The current incidence of neonatal early-onset sepsis (EOS) among infants born ≥37 weeks is relatively low (≈1/2000) and as much as 10-fold lower among well-appearing term infants.

There are three major approaches to EOS risk assessment among term infants: categorical consideration of risk factors, multivariate consideration of risk factors in combination with clinical condition, and consideration of the clinical condition alone as it evolves in the first 48 hours after birth.

Currently available laboratory tests lack sensitivity for predicting culture-confirmed EOS among term infants.

EOS-associated clinical activities have significant impact on early mother–newborn interaction and initiation of breastfeeding.

Depending on the local structure of care, EOS risk assessment activities are costly in terms of caregiver time, resource allocation, and monetary expenditures.

Preclinical animal and clinical human studies demonstrate an impact of perinatally administered antibiotics on the initial composition of the newborn gut microbiome.

Retrospective human epidemiologic studies associate perinatal and early infancy antibiotics with multiple morbidities in early childhood.

Introduction

Management of newborns at risk of early-onset bacterial sepsis (EOS) is one of the most common clinical tasks conducted by perinatal clinicians. Depending on the local structure of care, decisions are made by midwives, community pediatricians, resident house staff, newborn hospitalists, or neonatal intensive care specialists. EOS risk management begins with an assessment of whether the newborn is at a higher-than-average risk for EOS, continues to a decision to administer empiric antibiotic therapy, and ends with the decision to stop or extend empiric therapies, if given. Caregivers engage in this management to protect newborns from what may be a serious and even life-threatening infection. However, as the incidence of EOS has declined in the United States, risk management has become increasingly controversial, especially among initially well-appearing infants born at term. The incidence of EOS among all infants born ≥37 weeks’ gestation is now ≈1 case per 2000 live births; among well-appearing term infants born to mothers without concern for intrapartum infection, the incidence may be as low as 1 case in 25,000 births. Faced with a low-incidence, high-consequence condition, neonatal caregivers are challenged to determine the best approach to ensure newborn health. The difficulty of this task was brought forward in a recent national survey of EOS practices in American
Abstract
As the incidence of neonatal early-onset sepsis has declined, the approach to sepsis risk assessment practices has become increasingly controversial, particularly among initially well-appearing term infants. Current debate centers on several issues, including the proportion of newborns subjected to evaluation, the optimal use of available laboratory tests, unanticipated consequence of sepsis evaluation, and the risk and benefits of early antibiotic exposures.

Keywords
Neonatal early-onset sepsis
Risk assessment
Group B streptococcus
Perinatal antibiotics
Two newborn characteristics can be used to identify categories of infants at markedly higher risk of EOS compared with infants without such characteristics. The first is gestational age (or birth weight used as a surrogate for gestational age). Centers for Disease Control and Prevention (CDC) multistate surveillance data in the United States demonstrate that the incidence among infants born <37 weeks’ gestation is five to six times higher compared with the incidence among infants born ≥37 weeks’ gestation. The incidence of EOS among those born with birth weight <1500 g is ≈20 times higher than among those born at term. The microbiology of EOS also differs among premature infants: Despite widespread application of intrapartum antibiotic prophylaxis to prevent group B streptococcus (GBS)–specific EOS, GBS is the most common organism isolated in term infants with EOS. In contrast, *Escherichia coli* is the most common isolate among premature infants. The second characteristic predictive of EOS is infant clinical presentation. Escobar and colleagues evaluated the outcomes of EOS evaluation among 2875 newborns evaluated for EOS. Roughly half of the infants were evaluated due to clinical symptoms, and the other half were evaluated based on the presence of specific risk factors (e.g., maternal chorioamnionitis, rupture of membranes >18 hours). The unadjusted incidence of EOS was 10-fold higher among infants who were critically ill compared with those who were initially asymptomatic; on multivariate analysis, initial asymptomatic status predicted ≈60% lower risk of EOS compared with presentation with any degree of instability.

Despite a high relative risk of infection, not all premature infants are infected, and not all symptomatic term infants are infected. The challenge among such infants is to determine which infants *may not* require EOS evaluation and empiric antibiotics. Among term, well-appearing infants, in contrast, the primary challenge is to determine who, despite initial reassuring clinical condition, is at highest risk to develop symptomatic EOS. For these infants, the task is to determine which infants *may* require EOS evaluation and empiric antibiotics. In this chapter, we will evaluate the merits and limitations of different approaches to assessing the risk of EOS among term, well-appearing newborns.

**Approaches to EOS Risk Assessment Among Well- Appearing Term Infants**

*Categorical approaches to EOS risk assessment:* The first national consensus guidelines for EOS were issued by the American Academy of Pediatrics (AAP) in 1992, by the CDC in 1996, and by the American College of Obstetricians and Gynecologists in 1996. These guidelines were directed at reducing GBS-specific EOS incidence by interrupting mother-to-infant GBS transmission during labor. The evidence for specific chemoprophylaxis approaches to mediate such interruption and effectiveness of the various approaches were reviewed in each subsequent revision.11–18 Universal GBS screening and intrapartum chemoprophylaxis was recommended in the revised CDC guideline in 2002 and reaffirmed in the 2010 recommendations.18

These guidelines also contain recommendations for the management of infants after delivery with the goal of early identification of EOS cases and early initiation of antibiotics to halt the progression of disease. These recommendations use decision trees to direct management with a series of categorical consideration of risk factors, using these factors in dichotomous fashion with clear cutoff values. Decision trees ensure ease of clinical use and direct immediate decision making and are often used where time is a critical factor in determining success of outcome.19 This approach does not require computation or longitudinal monitoring. The aim of the categorical approach is to maximize sensitivity at the expense of specificity. With the goal to “not miss” EOS cases, a wide margin for categorizing infants as “at risk” is seen as beneficial, and the likelihood of overtreatment is judged to be acceptable. Whereas the CDC largely focuses on management strategies for infants in context of maternal

newborn nurseries. Wide variation was identified in most aspects of EOS risk management, with significant impact on the newborn and on the maternal–infant dyad.5
GBS-specific chemoprophylaxis, AAP guidelines have evolved to provide more holistic guidance for all bacterial causes of EOS.\textsuperscript{20–22} The specific criteria and tests recommended by the most recent guidelines are outlined in Table 1.1.

**Multivariate risk assessment:** This approach utilizes established risk factors and newborn clinical condition to estimate the individual infant’s risk of EOS. In their study of infants being evaluated for EOS using a CDC-recommended categorical approach, Escobar and colleagues demonstrated that a limited number of risk factors could be used to predict infection.\textsuperscript{7} Subsequently, these investigators used a cohort of 608,000 infants born at ≥34 weeks’ gestation to develop predictive models for culture-confirmed EOS based on objective data known at the moment of birth\textsuperscript{23} and the evolving newborn condition in the first 6 to 12 hours after birth.\textsuperscript{24} The objective data used include gestational age, highest intrapartum maternal temperature, maternal GBS status, duration of rupture of membranes (ROM), and type and duration of intrapartum antibiotics. The models were used to develop a web-based Sepsis Risk Calculator (SRC) with recommended clinical algorithms based on the final risk estimate.\textsuperscript{25} Blood culture and enhanced clinical observation are recommended for infants with EOS risk estimated at ≥1/1000, and blood culture and empiric antibiotics are recommended for infants with EOS risk estimated at ≥3/1000. The primary advantage of the multivariate approach is that it accounts for interactions between risk factors, providing differential information on an individual infant’s risk rather than placing infants in categories with a wide range of risk. A further advantage is that it uses only objective data, including maternal fever, without requiring obstetric clinical judgment with respect to clinical chorioamnionitis. If needed, the risk estimated can be recalculated during the first 6 to 12 hours as the newborn clinical condition evolves. Care pathways must be established to ensure that the risk estimate is accurately calculated and recorded at birth. The clinical care algorithms rely on enhanced clinical surveillance for infants with estimates 1/1000 requiring birth hospitalization for a minimum of 48 hours, as well as frequent vital signs and clinical nursing assessments. Institutions opting for this approach may set different risk thresholds for specific actions if local resources mandate more conservative algorithms (for example, setting the threshold for antibiotics at a risk estimate of 2/1000), but the use of more liberal thresholds has not been validated.

**Risk assessment based primarily on newborn clinical condition:** A third strategy for evaluating risk among well-appearing term infants consists of reliance on clinical signs of illness to identify infants with EOS. Such an approach is based on the observation that among term infants, asymptomatic condition at birth is associated with an ≈60% to 70% reduction in risk for EOS.\textsuperscript{7,24} EOS in persistently asymptomatic infants is uncommon. In their prospective SRC validation report, only 1/56,261 infants managed using the SRC had bacteremia despite never manifesting signs of illness.\textsuperscript{25} Other centers report the convergence of EOS with symptoms: In one report of 19,320 infants born at ≥35 weeks’ gestation, all 8 infants with EOS had clinical signs of illness at birth or developed illness before 48 hours of age.\textsuperscript{26} In another, 11 of 53,788 newborns of all gestational ages developed GBS-specific EOS; 5 of 11 were symptomatic at birth, and 6 became ill between 6 and 48 hours of age.\textsuperscript{27} Two

<table>
<thead>
<tr>
<th>Clinical Risk Factor</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric clinical diagnosis of chorioamnionitis</td>
<td>Blood culture at birth</td>
</tr>
<tr>
<td>Inadequate indicated GBS IAP and ROM ≥18 hr</td>
<td>CBC and differential (± CRP) at birth and/or at 6–12 hr age</td>
</tr>
<tr>
<td>Inadequate indicated GBS IAP and ROM &lt;18 hr</td>
<td>± Blood culture at birth</td>
</tr>
<tr>
<td>Adequate indicated GBS IAP</td>
<td>± CBC and differential, ± CRP at birth and/or at 6–12 hr age</td>
</tr>
<tr>
<td>Inadequate indicated GBS IAP and ROM ≥18 hr</td>
<td>Observation for minimum 48 hr</td>
</tr>
<tr>
<td>Inadequate indicated GBS IAP and ROM &lt;18 hr</td>
<td>Clinical observation for minimum 48 hr</td>
</tr>
<tr>
<td>Adequate indicated GBS IAP</td>
<td>Clinical observation for minimum 24–48 hr</td>
</tr>
</tbody>
</table>
centers in Italy have reported experience with strategies based on identification of at-risk newborns using categorical approaches to risk, accompanied by laboratory tests and serial examinations of at-risk newborns (Table 1.2). Both of these reports demonstrate decreases in laboratory test utilization and empiric antibiotic administration, with strategies relying on serial clinical examination of at-risk newborns.

### Areas of Controversy

EOS risk assessment for initially well-appearing term infants is a matter of considerable controversy among newborn caregivers, with debate centered on four main issues: (1) how many newborns is it acceptable to evaluate and empirically treat to identify one case of EOS; (2) what is the best way to use available laboratory tests to assess risk; (3) what are the economic and social costs of EOS risk assessment; and (4) what unintended consequences result from perinatal antibiotic administration?

**How many infants should be empirically evaluated and empirically treated for risk of EOS?** This judgment is perhaps the most controversial aspect of the categorical risk approach. The impact of using the recommendations contained within the CDC or AAP recommendations has been described in a variety of reports (Table 1.3). Depending on which categorical approach is taken, 5% to 20% of term and late preterm infants are evaluated with laboratory tests, and 5% to 10% are administered neonatal antibiotics for risk of EOS. The multivariate risk approach was predicted to result in fewer newborns evaluated and empirically treated with antibiotics. A prospective validation report including 204,685 infants born at ≥35 weeks’ gestation cared for in an integrated health care system demonstrates that blood culture testing declined by 66% and empiric antibiotic administration declined by 48% (to 2.6%) with use of the multivariate risk approach, compared with the use of a risk algorithm.

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**Table 1.2 CLINICAL OBSERVATION FOR WELL-APPEARING INFANTS AT RISK FOR EOS**

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Screening Policy</th>
<th>Years</th>
<th>Infants Included</th>
<th>Laboratory Tests (%)</th>
<th>Antibiotics (%)</th>
<th>EOS Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td><strong>First period:</strong> Laboratory tests (blood culture, CRP, CBC) for infants born to mothers with intrapartum fever or inadequate GBS IAP. Antibiotics for intrapartum fever or abnormal laboratory tests</td>
<td>2005–2007</td>
<td>Well at birth ≥35 weeks n = 9832</td>
<td>11.6</td>
<td>2.8</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td><strong>Second period:</strong> Laboratory tests for infants born to mothers with intrapartum fever or neonates with inadequate IAP and ≥2 additional risk factors</td>
<td>2009–2011</td>
<td>Well at birth ≥35 weeks n = 10,569</td>
<td>1.6</td>
<td>0.6</td>
<td>0.05</td>
</tr>
<tr>
<td>29</td>
<td><strong>First period:</strong> Laboratory tests (blood culture, CBC) and serial physical exam for infants born to mothers who are GBS positive (or have risk factors) and inadequate IAP</td>
<td>2004–2005</td>
<td>Well at birth ≥37 weeks n = 7625</td>
<td>6.9</td>
<td>1.2</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td><strong>Second period:</strong> Serial physical exam alone for infants born to mothers who are GBS positive (or have risk factors) and inadequate IAP</td>
<td>2005–2006</td>
<td>≥37 weeks n = 7611</td>
<td>0.6</td>
<td>0.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Management of the Asymptomatic Newborn at Risk for Sepsis

Based on CDC 2010 recommendations. No adverse impacts of the multivariate risk approach were noted during the birth hospitalization or after-birth hospital discharge. Hospital readmissions within 7 days of birth for culture-confirmed EOS were rare, occurring at a rate of ≈5/100,000 births, regardless of the approach taken for risk assessment at birth.25 Strategies based on clinical observation are predicted to result in very low rates of empiric antibiotic administration. In the two reports of using clinical observation for well-appearing infants deemed at risk for EOS on the basis of inadequate GBS intrapartum antibiotic prophylaxis (IAP), <1% of such infants were treated with empiric antibiotics for development of symptoms; neither of these reports provide data on use of antibiotics among infants symptomatic from birth.

Both the multivariate model and observation-based approach provide significant practical challenges compared with the categorical decision-tree approach. The SRC was designed for use with all live births ≥34 weeks; it is not validated for secondary assessment of infants flagged at risk by categorical approaches as has been done in retrospective studies.30,31 It does not rely on categorical risk flags but uses objective risk data to provide an estimated risk of EOS at the moment of birth. This estimate is subsequently adjusted based on the evolving newborn clinical condition. Centers adopting this approach must develop processes for ensuring that the data required for the multivariate risk estimate are available and that the SRC output is properly calculated, recorded, and communicated to caregivers. The SRC provides guidance on specific actions that can be taken at specific levels of risk. Observation-based approaches require centers to decide who is eligible for observation versus intervention; how to screen for risk (using a categorical or multivariate approach, with or without laboratory testing); and how serial clinical examinations will be conducted, recorded, and communicated. Furthermore, centers would need to develop explicit guidance for intervention based on specific changes in the newborn clinical condition. A National Institute of Child Health and Human Development–sponsored expert panel recently advocated for clinical observation of asymptomatic term infants born to mothers with suspected intrauterine infection,32 whereas the reports detailed in Table 1.3 and Table 1.4 used this approach for infants born in the context of intrapartum maternal fever, as well those born to mothers with inadequate indicated GBS IAP.33–36 Theoretically, a center could dispense with all EOS risk assessment and implement serial clinical observation for all well-appearing term newborns, intervening with laboratory testing and/or empiric antibiotics only when signs of illness became apparent. Such an approach would be predicted to result in very low utilization of laboratory testing and empiric antibiotic administration, but would significantly affect the structure of well-nursery care. The need for frequent clinical assessments and vital sign measurements would affect mother/infant couplet care and could result in increased labor costs resulting from increased demands on both nursing and pediatric providers.

**Table 1.3 OUTCOMES OF CATEGORICAL APPROACHES TO EOS RISK ASSESSMENT**

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Policy</th>
<th>Years</th>
<th>Infants Included</th>
<th>Laboratory Tests (%)</th>
<th>Antibiotics (%)</th>
<th>EOS Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>CDC</td>
<td>1996–1999</td>
<td>≥35 weeks n = 19,320</td>
<td>10.0</td>
<td>N/A</td>
<td>0.07</td>
</tr>
<tr>
<td>33</td>
<td>CDC</td>
<td>2008–2009</td>
<td>Well-appearing ≥35 weeks n = 7943</td>
<td>24</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>34</td>
<td>CDC</td>
<td>2013–2014</td>
<td>≥36 weeks n = 6544</td>
<td>13</td>
<td>12</td>
<td>0.04</td>
</tr>
<tr>
<td>25</td>
<td>CDC</td>
<td>2010–2012</td>
<td>≥35 weeks n = 95,354</td>
<td>14</td>
<td>5</td>
<td>0.06</td>
</tr>
<tr>
<td>35</td>
<td>AAP</td>
<td>2006–2012</td>
<td>≥35 weeks n = 12,121</td>
<td>4.6</td>
<td>4.6</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Laboratory testing defined as some combination of blood culture and/or CBC and/or CRP. Report includes only infants born in setting of chorioamnionitis.
Infectious Disease

Most importantly, clinicians using an observation-based approach to EOS risk assessment will need to view newborn transition from well appearing to symptomatic as an expected outcome and not a failure of care.

What is the best way to use available laboratory tests to assess EOS risk?
Clinicians seek to use laboratory tests to both predict and diagnose EOS. Bacterial culture; the white blood cell (WBC) count and differential (including absolute neutrophil count [ANC] and the ratio of immature to total neutrophil forms [I/T]); proinflammatory cytokines such as interleukins 1β, 6, 8, and 10 and tumor necrosis factor alpha; acute-phase reactants such as procalcitonin and C-reactive protein (CRP); and cell surface markers such as CD64 have been variably correlated with culture-proven, clinical, and viral sepsis. Most recently, molecular methods such as microarray and proteome analysis have sought to characterize molecular signatures that correlate with culture-confirmed infection.

• **Bacterial culture and the definition of EOS**: Epidemiologic studies of EOS are based on culture-confirmed isolation of pathogenic bacterial species from normally sterile compartments, most commonly blood and cerebrospinal fluid, and rarely in some circumstances, pleural or peritoneal fluid. Neonatal surface cultures taken at birth are generally considered to represent colonization; although used to test the efficacy of GBS IAP, cultures of the nares, inner ear, periumbilical and perianal regions, or swallowed amniotic fluid do not reflect invasive infection. Among symptomatic infants, evidence of surface colonization has been used to justify the diagnosis of “culture-negative sepsis” by arguing that blood cultures are sterile due to the use of maternally administered intrapartum antibiotic administration. Currently available blood culture systems use optimized enriched culture media with antimicrobial-inactivating elements that efficiently neutralize commonly used beta-lactam antibiotics as well as gentamicin. These culture systems detect bacteremia at a level of 1 to 10 colony-forming units if a minimum of 1 milliliter of blood is inoculated. Studies report no impact of intrapartum antibiotics on

### Table 1.4  WBC TESTING AMONG WELL-APPEARING NEWBORNS AT RISK FOR EOS

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Years</th>
<th>Infants With CBC</th>
<th>CBC Timing (hours)</th>
<th>Abnormal CBC Definition</th>
<th>Abnormal CBC (#)</th>
<th>EOS among Tested Infants, # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>1996–1999</td>
<td>≥35 weeks</td>
<td>&lt;4</td>
<td>WBC ≤5000 or ≥30,000</td>
<td>454/1665</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All EOS Risk</td>
<td></td>
<td>ANC &lt;1500 I/T &gt;0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>2008–2009</td>
<td>≥35 weeks</td>
<td>0–2</td>
<td>WBC ≤5000 I/T &gt;0.2</td>
<td>32/1062</td>
<td>3 (0.3)a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All EOS risk</td>
<td></td>
<td>At least one value abnormal of ANC, ATI, or I/T</td>
<td>686/692</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>35</td>
<td>2011–2012</td>
<td>≥35 weeks</td>
<td>0, 12, and 24</td>
<td>I/T &gt;0.2b</td>
<td>185/535</td>
<td>3 (0.6)c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposed to CAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 692</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>2006–2012</td>
<td>≥35 weeks</td>
<td>0 and 12</td>
<td>I/T &gt;0.2b</td>
<td>185/535</td>
<td>3 (0.6)c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposed to CAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 535</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>2004–2005</td>
<td>≥35 weeks</td>
<td>0–48</td>
<td>WBC ≤5000 or ≥15,000b</td>
<td>327/477</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All EOS risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 477</td>
<td></td>
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</tbody>
</table>

For each study, number of infants includes only those for whom the whole CBC was obtained. ANC, absolute neutrophil count; ATI, absolute immature neutrophil count; CAM, chorioamnionitis; CBC, complete blood count; EOS, early-onset sepsis; I/T; ratio of immature to total neutrophil forms; WBC, white blood count.

*None of the 3 cases of EOS were among the 32 infants with abnormal CBC.

In both reports clinicians also variably obtained CRP levels.

Although three cases of EOS were well appearing by 6 to 8 hours of age, all were depressed at birth, requiring positive pressure ventilation, continuous positive airway pressure (CPAP), or bag/mask ventilation.
blood culture time to positivity among bacteremic infants. Nonetheless, concern for culture-negative infection drives variable definitions of “clinical sepsis” or “culture-negative sepsis.” Some authors have advocated for a neonatal consensus diagnosis of EOS, based on the presence of symptoms and elevations of specific inflammatory markers. Both epidemiologic studies and clinical intervention trials may benefit from a neonatal consensus definition of EOS that extends beyond culture-confirmed disease, particularly among studies conducted in low-resource settings. Among adult patients, early recognition of sepsis syndrome and prompt initiation of volume resuscitation as well as antibiotics is critical to intact survival. However, there is no equivalent clinical imperative among well-appearing term newborns. The most straightforward approach to evaluating the predictive performance of laboratory tests is to use the outcome of culture-confirmed infection.

- **Complete blood count (CBC):** The most commonly used laboratory test to evaluate risk of EOS among newborns is the CBC and its components. Recent studies suggest this practice should be reconsidered. Multiple single centers have reported the poor sensitivity of total WBC and differential for identifying culture-confirmed EOS among initially well-appearing infants. The rates at which newborns are flagged with “abnormal” WBC vary widely, influenced by metric chosen, the definition of abnormal, and the time at which the test is obtained (see Table 1.4). Newman et al. addressed each of these issues in a multicenter study including 67,623 CBC/differential tests obtained within 1 hour of a blood culture, with 245 cases of culture-confirmed infection (incidence of EOS, 0.4% among tested infants). Test performance was analyzed using multiple approaches, including determining the mean values and distribution of values comparing infected and uninfected infants and sensitivity, specificity, and likelihood ratios for infection at different thresholds of “abnormal.” In addition, multiple models were built to determine if adjusting for age, birth weight, birth facility, year of birth, maternal diagnosis of preeclampsia, mode of delivery, and 5-minute Apgar score would improve test performance. The best test performance was obtained by accounting for age in hours after birth. The poorest test performance associated with values obtained immediately after birth was particularly notable: the receiver–operator curve for total WBC was 0.52 at <1 hour of age. Platelet count was also nonpredictive, even for values obtained >4 hours of age. The best test performance was obtained for extremely low WBC and ANC values obtained after 4 hours of age; the I/T (essentially the I/T divided by the ANC) was the only test characteristic with good performance independent of newborn age. A larger multicenter study including 293 centers in the Pediatrix Medical Group performed similar analyses: 168,604 blood cultures from infants admitted to a neonatal intensive care unit were matched to CBC obtained within 24 hours of the blood culture, including 2001 cases of culture-confirmed EOS. This study included infants of all gestational ages, with results provided in gestational age categories. Poor sensitivity was again found for WBC, the differential components, and the platelet count. Among infants born at ≥37 weeks’ gestation, the highest likelihood ratios were associated with WBC <5000, ANC <1500, and I/T >0.5, and platelet counts were nonpredictive. Despite this evidence, U.S. national recommendations continue to advocate for use of the WBC and differential in EOS risk assessment.

- **CRP and other markers of inflammation:** Most studies of inflammatory molecules and biomarkers have been performed on infants who are symptomatic and being evaluated for sepsis. None of these has yet proven useful in predicting infection in initially well-appearing infants. Nonetheless, CRP was the second most common laboratory test used to identify infants at risk for EOS in a national survey of neonatal providers. CRP is one of several acute-phase reactant proteins synthesized in the liver in response to proinflammatory cytokines. CRP is documented to rise and fall over the course of neonatal GBS infection with a variable course. A single measurement of CRP sent at the same time as blood culture lacks sensitivity for EOS, although serial measurements have a likelihood ratio of ≈3 for predicting culture-confirmed infection. CRP is particularly problematic for use in the immediate neonatal period, as it rises in response to other common neonatal...
conditions such as bruising and cephalohematoma and in generalized conditions of fetal distress that lead to meconium-stained amniotic fluid.49 Similarly, procalcitonin is an acute-phase reactant that increases earlier than CRP in the course of infection, but also rises in response to asphyxia, respiratory distress syndrome, and pneumothorax; procalcitonin also appears to naturally rise and decline in the first 48 hours after birth.50 A review of 18 neonatal procalcitonin studies demonstrated a wide range of cutoff values, definitions for outcomes, and ultimately variable test performance.51 Most recently, molecular methods have been utilized to identify a “molecular signature” of EOS. Sweeney and colleagues employed an 11-gene microarray to identify culture-confirmed early- and late-onset infection in retrospective analysis of three different study cohorts including a wide range of gestational ages. The study found high diagnostic accuracy in distinguishing culture-confirmed infection.52

What are the economic and social costs of EOS risk assessment? Many reports have focused on the economic impact of maternal GBS screening and IAP, but few have addressed the costs of neonatal assessment and treatment. Economic analysis of EOS risk activities is complicated by variation across centers in the both diagnostic and therapeutic approach and, importantly, whether newborns are admitted to higher-cost intensive care units or primarily cared for in well-nursery settings. We performed an economic analysis addressing the costs associated with EOS risk assessment among well-appearing infants born at ≥36 weeks’ gestation who were ultimately found to be uninfected. We estimated that a local algorithm aligned with the categorical approach recommended in the 2010 CDC GBS guidelines results in $110,000 to $150,000 in costs per 1000 live births.54 Extrapolated to ≈3.6 million term births per year in the United States, approximately $400 to $500 million is spent annually on EOS-associated procedures. The social costs are also considerable. In most perinatal centers, blood tests, intravenous line placement, and antibiotic administration are performed in neonatal care settings separate from maternal care settings, resulting in mother–infant separation after birth. In a survey of national EOS, 95% of respondents separate mother and infant to perform laboratory testing, and ≈40% of newborns receiving antibiotics for EOS are separated from the mother for the duration of care.5 Such separation has a significantly negative effect on the establishment of breastfeeding. In a study of 692 asymptomatic term infants separated from the mother for the evaluation of EOS, separation during the first 2 hours after birth resulted in significantly lower incidence of exclusive breastfeeding and increased use of formula in the absence of a medical indication.55 This unintended consequence of EOS evaluation among well-appearing newborns may have long-term child health implications.

Are there long-term consequences that result from perinatal antibiotic administration? Microbial exposure has been shown to have a role in determining host immune behavior as early as prenatal life, via the maternal microflora.54 This is followed by a postnatal period when the increase in microbial exposure at birth overlaps with the critical developmental window of immune cell programming.55–58 The roles of commensal microflora exposure in innate and adaptive immune pathways, including induction of toll-like receptor tolerance to exogenous endotoxin and production of short-chain fatty acid (SCFA) that stimulate the regulatory T-cell population, have been demonstrated in multiple studies.59,60 In preclinical studies, disruption of the early host microflora—either absolutely (as in germ-free mice) or partially by antibiotic exposure—results in an increased proinflammatory response in host gut to environmental irritants and an increased mortality when fighting invasive pathogens.61,62 Mice given subtherapeutic levels of antibiotics after weaning exhibit increased adiposity and increased bacterial SFCA metabolism and energy extraction.63,64 Early low-dose antibiotics combined with a high-fat diet cause even greater increases in adiposity.65,66 Many of these effects occur only during the newborn period, highlighting the importance of early-life microbiota and the potential for disruption to cause lasting adverse health outcomes. Intrapartum antibiotics are administered with the intent of altering colonization of the newborn with pathogenic bacterial species. An unintended consequence may be more global alteration of the early microbiota in both diversity and composition. Recently, multiple studies have documented the
impact of intrapartum antibiotics, with effects extending days to months (Table 1.5).67–78 Neonatal antibiotics administered for risk of EOS have not been as well studied to date, but are anticipated to have some impact on the developing microbiota as well. Epidemiologic studies have reported an association of early-life antibiotics with increased risk of multiple adverse outcomes, including obesity, diabetes, asthma, eczema and food allergies, altered response to subsequent infections, and decreased vaccine responses.55,79–89 Whether intrapartum and neonatal antibiotics specifically have enduring health consequences for the infant is a source of active research that will affect the risk/benefit balance of EOS risk assessment practices.

### Table 1.5 STUDIES ADDRESSING PERINATAL ANTIBIOTICS AND NEONATAL MICROBIOME

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Infant Population (#)</th>
<th>Exposure</th>
<th>Microbiota Source and Timing</th>
<th>Impact on IAP-Exposed Compared With Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>67–70</td>
<td>Term (52)</td>
<td>IAP (ampicillin)</td>
<td>Infant gut at 7 and 30 days</td>
<td>↑ Enterobacteriaceae and ↓ Bifidobacterium at both 7 and 30 days BF impact</td>
</tr>
<tr>
<td>71</td>
<td>Term (198)</td>
<td>IAP/VD (96) No IAP/VD (40) IAP/CS/P (17) IAP/CS/E (23)</td>
<td>Infant gut at 3 months and 1 year IAP impact</td>
<td>↑ Proteobacterium and Clostridia (especially CS) ↓ Bacteroidetes BF impact</td>
</tr>
<tr>
<td>72</td>
<td>Term dyads (262)</td>
<td>GBS status IAP</td>
<td>Infant gut at 1 and 6 months</td>
<td>↑ Clostridiaceae, Ruminococcaceae, Enterococcaceae in infants born to GBS + mothers when adjusting for IAP</td>
</tr>
<tr>
<td>73</td>
<td>Women at &lt;32 weeks’ gestation (27)</td>
<td>IAP for GBS and GBS unknown</td>
<td>Maternal vaginal microbiota</td>
<td>Most Lactobacillus in GBS+/no IAP Most Pseudomonas in GBS +/- IAP</td>
</tr>
<tr>
<td>74</td>
<td>Term dyads (36) Mothers with elevated BMI</td>
<td>IAP (cefaizolin or penicillin G)</td>
<td>Placenta Oral (mother and infant) Gut (mother)</td>
<td>↑ Proteobacteria ↓ Streptococcaceae, Gemellaceae, and Lactobacilli ↓ Maternal–infant similarity Both IAP and PROM ↓ Lactobacillus in infant ↓ Clostridia ↓ Enterobacteriaceae even when adjusting for prematurity</td>
</tr>
<tr>
<td>75</td>
<td>Term dyads (45)</td>
<td>Observational</td>
<td>Vertical transmission of Lactobacillus</td>
<td>Both IAP and PROM ↓ Lactobacillus in infant ↓ Clostridia ↓ Enterobacteriaceae even when adjusting for prematurity</td>
</tr>
<tr>
<td>76</td>
<td>Term (50)</td>
<td>IAP for GBS</td>
<td>Stool culture at day 3</td>
<td>Lactobacillus in infant</td>
</tr>
<tr>
<td>77, 78</td>
<td>Preterm (27) Term (13)</td>
<td>Prematurity</td>
<td>Longitudinal over 3 months</td>
<td>Maternal–infant similarity</td>
</tr>
</tbody>
</table>

BF, Breastfeeding; BMI, body mass index; CS/P, planned cesarean section delivery; CS/E, emergent cesarean section delivery; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; PROM, premature rupture of membranes; VD, vaginal delivery.

### REFERENCES


