INFECTION (LATE ONSET)

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 presenting >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

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 $\times$ 10^9/L (supportive but not diagnostic, and marginally more sensitive than a total white cell count)
- Platelet count of <100 $\times$ 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 – see https://www.nice.org.uk/guidance/ng224

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 in accordance with local formulary

- **Documentation**
- Always 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

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) 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:
- for babies with indwelling catheters and on parenteral nutrition, or to treat endotracheal secretion colonisation with CoNS

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 or as per microbiology advice
- 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
- If continuing antibiotics >48 hr for suspected late-onset neonatal infection despite negative blood culture, review the baby at least once every 24 hr
- at each review, decide whether to stop antibiotics, taking account of:
  - level of initial clinical suspicion of infection **and**
  - baby's clinical progress and current condition **and**

– levels and trends of C-reactive protein

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 Microbiology Consultant. Organisms such as group B streptococci 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 50 mg/kg every 12 hours 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 bacterium 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)

- Consider but 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).

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 early 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 (Fungizone®) starting at 1 mg/kg once daily. Can increase dose as tolerated to 1.5 mg/kg once daily. In renal failure can use liposomal amphotericin (AmBisome®) 1 mg/kg once daily increasing to a maximum of 5 mg/kg once daily (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.