Antibiotic Guideline for Early-onset & Late-onset neonatal infection

University Hospitals of Leicester NHS
NHS Trust

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Contents

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1. Introduction & Scope:

This guideline is aimed at all Health Care Professionals involved in the care of infants within the Neonatal Service. These guidelines detail the recommended antibiotic treatment for patients in UHL neonatal units, and those neonates transferred from NNU to the postnatal wards for ongoing management.

Early-onset neonatal bacterial infection (infection with onset within 72 hours of birth) is less common than late-onset neonatal infection (infection with onset after 72 hours of birth) but is often severe.

Key Points:

- Neonatal sepsis requires prompt treatment with antibiotics administered within 1 hour of the decision to treat.
- Start antibiotic treatment in babies with any ‘red flags’ or with two or more ‘non-red flag’ risk factors or clinical indicators.
- Measure C-reactive protein 18-24 hours after starting antibiotics.
- Refer to “Maternal pyrexia in labour” (Appendix 2) in addition to discussion with obstetrician to review maternal history, clinical status, antibiotic treatment and investigations (including CRP, blood culture if available)
- Reassess the need for antibiotics at or before 36 hours in early onset sepsis
- Reassess the need for antibiotics at 48 hours in late onset sepsis
- Consider viral infections, especially Herpes Simplex Virus (HSV), when evaluating any baby with signs of infection
- Microbiology authorisation code is required beyond recommended antibiotic duration (Table 7).
- Consider empiric Meropenem as per Appendix 3

Related UHL documents:

Antibiotics for Surgical Prophylaxis or Infection UHL Neonatal Guideline. Trust ref: C29/2015
Audiology Referral for High Gentamicin UHL Neonatal Guideline Trust ref: C30/2015
Pyrexia and Sepsis in Labour UHL Obstetric Guideline Trust ref: C21/2017

Gentamicin: Procedure for routine intravenous administration
Gentamicin Therapeutic drug monitoring
Prescription chart for: IV gentamicin only
Neonatal Formulary

2. Antibiotic Guideline for Early-Onset Neonatal Infection

Background:

Early-onset neonatal infection is usually caused by organisms from the mother's genital tract. Majority of early onset sepsis is caused by Group B beta-haemolytic streptococci (leading cause in UK with overall mortality of 10% and is even higher in premature babies) and Escherichia coli. Other less common organisms include Streptococci other than Group B, Staphylococcus aureus, Haemophilus influenzae, Listeria monocytogenes, Gram negative anaerobes, Chlamydia trachomatis.

Early-onset sepsis may develop suddenly and rapidly, and mortality is high, particularly in premature babies and those with low birth weight (birth weight between 1500 and 2499 grams). Even with antibiotic treatment, the mortality rate for early-onset infection in low birth weight babies is up to 26%. Babies who survive early-onset infection have prolonged hospital stays. Up to 7% of babies who survive GBS infection have a consequent disability [1].

Key points for early onset neonatal sepsis

- Do not routinely perform urine microscopy or culture or skin swab microscopy or culture (if no localised infection) as part of the investigations for EOS

- Perform a lumbar puncture before antibiotics if safe to do so when there is a strong clinical suspicion of EOS or there are clinical symptoms or signs suggesting meningitis

- Duration of antibiotics in EOS with positive blood culture or strong suspicion of sepsis is 7 days but can be stopped earlier when clinical review takes account of: the level of initial suspicion of infection and the baby's clinical progress and current condition and the levels and trends of CRP

2.1 Guidelines/Recommendations:

Review maternal and neonatal history and carry out a physical examination of the baby including an assessment of the vital signs without delay.

Intravenous antibiotic therapy should be started as soon as possible and always within the first hour of the decision to treat, after appropriate cultures and investigations have been taken.

All antimicrobial prescriptions should be reviewed daily. Microbiology authorisation code is required beyond recommended antibiotic duration (Refer to Table 7).

Recent maternal and infant microbiology results (where available) should be reviewed to identify if the patient is at risk of sepsis with a more resistant organism, which may not respond to standard first line therapy.

Follow guidance on timing of gentamicin assays and dosing provided in the IV monographs and pre-printed on the NNU prescription charts.

For recommended doses of antibiotics please refer to the neonatal drug doses policy and individual drug monographs available on NNU, and document management systems. If in doubt, contact your Pharmacist for further advice.

For information on contraindications, cautions, drug interactions and adverse effects refer to the British National Formulary for children or the drug Summary of Product Characteristics.

2.2 Indications to commence antibiotics in suspected early-onset neonatal sepsis

Refer to Table 1, 2, 3, and 4 to identify 'Red Flag' and 'Non red flag' risk factors and clinical indicators for early-onset neonatal infection.

In babies with any red flags (Table 1 and Table 2), or with two or more 'non-red flag' risk factors or clinical indicators (Table 3 and Table 4), perform investigations (see below) and start antibiotic treatment always within 1 hour of the decision to treat. Do not delay starting antibiotics pending the test results.

In babies without red flags and only one risk factor or one clinical indicator, using clinical judgement, consider

- whether it is safe to withhold antibiotics, and
- whether it is necessary to monitor the baby's vital signs and clinical condition for at least 12 hours

In babies being monitored for possible infection

- if clinical concern increases, consider performing necessary investigations and starting antibiotic treatment.

Use intravenous benzylpenicillin with gentamicin as the first choice antibiotic regimen for empirical treatment of suspected early-onset infection. Refer to Chart 1a, 1b and 1c for antibiotic guideline for suspected early-onset neonatal sepsis and necrotising enterocolitis (NEC).

If there is microbiological evidence of gram-negative bacterial sepsis, change benzylpencillin to cefotaxime and continue gentamicin.

Purulent eye discharge may indicate the presence of a serious infection (e.g. Chlamydia or Gonococcus) - start systemic treatment for possible gonococcal infection while awaiting the swab microbiology results (Refer to Table 7).

In babies with clinical signs of umbilical infection (for example, redness, increased skin warmth or swelling) - start intravenous flucloxacillin and gentamicin. Stop gentamicin if microbiology results do not indicate gram-negative infection.

Table 1. 'Red Flag' risk factors for early-onset neonatal infection

	Red Flag Risk Factors
1	Suspected or confirmed infection in another baby in the case of a multiple pregnancy

Table 2. 'Red Flag' clinical indicators of possible early-onset neonatal infection (observations and events in the baby)

	Red Flag Clinical Indicators
1	**Apnoea** **(in a term baby)**
2	Seizures
3	**Need for cardiopulmonary resuscitation**
4	Need for mechanical ventilation **(in a term baby)**
5	Signs of shock

Table 3. 'Non Red Flag' risk factors of possible early-onset neonatal infection

	Non Red Flag Risk Factors
1	Invasive group B streptococcal infection in a previous baby or maternal GBS colonisation, bacteriuria or infection in the current pregnancy
2	Preterm birth following spontaneous labour before 37 weeks gestation
3	Confirmed rupture of membranes for > 18 hours before a preterm birth
4	Confirmed pre-labour rupture of membranes at term for > 24 hours before onset of labour
5	Intrapartum fever* > 38°C if there is suspected or confirmed bacterial infection
6	Clinical diagnosis of chorioamnionitis

*Refer to "Maternal pyrexia in labour" (Appendix 2) in addition to discussion with obstetrician to review maternal history, clinical status, antibiotic treatment and investigations (including CRP, blood culture if available)

Table 4. 'Non Red Flag' clinical indicators of possible early-onset neonatal infection (observations and events in the baby)

	Non Red Flag Clinical Indicators
1	Altered behaviour or responsiveness
2	Altered muscle tone (e.g. floppiness)
3	Feeding difficulties (e.g. feed refusal)
4	Feed intolerance including vomiting, excessive gastric aspirates and abdominal distension
5	Abnormal heart rate (bradycardia and tachycardia)
6	Signs of respiratory distress (including grunting, recession, tachypnoea)
7	Signs of neonatal encephalopathy
8	Hypoxia (e.g. central cyanosis or reduced oxygen saturation level)
9	Jaundice within 24 hours of birth
10	Persistent pulmonary hypertension of newborns

11	Temperature abnormality (<36°C or >38°C) unexplained by environmental factors
12	Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulation
13	Altered glucose homeostasis (hypoglycaemia or hyperglycemia)
14	Metabolic acidosis (base deficit of ≥10 mmol/Litre)

a. Investigations for suspected early-onset sepsis

To consider before administering the first dose of antibiotics include:-

- Blood Culture
- Full blood count (FBC) and C - reactive protein (CRP) (repeat 18-24 hours)
- CXR only if clinical signs suggestive of respiratory distress
- Lumbar puncture (LP) before starting antibiotics if it is thought safe to do so and there is a strong clinical suspicion of infection, or there are clinical symptoms or signs suggesting meningitis.
- Perform surface/local swab only in the presence of purulent discharge or signs of periumbilical cellulitis
- Eye swab for Chlamydia and Gonococcus in the presence of purulent eye discharge
- Do not routinely perform urine culture/microscopy or surface/skin swabs as part of the investigation for early- onset neonatal infection in the absence of clinical signs.

If performing the lumbar puncture would unduly delay starting antibiotics, perform it as soon as possible after starting antibiotics. Contact microbiology to arrange urgent investigation.

Do not perform a repeat lumbar puncture in neonates who are receiving the antibiotic treatment appropriate to the causative organism and are making a good clinical recovery and/or before stopping antibiotic therapy if they are clinically well.

Meningitis should be diagnosed when there are clinical signs of sepsis and positive cerebro-spinal fluid (CSF) findings (increased white cells). Decreased CSF glucose & positive culture are additional features of meningitis. Refer to Appendix 1 for normal (mean and range) CSF values in preterm and term infants.

Pneumonia needs to be considered in infants with clinical signs of respiratory distress with x-ray changes. Always complete diagnostic investigations as above but in addition send endotracheal tube (ETT) secretions early in the course of treatment if baby is intubated and especially perinatal sepsis is suspected. Antibiotics are in line with early-onset sepsis as appropriate (Refer to chart 1a, 1b, 1c and Table 7).

If the ETT secretions are culture positive treat according to the organism. If no improvement, consult Microbiology and Neonatal Consultant.

If ETT secretions are culture negative and no improvement after 48 hours of early-onset sepsis antibiotics, consider changing antibiotics after discussion with Microbiology and Neonatal consultant.

If there is still no improvement, consider a) Ureaplasma, b) Chlamydia. It is important to take appropriate samples sooner than later for investigation

If positive ETT secretions, but clinically well/asymptomatic – no treatment may be required as this could represent colonisation rather than infection.

Ureaplasma Urealyticum- is known to colonise women's genital tract and has been shown to be associated with preterm neonates with bronchopulmonary dysplasia (BPD). Macrolide antibiotics are known to be effective against Ureaplasma species. The potential of azithromycin as a chemoprophylactic agent for BPD in preterm neonates is still under exploration. PCR from ET aspirates helps in the diagnosis.

2.4 Investigations during antibiotic treatment in early-onset sepsis

Measure the C-reactive protein concentration at 18-24 hours after presentation and first CRP

Consider performing a lumbar puncture to obtain CSF sample, if it is thought safe to do so, if the baby is receiving antibiotics and did not have a lumbar puncture at presentation and if baby:

- has a positive blood culture (other than coagulase negative staph) or
- does not respond satisfactorily to antibiotic treatment, or
- has strong clinical suspicion of infection, or
- has clinical symptoms or signs suggesting meningitis

Decision 36 hours after starting antibiotic treatment in early onset sepsis

For babies on the PNW, it's important to decide on the length of course of antibiotics. A review of results and clinical factors on day 1 and 2 by medical staff will assist with determining the length of antibiotic course required for an individual baby.

More than 90% babies who will have a positive blood culture will have this growth within 12 -24 hours of birth, sooner for significant pathogens. In the absence of clinical symptoms and no trend in CRP rise, a significant positive culture is even less likely.

Stop antibiotics at or before 36 hours if:

- the blood culture is negative, and
- the initial clinical suspicion of infection was not strong, and
- the baby's clinical condition is reassuring with no clinical indicators of possible infection, and
- the levels and trends of CRP are ≤ 10.

Where culture results may be available at 36 hours (lab in-hours times), active steps should be taken to avoid giving unnecessary gentamicin doses.

Duration of antibiotics in early onset sepsis without meningitis

The usual duration of antibiotic treatment for babies with a ***positive blood culture***, and for those with negative blood culture but in whom there has been ***strong suspicion*** of sepsis, should be 7 days. Refer to table 7 for further details and point at which microbiology authorisation code is required. **These babies will have often (though not always) required admission to NNU for some time in the early part of their stay.**

Consider continuing antibiotic for more than 7 days if:

- the baby has not yet fully recovered, or
- this is advisable, based on the pathogen identified on blood culture (seek expert microbiological advise if necessary)

If continuing antibiotics for longer than 36 hours despite negative blood cultures, review the baby at least once every 24 hours. For babies on the PNW, this may be completed by the midwifery team carrying out NEWTT observations. Any clinical concerns should be escalated for medical review. On each occasion using clinical judgement, consider whether it is appropriate to stop antibiotic treatment, taking account of:

- the level of initial clinical suspicion of infection and
- the baby's clinical progress and current condition, and
- the levels and trends of CRP.

In babies where there has been a raised CRP that is resolving and with negative blood or CSF cultures and where the baby has been clinically well throughout, a 5 day course of antibiotics is sufficient.

Medical teams are responsible for ensuring all midwifery and nursing concerns are addressed and to ensure a smooth discharge process including a discharge letter and crossing off the antibiotics as the final dose is given.

2.5 Management of early-onset meningitis in neonatal service

If a baby is admitted to NNU and meningitis is suspected but the causative pathogen is unknown (e.g. CSF is uninformative), treat with intravenous amoxicillin and cefotaxime.

If a baby's meningitis is shown to be due to gram negative infection either by CSF gram stain or culture, stop amoxicillin and treat with cefotaxime alone.

If a baby's meningitis is shown by CSF gram stain to be due to gram positive infection, continue treatment with intravenous amoxicillin and cefotaxime while awaiting the CSF culture result and seek expert microbiology advice.

If CSF culture is positive for GBS consider changing antibiotic treatment to benzylpenicillin for at least 14 days (Maximum 21 days). NICE guidance also suggests the addition of gentamicin treatment for 5 days.

If the blood culture or CSF culture is positive for Listeria, stop cefotaxime and treat with amoxicillin and gentamicin.

If the CSF culture identifies gram positive bacterium other than GBS or Listeria seek expert microbiological advice on management.

Chart 1a: Antibiotic guideline for early-onset neonatal sepsis (<3 days)

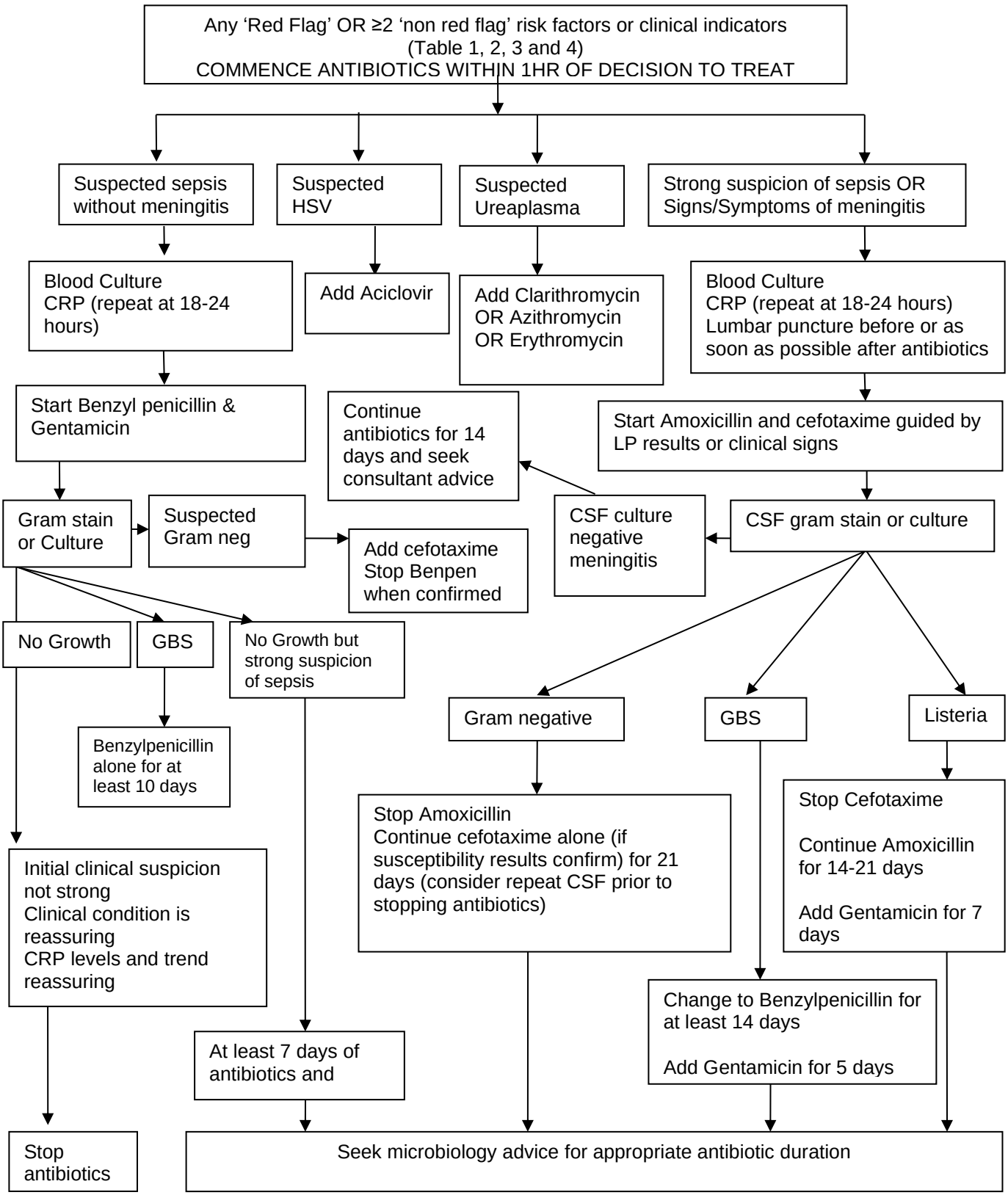


Chart 1b: Antibiotic guideline for possible early-onset and late-onset neonatal sepsis

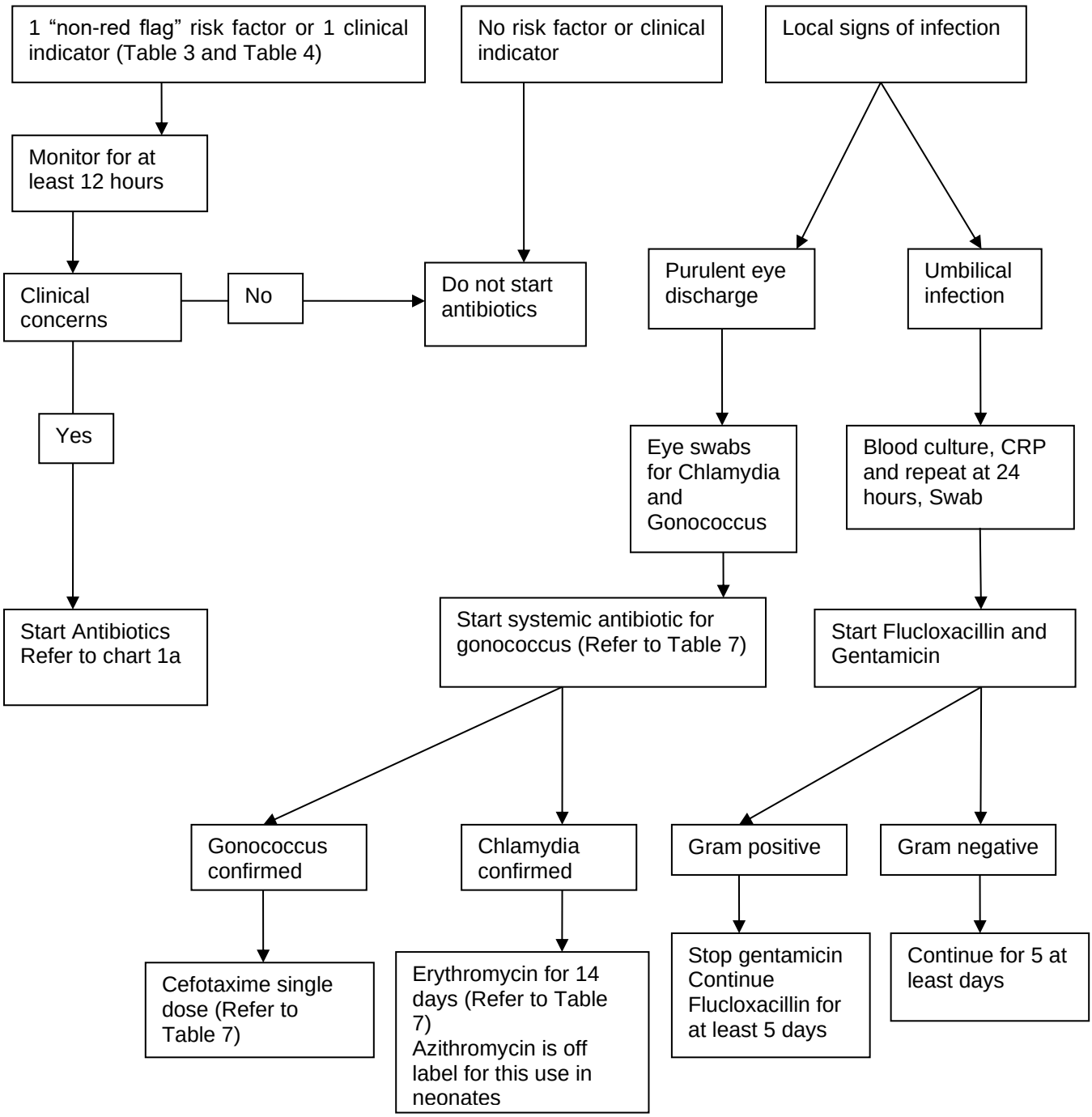
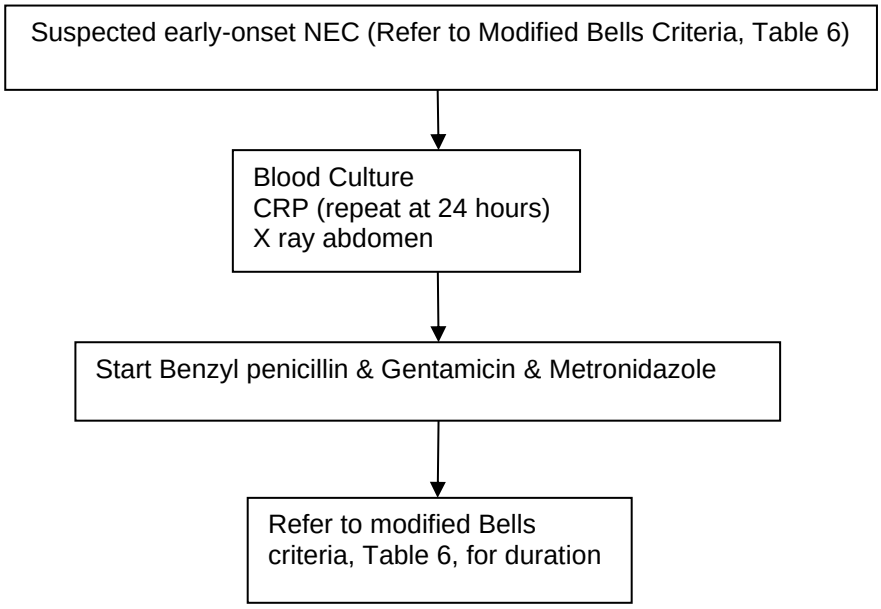


Chart 1c: Antibiotic guideline for suspected Necrotising Enterocolitis within 3 days after birth



3. Antibiotic Guideline for possible Late-onset Neonatal Infection

Background:

The incidence of late-onset neonatal infections (infection with onset after 72 hours of birth) is 4.4 per 1000 live births with a mortality rate of 9%. The incidence of meningitis in these infants is 9% [3]. The commonest organisms are (in order of decreasing frequency)[4]:-
Coagulase negative Staphylococcus species 55%, Staphylococcus aureus 9%, Enterococcus / group D Streptococcus 5%, Streptococcus agalactiae (Group B beta-haemolytic Streptococcus) 2%, Enterobacter 4%, Escherichia coli 4%, Klebsiella 4%, Pseudomonas 2%, Other Gram negatives 4%, Candida albicans 5%, Candida parapsilosis 2%.

Key points

- Birthweight ≤ 1500g or < 30 weeks - Start prophylactic oral nystatin when starting antibiotics for LOS.
- Do not routinely perform urine microscopy or culture or skin swab microscopy or culture (if no localised infection) as part of the investigations for LOS for babies in neonatal units.
- Perform urine microscopy and culture for babies outside of neonatal units in line with NICE guideline on urinary tract infection in under 16s.
- Perform a lumbar puncture before antibiotics if safe to do so when there is a strong clinical suspicion of infection or there are clinical symptoms or signs suggesting meningitis.
- Duration of antibiotics in LOS is 7 days but can be stopped earlier if: clinically improved and well, negative BC or BC growing skin type organisms (i.e. Coagulase negative Staphs).
- Reassess the need for antibiotic treatment at 48 hours. Blood cultures should be incubated for a full 48 hours before concluding negativity.

3.1 Guidelines/Recommendations:

Review the maternal and neonatal history and carry out a physical examination of the baby including an assessment of the vital signs without delay.

Intravenous antibiotic therapy should be started as soon as possible and always within the first hour of the decision to treat, after appropriate cultures and investigations have been taken.

All antimicrobials should be reviewed daily. Microbiology authorisation code is required beyond recommended antibiotic duration (Refer to Table 7)

Follow guidance on timing of vancomycin and gentamicin assays and dosing provided in the IV monographs and pre-printed on the NNU prescription charts.

Audiology assessment at 8 months is arranged for infants identified to have high gentamicin levels (pre dose greater than 2mg/l and/or post dose greater than 12mg/l) (Refer to guideline in related documents)

For recommended doses of antibiotics please refer to the neonatal drug doses policy and individual drug monographs available on NNU, on the document management system. If in doubt, contact your Pharmacist for further advice.

For information on contraindications, cautions, drug interactions and adverse effects refer to the British National Formulary for children or the drug Summary of Product Characteristics.

3.2 Indications to commence antibiotics in late-onset sepsis

Refer to Table 5 to identify clinical indicators for possible late-onset neonatal infection.

In babies with clinical indicators of possible late onset neonatal infection, perform investigations and start antibiotic treatment as per Chart 2.

Perform a lumbar puncture to obtain a cerebrospinal fluid sample before starting antibiotics if it is thought safe to do so and

- there is a strong clinical suspicion of infection, or
- there are clinical symptoms or signs suggesting meningitis

If performing the lumbar puncture would unduly delay starting antibiotics, perform it as soon as possible after starting antibiotics.

Do not delay starting antibiotics pending the test results. If a baby needs antibiotic treatment it should be given as soon as possible and always within 1 hour of the decision to treat

Refer to chart 2 and table 7 for appropriate antimicrobial guidance. Use intravenous Flucloxacillin with Gentamicin as the first choice antibiotic regimen for empirical treatment of suspected late-onset infection. Use intravenous Cefotaxime with Vancomycin as the antibiotic regimen when empirical changing over from Flucloxacillin and Gentamicin.

Table 5. Clinical indicators of possible late-onset neonatal infection (observations and events in the baby)

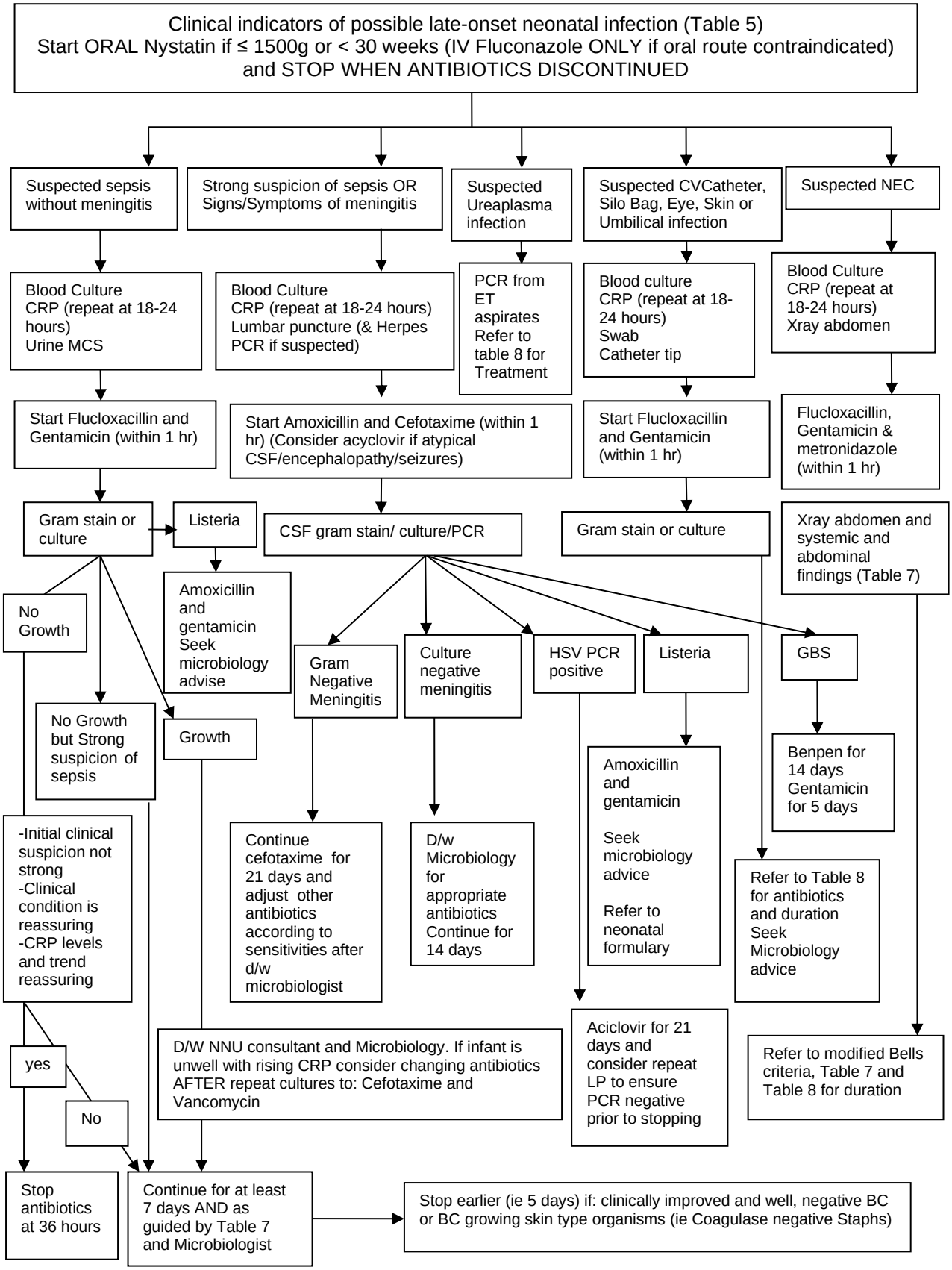
Category	Indicators
Behaviour	Parents or care-giver concern for change in behaviour Appears ill to a healthcare professional Does not wake, or if roused does not stay awake Weak high-pitched or continuous cry
Respiratory	Raised respiratory rate ≥ 60/min Grunting Apnoea Oxygen saturation <90% in air or increased oxygen requirement over baseline
Circulation and hydration	Persistent tachycardia: HR ≥160/min Persistent bradycardia: HR <100/min
Skin	Mottled or ashen appearance Cyanosis of skin, lips or tongue Non-blanching rash of skin
Other	Temperature ≥38˚C unexplained by environmental factors Temperature <36˚C unexplained by environmental factors Alterations in feeding pattern Abdominal distension Seizures Bulging fontanelle
Risk Factors	Needing or having had mechanical ventilation History of surgery Central catheter

3.3 Investigations in Late-onset sepsis

Before administering the first dose of antibiotics include:-

- Blood Culture
- Full blood count (FBC) and C-reactive protein (CRP) (repeat 18-24 hours)
- CXR only if clinical signs suggestive of pneumonia
- Lumbar puncture if it is thought safe to do so and there is a strong clinical suspicion of infection, or there are clinical symptoms or signs suggesting meningitis. Contact microbiology to arrange urgent investigation
- Local skin/surface swab only in the presence of clinical signs of a localised infection (purulent discharge or signs of periumbilical cellulitis)
- Do NOT routinely perform urine microscopy or culture as part of the investigations for LOS for babies in neonatal units

Chart 2: Antibiotic guideline for possible late-onset neonatal sepsis (> 3 days)



Meningitis should be diagnosed when there are clinical signs of sepsis and positive cerebro-spinal fluid (CSF) findings (increased white cells) (Refer to Appendix 1). Decreased CSF glucose & positive culture are additional features of meningitis.

Pneumonia needs to be considered in infants with clinical signs of respiratory distress with x-ray changes. Always complete diagnostic investigations as above but in addition send endotracheal tube (ETT) secretions if baby is intubated. Common organisms are coliforms, Pseudomonas, Group B Streptococcus and Staphylococcus aureus. Antibiotics are for late-onset sepsis as appropriate (Refer to chart 2 and Table 7 for further details).

If the ETT secretions are culture positive treat according to the organism. If no improvement, consult Microbiology and Neonatal Consultant.

If ETT secretions are culture negative and no improvement after 48 hours of late-onset sepsis antibiotics, consider changing antibiotics after discussion with Microbiology and Neonatal consultant.

If there is still no improvement, consider a) Ureaplasma, b) Chlamydia, c) pertussis (in unvaccinated mothers during current pregnancy) :- and d) Viruses – take NPA. It is important to take appropriate samples sooner rather than later for investigation

If positive ETT secretions, but clinically well / asymptomatic – treatment may not be required as this could represent colonisation rather than infection.

Ureaplasma Urealyticum - is known to colonise women's genital tract and has been shown to be associated with preterm neonates with bronchopulmonary dysplasia (BPD). Macrolide antibiotics are known to be effective against Ureaplasma species. The potential of azithromycin as a chemoprophylactic agent for BPD in preterm neonates is still under exploration. PCR from ET aspirates helps in the diagnosis.

Necrotising Enterocolitis - Table 6 below shows modified Bell's staging for NEC and provides a guide to antibiotic duration according to stage of NEC.

Table 6. Modified Bell´s Staging Criteria for Necrotizing Enterocolitis (NEC)

Stage	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics x 3 days
IB Suspected	Same as above	Grossly bloody stool	Same as above	Same as IA
IIA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics x 7 to 10 days
IIB Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites	NPO, antibiotics x 14 days
IIIA Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites	NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis
IIIB Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum	Same as IIA, plus surgery

DIC: disseminated intravascular coagulation
NPO: “nil per os” or nothing by mouth

Endocarditis should be suspected when there is evidence of systemic infection and there is either a congenital (or acquired) cardiac abnormality or when there is a central venous line in place. In general it requires clinical, laboratory and echocardiographic evidence of infection. Ensure at least three separate blood cultures are taken prior to antibiotic therapy (but do not delay antibiotic therapy if the infant is unwell).

Special circumstances (consult microbiology department.):

Encephalopathic/seizures: Consider CSF/plasma for HSV PCR and virology screening.

Ventriculo-peritoneal shunt in situ: Request CSF gram stain for appropriate antibiotics (Refer to Table 7).

3.4 Investigations during antibiotic treatment in late-onset sepsis

In babies given antibiotics because of clinical indicators of possible infection, measure the C-reactive protein concentration 18-24 hours after presentation.

Consider performing a lumbar puncture to obtain CSF sample in a baby who did not have a lumbar puncture at presentation is receiving antibiotics, if it is thought safe to do so and if the baby:

- has a positive blood culture (other than coagulase negative staph) or
- does not respond satisfactorily to antibiotic treatment, or
- has strong clinical suspicion of infection, or
- has clinical symptoms or signs suggesting meningitis

Decision 48 hours after starting antibiotic treatment in late-onset sepsis

In babies given antibiotics because of clinical indicators of possible infection, consider stopping the antibiotics at 48 hours if:

- the blood culture is negative, and
- the initial clinical suspicion of infection was not strong, and
- the baby's clinical condition is reassuring with no clinical indicators of possible infection, and
- the levels and trends of CRP are reassuring

Duration of antibiotics in late-onset sepsis without meningitis

The usual duration of antibiotics in LOS with a positive blood culture, and for those with negative blood culture but in whom there has been strong suspicion of sepsis is 7 days but can be stopped at 5 days if:

- clinically improved and well,
- negative BC or BC growing skin type organisms (i.e. Coagulase negative Staphs)

Refer to table 7 for further details and point at which microbiology authorisation code is required.

Consider continuing antibiotic for more than 7 days if:

- the baby has not yet fully recovered, or
- this is advisable, based on the pathogen identified on blood culture (seek expert microbiological advise if necessary)

If continuing antibiotics for longer than 48 hours despite negative blood cultures, review the baby at least once every 24 hours. On each occasion using clinical judgement, consider whether it is appropriate to stop antibiotic treatment, taking account of:

- the level of initial clinical suspicion of infection

- the baby's clinical progress and current condition, and
- the levels and trends of CRP

3.5 Management of late-onset meningitis for baby's in neonatal service

In a baby with suspected sepsis AND meningitis (CSF shows a meningitis picture) add cefotaxime IV to any current antibiotics, then adjust according to identification and sensitivities after discussion with microbiologist.

Prescribing antimicrobials

Table 7 gives details of the first line antimicrobials recommended for specific neonatal infection, and the required duration of treatment. Antimicrobials used in line with these recommendations can be initiated without prior microbiologist approval. Duration of treatment is restricted to that detailed in the table. If you wish to continue treatment beyond this period authorisation MUST be sought from microbiology and documented on the drug chart and in the medical records.

Certain antimicrobials cannot be initiated without prior microbiology approval because of factors including: High risk of unwanted effects, Limited availability, Expense & Unique mechanism of action to be reserved for the treatment of organisms resistant to standard antimicrobials.

These antimicrobials, along with details of their restrictions, are listed on the Trust Antimicrobial website via antimicrobial drug monograph section

Prescribers MUST seek microbiological approval for permission to prescribe an antimicrobial from the Trust-designated 'restricted list of antimicrobials', prior to starting treatment. This approval must be sought even out of hours and must be recorded (as a verification number) on the antimicrobial prescription and in the medical notes by the prescriber.

This restricted use of antimicrobials also helps to reduce antimicrobial burden and ensure the choice of antimicrobial is clinically appropriate.

Table 7 Antimicrobial guidance for UHL neonatal services

Infection	First Line antimicrobial(s)	Recommended Duration	Notes	Point at which microbiology verification is required
Presumed early onset sepsis ─ with signs presenting within 72 hours of birth • (Any 'Red Flag' OR ≥2 'non red flag' risk factors or clinical indicators (Table 1,2,3 and 4)	Benzylpenicillin IV & Gentamicin IV	Stop if culture negative at 36 hours. If positive continue treatment for 7 days, antibiotic choice guided by sensitivities.	If on-going signs of sepsis at 48 hours of treatment discuss with microbiology.	Treatment beyond 7 days
• gram –ve infection confirmed	Add Cefotaxime IV if gram –ve infection confirmed. Stop Benzylpenicillin			Treatment beyond 7 days
Presumed early onset sepsis – with signs presenting within 72 hours of birth • (1 'non red flag' risk factor or 1 'non red flag' clinical indicator (Table 3 and 4) and clinical concerns increases during monitoring period)	Benzylpenicillin IV & Gentamicin IV Add Cefotaxime IV if extra gram –ve cover needed. Stop Benzylpenicillin	Stop if culture negative at 36 hours. If positive continue treatment for 7 days, antibiotic choice guided by sensitivities.	If on-going signs of sepsis at day 5 of treatment discuss with microbiology.	Treatment beyond 7 days

	Add cefotaxime IV if gram –ve infection confirmed Stop Benzylpenicillin			Treatment beyond 7 days
Presumed late onset sepsis. Presenting after the first 72 hours of life • Clear evidence of localised infection, e.g. umbilical flare.	Flucloxacillin IV & Gentamicin IV	Stop if culture negative at 36 hours. If positive continue for 7 days, antibiotic choice guided by sensitivities.	If on-going signs of sepsis at day 7 of treatment discuss with microbiology.	Treatment beyond 7 days
Presumed late onset sepsis. Presenting after the first 72 hours of life • Suspected sepsis AND meningitis	Add Cefotaxime to any current antibiotics or commence Amoxicillin, cefotaxime and gentamicin	Depends upon identification and sensitivities after discussion with microbiologist.		Treatment beyond 21 days
Meningitis, initial treatment when causative pathogen unknown (blind treatment)	Amoxicillin IV & Cefotaxime IV	See below	Notify public health. If subsequently confirmed gram –ve infection can stop amoxicillin	See below
Meningitis – confirmed gram –ve infection	Cefotaxime IV (guided by CSF antimicrobial	For at least 21 days. If clinical progress is slow, consider extending	Notify public health.	Treatment beyond 21 days

	susceptibilities when available) (Stop Amoxicillin)	duration of treatment (Consider repeat CSF prior to stopping antibiotics)	Seek expert microbiology advice	
Meningitis – Group B streptococcus on culture	Benzylpenicillin IV Plus gentamicin for 5 days	Benzylpenicillin for at least 14 days	Notify public health	Treatment beyond 14 days
Listeria meningitis - Blood or CSF culture +ve	Amoxicillin IV for 14-21 days (Stop cefotaxime) plus gentamicin x 7days	For 14-21 days	Notify public health	Treatment beyond 21 days
Culture negative meningitis	Amoxicillin IV & Cefotaxime IV D/w Microbiology and switch to appropriate antibiotics	For 14 days	Notify public health	Treatment beyond 14 days
Suspected Herpes Simple Virus (HSV)-Encephalopathy/seizures/atypical CSF	Aciclovir IV	For 21 days if herpes PCR positive and review	Discuss with Consultant Virologist	Treatment beyond 21 days
Group B streptococcal septicaemia (Blood culture +ve or baby symptomatic)	Benzylpenicillin IV (Stop Gentamicin IV)	For 10 days.		Treatment beyond 10 days
Group B streptococcal osteomyelitis	Benzyl penicillin IV	For 4 weeks		Treatment beyond 4 weeks

Neonatal pneumonia (presenting within 72 hrs of birth) - Neonatal pneumonia (presenting after 72 hrs of birth) -	Benzylpenicillin IV & Gentamicin IV Cefotaxime IV & Amoxicillin IV	For 7 days, antibiotic choice guided by sensitivities.	If ongoing signs of sepsis at day 7 of treatment discuss with microbiology.	Treatment beyond 7 days
Staphylococcal aureus septicaemia	Flucloxacillin IV	For at least 14 days	Duration will depend on focus of infection. Discuss all cases with microbiology.	Treatment beyond 14 days
Coagulase negative staphylococcal septicaemia	Vancomycin IV (must request vancomycin sensitivities from microbiology)	For 7-10 days		Treatment beyond 10 days
Nosocomial infection -unknown cause	Flucloxacillin IV & Gentamicin IV	Stop if culture negative at 36 hours. If positive continue for 7 days, and review antibiotic choice guided by sensitivities.	If ongoing signs of sepsis at day 7 of treatment discuss with microbiology.	Treatment beyond 7 days

Nosocomial Infection -Central venous catheter related sepsis	Cefotaxime IV & Vancomycin IV Consider removal of central line	Continue for a minimum of 7 days Switch to appropriate antibiotics guided by sensitivities/microbiologist for remainder of course		Treatment beyond 7 days
Necrotising enterocolitis at < 72 hours of age	Benzylpenicillin IV, Gentamicin IV, Metronidazole IV	For up to 14 days	Authorisation code not required.	Treatment beyond 14 days
Necrotising enterocolitis at 72 hours of age or greater	Flucloxacillin IV, Gentamicin IV, Metronidazole IV	For up to 14 days	Authorisation code not required.	Treatment beyond 14 days
Neonatal Herpes Simplex Virus	Aciclovir IV	For 14 days. Give for 21 days if CNS involvement. Consider repeat LP to ensure herpes PCR negative prior to stopping aciclovir. Consider 6 months of oral aciclovir to prevent relapse	Discuss all cases with Virology.	Treatment beyond 21 days
Silo bag infection ("silo" is a bag made from silastic or similar material which allows gravity to slowly return the exposed intestines to the abdominal cavity in conditions such as omphalocele, exomphalos and gastroschisis)	Flucloxacillin IV, Gentamicin IV and Metronidazole IV	For 14 days guided by sensitivities.	If recent course of flucloxacillin substitute cefotaxime IV	Treatment beyond 14 days

Candidaemia	Fluconazole IV	14- 21 days.	Discuss with microbiology	Treatment beyond 21 days
Staphyloccus aureus osteomyelitis	Flucloxacillin IV	6 weeks		Treatment beyond 6 weeks
Urinary tract infection [7, 8]	Gentamicin IV & amoxicillin IV	Up to 7 days –change antibiotic if necessary once sensitivity known.		Treatment beyond 7 days
Urinary tract infection prophylaxis after recurrent infection where no underlying pathophysiology	Trimethoprim oral once daily. Change antibiotic if necessary once sensitivity known.	Management guided by specialist renal clinic		Before commencing treatment
Urinary tract infection prophylaxis where underlying pathophysiology known	Trimethoprim oral once daily. Change antibiotic if necessary once sensitivity known.	Management guided by specialist renal clinic.		Not required
Bacterial Endocarditis	Discuss with microbiology before treatment	4-6 weeks and review with clinical course and blood cultures		Treatment beyond 6 weeks
Pseudomonas pneumonia	i.v Ceftazidime	For 7 days. Review with sensitivities from respiratory culture		Treatment beyond 7 days

Suspected Ureaplasma Pneumonia First line-Clarithromycin Second line-Azithromycin/Erythromycin	Clarithromycin IV if oral route not available OR	For 10 days Switch to oral route when appropriate		Treatment beyond 10 days
	Azithromycin PO OR	For 10 days.		Treatment beyond 10 days
	Erythromycin IV	For 10 days		Treatment beyond 10 days
Chlamydia Pneumonia Or Conjunctivitis	Erythromycin PO/IV (First Line)	For 14 days		Treatment beyond 14 days
	Azithromycin PO (Off label)	For 3 days		Treatment beyond 3 days
VP shunt Gram stain shows a *Staphylococcus species*.	Vancomycin IV Rifampicin PO	For 14 days.		Treatment beyond 14 days

VP shunt Gram stain shows Coliforms	Cefotaxime IV Gentamicin IV	For 14 days		Treatment beyond 14 days
VP shunt Gram stain shows no bacteria	Vancomycin IV Cefotaxime IV	For 14 days		Treatment beyond 14 days
Conjunctivitis with purulent eye discharge in 1st 72 hours (possible congenital gonococcal infection)	Cefotaxime 100mg IV /IM	Single dose	Take swabs urgently for microbiological investigation to include Chlamydia and gonococcus. Start systemic treatment with cefotaxime whilst awaiting swab results.	Not required
Umbilical infection	Flucloxacillin IV and gentamicin IV	For at least 5 days	Stop gentamicin if swab culture indicates no gram –ve infection	Treatment beyond 5 days

4. Audit standards

1. Microbiology authorisation code requested when giving antibiotics beyond recommended duration.
2. Give intravenous antibiotics within 1 hour of decision to treat
3. Intravenous Benzylpenicillin and Gentamicin is used as first line antibiotics for early-onset neonatal sepsis
4. Intravenous Flucloxacillin and Gentamicin is used as first line antibiotics for late-onset neonatal infection
5. Give oral nystatin during antibiotic treatment for LOS in ≤ 1500g or < 30 weeks
6. Early onset sepsis: Stop antibiotics at or before 36 hours if: the blood culture is negative, and the initial clinical suspicion of infection was not strong, and the baby's clinical condition is reassuring with no clinical indicators of possible infection, and the levels and trends of CRP are ≤ 10
7. Late onset sepsis: Stop antibiotics at 48 hours if blood culture is negative, CRP level and trend is normal, clinical condition good and initial suspicion was not strong
8. Annual review of meropenem use on the neonatal unit

5. Annual Surveillance

1. Incidence of early, late and nosocomial infection (blood positive and negative)
2. Resident bacterial flora and sensitivities to antibiotics.
3. Long line sepsis incidence, organisms, and antibiotic sensitivities

6. References

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5. Stoll BJ, Gordon T, Korones SB et al. Early-onset sepsis in very low birth weight neonates: a report from the NICHHD Neonatal Research Network. Journal of Pediatrics 1996; 129:1093-1099
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7. Key Words

Antibiotics, Bacterial Endocarditis, Candidaemia, Chlamydia, Conjunctivitis, Gonococcus, Group B streptococcal, Herpes Simplex Virus, Lumbar Puncture, Meningitis, Necrotising enterocolitis, Neonatal Sepsis, Pneumonia, Staphylococcal, Umbilical Infection, Ureaplasma, Urinary Tract Infection, Viral Infection, VP Shunt

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

EDI Statement

We are fully committed to being an inclusive employer and oppose all forms of unlawful or unfair discrimination, bullying, harassment and victimisation.

It is our legal and moral duty to provide equity in employment and service delivery to all and to prevent and act upon any forms of discrimination to all people of protected characteristic: Age, Disability (physical, mental and long-term health conditions), Sex, Gender reassignment, Marriage and Civil Partnership, Sexual orientation, Pregnancy and Maternity, Race (including nationality, ethnicity and colour), Religion or Belief, and beyond.

We are also committed to the principles in respect of social deprivation and health inequalities.

Our aim is to create an environment where all staff are able to contribute, develop and progress based on their ability, competence and performance. We recognise that some staff may require specific initiatives and/or assistance to progress and develop within the organisation.

We are also committed to delivering services that ensure our patients are cared for, comfortable and as far as possible meet their individual needs.

Contact and review details	
Guideline Lead (Name and Title) V.Kairamkonda – Consultant Neonatologist L.Stachow - Pharmacist S Koo – Consultant Microbiologist	**Executive Lead** Chief Medical Officer

Details of Changes made during review:

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
August 2021	**3**	Neonatal guidelines group Neonatal Governance	Added to main key points- refer to maternal pyrexia in labour g/l and discuss maternal history with obstetrician **ABX guidance** Added - start oral nystatin if ≤ 1500g or < 30 weeks (iv flucanazole only if oral route contraindicated) and stop when antibiotics discontinued Added listeria & GBS pathways to the Late onset flowchart. Increased ABX duration for Gram stain + from 5 to 7 days Meningitis GBS on culture – add Gentamicin for 5 days Specified to Add Cefotaxime IV if gram –ve infection confirmed. Listeria meningitis – add gentamicin for 7 days Nosocomial infection –unknown cause, duration of ABX increased from 5 to 7 days **EOS** Added key points - • not for routine urine microscopy • For LP before ABX if safe to do so • 7 day duration of ABX but can be stopped earlier if appropriate Added to when commencing ABX, if there is microbiological evidence of gram-negative bacterial sepsis, change benzylpencillin to cefotaxime and continue gentamicin Removed Resp distress starting >4hrs after birth from red flag indicators, replaced with apnoea and need for cardiopulmonary resuscitation. Non-red flag risk factors - Clarified duration and gestation in cases of ruptured membranes Non-red flag indicators in baby- Removed ; apnoea, need for cardiopulmonary resus (now a red flag), need for mechanical ventilation in preterm, oliguria and local signs of infection Investigations- Removed - take NPA and viral cultures for Pertussis and viruses if not improving When considering performing LP whilst baby is receiving ABX – removed CRP ≥10 as an indicator. Amended positive blood culture to positive blood culture(other than coagulase negative staph). Added has clinical symptoms or signs suggesting meningitis Management of early onset meningitis now includes Gentamicin Added suspected gram –ve pathway to ABX guide flow chart In cases of confirmed chlamydia, now advises that Azithromycin is off label for this use in neonates

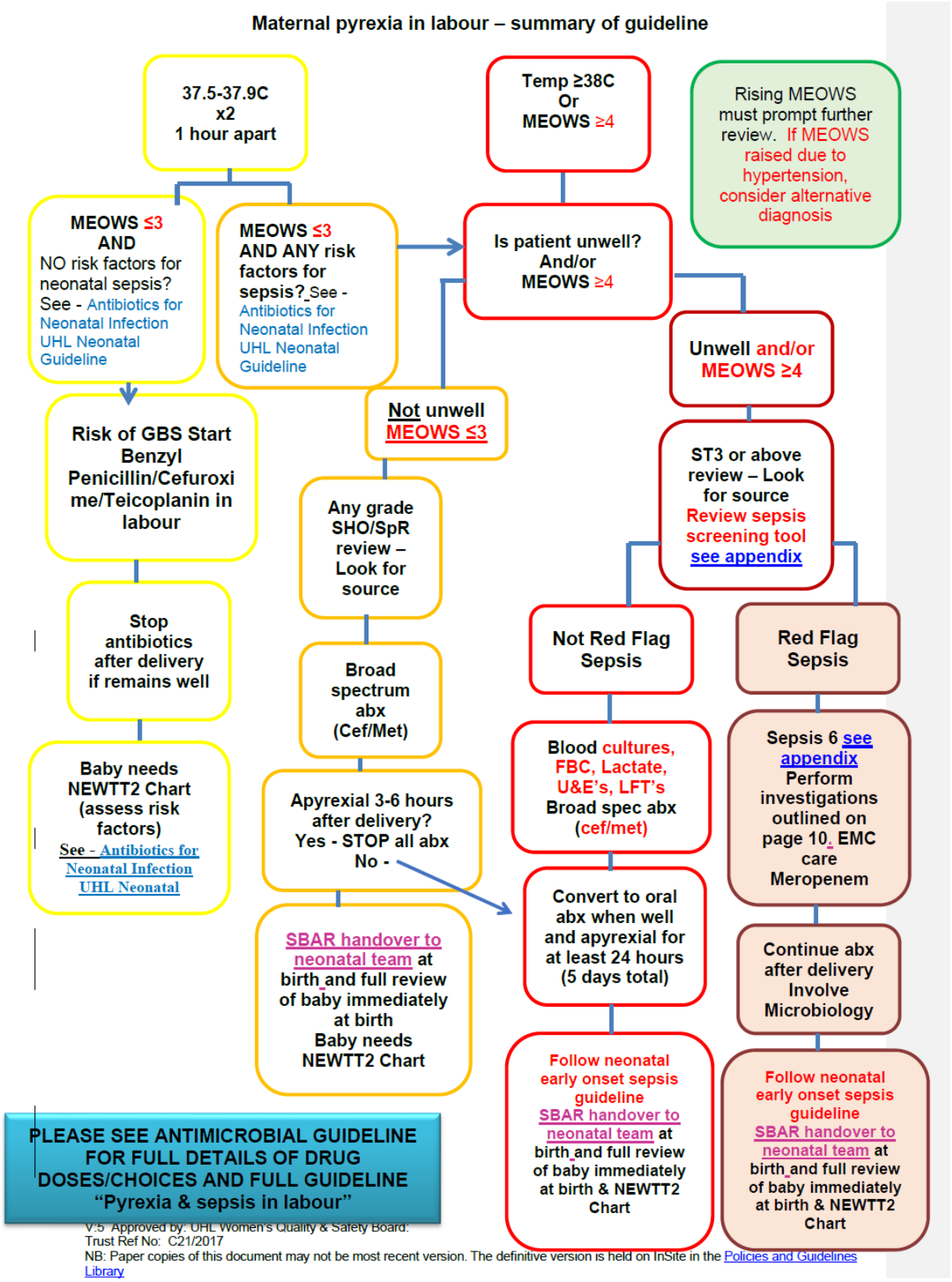
			<u>Late onset</u> Key points added: Birthweight ≤ 1500g or < 30 weeks - Start prophylactic oral nystatin when starting antibiotics for LOS. Do not routinely perform urine microscopy or culture or skin swab microscopy or culture (if no localised infection) Perform urine microscopy and culture for babies outside of neonatal units in line with NICE guideline on urinary tract infection in under 16s. Perform a lumbar puncture before antibiotics if safe to do so when there is a strong clinical suspicion of infection or there are clinical symptoms or signs suggesting meningitis. Duration of antibiotics in LOS is 7 days but can be stopped earlier if indicated Removed separation of 'strong' & 'suggestive' clinical indicators and updated clinical indicators in line with NICE Removed advise re- sampling urine as no longer routinely performed When considering performing LP whilst baby is receiving ABX Late onset same guidance as EOS Removed reference to UTI
Dec 2024	**4**	Neonatal guidelines group Neonatal Governance	Reassess the need for antibiotics at or before 36 hours in early onset sepsis. Reassess the need for antibiotics at 48 hours in late onset sepsis. **2.3 Investigations for suspected early-onset sepsis, added** • CXR only if clinical signs suggestive of respiratory distress 3. Late onset added - Clinical indicators of possible late-onset neonatal infection- added, risk factors Needing or having had mechanical ventilation, History of surgery, Central catheter. Antimicrobial table updated specifically re- neonatal pneumonia, Central venous catheter related sepsis & Pseudomonas pneumonia

Appendix 1: Normal CSF values (Mean and Range) [2]:

Type of Infant	WBC / mm^3	Protein (g/l)	Glucose (mmol/l)
Preterm < 28 days	9 (0-30)	1 (0.5-2.5)*	3 (1.5-5.5)
Term < 28 days	6 (0-21)	0.6 (0.3-2.0)*	3 (1.5-5.5)
*Protein values are higher in the first week of life and depend on the red cell count. A white cell count of more than 21/mm^3 with a protein value of more than 1 g/l with less than 1000 red cells is suspicious of meningitis.			

NB. Plasma glucose should be taken immediately prior to the LP. CSF glucose is usually 70-80% of plasma glucose (normal). A low CSF glucose can persist for many weeks following IVH. If CSF results are suspicious then always consider a repeat LP in next 12-24 hours (discuss with Consultant). Antibiotic therapy should initially be according to the unit guidelines (Refer to Chart 1) but will subsequently be guided by the CSF Gram stain and, later, by culture results.

Appendix 2: Pyrexia and Sepsis in Labour UHL Obstetric Guideline



Appendix 3. Criteria for empiric meropenem use on neonatal unit

Good practice points (points 1, 2 and 3 must be fulfilled):

1) There should be clear documentation in the clinical notes of the reason/rationale for use of meropenem

2) The initiation of meropenem would be a decision made by a neonatal consultant. The first meropenem dose can be given empirically, but subsequent doses would require a discussion with microbiology for a microbiology authorisation code.

3) It is relatively unusual for a neonate to be moved from 1st line antibiotic regime to meropenem with the exception of neonates that fulfils the following criteria:

· Severely unwell (inc CNS infection could not be ruled out) – clear signs of severe sepsis (requiring cardiovascular support) and overwhelming/ quick clinical deterioration despite initial dose(s) of empiric therapy

AND/OR (these criteria would add weight for consideration of meropenem use)

· Admitted from neonatal unit where ESBL endemic OR

· Known to be colonised or previously isolated an ESBL-producing organism, 3rd generation cephalosporin resistant isolate or previously isolated organisms with highly inducible AmpC (Enterobacter spp, Klebsiella aerogenes, Citrobacter freundii, Hafnia alvei) OR

· Mother known to be colonised with ESBL, 3rd generation cephalosporin resistant isolate or previously isolated organisms with highly inducible AmpC (Enterobacter spp, Klebsiella aerogenes, Citrobacter freundii, Hafnia alvei) OR

· Unit has a problem with ESBL or highly inducible AmpC organism OR

Less strict criteria (may not need to be fulfilled but worth considering)

· Mother and/or father is a healthcare worker OR

· Asian/South East Asian background OR

· Other less inducible AmpC organism isolated (Serratia marcescens, Morganella morganii, Providencia spp) – if susceptible to all 3rd gen cephalosporins on testing, monotherapy with any of the 3rd gen cephalosporins may infrequently select out for mutants