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:

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

- 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 >20,000cells/microliter (or >15,000cells/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/Symptoms 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/symptoms of respiratory distress after birth
- **Respiratory rate >60 bpm** (**or other signs/symptoms of respiratory distress) persisting for >3-6 hours after birth**
- Bradycardia, tachycardia, arterial hypotension
- **Signs of shock**
- Poor feeding, vomiting, other signs/symptoms of abdominal pathology
- 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 encephalopathy
- **Seizures**

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 (<2-2.5x10^9/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/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/symptoms (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. 95^{th} 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. 95^{th} 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^{th} 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^{th} 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

Dipstick	Leukocyte esterase positive	Leukocyte esterase negative
Nitrite positive	• UTI confirmed until proven otherwise • Send off sample for cell count and culture	• Treat as confirmed UTI, if baby unwell • Attempt SPA/catheter sampling • Send off sample for cell count and culture if successful • Subsequent management will depend upon the result of urine culture
Nitrite negative	• Treat as confirmed UTI, if baby unwell • Attempt SPA/catheter sampling • Send off sample for cell count and culture if successful • Subsequent management will depend upon the result of urine culture • Leukocyte esterase may be indicative of an infection outside the urinary tract	• UTI not confirmed until proven otherwise • Send off sample for cell count and culture

Microscopy	Pyuria positive	Pyuria negative
Bacteriuria positive	UTI until proven otherwise	UTI, if clinically unwell
Bacteriuria negative	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

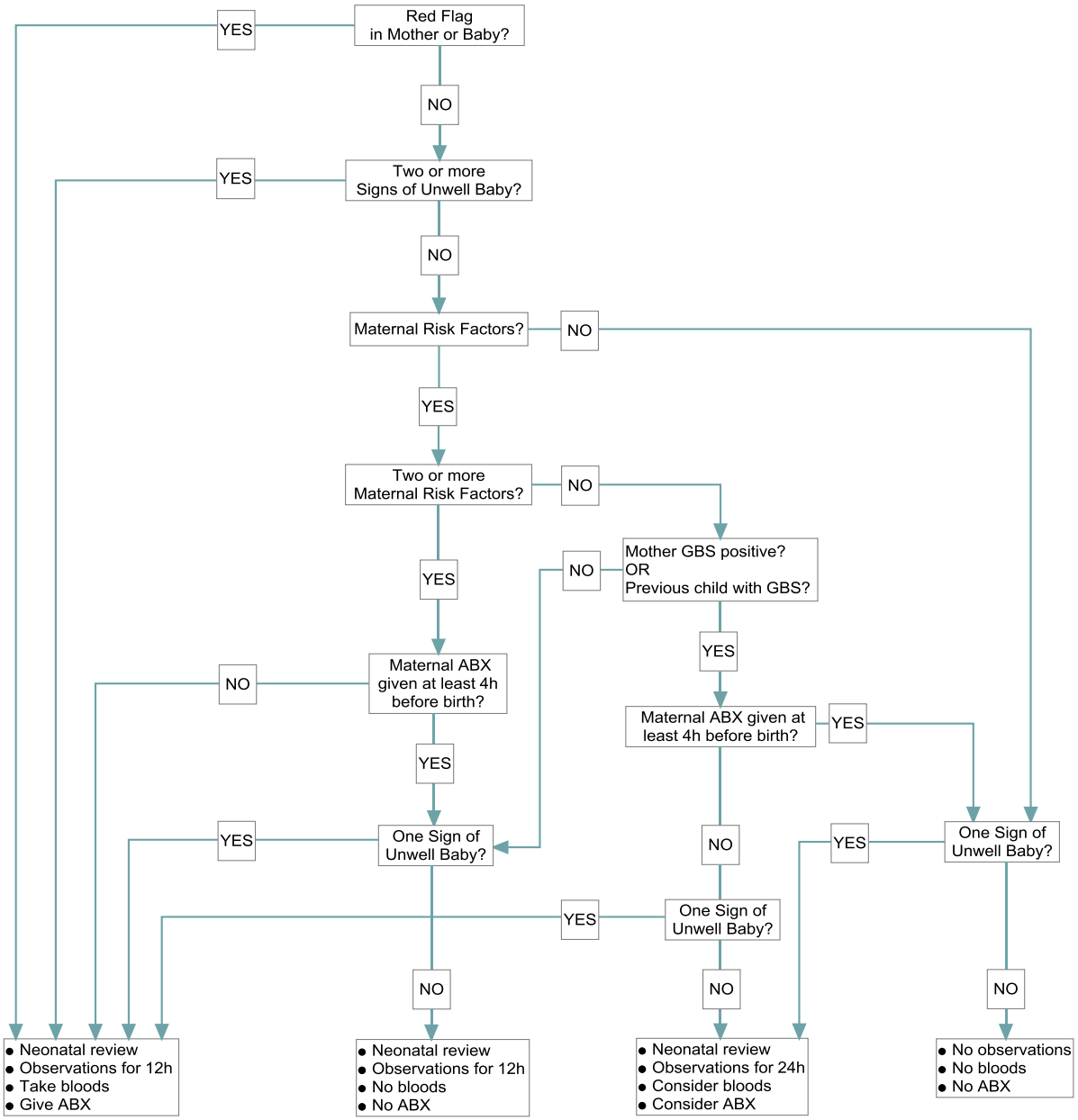
Recommended antibiotic treatment:

- 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 or NEC

- 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



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

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 CPR or mechanical ventilation	
Neonatal apnoea or abnormal saturations	
Neonatal respiratory rate >60bpm (or other signs of respiratory distress) for >3-6h after birth	
Signs/symptoms of neonatal shock	
Neonatal seizures	
Maternal Risk Factors	
Previous baby with invasive GBS infection	
GBS colonisation, bacteriuria or infection this pregnancy	
Maternal PROM	
Maternal fever	
Prematurity <35wks gestation and <2500g birthweight	
Thick (particulate) meconium in liquor at birth	

Unwell Baby	
Temperature instability (<36.6 - >37.2°C)	
Abnormal vigilance state, irritability, lethargy	
Respiratory rate >60 bpm or other signs of respiratory distress after birth	
Bradycardia, tachycardia, arterial hypotension	
Poor feeding, vomiting, other signs of abdominal pathology	
Oligouria >24h after birth	
Hypo-/hyperglycaemia, metabolic acidosis	
Petechiae, other signs of bleeding disorder	
Jaundice <24h, umbilical flare, signs of local infection	
Abnormal muscle tone, abnormal movements, signs of encephalopathy	