Introduction

During the last two decades, dramatic improvement in survival of newborns, especially the extremely premature group, resulted from major advances such as antenatal steroids and surfactant, as well as from many other less dramatic improvements in care. As fewer babies died of respiratory failure and smaller babies survive, infection has become an increasingly important cause of mortality and morbidity.

Infection naturally falls into two main categories: early onset (generally acquired from the mother), and late onset (generally acquired from nursery environment). Congenital infection will be dealt with in a separate guideline. The line between Early and Late is usually taken as 48 hr. The frequency of infection, and the microorganisms causing these infections is shown for both early and late infection in the following figures. This data is for true positive blood cultures in John Spence Nursery from 1992-2000. During this period, when there were about 40,000 live births, a screening policy for Group B strep was in place.

Figure 1. Organisms causing early infection
Figure 2. Organisms causing late infection

Incidence

Isaacs et al.\(^1\)\(^2\) provide excellent reviews of neonatal infection. Additionally, annual reports from the Australian and New Zealand Neonatal Network (ANZNN)\(^3\) showed that for all network babies <32 weeks gestation at birth, the median incidence of definite septicaemia was 18, 20, and 20% for the years 1995, 1996 and 1997 respectively (Interquartile ranges: 15-22, 16-36, and 14-27 respectively). Results were also given for individual nurseries, and for this nursery they were 16, 18, and 14% respectively. The strong relationship between gestational age and susceptibility to infection is shown in Figure 3.

Figure 3. The percent of babies with true positive blood cultures prior to discharge or death, as a proportion of all babies born at Royal Prince Alfred Hospital from 1992 to 2000, by gestational age.
Babies born at less than 30 weeks, but particularly those born at 24-25 weeks, would have a higher percentage of infection if those dying in the first few days for non-infective causes such as IVH were excluded.

**Risk Factors**

1. **Any stage**
   - Prematurity - risk proportional to the degree
   - Neutropenia due to non-infective causes, eg pre-eclampsia

2. **Early**
   - maternal carrier Group B Strep (vaginal swab, msu, previous pregnancy)
   - unexplained preterm labour
   - preterm premature rupture of membranes
   - prolonged rupture of membranes
   - maternal fever
   - discoloured liquor
   - clinical chorioamnionitis

3. **Late**
   - Damaged skin, immature immune defences in ELBW infants
   - Central lines, esp UVC > 10 days
   - Overcrowded nursery (close physical proximity, high patient/staff ratio)
   - Colonisation of patients by certain microorganisms
   - Inadequate hand washing by staff and visitors

**Consequences**

The consequences of infection in the newborn vary according to the gestational age, site of the infection, and micro-organism(s) involved. In general, due to the immaturity of the immune system in extremely premature babies, they have the worst incidence of mortality and significant morbidity. The site of infection is an important consideration:

- **Blood**: Isolated septicaemia is the most common form of severe infection encountered in the NICU. The majority of late-onset isolates in this nursery (and others in Australia and New Zealand) are due to Staph epidermidis. Fortunately, this is generally a low-grade bacterium, and recovery without sequelae is usual outcome. This is in contrast to most gram-negative organisms, where septic shock and death are not uncommon.

- **CSF**: Meningitis in premature babies is a devastating occurrence. Death occurs in about 50% of
cases\(^2\), and survivors are at risk of significant brain injury, with deafness and/or mental retardation.

- **Pneumonia:** Newborns with congenital pneumonia have high mortality. Infections are most commonly due to GBS and E coli. They have high ventilator requirements, and the course is commonly complicated by persistent fetal circulation. Blood cultures are positive in about 50% of cases. The mother has often received intrapartum antibiotics because of chorioamnionitis and/or ruptured membranes. Acquired pneumonia may be bacterial, eg Pseudomonas, or viral, eg RSV.

- **Bone:** Osteomyelitis may have serious long-term sequelae, but fortunately it has become very rare since infection due to Staphylococcus aureus has become very uncommon in our nursery.

### Diagnosis

- **Clinical:** The response of premature infants to infection can be subtle or dramatic in onset. Subtle signs include worsening apnoea, worsening skin perfusion leading to a less pink colour, worsening tolerance of intragastric feeds, and increasing lethargy. This is commonly seen with low-grade infections such as Staph epidermidis. Term or near-term babies can respond with fever, while preterm infants tend more to have temperature instability. In contrast, the onset can be that of septic shock with associated cardiovascular collapse, as seen with gram-negative organisms such as Escherichia coli or Pseudomonas aeruginosa.

- **Laboratory:** The typical response of the preterm infant to infection is the consumption of white cells and platelets, leading to neutropenia and thrombocytopenia. Red cells also commonly fall in severe infection. As the neutrophils drop, the proportion which are immature (bands, myelocytes, promyelocytes, metamyelocytes) become higher. The ratio of the immature forms over the total of neutrophils + immature forms, the I/T ratio\(^5\), is an early predictor of infection during the first week or two of life. The C-Reactive Protein (CRP) is another marker of infection, but appears more useful in monitoring response to treatment of infection rather than in its diagnosis.

- **Specific tests**
  - **Early**
    - Ear swab
    - Blood cultures
    - Lumbar punctures (positive blood culture or clinically indicated)
    - Chest X-ray
  - **Late**
    - Blood cultures
    - Lumbar punctures (positive blood culture or clinically indicated)
    - Urine culture
    - Chest X-ray

### Interventions

1. **Prevention**
   - **Intrapartum Prophylaxis**

     - **Group B Streptococcus (GBS) carriers.**

     Mothers identified via the GBS universal screening programme, or those with a history of urine infection due to GBS, or those previously noted to be colonised with GBS, or those which a previous baby with early-onset GBS infection, are given ampicillin 1g IVI at the start of labour (or induction of anaesthetic for elective caesarean sections) and then every 6 hours while labour continues. Cefazolin is given if there is a history of
- **Mothers with rupture of membranes**

Vaginal pathogens should be determined by a vaginal swab taken on admission, and at about weekly intervals prior to onset of labour or decision to deliver. Signs of evolving chorioamnionitis should be carefully sought, eg fever, abdominal pain, change in colour of discharge, fetal tachycardia, or other signs of distress on cardiotocographs. Appropriate or best guess antibiotics should be given according to the obstetric department’s policy for rupture of membranes.

- **Mothers with other recognisable risk factors for infection.**

Other mothers with risk factors for infection following the onset of labour (eg fever, unexplained preterm labour, fetal tachycardia, purulent discharge) should be given intrapartum antibiotic prophylaxis.

**Handwashing and other general measures**

A considerable amount of observational data links the spread of pathogenic bacteria to inadequate handwashing, and outbreaks with multiresistant Staph and Klebsiella have been controlled following re-introduction of adequate handwashing practices. Nursery design is important, as strategic placement of sinks will facilitate handwashing. The wearing of protective gowns has not been shown to prevent infection. Overcrowding of infants and/or understaffing has been shown to exacerbate problems with cross-infection.

- **Breast milk**

Neonatal infection is significantly reduced in babies fed breast milk compared with formula-fed controls. The incidence of necrotising enterocolitis has also shown to be significantly reduced in breast milk fed infants. Caution needs to be exercised, as contaminated milk can cause infection when it has been collected or stored sub-optimally.

- **Prophylactic IVIG**

Prophylactic administration of intravenous immunoglobulin to prevent infection in preterm infants has been extensively studied, and a meta-analysis of randomised controlled trials has appeared. In summary, IVIG administration results in a statistically significant reduction (3-4%) in sepsis and/or any serious infection, but is not associated with reductions in other morbidities: NEC, IVH, length of hospital stay or mortality. Currently in Australia, the availability of IVIG is restricted, and is approved for treatment of severe infection but not for prophylaxis.

- **Prophylactic GM-CSF**

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), given prophylactically for 5 days to preterm infants (<32 weeks), completely abolished post-natal neutropenia and sepsis-induced neutropenia. However, this study did not have the power to demonstrate significant reductions in either proven infection or mortality, and the agent needs further evaluation.

- **Prophylactic antibiotics**

  - **Sepsis in general**
    
    A meta-analysis of RCTs of intravenous vancomycin prophylaxis against sepsis in preterm infants showed a statistically significant reduction in the number of nosocomial infections, but no significant difference in mortality or length of stay. Hearing, as
judged by brainstem auditory evoked responses, was not different. Given the unknown risk of encouraging the development of vancomycin resistance, the authors concluded that routine prophylaxis with vancomycin should not be undertaken at present.

- **NEC**
  
  The prevention of NEC with enteral antibiotics has also been the subject of a meta-analysis. Again, there was a statistically significant reduction in NEC and a borderline reduction in NEC-related deaths, but not in all deaths. However, there was a statistically significant increase in colonisation with resistant bacteria. In summary, the reviewers concluded that there is insufficient evidence to support the use of enteral antibiotics for NEC in routine clinical practice.

- **Neutropenic Babies:**
  
  Babies of mothers with hypertensive disease of pregnancy have a high incidence of neutropenia (<1.0 x 10^9/L), and this is proportional to the severity of the disease, as well as the degree of growth restriction. Such babies have been shown to have an increased incidence of nosocomial infection, justifying a policy of prophylactic vancomycin and gentamycin while they remain neutropenic.

**Postnatal prophylactic emollient ointment**

In two small randomised studies, prophylactic application of emollient ointment decreased the risk of suspected and proven sepsis. However, in a recent multicentre randomised controlled trial, the application of Aquaphor was associated with increased infection (mainly S. epidermidis) in babies from 501-750 grams. (RR 1.54, CI 1.04, 2.30). However, skin integrity was significantly better in treated babies. In our nursery, a study performed after the introduction of our "Small Baby Policy", had shown a lower rate of infection. Because of these conflicting results, our use of Eucerin emollient will be carefully monitored.

2. **Treatment**

- **Antibiotics - General considerations**
  
  While one would always endeavour to treat an infected infant with the most effective antibiotic available in accordance with our duty of care, on the other hand thought has to be given to discouraging the emergence of resistant organisms, since worse morbidity and mortality may result if the nursery is allowed to become colonised with multiply-resistant organisms. Broad-spectrum cephalosporin antibiotics are particularly prone to encourage the emergence of resistance if used indiscriminately. This was demonstrated by a cross-over study where two neonatal ICUs used in turn tobramycin/flucloxacillin or ampicillin/cefotaxime for treatment of suspected late sepsis. In both nurseries, the latter combination led to 18 times the incidence of resistant bacteria (mainly Klebsiella). For this reason, cephalosporin antibiotics and imipenem are reserved for cases of severe infection where evidence suggests their use is warranted.

- **Antibiotic treatment - Early-Onset**
  
  Babies considered at risk of infection should be commenced on penicillin and gentamicin as soon as can be arranged following admission to the nursery. If the mother's vaginal swab was positive for a gram negative organism such as E. coli, this could be revised to cefotaxime and gentamicin. Blood should be taken for blood culture and full blood count, and gastric aspirate and ear swab sent for culture prior to the first dose of antibiotics. If there is difficulty achieving a satisfactory blood culture for any reason, it is safer to commence antibiotics without the culture rather than delay treatment.

- **Antibiotic treatment - Late-Onset**
  
  The current choice of antibiotics for late infection is vancomycin and gentamicin, covering staph epidermidis (frequently resistant to flucloxacillin) and most coliforms. The main weakness
with this combination is that cover for gram-negative meningitis is poor, because gentamicin only penetrates inflamed meninges. As Pseudomonas aeruginosa is the most common cause of septic shock, or death due to infection, in this nursery, ceftazidime or imipenem should be urgently added if a baby with septic shock is not showing an early favourable response to the usual antibiotics.

- **Intravenous immunoglobulin**

  Two meta-analyses have appeared examining the role of IVIG in the treatment of sepsis.

  - In the first meta-analysis\(^\text{17}\) (n = 7 trials), there was a significant reduction in mortality in neonates with suspected or subsequently proven infection (RR 0.52; 0.28-0.98), but when a quasi-randomised trial was excluded, or only proven cases of sepsis were included, the odds ratio was similar but significance was lost. The authors felt the evidence was insufficient to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proven infection.

  - The second meta-analysis\(^\text{18}\) (n = 23 trials) examined treatment of severe sepsis or septic shock in patients of all ages. Overall mortality was significantly reduced (RR 0.60; 0.47-0.76), but in the subset analysis for neonates, significance was lost (RR 0.60; 0.31-1.14). The authors recommended that polyclonal IVIG be used as an adjuvant treatment for severe sepsis and septic shock.

  - A new international, multi-centre RCT (INIS Trial) has commenced, and hopefully will remove the existing uncertainty.

- **Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)**

  Two recent randomized trials have described the treatment of sepsis with GM-CSF. The first\(^\text{19}\) involved 30 patients (all gestations) in each group, and showed a trend to reduced mortality and shortened hospital stay. The second\(^\text{20}\) involved early-onset infection only, and had 22 patients (<2000 g) in each group. There was no difference in mortality, but fewer infections during the 2 weeks following treatment. Neither study had the power determine whether this new agent has a role in the treatment of sepsis in the newborn. The agent needs to be tested in a population of extremely premature infants with higher risk of infection, with sufficient power to give an answer.

### Key Points

| Intrapartum antibiotic prophylaxis reduces the risk of infection in at-risk newborns | 24 |
| Risk of infection is significantly reduced by exclusive feeding with expressed breast milk | 6, 9 |
| Risk of infection is significantly reduced by good handwashing practices, and the avoidance of overcrowding | 21 |
| Newborns at risk of early-onset infection are treated with penicillin and gentamicin | 1 |
| Infants with suspected late-onset infection are treated with vancomycin and gentamicin | 1 |
| Patients (all ages) with severe sepsis, especially septic shock, should be treated with IVIG. However, evidence lacking in neonates: effect | 18 |
References


11. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low birthweight infants. The Cochrane Library 2000; Issue 2


17. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. The Cochrane Library 2000; Issue 2


Last Revision: January 2002