity of the organisms to ampicillin as a single agent to see whether gentamicin improved empiric coverage. All isolates of GBS, enterococcus, and pneumococcus were sensitive to ampicillin. Of the 72 blood isolates, 7 were resistant to ampicillin. Two of these 7 blood isolates were ampicillin-resistant *E coli* susceptible to gentamicin, 1 asymptomatic and 1 with symptoms, and the other 5 were Gram-positive organisms resistant to gentamicin. Therefore, of 3423 asymptomatic infants who received ampicillin and gentamicin for 2 to 3 days, only one infant benefitted from the addition of gentamicin as a second antibiotic.

To assess the value of the WBC count and differential in predicting bacteremia, we compared bacteremic infants with a cohort having these tests done but having only contaminants isolated. The total WBC count and the I:T neutrophil ratio were significantly different between the bacteremic and comparison groups. In the bacteremic group, the total WBC count was less than that in the control group (13 500 ± 9400 vs 17 400 ± 7000; $P = .007$). In addition, more bacteremic patients were leukopenic (WBCs <5000/mm$^3$) than control infants (12 of 67 vs 0 of 66; $P < .001$). As a diagnostic test, leukopenia has a sensitivity of 18% (95% CI, 10% to 29%) and a specificity of 100% (95% CI, 95% to 100%). The I:T neutrophil ratio was also greater in the bacteremic group (0.35 ± 0.27 vs 0.13 ± 0.13; $P < .001$).

In evaluating an ROC curve, a sharp break point in the upper left corner would represent an excellent value for defining an abnormal test result, whereas a diagonal line through the origin would signify that the diagnostic test has an ill-defined cutoff point. Our results (Fig 2) do not show a sharp break point. On review of the ROC curve for the I:T neutrophil ratio, the best cutoff point occurred at 0.4, which

### Table 1. Bacterial Pathogens and Contaminants in Blood of Symptomatic and Asymptomatic Full-term Newborns Within 7 Days of Birth*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
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<tbody>
<tr>
<td>Pathogens†</td>
<td>55</td>
<td>17</td>
</tr>
<tr>
<td>Contaminants‡</td>
<td>26</td>
<td>42</td>
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* $P < .0001$, $\chi^2$ with Yates correction.
† Group B streptococci (n = 32), *Escherichia coli* (n = 10), *Streptococcus faecalis* (n = 7), *Streptococcus pneumoniae* (n = 6), *Streptococcus* sp (n = 7), *Bacteroides* sp (n = 3), *Neisseria meningitidis* (n = 1), *Haemophilus influenzae* (n = 1), *Staphylococcus aureus* (n = 2), and *Staphylococcus epidermidis* (n = 3).
‡ *S. epidermidis* (n = 28), *Streptococcus sanguis* (2), and *Bacteroides fragilis* (1).
resulted in a sensitivity of 37% and a specificity of 94%. Hence, almost 63% of the cases with bacteremia would not be detected with this cutoff value.

During the 7-year study period, 3423 LPs were performed in asymptomatic infants, none of whom had meningitis but 35 of whom had contaminants. At our hospital an LP costs approximately $294, including physician and laboratory charges. With 3700 deliveries and 520 sepsis evaluations in asymptomatic full-term newborns per year, approximately $150 000 per year would be saved by omitting the LP. In addition, about five infants per year are detained an additional 48 to 72 hours awaiting results of second LPs after the first grows a contaminant.

**DISCUSSION**

The results of this study confirm numerous reports that show GBS as the most common cause of neonatal sepsis in full-term infants. In our 7-year study of 24 452 consecutive full-term deliveries, a surprisingly high percentage (21%) had sepsis evaluations. Blood culture within 7 days of birth showed GBS as the most common pathogen, followed by *E coli*, *Streptococcus faecalis*, and pneumococcus. Our study noted a 43% decrease in the incidence of GBS sepsis after the introduction of intrapartum prophylaxis, which agrees with the decline originally shown by Boyer and Gotoff. Our incidence of GBS bacteremia in full-term infants was 0.13%, less than reported in the 1992 study by Weisman et al, who included preterm infants and noted an incidence of 0.32%. They reported that this was in the upper range of the 12 largest US case studies since the early 1960s, which indicated that the incidence of GBS sepsis was not decreasing. They also reported a survival rate of 88%, similar to our rate of 93% in full-term newborns.

GBS sepsis has a high incidence of coexistent meningitis; therefore, an LP to exclude the possibility of meningitis has traditionally been included in the evaluation of newborns born to GBS-colonized women who have fever or prolonged rupture of membranes, although previous studies have been in mixed preterm and full-term infants, whereas ours was exclusively in full-term newborns. In our study, 3423 LPs were done in asymptomatic full-term infants, of which none revealed meningitis, but 35 had contaminants (0.96%). Eleven cases of meningitis were identified, and all were in symptomatic infants. Neonates with meningitis most commonly presented with non-neurologic complications, such as respiratory distress, perfusion problems, and temperature instability, although many also had neurologic symptoms of lethargy or irritability, and we think that all such neonates should be classified as symptomatic.

Results similar to ours were found in four previous studies. Fieckow et al reviewed 1073 consecutive CSF cultures in 10 years in full-term and preterm infants younger than 7 days. As in our study, none of the 284 asymptomatic infants in their study had meningitis, although 1.8% had contaminants. The rate of meningitis in asymptomatic infants was approximately 2%, similar to our rate of 0.6%. They concluded that LP is not indicated in asymptomatic full-term or preterm infants born to high-risk mothers. In the study of Weiss et al, 2156 premature infants with respiratory distress had 1495 successful LPs at admission. A rate of early-onset meningitis of 0.27% was found, and a contamination rate of 1.3% was found. They did not perform LP in asymptomatic infants. Blood cultures were positive in three of the four cases of meningitis. They concluded, as did Eldadah et al in 1987, that LP should be reserved for infants with positive blood cultures, central nervous system symptoms, or positive urine GBS antigen test results. Schwersenski et al showed similar findings, but also noted that the yield of LP increased fivefold when performed in symptomatic infants after the first week of life. Even in the one study that separately analyzed newborns weighing less than 1500 g, only one case of meningitis was found in 773 infants on day 1 of life. They concluded that “LP should only be carried out during the newborn period when there are clinical signs and symptoms of severe sepsis and not as a routine on all low birth weight babies.”

In contrast to these four studies, in 1995 Wiswell et al concluded from a review of 169 000 births in US Army hospitals that asymptomatic neonates frequently have meningitis. They identified 43 cases of meningitis in the first 72 hours, including 7 in infants born at 36 or less weeks and 36 in infants born at more than 36 weeks. Seven (16%) of 43 infants with meningitis were asymptomatic, which would suggest that early meningitis may often be asymptomatic. Even more worrisome, 4 of the 7 asymptomatic infants with meningitis had negative blood cultures. In view of the results of our study and the four studies cited above, this raises the question of whether some of these organisms were CSF contaminants. The authors do not provide data on the contamination rate, nor do they state whether second LPs were performed in any of the asymptomatic infants. The data on whether CSF pleocytosis or abnormal glucose or protein levels were present are also not provided. Given that we found a ratio of CSF contaminants to pathogens of 3:1, and Weiss et al found a ratio of 4.7:1 in premature infants, it is pos-
sible that some of the isolates of Wiswell et al\textsuperscript{9} were contaminants. Organisms that can be pathogenic were shown to be contaminants by second LP, including \textit{Enterobacter}, \textit{Streptococcus mitis}, and \textit{S aureus}. Wiswell et al\textsuperscript{9} do not identify the organisms that grew in cases of “asymptomatic meningitis,” or state whether second LPs were performed.

Recent guidelines from the Centers for Disease Control and Prevention do not include the use of any antibiotics in infants whose mothers received ampicillin more than 4 hours before delivery;\textsuperscript{7} however, at the time of our study both ampicillin and gentamicin were used at our hospital and many others while awaiting culture results. Because gentamicin may cause ototoxicity, we examined whether ampicillin alone provided adequate empiric coverage of sepsis in the full-term infant. All isolates of \textit{GBS}, enterococci, and pneumococci were sensitive to ampicillin, but 2 of 10 strains of \textit{E coli} were ampicillin-resistant and susceptible to gentamicin. Addition of gentamicin would have increased antibiotic coverage from 90% to 93% of infants, but at a cost of exposing more than 3400 asymptomatic newborns to gentamicin. Because the incidence of ampicillin-resistance may vary among hospitals, there may be centers where empiric gentamicin use is warranted. Broad-spectrum antibiotic coverage is indicated in infants who are symptomatic and in infants born at 34 weeks or earlier while awaiting culture results.\textsuperscript{1} Genta-micin should also be added when blood or CSF cultures grow enterococcus for synergism, but ampicillin is adequate initial therapy.

An ideal diagnostic test to establish neonatal sepsis should have high sensitivity, so no case of sepsis is missed, and a high negative predictive value, to exclude sepsis when the test is negative. In our study, a control group was compared with bacteremic infants, and when leukopenia (WBCs <5000) was analyzed, it had a sensitivity of 18% and a specificity of 100%. In 1984, Engle and Rosenfeld\textsuperscript{15} showed that factors other than sepsis could cause leukopenia in infants with sepsis. For example, infants with asphyxia whose mothers had pregnancy-induced hypertension had higher rates of leukopenia than infants with sepsis. The I:T neutrophil ratio, on the other hand, was elevated in 61% of septic infants but in only 12% of infants whose mothers had pregnancy-induced hypertension and 22% of asphyxiated infants. A review article\textsuperscript{16} on premature infants reported that an I:T neutrophil ratio of greater than 0.2 had a wide range of sensitivity (58% to 90%) and specificity (31% to 78%). Only when the I:T ratio exceeded 0.4 in our study was the specificity high enough to be clinically useful. Thus, our study showed limited usefulness of the I:T ratio as a diagnostic test to establish sepsis.

In conclusion, we have shown that asymptomatic full-term infants whose mothers are treated during birth with ampicillin are at extremely low risk of having meningitis within 7 days of birth. In more than 24 000 consecutive full-term deliveries, no infant had Gram-negative enteric meningitis. Ninety percent of all pathogens isolated from blood or CSF were susceptible to ampicillin as a single agent. The new guidelines from the Centers for Disease Control and Prevention\textsuperscript{1} recommend either universal maternal screening for \textit{GBS} colonization or a policy of using intrapartum risk factors to decide which mothers require intrapartum ampicillin. In hospitals such as ours, which have used antepartum risk factors in \textit{GBS}-colonized mothers as indications for a sepsis evaluation and 48 hours of broad-spectrum antibiotics, the new guidelines would reduce the number of newborns evaluated because, they specify that only those treated less than 4 hours before delivery need to be evaluated. The guidelines leave the issue of LP to the clinical judgment of the physician. Our data indicate that LP in an asymptomatic full-term newborn has a very low yield, even though we know that not all of our at-risk mothers with \textit{GBS} received ampicillin more than 4 hours before delivery. A subsequent study would be desirable to determine: (1) the incidence of sepsis and meningitis in full-term newborns treated with intrapartum antibiotics, but not treated after birth, and (2) the yield of LPs in asymptomatic full-term newborns whose mothers receive ampicillin less than 4 hours before delivery.

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