Case Based Teaching – Sepsis
St. Joseph’s CTU

Objectives:

Medical Expert:
1. Review the different causes of sepsis in a newborn
2. Understand the indications and interpretation of investigations for sepsis
3. Review the initial investigations to come to a diagnosis
4. Understand the choice of antibiotics

Communicator:
1. Learn how to explain to parents why the team is concerned about infection
2. Learn the information needed to counsel around the impact of treatment for sepsis in the case of culture negative and culture positive sepsis.

Resources:

Case Review:
- 39 5/7 week gestational infant
- Born to 37 G3T1A1L1 mother
- VDRL, Hep B, HIV GBS neg
- O +ve Rubella immune
- Normal antenatal US, No blood sugar or blood pressure issues
- Induced for unstable lie
- ROM for 13 hrs
- SVD
- APGARS 9, 9
- BW 3400 grams
- Cord gas
- Art 7.16/66/19/24
- Ven 7.28/40/46/19
  - 12 hrs later (midnight) call from NCR to peds.
  - Pt was born after they completed rounds and had not yet had newborn exam
  - Nurses called with tachypnea that developed at 10hrs of age
  - RR reported to be 80
  - Infant feeding well

On exam:
  - RR 84 no indrawing, HR 140 SpO2 99%
  - Occasional grunt
  - Infant responsive good tone
  - Good cap refill
  - No murmur normal femoral pulses
  - Good air entry no extra sounds

Discussion
  Is this a normal respiratory rate?
  What is your differential diagnosis at this time?
  What tests if any would you order?

Case
  CBC ordered at 0100, clotted times two
  Now 3 a.m. infant still grunting HR 180's BP 68/32 MAP 40 SPO2 95% caprefill 3-5 sec.

Discussion
  What would you do now?
  If you decided to start antibiotics which would you choose?
  What are the most common organisms that cause sepsis in neonates?
  Would your antibiotic choice be different if this infant was in the NICU for the past 7 days?
  How do you calculate the IT ratio? What is the significance of the IT ratio?
  Would you order a CRP?, How do you interpret the CRP?
  What is your interpretation of the blood gas? What intervention if any would you consider with the physical exam findings?

Results:

<p>| CORRECTED LKCS | 3.7 | X10 9/L |
| Corrected Leukocyte count appears when the Nucleated Erythrocyte count is greater than 5. |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LKCS</td>
<td>4.2</td>
<td>L 5.0-21.0 x10 9/L</td>
</tr>
<tr>
<td>ERCS</td>
<td>4.44</td>
<td>4.0-6.6 x10 12/L</td>
</tr>
<tr>
<td>HB</td>
<td>169</td>
<td>145-225 g/L</td>
</tr>
<tr>
<td>HCT</td>
<td>0.479</td>
<td>0.450-0.670</td>
</tr>
<tr>
<td>MCV</td>
<td>107.9</td>
<td>95-121 fL</td>
</tr>
<tr>
<td>MCH</td>
<td>38.1</td>
<td>28-40 pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>353</td>
<td>290-360 g/L</td>
</tr>
<tr>
<td>RDW</td>
<td>16.3</td>
<td>H 11.5-15.0 %</td>
</tr>
<tr>
<td>PLT</td>
<td>150</td>
<td>150-400 x10 9/L</td>
</tr>
<tr>
<td>MPV</td>
<td>8.4</td>
<td>7.4-10.4 fL</td>
</tr>
<tr>
<td>SMEAR EXAMINE</td>
<td>Blood film made</td>
<td></td>
</tr>
<tr>
<td>MANUAL DIFF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NERCS</td>
<td>14</td>
<td>/100 LKC</td>
</tr>
<tr>
<td>ABSOLUTE BANDS</td>
<td>0.8</td>
<td>x10 9/L</td>
</tr>
<tr>
<td>ABSOLUTE NEUTS</td>
<td>0.9</td>
<td>L 1.5-10.0 x10 9/L</td>
</tr>
<tr>
<td>ABSOLUTE LYMPHES</td>
<td>1.6</td>
<td>L 2.0-17.0 x10 9/L</td>
</tr>
<tr>
<td>ABSOLUTE MONOS</td>
<td>0.1</td>
<td>L 0.5-1.9 x10 9/L</td>
</tr>
<tr>
<td>ABSOLUTE MYELOS</td>
<td>0.1</td>
<td>x10 9/L</td>
</tr>
<tr>
<td>ABSOLUTE METAS</td>
<td>0.2</td>
<td>x10 9/L</td>
</tr>
</tbody>
</table>

CRP 40.8
Blood gas 7.18/46/47/17/-11
- Blood GBS positive after 7 hrs
- CSF done June 18th
  - BS 5.9 mmol/L
  - Protein 2.28 g/L
  - Leuks 3248
  - RBC 4
- Gram Stain Pus cells Gram positive Cocci
- CSF culture neg
Take Home Messages:

• No Risk factors does not mean no chance of infection
• Don’t rely on labs to make clinical decisions
• Be wary of respiratory rates that are normal at birth and increase subsequently
• Review the importance of doing a full septic workup in the case of suspected sepsis.
Diagnostic tests in neonatal sepsis
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Purpose of review
The present review examines the major developments in early detection of neonatal sepsis, with an emphasis on the utility of diagnostic laboratory markers in clinical practice.

Recent findings
Measures of acute phase proteins, cytokines, cell surface antigens, and bacterial genomes have been used alone or in combination to improve diagnosis of neonatal sepsis. Most studies evaluating laboratory diagnostic markers are retrospective cohorts or single center experience with relatively small sample size. Interpretation of these studies is confounded by inconsistent definitions of sepsis, heterogeneous sample populations, and different thresholds for diagnostic markers. Furthermore, many diagnostic markers are not available for routine care, they require specialized analytical procedures, and are expensive to perform.

Summary
A better understanding of the neonatal inflammatory response to sepsis and identification of sensitive and specific markers of inflammation or rapid microbe-specific diagnostic tests would assist in the early detection of neonatal sepsis and in safely withholding antibiotics for patients in whom sepsis is unlikely.

Keywords
acute phase reactant, cell surface antigens, cytokines, neonatal sepsis, polymerase chain reaction

Introduction
The diagnosis of sepsis in infants is difficult because clinical signs, particularly early in the course of disease, are subtle and nonspecific, and laboratory tests including blood culture, the 'gold standard', are not always reliable [1]. Clinicians have long sought reliable markers to detect sepsis early in its course and to exclude diseases of noninfectious origin [2–4]. Recent studies propose new diagnostic laboratory markers used alone or in combination to improve sensitivity and specificity for early detection of sepsis.

Clinical and laboratory scores
The clinical signs of neonatal sepsis are nonspecific. Fanaroff \textit{et al.} [5] with the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network found that increasing apnea, feeding intolerance, abdominal distension or heme-positive stools, increased respiratory support, lethargy, and hypotonia were the most common presenting signs of late onset sepsis (LOS). None was found to have high predictive accuracy [5]. However, many neonatologists, particularly those practicing in clinical settings with limited resources, use clinical judgment or scores combined with complete blood count (CBC) and blood cultures for the detection of neonatal sepsis [6,7]. Components of the CBC that may become abnormal in sepsis have a positive predictive value (PPV) as low as 11% [1]. This may be explained by inter-observer variability in immature and mature neutrophil identification [8], factors other than sepsis that cause abnormalities of the CBC, and timing of the CBC that is often normal at the time of initial evaluation but abnormal a few hours later. Okascharoen \textit{et al.} [6] devised and tested a scoring system for the diagnosis of LOS in preterm infants composed of the following five clinical indicators: hypotension, hypothermia, hyperthermia, respiratory insufficiency, and umbilical venous catheters between 1 and 7 days or more than 7 days; and the two following hematological parameters: immature neutrophil count more than 1% and platelet count less than 150 000/ml\textsuperscript{3}. The clinical score had an acceptable predictive performance [PPV 43%, negative predictive value (NPV) 96%] but was no better than the clinicians’ estimate of LOS risk. The addition of C-reactive protein (CRP) and micro erythrocyte sedimentation rate (mESR) to a clinical score in detecting LOS had a high sensitivity (95%) but a low specificity (18%). The positive likelihood ratio (a measure of predictive value that is independent of prevalence) was 1.61 (Table 1) [7,9–19].
A recent advance in the diagnosis of neonatal sepsis is heart rate characteristic (HRC) that monitors the presence of reduced variability and transient decelerations, which occur with increased frequency in the preclinical phases of septicemia [20,21,22,23]. The HRC index demonstrated a significant association with both blood culture proven sepsis and clinical LOS in neonates. The odds ratio for the prediction of neonatal sepsis with high HRC index was more than two. Both the clinical score and the HRC index rose before the clinical diagnosis of illness, with HRC being first [21]. This noninvasive and inexpensive index has the advantage of being available through continuous electrocardiogram monitoring and can add information to conventional measures in the early diagnosis of neonatal sepsis [23]. There is currently a large, multicenter randomized controlled trial underway to evaluate the impact of HRC monitoring on initiation of timing of treatment for sepsis and infection-related morbidities [impact of heart rate characteristics monitoring in neonates (HeRO)3. ClinicalTrials.gov Identifier: NCT00307333].

Acute phase reactants

Acute phase reactants are endogenous peptides produced by the liver as part of an immediate response to infection or tissue injury. The most widely used in neonates is CRP [24–27]. Given that there is a time lag of 12–24 h in the response of CRP to infection, some clinicians use it in combination with another serum marker such as interleukins [26,27]. The specificity of CRP is low for early onset sepsis (EOS), as a number of prenatal conditions (maternal fever, fetal distress or stressful delivery, and vacuum delivery) may lead to its elevation in the absence of systemic infection. Recent studies, using CRP cutoff values of 1.2–6 mg/dl to diagnose sepsis and guide duration of therapy in EOS and LOS, showed specificity between 84–96% and a NPV range of 93–99%. The clinical practice of using higher CRP cutoff values led to fewer days of antibiotics without an evidence of infection relapse [24,25,27].

Procalcitonin (PCT) is an acute phase reactant produced by monocytes and hepatocytes. PCT begins to rise 4 h after exposure to bacterial endotoxin, peaks at six to eight, and remains elevated for at least 24 h [28]. In adults, it has been used for almost a decade to diagnose the severity of systemic inflammatory response, to determine the progression of infection to sepsis and septic shock, to assess responsiveness to treatment, and to estimate prognosis [28]. A number of recent studies of preterm infants confirmed that PCT compared with CRP and proinflammatory cytokines had equivalent or better sensitivity for diagnosis of LOS, but with lower values of NPV and likelihood ratio [9–11,29] (Table 1). A recent study showed that PCT had a lower diagnostic utility (sensitivity 81.4%, specificity 80.6%) at the time of suspicion of sepsis. Therefore, PCT is not sufficiently reliable to be the sole marker of LOS, but may be useful as part of an evaluation for sepsis in a neonate [11]. The diagnostic utility of PCT in EOS is limited by its rapid physiological postnatal endogenous increase [30,31]. For this reason, age-related nomograms of PCT values were proposed during the first days of life [30]. In summary, PCT level is elevated during EOS and LOS and its overall diagnostic utility is comparable with CRP.

Serum amyloid A (SAA) is an acute phase protein induced by the inflammatory cytokines IL-1 and IL-6, and tumor necrosis factor (TNF)-α in response to lipopolysaccharide (LPS) gram-negative bacteria infection. There is a robust increase in SAA levels from 8 to 24 h after the onset of sepsis. Arnon et al. [12] showed that SAA had a better diagnostic accuracy than CRP at septic evaluation in EOS (~5 h after birth) (Table 1). However, vaginal delivery

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**Table 1 Accuracy of diagnostic tests at the time of sepsis evaluation**

<table>
<thead>
<tr>
<th>Diagnostic test [reference]</th>
<th>No. of patients</th>
<th>No. of infected patients</th>
<th>EOS/LOS</th>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Positive LR</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical+CBC+CRP+ mESR [7]</td>
<td>220</td>
<td>60</td>
<td>LOS</td>
<td>NA</td>
<td>95</td>
<td>1.61</td>
<td>91</td>
</tr>
<tr>
<td>IL-6+CRP [9]</td>
<td>92</td>
<td>37</td>
<td>LOS</td>
<td>60 pg/ml, 1.4 mg/dl</td>
<td>92</td>
<td>1.56</td>
<td>90</td>
</tr>
<tr>
<td>PCT+CRP [10]</td>
<td>85</td>
<td>29</td>
<td>LOS</td>
<td>0.5 µg/l, 1 mg/dl</td>
<td>93</td>
<td>1.18</td>
<td>80</td>
</tr>
<tr>
<td>PCT [11]</td>
<td>100</td>
<td>61</td>
<td>LOS</td>
<td>0.59 µg/l</td>
<td>81</td>
<td>4.26</td>
<td>72</td>
</tr>
<tr>
<td>SAA [12]</td>
<td>104</td>
<td>23</td>
<td>EOS</td>
<td>0.8 mg/dl</td>
<td>96</td>
<td>19</td>
<td>99</td>
</tr>
<tr>
<td>CRP [13]</td>
<td>116</td>
<td>42</td>
<td>LOS</td>
<td>1 mg/dl</td>
<td>32</td>
<td>10.6</td>
<td>74</td>
</tr>
<tr>
<td>SAA [13]</td>
<td>116</td>
<td>42</td>
<td>LOS</td>
<td>1 mg/dl</td>
<td>95</td>
<td>13.5</td>
<td>97</td>
</tr>
<tr>
<td>CRP [14]</td>
<td>25</td>
<td>8</td>
<td>EOS</td>
<td>2.1 mg/dl</td>
<td>98</td>
<td>99.9</td>
<td>96</td>
</tr>
<tr>
<td>LPB [14]</td>
<td>25</td>
<td>8</td>
<td>EOS</td>
<td>21.5 mg/l</td>
<td>100</td>
<td>16.6</td>
<td>100</td>
</tr>
<tr>
<td>LPB [14]</td>
<td>22</td>
<td>8</td>
<td>EOS</td>
<td>17.1 mg/l</td>
<td>92</td>
<td>8.3</td>
<td>97</td>
</tr>
<tr>
<td>CRP [15]</td>
<td>338</td>
<td>115</td>
<td>EOS</td>
<td>6136 antibody PE molecules bound/cell</td>
<td>79</td>
<td>7.18</td>
<td>93</td>
</tr>
<tr>
<td>CD64 [16]</td>
<td>110</td>
<td>32</td>
<td>LOS</td>
<td>4000 antibody PE molecules bound/cell</td>
<td>95</td>
<td>12</td>
<td>97</td>
</tr>
<tr>
<td>IL-8 [17]</td>
<td>249</td>
<td>61</td>
<td>EOS</td>
<td>18,000 pg/ml</td>
<td>97</td>
<td>19.4</td>
<td>99</td>
</tr>
<tr>
<td>IL-8+CRP [18]</td>
<td>1291</td>
<td>13</td>
<td>EOS</td>
<td>70 pg/ml, 1 mg/dl</td>
<td>80</td>
<td>6.15</td>
<td>93</td>
</tr>
<tr>
<td>PCR, 16S rRNA [19]</td>
<td>172</td>
<td>8</td>
<td>LOS</td>
<td>NA</td>
<td>100</td>
<td>50</td>
<td>98</td>
</tr>
</tbody>
</table>

CBC, complete blood count; CRP, C-reactive protein; EOS, early onset sepsis; IL, interleukin; LPB, lipopolysaccharide-binding protein; LOS, late onset sepsis; LR, likelihood ratio; mESR, micro erythrocyte sedimentation rate; NA, not available; NPV, negative predictive value; PCR, polymerase chain reaction; PCT, procalcitonin; PE, phycoerythrin; rRNA, ribosomal ribonucleic acid; SAA, serum amyloid A.

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that produces a transient elevation of SAA levels, even higher than the cutoff point for the detection of sepsis [32], might affect the diagnostic accuracy of SAA in EOS. The same group of investigators showed that SAA levels during LOS had a high sensitivity and NPV, suggesting it may be a superior marker compared with CRP [13] (Table 1). Recently, rapid SAA measurement has been facilitated by the development of a fully automated kit that required no specialized instrumentation and can be done in any service laboratory [12].

Lipopoly saccharide-binding protein (LBP), a 50-kDa acute-phase protein, is mainly synthesized in the liver. It binds with high affinity to LPS in the plasma, transfers LPS to membrane bound or soluble CD14, and modulates the microbial-induced activation of the inflammatory host response [33]. It was recently reported that LBP has a better sensitivity and specificity for detecting sepsis than LPS-soluble, CD14 complexes, and PCT in EOS, but equally effective to CRP in detecting sepsis of infants older than 48 h [14] (Table 1).

A number of acute phase proteins including α1-antitrypsin, fibronectin, haptoglobin, lactoferrin, neopterin, inter-α inhibitor proteins (Iαp), granulocyte colony stimulating factor (G-CSF), orosomucoid, and antithrombin have been evaluated in relation to neonatal sepsis [34]. Although these acute phase proteins may be candidate biomarkers for sepsis, none has been routinely used clinically or studied on a large scale.

Cell surface antigens

In recent years, flow cytometric analysis of cell surface antigens [CD11b, Fcy receptors I-II (CD64, CD32, and CD16), CD69] has been performed to detect congenital sepsis, EOS, and LOS [15,16,35]. For detection of EOS, CD64 was shown to have a sensitivity of 81% and a NPV of 89% [15] (Table 1). Twenty-four hours after onset of sepsis, the sensitivity and NPV rose to 96 and 97%, respectively. A large cohort study, assessing two neutrophil (CD11b and CD64) and two lymphocyte surface markers (CD25 and CD45RO) for the diagnosis of LOS, showed that CD64 had the highest sensitivity (95–97%) and specificity (88–90%) for detecting sepsis at the onset of infection and 24 h later [16] (Table 1). Combining CD64 with IL-6 or CRP further enhanced the ability to diagnose localized infections and improved the sensitivity and NPV to 100% [31]. In response to infection, preterm infants increase cell numbers of lymphocyte populations (CD3, CD19, CD25, CD26, and CD71) and human leukocyte antigen (HLA)-DR expression on monocytes, and upregulate neutrophil surface antigens (CD11b, CD11c, CD13, CD15, CD33, CD64, and CD66b) [35,36*]. However, to date, no cell surface markers alone or in combination have been tested and shown to be sensitive and specific enough to allow neonatologists to withhold antibiotic treatment in an infant with clinical signs suggestive of infection. Furthermore, analysis of cell surface markers in the clinical setting requires specialized equipment and qualified personnel. Blood specimens, must be processed immediately to avoid neutrophil apoptosis and downregulation of surface molecules [36*]. This limits the practical application of this technology in the clinical setting.

Chemokines and cytokines

The regulation and trafficking of leukocytes into specific body tissues are principally controlled by chemokines or cytokines, which are mainly divided into two subsets. Proinflammatory cytokines [IL-2, IL-6, interferon (IFN)γ, TNFα] that are primarily responsible for initiating an effective defense against exogenous pathogens and anti-inflammatory cytokines (IL-4 and IL-10) that are crucial for downregulating the exacerbated inflammatory process and maintaining homeostasis for proper functioning of vital organs. A study analyzing 127 episodes of suspected LOS in very low birth weight (VLBW) infants found both proinflammatory and anti-inflammatory cytokines significantly increased in infected infants compared with noninfected infants [37]. The very short half-life of circulating cytokines increases the risk of false negative results. For this reason, whole blood IL-8 (cell-bound and extracellular IL-8) [17] (Table 1) or cytokines combined with other more sustained markers of inflammation [9,38] have been suggested as a better diagnostic tool. A multicenter, randomized, controlled trial of 1291 infants suspected of EOS by at least one clinical sign showed that the use of IL-8 more than 70 pg/ml and/or CRP more than 10 mg/l to diagnose sepsis significantly reduced antibiotic therapy from 49.6 to 36.1% (P < 0.05) and increased the diagnostic utility of these markers [18] (Table 1). No infection was missed and no significant difference in the diagnostic accuracy was observed between the untreated group and the control group [18]. In VLBW infants with suspected sepsis, plasma IL-10 (>208 ng/l), IL-6 (>168 ng/l), and regulated upon activation normal T-cell expressed and secreted (RANTES) (<3110 ng/l) had sensitivity, specificity, PPV, and NPV of 100, 97, 85, and 100%, respectively, for identifying infected patients who subsequently developed disseminated intravascular coagulation [39]. Another recent study by the same group of researchers revealed that four markers of a panel of key chemokines and cytokines (IP-10, MIG, IL-6, IL-10) achieved a sensitivity of more than 80% and a specificity of more than 75%, for detecting sepsis for each tested marker. Among them, the IP-10 with a cutoff value of at least 1250 pg/ml exhibited the best sensitivity (93%) and specificity (89%) [40**]. Owing to the rapid decline of these inflammatory biomarkers after the onset of sepsis, 24 h measurements had lower predictive values.
Molecular biomarkers

Nucleic acid amplification tests such as PCR have been used successfully to diagnose a wide range of bacterial, yeast, viral, and protozoal infectious diseases. In recent years, PCR analysis has exploited the highly conserved bacterial 16S ribosomal ribonucleic acid (rRNA) gene to diagnose EOS and LOS. Shang et al. [19] used bacterial 16S rRNA gene PCR and DNA microarray analysis in 172 neonates with suspected sepsis and found a sensitivity of 100% and specificity of 97.8% (Table 1). Although the 16S rDNA PCR in near-term infants with EOS had high specificity (97.5%) and NPV (99.2%) compared with blood cultures, it failed to detect 59% of infants with positive blood culture (sensitivity 41%, PPV 19%) [42,43]. The use of staphylococcus-specific PCR to detect bloodstream infection had comparable specificity (94.7–100%) and NPV (95.4–98%) with inconsistent sensitivity of 57.1–69.2% and PPV of 53.3–100% [44,45]. The main advantage of PCR over blood cultures is that it is rapid (4–6 h versus ≥18 h, respectively) and requires small blood volume (0.2–0.3 ml versus 1 ml respectively). PCR amplification does require specialized instrumentation and training and it is not routinely available in many microbiology laboratories. A recent study [46] showed that approximately eight antibiotic doses and 85 neonatal intensive care unit (NICU) hours per infant could be saved using negative PCR results. Therefore, due to the high NPV of PCR methods, it may influence clinical practices and decision-making, leading to fewer antibiotic doses per patient and shorter hospital stay.

Proteomic biomarker of intra-amniotic inflammation

Recent advances in proteomics present a new opportunity to search for biomarkers and generation of protein profiles that can rapidly (1–3 h) aid in the prediction of amniotic fluid inflammation and early neonatal sepsis. The use of specific biomarkers to identify neonates with increased risk for sepsis in utero would aid in the initiation of appropriate therapy. Buhimschi et al. [47] showed that proteomic mapping of amniotic fluid, a profile designed as the mass restricted score, is highly characteristic of intra-amniotic inflammation. The profile comprised four protein biomarkers (neutrophil defensin-1 and neutrophil defensin-2, calgranulin A and C) that provide qualitative information (from a scale of 0–4 depending on the presence or absence of these 4 proteins) on the presence or absence of intra-amniotic inflammation. Furthermore, high mass restricted score (3–4) significantly correlated with suspected or confirmed EOS. The strongest association was for calgranulin A with a sensitivity, specificity, PPV, and NPV of 55, 80, 44, and 86%, respectively [48,49]. Although intriguing, these findings need to be validated in larger prospective studies of neonates suspected of having sepsis.

Conclusion

A better understanding of the neonatal inflammatory response to infection has led to the identification of multiple candidate biomarkers to improve diagnosis of sepsis. At present, no single biomarker or panel of biomarkers is sufficiently reliable for early detection of neonatal sepsis. Complicated analytical measurement further limits the utility of many biomarkers in clinical practice. The use of biomarkers as a diagnostic tool for the early discontinuation of empirical antibiotic treatment for infants with suspected sepsis is promising, but requires additional study.

Moorman JR, Lake DE, Griffin MP. Heart rate characteristics monitoring for neonatal sepsis and points out that the former is adjunctive and not a substitute for early diagnosis of bacterial infections in newborn infants. Pediatr Infect Dis J 2006; 25:946–952.


Summarizing the different flow cytometric markers to detect neonatal sepsis and their clinical and laboratory characteristics, the study stresses the role of cell surface antigens to stop antibiotics when the child is healthy and the lack of accuracy of these markers to withhold antibiotics when the child is sick and suspected of having sepsis.


A well designed study showing that preterm infants have the ability to induce a robust chemokine and cytokine response during sepsis, with IP-10 being a sensitive early marker of infection.


CLINICAL REPORT

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

abstract

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 (≥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! 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 ≤3 days of age.
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.2 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/mm³), 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%).3 Furthermore, most of these women with histologic chorioamnionitis do not have a positive placental culture.4 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.4 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).5 At term gestation, less than 1% of women with intact membranes will have organisms cultured from amniotic fluid.6 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).6 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%.7 Many of the pathogens recovered from amniotic fluid in women with preterm labor or PPROM (eg, Ureaplasma species or Mycoplasma species) do not cause early-onset sepsis.8–10 However, both Ureaplasma and Mycoplasma organisms can be recovered from the bloodstream of infants whose birth weight is less than 1500 g.11 When a pathogen (eg, GBS) is recovered from amniotic fluid, the attack rate of neonatal sepsis can be as high as 20%.12 Infants born to women with PPROM who are colonized with GBS have an estimated attack rate of 33% to 50% when intrapartum prophylaxis is not given.13

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.14–16 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.17 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.18

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,19,20 bacteremia can occur in the absence of clinical signs.21 Available diagnostic testing is not helpful in deciding which neonate requires empirical antimicrobial therapy but can assist with the decision to discontinue treatment.22

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.
from a peripheral vein. Furthermore, up to 25% of infants with sepsis have low colony count bacteremia (≤4 CFU/mL), and two-thirds of infants younger than 2 months of age have colony counts <10 CFU/mL. Neel et al demonstrated that more than half of blood specimens inoculated into the aerobic bottle were less than 0.5 mL. A study by Connell et al indicated that blood cultures with an adequate volume were twice as likely to yield a positive result. A blood culture obtained through an umbilical artery catheter shortly after placement yielded a contaminant is greater than 25% of infants with sepsis. Neal et al demonstrated that blood cultures with an adequate volume were twice as likely to yield a positive result. 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 the umbilical vein. The risk of recovering a contaminant is greater with a blood culture drawn from an umbilical vein. 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.

**Urine Culture**

A urine culture should not be part of the sepsis workup in an infant with suspected early-onset sepsis. 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. Gram stains of gastric aspirates to identify bacteria are of limited value and are not routinely recommended.

**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.

**Tracheal Aspirates**

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

**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. 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. However, in bacteremic infants, the incidence of meningitis may be as high as 23%. 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. 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/mL. Cell counts 2 standard deviations from the mean were generally less than 20 cells/mL. 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/mm³. 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/mm³. 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. 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). In addition, the number of bands in a CSF specimen does not predict meningitis. With a delay in analysis (>2 hours), white blood cell counts and glucose concentrations decrease significantly.

Protein concentrations in uninfected, term newborn infants are <100 mg/dL. 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. 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.
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. 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. The definitions for neutropenia vary with gestational age, type of delivery (infants born by cesarean delivery without labor have lower counts than infants delivered vaginally), site of sampling (neutrophil counts are lower in samples from arterial blood), and altitude (infants born at elevated altitudes have higher total neutrophil counts). In late preterm and term infants, the definition for neutropenia most commonly used is that suggested by Manroe et al (<1800/mm\(^3\) at birth and <7800/mm\(^3\) at 12–14 hours of age). Schmutz et al reinvestigated these reference ranges using modern cell-counting instrumentation in 30,254 infants born at 23 to 42 weeks’ gestation. Infants with diagnoses known to affect neutrophil counts (e.g., 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\(^3\) in infants born at >36 weeks’ gestation, 1000/mm\(^3\) in infants born at 28 through 36 weeks’ gestation, and 500/mm\(^3\) 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\(^3\), 3500/mm\(^3\), and 1500/mm\(^3\) for infants born at >36 weeks’ gestation, 28 to 36 weeks’ gestation, and <28 weeks’ gestation, respectively. 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\(^3\) at birth to 1500 cells/mm\(^3\) at 12 hours of age. Absolute immature counts have a poor sensitivity and positive predictive accuracy for early-onset sepsis. Furthermore, if exhaustion of bone marrow reserves occurs, the number of immature forms will remain depressed. 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. The I/T ratio is <0.22 in 96% of healthy preterm infants born at <32 weeks’ gestational age. 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. In healthy term infants, the 90th percentile for the I/T ratio is 0.27. A single determination of the I/T ratio has a poor positive predictive accuracy (approximately 25%) but a very high negative predictive accuracy (99%). The I/T ratio may be elevated in 25% to 50% of uninfected infants. 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.

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.

Platelet Counts

Despite the frequency of low platelet counts in infected infants, they are a nonspecific, insensitive, and late indicator of sepsis. 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. CRP concentration increases within 6 to 8 hours of an infectious episode in neonates and peaks at 24 hours. 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. 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. 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 (≥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. 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). Procalcitonin concentration has a modestly better sensitivity than does CRP concentration but is less specific. Chiesa and colleagues have published normal values for procalcitonin concentrations in term and preterm infants. 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.

**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 <150,000/mm³, and pronounced degenerative changes (ie, toxic granulations) in PMNs. In this study, two-thirds of preterm infants and 90% of term infants with a hematologic score ≥3 did not have proven sepsis.

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. 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. 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*. 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*. 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, and extensive/prolonged use of third-generation cephalosporins is a risk factor for invasive candidiasis. 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. 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.

**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. 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:

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 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. 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. 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. Therefore,
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.

FIGURE 2
Evaluation of asymptomatic infants ≥37 weeks’ gestation with risk factors for sepsis. a 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. b 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 ≥37 weeks’ gestation with risk factors for sepsis (no chorioamnionitis). a Inadequate treatment: Defined as the use of an antibiotic other than penicillin, ampicillin, or if duration of antibiotics before delivery was <4 h. b 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.

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.
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Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease

COMMITTEE ON INFECTIOUS DISEASES AND COMMITTEE ON FETUS AND NEWBORN

Pediatrics; originally published online August 1, 2011;
DOI: 10.1542/peds.2011-1466

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2011/07/28/peds.2011-1466
POLICY STATEMENT

Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease

abstract

The Centers for Disease Control and Prevention (CDC) guidelines for the prevention of perinatal group B streptococcal (GBS) disease were initially published in 1996. The American Academy of Pediatrics (AAP) also published a policy statement on this topic in 1997. In 2002, the CDC published revised guidelines that recommended universal antenatal GBS screening; the AAP endorsed these guidelines and published recommendations based on them in the 2003 Red Book. Since then, the incidence of early-onset GBS disease in neonates has decreased by an estimated 80%. However, in 2010, GBS disease remained the leading cause of early-onset neonatal sepsis. The CDC issued revised guidelines in 2010 based on evaluation of data generated after 2002. These revised and comprehensive guidelines, which have been endorsed by the AAP, reaffirm the major prevention strategy—universal antenatal GBS screening and intrapartum antibiotic prophylaxis (IAP) for culture-positive and high-risk women—and include new recommendations for laboratory methods for identification of GBS colonization during pregnancy, algorithms for screening and intrapartum prophylaxis for women with preterm labor and premature rupture of membranes, updated prophylaxis recommendations for women with a penicillin allergy, and a revised algorithm for the care of newborn infants. The purpose of this policy statement is to review and discuss the differences between the 2002 and 2010 CDC guidelines that are most relevant for the practice of pediatrics. Pediatrics 2011;128:000

INTRODUCTION

Group B streptococcal (GBS) disease has been a leading cause of neonatal morbidity and mortality since the 1970s. Maternal colonization with GBS in the genitourinary or gastrointestinal tract and transmission to the infant during the labor-and-delivery process is the principal risk factor for early-onset invasive GBS disease. Women who are identified as being GBS-colonized through culture-based screening are more than 25 times more likely to deliver an infant with early-onset infection than are women with negative prenatal cultures. Identification of maternal colonization through universal, culture-based screening with intrapartum antibiotic prophylaxis (IAP) for women with positive screening results has been recommended since 2002. This strategy, endorsed by the American Academy of Pediatrics, has been widely adopted in the United States and has resulted in an estimated 80% decrease in early-onset GBS infection.
However, even in the era of universal screening, cases of GBS disease continue to occur.7–11 To evaluate data published after the Centers for Disease Control and Prevention (CDC) issued guidelines for the prevention of GBS perinatal disease in 2002, the CDC called a meeting of clinical and public health representatives in June 2009. The goal of the meeting was to identify potentially modifiable reasons for continued GBS disease and to address these issues. The American Academy of Pediatrics was represented by members of its Committee on Infectious Diseases and Committee on Fetus and Newborn. The purpose of this policy statement is to review and discuss the differences between the 2002 and 2010 CDC guidelines that are most relevant for the practice of pediatrics. Table 1 outlines the evidence-based rating system that supports each recommendation; strength (indicated by a letter) and quality (indicated by a roman numeral) of evidence are shown in parentheses. The 2010 CDC guidelines can be accessed online (www.cdc.gov/groupbstrep/guidelines/guidelines.html).

### LABORATORY DIAGNOSIS OF GBS COLONIZATION

The 2002 guidelines from the CDC recommended universal culture-based screening for GBS at 35 to 37 weeks of gestation. In the intervening years, new diagnostic technologies have been developed, including pigmented enrichment broths, chromogenic agars, DNA probes, and nucleic acid amplification tests (NAATs). These methods have been validated for antenatal testing for GBS colonization and are used in many clinical laboratories, which enables more rapid identification of GBS. A positive test result for GBS by culture, DNA probe, or NAAT performed during antenatal screening indicates colonization, and the woman should receive IAP. However, infants with early-onset GBS can be born to women with negative antenatal screening results, because all laboratory-screening methods are imperfect. Culture-based screening, especially if processing in the laboratory does not always follow the CDC guidelines, may not identify all colonized women.7,11 Infants with signs and symptoms of sepsis should be managed according to the neonatal algorithm (Fig 1) and receive an initial antibiotic regimen that includes ampicillin regardless of maternal screening results.

### Recommendations

- Options for GBS identification from culture of maternal vaginal/rectal swabs have been expanded to include a positive identification from chromogenic agar media. Identification of GBS directly by nucleic acid amplification tests (NAATs), such as commercially available polymerase chain reaction assays, can also be used after broth enrichment if laboratories have validated their NAAT performance and instituted appropriate quality controls (CII).

### INTRAPARTUM ANTIBIOTIC PROPHYLAXIS

Penicillin and ampicillin have each been demonstrated in controlled clinical trials to be effective in preventing early-onset GBS disease when administered during labor.12,13 Penicillin and ampicillin at the recommended doses for IAP rapidly achieve therapeutic concentrations in the fetal circulation and then amniotic fluid. Cefazolin has similar pharmacokinetics when compared with penicillin, and IAP dos-
Signs of neonatal sepsis? 

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Maternal chorioamnionitis?c 

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GBS prophylaxis indicated for mother?* 

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Mother received ≥24 h of penicillin, ampicillin, or cefazolin IV? 

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≥37 wk and duration of membrane rupture < 18 h? 

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Either <37 wk or duration of membrane rupture ≥ 18 h? 

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**FIGURE 1**


- **Limited evaluation** includes blood culture (at birth) and CBC count with white blood cell differential and platelet counts; chest radiograph (if respiratory abnormalities are present); and lumbar puncture (if the patient is stable enough to tolerate procedure and sepsis is suspected). Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other Gram-negative pathogens) and should take into account local antibiotic-resistance patterns.
- **Full diagnostic evaluation** includes a blood culture; CBC count, including white blood cell differential and platelet counts; chest radiograph (if respiratory abnormalities are present); and lumbar puncture (if the patient is stable enough to tolerate procedure and sepsis is suspected). Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other Gram-negative pathogens) and should take into account local antibiotic-resistance patterns.

Women at low risk of anaphylaxis, current data indicate that approximately 20% of GBS isolates are resistant to clindamycin. Clindamycin should never be used for IAP if susceptibility testing of the mother’s GBS isolate has not been performed. Several recent studies have revealed that susceptibility testing is rarely performed on GBS isolates and early-onset GBS disease has been reported in infants born to mothers who have received clindamycin IAP.

**Recommendations**

- Penicillin remains the agent of choice for IAP, and ampicillin is an acceptable alternative.
- Penicillin-allergic women who do not have a history of anaphylaxis, angioedema, respiratory distress, or urticaria after administration of penicillin or a cephalosporin should receive cefazolin.
- Penicillin-allergic women at high risk of anaphylaxis should receive clindamycin if their GBS isolate is susceptible or vancomycin if their GBS isolate is intrinsically resistant to clindamycin.
- The definition of adequate IAP has been clarified to be at least 4 hours of penicillin, ampicillin, or cefazolin.
- The initial intravenous dose of penicillin is 5 million units; for ampicillin and cefazolin, the initial dose is 2 g.
- All other antibiotics, doses, or durations are considered inadequate for the purposes of neonatal management.

**PREVENTION OF EARLY-ONSET GBS DISEASE**

The revised 2010 GBS American Academy of Pediatrics guidelines for neonatal management were designed to broaden the scope to include all neonates, to increase the clarity of the recommendations, and to decrease un-
necessary laboratory evaluations and empirical antibiotics for infants at low risk. Although this strategy will never prevent all infections, the revised guidelines should result in a further decrease in cases of perinatal GBS disease. The management of neonates continues to be based on clinical signs, the presence of maternal risk factors for GBS neonatal disease, and the likely efficacy of IAP (or maternal antimicrobial treatment in the case of clinical or occult chorioamnionitis) in preventing early-onset disease. The revised infant management algorithm (Fig 1) is derived from recent data summarized in the published CDC document regarding the epidemiology of GBS disease and the usefulness of a “limited evaluation” of well-appearing neonates.

All newborn infants with signs suggestive of sepsis should have a full diagnostic evaluation, including a lumbar puncture if the infant is stable enough to undergo the procedure; 15% to 38% of infants with early-onset meningitis have sterile blood cultures, so evaluating the cerebrospinal fluid is required for optimal diagnostic sensitivity.18–21 If the care provider believes that a noninfectious condition is responsible for the infant’s signs (eg, transient tachypnea of the newborn) and there are no maternal risk factors for sepsis in an otherwise well-appearing infant, the lumbar puncture can be deferred or eliminated. Empirical antimicrobial therapy, typically intravenous ampicillin and gentamicin (unless local antibiotic-resistance patterns suggest the need for another combination), should be initiated promptly. Chorioamnionitis continues to be a significant risk factor for early-onset GBS sepsis in infants born to GBS-colonized women. All well-appearing newborn infants born to women who have a clinical diagnosis of chorioamnionitis from their obstetric provider should undergo a “limited evaluation,” which includes a complete blood cell (CBC) count and differential and a blood culture before initiation of empirical antimicrobial therapy. The sensitivity of the CBC count is improved if delayed for 6 to 12 hours after birth. Empirical therapy should be discontinued as soon as the clinical course and laboratory evaluation exclude sepsis.

The indications for maternal IAP remain unchanged and include 1 of more of the following: (1) GBS culture–positive within preceding 5 weeks; (2) GBS status unknown with 1 or more intrapartum risk factors including less than 37 weeks’ gestation, prolonged rupture of membranes for ≥18 hours, or temperature of ≥100.4°F (38.0°C); (3) GBS bacteriuria during current pregnancy; and (4) history of a previous infant with GBS disease. When a cesarean delivery is performed before onset of labor with intact amniotic membranes, the risk of early-onset GBS disease among infants is extremely low22,23; therefore, IAP is not recommended as a routine practice for cesarean deliveries performed under these circumstances, regardless of the GBS colonization status of the woman or the gestational age of the infant.

In well-appearing newborn infants born to women without an indication for IAP, routine clinical care is indicated unless signs of sepsis develop. For well-appearing term newborn infants born to mothers with an indication for IAP to prevent GBS disease and receipt of 4 or more hours of penicillin, ampicillin or cefazolin at the appropriate doses before delivery, routine care, and 48 hours of observation continue to be recommended. However, if these infants meet other discharge criteria, including term birth and ready access to medical care, discharge can occur as early as 24 hours after birth. In this latter circumstance, follow-up care by a care provider within 48 to 72 hours is recommended.

In well-appearing term newborn infants whose mothers had an indication for GBS prophylaxis and rupture of membranes for <18 hours but who received inadequate IAP—either by duration before delivery or by inappropriate agent or dose—observation in the hospital for at least 48 hours is recommended. These infants would include infants born to women with a serious penicillin allergy who received either clindamycin or vancomycin. This revised recommendation is based on the poor sensitivity of the “limited-evaluation” assessments in this circumstance and also data indicating that signs of early-onset GBS sepsis appear in more than 98% of neonates within this interval of hospitalization. The authors of several studies have reported the sensitivity of an abnormal CBC count in predicting GBS sepsis to range from 41% to 68%, whereas the presence of clinical signs has a sensitivity of 92%.24–27 The yield of blood culture can be low among newborn infants exposed to intrapartum antibiotics.28 Finally, for all preterm neonates (<37 weeks of gestation) or for term newborn infants born in the setting of rupture of membranes 18 hours or more before delivery without adequate maternal IAP, a limited evaluation and observation for at least 48 hours is recommended.

**Recommendations for Management of Newborn Infants**

- All newborn infants with signs of sepsis should undergo a full diagnostic evaluation (including a lumbar puncture) and receive empirical antimicrobial therapy (AII).
- All well-appearing newborn infants born to women given a diagnosis of chorioamnionitis by their obstetrical provider should undergo a
limited diagnostic evaluation (no lumbar puncture) and receive empirical antimicrobial therapy (All).

- For all women who received adequate IAP defined as penicillin (preferred), ampicillin, or cefazolin (penicillin-allergic women at low risk of anaphylaxis) for 4 or more hours before delivery, their newborn infants require only routine care and observation in the hospital for 48 hours (BIII). If these infants meet other discharge criteria, including term birth and ready access to medical care, discharge can occur as early as 24 hours after birth with follow-up care by a care provider within 48 to 72 hours (CII).

- Well-appearing term newborn infants whose mothers received no or inadequate IAP (including clindamycin or vancomycin) and had rupture of membranes for less than 18 hours require only observation for 48 hours (BIII).

- Well-appearing term newborn infants born to women with no or inadequate IAP and rupture of membranes for 18 or more hours before delivery should undergo a “limited evaluation” (ie, blood culture and CBC count with differential and platelets at birth) and observation for at least 48 hours (BIII).

- All preterm infants born to women with no or inadequate IAP should undergo a limited evaluation and observation for at least 48 hours (BIII).

REFERENCES


Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease

COMMITTEE ON INFECTIOUS DISEASES AND COMMITTEE ON FETUS AND NEWBORN

Pediatrics; originally published online August 1, 2011;
DOI: 10.1542/peds.2011-1466

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Neonatal sepsis continues to cause a significant proportion of perinatal mortality and long-term morbidity in the term and preterm infant population. The most common single organism that causes early-onset neonatal sepsis is the group B streptococcus (GBS or *Streptococcus agalactiae*) (1). Invasive early-onset GBS disease has an incidence of approximately two per 1000 live-born infants in the absence of intrapartum antibiotic prophylaxis (IAP) (2,3), with a case-fatality rate of between 2% and 13% in recent studies (4-6). Therefore, preventive strategies have been promoted and recently endorsed by the Society of Obstetricians and Gynaecologists of Canada (7). It has been demonstrated that the administration of intravenous penicillin at least 4 h before delivery to mothers colonized with GBS is highly effective in preventing perinatal transmission and early-onset invasive infection in the newborn (8). The recommendations are to screen all mothers with rectovaginal cultures at 35 to 37 weeks, and treat those with positive cultures for GBS at the time they present in labour. This strategy leads to as many as 22% of all mothers in labour at term being treated with IAP to prevent disease in 0.2% of infants and prevent mortality in 0.01% of infants (9). In the United Kingdom, it was calculated that it would require 24,000 antepartum cultures and 7000 women in labour treated with antibiotics to prevent one neonatal death (10). As a consequence, other authorities have developed different recommendations, questioning whether routine IAP is an appropriate use of resources (10,11), and whether the pressure exerted for the development of bacterial resistance is justified. In Canada, the current incidence of invasive neonatal GBS disease is uncertain because there is no centralized or mandatory reporting system.

**PURPOSE OF THE STATEMENT**

The aim of the present statement is to develop evidence-based practice guidelines answering the following question: How should an infant be monitored, investigated and treated given the presence of clinical signs of sepsis, the GBS culture status of the mother (positive, negative or unknown), the treatment status of the mother (completed, incomplete or no IAP), and the presence or absence of maternal risk factors for neonatal sepsis?

**METHODS OF STATEMENT DEVELOPMENT**

A search was carried out in MEDLINE and the Cochrane library, and last updated in January 2006. The MEDLINE search terms were ‘*Streptococcus agalactiae*’ and ‘newborn’. The hierarchy of evidence from the Centre for Evidence-Based Medicine (United Kingdom) was applied and, for this statement, the levels of evidence for treatment, prognosis and diagnosis were used (www.cebm.net, click on the EBM Tools tab or www.cebm.net/levels_of_evidence.asp#levels).

**DEFINITIONS**

**Limited diagnostic evaluation**

Limited diagnostic evaluation consists of a complete blood count (CBC), and observation of vital signs every 4 h for a period of 24 h. The newborn can be cared for and observed in the mother’s postpartum room. If the CBC shows a low total white blood cell (WBC) count of less than $5.0 \times 10^9/L$, then the risk of sepsis is substantially increased and a full diagnostic evaluation and initiation of therapy would usually be indicated.

**Full diagnostic evaluation**

Full diagnostic evaluation consists of a CBC, blood culture and lumbar puncture (LP); a chest x-ray should be obtained if respiratory difficulties are present. LP can be deferred in unstable infants, and performed later to ascertain the presence of hypoglycorrhachia or pleocytosis. Infants whose only sign of sepsis is respiratory distress may also be considered for deferment of LP if close follow-up can be ensured.

**THE UNWELL INFANT**

The initial signs of sepsis may be subtle, and may include temperature instability, tachycardia, poor peripheral perfusion and respiratory distress. Because the progression of invasive disease is very rapid, any infant with clinical signs suggestive of infection should be treated immediately following a prompt full diagnostic evaluation; delay between presentation and therapy increases the risk of a poor outcome (12) (evidence level 2b). There is no clear distinction in the clinical signs present when the infant has GBS sepsis compared with any other invasive organism.

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Although IAP with a penicillin dramatically reduces the frequency of early-onset invasive GBS disease, it does not affect the frequency of sepsis caused by other organisms (1,13) (evidence level 2b). Of note, invasive GBS can still occur in infants of mothers who have had a negative screening culture at 35 to 37 weeks; now that IAP is widespread and effective, the majority of the remaining infants with invasive GBS are those whose maternal cultures were negative (14), but who became colonized between screening and delivery (evidence level 2b). Also, invasive GBS disease is still possible, even if very rare, in mothers who received adequate IAP (15) (evidence level 4). Thus, neither the maternal screening history nor intrapartum exposure to antibiotics should affect the approach to the management of the infant with clinical signs of sepsis (recommendation category B). Therefore, prospective therapy, while awaiting culture results, should cover the most common bacteria: GBS, other streptococci, *Escherichia coli*, other Gram-negative organisms and *Listeria monocytogenes*.

An infant with signs of sepsis does not require confirmatory tests other than obtaining cultures before commencing therapy, because no other tests have an adequately high negative predictive value to avoid therapy (evidence level 2a). In particular, a normal WBC count or differential should not prevent treatment in such an infant because the negative likelihood ratio of a normal CBC is approximately 0.7 (recommendation grade B) (16).

**Empirical therapy**

There are no good prospective studies to indicate optimal choice of therapy in the newborn infant with possible sepsis (17), but ampicillin and gentamicin are usually appropriate based on the usual susceptibilities of the predominant organisms causing early-onset sepsis (evidence level 4). Infants with a positive cerebrospinal fluid (CSF) evaluation or with clinical signs of meningitis if the LP has been deferred, should be treated with antibiotics which both penetrate the CSF and are active against the likely organisms (Table 1). If there is information from the maternal history suggesting an organism that is unlikely to respond to these antibiotics, empirical therapy should be adjusted appropriately. Blood cultures using modern automated systems are almost always positive by 48 h (18). Therefore, if the laboratory results and clinical course do not indicate bacterial infection, therapy may be discontinued after 48 h. The majority of antibiotic courses are given to infants who eventually prove not to have had sepsis; strategies for further reduction of the duration of antibiotic therapy in such infants should be considered. For example, because gentamicin is usually now given once per day in the full-term infant, and ampicillin is given every 12 h, the initial antibiotic order could be to give ampicillin for four doses every 12 h and gentamicin for two doses every 24 h, followed by reassessment after verification of culture results at 48 h, and reordering the antibiotics in case of positive cultures (or ongoing signs of sepsis).

**WELL-APPEARING INFANT OF A GBS-POSITIVE MOTHER, WHO RECEIVED IAP MORE THAN 4 H BEFORE DELIVERY**

IAP with a penicillin for least 4 h is highly effective at eradicating GBS transmission (19), and thus preventing the majority of invasive neonatal GBS disease (evidence level 2b) (20). Therefore, if a GBS-positive woman receives intrapartum antibiotics for at least 4 h before delivery and if the newborn appears healthy and is more than 35 weeks gestational age, the newborn requires no therapy for prevention of early-onset GBS (recommendation grade A).

If the baby remains well at 24 h of age and is otherwise eligible for discharge at this time, early discharge can be contemplated provided the caregiver knows the appropriate resources in the community for accessing health care and is able to transport the baby immediately to a health care facility if clinical signs of sepsis develop.

There is insufficient information regarding the efficacy of alternative antibiotics (used when the mother is at risk of anaphylaxis from penicillin). Such infants should be managed as if the mother received incomplete IAP (next heading) until further data are available.

### Table 1

<table>
<thead>
<tr>
<th>CSF Findings</th>
<th>Most Common Organisms</th>
<th>Suggested Expectant Antimicrobials for Early-Onset Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive cocci</td>
<td>Group B streptococci, less commonly: <em>Staphylococcus species or enterococci</em></td>
<td>Ampicillin or penicillin plus gentamicin</td>
</tr>
<tr>
<td>Gram-positive rods</td>
<td><em>Listeria monocytogenes</em></td>
<td>Ampicillin plus gentamicin</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td><em>Escherichia coli</em>, less commonly: <em>Klebsiella</em>, <em>Pseudomonas</em> and <em>Citrobacter</em></td>
<td>Cefotaxime plus gentamicin</td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td>Uncommon</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Pleocytosis, or other findings strongly suggestive of meningitis, but Gram stain-negative, or too unstable to have an LP</td>
<td>Any of the above are possible</td>
<td>Ampicillin plus gentamicin</td>
</tr>
</tbody>
</table>

*LP Lumbar puncture. Source: Canadian Paediatric Society, 2007*
WELL-APPEARING INFANT OF A GBS-POSITIVE MOTHER WHO RECEIVED IAP LESS THAN 4 H BEFORE DELIVERY OR NOT AT ALL

The risk of invasive early-onset GBS disease in an infant whose mother is GBS-positive and does not receive IAP is approximately 1% (21). Only one-quarter of these babies are asymptomatic at birth. This risk of significant disease probably does not justify routine empirical treatment in these circumstances, and careful observation with treatment at the first clinical sign of infection appears to be reasonable. Ninety-five per cent of infants with early-onset GBS infection present with clinical signs within 24 h (22) (either temperature instability, tachycardia, poor peripheral perfusion, respiratory distress or abnormal CBC). Four per cent of infected infants present between 24 h and 48 h of age, with only 1% developing signs after 48 h of age. Thus, prolonging hospitalization from 24 h to 48 h would require the observation of more than 2000 infants to detect each case of invasive infection. Therefore, if careful assessment of the infant at 24 h confirms that they remain well, discharge at that time may well be appropriate as long as adequate patient education and follow-up are ensured.

The use of the CBC is sometimes promoted for determining risk, both for GBS and for other organisms, among infants who are at elevated risk but appear well. However, the positive predictive value of an abnormal CBC is low in the newborn and it is, therefore, uncertain how to proceed when an infant is clinically well but has an abnormal CBC; unfortunately, most studies investigating the usefulness of the CBC have not been confined to well-appearing infants and, therefore, their usefulness in this specific situation is somewhat conjectural. One study (23) confined to well-appearing term infants showed a positive predictive value of 1.5% of an ‘abnormal’ CBC (total WBC of 5.0 × 10^9/L or lower, or 30 × 10^9/L or greater, or an absolute polymorphonuclear cell count of less than 1.5 × 10^9/L or an immature to mature polymorphonuclear cell ratio greater than 0.2) in identifying the development of ‘clinical sepsis’ in 1665 healthy term infants who were at risk; of note, none of these infants developed a positive blood culture (evidence level 2b).

Several scoring systems have been developed for analyzing CBC results (24), and all involve analysis of the count of immature neutrophils, but there is very wide interobserver variability in the identification of immature or ‘band’ neutrophils (25). Even the best scoring system only achieves a likelihood ratio of between four and eight (24) (evidence level 2a). Finding a ‘left-shift’ or an elevated total WBC count is not sufficiently predictive to alter management. The individual finding on a CBC with the highest positive predictive value is a low total WBC count of less than 5.0 × 10^9/L; if this finding is present, the likelihood ratio is between 10 and 20 (16), leading to a post-test probability of sepsis of approximately 10% to 20% (evidence level 2b) and, therefore, probably justifying treatment even in a well-appearing infant after a full diagnostic workup. However, only between 22% and 44% of infants with sepsis will have such a low total WBC count (16).

WELL-APPEARING INFANT OF A GBS-NEGATIVE MOTHER WHO HAD RISK FACTORS AT DELIVERY

Before the recommendation for universal culture-based screening, IAP was recommended for mothers with any one of the following five risk factors: over 18 h rupture of membranes, pyrexia higher than 38°C, premature labour at less than 36 weeks, GBS bacteriuria at anytime during pregnancy or previous child with invasive GBS disease. These risk factors were present in as many as 22% of mothers, and only identified approximately 50% of infants who eventually developed invasive GBS disease (26,27) (evidence level 2b).

Although invasive GBS disease does occur in infants whose mothers have negative screening cultures at 35 to 37 weeks, the risk is very low even in those with prolonged rupture of membranes or intrapartum pyrexia (28) (evidence level 2b). It is suggested that a limited diagnostic evaluation be performed in this newborn population (recommendation grade B).

WELL-APPEARING INFANT OF A MOTHER WITH UNKNOWN GBS STATUS AND NO RISK FACTORS

A mother who has not had an antenatal GBS culture or whose results are not readily available, and her newborn baby, should be managed according to the risk factors listed in the previous section. In the absence of these risk factors, and if the baby remains well, no specific intervention is required (recommendation grade B).

WELL-APPEARING INFANT OF A MOTHER WITH UNKNOWN GBS STATUS WITH RISK FACTORS

The five risk factors mentioned above occur in approximately 20% of deliveries at term, and are present in approximately 50% of infants with invasive GBS disease (26,27). This fourfold increase in risk to the infant in a mother with unknown GBS status has led to the recommendation that she should receive IAP (7). In this circumstance, the infant should be treated in the same way as he or she would be treated if the mother were GBS-positive (ie, IAP more than 4 h before delivery and routine neonatal care; IAP less than 4 h or no IAP, limited diagnostic evaluation and minimum 24 h observation) (recommendation grade B).

THE LATE PRETERM INFANT

The mother who delivers at less than 37 weeks will often not have results of antenatal GBS screening available. In such a case, the infant has a ‘risk factor’ (prematurity) for invasive GBS disease and, if he or she appear well, should have a limited diagnostic evaluation. Infants of this gestational age should not be discharged before 48 h at the earliest (Figure 1).

CHORIOAMNIONITIS

Chorioamnionitis is a difficult condition to diagnose because the prevalence of pyrexia during labour is high.
Figure 1) Algorithm for the management of newborn babies who may be at risk for neonatal sepsis. Source: Canadian Paediatric Society, 2007

GBS Group B streptococcus

IAP Intrapartum prophylaxis with penicillin or ampicillin

Close observation = 4 h check of pulse rate, respiratory rate and temperature at mother’s bedside

Full diagnostic evaluation = blood culture, spinal tap ± chest x-ray (urine culture not indicated)

Risk factors for sepsis = maternal fever or signs of chorioamnionitis, ruptured membranes >18 h, previous child with GBS sepsis or preterm labour (<36 weeks)

Routine neonatal care and discharge with relevant parental counselling

Baby remains well?

Yes

No

Immediate full diagnostic evaluation

Findings or progress consistent with sepsis?

Yes

Empirical antibiotic therapy for up to and including 36 h. Consider consultation

Antibiotic therapy to cover underlying illness for at least 5 days. Consider consultation

No

Check CBC: Is the total WBC count <5.0×10^9/L?

Yes

No

Close observation

Check CBC

Are there perinatal risk factors for sepsis?

No

Yes

Did the mother receive more than 4 h of IAP?

No

Yes

Is the mother colonized with GBS?

Known to be negative

GBS status not known

Known to be positive

Is the baby unwell?

Yes

No
WBC and lower uterine tenderness is present. 'Definite', when the classical triad of fever, left-shift in the WBC and lower uterine tenderness is present. When the classical triad of fever, left-shift in the WBC and lower uterine tenderness is present. Therefore, chorioamnionitis is frequently classified as 'possible', when the main sign is fever, and 'definite', when the classical triad of fever, left-shift in the WBC and lower uterine tenderness is present.

The risk of sepsis (which may be due to a variety of different organisms, including GBS, E coli and other Gram-negative organisms) in an infant whose mother had definite chorioamnionitis is approximately 8%, and is approximately 3% to 4% if 'possible' and 'definite' chorioamnionitis are considered together (31,32) (evidence level 2b); among all mothers with fever, the incidence is 2% to 6% depending on the height of the fever (31) (evidence level 2b). Infants who do not have signs at birth are unlikely to develop sepsis, the odds ratio for sepsis among infants who are well at birth is 0.26 (95% CI 0.11 to 0.63) (31). The incidence of invasive infection in the present study in an initially well-appearing infant with a maternal history of fever or chorioamnionitis was less than 2%, and this is confirmed by other data (33) (evidence level 2b). Therefore, it seems reasonable to perform a CBC and closely observe such an infant, and to only perform a full diagnostic evaluation and treat with antibiotics if the CBC is strongly suggestive of infection (low total WBC count) or if clinical signs develop. A requirement for extensive resuscitation at birth should be considered a sign of possible infection in such infants (32,33).

RECOMMENDATIONS

- Any newborn infant with clinical signs suggestive of sepsis should have an immediate full diagnostic evaluation followed by the institution of empirical antibiotic therapy without delay (recommendation category B).

- If a mother who is GBS-positive receives IAP with a penicillin more than 4 h before delivery, no further evaluation or observation for invasive GBS disease in a well-appearing infant is required (recommendation category A).

- If a GBS-positive woman receives IAP less than 4 h before delivery (or receives no antibiotics or a nonpenicillin regimen), then a limited diagnostic evaluation is required, and the infant should not be discharged before 24 h of age. At the time of discharge, the infant should be evaluated and the parents should be educated regarding signs of sepsis in the newborn. Discharge at 24 h to 48 h is conditional on the parents’ ability to immediately transport the baby to a health care facility if clinical signs of sepsis develop (recommendation grade B).

- If the CBC reveals a total WBC count less than 5.0x10⁹/L, full diagnostic evaluation and empirical antibiotic therapy should be considered (recommendation grade B).

- If a GBS-negative woman with risk factors delivers a baby who remains well, the infant does not require evaluation for GBS (recommendation grade B).

- If a woman with unknown GBS status and with risk factors at the time of delivery receives IAP more than 4 h before delivery, the infant requires no specific intervention (recommendation grade B).

- If a woman with unknown GBS status and with risk factors at the time of delivery receives IAP less than 4 h before delivery, limited diagnostic evaluation is required and the infant is not discharged before 24 h of life (recommendation grade B).

- The well-appearing infant born at less than 36 weeks gestation with an unknown maternal GBS status should have a limited diagnostic evaluation and is not a candidate for early discharge.

- The well-appearing infant of a mother with possible chorioamnionitis requires a limited diagnostic evaluation for sepsis (recommendation grade B).

REFERENCES


ACKNOWLEDGEMENTS: The present position statement was reviewed by the Canadian Paediatric Society Community Paediatrics Committee and the Infectious Diseases and Immunization Committee.


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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. Internet addresses are current at time of publication.