MANAGEMENT OF
NEWBORNS AT RISK OF EARLY AND LATE NEONATAL INFECTIONS

General Considerations

Definitions:
- Early-onset neonatal infection: Infection with onset in the first 72h of life
- Late-onset neonatal infection: Infection with onset after the first 72h of life
- Prolonged rupture of membranes: >24h in any gestation

Background:

<table>
<thead>
<tr>
<th>Type of GBS Infection</th>
<th>Clinical Presentations</th>
<th>Survival</th>
<th>Longterm Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset GBS infection</td>
<td>Septicemia (25-40%)</td>
<td>5-20% mortality</td>
<td>25-30% major neurologic sequelae 50-60% are normal</td>
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<tr>
<td></td>
<td>Meningitis (5-15%)</td>
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<td>Respiratory illness (35-55%)</td>
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<tr>
<td>Late-onset GBS infection</td>
<td>Bacteremia without focus (40-50%)</td>
<td>2-6% mortality</td>
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<tr>
<td></td>
<td>Meningitis (30-40%)</td>
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<td></td>
<td>Osteomyelitis/septic arthritis (5-10%)</td>
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</table>

- 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

Maternal risk factors (Red Flags in BOLD):
- 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
  - White blood cell count <4,000 or >20,000 cells/microliter (or >15,000 cells/microliter and rising, or >10% immature bands)
  AND two or more of the following:
    - Temperature >37.5°C on two or more occasions at least 1 hour apart or a single temperature >38°C before giving birth or temperature <36°C
    - Acute change in mental state
    - Respiratory rate >20 to 25 breaths/min
    - Heart rate >100 to 130 beats/min
    - Systolic BP >90 to 100mmHg
    - Not passed urine in the past 12 - 18h
  OR one or more of the following:
    - Altered mental state
    - Respiratory rate >25 breaths/min or oxygen requirement
    - Heart rate >130 beats/min
    - Systolic BP ≤90mmHg (or drop >40 mmHg from normal)
    - Not passed urine in the past 18h
    - Lactate ≥2mmol/l
- **Maternal Sepsis with Chorioamnionitis:**
  - See above
  - **AND** one or more of the following:
    - Uterine tenderness
    - Foul-smelling amniotic fluid
- **Antibiotic treatment for suspected infection [not prophylaxis] 24h before to 24h after birth**
- Prematurity <35 weeks gestation and low birth weight (<2500 g)
- Meconium stained liquor
- **Unwell sibling requiring antibiotics in multiple-pregnancy**

**Adequate maternal antibiotics:**
- Correct intravenous antibiotic and dose ≥ 4 hours before birth

**Observations:**
- Every 1 & 2 hours followed by 2 hourly observations for 10 hours.
- These should include:
  - 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

**Clinical signs of an Unwell Baby (Red Flags in BOLD):**
- Temperature instability (<36.6 - >37.2°C)
- Abnormal vigilance state, irritability, lethargy
- **Need for cardio-pulmonary resuscitation or mechanical ventilation**
- **Apnoea or abnormal saturations**
- Respiratory rate >60 bpm or other signs or symptoms of respiratory distress
- **Respiratory rate >60 bpm (or other signs or symptoms of respiratory distress) after or persisting for >3-6 hours after birth**
- Bradycardia, tachycardia, arterial hypotension
- **Signs of shock**
- Poor feeding, vomiting, other signs or symptoms of abdominal pathology
- Oligouria >24h after birth
- Hypo/hyperglycaemia, metabolic acidosis (BE >-7mmol/l)
- Petechiae, other signs or symptoms of bleeding disorder (e.g. INR >2.0)
- Jaundice < 24h, umbilical flare, other signs of local infection (e.g. purulent eye discharge)
- Abnormal muscle tone, abnormal movements, symptoms and signs of encephalopathy
- **Seizures**

**Investigations:**
- Always ensure adequate analgesia for procedures
- **Blood**
  - FBC, CRP, Blood culture (min. 1 ml) before start of antibiotics; consider LFTs, etc.
  - Repeat FBC and CRP >6h <24h after the first blood test
    - Neutropenia within the first 48h of life (<2-2.5x10^9/l) suggests bacterial infection and neutropenia or neutrophilia (>7.8-8.0x10^9/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 100x10^9/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 or symptoms present
- CSF – LP, if it does not delay treatment, for:
  - Septic shock (very unwell newborn) irrespective of CRP
  - Unwell baby with a CRP ≥10 – 20 mg/l
  - Any baby with high CRP ≥20mg/l
  - Positive blood culture irrespective of CRP
  - CNS signs (encephalopathic) irrespective of CRP considering differential diagnoses
  - Poor response to antibiotic treatment present
    - 40% of infants with meningitis <35 weeks do not have a positive blood culture result at the time of diagnosis
    - 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/microliter (approx. 95th centile) have a sensitivity and specificity of 80% to predict culture-proven meningitis in newborns ≥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. 95th 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. 95th 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 95th centile in newborns ≥35 weeks gestation are: >15 cells/microliter (7-21 days) and >10 cells/microliter (>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
  - Use catheter or SPA for collecting urine, if initial results are inconclusive or suggestive of UTI (see table)
  - 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
<table>
<thead>
<tr>
<th>Dipstick</th>
<th>Leukocyte esterase positive</th>
<th>Leukocyte esterase negative</th>
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<td>Nitrite positive</td>
<td>• UTI confirmed until proven otherwise</td>
<td>• Treat as confirmed UTI, if baby unwell</td>
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<tr>
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<td>• Send off sample for cell count and culture</td>
<td>• Attempt SPA/catheter sampling</td>
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<td>• Subsequent management will depend upon the result of urine culture</td>
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<td>• Leukocyte esterase may be indicative of an infection outside the urinary tract</td>
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<tr>
<td>Nitrite negative</td>
<td>• Treat as confirmed UTI, if baby unwell</td>
<td>• UTI not confirmed until proven otherwise</td>
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<th>Pyuria positive</th>
<th>Pyuria negative</th>
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<td>Bacteriuria positive</td>
<td>UTI until proven otherwise</td>
<td>UTI, if clinically unwell</td>
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<td>Bacteriuria negative</td>
<td>UTI, if clinically unwell</td>
<td>No UTI</td>
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- Skin or eye swabs only if signs of local infection or for specific indications, e.g. suspected HSV.
- No surface swabs or gastric aspirates.

**Recommended antibiotic treatment:**
- Start treatment within 1h of decision to treat

**EOS - see EOS algorithm below**
- 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

**LOS:**
- 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
Consider adding Aciclovir or Fluconazole in case of unusual skin rash, severe thrombocytopenia, abnormal liver function tests and/or other findings suggestive of a possible viral or fungal infection (see separate guidance for prophylaxis and management of confirmed viral or fungal infections)

- **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
Early Onset Sepsis Algorithm

[Diagram showing decision tree for early onset sepsis with red flags in mother or baby, maternal risk factors, and neonatal outcomes]

Red Flags in Mother or Baby
- Maternal Sepsis (+/- chorioamnionitis)
- Maternal antibiotic treatment for suspected infection [not prophylaxis] 24h before to 24h after birth
- Unwell sibling requiring antibiotics in multiples
- Neonatal cardio-pulmonary resuscitation or mechanical ventilation
- Neonatal apnoea or abnormal saturations
- Neonatal respiratory rate >60 bpm (or other signs of respiratory distress) after or persisting for >3-6h after birth
- Signs of neonatal shock
- Neonatal seizures

Maternal Risk Factors
- Previous baby with invasive GBS infection
- Maternal GBS colonisation, bacteriuria or infection in this pregnancy
- Maternal PROM
- Maternal fever
- Prematurity <35 weeks gestation and <2500 g birthweight
- Meconium stained liquor

NB: Babies born by elective section (no labour and intact membranes) do not need observations.