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Epidemiology, Risk Factors, and Prevention Strategies for Neonatal Sepsis: A Review

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Abstract

Systemic invasion of pathogenic microorganism during the neonatal period causing inflammatory response is referred to as neonatal sepsis. Sepsis is one of the main causes for neonatal mortality and morbidity all over the globe, predominately in the middle- and low-income countries due to improper infection control procedures and inconsistent hygiene habits. Clinical features of sepsis in neonates are non-specific compared to children and adults making timely diagnosis challenging. This review emphasizes the contributing factors epidemiological trends, and pathogenic mechanisms associated with neonatal sepsis. On the basis of manifestation of clinical symptoms neonatal sepsis is categorized into two groups, Early onset of sepsis (EOS) <72hr and late onset of sepsis (LOS) >72hr. In high income countries both EOS and LOS have distinct causative agents and risk profiles while the EOS is supposed to be primarily caused due to maternal risk factors such as chorioamnionitis, preterm labor, and prolonged rupture of membrane while LOS is associated with hospital acquired infections exacerbated by inadequate infection control measures in healthcare settings. The critical need for improved prenatal care, stringent infection control protocols, and effective antibiotic stewardship to mitigate the incidence of neonatal sepsis. Additionally, disparities in healthcare infrastructure are highlighted as barriers to effective management and prevention.

Keywords: Neonatal sepsis; Child mortality India; Maternal health; Prenatal care; Socio-economic disparities; Antibiotic stewardship; Multi-drug resistant organisms

Introduction

Sepsis is one of the primary causes of mortality and morbidity in newborns worldwide [1], posing a significant health burden. In middle- and low-income countries, neonatal sepsis leads to distressing outcomes [2]. Neonatal sepsis accounts for nearly 203,000 deaths annually, with approximately 1.3 million cases reported globally [3], causing a significant financial burden [4]. The prevalence of sepsis is notably higher in preterm and low-weight newborns, with a reported mortality rate of 17.6% [5]. Studies have observed that 24% of these cases are caused by severe infections [6].

In high-income countries (HIC), neonatal sepsis is well-studied and documented. However, there is a lack of information on its incidence in low- and middle-income countries (LIC and MIC) [7,8]. Neonatal sepsis is a systemic infection caused by invading microorganisms during the first four weeks of life [9]. It encompasses conditions such as bloodstream infections (septicemia), pneumonia, meningitis, and other widespread infections.

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Diagnosing sepsis in neonates is particularly challenging because, unlike in older children and adults, its symptoms are often vague and non-specific [10]. During neonatal period, newborns may experience health issues resulting from birth and labor trauma. Research has revealed several factors associated with an increased risk of neonatal sepsis, including low birth weight, preterm birth (before 37 weeks of gestation), premature rupture of membranes (PROM), complications during labor such as perinatal asphyxia, low socioeconomic conditions, poor sanitation, poor maternal nutritional status, and suboptimal infection control practices [1,6,11,12].

Neonatal sepsis is categorized into two types on the basis of manifestation of clinical symptoms: Early-onset sepsis (EOS); Occurring within the first 72 hours of life, caused by microorganisms transmitted vertically from mother to infant and Late-onset sepsis (LOS); Occurring in neonatal intensive care unit (NICU) infants after the first 72 hours of life [12,13]. The primary diagnostic method for sepsis involves traditional blood cultures, which classify sepsis into two main categories: 'culture-positive' sepsis, where one or more pathogens are identified, and 'culture-negative' sepsis, where no pathogens are detected, but clinical symptoms and/or additional laboratory findings suggest the presence of sepsis [14,15]. In the urban conglomerate of Delhi NCR, the challenges are compounded by population density, diverse socio-economic conditions, and varying levels of healthcare access and quality. This review aims to provide a comprehensive overview of neonatal sepsis, focusing on its pathophysiology, risk factors, bacterial profiles, and management strategies. It highlights the significant burden of neonatal sepsis and explores the various factors contributing to its prevalence and management challenges.

Review

Epidemiology

In high-income countries (HIC), the occurrence of neonatal sepsis is estimated to range from 1 to 8 cases per 1,000 live births, with a mortality rate of 14 per 100,000 live births [16,17]. According to the investigators of the DeNIS study, the incidence of neonatal sepsis in Indian public sector hospitals is approximately 14.3%, of which 6.2% of cases were culture-positive. Additionally, 83% of the episodes were early-onset sepsis (EOS). It was found that the overall mortality in culture-positive sepsis, culture-negative sepsis, and meningitis is around 25.6%. Chaurasia et al. reported that the incidence of culture-positive sepsis in South Asia is approximately 15.7%, with a case fatality rate of 34.4%, which is 2 to 3 times higher than in the UK and USA [18].

When comparing the incidence of sepsis in HICs to that in low- and middle-income countries (LMICs), it has been observed that morbidity and mortality are significantly higher in LMICs. The factors contributing to these substantial differences include insufficient essential equipment and supplies, such as soap, sinks, running water, and disposables; overcrowding and staff shortages; and inadequate disinfection practices [1,19].

Pathophysiology

Neonatal sepsis is a clinical syndrome defined by the presence of infection-related signs and symptoms, often accompanied by bacteraemia, leading to a systemic inflammatory response and eventually resulting in multiorgan dysfunction [20]. Oranges et al. [21] and Wynn and Wong [22], studied that the skin creates physical barrier from the environment and the body but the stratum which is the outer layer of epidermis is not well developed till 10 days of birth and vernix which is complex natural material present on the skin can act as a barrier but is absent in preterm neonates which makes new-borns susceptible to sepsis [21,22]. Both early and late onset of sepsis have different microbial profile, while the former was supposed to be caused by *Group B Streptococcus* (GBS), *Escherichia coli*, and *Listeria monocytogenes,* infection in the foetus occurs through vertical transmission of maternal bacteria from the lower genital tract to the uterus. This results in contamination of the amniotic fluid, leading to hematogenous spread, which causes fetal bacteremia and sepsis [3], while the later was observed to be caused by ESKAPE pathogens which are horizontally transferred from hospital environment [1,23].

The pathogenesis of neonatal sepsis is influenced by several maternal and neonatal risk factors.

Maternal Risk Factors: Maternal infections, such as chorioamnionitis, urinary tract infections (UTIs), and GBS colonization, increase the likelihood of transmitting pathogens to the neonate. Other maternal conditions like premature rupture of membranes, premature labor, and low socioeconomic status have also been identified as major risk factors for neonatal sepsis [24,25]. A study conducted by Raturi A and Chandran S highlighted that prolonged rupture of membranes exceeding 18 hours, chorioamnionitis or intra-amniotic infection, and maternal infections (primarily urinary tract infections followed by vulvovaginitis) during pregnancy are significant risk factors to take into account [17]. Other studies also suggest the same [26,27]. Salama and Tharwat [28] Showed that primiparous mother are at a higher risk having neonatal sepsis than multiparous mothers, neonates delivered through C-section are at a 2.5 times high risk than neonates born vaginally [28].

Neonatal Risk Factors: Salama and Tharwat [28] showed that Premature birth (<37 weeks' gestation) increases the risk of neonatal sepsis 3.4 times than the full term neonate, males are at 1.7 times higher risk to develop neonatal sepsis

than females low birth weight (LBW) increases the risk to 3.5 times, and congenital anomalies place neonates at increased risk due to their underdeveloped immune systems. Premature neonates are particularly susceptible to infections, as their immune responses are not fully matured, and their exposure to invasive medical procedures such as intubation and catheterization increases the risk of nosocomial infections [28-31].

Once pathogens enter the neonate's bloodstream, they may spread to various organs, causing symptoms in multiple systems, including gastrointestinal, urological, cardiovascular, metabolic, and central nervous systems. The systemic inflammatory response leads to clinical manifestations such as fever, lethargy, respiratory distress, and poor feeding, which can progress to severe sepsis and multiorgan failure in extreme cases [20].

Risk Factors Associated with Neonatal Sepsis

Neonatal sepsis is a multifactorial condition, and its occurrence is influenced by a range of maternal, neonatal, and healthcare-related risk factors Multiple studies have established that neonatal sepsis involves both neonatal and maternal risk factors. This is further corroborated by evidence from a systematic review article [32].

Maternal Risk Factors

Prolonged rupture of membranes (PROM): The risk of neonatal infection increases when the membranes rupture more than 18 hours before delivery, allowing bacteria to ascend from the vaginal canal into the amniotic sac. This significantly raises the risk of early-onset neonatal sepsis [33,34]. A study conducted a meta-analysis examining three factors: gestational age, mode of delivery, and premature rupture of membranes (PROM). The analysis revealed that gestational age less than 37 weeks (OR: 2.05; 95% CI: 1.40–2.99; $I^2 = 77\%$) and PROM (OR: 11.14; 95% CI: 5.54–22.38; $I^2 = 0$) were significantly associated with increased odds of neonatal sepsis [12]. Another study supports that maternal factor, including preterm delivery (gestational age <37 weeks) and premature rupture of membranes (PROM), are significant risk factors for neonatal early-onset sepsis (EOS). A meta-analysis reported an odds ratio (OR) of 2.3 (95% CI: 1.0–5.4; $I^2 = 93.4\%$) for preterm delivery and an adjusted odd ratio (aOR) of 4.9 (95% CI: 1.9–12.8) for PROM [35,36], found out that the patient having PROM >18 hours are at 5 times higher risk of developing sepsis and the data was found to be consistent with the other studies, prolonged PROM leads the microbe to enter the amniotic sac and predisposes neonate to infection [37].

Urinary Tract Infection (UTI): UTI is common health issue during pregnancy with high prevalence rate in LMIC and leads to maternal and neonatal health problems all over the globe, it has been implicated to cause premature birth, perinatal death, it has been observed that maternal UTI increases the risk of neonatal UTI almost 5 times [38].

Chorioamnionitis and Intrapartum Fever: Chorioamnionitis and Intrapartum fever indicates the infections that can transfer to neonate while delivery study revealed that neonates whose mothers experienced a fever during labor had 3.42 times greater odds of developing sepsis compared to those born to mothers without a fever during labor [39,40].

Premature labor: Infants born prematurely (<37 weeks) are highly susceptible to infections due to their immature immune systems and the need for invasive procedures during hospitalization. Meta-analyses identified several risk factors for neonatal sepsis, including male sex (OR: 1.3; 95% CI: 1.02–1.68), being out born (OR: 5.5; 95% CI: 2.39–12.49), need for artificial ventilation (OR: 5.61; 95% CI: 8.21–41.18), gestational age less than 37 weeks (OR: 2.05; 95% CI: 1.40–2.99), and premature rupture of membranes (OR: 11.14; 95% CI: 5.54–22.38) [32].

Socio-economic status: Low socio-economic status has been linked to poor prenatal care and increased maternal infections, further elevating the risk of neonatal sepsis [32,33]. Reviews have highlighted that maternal colonization or infection, prolonged rupture of membranes exceeding 18 hours, and the use of intrapartum antibiotic prophylaxis significantly increase the risk of early-onset neonatal infections (EOS). Neonates are particularly vulnerable to EOS, which can result from the direct transmission of maternal colonizers, such as bacteria from the maternal vaginal tract, to the newborn during delivery [41,42].

Neonatal Risk Factors

Low birth weight (LBW): Infants weighing less than 2.5 kg at birth are more vulnerable to sepsis due to their underdeveloped immune systems and the increased likelihood of requiring invasive interventions. A study conducted by Murthy et al. [12], concluded that birthweight and gestational age at delivery were the most commonly reported factors associated with neonatal outcomes [24]. Ganfure and Lencha showed that neonate with birthweight >2.5 kg have 6 times higher chances of developing sepsis than normal birth weight [43].

Low APGAR Score: Studies associated with APGAR scores discovered that low first minute APGAR will increase the risk of sepsis by 3.33 times and low APGAR score in 5 minute will increase the risk by 4 times [44-46].

Prematurity: Premature infants are at high risk of infection due to their underdeveloped immune responses and prolonged hospital stays, which increase exposure to nosocomial pathogens [25].

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Hospital-Related Risk Factors

Infection control practices: Inadequate sterilization of medical equipment and inconsistent hygiene practices in NICUs are significant contributors to the incidence of hospital-acquired infections. Poor adherence to infection control protocols often leads to nosocomial neonatal sepsis, particularly in low-resource settings like India [47].

Antibiotic resistance: The overuse and misuse of antibiotics in NICUs contribute to the growing problem of multidrug-resistant (MDR) organisms, which complicate the management of neonatal sepsis. The study from Gupta S et al. [48], also identified a significant prevalence of multidrug-resistant (MDR) bacteria contributed significantly to the rising sepsis rates. Studies by Mohakud et al. [49] and Sethi et al. [13] also highlight and emphasize the prevalence of multidrug-resistant organisms in sepsis and the associated mortality risk.

Bacteriological Profile

Early-Onset Sepsis (EOS): The predominant pathogens for EOS are *Group B Streptococcus* (GBS), *Escherichia coli*, and *Klebsiella* species. These organisms are typically acquired from the maternal genital tract during delivery [24].

Late-Onset Sepsis (LOS): LOS, occurring after 72 hours of life, is often associated with hospital-acquired infections. Common pathogens include *Coagulase-negative Staphylococci* (CONS), *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* species. Increasing prevalence of MDR organisms has become a growing concern, emphasizing the need for stringent infection control measures in NICUs [25].

Study done by Vimal (2024) emphasized the role of multidrug-resistant pathogens, such as *Klebsiella* and *Escherichia coli*, in complicating the treatment of neonatal sepsis in Indian hospitals. This aligns with findings from Gupta S et al. [48], who noted that *coagulase-negative Staphylococcus* and *Klebsiella pneumoniae* were the most common bacterial isolates associated with neonatal sepsis.

Additionally, Studies by Mohakud et al. [49] and Sethi et al. [13] highlight *Staphylococcus aureus* as the predominant pathogen in sepsis, followed by *Coagulase-negative Staphylococcus* and *Enterococcus spp*. among Gram-positive isolates. Gram-negative pathogens, including *E. coli* and *Klebsiella pneumoniae*, were also significant, with high resistance to ampicillin and 68% resistance to cephalosporins. These studies reinforce the need for early detection, proper management, and improved infection control practices to reduce neonatal sepsis mortality in this region [13,49].

The epidemiology and risk factors associated with neonatal sepsis in Delhi NCR align with findings from several studies, highlighting the major burden of this condition. Studies have identified key risk factors, including preterm birth, low birth weight, and maternal infections such as GBS colonization and chorioamnionitis. These risk factors, combined with inadequate prenatal care and poor infection control practices, contribute to the high incidence of neonatal sepsis in the region.

Management Strategies

Effective management of neonatal sepsis requires a multifaceted approach that includes prompt diagnosis, appropriate antimicrobial therapy, and comprehensive infection control measures.

Early Diagnosis: Prompt identification of neonatal sepsis is crucial for improving outcomes. Common clinical signs include fever, respiratory distress, lethargy, and poor feeding. Laboratory tests such as blood cultures, C-reactive protein (CRP), and complete blood count (CBC) can aid in diagnosis. However, culture results may take time, so empirical antibiotic therapy is often initiated based on clinical suspicion until results are available [25]. A study by Arup Jana highlighted significant cross-state disparities in the prevalence of low birth weight (LBW) and preterm birth (PTB) in India, with 12% of children being LBW and 18% PTB during 2019–21. Maternal factors, including inadequate antenatal care, prior cesarean delivery, and maternal short stature, were positively associated with these adverse outcomes. Interestingly, some correlates were found to influence PTB and LBW differently, emphasizing the need for targeted interventions to address regional and maternal disparities in birth outcomes [50]. A study by the National Neonatology Forum (NNF) India highlights the importance of early diagnosis and appropriate management of neonatal sepsis. It emphasizes the use of timely blood cultures and biomarkers for more accurate sepsis diagnosis. It also stresses the significance of improving maternal care, proper hygiene, and timely interventions in Neonatal Intensive Care Units (NICUs) to reduce the burden of neonatal sepsis [51]. Collectively, these studies emphasize the role of timely diagnosis, appropriate antibiotic therapy, and prevention strategies such as improved antenatal care and hospital hygiene in reducing the impact of neonatal sepsis.

Antibiotic Therapy: Empirical antibiotic therapy should target the most common pathogens identified in the specific setting. In India, where Gram-negative organisms like *E. coli* and *Klebsiella* are prevalent, broad-spectrum antibiotics such as ampicillin and gentamicin are typically used which is mentioned in the WHO's access category as the first line antibiotics for EOS, while vancomycin or linezolid may be added for suspected nosocomial infections in LOS cases [20,52]. The emergence of antibiotic-resistant pathogens highlights the importance of continuous surveillance and

antibiotic stewardship programs to minimize resistance and improve outcomes [53]. A study by Sachan et al. [54] on 332 neonates found that 89 were diagnosed with clinical sepsis, with 64.9% presenting with early onset sepsis. Notably, 68.5% of these neonates had a birth weight of less than 2.5 kg, a key risk factor identified in multiple studies. The study also revealed that Gram-positive organisms were sensitive to vancomycin and linezolid, while Gram-negative organisms showed resistance to common antibiotics such as cephalosporins and piperacillin-tazobactam [54]. This underscores the importance of antibiotic resistance in neonatal sepsis in the region, as similarly observed by Jatsho et al. [55], who found a high resistance to carbapenems in Acinetobacter species, with a mortality rate of 88.9% in cases of Gram-negative sepsis [55]. These studies emphasize the importance of infection control practices and antibiotic stewardship to mitigate these risks.

Infection Control: Stringent infection control measures are critical in reducing the incidence of neonatal sepsis, particularly in NICUs. Regular hand hygiene, proper sterilization of medical equipment, and the use of personal protective equipment (PPE) are essential. Additionally, infection control protocols should be strictly adhered to, with regular audits and training for healthcare providers [47].

Antibiotic Stewardship: Antibiotic stewardship programs are designed to optimize the use of antibiotics in healthcare settings, minimizing the risk of resistance. In NICUs, these programs involve guidelines for empirical therapy, de-escalation of treatment based on culture results, and monitoring of local resistance patterns [56]. Such programs can significantly reduce the incidence of MDR infections in neonatal sepsis cases.

Prenatal Care: Improving prenatal care is essential in reducing the incidence of neonatal sepsis. Routine screening for maternal infections such as UTIs, GBS, and chorioamnionitis can significantly reduce the risk of early-onset sepsis. Educating expectant mothers about the importance of prenatal care and institutional deliveries is critical for early detection and prevention of maternal infections [57,58].

Conclusion

In conclusion, a multi-pronged approach focusing on improving maternal health, strengthening infection control in healthcare settings, and enhancing public health awareness is crucial in reducing neonatal sepsis in Delhi NCR. Despite advancements in healthcare, factors such as inadequate prenatal care, socioeconomic disparities, and inconsistent infection control practices continue to contribute to high rates of neonatal sepsis. Effective prevention and management require a multifaceted approach, including enhanced prenatal care, strict adherence to infection control protocols, and the implementation of antibiotic stewardship programs. Moreover, strengthening healthcare infrastructure, particularly in peripheral hospitals, and promoting regular training for healthcare providers are essential for improving outcomes. Government initiatives and collaborations with private healthcare providers and NGOs can further bridge the gaps in healthcare delivery, ensuring that all new-borns receive the care they need to thrive. Addressing these challenges holistically will be vital in reducing the burden of neonatal sepsis and improving neonatal health outcomes across regions.

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