

Position Statement

Management of term infants at increased risk for early-onset bacterial sepsis

Ann L. Jefferies; Canadian Paediatric Society, Fetus and Newborn Committee, Ottawa, Ontario

Correspondence: Canadian Paediatric Society, 100-2305 St Laurent Blvd, Ottawa, Ontario K1G 4J8. E-mail info@cps.ca, website www.cps.ca.

Abstract

Early-onset neonatal bacterial sepsis (EOS) is sepsis occurring within the first 7 days of life. This statement provides updated recommendations for the care of term (≥ 37 weeks' gestational age) newborns at risk of EOS, during the first 24 hours of life. Maternal Group B streptococcus (GBS) colonization in the current pregnancy, GBS bacteriuria, a previous infant with invasive GBS disease, prolonged rupture of membranes (≥ 18 hours) and maternal fever (temperature $\geq 38^\circ\text{C}$) are the factors most commonly associated with EOS. These risk factors are additive; the presence of more than one factor increases the likelihood of EOS. At present, there is no laboratory test, including white blood cell indices, that has sufficient sensitivity to allow clinicians to safely rule out EOS. All unwell infants with clinical signs suggesting sepsis must be treated empirically with antibiotics, once cultures have been taken. The management of well-appearing, at-risk term infants depends on the number of risk factors (including maternal GBS colonization) and whether maternal intrapartum antibiotic prophylaxis for GBS was used. In some cases, management should be individualized. Careful assessment and observation of these at-risk infants are a fundamental component of appropriate care.

Keywords: Chorioamnionitis; Early-onset sepsis; Group B streptococcus; Newborn

BACKGROUND

Early-onset neonatal bacterial sepsis (EOS) has been defined as sepsis occurring within the first 7 days of life (1); most infants become symptomatic within 24 hours of birth (2–4). EOS usually results from vertical transmission and, consequently, is associated with organisms that colonize the birth canal. Organisms can ascend to the amniotic fluid, colonizing the infant or the infant may become colonized during passage through the birth canal. Invasive infection may occur if the skin barrier is breached. Aspiration of infected fluid or transplacental passage of organisms may also result in invasive infection. Following implementation of universal maternal screening for Group B streptococcus (GBS) and intrapartum antibiotic prophylaxis (IAP), the incidence of early-onset GBS (EOGBS) infection has decreased without concomitant decrease in the incidence of other pathogens. The net result has been an overall decrease in the incidence of EOS. In 2013, 0.5% of infants admitted to Canadian neonatal intensive care units had EOS (5). In the USA, the overall incidence of EOS has been estimated at 0.77 cases per 1000 live births, with a case fatality rate of 10.9% (6). Incidence and case fatality rates decrease with increasing gestational age (GA).

In 2007, the Canadian Paediatric Society published recommendations for management of infants at increased risk of EOS (7). Subsequently, guidelines were published by the United States Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) (1,8–10). As the incidence of EOS is declining, new questions are being raised about the utility of predictive tools and the exposure of well-appearing newborns to antibiotics (11,12). This statement provides updated recommendations for the care of term (≥ 37 weeks' GA) newborns with risk factors for EOS, during the first 24 hours of life.

METHODS

A search of MEDLINE and the Cochrane database was undertaken and updated in 2015. Search terms included 'early-onset sepsis', 'neonatal sepsis', 'neonatal meningitis', 'chorioamnionitis', 'intrapartum fever' and 'prolonged rupture of membranes'. Reference lists of published guidelines and articles were reviewed. Chosen articles focused on term populations; those restricted to late-onset sepsis were excluded. A modification of the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system was used to describe the recommendations (13).

MATERNAL AND NEONATAL RISK FACTORS FOR EARLY-ONSET SEPSIS

Risk factors

The risk factors associated most frequently with EOS in term infants are summarized in Table 1 (1,14,15). The presence of more than one factor increases the likelihood of EOS (15–17). Recent case-control studies have shown 'dose-dependent' rather than dichotomous relationships between the degree of maternal fever, duration of ruptured membranes and lower GA with increasing risk of EOS (17,18). Puopolo et al. have developed a calculator which considers maternal GBS status, intrapartum antibiotic exposure, GA, highest maternal temperature and duration of membrane rupture to estimate the probability of EOS for asymptomatic babies (17,19). Validation of this algorithm is in progress.

Table 1. Maternal and neonatal risk factors for early-onset bacterial sepsis in term infants

- Maternal intrapartum GBS colonization during the current pregnancy
- GBS bacteriuria at any time during the current pregnancy
- A previous infant with invasive GBS disease
- Prolonged rupture of membranes ≥ 18 h
- Maternal fever (temperature $\geq 38^\circ\text{C}$)

GA Gestational age; GBS Group B streptococcus

GBS colonization and IAP

In the absence of IAP, approximately 1% to 2% of infants born to mothers colonized with GBS develop EOGBS sepsis. Current guidelines recommend screening pregnant women for GBS colonization at 35 weeks' to 37 weeks' GA and providing IAP for those who screen positive as well as for those with GBS bacteriuria or a previous GBS-infected infant (1,14). If GBS status is unknown, IAP should be offered if any other risk factors (Table 1) are present. Adequate IAP consists of at least one dose given at least 4 hours before birth of:

- IV penicillin G (initial dose 5 million units) or ampicillin (initial dose 2 g)

OR

- IV cefazolin (initial dose 2 g) if the mother is allergic to penicillin but at low risk for anaphylaxis

Penicillin-allergic women with a high risk of anaphylaxis should be treated with IV clindamycin when the GBS isolate is sensitive to clindamycin and erythromycin OR with IV vancomycin when the isolate is resistant to clindamycin or susceptibilities are unknown. Because the efficacy of the latter two regimes has not been confirmed in clinical trials, they should be considered inadequate IAP when managing the neonate (1). IAP is not recommended when a caesarean section is performed before onset of labour when membranes are intact, regardless of GBS status (1). It should be noted that IAP does not reduce the incidence of late-onset GBS disease.

INVESTIGATIONS FOR EARLY-ONSET SEPSIS

Bacterial cultures

A positive neonatal blood culture remains the gold standard for diagnosing neonatal sepsis, recognizing that maternal antimicrobial therapy may inhibit bacterial growth. Blood may be drawn by peripheral venous or arterial puncture or from a newly inserted catheter, using aseptic technique. An *in vitro* study showed that at least 1 mL of blood is required for optimal recovery of microorganisms in low-colony-count sepsis (20). Drawing blood cultures from multiple sites does not appear to improve the yield of pathogens (21).

Meningitis is uncommon in newly born infants (incidence 0.25 to 1 per 1000 live births) (22) and it remains controversial whether a lumbar puncture (LP) should be performed routinely as part of the initial investigation for EOS, particularly for term infants (23,24). In asymptomatic term infants investigated for EOS, no cases of meningitis were reported in three large observational studies (2,21,22). Meningitis was similarly very uncommon (0% to 0.3%) in preterm infants investigated for EOS because of respiratory distress (25,26). However, newborns with positive blood cultures are more likely to have meningitis (27–29). Furthermore, 8% to 40% of infants with early-onset meningitis are reported to have negative blood cultures (27–30). These data suggest that an LP should be performed at the outset when there is a strong clinical suspicion of EOS or when signs of meningitis (seizures, bulging fontanelle, irritability, altered neurological status) are present. The LP can be deferred in unstable infants until their condition improves. For term newborns with respiratory distress only, the LP could also be deferred if the infant is monitored closely. An LP must be done whenever the blood culture is positive. The cerebrospinal fluid (CSF) culture may be negative when the LP is performed after antibiotics have been started but pleocytosis,

low glucose and/or elevated protein concentration may be observed with meningitis. In term infants, a CSF white blood cell (WBC) count of >20 to 25 cells/ mm^3 is considered abnormal; this value has a sensitivity of 79% and specificity of 81% for diagnosing bacterial meningitis (29). Culture-positive bacterial meningitis may be present with a normal CSF WBC count (29,30).

Cultures of urine, gastric aspirates and body surface have limited value in the evaluation for EOS and are not recommended for newly born infants (16).

Biomarkers

A complete blood count (CBC) is the most readily available, rapid and economical investigative test for sepsis. Studies have examined individual WBC indices, including total WBC count, absolute neutrophil count (ANC) and ratio of immature to total neutrophils (I:T ratio), as well as combinations. Following birth, the neutrophil count of healthy term neonates rises, peaking between 6 and 8 hours of age; higher counts are associated with labour and duration of labour, likely because increasing catecholamine levels stimulate demargination of neutrophils (31–33). Four recent studies examined large cohorts of term and late preterm infants, many of whom were asymptomatic but investigated because of septic risk factors (4,33–35). A low total WBC count ($<5 \times 10^9/\text{L}$) or low ANC ($<1.5 \times 10^9/\text{L}$) was more likely to be associated with EOS than an increased I:T ratio (>0.2) or high total WBC ($>30 \times 10^9/\text{L}$). The positive predictive accuracies of all WBC indices were low, as were the sensitivities, the latter drawing into question the tests' role in allowing clinicians to confidently rule out sepsis (35).

The predictive abilities of WBC indices improve with time after birth. After 4 hours, the likelihood ratio in detecting sepsis for a WBC count $<5 \times 10^9/\text{L}$ was 80.5, for ANC $<1 \times 10^9/\text{L}$ was 115, and for an I:T ratio >0.6 was 10.7 (33). This means that in newborns with an abnormal test, the post-test probability of sepsis increased significantly. However, for most asymptomatic infants, who have a low pre-test probability for sepsis, WBC indices demonstrate only modest likelihood ratios which are not helpful for confidently ruling in or ruling out sepsis (33,36). When there is clinical uncertainty in well infants (e.g., multiple risk factors, chorioamnionitis), WBC indices, particularly in combination, may be of some help if obtained after 4 hours of age (18,33,36). Waiting to obtain a CBC should never delay investigation and starting antibiotics when clinical signs of sepsis are present.

Reported sensitivities for EOS of C-reactive protein (CRP), an acute-phase protein synthesized in response to tissue injury, vary widely; sensitivity is lowest early in the infectious process (37). The diagnostic accuracy of a single CRP at the time of initial investigation is poor, and a normal result should not delay initiation of antibiotics for a symptomatic infant. CRP measured serially may be helpful in determining duration of empiric antibiotic therapy. However, multiple conditions can be associated with the inflammatory response and a single elevated CRP should not be used to prolong antibiotic therapy (38). Although procalcitonin, a peptide precursor of calcitonin, has shown moderate-to-good accuracy in the diagnosis of EOS (39,40), it is not readily and rapidly available. The utility of other biomarkers, including interleukin-6, interleukin-8, tumour necrosis factor and neutrophil CD64, on their own or combined with WBC indices, requires confirmation.

MANAGEMENT

Unwell infants

Initial signs of sepsis may be subtle and include respiratory distress, temperature instability, tachycardia, seizures, hypotonia, lethargy, poor peripheral perfusion, hypotension and acidosis. In an analysis of 2785 symptomatic and asymptomatic infants with birth weights ≥ 2000 g, the sensitivity and negative predictive value of clinical signs were 92% and 99%, respectively, in contrast to sensitivities of $<50\%$ for low ANC and increased I:T ratio (2). Because invasive disease can progress rapidly, all infants with clinical signs of sepsis must be treated immediately with intravenous antibiotics following prompt investigation that includes a CBC, blood culture and LP as well as chest x-ray if respiratory distress is present. No screening tests have sufficiently high sensitivity to prevent therapy. Although the CBC is not a useful screening test, septic infants frequently have abnormal values and a CBC should be done at the time of initial blood culture.

Negative maternal GBS cultures or use of intrapartum antibiotics, including GBS IAP, should not change management of symptomatic infants. GBS disease occurs in the presence of negative maternal GBS cultures (9) and, occasionally, following adequate IAP. IAP does not affect the frequency of sepsis caused by other organisms (41).

Respiratory distress is a common initial presentation of many term newborns, especially after caesarean section, and often resolves within several hours. Infants who appear stable and lack perinatal risk factors for sepsis can be observed closely for up to 6 hours to determine whether respiratory distress resolves before investigating for sepsis and starting antibiotics (18).

Empirical antibiotic therapy should be directed toward the most common bacteria associated with EOS. In term infants born in Canada and the USA, the most common pathogen is GBS followed by *Escherichia coli*, *Streptococcus viridans*, *Streptococcus pneumoniae*, *Enterococcus*, *Enterobacter*, *Staphylococcus aureus* and *Haemophilus influenzae* (42). EOS as a result of *Listeria monocytogenes* is now very uncommon, but incidence may increase during outbreaks related to food contamination. Ampicillin and an aminoglycoside provide coverage for GBS, *E coli* and most other common pathogens. Knowledge of maternal symptoms and culture results, as well as local sensitivity patterns, should be taken into account. When meningitis is suspected, infants should receive antibiotics that penetrate into CSF, in appropriate doses. When cultures are positive and sensitivities determined, therapy can be modified to the most appropriate antimicrobial agents.

Well-appearing term infants with risk factors

The incidence of EOS in asymptomatic term infants with risk factors (Table 1), including maternal GBS colonization, is very low (~1%) (2,4), but is still higher than for the general birth population. Clinicians must balance not treating the small number of infected infants with minimizing invasive investigation and antibiotic exposure for many at-risk but well infants without infection (Figure 1).

GBS-positive mothers with adequate IAP, no additional risk factors

If a GBS-positive woman receives adequate IAP and her infant appears healthy, no investigation or treatment is necessary. Antibiotic use during labour does not appear to delay the onset of clinical signs of infection, with 95% of septic newborns presenting in the first 24 hours of life regardless of antibiotic exposure (3). Berger et al. has estimated that prolonging hospitalization for these infants from 24 to 48 hours has minimal effects on health outcomes but substantially increases cost (43). If other discharge criteria are met, these infants can be discharged home after 24 hours, providing they remain well, there is ready access to health care, and parents understand the signs of sepsis and when to seek medical care.

GBS-positive mothers with inadequate IAP, no additional risk factors

The risk of invasive EOGBS disease in infants born to GBS-positive mothers who received inadequate or no IAP is 1% to 2% (1). In three studies comprising 3101 infants born to mothers with inadequate or no IAP, only two infants (0.06%) had EOGBS sepsis; both were symptomatic within the first 24 hours (44–46). The CBC was of limited value. These infants should have a careful physical assessment after birth, close in-hospital observation (including vital signs every 3 to 4 hours) for at least 24 hours, and reassessment to confirm well-being if discharge is planned between 24 and 48 hours. A CBC is not indicated because the sensitivity of clinical signs is higher than that of WBC indices.

Infants who are well when reassessed after 24 hours and have met other discharge criteria can be discharged home, providing parents have been counselled about signs of sepsis and have ready access to health care. Parental understanding of when to seek medical care should be confirmed. If these conditions cannot be met, infants should be observed in hospital until 48 hours of age.

GBS-positive mothers with additional risk factors, with and without IAP

Maternal fever and prolonged rupture of membranes increase the likelihood of EOS in infants born to women colonized with GBS (47). Although IAP decreases the risk of EOGBS infection in these infants, their risk is still higher compared with

infants born to GBS-positive mothers without additional risk factors (2,15,17,48). Currently, there is insufficient information to specifically guide practice when multiple risk factors are present. Clinicians should consider the severity of each factor as well as intrapartum antibiotic exposure and the clinical status of each infant to determine an individualized management plan. At a minimum, these infants should be closely observed in hospital for 24 to 48 hours, with reassessment before discharge. Investigation and treatment for sepsis may be warranted for some infants. A CBC performed after 4 hours of age may be of some help in decision-making. In future, a sepsis calculator will likely be helpful (17–19).

Mothers who are GBS-negative or GBS-unknown status, with other risk factors

Risk factors (Table 1) increase the likelihood of EOS for babies born to mothers with negative or unknown GBS status and are indications for IAP when GBS status is unknown (9). In asymptomatic newborns, the likelihood of EOS remains low (4,49). In the era of universal GBS screening, most EOGBS sepsis in term infants occurs in newborns born to mothers who screened GBS-negative (17,27). Antibiotics given during labour decrease the incidence of both EOGBS and non-GBS EOS, but to a lesser extent with non-GBS infection, with a reported efficacy of 85% for GBS disease and 68% for non-GBS disease, adjusted for maternal fever (50).

When maternal GBS status is unknown or negative and a single risk factor is present, asymptomatic infants can be managed in the same manner as infants born to GBS-positive mothers, depending on whether IAP was adequate, inadequate or not given. If multiple risk factors are present, management should be individualized.

Chorioamnionitis

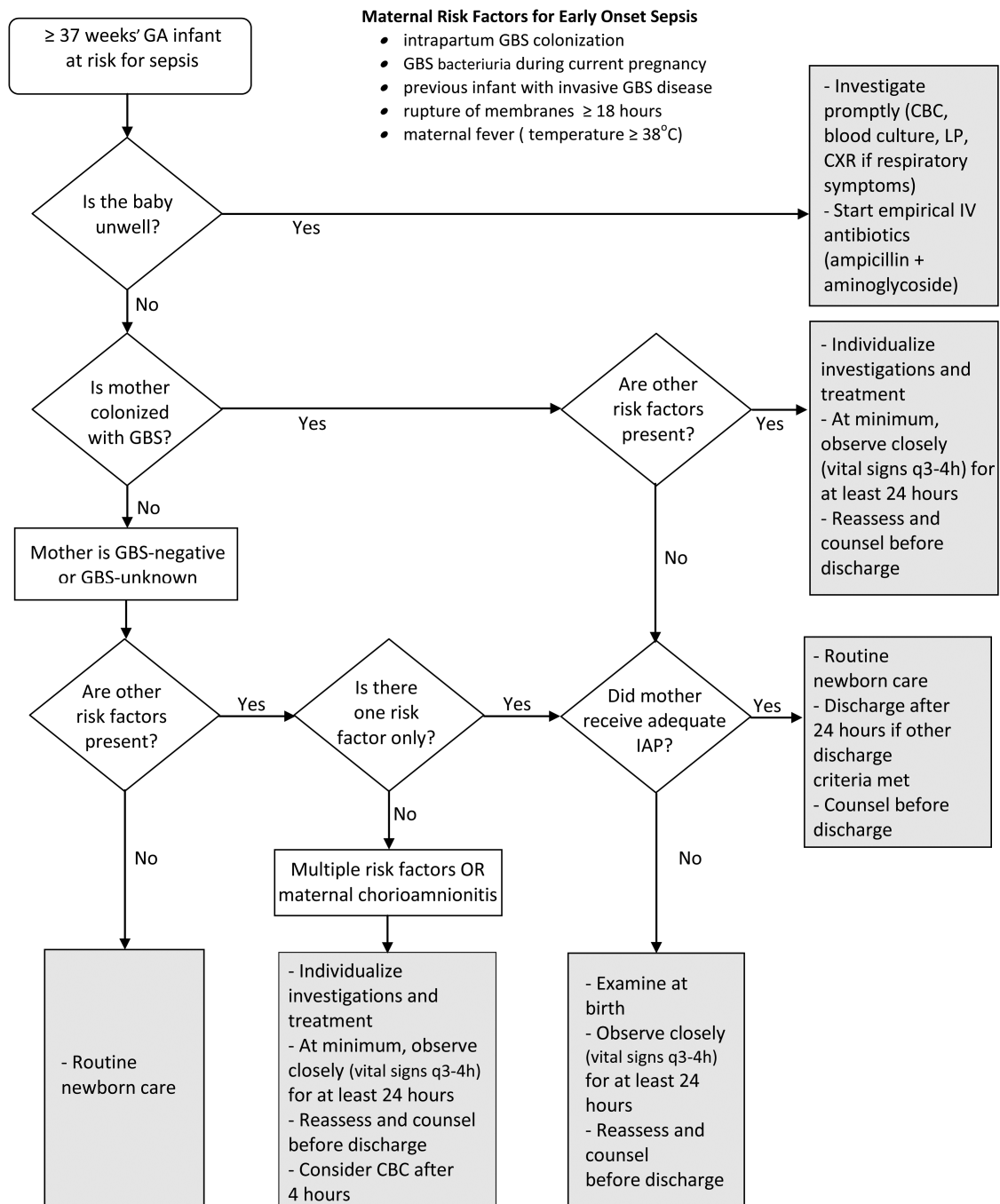
Chorioamnionitis (acute inflammation of the fetal membranes) is usually diagnosed on the basis of maternal temperature >38°C plus two other signs (uterine tenderness, maternal or fetal tachycardia, foul/purulent amniotic fluid, maternal leukocytosis) (51). Chorioamnionitis remains difficult to diagnose clinically because the prevalence of maternal fever during labour is high, especially after epidural analgesia (52) or prolonged labour.

The incidence of EOS in term infants born to mothers with chorioamnionitis is low. Three studies comprising 1892 neonates ≥ 35 weeks' GA exposed to maternal chorioamnionitis identified 15 infants (0.8%) with positive blood cultures (34,53,54), and a further study reported no EOS in asymptomatic term infants born after histologic chorioamnionitis (55). Broad-spectrum intrapartum antibiotics reduce the risk of EOS in general by 82% and EOGBS sepsis by 86% (15). Escobar reported that chorioamnionitis was not associated with EOS if mothers received antibiotics during labour (2).

Although both the CDC and the AAP currently recommend that all term infants born to women with suspected chorioamnionitis have cultures and antibiotic therapy (1,8–10), a recent commentary suggested that alternative approaches be considered (11,56). More individualized strategies may allow the number of infants treated with antibiotics to be decreased safely, as shown in a recent retrospective review of 698 infants born to mothers with chorioamnionitis (57). If term infants are examined after birth and are well, close observation in hospital for at least 24 hours is a reasonable approach. When a mother has multiple risk factors, including chorioamnionitis, has not received intrapartum antibiotics and/or is herself unwell, clinicians may consider investigation and antibiotic therapy for the infant. The LP can be deferred for asymptomatic infants.

Late preterm infants

Preterm birth <37 weeks' GA is considered a risk factor for infection, and women should receive IAP if GBS colonization is unknown (1,14). Although specific evidence to guide practice is lacking, infants 35 to 36 weeks' gestation who are stable enough to be admitted to a mother and baby unit (normal newborn nursery) rather than a special care nursery or neonatal intensive care unit, can be managed in a similar manner to infants ≥ 37 weeks' GA (10). These late preterm infants should be observed for at least 48 hours before being discharged home (58).

Figure 1. Management of term infants ≥ 37 weeks' gestational age who are at risk for early onset bacterial sepsis

CBC Complete blood count; CXR chest x-ray; GA Gestational age; GBS Group B streptococcus; IAP Intrapartum antibiotic prophylaxis; LP Lumbar puncture

RECOMMENDATIONS

Recommendations are graded using the GRADE system (13). It should be noted that this is an area in which few prospective and high-quality comparative studies have been done; hence the low-quality evidence.

Newly born *unwell* term infants (≥ 37 weeks' GA)

1. Infants with clinical signs of sepsis (respiratory distress, temperature instability, tachycardia, seizures, hypotonia, lethargy, poor peripheral perfusion, hypotension, acidosis) require prompt investigation, including CBC, blood culture and LP, and initiation of empirical IV antibiotic therapy. Ampicillin and an aminoglycoside provide coverage for the most common pathogens

associated with early-onset sepsis (EOS). Infants who have respiratory signs should also have a chest x-ray (*strong recommendation, moderate-quality evidence*).

2. Infants with early respiratory signs only and without risk factors for sepsis may be observed for up to 6 hours before initiating investigations for sepsis and antibiotic therapy (*strong recommendation, low-quality evidence*).

Newly born *well-appearing* infants (≥ 37 weeks' GA)

1. WBC indices (total WBC count, ANC, ratio of immature to total neutrophils) or a single CRP should not be used routinely as screening or diagnostic tests for EOS, nor to routinely exclude EOS (*strong recommendation, moderate-quality evidence*).

- For GBS-positive mothers with adequate IAP, no additional risk factors OR mothers who are GBS-negative or GBS-unknown status, with one other risk factor and adequate IAP: Infants do not require investigation or treatment for sepsis. They may be discharged home after 24 hours if they remain well, meet other discharge criteria and if parents understand signs of sepsis and when to seek medical care (*strong recommendation, high-quality evidence for GBS-positive mother, adequate IAP; low-quality evidence for GBS-negative or GBS-unknown mothers*).
- For GBS-positive mothers with inadequate IAP and no additional risk factors OR mothers who are GBS-negative or GBS-unknown status, with one other risk factor and inadequate IAP: Infants should be examined at birth, observed closely in hospital with vital signs every 3 to 4 hours and reassessed before discharge home. They may be discharged home after 24 hours if they remain well and meet other discharge criteria, providing there is ready access to health care and the parents understand and are able to seek medical care if the infant develops signs of sepsis. Routine investigation or treatment is not required (*strong recommendation, low-quality evidence*).
- Multiple risk factors for sepsis and/or chorioamnionitis: Infants should be investigated and treated using an individualized approach that includes consideration of the severity of risk factors and maternal antibiotic therapy. At minimum, infants should have close observation in hospital for at least 24 hours with vital signs every 3 to 4 hours and reassessment before discharge. A CBC done after 4 hours of age may be helpful; WBC $<5 \times 10^9/L$ and ANC $<1.5 \times 10^9/L$ have the highest positive predictive value. Some infants may warrant investigation and antibiotic therapy (*weak recommendation, low-quality evidence*).

Well late preterm infants 35 to 36 weeks' GA

- If infants are stable enough to remain with their mother in a mother and baby unit, they can be managed similar to infants ≥ 37 weeks' GA but should be observed in hospital for at least 48 hours (*weak recommendation, low-quality evidence*) (Figure 1).

Acknowledgements

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Principal author: Ann L. Jefferies MD