Neonatal sepsis
Alison R Bedford Russell

Abstract
Infection is a leading cause of mortality and morbidity in the newborn. The smaller and more preterm the baby, the higher the risk of infection and its consequences. Babies with risk factors or symptoms of infection should be screened and treated promptly. Group B streptococcus remains the leading cause of early onset infection. Late onset infection is predominated by coagulase negative staphylococci and gram-negative pathogens with increasingly resistant and unusual profiles. Increasing antimicrobial resistance is a global issue, and must be combated by robust infection control measures and implementation of antibiotic stewardship programmes including surveillance of infection episodes. While early detection and prompt management are vital in the prevention of adverse consequences of neonatal infection, it is imperative that antibiotic therapy is appropriately targeted to reduce the short and long term consequences of antibiotic use.

Keywords breastfeeding; coagulase-negative staphylococci (CONS); early onset neonatal sepsis; group B streptococcus (GBS); infection surveillance; late-onset neonatal sepsis

Definition
Neonatal sepsis refers to infection occurring within the neonatal period i.e. the first 28 days of life for a term baby, and up to 4 weeks beyond the expected date of delivery in a preterm baby. Sepsis is broadly classified into early or late onset neonatal sepsis:

Early-onset sepsis (EOS)
Early onset sepsis is variably defined as sepsis (bacteraemia and/or meningitis), within 48–72 hours of birth. Some define it as less than 7 days. It may present with subtle early signs or as a fulminating septicemia illness. Pneumonia is the commonest focal infection. The main routes of transmission are via transplacental or ascending vaginal routes from the mother.

The incidence of culture-positive EOS (defined as sepsis in the first 48 hours of life) is around 0.9 per 1000 livebirths and 9/1000 neonatal admissions. In the UK, organisms causing EOS are predominated by Group B Streptococcus (GBS), as shown in Table 1. This is followed by Gram-negative isolates (25%, predominantly Escherichia coli) and then in similar proportions, other streptococci and Staphylococcus aureus (6 and 5% respectively). Listeria monocytogenes is isolated less frequently but carries significant mortality, and is an important cause of meningitis.

The incidence of early onset GBS infection in countries which screen for GBS and offer intrapartum antibiotic prophylaxis to those women who are colonized with GBS, has continued to decline, while that in the UK has at best stayed stable, in spite of a Royal College of Obstetricians and Gynaecologists (RCOG) risk factor based prevention strategy.

The National Institute for Health and Clinical Excellence (NICE) clinical guideline development group (CGDG) developed a guideline in which risk factors and clinical indicators for early onset sepsis are stratified and attributed ‘Red Flags’ to indicators that should prompt a high level of concern (Table 2). Any baby with one Red Flag indicator or Risk factor, or two or more ‘Non-red flag’ indicators should be promptly assessed for infection and treated with antibiotics without delay.

Late-onset sepsis
Late-onset infection in neonates is most frequently defined as infection occurring at more than 48–72 hours of age after birth, and is usually the result of nosocomially acquired organisms, hence the term “Health Care Acquired Infection” (HCAI). Late onset GBS infection is defined as being from 7 days of life.

In the UK, the incidence of late onset infection is approximately 8/1000 livebirths, and affects approximately 7% of neonatal unit admissions. The majority of LOS occurs in premature (less than 37 weeks gestation) and low birthweight (less than 2500 g) babies, the risk being greater for the smallest and most immature babies. The incidence of late onset sepsis among VLBW infants ranges between 16 and 30% and approaches 50% in infants with birthweights less than 1000 g. Pathogens are predominated by coagulase negative staphylococci (CoNS) in approximately 50% of all LOS cases (see Table 3). The majority of other LOS isolates are S. aureus, E. coli, Enterococcus, and Enterobacteriaceae (Table 3).

Meningitis is more frequently a feature of late-onset than in early-onset sepsis.

Candida infections are relatively infrequent in the UK (as opposed to in the USA) even in extremely low birthweight (ELBW) babies.

Pathogen burden varies between countries, as well as within countries, and comparative rates of pathogen profiles causing EOS and late onset sepsis (LOS) in the UK and USA are summarized in Tables 1 and 3.

Risk factors
The risk of infection increases significantly the smaller and more immature the baby is. Risk factors for EOS, are essentially those for GBS and include intrapartum fever, prolonged rupture of membranes, (PROM) more than 18 hours, prematurity less than 37 weeks and having a previous infant with GBS. Infection is one of the commonest identifiable reasons for spontaneous preterm labour; thus spontaneous vaginal delivery of a baby at less than 37 weeks by definition is a risk factor for sepsis. Mothers with urinary tract infections are most commonly infected by E. coli, which in turn is the second most common cause of EOS.

Factors predisposing to nosocomial infection include being in intensive care, not receiving enteral feeds, not receiving maternal breast milk, having an indwelling catheter, or receiving parenteral nutrition (PN). Babies who have had gut surgery or gut-related problems have a significant risk of nosocomial sepsis, probably related to being unable to feed enteraly.

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Conflicts of interest: none declared.
Pathogens causing EOS: a comparison between NICHD data from the USA and NeonIN data from the UK

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>NICHD 2002–3 Incidence/1000 VLBW</th>
<th>NeonIN 2007–8 Incidence/1000 VLBW</th>
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<td>8</td>
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<td>Candida albicans</td>
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Table 1

Prolonged use of all antibiotics, but especially broad spectrum antibiotics, can result in an increase in antibiotic resistance among normal commensal organisms, or the emergence of other pathogens. Widespread use of broad spectrum antibiotics within maternity units has been shown to increase local persistence of resistant organisms, and favour opportunistic transmission within the unit. Antibiotic therapy therefore may simply replace one pathogen for another pathogen, which itself may be more hazardous. Moreover, prolonged duration of initial empirical antibiotic treatment (defined as more than 5 days), is also associated with increased rates of necrotising enterocolitis and death in extremely low birthweight infants, with each day of empirical treatment being associated with increased odds ratios for these adverse outcomes. Antibiotic use may also predispose a baby to fungal infection.

Risk factors for candida infection include birthweight less than 1500 g, PN, presence of indwelling catheters, not receiving enteral feeds, mechanical ventilation, H-2 Receptor antagonists,

Organisms causing LOS: comparison between USA NICHD and UK NeonIn surveillance data. (N = number of infection episodes for which data is available)

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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Pseudomonas</td>
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<tr>
<td>Candida spp</td>
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</table>

P values represent significant differences between NICHD and NeonIn data. Enterobacteriaceae include Klebsiella, Enterobacter, and Serratia.

Table 3

abdominal surgery, peritoneal dialysis, exposure to broad-spectrum antibiotics especially third generation cephalosporins, and exposure to antenatal antibiotics. If fungal infection is suspected or diagnosed, further evaluation of the extent of infection should include abdominal and renal USS, cerebral USS, fundoscopy and echocardiogram.

Presentation
Clinical signs in the early stages of any infection may be very subtle. Tachypnoea, apnoea or other respiratory distress are the most common presenting signs of infection. However, a baby may simply not be feeding well or possibly be excessively sleepy. A ventilated baby may manifest with increasing ventilatory requirements, having previously been stable or improving.

Although pneumonia is the most common cause of such respiratory distress, the differential diagnoses include generalized sepsis, meningitis, cardiac disease and metabolic conditions which give rise to acidosis. More fulminant infection may present with respiratory failure, cyanosis and shock.

Early onset infection may be clinically indistinguishable from hypoxic ischaemic encephalopathy at delivery, and infection is increasingly recognized as a risk factor for neonatal encephalopathy. Progression from mild symptoms to death can occur in less than 24 hours with bacteria such as GBS and E. coli which provoke brisk cytokine responses. GBS infection should always be suspected in a baby who has more severe respiratory distress syndrome (RDS) than would have been anticipated, as RDS and GBS pneumonia are radiologically indistinct. In severe cases, persistent pulmonary hypertension of the newborn (PPHN), hypotension, metabolic acidemia, tachycardia and poor peripheral perfusion may develop and are poor prognostic features.

While an abnormal environmental temperature may be responsible, temperatures below 36°C or above 37.8°C, sustained

NICE Red Flag risk factors and clinical indicators for EONS

Risk factor
Parenteral antibiotic treatment to woman for confirmed or suspected invasive bacterial infection at any time during labour or in the 24 hour periods before and after the birth
Suspected or confirmed infection in another baby in the case of a multiple pregnancy

Clinical indicators
Respiratory distress starting >4 hours after birth
Seizures
Need for mechanical ventilation in a term baby
Signs of shock

Table 2
for more than an hour, must be regarded as probably due to infection until proved otherwise. An unrelenting fever is likely to be viral in origin. Milk intolerance and abdominal distension are common features of generalized sepsis and are usually secondary to functional ileus, though must be distinguished from necrotising enterocolitis (NEC).

**Physical examination**

A baby should be undressed and examined in a warm environment, as subtle signs will otherwise be missed. An assessment should include evaluating the posture and tone, colour, level of activity, and capillary refill time as a marker of perfusion. There may be erythema, petechiae, or mottling. Signs of respiratory distress include tachypnoea (more than 60 breaths per minute), grunting, moaning, recession, and abnormal breath sounds. Tachypnoea is easily missed if the baby is not observed at rest for some minutes.

Tachycardia is a non-specific sign which frequently accompanies fever or poor perfusion. More recently Heart Rate observation (HeRo) monitoring has been introduced into units in the USA and Europe as a tool to aid in the earlier detection of sepsis. Bradycardia is a more ominous sign of advanced sepsis. Abdominal palpation may be uncomfortable for the baby, especially if the abdomen is tense. Bowel sounds may be relatively silent in both NEC and functional ileus. A high pitched cry, abnormal movements, back-arching, and tense fontanelle, are late features of neonatal meningitis. In evaluation for LOS, the limbs and joints should be examined for signs of osteomyelitis and septic arthritis.

**Investigations**

**Blood culture**

Blood for culture should be drawn from a freshly punctured blood vessel using strict aseptic technique and a closed system. The greater the volume of blood the higher the yield of organisms, but 0.5 ml of blood is usually sufficient for a successful culture. False-positive diagnoses of infection can be reduced by taking two cultures from separate sites. Cultures may be negative even in the face of symptoms and signs of infection. Most significant blood cultures are positive by 48 hours.

**Surface swabs, tracheal secretions, endotracheal tube-tip culture and gastric aspirates**

Routine swabbing of sites such as the umbilicus, groin, ear, nose, throat, pharynx and rectum are informative about colonization, but the results of surface cultures are of limited value as colonization of babies without clinical signs of infection does not warrant antibiotic treatment.

The same applies to gastric aspirates and maternal vaginal swabs which are indicative of colonization but not invasive infection.

**Urine**

Obtaining uncontaminated urine specimens in babies is difficult but important; a true positive result warrants further invasive investigation. It is ideal to collect a suprapubic aspiration of urine (SPA), fresh catheter specimen urine or a clean catch sample from a child following thorough skin cleansing.

**Lumbar puncture**

A lumbar puncture (LP) should be performed as part of the sepsis screen in LOS and considered in any other ill baby as part of sepsis screening. Some experts advocate that an asymptomatic term baby undergoing investigation for EOS may not require an LP as a routine, but will if CRP is raised or there are symptoms suggestive of meningitis. Some experts also exempt babies with overt localized infection, e.g. pneumonia complicating chronic lung disease, NEC, and babies who would not be able to tolerate the procedure. Thrombocytopenia is a relative contraindication to LP; if essential a platelet transfusion should be given to cover the procedure.

**Radiology**

Chest radiograph (CXR) should be considered in a baby undergoing EOS screening as pneumonia may be present with limited clinical signs. An abdominal radiograph (AXR) may be helpful in the differentiation between septic ileus and NEC.

**Haematological investigation**

**Neutrophil count**

Infection may result in neutropenia or neutrophilia (less than 5 × 10^9/litres or more than 20 × 10^9/litres respectively).

Mortality rates are high in neonates who fail to mount a neutrophil response to infection or whose neutrophil supply becomes exhausted by severe infection. Neutrophil counts in babies born small for gestational age, and those born to mothers with pregnancy-induced hypertension are frequently lower then those born at weights appropriate for gestational age.

Immature circulating neutrophils, known as band forms, appear in peripheral blood in response to infection. The ratio of immature to total neutrophils (I/T ratio), may be useful in diagnosing and monitoring infection. The maximum normal value is 0.16 during the first 24 hours, 0.14 by 48 hours, and 0.13 by 60 hours, where it remains until 5 days of age. Thereafter, the maximum normal I/T ratio is 0.12 until the end of the first month. Several studies have found that an I/T ratio of more than 0.2 is a useful marker of infection. Another feature suggesting infection is the presence of toxic granulation in the neutrophils.

**Platelet count**

Thrombocytopenia is a common feature of generalized infection and necrotising enterocolitis, but is also a feature of non-infective conditions such as hypoxic ischaemic encephalopathy. Viral infections, e.g. rubella, CMV and herpes, and enterovirus, may cause a profound thrombocytopenia. Conversely thrombocytosis is a manifestation of chronic inflammation, particularly within the gut.

**Acute phase reactants**

CRP is the most commonly available acute phase reactant and levels rise in response to IL-6. Babies with positive blood cultures may have negligible CRP results at birth, but the CRP may rise some 12–24 hours later. Whilst some babies do not mount a CRP response, serial measurements of CRP are recommended within the NICE guideline for early onset infection at the time of the infection screen and again at 18–24 hours in order to facilitate decisions regarding lumbar puncture (if initial [CRP] more than 10 mg/litres), and decision-making at 36 hours, regarding
duration of antibiotic therapy. Serial CRP measurements may be similarly useful in monitoring the progress of late onset infection, or other inflammatory conditions such as NEC. Persistently elevated CRP during antibiotic therapy for presumed bacterial infection suggests ongoing infection or inflammation.

Procalcitonin measurements appear to be more sensitive and specific in the differentiation between neonatal infection and inflammation than CRP, and may also differentiate between bacterial and viral infection, but there has been a high level of statistical heterogeneity among studies analysed and so has not been recommended by NICE.

**Polymerase chain reaction (PCR)**

PCR is used to measure highly conserved DNA sequences from a variety of Gram-positive and Gram-negative organisms, and many viruses. This method has the potential to provide more rapid diagnosis of bacteraemia and viraemia but while studies are demonstrating increasing benefit, such tools are not available in all microbiology departments.

**Treatment of neonatal sepsis**

There are no definitive randomized controlled trials to inform practitioners of the best antibiotic regimens for the newborn. Each antibiotic has benefits and side effects which must be evaluated every time antibiotics are prescribed. In general, narrow spectrum antibiotics should be used wherever possible, and only used when significant infection is likely.

**Antibiotic choices for early-onset infection**

Benzyl penicillin with an aminoglycoside such as gentamicin provides excellent coverage for UK EOS pathogens while maintaining a relatively narrow spectrum. Cephalosporin based combinations do not provide significantly better coverage of likely bacteria yet are associated with a broader spectrum of activity, and therefore are of greater potential harm. Flucloxacillin should be substituted for benzylpenicillin if *S. aureus* is suspected. The antibiotic regimen should be targeted appropriately once culture results are available. If *L. monocytogenes* is suspected for example, amoxicillin is usually given in place of benzyl penicillin.

**Antibiotic choices for late-onset infection**

The majority of the leading causes of LOS other then CoNS can be appropriately treated by a relatively narrow combination such as flucloxacillin and gentamicin. Vancomycin and teicoplanin are the antibiotics of choice for CoNS infections but their excessive use has been associated with the development of vancomycin-resistant enterococcal infections and resistant gram-negative infections. Empirc use of these agents should target only to those babies with the highest risk of complicated CoNS infections so as to minimize antibiotic exposure in the neonatal unit.

Flucloxacillin is the best antibiotic to treat Meticillin sensitive *S. aureus*, the second most common cause of LO bacteraemia and an organism capable of causing overwhelming infection if not treated early. Gentamicin will treat most Gram-negative bacteria, some of which e.g. *Pseudomonas* sp., give rise to significant mortality.

A cephalosporin given either alone or in combination with amoxicillin may not adequately cover a number of *Enterobacteriaceae*. If there is inadequate clinical improvement or deterioration, repeat cultures should be taken and antibiotic therapy changed. A change from flucloxacillin to vancomycin or teicoplanin should be considered, together with another antibiotic with broader activity against gram-negative bacteria e.g. piperacillin/tazobactam (Tazocin). Vancomycin in combination with gentamicin provides good gram-negative and gram-positive cover but potentially has additive toxicity, so should be used with caution.

Antibiotic therapy should be stopped after 36–48 hours if cultures are negative and the baby is asymptomatic. Conversely if a blood culture is positive, treatment should be adapted to ensure that an appropriate antibiotic with the narrowest spectrum possible is being used.

**Monitoring response to therapy**

If the baby remains unwell, or in the presence of other laboratory indicators including: persisting thrombocytopenia and/or neutropenia, raised C-reactive protein (CRP), procalcitonin, or plasma lactate; and always if there is persistence of positive blood cultures, further investigation should be undertaken.

Consideration should also be given to therapeutic options such as optimizing antibiotic doses, changing antibiotic regimens or removing indwelling catheters.

**Length of treatment**

While antibiotic therapy should be commenced promptly for suspected infection, they should be stopped as soon as sepsis has been excluded. Clinical response, type of organism if cultures are positive, antibiotic levels, and the presence of indwelling catheters should be used to determine length of treatment. There is little published evidence to inform of optimal length of course of antibiotics for culture-proven infection in neonates, and this remains a research area.

As a general rule, if antibiotics are started because of the possibility of infection, but the baby is asymptomatic for infection, and cultures are all negative at 36–48 hours, antibiotics should be stopped. If antibiotics are started on suspicion of infection, but cultures are negative, yet the clinical impression at the start of treatment was that sepsis was likely, then a longer course may be warranted — usually 5 days. If there is pneumonia on a chest radiograph (CXR), but blood cultures are negative, a 5 day course may be appropriate. If blood cultures are positive and cerebrospinal fluid (CSF) cultures are negative, treatment should be for a minimum of 10 days. Treatment should be for at least 14 days for *S. aureus*, because of its propensity to seed other tissues, but this decision should be taken in partnership with microbiology or infectious diseases colleagues, if possible. For a baby with positive CSF cultures, or a clinical diagnosis of meningitis, then treatment may be required for at least 21 days, depending on the organism. Osteomyelitis, endocarditis and deep abscesses which are not surgically drained, may require several weeks of antibiotic therapy. The length of treatment course may require extension in those with slow clinical and microbiological resolution, and requires specialist input.
Potential hazards of antibiotics

Gentamicin has a narrow therapeutic window and may result in ototoxicity and sensorineural hearing loss. There are two mechanisms for gentamicin-associated toxicity: the result of sustained high trough gentamicin concentrations; and genetically determined ototoxicity. Gentamicin also continues to be a significant source of medication errors (NPSA). Approximately 1:500 of the population carry the mitochondrial DNA mutation m.1555A → G associated and have permanent and profound hearing loss after receiving aminoglycosides even when drug levels are within the therapeutic range.

All antibiotics, particularly broad-spectrum antibiotics, alter the natural microflora of the patient, particularly in the gastrointestinal tract. This may result in an increase in antibiotic resistance among normal commensal organisms or the emergence of other pathogens. One pathogen may simply be replaced by another pathogen, which itself may be more hazardous, and the total burden of neonatal infection may be unchanged. Widespread use of broad spectrum antibiotics within a maternity unit will also increase local persistence of resistant organisms, and favour opportunistic transmission within the unit and even in the community.

The substantial increase in the incidence of allergic and autoimmune disease in young children of the developed world over the past three decades has been linked with peripartum antibiotic usage. The suggestion is that immune development becomes abnormal because the naive immune system is exposed to abnormal bacterial challenge, as a result of obstetric practices and inappropriate antibiotic use.

Feeding and infection prevention

The earlier enteral feeds are commenced, and the sooner a baby is receiving full enteral feeds, the less likely that baby is to develop nosocomial (late-onset) infection. The effect of early feeding is independent of the increased risk of infection with indwelling catheters (long lines, umbilical venous and arterial lines), and total parental nutrition (TPN). Breast milk has also been shown to protect babies from late onset infection Introducing even 0.5 ml/kg of “trophic” breast milk (and only breast milk) in the first hours of life, in very immature babies, will facilitate the naive gut becoming colonised with normal bacteria (lactobacilli and bifidobacteria). Such bacteria are critical for the development not only of the immune system, but also for bringing about the development of mucosal barrier function, gut motility and digestive functions.

Summary and practice points

Neonatal infection remains a significant cause of morbidity and mortality. The implementation of care bundles and an antibiotic stewardship program has been shown to reduce infection rates and inappropriate antibiotic use. The optimal program for neonatal units still need to be developed, however the following principles could be considered in order to limit the risk of infection and increase the judicious use of antibiotic therapy:

- Expose babies to at the very least trophic amounts of maternal breast milk as soon as it is available, regardless of weight, gestation and clinical condition.
- Develop a policy to use narrow spectrum empiric antibiotics and audit compliance.
- Stop empiric antibiotics in asymptomatic babies when blood cultures are negative, supported by microbiologists and pharmacists.
- Remove central catheters and stop parenteral nutrition (PN) as soon as full milk feeds have been achieved, and baby no longer requires PN to grow.
- Establish regular infection surveillance systems of bloodstream infections, e.g. through a network such as neonIN (neonin@sgul.ac.uk). In England all sepsis screens should be entered into the Badger neonatal electronic data collecting system).
- Review infection control strategies weekly and audit antibiotic use in partnership with microbiology, infection control and pharmacy teams.
- Identify a panel of consultant decision-only antibiotics, such as third generation cephalosporins, vancomycin and meropenem.

FURTHER READING

Bedford Russell AR, Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? BJOG 2006; 113: 758–65.

