Chapter 7

Opportunities for improvement of prevention of GBS-EOD

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Submitted

ABSTRACT

Despite considerable efforts and economic resources spent on prevention of early-onset group B streptococcal disease (GBS-EOD), it is still an important cause of neonatal infection and early neonatal mortality within the first seven days of life.

In this article, we identify potential areas for improvement of prevention of GBS-EOD. Opportunities for improvement can be found in development and implementation of local prevention protocols as well as in optimal timing of screening, the correct choice of sampling sites, the best conditions of transport of swabs and culture procedures and the best choice of antibiotics. Knowledge about the route to disease and the possible preventive measures as well as training in recognizing GBS-EOD is important. Caregivers should be aware that there are a lot of little steps in the chain of prevention where improvement of prevention of GBS-EOD can be made.

INTRODUCTION

Invasive Group B streptococcal disease emerged in the 1970's as a leading infectious cause of perinatal morbidity and mortality.(1) Vertical transmission of GBS from mother to child occurs during labor. The gastrointestinal tract of the mother has been recognized as the source of vaginal GBS colonization. The frequency of GBS colonization ranges from 10% to 35% in women of reproductive age.(2;3) Studies on vertical GBS transmission in colonized mothers during labor report incidences of colonization of the infant between 16 and 69%.(4-9) Early-onset group B streptococcal disease (GBS-EOD) occurs in approximately 1% of newborns who are colonized with GBS and typically presents with sepsis, pneumonia or meningitis.(10) Risk factors for acquiring GBS-EOD are prolonged rupture of membranes, preterm labor, intrapartum fever, GBS bacteriuria during pregnancy or a previous child with GBS.(11)

Because infants with early onset group B streptococcal disease (GBS-EOD) are infected during labor, the opportunity for timely prevention is limited. Prevention of disease rather than treatment is the focus of attempts to reduce neonatal GBS infections and the burden of the disease.

Intrapartum antibiotic prophylaxis (IAP) given to women at risk of transmitting GBS to their baby can prevent GBS-EOD.(9;12) Identifying these mothers at risk may be performed by screening (taking a culture during pregnancy to detect maternal colonization) and/ or by identifying women during labor with one of the established risk factors for GBS-EOD.

Today, after implementation of prevention strategies, the overall incidence of GBS-EOD in many countries has declined progressively.(2-5) However, current strategies for prevention of GBS-EOD are still subject of controversy. Despite considerable efforts and economic resources spent on prevention of GBS-EOD, it is still an important cause of neonatal infection and mortality within the first seven days of life.(1-3;6-14)

Factors contributing to ongoing disease

Nowadays, as shown in several recent studies, in countries where culture based screening is performed, GBS-EOD mainly occurs in term infants born to mothers screened negative for GBS colonization and in preterm infants born to mothers who were not screened and did not receive IAP.(3;14;15) Missed opportunities for prevention of GBS-EOD in case of a screening based strategy were identified in a recent study by Stoll et al(13) and revealed failure to screen all women during pregnancy, failure to provide antibiotics to all colonized women or to those who delivered preterm with unknown colonization status, and false negative GBS screens among some women who deliver infants with GBS infection.

Negative GBS screens among women who deliver infants with GBS-EOD are particularly troubling and may be attributable to insufficient sampling, delay in processing, suboptimal laboratory techniques, recent antibiotic use or colonization after screening was performed,

ie wrong timing of antenatal cultures. This, together with several other aspects of antenatal and perinatal clinical practice, including lack of guidelines, lack of communication, improper implementation of IAP and microbiological factors including antibiotic resistance, may all contribute to ongoing disease.

Opportunities for improvement of prevention of GBS-EOD

With regard to the remaining burden of disease it is important to identify potential areas for improvement in the total process from antenatal care to discharge of a healthy women with a healthy baby.

Prevention Strategy

Among all opportunities for improvement, one of the most important factors in decreasing GBS-EOD is that there is at least a nationwide guideline for preventing GBS-EOD, ideally translated into protocols for each region or each hospital.

The best prevention strategy maximizes treatment in women who need it, and refrains from treatment in women who do not need it. Wilson and Jugner defined in 1968 criteria for appraising validity of a screening programme, which still upheld today as classics; the gold standard of screening. (Table 1)(14)

However, several adaptations have been made to the classic criteria of Wilson and Jungner, and several new criteria have also emerged. Emerging criteria reflect broader trends that have shaped both Western medicine and society more generally over the past generation (e.g. increased consumerism, the shift away from paternalism towards informed choice, a focus on evidence-based health care, and the rise of managed care models that emphasize cost-effectiveness, quality assurance, and accountability of decision-makers.(15) All these

Table 1 The Wilson-Jungner criteria for appraising the validity of a screening program.(14)

1.	The condition being screened for should be an important health problem
2.	The natural history of the condition should be well understood
3.	There should be a detectable early stage
4.	Treatment at an early stage should be of more benefit than at a later stage
5.	A suitable test should be devised for the early stage
6.	The test should be acceptable
7.	Intervals for repeating the test should be determined
8.	Adequate health service provision should be made for the extra clinical workload resulting from screening
9.	The risks, both physical and psychological, should be less than the benefits
10.	The costs should be balanced against the benefits

criteria should be taken into account when a nationwide guideline or local protocol is established.

Management strategy to prevent GBS-EOD depends on local factors, including the percentage of GBS carriers and the percentage of pregnant women with perinatal risk factors within the population, the organization of perinatal care and the availability of laboratory facilities. The choice for a prevention strategy is based on rationality, cost-effectiveness, current knowledge and implementation and should be in line with criteria for screening.

In this article, we will not particularly describe pros and cons of different prevention strategies of GBS-EOD, but focus on identifying GBS carriage, different aspects of IAP and identifying GBS-EOD in newborns.

Improvement of prenatal screening

Accuracy of GBS prenatal screening can be improved. The aim of GBS screening is to predict vaginal GBS colonization at time of delivery. Methods that maximize the likelihood of GBS recovery are required, and specific culture media are needed. Critical factors that influence the accuracy of detecting GBS maternal colonization include anatomic sites of samplng the GBS bacteria, timing sampling in pregnancy, transport conditions of swabs and culture procedures. In addition, failure to culture GBS may be caused by maternal factors, such as use of oral antibiotics before specimen collection.

Sampling sites

The recommended method of collection of GBS is based on a 1977 study in which was shown that the gastrointestinal tract was the primary site of GBS colonization. In 17.9% of rectal cultures from pregnant women GBS was found, compared to 10.2% of vaginal cultures.(16) Results from later studies showed that swabs taken from both the anorectum and the vaginal introitus increase the likelihood of GBS isolation by 5-27% over vaginal culture alone.(19-21) In recent cohort studies similar detection rates were found when the vaginal-rectal collection method was compared with the vaginal-perianal collection method.(22-24) Patients indicated less pain and discomfort with the vaginal-perianal collection method. Therefore, vaginal-perianal cultures may be reasonable, patient-preferred alternatives for the recommended vaginal-rectal cultures for detection of GBS during pregnancy.(17)

Transport

For shipment from outpatient clinics to a microbiology laboratory it is important to know how long Group B streptococci in swabs will survive at room temperatures.

The CDC guidelines state specifically that the viability of GBS can be maintained for up to 4 days in appropriate transport media, i.e. Amies transport medium.(3) There are few data, which support this statement. One study showed that there will be a loss of positive culture

results if the GBS colony density is low or if the room ambient temperature is relatively high (> 30^0C).(18) Even when appropriate transport media are used, the sensitivity of culture is best when the specimen is stored at 4 ^{0}C before culture and processed within 24 hours of collection.(19) Further research is needed to know more about best transport and storage conditions.

Culture Procedures

The use of selective broth media (i.e. broths containing antimicrobial agents to inhibit competing organisms) is essential. In these media, the yield of screening cultures increases by as much as 50%.(28;29) Appropriate selective broth media, either SBM broth or Lim broth, are commercially available. Of course, it is important that the person who sends the swab to the laboratory clearly indicates that a GBS screening is requested, so that the appropriate media are used.

Timing

In countries were a screening regimen is followed, GBS-EOD mainly occurs in term infants born to mothers screened negative for GBS colonization and in preterm infants born to mothers who were not screened.(20-22) As GBS carriage is highly variable, antenatal GBS cultures are not always good predictors of maternal GBS carriage during delivery. Whether these negative cultures were false negative or the mothers acquired GBS in the interval between the screening culture and the time of delivery is unknown. Negative GBS screens may provide a false sense of reassurance both to the patient and her caregivers. In addition, women with GBS may not be colonized at the time of labor and thus receive IAP unnecessarily.

After a systematic review we confirmed recommendations to screen all pregnant women for colonization of GBS at 35-37 weeks gestation. However, one should be aware of the limitations of screening. Positive predictive values for antenatal GBS-cultures at gestation of 35-37 weeks ranged from 43-100% (mean 69%) and negative predictive values from 80-100% (mean 94%). GBS-cultures collected in late pregnancy correspond with high positive predictive values for colonization during delivery. The negative predictive value is high and relatively constant with regard to gestational age, but still 6% of GBS carriers during delivery remains undetected.(23)

Several studies have confirmed the benefit of using a reliable, highly sensitive, easy to perform, rapid test. To allow a timely and targeted IAP to GBS-positive women screened during labor, turnaround time of such tests should be short. These tests should be available 24 hours a day, 7 days a week. An accurate rapid test for GBS colonization proved difficult to develop. Despite the development of antigenic and hybridization-based tests in the last

two decades, a rapid and accurate culture method for GBS colonization is still unavailable. Although these tests have good specificities, they have disappointing performance with low sensitivities, which only increase with heavy colonization.

Communication and Implementation

In a recent prospective surveillance study from the USA all cases of GBS-EOD during 4 years in a cohort of 400 000 live births were reported. Despite CDC recommendations for universal antenatal screening for GBS, only 58% of mothers who delivered infants with GBS-EOD were screened. (in 63% of term deliveries and in 44% of preterm deliveries) Only 76% of mothers with GBS bacteriuria, 76% with a positive GBS screen and 66% with unknown GBS colonization status and a risk factor (gestation < 37 weeks, ROM more than 18 hours before delivery, maternal temperature > 38.0^0C) received intrapartum antibiotics.(13)

Guidelines are adressed to obstetric and neonatal-care practitioners, laboratories and labor-and delivery facilities. For ideal implementation of guidelines, good collaboration and communication is extremly important. Each hospital should have a protocol for prevention of GBS-EOD which is known to all professionals involved in the care of pregnant women. This protocol should document the way of selection of mothers to whom administration of IAP is advised, complete with documentation of risk factors (in case of risk factor based strategy), procedures for collecting specimens for culture of GBS at 35-37 weeks of gestation (in case of a screening strategy), transport and laboratory procedures, mode of administering IAP, dosage and duration and way of secondary prevention of GBS-EOD among newborn infants (i.e. observation vs treatment).

Results should be easily available for clinical workers on the floor, who ideally have been trained in the protocol and exactly know what to do in patients with risk factors for GBS-EOD or positive screening results. Health-care providers should inform women about recommended interventions.

Good implementation of guidelines requires knowledge of and adherence to the protocol for both the patient and caregivers.

Choice of antibiotics

Penicillin is the preferred antibiotic for IAP to prevent GBS-EOD. It is the first choice before ampicillin or amoxicillin, because of its narrower spectrum of antimicrobial activity, its decreased potential for selection of resistant organisms and its likely minor effect on enteric bacterial species. The efficiacy of all three agents administered intravenously for the prevention of GBS-EOD has been reported in clinical studies.(12)

Dosage

Proper dosing of antibiotics is essential to prevent the fetus from infection. In various countries with different prevention protocols, several dosing regimen recommendations exist and

are currently used. The rationale behind these regimens is not always clear nor evidence based. There is strikingly little information available on the pharmacokinetics of antibiotics in pregnancy in general and in the peripartal period in particular. Future studies should focus on research on pharmacokinetics of antibiotics during pregnancy and childbirth.

The CDC recommends penicillin G in a dosing regimen of 5 million units iv, followed by 2.5-3.0 million units iv every 4 hours. The range of 2.5-3.0 million units after the first 5 million units is recommended to achieve adequate drug levels in the fetal circulation and amniotic fluid while avoiding neurotoxicity. In order to reduce the need for pharmacies to specially prepare doses, the choice of dose should be guided by which formulations of penicillin G are readily available.(5)

As an alternative but equally recommended is Ampicillin in a 2 gram initial dose, followed by 1 gram every 4 hours until delivery. (Figure 1)

Outside the USA, intravenous amoxicillin is sometimes used in the prevention of neontal GBS disease.

Amoxicillin dosing regimens have been derived from studies using ampicillin, a beta-lactam antibiotic closely related to amoxicillin. Since the consequences of changes in

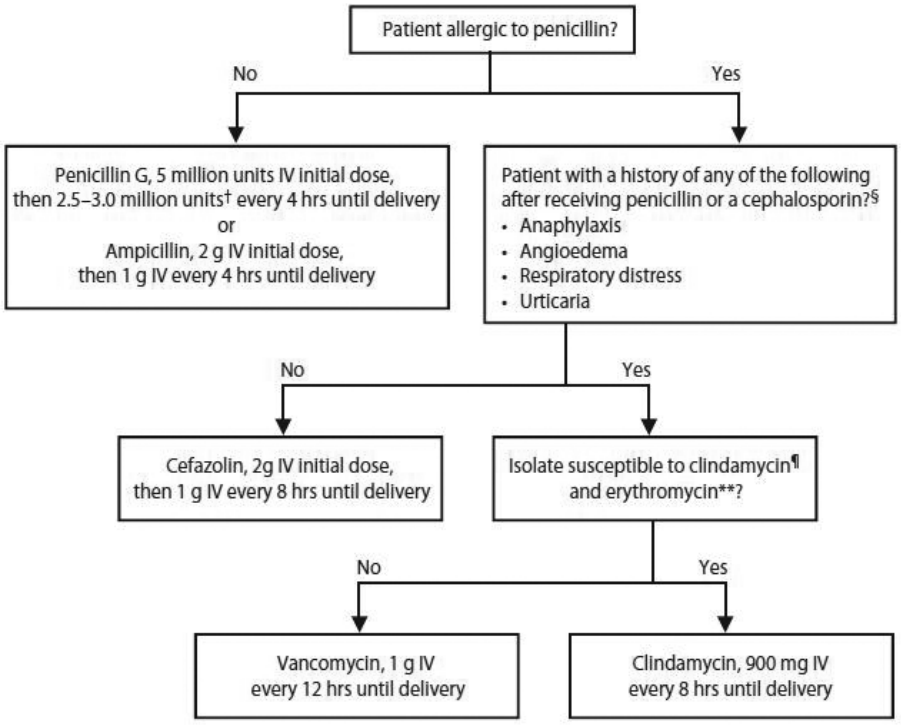

Figure 1 Algorithm for intrapartum antibiotic prophylaxis for prevention of GBS-EOD(5)

antibiotic dosing are unknown, it is not possible to study different regimens in pregnant women. Computer-simulations using data of the prescribed regimens are an accepted alternative, particularly when detailed information on the pharmacokinetics and the inherent inter-individual variation are avilable.

Muller et al. described in a simulation model in women with preterm prelabor rupture of membranes that a dosing regimen of bolus injections of 1 gram amoxicillin every 6 hours was predicted to be adequate for the prevention of GBS infection in pregnant patients.(24) This regimen was described as the usual regimen in a former review of the Cochrane Library.(25) After revision, the Library doesn't provide recommendations for antibiotic dosing regimens anymore. A 2 gram loading dose does not seem to be beneficial and the 1 gram doses can safely be administered by bolus injection increasing the comfort of the patient and facilitating prophylaxis.(31) The remaining difference between the CDC regimen and the former Cochrane regimen is the dosing interval of 4 hours versus 6 hours. Muller advises a 4-hour dosing regimen instead of a 6-hour dosing interval, since the common urgency of care in delivery rooms can easily result in inaccuracies in the administration. Using a 4-hour dosing interval results in a higher probability of target attainment, even when doses are accidentally skipped.

Dutch guidelines advise benzylpenicillin, in an initial dose of 2 million Units and subsequent doses of 1 million Units every four hours. As an alternative guidelines mention an initial dose of 2 gram amoxicillin or ampicillin, followed by 1 gram every four hours until delivery.(26)

Alternatives in penicillin-allergic patients

Considering a prevalence of GBS colonization of 20% and a prevalence of penicillin allergy of 10%, it is estimated that 2% of the pregnant women is both GBS colonized and penicillin allergic.

Penicillin skin testing can be performed in pregnant women, so that penicillin can be administered safely if the result is negative.(27)

To select the antibiotic prophylaxis for penicillin allergic women at high risk of anaphylaxis properly , antimicrobial susceptibility testing of GBS isolates is essential and should be documented. An antibiotic that is frequently prescribed in women with penicillin allergy is clindamycine. However, there is increasing resistance among GBS isolates. Resistance of GBS isolates to erythromycin and clindamycin has been reported many times.(28-31)

Resistance to erythromycin and clindamycin in a multicultural population of pregnant women in The Hague in the Netherlands was found in 8% and 7%, respectively. (30)

Nevertheless, susceptibility testing to macrolides is rarely performed (< 1% of colonized women who are allergic to penicillin) and clindamycin is administered to 70% of women allergic to penicillin.(21)

CDC guidelines recommend that penicillin-allergic women at high risk for anaphylaxis (i.e. a history of anaphylaxis, angioedema, respiratory distress or urticaria following administration of a penicillin or a cephalosporin) should receive clindamycine if their GBS isolate is susceptible to clindamycine and erythromycin, as determined by antimicrobial susceptibilitytesting; if the isolate is sensitive to clindamycin but resistant to erythromycin, clindamycine may be used if testing for inducible clindamycin resistance is negative.

However, data on the pharmacokinetics of clindamycine in pregnant women and non pregnant individuals are scarce.(39-41) Data suggest that in pregnant women the current dosing regimen of 900 mg every 8 hours reach adequate concentrations, but the concentration-time profiles in the fetus might be inadequate. More pharmacokinetic studies including data of both the mother and the neonate are needed to investigate whether the currently advised regimen is adequate to prevent GBS-EOD.

Penicillin-allergic women at high risk for anaphylaxis should receive vancomycine 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. (Figure 1)

Duration of administration of antibiotics

The Centre for Disease Control and Prevention (CDC) issued recommendations for the prevention of GBS-EOD specifying that profylaxis is considered adequate only if antibiotic administration is started at least 4 hours prior to delivery. Because of various delivery circumstances, as many as 50% of GBS carriers women may not get IAP 4 hours before delivery.(42) As a consequence, soon after birth healthy-appearing infants born to mothers who received inadequate IAP routinely undergo invasive testing (including white blood cell count and blood culture) to exclude infection. Only a few studies have evaluated the influence of timing of profylaxis on neonatal colonization and the reported rates of transmission are quite heterogeneous. In a systematic review a rationale for the 4 hour threshold of the CDC guidelines was not found.(32) A recent prospective cohortstudy described colonization rates of infants born to mothers who received inadequate or no profhylaxis. Among 137 infants born to mothers who received inadequate prophylaxis, 3.6% were colonized. Eighty-two women received prophylaxis < 2 hours before delivery and two of their infants (2.4%) were colonized. Of 30 infants who were not exposed to prophylaxis, 60% were colonized. Colonization was significantly more frequent among infants born to untreated mothers compared with infants born to women who received inadequate profylaxis. This suggests that inadequate prophylaxis may effectively interrupt GBS transmission. IAP should therefore

always been given to women with higher risk of neonatal GBS-EOD, even if delivery is expected to be within a few hours.(44)

To conclude, research on the pharmacokinetics of various antibiotics should be continued for optimization of the GBS disease prophylaxis.

Secondary prevention of GBS-EOD among newborn infants

Prevention strategies will never prevent all cases of GBS-EOD. Rapid detection of neonatal infections and initiation of appropriate treatment is needed to minimize morbidity and mortality. The detection of GBS-EOD poses certain clinical challenges, because neonatal care providers must take into account the clinical appearance of the infant, the presence of maternal risk factors for GBS-EOD and infant exposure to intrapartum antibiotics. Figure 2 describes the algorithm for managing infants with signs of sepsis, infants born to women with chorioamnionitis and well-appearing infants exposed to inadequate intrapartum antibiotics.(5)

Detection of disease after IAP

As use of IAP to prevent GBS-EOD increased, concern was expressed that signs of sepsis in the newborn could be delayed or masked, impairing the ability of clinicians to detect GBS-EOD. (45;46) However, several studies conducted since 1996 did not find significant difference in the clinical presentation of GBS-EOD between infants exposed to IAP and those not exposed.(22;33-36) Approximately 90% of cases of GBS-EOD continue to manifest within the first 24 hours of life.

Neonatal infection is diagnosed by laboratory tests, i.e. CRP (routinely) or procalcitonin (PCT) concentrations (sporadically). The concentrations of both proteins are increased in cord blood in response to infection. Measurements of CRP and PCT levels in cord blood plasma contribute to the diagnosis EOD.(37-40) There are significant differences between infected and uninfected neonates in levels of CRP and PCT levels in cord blood, also when prenatal antibiotic therapy was administered.

Knowledge, training and awareness

Training in recognizing GBS-EOD and knowledge about the route to disease and the possible preventive measures deserve continued attention of all workers in obstetric care, either in hospitals or at home. Parents need to be informed about the disease so that they can recognize alarm symptoms when they are alone with their baby.

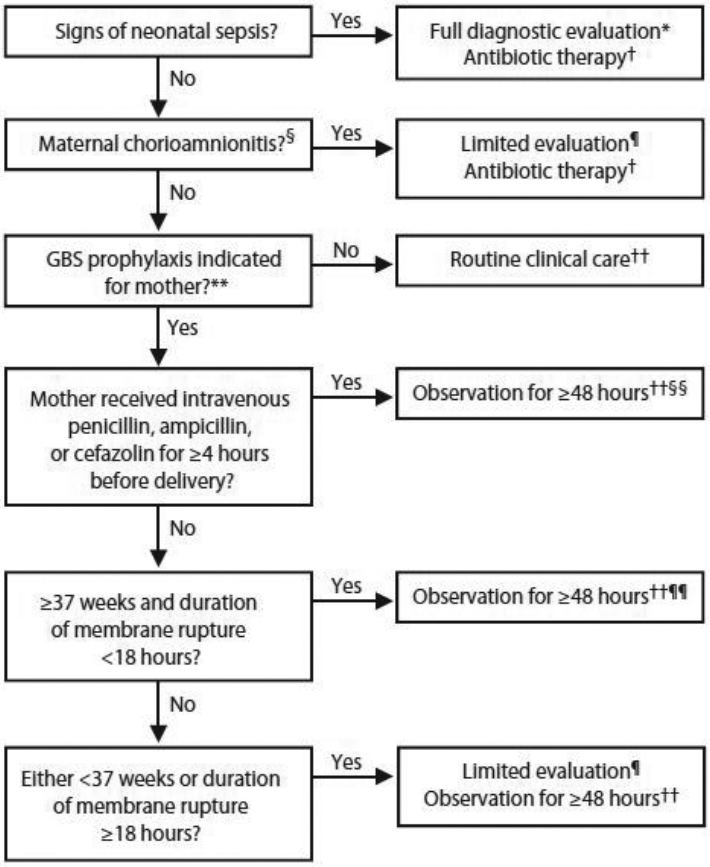

Figure 2 Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns(5)

* 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).

†† 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.

CONCLUSION

To identify potential areas for improvement of prevention of GBS-EOD, training in recognizing GBS-EOD is important. Opportunities for improvement can be found in development and implementation of local prevention protocols as well as in optimal timing of screening, a correct choice of sampling sites, the best conditions of transport of swabs and culture procedures and the best choice of antibiotics. Knowledge about the route to disease and the possible preventive measures deserve continued attention of all workers in obstetric care, either in hospitals or at home. Caregivers need to be aware that there are a lot of little steps in the chain of prevention where improvement can be made.

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