INFECTION (LATE ONSET) ● 1/5

Late-onset neonatal infection (infection arising >72 hr after birth) has a higher incidence than early-onset neonatal infection (infection arising within 72 hr of birth) and the spectrum of causative micro-organisms is broader than in early-onset infection

DEFINITION

- Infection >72 hr after birth
- When acquired in hospital – most commonly Gram-positive organisms. Coagulase-negative staphylococci (CoNS) account for approximately 50% of all late onset infections
- Gram-negative bacteria accounts for 20–40% and these are increasingly resistant to gentamicin (*Klebsiella>Serratia>Enterobacter>Pseudomonas>E.coli* and *Acinetobacter*)

Risk factors

- Prematurity
- Low-birth-weight
- Mechanical ventilation
- History of surgery
- Presence of central catheter
- Parenteral nutrition
- Delayed introduction of enteral feeds is associated with higher infection rates
- Increased risk of sepsis after gut surgery especially if enteral feeds slow to establish e.g. post-gastroschisis or necrotising enterocolitis (NEC) with stoma
- Think about infection in the other babies when one baby from a multiple birth has infection

PREVENTION

- Bare below elbow
- no jewellery except wedding band
- **Strict hand washing and alcohol hand rubs**
- Follow WHO **5 moments of hand hygiene** recommendations
- Meticulous regimen for changing IV fluid administration sets and 3-way taps
- Initiate enteral feeds with maternal breast milk within 6 hr of birth

PRESENTATION

- Can be vague and non-specific

Signs

Behaviour

- Parent or care-giver concern for change in behaviour
- Appears ill to healthcare professional
- Does not wake, or if roused does not stay awake
- Weak high-pitched or continuous cry

Respiratory

- Raised respiratory rate: ≥60 breaths/min
- Grunting and other signs of increased work of breathing
- Apnoea
- Oxygen saturation of <90% in air or increased oxygen requirement over baseline

Circulation and hydration

- Persistent tachycardia: heart rate ≥160 beats/min
- Persistent bradycardia: heart rate <100 beats/min

Skin

- Mottled or ashen appearance
- Cyanosis of skin, lips or tongue
- Non-blanching rash

GI

- Alteration in feeding pattern
- Distension and tenderness
- Reduced or absent bowel sounds
- Blood in stool

INFECTION (LATE ONSET) ● 2/5

Other

- Temperature <36°C **or** ≥38°C, unexplained by environmental factors
- Reluctance to move joint or limb (suggestive of osteomyelitis or septic arthritis)
- Septic spots in eyes, umbilicus, nails or skin
- Bulging fontanelle suggesting raised intracranial pressure (rarely detectable in babies with neonatal meningitis)
- Seizures
- Petechiae

INVESTIGATIONS (perform before starting antibiotics)

Swabs or ETT secretions for culture

- Swab any suspicious lesion (e.g. skin, umbilicus or nails)
- Refer to recent swabs or ETT secretion cultures to guide antibiotic therapy

Blood cultures

- From a peripheral vein, using a **closed system**, non-touch, aseptic technique
- If blood collected from cannula hub risk of culturing CoNS skin contaminants

Full blood count

- A neutrophil count <2 or >15 × 10^9/L (supportive but not diagnostic, and marginally more sensitive than a total white cell count)
- Platelet count of <100 × 10^9/L
- Toxic granulation in neutrophils [or if measured, an immature:total (I:T) neutrophil ratio >0.2]

Clotting profile

- If evidence of bleeding diathesis or in severe infection/septicaemia

CRP

- Acute phase protein synthesised in the liver in response to inflammatory cytokines
- Generally a delay of 18−24 hr between onset of symptoms and rise in serum CRP
- Take sample at presentation and further sample 18–24 hr after first CRP sample; use this together with later readings to assess the likelihood of infection and response to treatment

Urine microscopy, culture and sensitivity

- Do not routinely perform urine microscopy or culture as part of the investigations for late-onset neonatal infection for babies in neonatal units
- For babies outside of neonatal units follow the NICE guideline on urinary tract infection in under 16s (CG54)

Lumbar puncture (LP)

- If safe to do so, perform LP to obtain cerebrospinal fluid sample when:
- strong clinical suspicion of neonatal infection or
- clinical symptoms or signs suggesting meningitis
- If baby unstable, deranged clotting or thrombocytopenia, discuss advisability with consultant
- Send CSF for urgent Gram-stain and culture (MC&S), protein and glucose
- PCR for bacteria and viruses where indicated
- In critically ill baby, consider PCR for HSV, especially term babies

Others

- Chest X-ray
- If abdominal distension noted, abdominal X-ray
- Consider removing central lines for all infections (unless access major issue). Line removal should be a considered decision
- If line 'precious' and baby responding to treatment, consider infusing vancomycin down long line and leaving it to dwell for 1 hr before flushing

Documentation

- Always contemporaneously document symptoms and signs of infection **at the time of taking all blood and CSF cultures** (and abdominal radiographs) on **BadgerNet** ad-hoc reporting field

EMPIRICAL TREATMENT

INFECTION (LATE ONSET) ● 3/5

Do not use oral antibiotics to treat infection in babies
Consult local microbiology department for current recommendations. These may differ between units according to local resident flora

Late onset sepsis
Antibiotics

- **If decision made to give antibiotics, aim to start within <30 min and always within ≤1 hr of decision**
- **First line**: give combination of IV antibiotics (e.g. flucloxacillin plus gentamicin) (see **Neonatal Formulary** for dose) based on local or national susceptibility and resistance data
- Give antibiotics effective against both Gram-negative and Gram-positive bacteria
- If necrotising enterocolitis suspected, include antibiotic that is active against anaerobic bacteria (e.g. metronidazole) (see **Necrotising enterocolitis** guideline)
- **Second line suggested:** vancomycin + gentamicin − review local antibiotic susceptibility and resistance data (or national data if local data inadequate)
- **Third line** or if cultures dictate: meropenem +/- vancomycin, tazobactam + piperacillin alternative for Gram-negative infection
- **Do not use vancomycin routinely (consult local policy):**
  - for babies with indwelling catheters and on parenteral nutrition, unless they are very unwell
  - to treat endotracheal secretion colonisation with CoNS

Antifungals

- Give prophylactic oral nystatin to babies treated with antibiotics for suspected late-onset neonatal bacterial infection if:
  - birth weight ≤1500 g **or**
  - born <30 weeks' gestation
- Consider antifungals in post gut surgery babies at any gestation
- If oral administration of nystatin is not possible, give fluconazole IV

Review treatment at 36 hr

- Stop antibiotics if:
  - initial clinical suspicion of infection was not strong **and**
  - negative blood culture **and**
  - baby is well with no clinical indicators of possible infection **and**
  - levels and trends of CRP are reassuring i.e. CRP <15 mg/L on both tests

Treatment duration for late-onset neonatal infection without meningitis

- When culture results available, always change to narrowest spectrum antibiotic
- If positive blood culture, give for 7 days
- consider continuing antibiotic treatment >7 days if:
  - baby not yet fully recovered **or**
  - longer treatment required due to pathogen identified on blood culture (e.g. Gram-negative bacteria or *Staphylococcus aureus;* seek expert microbiological advice if necessary) **or**
  - longer treatment required due to site of infection (e.g. intra-abdominal co-pathology, necrotising enterocolitis, osteomyelitis or infection of a central venous catheter)
- If baby makes prompt recovery, and either no pathogen identified/pathogen identified is a common commensal (e.g. coagulase negative staphylococcus), treat <7 days

SPECIFIC INFECTIONS

Discharging eyes

- See **Conjunctivitis** guideline

Umbilicus sepsis (omphalitis)

- Systemic antibiotics required **only** if local induration or surrounding reddening of the skin

Meningitis

For all babies with a positive blood culture, other than CoNS, discuss the need for an LP with an experienced clinician. Organisms such as group B streptococcus and E. coli penetrate the CSF readily

Empirical treatment whilst CSF results pending

- If meningitis suspected but causative pathogen unknown, treat with amoxicillin IV and cefotaxime IV
- If meningitis caused by a Gram-negative infection, stop amoxicillin and treat with cefotaxime alone
- If meningitis caused by Gram-positive organism, continue with amoxicillin and cefotaxime until culture result confirmed
- Seek microbiological advice where possible
- If CSF culture positive for group B streptococcus, consider changing antibiotic treatment to benzylpenicillin for at least 14 days and gentamicin IV for 5 days
- If blood culture or CSF positive for *Listeria,* consider stopping cefotaxime and treating with amoxicillin and gentamicin
- If CSF culture identifies a Gram-positive bacteria other than group B streptococcus or *Listeria* seek microbiological advice

Table of normal CSF values

Gestation	White cell count (count/mm^3)	Protein (g/L)	Glucose (mmol/L)
Preterm <28 days	9 (0–30)	1.0 (0.5–2.5)	3.0 (1.5–5.5)
Term <28 days	6 (0–21)	0.6 (0.3–2.0)	3.0 (1.5–5.5)

- Values are mean (range)
- **Note**: protein levels are higher in first week of life and depend on RBC count. WBC of >21/mm^3 with a protein of >1.0 g/L with <1000 RBC is suspicious of meningitis
- If traumatic LP and strong suspicion of meningitis, repeat LP after 24–48 hr
- Manage baby as if he/she has meningitis. None of the 'correcting' formulae are reliable

Urinary tract infection (UTI)

- Do not routinely perform urine microscopy or culture in babies suspected of late onset sepsis on neonatal units
- if a urine microscopy and culture are requested this specimen should be a clean catch specimen. When it is not possible to collect urine by non-invasive methods catheter samples or suprapubic aspiration should be used

Necrotising enterocolitis

- See **Necrotising enterocolitis (NEC)** guideline

Fungal infection

- Mostly late onset
- Incidence in UK up to 1.2% in very-low-birth-weight babies and 2.6% in extremely-low-birth-weight babies (versus up to 28% in the USA), hence no routine prophylaxis in the UK

Risk factors

- <1500 g
- Parenteral nutrition
- Indwelling catheter
- No enteral feeds
- Ventilation
- H2 antagonists
- Exposure to broad spectrum antibiotics, especially cephalosporins
- Abdominal surgery
- Peritoneal dialysis

Symptoms and signs

- Non-specific
- as for late onset infection

Additional investigations

- If fungal infection suspected or diagnosed, end-organ evaluation to include:
- abdominal ultrasound
- cerebral ultrasound
- lumbar puncture
- fundoscopy
- echocardiogram
- blood cultures 24–48 hrly to confirm clearance

- suprapubic or catheter specimen of urine

Treatment
First choice
- Standard amphotericin starting at 1 mg/kg. Can increase dose as tolerated to 1.5 mg/kg. In renal failure can use liposomal amphotericin 1 mg/kg, increasing to a maximum of 5 mg/kg (see **Neonatal Formulary** for doses and intervals)
- Alternatives fluconazole and micafungin – see local formulary

ADJUNCTIVE THERAPY
- No substantive trials to date show benefit of immunoglobulin IV, recombinant cytokines etc.