Group B Streptococcus and Early-Onset Sepsis in the Era of Maternal Prophylaxis

Joyce M. Koenig, MD*, William J. Keenan, MD

KEYWORDS
• Group B Streptococcus • Sepsis • Pneumonia • Meningitis
• Neonate • Newborn • Review

HISTORICAL ASPECTS OF MATERNAL Puerperal SEPSIS AND GROUP B STREPTOCOCCUS AS A CAUSATIVE AGENT

Puerperal sepsis (or “childbed fever”) has been associated with maternal morbidity and mortality for centuries.¹ The controversial figure, Ignác Semmelweiss, a Hungarian obstetrician who practiced in Vienna in the early to mid-1800s, was the first to identify an infectious mode of transmission of puerperal sepsis.²,³ Semmelweiss, in a key observation, linked the septic death of a colleague after an autopsy of a woman with puerperal sepsis to an infectious agent in “decaying matter,” a contentious idea at a time when puerperal sepsis was thought to occur solely in women. His observations led to his strong espousal of hand washing before the examination of patients. These speculations of an organic causative agent in puerperal sepsis helped to lay the groundwork for the germ theory of infection several decades later.⁴,⁵

Group B Streptococcus (Streptococcus agalactiae; GBS) was first identified as a cause of puerperal sepsis in 1935 when Lancefield and Hare⁶ observed differences in the hemolytic culture characteristics of two types of streptococci obtained from autopsies of women who had puerperal sepsis. Fry⁷ subsequently reported several cases of fatal puerperal sepsis related to group B streptococcal disease. The use of antibiotics, initially sulfa drugs, followed by penicillin, dramatically decreased mortality attributable to puerperal sepsis. It was not until the early 1960s, however, that an association was observed between GBS infection in mothers and their newborn infants.⁸,⁹ Subsequent studies showed that although all known GBS serotypes could cause maternal infection, type III was associated with most invasive neonatal disease (meningitis).¹⁰

This work was supported in part by grant HD047401 from the National Institutes of Health and the Pediatric Research Institute, Cardinal Glennon Children’s Medical Center Foundation. Division of Neonatal-Perinatal Medicine, Department of Pediatrics, E. Doisy Research Building, Saint Louis University, 1100 South Grand Boulevard, Saint Louis, MO 63104, USA
* Corresponding author.
E-mail address: koenijm@slu.edu (J.M. Koenig).
GBS can cause significant maternal morbidity, particularly endometritis, chorioamnionitis, and bacteremia.\textsuperscript{11} In a multiregional surveillance study that followed the initial recommendations (1992) of the American Academy of Pediatrics (AAP) for GBS prophylaxis (but before the 1996 Centers for Disease Control and Prevention [CDC] consensus guidelines), Zaleznik and colleagues\textsuperscript{12} determined a maternal GBS attack rate of 0.3 per 1000 deliveries. The incidence of maternal GBS infection showed wide variation among sites, ranging from 0.1 per 1000 deliveries in Seattle to 0.8 per 1000 deliveries in Houston, a difference thought to reflect regional obstetric practices. Most (96%) women presented with bacteremia, and there was no associated mortality. Maternal disease had an adverse effect on fetal or neonatal outcome, however; 28% of affected mothers had pregnancy loss attributable to miscarriage or stillbirth or delivered an infant who developed GBS early-onset sepsis (EOS).

Historically, GBS began to be described in the 1960s as a significant causative organism for life-threatening infections in infants less than 3 months of age.\textsuperscript{11} GBS was the most commonly identified organism in infected neonates in the first week of life before the establishment of universal screening of pregnant women for GBS colonization and prophylactic measures. In a 2000 multisite surveillance study conducted in eight states, the incidence of invasive GBS disease was lowest in children aged 3 months to 14 years, representing 2% of total cases compared with 20% occurring in the first week after birth. The risk for dying from GBS disease was twice as high in the older infants compared with the neonates, however.\textsuperscript{13} In addition, GBS disease was responsible for 33% of infections in subjects 65 years of age or older, who had the highest case fatality rate (15%) compared with all other age groups. Although universal screening measures and aggressive maternal GBS prophylaxis have accounted for both a significant decrease in the incidence of invasive EOS GBS disease in neonates and of invasive disease in pregnant women, GBS remains a prominent cause of infection-related morbidity and mortality in the elderly with underlying chronic disease and in immunocompromised hosts.\textsuperscript{14–17}

GBS infection acquired from the colonized birth canal during labor or after membrane rupture can lead to miscarriage, stillbirth, prematurity, or invasive neonatal disease.\textsuperscript{11} Early-onset GBS infections are strongly linked to maternal colonization, although only a fraction of cases of late-onset disease in infants have a similar association.\textsuperscript{11,18} Vaginal colonization with GBS is acquired from the gastrointestinal tract, and a large proportion of healthy adults are reportedly colonized.\textsuperscript{19} Colonized women are typically asymptomatic, and urinary tract infections with GBS may also have few associated clinical symptoms.\textsuperscript{20–22} In the absence of intrapartum antibiotic prophylaxis (IAP), exposure of the term newborn to the colonized mother infrequently causes infection and leads to asymptomatic neonatal colonization without infection in approximately 75% of exposed infants.\textsuperscript{18} The neonatal attack rate of GBS infection through this vertical transmission ranges from 1 to 2 per 1000 live births. In the 1980s, Boyer and Gotoff\textsuperscript{23} determined that women colonized with GBS in the presence of other risk factors (birth weight [BW] <2.5 kg, ruptured membranes for >18 hours, intrapartum fever) versus women who were GBS culture-negative before delivery were 24 times more likely to have neonates with EOS attributable to GBS. Maternal GBS bacteruria has been associated with a high risk for neonatal EOS.\textsuperscript{20}

**NEONATAL RISK FOR INVASIVE GROUP B \textit{STREPTOCOCCUS} DISEASE:**

**HOST IMMUNOLOGIC FACTORS**

As a group, neonates are at risk for infections, and this is particularly so in preterm neonates.\textsuperscript{24–26} When compared with older children and adults, neonates have an
intrinsic limitation in their capacity to produce neutrophils and a subsequent susceptibility to exhaustion of marrow reserves during times of increased use, such as sepsis. In addition, those neutrophils that are produced have impairments of numerous functions important to the clearance of microbes, including marrow egress, adhesion to the microvascular endothelium, chemotaxis, and bactericidal function. Perhaps as a compensatory mechanism, neonatal neutrophils have a prolonged functional life span, which can potentially delay their clearance and prolong inflammatory and cytotoxic processes. Relative deficiencies in circulating levels of GBS-specific antibody and complement in the context of neutrophil dysfunction heighten the neonatal susceptibility to GBS infection. Furthermore, studies have also shown that vernix caseosa, which is sparse in the preterm infant, contains proteins important to host defense functions, including antimicrobial peptides and factors that promote opsonization and inhibit protease activity.

NEONATAL RISK FOR INVASIVE GROUP B STREPTOCOCCUS DISEASE: BACTERIAL VIRULENCE FACTORS

Capsular polysaccharides (CPSs) expressed by GBS and identified by serotyping assist in bacterial evasion of host defense by interfering with their ingestion by phagocytes. More virulent strains of encapsulated GBS can produce increased amounts of polysaccharides. Lancefield and Hare was the first to serotype GBS, and she identified the prominence of serotype III in neonatal meningitis, subsequently confirmed by others. GBS expresses 9 (and possibly 10) unique serotypes, and most invasive neonatal GBS disease in the United States has been associated with types Ia, II, and III in addition to a more recent prevalence of type V.

Another important virulence factor of GBS is related to its ability to attach to the vascular endothelium and epithelium, particularly of the vaginal tissue and chorionic membranes in addition to the neonatal lungs, which is a prerequisite for invasiveness and disease. The more virulent invasive strains of GBS have been found to have a greater capacity for adherence, and this has been particularly evident in studies of serotype III GBS. Environmental factors, including ambient oxygen concentration, may contribute to bacterial adherence as well. Additional virulence factors have been reviewed.

NEONATAL EARLY-ONSET INFECTION AND GROUP B STREPTOCOCCUS

Neonatal EOS is an infection occurring in the first week of life in term newborns and in the first 72 hours of life in very low birth weight (VLBW) neonates. This gestational age-adjusted difference in the definition of EOS accounts for the higher acquisition of nosocomial organisms as causative agents of sepsis in VLBW neonates after 3 days of hospitalization. Gram-positive bacteria were the most commonly identified causative organisms of neonatal sepsis in the early part of the twentieth century. Lancefield and Hare identified GBS as a contributing factor in often-fatal puerperal and neonatal sepsis in the 1930s. In the 1970s, GBS became the most common causative agent of EOS, whereas gram-negative organisms had been the most common cause of EOS in the early antibiotic era. Before the era of maternal prophylaxis, GBS had a national incidence of approximately 2 per 1000 live births and was associated with 50% mortality in affected neonates. Over the past decade, the approaches to maternal prophylaxis have resulted in a remarkable decrease in the incidence of GBS to its current rate of 0.3 per 1000 live births. Early-onset invasive disease attributable to GBS most commonly presents in neonates during the first day after birth (60%–70% of cases reported in multicenter
One third (32%) of cases were identified between 24 and 48 hours of life, whereas only 8% of cases occurred in infants greater than 2 days of age. Early-onset GBS infections may be invasive and cause nonfocal bacteremia (the most common presentation), pneumonia (Fig. 1), or meningitis and, less commonly, joint and bone involvement. In contrast, infants with GBS infections after the first week of life (“late-onset sepsis”) commonly present with bacteremia but more frequently (nearly one quarter of cases) develop meningitis (Fig. 2) than infants who have EOS caused by GBS.

**EARLY-ONSET SEPSIS AND RISK FOR NEONATAL DEATH**

Death attributable to EOS is inversely related to gestational age and birth weight. Surveillance data obtained before the release of the initial 1996 CDC consensus statement showed an overall case fatality rate of 16% for infants who had GBS EOS. Approximately 65% of these deaths occurred in neonates weighing less than 2500 g. The CDC assessed the effects of IAP on EOS and late-onset sepsis occurring in two periods (1985–1991 and 1995–1999) using a national data set. Mortality attributable to EOS decreased from 24.9 per 100,000 live births to 15.6 per 100,000 live births, potentially reflecting adherence to GBS prophylactic regimens.

**GROUP B STREPTOCOCCUS, EARLY-ONSET SEPSIS, AND THE ROLE OF INTRAPARTUM PROPHYLAXIS**

In the 1970s, Larsen and Sever used a rhesus monkey model to investigate the biology of peripartum GBS infection. Cerebral inoculation of GBS types 1c and III was uniformly fatal, whereas intravenous or intra-amniotic inoculation with GBS just before delivery resulted in neonatal pneumonia and meningitis but variable mortality. Studies designed to assess the utility of antibiotics under these conditions showed a significant protective effect, even in the presence of intracerebral infection. In 1979, Yow and colleagues showed the effectiveness of single-dose ampicillin in averting the peripartum transmission of GBS by colonized mothers to their neonates. In that study of women colonized with GBS, none of the 34 women who received

---

**Fig. 1.** Typical chest radiograph of a newborn with GBS pneumonia. CXR of a term infant with GBS and a small left-sided pneumothorax. Infant was delivered to a mother with unknown GBS and ruptured membranes for 7 hours. Infant required mild resuscitation, then developed progressive respiratory distress and required intubation. A sepsis work-up was performed and antibiotics were started; culture of a tracheal aspirate was positive for GBS. Infant was discharged home in good health on DOL 11. (Courtesy of A. Ali, MD, St. Louis, MO.)
intrapartum ampicillin during labor delivered colonized infants. In contrast, 58% of infants born to the untreated cohort were colonized. Subsequent clinical trials confirmed the utility of intrapartum antibiotics in significantly preventing neonatal EOS attributable to GBS. In these trials, the treatment of colonized women with intrapartum ampicillin or penicillin dramatically reduced the incidence of EOS attributable to GBS, with reported ranges of effectiveness from 25% to 100%. In one study, Boyer and Gotoff observed that colonized women identified at 26 to 28 weeks of gestation who received intrapartum parenteral antibiotics during labor (and who exhibited other risk factors, including preterm labor, prolonged membrane rupture, or fever) had a reduction in the rate of vertically transmitted colonization from 51% to 9% and a decrease in EOS from 6% to 0%.

In 1992, the American Academy of Pediatrics made recommendations for a prophylactic treatment approach to maternal GBS colonization to diminish the incidence of neonatal infection. In an early multiregional surveillance study after these initial recommendations, Zaleznik and colleagues reviewed data in pregnant women and neonates from indigent care and private facilities in Seattle, Minneapolis/St. Paul, Pittsburgh, and Houston during a period from 1993 to 1996. The combined attack rate for GBS EOS in all study sites was lower (0.8 per 1000 live births) than the expected rate of 2 per 1000 live births, based on earlier surveillance data. Attack rates depended on the region, however, ranging from the highest rate of 1.3 per 1000 live births in Houston to a rate of 0.6 per 1000 live births in Minneapolis/St. Paul. Attack rates were highest for African-American and Hispanic women. Low birth weight (<2500 g) was a significant risk factor for GBS EOS (2.1 versus 0.7 per 1000 live births for infants weighing ≥2500 g); however, 75% of the cases occurred in near-term or term infants.

The 1992 AAP recommendations received uneven acceptance. In 1996, the CDC released a consensus statement developed with the ACOG and AAP. In that policy statement, strategies that involved universal screening of pregnant women for GBS colonization at 35 to 37 weeks of gestation or a risk-based approach (fever ≥38°C

---

**Fig. 2.** Head CT scan of a 3-week-old male newborn after late-onset GBS meningitis. The CT scan performed 27 days later showed virtually no normal cortex. He was able to breathe without a respirator but was unable to suck. (Courtesy of Carol J. Baker, MD, Houston, TX.)
[104.5°F], premature membrane rupture ≥18 hours, <37 weeks of gestation, or established GBS colonization) were equally acceptable alternatives. Subsequent surveillance studies revealed that almost 50% of neonatal EOS GBS infections were not identified using the risk-based approach.73,74 A multicenter analysis of surveillance data (1993–1998) showed a striking (65%) decline in the incidence of GBS EOS, confirming the efficacy of screening-triggered treatment of colonized mothers (Fig. 3).13 The general protective effect of GBS prophylaxis was also confirmed by the CDC in its report of national surveillance data for GBS disease in 12.5 million persons during a similar time period.

A large (n = 600,000) retrospective cohort study conducted by the Active Bacterial Core Surveillance Team at the CDC suggested the greater efficacy of universal screening over the risk-based approach. Based on the results of these and other studies, the CDC reissued its most current guidelines in 2002, endorsed by the AAP and ACOG, specifically to promote universal screening for GBS at 35 to 37 weeks of gestation and the treatment of colonized women with IAP.75,76 To help narrow the use of intrapartum antibiotics, the guidelines did not recommend that women with GBS-negative cultures within 5 weeks of delivery receive GBS prophylaxis in the presence of intrapartum risk factors. In an attempt to enhance the sensitivity of rectovaginal cultures, the revised guidelines outlined a detailed approach to the collection and processing of cultures. In addition, new algorithms were included regarding GBS prophylaxis for threatened preterm delivery and the management of neonates exposed to intrapartum prophylaxis. This refocused approach led to an additional decline in GBS-related EOS to a reported incidence of 0.3 per 1000 live births in term neonates, which has surpassed the established goals of Healthy People 2010 of achieving an incidence of 0.5 per 1000 live births for EOS (Fig. 4).13,77 Concurrently, mortality associated with GBS EOS in term infants also dropped dramatically. Although the initial dramatic decrease in the incidence of GBS EOS was reflective of declines among African-American neonates, analysis of more recent data continues to reveal a several-fold higher incidence of GBS EOS in African-American versus white infants.13,60,78,79

Fig. 3. Incidence of early- and late-onset invasive GBS in three active surveillance areas (California, Georgia, and Tennessee), 1990 through 1998, and activities for the prevention of GBS. Live births for 1998 were approximated on the basis of 1997 data. Arrows designate the dates when prevention activities occurred. (From Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000;342:16; with permission.)
Despite the significant decrease in the incidence of GBS EOS after the inception of the 1996 CDC guidelines for prophylaxis, a sizable number of infants develop GBS disease annually, particularly in the VLBW infant population. Of concern are reports that many of these infants developed GBS EOS in the absence of evidence for maternal colonization. Potential explanations for these occurrences may be related to the acquisition of colonization after a negative screen result (in one study, 8.5% of women with initially negative cultures were colonized at delivery), discordance between antenatal screening and colonization (studies have determined that some women who are negative at their initial screening may be colonized at delivery), effects of undocumented outpatient antibiotics, and uneven techniques in the acquisition or processing of specimens for culture. False-negative rates ranging from 4% to 8% have been reported.

Puopolo and colleagues prospectively reviewed single-center data from three periods encompassing the years 1997 to 2003, which reflected changes in obstetric approaches to GBS prophylaxis, using a screening-based protocol. In this study, the attack rate for GBS EOS was 0.37 per 1000 live births, a decrease in incidence that mirrored rates reported for other institutions. In affected neonates, nearly two thirds of mothers (82% of term gestations) had a negative GBS culture screen. Nineteen of 25 GBS-negative mothers of infected neonates presented with at least one intrapartum risk factor, but only a small fraction (<20%) received intrapartum prophylaxis and in only one case was prophylaxis initiated more than 4 hours before delivery. Twelve of 17 infected term infants had no or mild symptoms. Those treated empirically based on risk factors with subsequent positive blood cultures remained clinically stable. In contrast, 7 of 8 preterm infants with GBS EOS presented with clinical evidence of sepsis. These data indicated a protective effect of early empiric antibiotic therapy in neonates at risk for EOS and underscored the importance of evaluating even well-appearing infants for possible sepsis in the presence of any maternal risk factors, despite a negative GBS status in the mother. These researchers...
concluded that the relatively high false-negative maternal screening incidence indicates the need for rapid identification of at-risk deliveries.

EFFECT OF UNIVERSAL SCREENING FOR GROUP B STREPTOCOCCUS IN VERY LOW BIRTH WEIGHT NEONATES

Despite the dramatic impact of universal screening at 36 weeks of gestation on the incidence of and mortality associated with GBS EOS in term infants, its effect in VLBW neonates has been less apparent. Data from several multicenter surveillance studies associated with the National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network VLBW registry from three study periods have been compared: 1991 to 1993, 1998 to 2000, and 2002 to 2003. Stoll and colleagues reported that the attack rate of EOS attributable to GBS declined significantly between the first two periods (from 5.9 to 1.7 per 1000 live births) but did not change between the last two study periods (1.8 per 1000 live births). The case fatality rate markedly dropped during the first periods (the most recent data report a rate of 2.6%), although GBS EOS remains a significant cause of neonatal death in the preterm population (19.9%), with the highest mortality observed in VLBW neonates (35% in a 2003 study).

Therapeutic approaches to GBS-colonized women identified early in gestation and who present with premature membrane rupture or are in labor have lacked consistency and have been hampered by a lack of data. Although prophylactic antibiotics reduce transmission of GBS from a colonized mother to her infant, this approach may not completely prevent neonatal disease. The cause(s) of the disparate prophylactic effectiveness of maternal GBS screening between term and VLBW neonates remain(s) enigmatic. One potential explanation involves the pronounced immunoincompetence of fetuses and extremely premature neonates. In addition, screening early in gestation and prophylaxis may be ineffective. Boyer and colleagues reported that 8.5% of women with negative cultures at 26 to 28 weeks of gestation were GBS-positive at the time of delivery.

GROUP B STREPTOCOCCUS PROPHYLAXIS AND ALTERATIONS IN THE PROFILE OF CAUSATIVE ORGANISMS IN EARLY-ONSET SEPSIS

Mounting evidence shows that the increasing use of intrapartum antibiotics as part of GBS prophylaxis has altered the profile of microorganisms causing EOS. Universal screening measures and IAP have resulted in a dramatic decrease in GBS as a causative organism, but there has been a dramatic shift toward gram-negative organisms as a cause of EOS in VLBW infants.

Surveillance data were prospectively collected from 16 centers belonging to the NICHD Neonatal Research Network VLBW registry during a 13-year period. Stoll and colleagues reviewed these data during three time periods to assess the pathogens associated with EOS in VLBW neonates. In VLBW neonates, EOS was described as infection occurring in the first 72 hours of life in the presence of clinical symptoms and a positive blood culture. In the latter two periods, there were no changes in birth weight, gender, or gestational age among cohorts. The rate of EOS in neonates weighing 401 to 1500 g remained relatively stable during this period (15–19 of 1000 live births); however, the pattern of distribution for associated pathogens underwent a significant change.

Gram-positive organisms predominated during the first period, causing 56% of EOS; this was primarily attributable to GBS. After the 1996 institution of CDC
guidelines, there was a precipitous decline in the attack rate of GBS, from 5.9 per 1000 live births in 1991 to 1993 to 1.7 per 1000 live births in 1998 to 2000; this did not change further in the last period evaluated (1.8 per 1000 live births) (Table 1). The incidence of EOS attributable to Escherichia coli more than doubled between these two periods, from 3.2 to 6.8 per 1000 live births, and did not change in the last period evaluated (7.0 per 1000 live births). In 1998 to 2000, EOS was primarily associated with gram-negative bacteria (61%), and nearly three-quarters of these cases were attributable to E. coli, followed by Hemophilus influenzae (8%), Citrobacter (2%), and others (Table 2). Less than half (37%) of EOS infections were attributable to gram-positive infections, with 11% of the total attributable to GBS. One disturbing trend over the periods studied was the gradual increase in the incidence of EOS attributable to coagulase-negative Staphylococcus, which accounted for nearly 15% of gram-positive EOS in the period from 2002 to 2003.

GROUP B STREPTOCOCCUS PROPHYLAXIS AND THE EMERGENCE OF BACTERIAL RESISTANCE

Increasing evidence has linked the administration of maternal intrapartum antibiotics with the emergence of resistant bacterial strains. GBS remains sensitive to penicillin. Cases of resistance to erythromycin and clindamycin, antibiotics frequently given to women with documented penicillin allergy, have been reported, however. In 2002, recommendations were made in partial response to the emerging frequency of GBS resistance to erythromycin and clindamycin to measure antibiotic sensitivities of GBS in high-risk penicillin-sensitive women.

A major concern is the increasing incidence of antibiotic resistance in gram-negative organisms, particularly E. coli. In the NICHD VLBW registry, analysis of 39 isolates in the cohort from 2002 to 2003 showed an 85% resistance to ampicillin. Analysis of maternal intrapartum antibiotic exposure showed a marked increase in antibiotic use from the earliest cohort studied compared with 69% of mothers who received antibiotics in 2002 to 2003. A significantly higher proportion of neonates with E. coli sepsis were born to mothers who had received ampicillin within 72 hours of delivery (1.1% versus 0.4%). Although the CDC guidelines for IAP outline the preferential use of penicillin in the absence of known allergy, surveillance data indicated that ampicillin was used for IAP in 49% of cases.

The results of the VLBW registry analysis have reflected similar trends in other institutions. In a single-institution retrospective review of three periods encompassing 1979 to 2006, Bizzarro and colleagues observed an increase in antibiotic use (from 16% to 85%) paralleling the adoption of the CDC guidelines for GBS prophylaxis. In VLBW neonates, the incidence of ampicillin-resistant E. coli increased dramatically, from 0% in the first period (1979–1992) to 64% in the latest period (1997–2006). Colonization with resistant organisms was associated with lower birth weights, lower gestational ages, and exposure to antenatal antibiotics. In an analysis of data (1998–2000) from San Francisco and Atlanta for the CDC Active Bacterial Core surveillance, the rates of ampicillin-resistance in EOS attributable to E. coli in preterm infants increased from 29% (2 of 7 infants) in 1998 to 84% (16 of 18 infants) in 2000. Ampicillin-resistant E. coli-associated mortality tended to be more common in ampicillin-resistant cases (26%) compared with those that were sensitive to ampicillin (5%). Ampicillin-resistant E. coli infections increased during the study period in preterm but not term infants, a possible reflection of prolonged exposure of the preterm group to antibiotics.

Eighty-two percent of mothers who delivered preterm infants with EOS with an ampicillin-resistant organism had received antenatal antibiotics compared with 40% of mothers of term infants with resistant disease.
### Table 1

<table>
<thead>
<tr>
<th>Early-Onset Sepsis</th>
<th>1991–1993</th>
<th>Rate Per 1000 Live-Born VLBW Infants</th>
<th>1998–2000</th>
<th>Rate Per 1000 Live-Born VLBW Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Infected/Total No.</td>
<td></td>
<td>No. Infected/Total No.</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>147/7606</td>
<td>19.3</td>
<td>84/5447</td>
<td>15.4</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>83/7606</td>
<td>10.9</td>
<td>31/5447</td>
<td>5.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>45/7606</td>
<td>5.9</td>
<td>9/5447</td>
<td>1.7&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>63/7606</td>
<td>8.3</td>
<td>51/5447</td>
<td>9.4</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>24/7606</td>
<td>3.2</td>
<td>37/5447</td>
<td>6.8&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fungus</td>
<td>1/7606</td>
<td>0.1</td>
<td>2/5447</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Data from the period from 1991 to 1993 are from Stoll and colleagues. $P = .007$ for the change in the distribution of pathogens between the two periods; there was no significant change in the overall rate of sepsis. VLBW infants are defined as infants weighing between 401 and 1500 g. When the three centers that were not included in the earlier birth cohort are excluded from the analysis, the rates of group B streptococci and *E. coli* in the more recent birth cohort are 2.1 per 1000 live-born VLBW infants and 7.3 per 1000 live-born VLBW infants, respectively, and the changes remain significant ($P = .003$).

<sup>a</sup> $P = .002$ for the comparison with the earlier period.<br>
<sup>b</sup> $P < .001$ for the comparison with the earlier period.<br>
<sup>c</sup> $P = .004$ for the comparison with the earlier period.

Conversely, Schrag and colleagues\textsuperscript{88} reported a lack of an association between IAP and EOS attributable to ampicillin-resistant \textit{E. coli}. Although more than half of infected subjects had been exposed to intrapartum antibiotics, those with ampicillin-resistant \textit{E. coli} did not have a greater exposure to intrapartum antibiotics in general, although they were exposed to more doses of penicillin or ampicillin, possibly a reflection of factors linked to prematurity or maternal infection. The strongest identified risk factors for \textit{E. coli} sepsis were prematurity, particularly 33 weeks or less of gestation, followed by maternal fever and prolonged membrane rupture. Univariate analysis controlling for intrapartum fever revealed an association between IAP and \textit{E. coli} infection in general (ampicillin-resistant and ampicillin-sensitive). When separating the analysis based on gestational age, exposure to IAP for 4 or more hours actually reduced the odds for \textit{E. coli} infection in term infants, indicative of a protective effect.

Increased emergence of ampicillin-resistant \textit{E. coli} EOS has also been reported in other countries. Analysis of single-institution data from Madrid showed a preferential increase of resistant \textit{E. coli} EOS among preterm but not term neonates, a finding that was not paralleled by a significantly greater use of intrapartum antibiotics.\textsuperscript{89} Retrospective analysis in one hospital in New Zealand confirmed the preponderance of

\begin{table}
\centering
\begin{tabular}{|l|c|}
\hline
Organism & No. With Sepsis (%) \\
\hline
\textbf{Gram-negative organisms} & \\
\textit{Escherichia coli} & 51 (60.7) \\
\textit{Haemophilus influenzae} & 7 (8.3) \\
\textit{Citrobacter} & 2 (2.4) \\
Other\textsuperscript{a} & 5 (6.0) \\
\hline
\textbf{Gram-positive organisms} & \\
\textit{Group B Streptococcus} & 31 (36.9) \\
Viridans \textit{Streptococcus} & 9 (10.7) \\
Other streptococci\textsuperscript{b} & 3 (3.6) \\
\textit{Listeria monocytogenes} & 4 (4.8) \\
\hline
\textbf{Coagulase-negative \textit{Staphylococcus}}\textsuperscript{c} & \\
Other\textsuperscript{d} & 2 (2.4) \\
\hline
\textbf{Fungi} & \\
\textit{Candida albicans} & 2 (2.4) \\
\hline
\textbf{Total} & 84 (100) \\
\hline
\end{tabular}
\caption{Distribution of pathogens among 84 cases of early-onset sepsis occurring in 5447 infants born between September 1, 1998, and August 31, 2000}
\end{table}

Seven of the 84 infants had two positive blood cultures for the same organism.

\textsuperscript{a} Other gram-negative organisms included \textit{Klebsiella} (in 1 infant), \textit{Bacteroides} (in 2 infants), \textit{Eikenella corrodens} (in 1 infant), and \textit{Stenotrophomonas maltophilia} (in 1 infant).

\textsuperscript{b} Other streptococci included group A \textit{Streptococcus} (in 1 infant) and three cases in which the species was unknown.

\textsuperscript{c} Of 18 positive blood cultures for coagulase-negative \textit{staphylococci}, 1 met the criteria for definite infection and 8 met the criteria for possible infection; in the other 9 cultures, the organism was considered to be a contaminant (see the Methods section).

\textsuperscript{d} Other gram-positive organisms included \textit{Staphylococcus aureus} (in 1 infant), \textit{Bacillus} (in 2 infants), and \textit{Peptostreptococcus} (in 1 infant).

E. coli infection in premature infants, with more than half being resistant to amoxicillin.90

ECONOMIC COSTS OF PERIPARTUM GROUP B STREPTOCOCCUS DISEASE AND ITS PREVENTION

Peripartum GBS infection is associated with significant morbidity and mortality and causes maternal septicemia, septic abortion, stillbirth, and premature delivery. In addition, neonatal GBS infection significantly prolongs hospitalization and has been associated with developmental delay, blindness, deafness, and other neurologic impairments. Although the emotional toll of these complications cannot be numerically assessed, the economic costs are significant. A study of one California health maintenance organization correlated an incidence of EOS GBS of 0.1% from 1989 to 1983 with a calculated cost of $2.8 million.91 The initiation of a risk-based approach (1994–1995) resulted in a decreased incidence of EOS paralleling those reported in multicenter surveys (0.04%). The investigators estimated that nearly two thirds of EOS GBS cases had been prevented by this strategy, representing 65.5 life-years saved attributable to averted cases and a net cost savings of $1.1 million.

Studies of the economic impact of strategies to prevent GBS EOS have determined a marked increase in the use of maternal intravenous antibiotics (in one study, from 27% in 1998 to 41% in 2002) and have cataloged the contribution of this practice to the emergence of resistant organisms.92,93 Maternal prophylaxis has also been associated with increased early antibiotic use in term neonates and a longer hospital stay.92,94 A recent single-institution study from Switzerland assessed GBS early-onset disease in the context of risk factors and cost-effectiveness of different preventative strategies.95 From March 2005 to 2006, the maternal colonization rate was 21% and risk factors were present in 37% of women at the time of delivery. Although the risk-based approach was associated with a lower direct cost compared with a screening approach, these researchers suggested universal screening as the more effective regimen in the presence of a high maternal colonization rate.

ALTERNATIVE STRATEGIES TO PREVENTION OF GROUP B STREPTOCOCCUS EARLY-ONSET SEPSIS

Although universal screening measures have had a significant and positive impact on EOS attributable to GBS, this approach is not fail-safe and early-onset GBS disease remains a major public health issue. In addition, evidence has linked the emergence of resistant organisms to IAP administration. An increasing number of investigators have become proponents of alternative approaches to minimize the need for antenatal prophylaxis and its attendant risks.

Combination approaches to the screening or prophylaxis of mothers and their newborns have been explored with some success. In one trial from Italy, neonates delivered to screened mothers were themselves cultured and treated with a course of prophylactic amoxicillin, resulting in a decrease in EOS and late-onset GBS disease (from an incidence of 0.74 to 0.048 per 1000 live births at the end of the study). Further studies are required to assess the cost-benefits of targeted approaches, in addition to unintended consequences, however, particularly with respect to microbial resistance patterns. For example, prophylactic oral administration of amoxicillin-clavulanate for prematurely ruptured membranes or preterm labor was associated with an increased risk for necrotizing enterocolitis.96

The administration of prophylactic vaccines is the most promising approach to the prevention of neonatal GBS disease.97 A major rationale for the vaccination of women
against GBS is the fact that most (85%–90%) pregnant women lack protective antibodies at the time of delivery. In a decision analytic model, effective maternal vaccination in combination with a screening approach was predicted to prevent 66% of peripartum GBS infections and 1 of 25 preterm births. Vaccines based on CPS expression and conjugated to tetanus toxoid have shown particular therapeutic potential. In early trials, maternal immune responses to polysaccharide vaccines were variable, although in a study directed by Baker and colleagues, 75% of infants born to women who responded to a type III polysaccharide vaccine had protective antibody levels 2 months after delivery. Conjugation of CPS vaccines to tetanus toxoid has improved antigenic responses in recipients. A high proportion (93%–100%) of immunized women exhibited a fourfold increase in type-specific antibody responses after immunization, although this number was lower (80%) for those receiving the type 1b conjugated vaccine. Importantly, antibody levels were detectable 2 years after immunization. Nevertheless, although substantial evidence has shown these vaccines to be promising deterrents to GBS disease in the United States, the participation by pharmaceutical companies has been hesitant. The goal of a universally effective vaccine and a successful immunization strategy remains elusive. The development of efficacious vaccines with global relevance has been hindered by changes in the prominence of various GBS serotypes and antigenicity patterns over time, in addition to regional variations in human populations.

Conventional approaches to the development of numerous vaccines have been augmented by novel DNA, genomic, and protein technologies and are rapidly being superseded by such techniques as reverse vaccinology, in which pathogen-specific genomic sequences are used to screen for potential protein candidates for vaccine development. A thorough discussion of GBS vaccine development and novel approaches, which is beyond the scope of this article, has been elegantly reviewed elsewhere.

Alternative approaches to the eradication of GBS colonization have been considered, including the development of topical agents that can target GBS. One approach involving the use of chlorhexidine as a vaginal disinfectant has been favored by some because of low cost, lack of impact on the development of antibiotic resistance, and its potential use in undeveloped areas. Although a systematic review of the literature was consistent with a decrease in neonatal GBS colonization of neonates, this was not associated with a reduction in early-onset neonatal disease. One novel agent, aqueous allicin, a substance derived from garlic, has been shown to have potent bactericidal activity against GBS isolates in culture. Another consideration involves bacteriophage lysins, which are cell wall hydrolases that render bacteria vulnerable to lysis. In vivo studies in neonatal mice have shown the potent and wide-spectrum bactericidal activity of a bacteriophage lysin, PlyGBS, against GBS colonization. Interesting possibilities of this approach include potential utility in cases of antibiotic resistance, its rapid action, and the apparent lack of toxicity.

An approach involving the use of rapid diagnostic tests could help to guide management shortly before delivery, particularly in cases in which GBS status is unknown or when cultures are negative in the presence of risk factors. One such test involves a rapid polymerase chain reaction (PCR) assay, which has been shown to match or exceed the sensitivity of culture-based approaches, the commercial version of which has been approved by the US Food and Drug Administration (FDA) for this purpose. In a Stanford University cost analysis of a hypothetical cohort, a PCR-based strategy resulted in a net cost benefit, less maternal antibiotic use, fewer neonatal GBS infections, and a lower incidence of GBS-related infant death and disability compared with the current universal screening approach.
SUMMARY

The changing face of EOS has been associated with the wide adoption of consensus guidelines to detect and treat women with GBS colonization. The utility of these guidelines, promulgated by the CDC and endorsed by the AAP and ACOG, has stood the test of time and experience. Faithful adherence to a universal screening approach across institutions has dramatically decreased maternal and early-onset neonatal GBS disease and has lowered the incidence of GBS EOS to a level that achieves the goal outlined in Healthy People 2010. Unintended consequences of increased intrapartum antibiotic exposure, particularly to ampicillin, include an increasing prevalence of gram-negative bacteria causing EOS, particularly of resistant strains, however. Morbidity and mortality attributable to EOS related to GBS and other organisms remain significant, especially in VLBW neonates.

Despite an era of marked success with universal screening, GBS continues to be an important cause of EOS, and thus remains a significant public health issue. Measures that augment its diagnosis and prevention are imperative. Improved eradication of GBS colonization and disease may involve universal screening in conjunction with rapid diagnostic technologies or other novel approaches. Given the complications and potential limitations associated with maternal intrapartum prophylaxis, however, vaccines may be the most effective means of preventing neonatal GBS disease. Although efficacious against most serotypes associated with GBS disease in the United States, the global utility of conjugated GBS vaccines may be hampered by the variability of serotypes in diverse populations and geographic locations. Modern technologies, such as those involving proteomics and genomic sequencing, are likely to hasten the development of a universal vaccine against GBS.

REFERENCES


