Group B Streptococcal Disease: From Trials and Tribulations to Triumph and Trepidation

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Group B streptococci garnered attention during the 1970s when they surpassed *Escherichia coli* and *Staphylococcus aureus* to become the principal causes of sepsis in early infancy. During the 1980s, several clinical trials demonstrated that administration of antimicrobial agents during labor could interrupt vertical transmission and prevent invasive disease in the first week of life (i.e., early-onset disease). However, prophylaxis was not widely used during the next 10 years. On the basis of efforts by clinician-researchers, professional organizations, community-based parent advocacy groups, and the public health community, consensus recommendations for group B streptococcal prophylaxis were finally issued in 1996. By the end of 1999, the incidence of early-onset disease in selected counties within the United States had decreased by 70%, and the gap between black and white persons with disease narrowed by 75%. This recent triumph leaves the professional community treading lightly, alert to the need to monitor for unintended consequences that may threaten recent progress.

Research on group B streptococci began at approximately the same time that Dr. Joseph Smadel completed his medical training (in 1931) and started his research career in rickettsial and viral diseases, and like Dr. Smadel, group B streptococci also has a Rockefeller connection. That institution was home to Dr. Rebecca Lancefield, whose career at Rockefeller spanned 7 decades. In 1933, she reported development of the grouping system for hemolytic streptococci [1]; this landmark work permitted differentiation of group A streptococci (*Streptococcus pyogenes*), which was the major pathogen associated with puerperal sepsis at the time, from group B streptococci (*Streptococcus agalactiae*), which were initially identified in postpartum specimens obtained after uncomplicated deliveries [2]. The organism was initially considered to be a commensal, but by the end of the decade, Fry [3] reported fatal human sepsis associated with group B streptococci. By the 1960s, numerous reports had linked neonatal infections with this organism [4–6]. However, during the 1970s, the magnitude of disease and attention to group B streptococci changed dramatically when separate reports from Baker et al. [7], Franciosi et al. [8], and Barton et al. [9] announced that group B streptococci had emerged as the leading cause of neonatal sepsis in nurseries around the United States. I will focus on the most recent chapters of the group B streptococci story, which took place from the 1980s through the end of the 20th century, a time during which attention to group B streptococcal disease shifted its focus from trials and tribulations to triumph and trepidation.

Approximately 10%–35% of women are asymptomatic carriers of group B streptococci in the genital and gastrointestinal tracts [10]. At birth, 1 in 2 infants who are born to colonized mothers will themselves be colonized on the skin or mucosal surfaces [11]. Approximately 98% of colonized newborns are without symptoms, but 1%–2% develop early-onset disease, in which sepsis, pneumonia, or meningitis occur during the first week of life. The vast majority of early-onset infections are evident within hours of birth. During the 1970s, ~50% of infants who developed early-onset group B streptococcal infection died of their illness, and many patients who survived meningitis had permanent neurological sequelae. However, by the 1980s, improved recognition of symptoms, prompt treatment, and other improvements in neonatal care reduced the fatality rate to ~15%. The fatality rate remains higher among infants who...
are born prematurely, and such infants also remain at higher risk of long-term consequences of intrauterine infection, such as cerebral palsy and chronic lung disease. Therefore, with the overall improvements in the survival rates, the clinical community turned attention to research on disease prevention. Researchers explored administration of antimicrobial agents to women during pregnancy [12] and to babies after delivery [13], but the most promising results involved use of antibiotic prophylaxis intrapartum, which is defined here as after onset of labor or rupture of the amniotic membranes.

TRIALS

Investigators conducted a number of clinical trials of intrapartum antimicrobial prophylaxis, although not all were randomized or used prospectively enrolled control subjects [14–21]. For efficiency, most studies used inclusion criteria that focused on higher-risk women, such as those who had been detected as prenatal carriers of group B streptococci or those with high density of colonization, which was determined on the basis of first-generation methods for the rapid identification of group B streptococci after rupture of the membranes or preterm labor. Investigators measured the effect of intrapartum antimicrobial prophylaxis against neonatal colonization—a surrogate for disease risk—as well as against laboratory-confirmed, early-onset group B streptococcal disease. One study used postpartum maternal febrile illness as a secondary end point [18]. The trials consistently demonstrated that intrapartum antimicrobial prophylaxis interrupts maternal transmission of the organism to the child [14–19], and the trials that were sufficiently large demonstrated that intrapartum antimicrobial prophylaxis reduces the incidence of early-onset group B streptococcal disease in newborns [18, 20, 21].

The trial by Boyer and Gotoff [18] deserves particular mention, because it was considered by many to be pivotal. The main study was a randomized controlled trial of treatment with ampicillin versus placebo for women who had been identified as prenatal carriers of group B streptococci (on the basis of vaginal and rectal swab samples obtained for culture at 26–28 weeks’ gestation) and who had a threatened delivery at <37 weeks’ gestation or had an interval of >12 h between rupture of the amniotic membranes and delivery. This trial, which was funded by the National Institutes of Health, was halted after an interim analysis revealed significant protection among ampicillin recipients. The decision was based on ethical concerns regarding the withholding of intervention from control subjects any longer. After results were published in the New England Journal of Medicine in 1986, one might have expected wide-scale adoption of this apparently successful intervention strategy.

TRIBULATIONS

What was the immediate impact of the family of prevention trials? During the 1980s, there was no large-scale surveillance for early-onset group B streptococcal infections, so data regarding group B streptococcal disease from this period are limited to reports from a few major hospitals. Group B streptococci continued to be the principal cause of early-onset neonatal sepsis in large hospitals around the country. Even in institutions in which trials had been conducted, intrapartum prophylaxis was not initially adopted. Barriers to implementation included the complexity of the interventions that had been tested—some relied on cumbersome intrapartum detection tests and others used prenatal cultures, which were considered far from perfect. Clinicians with faith in biotechnology probably thought that a simple and accurate detection method would be available soon and that prevention could wait. But a perfect detection method was not revealed during the next decade [22], and the accuracy of prenatal cultures could be optimized with attention to timing and site of specimen collection [23–25] as well as microbiological technique used in processing cultures [26]. The magnitude of disease caused by group B streptococci was not well appreciated outside a small number of clinical centers, which limited the priority given to this condition by the general medical and public health communities. Complicating the situation further, there was diffused responsibility for group B streptococcal disease among clinicians: pediatric caregivers bore the burden of treatment of newborns with life-threatening infections, but obstetrical caregivers who were responsible for intrapartum care had to implement prevention strategies.

Public pressure for prevention of group B streptococcal disease was largely absent during the 1980s. During the 1990s, a number of forces converged on the group B streptococcal front. Public advocacy groups formed in the United States (e.g., the Group B Strep Association and the Jesse Cause) and Canada (Canadian Group B Strep Association); their efforts led to local and national media attention. Economic analyses suggested that a number of intervention strategies were likely to save money, compared with the staggering costs of caring for ill newborns with group B streptococcal infections as well as those with long-term sequelae of newborn infection [27–30]. Several state legislatures considered bills related to prevention of group B streptococcal infection, which was one of the avenues that had been addressed by the parents’ groups. The California assembly passed a bill in 1995 that mandated the health department to hold a consensus conference, the results of which would guide California policy and clinical recommendations on this issue. Some parents sought a voice through political channels, and others sought legal settlements; the issue reached prominence that was sufficient for step-by-step guidance for these cases to appear in the legal journal Trial [31].
Finally, in 1996, consensus recommendations for the prevention of group B streptococcal disease were issued by the 2 key professional organizations, the American College of Obstetricians and Gynecologists [32] and the American Academy of Pediatrics [33], together with the Centers for Disease Control and Prevention (CDC) [34]. The consensus guidelines urged institutions and caregivers to adopt a prevention strategy for group B streptococcal disease and recommended the following 2 appropriate approaches as acceptable alternatives (table 1): the screening-based strategy and the risk-based strategy. Even though the proportion of cases that would be preventable by use of the screening-based strategy was theoretically greater [35], the relative effectiveness of the 2 strategies in practice was not clear. Because the screening-based strategy is more complex—it requires prenatal measures, accurate laboratory testing, and communication from laboratories to labor and delivery—it may be less effective in practice than it is in theoretical estimates.

In Contemporary Ob/Gyn, the guidelines were heralded and clinicians were warned, “If you don’t heed the CDC recommendations and a baby you delivered develops a group B streptococcal infection, it will be just a matter of where they place the decimal point in the out-of-court settlement” [36]. The critical issue at this point was whether practitioners would actually implement the guidelines and what consequences implementation would yield. In contrast to the situation during which the first prevention trials were published, by this point, the United States did have a large-scale surveillance system in place poised to monitor impact.

TRIUMPH

Hospital authorities and practitioners alike viewed the consensus recommendations as a new standard. The proportion of hospitals that adopted prevention policies regarding group B streptococci increased from 13% in 1992 to nearly 60% in 1997 [37]. From 1993 through 1998, the incidence of early-onset group B streptococcal disease decreased by 65%, whereas the incidence of invasive group B streptococcal disease in adults and of late-onset disease in infants who were 7–90 days of age remained stable [38]. In 1993, the rate of early-onset disease among African American persons was nearly twice that of white infants; by 1998, this gap in incidence had narrowed by 75%. There was a direct association between implementation of a new prevention policy and a decrease in the incidence of disease: hospitals with new or revised policies in 1996 had approximately half the incidence of disease in 1997 that they had in earlier years, whereas hospitals with no policy in 1996 had no significant decrease in the number of cases by 1997 [39]. The incidence of disease continued to decrease from 1997 through 1999, but the proportion of hospitals that had implemented policies did not continue to increase during this time period [40]. An explanation for this discrepancy is the finding that, by 1999, more hospitals had introduced systemwide features, such as standing orders, to promote compliance with policies that they had already adopted [40]. Individual practitioners were even more likely than institutions to have policies; many hospitals claimed that their policy was to encourage obstetrical caregivers to implement prevention policies [41, 42]. Although practitioners in some areas were more likely to have adopted the screening-based approach, in others, the risk-based strategy predominated [41]. There were also geographic differences in implementation of appropriate screening methods in clinical laboratories [43]. CDC is currently collaborating with investigators in 8 states where active surveillance for group B streptococcal disease is ongoing on special projects to track actual compliance with the screening-based and risk-based strategies and to compare the relative effectiveness of these approaches.

TREPIDATION

The good news regarding disease prevention and practice changes must be tempered with concern about unintended

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<th>Approach</th>
<th>Prenatal component</th>
<th>Intrapartum component</th>
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<tr>
<td>Screening-based strategy</td>
<td>Obtain vaginal and rectal swab specimens at 35–37 weeks’ gestation and inoculate in selective broth media; assess history of previous infant with group B streptococcal disease and presence of GBS bacteriuria during current pregnancy.</td>
<td>Offer intrapartum penicillin(^a) to women with GBS identified on prenatal cultures, previous infant with GBS disease, GBS bacteriuria during this pregnancy, or unknown screening results and threatened delivery at gestation of &lt;37 weeks, rupture of membranes for (\geq)18 h, or intrapartum temperature of &gt;38°C.</td>
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<tr>
<td>Risk-based strategy</td>
<td>Determine history of previous infant with group B streptococcal disease and presence of GBS bacteriuria during current pregnancy.</td>
<td>Offer intrapartum penicillin(^a) to women with previous infant with GBS disease, GBS bacteriuria during this pregnancy, threatened delivery at gestation of &lt;37 weeks, rupture of membranes for (\geq)18 h, or intrapartum temperature of &gt;38°C.</td>
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\(^a\) Penicillin was recommended as first-line agent with ampicillin as acceptable alternative; clindamycin or erythromycin were recommended for women who were allergic to penicillin.
consequences. A critical component of success in control of group B streptococcal disease is the use of antimicrobial prophylaxis during labor and delivery. Implementation of prevention guidelines appears to double the rates of use of antibiotics during labor. While the guidelines were being developed, authorities voiced concern about adverse effects of increased use of antibiotics, such as severe anaphylactic reactions or the possible emergence of antimicrobial resistance in either group B streptococci or other perinatal pathogens. One unanticipated problem was a shortage of iv penicillin G, the drug of choice for prophylaxis, which occurred in 1999 after a main supplier in the United States halted production because of manufacturing irregularities [44]. A national survey of obstetrician-gynecologists suggested that two-thirds of the providers who had been using penicillin as their first-line prophylaxis agent were affected by the shortage; they usually substituted use of a broader-spectrum agent during the interim period [42]. Although the increased demand for group B streptococcal prophylaxis that grew out of the consensus recommendations was not the cause of the sudden shortage, the problem points to the tenuous state of generic drug availability and highlights a major concern for infectious disease practitioners.

Resistance has been a concern as well. As of 2001, no penicillin-resistant isolates of group B streptococci have been detected. However, resistance to erythromycin and clindamycin has become relatively common in both genital tract isolates and invasive strains [45–47]. Additional concerns relate to the potential for increased antibiotic use to lead to more infections caused by pathogens other than group B streptococci, by filling the niche vacated by this organism. Escherichia coli is the second-most-common cause of neonatal sepsis in the first week of life, after group B streptococci, and sepsis due to ampicillin-resistant E. coli has a worse clinical outcome than does sepsis due to group B streptococci [48, 49]. A small study from California found that, when the number of cases of sepsis due to group B streptococci decreased in 1 hospital, the number of cases of other types of early-onset sepsis actually increased [50]. In a larger observational study from Australia, rates of sepsis caused by organisms other than group B streptococci decreased significantly during the period when the incidence of group B streptococcal sepsis dropped [51]. CDC’s Active Bacterial Core surveillance (ABCs) is tracking all causes of early-onset sepsis in a few states; no increase in the incidence of infection with E. coli or of other infections has been detected to date. The possibility that other infections—in particular, those due to resistant pathogens—will emerge suggests the need for continued surveillance.

To determine whether additional opportunities for prevention of group B streptococcal disease exist, CDC’s ABCs, part of the Emerging Infections Program Network, has been tracking detailed information on early-onset cases that have occurred in recent years, despite the prevention guidelines. A review of >300 cases from 1998 and 1999 in a population with ~300,000 births annually found that approximately one-fifth of cases occurred despite administration of intrapartum antibiotics [52]. These cases may represent antibiotic failures; however, in some instances, administration of antibiotics earlier during labor might have been more effective. Only 35% of case-mothers had been screened prenatally for group B streptococcal colonization, and only 44% of case-mothers had a risk factor evident at the time of labor. Forty percent of case-mothers presented with none of the risk-based criteria for prophylaxis and without having been screened for group B streptococcal colonization. Recent cases represent a mixture of missed opportunities for prevention, protocol failures, and cases that would not be preventable even under perfect implementation of prophylaxis strategies.

**PROGRESS AND PRIORITIES**

During 1999, an estimated 1600 cases of early-onset group B streptococcal disease occurred in the United States. On the basis of disease burden in the era before prevention standards, an estimated 4500 cases and 225 deaths due to early-onset group B streptococcal disease were prevented in 1999. The decrease in the incidence of disease resulted from provision of penicillin—an antibiotic that has been available for more than half a century—to selected women during childbirth by means of a strategy that had been demonstrated to be effective a decade before it was widely accepted as a standard of care. Behind the statistics lies the message that biotechnological breakthroughs are not always needed to make major differences in health.
Sometimes what is needed is a decision that the problem is worth addressing.

Today, the antimicrobial prophylaxis strategies are making a difference, but they may not be the ultimate solution to prevention of group B streptococcal infection. They were proposed as interim strategies while development of more comprehensive tools continues. Antimicrobial prophylaxis will not prevent all cases of early-onset disease. Prenatal cultures are not always predictive of colonization at delivery, and antibiotics are not 100% effective. Intrapartum prophylaxis has not reduced the occurrence of late-onset group B streptococcal disease and does not prevent stillbirths, miscarriages, or preterm deliveries attributable to group B streptococci [53]. In addition, the sustainability of frequent use of antimicrobial agents for prophylaxis during labor is not assured; potential risks of this approach, such as emergence of problems with resistance and adverse effects, may eventually outweigh the current benefits. Additional syndromes, such as invasive group B streptococcal disease in nonpregnant adults, will not be addressed through this strategy. Adults, primarily those with chronic medical conditions or the elderly, now experience most of the illness and death caused by this pathogen (figure 1) [54]. These concerns motivate continued interest and activity in evaluation of group B streptococcal vaccines.

A few lessons learned from the past 2 decades of perinatal group B streptococcal disease may be generalizable to other health concerns. It is essential that research trials are linked to subsequent clinical practice. The tribulations that are a common part of public health can be exploited if we learn to use controversy as a springboard to forging consensus. Triumphs may be rare, but when they occur, they should not only be celebrated but they should be used to convert skeptics to the idea that change is possible. The future may be filled with trepidation, but if we expect the unexpected, we can be better prepared to respond to it effectively.

References