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Prevention of Perinatal Group B Streptococcal Disease Revised Guidelines from CDC, 2010



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Prevention of Perinatal Group B Streptococcal Disease

Revised Guidelines from CDC, 2010

Prepared by

Jennifer R. Verani, MD

Lesley McGee, PhD

Stephanie J. Schrag, DPhil

Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases

Summary

Despite substantial progress in prevention of perinatal group B streptococcal (GBS) disease since the 1990s, GBS remains the leading cause of early-onset neonatal sepsis in the United States. In 1996, CDC, in collaboration with relevant professional societies, published guidelines for the prevention of perinatal group B streptococcal disease (CDC. Prevention of perinatal group B streptococcal disease: a public health perspective. *MMWR* 1996;45[No. RR-7]); those guidelines were updated and republished in 2002 (CDC. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. *MMWR* 2002;51[No. RR-11]). In June 2009, a meeting of clinical and public health representatives was held to reevaluate prevention strategies on the basis of data collected after the issuance of the 2002 guidelines. This report presents CDC's updated guidelines, which have been endorsed by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the American College of Nurse-Midwives, the American Academy of Family Physicians, and the American Society for Microbiology. The recommendations were made on the basis of available evidence when such evidence was sufficient and on expert opinion when available evidence was insufficient. The key changes in the 2010 guidelines include the following:

- expanded recommendations on laboratory methods for the identification of GBS,
- clarification of the colony-count threshold required for reporting GBS detected in the urine of pregnant women,
- updated algorithms for GBS screening and intrapartum chemoprophylaxis for women with preterm labor or preterm premature rupture of membranes,
- a change in the recommended dose of penicillin-G for chemoprophylaxis,
- updated prophylaxis regimens for women with penicillin allergy, and
- a revised algorithm for management of newborns with respect to risk for early-onset GBS disease.

Universal screening at 35–37 weeks' gestation for maternal GBS colonization and use of intrapartum antibiotic prophylaxis has resulted in substantial reductions in the burden of early-onset GBS disease among newborns. Although early-onset GBS disease has become relatively uncommon in recent years, the rates of maternal GBS colonization (and therefore the risk for early-onset GBS disease in the absence of intrapartum antibiotic prophylaxis) remain unchanged since the 1970s. Continued efforts are needed to sustain and improve on the progress achieved in the prevention of GBS disease. There also is a need to monitor for potential adverse consequences of intrapartum antibiotic prophylaxis (e.g., emergence of bacterial antimicrobial resistance or increased incidence or severity of non-GBS neonatal pathogens). In the absence of a licensed GBS vaccine, universal screening and intrapartum antibiotic prophylaxis continue to be the cornerstones of early-onset GBS disease prevention.

Introduction

In the 1970s, the bacterium group B *Streptococcus* (GBS) emerged as the leading infectious cause of early neonatal morbidity and mortality in the United States (1–4). Initial case series reported case-fatality ratios as high as 50% (5). Maternal

colonization with GBS in the genitourinary or gastrointestinal tracts is the primary risk factor for disease. Beginning in the mid 1980s, clinical trials and well-designed observational studies demonstrated that administering intravenous antibiotics during labor to women at risk for transmitting GBS to their newborns could prevent invasive disease in the first week of life (i.e., early-onset disease) (6–11). As a result of the collaborative efforts of clinicians, researchers, professional organizations, parent advocacy groups, and the public health community in the 1990s, recommendations for intrapartum prophylaxis to prevent perinatal GBS disease were issued in 1996 by the American College of Obstetricians and Gynecologists (ACOG) (12) and CDC (13) and in 1997 by the American Academy of

The material in this report originated in the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director, and the Division of Bacterial Diseases, Rana Hajjeh, MD, Director.

Corresponding preparer: Jennifer R. Verani, MD, National Center for Immunization and Respiratory Diseases, CDC, 1600 Clifton Road, N.E., MS C-23, Atlanta, GA 30333. Telephone: 404-639-8652; Fax: 404-639-3970; E-mail: jverani@cdc.gov.

Pediatrics (AAP) (14). Revised guidelines for the prevention of early-onset GBS disease issued in 2002 recommended universal culture-based screening of all pregnant women at 35–37 weeks' gestation to optimize the identification of women who should receive intrapartum antibiotic prophylaxis (15).

Before active prevention was initiated, an estimated 7,500 cases of neonatal GBS disease occurred annually in the United States (16). Striking declines in disease incidence coincided with increased prevention activities in the 1990s (17), and a further reduction occurred following the issuance of the recommendation for universal screening in 2002 (18). However, GBS disease remains the leading infectious cause of morbidity and mortality among newborns in the United States (19,20). The continued burden of disease and newly available data relevant to early-onset GBS disease prevention from the fields of epidemiology, obstetrics, neonatology, microbiology, molecular biology, and pharmacology prompted revision of the guidelines for early-onset GBS disease prevention.

Methods

In November 2008, CDC formed a technical working group* to revise the 2002 guidelines (15). The group consisted of representatives from the ACOG Committee on Obstetric Practice, the American College of Nurse-Midwives (ACNM), the AAP Committee on Infectious Diseases and Committee on the Fetus and Newborn, the American Academy of Family Physicians (AAFP), the Society for Healthcare Epidemiology of America, the American Society for Microbiology (ASM), and CDC's Active Bacterial Core surveillance system, as well

* A list of the members appears on page 32 of this report.

as experts in GBS epidemiology, clinical microbiology, and pharmacology. The group held regular telephone conference calls to identify potential areas of change in the recommendations to prevent GBS disease, and to define sources of newly available data (published and unpublished) to inform the revision of the guidelines.

The working group identified a subset of topics for in-depth review, including areas in which new technologies and/or evidence had become available since the publication of the 2002 guidelines, areas in which implementation of the 2002 guidelines was found to be suboptimal on the basis of published and unpublished data, and areas in which interpretation of the 2002 guidelines was found to be variable on the basis of inquiries received at CDC and the experience of experts in the field. For these topics, a thorough review was conducted of published literature through PubMed searches, other sources (including abstracts and conference proceedings), and unpublished data from ongoing surveillance and research activities of which the working group was aware. For topics on which several sources of data were available, evidence was summarized in tables. For topics on which relatively little new evidence was available, summaries of pertinent data were provided to working group members. Expert opinion was sought from working group members regarding topics on which no new evidence was available.

In June 2009, an in-person meeting of the technical working group was held to review available data and develop updated recommendations using an evidence-based approach when possible and relying on expert scientific opinion when sufficient data were lacking (Table 1). These updated guidelines replace CDC's 2002 guidelines. They are intended for providers of prenatal, obstetric, and neonatal care; supporting microbiol-

TABLE 1. Evidence-based rating system used to determine strength of recommendations

Category	Definition	Recommendation
Strength of recommendation		
A	Strong evidence for efficacy and substantial clinical benefit	Strongly recommended
B	Strong or moderate evidence for efficacy but only limited clinical benefit	Generally recommended
C	Insufficient evidence for efficacy or efficacy does not outweigh possible adverse consequences	Optional
D	Moderate evidence against efficacy or for adverse outcome	Generally not recommended
E	Strong evidence against efficacy or for adverse outcome	Never recommended
Quality of evidence supporting recommendation		
I	Evidence from at least one well-executed randomized, controlled trial or one rigorously designed laboratory-based experimental study that has been replicated by an independent investigator	
II	Evidence from at least one well-designed clinical trial without randomization, cohort or case-controlled analytic studies (preferably from more than one center), multiple time-series studies, dramatic results from uncontrolled studies, or some evidence from laboratory experiments	
III	Evidence from opinions of respected authorities based on clinical or laboratory experience, descriptive studies, or reports of expert committees	

Source: Adapted from LaForce FM. Immunizations, immunoprophylaxis, and chemoprophylaxis to prevent selected infections. US Preventive Services Task Force. JAMA 1987;257:2464–70.

ogy laboratories, hospital administrators, and managed-care organizations; childbirth educators; public health authorities; and expectant parents and their advocates.

Invasive Group B Streptococcal Disease

Group B *Streptococcus*, or *Streptococcus agalactiae*, is a gram-positive bacterium that causes invasive disease primarily in infants, pregnant or postpartum women (19,21–27), and older adults, with the highest incidence among young infants (19). Infections in newborns occurring within the first week of life are designated early-onset disease. Late-onset infections occur in infants aged >1 week, with most infections evident during the first 3 months of life. Because of the burden of disease among infants and the availability of effective interventions to prevent early-onset GBS disease, these guidelines concern only early-onset disease. The measures used to prevent early-onset GBS disease also might prevent some perinatal maternal infections (17,28); however, they do not prevent late-onset infant disease (29).

Early-Onset GBS Disease

GBS is the leading infectious cause of morbidity and mortality among infants in the United States. As a result of prevention efforts, incidence of GBS has declined dramatically over the past 15 years, from 1.7 cases per 1,000 live births in the early 1990s to 0.34–0.37 cases per 1,000 live births in recent years (Figure 1). On the basis of data from CDC's Active Bacterial Core surveillance (ABCs) system, a network of 10 sites across the United States that conduct active, population-based surveillance, CDC estimates that in recent years, GBS has caused approximately 1,200 cases of early-onset invasive disease per year (30); approximately 70% of cases are among babies born at term (≥ 37 weeks' gestation) (19).

Infants with early-onset GBS disease generally present with respiratory distress, apnea, or other signs of sepsis within the first 24–48 hours of life (3,31). The most common clinical syndromes of early-onset disease are sepsis and pneumonia; less frequently, early-onset infections can lead to meningitis. The case-fatality ratio of early-onset disease has declined from as high as 50% in the 1970s

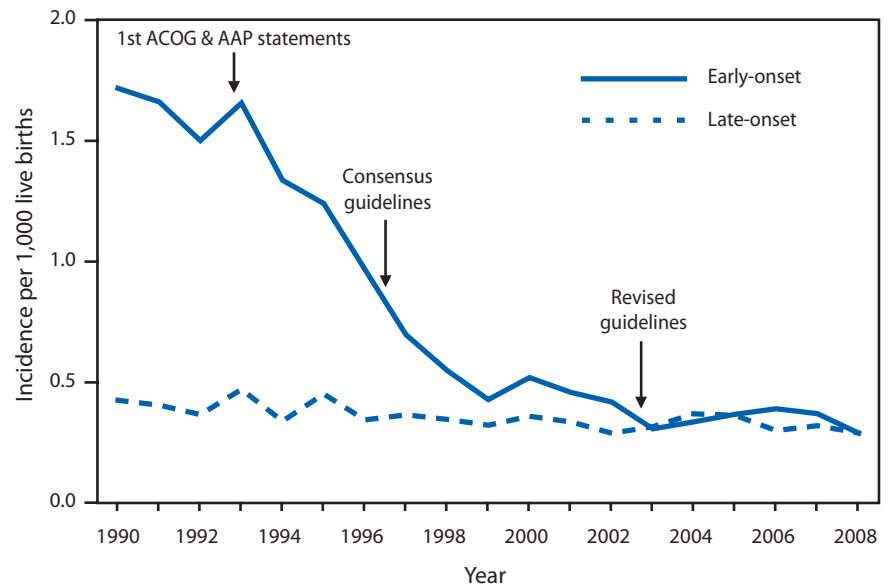
(5) to 4%–6% in recent years, primarily because of advances in neonatal care (17,19). Mortality is higher among preterm infants, with case-fatality rates of approximately 20% and as high as 30% among those ≤ 33 weeks' gestation, compared with 2%–3% among full-term infants (17,19).

Early-onset infections are acquired vertically through exposure to GBS from the vagina of a colonized woman. Neonatal infection occurs primarily when GBS ascends from the vagina to the amniotic fluid after onset of labor or rupture of membranes, although GBS also can invade through intact membranes (32,33). GBS can be aspirated into the fetal lungs, which in turn can lead to bacteremia. Infants also can become infected with GBS during passage through the birth canal; infants who are exposed to the organism through this route can become colonized at mucus membrane sites in the gastrointestinal or respiratory tracts, but these colonized infants most commonly remain healthy.

Risk Factors for Early-Onset GBS Disease

Maternal intrapartum GBS colonization is the primary risk factor for early-onset disease in infants. A classic prospective cohort study conducted during the 1980s revealed that pregnant women with GBS colonization were >25 times more likely

FIGURE 1. Incidence of early- and late-onset invasive group B streptococcal (GBS) disease — Active Bacterial Core surveillance areas, 1990–2008, and activities for prevention of GBS disease



Abbreviations: ACOG = American College of Obstetricians and Gynecologists and AAP = American Academy of Pediatrics.

Source: Adapted from Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease. *Pediatr Infect Dis J* 2008;27:1057–64.

* Incidence rates for 2008 are preliminary because the live birth denominator has not been finalized.

than pregnant women with negative prenatal cultures to deliver infants with early-onset GBS disease (34). In the absence of any intervention, an estimated 1%–2% of infants born to colonized mothers develop early-onset GBS infections (13,34,35). Approximately 10%–30% of pregnant women are colonized with GBS in the vagina or rectum (36–38). GBS colonization during pregnancy can be transient, intermittent, or persistent (39–41). Although some women with GBS colonization during a pregnancy will be colonized during subsequent pregnancies, a substantial proportion will not (42,43). The gastrointestinal tract serves as the primary reservoir for GBS and is the likely source of vaginal colonization. Heavy colonization, defined as culture of GBS from direct plating rather than from selective broth only, is associated with higher risk for early-onset disease (44,45). GBS identified in clean-catch urine specimens during any trimester is considered a surrogate for heavy maternal colonization and also is associated with a higher risk for early-onset GBS disease (46–50).

In addition to maternal colonization with GBS, other factors that increase the risk for early-onset disease include gestational age <37 completed weeks, longer duration of membrane rupture, intra-amniotic infection, young maternal age, black race, and low maternal levels of GBS-specific anticapsular antibody (51–58). Previous delivery of an infant with invasive GBS disease is a risk factor for early-onset disease in subsequent deliveries (59–62). In a 1985 report of predictors of early-onset disease, women with gestation <37 weeks, membrane rupture of >12 hours, or intrapartum temperature >99.5°F (>37.5°C) had 6.5 times the risk for having an infant with early-onset GBS disease compared with women who had none of these risk factors (34). Of note, women who had one of these risk factors but who had negative prenatal screening cultures were at relatively low risk for early-onset GBS disease (incidence: 0.9 cases per 1,000 births) compared with women who were colonized prenatally but had none of the risk factors (incidence: 5.1 cases per 1,000 births) (34).

Some observational studies have reported an association between early-onset GBS disease and certain obstetric procedures, such as the use of internal fetal monitoring devices (58,63) and more than five or six digital vaginal examinations after onset of labor or rupture of membranes (55,63). However, lack of randomization in observational studies can result in confounding, because certain procedures might be used more frequently in high-risk settings (64). Although concern has been raised about performing other obstetric procedures (e.g., membrane stripping and mechanical and/or pharmacologic cervical ripening) on GBS-colonized women, available data are not sufficient to determine whether these procedures are associated with an increased risk for early-onset disease (65,66).

Prevention of Early-Onset Group B Streptococcal Disease

Intravenous Intrapartum Antibiotic Prophylaxis

The use of intravenous intrapartum antibiotic prophylaxis to prevent early-onset GBS disease in the infant was first studied in the 1980s. Clinical trials and well-designed observational studies found that intrapartum antibiotic prophylaxis reduced vertical transmission of GBS, as measured by infant colonization (6,8,11,67) or by protection against early-onset disease (6–11). Early trials suggested an efficacy of 100% for intrapartum antibiotic prophylaxis to prevent early-onset disease among infants born to women with GBS colonization (7,8,10,11). Subsequent observational studies have found the effectiveness to be 86%–89% among infants born to women who received intrapartum GBS prophylaxis (62,68).

Other strategies to reduce maternal colonization and vertical transmission have been studied, including intramuscular intrapartum antibiotic prophylaxis (67), antenatal (oral or intramuscular) antibiotics (69–71), and chlorhexidine vaginal wipes or douches (72–76); however, none has proven to be effective at preventing early-onset disease. Although some nonrandomized studies on chlorhexidine have yielded promising results (72,75), randomized clinical trials have found no protection against early-onset GBS disease or neonatal sepsis (76,77).

Intrapartum Antibiotic Prophylaxis Agents

The efficacy of both penicillin (10) and ampicillin (7) as intravenously administered intrapartum agents for the prevention of early-onset neonatal GBS disease was demonstrated in clinical trials. Penicillin has a narrower spectrum of antimicrobial activity and therefore might be less likely to select for resistant organisms, although one clinical trial found that penicillin and ampicillin administered intravenously intrapartum were associated equally with the presence of ampicillin-resistant gram-negative organisms on postpartum vaginal-perineal culture (78). The dosages of penicillin and ampicillin used for intrapartum GBS prophylaxis are aimed at achieving adequate levels in the fetal circulation and amniotic fluid rapidly while avoiding potentially neurotoxic serum levels in the mother or fetus (79–83). Although the exact duration of antibiotics needed to prevent vertical transmission of GBS has been debated (84,85), beta-lactam antibiotics for GBS prophylaxis administered for ≥4 hours before delivery have been found to be highly effective at preventing vertical transmission of GBS (86) and early-onset GBS disease (68). Shorter durations of appropriate antibiotics might provide some protection; in

particular, colonization data suggest durations of ≥ 2 hours before delivery might confer some protection (86).

The efficacy of alternatives to penicillin or ampicillin that have been used to prevent early-onset GBS disease among infants born to penicillin-allergic mothers (including cefazolin, clindamycin, erythromycin, and vancomycin) has not been measured in controlled trials. Cefazolin has a relatively narrow spectrum of activity, similar pharmacokinetics and dynamics to penicillin and ampicillin, and achieves high intra-amniotic concentrations (87–89). However, an estimated 10% of persons with penicillin allergy also have immediate hypersensitivity reactions to cephalosporins (90). In contrast, data on the ability of clindamycin, erythromycin and vancomycin to reach bactericidal levels in the fetal circulation and amniotic fluid are very limited; available data suggest that erythromycin and clindamycin provided to pregnant women do not reach fetal tissues reliably (91–95).

Safety

Maternal anaphylaxis associated with GBS intrapartum chemoprophylaxis occurs but is sufficiently rare that any morbidity associated with anaphylaxis is offset greatly by reductions in the incidence of maternal and neonatal invasive GBS disease. Anaphylaxis-related mortality is likely to be a rare event because the majority of women receiving intrapartum antibiotics will be in hospital settings where rapid intervention is readily available. Allergic reactions occur in an estimated 0.7%–4.0% of all treatment courses with penicillin, the most common of which is a maculopapular rash (96). Estimates of the rate of anaphylaxis caused by penicillin range from four per 10,000 to four per 100,000 recipients (96). Maternal anaphylaxis associated with GBS prophylaxis was reported in the early 1990s (97); since the release of the 1996 guidelines, four reports of nonfatal cases of anaphylaxis associated with GBS chemoprophylaxis in the United States have been published (98–101). In a CDC multistate sample of approximately 5,000 live births occurring during 1998–1999, a single, nonfatal anaphylactic reaction was noted among the 27% of deliveries in which intrapartum antibiotics were administered (62). In that case, a single dose of penicillin was administered approximately 4 hours before a preterm cesarean delivery, and an anaphylactic reaction occurred shortly after the mother received a single dose of a cephalosporin following umbilical cord clamping. A similar sample of approximately 7,600 live births occurring during 2003–2004 revealed no cases of anaphylaxis among the 32% of deliveries in which mothers received intrapartum antibiotic prophylaxis for GBS (102).

Because a fetus or newborn is unlikely to have had a previous exposure to the antibiotic, and because specific maternal IgE antibodies are not transmitted across the placenta (103), there

is no risk for anaphylaxis in the fetus or newborn resulting from intrapartum antibiotic prophylaxis. Although limited data are available on the impact of intrapartum antibiotics on neonatal gastrointestinal flora, one study comparing stool from infants born to women who received intrapartum GBS prophylaxis with stool from infants whose mothers received no intrapartum antibiotics found no significant difference in colonization with antibiotic-resistant enterobacteria between the two groups (104).

Antibiotic Resistance of GBS

The widespread use of intrapartum antibiotic prophylaxis to prevent early-onset GBS disease has raised concern about the development of antibiotic resistance among GBS isolates. GBS continues to be susceptible to penicillin, ampicillin, and first-generation cephalosporins (19,105–109). However, isolates with increasing minimum inhibitory concentrations (MICs) to penicillin or ampicillin have been reported, including 14 noninvasive isolates during 1995–2005 among adults in Japan (110), and 11 (0.2%) of 5,631 invasive isolates recovered during 1999–2005 from patients of varying ages in the United States (111). Alterations in a penicillin-binding protein (PBP 2X) were found in all of the isolates from Japan and four of those from the United States. The measured MICs from the 11 invasive isolates from the United States are just at the threshold of susceptibility ($\leq 0.12 \mu\text{g/ml}$ for penicillin and $\leq 0.25 \mu\text{g/ml}$ for ampicillin) (112), but the clinical significance of these MIC values is as yet unclear.

Relatively elevated MICs to cefazolin ($1 \mu\text{g/ml}$) also were reported among three (0.05%) of 5,631 invasive GBS isolates collected through CDC's active surveillance during 1999–2005; two of the three isolates also had elevated MICs to penicillin ($0.12 \mu\text{g/ml}$) (111). Although Clinical and Laboratory Standards Institute guidelines do not specify susceptibility breakpoints for cefazolin, they recommend that all isolates susceptible to penicillin be considered susceptible to cefazolin (112). As with the elevated MICs to penicillin and ampicillin, the clinical significance of higher MICs to cefazolin among GBS isolates remains unclear.

The proportions of GBS isolates with *in vitro* resistance to clindamycin or erythromycin have increased over the past 20 years. The prevalence of resistance among invasive GBS isolates in the United States ranged from 25% to 32% for erythromycin and from 13% to 20% for clindamycin in reports published during 2006–2009 (19,106,108). Resistance to erythromycin is associated frequently but not always with resistance to clindamycin. One longitudinal study of GBS early-onset sepsis found that although the overall rate of GBS early-onset disease declined over time, erythromycin-resistant GBS caused an increasing proportion of disease during this interval; however,

the incidence of antibiotic-resistant GBS early-onset sepsis remained stable (105).

Vaccines to Prevent GBS Disease

GBS vaccines have been investigated as a tool for reducing maternal colonization and preventing transmission to neonates (113,114); however, no licensed vaccine is available currently. Sufficient amounts of GBS capsular polysaccharide type-specific serum IgG in mothers have been shown to protect against invasive disease in their infants (51,115–118). Phase I and II clinical trials among healthy, nonpregnant adults of monovalent polysaccharide-protein conjugate vaccines of GBS disease-associated types have shown these vaccines to be well tolerated and immunogenic (116–121). A recent, double-blind randomized trial of a conjugate vaccine against GBS serotype III among nonpregnant women of reproductive age found a significant delay in acquisition of colonization with the vaccine-serotype among vaccine recipients (122). Although an effective GBS vaccine would be a powerful tool against GBS disease, no licensed vaccine is yet available.

Identification of Candidates for Intrapartum Antibiotic Prophylaxis Culture- Versus Risk-Based Screening

Early guidelines recommended the use of one of two approaches to identifying women who should receive intrapartum antibiotic prophylaxis: a risk-based approach or a culture-based screening approach (13). Providers using the risk-based method identified candidates for intrapartum chemoprophylaxis according to the presence of any of the following intrapartum risk factors: delivery at <37 weeks' gestation, intrapartum temperature $\geq 100.4^{\circ}\text{F}$ ($\geq 38.0^{\circ}\text{C}$), or rupture of membranes for ≥ 18 hours. Providers using the culture-based screening method screened all pregnant women for vaginal and rectal GBS colonization between 35 and 37 week's gestation. Colonized women were offered intrapartum antibiotics at the time of labor onset or rupture of membranes if before labor. Under both strategies, intrapartum antibiotic prophylaxis was recommended for women with GBS bacteriuria at any time during their current pregnancy or for women who had given birth previously to an infant with invasive early-onset GBS disease.

A large population-based study conducted during 1998–1999 demonstrated the superiority of culture-based screening over the risk-based approach to prevention of early-onset GBS disease (62). The study found that culture-based screening resulted in the identification of a greater proportion of women

at risk for transmitting GBS to their newborns. Furthermore, women with a positive antenatal GBS culture were more likely to receive intrapartum antibiotic prophylaxis than those women with a risk-based indication for chemoprophylaxis. In 2002, CDC's guidelines for GBS prevention were updated to recommend universal culture-based screening to determine which women should receive intrapartum GBS chemoprophylaxis (15). CDC recommended that women with unknown GBS colonization status at the time of delivery be managed according to the presence of intrapartum risk factors.

Preterm Delivery

Because preterm (at <37 weeks and 0 days' gestation) delivery is an important risk factor for early-onset GBS disease, and because assessing whether preterm labor or rupture of membranes will result in preterm delivery can be difficult, management of intrapartum antibiotic prophylaxis for women with threatened preterm delivery is challenging. Assessing the need for intrapartum prophylaxis for these women also can be difficult because GBS colonization status often is unknown when labor or rupture of membranes occur before 35–37 weeks' gestation. In addition, appropriate use of antibiotic prophylaxis for women with threatened preterm delivery is critical. For women remote from term with premature rupture of membranes, clinical trials have demonstrated that certain antibiotic regimens prolong latency (123,124). However, data from clinical trials also have suggested that certain antibiotics administered for preterm premature rupture of membranes can be associated with necrotizing enterocolitis in the neonate (125,126) and that antibiotics administered in the setting of spontaneous preterm labor can be associated with adverse neonatal outcomes, such as increased need for supplementary oxygen (127) or cerebral palsy (128).

The 2002 guidelines recommended that if GBS colonization status from the current pregnancy is not known, and if onset of labor or rupture of membranes occurred before 37 weeks' gestation with a substantial risk for preterm delivery, then GBS screening should be performed and intrapartum antibiotic prophylaxis for GBS should be provided pending culture results. The implementation of those recommendations has been suboptimal, with limited GBS screening on hospital admission and limited administration of intrapartum antibiotic prophylaxis (102). However, when penicillin, ampicillin, or cefazolin prophylaxis was administered for ≥ 4 hours before delivery to women delivering at <37 weeks' gestation, antibiotic prophylaxis was 78% (95% confidence interval: 44%–91%) effective in preventing early-onset GBS disease (CDC, unpublished data, 2009). No data are available on the effectiveness of antibiotics given before the intrapartum

period in GBS-colonized women with preterm premature rupture of membranes for preventing early-onset GBS disease in the infant.

Bacteriuria

GBS is found in the urine of 2%–7% of pregnant women (46–48,129,130). GBS bacteriuria in a pregnant woman is a marker for heavy genital tract colonization, and maternal GBS bacteriuria (including pure and predominant growth of GBS in the urine) has been associated with GBS colonization and an increased risk for early-onset disease in the newborn (46–50,129). Although some women receive antibiotics to treat GBS bacteriuria during pregnancy, antibiotics do not eliminate GBS from the genitourinary and gastrointestinal tracts, and recolonization after a course of antibiotics is typical (71,131,132). Studies have found that some women with GBS bacteriuria during the first trimester might not have vaginal-rectal colonization detected at 35–37 weeks' gestation (130) or at the time of delivery (133). However, maternal GBS bacteriuria at any point during pregnancy is a recognized risk factor for early-onset GBS disease and therefore has been included as an indication for intrapartum antibiotic prophylaxis since 1996 (13,15).

The 1996 guidelines did not specify a colony-count threshold for defining GBS bacteriuria. In 2002, the guidelines recommended that laboratory personnel report GBS present in any concentration in the urine. Most data on the risk for early-onset GBS disease among infants born to women with GBS bacteriuria are derived from studies of significant GBS bacteriuria (generally $>10^5$ colony-forming units per millimeter of urine) (47–49). Although lower concentrations ($<10^4$ cfu/ml) of GBS in the urine can be associated with vaginal-rectal colonization (134), relatively few data are available on the risk for early-onset GBS disease among infants born to women with low colony-count GBS bacteriuria (48). One study from a vertically integrated health system in Utah found an elevated risk for early-onset GBS disease among infants born to women with low colony-count GBS bacteriuria compared with those whose mothers did not have GBS bacteriuria (135). However, because the majority of pregnant women in the study population had no urine culture performed, those with urine culture results might have been a biased subset. Therefore, the findings on women with low colony-count bacteriuria in this study might not be generalizable to all pregnant women with low colony-count bacteriuria. The recommendation to report any colony count of GBS in the urine represents increased workload for clinical microbiology laboratories, which generally do not report bacterial growth in urine of other pathogens at concentrations $<10^4$ cfu/ml (136) and rarely know whether

urine samples are from pregnant women; as a result, some laboratories search for any GBS colonies in urine cultures from all women of reproductive age. Routine screening for asymptomatic bacteriuria is recommended in pregnant women (137); the identification of GBS through this screening represents an opportunity to detect women at high risk for transmitting GBS to their infant. However, in the context of universal late antenatal GBS screening, it is unclear how much additional disease is prevented by screening for low colony-count GBS bacteriuria and whether identification of low colony-count bacteriuria is cost-effective.

Cesarean Delivery Performed Before Labor Onset on a Woman With Intact Amniotic Membranes

Cesarean delivery does not prevent mother-to-child transmission of GBS because GBS can cross intact amniotic membranes (32,33). A risk does exist for transmission of GBS from a colonized mother to her infant during a cesarean delivery. However, a retrospective study at a single hospital (138), a national population-based study from Sweden (139), and a review of CDC active, population-based surveillance data (CDC, unpublished data, 1998–1999 and 2003–2004) indicated that when a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes, the risk for early-onset GBS disease among full-term infants is extremely low. Data on risk for transmission to preterm infants born via cesarean delivery performed before onset of labor on a woman with intact amniotic membranes are limited; however, the risk for transmission is likely much lower than in the setting of vaginal delivery or cesarean delivery following rupture of membranes or onset of labor.

Specimen Collection and Processing for GBS Screening

Timing of Screening

Because GBS colonization status can change over the course of a pregnancy, the timing of specimen collection for determination of colonization status is important. Because colonization can be transient, colonization early in pregnancy is not predictive of early-onset GBS disease (44). Late third trimester colonization status has been used as a proxy for intrapartum colonization (140). The negative predictive value of GBS cultures performed ≤ 5 weeks before delivery is 95%–98%; however, the clinical utility decreases when a prenatal culture is performed more than 5 weeks before delivery because the negative predictive value declines (37).

Specimen Collection

Swabbing both the lower vagina and rectum (through the anal sphincter) increases the culture yield substantially compared with sampling the cervix or the vagina without also swabbing the rectum (40,141–146). Although a small number of studies have examined the ability of perianal or vaginal-perianal cultures to detect GBS colonization (147,148), the available data on their performance compared with vaginal-rectal cultures are limited. Studies have indicated that when women in the outpatient clinic setting collect their own vaginal-rectal screening specimens, with appropriate instruction, GBS yield is similar to when specimens are collected by a health-care provider (149–152).

The use of appropriate transport media can help sustain the viability of GBS in settings where immediate laboratory processing is not possible (153,154). GBS isolates can remain viable in transport media for several days at room temperature; however, the recovery of isolates declines during 1–4 days, particularly at high temperatures. Even when appropriate transport media are used, the sensitivity of culture is greatest when the specimen is stored at 4°C before culture and processed within 24 hours of collection (139,155–157).

Specimen Processing

Regardless of the test selected to identify GBS, use of an enrichment broth improves detection substantially. When direct agar plating is used instead of selective enrichment broth, as many as 50% of women who are GBS carriers have false-negative culture results (143,144,158,159). Examples of selective enrichment broths include Todd-Hewitt broth supplemented either with gentamicin (8 µg/ml) and nalidixic acid (15 µg/ml) [TransVag broth] or with colistin (10 µg/ml) and nalidixic acid (15 µg/ml) [Lim broth] (160). Although TransVag and Lim broth media are often available without blood, the addition of 5% sheep blood can increase the recovery of GBS (161). Selective enrichment broth also can contain chromogenic substrates that provide for a change in color in the setting of beta-hemolytic GBS. Such broths can facilitate the identification of beta-hemolytic GBS; however, nonhemolytic isolates will not be detected by these broths alone (162–168). Among 265 GBS isolates from invasive early-onset cases that occurred in the 10 ABCs system areas during 2006–2008, a total of 4% were nonhemolytic (CDC, unpublished data, 2006–2008).

Following enrichment, the conventional means for identifying GBS is through isolation on subculture to blood agar plates and presumptive identification by the CAMP test (169) or serologic identification using latex agglutination with group B streptococcal antisera (170). More recently, chromogenic agars

that undergo color change in the presence of beta-hemolytic colonies of GBS have become available (171,172). As with pigmented enrichment broths, these chromogenic agars can facilitate detection of beta-hemolytic GBS, but the majority will not detect nonhemolytic strains. In addition more rapid techniques for identifying GBS directly from enrichment broth, or after subculture have been developed, including DNA probes (173–176) and nucleic acid amplification tests (NAAT) such as polymerase chain reaction (177,178).

Published studies on the performance of commercially available NAAT on nonenriched samples have demonstrated varying sensitivities (range: 62.5%–98.5%) and specificities (range: 64.5%–99.6%) compared with the gold standard of enrichment followed by subculture (179–188) (Table 2). Three studies have compared both intrapartum NAAT on nonenriched samples and late antepartum enriched culture results to intrapartum enriched culture (179,182,185). When comparing swabs collected at the two different time points, two of the studies found intrapartum NAAT to be slightly more sensitive (95.8% and 90.7%, respectively) than antepartum culture (83.3% and 84.3%, respectively) (182,185), although with widely overlapping confidence intervals. One study reported a statistically significant difference between the sensitivity of swabs collected intrapartum and tested with NAAT (94.0%) compared with enriched culture performed on swabs collected prenatally (54.3%) (179). The sensitivity of NAAT for GBS increases to 92.5%–100.0% with use of an enrichment step before testing the sample (177,178,188). Use of an enrichment step lengthens the time to obtain a final result; however, for antenatal testing, the accuracy of results is much more important than timeliness.

Despite the availability of NAAT for GBS, utility of such assays in the intrapartum setting remains limited. Although a highly sensitive and specific test with rapid turnaround time could be used to assess intrapartum GBS colonization and therefore obviate the need for antenatal screening, data on currently available assays do not support their use in replacement of antenatal culture or risk-based assessment of women with unknown GBS status on admission for labor. The additional time required for enrichment of samples makes it not feasible for intrapartum testing, and the sensitivity of assays in the absence of enrichment is not adequate in comparison to culture. In addition, concerns remain regarding real-world turnaround time, test complexity, availability of testing at all times, staffing requirements, and costs. In settings that can perform NAAT, such tests might prove useful for the limited circumstance of a woman at term with unknown colonization status and no other risk factors. Even optimal NAAT would have drawbacks in the intrapartum setting, including a delay in administration of antibiotics while waiting for the result,

TABLE 2. Performance of Nucleic Acid Amplification Tests* (NAAT) compared with enriched culture for detecting group B *Streptococcus* (GBS)

Test	Swab for NAAT and culture		No. positive by NAAT/ No. positive by culture	NAAT sensitivity [†]	No. negative by NAAT/ No. negative by culture	NAAT specificity [†]
	Timing	Type				
NAAT performed on nonenriched samples						
IDI-Strep [§]	IP	VR	140/149	94.0%	626/653	95.9%
IDI-Strep [¶]	IP	V	35/56	62.5%	252/259	97.3%
IDI-Strep ^{**}	AP/IP	VR	59/68	86.8%	157/165	95.2%
GeneXpert ^{††}	IP	VR	23/24	95.8%	20/31	64.5%
IDI-Strep ^{§§}	AP/IP	VR	149/188	79.3%	575/603	95.4%
GeneXpert ^{§§}	AP/IP	VR	173/190	91.1%	570/594	96.0%
BD GeneOhm ^{¶¶}	AP	V	64/83	77.1%	99/117	84.6%
BD GeneOhm ^{***}	IP	VR	49/54	90.7%	121/124	97.6%
GeneXpert ^{†††}	AP/IP	V	135/137	98.5%	723/726	99.6%
IDI-Strep ^{§§§}	IP	VR	38/42	90.5%	148/154	96.1%
NAAT performed on enriched^{¶¶¶} samples						
BD GeneOhm ^{****}	AP	VR	49/53	92.5%	136/147	92.5%
BD GeneOhm ^{††††}	AP	VR	§§§§	100.0%	§§§§	99.3%
BD GeneOhm ^{††††}	AP	VR	§§§§	92.5%	§§§§	99.3%
BD GeneOhm ^{¶¶¶¶}	AP	V/VR	136/141	96.4%	349/357	97.8%

Abbreviations: AP = antepartum, IP = intrapartum, V = vaginal only, and VR = vaginal-rectal.

* Includes only those NAAT that are approved for use by the Food and Drug Administration.

† Compared with enriched culture of specimen collected at the same time as that used for NAAT.

§ **Source:** Davies HD, Miller MA, Faro S, Gregson D, Kehl SC, Jordan JA. Multicenter study of a rapid molecular-based assay for the diagnosis of group B *Streptococcus* colonization in pregnant women. *Clin Infect Dis* 2004;39:1129–35.

¶ **Source:** Aziz N, Baron EJ, D'Souza H, Nourbakhsh M, Druzin ML, Benitz WE. Comparison of rapid intrapartum screening methods for group B streptococcal vaginal colonization. *J Matern Fetal Neonatal Med* 2005;18:225–9.

** **Source:** Atkins KL, Atkinson RM, Shanks A, Parvin CA, Dunne WM, Gross G. Evaluation of polymerase chain reaction for group B *Streptococcus* detection using an improved culture method. *Obstet Gynecol* 2006;108(3 Pt 1):488–91.

†† **Source:** Gavino M, Wang E. A comparison of a new rapid real-time polymerase chain reaction system to traditional culture in determining group B *Streptococcus* colonization. *Am J Obstet Gynecol* 2007;197:388e1–4.

§§ **Source:** Edwards RK, Novak-Weekley SM, Koty PP, Davis T, Leeds LJ, Jordan JA. Rapid group B streptococci screening using a real-time polymerase chain reaction assay. *Obstet Gynecol* 2008;111:1335–41.

¶¶ **Source:** Smith D, Perry JD, Laine L, Galloway A, Gould FK. Comparison of BD GeneOhm real-time polymerase chain reaction with chromogenic and conventional culture methods for detection of group B *Streptococcus* in clinical samples. *Diagn Microbiol Infect Dis* 2008;61:369–72.

*** **Source:** Money D, Dobson S, Cole L, et al. An evaluation of a rapid real time polymerase chain reaction assay for detection of group B *Streptococcus* as part of a neonatal group B *Streptococcus* prevention strategy. *J Obstet Gynaecol Can* 2008;30:770–5.

††† **Source:** El Helali N, Nguyen JC, Ly A, Giovangrandi Y, Trinquart L. Diagnostic accuracy of a rapid real-time polymerase chain reaction assay for universal intrapartum group B *Streptococcus* screening. *Clin Infect Dis* 2009;49:417–23.

§§§ **Source:** Alfa MJ, Sephiri S, De Gagne P, Helawa M, Sandhu G, Harding GK. Real-time PCR assay provides reliable assessment of intrapartum carriage of group B *Streptococcus*. *J Clin Microbiol* 2010;48:3095–9.

¶¶¶ Duration of incubation in selective enrichment broth varied (range: 4–24 hours).

**** **Source:** Goodrich JS, Miller MB. Comparison of culture and 2 real-time polymerase chain reaction assays to detect group B *Streptococcus* during antepartum screening. *Diagn Microbiol Infect Dis* 2007;59:17–22.

†††† **Source:** Block T, Munson E, Culver A, Vaughan K, Hryciuk JE. Comparison of carrot broth- and selective Todd-Hewitt broth-enhanced PCR protocols for real-time detection of *Streptococcus agalactiae* in prenatal vaginal/anorectal specimens. *J Clin Microbiol* 2008;46:3615–20.

§§§§ Primary data unavailable.

¶¶¶¶ **Source:** Scicchitano L, Bourbeau P. Comparative evaluation of the AccuProbe group B *Streptococcus* culture test, the BD GeneOhm Strep B assay, and culture for detection of group B streptococci in pregnant women. *J Clin Microbiol* 2009;47:3021–3.

and no antimicrobial susceptibility testing for penicillin-allergic women. Other rapid tests in addition to NAAT have been developed to detect GBS rapidly from nonenriched samples, including optical immunoassays and enzyme immunoassays; however, none is sufficiently sensitive when used on a direct specimen to detect GBS colonization reliably in the intrapartum setting (180,189–192).

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing of GBS isolates is crucial for appropriate antibiotic prophylaxis selection for penicillin-

allergic women who are at high risk for anaphylaxis because resistance to clindamycin, the most common agent used in this population, is increasing among GBS isolates. In addition, appropriate methodologies for susceptibility testing are important because inducible clindamycin resistance can occur in some strains that appear susceptible in broth susceptibility tests (193,194). D-zone testing using the double-disk diffusion method has been used to identify isolates that are erythromycin-resistant and clindamycin-susceptible, yet have inducible resistance to clindamycin (195). Isolates that are D-zone positive are considered to have inducible clindamycin

resistance and are presumed to be resistant although the clinical significance of this resistance is not clear (196).

Secondary Prevention of Early-Onset GBS Among Infants

Currently available GBS prevention strategies will not prevent all cases of early-onset disease. Rapid detection of neonatal infections and initiation of appropriate treatment is needed to minimize morbidity and mortality among the cases that continue to occur. The detection of early-onset GBS disease poses certain clinical challenges, because neonatal providers must take into account the clinical appearance of the infant, the presence of maternal risk factors for GBS disease, and infant exposure to intrapartum antibiotics.

Infants with Signs of Sepsis

As use of intrapartum antibiotics to prevent early-onset GBS disease increased, concern was expressed that signs of sepsis in the newborn could be delayed or masked, impairing the ability of clinicians to detect early-onset GBS disease (197–199). However, several studies conducted since 1996 have found no significant difference in the clinical presentation of early-onset GBS disease between infants exposed to intrapartum antibiotics and those not exposed (200–204). Approximately 90% of cases of early-onset disease continue to manifest within the first 24 hours of life.

Although maternal GBS colonization might increase clinical suspicion for early-onset GBS disease in an infant, in the era of universal screening, >60% of early-onset GBS cases have occurred among infants born to women who had a negative prenatal GBS culture screen (102,203,204). False-negative cases are not unexpected because culture at 35–37 weeks' gestation will fail to detect some women with intrapartum GBS colonization. As effective prevention strategies are increasingly implemented, a growing proportion of the remaining relatively low burden of disease will reflect inherent limitations in the strategies. Signs of sepsis in any newborn can be an indication of early-onset GBS disease, regardless of maternal colonization status.

Among infants with signs of early-onset disease, the detection of GBS can be increased by performing culture of both blood and cerebrospinal fluid (CSF). Blood cultures can be sterile in as many as 15%–33% of newborns with meningitis (205–209), and the clinical management of an infant with abnormal CSF findings differs from that of an infant with normal CSF.

Infants Born to Women with Chorioamnionitis

Chorioamnionitis is an important risk factor for early-onset GBS disease in women with GBS colonization and can reflect an intrauterine onset of infection in the neonate (45,63,210–212). Intrapartum fever, one sign of chorioamnionitis in parturient women, has been associated with failure of intrapartum antibiotics to prevent GBS disease in the newborn (68,213). Intrapartum treatment of chorioamnionitis can prevent neonatal sepsis (214,215). The diagnosis of chorioamnionitis usually is made clinically on the basis of signs and symptoms such as fever (which might be low-grade), uterine tenderness, fetal tachycardia, maternal tachycardia, and foul-smelling or purulent amniotic fluid. In an effort to avert neonatal infections, maternal fever alone in labor may be used as a sign of chorioamnionitis and hence indication for antibiotic treatment, particularly among women with a significant risk factor for chorioamnionitis (e.g., prolonged labor or prolonged rupture of membranes).

Because an association has been observed between epidural labor analgesia and fever, chorioamnionitis might be overdiagnosed in women with epidurals, which could lead to unnecessary diagnostic evaluations and unnecessary exposure to empirical antibiotics in neonates (216). However, multistate surveillance data suggest that although epidural use is common (in 67% of births), intrapartum temperature of $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$] (3.3% of births) and physician diagnoses of chorioamnionitis (3.1% of births) remain relatively rare (102) (CDC, unpublished data, 2009). Consultation with obstetric providers to determine whether chorioamnionitis is suspected is important for guiding neonatal management.

Well-Appearing Infants Exposed to Inadequate Intrapartum Antibiotics

The management of well-appearing infants whose mothers received inadequate intrapartum antibiotic prophylaxis (because of either a short duration of exposure before delivery or use of an agent with limited efficacy data) can be challenging. Previous GBS prevention guidelines have recommended that infants whose mothers received inadequate intrapartum antibiotic prophylaxis and those <35 weeks' gestational age exposed to intrapartum antibiotics be evaluated with a blood culture and complete blood count (CBC) with differential (13,15). There are limitations to this diagnostic approach. The sensitivity of blood culture can be low among newborns exposed to intrapartum antibiotics (217,218). Available data on the performance of the CBC as a screening test for neonatal sepsis suggest that although the negative predictive value is

high, the positive predictive value is low, particularly among healthy-appearing term infants (219–221). The sensitivity of the CBC is lowest immediately after birth, and its performance as a screen for sepsis can be improved by obtaining the blood specimen between 6–12 hours of life (220,222,223). Clinical signs of sepsis have been found to be a more sensitive indicator of neonatal sepsis than hematologic tests (201).

Certain centers provide intramuscular penicillin to asymptomatic infants within 1 hour of birth; this practice is based on results of observational studies demonstrating declines in early-onset GBS disease coincident with a policy of universal administration of intramuscular penicillin to newborns (224–226). However, because the studies used historic control groups and were conducted at a single center that does not screen pregnant women routinely for antenatal GBS colonization, the findings are not generalizable to other settings.

Implementation and Impact of GBS Prevention Efforts

Implementation of the 2002 Guidelines

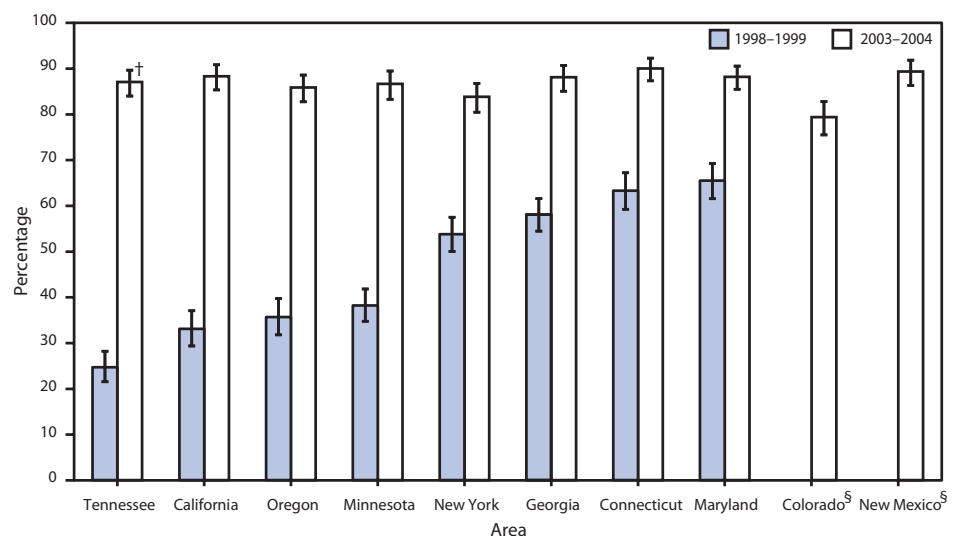
After the issuance of the 2002 recommendation for universal culture screening, implementation was rapid and widespread. The most robust evaluation comes from a multistate, population-based analysis of 819,000 live births during 2003–2004 (102) and a similarly designed study of births during 1998–1999 (62). The proportion of infants whose mothers were screened for GBS colonization before delivery increased from 48.1% during 1998–1999 to 85.0% during 2003–2004 (Figure 2); among women screened during 2003–2004, a total of 98.4% had a result available at labor. Among screened women, 24.2% were documented as GBS-positive, within the range of expected colonization rates. The proportion of mothers with an indication for intrapartum antibiotic prophylaxis who received them also increased substantially, from 73.8% during 1998–1999 to 85.1% during 2003–2004 (Figure 3).

Despite widespread uptake of universal screening, implementation fell short in several key areas. Infants born preterm have an elevated risk for early-onset disease, and because antenatal

screening is recommended at 35–37 weeks of gestation, only 50.3% of women delivering preterm had a known colonization status at the time of hospital admission. Although it is recommended that women with unknown GBS status who deliver preterm receive intrapartum antibiotic prophylaxis, only 63.4% received prophylaxis. In addition, intrapartum antibiotic prophylaxis administration for the indications of GBS bacteriuria or having delivered a previous infant with GBS disease was also low (73.5%) among preterm deliveries. Intrapartum antibiotic prophylaxis was provided to a greater proportion (84.5%) of women delivering preterm who had a positive GBS screening result. Screening for GBS on admission among women with threatened preterm delivery and unknown colonization status was suboptimal; only 18% of women who progressed to delivery and 31% of women who did not progress to delivery were screened despite a recommendation to perform cultures for GBS at hospital admission for this population (15,102).

As anticipated, the proportion of laboring women who received intrapartum antibiotics increased only slightly, from 26.8% to 31.7%, under universal screening. Penicillin and ampicillin, the recommended agents for intrapartum GBS prophylaxis for women with no allergy to penicillin, remained the most common agents administered (76.7% of women receiving intrapartum antibiotic prophylaxis received these agents). However, among penicillin-allergic women, the agents most often administered did not reflect the 2002 recommendations.

FIGURE 2. Percentage of pregnant women screened for group B streptococcal colonization — Active Bacterial Core surveillance areas, 1998–1999 and 2003–2004*



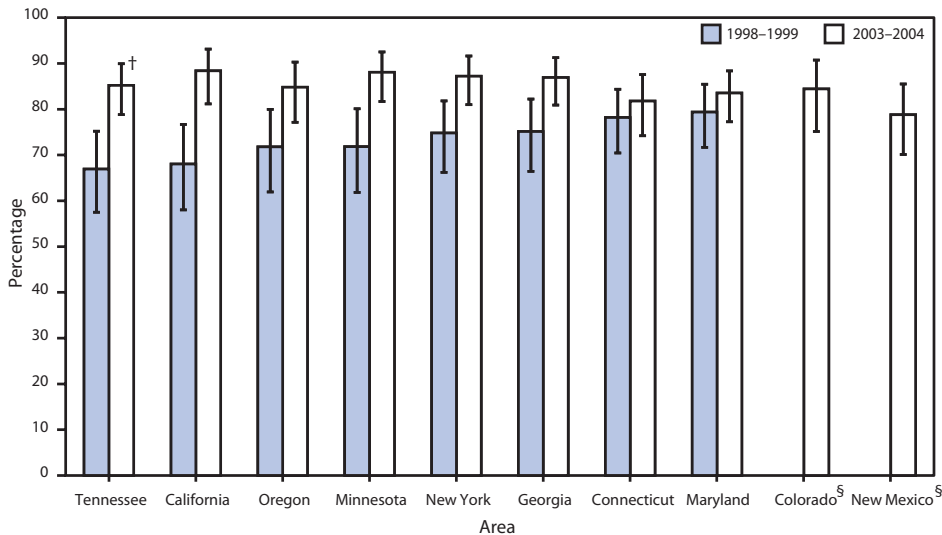
Source: Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B *Streptococcus*. *N Engl J Med* 2009;360:2626–36.

* Reported values are weighted to account for the stratified survey design. The number of charts abstracted was 5,144 for 1998–1999 and 7,691 for 2003–2005.

† 95% confidence interval.

§ Data for 1998–1999 not available.

FIGURE 3. Percentage of women with an indication who received intrapartum antibiotic prophylaxis — Active Bacterial Core surveillance areas, 1998–1999 and 2003–2004*



Source: Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS, et al. Evaluation of universal antenatal screening for group B *Streptococcus*. *N Engl J Med* 2009;360:2626–36.

* Reported values are weighted to account for the stratified survey design. The number of charts abstracted was 5,144 for 1998–1999 and 7,691 for 2003–2005.

[†] 95% confidence interval.

[§] Data for 1998–1999 not available.

In particular, only 13.8% of penicillin-allergic women who were not at high risk for anaphylaxis received cefazolin, despite a recommendation that this more effective agent be used. Clindamycin remained the leading agent among penicillin-allergic women (69.9% of those at low risk for anaphylaxis and 83.5% of those at high risk). Among women receiving clindamycin for prophylaxis, clindamycin and erythromycin susceptibility testing were performed rarely despite recommendations that susceptibility testing be conducted on all vaginal-rectal specimens from women who are allergic to penicillin and at high risk for anaphylaxis (15,102). A single-hospital study in Rhode Island reported similar findings (227).

The multistate population-based study conducted during 2003–2004 also identified a greater-than-expected number of cases of early-onset GBS occurring among infants born to women with negative prenatal screening results (61% observed compared with 23%–46% expected cases of early-onset GBS disease among full-term infants) (102). Some false-negative results are expected because culture is not perfectly sensitive and GBS can be acquired by the mother during the period between screening and delivery. However, the high proportion of cases born to women with negative screening results suggests possible problems in the steps required to identify GBS colonization. Suboptimal specimen collection timing, methods, transport, and/or laboratory processing might be contributing factors.

Among screened women, the date of the antenatal screening test was missing from 36% of labor and delivery charts. Documentation of the date allows for an assessment of whether screening was performed during the recommended gestation time window.

Trends in Neonatal GBS Disease

Incidence of invasive early-onset GBS disease has declined approximately 80% (Figure 1) since the early 1990s, when implementation of intrapartum antibiotic prophylaxis to prevent GBS disease began. Nationally representative hospital discharge diagnostic code data also demonstrated a steady decrease in clinical sepsis rates during 1990–2002, with a marked decline in clinical sepsis among term infants during the 2 years following the issuance of the 1996 GBS prevention guidelines (228); these data

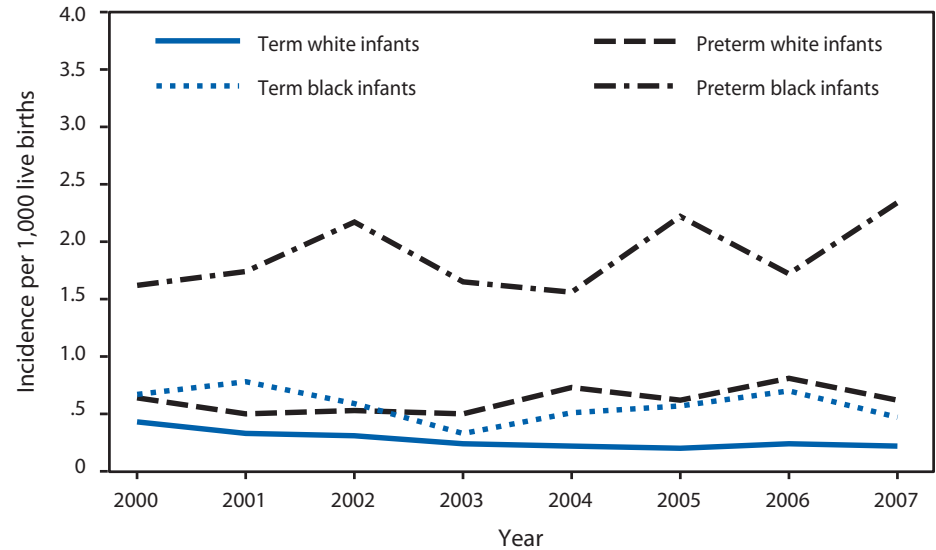
suggest that the observed decline in early-onset GBS disease is a result of prevented cases of illness and not simply of sterilization of neonatal blood cultures as a result of exposure to maternal antibiotics. During 1999–2001, incidence of early-onset GBS disease achieved a plateau of approximately 0.5 cases per 1,000 live births. After the 2002 guidelines were issued, incidence declined further and in recent years has ranged from 0.3 to 0.4 cases per 1,000 live births. This additional decline of 20%–40% is consistent with that predicted for the transition from the 1996 prevention strategy to the universal screening approach recommended in 2002 (62). Similar trends have been reported among infants delivered in all U.S. military hospitals (229). However, the disparity in early-onset GBS disease incidence between black and white infants has persisted (Figure 4) and is evident among both term and preterm infants (18,20). Preliminary surveillance data from 2008 suggest that the racial disparity was reduced somewhat in 2008 (30). Incidence among all black infants declined to 0.49 cases per 1,000 live births, showing progress towards the *Healthy People 2010* objective of 0.5 cases per 1,000 live births for all racial and ethnic groups (230). However final data from 2008, including enhanced race/ethnicity reporting on cases and the 2008 live birth denominators, and more years of data are needed to determine whether this trend is sustained.

Trends in Non-GBS Pathogens

Decreases in the incidence of early-onset GBS sepsis have not been accompanied by increases in incidence of early-onset sepsis caused by other pathogens, including those that are antimicrobial-resistant. Most studies, including population-based multicenter studies, have found stable (231–239) or decreasing (240,241) rates of non-GBS early-onset sepsis during a period of increasing use of intrapartum antibiotic prophylaxis for GBS. Increases in invasive *Escherichia coli* infections have been reported among preterm and low-birth-weight or very low-birth-weight infants (242–246), and some studies have found an increasing proportion of ampicillin-resistant isolates among preterm or very low birth-weight infants with *E. coli* sepsis (235,245,247). However, the trends have not been consistent over time or across studies. A multicenter study of sepsis in preterm infants that reported an increase in *E. coli* incidence from 1991–1993 to 1998–2000 (246) found stable rates of *E. coli* sepsis from 1998–2000 to 2002–2003 and reported no significant change in the proportion of *E. coli* isolates that were resistant to ampicillin (248). Whether any observed increase in ampicillin-resistant *E. coli* is attributable to the use of intrapartum antibiotics for GBS prophylaxis is unclear because ampicillin resistance among *E. coli* isolates has increased communitywide (249). Currently available evidence does not suggest any increase in non-GBS early-onset sepsis among term infants.

An association between intrapartum antibiotic exposure and ampicillin resistance in newborns with *E. coli* or other non-GBS early-onset sepsis has been observed in several studies among all newborns (55,239,242,250–252) and among preterm or very low birth-weight infants (245,246). However, studies using infants infected with nonresistant pathogens as a control group do not account for ampicillin-susceptible infections prevented by intrapartum antibiotic prophylaxis and therefore might overestimate an association between antibiotic exposure and antibiotic resistance (253). A multicenter case-control study of early-onset *E. coli* cases that enrolled uninfected infants born at the same hospitals found no association between intrapartum antibiotic prophylaxis exposure and infection with ampicillin-resistant *E. coli* (254).

FIGURE 4. Incidence of early-onset invasive group B streptococcal disease, stratified by race and term — Active Bacterial Core surveillance areas, 2000–2007



Source: Adapted from CDC. Trends in perinatal group B streptococcal disease—United States, 2000–2006. MMWR 2009;58:109–12.

The reported increases in *E. coli* early-onset sepsis among preterm infants and antibiotic-resistant early-onset infections are not of sufficient magnitude to outweigh the benefits of intrapartum antibiotic prophylaxis to prevent early-onset GBS disease. Among all neonates, rates of *E. coli* early-onset sepsis have remained stable and lower than those of GBS early-onset disease, despite declines in GBS (CDC, unpublished data, 2009). However, to ensure early detection of increases in the rate of disease or deaths caused by organisms other than GBS, continued surveillance of neonatal sepsis caused by organisms other than GBS is needed.

Impact of GBS Prevention Efforts on Infant Management

Provider surveys conducted in the early to mid 1990s indicated that pediatricians and neonatologists were more likely to conduct diagnostic evaluations and initiate empiric antibiotics for an infant whose mother received intrapartum antibiotic prophylaxis than they were for an infant whose mother who did not receive prophylaxis (197–199). Results of studies conducted during 1996–2002 were inconsistent, reporting increased (255), stable (256), or decreased (257) use of health services (including diagnostic tests, antibiotics, and/or length of hospital stay) for neonates born to women receiving intrapartum antibiotics. No studies have reported on the impact of the 2002 guidelines

on health-care services for neonates. Continued monitoring of the influence of GBS prevention recommendations on the management of newborns is needed.

Recommendations

The following updated recommendations for the prevention of early-onset GBS disease are based on critical appraisal of data that have become available since publication of previous CDC (13,15) and ACOG (258) recommendations and replace previous recommendations from CDC. These recommendations have been endorsed by ACOG, AAP, ACNM, AAFP, and ASM. After each recommendation, its strength (indicated by a letter) and the quality of supporting evidence (indicated by a Roman numeral) are shown in parentheses according to the evidence-based rating system used (Table 1).

Obstetric and neonatal health-care providers, in conjunction with supporting laboratories and labor and delivery facilities, should adopt the following recommendations for the prevention of early-onset GBS disease.

Identification of Candidates for Intrapartum Antibiotic Prophylaxis

Universal Screening for GBS

Candidates to receive intrapartum antibiotic prophylaxis to prevent early-onset GBS disease should be identified according to the indications and nonindications provided (Table 3).

The following are key components of the screening strategy:

- Women with GBS isolated from the urine at any time during the current pregnancy or who had a previous infant with invasive GBS disease should receive intrapartum antibiotic prophylaxis and do not need third trimester screening for GBS colonization (AII). Women with symptomatic or asymptomatic GBS urinary tract infection detected during pregnancy should be treated according to current standards of care for urinary tract infection during pregnancy and should receive intrapartum antibiotic prophylaxis to prevent early-onset GBS disease (AIII).
- All other pregnant women should be screened at 35–37 weeks' gestation for vaginal and rectal GBS colonization (AII).
- At the time of labor or rupture of membranes, intrapartum antibiotic prophylaxis should be given to all pregnant women who tested positive for GBS colonization (AII), except in the instance of cesarean delivery performed before onset of labor on a woman with intact amniotic membranes.
- For circumstances in which screening results are not available at the time of labor and delivery, intrapartum antibiotic prophylaxis should be given to women who are <37 weeks and 0 days' gestation, have a duration of membrane rupture ≥ 18 hours, or have a temperature of $\geq 100.4^\circ\text{F}$ ($\geq 38.0^\circ\text{C}$) (AII).
- In the absence of GBS urinary tract infection, antimicrobial agents should not be used before the intrapartum period to eradicate GBS genitorectal colonization, because such treat-

TABLE 3. Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease

Intrapartum GBS prophylaxis indicated	Intrapartum GBS prophylaxis not indicated
<ul style="list-style-type: none"> • Previous infant with invasive GBS disease • GBS bacteriuria during any trimester of the current pregnancy* • Positive GBS vaginal-rectal screening culture in late gestation[†] during current pregnancy* • Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: <ul style="list-style-type: none"> – Delivery at <37 weeks' gestation[‡] – Amniotic membrane rupture ≥ 18 hours – Intrapartum temperature $\geq 100.4^\circ\text{F}$ ($\geq 38.0^\circ\text{C}$)[§] – Intrapartum NAAT** positive for GBS 	<ul style="list-style-type: none"> • Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy) • GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy) • Negative vaginal and rectal GBS screening culture in late gestation[†] during the current pregnancy, regardless of intrapartum risk factors • Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age

Abbreviation: NAAT = Nucleic acid amplification tests

* Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes.

[†] Optimal timing for prenatal GBS screening is at 35–37 weeks' gestation.

[‡] Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 5 and 6.

[§] If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

** NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture at ≥ 18 hours, or temperature $\geq 100.4^\circ\text{F}$ [$\geq 38.0^\circ\text{C}$]) is present, then intrapartum antibiotic prophylaxis is indicated.

ment is not effective in eliminating carriage or preventing neonatal disease and can cause adverse consequences (DI).

- Intrapartum antibiotic prophylaxis to prevent early-onset GBS disease is not recommended as a routine practice for cesarean deliveries performed before labor onset on women with intact amniotic membranes, regardless of the GBS colonization status of the woman or the gestational age of the pregnancy (CIII). The use of perioperative prophylactic antibiotics to prevent infectious complications of cesarean delivery should not be altered or affected by GBS status. Women expected to undergo cesarean deliveries should undergo routine vaginal and rectal screening for GBS at 35–37 weeks' gestation because onset of labor or rupture of membranes can occur before the planned cesarean delivery, and under those circumstances GBS-colonized women should receive intrapartum antibiotic prophylaxis (AII).

- Health-care providers should inform women of their GBS screening test result and the recommended interventions (BIII).

The following key changes were made from the 2002 guidelines:

- Guidance regarding cesarean deliveries performed before onset of labor on a woman with intact amniotic membranes is clarified as applying to cesarean deliveries performed at any gestational age (CIII).
- In settings in which NAAT for GBS is available, obstetric providers can choose to perform intrapartum testing of vaginal-rectal samples from women with unknown GBS colonization status and no intrapartum risk factors (temperature of $\geq 100.4^\circ\text{F}$ [$\geq 38.0^\circ\text{C}$] or rupture of amniotic membranes ≥ 18 hours) at the time of testing and who are delivering at term (CII). If an intrapartum risk factor subsequently develops, antibiotic prophylaxis should be administered regardless of the intrapartum testing results (AIII).
- Women with positive intrapartum NAAT results for GBS should receive antibiotic prophylaxis (AII). NAAT testing is optional and might not be available in all settings.

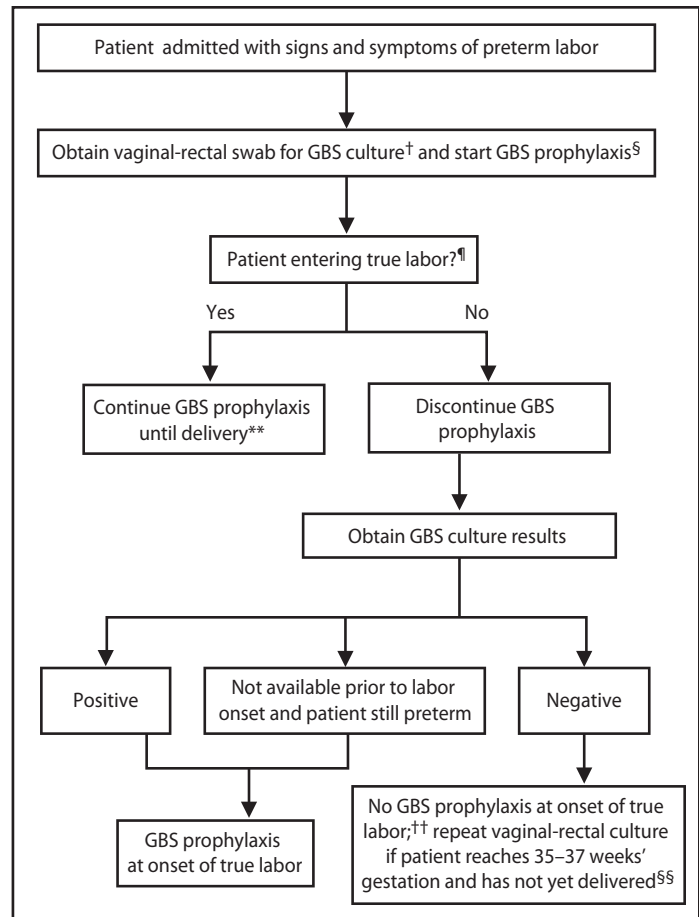
Threatened Preterm Delivery

Women admitted with signs and symptoms of preterm labor (before 37 weeks and 0 days' gestation) should be managed according to the algorithm provided (Figure 5). Women with rupture of membranes at <37 weeks and 0 days' gestation should be managed according to the algorithm provided (Figure 6).

The following are key components of threatened preterm delivery GBS management:

- Women admitted with signs and symptoms of labor or with rupture of membranes at <37 weeks and 0 days' gestation should be screened for GBS colonization at hospital admis-

FIGURE 5. Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm* labor (PTL)



* At <37 weeks and 0 days' gestation.

† If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

§ See Figure 8 for recommended antibiotic regimens.

¶ Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.

** If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis.

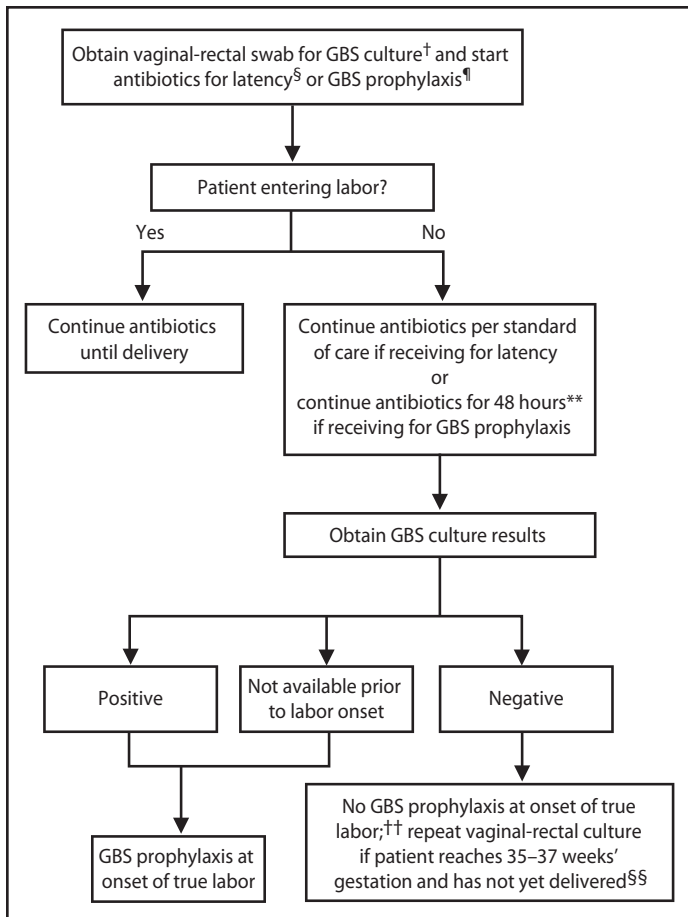
†† Unless subsequent GBS culture prior to delivery is positive.

§§ A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time.

sion unless a vaginal-rectal GBS screen was performed within the preceding 5 weeks (AII).

- Women admitted with signs and symptoms of preterm labor who have unknown GBS colonization status at admission or a positive GBS screen within the preceding 5 weeks should receive GBS prophylaxis at hospital admission (AII).
- Antibiotics given for GBS prophylaxis to a woman with preterm labor should be discontinued immediately if at any

FIGURE 6. Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm* premature rupture of membranes (pPROM)



* At <37 weeks and 0 days' gestation.

† If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

§ Antibiotics given for latency in the setting of pPROM that include ampicillin 2 g intravenously (IV) once, followed by 1 g IV every 6 hours for at least 48 hours are adequate for GBS prophylaxis. If other regimens are used, GBS prophylaxis should be initiated in addition.

¶ See Figure 8 for recommended antibiotic regimens.

** GBS prophylaxis should be discontinued at 48 hours for women with pPROM who are not in labor. If results from a GBS screen performed on admission become available during the 48-hour period and are negative, GBS prophylaxis should be discontinued at that time.

†† Unless subsequent GBS culture prior to delivery is positive.

§§ A negative GBS screen is considered valid for 5 weeks. If a patient with pPROM is entering labor and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time.

point it is determined that she is not in true labor or if the GBS culture at admission is negative (AII).

- Negative GBS colonization status should not affect the administration of antibiotics for other indications (AIII).
- Women with threatened preterm delivery who have a GBS screen performed that is positive and do not deliver at that time should receive GBS prophylaxis when true labor begins (AII).
- Women with threatened preterm delivery who have a GBS screen performed that is negative but do not deliver at that time should undergo repeat screening at 35–37 weeks' gestation. If such women are re-admitted at a later date with threatened preterm delivery, they should undergo repeat screening if the previous culture was performed >5 weeks prior (AIII).

The following key changes were made from the 2002 guidelines:

- Separate algorithms are presented for GBS prophylaxis in the setting of threatened preterm delivery, one for spontaneous preterm labor (Figure 5) and one for preterm premature rupture of membranes (Figure 6).
- GBS prophylaxis provided to women with signs and symptoms of preterm labor should be discontinued if it is determined that the patient is not in true labor (AI).
- Antibiotics given to prolong latency for preterm premature rupture of membranes with adequate GBS coverage (specifically 2 g ampicillin administered intravenously followed by 1 g administered intravenously every 6 hours for 48 hours) are sufficient for GBS prophylaxis if delivery occurs while the patient is receiving that antibiotic regime (CIII). Oral antibiotics alone are not adequate for GBS prophylaxis (DII).
- Women with preterm premature rupture of membranes who are not in labor and are receiving antibiotics to prolong latency with adequate GBS coverage should be managed according to standard of care for preterm premature rupture of membranes; GBS testing results should not affect the duration of antibiotics (BIII).
- Women with preterm premature rupture of membranes who are not in labor and are not receiving antibiotics to prolong latency (or are receiving antibiotics that do not have adequate GBS coverage) should receive GBS prophylaxis for 48 hours, unless a GBS screen performed within the preceding 5 weeks was negative (CIII). If the results from a GBS screen performed on admission become available during that 48-hour period and are negative, then GBS prophylaxis should be discontinued at that time.

GBS Specimen Collection and Processing

GBS specimen collection and processing should be conducted according to the recommendations provided (Boxes 1–3 and Figure 7).

The following are key components of specimen collection and processing:

- GBS colonization status should be determined by collecting both vaginal and rectal specimens at 35–37 weeks' gestation. A single combined vaginal-rectal specimen can be collected (AII).
- Specimens should undergo 18–24 hour incubation at 35°–37°C in an appropriate enrichment broth medium to enhance the recovery of GBS (AI).
- Accurate results are more important than rapid turnaround time for antenatal screening (AIII).
- To ensure proper testing of specimens, clinicians must inform laboratories when submitted urine specimens are from pregnant women (AIII).
- Antimicrobial susceptibility testing should be performed on antenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis because of a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of a penicillin or a cephalosporin. (AII) (Box 3).

The following key changes were made from the 2002 guidelines:

- Specimen transport options and timing until processing are clarified.
- GBS identification options are expanded to include a positive identification from chromogenic media and identification directly from enriched broth. NAAT, such as commercially available PCR assays, can also be used after enrichment, if laboratories have validated NAAT performance and instituted appropriate quality controls (CII).
- A direct plating option can be included in addition to enriched culture (CII). Direct plating has a lower sensitivity than enriched culture and should not be used as sole means to identify GBS.
- Testing for inducible clindamycin resistance should be performed on antenatal GBS isolates that are susceptible to clindamycin, resistant to erythromycin, and are from penicillin-allergic women at high risk for anaphylaxis (CIII).
- Laboratories should report GBS in urine culture specimens when present at concentrations of $\geq 10^4$ colony-forming units/ml in pure culture or mixed with a second microorganism (AII) (Box 4).

BOX 1. Procedures for collecting clinical specimens for culture of group B *Streptococcus* (GBS) at 35–37 weeks' gestation

- Swab the lower vagina (vaginal introitus), followed by the rectum (i.e., insert swab through the anal sphincter) using the same swab or two different swabs. Cultures should be collected in the outpatient setting by the health-care provider or, with appropriate instruction, by the patient herself. Cervical, perianal, perirectal or perineal specimens are not acceptable, and a speculum should not be used for culture collection.
- Place the swab(s) into a nonnutritive transport medium. Appropriate transport systems (e.g., Stuart's or Amies with or without charcoal) are commercially available. GBS isolates can remain viable in transport media for several days at room temperature; however the recovery of isolates declines over one to four days, especially at elevated temperatures, which can lead to false-negative results. When feasible, specimens should be refrigerated before processing.
- Specimen requisitions should indicate clearly that specimens are for group B streptococcal testing. Patients who state that they are allergic to penicillin should be evaluated for risk for anaphylaxis. If a woman is determined to be at high risk for anaphylaxis,* susceptibility testing for clindamycin and erythromycin should be ordered.

* Patients with a history of any of the following after receiving penicillin or a cephalosporin are considered to be at high risk for anaphylaxis: anaphylaxis, angioedema, respiratory distress, or urticaria.

Intrapartum Antibiotic Prophylaxis

Intrapartum antibiotic prophylaxis agents and dosing should be administered according to the recommendations provided (Figure 8).

The following are key components of intrapartum antibiotic prophylaxis agents and dosing:

- Penicillin remains the agent of choice for intrapartum antibiotic prophylaxis, with ampicillin as an acceptable alternative (AI).
- Penicillin-allergic women who do not have a history of anaphylaxis, angioedema, respiratory distress or urticaria following administration of a penicillin or a cephalosporin should receive cefazolin (BII).
- Antimicrobial susceptibility testing should be ordered for antenatal GBS cultures performed on penicillin-allergic women at high risk for anaphylaxis because of a history of anaphylaxis, angioedema, respiratory distress or urticaria

BOX 2. Procedures for processing clinical specimens for culture of group B *Streptococcus* (GBS) (see Figure 7)

- Remove swab(s) from transport medium.* Inoculate swab(s) into a recommended selective broth medium, such as Todd-Hewitt broth supplemented with either gentamicin (8 µg/ml) and nalidixic acid (15 µg/ml) [TransVag broth], or with colistin (10 µg/ml) and nalidixic acid (15 µg/ml) [Lim broth]. TransVag broth may be supplemented with 5% defibrinated sheep blood to increase the recovery of GBS.† As an alternative, swabs may be inoculated into selective enrichment broth that incorporates chromogenic pigments for the detection of beta-hemolytic GBS using color detection. Examples of appropriate commercially available options include StrepB carrot broth or Granada Biphasic broth.§
- Incubate inoculated selective broth for 18–24 hours 35°–37°C in ambient air or 5% CO₂.
- For TransVag or Lim broth, subculture the incubated broth to an appropriate agar plate (e.g., tryptic soy agar with 5% defibrinated sheep blood, Columbia agar with colistin and nalidixic acid, or a commercial chromogenic agar). For chromogenic broth, monitor for color change indicative of GBS per product instructions. GBS detection using chromogenic broth is possible only for beta-hemolytic strains,¶ and therefore all broths that are negative (i.e., no color detection) should be subcultured to a sheep blood agar plate with 5% sheep blood or tested for GBS antigen or by DNA probe to further identify nonhemolytic GBS strains.
- Inspect agar plates and identify organisms suggestive of GBS (e.g., narrow zone of beta hemolysis on blood agar, gram-positive cocci, catalase-negative, and/or hippurate-positive). Note that hemolysis can be difficult to observe, so typical colonies without hemolysis should also be further tested. If GBS is not identified after incubation for 18–24 hours, then reincubate plates overnight and examine for suspected GBS colonies.
- Various streptococcal grouping latex agglutination tests or other tests for GBS detection (e.g., GBS Accuprobe) may be used for specific identification, or the CAMP test can be employed for presumptive identification.
- Optional direct broth testing:** Detection of GBS can be determined directly from broth media using latex agglutination, probes or nucleic acid amplification tests (NAAT) such as PCR.

* Before the inoculation step, laboratories may choose to roll the vaginal-rectal swab(s) on a blood agar plate with or without colistin and nalidixic acid or commercially available chromogenic agar (appropriate recommendations include chromID Strepto B [which might detect both hemolytic and nonhemolytic GBS] or Granada Agar [which detects hemolytic GBS]. **Source:** Tazi A, Réglier-Poupet H, Dautezac F, Raymond J, Poyart C. Comparative evaluation of Strepto B ID chromogenic medium and Granada media for the detection of group B *Streptococcus* from vaginal samples of pregnant women. *J Microbiol Methods* 2008;73:263–5). This approach should be taken only in addition to, and not instead of, inoculation into selective broth. The directly inoculated blood agar plate should be streaked for isolation, incubated at 35°–37°C in ambient air or 5% CO₂ for 18–24 hours and inspected for organisms suggestive of GBS as described above. If suspected colonies are confirmed as GBS, the selective broth can be discarded, thus shortening the time to obtaining culture results. The directly inoculated chromogenic agar should be streaked for isolation and incubated at 35°–37°C for 18–24 hours. Hemolytic GBS isolates are identified by colored colonies as directed by specific manufacturers' instructions, and selective broth can be discarded if GBS positive.

† **Source:** Fenton LJ, Harper MH. Evaluation of colistin and nalidixic acid in Todd-Hewitt broth for selective isolation of group B streptococci. *J Clin Microbiol* 1979;9:167–9. Although Trans-Vag medium often is available without sheep blood, direct comparison of medium with and without sheep blood has shown higher yield when blood is added. Lim broth also might benefit from the addition of sheep blood, although the improvement in yield is smaller, and sufficient data are not yet available to support a recommendation.

§ **Sources:** Church DL, Baxter H, Lloyd T, Miller B, Elsayed S. Evaluation of StrepB carrot broth versus Lim broth for detection of group B *Streptococcus* colonization status of near-term pregnant women. *J Clin Microbiol* 2008;46:2780–2. Martinho F, Prieto E, Pinto D, Castro RM, Morais AM, Salgado L, Exposto Fda L. Evaluation of liquid biphasic Granada medium and instant liquid biphasic Granada medium for group B *Streptococcus* detection. *Enferm Infecc Microbiol Clin* 2008;26:69–71.

¶ **Source:** de la Rosa M, Perez M, Carazo C, Pareja L, Peis JJ, Hernandez F. New Granada medium for detection and identification of group B streptococci. *J Clin Microbiol* 1992;30:1019–21.

** Direct latex agglutination, probe detection or nucleic acid amplification testing on enriched selective broth is an additional option. **Sources:** Guerrero C, Martinez J, Menasalvas A, Blazquez R, Rodriguez, Segovia M. Use of direct latex agglutination testing of selective broth in the detection of group B streptococcal carriage in pregnant women. *Eur J Clin Microbiol Infect Dis* 2004;23:61–2. Goodrich JS, Miller MB. Comparison of culture and 2 real-time polymerase chain reaction assays to detect group B *Streptococcus* during antepartum screening. *Diagn Microbiol Infect Dis* 2007;59:17–22. Block T, Munson E, Culver A, Vaughan K, Hryciuk JE. Comparison of carrot broth- and selective Todd-Hewitt broth-enhanced PCR protocols for real-time detection of *Streptococcus agalactiae* in prenatal vaginal/anorectal specimens. *J Clin Microbiol* 2008;46:3615–20. Montague NS, Cleary TJ, Martinez OV, Procop GW. Detection of group B streptococci in Lim broth by use of group B *Streptococcus* peptide nucleic acid fluorescent in situ hybridization and selective and nonselective agars. *J Clin Microbiol* 2008 46:3470–2. If a rapid test performed on enriched broth yields positive results and antimicrobial susceptibility testing is recommended (for penicillin-allergic women at high risk for anaphylaxis), the enriched broth should be subcultured to obtain an isolate.

BOX 3. Procedures for clindamycin and erythromycin susceptibility testing of group B streptococcal (GBS) isolates, when ordered for penicillin-allergic patients

- The Clinical and Laboratory Standards Institute (CLSI) recommends disk diffusion or broth microdilution testing for susceptibility testing of GBS.* Commercial systems that have been cleared or approved for testing of streptococci other than *S. pneumoniae* also may be used.
- To ensure accurate results, laboratories should include a test for detection of inducible clindamycin resistance. The double-disk diffusion method (D-zone test) is recommended for testing erythromycin-resistant and clindamycin-susceptible GBS.† Other validated tests to detect inducible clindamycin resistance in GBS may be used in place of the D-zone test.
- Use a cotton swab to make a suspension from 18–24 hour growth of the organism in saline or Mueller-Hinton broth equal to a 0.5 McFarland turbidity standard.
- Within 15 minutes of adjusting the turbidity at room temperature, dip a sterile cotton swab into the adjusted suspension. The swab should be rotated several times and pressed firmly on the inside wall of the tube above the fluid level. Use the swab to inoculate the entire surface of a plate of Mueller-Hinton agar with 5% sheep blood.

After the plate is dry, use sterile forceps to place a clindamycin (2 µg) disk and an erythromycin (15 µg) disk 12 mm apart for D-zone testing (Note: This differs from recommended 15–26 mm for staphylococci and a disk dispenser cannot be used to place disks on the plate for streptococci testing).

- Incubate inoculated agar plate at 35°C in 5% CO₂ for 20–24 hours.
- Isolates with blunting of the inhibition zone around the clindamycin disk adjacent to the erythromycin disk (D-zone positive) should be considered to have inducible clindamycin resistance and are presumed to be resistant. (Note: Other validated tests to detect GBS with inducible clindamycin resistance may be used.)
- The following comment could be included in patient reports for isolates that show inducible clindamycin resistance: “This isolate is presumed to be resistant on the basis of detection of inducible clindamycin resistance. Clindamycin still might be effective clinically in some cases.”

* Source: Clinical and Laboratory Standards Institute. Performance standard for antimicrobial susceptibility testing, M100-S20, Table 2H-1, Wayne, Pa: Clinical and Laboratory Standards Institute; 2010. CLSI recommends disk diffusion (M-2) or broth microdilution testing (M-7) for susceptibility testing of GBS. Commercial systems that have been cleared or approved for testing of streptococci other than *S. pneumoniae* may also be used. Interpret according to CLSI guidelines for *Streptococcus spp.* Beta-hemolytic Group (2010 breakpoints for disk-diffusion: for clindamycin: ≥19 mm = susceptible, 16–18 mm = intermediate, and ≤15 mm = resistant; for erythromycin: ≥21 mm = susceptible, 16–20 mm = intermediate, and ≤15 = resistant; for broth microdilution: clindamycin: ≤0.25 µg/ml = susceptible, 0.5 µg/ml = intermediate, and ≥1.0 µg/ml = resistant; and for erythromycin: ≤0.25 µg/ml = susceptible, 0.5 µg/ml = intermediate, and ≥1.0 µg/ml = resistant).

† Sources: Tang P, Ng P, Lum M, et al. Use of the Vitek-1 and Vitek-2 systems for detection of constitutive and inducible macrolide resistance in Group B streptococci. *J Clin Microbiol* 2004;42:2282–4. Richter SS, Howard WJ, Weinstein MP, et al. Multicenter evaluation of the BD Phoenix automated microbiology system for antimicrobial susceptibility testing of *Streptococcus* species. *J Clin Microbiol* 2008;45:2863–71.

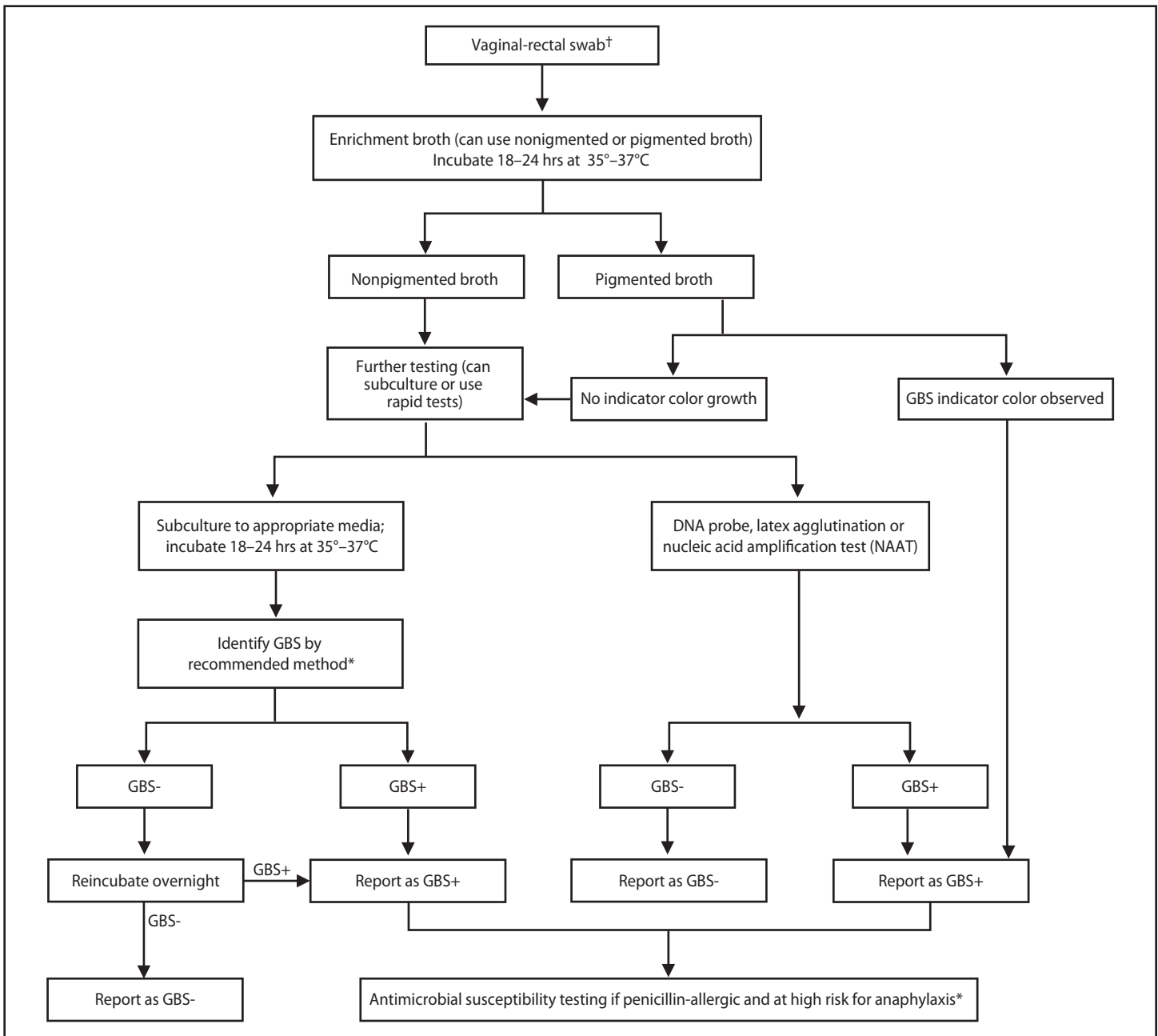
following administration of a penicillin or a cephalosporin (AII). To ensure proper testing, clinicians must inform laboratories of the need for antimicrobial susceptibility testing in such cases (AIII).

- Penicillin-allergic women at high risk for anaphylaxis should receive clindamycin if their GBS isolate is susceptible to clindamycin and erythromycin, as determined by antimicrobial susceptibility testing; if the isolate is sensitive to clindamycin but resistant to erythromycin, clindamycin may be used if testing for inducible clindamycin resistance is negative (CIII). Penicillin-allergic women at high risk for anaphylaxis should receive vancomycin if their isolate is intrinsically resistant to clindamycin as determined by antimicrobial susceptibility testing, if the isolate demonstrates inducible resistance to clindamycin, or if susceptibility to both agents is unknown (CIII) (Box 3).

The following key changes were made from the 2002 guidelines:

- The definition of high risk for anaphylaxis is clarified as a history of anaphylaxis, angioedema, respiratory distress or urticaria following administration of a penicillin or a cephalosporin.
- The recommended dosing regimen of penicillin G is 5 million units intravenously, followed by 2.5–3.0 million units intravenously every 4 hours (AII). The range of 2.5–3.0 million units is recommended to achieve adequate drug levels in the fetal circulation and amniotic fluid while avoiding neurotoxicity. The choice of dose within that range should be guided by which formulations of penicillin G are readily available in order to reduce the need for pharmacies to specially prepare doses.

FIGURE 7. Algorithm for recommended laboratory testing for prenatal screening for group B streptococcal (GBS) colonization*



* See Boxes 1–3 for details on specimen processing and antimicrobial susceptibility testing.

† Direct plating with appropriate media may be done in addition to enriched culture. Direct plating should not be used as the sole means to identify GBS.

- Erythromycin is no longer an acceptable alternative for intrapartum GBS prophylaxis for penicillin-allergic women at high risk for anaphylaxis.

Other Obstetric Management Issues

- Available data are not sufficient to suggest that GBS colonization should differentially affect the use of obstetric procedures for monitoring, cervical ripening or labor induction. These procedures should be reserved for appropriate indications and not altered for GBS-colonized women (CIII).
- Data are not sufficient to make recommendations regarding the timing of procedures intended to facilitate progression of labor, such as amniotomy, in GBS-colonized women. Intrapartum antibiotic prophylaxis is optimal if administered

for at least 4 hours before delivery; therefore, such procedures should be timed accordingly, if possible (CIII).

- No medically necessary obstetric procedure should be delayed in order to achieve 4 hours of GBS prophylaxis before delivery (AIII).

Secondary Prevention Among Infants

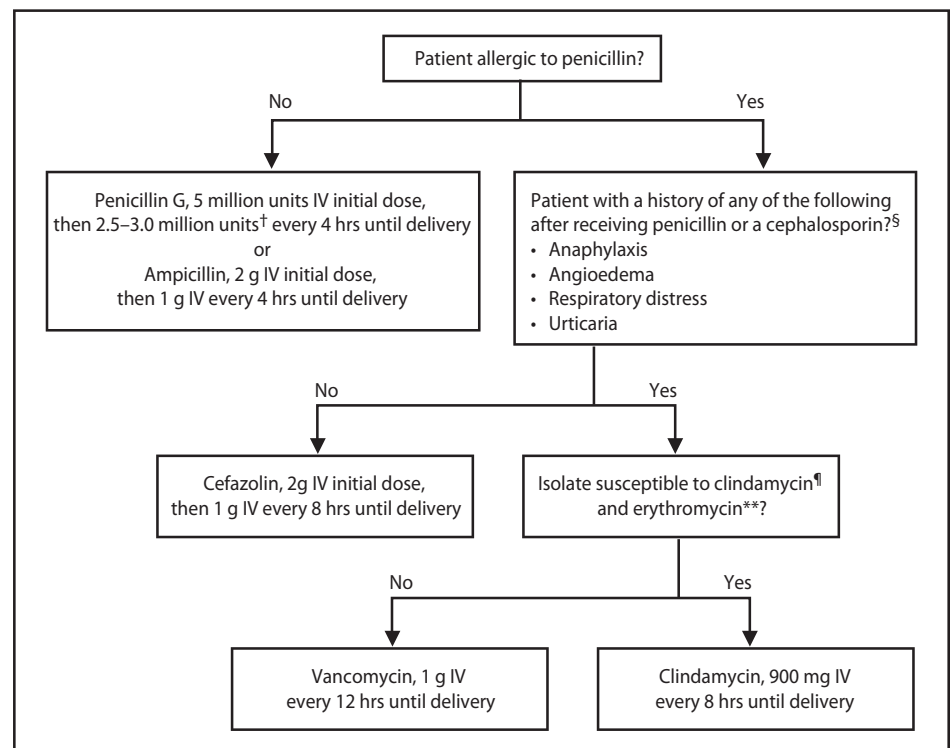
To detect potential sepsis cases in newborns as early as possible, newborns should be managed according to the algorithm provided (Figure 9). The following are key components of the neonatal management algorithm:

- Any newborn with signs of sepsis should receive a full diagnostic evaluation and receive antibiotic therapy pending the results of the evaluation. The evaluation should include a blood culture; a CBC including white blood cell differential and platelet count; a chest radiograph if any abnormal respiratory signs are present; and a lumbar puncture if the newborn is stable enough to tolerate the procedure and sepsis is suspected. Therapy for the infant should include antimicrobial agents active against GBS (including intravenous ampicillin) as well as other organisms that might cause neonatal sepsis, such as *E. coli* (AII).
- Well-appearing newborns whose mothers had suspected chorioamnionitis should undergo a limited evaluation and receive antibiotic therapy pending culture results (AII). The evaluation should include a blood culture and a CBC including white blood cell differential and platelet count; no chest radiograph or lumbar puncture is needed. Consultation with obstetric providers to assess whether chorioamnionitis was suspected is important to determine neonatal management (CIII).
- Well-appearing infants whose mothers had no chorioamnionitis and no indication for GBS prophylaxis should be managed according to routine clinical care (CIII).

BOX 4. Identification of group B *Streptococcus* (GBS) bacteriuria in pregnant women

- Routine screening for asymptomatic bacteriuria is recommended in pregnant women, and laboratories should screen urine culture specimens for the presence of GBS in concentrations of 10^4 colony-forming units (cfu)/ml or greater.
- Laboratories should identify GBS when present at $\geq 10^4$ cfu/ml in pure culture or mixed with a second microorganism.

FIGURE 8. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease*



Abbreviation: IV = intravenously.

* Broader spectrum agents, including an agent active against GBS, might be necessary for treatment of chorioamnionitis.

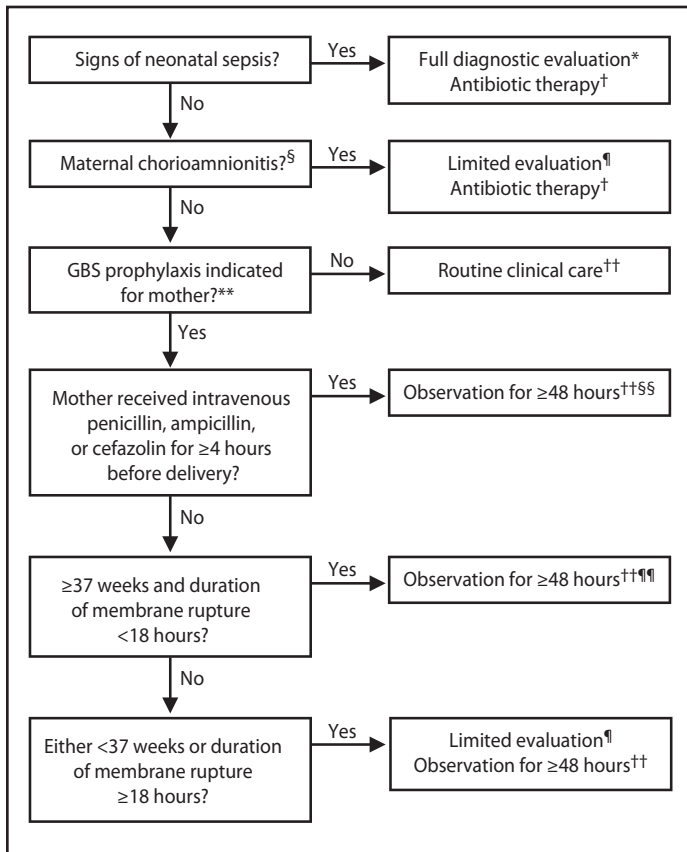
† Doses ranging from 2.5 to 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. The choice of dose within that range should be guided by which formulations of penicillin G are readily available to reduce the need for pharmacies to specially prepare doses.

§ Penicillin-allergic patients with a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillin or a cephalosporin are considered to be at high risk for anaphylaxis and should not receive penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. For penicillin-allergic patients who do not have a history of those reactions, cefazolin is the preferred agent because pharmacologic data suggest it achieves effective intraamniotic concentrations. Vancomycin and clindamycin should be reserved for penicillin-allergic women at high risk for anaphylaxis.

¶ If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing (Box 3) should be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If no susceptibility testing is performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis.

** Resistance to erythromycin is often but not always associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin, resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be used for GBS intrapartum prophylaxis instead of vancomycin.

FIGURE 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

** See table 3 for indications for intrapartum GBS prophylaxis.

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

- Well-appearing infants of any gestational age whose mother received adequate intrapartum GBS prophylaxis (≥4 hours of penicillin, ampicillin, or cefazolin before delivery) should be observed for ≥48 hours, and no routine diagnostic testing is recommended (BIII). Such infants can be discharged home as early as 24 hours after delivery, assuming that other discharge criteria have been met, ready access to medical care exists, and that a person able to comply fully with instructions for home observation will be present (CIII).
- For well-appearing infants born to mothers who had an indication for GBS prophylaxis but received no or inadequate prophylaxis, if the infant is well-appearing and ≥37 weeks and 0 days' gestational age and the duration of membrane rupture before delivery was <18 hours, then the infant should be observed for ≥48 hours, and no routine diagnostic testing is recommended (BIII). If the infant is well-appearing and either <37 weeks and 0 days' gestational age or the duration of membrane rupture before delivery was ≥18 hours, then the infant should undergo a limited evaluation and observation for ≥48 hours (BIII).

The following key changes were made from the 2002 guidelines:

- The algorithm now applies to all newborns.
- The definition of adequate intrapartum antibiotic prophylaxis is clarified as ≥4 hours of IV penicillin, ampicillin, or cefazolin before delivery (AII). All other agents or durations are considered inadequate for purposes of neonatal management.
- Well-appearing infants whose mother had an indication for GBS prophylaxis but received no or inadequate intrapartum antibiotics can be managed with observation for ≥48 hours, unless the infant is <37 weeks and 0 days' gestational age or membranes were ruptured ≥18 hours before delivery, in which case a limited evaluation and observation for ≥48 hours is recommended (BIII).
- Well-appearing infants with a gestational age of 35–36 weeks whose mothers received adequate intrapartum antibiotic prophylaxis do not routinely require diagnostic evaluations (CIII).

Monitoring Implementation and Impact of Guidelines

- Local and state public health agencies, in conjunction with appropriate groups of hospitals, are encouraged to establish surveillance for early-onset GBS disease and to take other steps to promote perinatal GBS disease prevention and education to reduce the incidence of early-onset GBS disease in their states (CIII).

- Efforts to monitor the emergence of perinatal infections caused by other organisms are also encouraged (CIII).

Future of GBS Prevention

Although much progress has been made in the prevention of early-onset GBS disease, important challenges remain. Early-onset disease has declined among all racial and ethnic groups, yet significant disparities persist. Research aimed at better understanding racial or ethnic differences in GBS disease might lead to opportunities for more effective prevention efforts. In addition, the evidence is incomplete for several key areas related to GBS prevention, including: strategies to prevent early-onset GBS disease among preterm infants, the role of bacteriuria as a risk factor in the era of universal screening, effectiveness of recommended intrapartum antibiotic prophylaxis agents for penicillin-allergic women at high risk for anaphylaxis, the impact and effectiveness of recommendations for secondary prevention of early-onset GBS disease among neonates, and factors contributing to the higher-than-anticipated proportion of early-onset GBS disease cases occurring among infants born to women with negative prenatal GBS screens.

The development of relatively rapid laboratory tests to identify GBS moves us closer to the possibility of an intrapartum test for GBS colonization screening. A highly sensitive, low-complexity test with a rapid turnaround time could be used to determine intrapartum GBS colonization, thereby overcoming some of the inherent limitations in late antenatal screening. Although available NAATs have demonstrated high sensitivity when performed on enriched samples, enrichment is not feasible in the intrapartum setting when results are needed quickly. Manufacturers and some researchers (180,185) have reported turn-around-times of <2 hours; however, the complexity of available NAAT for GBS is still moderate to high. To be clinically useful in the intrapartum period, a screening test for GBS should consist of a simple bedside kit that enables labor and delivery staff to perform a test, have a turn-around time of <30 minutes, and have a sensitivity and specificity of $\geq 90\%$. Ideally, a rapid test for intrapartum use also would be able to detect mutations likely to confer resistance to clindamycin and/or erythromycin in order to guide antibiotic choice for penicillin-allergic women.

Universal screening and intrapartum antibiotic prophylaxis have had no measurable impact on late-onset GBS disease, prenatal-onset disease (including stillbirths and miscarriages), or GBS disease among nonpregnant adults. Because of declines in early-onset GBS disease, the burden of late-onset disease is now similar to that of early-onset disease. More research on preventive measures against late-onset disease is needed. The

burden of prenatal-onset GBS disease has not been assessed adequately (32,33,259–262), and no effective prevention tools have been identified before the intrapartum period. GBS disease among nonpregnant adults has increased in recent years. Although GBS vaccines might be expected to aid in reduction of racial disparities and prevention of invasive GBS disease among adults and infants (both early- and late-onset), continued exploration of other means to improve and strengthen GBS prevention efforts is warranted.

Until a safe and efficacious vaccine achieves licensure, continued monitoring for potential unintended consequences of intrapartum antibiotic chemoprophylaxis is needed, with an emphasis on tracking key sentinel events signaling a need for revision of the guidelines. Such sentinel events include the emergence of penicillin resistance among GBS isolates and an increase in the incidence of disease or deaths due to neonatal pathogens other than GBS that offsets the burden of early-onset disease prevented by intrapartum antibiotic prophylaxis. Monitoring for the latter will require long-term surveillance of a large population of term and preterm births (246,248).

States are encouraged to monitor incidence of GBS disease, to promote activities that enhance perinatal GBS disease prevention and education, and to assess progress toward national objectives for disease reduction, such as objectives for *Healthy People 2010* (230) and the forthcoming *Healthy People 2020* (263). Practical tools to assist with monitoring for missed opportunities for perinatal GBS prevention within hospitals have been published (264); additional prevention information and tools for providers, patients and clinical microbiologists are available at <http://www.cdc.gov/groupbstrep>, <http://www.acog.org>, <http://www.aap.org>, <http://www.aafp.org>, <http://www.midwife.org>, and <http://www.asm.org>.

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Group B *Streptococcus* Technical Working Group*

Members: Kathryn Arnold, MD, Georgia Division of Public Health, Barbara Stoll, MD, Yun Wang, MD, PhD, Emory University School of Medicine, Atlanta Georgia; Carol Baker, MD Baylor College of Medicine, Houston, Texas; Carrie Byington, MD, American Academy of Pediatrics/Committee on Infectious Diseases, Richard Polin MD, American Academy of Pediatrics/Committee on Fetus and Newborn, Elk Grove Village, Illinois; Ronald Gibbs, MD, University of Colorado School of Medicine, Denver, Colorado; Jeanne Jordan, PhD, George Washington University School of Public Health and Health Services, Sarah Kilpatrick, MD, PhD, American College of Obstetricians and Gynecologists, District of Columbia; Geraldine Hall, PhD, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio; Tekoa King, MPH, American College of Nurse Midwives, Silver Spring, Maryland; Ruth Lynfield, MD, Minnesota Department of Health, Minneapolis, Minnesota; Marti Perhach, Group B Strep International, Pomona, California; Laura Riley, MD, Massachusetts General Hospital, Boston, Massachusetts; Pablo Sanchez, MD; Society for Healthcare Epidemiology of America, Arlington, Virginia; Pamela Simms, PhD, PharmD, Samford University McWhorter School of Pharmacy, Birmingham, Alabama; Julie Wood, MD, American Academy of Family Physicians, Leawood, Kansas; Rex Astles, PhD, Bernard Beall, PhD, Roberta Carey, PhD, Janine Corey, MPH, Lee Hampton, MD, Denise Jamieson, MD, Melissa Lewis, MPH, Michael Miller, PhD, Christine Olson, MD, Alison Patti, MPH, Emily Weston, MPH, Cynthia Whitney, MD, Elizabeth Zell, MStat, CDC, Atlanta, Georgia.

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