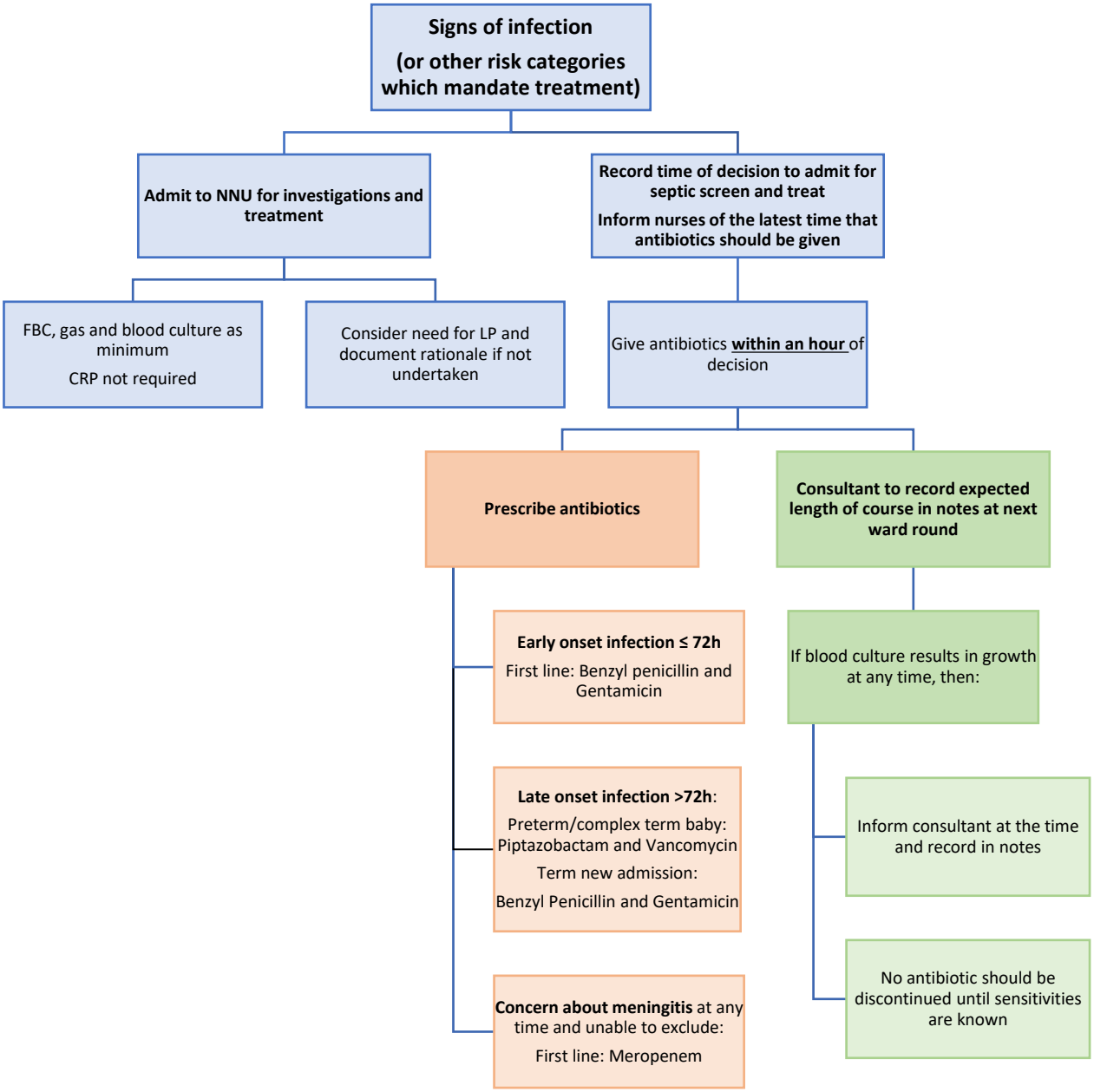
Neonatal Infection

Risk factors



This guideline was developed after review of NICE guidance (Neonatal infection: antibiotics for prevention and treatment, 2021) and consensus consultant opinion at Simpson Centre for Reproductive Health (SCRH). There is some variation between NICE guideline and suggested practice; most notably an increased emphasis on antibiotic stewardship and monitoring infants at risk of infection with

no clinical signs, as opposed to empirically commencing antibiotics based on risk factors alone.

- **Background**
- **Clinical presentation**
- **Risk factors**
- **Decision to investigate and treat**
- **Investigation**
- **Treatment**
    - Antibiotic Policy for Suspected Neonatal Infection
    - Automatic Stop Order (Autostops)
        - Antibiotic Policy – Features Specific to St John's Hospital
    - Duration of Antibiotic Treatment
    - Specific Infections
        - Sepsis – Blood culture positive and negative
        - Suspected Meningitis
        - Herpes Simplex
        - Skin Infections
        - Pneumonia
        - Necrotising Enterocolitis
        - Omphalitis
        - Urinary Tract Infection
- **Fungal Prophylaxis**
- **Communication with Parents**

Background

Neonatal infection occurs in1 to 8 per 1000 live births. Infection must be considered as a possible cause in any unwell baby. The presentation of infection can be subtle with non-specific signs, or can be acute and rapidly progressive. The consequences of untreated sepsis are devastating, so **antibiotic treatment must be commenced as soon as possible and, at the latest, within one hour of the decision to treat.**

For this guidance, neonatal infection is classified by age of onset of signs:

A. Early Onset: up to 72 hours of age (transplacentally or perinatally acquired):

- prior to delivery due to maternal sepsis/chorioamnionitis
- during delivery through contact with organisms in the vagina, or
- after delivery through exposure to organisms in the environment

Group B Streptococcus (*Streptococcus agalactiae*) is the most common organism. Other organisms include *Escherichia coli* and (less commonly) *Listeria sp.and Staphyloccus Aureus*

B. Late Onset: > 72 hours of age (postnatally acquired or nosocomial)

- acquired from the environment, including through central and peripheral venous lines, ETT and skin punctures

Coagulase negative Staphylococci are the commonest organisms in preterm infants. Other organisms such as *Group B Streptococcus*, *Staphylococcus aureus, Klebsiella sp., Serratia sp., E.coli, enterococci* can all cause late onset infection. Candidal infection must also be considered in extreme preterm babies.

Clinical Presentation

The following are signs of both early and late onset infection, but alone do not always necessitate investigation and treatment if assessment reassures:

- Any unexpected deterioration including on the neonatal unit
- Cardiovascular: tachycardia, episodic bradycardia, poor perfusion including pallor, cyanosis, hypotension and reduced urine output, persistent pulmonary hypertension, poor tolerance of handling
- Respiratory: tachypnoea, apnoea, respiratory distress (including grunting), increase in respiratory support, central cyanosis or desaturations
- Neurological: altered behaviour/responsiveness, low/high tone, encephalopathy, lethargy or irritability, high pitched cry, seizures, bulging fontanelle.
- Gastrointestinal: poor feeding, vomiting, excessive gastric aspirates and abdominal distension
- Haematology: unexplained bruising, petechiae or excessive bleeding from puncture sites, neutropenia, thrombocytopenia, or abnormal coagulation
- Local signs of infection e.g. paronychia
- Miscellaneous:
    - Jaundice – in particular when present within 24hours of birth
    - Temperature abnormality (< 36°C or >38°C) unexplained by environmental factors
    - Hypoglycaemia and hyperglycaemia
    - Metabolic acidosis (base deficit equal or > 10 mmol/litre)
    - Altered glucose homeostasis (hypoglycaemia/hyperglycaemia)
    - Rash
    - Parent/caregiver concern about behavioural change or appearing ill

Risk factors

The following features increase the risk of developing infection and if present, babies should be considered for investigation and treatment. None of these risk factors alone are a mandate to investigate and treat for infection but represent the need for greater surveillance and lower threshold for initiating a septic screen and starting antibiotics.

Early Onset Infection:

- Prolonged rupture of membranes (>18 hours)
- Preterm birth following spontaneous preterm labour (before 37 weeks)
- Fetal distress without adequate explanation
- Maternal pyrexia (>38°C on two occasions 1 hour apart or one temp >38.5°C)
- Maternal sepsis in labour or < 24h from birth, particularly if not had antibiotics
- Clinical diagnosis of chorioamnionitis
- Maternal Group B strep colonisation, bacteriuria or infection in current pregnancy

Late Onset Infection:

- Maternal Group B strep colonisation, bacteriuria or infection in current pregnancy
- Prolonged hospitalisation
- Foreign bodies e.g. intravenous catheters, endotracheal tubes
- Congenital anomalies e.g.urinary tract anomalies, neural tube defects
- Parenteral nutrition

Decision to investigate and treat

The decision to investigate and treat for neonatal infection is made on the basis of risk factors and the clinical condition of the baby as outlined above. These should be clearly documented when a baby is investigated for infection.

Risk categories which mandate investigation and treatment

The following clinical scenarios always warrant investigation and treatment for neonatal infection:

- Suspected or confirmed infection in another baby in the case of a multiple pregnancy
- Respiratory distress commencing >4hours after birth
- A term infant requiring mechanical ventilation
- Signs of shock or any critically unwell baby.
- Any baby with neonatal encephalopathy (eg seizures or HIE)
- Sudden unexpected postnatal collapse.
- Spontaneous onset labour in < 32 week gestation infant
- Definite Group B strep infection in a previous baby (sibling) with no maternal intrapartum antibiotics in this labour.
- Apnoea
- Need for CPR

Any infant with any risk factors or clinical features who is deemed not to require investigation and treatment and who is being managed on the postnatal wards should be commenced on a **Neonatal Early Warning Score (NEWS) chart**. If in doubt as to whether or not to investigate and treat for infection, discuss the patient with a senior colleague.

Antibiotics are not routine in (but may be considered):

- Well preterm babies born by pre-labour caesarean section in whom there are no additional risk factors for infection.
- Well preterm infant ≥32 weeks without clinical signs of illness, where there are no other risk factors other than spontaneous onset preterm labour.

Investigation

Once the decision has been made to investigate and treat for neonatal infection the following investigations should be undertaken immediately and **antibiotics administered within 1 hour of this decision**.

Failure to obtain the desired samples by an appropriately senior member of staff (most commonly a blood culture) MUST NOT delay commencing antibiotics.

- **Blood gas** – including glucose and lactate
- **Full blood count**
- **Blood** culture – always using closed system technique
- Investigation always includes a full history including information about maternal infections (including HSV) and top to toe examination.

The following investigations should then also be considered:

- **Lumbar puncture** –meningitis should always be considered if there is strong clinical suspicion of infection **and** or clinical signs which may indicate meningitis.
  - Where a decision is made not to perform a LP at the time of a septic screen, the rationale should be documented in the notes.
  - LP may be deferred if:
    - babies are considered not able to tolerate the procedure
    - if platelets < 50 or significant coagulopathy. If not available, FBC results are not required prior to LP unless clinical evidence of deranged haemostasis.
    - concern about raised intracranial pressure or a non-communicating hydrocephalus
    - local infection over the LP site
  - Blood culture positive sepsis with a known pathogen is an indication for an LP.
  - There is no evidence to support a specific CRP value for undertaking a LP. The key factors for undertaking an LP are clinical concerns about abnormal behaviour and/or culture of a known pathogen from the blood. Clinically well babies with negative blood cultures but with elevated CRPs do not need LP because of the CRP alone. An LP may be considered necessary in some infants where the clinical suspicion of bacterial infection remains high.

  If a lumbar puncture is deferred, or attempted but not successful or not interpretable, this should be escalated to the consultant so that a decision can be made about whether or not antibiotic cover to cover meningitis is required. Whether antibiotic cover is started or not the Consultant will convey the associated uncertainty and explain to the family that the situation will be discussed in the senior team during daytime hours to reach a consensus recommendation rather than start a 2 week course of treatment that must be completed. **All decisions should be clearly documented in the notes.**

- CSF results:
    - A blood glucose should always be measured prior to CSF sampling
    - A white cell count of greater than 20 in the absence of blood contamination should be escalated to the consultant.
    - Protein and glucose results are not helpful if the CSF is bloodstained.
    - A raised protein with a decrease in the CSF/ blood glucose ratio should be escalated to the consultant.
    - Viral PCR for herpes virus and VZV is not performed routinely.
    - If there remain clinical concerns about bacterial meningitis but culture is negative, the consultant should discuss with the duty microbiology consultant. In some cases it might be helpful to request for the specimen to be sent to Great Ormond Street Hospital for 16S r RNA pan-bacterial PCR, Group B Streptococci and Enterobacteriaceae PCR (turn-around time is 5-7d).
    - When clinical concern about serious infection is high but CSF results are negative there may be value in molecular testing of CSF but this will not generally be requested when the level of clinical concern is low because the value is uncertain, the test requires at least 0.5ml (10 drops) of CSF, and the results take a 7-10 days to come back.

- **Chest X-Ray** if there are any respiratory signs or symptoms
- **Abdominal X-Ray** if there are any abdominal signs or symptoms
- **Skin swabs** should be considered if there are areas of inflamed skin or pustular lesions. If pustules are present, send an MRSA swab. If there is a family history of *S. aureus* Panton-Valentine Leukocydin (PVL) producer carriage (check Trak notes of relatives if unsure) add clindamycin and inform the consultant neonatologist/microbiologist. Consider isolation until culture results are available. Mildly erythematous peri-umbilical areas should not be swabbed routinely. Herpes simplex virus should be considered and relevant history obtained from the baby's mother (bearing in mind that the majority of affected babies do not have cutaneous signs of infection).
- **Eye swabs** should not be sent unless requested by a consultant
- **Stool culture/virology** should not be sent unless requested by a consultant
- **ET or NPA culture/virology** should not be sent unless requested by a consultant
- **Suprapubic aspirate (SPA)** is the gold standard for urine culture but this is not performed routinely and should be discussed with a consultant if it is indicated. SPA should be considered in infants over 7 days of age.

Treatment

1. **Antibiotic Policy for Suspected Neonatal Infection**

The neonatal service antibiotic policy is based on knowledge of local organisms and their sensitivities and is reviewed on a regular basis. A disciplined and consistent approach to antibiotic usage is necessary to provide optimal broad-spectrum cover in suspected sepsis and to limit the emergence of resistant organisms in areas of high usage.

It is essential that all babies undergo CRA and MRSA/CPE screening on admission.

Once the decision is made to commence antibiotics, they must be given as soon as possible and always within 1 hour of this decision.

Treatment is determined by the age of the baby (≤ or > 72hours):

- ≤ 72 hours of age: commence Benzylpenicillin and Gentamicin
- > 72 hours of age:
    - Babies admitted from the PNW or home who *have not previously had antibiotics* should receive benzylpenicillin and gentamicin
    - Babies who have spent time at a tertiary NNU within Scotland, have had antibiotics or who have previously had a central line, surgery or NEC treatment should receive Piperacillin/tazobactam and Vancomycin. Piperacillin/tazobactam provides broad cover including Gram negative, enterococci and anaerobes and should also be used in NEC, skin infections and post-surgical sepsis.
    - Term infants whose mothers are known to have or be colonised with healthcare-associated organisms, should be given Piperacillin/tazobactam and Vancomycin.
- At any age: Empirical treatment of meningitis is Meropenem

2. Autostops

- Autostops are an effective way to reduce unnecessary exposure to antibiotics in infants treated for suspected infection. All infants will have an Autostop stamp applied on initial prescription to curtail antibiotics to 24-36h in the face of negative cultures and a low index of suspicion about infection. A CRP will be performed between 24-36h to coincide with other blood tests where possible.

- If ongoing suspicion of infection, antibiotics will be re-prescribed and a decision about the length of course or review date will be documented. No infant will be discharged home without knowledge of culture results. Infants may be discharged home immediately if cultures are negative. All parents should receive worsening advice on discharge.

Specific to St John's Hospital -Automatic Stop Orders are not used- follow this guidance when considering stopping antibiotics.

- Antibiotics are reviewed on a daily basis and stopped as soon as clinically indicated.
- Due to practical differences in laboratory services, it may not be until 70 hours that full negative blood culture results are available from the lab, although all positive blood cultures are phoned back over the weekend during the below lab opening ours.
- Blood cultures are placed on the analyser between 9am-5pm Monday to Friday, and 9am-12md weekends, and negative results are automatically available on Trak 48 hours later.
- A CRP will be performed between 24 and 48 hours to coincide with other blood tests and to minimise workload where possible.
- At 48-72 hours if blood culture is negative and CRP result is <10 and there is no significant clinical concern of sepsis antibiotics can be stopped, there is no need to administer any further doses due and the antibiotic prescription can be terminated.
- Blood and other culture results will be sought and recorded in the infant notes from 36-70 hours.
- Parents should be advised that they need to stay in hospital until the blood culture result is known. No infant will be discharged home without knowledge of culture results. Once these are known, infants may be discharged home immediately if cultures are negative.
- If cultures are positive or there is continuing clinical concern about infection, antibiotics should be continued for a longer course. It is essential that at the time of initial prescription that there is good documentation about the scope of clinical concern in order to aid decision-making in the following days.

3. Duration of Antibiotic Treatment

The threshold for starting antibiotic treatment is necessarily low in neonatal care. As such, many infants are commenced on antibiotics who are later found not to have an infection. Continuing treatment beyond 36h should be restricted to infants with proven or highly probable sepsis because continuing empiric treatment unnecessarily is associated with mortality and morbidity and increases the risk of resistant organisms.

An expected timescale for length of antibiotics should be recorded in the notes by the consultant at the first ward round after admission.

In the absence of proven or highly probable infection, there is **no** place for continuing empiric antibiotic treatment beyond 24-36h.

On completing a course of antibiotic treatment, well babies should be discharged promptly from hospital with worsening advice for parents.

a. C-Reactive Protein

CRP is an acute-phase protein and a key component of the innate immune response to infection and inflammation. It increases 4-6h after an inflammatory trigger and peaks at 36-48h. Healthy infants have levels of <10mg/l, and any elevation indicates endogenous production because placental transfer is negligible.

- CRP≤10: The NPV of CRP at 24-48 hours after sepsis evaluation is around 99%. If CRP<10 and symptoms have completely resolved then antibiotics can be stopped, however the baby should remain in hospital until blood culture is negative at 48 hours. CRP cannot be relied upon to identify all cases of infection, and antibiotics should not be stopped on the basis of low CRP if there is a highly suggestive clinical picture

- CRP>10: there should be discussion with the consultant about antibiotic duration and any additional investigations. The sensitivity of CRP for predicting bloodstream infection at the time of evaluation for sepsis is in the order of 60% so a raised CRP may be due to another reason. A mildly elevated CRP in an otherwise well baby without major concerns at initial presentation does not require antibiotics to be continued.

- There is no specific CRP cut off for the need to do a lumbar puncture; this decision is based on the whole clinical picture.

Specific Infections

If growth of organisms is reported in blood or CSF, then **this should be documented and the consultant should be informed at the time.**

In culture positive sepsis, no antibiotic should be discontinued until sensitivities are known.

Please see below for guidance in different clinical scenarios

i. Sepsis: Blood culture positive or negative (without concern about meningitis)

- **Coagulase Negative Staphylococcus (CoNS)** can cause disease but are also a common contaminant. It is important to establish whether CoNS represents true bloodstream infection. Treat for 5d where true infection is suspected and 7d where central lines in situ.
- **Group B strep:** treat for 7-10d.
- **Gram negative organisms:** treat for 7 – 10d.

- **Staphylococcus aureus:** treat for 14-21d. Further investigations to find a focus of infection may be required.
- **Culture negative and CRP raised but minimal suspicion of sepsis:** A mildly elevated CRP in an otherwise well baby without major concerns at initial presentation does not require antibiotics to be continued.
- **Culture negative but strong suspicion of sepsis:** treat for 5-7d.

ii. Suspected meningitis (early or late onset)

- **Negative culture/PCR but elevated CSF WCC**: Meropenem for 14d

- **Confirmed meningitis**
  - Gram-negative bacillus: Meropenem for at least 14d & Gentamicin for 5-7d (see below)
  - Group B Streptococcus: Meropenem for at least 14d & Gentamicin for 5-7d (see below)
  - Listeria monocytogenes: Amoxicillin for 21d and Gentamicin for 5-7d (see below).

In all cases of meningitis:
- Discuss antibiotic choice and duration of treatment with the consultant neonatologist and consultant microbiologist.
- If clinical improvement, gentamicin can be stopped after 5-7d.
- It is not routine to repeat lumbar puncture toward the end of the antibiotic course to ensure reduction in pleocytosis and negative CSF culture. Consider repeat if lack of clinical improvement.
- CRP lags behind clinical improvement and normal CRP is not required to stop treatment.

iii. Herpes Simplex Virus: 14-21d dependent on whether there is local or disseminated/CNS disease.
iv. Skin infections: at least 5-7d until clinical improvement.
v. Pneumonia: treat for 5d
vi. Necrotising Enterocolitis (NEC): treatment duration will be determined by ongoing condition and jointly by neonatal and surgical teams.
vii. Omphalitis: mild cases- oral Flucloxacillin for 5-7d. In more severe cases give empirical Piperacillin/tazobactam and Vancomycin until culture results known- for at least 48h intravenous before changing to oral treatment.
viii. Urinary Tract Infection: give empirical Piperacillin/tazobactam and Vancomycin and refine when the culture/sensitivities known. Treat for a minimum of 5 days. In term infants with suspected renal tract malformations consider starting prophylactic Trimethoprim until investigations are complete.
ix. Eyes: Minor conjunctivitis is common and often benign, If the eye looks inflamed and purulent discuss with consultant.

Fungal Prophylaxis

Oral and nasogastric Nystatin and topical Clotrimazole to the nappy area is given as routine prophylaxis to all infants < 27 weeks for 7 days after birth, and to those

receiving Piperacillin/tazobactam or other broad spectrum antibiotics and for at least 48h after these antibiotics have been stopped.

Additionally, give IV fluconazole prophylaxis to all infants <25w for 7d after birth.

Communication with parents

Parents (and the midwifery team) should be involved and informed of decisions about monitoring or treatment of neonatal infection.

a. **NEWS monitoring:** Whichever team starts NEWS monitoring should explain the rationale to parents. Following a period of reassuring NEWS monitoring the midwifery team should provide the parents with the information leaflet on **Going home after your baby has been monitored or treated for infection' neonatal infection.**

b. **Antibiotic treatment:** the rationale should be discussed with the family. Encourage their ongoing involvement in caring for and holding their baby unless if clinically stable. Keep parents informed of investigations, duration of treatment, whether long term effects may develop, if follow up is required and signpost to additional psycho-social or emotional support. Communication with parents should be documented on Badger.

c. **Going home**:

i. Antibiotics will be commenced in the neonatal unit, but the majority of term babies will be transferred back to the postnatal wards to complete the course and some may be discharged home from the neonatal unit following completion. It is the responsibility of the neonatal team to provide the parents with the information leaflet on **'Going home after your baby has been monitored or treated for infection'** and discuss reasons to seek medical help once discharged.

ii. **Maternal or baby group B streptococcus colonisation:** Midwifery teams should give parents the RCOG '**Group B Streptococcus (GBS) in pregnancy and newborn babies**' parent leaflet before discharge GBS in pregnancy and newborn babies - Patient information leaflet (rcog.org.uk)

Title: Neonatal Infection
Review Authors': David Quine, Neonatal Consultant; Claire Smith, Neonatal Consultant; Robin Dawson, Specialist Trainee.
Previous significant contributors: James Boardman/Julie-Clare Becher, Neonatal consultants.
Implementation Date: 24/04/2023