# Changing patterns of neonatal sepsis

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Despite major advances in neonatology during the past few decades, many infants still develop life-threatening infections during the first month of life. The increasing population of very low birth weight (VLBW) premature infants, who now survive due to improved neonatal care, represent the group at highest risk for neonatal infection.

Infection, either as a primary pathology or a complication of other illness, is a major cause of neonatal mortality and morbidity throughout the world. Neonatal bacteraemia is estimated to occur in 1-8 infants per 1000 live births and the incidence of neonatal bacterial meningitis is in the order of four infants per 10,000 live births[1]. A comprehensive study of systemic bacterial and fungal infections in neonatal units in Australia show incidence figures of 2.2 per 1000 live births for early-onset (<48 hours of birth) sepsis and 4.4 per 1000 live births for late-onset (>48 hours of birth) sepsis[2]. The mortality rate for early-onset sepsis was 15% and for late-onset sepsis 9%[2]. Among VLBW babies undergoing prolonged intensive care, the rate of culture-proven sepsis may be as high as 30% with a mortality rate of 30%[3]. Additionally, 20-30% of the survivors of neonatal bacteraemia and 40% or more of those with meningitis exhibit neurological sequelae[1].

In the developing world neonatal sepsis is a greater problem. A recent study from Malaysia reported rates of neonatal sepsis of 5-10% with case fatality rates of 23-52%. Septicaemia accounted for 11-30% of all neonatal deaths[4].

**Classification**

Classification of neonatal sepsis is useful as it facilitates consideration of common principles of causation, presentation and treatment. The most helpful classification is given below.

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**1. Early-onset sepsis (EOS)**

Infections presenting within the first 48 hours of life are generally classified as early-onset infections although definitions range from 24 hours to 7 days. This category of infections is commonly caused by microorganisms acquired from the mother before or during birth (vertically transmitted and perinatally acquired).

**2. Late-onset sepsis (LOS)**

Infections presenting after 48 hours of age are considered late-onset infections and are generally caused by microorganisms acquired from the environment rather than from the mother (nosocomial and horizontally transmitted).

**Common organisms causing neonatal septicaemia**

The microorganisms responsible for EOS differ from those responsible for LOS although some pathogens including group B streptococcus (GBS) and Escherichia coli (E.coli) are known to cause both severe EOS and LOS[1]. During the past few decades there have been changes in the predominant bacteria that cause EOS and LOS[5]. The main contributory factors for these changes are the development and usage of new antibiotics, the clustering of sick neonates within relatively small areas, and the prolonged survival of VLBW pre-term babies who previously would have died.

In the pre-antibiotic era, two gram-positive organisms, group A betahaemolytic streptococcus and staphylococcus aureus predominated[5]. However, in the 1940s and 1950s, gram-negative organisms, particularly E.coli, became the most common cause of neonatal sepsis[5]. Over the past 3 decades, the most prominent organism responsible for neonatal bacteraemia and meningitis has been GBS[6]. However, the incidence of EOS appears to be falling in the developed world possibly due to intrapartum antibiotic prophylaxis for GBS infection[3]. *E.coli, Listeria monocytogenes, Haemophilus influenzae,*

*Enterobacter spp., Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus* are the other microorganisms commonly isolated from infants with EOS.

In general, the organisms responsible for LOS are those nosocomially acquired from the environment. In the developed world Coagulase-negative staphylococci (CoNS) and Candida albicans are the leading causes of LOS[2,7]. Both are normally benign, skin-colonizing organisms. The recent transition of these organisms from commensals to true pathogens is associated with the creation of a highly susceptible population of VLBW premature infants who now survive due to neonatal intensive care. The risk of infection is inversely related to gestational age and birth weight[8]. The presence of centrally placed vascular lines, use of intravenous lipid emulsions and ventilation which are integral parts of modern neonatal intensive care have been identified as major risk factors for the development of infection with these opportunistic pathogens[9,10].

The picture as regards LOS in the developing world is quite different. Gram-negative organisms (E. coli, Klebsiella and Pseudomonas aeruginosa) still predominate[11]. A study carried out in the University Neonatal Unit, De Soysa Hospital for Women, Colombo, over a period of 24 months (1995-1997) identified E. coli (52%) and Klebsiella (22%) as responsible for over 70% of LOS[12]. However, as countries implement modern neonatal medical practices, CoNS seem to emerge as the most important pathogens[13].

**Risk factors for infection**

Maternal risk factors for neonatal septicaemia include spontaneous premature rupture of membranes, prolonged rupture of membranes (12-18 hours or more), maternal fever, maternal urinary tract infection, vaginal colonization with GBS, low levels of maternal antibody to GBS, and the presence of chorioamnionitis[14,15,16,17]. In an otherwise healthy term baby, none of these factors individually should warrant a complete septic workup. However, the combination of these risk factors greatly increases the probability of infection and should heighten the clinical suspicion of sepsis. Furthermore, the presence of any single risk factor in a sick newborn should prompt an evaluation for sepsis.

Prematurity is the most important infant risk factor for infection[17]. There is a direct correlation between the degree of prematurity and the risk of infection. Infants born at less than 32 weeks gestation are 4 to 25 times more likely to develop EOS than their more mature counterparts[18]. Other risk factors for sepsis include resuscitation at birth, ventilation, parenteral nutrition, prolonged courses of broad-spectrum antibiotics and surgical procedures[17].

**Clinical manifestations of infection**

The signs and symptoms of systemic infection are usually subtle and non-specific. Infected foetuses may demonstrate pronounced tachycardia or decreased beat-to-beat variability on fetal heart monitoring, be depressed at birth, require resuscitation and have low Apgar scores. Lethargy, decreased alertness and responsiveness and decreased activity are common early features of neonatal sepsis. Both hypothermia and hyperthermia are recognised manifestations of infection. Hypoglycaemia or more commonly hyperglycaemia is frequently noted. Systemic hypotension is often associated with severe infection. Respiratory symptoms ranging from apnoea, respiratory distress and need for assisted ventilation, occur in more than half of infants with culture proven sepsis. Other features include abdominal distension, feed intolerance, increasing gastric aspirate, vomiting and hepatosplenomegaly[1]. Seizures should prompt investigation for neonatal meningitis. Virtually all signs and symptoms attributable to neonatal infection could be indicative of conditions other than systemic infection.

**Diagnosis of septicaemia**

The diagnosis of systemic infection in a neonate is difficult to make solely on historical or clinical grounds. Laboratory evaluation assists in the diagnosis and confirmation of infection. Positive cultures of blood, CSF or urine are the gold standards for confirming sepsis. However, in a considerable proportion of neonates at risk of infection, culture results may be influenced by previous antibiotic exposure.

Blood is the most often examined body fluid for suspected sepsis. With current blood culture systems, at least 95% of positive cultures will be positive within 48 hours of inoculation into media[19]. One notable exception is Candida albicans, which may take as long as 3 to 5 days to grow in blood culture media. Culture specimens should be obtained from peripheral veins and not from indwelling catheters. Although it is optimal to obtain at least 2 blood samples for cultures from different peripheral sites, inordinate delays in instituting antibiotic therapy should not occur because the clinician is trying to

obtain blood from more than one site in a sick neonate.

What is the volume of blood needed to detect bacteraemia in neonates? Most common pathogens can be detected when volumes of 0.5-1ml are inoculated into culture media[20]. However it is worth sending even smaller volumes for culture in a sick neonate.

A positive blood culture may not always indicate true bacteraemia. Distinguishing true bacteraemia from contamination is an increasingly common problem encountered in VLBW preterm infants with suspected LOS. When an unusual organism or one with low virulence is isolated from blood, the clinician is in a dilemma as to the significance of the culture result. The presence of the same pathogen in both bottles of a blood culture set and multiple positive blood cultures with the same organism, increase the likelihood of true bacteraemia.

Urinary tract infections (UTI) are relatively uncommon among infants with EOS but common among those with LOS. Urine should be cultured whenever there is suspicion of LOS. The best method of obtaining urine for culture is via suprapubic aspiration of the bladder. A bag specimen, if negative, is adequate to exclude UTI, but positive results should be confirmed by culture of a suprapubic sample.

The neonatal period carries the highest risk of meningitis of all age groups. Although meningitis represents a rare infection (4-10 per 10,000 live births), the high mortality rate and the substantial risk of adverse neurological sequelae warrant an aggressive approach to exclude this possibility. Some neonatologists limit lumbar puncture (LP) to infants who have a positive blood culture or who demonstrate symptoms specific to the central nervous system. However, up to 61% of infants with meningitis do not have concomitant bacteraemia[21]. Lumbar puncture is a low-risk procedure and the consequences of missed or delayed diagnosis of meningitis are considerable. Thus, it is prudent that a LP be performed as part of the septic screen. If the infant is considered too unstable to tolerate an LP, it could be performed once the infant is more stable.

The value of surface swabs in the evaluation of neonatal sepsis is questionable. Cultures from diverse sites such as skin surface, gastric fluid, ear canal, umbilical cord and tracheal aspirates have been included in the septic screen. Surface swabs are informative about colonization, but not necessarily of infection. Several studies have shown that the results of surface cultures are limited in the diagnosis of neonatal sepsis[22,23]. Occasional studies have concluded differently[24]. The value of routine surveillance cultures in early detection of hospital-acquired infection, too, is questionable. There is little correlation between organisms colonizing the skin and devices such as endotracheal tubes and organisms grown from the blood of septic neonates[25]. Surveillance cultures do not decrease morbidity or mortality from neonatal sepsis, nor are they cost-effective. On the balance, it seems reasonable to limit routine surface cultures to a throat and ear swab in the evaluation of EOS.

**Early diagnosis of sepsis - use of adjunctive tests**

A number of studies have been advocated as providing useful information in the early diagnosis of sepsis. Multiple parameters are combined and performed together as a septic screen to improve the predictive accuracy of diagnosing neonatal sepsis before culture results are obtained. Unfortunately the positive predictive value of most septic screens is less than 30%[26]. The main value of septic screens is in the identification of infants at low risk who may not require antibiotics or in whom antibiotics can be discontinued.

Urine latex particle agglutination (LPA) tests for GBS were popular during the 1980s and early 1990s. However these tests have unacceptable high rates of both false-negative and false-positive results[27]. The Food and Drug Administration of USA published a safety alert in 1997 recommending that urine LPA tests not be performed in infants.

A chest x-ray should be an essential component of the neonatal septic screen. Pneumonia is found in the majority of infants who die from culture-proven EOS[18].

White cell count, total neutrophil count, band count, immature to total granulocyte ratio (I:T ratio) and platelet count are some of the haematological parameters used in assessing neonatal sepsis. Findings that have been associated with culture proven bacteraemia include an increased I:T ratio (>0.2), a high band count (>2 x $10^9$/l), neutropenia (total neutrophil count <1.75 x $10^9$/l), exceptionally high (>25 x $10^9$/l) or low (<5 x $10^9$/l) total white cell count, and thrombocytopenia (platelet count <100 x $10^9$/l)28. Newborns with CoNS sepsis often have blood counts that are unremarkable. Buffy coat smears may reveal bacteria several hours before the culture results are positive. However, although the

sensitivity of these indices is reasonably good (e.g., I:T >90%), their specificity is not consistently high enough to be the sole basis for diagnosing neonatal sepsis[29].

A wide range of parameters including blood levels of various acute phase reactants (CRP, haptoglobin, fibronectin), cytokines and cytokine receptors (IL-6 is the most widely used) and procalcitonin have been used as supporting the diagnosis of neonatal septicaemia. Of these CRP is a more accurate predictor of infection than WBC indices[30]. Culture proven sepsis is most unlikely if the CRP does not rise within 24-48 hours of the onset of sepsis. Serial CRP measurements are useful in assessing the effectiveness of therapy[31]. Although the sensitivity of IL-6 is greater than 90% when early measurements are made, normal values need to be determined and the methodology standardized before this test can be incorporated into routine practice. At present, none of the others (procalcitonin, intercellular adhesion molecule 1, soluble IL receptors) have been evaluated sufficiently in infected babies to make them clinically useful. The measurement of granulocyte colony-stimulating factor (G-CSF)[32] and polymerase chain reaction to detect bacterial DNA[33] are the recent additions to the long list of adjunctive tests to assist early diagnosis of neonatal sepsis

**Treatment**

Urgent therapy is indicated due to the rapid progression of infection, associated high morbidity and mortality, and the difficulties in differentiating infection from other disorders. Treatment should begin immediately after the cultures are obtained, even with relatively minimal indications of sepsis. Estimates are that only 1 in 6 to 1 in 20 infants who are treated for suspected sepsis end up having positive cultures[28]. Nonetheless, this apparent over treatment is permissible in view of the adverse consequences of missed or delayed diagnosis of neonatal sepsis. Although antibiotics are potentially lifesaving, they have inherent risks when used in neonates, including drug toxicity, emergence of resistant organisms and super-infection. The critical task is to reduce overuse of antibiotics by cutting down on the duration of therapy whenever possible.

The initial choice of antibiotics depends on the knowledge of prevalent organisms responsible for infection within a geographical area, as well as the pattern of specific antimicrobial susceptibility. Typically the initial therapy for suspected EOS should include coverage of GBS and gram-negative enteric bacilli. The combination of C. Penicillin and an aminoglycoside (usually gentamicin) is usually adequate. When meningitis is suspected initially, the combination of cefotaxime with penicillin is an acceptable alternative.

The choice of antibiotics for use in LOS would depend on the organisms generally responsible for such infections in individual units. The combination of an aminoglycoside with flucloxacillin/cloxacillin has been the standard therapy for suspected LOS. However, in most of the developed world CoNS are the main organisms responsible for LOS, and are often resistant to multiple antibiotics including methicillin. Therefore, an increasing tendency is seen to use vancomycin in combination with the aminoglycoside or cephalosporin as initial blind therapy. In addition, removal of indwelling intravenous catheters and other devices may be necessary to eradicate the infection if antibiotics alone are not successful. Several newer antibiotics are finding a place in difficult cases. Aztreonam[34] and imipenem[35] are valuable in the treatment of gram-negative sepsis. When necrotising enterocolitis is suspected, it is usual to add metronidazole to cover anaerobes. When budding yeasts are seen in urine, systemic candidiasis should be suspected and anti-fungal therapy with amphotericin B initiated pending culture results. When cultures are positive and sensitivities available, treatment should be modified to reflect the susceptibility of the isolated organism.

The duration of therapy depends on the culture results as well as the initial response to therapy. In the majority of infants evaluated for sepsis, culture results will be negative after 48 hours. At that time, if the child appears well and infection was an unlikely cause of original symptoms, antibiotics may be discontinued. However, if the clinical condition of the infant remains unstable and a strong suspicion of sepsis still remains despite negative cultures, a longer course of antibiotics is appropriate. If cultures are initially positive, repeat cultures should be sent after 48 hours of starting appropriate therapy to assess the response to therapy. Monitoring of drug levels and appropriate adjustments to dosage is accepted practice in view of the toxicity of the antibiotics used. For bacteraemia, the duration of therapy is usually 7-10 days or 7 days after the initial negative results are obtained. For meningitis, the duration of therapy is 14 to 21 days. For Candida sepsis unaccompanied by meningitis, 2-4 week or longer courses have been used. In the presence of candidal meningitis addition of 5-flucytosine is recommended because of its excellent penetration into CSF. In the presence of endocarditis and osteomyelitis longer courses of antibiotics are needed.

Much of the treatment of neonatal sepsis is supportive. Maintaining good oxygenation and ventilation, providing metabolic and blood pressure support and optimising nutrition are all important in achieving a successful outcome.

Various adjunctive therapies have been used in the treatment of neonatal sepsis. These include granulocyte transfusion, exchange transfusion, intravenous immunoglobulin[36] and administration of haemopoietic growth factors (G-CSF and GM-CSF)[37]. There is no conclusive evidence for the effectiveness of these substances in neonatal sepsis. In addition, these substances carry a potential for substantial adverse effects. Therefore, at present, these should be used only under an investigational protocol or in a desperate situation following informed consent and counselling of the parents.

### Prevention of infection

Selective intrapartum administration of antibio-tics to women in labour has been shown to be effective in preventing early-onset GBS disease[38]. Intrapartum antibiotics are most effective when administered at least 4 hours before delivery and when at least 2 doses have been given. Currently, two equally acceptable strategies (screening based and risk based) have been recommended by the Centres for Disease Control and Prevention[39]. If the mother has been given intrapartum antibiotic chemoprophylaxis for GBS, the neonates should be observed for a minimum of 48 hours after delivery. If signs of sepsis appear, a full diagnostic evaluation and empirical therapy should be initiated[40].

Nosocomial infections account for an increasingly large proportion of neonatal infections. Meticulous attention to hand washing is the most effective measure in reducing hospital infection[41]. Jewellery, wristwatches and all other ornaments should be removed and hands scrubbed from elbow downwards with an iodine containing solution before entering the neonatal unit. Hand washing should not only be done before and between handling infants, but also after handling potentially contaminated sites including one's face or hair, pens, bed head tickets, telephones etc. A written hand washing policy sited above the wash area may help the staff to adhere to correct technique. Proper staffing, adequate space in neonatal units, controlling admissions, aseptic care of catheters and appropriate limitation of antibiotic usage, are some of the other measures helpful in reducing hospital acquired infections. Wearing of protective clothing by parents and staff is not an effective method of infection reduction.

Communal equipment such as thermometers, stethoscopes and suckers are a major source of cross-infection. Ideally individual pieces of equipment should be provided. If equipment has to be shared it should be wiped clean between patients.

### Key Points

- Neonatal sepsis is an emergency - empirical treatment should be started on clinical suspicion.

- In the VLBW baby it is unwise to ignore a positive blood culture with an unusual organism.

- Antibiotics may be discontinued after 48 hours if the cultures are negative and the infant clinically stable.
- Meticulous attention to hand washing is the most effective method of reducing hospital-acquired infections.

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