Antimicrobial Prevention of Early-onset Group B Streptococcal Sepsis: Estimates of Risk Reduction Based on a Critical Literature Review

William E. Benitz, MD*; Jeffrey B. Gould, MD§; and Maurice L. Druzin, MD‡

ABSTRACT. Objective. To identify interventions that reduce the attack rate for early-onset group B streptococcal (GBS) sepsis in neonates.

Study Design. Literature review and reanalysis of published data.

Results. The rate of early-onset GBS sepsis in high-risk neonates can be reduced by administration of antibiotics. Treatment during pregnancy (antepartum prophylaxis) fails to reduce maternal GBS colonization at delivery. With the administration of intravenous ampicillin, the risk of early-onset infection in infants born to women with preterm premature rupture of membranes is reduced by 56% and the risk of GBS infection is reduced by 36%; addition of gentamicin may increase the efficacy of ampicillin. Treatment of women with chorioamnionitis with ampicillin and gentamicin during labor reduces the likelihood of neonatal sepsis by 82% and reduces the likelihood of GBS infection by 86%. Universal administration of penicillin to neonates shortly after birth (postpartum prophylaxis) reduces the early-onset GBS attack rate by 68% but is associated with a 40% increase in overall mortality and therefore is contraindicated. Intrapartum prophylaxis, alone or combined with postnatal prophylaxis for the infants, reduces the early-onset GBS attack rate by 80% or 95%, respectively.

Conclusions. Women with chorioamnionitis or preterm premature rupture of membranes and their infants should be treated with intravenous ampicillin and gentamicin. Intrapartum antimicrobial prophylaxis may be appropriate for other women whose infants are at increased but less extreme risk, and supplemental postpartum prophylaxis may be indicated for some of their infants. Selection of appropriate candidates and prophylaxis strategies requires careful consideration of costs and benefits for each patient.

ABBREVIATIONS. EOGBS, early-onset neonatal group B streptococcus, neonatal sepsis, early-onset sepsis, prevention, prophylaxis.

Methods

Prevention of early-onset neonatal group B streptococcal (EOGBS) sepsis requires the identification of infants who are at high risk and the use of effective preventive intervention. The American Academy of Pediatrics (AAP),1,2 American College of Obstetricians and Gynecologists (ACOG),3,4 and Centers for Disease Control and Prevention (CDC)5 agree that this intervention should be intrapartum antibiotic treatment. The commentaries that accompany those recommendations and several recent cost-benefit or efficacy analyses implicitly1-7 or explicitly8-11 assume that intrapartum antimicrobial prophylaxis is 100% effective, but reports of at least 50 cases of EOGBS disease in infants whose mothers received intrapartum prophylaxis12-15 demonstrate that this cannot be correct. The decision analysis cited by the CDC recommendations16 estimated that intrapartum prophylaxis reduces the attack rate by 93.75%, from 16 to 1/1000 live births. A critical review17,18 has questioned whether intrapartum prophylaxis is effective at all. Reviews that support efficacy have not distinguished consistently treatment of mothers during labor alone from treatment of both mothers during labor and infants after delivery.5,19,20 Amstey and Gibbs,21 as well as the CDC,5 have advocated the use of penicillin instead of ampicillin for intrapartum prophylaxis,21 but this regimen has not been evaluated extensively. Because of uncertainty about the efficacy of intrapartum prophylaxis, Wedgwood et al22 and Siegel and Cushion23 have advocated reconsideration of universal postpartum prophylaxis, and Gotoff and Boyer24 have proposed a strategy based on a combination of intrapartum maternal prophylaxis and postpartum neonatal prophylaxis. These proposals indicate that the AAP, ACOG, and CDC recommendations have not been universally accepted. To better understand the scientific basis for proposed prevention strategies, we have reviewed published trials of methods for prevention of neonatal group B streptococcus (GBS) infection to establish estimates for the effectiveness of each prophylaxis regimen in reducing the rate of EOGBS infection.

METHODS

Trials of regimens for prevention of EOGBS infection were identified using a MEDLINE search, as well as reference lists for those articles and recent reviews.25-30 Studies were considered relevant only if enrollment criteria were explicit and applied equally to both treatment and nontreatment (control) subjects, and if GBS disease was observed in at least 1 subject. Neonatal sepsis or GBS sepsis was diagnosed only if pathogenic bacteria or GBS, respectively, were recovered from cultures of blood, cerebrospinal...
fluid, or a tracheal aspirate. Infants who had only clinical findings consistent with sepsis and/or GBS antigen in their urine were not considered to have sepsis. Only early-onset cases (diagnosed within the first 7 days after birth) were included. Because spontaneous waxing and waning of GBS attack rates make sequential designs inappropriate for studies of this disease, studies that relied on historical controls were evaluated primarily for evidence of adverse effects. Effects on neonatal mortality were also evaluated if possible. Because of heterogeneity in study designs, differences in therapeutic regimens, inconsistent criteria for diagnosis of sepsis, and implementation flaws, formal metaanalysis of treatment and prevention strategies is not practical. We included all studies that meet these relevance and diagnostic criteria, but doing so may overestimate treatment efficacy because of ascertainment bias.

Differences in outcomes were evaluated using the G test of independence, an alternative to the $\chi^2$ or Fisher exact tests preferred for contingency tables in which marginal totals are not fixed by experimental design. CIs for ORs were calculated using the method of Cornfield (see reference), typical ORs and confidence limits for data pooled from multiple studies were calculated by the method of Mantel and Haenszel after testing for heterogeneity by the method of Woolf (see reference), and relative risks were calculated by the method of Rothman and Boice (see reference). If no events were observed, we calculated one-tailed confidence limits for ORs using the method of Cornfield, we calculated OR point estimates by adding .5 to each entry in the contingency table, and we calculated CIs for attack rates using the normal or binomial distributions. Probabilities of type II errors were calculated as described by Sokol and Rohlf. All $P$ values are two-tailed.

RESULTS

Measures intended to prevent early-onset neonatal sepsis fall into two groups: treatment with broad-spectrum antibiotics with the intent of preventing any early-onset infection and prophylaxis using monotherapy specifically to prevent GBS transmission. The first group, in which antepartum or intrapartum antibiotic use is the primary intervention, has been categorized according to the clinical indication for treatment (preterm premature rupture of membranes or chorioamnionitis). The second group includes antepartum, intrapartum, postpartum, and combined intrapartum and postpartum prophylaxis regimens.

Intrapartum Treatment for Preterm Premature Rupture of Membranes

Thirteen studies describing the effects of intrapartum intravenous antibiotics and two studies describing the effects of oral antibiotic therapy on the prevalence of neonatal sepsis and/or GBS sepsis after preterm (<37 weeks gestation) premature (before the onset of labor) rupture of membranes were identified. Neither study of oral therapy demonstrated any impact on neonatal infection. Three studies of intravenous therapy that did not report the number of infants with culture-proven bacteremia were excluded. The remaining studies are summarized in Table 1. Two individual studies, one a randomized prospective trial, as well the pooled data, indicate that antibiotic treatment of women with preterm premature rupture of membranes before delivery reduced the rate of culture-proven sepsis among their infants. In several of these studies, GBS-colonized women were excluded or were given intrapartum prophylaxis. In three trials in which intervention was not contingent on GBS colonization status, there were no cases of early-onset GBS infection in 104 infants whose mothers received intrapartum antibiotics and 7 cases in 152 infants born to women who were not given antibiotics ($P > .05$). When combined with a recent study from which GBS-colonized women were excluded, these studies imply that administration of antibiotics to women with preterm premature rupture of membranes reduces the risk of early-onset sepsis by 56% and reduces the risk of GBS sepsis by 36% (Table 1). Because the latter study may overlook benefits in GBS-colonized patients, benefits of intrapartum treatment of women with preterm premature rupture of membranes may be underestimated. The observation that intrapartum ampicillin reduced the rate of early-onset clinical sepsis in infants born to GBS-colonized women but not in infants born to women who were not GBS-colonized suggests that broad-spectrum antimicrobial coverage may be required for these patients.

Intrapartum Treatment of Chorioamnionitis

The effects of the intrapartum treatment of women with chorioamnionitis on the risk of neonatal infection are addressed by several studies (Table 2). In a prospective, nonrandomized study, Sperling et al evaluated rates of early-onset sepsis in infants born to women with chorioamnionitis that was diagnosed based on intrapartum fever >100°F (37.8°C) and at least two additional clinical findings: maternal tachycardia, uterine tenderness, fetal tachycardia, purulent amniotic fluid, or leukocytosis. Bacteremia was less common ($P < .001$) in infants whose mothers received penicillin and gentamicin before delivery (Table 2). All infants were treated with ampicillin and gentamicin until infection was excluded. Treatment was not random, the antepartum treatment group included fewer low birth weight infants and had a longer time from diagnosis of chorioamnionitis to delivery, and there were no significant effects on neonatal sepsis in infants with birth weights <2000 g nor any difference in EOGBS rates between early and delayed treatment groups; therefore, it is not clear that the observed difference in sepsis rates was attributable to treatment. Gilstrap et al retrospectively examined outcomes of infants born to women with chorioamnionitis diagnosed using similar criteria. Infants born to women who had been given antibiotics before delivery were less likely to have GBS bacteremia, but there was no significant effect on the total bacteremia rate (Table 2). Gibbs et al prospectively randomized women with chorioamnionitis, diagnosed as above, to treatment during labor or only after cord clamping. Infants in both groups were treated with ampicillin and gentamicin until infection was excluded by negative blood cultures at 72 hours or for 10 days in those with confirmed sepsis. This series was too small to detect a significant effect on the rate of EOGBS infection, but treatment before delivery was associated with a significant reduction in neonatal sepsis in general (Table 2), providing the most compelling evidence that intrapartum treatment of such women is beneficial to their infants. In the above studies, treatment consisted of penicillin or
ampicillin in combination with gentamicin. Treatment with a penicillin alone cannot be recommended, because 4 cases of infection attributable to ampicillin-resistant Enterobacteriaceae after prophylactic treatment of women with chorioamnionitis using ampicillin or amoxicillin alone have been reported.58 Considered collectively, these studies indicate that intrapartum treatment of women with chorioamnionitis, using ampicillin and gentamicin, reduces the risk of EOGBS sepsis by 86% and reduces the risk of early-onset sepsis in general by 82% (Table 2).

### Antepartum Prophylaxis

As the relationship between maternal GBS colonization and early-onset neonatal infection became apparent in the early 1970s, the potential for prevention of neonatal disease by identification and treatment of GBS carriers during pregnancy was recognized quickly.59,60 In promising but uncontrolled observations, Franciosi et al described eradication of GBS colonization in 13 of 14 colonized women and their husbands after treatment with intramuscular benzathine penicillin G.60 In a randomized controlled trial of treatment of GBS-colonized women with oral ampicillin for 1 week during pregnancy, Hall et al61 demonstrated reduced maternal colonization 3 weeks after treatment, but neither maternal (Table 3) nor neonatal colonization rates were reduced at delivery. Treatment of GBS-colonized women and their husbands with oral penicillin for 14 days during the third trimester also did not reduce maternal colonization rates at delivery.62 In a unique trial in which treatment of GBS-colonized women and their husbands was continuous from 38 weeks gestation until delivery, Merenstein et al63 described a marked reduction in maternal colonization at delivery, but they recommended additional studies before these observations were applied to clinical practice and emphasized that this approach did not address the high-risk population of infants who deliver before screening at 38 weeks gestation. Lewin and Amstey64 reported that treatment of colonized women and their husbands...
bands with benzathine penicillin/procaine penicillin injection in the third trimester was effective in reducing the colonization rate at delivery. Weeks et al\(^6\) have recently reported a 72% reduction in GBS colonization rate and eradication of heavy GBS colonization at delivery after administration of benzathine penicillin G to women with GBS colonization at various times between 16 and 37 weeks gestation, but follow-up was unavailable for nearly a third of their subjects and no control group was studied. Now, it is generally accepted that it is extremely difficult or impossible to eradicate GBS from mucosal surfaces,\(^6\) and that vaginal recolonization after a course of antibiotic therapy is exceedingly common, as initially reported by Hall et al.\(^6\) No studies have demonstrated an effect on neonatal infections.

**TABLE 2.** Intrapartum Versus Postpartum Treatment of Chorioamnionitis: Effects on Early-Onset Sepsis (Sepsis) and EOGBS

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Regimen</th>
<th>Intrapartum Sepsis</th>
<th>Postpartum Sepsis</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperling, 1987</td>
<td>Mothers: Penicillin 5 MU IV every 6 h plus gentamicin 1.5 mg/kg every 8 h. Neonates: Ampicillin 75 mg/kg IV every 12 h plus gentamicin 2.5 mg/kg IV every 12 h until infection was excluded.</td>
<td>6</td>
<td>211</td>
<td>9</td>
<td>46</td>
<td>.12 (.04–.35)</td>
</tr>
<tr>
<td>Gilstrap, 1988</td>
<td>Mothers: Various regimens. Infants: Treatment not specified.</td>
<td>2</td>
<td>152</td>
<td>8</td>
<td>160</td>
<td>.25 (.06–1.1)</td>
</tr>
<tr>
<td>Gibbs, 1988</td>
<td>Mothers: Ampicillin 2 g IV every 6 h plus gentamicin 1.5 mg/kg IV every 8 h. Neonates: Ampicillin 75 mg/kg IV every 12 h plus gentamicin 2.5 mg/kg IV every 12 h until infection was excluded.</td>
<td>0</td>
<td>26</td>
<td>4</td>
<td>19</td>
<td>.065 (0–.42)</td>
</tr>
</tbody>
</table>

**Pooled OR**: \(.138 (.06–.30)\)

**Relative Risk** = \(.181\)

*Because of assumptions implicit in the Mantel-Haenszel method, pooled ORs must be viewed with caution (95% CI).

**TABLE 3.** Effects of Antepartum Regimens on Maternal Colonization at Delivery (GBS +) and EOGBS

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Regimen</th>
<th>Treatment</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall, 1976</td>
<td>Ampicillin 500 mg orally qid (\times 7) d for GBS+ women in third trimester</td>
<td>8</td>
<td>23</td>
<td>13</td>
<td>29</td>
<td>.66 (.22–2.0)</td>
</tr>
<tr>
<td>Gardner, 1978</td>
<td>Penicillin or erythromycin 250 mg orally qid (\times 12–14) d during third trimester</td>
<td>27</td>
<td>40</td>
<td>12</td>
<td>19</td>
<td>1.2 (.40–3.7)</td>
</tr>
<tr>
<td>Merenstein, 1980</td>
<td>Penicillin or erythromycin 500 mg orally qid from 38 wk gestation until delivery</td>
<td>0</td>
<td>19</td>
<td>12</td>
<td>22</td>
<td>.02 (0–15)</td>
</tr>
<tr>
<td>Lewin, 1981</td>
<td>CR-Bicillin 2.4 M units for GBS+ women and their husbands in the third trimester</td>
<td>2</td>
<td>11</td>
<td>9</td>
<td>12</td>
<td>.07 (.01–.51)</td>
</tr>
</tbody>
</table>

**Pooled OR**: Not calculated, groups heterogenous

**TABLE 3.** Effects of Antepartum Regimens on Maternal Colonization at Delivery (GBS +) and EOGBS

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Regimen</th>
<th>Treatment</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merenstein, 1980</td>
<td>See above</td>
<td>0</td>
<td>20</td>
<td>1</td>
<td>24</td>
<td>.38 (0–3.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Regimen</th>
<th>Treatment</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merenstein, 1980</td>
<td>See above</td>
<td>0</td>
<td>20</td>
<td>1</td>
<td>24</td>
<td>.38 (0–3.3)</td>
</tr>
</tbody>
</table>

**Intrapartum Prophylaxis**

A total of 17 reports describing intrapartum prophylaxis were identified. Of the reports, 3, in which both intrapartum maternal and postpartum neonatal prophylaxis was administered,\(^6\) are considered separately. Of the reports, 9 were excluded: 4 had no control subjects\(^7\), or only historical controls,\(^7\), 2 used clinical\(^7\) or unspecified\(^6\) criteria to diagnose sepsis, 1 did not report the number of recipients of prophylaxis,\(^7\) and 2 were duplicate reports.\(^7\) The 5 remaining studies\(^7\) are summarized in Table 4. In the study by Allardice et al,\(^8\) 28 women who were
prospectively identified as GBS carriers by vaginal culture at 28 to 34 weeks gestation were confirmed to have GBS colonization at delivery and were given intrapartum ampicillin prophylaxis; none delivered infants with invasive GBS disease. Among 136 women who had vaginal GBS colonization at delivery but who did not receive intrapartum prophylaxis because they had not been identified previously as GBS carriers, 9 had infants with invasive GBS disease \((P = .08)\). Morales et al\(^75\) randomly assigned women with positive coagglutination screening tests for GBS colonization to treatment with intravenous ampicillin or no intervention and reported elimination of superficial colonization and invasive GBS disease in infants born to treated mothers \((P = .13)\). Among infants born to women with heavy GBS colonization, ascertained using a rapid latex agglutination test on admission with labor, Tuppurainen and Hallman reported significantly fewer cases of clinical sepsis in those infants who were assigned randomly to treatment with intravenous penicillin.\(^82\) There was 1 case of culture-proven GBS infection in 88 infants born to treated women and 5 cases of culture-proven GBS infection among 111 infants born to untreated women \((P = .16)\). Among 157 women with positive latex agglutination tests who could not be randomized because delivery occurred before screening test results were available, only 1 woman had an infant with GBS bacteremia; therefore, the relatively high attack rate in the group randomized to no treatment may have been anomalous. Matorrás et al\(^79\) observed no invasive GBS disease in 60 infants born to GBS-colonized women assigned randomly to treatment with intrapartum intravenous ampicillin and 3 cases in 65 infants whose mothers were randomized to no treatment \((95\%\ CI\ for\ OR\ 0–.90,\ but\ P = .06\ by\ G\ test)\). Pylipow et al\(^83\) documented GBS bacteremia in 5 of 54 infants whose mothers were GBS colonized, had at least one intrapartum risk factor (fever or amnionitis, preterm labor, or rupture of membranes for >6 hours), and did not receive intrapartum antibiotics. Only 1 infant born to 79 such mothers who received intrapartum ampicillin had a blood culture positive for GBS. This difference is significant \((P = .05)\), but treatment assignment was not random. It is notable that nontreatment subjects were enrolled preferentially in the last 6 months of this 21-month study, which was conducted during a period when attack rates were not stable at that hospital.\(^80\) Differences between attack rates in treatment and nontreatment groups are statistically significant only in the last of these studies,\(^83\) which was not a randomized trial. Studies in which treatment was randomized\(^79,81,82\) did demonstrate a significant reduction in EOGBS \((OR: .11; 95\%\ CI: .02–.62)\). Studies of intrapartum prophylaxis have been criticized because of nonrandom assignment of penicillin-allergic subjects to the control group\(^81\) (although no biological mechanism by which maternal penicillin allergy could increase the risk of neonatal infection is apparent\(^84\)), failure to provide comparison data on the study groups or to describe fully the randomization procedure,\(^79,82\) omission of statistical methods,\(^82\) and multiple outcome analyses.\(^82\) Although there are many potential sources of error, including bias and selective publication as well as those noted above, these studies provide reasonable evidence that intrapartum antibiotic prophylaxis reduces the risk of EOGBS sepsis by 80%.

The timing or duration of intrapartum prophylaxis is an additional concern. The 1992 AAP guidelines suggested beginning intrapartum prophylaxis at least 4 hours before delivery,\(^1\) and the CDC\(^5\) recommends diagnostic evaluation for infants whose mothers were treated with antibiotics for ≤4 hours before delivery. The revised AAP guidelines indicate that treatment is not necessary for infants whose mothers received at least 2 doses of prophylactic antibiotics before delivery.\(^2\) We are unable to identify data to support these recommendations. The prevalence of GBS colonization of infants born to colonized mothers decreases with increasing duration of intrapartum therapy, from nearly 50% without therapy or within 1 hour of initiation of therapy to 28% after 1 to 2 hours, 2.9% after 2 to 4 hours, and 1.2% after >4 hours \((P < .005)\).\(^76\) Treatment for <1 hour did not

**TABLE 4.** Effects of Intrapartum Prophylaxis on EOGBS

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Regimen</th>
<th>Treatment Total</th>
<th>No Treatment Total</th>
<th>OR (95% CI)</th>
<th>(P)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allardice, 1982</td>
<td>Ampicillin 500 mg IV every 6 h during labor for women with GBS+ antepartum cultures</td>
<td>0/28</td>
<td>9/136</td>
<td>.24 (0.14)</td>
<td>.08</td>
<td>80</td>
</tr>
<tr>
<td>Morales, 1986</td>
<td>Ampicillin 1 g IV every 6 h during labor for women with positive rapid screening tests</td>
<td>0/135</td>
<td>2/128</td>
<td>.19 (0.13)</td>
<td>.13</td>
<td>81</td>
</tr>
<tr>
<td>Tuppurainen, 1989</td>
<td>Penicillin 5 M units IV every 6 h during labor for women with GBS+ intrapartum latex agglutination tests</td>
<td>1/88</td>
<td>5/111</td>
<td>.24 (0.14-1.6)</td>
<td>.16</td>
<td>82</td>
</tr>
<tr>
<td>Matorrás, 1991</td>
<td>Ampicillin 1 g IV every 6 h during labor for women with GBS+ antepartum cultures</td>
<td>0/60</td>
<td>3/65</td>
<td>.15 (0.09-0.95)</td>
<td>.06</td>
<td>79</td>
</tr>
<tr>
<td>Pylipow, 1994</td>
<td>Ampicillin 2 g IV x 3, then 1 g every 6 h during labor for women with GBS+ antepartum cultures and fever, prematurity, or prolonged rupture of membranes</td>
<td>1/70</td>
<td>5/54</td>
<td>.14 (0.02-0.96)</td>
<td>.05</td>
<td>83</td>
</tr>
</tbody>
</table>

*Pooled OR, .188 (.07–53) Relative Risk = .198

* Because of assumptions implicit in the Mantel-Haenszel method, pooled odds ratios must be viewed with caution (95% CI).
affect the rate of infant colonization, and colonization rates after >4 hours of treatment were not different statistically from those after 2 to 4 hours of treatment. In that study, there were no cases of early-onset GBS disease in infants whose mothers received antibiotics at any time before delivery and only 1 case among 253 infants whose mothers did not receive antepartum antibiotics; therefore, no relationship between the risk of disease and duration of therapy can be established. Pylipow et al83 noted that the 2 infants in their survey who developed sepsis despite intrapartum prophylaxis had mothers who received antibiotics <2.5 hours before delivery. They also described a reduction in neonatal colonization after intrapartum prophylaxis (P < .05), and reported that colonization (6.9% vs 9%) and neonatal sepsis (4.7% vs 7%) rates were not significantly higher in infants whose mothers received only 1 intrapartum antibiotic dose than in those whose mothers received 2 doses (P > .5). Others have reported prophylaxis failures after antibiotic administration for >4 hours before delivery. Weisman et al reported prophylaxis failures in preterm infants even after antibiotic administration for up to 48 hours before delivery, as well as in term infants who received antibiotics for <4 hours before delivery.12,14 In a series of intrapartum prophylaxis failures reported by Ascher et al,13 6 of 16 occurred in term infants treated for 4 to 7 hours before delivery. No studies report either the number of women who received intrapartum treatment for longer intervals or the number of women who were treated for a short time and whose infants were not infected. The 1992 AAP recommendation is supported by the rationale that >4 hours may be required to allow achievement of optimal ampicillin levels in the amniotic fluid and placental circulation, presumably producing a reduction in amniotic fluid bacterial counts.1 Although bactericidal levels of ampicillin are achieved in fetal serum and amniotic fluid as soon as 5 minutes after maternal ampicillin administration,85 there are no data relating these ampicillin levels to neonatal outcomes, and Silver et al found “no significant relationship between quantitative amniotic fluid GBS cultures and neonatal outcome.”86 Because the available data do not permit stratification of residual risk based on either the number of doses given or the duration of treatment before delivery, we conclude that it is impossible to determine the minimum duration of intrapartum treatment required to achieve detectable or optimal efficacy.

Postpartum Prophylaxis

The serendipitous observation that GBS infections were rare at centers in which newborn infants were given penicillin injections routinely to prevent gonococcal ophthalmia suggested that this intervention might also prevent EOGBS disease.87–89 Several studies tested this hypothesis (Table 5). Lloyd et al described a significant reduction in the GBS attack rate after institution of routine penicillin prophylaxis for premature (<35 weeks) or low birth weight (<2500 g) infants.90 In a prospective trial, Siegel et al demonstrated that postpartum penicillin prophylaxis significantly reduced the prevalence of EOGBS disease.91,92 Patel et al reported a lower rate of EOGBS disease during an 18-month period when intramuscular penicillin prophylaxis at birth was routine, compared with the 18 months after the discontinuation of that practice.93 Siegel and Cushion23 and Wedgwood et al22 have recently advocated reconsideration of universal penicillin prophylaxis at birth. Siegel and Cushion23 presented comprehensive data on GBS attack and mortality rates for infants delivered at Parkland Memorial Hospital between the start of their previously reported clinical trial on December 4, 1977 and the end of 1994.23 Data gathered retrospectively for the period before the clinical trial were not considered in this analysis. Data from the clinical trial (December 1977 through May 1981), for infants who received penicillin prophylaxis after birth in June 1981 through October 1986, and for infants delivered in November 1986 through December 1994, who did not receive penicillin prophylaxis, are summarized in Table 6. The GBS attack rate was significantly lower during the penicillin prophylaxis periods both during and after the prospective trial (Table 5). Attack rates for invasive disease attributable to penicillin-sensitive bacteria were lower in penicillin-treated infants (Table 6). Mortality associated with EOGBS disease or with penicillin-sensitive organisms during the first month of life was not

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Regimen</th>
<th>Treatment Controls OR (95% CI)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lloyd, 1979</td>
<td>Penicillin 50 000–100 000 units/kg/day IV or IM × 48 h in infants &lt; 2.5 kg</td>
<td>0 537 11</td>
<td>1208 .10 (.05–.55)</td>
<td>.006</td>
</tr>
<tr>
<td>Pyati, 1983</td>
<td>Penicillin 100 000 units/kg IM × 1 within 90 min of birth for infants &lt; 2 kg in weight</td>
<td>10 589 14</td>
<td>598 .72 (.32–1.6)</td>
<td>.44</td>
</tr>
<tr>
<td>Patel, 1994</td>
<td>Penicillin 25 000 or 50 000 units (for infants &lt; or ≥2.5 kg, respectively) IM × 1 immediately after delivery</td>
<td>8 5892 32</td>
<td>5865 .25 (.12–.53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Siegal, 1982 and 1996</td>
<td>Penicillin 25 000 or 50 000 units (for infants &lt; or ≥2 kg, respectively) IM × 1 immediately after delivery (1977–1981)</td>
<td>4 16 082 19</td>
<td>15 976 .21 (.07–.59)</td>
<td>.0012</td>
</tr>
<tr>
<td>Siegal, 1996</td>
<td>As above (1982–1994)</td>
<td>40 63 727 234</td>
<td>119 931 .32 (.23–.45)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Because of assumptions implicit in the Mantel-Haenszel method, pooled ORs must be viewed with caution (95% CI).
TABLE 6. Effects of Postpartum Prophylaxis for EOGBS on Other Neonatal Outcomes 23

<table>
<thead>
<tr>
<th>Bacterial Infection in First Month of Life</th>
<th>Mortality Attributable to Bacterial Infection</th>
<th>Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvicillin-sensitive</td>
<td>Pellicillin-resistant</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1977–1981</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>No penicillin</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>.29 (1.58–58)</td>
<td>1.3 (81–2.2)</td>
</tr>
<tr>
<td><strong>1982–1994</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>70</td>
<td>132</td>
</tr>
<tr>
<td>No penicillin</td>
<td>304</td>
<td>396</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>.43 (33–56)</td>
<td>.63 (35–76)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pooled OR*</td>
<td>.41 (33–52)</td>
<td>Heterogenous</td>
</tr>
</tbody>
</table>

* Because of assumptions implicit in the Mantel-Haenszel method, pooled ORs must be viewed with caution (95% CI).

TABLE 7. Neonatal Outcomes in a Randomized Controlled Trial of Combined Intrapartum and Postpartum Prophylaxis 69

<table>
<thead>
<tr>
<th>Neonatal Outcome Measure</th>
<th>Ampicillin Group</th>
<th>Control Group</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS colonization</td>
<td>8</td>
<td>40</td>
<td>.10 (.04–.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heavy GBS colonization</td>
<td>3</td>
<td>24</td>
<td>.08 (.03–.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GBS bacteremia</td>
<td>0</td>
<td>5</td>
<td>.08 (0–.48)</td>
<td>.009</td>
</tr>
<tr>
<td>Clinical signs of pneumonia</td>
<td>0</td>
<td>4</td>
<td>.10 (0–.61)</td>
<td>.021</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2</td>
<td>.18 (0–1.3)</td>
<td>.12</td>
</tr>
</tbody>
</table>
who received combined intrapartum and neonatal ampicillin prophylaxis (Table 8; upper 95% confidence limit for the OR: .81 by the binomial distribution).

Garland and Fliegner compared neonatal outcomes for 30,197 public clinic patients who had screening cultures at 32 weeks gestation to those for 26,915 private clinic patients who were not screened for GBS colonization.70 GBS-colonized public patients were given penicillin during labor, and their infants received a single injection of penicillin after birth.70 There were 25 cases of EOGBS disease in infants of untreated asymptomatic women (5 cases in public patients who were GBS-colonized women but did not receive prophylaxis attributable to protocol deviations and 20 cases in private patients). There were no EOGBS cases in infants born to GBS-colonized women who received prophylaxis. The number of women who were GBS-colonized or who received intrapartum treatment were not specified, but the OR (Table 8) can be estimated by assuming that rates of delivery at ≤32 weeks gestation (~2%) and GBS colonization (~14%; S. Garland, personal communication) were the same in treated and untreated women. Remarkably, neither the OR nor its confidence limits are sensitive to assumed values for these rates. From the binomial distribution,39 the upper 95% confidence limit for the OR for GBS cases among infants born to women who received intrapartum prophylaxis, compared with those who did not, is .20.

The data of Boyer et al.69 and Garland and Fliegner70 strongly support the inference that combined intrapartum and postpartum prophylaxis reduces the risk of early-onset GBS disease in neonates by 95% (Table 8). Because these studies have fewer methodologic weaknesses than those studies that used intrapartum prophylaxis alone, the efficacy of combined intrapartum and postpartum prophylaxis may be both greater and better established than that of intrapartum prophylaxis alone.

**DISCUSSION**

To better understand the scientific basis for the recommendations of the CDC,5 ACOG,4 and AAP,2 we have systematically evaluated all studies that met criteria for clinical relevancy and diagnostic specificity. There are few data from randomized controlled trials, and no studies directly address relative efficacies of different regimens. Because of heterogeneous study designs, different therapeutic regimens, inconsistent diagnostic criteria, and implementation flaws, reports of strategies for prevention of EOGBS disease are not suitable for formal metaanalysis.17,18,32 Despite these shortcomings, we do not believe that the available data are compromised beyond utility, and we have attempted to use as much of the data as feasible to quantitate the extent to which treatment or prophylaxis regimens reduce attack rates for early-onset neonatal sepsis in general and for EOGBS sepsis in particular. This inclusive approach increases the potential for ascertainment, diagnostic, and reporting biases33,34 and, consequently, may overestimate efficacy.17 Ascertainment error is of particular concern for retrospective studies, of which only three are considered in these analyses.46,56,93 Errors attributable to ascertainment bias are likely to be few for the studies in which blood cultures were performed uniformly on all enrolled infants46,57,69,94,98. In one study, blood cultures were obtained routinely from infants who received postpartum penicillin prophylaxis, but not from infants reported as historical control subjects,90 creating the potential for overascertainment in the penicillin-treated group. The potential for ascertainment errors in prospective studies in which blood cultures were obtained only if the infant was judged to be clinically ill47,53,79,81,83,89 at the discretion of the attending neonatologist,49 or according to unspecified criteria23,51,52,63,70,80,82,91,92 depends on the duration of observation and the proportion of infants for whom complete outcome data were available. All but two of these studies were prospective trials with apparently complete data on early-onset neonatal bacteremia; the other two studies were hospital-based studies that included data for the entire birth cohort. Because most infants with EOGBS sepsis are symptomatic within the first 24 hours,99 few are likely to have been discharged before clinical signs prompted evaluation with blood cultures. To minimize the effects of preferential diagnosis of clinical sepsis in untreated infants, the diagnosis of sepsis was restricted to infants from whom pathogenic bacteria were recovered in nonpermissive cultures. Positive culture results can be ascertained reliably, ie, by review of laboratory summaries,91 so there should have been few failures to identify bacteremic infants.
with EOGBS infection. In making objective determinations of bacterial growth, laboratory personnel are unlikely to be influenced by knowledge of antimicrobial interventions, but clinicians are likely to use such knowledge to reach or exclude a diagnosis of sepsis, which is often based on subjective and nonspecific clinical observations. This criterion may lead to overestimation of the benefits of treatment because of the suppression of bacterial growth in cultures without concomitant reduction of other morbidities of bacterial infection. There are no reliable strategies for recognition of underreporting of negative trials. The effects of interventions on neonatal mortality secondary to early-onset sepsis are described in only a few studies including those of treatment of chorioamnionitis,56,57,98 preterm premature rupture of membranes,47,49–52 postpartum prophylaxis,23,81,92 and combined intrapartum and postpartum prophylaxis.69 Only the very large dataset of Siegel et al included enough subjects to detect an effect on mortality rate,23 and only one study gathered empirical data on infection-related morbidity and cost.100 Future studies, including postimplementation surveillance of GBS prevention strategies, should report complete outcome data, particularly relating to neonatal mortality and hospitalization experiences.

This review identified two types of interventions that may reduce the rate of EOGBS. The first type consists of interventions initiated in response to relatively low prevalence conditions associated with a very high risk of neonatal GBS infection, including preterm premature rupture of membranes (particularly in GBS-colonized women), chorioamnionitis, GBS bacteriuria during pregnancy, and invasive GBS disease in a twin or sibling.101 These interventions could be considered treatment for apparent disease. The second group includes interventions provoked by more common conditions associated with a moderately increased risk of neonatal GBS infection. These interventions are more appropriately considered to be prophylaxis, because few infants with these conditions would become infected even without intervention. Such conditions include maternal vaginal colonization with GBS at delivery, prematurity and low birth weight, prolonged rupture of membranes, and intrapartum maternal fever.101 We considered these two categories of interventions separately, because infants in the highest risk category may require aggressive treatment rather than prophylactic measures.

We found that interventions in the first category are effective in reducing the rate of sepsis in general and GBS sepsis in particular. In a recent metaanalysis of strategies for management of preterm premature rupture of membranes, Egarter et al102 also concluded that antibiotic therapy is effective in reducing the risk of clinical sepsis defined as fever, leukocytosis, and C-reactive protein elevation (a positive blood culture was not considered sufficient and apparently was not required). Most of the reported regimens continued treatment either until delivery or until cultures excluded GBS colonization. We recommend treating women with preterm premature rupture of membranes with ampicillin and gentamicin beginning at diagnosis and continuing until delivery occurs or at least until maternal vaginal cultures exclude GBS colonization. Antibiotic treatment of women with chorioamnionitis reduces the risk of early-onset sepsis in general as well as GBS sepsis in particular, so these patients also should be treated with intravenous ampicillin and gentamicin, beginning at diagnosis and continuing until delivery. Nearly all (44 of 50) reported cases in which intrapartum antibiotic treatment failed to prevent EOGBS sepsis occurred in infants born to mothers with chorioamnionitis,12–15 so complete evaluation and empiric treatment of infants with chorioamnionitis is also a necessity until neonatal sepsis is excluded.

There have been no studies of GBS prevention in infants born to women with GBS bacteriuria during pregnancy. Patients with asymptomatic GBS bacteriuria reported by Møller et al and by Persson et al apparently did not receive antibiotic therapy before delivery,103,104 and Wood and Dillon were explicit that the mother of the infant with GBS infection in their series did not receive antibiotic therapy before delivery; therefore, potential effects of treatment at the time GBS bacteriuria is diagnosed are unclear. However, antepartum treatment of women with GBS bacteriuria is unlikely to prevent neonatal infection reliably because bacteriuria may reflect heavy colonization,101 it is extremely difficult to eradicate GBS from the lower intestinal tract,46,67 and recolonization of vagina after antibiotic therapy is common.61 Because intrapartum treatment for preterm premature rupture of membranes and chorioamnionitis and intrapartum prophylaxis both are effective, we recommend intrapartum administration of a penicillin to women with a history of GBS bacteriuria during pregnancy. Because the neonatal risk is apparently very high, and neither intrapartum therapy nor prophylaxis is completely effective, we also recommend empiric treatment with a penicillin for their infants until a diagnosis of invasive GBS disease can be confidently excluded.

When 1 infant from a multiple birth is diagnosed with invasive GBS disease, the apparent very high risk in the others justifies empiric treatment. Until there are empiric data to guide management, the minimum intervention should include a complete diagnostic evaluation and initiation of empiric therapy, using ampicillin or penicillin if GBS infection has been specifically diagnosed, and adding gentamicin if the sepsis is suspected only because of other clinical findings. Because of the unavoidable delay in availability of results and the potential for false-negative results, it would appear ill-advised to require confirmation of the diagnosis by positive cultures in the index case before initiating treatment of the other infant(s). Subsequent infants born to mothers of neonates with EOGBS disease also may be at very high risk,101 so intrapartum prophylaxis in subsequent pregnancies is apparently prudent. There are no data to address the question of whether it is sufficient to treat an at-risk twin or sibling only until cultures are found to be negative or whether a longer course of therapy is needed. Given the very high attack rate in
initially asymptomatic twins, a full course of treatment may be appropriate. Extended treatment may not be necessary for siblings of previously affected infants, because the magnitude of their risk is unknown.

We also found that interventions in the second category are effective, providing opportunities to prevent infection in infants at moderately increased risk. Antepartum prophylaxis has appropriately been abandoned. Because the largest reported experience shows an increased mortality rate with postpartum prophylaxis, this strategy should be abandoned, as well. Ohlsson and Myhr detailed deficiencies of intrapartum prophylaxis trials and concluded that “intrapartum chemoprophylaxis . . . is not supported by conclusive evidence from well designed and conducted randomized, controlled trials”. Although published trials are imperfect, we have concluded that intrapartum prophylaxis is effective, in concurrence with several other reviews and meta-analyses. The necessity of distinguishing between intrapartum prophylaxis alone and in tandem with postpartum prophylaxis in the neonate has been almost universally overlooked, having been noted in print only by Ohlsson and Myhr. Intrapartum prophylaxis alone reduces the risk of EOGBS sepsis by 80% (Tables 4, 7 and 8), and addition of postnatal prophylaxis increases this reduction in GBS disease to 95% (Table 8). The evidence that combined prophylaxis is superior to intrapartum prophylaxis alone is not conclusive (P = .14), but evidence supporting the former is arguably stronger than that supporting the latter. Considering the reported failures of intrapartum prophylaxis, we concur with Boyer and Gotoff and Garland and Fliegner that postpartum prophylaxis may be a useful supplement to intrapartum prophylaxis. Because neither Boyer et al nor Garland and Fliegner reported any cases of early-onset GBS disease in infants given 4 doses of ampicillin or 1 dose of penicillin after intrapartum prophylaxis, a single postpartum antibiotic dose may be sufficient. As the length of hospital stay after vaginal deliveries decreases, more neonates may be discharged before a scheduled 4th antibiotic dose at 36 hours of age. Reported cases of intrapartum prophylaxis failure have been characterized by a high prevalence of chorioamnionitis (44 of 50 cases), onset of symptoms before 1 hour of age in 15 of 16 patients reported by Ascher et al, admission to the NICU at 4 to 7 days of age in the 25 patients reported by Weisman et al, and at least one of these findings in all the infants described by Ascher et al. Because continued treatment is recommended for infants whose mothers had chorioamnionitis and for those who are asymptomatic, missed GBS cases will be unlikely if asymptomatic infants whose mothers received intrapartum prophylaxis are given intramuscular ampicillin every 12 hours until discharge from the hospital, up to a maximum of 4 doses.

The choice of agent for intrapartum prophylaxis remains controversial. The CDC recommends use of penicillin “because it has a narrower spectrum and thus is less likely to select for antibiotic resistant organisms”, Amstey and Gibbs also advocated use of penicillin rather than ampicillin, because of its favorable pharmacokinetics and narrower spectrum of antimicrobial activity, citing a report of 4 infants who developed infections with ampicillin-resistant strains of Escherichia coli (3 cases) or Klebsiella pneumoniae (1 case) after prophylactic treatment with ampicillin or amoxicillin. The mothers of those infants had clinical chorioamnionitis 3 to 12 days after initiation of antibiotic therapy for premature rupture of membranes, but only 1 received intravenous therapy and none received an aminoglycoside. Had these women been treated with intravenous ampicillin and gentamicin, either for preterm premature rupture of membranes while cultures were pending or for chorioamnionitis, it is much less likely that their infants would have developed infection with resistant organisms, so these observations may not be relevant to the use of intravenous ampicillin for GBS prophylaxis. Trials of intrapartum prophylaxis and postpartum prophylaxis have not included sufficient patient numbers to detect increased infections with resistant organisms or higher mortality, and data on these outcomes are rarely reported. Joseph et al recently reported increases in the prevalence of ampicillin resistance, the frequency of maternal ampicillin therapy, and the virulence of disease among infants with early-onset E coli sepsis in the 5 years after implementation of routine intrapartum ampicillin prophylaxis. Although death from infection was more likely among infants with resistant organisms than in those whose organism was ampicillin-sensitive, there was no increase in the overall rate of E coli infection or neonatal mortality. Until data are available, extrapolation from postpartum penicillin prophylaxis suggests that ampicillin should be the preferred agent for intrapartum prophylaxis, as well as for adjunctive postpartum prophylaxis. The AAP, ACOG, and CDC recommendations indicate that erythromycin or clindamycin may be appropriate alternatives, but the efficacy of these agents has not been studied.

The current AAP guidelines advise that “neonates with signs of septicemia should have a complete diagnostic evaluation and initiation of empiric antimicrobial therapy”, and the CDC concurs that antibiotic therapy “is appropriate for those infants suspected clinically of having sepsis”. Management of asymptomatic infants is more problematic. Pediatric practice has been inconsistent and at times illogical. For example, pediatricians may be more rather than less likely to prescribe antibiotic therapy for infants whose mothers have received intrapartum prophylaxis, even though prophylaxis reduces the risk of disease. The revised AAP guidelines recommend limited evaluation (blood count, differential, and blood culture) if fewer than 2 doses of intrapartum chemoprophylaxis were given, or the infant is <35 weeks gestation and has received no treatment otherwise. The rationale for these recommendations is not apparent, because no published data permit risk stratification based on the number of intrapartum antibiotic doses given or on a week-by-week for gestational age basis. The strategy of limited evalu-
ation for infants treated for ≤4 hours or with fewer than 2 doses of antibiotic before delivery is also compromised by the low sensitivity of blood counts in diagnosis of neonatal sepsis.11 Until additional data are available, management of asymptomatic infants whose mothers have received intrapartum prophylaxis will have to be individualized. For some, observation alone may be sufficient. Others may be managed appropriately with intramuscular prophylaxis alone or in concert with screening tests for infection, and those at highest risk may need full diagnostic evaluations and empiric therapy. These choices may be influenced by the expected marginal costs and benefits of interventions for each infant and are considered in greater detail in the third part of this series.112

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