

# MANAGEMENT OF NEWBORNS AT RISK OF EARLY AND LATE NEONATAL INFECTIONS

## Background

- Early-onset neonatal infection: Infection with onset in the first 72h of life.
  - Early-onset GBS infection: respiratory illness 35-55%, septicaemia 25-40%, meningitis 5-15%; major neurologic sequelae 25-30%, normal 50-60%; mortality 5-20%
- Late-onset neonatal infection: Infection with onset after the first 72h of life
  - Late-onset GBS infection: bacteraemia without focus 40-50%, meningitis 30-40%, osteomyelitis/septic arthritis 5-10%, mortality 2-6%
- Gram-negative meningitis: 20-30% mortality rate, 35-50% neurologic sequelae (30% hydrocephalus, 30% seizures, 25% developmental delay/cerebral palsy and 15% hearing loss, 10% severe sequelae)
- 40% of infants with meningitis <35 weeks do not have a positive blood culture result at the time of diagnosis

## General Sepsis Management

### **Observations**

- At 1 & 2 hours followed by 2 hourly observations for 10 hours, then 4 hourly depending on risk factors, clinical condition and antibiotic treatment. See also NEWS on postnatal ward:
  - Body temperature and overall wellbeing and behaviour
  - Skin colour, including capillary refill time
  - Grunting, nasal flaring, chest movements, respiratory rate, heart rate, feeding
  - Muscle tone

### **Investigations**

- Always ensure adequate analgesia for procedures
- Blood:
  - FBC, CRP, Blood culture (min. 1ml) before start of antibiotics; Blood PCR (min. 1ml) before start of antiviral treatment; consider LFTs, etc.
  - Repeat FBC and CRP >6h <24h after the first blood test
    - Neutropenia within the first 48h of life ( $<2-2.5 \times 10^9/l$ ) suggests bacterial infection and neutropenia or neutrophilia ( $>7.8-8.0 \times 10^9/l$ ) after 48h of age are also useful predictors.
    - Ratio of immature to total neutrophil count (I/T ratio)  $>0.2$  suggests infection. A high ratio in presence of low overall neutrophil count makes infection more likely.
    - Toxic granulation of neutrophils on film suggests infection
    - In 50% of babies with bacterial infection the platelet count will fall below  $100 \times 10^9/l$  but this is often a late finding.
    - Viral infections, e.g. CMV and HSV can cause profound thrombocytopenia and/or abnormal liver function tests
- Chest x-ray if chest pathology signs/symptoms present
- CSF – LP, if it does not delay treatment, for:
  - Septic shock (very unwell newborn) irrespective of CRP
  - Unwell baby with a CRP  $\geq 10-20$  mg/l
  - Any baby with high CRP  $\geq 20$  mg/l
  - Positive blood culture irrespective of CRP
  - CNS signs/symptoms (encephalopathic) irrespective of CRP considering differential diagnoses
  - Poor response to antibiotic treatment present
    - Normal CSF does not always rule out bacterial meningitis and, therefore repeat CSF analysis should be considered and antimicrobial therapy reviewed.
    - A positive Gram stain can suggest bacterial meningitis before culture results are available. However, a negative Gram stain does not exclude the diagnosis.
    - CSF WBC count  $>20$  cells/mcl (95<sup>th</sup> centile) have a sensitivity and specificity of 80% to predict culture-proven meningitis in newborns  $\geq 35$  weeks gestation in first week of life.

- CSF WBC count is typically greater in neonates with gram-negative meningitis than with gram-positive meningitis.
- CSF protein is highly variable, but a value >130 mg/dl (approx. 95<sup>th</sup> centile) in newborns ≥35 weeks gestation in first week of life has a sensitivity of 75% and specificity of 60% to predict culture-proven meningitis is consistent with bacterial meningitis.
- CSF glucose is highly variable, but a value <30 mg/dl (1.7 mmol/l) (approx. 95<sup>th</sup> centile) in first week of life has a sensitivity of 90% and specificity of 20% to predict culture-proven meningitis is consistent with bacterial meningitis.
- CSF values for WBC and protein fall with postnatal age whilst glucose remains static. Approximate values for 95<sup>th</sup> centile in newborns ≥35 weeks gestation are: >15 cells/mcl (7-21 days) and >10 cells/mcl (>21 days); >120 mg/dl (7-21 days) and >100 mg/dl (>21 days)
- CSF WBC count and glucose in preterm infants are not significantly different at birth and with advancing postnatal age (see values above). CSF protein is significantly higher at birth and declines more slowly with postnatal age in preterm infants; a CSF protein value >150 mg/dl at birth is suggestive of meningitis
- The chance of growing bacteria reduces after only 1–2 hours of antibiotic, but CSF samples taken up to 96 hours after treatment started may give useful results regarding CSF white cell count.
- Adjustment of CSF WBC count with a traumatic LP does not improve diagnostic utility and can result in loss of sensitivity with a marginal gain in specificity; this also applies to protein and glucose.
- The ratio of CSF to serum glucose is not useful in acutely unwell neonates
- Urine - only after the first 72h of life except if there is a predisposition to UTI:
  - Dipstick urine collected from bag or mid-stream, if no catheter in situ.
  - Dipstick test for UTI has a negative predictive value of 98.7%. Adding microscopy increases the NPV to 99.2% but results in 8 false-positives for every UTI missed.
  - Use catheter or SPA for collecting urine, if initial results are inconclusive or suggestive of UTI (see table):

Dipstick	Leukocyte esterase positive	Leukocyte esterase negative
<b>Nitrite positive</b>	<ul style="list-style-type: none"> <li>• UTI confirmed until proven otherwise</li> <li>• Send off sample for cell count and culture</li> </ul>	<ul style="list-style-type: none"> <li>• Treat as confirmed UTI, if baby unwell</li> <li>• Attempt SPA/catheter sampling</li> <li>• Send sample for cell count and culture if successful</li> <li>• Subsequent management will depend upon urine culture result</li> </ul>
<b>Nitrite negative</b>	<ul style="list-style-type: none"> <li>• Treat as confirmed UTI, if baby unwell</li> <li>• Attempt SPA/catheter sampling</li> <li>• Send sample for cell count and culture</li> <li>• Subsequent management will depend upon the urine culture result</li> <li>• Leukocyte esterase may be indicative of an infection outside the urinary tract</li> </ul>	<ul style="list-style-type: none"> <li>• UTI not confirmed until proven otherwise</li> <li>• Send sample for cell count and culture</li> </ul>

Microscopy	Pyuria positive	Pyuria negative
<b>Bacteriuria positive</b>	UTI until proven otherwise	UTI, if clinically unwell
<b>Bacteriuria negative</b>	UTI, if clinically unwell	No UTI

- Skin or eye swabs only if signs/symptoms of local infection or for specific indications, e.g. suspected HSV
- No surface swabs or gastric aspirates

## Early Onset Sepsis Management

- Assess for risk factors for sepsis in either the mother or baby. Risk factors in **RED** are considered **RED FLAGS**.
- Start antibiotics on **ANY NEONATE WITH RED FLAGS**.

### **Maternal Risk Factors**

- Previous baby with invasive GBS infection
- Maternal GBS colonisation, bacteriuria or infection in this pregnancy
- Maternal rupture of membranes for >24h in any newborn (PROM)
- Maternal fever (>37.5°C on two or more occasions at least 1 hour apart, or a single temperature >38°C) before or during birth
- **MATERNAL SEPSIS**
  - Clinical suggestion of infection (e.g. non-blanching rash)

#### AND

- WBC <4,000 or >20,000cells/mcl (or >15,000cells/mcl and rising, or >10% immature bands)

#### AND at least two of the following:

- Temperature >37.5°C at least twice 1h apart or >38°C once or <36°C once
- Respiratory rate >20-25 bpm
- Heart rate >100-130 bpm
- Systolic BP <90-100mmHg
- Not passed urine in the past 12-18h
- Acute change in mental state

#### OR at least one of the following:

- Respiratory rate >25 bpm or oxygen requirement
- Heart rate >130 bpm
- Systolic BP ≤90mmHg (or drop >40 mmHg from normal)
- Not passed urine in the past 18h
- Lactate ≥2mmol/l
- Altered mental state

- **CHORIOAMNIONITIS**

- Temperature >37.5°C at least twice 1h apart or >38°C once or <36°C once

#### AND at least one of the following:

- Uterine tenderness
- Foul-smelling amniotic fluid
- Foetal tachycardia

- Prematurity <35 weeks gestation and low birth weight (<2500 g)
- Thick particulate meconium stained liquor

- **UNWELL SIBLING REQUIRING ANTIBIOTICS IN MULTIPLE-PREGNANCY**

### **Neonatal Risk Factors**

- **APGAR SCORE <5 @ 5 MINUTES**
- **PERSISTENT NEED FOR CONTINUOUS RESPIRATORY SUPPORT (PRESSURE SUPPORT AND/OR SUPPLEMENTAL OXYGEN TO MAINTAIN OXYGEN SATURATIONS >89%) AFTER INITIAL STABILISATION AT BIRTH**
- **HAEMODYNAMIC INSTABILITY REQUIRING VASOACTIVE DRUGS AFTER BIRTH**
- **NEONATAL ENCEPHALOPATHY/PERINATAL DEPRESSION +/- SEIZURES**
- Temperature instability (<36.4 - >37.9°C)
- Respiratory distress (respiratory rate >60bpm, grunting, flaring, or retracting) not requiring supplemental oxygen after birth
- Bradycardia (<120bpm) or tachycardia (≥160bpm)
- Poor feeding, vomiting, other signs/symptoms of abdominal pathology (e.g. abdominal distension, large gastric aspirates)
- Oligouria >24h after birth

- Hypo-/hyperglycaemia, metabolic acidosis (BE >-7mmol/l)
- Petechiae, other signs/symptoms of bleeding disorder (e.g. INR >2.0)
- Jaundice <24h, umbilical flare, signs/symptoms of local infection (e.g. purulent eyes)
- Abnormal muscle tone, abnormal movements, signs/symptoms of mild encephalopathy
- Abnormal vigilance state, irritability, lethargy

**Early Onset Sepsis Calculator**

- For **NON-RED FLAG** sepsis risk factors use the calculator. It provides an EOS risk/1000 births.
- Set the background infection rate at 0.5/1,000 and enter the following information:
  - Highest maternal antepartum temperature (°C)
  - Duration of rupture of membranes (hours)
  - Maternal GBS status
  - Maternal intrapartum antibiotic prophylaxis
  - Gestational age

<https://neonatalesepsiscalculator.kaiserpermanente.org/InfectionProbabilityCalculator.aspx>

- Follow the management pathway as indicated by the calculator (**Green/Amber/Red**) combined with the classification of the clinical examination **Well/ Equivocal/ Clinically Unwell** as defined by the calculator: N.B Temperature instability (> 100.4°F or < 97.5°F) = (<36.4 - >37.9°C)

<b>No culture No antibiotics</b>	<ul style="list-style-type: none"> <li>• Observations at 1 &amp; 2 h followed by 2 hourly observations for 10 h (total 12 h).</li> <li>• Babies with abnormal observations or other concerning signs will require a neonatal review.</li> <li>• Babies with completely normal observations will need a final neonatal review before discharge.</li> </ul>
<b>No culture No antibiotics</b>	<ul style="list-style-type: none"> <li>• Observations at 1 &amp; 2 h followed by 2 hourly observations for 10 h and then 4 hourly observations for 12 h (total 24 h).</li> <li>• Babies with abnormal observations or other concerning signs will require a neonatal review.</li> <li>• Babies with completely normal observations will need a final neonatal review before discharge.</li> </ul>
<b>Blood Culture</b>	<ul style="list-style-type: none"> <li>• Observations at 1 &amp; 2 h followed by 2 hourly observations for 10 h and then 4 hourly observations for 12 h (total 24 h).</li> <li>• Investigations: FBC, CRP, Blood culture. Consider chest x-ray if chest pathology signs/symptoms present.</li> <li>• Hold IV antibiotics pending results.</li> <li>• Repeat FBC and CRP &gt;6 h &lt;24 h after the first blood test.</li> <li>• Babies with abnormal investigations or observations or other concerning signs will require a neonatal review and consideration of IV antibiotics.</li> <li>• Discharge only once all results are back and reassuring.</li> <li>• Babies with completely normal observations and not started on IV antibiotics will need a final neonatal review before discharge.</li> </ul>
<b>Empiric antibiotics</b>	<ul style="list-style-type: none"> <li>• Observations at 1 &amp; 2 h followed by 2 hourly observations for 10 h and then 4 hourly observations until antibiotics stopped.</li> <li>• Investigations: FBC, CRP, Blood culture. Consider chest x-ray if chest pathology signs/symptoms present.</li> <li>• Aim to administer IV antibiotics within 1h of the decision to treat.</li> <li>• Repeat FBC and CRP &gt;6 h &lt;24 h after the first blood test.</li> <li>• Babies started on IV antibiotics should remain on 4 h observations until antibiotics are stopped.</li> <li>• Discharge once results are back, reassuring and antibiotic treatment completed.</li> </ul>

- Document the clinical examination as well as the Sepsis Calculator outcome in the baby's notes.
- Give the parental information leaflet and explain the management pathway.
- Post-natal doctor/ANNP to complete and update the EOS audit tool. (T drive/TMBUSHO/Postnatal Ward Handover/KP Audit Data Collection).

### **Antibiotic Treatment**

- Early-Onset Sepsis:
  - Benzylpenicillin and Gentamicin for NICU/HDU (see formulary)
  - Cefotaxime for postnatal ward and PRH SCBU (see formulary)
  - Amoxicillin and Gentamicin for suspected Listeria sepsis
  - Amoxicillin and Cefotaxime for suspected meningitis (see formulary)
  - Consider adding Aciclovir in case of unusual skin rash, severe thrombocytopenia, abnormal liver function tests and/or unexplained encephalopathy
- Late-Onset Sepsis:
  - Cefotaxime (first-line)
  - Piperacillin and Tazobactam (second-line)
  - Meropenem (third-line or second-line in case of bacterial meningitis)
  - Consider adding Vancomycin for suspected CVL sepsis
    - Remove CVL, if possible or alternatively start Vancomycin infusion
  - Consider adding Metronidazole for gastrointestinal infection with sepsis or NEC
  - Consider adding Aciclovir or Fluconazole in case of unusual skin rash, severe thrombocytopenia, abnormal liver function tests and/or unexplained encephalopathy
- Focal Infection:
  - Flucloxacillin (+/- Gentamicin) for soft tissue infection incl. omphalitis
  - Chloramphenicol (topical) for bacterial conjunctivitis
- A minimum of 36-48h of antibiotics is recommended in any case
- Stop treatment after 36-48h, if blood culture negative
  - AND
  - low level of suspicion
  - AND
  - well baby
  - AND
  - CRP <10mg/l and no other abnormal laboratory markers
- Continue treatment otherwise:
  - for as long as needed, if blood culture negative, but baby is unwell (review need for antibiotics every 24h)
  - for 7 days if blood culture positive
  - for >7-10 days if blood culture positive and baby unwell
  - for 14 days if GBS meningitis present
  - for 21 days if Gram-negative meningitis present
- Discuss with Microbiology Consultant as needed