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

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Historical aspects of maternal puerperal sepsis and GBS as a causative agent

Puerperal sepsis (or “childbed fever”) has been associated with maternal morbidity and mortality for centuries (reviewed in [1]). The controversial figure, Ignác Semmelweis, a Hungarian obstetrician who practiced in Vienna in the early to mid-1800’s, was the first to identify an infectious mode of transmission of puerperal sepsis [2,3]. Semmelweis, in a key observation, linked the septic death of a colleague following 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 prior to the examination of patients. These speculations of an organic causative agent in puerperal sepsis helped 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 Hare observed differences in the hemolytic culture characteristics of two types of streptococci obtained from autopsies of women with puerperal sepsis [6]. Fry subsequently reported several cases of fatal puerperal sepsis related to group B streptococcal disease [7]. The use of antibiotics, initially sulfa drugs followed by penicillin, dramatically decreased mortality from puerperal sepsis. However, it was not until the early 1960’s that an association was observed between GBS infection in mothers and their newborn infants [8,9]. Subsequent studies showed that while all known GBS serotypes could cause maternal infection, Type III was associated with the large majority of invasive neonatal disease (meningitis) [10].

GBS can cause significant maternal morbidity, particularly endometritis, chorioamnionitis and bacteremia [11]. In a multi-regional surveillance study that followed the initial (1992) AAP

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and ACOG recommendations for GBS prophylaxis (but before the 1996 CDC consensus guidelines), Zalesnik and colleagues determined a maternal GBS attack rate of 0.3/1000 deliveries [12]. The incidence of maternal GBS infection showed wide variation between sites, ranging from 0.1/1000 in Seattle to 0.8/1000 in Houston, a difference thought to reflect regional obstetrical practices. The majority (96%) of women presented with bacteremia and there was no associated mortality. However, maternal disease had an adverse effect on fetal or neonatal outcome; 28% of affected mothers had pregnancy loss due to miscarriage or stillbirth, or delivered an infant who developed GBS EOS.

Historically, group B *Streptococcus* (*Streptococcus agalactiae*; GBS) began to be described in the 1960's as a significant causative organism for life threatening infections in infants less than 3 months of age [11]. GBS was the most commonly identified organism in infected neonates in the first week of life prior to the establishment of universal screening of pregnant women for GBS colonization and prophylactic measures. In a 2000 multi-site surveillance study conducted in eight states, the incidence of invasive GBS disease was lowest in children aged 3 months to 14 years (2% of total cases compared with 20% in the first week of after birth). However the risk of dying from GBS disease was twice as high in the older infants compared to neonates [13]. In addition, GBS disease was responsible for 33% of infections in subject's ≥ 65 years of age, who had the highest case-fatality rate (15%) compared to all other age groups. While universal screening measures and aggressive maternal GBS prophylaxis have accounted for 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 [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 [11]. Early-onset GBS infections are strongly linked to maternal colonization, while only a fraction of late-onset disease in infants have a similar association [11,18]. Vaginal colonization with GBS is acquired from the gastrointestinal tract and a large proportion of healthy adults are reportedly colonized [19]. Colonized women are typically asymptomatic, and urinary tract infections with GBS, may also have few associated clinical symptoms [20-22]. In the absence of intrapartum antibiotic prophylaxis, 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 [18]. The neonatal attack rate of GBS infection through this vertical transmission ranges from 1-2/1000 live births.. In the 1980's, Boyer and Gotoff determined that women colonized with GBS in the presence of other risk factors (BW < 2.5 kg, ruptured membranes > 18 hours, intrapartum fever) versus women who were GBS culture negative prior to delivery were 24 times more likely to have neonates with EOS due to GBS [23]. Maternal GBS bacteruria has been associated with a high risk for neonatal EOS [20].

Neonatal risk for invasive GBS disease: host immunologic factors

Neonates as a group are at risk for infections, and this is particularly so in preterm neonates (reviewed in [24-26]). When compared to 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 utilization, such as sepsis [27,28]. 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 [24,28-36]. 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 [37-39]. Relative deficiencies in circulating levels of GBS-specific antibody and complement in the context of neutrophil

dysfunction heighten the neonatal susceptibility to GBS infection [24,40-51]. 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 [52].

Neonatal risk for invasive GBS disease: bacterial virulence factors

Capsular polysaccharides (CPS) expressed by GBS and identified by serotyping, assist bacterial evasion of host defense by interfering with their ingestion by phagocytes. More virulent strains of encapsulated GBS can produce increased amounts of polysaccharide. Lancefield was the first to serotype GBS, and she identified the prominence of serotype III in neonatal meningitis, subsequently confirmed by others [6,53,54]. GBS express nine (and possibly ten) unique serotypes, and the majority of invasive neonatal GBS disease in the United States has been associated with types Ia, II, III and a more recent prevalence of type V (reviewed in [55]).

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 as well as the neonatal lungs, and which is a prerequisite for invasiveness and disease [56]. 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 [55-57]. Environmental factors, including ambient oxygen concentration, may contribute to bacterial adherence as well [58]. Additional virulence factors have been reviewed [59].

Neonatal early-onset infection and GBS

Neonatal early-onset sepsis (EOS) is an infection occurring in the first week of life in term infants and in the first 72 hours of life in very low birth weight (VLBW) neonates [60]. 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 after three days of hospitalization. Gram-positive bacteria were the most commonly identified causative organisms of neonatal sepsis in the early part of the twentieth century (reviewed in [11]). Lancefield and Hare identified GBS as a contributing factor in often-fatal puerperal and neonatal sepsis in the 1930's [6]. In the 1970's, GBS became the most common etiologic agent of EOS, whereas gram-negative organisms had been the most common causes of EOS in the early antibiotic era. Prior to the era of maternal prophylaxis, GBS had a reported national incidence of approximately 2 per 1000 live births and was associated with a 50% mortality rate in affected neonates [18,61]. Over the past decade the approaches to maternal prophylaxis has resulted in a remarkable drop in incidence to its current rate of 0.3/1000 [62].

Early-onset invasive disease due to GBS most commonly presents in neonates in the first day of life (60-70% of cases reported in multi-center trials) [12,13]. A third (32%) of cases were identified between 24-48 hours of life, while only 8% of cases occurred in infants greater than two days of age [12]. Early-onset GBS infections may be invasive and cause non-focal bacteremia (the most common presentation), pneumonia (Fig. 3) or meningitis, and less commonly joint and bone involvement [11]. In contrast, infants with GBS infections after the first week of life ("late-onset sepsis") commonly present with bacteremia but more frequently (nearly a quarter of cases) develop meningitis (Fig. 4) than infants with EOS caused by GBS.

EOS and risk for neonatal death

Death from 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 with GBS EOS [12]. Approximately 65% of these deaths

occurred in neonates weighing < 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 [63]. Mortality for EOS decreased from 24.9/100,000 live births to 15.6, potentially reflecting adherence to GBS prophylactic regimens.

GBS, EOS and the role of intrapartum prophylaxis

In the 1970's, Larsen and colleagues utilized a rhesus monkey model to investigate the biology of peripartum GBS infection (reviewed in [64]). Cerebral inoculation of types 1c and III GBS was uniformly fatal, while intravenous or intra-amniotic inoculation with GBS administration just prior to delivery resulted in neonatal pneumonia and meningitis but variable mortality [65]. 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 *et al.* showed the effectiveness of single-dose ampicillin in averting the peripartum transmission of GBS by colonized mothers to their neonates [66]. In that study of women colonized with GBS, none of the 34 who received 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 due to GBS [67-70]. In these trials, the treatment of colonized women with intrapartum ampicillin or penicillin dramatically reduced the incidence of EOS due to GBS, with reported ranges of effectiveness from 25 – 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 percent, and a decrease in EOS from 6 to 0 percent [67].

In 1992, the American Academy of Pediatrics made recommendations for a prophylactic treatment approach to maternal GBS colonization in order to diminish the incidence of neonatal infection [71]. In an early multiregional surveillance study following these initial recommendations, Zalesnik 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 1993-1996 [12]. The combined attack rates for GBS EOS in all study sites was lower (0.8 per 1000 births) than the expected rate of 2/1000, based on earlier surveillance data. However, attack rates were region-dependent, ranging from the highest rate of 1.3/1000 in Houston to a rate of 0.6/1000 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 (2.1/1000 vs. 0.7/1000 for infants weighing $\geq$ 2500 g). However, 75% of the cases occurred in near-term or term infants.

The 1992 AAP recommendations received uneven acceptance. In 1996 the Centers for Disease Control and Prevention (CDC) released a consensus statement developed with ACOG and AAP [72-74]. In that policy statement strategies that involved either *universal screening* of pregnant women for GBS colonization at 35-37 weeks of gestation, or a *risk-based approach* (fever $\geq$ 38° C (104.5° F), PROM $\geq$ 18 hours, < 37 weeks of gestation, 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 [75]. A multi-center analysis of surveillance data (1993-1998) showed a striking (65%) decline in the incidence of GBS EOS, confirming the efficacy of a screening triggered treatment of colonized mothers (FIG. 1) [13]. The general protective effect of GBS prophylaxis was also confirmed by the CDC in their report of national surveillance data for GBS disease in 12.5 million persons during a similar time period.

A large (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, in 2002 the CDC reissued their most current guidelines (accessed at http://www.cdc.gov/groupbstrep/hospitals/hospitals_guidelines.htm), endorsed by the AAP and ACOG, to specifically promote universal screening for GBS at 35 -37 weeks and the treatment of colonized women with intrapartum antibiotic prophylaxis (IAP) [76,77]. 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 on the collection and processing of cultures. In addition, new algorithms were also 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 thousand in term neonates, and one which has surpassed the established goals of Healthy People 2010 of achieving an incidence of 0.5 per 1000 for EOS (FIG. 2) [13][78]. 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 [13,79-81].

Persistence of GBS disease despite universal screening

Despite the significant decrease in the incidence of GBS EOS following the inception of the 1996 CDC guidelines for prophylaxis, a sizable number of infants develop GBS disease annually, particularly in the VLBW infant population [60,82]. 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 following a negative screen (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 and/or processing of specimens for culture [83]. False-negative rates ranging from 4-8% have been reported [84].

Puopolo *et al.* prospectively reviewed single-center data from three periods encompassing the years 1997-2003 and which reflected changes in obstetrical approaches to GBS prophylaxis using a screening-based protocol [84]. In this study, the attack rate for GBS EOS was 0.37/1000, 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 only in only one case was prophylaxis initiated more than 4 hours prior to delivery. Twelve of seventeen 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, seven of eight 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. The authors 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 GBS in VLBW neonates

Despite the dramatic impact of universal screening at 36 weeks on the incidence of and mortality associated with GBS EOS in term infants, its effect in VLBW has been less apparent. Data from several multi-center surveillance studies associated with the NICHD Neonatal Research Network VLBW registry from three study periods have been compared: 1991-1993; 1998-2000; 2002-2003 [82,85]. Stoll and colleagues reported that the attack rate of EOS due to GBS dropped significantly between the first two periods (from 5.9/1000 to 1.7/1000) but did not change between the last two study periods (1.8/1000). 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 and/or who are in labor have lacked consistency and have been hampered by a lack of data. While prophylactic antibiotics reduce transmission of GBS from a colonized mother to her infant, this approach may not completely prevent neonatal disease [86]. The cause(s) of the disparate prophylactic effectiveness of maternal GBS screening between term and VLBW remain(s) enigmatic. One potential explanation involves the pronounced immunoincompetence of fetuses and very premature neonates [24,26]. In addition, screening early in gestation and prophylaxis may be ineffective. Boyer *et al.* reported that 8.5% of women with negative cultures at 26-28 weeks of gestation were GBS-positive at the time of delivery [83].

GBS prophylaxis and alterations in the profile of etiologic organisms in EOS

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 towards gram-negative organisms as an etiology of EOS in VLBW infants.

Surveillance data was prospectively collected from 16 centers belonging to the National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network VLBW registry during a 13 year period [82,85]. Stoll and colleagues reviewed this 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, sex or gestational ages between cohorts. The rate of EOS in neonates weighing 401-1500 g remained relatively stable during this period (15-19/1000 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 due to GBS. Following the 1996 institution of CDC guidelines, there was a precipitous drop in the attack rate of GBS, from 5.9/1000 live births in 1991-1993 to 1.7/1000 in 1998-2000; this did not change further in the last period evaluated (1.8/1000) (TABLE 1) [83]. The incidence of EOS due to *E. coli* more than doubled between these two periods, from 3.2/1000 to 6.8/1000, and did not change in the last period evaluated (7.0/1000). In 1998-2000, EOS was primarily associated with gram-negative bacteria (61%) and nearly three-quarters of these were due to *E. coli*, followed by *Hemophilus influenzae* (8%), *Citrobacter* (2%) and others (TABLE 2). Less than half (37%) of EOS infections were due to gram-positive infections, with 11% of the total due to GBS. One disturbing trend over the periods studied was the gradual increase in the incidence of EOS due to coagulase-negative staphylococcus (CONS), which accounted for nearly 15% of gram positive EOS in the 2002-2003 period rate.

GBS 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. However, cases of resistance to erythromycin and clindamycin, antibiotics frequently given to women with documented penicillin allergy, have been reported [87]. 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 woman [76].

A major concern is the rising the incidence of antibiotic resistance in gram-negative organisms, particularly *E. coli*. In the NICHD VLBW registry, analysis of 39 isolates in the 2002-2003 cohort showed an 85% resistance to ampicillin [82]. Analysis of maternal intrapartum antibiotic exposure showed a marked increase in antibiotic usage from the earliest cohort studied compared with 69% of mothers who received antibiotics in 2002-2003. 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% vs. 0.4 percent). 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% 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, Bizarro et al. observed an increase in antibiotic use (from 16% to 85%) paralleling the adoption of the CDC guidelines for GBS prophylaxis [88]. In VLBW neonates the incidence for 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 due to *E. coli* in preterm infants increased from 29% (2 of 7) in 1998 to 84% (16 of 18) in 2000 [89]. *E. coli*-associated mortality tended to be more common in ampicillin-resistant cases (26%) compared to 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. 82% of mothers who delivered preterm infants with EOS with an ampicillin resistant organism had received antenatal antibiotics compared to 40% of mothers of term infants with resistant disease.

On the other hand, Schrag *et al.* reported a lack of an association between IAP and EOS due to ampicillin-resistant *E. coli* [90]. While over half of infected subjects had been exposed to intrapartum antibiotics, those with ampicillin-resistant *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 *E. coli* sepsis were prematurity, particularly ≤ 33 weeks of gestation, followed by maternal fever and prolonged membrane rupture. Univariate analysis controlling for intrapartum fever revealed an association between IAP and *E. coli* infection in general (both ampicillin-resistant and -sensitive). When separating the analysis based on gestational age, exposure to IAP for 4 or more hours actually reduced the odds for *E. coli* infection in term infants, indicative of a protective effect.

Increased emergence of ampicillin-resistant *E. coli* EOS has also been reported in other countries. Analysis of single-institution data from Madrid showed a preferential increase of resistant *E. coli* EOS among preterm but not term neonates, a finding which was not paralleled by a significantly greater usage of intrapartum antibiotics [91]. Retrospective analysis in one

hospital in New Zealand confirmed the preponderance of *E. coli* infection in premature infants with over half being resistant to amoxicillin [92].

Economic costs of peripartum GBS 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 neurological impairments. While the emotional toll of these complications cannot be numerically assessed, the economic costs are significant. A study of one California HMO correlated an incidence of EOS GBS of 0.1% from 1989-1993, with a calculated cost of \$2.8 million [93]. The initiation of a risk-based approach (1994-1995) resulted in a decreased incidence of EOS paralleling those reported in multi-center surveys (0.04%). The authors estimated that nearly two-thirds of EOS GBS cases had been prevented by this strategy, representing 65.5 life-years saved due 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 catalogued the contribution of this practice to the emergence of resistant organisms [94,95]. Maternal prophylaxis has also been associated with increased early antibiotic use in term neonates and a longer hospital stay [94,96]. 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 [97]. From March 2005 to 2006, 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 to a screening approach, the authors suggested universal screening as the more effective regimen in the presence of a high maternal colonization rate.

Alternative strategies to prevention of GBS EOS

While universal screening measures have significantly and positively impacted EOS due 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 and/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 both EOS as well as late onset GBS disease (from an incidence of 0.74/1000 to 0.048/1000 at the end of the study). However, further studies will be required to assess the cost-benefits of targeted approaches, as well as unintended consequences, 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 of necrotizing enterocolitis [98].

The administration of prophylactic vaccines are the most promising approach to the prevention of neonatal GBS disease [99]. A major rationale for the vaccination of women against GBS is the fact that the majority (85-90%) of pregnant women lack protective antibodies at the time of delivery [100]. In a decision analytical 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 [101]. Vaccines based on CPS expression and conjugated to tetanus toxoid have shown particular therapeutic potential [100,102-107]. In early trials maternal immune

responses to polysaccharide vaccines were variable, although in a study directed by Baker *et al.*, 75% of infants born to women who responded to a type III polysaccharide vaccine had protective antibody levels two months after delivery [104,108]. Conjugation of capsular polysaccharide vaccines to tetanus toxoid has improved antigenic responses in recipients. A high proportion (93-100%) of immunized women exhibited a four-fold increase in type-specific antibody responses post-immunization, although this number was lower (80%) for those receiving the type 1b conjugated vaccine [109]. Importantly, antibody levels were detectable two years after immunization. However, 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 [110]. 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, as well as by regional variations in human populations [111-113].

Conventional approaches to the development of numerous vaccines have been augmented by novel DNA, genomic and protein technologies and are being rapidly superseded by techniques such as reverse vaccinology, in which pathogen-specific genomic sequences are used to screen for potential protein candidates for vaccine development [113-115]. A thorough discussion of GBS vaccine development and novel approaches, beyond the scope of this chapter, have been elegantly reviewed elsewhere [109,113].

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. While 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 [116]. One novel agent, aqueous allicin, a substance derived from garlic, has been shown to have potent bactericidal activity against GBS isolates in culture [117]. Another consideration involves bacteriophage lysins, which are cell wall hydrolases that render bacteria vulnerable to lysis [118]. 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 guide management shortly before delivery, particularly in cases when 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 [119], the commercial version of which has been approved by the FDA for this purpose [120]. 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 to the current universal screening approach [121].

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, have 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. However, unintended consequences of increased intrapartum antibiotic exposure, particularly to ampicillin, include an increasing prevalence of gram-negative bacteria causing EOS, particularly of resistant strains. Morbidity and mortality due to EOS related to GBS and other organisms remains significant, especially in VLBW neonates.

Despite an era of 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. However, given the complications and potential limitations associated with maternal intrapartum prophylaxis, vaccines may be the most effective means of preventing neonatal GBS disease. Although efficacious against the majority of the 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.

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Fig. 1. Incidence of early- and late-onset invasive Group B Streptococcal Disease in three active surveillance areas (California, Georgia and Tennessee), 1990 through 1998, and activities for the prevention of Group B streptococcal disease

Live births for 1998 were approximated on the basis of 1997 data. Arrows designate the dates when prevention activities occurred. ACOG denotes the American College of Obstetricians and Gynecologists, and AAP the American Academy of Pediatrics.

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Fig. 2. Incidence of early-onset invasive Group B Streptococcal disease in black neonates and white neonates in four active surveillance areas (California, Georgia, Tennessee and Maryland), 1993 through 1998

The Healthy People 2010 objectives, released by the U.S. Department of Health and Human Services, constitute a national prevention strategy for substantially improving the health of people in the United States. Live births for 1998 were approximated on the basis of 1997 data. Copied with permission from: NEJM 2000; 3342:15-42.

GBS Pneumonia

CXR of a term infant delivered to a mother with unknown GBS. Infant required mild resuscitation

Term Infant 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.

Photo courtesy of Dr. Ayoob Ali, Cardinal Glennon Children's Medical Center, St. Louis, MO.

Fig. 3.

Typical chest radiograph of a newborn with GBS pneumonia. (Courtesy of Dr. Ayoob Ali, Cardinal Glennon Children's Medical Center, St. Louis, MO.)

Fig. 4. Head CT scan of a 3-week-old male following late-onset GBS meningitis

CT scan performed 27 days later showed virtually no normal cortex. He was able to breathe without a respirator, but was unable to suck. (Image courtesy of Dr. Carol J. Baker, Baylor College of Medicine)

Table 1

Rates of early-onset sepsis and associated pathogens in 1991-1993 and 1998-2000.*

Copied with permission from: NEJM 2002; 347:240-247.

Early-Onset Sepsis	1991–1993		1998–2000	
	NO. INFECTED/TOTAL NO.	RATE/ 1000 LIVE- BORN VLBW INFANTS	NO INFECTED/TOTAL NO.	RATE/ 1000 LIVE- BORN VLBW INFANTS
Any	147/7606	19.3	84/5447	15.4
Gram-positive	83/7606	10.9	31/5447	5.7 [†]
Group B streptococci	45/7606	5.9	9/5447	1.7 [‡]
Gram-negative	63/7606	8.3	51/5447	9.4
<i>Escherichia coli</i>	24/7606	3.2	37/5447	6.8 [§]
Fungus	1/7606	0.1	2/5447	0.4

* Data from the period from 1991 to 1993 are from Stoll et al.¹ P=0.007 for the change in the distribution of pathogens between the two periods; there was no significant change in the overall rate of sepsis. Very-low-birth-weight (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 recent birth cohort are 2.1 per 1000 live-born very-low-birth-weight infants and 7.3 per 1000 live-born very-low-birth-weight infants, respectively, and the changes remain significant (P=0.003).

[†] P=0.002 for the comparison with the earlier period.

[‡] P<0.001 for the comparison with the earlier period.

[§] P=0.004 for the comparison with the earlier period.

Table 2

Distribution of pathogens among 84 cases of early-onset sepsis occurring in 5447 infants born between September 1, 1998, and August 31, 2000.*

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Organism	No. with Sepsis (%)
Gram-negative organisms	51 (60.7)
<i>Escherichia coli</i>	37 (44.0)
<i>Haemophilus influenzae</i>	7 (8.3)
Citrobacter	2 (2.4)
Other [†]	5 (6.0)
Gram-positive organisms	31 (36.9)
Group B streptococcus	9 (10.7)
Viridans streptococcus	3 (3.6)
Other streptococci [‡]	4 (4.8)
<i>Listeria monocytogenes</i>	2 (2.4)
Coagulase-negative staphylococcus [§]	9 (10.7)
Other [¶]	4 (4.8)
Fungi	2 (2.4)
<i>Candida albicans</i>	2 (2.4)
Total	84 (100)

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

[†] Other gram-negative organisms included klebsiella (in one infant), bacteroides (in two infants), *Eikenella corrodens* (in one infant), and *Stenotrophomonas maltophilia* (in one infant).

[‡] Other streptococci included group A streptococcus (in one infant) and three cases in which the species was unknown.

[§] Of 18 positive blood cultures for coagulase-negative staphylococci, 1 met the criteria for definite infection and 8 for possible infection; in the other 9 cases, the organism was considered to be a contaminant (see the Methods section).

[¶] Other gram-positive organisms included *Staphylococcus aureus* (in one infant), bacillus (in two infants), and peptostreptococcus (in one infant).