

**Title:** THERAPEUTIC GUIDELINES IN NEONATAL INFECTION  
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**Consultation:** Neonatal Consultants, Pharmacy, Neonatal Guideline Group  
**Distribution:** Neonatal Units, Postnatal Wards and Labour NUH NHS Trust.  
**Risk managed:** Prevention and treatment of infection in infants on the Neonatal Units

**Clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague. Caution is advised when using guidelines after a review date. This guideline has been registered with the Nottingham City Hospital Trust.**

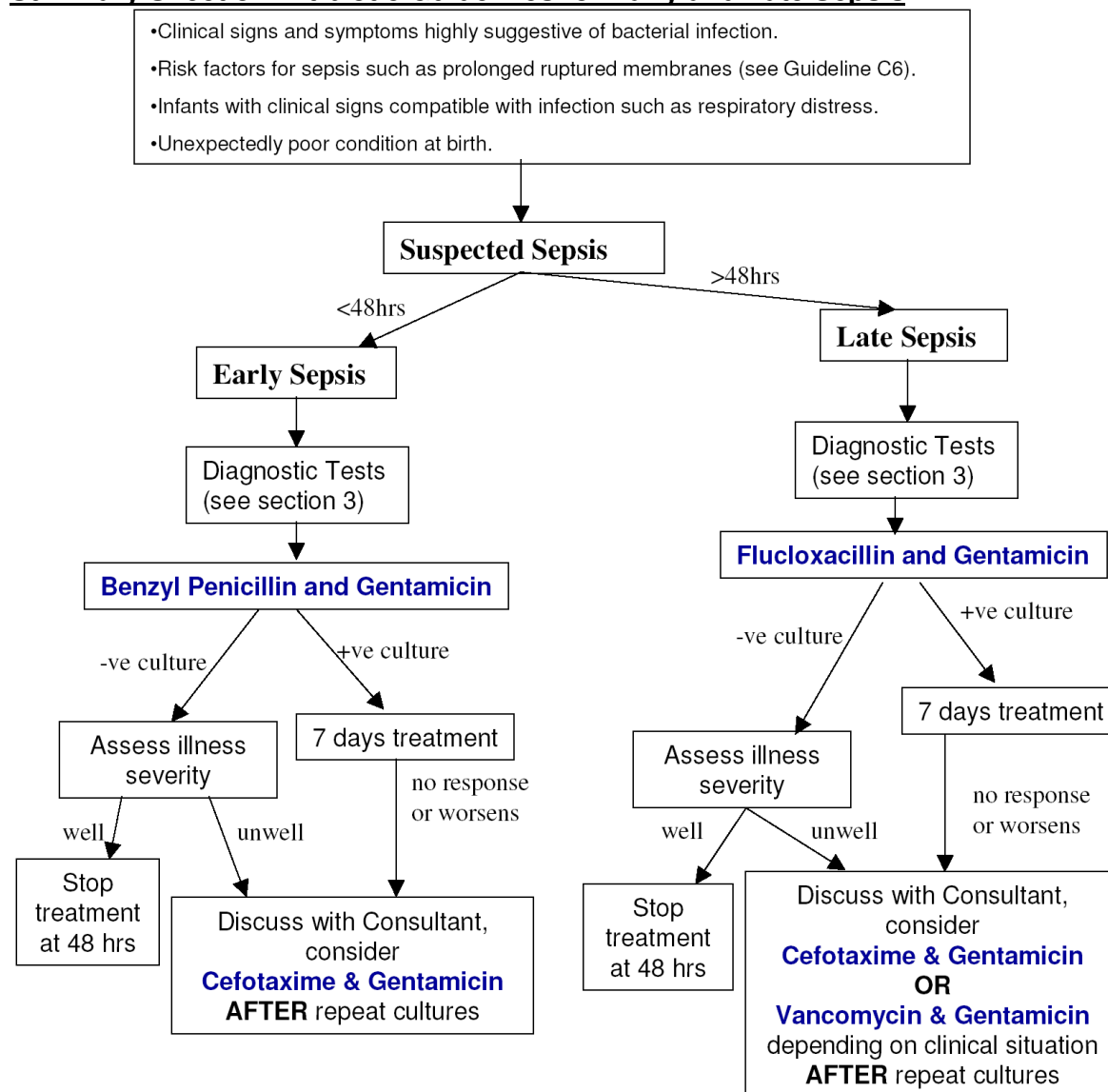
## **1. Introduction / Background**

Neonatal infection is a major cause of mortality and morbidity. The incidence of early infection (<48 hours) is approximately 2-3 per 1000 live births with a mortality of 15%. The incidence of meningitis in these infants is 23% [1]. The incidence of late infections (after 48 hours) is 4.4 per 1000 live births with a mortality rate of 9%. The incidence of meningitis in these infants is 9% [1]. Most sepsis on the neonatal unit is late sepsis in preterm infants and life threatening late-onset infections in term infants are rare. The commonest organism causing sepsis on the neonatal unit is coagulase negative *Staphylococcus* reflecting the fact that most infection is late in onset and probably nosocomial.

Symptoms and signs of infection are notoriously vague and ill defined, and range from jaundice, to respiratory distress, to septic shock. Although the commonest symptom is a non-specific 'going off' when the mother or an experienced nurse feels the infant is just not 'right'. It is important to have a low threshold for starting antibiotics particularly in preterm infants.

Traditionally in infants suspected to have sepsis 48 hours of antibiotic therapy has been recommended, before re-evaluating the need for continued antibiotics, pending negative blood cultures, and good clinical condition. Over the last decade, the role of supportive laboratory tests such as CRP's and differential white cell counts has increased, and decisions about therapy may be based on information gained from multiple sources. It is important to stop antibiotics promptly when indicated so as not to prolong antibiotic exposure and increase the antibiotic burden and thus increase the likelihood of the development of resistant organisms.

The bacteria infecting neonates vary from place to place, and between populations. These guidelines have been created on advice from the microbiology department in Nottingham, and are based on current bacterial prevalence and sensitivity profiles from our population of neonates.

**Summary Sheet of Antibiotic Guidelines for Early and Late Sepsis**

**NB: If positive culture or clinical suspicion of specific site infection see guideline details** (Pneumonia, Necrotising Enterocolitis, Meningitis, UTI, Endocarditis, Bone & Joint)

**2. Patient Group**

Infants suspected of having sepsis, including:-

- Clinical signs and symptoms highly suggestive of bacterial infection.
- Risk factors for sepsis such as prolonged ruptured membranes (see Guideline C6).
- Infants with clinical signs compatible with infection such as respiratory distress.
- Unexpectedly poor condition at birth.

**3. Identification / Diagnosis**

Infants in the above groups should have the following investigations:-

- Blood Culture
- Full blood count (FBC) and C-Reactive protein (CRP)
- CXR
- Lumbar puncture (may be omitted if the infant is less than 48 hours old and only has respiratory symptoms and no other risk factors).
- Urine supra-pubic aspirate for culture and sensitivity should be considered (not essential in early onset sepsis)

#### 4. Antibiotic Management

##### i.) Early Sepsis

The commonest organisms in this group of infants are (in order of decreasing frequency):-

<i>Streptococcus agalactiae</i> (Group B, $\beta$ Haemolytic)	approx 30-50%
<i>Escherichia coli</i> ( <i>E. coli</i> ),	
<i>Streptococci</i> other than Group B	
<i>Staphylococcus aureus</i>	
<i>Haemophilus influenzae</i>	
<i>Listeria monocytogenes</i>	
Gram negative anaerobes	
Fungi	
<i>Chlamydia trachomatis</i>	

If there are clinical signs of early respiratory distress such as grunting, tachypnoea, oxygen requirement, or nasal flaring OR clinical signs of sepsis in an infant < 5 days old

#### **BENZYL PENICILLIN AND GENTAMICIN**

Duration: If positive cultures – minimum 7 days of appropriate antibiotic.  
 If negative cultures, and clinically well, with normal CRP – stop after 48 hours  
 If negative cultures, but not clinically well, abnormal CXR or elevated CRP – discuss with Neonatal Consultant.

If no improvement after 48 hours, or worsens, discuss with Consultant and **AFTER** repeating blood cultures and considering further investigations, consider changing to:

#### **CEFOTAXIME AND GENTAMICIN**

##### ii.) Late Onset Sepsis

The commonest organisms in this group of infants are (in order of decreasing frequency) [2]:-

Coagulase negative <i>Staphylococcus spp.</i>	55%
<i>Staphylococcus aureus</i>	9%
<i>Enterococcus</i> / group D <i>Streptococcus</i>	5%
<i>Streptococcus agalactiae</i> (Group B, $\beta$ Haemolytic)	2%
<i>Enterobacter</i>	4%
<i>Escherichia coli</i>	4%
<i>Klebsiella</i>	4%
<i>Pseudomonas</i>	2%
Other Gram negatives	4%
<i>Candida albicans</i>	5%
<i>Candida parapsilosis</i>	2%

A recent review of positive blood cultures from both Nottingham Neonatal units supports these commonly quoted figures with coagulase negative *Staphylococcus* predominating. The majority of (but not all) coagulase negative *Staphylococcus* in both units is resistant to Flucloxacillin. Coagulase negative *Staphylococcus* is, to date, entirely sensitive to Vancomycin. If there are clinical signs of sepsis in an infant more than 5 days old:

#### **FLUCLOXACILLIN AND GENTAMICIN**

Duration: As before (see early onset sepsis)  
 If the infant has positive blood cultures (particularly with coagulase negative *Staphylococcus*), but is clinically well with a normal CRP – discuss with Neonatal Consultant.

Antibiotics may need to be changed when the sensitivities become known. Consider using **VANCOMYCIN** when coagulase negative *Staphylococcus* is cultured (discuss with Neonatal Consultant and / or Microbiology Consultant). Consider removing central venous lines (discuss with Neonatal Consultant).

If no improvement after 48 hours, or the infant's condition worsens, repeat blood cultures/re-screen and consider changing antibiotics to:

**VANCOMYCIN AND GENTAMICIN**  
**OR**  
**CEFOTAXIME AND GENTAMICIN**  
*Dependant upon the clinical situation*

If the infant remains unwell or deteriorates whilst on Cefotaxime and Gentamicin (or Vancomycin and Gentamicin) discuss with Neonatal Consultant. Always consider removal of central venous lines but discuss this with Consultant first.

### iii.) Pneumonia

Needs to be considered in infants with clinical signs of respiratory distress with x-ray changes. Always complete investigations as above but in addition send endotracheal tube (ETT) secretions. Antibiotics are as for late or early sepsis (see above) as appropriate.

If the ETT secretions are culture positive:

- Coliforms – **CEFOTAXIME AND GENTAMICIN**
- *Pseudomonas* – **CEFTAZIDIME AND GENTAMICIN**
- Group B *Streptococcus* – **BENZYL PENICILLIN AND GENTAMICIN**
- *Staphylococcus aureus* – **FLUCLOXACILLIN AND GENTAMICIN** (await sensitivities)

If no improvement, consult Microbiology and Neonatal Consultant.

If ETT secretions are culture negative:

- Infant < 5 days old **BENZYL PENICILLIN AND GENTAMICIN**
- Infant > 5 days old **FLUCLOXACILLIN AND GENTAMICIN**  
(or on second course of antibiotics)

If no improvement after 48 hours consider changing to (after repeat blood culture):  
**CEFOTAXIME AND GENTAMICIN**

If there is still no improvement, consider:

*Ureaplasma* and *Chlamydia*:- take appropriate samples for investigation and commence:  
**ERYTHROMYCIN**

Viruses – take NPA and viral cultures

Duration: 7 days of appropriate antibiotics

*Note: if positive ETT secretions, but clinically well / asymptomatic – no treatment.*

**iv.) Necrotising Enterocolitis.**

This should be suspected when there are clinical signs of sepsis, abdominal signs and / or x-ray changes suggestive of intra-abdominal pathology (see Neonatal Guideline G14)

***BENZYL PENICILLIN, GENTAMYCIN AND METRONIDAZOLE***

If no improvement after 48 hours, discuss with Neonatal Consultant and Microbiology. Flucloxacillin prescribed for a late onset infection should be changed to Benzylpenicillin if NEC subsequently becomes probable or confirmed.

Duration: Consider 10 days antibiotics (Discuss with Neonatal Consultant).

**v.) Meningitis**

This should be considered when there are clinical signs of sepsis and positive cerebro-spinal fluid (CSF) findings (increased white cells, decreased glucose, positive culture etc.).

Normal CSF values [3]:

<b>Infant</b>	<b>RBC / mm<sup>3</sup></b>	<b>WBC / mm<sup>3</sup></b>	<b>Protein (g/l)</b>	<b>Glucose (mmol/l)</b>
Preterm < 7 days	30 (0-333)	9 (0-30)	1 (0.5-2.9), usually < 2g/l	3
Preterm > 7 days	30	12 (2-70)	0.9 (0.5-2.6), usually < 1.5g/l	3
Term < 7 days	9 (0-50)	5 (0-30)	0.6 (0.3-2.5)	3
Term > 7 days	<10	3 (0-10)	0.5 (0.2-0.8)	3

NB. CSF Glucose is usually 70-80% of plasma Glucose (normal). Plasma Glucose should be taken immediately prior to the LP. 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 above guidelines but will subsequently be guided by the CSF Gram stain (indicated below):

- Group B *Streptococcus* (gram +ve cocci)      ***BENZYL PENICILLIN AND GENTAMICIN***
- Coliforms (gram –ve bacilli)                      ***CEFOTAXIME AND GENTAMICIN***
- *Listeria* (gram +ve bacilli)                        ***AMOXICILLIN AND GENTAMICIN***
- No bacteria seen                                        ***CEFOTAXIME AND GENTAMICIN***

Duration (discussion with Neonatal Consultant should follow as to when to repeat LP during the course of treatment):

- Group B *Streptococcus* 14 to 21 days of appropriate antibiotic
- Coliforms – 21 days of appropriate antibiotic
- *Listeria* – 14 – 21 days of appropriate antibiotic
- No positive culture but abnormal CSF findings – discuss with Neonatal Consultant and Microbiology.

Special circumstances (consult microbiology dept.):

a.) Ventriculo-peritoneal shunt in situ:

If the Gram stain shows a *Staphylococcus* spp.

***VANCOMYCIN IV AND RIFAMPICIN (ORALLY)***

If the Gram stain shows Coliforms

***CEFOTAXIME AND GENTAMICIN***

If the Gram stain shows no bacteria

***VANCOMYCIN AND CEFOTAXIME***

b.) External Ventricular Drain in situ:

**PTO**

If the Gram stain shows *Staphylococcus spp.*:

**INTRATHECAL VANCOMYCIN, AND INTRAVENOUS VANCOMYCIN WITH ORAL RIFAMPICIN.**

If the Gram stain shows Coliforms:

**CEFOTAXIME AND GENTAMICIN**

If the Gram stain shows no bacteria

**VANCOMYCIN AND CEFOTAXIME**

Consult with microbiology for duration of antibiotics

c.) Encephalopathic/seizures:

Consider CSF/plasma for Herpes PCR and virology screening.

Consider adding in

**ACICLOVIR**

(See Guideline E10 and Pocket Neonatology for reference)

#### **vi.) Urinary Tract Infections (UTI)**

The signs and symptoms of UTI in the neonate are not distinguishable from generalised sepsis (and it is often associated with generalised sepsis) therefore a urine sample should always form part of the assessment of a possible septic neonate. UTI in the neonate has long-term implications and the diagnosis must be carefully confirmed. It is essential therefore to confirm bacteria and pus cells on microscopy from a supra-pubic aspirate (SPA) or a clean catheter specimen of urine. Bag specimens or clean catches are not suitable or impractical.

**AMOXICILLIN AND GENTAMICIN**

Route: Intravenous

Duration: 5 – 7 days

Prophylaxis for infants considered at risk of UTI e.g. reflux nephropathy:

**ORAL TRIMETHOPRIM in Term infants (ie. >36/40)**

**ORAL CEPHRADINE in Preterm infants (ie. <36/40)**

#### **vii.) Endocarditis**

This 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.

To confirm the diagnosis and infecting organism ensure at least three separate blood cultures prior to antibiotic therapy (but do not delay antibiotic therapy if the infant is unwell).

**VANCOMYCIN AND GENTAMICIN**

If no improvement after 48 hours repeat blood cultures and add

**CEFOTAXIME**

Duration: 4 – 6 weeks, but depends on blood cultures and clinical course.

Manage in conjunction with the microbiology dept.

**viii.) Bone And Joint Infections**

This should be suspected when there is clinical evidence of sepsis with a painful limb / bony area, or a swollen joint. Antibiotic treatment:-

***FLUCLOXACILLIN AND GENTAMICIN***

If there is no improvement or the infant's condition worsens over the next 48 hours repeat blood cultures and change to

***CEFOTAXIME AND GENTAMICIN***

Duration: 4 – 6 weeks.

**ix.) Fungal Infection**

Newborn infants are susceptible to fungal infections because of their relative immunodeficiency. Invasive Candidiasis has been reported in as high a proportion as 4.5% [4]. *C. albicans* accounts for about 75% of all neonatal fungal infections with *C. parasilosis* and *C. tropicalis* accounting for most of the rest [5].

Fungal infection presents in much the same way as bacterial infection in the preterm neonate but often has an insidious onset often associated with thrombocytopenia and abdominal distension. The spectrum of illness includes pneumonia, septicaemia, with or without endocarditis, septic arthritis, osteomyelitis, intra-peritoneal infection, liver abscesses, meningitis and renal tract infection. Most infants with systemic fungal infection have indwelling central lines and have been treated with antibiotics for some time[6].

Fungal infection is harder to diagnose than bacterial infection as positive blood cultures are less common. Even when organisms are in the blood it takes several days longer for cultures to become positive. It is therefore vital to ensure all specimens are collected and repeated if fungal infection is suspected including blood, urine and CSF.

At present if fungal sepsis is proven, full discussion with Neonatal Consultant and Microbiology Consultant must take place to decide on appropriate antifungal agent(s), monitoring of side-effects and duration of treatment. When Candida is grown in blood culture(s) an Echocardiograph must be ordered to exclude Endocarditis. When Candida is grown from urine culture a Renal USS should be considered.

In terms of antifungal prophylaxis further evidence is awaited before changing our current approach. At present we are using Oral Miconazole gel (Daktarin) and topical Nystatin together in any baby receiving any antibiotic other than benzyl penicillin, flucloxacillin or gentamicin **OR** receiving **ANY** antibiotics for more than a 5 day course. In most situations the antifungal treatment should be continued for 48 hours beyond the cessation of the antibiotic course. This may help to establish a more normal bowel flora although there is little evidence for this.

**5. Audit Points:**

Incidence of systemic sepsis – early and late.

Incidence of sepsis in infants with intravenous long lines and other central lines.

Proportion of positive blood cultures, identity of organisms and antibiotic sensitivity.

Proportion of negative blood cultures but clinical evidence of sepsis with elevated CRP and antibiotic therapy continued for > 48 hours.

Proportion of septic screens involving a suitable urine culture – and significance of sterile pyuria in this population.

**6. Allied Guidelines:**

Management of infants born to women known to carry GBS. Policy C6

Management of babies born after prolonged rupture of membranes. Policy C6

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