Management of the infant at increased risk for sepsis

Canadian Paediatric Society

Neonatal sepsis continues to cause a significant proportion of perinatal mortality and long-term morbidity in the term and preterm infant population. The most common single organism that causes early-onset neonatal sepsis is the group B streptococcus (GBS or *Streptococcus agalactiae*) (1). Invasive early-onset GBS disease has an incidence of approximately two per 1000 live-born infants in the absence of intrapartum antibiotic prophylaxis (IAP) (2,3), with a case-fatality rate of between 2% and 13% in recent studies (4-6). Therefore, preventive strategies have been promoted and recently endorsed by the Society of Obstetricians and Gynaecologists of Canada (7). It has been demonstrated that the administration of intravenous penicillin at least 4 h before delivery to mothers colonized with GBS is highly effective in preventing perinatal transmission and early-onset invasive infection in the newborn (8). The recommendations are to screen all mothers with rectovaginal cultures at 35 to 37 weeks, and treat those with positive cultures for GBS at the time they present in labour. This strategy leads to as many as 22% of all mothers in labour at term being treated with IAP to prevent disease in 0.2% of infants and prevent mortality in 0.01% of infants (9). In the United Kingdom, it was calculated that it would require 24,000 antepartum cultures and 7000 women in labour treated with antibiotics to prevent one neonatal death (10). As a consequence, other authorities have developed different recommendations, questioning whether routine IAP is an appropriate use of resources (10,11), and whether the pressure exerted for the development of bacterial resistance is justified. In Canada, the current incidence of invasive neonatal GBS disease is uncertain because there is no centralized or mandatory reporting system.

PURPOSE OF THE STATEMENT

The aim of the present statement is to develop evidence-based practice guidelines answering the following question: How should an infant be monitored, investigated and treated given the presence of clinical signs of sepsis, the GBS culture status of the mother (positive, negative or unknown), the treatment status of the mother (completed, incomplete or no IAP), and the presence or absence of maternal risk factors for neonatal sepsis?

METHODS OF STATEMENT DEVELOPMENT

A search was carried out in MEDLINE and the Cochrane library, and last updated in January 2006. The MEDLINE search terms were '*Streptococcus agalactiae*' and 'newborn'. The hierarchy of evidence from the Centre for Evidence-Based Medicine (United Kingdom) was applied and, for this statement, the levels of evidence for treatment, prognosis and diagnosis were used (www.cebm.net, click on the EBM Tools tab or www.cebm.net/levels_of_evidence.asp#levels).

DEFINITIONS

Limited diagnostic evaluation

Limited diagnostic evaluation consists of a complete blood count (CBC), and observation of vital signs every 4 h for a period of 24 h. The newborn can be cared for and observed in the mother's postpartum room. If the CBC shows a low total white blood cell (WBC) count of less than 5.0×10^9/L, then the risk of sepsis is substantially increased and a full diagnostic evaluation and initiation of therapy would usually be indicated.

Full diagnostic evaluation

Full diagnostic evaluation consists of a CBC, blood culture and lumbar puncture (LP); a chest x-ray should be obtained if respiratory difficulties are present. LP can be deferred in unstable infants, and performed later to ascertain the presence of hypoglycorrhachia or pleocytosis. Infants whose only sign of sepsis is respiratory distress may also be considered for deferment of LP if close follow-up can be ensured.

THE UNWELL INFANT

The initial signs of sepsis may be subtle, and may include temperature instability, tachycardia, poor peripheral perfusion and respiratory distress. Because the progression of invasive disease is very rapid, any infant with clinical signs suggestive of infection should be treated immediately following a prompt full diagnostic evaluation; delay between presentation and therapy increases the risk of a poor outcome (12) (evidence level 2b). There is no clear distinction in the clinical signs present when the infant has GBS sepsis compared with any other invasive organism.

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Table 1
Empirical therapy for infants with positive cerebrospinal fluid (CSF) evaluation

CSF findings	Most common organisms	Suggested expectant antimicrobials for early-onset meningitis
Gram-positive cocci	Group B streptococci, less commonly: *Staphylococcus* species or enterococci	Ampicillin or penicillin plus gentamicin
Gram-positive rods	*Listeria monocytogenes*	Ampicillin plus gentamicin
Gram-negative rods	*Escherichia coli,* less commonly: *Klebsiella, Pseudomonas* and *Citrobacter*	Cefotaxime plus gentamicin
Gram-negative cocci	Uncommon	Cefotaxime
Pleocytosis, or other findings strongly suggestive of meningitis, but Gram stain-negative, or too unstable to have an LP	Any of the above are possible	Ampicillin plus gentamicin

LP Lumbar puncture. Source: Canadian Paediatric Society, 2007

Although IAP with a penicillin dramatically reduces the frequency of early-onset invasive GBS disease, it does not affect the frequency of sepsis caused by other organisms (1,13) (evidence level 2b). Of note, invasive GBS can still occur in infants of mothers who have had a negative screening culture at 35 to 37 weeks; now that IAP is widespread and effective, the majority of the remaining infants with invasive GBS are those whose maternal cultures were negative (14), but who became colonized between screening and delivery (evidence level 2b). Also, invasive GBS disease is still possible, even if very rare, in mothers who received adequate IAP (15) (evidence level 4). Thus, neither the maternal screening history nor intrapartum exposure to antibiotics should affect the approach to the management of the infant with clinical signs of sepsis (recommendation category B). Therefore, prospective therapy, while awaiting culture results, should cover the most common bacteria: GBS, other streptococci, *Escherichia coli*, other Gram-negative organisms and *Listeria monocytogenes*.

An infant with signs of sepsis does not require confirmatory tests other than obtaining cultures before commencing therapy, because no other tests have an adequately high negative predictive value to avoid therapy (evidence level 2a). In particular, a normal WBC count or differential should not prevent treatment in such an infant because the negative likelihood ratio of a normal CBC is approximately 0.7 (recommendation grade B) (16).

Empirical therapy
There are no good prospective studies to indicate optimal choice of therapy in the newborn infant with possible sepsis (17), but ampicillin and gentamicin are usually appropriate based on the usual susceptibilities of the predominant organisms causing early-onset sepsis (evidence level 4). Infants with a positive cerebrospinal fluid (CSF) evaluation or with clinical signs of meningitis if the LP has been deferred, should be treated with antibiotics which both penetrate the CSF and are active against the likely organisms (Table 1). If there is information from the maternal history suggesting an organism that is unlikely to respond to these antibiotics, empirical therapy should be adjusted appropriately. Blood cultures using modern automated systems are almost always positive by 48 h (18). Therefore, if the laboratory results and clinical course do not indicate bacterial infection, therapy may be discontinued after 48 h. The majority of antibiotic courses are given to infants who eventually prove not to have had sepsis; strategies for further reduction of the duration of antibiotic therapy in such infants should be considered. For example, because gentamicin is usually now given once per day in the full-term infant, and ampicillin is given every 12 h, the initial antibiotic order could be to give ampicillin for four doses every 12 h and gentamicin for two doses every 24 h, followed by reassessment after verification of culture results at 48 h, and reordering the antibiotics in case of positive cultures (or ongoing signs of sepsis).

WELL-APPEARING INFANT OF A GBS-POSITIVE MOTHER, WHO RECEIVED IAP MORE THAN 4 H BEFORE DELIVERY

IAP with a penicillin for least 4 h is highly effective at eradicating GBS transmission (19), and thus preventing the majority of invasive neonatal GBS disease (evidence level 1b) (20). Therefore, if a GBS-positive woman receives intrapartum antibiotics for at least 4 h before delivery and if the newborn appears healthy and is more than 35 weeks gestational age, the newborn requires no therapy for prevention of early-onset GBS (recommendation grade A).

If the baby remains well at 24 h of age and is otherwise eligible for discharge at this time, early discharge can be contemplated provided the caregiver knows the appropriate resources in the community for accessing health care and is able to transport the baby immediately to a health care facility if clinical signs of sepsis develop.

There is insufficient information regarding the efficacy of alternative antibiotics (used when the mother is at risk of anaphylaxis from penicillin). Such infants should be managed as if the mother received incomplete IAP (next heading) until further data are available.

WELL-APPEARING INFANT OF A GBS-POSITIVE MOTHER WHO RECEIVED IAP LESS THAN 4 H BEFORE DELIVERY OR NOT AT ALL

The risk of invasive early-onset GBS disease in an infant whose mother is GBS-positive and does not receive IAP is approximately 1% (21). Only one-quarter of these babies are asymptomatic at birth. This risk of significant disease probably does not justify routine empirical treatment in these circumstances, and careful observation with treatment at the first clinical sign of infection appears to be reasonable. Ninety-five per cent of infants with early-onset GBS infection present with clinical signs within 24 h (22) (either temperature instability, tachycardia, poor peripheral perfusion, respiratory distress or abnormal CBC). Four per cent of infected infants present between 24 h and 48 h of age, with only 1% developing signs after 48 h of age. Thus, prolonging hospitalization from 24 h to 48 h would require the observation of more than 2000 infants to detect each case of invasive infection. Therefore, if careful assessment of the infant at 24 h confirms that they remain well, discharge at that time may well be appropriate as long as adequate patient education and follow-up are ensured.

The use of the CBC is sometimes promoted for determining risk, both for GBS and for other organisms, among infants who are at elevated risk but appear well. However, the positive predictive value of an abnormal CBC is low in the newborn and it is, therefore, uncertain how to proceed when an infant is clinically well but has an abnormal CBC; unfortunately, most studies investigating the usefulness of the CBC have not been confined to well-appearing infants and, therefore, their usefulness in this specific situation is somewhat conjectural. One study (23) confined to well-appearing term infants showed a positive predictive value of 1.5% of an 'abnormal' CBC (total WBC of 5.0×10^9/L or lower, or 30×10^9/L or greater, or an absolute polymorphonuclear cell count of less than 1.5×10^9/L or an immature to mature polymorphonuclear cell ratio greater than 0.2) in identifying the development of 'clinical sepsis' in 1665 healthy term infants who were at risk; of note, none of these infants developed a positive blood culture (evidence level 2b).

Several scoring systems have been developed for analyzing CBC results (24), and all involve analysis of the count of immature neutrophils, but there is very wide interobserver variability in the identification of immature or 'band' neutrophils (25). Even the best scoring system only achieves a likelihood ratio of between four and eight (24) (evidence level 2a). Finding a 'left-shift' or an elevated total WBC count is not sufficiently predictive to alter management. The individual finding on a CBC with the highest positive predictive value is a low total WBC count of less than 5.0×10^9/L; if this finding is present, the likelihood ratio is between 10 and 20 (16), leading to a post-test probability of sepsis of approximately 10% to 20% (evidence level 2b) and, therefore, probably justifying treatment even in a well-appearing infant after a full diagnostic workup. However, only between 22% and 44% of infants with sepsis will have such a low total WBC count (16).

WELL-APPEARING INFANT OF A GBS-NEGATIVE MOTHER WHO HAD RISK FACTORS AT DELIVERY

Before the recommendation for universal culture-based screening, IAP was recommended for mothers with any one of the following five risk factors: over 18 h rupture of membranes, pyrexia higher than 38°C, premature labour at less than 36 weeks, GBS bacteriuria at anytime during pregnancy or previous child with invasive GBS disease. These risk factors were present in as many as 22% of mothers, and only identified approximately 50% of infants who eventually developed invasive GBS disease (26,27) (evidence level 2b).

Although invasive GBS disease does occur in infants whose mothers have negative screening cultures at 35 to 37 weeks, the risk is very low even in those with prolonged rupture of membranes or intrapartum pyrexia (28) (evidence level 2b). It is suggested that a limited diagnostic evaluation be performed in this newborn population (recommendation grade B).

WELL-APPEARING INFANT OF A MOTHER WITH UNKNOWN GBS STATUS AND NO RISK FACTORS

A mother who has not had an antenatal GBS culture or whose results are not readily available, and her newborn baby, should be managed according to the risk factors listed in the previous section. In the absence of these risk factors, and if the baby remains well, no specific intervention is required (recommendation grade B).

WELL-APPEARING INFANT OF A MOTHER WITH UNKNOWN GBS STATUS WITH RISK FACTORS

The five risk factors mentioned above occur in approximately 20% of deliveries at term, and are present in approximately 50% of infants with invasive GBS disease (26,27). This fourfold increase in risk to the infant in a mother with unknown GBS status has led to the recommendation that she should receive IAP (7). In this circumstance, the infant should be treated in the same way as he or she would be treated if the mother were GBS-positive (ie, IAP more than 4 h before delivery and routine neonatal care; IAP less than 4 h or no IAP, limited diagnostic evaluation and minimum 24 h observation) (recommendation grade B).

THE LATE PRETERM INFANT

The mother who delivers at less than 37 weeks will often not have results of antenatal GBS screening available. In such a case, the infant has a 'risk factor' (prematurity) for invasive GBS disease and, if he or she appear well, should have a limited diagnostic evaluation. Infants of this gestational age should not be discharged before 48 h at the earliest (Figure 1).

CHORIOAMNIONITIS

Chorioamnionitis is a difficult condition to diagnose because the prevalence of pyrexia during labour is high
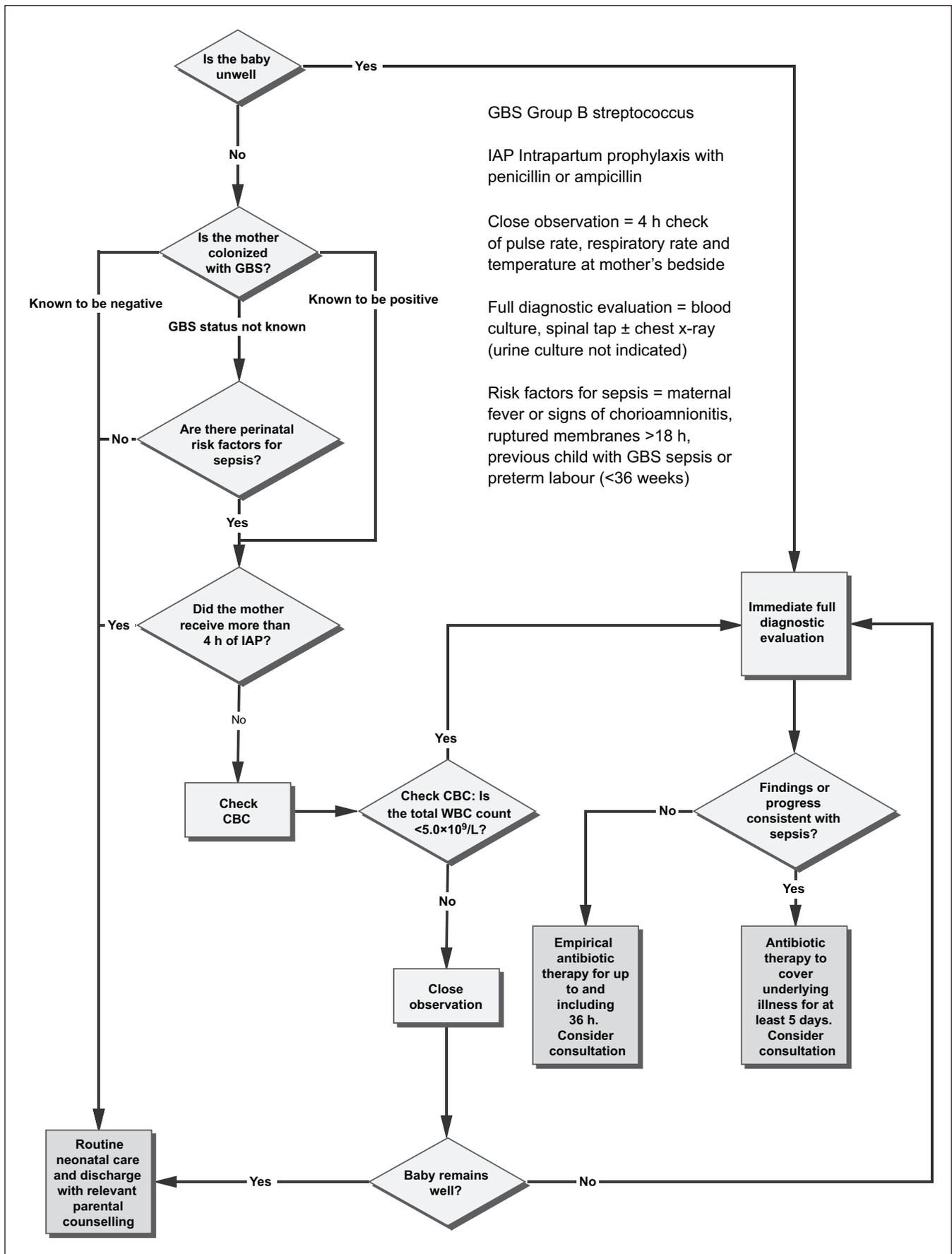
Is the baby unwell — Yes

No

Is the mother colonized with GBS?

Known to be negative

Known to be positive

GBS status not known

Are there perinatal risk factors for sepsis? — No

Yes

Did the mother receive more than 4 h of IAP? — Yes

No

Check CBC

Check CBC: Is the total WBC count <5.0×10⁹/L? — Yes

No

Close observation

GBS Group B streptococcus

IAP Intrapartum prophylaxis with penicillin or ampicillin

Close observation = 4 h check of pulse rate, respiratory rate and temperature at mother's bedside

Full diagnostic evaluation = blood culture, spinal tap ± chest x-ray (urine culture not indicated)

Risk factors for sepsis = maternal fever or signs of chorioamnionitis, ruptured membranes >18 h, previous child with GBS sepsis or preterm labour (<36 weeks)

Immediate full diagnostic evaluation

Findings or progress consistent with sepsis? — No

Yes

Empirical antibiotic therapy for up to and including 36 h. Consider consultation

Antibiotic therapy to cover underlying illness for at least 5 days. Consider consultation

Routine neonatal care and discharge with relevant parental counselling — Yes

Baby remains well? — No

Figure 1) *Algorithm for the management of newborn babies who may be at risk for neonatal sepsis. Source: Canadian Paediatric Society, 2007*

(29), especially if the mother has had epidural analgesia (30). Other signs of chorioamnionitis are less frequent; there is poor correlation between clinical signs of chorioamnionitis and histology (29). Therefore, chorioamnionitis is frequently classified as 'possible', when the main sign is fever, and 'definite', when the classical triad of fever, left-shift in the WBC and lower uterine tenderness is present.

The risk of sepsis (which may be due to a variety of different organisms, including GBS, *E coli* and other Gram-negative organisms) in an infant whose mother had definite chorioamnionitis is approximately 8%, and is approximately 3% to 4% if 'possible' and 'definite' chorioamnionitis are considered together (31,32) (evidence level 2b); among all mothers with fever, the incidence is 2% to 6% depending on the height of the fever (31) (evidence level 2b). Infants who do not have signs at birth are unlikely to develop sepsis, the odds ratio for sepsis among infants who are well at birth is 0.26 (95% CI 0.11 to 0.63) (31). The incidence of invasive infection in the present study in an initially well-appearing infant with a maternal history of fever or chorioamnionitis was less than 2%, and this is confirmed by other data (33) (evidence level 2b). Therefore, it seems reasonable to perform a CBC and closely observe such an infant, and to only perform a full diagnostic evaluation and treat with antibiotics if the CBC is strongly suggestive of infection (low total WBC count) or if clinical signs develop. A requirement for extensive resuscitation at birth should be considered a sign of possible infection in such infants (32,33).

RECOMMENDATIONS

- Any newborn infant with clinical signs suggestive of sepsis should have an immediate full diagnostic evaluation followed by the institution of empirical antibiotic therapy without delay (recommendation category B).

- If a mother who is GBS-positive receives IAP with a penicillin more than 4 h before delivery, no further evaluation or observation for invasive GBS disease in a well-appearing infant is required (recommendation category A).

- If a GBS-positive woman receives IAP less than 4 h before delivery (or receives no antibiotics or a nonpenicillin regimen), then a limited diagnostic evaluation is required, and the infant should not be discharged before 24 h of age. At the time of discharge, the infant should be evaluated and the parents should be educated regarding signs of sepsis in the newborn. Discharge at 24 h to 48 h is conditional on the parents' ability to immediately transport the baby to a health care facility if clinical signs of sepsis develop (recommendation grade B).

- If the CBC reveals a total WBC count less than 5.0×10^9/L, full diagnostic evaluation and empirical antibiotic therapy should be considered (recommendation grade B).

- If a GBS-negative woman with risk factors delivers a baby who remains well, the infant does not require evaluation for GBS (recommendation grade B).

- If a woman with unknown GBS status and with risk factors at the time of delivery receives IAP more than 4 h before delivery, the infant requires no specific intervention (recommendation grade B).

- If a woman with unknown GBS status and with risk factors at the time of delivery receives IAP less than 4 h before delivery, limited diagnostic evaluation is required and the infant is not discharged before 24 h of life (recommendation grade B).

- The well-appearing infant born at less than 36 weeks gestation with an unknown maternal GBS status should have a limited diagnostic evaluation and is not a candidate for early discharge.

- The well-appearing infant of a mother with possible chorioamnionitis requires a limited diagnostic evaluation for sepsis (recommendation grade B).

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