EVIDENCE-BASED NEONATAL INFECTIONS

David Isaacs
Evidence-Based Neonatal Infections
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Evidence-Based Neonatal Infections

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David Isaacs was born in London and has an identical twin brother, Stephen, who is a child psychiatrist. They went to different schools and once swapped schools for a day. His mother was also a child psychiatrist and his father, Alick Isaacs, discovered interferon in 1957.

David trained as a general paediatrician in London and Sydney and in paediatric infectious diseases in Oxford. He moved to Sydney in 1989 to head the new Department of Immunology and Infectious Diseases at the Royal Alexandra Hospital for Children, but was the only member of the Department. He is a Clinical Professor in Paediatric Infectious Diseases at the Children’s Hospital at Westmead and at the University of Sydney. His research is mainly in neonatal infections, respiratory viral infections, immunization and bioethics. He loves writing and has published extensively, over 300 original peer-reviewed papers and 10 books on paediatric infectious diseases, neonatal infections, immunizations and ethics. This is the third book he has written on neonatal infections, but the first to use a systematic evidence-based approach.
Preface

This book is aimed primarily at clinicians working with neonates, although I hope policymakers will also be interested. It is based on evidence from the literature but also on over 30 years attending neonatal unit ward rounds to learn, advise and teach about neonatal infections.

My special thanks to Dr Phil Britton and Dr David Andresen of the Children’s Hospital at Westmead for their extraordinary but characteristic generosity in reading all the chapters and their invariably helpful and incisive advice. I would also like to thank Professor Craig Mellis of the University of Sydney and Professor Ruth Gilbert of the Institute of Child Health in London for help with the chapter on evidence and Associate Professor Ben Marais of the Children’s Hospital at Westmead for his help with the section on tuberculosis. I would also like to thank John Yeats and Paul de Sensi from the Children’s Hospital at Westmead for help with medical imaging.

I would like to thank my wife Carmel and my children for putting up with me spending long hours researching and writing this book.

Finally, I would like to acknowledge all my colleagues in neonatology who have shared their knowledge and discussed the management of neonatal infections. I dedicate this book to you, the neonatologists at the coal face making the difficult clinical decisions. I hope this book helps a bit.

David Isaacs
University of Sydney
CHAPTER 1
How to search for evidence

1.1 Obstacles to searching for evidence

Clinicians who do not search the literature for evidence quote lack of time\(^1-3\) and lack of knowledge as the main constraints.\(^6,7\)

In this brief chapter, we will suggest a rapid and easy approach to searching for evidence. For more detail, one journal publication\(^8\) and three books\(^9-11\) can be consulted.

1.2 Sources of evidence

1.2.1 The Cochrane library

The Cochrane Collaboration was established in 1993 and named for the British epidemiologist Archie Cochrane. It is an international non-profit making organization which publishes online evidence about health care in the Cochrane Library including almost 5000 systematic Cochrane Reviews. Cochrane Reviews of treatment interventions are usually restricted to randomized controlled trials (RCTs) because this is the best study design to avoid bias. The Cochrane Library is free in developing countries, in the United Kingdom (where the NHS pays for it) and in Australia (paid for by the Federal Government). In the United States, access requires a subscription, but many libraries and hospitals subscribe so that it is readily available to many clinicians. The Cochrane Library website is http://www.thecochranelibrary.com/.

For the evidence for an intervention, search the Cochrane Library (Figure 1.1) first by typing your topic into the box marked SEARCH THE COCHRANE LIBRARY and clicking on Go. Try different search terms because they will give different information.

1.2.2 Medline and PubMed

PubMed is provided free by the US National Library of Medicine and the National Institutes of Health and gives access to the comprehensive database Medline to anyone with internet access. The website is http://www.pubmed.gov/.

The best approach to find evidence is to use the Clinical Queries option in PubMed. Click on Clinical Queries, under PubMed Tools, currently in the centre of the PubMed home page (Figure 1.2), which brings up a new screen (Figure 1.3). Enter your search terms into the Search box and click on SEARCH. PubMed automatically finds RCTs in the first column (set the Category to “therapy” and Scope to “narrow” to find RCTs) and systematic reviews including Cochrane reviews in the middle column (Figure 1.3). Ignore the third column (only used by geneticists). Experiment with search terms until you find the best ways of expanding or narrowing the search to find what you want.

1.3 Statistical terms and explanations

Cluster randomized trial: a trial in which a group of individuals is randomized. For example, whole villages could be randomized to have a study intervention or no intervention, rather than individuals. The village becomes the unit of randomization. Outcomes are compared between those who do and do not receive the intervention.

Confidence Intervals (CI): a way of quantifying measurement uncertainty. This is usually expressed as the 95% CI, which means that the true value will be within the range 95% of the time. If the Relative Risk of dying with treatment compared with placebo is 0.50 (95%
CI 0.20–0.75), the treatment reduces the risk of dying by 50%, and 95% of the time it will reduce the risk by somewhere between 20% and 75%.

**Negative predictive value (NPV):** the proportion of subjects with a negative test result who are correctly diagnosed. The negative predictive value of a test for sepsis is a reflection of the test sensitivity and the incidence of sepsis in the population. The higher the negative predictive value of a test, the safer it is to use a negative test result as a basis to withhold treatment. If a test for sepsis has an NPV of 100%, then no child with sepsis will have a false negative result and all septic children will be identified by the test.

**Number Needed to Treat (NNT):** the number of patients you need to treat in order to achieve one extra favourable outcome. For example, if 19 of 20 patients treated with antibiotics for an infection get better compared with 14 of 20 treated with placebo, five extra patients get better for every 20 treated so the NNT is 20/5 or 4.

**Odds Ratio (OR):** the ratio of the odds of having the outcome in the treated group compared to the odds of having it in the control group. For example:
- If 100 of 1000 treated patients have persistent symptoms, the odds of persistent symptoms are 100/900 or 0.11 (11%).
- If 300 of 1000 untreated/placebo patients in the same study have persistent symptoms, the odds are 300/700 or 0.43 (43%).
- The odds ratio (OR) is 0.11/0.43 which is 0.26.

**Positive predictive value (PPV):** the proportion of subjects with a positive test result who are correctly
diagnosed. The positive predictive value of a test for sepsis is a reflection of the test specificity and the incidence of sepsis in the population. If all infants with a positive test result receive antibiotics, for example, the higher the positive predictive value of a test for sepsis, the fewer children without sepsis will receive antibiotics.

Relative Risk or Risk Ratio (RR): the ratio of the risk in the treated group to the risk in the control group. For example:
- If 100 of 1000 treated patients have persistent symptoms, the risk of persistent symptoms is 100/1000 or 0.1 (10%).
- If 300 of 1000 untreated/placebo patients in the same study have persistent symptoms, the risk is 300/1000 or 0.3 (30%).
- The Relative Risk or Risk Ratio is 0.1/0.3 which is 0.33.

When the event rate is 10% or lower, the OR and RR are similar. For more common events, the difference between OR and RR becomes wider, with the RR always closer to one. In general, it is preferable to use RR.11

Sensitivity: the sensitivity of a test is the proportion of true positives correctly identified by the test (e.g. the percentage of infected infants who are correctly identified as having infection).

Specificity: the specificity of a test is the proportion of negatives correctly identified by the test (e.g. the percentage of healthy infants who are correctly identified by a sepsis test as not having infection).

1.4 Useful websites

The Cochrane Library: www.thecochranelibrary.com
Clinical Evidence: www.clinicalevidence.com
MEDLINE via PubMed: www.pubmed.gov
GRADE working group:
www.gradeworkinggroup.org
[N.B. This chapter is adapted from Chapter 1 of reference 10 and we acknowledge some repetition.]

References
2. Riordan FAI, Boyle EM, Phillips B. Best paediatric evidence; is it accessible and used on-call?. Arch Dis Child 2004; 89:469–471.
CHAPTER 2

Epidemiology

2.1 Incidence and mortality

Neonatal infections are an important and sadly neglected cause of mortality and morbidity globally. In 2008, neonatal infections caused an estimated 29% of the 3.6 million neonatal deaths worldwide (see Figure 2.1 and Table 2.1) or about one million deaths, almost all in developing countries. Neonates comprised 41% of the estimated 8.8 million deaths in children under 5 years old worldwide in 2008. Community-based studies in developing countries attribute up to 42% of neonatal deaths in the community to infection.

The mortality from neonatal infections is considerably lower in resource-rich countries. Intrapartum antibiotic use to prevent group B streptococcus (GBS) infection has reduced mortality significantly in countries with a high incidence.

Newborn babies have rates of infection as high as children and adults whose immunity is compromised for almost any other reason, including most oncology patients and the elderly. Although newborn babies, and particularly pre-term newborns, are immunocompromised, additional factors contribute to the high rates of neonatal infection and will be considered in Section 2.2.

Knowledge of the incidence of neonatal infections is important for planning preventive and intervention strategies and for comparisons within and between countries, which can help inform clinical practice and help assess the quality of care. However, such comparisons are not necessarily straightforward.

In developing countries, most deliveries occur in the home, so hospital-based studies of incidence and aetiology may give misleading or inaccurate results. Infections are usually diagnosed clinically without cultures, and deaths from infection are frequently underreported. Community studies report rates of clinical neonatal sepsis ranging from 49 per 1000 live births in babies >24 hours old in Guatemala to 170 per 1000 live births in rural India. The reported rate of blood culture-confirmed cases is far lower: a minimum of 5.5 per 1000 live births in a rural hospital in Kenya, a highly uncertain figure because of incomplete sampling. Infection-specific mortality rates reported in 32 studies varied from 2.7 per 1000 live births in South Africa to 38.6 per 1000 in Somalia.

In industrialized Western countries where most deliveries occur in hospital, hospital-based studies of incidence are more representative.

The reported incidence of neonatal infection depends on how neonatal infection is defined and reported. Definitions may vary considerably. Examples include how contaminants in blood cultures and cerebrospinal fluid (CSF) are defined; whether or not contaminants are excluded; whether or not clinical sepsis with evidence of raised inflammatory markers is accepted as being infection; and whether infections are confined to positive cultures of blood and/or CSF or also include positive cultures from normally sterile sites, such as urine, bone, joint fluid or pulmonary fluid.

2.1.1 Early-onset infection

It is conventional to divide the reporting of neonatal infections into early- and late-onset infections. Early infections are presumed to be due to organisms acquired from the mother shortly before (e.g. Listeria) or at the time of birth (e.g. GBS) whereas...
late infections are primarily caused by environmental organisms, acquired nosocomially (i.e. in hospital) or in the community. However, ‘early onset’ has been defined as anything from the first 2 days to the first 7 days after birth. Furthermore, environmental organisms may grow from blood cultures in the first 48 hours after birth, while the classic early-onset organisms like GBS and Listeria can cause late- as well as early-onset sepsis. Methicillin-resistant *Staphylococcus aureus* (MRSA), originally confined to hospitals or patients associated with hospitals, is a common community-acquired pathogen in many countries and can colonize pregnant women and cause both early- and late-onset neonatal infections.

There are two major considerations in defining early-onset infection, clinical and epidemiologic.

### Table 2.1 Causes of death in neonates globally.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of deaths in millions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term birth complications</td>
<td>1.033 (29%)</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>0.814 (22%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.521 (15%)</td>
</tr>
<tr>
<td>Other</td>
<td>0.409 (11%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.386 (11%)</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>0.272 (8%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.079 (2%)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>0.059 (2%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3.575</td>
</tr>
</tbody>
</table>

*Source: Adapted from Reference 1 with permission from Elsevier. Copyright © 2010 Elsevier.*

**Question: Does it matter how we define early-onset infection clinically?**

The clinical problem with defining early-onset infection as infections in the first 7 days after birth, as opposed to those in the first 48 hours say, comes if the empiric antibiotic regimen for early-onset sepsis does not cover organisms that may be acquired from 3 to 7 days. For example, say penicillin and gentamicin are recommended for early-onset sepsis, gentamicin has only modest anti-staphylococcal activity so this regimen provides little cover against *S. aureus* infections. Yet data from Western countries\(^6\),\(^7\) show that *S. aureus* bloodstream infections are not uncommon between days 3 and 7 (Figures 2.2 and 2.3).

**Recommendation:** It is critical for the clinician that empiric antibiotic regimens reflect the local epidemiology and cover the organisms likely to cause sepsis.

**Question: Is there a correct way of reporting early-onset infection?**

The incidence of early-onset infections is conventionally reported as the number of infections per 1000 live births in a defined period, for example, the number of infections in babies born in a maternity hospital (excluding babies transferred from other hospitals or home) divided by the number of live births over a...
defined time period. Various countries have established neonatal infection surveillance networks, including Australia, the United Kingdom, Canada (http://www.canadianneonatalnetwork.org/portal/), the US National Institute of Child Health and Human Development (http://www.nichd.nih.gov), Germany (http://www.nrz-hygiene.de/surveillance/kiss/neon-kiss/) and the Vermont Oxford Network (http://www.vtoxford.org/) has established a global network. The Australian, Canadian and US NICHD report all neonatal infections, whereas the other networks focus on low birth-weight babies in tertiary centres. Comparisons depend on definitions and completeness of reporting.

Data on early infections inform public health interventions. For example, the rate of early-onset GBS infection determines whether or not prevention strategies are cost-effective. Epidemiology should be a critical driver of public health.

The clinician wants data to inform empiric choice of antibiotics. Whether organisms are reported separately (Figure 2.2) or all organisms combined on a single day (Figure 2.3), clearly there is some overlap between organisms likely to have been maternally and those probably nosocomially acquired. An alternative approach is to separate infections into those in babies <48 hours old (early onset), in babies aged 3–7 days (intermediate sepsis) and in babies >7 days (late sepsis).

Failure to exclude contaminants can give misleading results. For example, one single-centre study reported coagulase-negative staphylococci (CoNS) as their commonest cause of early-onset neonatal infection. Excluding all likely contaminants (e.g. CoNS, diphtheroids, micrococci, α-haemolytic streptococci and anaerobes) is probably not valid, because these organisms occasionally cause serious infection, even

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**Figure 2.2** Timing of neonatal infection by organism. Adapted from Reference 6. CoNS, Coagulase-negative staphylococci; Other GNB, Other Gram-negative bacilli; Gp B Strep, Group B streptococci.
Figure 2.3 Pathogens according to the day of onset of infection, UK 2006–2008. Reprinted from Reference 7 with permission. CoNS, Coagulase-negative staphylococci; GBS, Group B streptococci.
Epidemiology

meningitis. One option is to include all organisms cultured while acknowledging most are probably contaminants.7 Another possibility is to use a combined clinical and laboratory definition of infection, and only report likely contaminants if the baby also has abnormal laboratory parameters, for example, elevated C-reactive protein (CRP), abnormal white cell or platelet count.6

In Western countries, early-onset infection is mainly due to GBS, although less frequently in countries using intrapartum antibiotic chemoprophylaxis, Gram-negative enteric bacilli (Enterobacteriaceae), notably *Escherichia coli*, and miscellaneous other organisms, including streptococci, which are mostly sensitive to penicillin or gentamicin.4, 6, 7

In stark contrast, most early-onset infections in developing countries are due to Klebsiella species, *E. coli*, other Gram-negative enteric bacilli and *S. aureus*.13 Intriguingly, and for unknown reasons, this pattern of organisms, with little variation, is reported commonly from Africa, Asia, Latin America and the Middle East.13 GBS is rare in resource-poor countries,13 although an important cause of early-onset sepsis in some Asian countries.9

Self-evidently, it is vital to know the local organisms and their resistance patterns to develop rational empiric antibiotic policies for babies with suspected sepsis.

**Recommendation: There is no single correct epidemiologic way of reporting early-onset infection, but reporting the date of onset would improve comparison of rates.**

### 2.1.2 Late-onset infection

Late-onset neonatal infection can be caused by organisms associated with neonatal intensive care and acquired nosocomially (*nosocomos* means hospital in Greek), for example, CoNS and water-loving Gram-negative bacilli; by maternally acquired organisms that colonize the baby at birth and invade later, for example, GBS and Listeria; or by community organisms, including respiratory, gastrointestinal and Salmonella and skin organisms.13

In industrialized Western countries, the major burden of late-onset neonatal sepsis is in babies in neonatal intensive care units (NICU). The incidence of late sepsis is inversely related to gestational age and birth weight14 (see Figure 2.4). Incidence can also be reported in terms of the proportion of babies admitted to NICU who develop sepsis, usually around 2–5%, depending on the NICU population.7–14 In one study, annual rates of late sepsis ranged from 2.4% to 4.5% of NICU admissions in different NICUs, a difference which was statistically significant, but no longer significant after stratifying for birth weight.14

Rates of late-onset neonatal sepsis in industrialized countries may be reported as the proportion of babies admitted to neonatal units who develop sepsis or the proportion of all live born babies who develop sepsis, if these data are known. However, even after allowing for birth weight, the comparisons may be confounded by population variation. The risk of infection increases with the duration of neonatal unit stay, particularly if intensive care is needed. Stratification by birth weight allows for this, because low birth-weight infants stay longer. However, other more mature infants may require intensive care, for example, those needing gastrointestinal surgery.

In industrialized countries, the reported rate of late-onset neonatal infection in neonatal units is most useful when definitions of sepsis are standardized. Even then, comparisons between hospitals are only truly valid when variations in patient populations have been taken into account.15, 16

A refinement of crude comparisons of overall rates of late sepsis is to compare specific infections that are felt to reflect good hygiene in intensive care. An example is the use of rates of *central line-associated bacteraemia* (CLAB), also called *central line-associated bloodstream infections* (CLABSI).15 A CLAB is defined as a bacteraemic infection caused by an organism like CoNS in a baby with a central line *in situ* and no other explanation for the infection. The rate can be reported as the number of CLAB’s per 1000 line days, which

![Figure 2.4 Incidence of late-onset neonatal infection by birth weight. Data from Reference 14.](image)
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makes allowance for varying duration of exposure (see Section 20.2.1).

Widespread use of artificial surfactant in resource-rich countries has permitted early extubation of almost all pre-term infants, who are then managed with nasal continuous positive airways pressure (CPAP). Infants on CPAP are at low risk of ventilator-associated pneumonia (VAP), so VAP is no longer a useful measure of nosocomial infection in newborns (see Chapter 8).

In developing countries, the reliability of reported infection rates depends on factors such as definitions, case ascertainment, population selection, whether or not babies are cultured and the reliability of the microbiology laboratory. A review of 32 studies from developing countries found considerable study heterogeneity, making comparisons difficult. Many studies did not distinguish early from late sepsis. Clearly, more accurate data based on standardized methods are needed.

2.1.2.1 Organisms causing late sepsis
In most Western countries, CoNS now cause just over 50% of all late-onset neonatal infections, even when likely contaminants are excluded. Most CoNS infections occur in low birth-weight infants and are central line-associated. The major pathogens causing the remainder of late-onset infections are Gram-negative enteric bacilli (Enterobacteriaceae) and S. aureus (methicillin-sensitive or MRSA). Other important but rarer causes of late-onset sepsis include enterococci (faecal streptococci), Listeria, Candida and miscellaneous rarer organisms.

In developing countries, there are limited data on home deliveries, but in a non-Cochrane review the four most common pathogens reported with almost equal frequency after 7 days of age were S. aureus, GBS, Streptococcus pneumoniae and non-typhoidal Salmonella species.

2.2 Pathogenesis

2.2.1 Pregnancy
Pregnancy is an immunosuppressed state. The pregnant woman does not want to mount an immune response that would harm the foetus, so her cell-mediated immunity is reduced. Evidence of this impairment is the pregnant woman’s increased susceptibility to infections which require cellular immunity for optimal recovery, such as viral infections (e.g. chickenpox, influenza, HIV) and intracellular bacterial infections (Listeria, tuberculosis). If the pregnant woman is infected with an intracellular pathogen during pregnancy, the baby may be infected transplacentally (e.g. Listeria monocytogenes, Mycobacterium tuberculosis; congenital infections caused by CMV, rubella, Toxoplasma gondii, Treponema pallidum, VZV) or perinatally (e.g. HIV, HSV, VZV, M. tuberculosis).

2.2.2 Chorioamnionitis
Chorioamnionitis is one of several terms used for intrauterine infection in the second half of pregnancy, others being intra-amniotic infection, amniotic fluid infection, placental infection and intrapartum infection. Clinical chorioamnionitis, with signs such as fever, tachycardia, uterine tenderness and foul-smelling amniotic fluid, occurs in anything from 1% to 10% or more of pregnancies, depending on the population studied. Membrane rupture and/or labour frequently ensue.

Romero described four stages of ascending intrauterine infection, (a) cervical colonization/infection with pathologic bacteria, including bacterial vaginosis; (b), ascending infection from the cervix or vagina to the decidua (endometrium), (c) bacterial invasion of chorionic blood vessels and amniotic fluid and (d) foetal infection to cause pneumonia and often bacteraemia. Histopathologic chorioamnionitis can be diagnosed by histologic examination of the placenta and precedes defined clinical chorioamnionitis.

Only a relatively small proportion of babies born to mothers diagnosed with chorioamnionitis have proven early-onset bacteraemia. Nevertheless, chorioamnionitis has a profound effect on neonatal outcome because it can induce pre-term labour, probably because the causative microorganisms produce prostaglandins and related substances. Pre-term birth predisposes the baby to early- and late-onset infections, and is associated with an increased risk of cerebral palsy and bronchopulmonary dysplasia.

A Cochrane systematic review provides strong evidence that giving maternal antibiotics for pre-term rupture of membranes significantly reduces chorioamnionitis (by 34%) and reduces the numbers of babies born within 2 days (29% reduction) and 7 days (21% reduction). Neonatal infection is also reduced...
by a third (Relative Risk, RR = 0.67, 95% CI 0.52–0.85). Interestingly, β-lactam antibiotics, particularly amoxicillin–clavulanic acid, were associated with a more than fourfold increased risk of neonatal necrotizing enterocolitis (RR 4.72, 95% CI 1.57–14.23), whereas erythromycin was not, an observation driven by the findings of the large ORACLE study.21

2.2.3 Early-onset sepsis

The intrauterine environment is usually sterile. However, if chorioamnionitis leads to ascending infection, although the foetus does not breathe in utero, the foetal lungs are fluid-filled and thus exposed to infected amniotic fluid. Early-onset sepsis caused by GBS, one of the major causes of early sepsis, almost always presents with early-onset pneumonia, even if the baby may sometimes also be bacteraemic and may even develop meningitis. This implies that the commonest route of infection in early-onset GBS infection is via the lung, either antenatally or by aspiration of maternal secretions during the birth process.

Other organisms associated with chorioamnionitis, such as *E. coli*, other Gram-negative bacilli, enterococci and anaerobes, generally cause early-onset sepsis without pneumonia. Indeed, apart from GBS pneumonia, most early-onset bacterial infections are non-focal. This implies that the intra-amniotic organism is able to invade the baby’s bloodstream. A baby with early-onset septicaemia is almost without exception colonized with the same organism, implying that colonization of the foetus’ mucosal surfaces commonly precedes bacteraemia.

Transplacental infection is also possible. Babies born with *L. monocytogenes* infection are often bacteraemic and may present with rash and hepatosplenomegaly, suggesting transplacental infection. Their mothers are often febrile and sometimes shown to be bacteraemic, reinforcing the importance of transplacental *Listeria* infection. However, babies born with *Listeria* infection do sometimes have a significant respiratory illness with radiologic changes, suggesting that pulmonary aspiration may sometimes play a role in the pathogenesis of early-onset neonatal *Listeria* infection.

The maternal birth canal is colonized with a great variety of organisms that usually do not infect the mother but can potentially infect the baby. Babies not already exposed to intrauterine infection become colonized perinatally with bacteria and other organisms. While these usually remain commensals, they may occasionally cause late infection. If the mother’s birth canal or perineum is colonized with potentially virulent organisms (e.g. MRSA, Salmonella, *Pseudomonas*) a baby colonized perinatally may develop sepsis rapidly.

Whenever considering why one person and not another develops an infection, it is necessary to consider three main factors: the host, the environment and the organism. The risk factors for early-onset sepsis reflect a combination of host factors (the more pre-term the baby, the higher the risk of sepsis), environmental risk factors (maternal risk factors) and virulence of the organism (maternal colonization with potent neonatal pathogens such as GBS, group A streptococci, HSV, etc.).

### Risk factors for developing early-onset neonatal infection

A literature search of Medline via PubMed and Clinical Queries for systematic reviews and observational studies using the search term ‘early-onset neonatal infections’, category ‘prognosis’, scope ‘broad’ found 23 systematic reviews and 320 studies. Most of the studies were not relevant, but it was possible to identify risk factors from selected papers (Table 2.2). Although cohort studies are generally more valid for ascertaining risk factors, a case-control study is a more practical study design because early-onset sepsis is relatively uncommon.

Prior to intrapartum antibiotic prophylaxis, a systematic review of a number of studies of risk factors for early-onset neonatal GBS infection identified maternal colonization with GBS and prematurity as the major risk factors.22 The risk increased with decreasing gestational age; the OR for infection was 4.8 for any baby <37 weeks of gestation and 21.7 for babies <28 weeks of gestation.22 Other risk factors were prolonged rupture of membranes (PROM) >18 hours (OR 7.3), and intrapartum maternal fever >37.5°C (OR 4.0).22

A subsequent large nested case-control study of babies of 34 weeks of gestation or more concentrated on maternal risk factors.23 There was no increased risk of early-onset neonatal infection when the highest maternal temperature was <38°C, but the risk increased rapidly above 38°C and was highest >39°C, although such fever was rare. The risk of sepsis
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Table 2.2 Risk factors for early-onset neonatal infection.

<table>
<thead>
<tr>
<th>Risk factors for early-onset neonatal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity: risk increases with decreasing gestation and birth weight</td>
</tr>
<tr>
<td>Spontaneous pre-term onset of labour</td>
</tr>
<tr>
<td>Spontaneous pre-term rupture of membranes</td>
</tr>
<tr>
<td>Prolonged rupture of membranes (increases with increasing duration &gt; 12 hours)</td>
</tr>
<tr>
<td>Maternal intrapartum fever &gt; 38°C</td>
</tr>
<tr>
<td>Maternal clinical chorioamnionitis</td>
</tr>
<tr>
<td>Vaginal examinations during labour</td>
</tr>
<tr>
<td>Maternal urinary tract infection</td>
</tr>
<tr>
<td>Maternal vaginal discharge</td>
</tr>
<tr>
<td>Maternal colonization with group B streptococcus (GBS)</td>
</tr>
<tr>
<td>Previous baby with early-onset GBS infection</td>
</tr>
</tbody>
</table>

Source: From References 22–25.

increased steadily with increasing duration of rupture of membranes greater than 12 hours. The relationship between gestational age and sepsis showed a U-shaped curve, with the risk increasing with decreasing gestational age and increasing when gestation exceeded 42 weeks. Any intrapartum antibiotic given > 4 hours before delivery decreased the risk of early-onset neonatal infection compared with no antibiotic or antibiotic < 4 hours before delivery.

A case-control study from Pakistan found that maternal fever and vaginal examinations during labour were risk factors for early-onset sepsis, as in Western countries, but also found maternal urinary tract infection and vaginal discharge were risk factors in the developing country setting studied.

2.2.4 Late-onset sepsis

The risk factors for late-onset sepsis reflect a combination of host factors (the more pre-term the baby, the higher the risk of sepsis), environmental risk factors (exposure to organisms and to factors like indoor pollution) and virulence of the organism (e.g. Pseudomonas in neonatal units, GBS acquired at birth or post-natally and causing invasive disease later in the first month, and M. tuberculosis in developing countries).

The major risk factors for late-onset sepsis in industrialized countries relate to neonatal intensive care, because although only about 5–9% of babies in Europe and 12–13% of babies in the United States are born pre-term, they are by far the most numerous babies to develop late-onset neonatal infection.

In resource-poor countries, most babies are born at home, and very different risk factors apply. However, although hospital-acquired neonatal infections in developing countries have the same risk factors as in Western countries, reported rates are 3–20 times higher than in Western countries.

Host risk factors common to neonates in resource-poor and resource-rich countries are prematurity and anatomic abnormalities. Babies born with abnormal urinary tracts are at increased risk of urinary tract infection, babies with abnormal gastrointestinal tracts are at increased risk of obstruction and of ischemic damage leading to infection and babies with obstructive pulmonary abnormalities such as sequestration are at increased risk of pneumonia (Table 2.3).

Risk factors for developing late-onset neonatal infection

A search of Medline via PubMed and Clinical Queries (see Chapter 1) for systematic reviews and case-control studies using the search term ‘late-onset neonatal infections’, category ‘prognosis’, scope ‘broad’ found 12 systematic reviews and 180 studies.

A non-Cochrane review article on risk factors for late-onset sepsis in premature infants identified factors related to the causative organism, intensive care and preventative factors.

Late-onset bloodstream infections with Gram-negative bacilli and fungi are associated with increased mortality compared with matched, uninfected babies, whereas those with Gram-positive organisms, particularly CoNS, are not. Pseudomonas is more virulent than other Gram-negative bacilli, with a mortality of 52–74% compared with 10–25% for other Gram-negative bacilli.

The use and duration of central venous catheters is a clear risk factor for bloodstream infections with bacteria, notably CoNS, S. aureus and Gram-negative bacilli and with Candida. The review article noted that in a study of nosocomial infections in infants <1500 g,
Epidemiology

Table 2.3 Risk factors for late-onset neonatal infection.

<table>
<thead>
<tr>
<th>Risk factors for late-onset neonatal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All babies:</strong></td>
</tr>
<tr>
<td>Prematurity: risk increases with decreasing gestation and birth weight</td>
</tr>
<tr>
<td>Anatomical, for example, urinary tract or gastrointestinal abnormalities</td>
</tr>
<tr>
<td>Exposure to organisms of high pathogenicity</td>
</tr>
<tr>
<td><strong>Hospital-based:</strong></td>
</tr>
<tr>
<td>Use and duration of parenteral nutrition</td>
</tr>
<tr>
<td>Use and duration of invasive mechanical ventilation</td>
</tr>
<tr>
<td>Use and duration of central venous catheters</td>
</tr>
<tr>
<td>Use of H2 blocker/proton pump inhibitors</td>
</tr>
<tr>
<td>Poor infection control</td>
</tr>
<tr>
<td>Colonization with virulent organisms, for example, Pseudomonas</td>
</tr>
<tr>
<td><strong>Community-based:</strong></td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Exposure to indoor air pollution (tobacco, chimney stoves)</td>
</tr>
</tbody>
</table>

*Source: From References 28–31.*

infection was significantly associated with lower birth weight, respiratory distress syndrome and duration of parenteral nutrition and was significantly lower if enteral feeds were started earlier.33

Risk factors for late-onset Gram-negative sepsis were considered in two case-control studies. A US study of low birth-weight infants (<1500 g) reported significant associations with the duration of central venous catheter >10 days, nasal CPAP, use of H2 blocker/proton pump inhibitors and gastrointestinal tract pathology.34 A UK study found that mechanical ventilation, the use and duration of total parenteral nutrition, and the use and duration of a central venous catheter were significantly associated with Gram-negative infection by univariate analysis, but only the duration of total parenteral nutrition before infection remained significant by multivariate logistic regression analysis.35

An intriguing retrospective cohort analysis of twins born from 1994 to 2009 examined concordance rates for late-onset neonatal sepsis in monozygotic and dizygotic twins, and used logistic regression to look at genetic and non-genetic factors. They found that decreasing birth weight, occurrence of respiratory distress syndrome and the duration of total parenteral nutrition were significant non-genetic risk factors for infection.36 Further analysis suggested that 49% of the variance in risk of sepsis was due to genetic factors and 51% due to environmental factors.37

There is intense research interest in how genetic factors influence the risk of neonatal sepsis. A study of T-cell cytokine production from 1 to 21 days of age in 996 extremely low birth-weight babies <1000 g found babies with bloodstream infection had significantly lower levels of the inflammatory cytokine IL-17 and higher levels of the regulatory cytokines IL-6 and IL-10. After adjusting for confounding variables, the ratio of regulatory to inflammatory cytokines was a significant risk factor for developing late-onset sepsis.36 The genetic basis for the differing cytokine patterns awaits elucidation.

Some of the above-mentioned risk factors are effectively unavoidable once the baby is born: small, sick pre-term babies are at increased risk of infection. However, it may be possible to initiate early enteral feeds and thereby shorten the duration of parenteral nutrition and central venous catheters and it is also possible to avoid using H2 blocker/proton pump inhibitors.

In developing countries, the bulk of late-onset neonatal infections occur at home and are caused by bacterial infection, pneumonia, diarrheal illness and tetanus1 (Figure 2.1). Factors that predispose to infection should be considered in terms of the host, the organism and the environment. Host factors include babies born prematurely and babies with underlying problems with immunity, particularly HIV infection. Exposure to organisms of high pathogenicity is an important issue which depends both on virulence of the organisms and environmental exposure. Newborns exposed to *M. tuberculosis* at or soon after birth are at high risk of developing tuberculosis. Other pathogenic organisms, including pyogenic organisms like *S. aureus* and group A streptococcus, intracellular bacteria like Salmonella, viruses and protozoa can cause late-onset neonatal infections. Environmental factors that increase the risk of the baby developing symptomatic infection include indoor air pollution from tobacco smoke and from open wood cooking fires.38
2.3 Outcome of neonatal infection

The long-term outcome of neonatal infections depends on many factors, of which the most important are the gestational age of the infant; early- versus late-onset infection; resource-rich versus resource-poor setting; presence of meningitis; and the timing and appropriateness of antibiotic therapy. Mortality was considered in Section 2.1 and many aspects of outcome will be considered under the relevant chapters regarding specific organs infected and specific organisms.

A large US multi-centre study conducted by the National Institute of Child Health Development Neonatal Research Network followed up 6093 infants born weighing 401–1000 g at 18–22 months of age. Infants were classified as uninfected (n = 2161), clinical infection alone (n = 1538), sepsis (n = 1922), sepsis and necrotizing enterocolitis (n = 279) or meningitis (n = 193). Compared with uninfected infants, all four infection groups were significantly more likely to have adverse neurodevelopmental outcomes, including cerebral palsy and visual impairment. Neo-

Natal infection was also associated with impaired head growth. The data were analysed by infecting organism group: CoNS, other Gram positive organisms, Gram negative bacilli and fungi. All adverse neurodevelopmental outcomes except hearing impairment but including microcephaly were higher among infected children in all pathogen groups. Hearing impairment was significantly higher in infants with Gram-negative and fungal infections.

2.4 Prevention of neonatal infections

Prevention of neonatal infections will be considered in detail in Chapters 22 and 23.

References

CHAPTER 3
Clinical manifestations

The clinical features of early-onset and late-onset neonatal septicaemia are generally non-specific and rarely indicate a specific bacteriologic or indeed microbiologic diagnosis.\textsuperscript{1–9} A list derived from published studies of the clinical features, which differ little between early- and late-onset sepsis, is given in Table 3.1. The frequency of signs and symptoms varies somewhat with gestational age and between developing\textsuperscript{1–4} and Western countries.\textsuperscript{5–9}

In developing countries, two systematic reviews concluded that in young infants under 60 days old brought to a health-care facility, the most valuable signs and symptoms of sepsis were feeding difficulty, convulsions, fever or hypothermia, change in level of activity, tachypnoea, severe chest in-drawing, grunting and cyanosis.\textsuperscript{8, 9} Pallor and poor capillary return were also positively associated with sepsis. These data help community health-care workers decide about hospital referral of sick infants.

In Western countries, septic infants usually present earlier with less florid signs. In a large US study of very low birth-weight infants the positive predictive value for most clinical signs varied from 14% to 20%, while hypotension had a positive predictive value of 31% but only occurred in 5% of babies.\textsuperscript{1}

A minority of septicaemic babies has a focal infection, for example, skin abscess or swollen joint, which will not only provide a strong diagnostic indicator but also a likely focus for biopsy and hence a microbiologic diagnosis.

Simple laboratory tests may yield clues to sepsis: 10% of very low birth-weight infants with sepsis had hypoglycaemia and 11% had metabolic acidosis (see Chapter 4).\textsuperscript{1}

3.1 Fever or hypothermia

Rectal temperatures measured with a mercury thermometer are the traditional ‘gold standard’ for temperature measurement in newborns. In one study, axillary temperatures were consistently about 0.27°C (SD 0.20°C) lower than rectal temperatures,\textsuperscript{10} but another study using the same electronic device found significant differences between axillary and rectal temperatures.\textsuperscript{11} An infrared skin thermometer gave similar readings to a rectal mercury thermometer below 37°C, but concordance was only 74% for readings ≥37°C.\textsuperscript{12} Most of these studies study mainly afebrile infants, yet febrile infants are the major clinical concern.

The incidence of fever and hypothermia is gestation-dependent and also differs somewhat between early- and late-onset sepsis. Full-term infants are far more likely to respond to infection with fever than pre-term infants while pre-term infants are more likely to develop hypothermia. In a study of infants with early-onset GBS bacteraemia, 12% of full-term infants had fever at the time of admission compared with only 1% of pre-term infants, whereas the figures for hypothermia were 3% and 13%, respectively.\textsuperscript{3} Significantly, about 85% of both full-term and pre-term infants with GBS sepsis had normothermia on admission.\textsuperscript{3}

In late-onset sepsis, the reported onset of fever is nearer 50%, while 10–15% of septic infants have hypothermia.\textsuperscript{1}
Clinical manifestations

Table 3.1  Clinical manifestations of neonatal septicemia and approximate frequency.

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Early-onset sepsis</th>
<th>Late-onset sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnoea</td>
<td>+++ +</td>
<td>+++ +</td>
</tr>
<tr>
<td>Fever</td>
<td>++ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>+ + +</td>
<td>+++ +</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Lethargy</td>
<td>+ + +</td>
<td>+ +</td>
</tr>
<tr>
<td>Irritability</td>
<td>+ + +</td>
<td>+ +</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Change in level of activity</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Hypotension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vomiting</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Meconium-stained liquor</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Convulsions</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Source: Data from References 1–9.

Key:
- 0 < 1%
- + 5–10%
- ++ 10–25%
- +++ 25–55%

Note: The frequency of signs varies with disease severity and between Western and developing countries (see text) but these are the approximate frequencies derived from a literature search.

Question: How significant is fever?

Clearly, the presence of fever or hypothermia may indicate infection, but it may also be due to poor temperature regulation in pre-term infants, or in infants with cerebral insults and possibly in dehydration.

Of 100 US infants who developed fever in the first 4 days, 10 had proven bacterial infection, 8 had other signs of infection. Infants were only investigated if fever recurred; the 35 with a single episode of fever remained well. Newborns with temperature ≥39°C had a significantly higher incidence of bacterial infection than newborns with temperature <39°C, but low-grade fever did not exclude infection. Appleton and Foo described a febrile, full-term, breastfed infant aged 3 days with tachycardia and irritability who had hypernatraemia. The baby fed ravenously from a bottle and the fever resolved. They called this ‘dehydration fever’. A retrospective case-control study of 122 Israeli infants aged 1–4 days with fever but no other signs or symptoms of infection found only one infant had infection (GBS in urine culture) and the study reported an association between fever and weight loss, breastfeeding, caesarean section and high birth weight.

Recommendations

- Full-term infants aged 0–4 days with fever <39°C and no other symptoms can be monitored closely without commencing antibiotics.
- If fever resolves and does not recur, the infant should be observed but the risk is low.
- Fever ≥39°C is more likely to indicate serious bacterial infection.
- Any infant with fever plus one or more other clinical signs of infection should be cultured and treated with empiric antibiotics.

3.2 Meconium

Meconium is usually sterile. There are two potential links between meconium and infection. Firstly, aspiration of thick meconium may cause airways obstruction and lung collapse, potentially complicated by bacterial pneumonia. There are no RCTs of antibiotics in meconium aspiration syndrome. Secondly, meconium-stained liquor, uncommon in pre-term labour, was described in early-onset Listeria monocytogenes neonatal infection and postulated as being specific to listeriosis. Subsequent studies show that meconium-stained liquor can occur with infection due to other organisms and is not common in Listeria infection. Obstetric studies have reported culturing Ureaplasma urealyticum, streptococci, Escherichia coli, Candida albicans and L. monocytogenes from amniotic fluid in association with meconium-stained liquor in pre-term labour. In a UK case-control study, early-onset infection was no more common in pre-term babies born after meconium-stained liquor than in controls. In Tanzania in contrast, meconium-stained liquor was an independent predictor of both early- and late-onset infection with Staphylococcus aureus and Gram-negative bacilli. It seems reasonable to conclude that meconium staining of the liquor in pre-term labour should alert the clinician to the possibility of infection with Listeria or other organisms and that empiric therapy if started should include ampicillin or penicillin to cover Listeria.
3.3 Jaundice

Jaundice is common in the first few days of life and likely to be physiologic or due to haemolysis. While it has been described in association with urinary tract infections it is debatable whether jaundice is a useful clinical sign in sepsis.

The two most pertinent clinical questions are:

**Question 1:** Is jaundice without other clinical features likely to be due to infection?

A highly selective case series from a tertiary Australian children’s hospital found 9 of 22 babies (41%) referred with late jaundice had UTI. In subsequent case series of babies with non-haemolytic jaundice, the incidence of UTI was 0 of 306 US babies <3 weeks, 12 of 217 (5.5%) Taiwanese infants <8 weeks and 12 of 160 (7.5%) afebrile jaundiced US infants <8 weeks, including 6 of 12 infants with onset of jaundice >8 days.

A prospective Israeli cohort study found 3 of 93 full-term infants with unexplained jaundice <7 days without other features suggestive of sepsis had bacteraemia.

In a Taiwanese cohort study 50 (2.3%) of 2128 infants with UTI had prolonged jaundice (28 unconjugated, 22 conjugated). All infants >6 weeks had conjugated hyperbilirubinemia.

**Recommendation:** It is reasonable to perform blood cultures on infants with unexplained early jaundice and urine cultures on infants with late jaundice, but the risk of UTI is low.

**Question 2:** How likely is it that a septicaemic baby will be jaundiced?

The incidence of jaundice in babies with proven septicaemia was ≤30% in early studies, but this has not proved a consistent or useful clinical feature. In developing countries, jaundice is not common in neonatal sepsis, nor predictive of severe infection. Jaundice was only present in 3–6% of septicaemic US babies and the sole sign of infection in fewer than half.

**Comment:** Jaundice is rare in septicaemic infants.

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3.4 Rash

If a baby is born with a petechial rash, congenital infections with cytomegalovirus (CMV), rubella and toxoplasmosis should be considered, as well as non-infectious causes. However, babies born infected with Listeria can present with a clinically similar rash, which is actually an embolic, granulomatous rash (Figure 3.1). Other clinical features such as maternal fever, meconium staining of the liquor, hepatosplenomegaly and respiratory distress may help suggest the diagnosis of Listeria infection. Later development of a petechial rash may be due to septicaemia, endocarditis or rarely meningococcal infection (see Section 14.4.1).

Pyogenic and septicaemia-associated skin lesions are considered in Chapter 13.

3.5 Respiratory signs or symptoms

3.5.1 Apnoea

Apnoea of prematurity occurs in most infants <30 weeks of gestation, in about 50% of babies 30–32 weeks
and 10% of infants at 34 weeks.\textsuperscript{29} The onset peaks between 5 and 7 days. Apnoea in a pre-term infant on the first day or after 2 weeks is unlikely to be physiologic and should trigger investigation and empiric treatment for sepsis.\textsuperscript{32}

In full-term infants, apnoea is a more sinister sign of respiratory or central nervous system pathology or sepsis.\textsuperscript{8, 9}

### 3.5.2 Respiratory distress

Symptoms and signs of respiratory distress include tachypnoea, grunting, chest wall or intercostal recession and cyanosis. Respiratory symptoms from birth in a pre-term baby may be due to hyaline membrane disease (surfactant deficiency), retained lung fluid (transient tachypnoea of the newborn) or sepsis. The radiographic appearance of pneumonia due to GBS or other bacterial pathogens can mimic hyaline membrane disease (see Chapter 8).

Later onset of respiratory distress may be due to bacterial pneumonia or viral or Chlamydial pneumonitis, but is also described in septic infants with normal chest radiographs.\textsuperscript{8, 9} Tachypnoea can be due to acidosis or central stimulation in meningitis. The need for empiric treatment will depend on circumstances, but the usual low threshold applies.

### References