Journal of Perinatology (2010) 30, 77–87

www.nature.com/jp

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Prevention of Group B Streptococcus early-onset disease: a toolkit by the California Perinatal Quality Care Collaborative

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The California Perinatal Quality Care Collaborative (CPQCC) was organized in 1996 in an effort to improve perinatal outcomes in California. CPQCC has a robust infrastructure of quality improvement resources and expertise and uses a database of demographic and outcome data from neonatal intensive care units in California. In 2004, CPQCC developed a toolkit to provide an evidence-based framework and supporting documents for hospitals to use in systematically addressing persistent early-onset disease (EOD) because of Group B Streptococcus (GBS) in their centers. The CPQCC toolkit was based on the 2002 Centers for Disease Control guideline, 'Prevention of Perinatal Group B Streptococcal Disease.' This article presents an updated version of the CPQCC toolkit reflecting several population studies published since the 2002 guideline. Current epidemiological trends in incidence of EOD with GBS, changes in antibiotic sensitivity and the potential value of newer strategies are discussed.
Journal of Perinatology (2010) **30,** 77–87; doi:10.1038/jp.2009.95; published online 6 August 2009

Keywords: group B; streptococcus; quality improvement; prevention; prophylaxis; early onset

Introduction

The California Perinatal Quality Care Collaborative (CPQCC) was organized in 1996 in an effort to improve perinatal outcomes in California. The strategy was based on the principle that data should inform improvement actions, adapted from the successful Vermont Oxford Network's improvement projects.[1–5] Using the pooled data from California's Neonatal Intensive Care Units, centers participating in the CPQCC had the opportunity to work together to identify problems, strategies for successfully overcoming them and means for implementing them locally. The process of collaboration among institutions was central to this regional effort.

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Received 28 January 2009; revised 29 April 2009; accepted 7 June 2009; published online 6 August 2009

The CPQCC approach relies heavily upon evidence-based toolkits that are developed by state or nationally recognized content experts on specific topics.[6] Each toolkit contains all of the components for a perinatal–neonatal unit to initiate quality improvement without painstaking and lengthy preparation. In the past, the toolkits were complemented by Quality Improvement Workshops, held throughout the state. Toolkits are divided into several sections, including evidence-based practice reviews with relevant citations and actual reprints when available for distribution, benchmarking data with instructions on how a unit can review and compare its own data with the benchmark, problem-identification worksheets for guiding chart reviews, a general structure for quality improvement followed by specific examples on how to organize teams, and appendices filled with such products as example policy and procedures, teaching aids and evaluation tools.[7]

In conjunction with the toolkits, Quality Improvement Workshops are used to pull together multidisciplinary teams from the various neonatal intensive care units with the goal of improving their performance. Participants are sent pre-meeting exercises that introduce them to using the problem-identification worksheet elements of the toolkit relevant to the meeting's topics. This ensures awareness of actual unit practice and facilitates the identification of local opportunities unique to the individual units. Strategies to address specific opportunities are also facilitated at the Quality Improvement Workshops.

This three step process, namely, (1) data collection and analysis; (2) toolkit development and (3) provision of workshops, has been applied successfully by CPQCC to numerous topics over the past several years. Topics have included improvements in antenatal steroid use,[8] nosocomial infection reduction, prevention of kernicterus, strategies to reduce chronic lung disease, including reduction of postnatal steroid use, management of the parenteral and enteral nutrition needs of the very low birth weight infant and prevention of Group B Streptococcus early-onset disease (GBS EOD). The remainder of this discussion will address the updated toolkit for the last of these, The Prevention of Group B Streptococcus Early Onset Disease.

Unlike most other topics addressed by the tookits, GBS EOD was not able to be benchmarked using center specific or statewide

data from the CPQCC database. With an incidence between 0.5 and 1 per 1000 births, the incidence at any given center was too low to give statistical validity to a single-center data. Moreover, as only select patients greater than 1500 g were reported to the database, accurate population-based incidence was not available until 2002 when all GBS episodes became reportable. However, the Collaborative decided to include GBS EOD as one of the priorities because it remained, at the level of the statewide population, an important cause of neonatal morbidity and mortality that could be reduced by proper implementation of screening and management strategies.

Guideline statement

The following recommendations for the prevention of GBS EOD are based on critical appraisal of multistate population-based observational data and several studies from individual institutions that prompted the latest revision of the Centers for Disease Control (CDC) guideline published in 2002.[9] For this update we surveyed the literature as of October 2008 and have included several studies evaluating the impact of the 2002 guideline. When released, the 2002 guideline shifted the focus from an optional risk-based or screening-based prophylaxis strategy to an exclusive strategy of universal screening (see section Sidebar 1).

Sidebar 1

CPQCC COMMENT. Priority should be given to those recommendations categorized as IA (strongly recommended for implementation and strongly supported by well-defined experimental, clinical or epidemiological studies). The rating system for this guideline is adapted from the 1999 USPHS/IDSA guideline for the prevention of opportunistic infections in persons infected with human immunodeficiency virus.[45] Explanation of categorical ratings is provided in the CDC Guideline, see Table 1.[9]

Both the American College of Obstetrics and Gynecology (http://www.acog.org/from_home/publications/press_releases/nr11-29-02-1.cfm) and American Academy of Pediatrics (http://www.aap.org/policy/groupb.html) have endorsed the 2002 CDC recommendation.

Before widespread use of intrapartum antibiotics for the prevention of GBS, invasive neonatal disease incidence ranged from 1 to 2 cases per 1000 live births, or as high as 3.6 cases when clinical sepsis and GBS colonization were included.[10,11] This incidence decreased by approximately 70% in the mid 1990s with the implementation of intrapartum antibiotic regimens based on either risk factors or culture results.[12–15] However, even with a substantial drop in the incidence of early-onset GBS disease, the residual rate of approximately 0.5 cases per 1000 live births was felt to be preventable. The adoption of the universal screening approach was based on the documentation of mothers with positive risk factors who did not receive intrapartum prophylaxis because of the absence of risk factors or failed implementation of the risk factor-based strategy.[16–18] (see section Sidebar 2).

Sidebar 2

CPQCC COMMENT. The use of clinical risk factors alone will inevitably result in missed opportunities for intrapartum antibiotic prophylaxis. Rosenstein and Schuchat[18] showed that 54% of mothers of infants diagnosed with GBS EOD did not have risk factors. Schrag *et al*. in 2002 compared the effectiveness of both the risk factor- and screening-based protocols in a large cohort study of over 600 000 births. They showed the relative risk of GBS EOD with the screening protocol to be 0.46 (95% confidence interval 0.36 to 0.60) compared with the risk factor-based protocol.[17] Additional studies have shown that a lack of compliance with risk factor-based protocol indicated that antibiotic prophylaxis, especially for rupture of membranes prolonged beyond 18 h and prematurely, is the major factor in risk factor-based strategy failure. In these cases, the superiority of the screening-based protocol was based on the elimination of human factors that lead to missed opportunities in a busy clinical setting with risk factor protocols.[46–48]

Since the publication of the revised guideline and implementation of the universal screening for GBS in the United States, the incidence of EOD has declined further. In an analysis of CDC surveillance data comparing early-onset sepsis (EOS) in 2000 to 2001, the period immediately before the universal screening, with the post-implementation period of 2003 to 2005, the incidence was shown to decrease further by 33%.[19] Other investigators, in a single-center observational studies, have also documented significant decreases in early-onset GBS disease after the implementation of universal screening at their institutions.[20,21] Of note, in the CDC surveillance data there appears to be a persistent and increasing trend of racial disparity in the incidence of EOS with the incidence in black infants increasing in the two reporting periods from 0.52 to 0.89 cases per 1000 live births. The incidence in white infants decreased from 0.26 to 0.22 cases per 1000 live births in the same period (see section Sidebar 3).

Sidebar 3

The Healthy People 2010 objectives include achieving rates of GBS EOD below 0.5 cases per 1000 live births for all racial populations. CDC data show that the rates of EOD among white infants reached this target in 1998 and have remained below this level since the universal recommendations were issued.[19] In 2003, the year after the recommendations were issued, incidence among black infants reached a record low (0.52 per 1000 live births) and suggested that the national health objectives might also be met for black infants. However, during the following 2 years, the incidence of EOD among black infants returned to levels observed before recommendations were issued, 0.89 cases per 1000 live births. Factors that might contribute to this disparity include higher maternal colonization rates in blacks, higher rates of preterm deliveries (a risk factor for neonatal GBS disease) among blacks and less access to prenatal care among black women compared with white women. However, a study that controlled for these factors indicated that the black race remained an independent risk factor for disease.[49]

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 CDC, 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) *MMWR Recomm Rep* 1999; **48** (RR-10): 1–66.

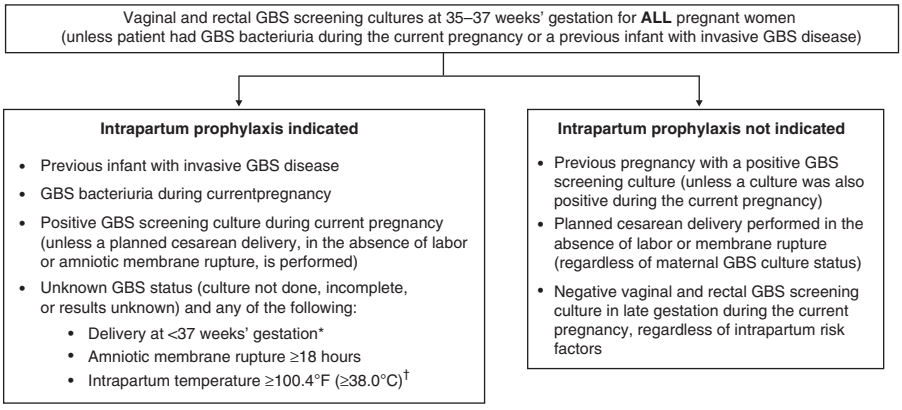

Figure 1 Indications for intrapartum antibiotic prophylaxis to prevent perinatal Group B Streptococcus (GBS) disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35 to 37 weeks' gestation from all pregnant women. *If onset of labor or rupture of amniotic membranes occurs at <37 weeks' gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided (Figure 2). †If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis. *Source*: Adapted from Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. *MMWR Recomm Rep* 2002; **51** (No. RR-11): 1–22.

The strength (indicated by a letter) and quality (indicated by a roman numeral) of evidence supporting each recommendation are shown in parentheses, according to the evidence-based rating system outlined in Table 1.[9] Obstetric-care practitioners, along with supporting laboratories and labor and delivery facilities, should adopt the following strategy for the prevention of perinatal GBS disease-based on prenatal screening for GBS colonization. The risk-based approach is no longer an acceptable alternative except for circumstances in which screening results are not available before delivery (AII).

Screening indications and schedule

- All pregnant women should be screened at 35 to 37 weeks' gestation for vaginal and rectal GBS colonization (Figure 1) (AII).[9] At the time of labor or rupture of membranes, intrapartum chemoprophylaxis should be given to all pregnant women identified as GBS carriers (AII). Colonization during a previous pregnancy is not an indication for intrapartum prophylaxis in subsequent deliveries. Screening to detect GBS colonization in each pregnancy will determine the need for prophylaxis in that pregnancy.

- Women with GBS isolated from the urine in any concentration during their current pregnancy should receive intrapartum chemoprophylaxis, because such women usually are heavily colonized with GBS and are at increased risk of delivering an infant with early-onset GBS disease (BII). Labels on urine specimens from prenatal patients should clearly state the patient's pregnancy status to assist laboratory processing and reporting of results. Prenatal culture-based screening at 35 to 37 weeks' gestation is not necessary for women with GBS bacteriuria. Women with symptomatic or asymptomatic GBS urinary tract infection detected during pregnancy should be treated according to the current standards of care for urinary tract infection during pregnancy (see section Sidebar 4).

Sidebar 4

Accuracy of screening. Although recommended by the CDC as the best available method for identifying mothers colonized with GBS, antepartum rectovaginal culture at 35 to 37 weeks is not a perfect test. As a screening test for a condition with a high prevalence, one can accept a low rate of false-positive tests as long as the rate of false negatives is close to zero. A false-positive test results in unnecessary antibiotic exposure for the mother, while a false-negative test means a GBS colonized mother will not receive intrpartum antibiotic prophylaxis and the infant is at risk for developing disease. Several studies have been reported that compare the accuracy of antepartum cultures at 35 to 37 post-menstrual age weeks with cultures during labor. Yancey *et al*., in 1996, were one of the first to study the accuracy of 35 to 37 week post-menstrual age cultures using cultures obtained during labor as the gold standard. They reported a positive predictive value of 87% (95% confidence interval 83 to 92) and an NPV of 96% (95% confidence interval 95 to 98). Thus 4% of mother testing negative at 35 to 37 weeks post-menstrual age were actually colonized with GBS at delivery.[27] Others have found similar results.[29,33,50]

- Women who have previously given birth to an infant with invasive GBS disease should receive intrapartum chemoprophylaxis; prenatal culture-based screening is not necessary for these women (BII).
- If the result of GBS culture is not known at the onset of labor, intrapartum chemoprophylaxis should be administered to women with any of the following risk factors: gestation <37 weeks, duration of membrane rupture >18 h or a temperature of >100.4 °F (>38.0 °C) (AII) (see section Sidebar 5).
- Women with known negative results from vaginal and rectal GBS screening cultures within 5 weeks of delivery do not require prophylaxis to prevent GBS disease even if any of the intrapartum risk factors develop.
- Women with threatened preterm (<37 weeks' gestation) delivery should be assessed for need for intrapartum prophylaxis to prevent perinatal GBS disease. An algorithm for the management of women with threatened preterm delivery is provided (Figure 2).[9] Other management approaches, developed by individual physicians or institutions, may be appropriate (CIII).
- Culture techniques that maximize the likelihood of GBS recovery are required for prenatal screening.[9] Collection of specimens for culture may be conducted in the outpatient clinic setting by either the patient, with appropriate instruction, or health-care provider (BII). This involves swabbing the lower vagina and rectum (that is, through the anal sphincter). Because lower vaginal as opposed to cervical cultures are recommended, cultures should not be collected by speculum examination. Specimens should be placed in a nonnutritive transport medium (for example, Amies or Stuart's without charcoal). Specimen labels should clearly identify that specimens are for GBS culture. If susceptibility testing is ordered for penicillin-allergic women (Box 1),[9] specimen labels should also identify the patient as penicillin allergic and should specify that if GBS is isolated, it should be tested for susceptibility to clindamycin and erythromycin. Specimens should be inoculated into a selective broth medium (examples of appropriate commercially available media include Trans-Vag Broth

Sidebar 5

CPQCC comment. Chorioamnionitis should be treated even if the GBS screening culture is negative. CPQCC commends the definition proposed by Newton. Choriamniotitis is defined as fever >38 °C and at least two clinical or laboratory findings suggesting intra-amniotic fluid infection (foul fluid, uterine tenderness, maternal WBC >15 000, fetal tachycardia >160 b.p.m. or maternal tachycardia >100 b.p.m.).[51]

CPQCC comment. Escobar *et al*.[52] noted the following relationship between antepartum fever or chorioamnionitis and neonatal infection rates in infants >2000 g at birth, even when the mother received intrapartum antibiotics.

Maternal temp		*Infection rate*
<99.5 °F	<37.5 °C	1.9%
99.5–100.4	37.5–38.0	2.5%
100.4–101.5	38.0–38.6	1.0%
101.5–101.9	38.6–38.8	5.5%
>102	⩾38.9	6.4%
Maternal Chorioamnionitis		
Possible	2.4%	
Probable	2.5%	
Definite	8.1%	

In women who receive intrapartum antibiotic prophylaxis for chorioamnionitis, CDC recommends a full sepsis evaluation and empiric antibiotic therapy. This is based on the above data showing that newborns whose mothers had chorioamnionitis had a high rate of sepsis, even when treated with intrapartum antibiotics.

supplemented with 5% defibrinated sheep blood or LIM broth), incubated overnight, and subcultured onto solid blood agar medium (AII). Methods of testing prenatal isolates from penicillin-allergic women for susceptibility to clindamycin and erythromycin are outlined in the CDC guideline.[9] Laboratories should report culture results (positive and negative) and susceptibility testing results to the anticipated site of delivery (when known) and to the health-care provider who ordered the test.

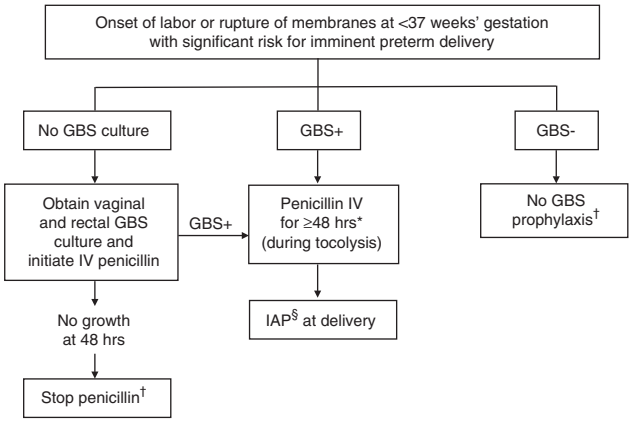

Figure 2 Sample algorithm for Group B Streptococcus (GBS) prophylaxis for women with threatened preterm delivery. This algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate. *Penicillin should be continued for a total of at least 48 h, unless delivery occurs sooner. At the physician's discretion, antibiotic prophylaxis may be continued beyond 48 h in a GBS culture-positive woman if delivery has not yet occurred. For women who are GBS culture positive, antibiotic prophylaxis should be reinitiated when labor likely to proceed to delivery occurs or recurs. †If delivery has not occurred within 4 weeks, a vaginal and rectal GBS screening culture should be repeated and the patient should be managed as described, based on the result of the repeat culture. §Intrapartum antibiotic prophylaxis. *Source:* Adapted from Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. *MMWR Recomm Rep* 2002; **51** (No. RR-11): 1–22.

- Health-care providers should inform women of their GBS screening test result and the recommended interventions. In the absence of GBS urinary tract infection, antimicrobial agents should not be used before the intrapartum period to treat GBS colonization. Such treatment is not effective in eliminating carriage or preventing neonatal disease and may cause adverse consequences resulting from overtreatment with antibiotics (DI).
- Group B Streptococcus-colonized women who have a planned cesarean delivery performed before rupture of membranes and onset of labor are at low risk for having an infant with early-onset GBS disease. These women should not routinely receive intrapartum chemoprophylaxis for perinatal GBS disease prevention (CII).
- For intrapartum chemoprophylaxis, the following regimen is recommended for women without penicillin allergy (Box 1): penicillin G, 5 million units intravenously initial dose, then 2.5 million units intravenously every 4 h until delivery (AII).[9] Because of its narrow spectrum of activity, penicillin is the preferred agent. An alternative regimen is ampicillin, 2 g intravenously initial dose, then 1 g intravenously every 4 h until delivery (AI).
- Intrapartum chemoprophylaxis for penicillin-allergic women takes into account increasing the resistance to clindamycin and

Box 1 Recommended regimens for intrapartum antimicrobial prophylaxis for perinatal GBS disease prevention[a]

Recommended	Penicillin G, 5 million units intravenously initial dose, then 2.5 million units intravenously every 4 h until delivery
Alternative	Ampicillin, 2 g intravenously initial dose, then 1 g intravenously every 4 h until delivery
If penicillin allergic[b]	
Patients not at high risk for anaphylaxis	Cefazolin, 2 g intravenously initial dose, then 1 g intravenously every 8 h until delivery
Patients at high risk for anaphylaxis[c]	
GBS susceptible to clindamycin and erythromycin[d]	Clindamycin, 900 mg intravenously every 8 h until delivery or Erythromycin, 500 mg intravenously every 6 h until delivery
GBS resistant to clindamycin or erythromycin or susceptibility unknown	Vancomycin[e], 1 g intravenously every 12 h until delivery

Source: Adapted from Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. *MMWR Recomm Rep* 2002; **51** (No. RR-11): 1–22.
[a]Broader-spectrum agents, including an agent active against Group B Streptococcus (GBS), may be necessary for treatment of chorioamnionitis.
[b]History of penicillin allergy should be assessed to determine whether a high risk for anaphylaxis is present. Penicillin-allergic patients at high risk for anaphylaxis are those with asthma or other diseases that would make anaphylaxis more dangerous or difficult to treat, such as persons being treated with β-adrenergic-blocking agents.
[c]If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis.
[d]Resistance to erythromycin is often but not always associated with clindamycin resistance. If a strain is resistant to erythromycin but appears susceptible to clindamycin, it may still have inducible resistance to clindamycin.
[e]Cefazolin is preferred over vancomycin for women with a history of penicillin allergy other than immediate hypersensitivity reactions, and pharmacological data suggest it achieves effective intramniotic concentrations. Vancomycin should be reserved for penicillin-allergic women at high risk for anaphylaxis.

erythromycin among GBS isolates (Box 1).[9] During prenatal care, history of penicillin allergy should be assessed to determine whether a patient is at high risk for anaphylaxis, that is, has a history of immediate hypersensitivity reactions to penicillin (for example, anaphylaxis, angioedema or urticaria) or history of asthma or other conditions that would make anaphylaxis more dangerous. Women who are not at high risk for anaphylaxis should be given cefazolin, 2 g intravenously initial dose, then 1 g intravenously every 8 h until delivery (BIII) (see section Sidebar 6). For women at high risk for anaphylaxis, clindamycin and erythromycin susceptibility testing, if available, should be performed on isolates obtained during GBS prenatal carriage screening. Women with clindamycin- and erythromycin-susceptible isolates should be given either clindamycin, 900 mg intravenously every 8 h until delivery; or erythromycin, 500 mg intravenously every 6 h until delivery. If susceptibility testing is not possible, susceptibility results are not known, or isolates are resistant to erythromycin or clindamycin, the following regimen can be used for women with immediate penicillin hypersensitivity: vancomycin, 1 g intravenously every 12 h until delivery (CIII).

- Routine use of antimicrobial prophylaxis for newborns whose mothers received intrapartum chemoprophylaxis for GBS infection is not recommended. However, therapeutic use of these agents is appropriate for infants with clinically suspected sepsis. An updated algorithm for the management of infants born to mothers who received intrapartum chemoprophylaxis for GBS infection is provided in the CDC guideline.[9] This revised algorithm is not an exclusive approach to management; variation that incorporates individual circumstances or institutional preferences may be appropriate (CIII) (see section Sidebar 7).
- Local and state public health agencies, along 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. Efforts to monitor the emergence of perinatal infections caused by other organisms are also encouraged.
- Before full implementation of this strategy can be expected in all health-care settings, all members of the health-care team will need to improve protocols for isolation and reporting of GBS culture results, to improve information management to ensure communication of screening results and to educate medical and nursing staff responsible for prenatal and intrapartum care. Within institutions, such efforts may take several months.
- Even with ideal implementation, cases of early-onset GBS disease will continue to occur (see section Sidebar 8).

Sidebar 6

Phares *et al*. in a review of population-based surveillance data from the Active Bacterial Core Surveillance/Emerging Infections Program Network over the period of 1999 to 2005 report an increasing pattern of resistance of GBS isolates to clindamycin and erythromycin. Of 4882 isolates tested for susceptibility, all were susceptible to penicillin, ampicillin and vancomycin, but 32 and 14% were resistant to erythromycin and clindamycin, respectively. Virtually all isolates resistant to clindamycin were also resistant to erythromycin.

CPQCC comment. In light of increasing resistance to erythromycin and clindamycin, the CDC guideline recommendation is even more important; that is, these agents should only be used when susceptibility testing has been performed on the colonizing isolate and sensitivity can be confirmed.

Sidebar 7

Efforts to monitor resistance. Concern has been raised regarding shifting patterns of antibiotic resistance because of the large volume of mothers receiving intrapartum prophylaxis with ampicillin or penicillin. Emergence of resistance may occur in two forms, either the development of resistance by GBS to penicillin, ampicillin and other previously used antibiotics or the emergence of other organisms resistant to ampicillin and penicillin. Regarding the former, some data have been reported in a single-center series suggesting the potential development of ampicillin or penicillin resistance.[53] However, larger population studies by the CDC Active Bacterial Core Surveillance/Emerging Infections Program Network have shown 100% sensitivity to ampicillin and penicillin.[54] The CDC data do confirm increasing resistance of GBS to erythromycin and clindamycin (see section Sidebar 6).

Emergence of ampicillin- and penicillin-resistant pathogenic organisms has been reported by numerous researchers. Most of the reports indicate a common thread, overall GBS EOD is decreased with widespread intrapartum prophylaxis, but EOD with ampicillin-resistant *Escherichia coli* and other resistant pathogens is increased in some populations. When newborns with EOS were stratified by birth weight or gestation, the probability of EOD with resistant pathogens increased substantially in premature infants.[55–57] Population-based studies have not shown a change in incidence of EOS with ampicilin-resistant pathogens in term infants.[20,58,59] Factors identified with ampicillin-resistant Gram-negative pathogens include intrapartum fever, ROM >18 h, intrapartum antibiotics given >24 h and clinical chorioamnionitis. These are the circumstance that present more often in preterm infants, accounting for much of the selective increase in that population.

CPQCC comment: Because of varying local experience with the emergence of resistant strains, we encourage each center to monitor their own trends, especially among their very low birth weight populations.

Sidebar 8
Persistent GBS Disease with Screening Protocols. Since the 2002 release of the current CDC guideline, data have been published documenting the incidence and possible etiologies for persistent GBS EOD adherence to the universal screening. In a single-center observational study, the incidence of GBS was 0.37 per 1000 live births after implementation of universal screening. Of term infants with GBS sepsis, 82% of the mothers had negative rectovaginal cultures.[26] Other investigators have shown a false-negative test rate of 4% between GBS cultures obtained at 33 to 39 weeks with cultures obtained at delivery.[27]

In light of the increasing trends of EOS in some demographic subgroups and the evidence of GBS occurring in term babies whose mothers had negative cultures, it would be prudent to consider the recommendation of Puopolo and others to treat GBS-negative mothers who have intrapartum risk factors with prophylactic antibiotics. This is not recommended by the CDC in the 2002 guideline. As there is no high level evidence to support this practice it is not formally recommended by the CPQCC either.

Additional educational and quality improvement materials

Tools to help promote prevention and educate parents of infants with early-onset GBS disease are available at http://www.cdc.gov/groupbstrep. Additional tools available to assist with prevention implementation are available at http://www.acog.org, Multiple copies of educational materials published by CDC are available at the Public Health Foundation, 1220L Street, NW Suite 350, Washington, DC 20005, telephone 877-252-1200, or online at http://bookstore.phf.org/advanced_search_result.php?keywords=Group+B+strep&x=5&y=7

The Centers for Disease Control, the American College of Obstetrics and Gynecology and the American Academy of Pediatrics websites have a variety of materials available to help with implementation.

The CDC site (http://www.cdc.gov/groupbstrep) contains the following:

- the Guidelines themselves
- **Clinical Issues and Introduction to the New Guidelines**
  Slide presentation geared toward health professionals that covers background on the epidemiology of perinatal GBS disease, the impact of prevention efforts in the 1990s, the rationale for revisions to the 1996 guidelines, and the recommendations in the CDC's 2002 guidelines. This is a downloadable powerpoint file and each slide includes brief speaker notes.
- **Laboratory Processing of Prenatal Group B Strep Specimens**
  Slide set presenting CDC's 2002 recommendations for laboratory processing of prenatal group B strep specimens, including photos outlining group B strep identification and susceptibility testing methods (Updated 2/03).
- Patient handout: 'GROUP B STREP—WHAT YOU NEED TO KNOW'
- Ready-to-print patient's education on group B strep screening, available at: http://www.cdc.gov/groupbstrep/docs/GBS_Patient_Info.pdf
- Instructions for the collection of a genital swab for the detection of a group B streptococcus (GBS)
  One page patient information sheet outlining instructions for self-collection of prenatal vaginal/rectal swabs in the outpatient setting for the detection of GBS. Courtesy of Suzanne Garland and Angela Guzys, Royal Women's Hospital, Melbourne Victoria, Australia.
- Other patient handouts
  - Group B Strep Awareness Flyer 'Babies, Beautiful, Healthy Babies' (2002) Pregnancy and GBS-Group B Streptococcal Low Literacy Brochure—English Version (August 2002)
  - What You Can Do to Keep Germs from Harming You and Your Baby—English Version (August 2002)
  - What You Can Do to Keep Germs from Harming You and Your Baby—Spanish Version (March 2000)
  - Group B Streptococcal Infection Patient Brochure—Spanish Version (August 1998)

The American College of Obstetrics and Gynecology site contains the following:

- A parent information sheet
- Group B Streptococcus and Pregnancy
- This pamphlet discusses the ways to help prevent GBS infection in newborns.

Supplementary material

The appendix (Supplementary Material Appendix) contains numerous supportive tools to assist local implementation of the guideline. There are fishbone diagrams outlining the process of implementation and problem identification worksheets to be used in local quality improvement projects involved with reducing the incidence of GBS EOD.

Future directions

Rapid detection methodology
Efforts to address the residual incidence of GBS EOD have prompted further analysis of the underlying causes for the failure of current prevention strategies. As discussed earlier (Sidebar 8, Persistent GBS Disease with Screening Protocols), the CDC reports that post-implementation monitoring in the period after the universal screening was recommended shows a residual incidence of GBS EOD to be approximately 0.5 cases per 1000 live births overall, and up to 0.89 cases per 1000 live births among African

Americans. It has been shown that intrapartum antibiotic prophylaxis is almost 100% effective in eliminating vertical transmission of GBS in colonized mothers, eliminating this phase of the guideline as a source of screening failures.[22–25] Numerous problems in identification of colonized mothers continue to exist. These are based on failures to screen, errors in tracking of results or the inherent limitations of antepartum cultures because of the intermittent nature of GBS colonization leading to false-negative screening tests.

Puopolo *et al*.[26] showed that in term infants with GBS EOD in the post-universal screening era, 82% of the mothers had negative rectovaginal cultures on antenatal screening. In early studies establishing the groundwork for GBS prevention protocols, Boyer *et al*. showed that when compared with intrapartum cultures, antenatal screening for GBS only had a positive predictive value of 72.5% and a negative predictive value (NPV) of 91.5%. These values were for cultures obtained at any time before delivery. These data also showed an inverse relationship with the interval between prenatal cultures and delivery, that is, the accuracy improved the closer to delivery cultures were obtained.[25] In several more recent studies, the relationship between screening cultures for GBS at 35 to 37 weeks and at delivery has been shown to have a positive predictive value of 67 to 87%, and an NPV of 91 to 96%.[27–29] Thus, 67 to 87% of mothers may be unnecessarily exposed to intrapartum antibiotics when they are not colonized at the time of delivery, and more importantly, 4 to 9% of mothers who are colonized at the time of delivery would miss intrapartum prophylaxis because their antenatal screening was negative.

One solution to this inherent problem with protocols based on antepartum screening is to use rapid intrapartum screening to identify only those mothers who are colonized at the time of delivery. Such a test would need to have a high NPV, so false negatives are essentially eliminated and have a reasonably high positive predictive value to avoid unnecessary intrapartum antibiotic administration. Such a test would also need to have rapid turnaround and be available 24 h day^{-1}, so colonized mothers could be identified more than 4 h before delivery to make the prophylaxis effective. Rapid testing for GBS colonization using rectovaginal specimens has been studied extensively. Rapid testing technology has evolved to a point where numerous independent investigators are consistently reporting accuracy much better with DNA PCR assays than with antepartum screening. These are recent reports, describing the likely evolution of DNA PCR technology that may be available in the near future. Sensitivity and specificity are reported in the range of 91 to 97% and 96 to 99%, respectively. Positive predictive value and NPV for real-time DNA PCR assays are reported to be in the range of 88 to 98% and 97 to 98%, respectively.[30,31] DNA PCR results are also reported to be available within less than 2 h and can be performed on the maternal unit, thus satisfying more essential requirements of a rapid screening test for GBS.[31–33] Although very promising, further evaluation of accuracy, feasibility and cost-effectiveness will still be necessary in larger population studies before these tests will replace the current antepartum screening protocols.

Group B Streptococcal vaccines

An effective vaccine against GBS would eliminate the need for risk-based and screening-based guidelines with their attendant limitations. It could also have additional benefits in preventing GBS-related stillbirths or prematurity by providing protection earlier in the gestation than the intrapartum prophylaxis strategies. It would provide a longer duration of immunity to the newborn, thus preventing late-onset GBS as well. Finally, an effective vaccine would also protect the mother against invasive GBS infection.[34]

The ideal GBS vaccine would be administered only once, before or during pregnancy. If given during pregnancy, it would need to have proven safety without toxicity or teratogenicity. Ideally, it would eliminate or reduce colonization with GBS in the maternal gastrointestinal and reproductive tract, reducing the risk of late-onset disease GBS, stillbirths resulting from GBS infection and EOD in premature infants born before placental antibody transfer.

The surface of the GBS organism is made up of the unique group-specific carbohydrate and a number of type-specific polysaccharides, Types I through VII. The capsular polysaccharide antigens are immunogenic, and susceptibility of the newborn to clinical disease is associated with levels of antibody to the different capsular polysaccharides.[35–37] In the United Kingdom and North America, EOD is associated with Type Ia, III and V, whereas late-onset disease is associated primarily with Type III. Polysaccharide antigen prevalence varies in other regions of the world, with reports of predominance of colonization with serotypes VI and VIII in Japan, Ib, Ic, II and III in the Netherlands and V in Gambia.[38–41] The immunogenicity of capsular polysaccharides and the relationship of certain serotypes to specific disease manifestations make the development of a GBS vaccine a feasible and desirable approach to prevention of disease. As all of the serotypes are associated with disease, vaccines would need to be multivalent, covering the serotypes prevalent in the specific region.

The current vaccine research and development is based on targeting of the capsular polysaccharides. The different carbohydrate molecules are bonded with protein carriers, most commonly tetanus toxoid, to enhance immunogenicity of the vaccine. Numerous Phase I and Phase II studies in humans have shown successful immunogenicity of these capsular polysaccharide–tetanus toxoid conjugate vaccines in healthy adult volunteers[42,43] and in pregnant women.[36,44]

Vaccines will not be ready for widespread distribution until Phase III testing has been completed with larger multicenter randomized controlled trials. Clinical research at this level will entail significant obstacles. As the background incidence of GBS is so low, at least 40 000 women would need to be enrolled for an 80% probability of showing a significant reduction in GBS

disease. As the standard prevention strategies involving intrapartum antibiotic prophylaxis are reasonably successful, this treatment cannot be withheld in a vaccine trial. Any Phase III trial will need to show incremental efficacy in patients already receiving intrapartum antibiotic prophylaxis, making the trial even larger. Another obstacle to the approval of a GBS vaccine is the need for administration during gestation. Owing to the background incidence of congenital malformations and stillbirths, the liability of testing a vaccine in the pregnant population presents overwhelming liability challenges, considering the fact that there is currently no legal protection for companies or institutions sponsoring such research. Some experts feel that the regulatory and legal challenges are too great to allow further progress in implementation of a GBS vaccine.[34]

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We thank Courtney Nisbet, MS, the CPQCC Quality Improvement Program Manager, for her helpful assistance in the preparation of the toolkit since its inception and along with Megan Sullivan, CPQCC Program Assistant, for their help and technical expertise in the preparation of this article. We also thank Paul Sharek, MD, the CPQCC Director of Quality for his support, many contributions and review of this article.

Abbreviations

CPQCC, California Perinatal Quality Care Collaborative; PIW, Problem Identification Worksheet; NICU, Neonatal Intensive Care Unit; CDC, Centers for Disease Control; GBS, Group B Streptococcus; PPV, Positive Predictive Value; NPV, Negative Predictive Value; DNA, Deoxyribonucleic Acid; PCR, Polymerase Chain Reaction; AAP, American Academy of Pediatrics; ACOG, American College of Obstetrics and Gynecology; E Coli, Escherichia Coli; ROM, Rupture of Membranes; PROM, Premature Rupture of Membranes; VLBW, Very Low Birth Weight; EOS, Early Onset Sepsis; EOD, Early-Onset Disease; PMA, Post Menstrual Age

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)

Appendix

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