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## **Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis**

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## CLINICAL REPORT

# Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis

## abstract

FREE

With improved obstetrical management and evidence-based use of intrapartum antimicrobial therapy, early-onset neonatal sepsis is becoming less frequent. However, early-onset sepsis remains one of the most common causes of neonatal morbidity and mortality in the preterm population. The identification of neonates at risk for early-onset sepsis is frequently based on a constellation of perinatal risk factors that are neither sensitive nor specific. Furthermore, diagnostic tests for neonatal sepsis have a poor positive predictive accuracy. As a result, clinicians often treat well-appearing infants for extended periods of time, even when bacterial cultures are negative. The optimal treatment of infants with suspected early-onset sepsis is broad-spectrum antimicrobial agents (ampicillin and an aminoglycoside). Once a pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed). Recent data suggest an association between prolonged empirical treatment of preterm infants ( $\geq 5$  days) with broad-spectrum antibiotics and higher risks of late onset sepsis, necrotizing enterocolitis, and mortality. To reduce these risks, antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low. The purpose of this clinical report is to provide a practical and, when possible, evidence-based approach to the management of infants with suspected or proven early-onset sepsis. *Pediatrics* 2012;129:1006–1015

## INTRODUCTION

“Suspected sepsis” is one of the most common diagnoses made in the NICU.<sup>1</sup> However, the signs of sepsis are nonspecific, and inflammatory syndromes of noninfectious origin mimic those of neonatal sepsis. Most infants with suspected sepsis recover with supportive care (with or without initiation of antimicrobial therapy). The challenges for clinicians are threefold: (1) identifying neonates with a high likelihood of sepsis promptly and initiating antimicrobial therapy; (2) distinguishing “high-risk” healthy-appearing infants or infants with clinical signs who do not require treatment; and (3) discontinuing antimicrobial therapy once sepsis is deemed unlikely. The purpose of this clinical report is to provide a practical and, when possible, evidence-based approach to the diagnosis and management of early-onset sepsis, defined by the National Institute of Child Health and Human Development and Vermont Oxford Networks as sepsis with onset at  $\leq 3$  days of age.

Richard A. Polin, MD and the COMMITTEE ON FETUS AND NEWBORN

### KEY WORDS

early-onset sepsis, antimicrobial therapy, group B streptococcus, meningitis, gastric aspirate, tracheal aspirate, chorioamnionitis, sepsis screen, blood culture, lumbar puncture, urine culture, body surface cultures, white blood count, acute phase reactants, prevention strategies

### ABBREVIATIONS

CFU—colony-forming units  
CRP—C-reactive protein  
CSF—cerebrospinal fluid  
GBS—group B streptococci  
I/T—immature to total neutrophil (ratio)  
PMN—polymorphonuclear leukocyte  
PPROM—preterm premature rupture of membranes

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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## PATHOGENESIS AND EPIDEMIOLOGY OF EARLY-ONSET SEPSIS

Before birth, the fetus optimally is maintained in a sterile environment. Organisms causing early-onset sepsis ascend from the birth canal either when the amniotic membranes rupture or leak before or during the course of labor, resulting in intra-amniotic infection.<sup>2</sup> Commonly referred to as “chorioamnionitis,” intra-amniotic infection indicates infection of the amniotic fluid, membranes, placenta, and/or decidua.

Group B streptococci (GBS) can also enter the amniotic fluid through occult tears. Chorioamnionitis is a major risk factor for neonatal sepsis. Sepsis can begin in utero when the fetus inhales or swallows infected amniotic fluid. The neonate can also develop sepsis in the hours or days after birth when colonized skin or mucosal surfaces are compromised. The essential criterion for the clinical diagnosis of chorioamnionitis is maternal fever. Other criteria are relatively insensitive. When defining intra-amniotic infection (chorioamnionitis) for clinical research studies, the diagnosis is typically based on the presence of maternal fever of greater than 38°C (100.4°F) and at least two of the following criteria: maternal leukocytosis (greater than 15 000 cells/mm<sup>3</sup>), maternal tachycardia (greater than 100 beats/minute), fetal tachycardia (greater than 160 beats/minute), uterine tenderness, and/or foul odor of the amniotic fluid. These thresholds are associated with higher rates of neonatal and maternal morbidity.

Nonetheless, the diagnosis of chorioamnionitis must be considered even when maternal fever is the sole abnormal finding. Although fever is common in women who receive epidural anesthesia (15%–20%), histologic evidence of acute chorioamnionitis is very common in women who become febrile after an epidural (70.6%).<sup>3</sup> Furthermore,

most of these women with histologic chorioamnionitis do not have a positive placental culture.<sup>3</sup> The incidence of clinical chorioamnionitis varies inversely with gestational age. In the National Institute of Child Health and Human Development Neonatal Research Network, 14% to 28% of women delivering preterm infants at 22 through 28 weeks' gestation exhibited signs compatible with chorioamnionitis.<sup>4</sup> The major risk factors for chorioamnionitis include low parity, spontaneous labor, longer length of labor and membrane rupture, multiple digital vaginal examinations (especially with ruptured membranes), meconium-stained amniotic fluid, internal fetal or uterine monitoring, and presence of genital tract microorganisms (eg, *Mycoplasma hominis*).<sup>5</sup>

At term gestation, less than 1% of women with intact membranes will have organisms cultured from amniotic fluid.<sup>6</sup> The rate can be higher if the integrity of the amniotic cavity is compromised by procedures before birth (eg, placement of a cerclage or amniocentesis).<sup>6</sup> In women with preterm labor and intact membranes, the rate of microbial invasion of the amniotic cavity is 32%, and if there is preterm premature rupture of membranes (PPROM), the rate may be as high as 75%.<sup>7</sup> Many of the pathogens recovered from amniotic fluid in women with preterm labor or PPRM (eg, *Ureaplasma* species or *Mycoplasma* species) do not cause early-onset sepsis.<sup>8–10</sup> However, both *Ureaplasma* and *Mycoplasma* organisms can be recovered from the bloodstream of infants whose birth weight is less than 1500 g.<sup>11</sup> When a pathogen (eg, GBS) is recovered from amniotic fluid, the attack rate of neonatal sepsis can be as high as 20%.<sup>12</sup> Infants born to women with PPRM who are colonized with GBS have an estimated attack rate of 33% to 50% when intrapartum prophylaxis is not given.<sup>13</sup>

The major risk factors for early-onset neonatal sepsis are preterm birth, maternal colonization with GBS, rupture of membranes >18 hours, and maternal signs or symptoms of intra-amniotic infection.<sup>14–16</sup> Other variables include ethnicity (ie, black women are at higher risk of being colonized with GBS), low socioeconomic status, male sex, and low Apgar scores. Preterm birth/low birth weight is the risk factor most closely associated with early-onset sepsis.<sup>17</sup> Infant birth weight is inversely related to risk of early-onset sepsis. The increased risk of early-onset sepsis in preterm infants is also related to complications of labor and delivery and immaturity of innate and adaptive immunity.<sup>18</sup>

## DIAGNOSTIC TESTING FOR SEPSIS

The clinical diagnosis of sepsis in the neonate is difficult, because many of the signs of sepsis are nonspecific and are observed with other noninfectious conditions. Although a normal physical examination is evidence that sepsis is not present,<sup>19,20</sup> bacteremia can occur in the absence of clinical signs.<sup>21</sup> Available diagnostic testing is not helpful in deciding which neonate requires empirical antimicrobial therapy but can assist with the decision to discontinue treatment.<sup>22</sup>

## Blood Culture

A single blood culture in a sufficient volume is required for all neonates with suspected sepsis. Data suggest that 1.0 mL of blood should be the minimum volume drawn for culture when a single pediatric blood culture bottle is used. Dividing the specimen in half and inoculating aerobic and anaerobic bottles is likely to decrease the sensitivity. Although 0.5 mL of blood has previously been considered acceptable, in vitro data from Schelonka et al demonstrated that 0.5 mL would not reliably detect low-level bacteremia

(4 colony-forming units [CFU]/mL or less).<sup>23</sup> Furthermore, up to 25% of infants with sepsis have low colony count bacteremia ( $\leq 4$  CFU/mL), and two-thirds of infants younger than 2 months of age have colony counts  $<10$  CFU/mL.<sup>24,25</sup> Neal et al demonstrated that more than half of blood specimens inoculated into the aerobic bottle were less than 0.5 mL.<sup>26</sup> A study by Connell et al indicated that blood cultures with an adequate volume were twice as likely to yield a positive result.<sup>27</sup> A blood culture obtained through an umbilical artery catheter shortly after placement for other clinical indications is an acceptable alternative to a culture drawn from a peripheral vein.<sup>28</sup> The risk of recovering a contaminant is greater with a blood culture drawn from an umbilical vein.<sup>29</sup> There are, however, data to suggest that a blood culture drawn from the umbilical vein at the time of delivery using a doubly clamped and adequately prepared segment of the cord is a reliable alternative to a culture obtained peripherally.<sup>30</sup>

### Urine Culture

A urine culture should not be part of the sepsis workup in an infant with suspected early-onset sepsis.<sup>31</sup> Unlike urinary tract infections in older infants (which are usually ascending infections), urinary tract infections in newborn infants are attributable to seeding of the kidney during an episode of bacteremia.

### Gastric Aspirates

The fetus swallows 500 to 1000 mL of amniotic fluid each day. Therefore, if there are white blood cells present in amniotic fluid, they will be present in gastric aspirate specimens at birth. However, these cells represent the maternal response to inflammation and have a poor correlation with neonatal sepsis.<sup>32</sup> Gram stains of gastric aspirates to identify bacteria are of limited value and are not routinely recommended.<sup>33</sup>

### Body Surface Cultures

Bacterial cultures of the axilla, groin, and the external ear canal have a poor positive predictive accuracy. They are expensive and add little to the evaluation of an infant with possible bacterial sepsis.<sup>34,35</sup>

### Tracheal Aspirates

Cultures and Gram stains of tracheal aspirate specimens may be of value if obtained immediately after endotracheal tube placement.<sup>36</sup> Once an infant has been intubated for several days, tracheal aspirates are of no value in the evaluation of sepsis.<sup>37</sup>

### Lumbar Puncture

The decision to perform a lumbar puncture in a neonate with suspected early-onset sepsis remains controversial. In the high-risk, healthy-appearing infant, data suggest that the likelihood of meningitis is extremely low.<sup>38</sup> In the infant with clinical signs that are thought to be attributable to a noninfectious condition, such as respiratory distress syndrome, the likelihood of meningitis is also low.<sup>39</sup> However, in bacteremic infants, the incidence of meningitis may be as high as 23%.<sup>40,41</sup> Blood culture alone cannot be used to decide who needs a lumbar puncture, because blood cultures can be negative in up to 38% of infants with meningitis.<sup>42,43</sup> The lumbar puncture should be performed in any infant with a positive blood culture, infants whose clinical course or laboratory data strongly suggest bacterial sepsis, and infants who initially worsen with antimicrobial therapy. For any infant who is critically ill and likely to have cardiovascular or respiratory compromise from the procedure, the lumbar puncture can be deferred until the infant is more stable.

Cerebrospinal fluid (CSF) values indicative of neonatal meningitis are controversial. In studies that have excluded

infants with “traumatic taps” (or nonbacterial illnesses), the mean number of white blood cells in uninfected preterm or term infants was consistently  $<10$  cells/mm<sup>3</sup>.<sup>44–50</sup> Cell counts 2 standard deviations from the mean were generally less than 20 cells/mm<sup>3</sup>.<sup>46</sup> In a study by Garges et al, the median number of white blood cells in infants who were born at greater than 34 weeks’ gestation and had bacterial meningitis was 477/mm<sup>3</sup>.<sup>43</sup> In contrast, the median number of white blood cells in infants who were born at less than 34 weeks’ gestation and had meningitis was 110/mm<sup>3</sup>.<sup>51</sup> Infants with meningitis attributable to Gram-negative pathogens typically have higher CSF white blood cell counts than do infants with meningitis attributable to Gram-positive pathogens.<sup>52</sup> Adjusting the CSF white blood cell count for the number of red blood cells does not improve the diagnostic utility (loss of sensitivity with marginal gain in specificity).<sup>53</sup> In addition, the number of bands in a CSF specimen does not predict meningitis.<sup>54</sup> With a delay in analysis ( $>2$  hours), white blood cell counts and glucose concentrations decrease significantly.<sup>55</sup>

Protein concentrations in uninfected, term newborn infants are  $<100$  mg/dL.<sup>44–50</sup> Preterm infants have CSF protein concentrations that vary inversely with gestational age. In the normoglycemic newborn infant, glucose concentrations in CSF are similar to those in older infants and children (70%–80% of a simultaneously obtained blood specimen). A low glucose concentration is the CSF variable with the greatest specificity for the diagnosis of meningitis.<sup>43,51</sup> Protein concentrations are higher and glucose concentrations are lower in term than in preterm infants with meningitis. However, meningitis occurs in infants with normal CSF values, and some of these infants have high bacterial inocula.<sup>43,51</sup>

## Peripheral White Blood Cell Count and Differential Count

Total white blood cell counts have little value in the diagnosis of early-onset sepsis and have a poor positive predictive accuracy.<sup>56,57</sup> Many investigators have analyzed subcomponents of the white blood cell count (neutrophil indices)—absolute neutrophil count, absolute band count, and immature to total neutrophil (I/T) ratio—to identify infected infants. Like most diagnostic tests for neonatal sepsis, neutrophil indices have proven most useful for excluding infants without infection rather than identifying infected neonates. Neutropenia may be a better marker for neonatal sepsis and has better specificity than an elevated neutrophil count, because few conditions besides sepsis (maternal pregnancy-induced hypertension, asphyxia, and hemolytic disease) depress the neutrophil count of neonates.<sup>58</sup> The definitions for neutropenia vary with gestational age,<sup>58–61</sup> type of delivery (infants born by cesarean delivery without labor have lower counts than infants delivered vaginally),<sup>61</sup> site of sampling (neutrophil counts are lower in samples from arterial blood),<sup>62</sup> and altitude (infants born at elevated altitudes have higher total neutrophil counts).<sup>63</sup> In late preterm and term infants, the definition for neutropenia most commonly used is that suggested by Manroe et al (<1800/mm<sup>3</sup> at birth and <7800/mm<sup>3</sup> at 12–14 hours of age).<sup>58</sup> Schmutz et al reinvestigated these reference ranges using modern cell-counting instrumentation in 30 254 infants born at 23 to 42 weeks' gestation.<sup>61</sup> Infants with diagnoses known to affect neutrophil counts (eg, those born to women with pregnancy-induced hypertension or those with early-onset sepsis) were excluded. In this study, the lower limits of normal for neutrophil values at birth were 3500/mm<sup>3</sup> in infants born at >36 weeks' gestation, 1000/mm<sup>3</sup> in infants born at

28 through 36 weeks' gestation, and 500/mm<sup>3</sup> in infants born at <28 weeks' gestation. Peak values occurred at 6 to 8 hours after birth; the lower limits of normal at that time were 7500/mm<sup>3</sup>, 3500/mm<sup>3</sup>, and 1500/mm<sup>3</sup> for infants born at >36 weeks' gestation, 28 to 36 weeks' gestation, and <28 weeks' gestation, respectively.<sup>61</sup> It is noteworthy that the study by Schmutz et al was performed at 4800 feet above sea level, whereas that of Manroe et al was performed at 500 feet above sea level.

The absolute immature neutrophil count follows a similar pattern to the absolute neutrophil count and peaks at approximately 12 hours of life. The number of immature neutrophils increases from a maximal value of 1100 cells/mm<sup>3</sup> at birth to 1500 cells/mm<sup>3</sup> at 12 hours of age.<sup>58</sup> Absolute immature counts have a poor sensitivity and positive predictive accuracy for early-onset sepsis.<sup>22</sup> Furthermore, if exhaustion of bone marrow reserves occurs, the number of immature forms will remain depressed.<sup>64</sup>

The I/T ratio has the best sensitivity of any of the neutrophil indices. However, with manual counts, there are wide interreader differences in band neutrophil identification.<sup>65</sup> The I/T ratio is <0.22 in 96% of healthy preterm infants born at <32 weeks' gestational age.<sup>66</sup> Unlike the absolute neutrophil count and the absolute band count, maximum normal values for the I/T ratio occur at birth (0.16) and decline with increasing postnatal age to a minimum value of 0.12.<sup>58</sup> In healthy term infants, the 90th percentile for the I/T ratio is 0.27.<sup>59</sup> A single determination of the I/T ratio has a poor positive predictive accuracy (approximately 25%) but a very high negative predictive accuracy (99%).<sup>66</sup> The I/T ratio may be elevated in 25% to 50% of uninfected infants.<sup>67</sup>

Exhaustion of bone marrow reserves will result in low band counts and lead to falsely low ratios. The timing of the white blood cell count is critical.<sup>68</sup>

Counts obtained 6 to 12 hours after birth are more likely to be abnormal than are counts obtained at birth, because alterations in the numbers (and ratios) of mature and immature neutrophils require an established inflammatory response. Therefore, once the decision is made to start antimicrobial therapy soon after birth, it is worth waiting 6 to 12 hours before ordering a white blood cell count and differential count.<sup>68,69</sup>

## Platelet Counts

Despite the frequency of low platelet counts in infected infants, they are a nonspecific, insensitive, and late indicator of sepsis.<sup>70,71</sup> Moreover, platelet counts are not useful to follow clinical response to antimicrobial agents, because they often remain depressed for days to weeks after a sepsis episode.

## Acute-Phase Reactants

A wide variety of acute-phase reactants have been evaluated in neonates with suspected bacterial sepsis. However, only C-reactive protein (CRP) and procalcitonin concentrations have been investigated in sufficiently large studies.<sup>72,73</sup> CRP concentration increases within 6 to 8 hours of an infectious episode in neonates and peaks at 24 hours.<sup>74,75</sup> The sensitivity of a CRP determination is low at birth, because it requires an inflammatory response (with release of interleukin-6) to increase CRP concentrations.<sup>76</sup> The sensitivity improves dramatically if the first determination is made 6 to 12 hours after birth. Benitz et al have demonstrated that excluding a value at birth, 2 normal CRP determinations (8–24 hours after birth and 24 hours later) have a negative predictive accuracy of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis.<sup>76</sup> If CRP determinations remain persistently normal, it is strong evidence that bacterial sepsis is unlikely, and antimicrobial agents can be safely discontinued. Data are insufficient to recommend following sequential CRP



concentrations to determine the duration of antimicrobial therapy in an infant with an elevated value ( $\geq 1.0$  mg/dL).

Procalcitonin concentrations increase within 2 hours of an infectious episode, peak at 12 hours, and normalize within 2 to 3 days in healthy adult volunteers.<sup>77</sup> A physiologic increase in procalcitonin concentration occurs within the first 24 hours of birth, and an increase in serum concentrations can occur with noninfectious conditions (eg, respiratory distress syndrome).<sup>78</sup> Procalcitonin concentration has a modestly better sensitivity than does CRP concentration but is less specific.<sup>73</sup> Chiesa and colleagues have published normal values for procalcitonin concentrations in term and preterm infants.<sup>79</sup> There is evidence from studies conducted in adult populations, the majority of which focused on patients with sepsis in the ICU, that significant reductions in use of antimicrobial agents can be achieved in patients whose treatment is guided by procalcitonin concentration.<sup>80</sup>

### Sepsis Screening Panels

Hematologic scoring systems using multiple laboratory values (eg, white blood cell count, differential count, and platelet count) have been recommended as useful diagnostic aids. No matter what combination of tests is used, the positive predictive accuracy of scoring systems is poor unless the score is very high. Rodwell et al described a scoring system in which a score of 1 was assigned to 1 of 7 findings, including abnormalities of leukocyte count, total neutrophil count, increased immature polymorphonuclear leukocyte (PMN) count, increased I/T ratio, immature to mature PMN ratio  $>0.3$ , platelet count  $\leq 150\,000/\text{mm}^3$ , and pronounced degenerative changes (ie, toxic granulations) in PMNs.<sup>81</sup> In this study, two-thirds of preterm infants and 90% of term infants with a hematologic score  $\geq 3$  did not have proven sepsis.<sup>81</sup>

Furthermore, scores obtained in the first several hours after birth have been shown to have poorer sensitivity and negative predictive value than scores obtained at 24 hours of age.<sup>67</sup> Sepsis screening panels commonly include neutrophil indices and acute-phase reactants (usually CRP concentration). The positive predictive value of the sepsis screen in neonates is poor ( $<30\%$ ); however, the negative predictive accuracy has been high ( $>99\%$ ) in small clinical studies.<sup>22</sup> Sepsis screening tests might be of value in deciding which “high-risk” healthy-appearing neonates do not need antimicrobial agents or whether therapy can be safely discontinued.

### TREATMENT OF INFANTS WITH SUSPECTED EARLY-ONSET SEPSIS

In the United States, the most common pathogens responsible for early-onset neonatal sepsis are GBS and *Escherichia coli*.<sup>17</sup> A combination of ampicillin and an aminoglycoside (usually gentamicin) is generally used as initial therapy, and this combination of antimicrobial agents also has synergistic activity against GBS and *Listeria monocytogenes*.<sup>82,83</sup> Third-generation cephalosporins (eg, cefotaxime) represent a reasonable alternative to an aminoglycoside. However, several studies have reported rapid development of resistance when cefotaxime has been used routinely for the treatment of early-onset neonatal sepsis,<sup>84</sup> and extensive/prolonged use of third-generation cephalosporins is a risk factor for invasive candidiasis.<sup>85</sup> Because of its excellent CSF penetration, empirical or therapeutic use of cefotaxime should be restricted for use in infants with meningitis attributable to Gram-negative organisms.<sup>86</sup> Ceftriaxone is contraindicated in neonates because it is highly protein bound and may displace bilirubin, leading to a risk of kernicterus. Bacteremia without an identifiable focus of infection is generally treated for 10 days.<sup>87</sup> Uncomplicated

meningitis attributable to GBS is treated for a minimum of 14 days.<sup>88</sup> Other focal infections secondary to GBS (eg, cerebritis, osteomyelitis, endocarditis) are treated for longer durations.<sup>88</sup> Gram-negative meningitis is treated for minimum of 21 days or 14 days after obtaining a negative culture, whichever is longer.<sup>88</sup> Treatment of Gram-negative meningitis should include cefotaxime and an aminoglycoside until the results of susceptibility testing are known.<sup>87,88</sup>

The duration of antimicrobial therapy in infants with negative blood cultures is controversial. Many women receive antimicrobial agents during labor as prophylaxis to prevent early-onset GBS infections or for management of suspected intra-amniotic infection or PPRM. In those instances, postnatal blood cultures may be sterile (false negative). When considering the duration of therapy in infants with negative blood cultures, the decision should include consideration of the clinical course as well as the risks associated with longer courses of antimicrobial agents. In a retrospective study by Cordero and Ayers, the average duration of treatment in 695 infants ( $<1000$  g) with negative blood cultures was  $5 \pm 3$  days.<sup>89</sup> Cotten et al have suggested an association with prolonged administration of antimicrobial agents ( $>5$  days) in infants with suspected early-onset sepsis (and negative blood cultures) with death and necrotizing enterocolitis.<sup>90</sup> Two recent papers also support this association.<sup>91,92</sup>

### PREVENTION STRATEGIES FOR EARLY-ONSET SEPSIS

The only intervention proven to decrease the incidence of early-onset neonatal sepsis is maternal treatment with intrapartum intravenous antimicrobial agents for the prevention of GBS infections.<sup>93</sup> Adequate prophylaxis is defined as penicillin (the preferred agent), ampicillin, or cefazolin given for

≥4 hours before delivery. Erythromycin is no longer recommended for prophylaxis because of high resistance rates. In parturients who have a nonserious penicillin allergy, cefazolin is the drug of choice. For parturients with a history of serious penicillin allergy (anaphylaxis, angioedema, respiratory compromise, or urticaria), clindamycin is an acceptable alternative agent, but only if the woman's rectovaginal GBS screening isolate has been tested and documented to be susceptible. If the clindamycin susceptibility is unknown or the GBS isolate is resistant to clindamycin, vancomycin is an alternative agent for prophylaxis. However, neither clindamycin nor vancomycin has been evaluated for efficacy in preventing early-onset GBS sepsis in neonates. Intrapartum antimicrobial agents are indicated for the following situations<sup>93</sup>:

1. Positive antenatal cultures or molecular test at admission for GBS (except for women who have a cesarean delivery without labor or membrane rupture)
2. Unknown maternal colonization status with gestation <37 weeks, rupture of membranes >18 hours, or temperature >100.4°F (>38°C)
3. GBS bacteriuria during the current pregnancy
4. Previous infant with invasive GBS disease

Management guidelines for the newborn infant have been published<sup>93</sup> and are available online (<http://www.cdc.gov/groupbstrep/guidelines/index.html>).

## CLINICAL CHALLENGES

### Challenge 1: Identifying Neonates With Clinical Signs of Sepsis With a “High Likelihood” of Early-Onset Sepsis Who Require Antimicrobial Agents Soon After Birth

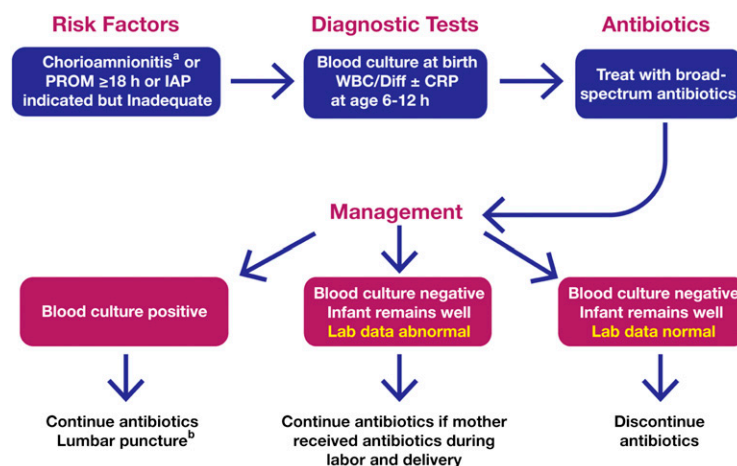
Most infants with early-onset sepsis exhibit abnormal signs in the first 24

hours of life. Approximately 1% of infants will appear healthy at birth and then develop signs of infection after a variable time period.<sup>21</sup> Every critically ill infant should be evaluated and receive empirical broad-spectrum antimicrobial therapy after cultures, even when there are no obvious risk factors for sepsis. The greatest difficulty faced by clinicians is distinguishing neonates with early signs of sepsis from neonates with noninfectious conditions with relatively mild findings (eg, tachypnea with or without an oxygen requirement). In this situation, data are insufficient to guide management. In more mature neonates without risk factors for infection who clinically improve over the first 6 hours of life (eg, need for oxygen is decreasing and respiratory distress is resolving), it is reasonable to withhold antimicrobial therapy and monitor the neonates closely. The 6-hour window should not be considered absolute; however, most infants without infection demonstrate some improvement over that time period. Any worsening of the infant's condition should prompt

starting antimicrobial agents after cultures have been obtained.

### Challenge 2: Identifying Healthy-Appearing Neonates With a “High Likelihood” of Early-Onset Sepsis Who Require Antimicrobial Agents Soon After Birth

This category includes infants with 1 of the risk factors for sepsis noted previously (colonization with GBS, prolonged rupture of membranes >18 hours, or maternal chorioamnionitis). GBS is not a risk factor if the mother has received adequate intrapartum therapy (penicillin, ampicillin, or cefazolin for at least 4 hours before delivery) or has a cesarean delivery with intact membranes in the absence of labor.<sup>93</sup> The risk of infection in the newborn infant varies considerably with the risk factor present. The greatest risk of early-onset sepsis occurs in infants born to women with chorioamnionitis who are also colonized with GBS and did not receive intrapartum antimicrobial agents. Early-onset sepsis does occur in infants who appear healthy at birth.<sup>21</sup> Therefore,



**FIGURE 1**

Evaluation of asymptomatic infants <37 weeks' gestation with risk factors for sepsis. <sup>a</sup>The diagnosis of chorioamnionitis is problematic and has important implications for the management of the newborn infant. Therefore, pediatric providers are encouraged to speak with their obstetrical colleagues whenever the diagnosis is made. <sup>b</sup>Lumbar puncture is indicated in any infant with a positive blood culture or in whom sepsis is highly suspected on the basis of clinical signs, response to treatment, and laboratory results. IAP, intrapartum antimicrobial prophylaxis; WBC, white blood cell; Diff, differential white blood cell count.

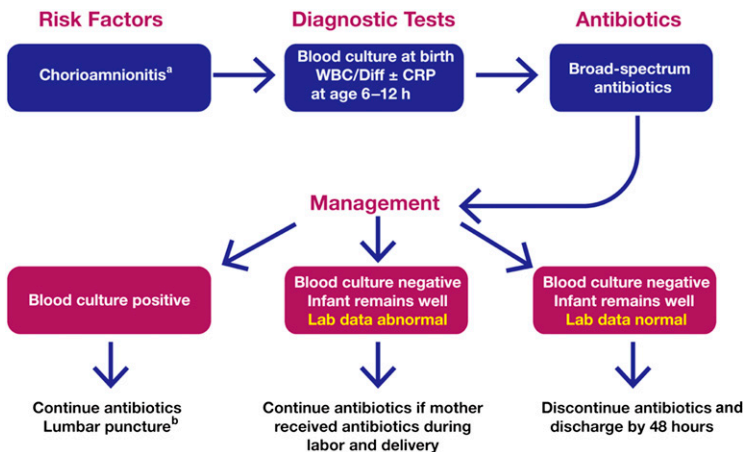
some clinicians use diagnostic tests with a high negative predictive accuracy as reassurance that infection is not present (allowing them to withhold antimicrobial agents). The decision of whether to treat a high-risk infant depends on the risk factors present, the frequency of observations, and gestational age. The threshold for

initiating antimicrobial treatment generally decreases with increasing numbers of risk factors for infection and greater degrees of prematurity. Suggested algorithms for management of healthy-appearing, high-risk infants are shown in Figs 1, 2, and 3. Screening blood cultures have not been shown to be of value.<sup>21</sup>

## CONCLUSIONS

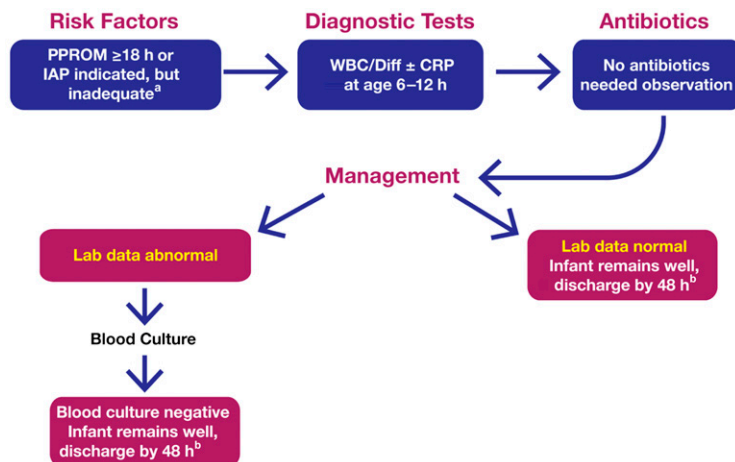
The diagnosis and management of neonates with suspected early-onset sepsis are based on scientific principles modified by the “art and experience” of the practitioner. The following are well-established concepts related to neonatal sepsis:

1. Neonatal sepsis is a major cause of morbidity and mortality.
2. Diagnostic tests for early-onset sepsis (other than blood or CSF cultures) are useful for identifying infants with a low probability of sepsis but not at identifying infants likely to be infected.
3. One milliliter of blood drawn before initiating antimicrobial therapy is needed to adequately detect bacteremia if a pediatric blood culture bottle is used.
4. Cultures of superficial body sites, gastric aspirates, and urine are of no value in the diagnosis of early-onset sepsis.
5. Lumbar puncture is not needed in all infants with suspected sepsis (especially those who appear healthy) but should be performed for infants with signs of sepsis who can safely undergo the procedure, for infants with a positive blood culture, for infants likely to be bacteremic (on the basis of laboratory data), and infants who do not respond to antimicrobial therapy in the expected manner.
6. The optimal treatment of infants with suspected early-onset sepsis is broad-spectrum antimicrobial agents (ampicillin and an aminoglycoside). Once the pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed).
7. Antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low.



**FIGURE 2**

Evaluation of asymptomatic infants  $\geq 37$  weeks' gestation with risk factors for sepsis. <sup>a</sup>The diagnosis of chorioamnionitis is problematic and has important implications for the management of the newborn infant. Therefore, pediatric providers are encouraged to speak with their obstetrical colleagues whenever the diagnosis is made. <sup>b</sup>Lumbar puncture is indicated in any infant with a positive blood culture or in whom sepsis is highly suspected on the basis of clinical signs, response to treatment, and laboratory results. WBC, white blood cell; Diff, differential white blood cell count.



**FIGURE 3**

Evaluation of asymptomatic infants  $\geq 37$  weeks' gestation with risk factors for sepsis (no chorioamnionitis). <sup>a</sup>Inadequate treatment: Defined as the use of an antibiotic other than penicillin, ampicillin, or cefazolin or if the duration of antibiotics before delivery was  $< 4$  h. <sup>b</sup>Discharge at 24 h is acceptable if other discharge criteria have been met, access to medical care is readily accessible, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 h and until discharge criteria are achieved. IAP, intrapartum antimicrobial prophylaxis; WBC, white blood cell; Diff, differential white blood cell count.



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## Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis

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