

PROTOCOL FOR SCREENING AND MANAGEMENT OF SUSPECTED NEONATAL SEPSIS.

Introduction

Neonatal sepsis occurs in 1 to 8 per 1000 live births with the highest incidence occurring among infants of very low birth weight and gestation. It is mandatory to have a high index of suspicion for the possibility of sepsis. The consequences of untreated sepsis or delaying treatment in an infant with sepsis can be catastrophic.

Early Onset Sepsis ((EOS) (There are different definitions)

EOS refers to an infection of the blood stream or meninges proven by culture. It is usually acquired vertically. Very early onset present in the first 24 hours, early onset day 1-7. The CDC defines EOS as a blood or CSF infection within the first 6 days. In VLBW babies EOS refers to infection within the first 3 days.

- Often present as pneumonia and/or septicaemia.
- The incidence is equal in male and female.
- Mortality is 10 to 30%.
- Often due to organisms acquired from the birth canal, E coli and Group B Streptococcal (GBS) particularly. GBS more common in term babies and E coli in preterm infants
- Occasionally intrapartum haematogenous spread occurs e.g. Listeria.

Risk Factors for Early Onset Sepsis

- Prolonged ruptured membranes (> 18 hours).
- Foetal distress.
- Chorio-amnionitis – Maternal temperature above 37.8° and any 2 of foetal tachycardia, offensive liquor or maternal leucocytes of > 12 500 /mm³ (Gibbs criteria).
- Maternal pyrexia (> 38° C) or overt infection e.g. UTI, gastroenteritis/diarrhoeal illness.
- Multiple obstetric procedures, including cervical sutures.
- Preterm delivery.
- History of GBS infection in previous infant, GBS bacteraemia in this pregnancy.

Recognition of Systemic Sepsis

Signs are often non-specific.

General features: pallor, lethargy, jaundice, temperature instability (1/3 of confirmed sepsis cases are normothermic) hypoglycaemia/hyperglycaemia, blood gas derangements.

Respiratory: tachypnoea, apnoea, grunting, cyanosis.

Cardiovascular system: tachycardia, bradycardic episodes, poor perfusion hypotension.

Cutaneous: petechiae, bruising, bleeding tendency.

GIT: poor feeding, vomiting, abdominal distension, feed intolerance, bilious aspirates/vomits, loose stools

CNS: lethargy, irritability, seizures

Any baby who is unwell must be considered at risk of sepsis and appropriate antibiotics commenced as soon as possible after taking cultures. Inability to obtain cultures should not delay administration of antibiotics.

Investigations

General investigations include parameters important in assessment of general wellbeing of the infant e.g. blood gases, blood glucose, electrolytes.

Infection related tests

Non-specific markers e.g. C-reactive protein (CRP), Full Blood Count 12 hours after birth.

CRP rises approximately 12 hours after onset of sepsis and returns to normal within 2 to 7 days of successful treatment. CRP is raised in 85 % of episodes of confirmed sepsis with a specificity of 90%. It can, therefore, be normal in cases of true sepsis and should be used in conjunction with clinical signs and culture results.

FBC -The Polymorph nucleocyte (PMN) count can be normal in 1/3 of cases of confirmed sepsis, but can also be elevated in the absence of infection. Neutropenia in the face of confirmed sepsis can indicate that the baby is extremely unwell. An increased in the immature to total white cell ratio (I: T ratio > 0.3) is about 85 % sensitive and specific - particularly for early onset sepsis.

Blood culture – is the gold-standard and test to identify the infective organism. Clean venepuncture site with 70% isopropyl ethyl alcohol. Apply tincture of iodine or 10% povidone-iodine and allow drying for at least 1 min, or clean the site with 2% chlorhexidine. Clean blood culture bottle injection site with alcohol only. Obtain 1–2 mL for a neonate, 1mL for a preterm. There is a higher culture yield with higher volume blood cultures.

Early Onset Sepsis

Blood culture (mandatory)

Lumbar puncture (LP) should be performed where the 'index of suspicion' of meningitis is high i.e. abnormal conscious state or seizures. LP may need to be delayed until after the infant's condition has stabilised sufficiently to tolerate the procedure and abnormalities of coagulation status have been controlled. If the initial blood culture is positive. LP must be performed to exclude meningitis since the presence of meningitis alters the length of antibiotic treatment as well as prognosis.

Do not do urine aspiration for culture, as haematogenous spread is the mechanism behind positive urine cultures in the first few days of life.

The following protocol is recommended initially. Antibiotic choice can then be rationalized on the basis of culture results and clinical course.

Treatment for early onset sepsis

Pen G and Amikacin

Pen G 100,000units/kg per dose IV infusion

Dosing interval

Post menstrual age (weeks)	Post Natal (days)	Interval
≤ 29	0-28	12
	>28	8
30-36	0-14	12
	>14	8
37-44	0-7	12
	>7	8
≥ 45	ALL	6

Amikin

Post menstrual age (weeks)	Post Natal (days)	Dose	Interval
≤ 29*	0-7	18	48
	8-28	15	36
	≥29	15	24
30-34	0-7	18	36
	≥8	15	24
≥35	ALL	15	24

*ALSO FOR BABIES WITH MODERATE TO SEVERE HIE OR TREATMENT WITH BRUFEN

Monitoring: Measure serum concentrations when treating for more than 48hours. Peak 30 minutes after infusion, trough just prior to next dose.

Peak: 20-30mcg/mL

Trough: 2-5mcg/mL

Late Onset Sepsis (LOS)

(After age 3 days in preterm infant After age 7days in term infants):

Incidence of LOS among healthy term infants is much less than early onset sepsis. However, preterm infants and term infants with various medical or surgical conditions are at greater risk for late onset sepsis.

More than 20% of infants with birth weight <1,500 grams will have at least one episode of late onset sepsis. Preterm infants are more severely affected with a mortality of up to 20%.

Risk Factors

- Overcrowding and lack of hand washing.
- Horizontal transmission of causative organisms.
- Endotracheal intubation.
- Indwelling urinary and vascular catheters, especially venous catheters.
- Lack of enteric feeding.
- Exposure to broad-spectrum antibiotics, which may alter normal flora and permit overgrowth and dissemination of fungal species and resistant bacteria.

Causative Organisms:

Gram-positive organisms are important in late neonatal sepsis. Coagulase-negative Staphylococcus species (common skin flora) are common isolates, especially among very preterm infants where they are often the causative pathogen.

Gram-negative bacteria (e.g., *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) also cause a significant proportion of late onset sepsis.

Fungal infections (with *Candida* species) occur often in small preterm infants.

Presentation in some cases of late onset sepsis is gradual. The first indications may be subtle signs such as feeding intolerance, need for increased environmental oxygen, or persistent tachycardia. Some infants become gravely ill very quickly (especially with *Pseudomonas* infections), and the presentation may include any signs mentioned above in Early Onset Sepsis.

Evaluation and Management:

Blood culture.

FBC with differential and platelet count. Calculate the I: T ratio. A value of < 0.2 has good negative predictive value therefore excluding disease.

Lumbar puncture with complete evaluation of CSF is essential. CNS infection is more likely with late onset sepsis,

Urine infection is frequent. Suprapubic needle aspiration urine should be collected for urinalysis and culture.

CRP lag behind the clinical signs, therefore CRP should be done 12h00 after the onset of clinical symptoms.

If the CRP is < 1.0 mg/dL at 12 and 36 hours after the onset of symptoms, the likelihood of proven or probable sepsis is 2.4%.

As soon as cultures have been obtained, antibiotic therapy should be instituted without delay.

When to Stop Antibiotics

- Duration of antibiotic treatment depends upon the clinical condition of the infant and the organism identified on culture.
- Where the likelihood of infection is low, with a baby in good condition and infective indices negative, antibiotics can be ceased if cultures are negative after 48 hours.
- Sepsis strongly suspected, despite negative blood culture at 48 hours. It is advisable to repeat blood culture and continue antibiotics for at least 5 days providing infective indices have normalised. Another approach is to continue antibiotics for 48 hours after indices have normalised.
- Proven gram negative bacteraemia, with clear CSF, treat for 10 days, antibiotics can be rationalised in the face of culture and sensitivities proven GBS bacteraemia, with clear CSF, 10 days treatment should be sufficient
- Meningitis, treat for 14 days for GBS and 21 days for gram negative organisms.
- UTI - treat with IV antibiotics for at least 5 days, a total of 10 days treatment is needed. The infant can be managed with appropriate oral antibiotics for the latter half of the treatment course if clinical condition is satisfactory. Ongoing prophylactic antibiotics will be needed until renal investigations (ultrasound and/or MCU) are completed.

Antibiotic Sensitivity

- Methicillin- resistant *Staphylococcus aureus* (MRSA): vancomycin, or linezolid for serious infections.
- *Enterobacter* spp. *Citrobacter* spp. *Pseudomonas aeruginosa* *Serratia* spp. *Providencia* spp *Morganella* spp: All are resistant to all cephalosporins. Since β -

lactamase inhibitors are potent inducers of cephalosporin resistance, they should not be used.

- Salmonella: Ampicillin/amoxicillin, TMP-SMX
- P. Aeruginosa Acinetobacter spp: usually susceptible to aminoglycosides
- Enterococci: Usually requires double-agent therapy for synergy and bacterial killing for invasive infections. Recommended therapy is ampicillin AND aminoglycoside for serious invasive infections. Other antibiotics with activity against enterococci include, piperacillin, and imipenem. Vancomycin if ampicillin resistant.
- Vancomycin-resistant enterococcus (VRE): VRE is usually Enterococcus faecium, although rarely E. faecalis. Linezolid is active against most enterococcal isolates, including VRE. The following antibiotics are not clinically active against enterococci: all cephalosporins, antistaphylococcal penicillins (e.g., oxacillin), macrolides, clindamycin, and quinolones.

Management

General Measures

In addition to the administration of antibiotics, great attention to supportive care is needed. Antibiotics should be considered as only part of the management of a septic neonate.

Of importance are: thermal care, incubator nursing, phototherapy if warranted, monitoring of oxygen saturation, heart rate and blood pressure.

Respiratory support is needed for hypoxia, hypercapnoea, respiratory distress and apnoea.

Cardiovascular inotropic support is often needed (see management of shock)

Correction of fluid, electrolyte, glucose and haematological derangements (including blood, platelets and clotting factors)

Only the very unstable infant usually needs enteral feedings withheld, consider parenteral alimentation if oral feeding is not possible.

The Group B Streptococcal (GBS) Colonised Mother

The incidence of GBS colonization in South Africa woman is unknown. From the literature it is known that up to 70% of infants born to colonised women are themselves colonised. Infection occurs in 1% of colonised infants. 75% of early onset GBS disease in neonates occurs in term babies. The incidence of GBS disease varies.

Screening for GBS remains the subject of heated debate, but it is known that intrapartum administration of antibiotics (penicillin or amoxycillin) reduces neonatal colonisation by 90%, and early onset GBS disease by 90%. The disadvantage of screening and antibiotic prophylaxis is the risk of maternal complications and the cost. (GBS rates of >0.5 per 1000 live births are needed to justify such an approach on a cost-effectiveness basis).

Recommendations for management of the infant where the mother was identified with Group B Streptococcal (GBS) infection.

Mothers who are to receive intrapartum antibiotic prophylaxis (Pen G, Ampicillin or Cefazolin) at the onset of labour and then 4hourly:

- Previous baby with GBS disease.
- GBS bacteriuria in present pregnancy
- Positive GBS screen at 35-37 week gestation.

Preterm baby where the mother received intrapartum prophylaxis: Admit and observe but special investigations and antibiotic is not indicated if the baby is asymptomatic.

Preterm baby where the mother did not receive intrapartum prophylaxis: Admit, observe, do special investigations as indicated and starts Pen G (Benzyl penicillin) 100 000U/kg/dose 12 hourly if <1 week old. Pen G (Benzyl penicillin) 100 000U/kg/dose 8 hourly if >1 week old.

Term baby where the mother received intrapartum prophylaxis: Observe for 24h00. Routine special investigations and antibiotics are not indicated if the baby is asymptomatic.

Term baby where the mother did not receive intrpartum prophylaxis: Admit the baby, do special investigations and start Pen G.

If the infant is initially (or becomes) symptomatic, or if significant prematurity (<35 weeks gestation) is present, the infant should undergo a septic evaluation and treatment with intravenous antibiotics despite maternal intrapartum prophylaxis. LP is indicated in all blood culture positive patients or if indicated on clinical grounds.

Meningitis: Pen G 100 000 U/kg/dose 8 hourly if < 1 week old.

Pen G 125 000 U/kg/dose 6 hourly if > 1 week old.

Prolonged Rupture of Membranes (PROM)

PROM for greater than 18 hours may lead to increased risk of infection in mother and baby. Babies born with a background of PROM need to be viewed as potentially at risk of sepsis.

Preterm infants, particularly those <35 weeks, are usually screened for sepsis and treated with IV antibiotics until infection in the baby has been excluded.

Term infants if there are no risk factors, apart from the PROM; the infant is usually observed closely and treated only if symptoms develop.

If there is a risk factor present in addition to PROM, such as GBS positive mother, maternal intrapartum fever or suspected chorioamnionitis that infant should be treated as potentially septic, even if completely asymptomatic.

Any symptomatic baby needs septic evaluation performed and treatment for infection regardless of the presence or absence of risk factors.

Fungal Sepsis

VLBW infants are at the highest risk. Risk factors include multiple courses of IV antibiotics, presence of central lines and extensive areas of skin breakdown. Consideration of fungal sepsis is particularly necessary when such infants deteriorate whilst receiving antibiotics. Empirical treatment with Fluconazole until cultures are reported as clear for fungal organisms is appropriate. SPA of urine must be performed prior to starting Fluconazole as bag specimens will often be contaminated with Candida colonising the skin. If fungal sepsis is confirmed, the sensitivity of the organism must be evaluated. If no clear improvement is evident consider changing to Amphotericin B. Duration of treatment depends upon the site of infection but generally ranges from 3 to 6 weeks or 21 days after the first negative blood culture. Ultrasound of the kidneys and formal fundoscopy should be performed.

Areas of Uncertainty

The role of antigen tests for GBS is controversial

Suprapubic urine specimens for GBS antigen can be positive when babies are colonised, while bag specimens can be contaminated with skin GBS colonisation that will result in a positive test. Antigen tests are more sensitive and specific for CSF specimens, but cannot be relied upon to exclude infection. Antigen testing results adds supplementary evidence of possible infection, but cannot be relied upon to prove or disprove GBS infection, and is therefore of limited value.

Antifungal prophylaxis

A recent Cochrane review failed to demonstrate a reduction in fungal colonisation among patients receiving prophylactic oral nystatin compared to placebo. All patients in these trials were immuno-compromised but beyond the neonatal period.

Prophylactic antifungal might select for resistance.

Treatment with Granulocyte Colony Stimulating Factor (G-CSF)

G-CSF has been shown to increase PMN counts in VLBW babies, but the effect on sepsis reduction or mortality from sepsis has not been demonstrated.

Intravenous immunoglobulin (IVIG)

Studies involving IVIG show a possible improvement in mortality in babies given IVIG as part of the treatment of sepsis. However, larger trials are needed to examine the role of IVIG in neonates with sepsis.

Late onset neonatal sepsis is mainly acquired nosocomially. Prevention, therefore, is ideal but despite optimal hand-washing, staffing and NICU design, premature infants will continue to develop late onset infection secondary to immature immune responses, invasive devices and opportunistic infections. Knowledge and surveillance of the organisms present in a Neonatal Intensive Care Unit may help clinicians to choose the right antibiotic for treating and preventing sepsis.

ANTIBIOTIC PROTOCOL FOR SUSPECTED AND / OR PROVEN NEONATAL SEPSIS.

Infection	Most probable organisms	Drug of Choice
Suspected early onset sepsis (Less ≤72h in preterm)	Community acquired E coli and GBS	Empiric choice Pen G & Amikacin
Group B Streptococcus sepsis	S agalactica	Pen G 100 000U/kg/dose q12h if <1 w Pen G 100 000U/kg/dose q8h if >1 w
Group B Streptococcus meningitis	S agalactica	Pen G 100 000U/kg/dose q8h if <1 w Pen G 120 000U/kg/dose q6h if >1 w
Suspected late onset sepsis Nosocomial sepsis in preterm infants		Empiric choice Piperacillin-tazobactam & Amikacin (for babies in ward more than 72h without previous treatment with Amikacin) or Meronem (in severe sepsis)
	Klebsiella pneumonia	Meronem
	Enterococcus spp	Piperacillin-tazobactam & Amikacin or Meronem (in severe sepsis)
	S. aureus (MRSA)	Vancomycin or Linizolid
	Proteus mirabilis	Piperacillin-tazobactam & Amikacin or Meronem (in severe sepsis)
	Pseudomonas aeruginosa	Colistin
	Acinetobacter spp	Tobromycin or Colistin
	Serratia spp.	Amikacin and Meronem
	S.epidermidis(coag neg) Confirm invasive disease	Vancomycin
Congenital syphilis		Procaine Penicillin 50 000 U/kg/day. Give once a day for 10days
Catheter related sepsis		Remove long IV-line Meronem Assess for invasive fungus infection
Meningitis	GBS	Pen G
	Listeria	Ampicillin
	Multi-resistant Klebsiella	Meronem
	Herpes	Acyclovir
	Candida	Amphotericine B
	No organism identified	Claforan (Cefotaxime)
NEC		Meronem Flagyl (if perforated)
Invasive fungus sepsis		Amphotericine B

The use of Colistin, Vancomycin, Linzolid and Amphotericin B must be discussed with the ward consultant.

Reference: Martin RJ, Fanaroff AA, Walsh MC Neonatal-Perinatal Medicine Diseases of the Fetus and Infant; 9th Edition. ELSEVIER. USA 2010
Remington JS, Klein JO. Infectious Diseases of the Fetus and Newborn Infant 7th Edition. ELSEVIER, USA 2010
Ampath's Bacterial Resistance Data -2009.

