

# Review Articles

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## Neonatal Sepsis – A Review

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### Introduction

Neonatal infection is an important cause of morbidity, prolonged hospital stay and mortality among infants, particularly those born preterm and of very low birth weight (VLBW).<sup>1, 2</sup>

Neonatal infections are unique in several ways. Infectious agents can be transmitted from the mother to the fetus or newborn infant by diverse modes. Newborn infants are less capable of responding to infection because of one or more immunologic deficiencies. Coexisting conditions often complicate the diagnosis and management of neonatal infections. The clinical manifestations of newborn infections vary and include sub-clinical infection, mild to severe manifestations of focal or systemic infection, and, rarely, congenital syndromes resulting from in utero infection. The timing of exposure, inoculum size, immune status, and virulence of the etiologic agent influence the expression of disease. Maternal infection which is the source of transplacental fetal infection often remain undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection. A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas. Immature, very low birthweight (VLBW) newborns have improved survival but remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections<sup>3</sup>.

As mentioned above, causative organisms of neonatal infections are diverse in their epidemiology, clinical presentation, diagnosis and management. However, in this updated review we will principally emphasize and focus on bacterial sepsis in the newborn.

### Epidemiology and Public Health Issues

Neonatal mortality is increasingly recognized as an important global public health challenge that must be addressed if we wish to reduce child death disparities between rich and poor countries. Most of the estimated 4 million neonatal deaths per year occur in low and middle income countries. More than one-third of neonatal deaths are estimated to be due to severe infections, and a quarter is due to the clinical syndrome of neonatal sepsis/pneumonia<sup>4</sup>.

The reported incidence of neonatal sepsis varies from 7.1 to 38 per 1000 live births in Asia, from 6.5 to 23 per 1000 live births in Africa, and from 3.5 to 8.9 per 1000 live births in South America and the Caribbean. By comparison, rates reported in the United States and Australia range from 1.5 to 3.5 per 1000 for early-onset sepsis and up to 6 per 1000 live births for late-onset sepsis, a total of 6 – 9 per 1000 for neonatal sepsis<sup>5</sup>.

Currently, neonatal mortality rate in Bangladesh is 32 per 1000 live births which accounts for 60% of all under-five deaths<sup>6</sup>. In a study assessing causes of neonatal deaths in rural Bangladesh it is shown that sepsis/meningitis constituted 12% of direct causes of neonatal deaths<sup>7</sup>. In another study conducted in Dhaka slums showed sepsis as a direct cause of neonatal deaths in 20% cases<sup>8</sup>. In another study in Bangladesh, estimated causes of mortality around the year 2010 for 102,000 neonatal deaths showed that severe infections (sepsis, meningitis, pneumonia and tetanus) contributed 20% of neonatal deaths<sup>9,10</sup>.

### Definition

Systemic illness caused by microbial invasion of normally sterile parts of the body is referred to as 'sepsis'<sup>11</sup>. This is a term that specifically serves to

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differentiate an illness of microbial origin from an identical clinical syndrome that can arise in several non-microbial conditions<sup>11</sup>. When accompanied by evidence of hypoperfusion or dysfunction of at least one organ system, this becomes 'severe sepsis'. Finally, where severe sepsis is accompanied by hypotension or need for vasopressors, despite adequate fluid resuscitation, the term 'septic shock' applies<sup>11</sup>. Within this terminology, the archaic term 'septicemia', which persists in the language of the non-specialist and layman, straddles the definitions of sepsis, severe sepsis, and septic shock<sup>11</sup>.

Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life<sup>12</sup>. The condition may be defined both clinically and/or microbiologically, by positive blood and/or cerebrospinal fluid cultures<sup>5</sup>.

**Classification**

Neonatal sepsis may be classified according to the time of onset of the disease: early onset (EOS) and late onset (LOS). The distinction has clinical relevance, as EOS disease is mainly due to bacteria acquired before and during delivery, and LOS disease to bacteria acquired after delivery (nosocomial or community sources). In the literature, however, there is little consensus as to what age limits apply. A few papers distinguish between very early onset (within 24 hours), EOS (24 hours to six days), and LOS (more than six days) sepsis<sup>5</sup>. Very late onset sepsis is demarcated by onset at >30 days of age.

**Risk factors**

Several obstetric and neonatal factors have been identified that may be associated with an increased risk of neonatal infection. The presence of any of these factors alone is not an indication for a complete sepsis

work-up and antibiotic therapy; however, combinations of risk factors are clearly additive and should greatly enhance the suspicion of sepsis.<sup>13</sup>

- Prematurity and low birthweight
- Premature or prolonged rupture of membranes (>18 h)
- Maternal peripartum fever (>100.4<sup>0</sup>F) or infection
- Resuscitation at birth
- Multiple gestation
- Invasive procedures
- Infants with galactosemia (predisposition to *E. coli* sepsis), immune defects, or asplenia.
- Other factors: Male sex (four times more affected than females), bottle-feeding (as opposed to breast-feeding), low socio-economic status, improper handwashing practice of NICU staff and family members etc.

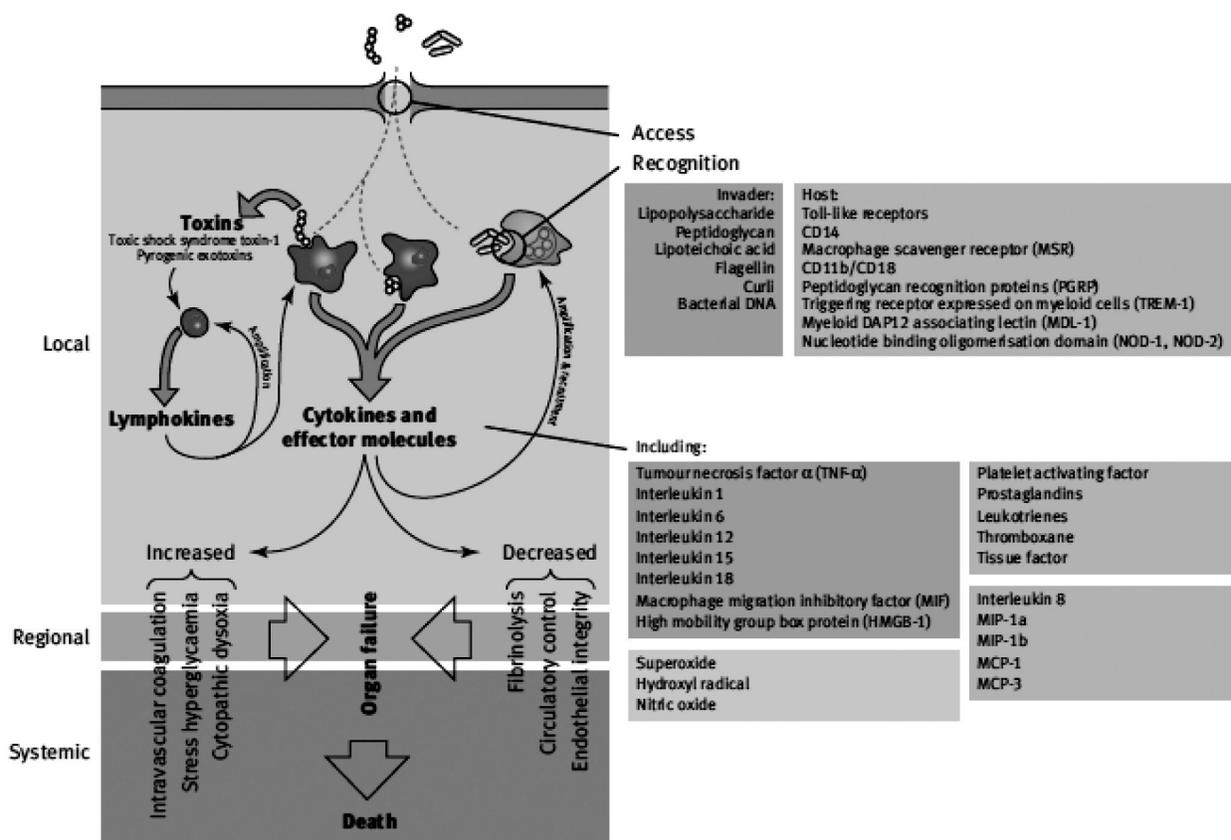
**Causative organisms**

Pathogens causing neonatal infections and their antibiotic susceptibility pattern may change over time<sup>14-16</sup> and differ between countries<sup>17</sup>.

Neonatal surveillance in developed countries generally identifies Group B Streptococcus (GBS) and *E. coli* as the dominant EOS pathogens and coagulase-negative staphylococci (CONS) as the dominant LOS pathogen followed by GBS and *Staph aureus*. In developing countries, overall, Gram negative organisms are more common and are mainly represented by Klebsiella, *E. coli* and *Pseudomonas*. Of the Gram positive organisms, *Staph aureus*, CONS, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* are most commonly isolated.<sup>18</sup> Agents that commonly cause nosocomial infection are coagulase-

*Characteristics of neonatal infection according to age at onset<sup>3</sup>*

| Characteristics                  | Early onset                                    | Late onset                              | Very late onset                         |
|----------------------------------|--|---|---|
| Age at onset                     | Birth to 7 days usually <72 hr                 | 7-30 days                               | >30 days                                |
| Maternal obstetric complications | Common   | Uncommon                                | Varies                                  |
| Prematurity                      | Frequent                                       | Varies                                  | Usual                                   |
| Organism source                  | Maternal genital tract                         | Maternal genital tract/ environment     | Environment/community                   |
| Manifestation Site               | Multisystem<br>Normal nursery, NICU, community | Multisystem or focal<br>NICU, community | Multisystem or focal<br>NICU, community |



Pathophysiological pathways of sepsis

negative staphylococci, gram-negative bacilli (E. coli, Klebsiella pneumonia, Salmonella, Enterobacter, Citrobacter, Pseudomonas aeruginosa, Serratia), Enterococci, and S. aureus<sup>3</sup>.

**Pathogenesis**

The pathophysiology of sepsis arises largely from the response of the host’s innate immune system under the influence of genetic factors. Sepsis originates from a breach of integrity of the host barrier, either physical or immunological, and direct penetration of the pathogen into the bloodstream, creating the septic state.<sup>11</sup>

Pathophysiological pathways of sepsis:<sup>11</sup>

**Clinical manifestations**

The signs and symptoms of sepsis are influenced by the virulence of the pathogen, the portal of entry, the susceptibility and response of the host, and the temporal evolution of the condition.<sup>11</sup>

Initial signs and symptoms of infection in newborn infants:<sup>3</sup>

- **General:** Fever, temperature instability, “not doing well”, poor feeding, edema

- **Gastrointestinal system:** Abdominal distension, vomiting, diarrhea, hepatomegaly
- **Respiratory system:** Apnea, dyspnea, tachypnea, retractions, flaring, grunting, cyanosis
- **Renal system:** Oliguria
- **Cardiovascular system:** Pallor, mottling; cold, clammy skin, tachycardia, hypotension, bradycardia
- **Central nervous system:** Irritability, lethargy, tremors, seizures, hyporeflexia, hypotonia, abnormal Moro reflex, irregular respirations, full fontanel, high-pitched cry
- **Hematologic system:** Jaundice, splenomegaly, pallor, petechiae, purpura, bleeding

Early-onset sepsis is usually a multisystem illness with prominent respiratory symptoms. It is characterized by a sudden onset and fulminant course that can progress rapidly to septic shock and death. Late-onset sepsis is usually more insidious but it can be fulminant at times. In addition to bacteremia, these infants may have an identifiable focus, most often meningitis in addition to sepsis.<sup>12</sup>

**Clinical criteria for the diagnosis of sepsis:<sup>3, 5</sup>**

| Criteria  | IMCI criteria for Severe bacterial infection* | WHO Young infant study group**      |
|---|---|-------------------------------------|
| Convulsions   | ×   | ×                                   |
| Respiratory rate >60 breaths/min  | ×   | × (divided by age group)            |
| Severe chest indrawing  | ×   | ×                                   |
| Nasal flaring   | ×   |                                     |
| Grunting  | ×   |                                     |
| Bulging fontanel  | ×   |                                     |
| Pus draining from the ear   | ×   |                                     |
| Redness around umbilicus extending to the skin  | ×   |                                     |
| Temperature >37.7 <sup>0</sup> C (or feels hot) or <35.5 <sup>0</sup> C (or feels cold) | ×   | ×                                   |
| Lethargic or unconscious  | ×   | × (not aroused by minimal stimulus) |
| Reduced movements   | ×   | × (change in activity)              |
| Not able to feed  | ×   | × (not able to sustain such)        |
| Not attaching to the breast   | ×   |                                     |
| No suckling at all  | ×   |                                     |
| Crepitations  |   | ×                                   |
| Cyanosis  |   | ×                                   |
| Reduced digital capillary refill time   |   | ×                                   |

\*Any of the signs listed below implies high suspicion for serious bacterial infection.

\*\*Each symptom or sign is associated with a score. The score indicates the probability of disease.

**Evaluation and Diagnosis**

Blood culture is the gold standard for the diagnosis of sepsis. However, it is not error free because it can be falsely sterile because of insufficient sample volumes, intermittent or low-density bacteremia, or suppression of bacterial growth by earlier antibiotic administration. Positive cultures reportedly range from 8 – 73% in the diagnosis of potential neonatal sepsis. On the other hand, high rates of culture contaminants have also been reported.<sup>18</sup>

**Evaluation of a newborn for infection or sepsis:<sup>3</sup>**

**History**

- Maternal infection during pregnancy and delivery: Urinary tract infection, Chorioamnionitis, type and duration of antibiotics
- Maternal colonization with group B streptococci and Neisseria gonorrhoeae
- Gestational age/birthweight
- Multiple births
- Duration of membrane rupture

- Complicated delivery
- Fetal tachycardia/distress
- Age at onset (in utero, birth, early postnatal, late)
- Location at onset (hospital, community)
- Medical intervention: vascular access, endotracheal intubation, parenteral nutrition, surgery

Evidence of Other Diseases that increase the risk of infection or may overlap with signs of sepsis

- Congenital malformations (heart disease, neural tube defects)
- Respiratory tract disease (respiratory distress syndrome, aspiration)
- Necrotizing enterocolitis
- Metabolic disease e.g. galactosemia

Evidence of Focal or Systemic Disease

- General appearance, neurologic status
- Abnormal vital signs
- Organ system disease
- Feeding, stools, urine output, extremity movement

**Laboratory Studies***Evidence of infection*

- Culture from a normally sterile site (blood, CSF, other)
- Demonstration of a microorganism in tissue or fluid
- Molecular detection (blood, urine, CSF)
- Autopsy

**Evidence of inflammation**

- Leukocytosis, increased immature/total neutrophil count ratio
- Acute-phase reactants: C-reactive protein, ESR
- Cytokines: interleukin-6, interleukin-8, tumor necrosis factor
- Pleocytosis in CSF or synovial or pleural fluid
- DIC: fibrin degradation products, D-dimer

**Evidence of multiorgan system disease**

- Metabolic acidosis: pH, PCO<sub>2</sub>
- Pulmonary function: PO<sub>2</sub>, PCO<sub>2</sub>
- Renal function: blood urea nitrogen, creatinine
- Hepatic function: bilirubin, ALT, AST, ammonia, PT, APTT
- Bone marrow function: neutropenia, anemia, thrombocytopenia

**Sepsis screen<sup>13</sup>**

Although diagnostic tests are frequently ordered to identify infants with probable sepsis, their main benefit is to exclude disease in infants with a low probability of infection. A combination of diagnostic tests improves the predictive values over use of a single test. One suggested sepsis screen is given below:

| Test                                 | Point value |
|--------------------------------------|-------------|
| Absolute neutrophil count <1,750/cmm | 1 point     |
| Total WBC <7,500 or >40,000/cmm      | 1 point     |
| I:T neutrophil ratio > 0.2           | 1 point     |
| I:T neutrophil ratio > 0.4           | 2 points    |
| CRP+ (> 1.0 mg/dL)                   | 1 point     |
| CRP+ (> 5.0 mg/dL)                   | 2 points    |

The screen result is considered positive if 2 or more points are present. It is important to recognize that no sepsis screen is perfect, and one should err on the side of caution with neonatal sepsis.

**Newer Diagnostic Tools***Candidate biomarkers for diagnosis of sepsis:<sup>11</sup>*

- Acute phase reactants: C-reactive protein, ferritin, lactoferrin, neopterin, procalcitonin, serum amyloid A
- Cytokines: tumor necrosis factor-alpha, Interleukins (1-alpha, 1-beta, 6, 8, 10, 18)

- Leucocyte surface markers: Cell differentiation antigen CD11b, Intercellular adhesion molecule (ICAM-1), CD63, CD64, CD66b
- Microbial products: endotoxin
- Polymerase chain reaction (PCR): 100% sensitivity and 95.6% specificity. However, diagnostic accuracy and cost-effectiveness should be established before implementation in clinical practice.<sup>18</sup>

**Differential diagnosis**

The differential diagnosis of neonatal sepsis is extensive and following noninfectious disorders should be considered in appropriate settings:<sup>3</sup>

*Differential diagnosis of Neonatal sepsis***CARDIAC**

Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)

Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN

**GASTROINTESTINAL**

Necrotizing enterocolitis, Spontaneous gastrointestinal perforation

Structural abnormalities

**HEMATOLOGIC**

Neonatal purpura fulminans

Immune-mediated thrombocytopenia

Immune-mediated neutropenia

Severe anemia

Malignancies (congenital leukemia)

Hereditary clotting disorders

**METABOLIC**

Hypoglycemia

Adrenal disorders: adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia

Inborn errors of metabolism: organic acidurias, lactic acidoses, urea cycle disorders, galactosemia

**NEUROLOGIC**

Intracranial hemorrhage Hypoxic-ischemic encephalopathy

Neonatal seizures, Infant botulism

**RESPIRATORY**

Respiratory distress syndrome

Aspiration pneumonia: amniotic fluid, meconium, or gastric contents

Lung hypoplasia

Tracheoesophageal fistula

Transient tachypnea of the newborn

## Management

### *Empirical treatment*

Treatment is most often started before a definitive causative agent is identified. It consists of a penicillin, usually ampicillin, plus an aminoglycoside such as gentamicin. In nosocomial sepsis, the flora of the NICU must be considered; however, generally, staphylococcal coverage with vancomycin plus an aminoglycoside such as gentamicin or amikacin is usually begun.<sup>12</sup>

### *Specific treatment*

Specific or continuing therapy is based on culture and sensitivity results, clinical course, and other serial laboratory studies. Monitoring for antibiotic toxicity is important as well as monitoring levels of aminoglycosides and vancomycin.<sup>12</sup> It is better to follow institutional guidelines as it is based on antibiogram which varies in different institutes.

### *Supportive care*<sup>12</sup>

- Thermal care: Thermo-neutral environment should be ensured
- Respiratory: Adequate oxygenation with blood gas monitoring, and initial oxygen therapy or ventilator support (if needed) must be ensured.
- Cardiovascular: Blood pressure and perfusion must be supported to prevent shock. Volume expanders like normal saline, and inotropes such as dopamine or dobutamine may be needed. Intake and output of fluids should be monitored.
- Hematologic: DIC and neutropenia should be treated as per standard protocol.
- CNS: Seizures and SIADH should be addressed with proper attention.
- Metabolic: Hypoglycemia, hyperglycemia and metabolic acidosis should be monitored and treated accordingly.

### **Advances in Therapy**

IVIG, G-CSF, GM-CSF, pentoxifylline, oral lactoferrin etc. are showing promising results in treating and in some instances, preventing neonatal sepsis in different studies. Immunotherapy progress continues in the development of vaccines as well as various hyperimmune globulins and synthetic monoclonal antibodies to specific pathogens e.g. antistaphylococcal antibodies. All these may prove to be significant adjuvants to the routine use of antibiotics for the treatment of sepsis.<sup>12</sup>

## Antimicrobial Resistance

Antibiotic resistance is now a global problem. Reports of multiresistant bacteria causing neonatal sepsis in developing countries are increasing, particularly in intensive care units. Studies show increasing resistance of organisms to commonly used antibiotics. Most Gram negative bacteria are now resistant to ampicillin and cloxacillin, and many are becoming resistant to gentamicin. However, reduced susceptibility to third generation cephalosporins and even to quinolones is emerging. In some countries, Staph aureus is the most common cause of neonatal sepsis and methicillin resistant strains (MRSA) are widespread.<sup>5</sup>

## Complications and Prognosis

- Bacteremic infections may lead to endocarditis, septic emboli, abscess formation, septic joints with residual disability, and osteomyelitis and bone destruction.<sup>3</sup>
- Later complications of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).<sup>3</sup>

Mortality rates from the sepsis syndrome depend on the definition of sepsis. As all bacteremic infections are included in the definition, reported mortality rates in neonatal sepsis are as low as 10%; but the rate may be as high as 50%. Several studies have documented that the sepsis case fatality rate is highest for gram-negative and fungal infections.<sup>19</sup>

The case fatality rate for neonatal bacterial meningitis is between 20% and 25%. A number of neurologic sequelae may be encountered in infants with sepsis but without meningitis, as a result of cerebritis or septic shock. Extremely LBW infants (<1000 g) with sepsis are at increased risk for poor neurodevelopment and growth outcomes in early childhood.<sup>3</sup>

## Prevention

Possible preventive strategies to be considered might include:<sup>5</sup>

- Intrapartum antibiotic prophylaxis
- Use of antiseptic solution to disinfect the birth canal, and

- Implementation of simple infection control methods of proven efficacy such as -
  - o Hand washing, and barrier nursing
  - o Promotion of clean deliveries
  - o Exclusive breast feeding
  - o Restriction of antibiotic use, and
  - o Rationalization of admissions to and discharges from neonatal units

Principles for the prevention of nosocomial infection in the NICU:<sup>20</sup>

- Universal precautions with all patient contact: Gloves, gowns, mask, and isolation as needed
- Nursery design engineering: Appropriate nursing: patient ratio, avoid overcrowding and excessive workload, readily accessible sinks, antiseptic solutions, soap, and paper towels
- Handwashing
- Minimizing central venous catheter contamination
- Meticulous skin care
- Encourage early and appropriate advancement of enteral feeding
- Education and feedback for nursery personnel
- Continuous monitoring and surveillance of nosocomial infection rates in the NICU

#### Future Developments and Research Priorities

There are a number of important gaps in our knowledge, and there is an urgent need for studies looking at simple and sustainable interventions to reduce the burden of neonatal infection. Longitudinal surveillance to describe the varied pathogens causing neonatal sepsis as well as their changing antibiotic susceptibility profile is important. Without such a platform, the introduction of new methods of prevention is difficult.<sup>5</sup>

Research is also ongoing into blocking some of the body's own inflammatory mediators that result in significant tissue injury, including endotoxin inhibitors, cytokine inhibitors, nitric oxide synthetase inhibitors, and neutrophil adhesion inhibitors. Studies are ongoing to test if probiotics with or without lactoferrin will be helpful in the prevention or modulation of neonatal sepsis.<sup>12</sup>

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