

Recommendations for term and late preterm infants at risk for perinatal bacterial infection

Revised guidelines of the Swiss Society of Neonatology in collaboration with the Paediatric Infectious Disease Group of Switzerland (PIGS): modified version based on a previous publication in the Journal of the Swiss Society of Paediatrics [1]*

Stocker Martin^a, Berger Christoph^b, McDougall Jane^c, Giannoni Eric^d
Taskforce for the Swiss Society of Neonatology and the Paediatric Infectious Disease Group of Switzerland

^a Neonatology, Children's Hospital Lucerne, Switzerland

^b Division Infectious Diseases, University Children's Hospital Zurich, Switzerland

^c Neonatology, University Children's Hospital Berne, Switzerland

^d Neonatology, University Children's Hospital Lausanne, Switzerland

Summary

Since publication of the initial guidelines for the prevention of group B streptococcal disease in 1996, the incidence of perinatal infection has decreased significantly. Intrapartum antibiotic prophylaxis together with appropriate management of neonates at increased risk for early-onset sepsis not only reduces morbidity and mortality, but also decreases the burden of unnecessary or prolonged antibiotic therapy. This article provides healthcare workers in Switzerland with evidence-based and best-practice derived guidelines for the assessment and management of term and late preterm infants (>34 weeks) at increased risk for perinatal bacterial infection. Management of neonates at increased risk for early-onset sepsis depends on clinical presentation and risk factors. Asymptomatic infants with risk factors for early-onset sepsis should be observed closely in an inpatient setting for the first 48 hours of life. Symptomatic neonates must be treated promptly with intravenous antibiotics. As clinical and laboratory signs of neonatal infection are nonspecific, it is mandatory to reevaluate the need for continued antibiotic therapy after 48 hours.

Key words: *Prevention; neonatal early-onset sepsis; group B streptococcus; management*

Introduction

Guidelines for the prevention of perinatal group B streptococcal (GBS) disease were initially published in the USA in 1996. They have been revised several times, most recently in 2010 [2]. Since publication of the original

guidelines, the incidence of perinatal GBS disease has decreased significantly in the USA [2, 3]. In addition, intrapartum antibiotic prophylaxis showed a beneficial effect in reducing the incidence of perinatal infection in other high-risk conditions (chorioamnionitis, prolonged rupture of membranes) [4].

The mortality rate for GBS sepsis ranges from 4% to 11% for term infants and is much higher for preterm infants [2, 3]. The incidence of proven (culture positive) neonatal early-onset sepsis, defined as onset of symptoms during the first 3 days of life, is 0.76–0.9 per 1000 live births [3, 5]. As a result of false negative culture results the actual incidence is probably higher. GBS is a major cause of early-onset sepsis, accounting for 38%–50% of perinatal bacterial infections [3, 5, 6]. Implementation of GBS screening programmes during pregnancy and intrapartum prophylaxis of GBS-positive mothers has led to an important reduction in the incidence of GBS-related sepsis. Consequently, the proportion of early-onset sepsis due to other bacteria such as gram-negative bacilli has increased. Therefore, it is important to formulate recommendations for the care of infants at risk of perinatal infection that do not only focus on GBS. Our position is in line with the new guidelines of the American Academy of Pediatrics (AAP) published in 2011 and 2012 [7, 8]. In addition, updated guidelines from Australia and New Zealand [9], and from the United Kingdom [10] were published recently.

Swiss Guidelines for the management of neonates whose mothers are colonised with GBS were published in 2001. Recent data and the 2010 revised CDC guidelines prompted the Swiss Society of Neonatology to commission a revision of the 2001 paper. In a first meeting in December 2011, members of the task force analysed and discussed guidelines and clinical studies published after 2001. The

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goal of the meeting was to identify topics that need to be reconsidered and potentially changed. Recently published guidelines and a focused literature search were used to evaluate and discuss new data that support each recommendation. As maternal GBS colonisation is not the only relevant risk factor for neonatal early-onset sepsis, the guidelines have been broadened to include the management of all neonates at increased risk for bacterial sepsis. In December 2012, the new guidelines were discussed independently within the Paediatric Infectious Disease Group of Switzerland and the Swiss Society of Neonatology and finally approved early 2013. The recommendations were previously published in the official Journal of the Swiss Society of Paediatrics, a nonpeer-reviewed and nonindexed journal written in German/French for members of the Swiss Society of Paediatrics [1]. This article is a modified version of the previous publication.

Purpose of the guidelines

The aim of this guideline is to assist healthcare workers providing care for neonates in the assessment and management of neonates at increased risk for early-onset sepsis. The goal is to prevent early-onset sepsis, to facilitate an early diagnosis and to avoid unnecessary or prolonged antibiotic therapy. Generally, preterm infants younger than 34–35 weeks gestation need special care and are hospitalised in neonatology units, and are therefore not discussed in these guidelines. This guideline focuses on term and late preterm infants (>34 weeks gestation) at risk for early-onset bacterial infection.

Management of neonates at increased risk for infection

The management of neonates at increased risk for infection depends on clinical presentation and underlying risk factors (fig. 1). The clinical signs of neonatal infection are often nonspecific and may be very subtle or even absent initially (table 1). Therefore, the assessment of risk factors for neonatal infection is crucial (table 2). In a prospective cohort study in an obstetric department in Switzerland, prevalence rate of GBS colonisation was 16.3% [11].

It is important to note that although intrapartum antibiotic prophylaxis has been shown to decrease the incidence of early-onset sepsis due to group B streptococcus, it does not eliminate the risk for neonatal infection entirely. Therefore, neonates born to mothers who meet the requirements for intrapartum antibiotic prophylaxis need to be closely observed for 48 hours postnatally [2, 7]. Over 90% of newborn infants with perinatally acquired bacterial infection will develop symptoms within the first 24–48 hours, emphasising the importance of this observation period [8, 12, 13]. If intrapartum prophylaxis is indicated but not administered, or administered less than 4 hours before delivery, newborns are considered at increased risk of perinatal infection and clinical observation is required, as for other risk factors.

Newborn infants with clinical signs suggestive of neonatal infection

The clinical signs of neonatal infection are diverse and non-specific and may be missed (table 1). Clinical signs are sensitive markers for neonatal infection, even when intrapartum antibiotic prophylaxis was administered, but have a low positive predictive value [2, 7–9, 12–14]. All newborn infants with signs suggestive of neonatal infection need empirical antibiotic treatment after blood cultures have been drawn [2, 7–9].

The positive and negative predictive values of single diagnostic laboratory tests are inadequate for early detection of neonatal infection [8, 13, 15–19]. Therefore, diagnostic laboratory tests cannot be used to decide whether antibiotics need to be started and a recommendation concerning routine laboratory evaluation is not justified [8, 9]. Several publications have shown a high negative predictive value for C-reactive protein (CRP) and procalcitonin (PCT) determined during the course of treatment, which can be used to stop empirically started antibiotic therapy early (see below under “Length of antibiotic therapy for suspected neonatal infection”) [15, 19–22].

Asymptomatic newborn infants with risk factors for early-onset sepsis

Asymptomatic neonates with risk factors for early-onset sepsis should be observed in an in-patient setting for the first 48 hours of life. This entails 4-hourly monitoring of vital signs (including temperature, peripheral perfusion and

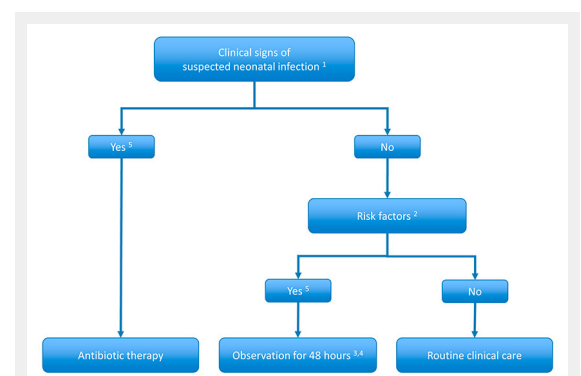


Figure 1

Management of term and late preterm infants (>34 weeks) at increased risk for neonatal bacterial infection (early-onset sepsis).

- (1.) Tachypnoea, respiratory distress, apnoea, tachycardia/bradycardia, poor peripheral perfusion, mottling, temperature instability, lethargy, irritability, changes in tone, vomiting, poor feeding.
- (2.) Maternal group B streptococcus (GBS) colonisation (vaginal/rectal swab: current or previous, bacteruria), preterm birth, prolonged rupture of membranes >18 hours, chorioamnionitis (maternal fever >38 °C plus two further symptoms: maternal leucocytosis, foetal tachycardia, painful or tender uterus, fetid amniotic fluid), required intrapartum prophylaxis missing or inadequate.
- (3.) Monitor vital signs every 4 hours: respiration, temperature, peripheral perfusion, colour.
- (4.) Elective Caesarean section (no rupture of membranes or contractions): no postnatal observation of baby necessary (regardless of maternal GBS status).
- (5.) If there are coexisting risk factors and/or the baby has clinical signs, discuss indication for laboratory tests with responsible neonatologist.

colour) by appropriately qualified staff. An effective intrapartum prophylaxis for GBS colonisation reduces but does not eliminate the risk of GBS infection [2, 7]. The risk of neonatal infection after an elective Caesarean section (no contractions or rupture of membranes) is minimal regardless of maternal GBS status, and thus both intrapartum prophylaxis and postnatal observation of the infant are not indicated [2, 7–9]. Contrary to the revised CDC recommendations, we do not recommend empirical antibiotic therapy for asymptomatic neonates whose mothers have signs of chorioamnionitis [2]. We recommend close observation for the first 48 hours, as for asymptomatic neonates with other risk factors for infection. This management is in agreement with the recent recommendations from Australia and New Zealand as well as the AAP 2012 guidelines for the management of neonates at increased risk for early-onset sepsis [8, 9]. The risk of neonatal infection increases with the number of coexisting risk factors and is highest for term infants of GBS positive mothers with chorioamnionitis [8]. Relevant clinical information should always be obtained from obstetricians and midwives. The indication for diagnostic tests (complete blood count, acute phase reactants) and empirical antibiotic therapy should be discussed with the responsible neonatologist. Close observation is mandatory.

Asymptomatic neonates with unknown maternal GBS status

If the GBS status is unknown at delivery (screening not performed or results unavailable), intrapartum antibiotic prophylaxis should be given and the infant should be monitored for 48 hours postnatally if other risk factors for neonatal infection are present (preterm birth <37 weeks, prolonged rupture of membranes >18 hours, signs of chorioamnionitis) [2, 7]. Based on the high recurrence rate of GBS colonisation, it is advisable to consider previous GBS colonisation as a risk factor for neonatal infection (e.g. in an earlier pregnancy) [23, 24].

Table 1: Clinical signs of early-onset sepsis.
(1.) Tachypnoea, respiratory distress, apnoea
(2.) Tachycardia/bradycardia, poor peripheral perfusion (i.e. capillary refill time >3 seconds), mottling
(3.) Temperature instability (hyperthermia >38.0 °C or hypothermia <36.0 °C)
(4.) Lethargy, irritability, altered muscular tone or floppiness
(5.) Vomiting, poor feeding

Table 2: Risk factors for early onset neonatal sepsis.
(1.) Maternal group B Streptococcus colonisation (vaginal/rectal swab), bacteriuria or infection in the current pregnancy
(2.) Signs of chorioamnionitis (maternal fever >38 °C plus at least two of the following symptoms: maternal leucocytosis (>15 G/l), foetal tachycardia (>160/min), uterine tenderness, foul-smelling amniotic fluid)
(3.) Prolonged rupture of membranes (>18 hours before delivery)
(4.) Preterm birth <37 weeks
(5.) Previous neonate with an invasive group B streptococcus infection
(6.) Suspected infection in a sibling in the case of a multiple pregnancy

Specific recommendations for antibiotic therapy

Maternal antibiotic prophylaxis

Maternal antibiotic prophylaxis is the responsibility of the attending obstetrician. Penicillin or amoxicillin are the antibiotics of choice for intrapartum GBS prophylaxis [7–10]. Erythromycin is no longer recommended owing to a prevalence of GBS resistance of 30% [11]. Cefazolin, which has similar pharmacokinetics to penicillin, is the antibiotic of choice for women with a known penicillin allergy and low risk of anaphylaxis. Vancomycin is recommended for women with penicillin allergy and high risk of anaphylaxis, whereas clindamycin is no longer recommended owing to a prevalence of GBS resistance of 25–30% [11]. Effective and adequate antibiotic prophylaxis is defined as intrapartum prophylaxis with penicillin, amoxicillin or cefazolin given at least 4 hours prior to delivery. There are limited data on the efficacy and pharmacokinetics of vancomycin [2].

Culture work-up of symptomatic neonatal infection

Blood cultures are mandatory in the work-up of symptomatic neonatal infection. The blood culture should be obtained before antibiotics are given and at least 1 ml blood should be drawn [8, 25]. The indication for a lumbar puncture is controversial [2, 7]. A lumbar puncture should always be performed if blood cultures are positive and/or in critically ill newborns. It should be borne in mind that cases of neonatal meningitis have been documented with negative blood cultures [8, 26]. Antibiotics can be started at meningitic doses to ensure adequate treatment of possible meningitis (amoxicillin 200 mg/kg/day instead of 100 mg/kg/day). The decision not to perform a lumbar puncture is always an active one, and should be documented in the patient chart. If there is doubt about the indication, the lumbar puncture can still be performed 1–2 days after onset of the infection and treatment [8]. Urine cultures, gastric aspirates and body surface cultures have no place in the work-up of early-onset sepsis.

Antibiotic therapy for suspected neonatal infection

An aminoglycoside (amikacin or gentamicin) combined with amoxicillin given intravenously is the standard empirical therapy. Appropriate doses for neonates within the first week of life are: gentamicin 4–5 mg/kg/dose or amikacin 15 mg/kg/dose intravenously every 24 hours and amoxicillin 50–100 mg/kg/dose intravenously every 12 hours. There is a need for therapeutic drug monitoring for aminoglycoside therapy. Cephalosporins should be avoided as first-line therapy because of the high risk of developing resistance and should be restricted to special cases [8, 27, 28].

Length of antibiotic therapy for suspected neonatal infection

As the clinical and laboratory signs of neonatal infection are nonspecific and symptomatic neonates are treated empirically with antibiotics, it is important to reevaluate the need for continued antibiotic therapy after 48 hours. In most cases, based on the clinical course, negative culture

results and laboratory parameters, a decision can be made to stop safely antibiotic therapy after this time [8, 15, 19–22]. The frequent observation that prolonged antibiotic therapy (>5 days) causes increased mortality and a higher incidence of necrotising enterocolitis in preterm infants emphasises the need to stop empirical antibiotic therapy in the absence of proven infection (negative culture and negative acute phase reactants) as early as possible and at the latest after 48–72 hours [29–31].

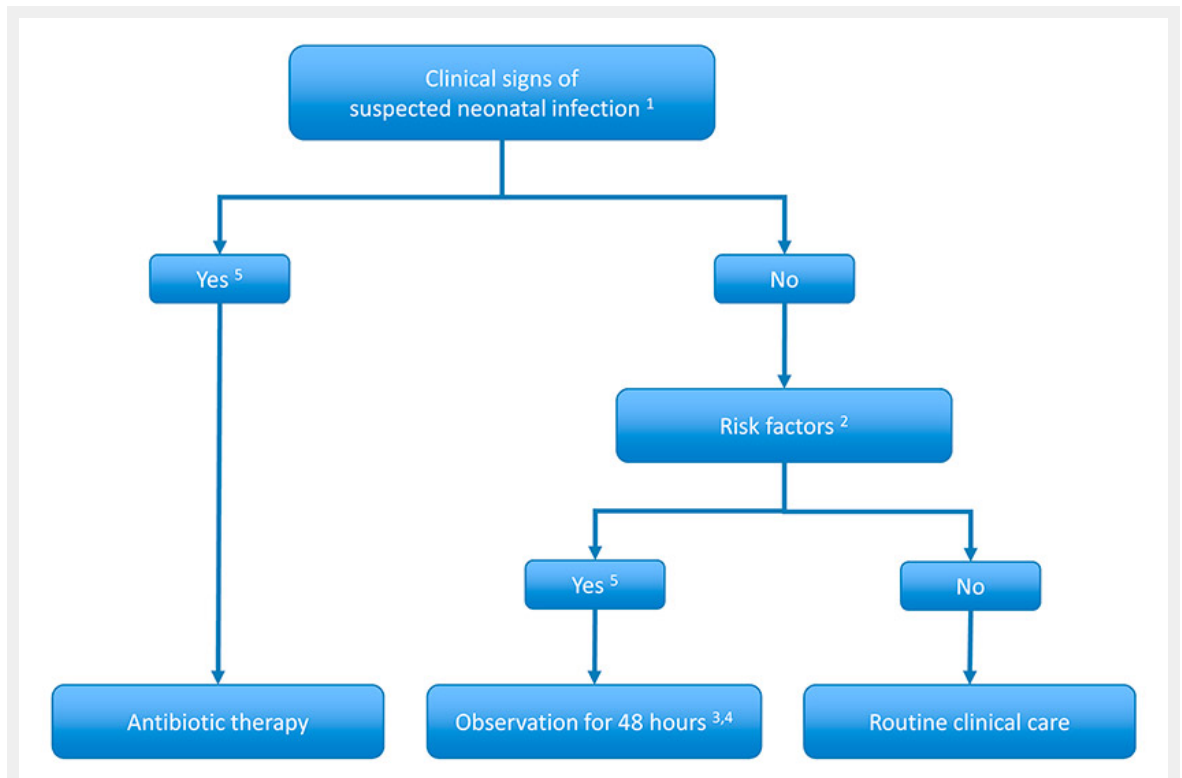
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Correspondence: Martin Stocker, MD, Neonatology, Children's Hospital Lucerne, CH-6000 Lucerne 16, Switzerland, [martin.stocker\[at\]luks.ch](mailto:martin.stocker[at]luks.ch)

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Figures (large format)

**Figure 1**

Management of term and late preterm infants (>34 weeks) at increased risk for neonatal bacterial infection (early-onset sepsis).

(1.) Tachypnoea, respiratory distress, apnoea, tachycardia/bradycardia, poor peripheral perfusion, mottling, temperature instability, lethargy, irritability, changes in tone, vomiting, poor feeding.

(2.) Maternal group B streptococcus (GBS) colonisation (vaginal/rectal swab: current or previous, bacteruria), preterm birth, prolonged rupture of membranes >18 hours, chorioamnionitis (maternal fever >38 °C plus two further symptoms: maternal leucocytosis, foetal tachycardia, painful or tender uterus, fetid amniotic fluid), required intrapartum prophylaxis missing or inadequate.

(3.) Monitor vital signs every 4 hours: respiration, temperature, peripheral perfusion, colour.

(4.) Elective Caesarean section (no rupture of membranes or contractions): no postnatal observation of baby necessary (regardless of maternal GBS status).

(5.) If there are coexisting risk factors and/or the baby has clinical signs, discuss indication for laboratory tests with responsible neonatologist.