Epidemiology of Neonatal Early-onset Sepsis
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Epidemiology of Neonatal Early-onset Sepsis

Karen M. Puopolo, MD, PhD*

Author Disclosure
Dr Puopolo has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/ investigative use of a commercial product/ device.

Objectives After completing this article, readers should be able to:

1. Describe the incidence and microbiology of neonatal early-onset sepsis (EOS).
2. Identify clinical risk factors for neonatal EOS.
3. Review the impact of group B streptococcal prophylaxis policies on the epidemiology of neonatal EOS.
4. Delineate the differences in incidence, risk, and microbiology of neonatal EOS between term and very low-birthweight infants.

Abstract
Neonatal early-onset sepsis (EOS) continues to be a significant source of morbidity and mortality among newborns, especially among very-low birthweight infants. Epidemiologic risk factors for EOS have been defined, and considerable resources are devoted to the identification and evaluation of infants at risk for EOS. The widespread implementation of intrapartum antibiotic prophylaxis for the prevention of early-onset neonatal group B Streptococcus (GBS) disease has reduced the overall incidence of neonatal EOS and influenced the microbiology of persistent early-onset infection. Most early-onset neonatal GBS disease now occurs in preterm infants or in term infants born to mothers who have negative GBS screening cultures. Ongoing clinical challenges include reassessment of clinical risk factors for EOS in the era of GBS prophylaxis; more accurate identification of GBS-colonized women; and continued surveillance of the impact of GBS prophylaxis practices on the microbiology of EOS, particularly among very low-birthweight infants.

Introduction
Bacterial sepsis and meningitis continue to be major causes of morbidity and mortality in newborns, particularly in very-low birthweight (VLBW) infants (birthweight <1,500 g). Neonatal early-onset sepsis (EOS) is defined by the Centers for Disease Control and Prevention (CDC) as blood or cerebrospinal fluid culture-proven infection occurring in the newborn who is younger than 7 days of age. (1) For the continuously hospitalized VLBW infant, EOS is defined as culture-proven infection occurring at fewer than 72 hours of age. (2) The alternative definition in VLBW infants is justified by two findings: 1) the risks for infection in VLBW infants after 72 hours of age primarily derive from the specifics of ongoing neonatal intensive care rather than from perinatal risk factors, and 2) the organisms causing infection after 72 hours of age among VLBW infants reflect the nosocomial flora of the neonatal intensive care unit (NICU) more than perinatally acquired maternal flora. (2)

The overall incidence of EOS in the United States in the past 10 years is 1 to 2 cases per 1,000 live births; the incidence is 10-fold higher in VLBW infants. (3)(4) Since

Abbreviations

BWH: Brigham and Women’s Hospital
CDC: Centers for Disease Control and Prevention
EOS: early-onset sepsis
GBS: group B Streptococcus
IAP: intrapartum antibiotic prophylaxis
MRSA: methicillin-resistant Staphylococcus aureus
NICHD: National Institute of Child Health and Development
NICU: neonatal intensive care unit
PCR: polymerase chain reaction
VLBW: very low birthweight

*Assistant Professor of Pediatrics, Harvard Medical School; Attending Physician, Channing Laboratory and Department of Newborn Medicine, Brigham and Women’s Hospital and Division of Newborn Medicine, Children’s Hospital, Boston.

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Sepsis has been the leading cause of death among newborns in the United States in 2000 to 2001. (5) Mortality from EOS decreased significantly in term infants with improvements in NICU care over the past 20 years, primarily due to advances in respiratory support (including surfactant replacement, high-frequency ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation). Mortality rates from EOS are higher among term infants compared with 19.9% of infants born before 37 weeks’ gestation, an eightfold increase in the risk of infection- attributable mortality. (1) Among VLBW infants, mortality is greater: 35% of VLBW infants who had EOS died in a 2002 to 2003 National Institute of Child Health and Development (NICHD) Neonatal Network cohort study compared with an overall 11% mortality among uninfected VLBW infants. (3) Finally, neonatal survivors of EOS may have severe neurologic sequelae, attributable to concomitant meningitis or from hypoxemia resulting from septic shock, persistent pulmonary hypertension, and hypoxic respiratory failure. Hypotension and increased concentrations of inflammatory cytokines during sepsis also may injure the developing neonatal central nervous system.

**Microbiology of EOS**

Since the 1980s, GBS has been the leading cause of neonatal EOS in the United States. Despite the widespread implementation of IAP, early-onset GBS disease remains the leading cause of EOS in term infants (Table 1). However, coincident with the increased use of IAP for GBS, gram-negative enteric bacteria have become the leading cause of EOS in preterm infants (Table 2). (3)(4)(6) In Table 1, data from the CDC Active Bacterial Core Surveillance program are compared with data from our single center (the Brigham and Women’s Hospital [BWH] in Boston). The CDC data were obtained from the Atlanta and San Francisco metropolitan areas in 1998 to 2000. The BWH is a large maternity hospital that has an average 9,000 deliveries per year. The BWH data encompass all cases of EOS occurring in infants cared for in the 50-bed Level III BWH NICU for the period 1990 to 2007. Both data sets reveal a similar spectrum of organisms, with a predominance of gram-positive organisms, primarily GBS and other streptococcal species. Table 2 compares data from the NICHD Neonatal Network and our single center. The NICHD data are from 16 centers over the period 2002 to 2003. Our single-center data include cases of EOS occurring in infants cared for in the BWH NICU from 1990 to 2007 whose birthweights were less than 1,500 g. Again, the data sets are strikingly similar, with a predominance of enteric bacilli, primarily *Escherichia coli* but including a spectrum of other Enterobacteriaceae.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Centers for Disease Control and Prevention (n=408)</th>
<th>%</th>
<th>Brigham and Women’s Hospital (n=307)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS</td>
<td>166</td>
<td>40.7</td>
<td>130</td>
<td>42.3</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>70</td>
<td>17.2</td>
<td>64</td>
<td>20.8</td>
</tr>
<tr>
<td>Other streptococci*</td>
<td>93</td>
<td>22.7</td>
<td>37</td>
<td>12.1</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>16</td>
<td>3.9</td>
<td>13</td>
<td>4.2</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>15</td>
<td>3.7</td>
<td>12</td>
<td>3.9</td>
</tr>
<tr>
<td>CONS</td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>4.6</td>
</tr>
<tr>
<td><em>Listeria</em></td>
<td>6</td>
<td>1.5</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td><em>Bacteroides</em></td>
<td>5</td>
<td>1.2</td>
<td>14</td>
<td>4.6</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>9</td>
<td>2.2</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>9</td>
<td>2.2</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>Other gram-negative*</td>
<td>16</td>
<td>3.9</td>
<td>6</td>
<td>1.6</td>
</tr>
<tr>
<td>Other*</td>
<td>3</td>
<td>0.7</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>Total gram-positive</td>
<td>299</td>
<td>73.3</td>
<td>211</td>
<td>68.7</td>
</tr>
<tr>
<td>Total gram-negative</td>
<td>109</td>
<td>26.7</td>
<td>96</td>
<td>31.3</td>
</tr>
</tbody>
</table>

CONS = coagulase-negative *Staphylococcus*, GBS = group B *Streptococcus*.

| *Other streptococci* include *S pneumoniae*, *S bovis*, *S mitis*, *Peptostreptococcus*, and viridans streptococci. |
| *Other gram-negative organisms include Pseudomonas, Proteus, Morganella, and Teratia. |
| Other organisms include *Bacillus* and *Clostridium*. |

1% to 2% of colonized infants develop invasive GBS. Mothers colonized with GBS are colonized at birth, and the absence of IAP, approximately 50% of infants born to mothers demonstrated that nearly 60% were colonized at any given time. A longitudinal study of GBS colonization in a cohort of primarily young, sexually active women demonstrated that nearly 60% were colonized at some time over a 12-month period. (8) In the United States currently is caused by types Ia, Ib, II, III, and V GBS. (1) Type III GBS more commonly are associated with late-onset sepsis and meningitis. GBS are facultative diplococci that are primarily intestinal tracts and the upper respiratory tract in young infants. GBS frequently colonizes the human genital and gastrointestinal tracts and the upper respiratory tract in young infants. GBS are facultative diplococci that are primarily identified by the Lancefield group B carbohydrate antigen. They are subtyped further into nine distinct capsular polysaccharide serotypes (types Ia, Ib, II, III, IV, V, VI, VII, VIII). A potential tenth polysaccharide type recently has been identified. (7) Most GBS EOS in the United States currently is caused by types Ia, Ib, II, III, and V GBS. (1) Type III GBS more commonly are associated with late-onset sepsis and meningitis.

Early-onset GBS infection is acquired in utero or during passage through the birth canal. Approximately 20% to 30% of American women are colonized with GBS at any given time. A longitudinal study of GBS colonization in a cohort of primarily young, sexually active women demonstrated that nearly 60% were colonized with GBS at some time over a 12-month period. (8) In the absence of IAP, approximately 50% of infants born to mothers colonized with GBS are colonized at birth, and 1% to 2% of colonized infants develop invasive GBS disease. Lack of maternally derived protective capsular polysaccharide-specific antibody is associated with the development of invasive GBS disease. Other factors predisposing the newborn to GBS disease are less well understood, but relative deficiencies in complement, neutrophil function, and innate immunity may be important.

A number of studies helped define maternal and neonatal risk factors for GBS EOS. Benitz and associates (9) performed a literature review and data reanalysis of studies of risk factors for GBS EOS from the 1970s to the 1990s to generate odds ratio estimates for several clinical factors (Table 3). Maternal GBS colonization alone was far more predictive than any other maternal or neonatal clinical characteristic, a finding that is the evidence base for the current recommendation for use of IAP according to maternal GBS colonization status.

Additional maternal clinical factors predictive of early-onset GBS disease include maternal intrapartum fever (temperature >99.5°F [37.5°C]), the clinical diagnosis of chorioamnionitis, and prolonged rupture of membranes (>18 h). Neonatal risk factors include prematurity (<37 weeks’ gestation) and low birthweight (<2,500 g), especially birthweight less than 1,000 g. Although once considered a risk factor for GBS disease, GBS frequently colonizes the human genital and gastrointestinal tracts and the upper respiratory tract in young infants. GBS are facultative diplococci that are primarily identified by the Lancefield group B carbohydrate antigen. They are subtyped further into nine distinct capsular polysaccharide serotypes (types Ia, Ib, II, III, IV, V, VI, VII, VIII). A potential tenth polysaccharide type recently has been identified. (7) Most GBS EOS in the United States currently is caused by types Ia, Ib, II, III, and V GBS. (1) Type III GBS more commonly are associated with late-onset sepsis and meningitis.

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Table 2. Organisms Causing Early-onset Sepsis in Very Low-birthweight Infants

<table>
<thead>
<tr>
<th>Organism</th>
<th>National Institute of Child Health and Development (n=102) %</th>
<th>Brigham and Women’s Hospital (n=95) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS</td>
<td>12</td>
<td>11.8</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>42</td>
<td>41.2</td>
</tr>
<tr>
<td>Other streptococci*</td>
<td>9</td>
<td>8.8</td>
</tr>
<tr>
<td>CONS</td>
<td>15</td>
<td>14.7</td>
</tr>
<tr>
<td>Listeria</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Other gram-positive*</td>
<td>8</td>
<td>7.8</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>N/A</td>
<td>9</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td><em>Citrobacter</em></td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Other gram-negative*</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Fungal</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Total gram-positive</td>
<td>46</td>
<td>45.1</td>
</tr>
<tr>
<td>Total gram-negative</td>
<td>54</td>
<td>52.9</td>
</tr>
</tbody>
</table>

CONS=coagulase-negative Staphylococcus, GBS=group B Streptococcus. *Other streptococci include S pneumoniae, S mitis, viridans streptococci, and group A Streptococcus. †Other gram-positive organisms include Bacillus, Corynebacterium, Staphylococcus aureus. ‡Other gram-negative organisms include Klebsiella, Pseudomonas, Acinetobacter, Proteus, Morganella, and Fusobacterium.


EOS Caused by GBS

GBS frequently colonizes the human genital and gastrointestinal tracts and the upper respiratory tract in young infants. GBS are facultative diplococci that are primarily identified by the Lancefield group B carbohydrate antigen. They are subtyped further into nine distinct capsular polysaccharide serotypes (types Ia, Ib, II, III, IV, V, VI, VII, VIII). A potential tenth polysaccharide type recently has been identified. (7) Most GBS EOS in the United States currently is caused by types Ia, Ib, II, III, and V GBS. (1) Type III GBS more commonly are associated with late-onset sepsis and meningitis.

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Table 3. Risk Factors for Early-onset GBS Sepsis in the Absence of IAP

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal GBS colonization</td>
<td>204 (100 to 419)</td>
</tr>
<tr>
<td>Birthweight &lt;1,000 g</td>
<td>24.8 (12.2 to 50.2)</td>
</tr>
<tr>
<td>Birthweight ≤2,500 g</td>
<td>7.37 (4.48 to 12.1)</td>
</tr>
<tr>
<td>Rupture of membranes &gt;18 h</td>
<td>7.26 (4.42 to 12.0)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>6.42 (2.32 to 17.8)</td>
</tr>
<tr>
<td>Intrapartum temperature &gt;99.5°F</td>
<td>4.05 (2.17 to 7.56)</td>
</tr>
</tbody>
</table>

GBS=group B Streptococcus, IAP=intrapartum antibiotic prophylaxis.

multiple gestation now is not considered an independent risk factor for EOS. (10) GBS bacteriuria during pregnancy is associated with heavy colonization of the rectovaginal tract and is considered a significant risk factor for EOS. Black race is associated with higher rates of GBS EOS, although it is not entirely clear whether this simply reflects the higher rate of GBS colonization in this population. The most recent CDC surveillance data demonstrate a fourfold increased incidence of neonatal GBS EOS among black infants compared with white infants. (1)

**IAP for the Prevention of Early-onset GBS infection**

After recognizing that maternal colonization with GBS was the greatest risk factor for neonatal GBS disease, multiple trials demonstrated that the use of intrapartum penicillin or ampicillin significantly reduced the rate of neonatal colonization with GBS and the incidence of early-onset GBS disease. The ability to prevent neonatal GBS colonization and neonatal EOS was demonstrated most dramatically in a trial of only 160 women in 1986. (11) IAP for the prevention of GBS EOS can be administered to pregnant women during labor based on specific clinical risk factors for early-onset GBS infection or the results of antepartum screening of pregnant women for GBS colonization. In 1996, the CDC published consensus guidelines for the prevention of neonatal GBS disease that endorsed the use of either a risk factor-based or screening-based approach. (10) The CDC later conducted a large retrospective cohort study of more than 600,000 births that demonstrated the superiority of the screening-based approach for the prevention of neonatal GBS disease. (12) Based on these results, the CDC issued revised guidelines for the prevention of early-onset GBS disease in 2002, recommending universal screening of pregnant women for GBS by rectovaginal culture at 35 to 37 weeks’ gestation and management of IAP based on screening results. (13) The revised guidelines can be accessed at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5111a1.htm or in PDF form at http://www.cdc.gov/mmwr/PDF/rr/rr5111.pdf.

The CDC guideline includes specific recommendations for pregnant women who have documented GBS bacteriuria or who previously delivered infants who had GBS disease and for the use of IAP in women experiencing threatened preterm labor. The revised guidelines also address concerns over the documented emergence of GBS resistance to erythromycin and clindamycin, antibiotics frequently used for IAP in women allergic to penicillin. The CDC continues to recommend penicillin or ampicillin for IAP. In those who have penicillin allergy, testing of GBS screening isolates for antibiotic susceptibility is recommended to guide the choice of antibiotic (erythromycin, clindamycin, cefazolin, or vancomycin) for IAP. “Adequate IAP” is defined as the administration of one of the endorsed antibiotics 4 or more hours prior to delivery. The revised CDC guideline also includes a recommended algorithm for the evaluation of infants born to mothers exposed to IAP.

**Current Status of GBS EOS**

CDC active surveillance data for the United States from 1999 to 2005 demonstrate that the incidence of GBS EOS has fallen to 0.34 cases per 1,000 live births in 2003 to 2005 (compared with 1.7 cases per 1,000 live births in 1993). (1) We recently evaluated the reasons for persistent GBS EOS despite the use of a screening-based approach to IAP at the BWH. (14)(15) We found that most GBS EOS in term infants now occurs in infants born to women who have negative antepartum screening results for GBS colonization. Many of the mothers in this study had other intrapartum risk factors for sepsis, underscoring the importance of continued evaluation of infants at risk for EOS in the era of GBS prophylaxis. There is a low incidence (approximately 4%) of noncordance between results of maternal GBS screening performed at 35 to 37 weeks’ gestation and repeat screening on presentation for delivery at term, (16) which may account for many cases of persistent GBS EOS.

Bacterial culture remains the CDC-recommended standard for detection of maternal GBS colonization. In 2002, the United States Food and Drug Administration approved the first polymerase chain reaction (PCR)-based rapid diagnostic test for use in detection of maternal GBS colonization. The test can be completed in 1 hour and potentially allows for screening of pregnant women on presentation for delivery. (17) Although this type of testing could address the risk of antenatal false-negative GBS screens, the costs and technicalities of providing continuous support for a real-time PCR-based diagnostic are considerable, and most obstetric services continue to rely on antenatal screening culture alone.

**EOS Caused by E coli**

*E coli* is the second most common organism isolated in EOS in all neonates and the single most common EOS organism in VLBW infants. (3)(6) *E coli* are facultative anaerobic gram-negative rods found universally in the human intestinal tract and commonly in the human vagina and urinary tract. There are hundreds of different organisms...
antigenic types of *E. coli*, but EOS *E. coli* infections, particularly those complicated by meningitis, are primarily due to strains that have the K1-type polysaccharide capsule. With the implementation of IAP against GBS, an increasing proportion of EOS cases are caused by gram-negative organisms. (4) Whether GBS IAP policies are contributing to an absolute increase in the incidence of EOS caused by gram-negative organisms, particularly ampicillin-resistant gram-negative organisms, is controversial.

In 2003, the CDC published a review of 23 reports of EOS in the era of GBS prophylaxis, (4) which concluded that there is no evidence of an increase in non-GBS EOS among term infants. A case-control study of 132 cases of neonatal EOS caused by *E. coli* occurring from 1997 to 2001 recently published by the CDC concluded that exposure to intrapartum antibiotic therapy did not increase the odds of invasive early-onset *E. coli* infection. (18) In fact, this study demonstrated a protective effect of intrapartum antibiotic exposure on the risk of *E. coli* EOS among term infants. However, worrisome increases in non-GBS EOS and ampicillin-resistant EOS in VLBW infants have been reported by single centers (19) and by the NICHD Neonatal Research Network. (20) The multicenter NICHD Network documented an increase in *E. coli* EOS in VLBW infants from 3.2 cases per 1,000 live births in 1991 to 1993 to 7.0 cases per 1,000 live births in 2002 to 2003.

Trends in the microbiology of EOS likely vary to some extent by institution and may be influenced by local obstetric practices as well as by local variation in indigenous bacterial flora. To address this important issue, the CDC Active Bacterial Core Surveillance Program and the NICHD Neonatal Research Network are conducting active surveillance for early-onset neonatal sepsis from 2007 to 2009 that will include data on intrapartum antibiotic exposure and collection of specific infecting bacterial isolates for microbiologic study. (21) Information from studies of this type may help guide clinical decisions regarding empiric antibiotic choice for EOS, particularly in VLBW infants. Currently, when there is strong clinical suspicion for sepsis in a critically ill infant, the possibility of ampicillin-resistant gram-negative infection suggests the consideration of empiric use of a third-generation cephalosporin such as cefotaxime or ceftazidime.

**Other Organisms Responsible for EOS**

In addition to GBS and *E. coli*, a number of other pathogens that cause EOS in the United States deserve special note. *Listeria monocytogenes* are gram-positive, beta-hemolytic, motile bacteria that most commonly infect humans via the ingestion of contaminated food. An association with prepared foods held at moderate temperature (particularly cheeses and deli meats) has been documented, occasionally in epidemic outbreaks. These bacteria do not cause significant disease in immunocompromised (ie, renal transplant patients), in pregnant women and their fetuses, and in newborns. The true incidence of listeriosis in pregnancy is difficult to determine because many cases are undiagnosed when they result in spontaneous abortion of the previable fetus. Obligate anaerobic bacteria (primarily the encapsulated enteric organism *Bacteroides fragilis*) can cause neonatal EOS and justify the use of both aerobic and anaerobic blood culture bottles in the evaluation of EOS. Although both methicillin-sensitive and methicillin-resistant *S. aureus* (MRSA) cause a large proportion of hospital-acquired infection in VLBW infants and represent an increasing issue in community-acquired pediatric infections, they remain a rare cause of neonatal EOS. A recent study of 5,732 pregnant women documented a 3.5% incidence of MRSA in GBS rectovaginal screening cultures but found no cases of MRSA neonatal EOS in delivered infants. (22) Finally, fungal organisms (primarily *Candida* sp) rarely cause neonatal EOS. Fungal EOS is found largely in preterm and VLBW infants and in our center is associated with very prolonged antibiotic (>24 h) exposure of pregnant mothers prior to delivery.

**Clinical Risk Factors for EOS**

Maternal and infant characteristics associated with the development of EOS have been studied most rigorously with respect to GBS EOS, but much of these data were obtained prior to the implementation of IAP for GBS prevention. Perhaps the most challenging clinical issue in the era of GBS prophylaxis is the identification and evaluation of the initially asymptomatic term and late preterm infant at risk for EOS. Escobar and associates (23) studied a cohort of more than 18,000 infants born in 1995 to 1996, cared for in a single health-care plan, whose birthweights were at least 2,000 g, and who had no major anomalies. Of these, 2,785 infants were evaluated for EOS with a complete blood count and blood culture. Multivariate analyses of predictors of EOS accounted for intrapartum antibiotic exposure and modeled maternal chorioamnionitis either as a clinical obstetric diagnosis or as an entity defined by prolonged rupture of membranes and maternal fever. Results of the latter model are shown in Table 4, but the overall findings were the same in each model: maternal intrapartum fever, the
clinical diagnosis of chorioamnionitis, low absolute neutrophil count, and the presence of meconium-stained amniotic fluid each were associated with increased risk of EOS, with some modification of these factors in the presence of maternal intrapartum antibiotic exposure. Although this study aids in our understanding the issues of overall EOS risk in the era of GBS prophylaxis, it also underscores the challenge of evaluating the initially asymptomatic infant. Only 1% of the initially asymptomatic infants in this study had EOS, and asymptomatic status predicted against infection. Yet, this incidence is 10-fold higher than the population risk of 1 to 2 cases per 1,000 live births, pointing out the importance of the clinical factors that prompted the evaluation for infection and confirming the concept that asymptomatic status alone cannot rule out infection.

Algorithm for the Evaluation of Asymptomatic Infants at Risk for EOS
The CDC 2002 guidelines for the use of IAP to prevent early-onset GBS disease address the evaluation of infants at risk for EOS, with some modification of these factors in the presence of maternal intrapartum antibiotic exposure. Although this study aids in our understanding the issues of overall EOS risk in the era of GBS prophylaxis, it also underscores the challenge of evaluating the initially asymptomatic infant. Only 1% of the initially asymptomatic infants in this study had EOS, and asymptomatic status predicted against infection. Yet, this incidence is 10-fold higher than the population risk of 1 to 2 cases per 1,000 live births, pointing out the importance of the clinical factors that prompted the evaluation for infection and confirming the concept that asymptomatic status alone cannot rule out infection.

Current Clinical Challenges in EOS
EOS remains an infrequent but potentially devastating clinical issue for term and preterm infants. The widespread implementation of IAP for the prevention of GBS early-onset disease has resulted in an overall decrease in neonatal EOS in the United States. There remain, however, a number of research questions that need to be addressed to optimize neonatal care further with respect to EOS. Considerable clinical time and economic resources are expended in the identification and evaluation of infants at risk for EOS. A multicenter reassessment of the clinical risk factors for EOS in the setting of proper implementation of a screening-based program for IAP should be performed. Such a study may allow clinicians to identify more accurately the initially asymptomatic infant who needs to be evaluated for infection in the era of GBS prophylaxis. The utility of real-time PCR-based GBS diagnostics, used either as a substitute for third trimester culture-based GBS screening or as an addition to culture-based screening, needs to be assessed on a national basis to determine if this test can lower the national incidence of early-onset GBS disease further. Finally, the CDC has endorsed the need for continued surveillance to assess the impact of GBS prophylaxis practices on the microbiology of EOS, particu-
larly among VLBW infants. Research into individual center obstetric practices as well as national surveillance may help identify the risks that may be associated with IAP to allow neonates to continue to benefit from this important advance in the prevention of EOS.

**References**


2. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very...
5. Widespread implementation of intrapartum antibiotic prophylaxis has altered the epidemiology of early-onset sepsis (occurring at less than 72 hours after birth) in the newborn. The incidence of group B Streptococcus (GBS) early-onset sepsis has decreased; the incidence of non-GBS early-onset sepsis is unchanged or decreasing. Of the following, the national incidence of GBS early-onset sepsis, as estimated in 2003 through 2005, is closest to:

A. 0.03 per 1,000 live births.
B. 0.30 per 1,000 live births.
C. 0.60 per 1,000 live births.
D. 0.90 per 1,000 live births.
E. 0.20 per 1,000 live births.

6. The spectrum of microorganisms causing early-onset sepsis in the era of intrapartum antibiotic prophylaxis is different between term neonates (>2,000 g birthweight) and very low-birthweight neonates (<1,500 g birthweight). Of the following, the most common microorganism attributable to early-onset sepsis in term neonates, as reported by the Centers for Disease Control and Prevention, is:

A. Coagulase-negative Staphylococcus.
B. Escherichia coli
C. Group B Streptococcus.
D. Haemophilus influenzae.
E. Listeria monocytogenes.

7. The spectrum of microorganisms causing early-onset sepsis in the era of intrapartum antibiotic prophylaxis is different between term neonates (>2,000 g birthweight) and very low-birthweight (VLBW) neonates (<1,500 g birthweight). Of the following, the most common microorganism attributable to early-onset sepsis in VLBW neonates, as reported by the National Institute of Health and Human Development Neonatal Research Network, is:

A. Coagulase-negative Staphylococcus.
B. Escherichia coli.
C. Group B Streptococcus.
D. Haemophilus influenzae.
E. Listeria monocytogenes.

8. Most cases of early-onset sepsis attributable to GBS in the United States currently are caused by GBS serotypes Ia, Ib, II, III, and V. Intrapartum antibiotic prophylaxis for prevention of GBS sepsis was advocated following several studies examining the maternal and neonatal risk factors for early-onset GBS sepsis. Of the following, the clinical risk factor most predictive of neonatal early-onset GBS sepsis in the absence of intrapartum antibiotic prophylaxis is:

A. Chorioamnionitis.
B. Extremely low birthweight (<1,000 g).
C. Intrapartum fever (temperature >99.5°F [37.5°C]).
D. Maternal GBS colonization.
E. Prolonged rupture of membranes (>18 hours).