Current guidelines recommendations for management of group B streptococcal infections in pregnant women

Abstract

Group B streptococcus (GBS) is one of the main cause of neonatal infections, especially in preterm neonates. GBS presence, both in mothers and neonates, has a remarkable impact on morbidity and mortality. Screening for GBS infection in mothers during pregnancy in the third trimester, monthly urinalysis and promptly initiation of antibiotic therapy intrapartum will lead to a significant decrease of early onset GBS disease.

Keywords: *Group B streptococcal infection, management, screening*

Raluca Jipa[1], Adriana Hristea[1,2], Victoria Arama[1,2]

1. „Prof. Dr. Matei Balș" National Institute for Infectious Diseases, Bucharest, Romania
2. „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Correspondence: Dr. Raluca Jipa
e-mail: ralucajipa@yahoo.com

All authors contributed equally in the writing of this article.

1. Introduction - epidemiology

GBS is a aerobic Gram-positive diplococcus, encapsulated, that produces clear areas of β-hemolysis on blood agar plates[2]. GBS colonies asymptomatically the gastrointestinal, genital and upper-respiratory tracts[3].

Vaginal GBS colonization varies worldwide from 12 to 27% and can be permanent, intermittent or transient[4]. In Europe, the rate of colonization varies between 4 and 36%[5]. Despite a transmission rate of 50%, only 1-2% of the colonized newborns will develop GBS disease[6]. Although the incidence rate of early-onset GBS decreased after the introduction of different guidelines, from 1.7 per 1000 live births to 0.4 per 1000 live births, the incidence rate of late-onset GBS disease remained unchanged (0.33 per 1000 live births)[7]. The mortality risk in newborns is associated both with low birth weight and length of pregnancy (see Table 1).

Transmission of GBS to neonates

The transmission of GBS from mother to neonates can be made by ascending route, through translocation of GBS through intact or ruptured membranes, with aspiration of GBS by the neonate and secondary occurrence of bacteraemia or at birth, during passage through the birth canal, with secondary colonization of the respiratory or gastrointestinal mucous membranes[8].

Risk factors associated with GBS infection

The most important risk factor is represented by maternal intrapartum colonization with GBS. Asymptomatic bacteriuria and urinary tract infections (UTI) with GBS are predictive factors for the presence of an important inoculum, and increase the risk of infection in newborns[9].

Table 1 Case-fatality rate in neonates*

Study	500-1000 gr	1001-1500gr	1501-2000gr	2001-2500gr	➢ 2500gr
Boyer (1973-1981)	90	25	29	33	3
Baker (1982-1989)	60	25	26	18	5
Weisman (1987-1989)	75	40	20	15	6
Schrag (1993-1998)		30 (< 33 S)		10 (34-36 S)	2 (> 37 S)
Phares (1999-2005)		20 (< 37 S)			3 (> 37 S)

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Other risk factors for GBS infections are: gestational age <37 weeks; longer duration of rupture membrane (>18 hours); intra-amniotic infections (fever >38° C); young maternal age; black race; low maternal levels of GBS specific anticapsular-antibody[9]; previous birth of a child with GBS infection[10-14].

2. Maternal clinical manifestations

Asymptomatic bacteriuria occurs in 2-10% of all pregnancies[15,16] and GBS is responsible for 20% of them[17]. The presence of asymptomatic bacteriuria during pregnancy is associated with increased risk of: low birth weight, preterm birth and pyelonephritis[16,18,19].

UTI are the most frequent bacterial infections during pregnancy and GBS is responsible for 10% pyelonephritis cases, especially in the second trimester[19].

The incidence of invasive disease in pregnant women is 0.12 in 1000 live births and can cause: bacteremia (31%), endometritis (8%), chorioamniotitis (4%) and pneumonia (2%)[20].

Chorioamniotitis can reflect the intramniotic onset of GBS infection in the fetus. The diagnosis of chorioamniotitis is frequently established clinically, based on signs and symptoms as fever, abdominal distension, uterine tenderness, fetal and maternal tachycardia and purulent amniotic fluid[1].

3. Neonatal clinical manifestations

GBS infection in neonates has a bimodal distribution: early-onset infection (day 1 to 6) and late-onset infection (day 7 to 89).

In 80% of neonates with bacteremia the initial signs are respiratory (apnea, tachypnea, cyanosis, grunting respirations). Hypotension is seen in 25% of neonates with bacteremia. Other signs include fever or hypothermia, lethargy, palor or jaundice, abdominal distension[21].

Respiratory signs in neonates with pneumonia due to GBS infection appear within the first 24 hours of life[22]. Suggestive image for surfactant deficiency or infiltrates suggesting congenital pneumonia are seen in one third of neonates; pleural effusion and cardiomegaly are infrequent (Table 2)[23].

The most common initial expression of meningitis during early-onset infection is respiratory distress[24]. Half of neonates develop seizures within 24 hours of life. Coma, persistent seizures and a high CSF protein concentration (>3g/l) are associated with a poor prognosis[25]. In late-onset infection, meningitis is preceded by upper respiratory tract infections in 20-30% of the cases and hypotension or apnea are seen in 15% of neonates[25,26]. Also, besides the risk factors listed above, the presence of hypotension

Table 2 Clinical characteristics of GBS infection: Early-onset vs Late-onset*

	Early-onset	Late-onset
Median age at onset	Day 1	Day 37
Incidence of prematurity	Increased	Increased
Maternal obstetric complications	Frequent (70%)	Preterm birth
Clinical manifestations	Septicemia (80-85%)	Meningitis (25-30%)
	Meningitis (5-10%)	Bacteremia (65%)
	Pneumonia (5-10%)	Soft tissue/bone/joint (5-10%)
Case-fatality rate	3-10%	2-6%

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Table 3 Characteristics of septic arthritis and osteomyelitis in GBS disease*

	SEPTIC ARTHRITIS	OSTEOMYELITIS
Mean age at diagnosis (days)	20 (5-37)	31 (8-60)
Mean duration of symptoms (days)	1.5 (<1-3)	9 (1-28)
M:F	2:5	2:3
Site (%)	Hip (56) Knee (38) Ankle (6)	Humerus (56) Femur (26) Tibia, talus (4)
Mean duration of treatment (weeks)	2 (2-3)	3 (2-7)
Physical examination	Fixed flexion of the involved extremity Mild edema, local pain ± erythema, warmth	

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and low neutrophil levels (<1000/mm^3), increase the neurological sequelae[25]. In Table 3 are described by comparison the clinical characteristics of septic arthritis and osteomyelitis in late-onset GBS infection.

In late-onset GBS infection, cellulitis or adenitis can be seen. The mean age at the time of diagnosis of cellulitis is 5 weeks (2-11 weeks) and unlike other manifestations of GBS infection, there is a male predominance (72%). The most common sites are the face, submandibular and parotid. Besides local signs as unilateral facial, preauricular or submandibular edema, local erythema and enlarged adjacent lymphnodes, nonspecific signs can be encountered (fever, irritability, poor-feeding)[27].

In 0.5-3% of neonates, relapse or recurrence of GBS infection can occur, but this cases are frequently responsive to retreatment with penicillin or ampicillin. Signs can develop during treatment for the initial episode or after the completion of therapy, in the next 3 to 90 days. Relapse or recurrence of infection can develop as a result of: undrained focus of infection, reinvasion from persistently colonized mucous membranes (the gastrointestinal tract) and re-exposure to the source of infection (breast feeding)[28-30].

4. Laboratory diagnosis

The most frequent method of diagnosis used to detect GBS infection in neonates or maternal colonization is represented by culture of the microorganism from blood, CSF or a site of suppurative focus (bone, joint fluid, soft tissue). As recommended, the specimen from the mother should be collected during weeks 35-37 of pregnancy. After collection, the sample is placed in a non-nutritive transport media (eg. Stuart). The specimen sensitivity is maximum when the sample is kept at 4°C and processed within 24 hours[31-33].

The sample is transferred on an enrichment broth: Todd-Hewitt broth enriched with colistin 10µg/ml and nalidixic acid 15 µg/ml (Lim broth) or Todd-Hewitt broth enriched with gentamicin 8µg/ml and nalidixic acid 15 µg/ml (TransVag broth); and incubated at 36.1° C for 24 hours. The addition of 5% sheep blood can increase the sensitivity of the test[34].

For GBS detection can also be used: CAMP test; latex agglutination with group B streptococcal antisera; nucleic acid amplification test, such as PCR (see Table 4). In Romania, these tests are not used on a large scale.

5. Treatment

Management of GBS bacteriuria during pregnancy

Antibiotic treatment for asymptomatic bacteriuria reduces the risk of pyelonephritis and low-birth weight, without reducing the risk of preterm birth. In text box 1 are described the recommendations established by the Society of Obstetricians and Gynaecologists of Canada

Table 4 Tests used for GBS detection

	Specificity	Sensitivity	Commercial method/Continent	Advantages/Disadvantages
CAMP test	88.9%	98%	CAMP test/USA, EU	-False positive tests
Latex agglutination	99.5% (98-100)	57.3%	GBS Accuproe (USA) Strep B Latex Kit (Europe)	+ Low cost + Easy to perform
PCR	86.8-100%	75.3-99.6%	cfb PCR, scp $_B$PCR USA, EU	-Increased cost + Increased accuracy

Table 5 Antimicrobial regimen for GBS infection in neonates*

Manifestation of Infection	Antibiotic	Daily dose(iv)	Duration
Bacteriemia (without meningitis)	Ampicilllin+Gentamicin	150-200mg/kgc + 7.5mg/kgc	Initial treatment before culture results (48-72h)
	Penicillin G	200.000U/kgc	Complete a total treatment couse of 10 d
Meningitis	Ampicillin+Gentamicin	300-400mg/kgc + 7.5mg/kgc	Initial treatment (until CSF is sterile)
	Penicillin G	500.000U/kgc	Complete a total treatment couse of 14 d†
Septic arthritis	Penicillin G	200.000U/kgc	2-3 weeks
Osteomyelitis	Penicillin G	200.000U/kgc	3-4 weeks
Endocarditis	Penicillin G	400.000U/kgc	4 weeks‡

†4 weeks for ventricilitis; ‡In association with Gentamicin for the first 14 days

**From Morven S. Edwards, Victor Nizet. Group B streptococcal infections. Infectious Diseases of the Fetus and Newborn Infant. Seventh Edition, 2010. Page 447*

Management of GBS bacteriuria.SOGC Clinical Practice Guideline, JOGC 2012, 34(5):482–486

- Treatment of any bacteriuria with colony counts ≥10^5/ml;
- Asymptomatic bacteriuria with colony counts <10^5/ml should not be treated with antibiotics;
- Pregnant women with documented GBS bacteriuria, don't require screening during the third trimester;
- Documented bacteriuria during pregnancy (regardless the colony count) it's an absolute indication for intrapartum antibiotic prophylaxis.

(published in JOCG in may 2012) for management of GBS bacteriuria during pregnancy.

6. Management of GBS infection in neonates

In Table 5 are described the antibiotic regimens recommended for treatment of GBS infection in infants.

7. Prevention of GBS infection in neonates. International guidelines recommendations

In November 2008, CDC formed a technical working group to revise the 2002 guidelines, consisting 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 as experts in GBS epidemiology, clinical microbiology, and pharmacology; in 2010 CDC published the revised guideline for prevention of GBS disease. In text box 2 a series of recommendations are detailed.

Recommendations for prevention of GBS disease

Screening for detection of GBS colonization should be performed between wk 35-37 of pregnancy.

Antibiotic intrapartum prophylaxis is recommended in case of:

- Previous birth of a child with GBS infection;
- GBS bacteriuria during pregnancy;
- Positive screening culture for GBS;
- Unknown GBS status at the onset of labor and any of the following: delivery at <37 wk gestation, amniotic membrane rupture ≥18 hours, intrapartum temperature ≥38.0°C, intrapartum RT-PCR positive for GBS.

Antibiotic prophylaxis is not indicated in case of:

- 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.

In case of signs or symptoms of preterm labor and preterm premature rupture membrane, the women should be managed according to algorithm in figure 1 and Figure 2 respectively (according to CDC. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010; 59 (No. RR-10) [pag 1-32]).

Agents used for intrapartum prophylaxis are described in Figure 3. The use of Erythromycin is no longer recommended, due to the risk of resistance. In USA the resistance rate is estimated between 25-32% and for Clindamycin between 13-20% (UK 10%); therefore is recommended the use of antimicrobial test susceptibility and D test.

The evaluation of newborns according to the algorithm in Figure 4 allows the early detection of sepsis.

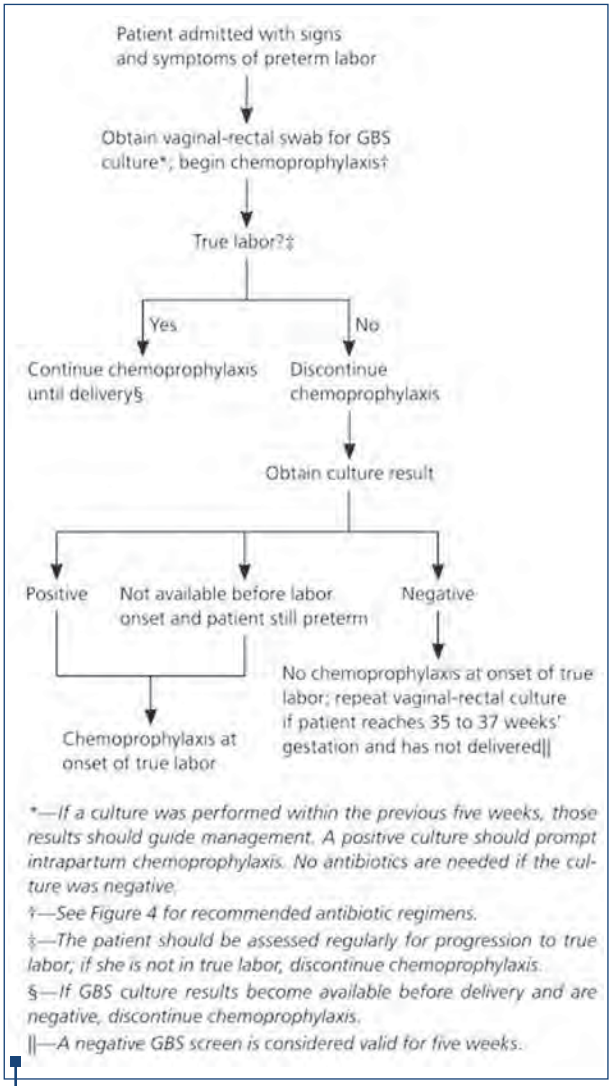


Figure 1. Algorithm for screening for GBS colonization and use of intrapartum prophylaxis for women with preterm labor - CDC. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010; 59(No. RR-10) [pag 1-32]

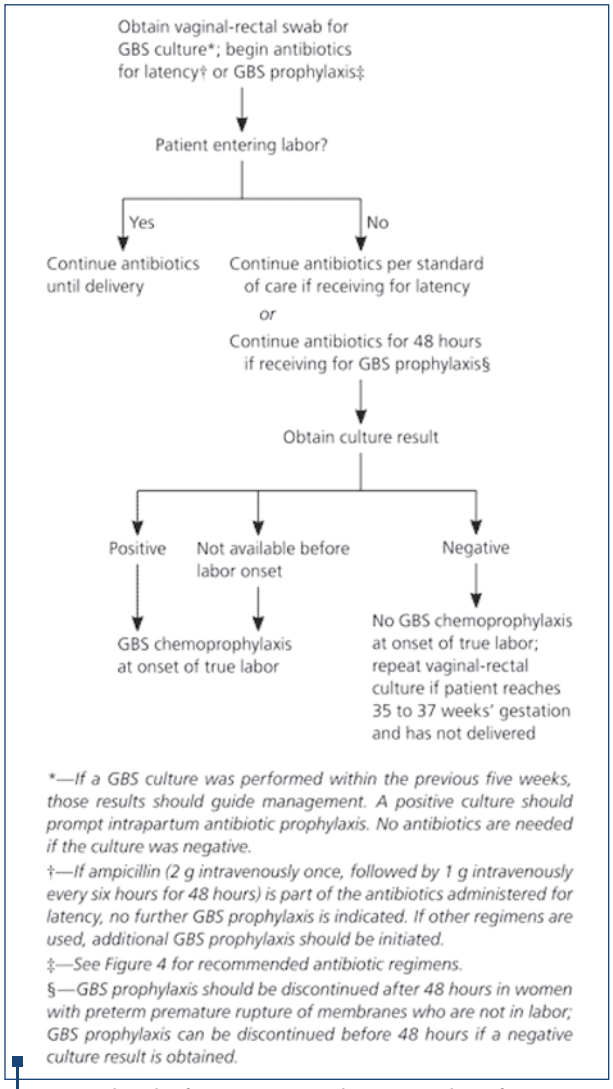


Figure 2. Algorithm for screening GBS colonization and use of intrapartum prophylaxis for women with preterm premature rupture of membrane (pROM) - CDC. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010; 59(No. RR-10) [pag 1-32]

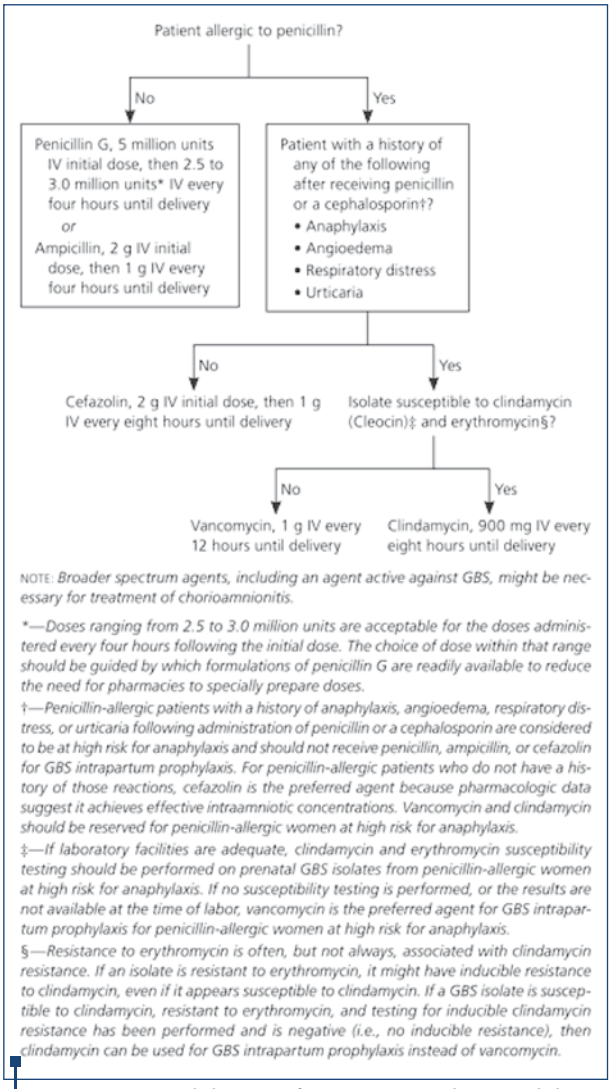


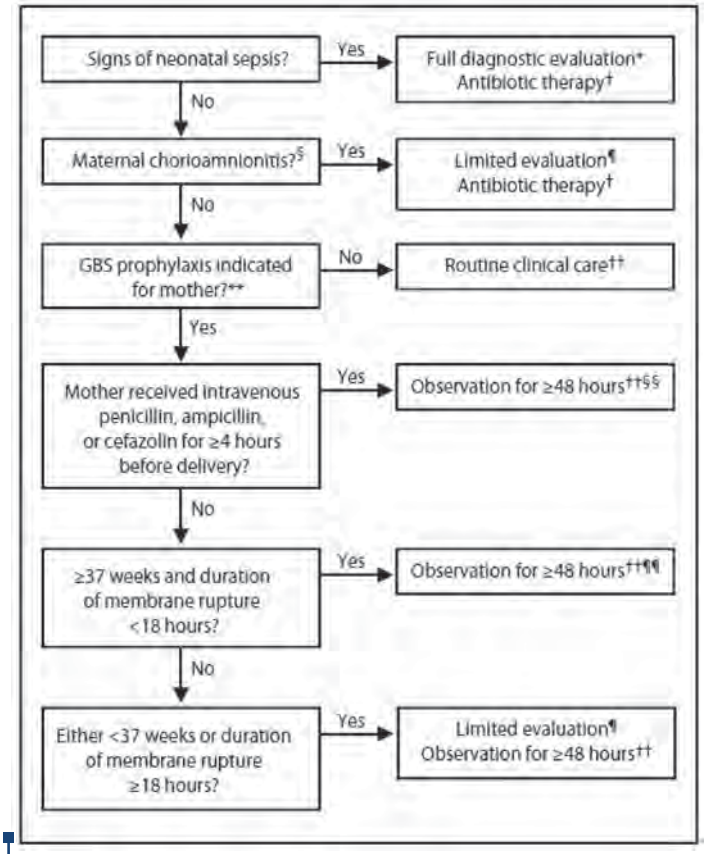
Figure 3. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset GBS - CDC. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010; 59(No. RR-10) (pag 1-32)

In Romania, screening for GBS infection is recommended during weeks 35-37 of pregnancy, but probably this is not performed systematically throughout the country. According to the Clinical Guide for Obstetrics and Gynecology no. 4, annex 12, published in the Official Monitor no. 88 bis/February 2010, antibiotic therapy is recommended in case of preterm labor or pROM (preterm rupture of membrane) if the patient had a positive culture with GBS during pregnancy, bacteriuria with GBS or previous birth of a child with GBS infection.

The main recommendations of the latest international guidelines for management of GBS infection are:

- Pregnant women should perform monthly urine summary and urine culture;
- Antibiotic therapy will be initiated in case of asymptomatic bacteriuria with ≥ 10^5 UFC/ml or symptomatic UTI;
- Pregnant women with symptomatic or asymptomatic bacteriuria will not perform screening culture in weeks 35-37 and they will receive intrapartum antibiotic prophylaxis;
- Screening culture will be performed during weeks 35-37 of pregnancy;
- In case of a positive screening culture, intrapartum antibiotic prophylaxis will be administered;
- The result of a culture is considered valid for 5 weeks; in case of an onset of labor after this period, intrapartum antibiotic prophylaxis will be initiated and an intrapartum culture will be performed;
- In case of preterm birth or premature rupture membrane, the algorithms described above should be followed.

GBS continues to be one of the major perinatal pathogen. Universal screening at weeks 35-37 of pregnancy and intrapartum antibiotic prophylaxis are the basis of the prevention strategy and should be implemented in all departments of obstetrics and gynecology. ■



*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 figure 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.

Figure 4. ***Algorithm for secondary prevention of early-onset GBS disease among newborns - CDC. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010; 59 (No. RR-10) (pag 1-32)***

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