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Management of the neonate at risk for early-onset Group B streptococcal disease (GBS EOD): new paediatric guidelines in Belgium.

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Abstract

Despite group B streptococcal (GBS) screening in late pregnancy and intrapartum antimicrobial prophylaxis, early onset sepsis in neonates remains a common source of neonatal morbidity and mortality especially in preterm neonates. The identification of neonates with early onset sepsis is usually based on perinatal risk factors. Clinical signs are aspecific and laboratory tests not sensitive. Therefore, many clinicians will overtreat at risk infants. Inappropriate treatment with antibiotics increases the risk for late onset sepsis, necrotizing enterocolitis, mortality and prolongs hospitalisation and costs. In 2003, the Belgian Health Council (BHC), published guidelines for the prevention of perinatal GBS infections. This report presents the Belgian paediatric management guidelines, which have been endorsed by the Belgian and Flemish societies of neonatology and paediatrics. The most imported changes in the 2014 guidelines are the following:

- recommendations for a lumbar puncture,
- clarification of normal spinal fluid parameters and blood neutrophil indices corrected for gestation age,
- specific timing for diagnostic testing after birth,
- no indication for diagnostic testing in asymptomatic newborns unless additional risk factors,
- a revised algorithm for management of neonates according to maternal and neonatal risk factors,
- premature infants described as those below 35 weeks instead of 37 weeks

The guidelines were made on the basis of the best evidence and on expert opinion when inadequate evidence exists.

Key Words: GBS; Belgium; Guideline; Paediatric; Management; Neonate

Introduction

Since the seventies, the incidence of neonatal group B streptococcal sepsis and meningitis has increased dramatically in all industrialized countries.[1] Today, GBS is identified as the leading cause of invasive bacterial infections in neonates. The reported attack rates for the early-onset disease (EOD) (birth to age 7 days) range from 0.5 to 4 cases per 1,000 live births. [2-4] In the late-onset form (LOD) occurring in infants aged > 1 week, the attack rate is close to 0.5 per 1,000 live births.

The early-onset form of GBS disease typically occurs in the first 24 h of life, with fulminant sepsis or pneumonia and less often with meningitis. Despite intensive supportive care, diagnostic and therapeutic progresses, these infections have remained associated to high mortality (5 - 20 %) and morbidity; more than 30 % of infants recovering of meningitis develop long term neurologic sequelae.[5]

In perinatal infections or EOD, GBS is transmitted vertically to the newborn from the vagina of a *typically asymptomatic* colonized woman during labour and delivery. In addition to colonization with GBS, other factors increase the risk for GBS EOD. These include prematurity (gestation < 37 weeks), intrapartum fever (temperature >= 38°C), duration of amniotic membrane rupture >= 18 hours, previous delivery of an infant with invasive GBS disease and GBS bacteriuria during current pregnancy.[6,7]

Because of the continuing magnitude and severity of GBS disease, several preventive strategies have been evaluated.[8,9] The reference recommendations were published by the CDC in 1996, re-evaluated and updated 2002 and further in 2010.[10] Universal screening at 35–37 weeks' gestation for maternal GBS colonization and use of intrapartum antibioprophylaxis is currently considered to be the most effective strategy to decrease the incidence of EOD. However the cost of prenatal screening and antibiotic prophylaxis, as well as the selective pressure that antibiotics may have on the bacterial flora of mother and newborn still generate much controversy.

In Belgium, as in many European countries, national guidelines for the GBS EOD prevention are currently available since 2003.[11] Indeed, most hospitals have implemented strategies to decrease perinatal GBS infections and obstetric programs already included a GBS prevention policy but not always according to CDC guidelines.[12] As in the United States of America, despite the Belgian implemented strategy for prevention of perinatal group B streptococcal (GBS) disease, GBS remains an important cause of GBS EOD.

The majority (95%) of children with GBS EOD will become ill within the first 24 hours after birth. The management of ill neonates and/or neonates at high risk of infection is well defined, but management of healthy-appearing neonates is more problematic. An updated approach for empirical management of infants born to women, who received or should have received intrapartum antibiotic prophylaxis (IAP) to prevent GBS EOD or to treat suspected chorioamnionitis, is provided (A 1) and was adapted from international guidelines.[10,13] Indeed, both prenatal exposure and postnatal prolonged therapy with antibiotics has been associated with the development of necrotizing enterocolitis.[14-17] The main objective of developing an algorithm for management of newborns is to minimize unnecessary evaluations and antimicrobial treatment in infants whose mothers received intrapartum antimicrobial prophylaxis (IAP).

Methods

This report was developed by a national GBS working group of paediatricians of the Belgian Superior Health Council in collaboration with gynaecologists and microbiologist according to the best available evidence (A 2) and on experts' opinion when inadequate evidence was present.[18] It represents the core of the paediatric section of the updated Belgian guidelines for prevention of perinatal GBS disease (not yet published). The level of evidence is presented between brackets

throughout the guideline. The guideline have been endorsed by the Belgian, Flemish and French speaking sections of neonatology and paediatrics.

Management of the neonate at risk for early-onset Group B streptococcal disease (GBS EOD).

1. **Neonates with signs of neonatal sepsis:**

In any infant with clinical signs of sepsis a full diagnostic evaluation should be done and empirical antibiotic therapy (ampicillin/ amoxicillin or penicillin + aminoglycoside) should be started regardless of IAP, other obstetrical risk factors or maternal GBS status (A-II).

Because of sub-optimal sensitivity and specificity, and of poor predictive value for infection, routine use of urine antigen, cultures of mucous membranes and gastric aspirates or body surfaces are not recommended.[19-22]

-***Clinical signs of sepsis****:* infant with a combination of signs as respiratory (apnea, grunting, tachypnea, cyanosis), cardiovascular (reduced capillary refill, hypotension, shock), central nervous system (lethargy, hypothermia, fever, seizures, apnoeic spells, irritability, bulging fontanel) or gastrointestinal (poor feeding, abdominal distension) disturbances.

-***Full diagnostic evaluation****:* full blood cell count (FBC) and differential, CRP level, blood culture, lumbar puncture (LP) if feasible (CSF analysis and culture), chest X-ray, endotracheal culture (in intubated infants or if respiratory distress or lung infiltrate) to guide antibiotic treatment in blood culture negative "pneumonia" cases. [23]

A lumbar puncture is indicated in all neonates with high suspicion of GBS infection especially in those with clinical signs of meningeal inflammation (seizures, apnoeic spells, irritability, bulging fontanel), in those who initially worsen with antimicrobial therapy, and all neonates with positive blood cultures. Indeed, 15% of infants with early onset GBS infection have meningitis and 20% of infants with proven GBS meningitis have a negative blood culture. [24,25]

In cases of clinical instability, antibiotic therapy should be administered and LP should be deferred and performed later until 48 hours for cell count, chemistry together with a blood glucose level for comparison and culture. An elevated CSF protein is the most sensitive parameter for GBS meningitis and a low CSF glucose is the most specific. Normal value depends on gestational age (see A 3 below). Of the infants with GBS meningitis 96% will have at least one abnormal CSF value. If meningitis is diagnosed, the dose of penicillin should be doubled and the duration of therapy extended to 2 weeks in GBS meningitis. Aminoglycosides should be stopped as soon as blood culture confirms GBS infection.

2. Healthy-appearing newborn

2.1. Neonates at high risk for early onset sepsis.

Neonates born to mothers with clinical **chorioamnionitis** predisposes to infection with Gram-negative organisms and increases the risk of GBS infection in GBS colonized women. If a mother received intrapartum antibiotics for treatment of suspected chorioamnionitis, a limited diagnostic evaluation consisting of blood culture, FBC (including WBC differential) + CRP at 12 hours and at 36 hours should be carried out; no chest radiograph or lumbar puncture is needed. Empiric antibiotic therapy (ampicillin/amoxicillin or penicillin + aminoglycoside) should be started in these newborns regardless of clinical condition at birth or other conditions (AII). The term “chorioamnionitis” is a clinical connotation of maternal fever (> 38 °C) during labor (with or without uterine tenderness), leukocytosis, foul smelling amniotic fluid, and/or fetal tachycardia (C-III).

2.2. Neonates at low risk of early onset sepsis.

Routine use of antimicrobial prophylaxis and routine additional laboratory testing, as defined in this document is not recommended for healthy-appearing newborns whose mother received IAP. An algorithm for the management of these newborns is suggested in figure 1.

If **no IAP was indicated** then no further diagnostic investigations or clinical observations are required (CIII).

If the mother **received adequate IAP**, that means penicillin, ampicillin or cefazolin at least 4 hours before delivery, without additional risk factors (PROM, preterm birth, and/or clinical chorioamnionitis) infants should be observed clinically in the mother's room without additional laboratory testing. When the newborn remains healthy he or she can be discharged from the hospital after 48 hours. In case the neonate is >= 37 weeks gestation observation can occur at home, already after 24 hours, only when a person who is able to comply fully with instructions for home observation and access to medical care is readily available and a FBC + CRP is negative after 24hrs.[26] Agents other then penicillin, ampicillin and cefazolin, as clindamycin and vancomycin, although used in penicillin-allergic patients with a history of anaphylactic reaction, have not been proven efficient for IAP and are considered inadequate for purposes of IAP (C-III). Indeed, data on the ability of clindamycin and vancomycin to reach bactericidal levels in the fetal circulation and amniotic fluid are very limited and available data suggest that clindamycin provided to pregnant women do not reach fetal tissues reliably. [27-31] Furthermore, in Belgium a high resistance level (> 25%) of the GBS strains to clindamycin is reported by the national reference centre for GBS.

If **no adequate maternal IAP** for GBS has been administered despite indication being present (e.g other antibiotics then penicillin, ampicillin and cefazolin for IAP, IAP < 4 hours before delivery, no IAP despite indication) then follow algorithm of Figure 1.

In case the infant is >= 35 weeks and duration of membrane rupture was < 18 hours, then the infant should be observed for at least 48 hours, and no routine diagnostic testing needs to be performed. If clinical signs of infection develop, a full diagnostic evaluation should be performed and

empirical antibiotic therapy (ampicillin/amoxicillin + aminoglycoside) should be started (see 2.2.1) (BIII).

In case the infant is < 35 weeks or duration of membrane rupture was >= 18 hours, then the infant should be observed for at least 48 hours, and limited diagnostic testing be performed. Again, if clinical signs of infection develop a full diagnostic evaluation, including cultures, should be undertaken and empirical antibiotic therapy (ampicillin/amoxicillin + aminoglycoside) should be started (see 2.1) (B-III).

Which and when laboratory testing?

Limited evaluation*:* Limited evaluation includes blood culture (at birth), FBC with differential and platelets (at 6 –12 hours of life) and CRP at 12 and 36 hours.

Because of the low sensitivity and specificity at birth, results of the full blood count (FBC) can provide more information about the presence of infection if the test is not performed before 6-12 hours after delivery.[32,33] Clinical signs are much more sensitive than any laboratory test of infection. Therefore, treatment should rather be based on clinical signs and on maternal risk factors, (e.g. in case of inadequate IAP: gestational age and PROM). Population data reveal that late preterm infants (35-36 weeks) are at low risk for GBS disease and related mortality compared to their more premature counterparts and even term infants.[34] Therefore, in the algorithm the cut-off was set at < 35 weeks and not at 37 weeks as the definition for prematurity. Thus laboratory tests should rather be seen as a confirmation of clinical judgment (e.g. positive laboratory tests in ill infants and negative tests in healthy-appearing neonates). In order to increase the diagnostic performance, serial measurements of CRP and full blood cell count should be undertaken at least at around 12 and 36 hours of life.[35]

Lower and upper limits of neutrophils count vary with postnatal age. The total and differential white blood cell count are affected by several factors besides infection, including infant age in hours (lower first hours), the method of blood sampling (lower via arterial blood sampling), the method of delivery (lower after caesarean section), maternal hypertension (lower), and infant's gender (lower in boys), infant's gestational age (lower in very low birth weight infants and premies). [36-38] Sepsis should be

suspected if leukopenia < 5000/mm^3, neutrophilia > 25x10^9/l, leukocytosis> 30x10^9/l immature to total neutrophil count (I/T ratio ≥ 0.30) or if neutropenia defined as absolute neutrophil count < 10th percentile adjusted for gestational age (Schmutz criteria) [A 4]. [39] Thrombocytopenia is not a sign of sepsis within 24 hours after birth. [32]

The sensitivity of C-reactive protein (CRP) to predict a bacterial infection increases rapidly after birth but at least 6 to 12 hours after the onset of infection are necessary to reach abnormal level. Therefore, if blood for CRP is taken for decision making regarding initiating antimicrobial therapy, then the drawing can better be delayed for a few hours. A significant increase (CRP level above 10 mg/l) between 2 serial measurements on samples taken over the first 8-48 hours of life has a sensitivity of almost 100% for an infectious status and normal levels for the 2 samples have a negative predictive value of 90 to 100% for an infectious status.[40] The normal upper level of CRP depends on the laboratory but in general a CRP > 10 mg/L is considered a positive level. In premature infants the increase of CRP may be delayed and the level may be lower because of immaturity of the liver. [41]
Sepsis should be suspected based on repeated clinical and laboratory evaluations and if sepsis is suspected, a full diagnostic evaluation should be done (see 2.1), including cultures, and empiric antibiotic therapy should be started.

Empiric antibiotic therapy

In Ill neonates are those at risk with abnormal laboratory tests should be treated with antimicrobial agents active against GBS as well as other organisms that might cause neonatal sepsis (e.g. ampicillin or penicillin + aminoglycoside). Antimicrobial switch to 3rd generation cephalosporin (e.g. cefotaxime) is necessary in case of Gram-negative sepsis/meningitis because of increasing ampicillin resistance of *E. coli*. Dosage and regimen of antimicrobial agents depend of diagnosis, post-natal age and birth weight. For dosages we refer to the Sanford guide.[42] Intravenous immunoglobulins do not improve morbidity nor mortality and are not indicated. [43]

Duration of antibiotic therapy varies depending on results of cultures and on the clinical course of the infant (A 5): If GBS infection is confirmed by culture and meningitis is excluded,

ampicillin should be replaced by the narrower spectrum penicillin and aminoglycoside should be discontinued. In case of GBS meningitis the dose of penicillin should be doubled. Combination therapy with aminoglycoside can be discontinued if CSF specimen obtained 48 hrs in therapy, is sterile.[44,45] Ventriculitis is a common complication of neonatal meningitis. There are no reliable clinical signs of ventriculitis, although evidence of increased intracranial pressure usually is present. It must be suspected on the basis of failure to respond clinically and bacteriologically to appropriate antimicrobial therapy; if ventriculitis results in obstruction to CSF flow, the access of systemic antibiotics to the ventricular CSF can be limited. Neuroimaging should be performed to make the diagnosis. Cranial sonography can demonstrate findings suggestive of ventriculitis or obstructed flow of CSF. Contrast-enhanced CT or MRI can demonstrate enhancement of the lining of the ventricles. Ventricular fluid aspiration is indicated for infants who have ventriculitis with an obstruction to the flow of CSF. In this setting, cultures of CSF often remain positive for the infecting organism for several days or longer. Treatment can involve direct instillation of an antimicrobial such as gentamicin or amikacin directly into the ventricle. The duration of antimicrobial therapy may extend several weeks longer than the time required to sterilize the ventricular CSF and can be as long as six to eight weeks.

Future perspectives

A major change in the new guideline is that asymptomatic term neonates should not have any laboratory testing when they do not have any additional risk factors such as PROM even when GBS prophylaxis was inadequate. This will decrease unnecessary evaluations and antibiotic exposure in healthy neonates. National long-term surveillance of early onset infections in both preterm and term infants remains of high value. Not only is this important to monitor the effect of intrapartum prophylaxis on the incidence of GBS disease but also to detect emergence resistance of GBS isolates and to find emerging neonatal pathogens causing early onset sepsis. As long there is no GBS vaccine available universal screening and intrapartum antimicrobial prophylaxis is the best option for the prevention of neonatal GBS disease and mortality. Future research should focus on the value of rapid

molecular testing in order to identify not only colonized mothers but also children at highest risk of invasive disease.

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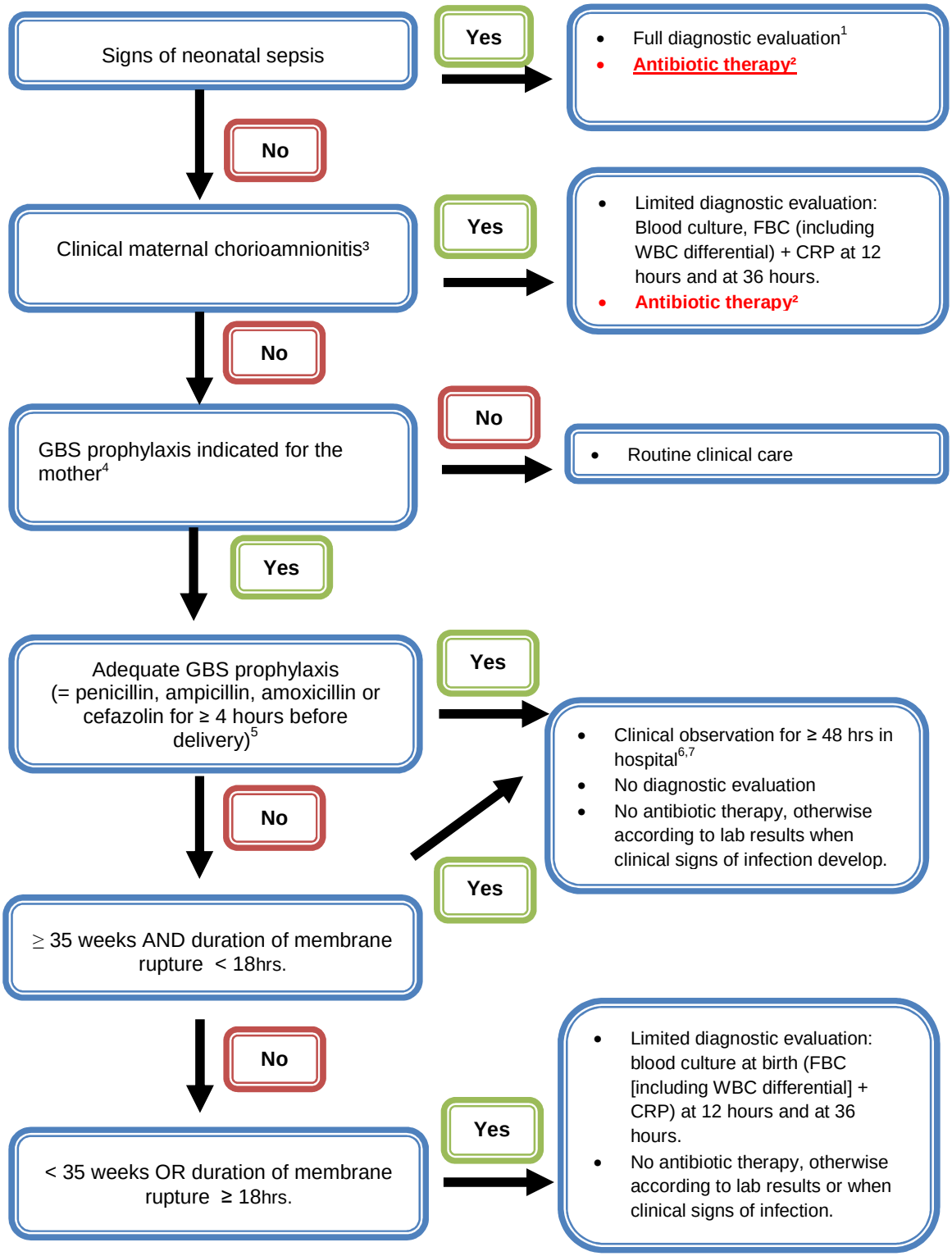
A 1. Algorithm for secondary prevention of early-onset GBS disease among newborns.



A1 Figure legend

[1] Full diagnostic evaluation: Blood culture, a full blood count (FBC) including white blood cell differential and platelet counts, CRP, chest X-ray (if respiratory symptoms are present), and lumbar puncture (at least if central nervous system signs are present, blood culture becomes positive and patient is stable enough to tolerate the procedure). Normal CSF values if < 37 weeks gestation: WBC < $0.026x10^9$/l glucose > 1.27 mmol/l, protein <15.1 g/l; if ≥37 weeks gestation: WBC < $0.023x10^9$/l, glucose >1.83 mmol/l, protein <17,1 g/l.

[2] Antibiotic therapy:
Ampicillin or Penicillin IV: double dose in case of meningitis or severe GBS sepsis.
Aminoglycoside IV: Measure serum concentration when treating for more than 48 hours.

[3] Consultation with obstetrician for clinical signs of chorioamnionitis (e.g. maternal fever > 38°C, uterine tenderness, leukocytosis> 15 $x10^9$/l, foul smelling amniotic fluid, and/or fetal tachycardia) is important. Beware for intrapartum fever due to epidural anaesthesia.

[4]Indication for intrapartum GBS antibiotic prophylaxis:

1. Previous infant with GBS disease.
2. GBS bacteriuria during this pregnancy.
3. GBS vagino-rectal culture positive during current pregnancy (35-37 wks) or intrapartum nucleic acid amplification test (NAAT) positive for GBS on vaginal specimen.
    - unless a cesarean delivery, is performed before onset of labor on a woman with intact amniotic membranes.
4. Unknown GBS status at the onset of labor and ≥ 1 risk factor at onset of labor:
    - < 37 weeks of gestation
    - Amniotic membrane rupture ≥ 18 hrs
    - Intrapartum temperature ≥ 38,0°C
    - Intrapartum nucleic acid amplification test (NAAT) positive for GBS

[5] The efficacy of other antibiotics (e.g. vancomycin, clindamycin) has not been studied and, for this reason, from the paediatric management point of view, they are considered as "inadequate" to protect the child against GBS infection. All oral antibiotics (e.g. azithromycin) should be considered as inadequate for GBS prophylaxis.

[6]Patient can be discharged home as early as 24 hrs after delivery if ≥ 37 weeks of gestation, assuming that other discharge criteria have been met, ready access to medical care exist and a person is able to comply fully with instruction for home observation (e.g. midwife, generalist) and an infection is excluded by FBC + CRP after 24 hrs .

[7] If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

A 2. Evidence-based rating system used to determine strength of recommendations.

Category	Definition	Recommended
Strength		
A	Strong evidence for efficacy and substantial clinical benefit	Strongly
B	Strong or moderate evidence for efficacy but only limited clinical benefit	Generally
C	Insufficient evidence for efficacy or efficacy does not outweigh possible adverse consequences	Optional
D	Moderate evidence against efficacy or adverse outcome	Generally not
E	Strong evidence against efficacy or adverse outcome	Never
Quality of evidence		
I	Evidence from at least one well-executed randomized, controlled trial or one rigorously designed laboratory-based experimental study that has been replicated by an independent investigator	
II	Evidence from at least one well-designed clinical trial without randomization, cohort or case-controlled analytic studies (preferably from more than one center), multiple time-series studies, dramatic results from uncontrolled studies, or some evidence from laboratory experiments	
III	Evidence from opinions of respected authorities based on clinical or laboratory experience, descriptive studies, or reports of expert committees	

Source: Adapted from La Force FM (18).

A 3. Normal cerebrospinal fluid parameters in neonates.

Gestational age (weeks)	White Blood Cell count (x 10^9/l)	Glucose* (mmol/l)	Protein (g/l)
< 37	< 0.026	> 1.27	< 15.1
≥ 37	< 0.023	> 1.83	< 17.1

**Glycorachia should be > 75% of serum glycaemia.*

A 4. Criteria for lower limits of neutrophils /mm^3 at 6- 8 hours after birth according to gestation. (Criteria according to Schmutz et al.).

Gestation	**<28 weeks**	**28 – 36 weeks**	**>36 weeks**
Neutrophil count (x 10^9/l)	1.5	3.5	7.5

A 5. Duration of antibiotic therapy.

Focus of infection	**Duration of therapy**
Suspected sepsis not confirmed by clinical, biological or bacteriological results	36-48 hours
Proven sepsis	7-10 days
Meningitis	minimum 14 days
Ventriculitis	28 days
Osteomyelitis	4-6 weeks