



Sepsis: A Multidisciplinary Approach to Early Recognition, Diagnosis, Management, and Prevention-An Updated Review

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Abstract

Background: Neonatal sepsis remains a major cause of morbidity and mortality, particularly during the first weeks of life. Early-onset sepsis (EOS), occurring within the first 72 hours after birth, is mainly associated with maternal and perinatal risk factors, whereas late-onset sepsis (LOS) is linked to healthcare exposure and neonatal vulnerability. Early recognition remains difficult because clinical manifestations are often nonspecific.

Aim: This review summarizes current evidence on the epidemiology, aetiology, risk factors, clinical presentation, diagnosis, prevention, treatment, and multidisciplinary management of neonatal sepsis, with emphasis on EOS and LOS.

Methods: A narrative literature review was conducted using PubMed/MEDLINE, EMBASE, and ClinicalKey. Evidence addressing neonatal sepsis definitions, risk factors, diagnostic approaches, biomarkers, antimicrobial therapy, prevention, complications, and antimicrobial stewardship was reviewed and synthesized.

Results: EOS is commonly associated with maternal Group B Streptococcus colonization, intra-amniotic infection, prolonged rupture of membranes, and prematurity. LOS is associated with prematurity, prolonged hospitalization, invasive procedures, and healthcare exposure. Clinical signs include respiratory, cardiovascular, neurological, and gastrointestinal abnormalities, but none reliably excludes infection. Blood culture remains central to diagnosis, while inflammatory biomarkers can support clinical assessment. Risk-based assessment and serial clinical observation can reduce unnecessary antibiotic exposure in well-appearing neonates. Suspected sepsis requires prompt cultures and empiric antimicrobial therapy, commonly involving ampicillin or benzylpenicillin with an aminoglycoside, followed by modification according to microbiological results and local resistance patterns. Supportive respiratory, circulatory, and metabolic management remains essential.

Conclusion: Effective neonatal sepsis care requires early recognition, risk-based assessment, timely antimicrobial treatment, infection prevention, and antimicrobial stewardship within a coordinated multidisciplinary pathway.

Keywords: neonatal sepsis; early-onset sepsis; late-onset sepsis; Group B Streptococcus; neonatal infection; biomarkers; antimicrobial therapy; antimicrobial stewardship; newborn; prevention.

Introduction

Sepsis is a major cause of morbidity and mortality across all age groups and remains a critical challenge in contemporary healthcare. Its clinical significance is particularly pronounced in neonates, in whom the disease is characterized by distinctive pathophysiological mechanisms and often nonspecific clinical manifestations related to the immaturity of the developing immune system.

Neonatal sepsis can be broadly defined as a life-threatening condition resulting from a dysregulated host inflammatory response to infection, particularly bloodstream infection, occurring during the first 28 days of life [1][2][3]. The vulnerability of neonates to severe infection is influenced by the incomplete maturation of both innate and adaptive immune responses, together with physiological characteristics that can facilitate rapid progression from localized

infection to systemic illness. Neonatal sepsis is conventionally classified according to the timing of disease onset into early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS generally develops within the first 72 hours after birth, whereas LOS occurs after the first 3 days of life [2][4]. This temporal distinction is clinically important because the two forms are associated with differences in causative microorganisms, routes of infection, epidemiological characteristics, risk factors, clinical presentation, therapeutic approaches, and outcomes. Early-onset disease is frequently associated with maternal and perinatal factors and exposure to microorganisms acquired before or during delivery, whereas late-onset disease is more commonly associated with postnatal environmental exposure and healthcare-related factors. Understanding these differences is essential for developing appropriate diagnostic, preventive, and therapeutic strategies.

Despite substantial advances in neonatal intensive care, neonatal sepsis continues to be associated with considerable morbidity and mortality. One of the major challenges in clinical practice is the difficulty of establishing an early and reliable diagnosis. The initial manifestations of neonatal sepsis are frequently subtle and nonspecific and may overlap with other neonatal conditions, making clinical recognition particularly difficult. Delayed diagnosis and treatment have historically contributed to disease progression and the development of serious complications [5][6]. Consequently, contemporary research has increasingly focused on identifying sensitive and specific biomarkers and developing rapid diagnostic technologies capable of detecting infection before the appearance of severe clinical deterioration. Advances in molecular diagnostics, inflammatory biomarkers, point-of-care testing, and other emerging technologies may improve the speed and accuracy of neonatal sepsis recognition. The management of neonatal sepsis also presents significant challenges because treatment decisions must balance the potentially fatal consequences of delayed antimicrobial therapy against the adverse effects associated with unnecessary antibiotic exposure. Increasing antimicrobial resistance has further complicated this clinical dilemma and represents an important global healthcare concern [6][7]. Optimizing antimicrobial selection, dosing, duration, and de-escalation while maintaining timely treatment is therefore an essential component of contemporary neonatal sepsis management. Prevention is equally important and requires attention to maternal infection screening, appropriate intrapartum practices, neonatal infection-control measures, hand hygiene, device-associated infection prevention, and antimicrobial stewardship.

Given the complexity of neonatal sepsis, effective management requires coordinated multidisciplinary care involving physicians, nurses,

laboratory professionals, pharmacists, radiologists, infection-control specialists, and health informatics professionals. Laboratory medicine contributes to microbiological confirmation and biomarker assessment, while radiology may support the identification of infectious foci and complications. Pharmacists play an important role in antimicrobial selection, dosing optimization, drug interactions, and antimicrobial stewardship, whereas nurses are central to continuous clinical monitoring, early recognition of deterioration, infection prevention, and supportive care. Health information systems can further facilitate early-warning tools, clinical decision support, data integration, and standardized sepsis pathways. This narrative review examines the epidemiology, etiology, pathophysiology, risk factors, clinical manifestations, diagnostic approaches, management strategies, and complications associated with both EOS and LOS. Particular attention is given to developments in early diagnosis, emerging biomarkers, rapid diagnostic technologies, antimicrobial resistance, prevention strategies, and multidisciplinary approaches to care. The review incorporates both established evidence and emerging research findings to provide a comprehensive clinical perspective on neonatal sepsis. An extensive literature search was conducted using PubMed/MEDLINE, EMBASE, and ClinicalKey. Relevant publications addressing established concepts and novel developments were screened according to their relevance and applicability to the principal themes of this review.

Epidemiology

Neonatal sepsis remains an important global cause of neonatal morbidity and mortality, although its incidence and outcomes vary substantially according to geographical region, socioeconomic conditions, healthcare infrastructure, maternal health, infection-prevention practices, and access to timely diagnosis and treatment. In the United Kingdom and other high-income countries, the reported incidence of neonatal sepsis is estimated at approximately 6–8 cases per 1000 live births [8][9]. In the United States, the incidence of early-onset sepsis (EOS) is substantially lower, reaching approximately 1 case per 1000 live births. Despite the relatively low incidence in these settings, neonatal bacterial sepsis continues to contribute to preventable mortality, with approximately 14 deaths per 100,000 live births reported in the United States in 2016 [10][11]. These figures demonstrate that neonatal sepsis remains clinically important even in healthcare systems with advanced neonatal services and established infection-prevention strategies. The global burden becomes considerably greater when low- and middle-income countries (LMICs) are considered. Neonatal sepsis and other neonatal infections (NSNIs) were responsible for nearly one-quarter of a million deaths worldwide in 2016 [12]. The distribution of this

burden is highly unequal, with LMICs experiencing substantially higher incidence and mortality than high-income countries. This disparity reflects differences in access to antenatal care, skilled birth attendance, neonatal intensive care, microbiological diagnostics, antimicrobial therapy, infection-control resources, and early recognition of clinical deterioration. In 2016, the incidence of culture-positive neonatal sepsis in hospitals across South Asia was reported to be approximately 15.8 cases per 1000 live births, representing approximately two to three times the incidence reported in Western countries [14]. Such differences emphasize the influence of healthcare resources and preventive practices on the epidemiology of neonatal infection.

Temporal trends have also demonstrated important regional differences. Although the global incidence of NSNIs increased by approximately 13% between 1990 and 2019, countries classified within middle, middle-high, and high sociodemographic index groups experienced declining incidence during the same period [12][13]. These contrasting trends suggest that improvements in maternal and neonatal healthcare, infection prevention, obstetric practices, and access to effective treatment may have contributed to reductions in neonatal infection in more developed healthcare systems. The implementation of systematic prevention strategies for EOS has been particularly important. Increased use of intrapartum antibiotic prophylaxis against Group B *Streptococcus* (GBS) in higher-income countries has contributed to reductions in GBS-associated EOS and has consequently influenced the overall epidemiology of neonatal sepsis [15][16]. The mortality burden remains disproportionately concentrated in LMICs. Approximately 99% of deaths associated with neonatal sepsis have been estimated to occur in these settings [17]. Sub-Saharan Africa represents one of the regions most severely affected, with an estimated 300,000 neonatal deaths attributed to sepsis annually [18]. The high mortality in these regions is influenced by multiple interconnected factors, including limited access to skilled maternal and neonatal care, delayed presentation to healthcare facilities, inadequate laboratory capacity, shortages of essential medicines, limited availability of neonatal intensive care, and increasing antimicrobial resistance. In addition, differences in the predominant causative organisms and antimicrobial susceptibility patterns may complicate the application of treatment recommendations developed in high-income countries to resource-limited settings. Despite the continuing global burden, mortality associated with neonatal sepsis has shown an overall decline in both developed and developing countries. This improvement has been associated with broader advances in maternal and neonatal healthcare, improved infection-prevention measures, enhanced understanding of neonatal sepsis, earlier recognition

of clinical deterioration, and advances in antimicrobial and supportive management [19][20]. Nevertheless, the condition remains a major contributor to mortality among young infants and is estimated to account for approximately 15% of deaths in this population [13][21]. The continuing burden highlights the need for sustained investment in prevention, early diagnosis, antimicrobial stewardship, neonatal intensive care, and standardized clinical pathways. Epidemiological differences between regions should also be considered when developing diagnostic algorithms and treatment protocols, as strategies effective in high-resource settings may require adaptation to the microbial, healthcare, and socioeconomic realities of LMICs.

Etiology

The etiology of neonatal sepsis varies according to the timing of disease onset, route of pathogen acquisition, gestational age, birth circumstances, healthcare exposure, and geographical and socioeconomic context. Early-onset sepsis (EOS) is predominantly associated with vertical transmission of microorganisms from the mother to the neonate. Infection may occur during passage through the infected birth canal or through ascending infection, in which microorganisms migrate from the vagina or cervix into the uterus and subsequently contaminate the amniotic fluid [22]. The fetus may therefore be exposed to pathogenic organisms before delivery, during labour, or at the time of birth. In contrast, late-onset sepsis (LOS) is more commonly associated with postnatal acquisition of microorganisms from the healthcare environment, healthcare workers, caregivers, invasive devices, or other sources of environmental exposure [1][22]. Group B *Streptococcus* (GBS) is an important cause of EOS and has historically been regarded as one of the predominant causative organisms in developed countries. GBS commonly colonizes the female gastrointestinal and genitourinary tracts and can be transmitted to the neonate during labour and delivery [23][24]. The widespread implementation of maternal GBS screening and intrapartum antibiotic prophylaxis has contributed to a reduction in GBS-associated EOS in many high-income countries. *Escherichia coli* is another major pathogen, accounting for approximately 10%–35% of EOS cases and, in some studies, occurring more frequently than GBS among affected neonates [23][24][25]. The importance of *E. coli* is particularly evident among very-low-birth-weight (VLBW) infants, in whom increasing isolation rates have been reported [25]. Other bacterial organisms implicated in EOS include *Staphylococcus aureus*, *Listeria monocytogenes*, coagulase-negative staphylococci (CoNS), and *Haemophilus influenzae*, although these organisms generally account for a smaller proportion of cases [2][22][23][24][26].

Antimicrobial susceptibility patterns are particularly important in the management of EOS because empirical treatment commonly includes an aminoglycoside, such as gentamicin, combined with ampicillin or penicillin. Contemporary surveillance data from developed countries indicate that GBS isolates remain highly susceptible to ampicillin and penicillin [25][27]. Although most *E. coli* isolates demonstrate susceptibility to gentamicin, resistance to commonly used empirical treatment remains a concern, with resistance to standard antimicrobial coverage reported in approximately 10% of isolates [25][27]. Continuous surveillance of local microbiological patterns is therefore essential for maintaining appropriate empirical treatment protocols and reducing unnecessary broad-spectrum antibiotic exposure. LOS has a different epidemiological and microbiological profile because infection is generally acquired after birth. Transmission may occur through contact with healthcare workers, caregivers, contaminated equipment, healthcare environments, or invasive medical devices. Coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, are among the most frequently identified pathogens in LOS [1][22][23][26][28]. Enterobacteriaceae, *S. aureus*, and *Candida* species are also important causes, particularly among hospitalized and premature neonates [1][22][23][26][28]. The clinical interpretation of CoNS-positive cultures can be challenging because these organisms may represent either genuine bloodstream infection or contamination during specimen collection [24]. Differentiating contamination from true infection is particularly important because unnecessary antimicrobial treatment can increase antibiotic exposure and contribute to antimicrobial resistance. Furthermore, CoNS frequently demonstrate greater resistance to conventional antimicrobial regimens than some other LOS pathogens, potentially necessitating modification or expansion of empirical antimicrobial coverage [24][29].

simplex virus (HSV) infection is particularly important because neonatal HSV can present with systemic manifestations and may initially be indistinguishable from bacterial sepsis [30][31][32]. Other viral pathogens implicated in neonatal sepsis or sepsis-like syndromes include cytomegalovirus (CMV), enteroviruses, and other agents associated with congenital infections within the TORCH spectrum [33][34]. CMV is an established cause of congenital infection, including sensorineural hearing loss and other neonatal complications, and has also been associated with bacterial neonatal sepsis [35][36]. Interactions between viral and bacterial infections may involve complex immune dysregulation, whereby the inflammatory and immunological effects of one infection may increase susceptibility to concurrent or subsequent infection with another pathogen [34][35][36][37]. Invasive fungal infection represents another important cause of LOS, particularly among extremely premature and VLBW infants. Invasive candidiasis is associated with substantial morbidity and mortality and has become an increasingly recognized cause of neonatal infection [38][39][40]. *Candida* species can colonize healthcare workers and the hospital environment, and *Candida* represents an important cause of LOS among VLBW infants [38][39][40]. The increased susceptibility of these neonates may be related to immaturity of epithelial and mucosal barriers, facilitating translocation of microorganisms into the bloodstream. Additional factors, including prolonged antibiotic exposure and corticosteroid therapy such as dexamethasone, may alter the neonatal microbiome and promote proliferation and pathogenic transformation of *Candida albicans*, including development of its more invasive filamentous form [40][41].

The microbial spectrum of neonatal sepsis also differs substantially between high-income and resource-limited settings. In developing countries, healthcare-associated infection is more frequent, and Gram-negative organisms such as *Klebsiella* species and *E. coli* account for a substantial proportion of neonatal sepsis cases, whereas GBS is comparatively less prominent [42][43]. Marked regional variation has also been demonstrated. For example, an analysis from sub-Saharan Africa identified *Salmonella enterica* and *Acinetobacter* species as important causes of EOS and reported no cases attributable to GBS [44]. These geographical differences highlight the importance of local epidemiological and antimicrobial susceptibility data when developing diagnostic and empirical treatment protocols. Consequently, neonatal sepsis should not be regarded as having a uniform microbial profile, and clinical management should consider the timing of onset, maternal and neonatal risk factors, healthcare exposure, regional pathogen distribution, and local antimicrobial resistance patterns.

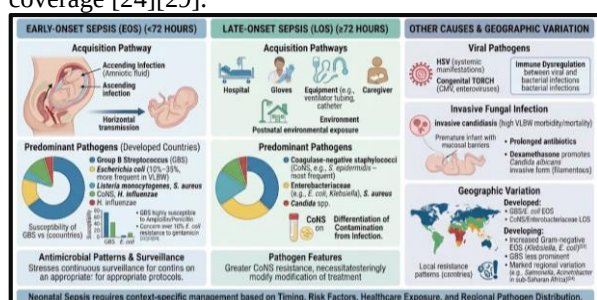


Figure 1: Etiology of neonatal Sepsis.

Although bacterial organisms constitute the principal causes of neonatal sepsis, viral infections should also be considered in neonates presenting sepsis-like illness. Viral sepsis is relatively uncommon but may produce clinical manifestations that closely resemble bacterial infection. Herpes

Pathophysiology and Risk Factors

Neonatal susceptibility to sepsis is strongly influenced by the immaturity of the developing immune system and the incomplete development of physical and biological barriers during the early postnatal period. This vulnerability is particularly pronounced in preterm infants, whose abbreviated gestational development limits the maturation of several protective mechanisms. The stratum corneum, the outermost epidermal barrier and an important component of innate immunity, does not achieve full functionality until approximately 10 days after birth and may require several additional weeks to mature in premature infants, depending on gestational age [45][46]. Extremely preterm neonates born before 28 weeks of gestation may also have inadequate vernix caseosa, which normally provides a mechanical barrier and contains antimicrobial peptides such as lactoferrin and lysozyme [47][48]. These deficiencies facilitate microbial invasion and contribute to the increased risk of infection in premature neonates. Prematurity also affects passive immune protection because most maternal immunoglobulin G (IgG) transfer occurs during the third trimester. Consequently, infants born prematurely receive lower concentrations of maternally derived antibodies at birth [45][49]. In addition, premature neonates may have impaired respiratory defense because increased goblet-cell density contributes to more viscous secretions and reduced mucociliary clearance, while reduced concentrations of protective surfactant proteins further compromise mucosal immunity [50][51]. Important maternal and perinatal risk factors for EOS include prolonged rupture of membranes, particularly for more than 18 hours, chorioamnionitis or intra-amniotic infection, maternal GBS colonization or infection, urinary tract infection, vulvovaginitis, and multiple vaginal examinations [52][53]. Maternal infection may contribute to neonatal infection through direct vertical transmission and may also influence fetal immune development through epigenetic mechanisms, including altered methylation of genes involved in immune regulation [55][56][57].

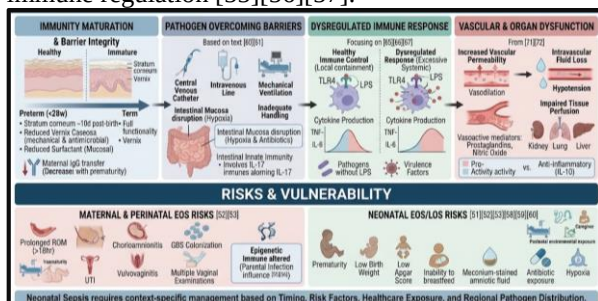


Figure-2: Pathophysiology of neonatal sepsis.

Additional neonatal risk factors include prematurity, low birth weight, low Apgar score, inability to breastfeed, and meconium-stained amniotic fluid [51][52][53][58][59]. LOS is similarly associated with immature host defenses but is

additionally influenced by healthcare exposure. Central venous catheters, intravenous lines, mechanical ventilation, repeated blood sampling, and inadequate handling of the infant or umbilical cord provide potential routes for pathogen entry [60]. Antibiotic exposure and hypoxia may further disrupt the intestinal mucosa and neonatal microbiota. These alterations are particularly relevant because intestinal innate immune mechanisms involving interleukin-17 (IL-17) contribute to both pathogen defense and regulation of inflammatory responses [61][62][63][64]. Once pathogens overcome local barriers and enter the bloodstream, neonatal sepsis develops through a complex and dysregulated interaction between microbial factors and host immunity. Sepsis can be viewed as failure to adequately contain infection locally, followed by excessive systemic immune activation and inflammatory responses [65]. Bacterial lipopolysaccharide (LPS), a pathogen-associated molecular pattern, activates Toll-like receptor 4 on myeloid cells and stimulates production of pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukin-6 [66]. Although this response is essential for pathogen clearance, excessive exposure to microbial products can produce uncontrolled inflammation, abnormal vascular responses, and tissue injury [67]. Pathogens lacking LPS can induce similar responses through other pathogen-associated molecular patterns, while specific virulence factors may facilitate tissue invasion and bloodstream dissemination [68]. Neonatal immune responses may be further impaired by reduced L-selectin expression and diminished neutrophil extracellular trap formation, limiting effective pathogen recruitment and killing [45][69][70]. Excessive production of vasoactive mediators, including prostaglandins, leukotrienes, and nitric oxide, increases vascular permeability and vasodilation, resulting in intravascular fluid loss, hypotension, impaired tissue perfusion, and potentially progressive organ dysfunction [71][72]. At the same time, anti-inflammatory mechanisms develop alongside pro-inflammatory responses. Excessive or premature anti-inflammatory activity, including increased interleukin-10 production, may suppress effective neutrophil recruitment and pathogen clearance and has been associated with poorer outcomes in experimental neonatal sepsis [45][73][74]. Thus, neonatal sepsis reflects a highly dynamic imbalance between pathogen invasion, immature host defenses, excessive inflammation, vascular dysfunction, and compensatory immunosuppression.

Presentation, Diagnosis and Biomarkers

Unlike adult sepsis, where systemic inflammatory response syndrome (SIRS) and quick Sequential Organ Failure Assessment (qSOFA) can identify clinical deterioration, these criteria are less suitable for neonatal sepsis because they depend on

signs of physiological instability that may occur relatively late, when mortality risk is already substantial [75]. Neonatal sepsis may also be clinically silent or present with nonspecific manifestations, making early recognition particularly challenging [76][77]. Common findings include poor feeding, respiratory distress with subcostal or intercostal retractions, bradycardia, tachycardia, vomiting, cyanosis, fever, hypotonia, jaundice, petechiae, seizures, lethargy, reduced sucking reflex, and grunting [78]-[80]. These features should prompt sepsis evaluation when alternative explanations are not evident. Blood culture remains the principal diagnostic investigation and should be obtained promptly when neonatal infection is suspected. For suspected early-onset sepsis (EOS), approximately 97%-100% of blood cultures become positive within 48 hours, supporting reassessment of empirical antibiotic therapy after 48 hours when cultures remain negative and clinical findings do not indicate ongoing infection [81][82]. According to National Institute for Health and Care Excellence (NICE) guidance, lumbar puncture should be performed following a positive blood culture. It should also be considered when there are signs of central nervous system dysfunction, poor response to antibiotics, or clinical and laboratory findings strongly suggestive of sepsis despite negative blood cultures [56][83][84]. False-negative cultures may occur because of slow-growing organisms, inadequate specimens, or previous antibiotic exposure [85].

Molecular techniques can complement conventional culture. Polymerase chain reaction (PCR) may identify pathogens in culture-negative cases, with one study detecting organisms in 45% of suspected EOS cases with negative cultures [86][87]. PCR and culture can also be performed using cerebrospinal fluid (CSF), while reduced CSF glucose and increased protein and white blood cell concentrations may support bacterial infection [2][88][89]. Hematological parameters provide supportive rather than definitive evidence. An immature-to-total neutrophil ratio below 0.27 has a high negative predictive value for neonatal sepsis, although an elevated ratio is frequently physiological and therefore less specific [90][91]. The ratio may nevertheless be more sensitive than absolute neutrophil or band counts [68]. Reduced leukocyte and platelet counts have also been associated with neonatal sepsis and may contribute to diagnostic assessment [92]. C-reactive protein (CRP) is an acute-phase protein involved in bacterial opsonization and complement activation [93][94]. However, CRP and other inflammatory markers can increase in noninfectious inflammatory conditions and during normal fetal and neonatal development [95][96]. Serial measurements are therefore more informative than a single value. Persistently normal CRP, particularly 36 hours after empirical antibiotics,

may provide useful exclusionary evidence [97]. Because CRP synthesis requires upstream inflammatory signaling, significant elevation generally occurs 10-12 hours after infection, limiting its value as an early biomarker [98][99]. Interleukin-6 (IL-6) rises earlier than CRP and may therefore support earlier recognition of infection, although its short half-life restricts its diagnostic window [98][100]. Procalcitonin (PCT) responds earlier to bacterial lipopolysaccharide and has demonstrated greater sensitivity than CRP. A 2019 meta-analysis reported approximately 8% higher sensitivity for EOS and 11.5% higher sensitivity for LOS compared with CRP [101][102]. Nevertheless, PCT sensitivity for EOS was only 73.6%, indicating that many infections remain undetected [102][103]. Current biomarkers therefore remain insufficiently sensitive for reliable early diagnosis, highlighting the need for high-sensitivity biomarkers and rapid molecular or point-of-care diagnostic approaches [24][104].

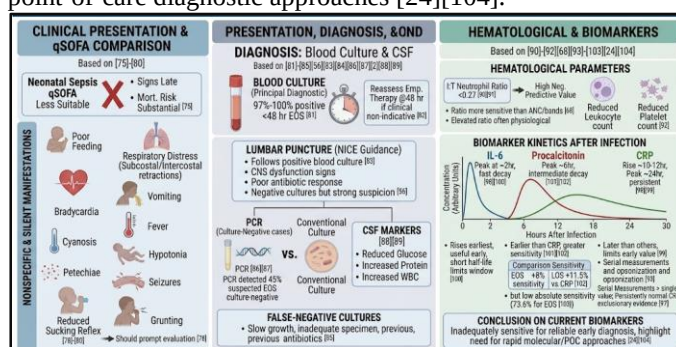


Figure 3: Diagnosis of Neonatal Sepsis.

Prevention, Treatment and Management

Prevention and early management are central to reducing neonatal sepsis morbidity and mortality. For early-onset sepsis (EOS), maternal intrapartum antibiotic prophylaxis with penicillin, or clindamycin in women with serious penicillin allergy, is recommended for mothers with established group B Streptococcus (GBS) infection or important risk factors. These include previous invasive GBS disease in an infant, GBS bacteriuria, prolonged rupture of membranes exceeding 18 hours, and maternal fever [56][105]. Prevention of prematurity through improved maternal nutritional status and comprehensive prenatal care may further reduce neonatal sepsis risk [106][107]. Suspected EOS requires prompt empirical broad-spectrum antimicrobial therapy after appropriate cultures have been obtained. Intravenous aminoglycosides combined with ampicillin in US practice or benzylpenicillin in UK practice provide coverage against common Gram-positive and Gram-negative pathogens [53][108]-[110]. In low- and middle-income countries, treatment may be complicated by high antimicrobial resistance, particularly among Gram-negative organisms, as well as limited diagnostic resources that restrict transition from empirical to pathogen-directed therapy [111].

Consequently, local microbiological surveillance and antimicrobial susceptibility data are important for selecting appropriate empirical regimens.

Prevention of late-onset sepsis (LOS) depends largely on reducing healthcare-associated transmission and minimizing potential routes of pathogen entry. Strategies include avoiding unnecessary invasive procedures, limiting inappropriate manipulation or premature replacement of central venous lines, and maintaining rigorous hand hygiene and infection-control practices within neonatal intensive care units [28][112][113]. Treatment of LOS should be guided by local epidemiology and antimicrobial susceptibility patterns. In addition to regimens used for EOS, cephalosporins and vancomycin may be required when resistant Gram-positive organisms, including beta-lactamase-producing staphylococci, are suspected [53][114]. Recommendations for investigating and treating neonatal sepsis differ between countries and clinical guidelines. NICE recommendations emphasize combinations of maternal and neonatal risk factors with clinical indicators, whereas American Academy of Pediatrics (AAP) approaches incorporate multivariable risk assessment, risk-factor assessment, or serial clinical observation [66][108][115]. The Kaiser Permanente Sepsis Risk Calculator (SRC) integrates local EOS incidence, maternal GBS status, intrapartum temperature, duration of membrane rupture, prophylaxis, gestational age, and neonatal clinical condition to estimate the need for antibiotic treatment. However, its use is generally limited to infants born at more than 34 weeks of gestation [113][116][117].

Antimicrobial resistance represents a major challenge in neonatal sepsis management. Multidrug-resistant (MDR) organisms were estimated to account for approximately 30% of neonatal sepsis deaths globally in 2016, while one Singapore healthcare setting reported MDR isolates in 47% of neonatal sepsis infections [118][119]. Increasing resistance among Gram-negative organisms has reduced the effectiveness of conventional first- and second-line antimicrobial regimens worldwide [118][120]-[122]. This may necessitate the use of less commonly prescribed or older agents, such as fosfomycin, for which neonatal safety and optimal dosing data remain limited [118][121]. Antimicrobial stewardship is therefore essential to maintain effective treatment while reducing resistance and drug-related harm. Antibiotic exposure itself may contribute to neonatal complications, including necrotizing enterocolitis, altered immune development, and other long-term effects [123]-[125]. Antibiotics can disrupt the developing intestinal microbiome, alter inflammatory mediator availability, promote expansion of pathogenic organisms, and influence neonatal immune maturation [126]. Microbiome disturbances may also affect the gut-lung, gut-skin, and gut-brain

axes, potentially contributing to subsequent disease processes [127][128]. Therefore, antibiotic therapy should be regularly reassessed. The SRC is increasingly used to reduce unnecessary antibiotic exposure, while serial clinical observations can support safe discontinuation or modification of therapy when infection becomes unlikely [108][129].

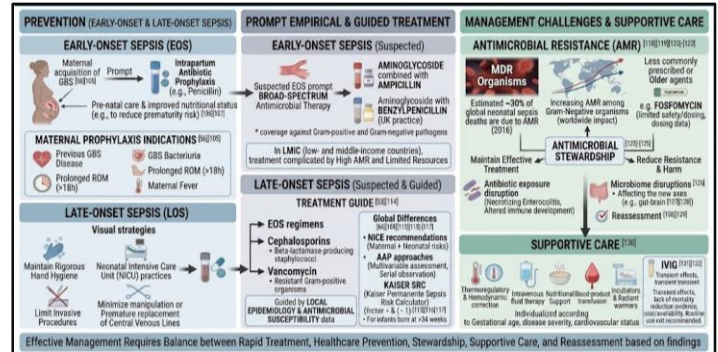


Figure-4: Treatment and Management of neonatal sepsis.

Supportive care is equally important in infants with suspected or confirmed sepsis. Thermoregulatory and hemodynamic disturbances associated with systemic inflammatory responses require prompt recognition and correction to reduce mortality [130]. Management may include appropriate intravenous fluid therapy, nutritional support, blood-product transfusion when clinically indicated, and maintenance of appropriate temperature and humidity using incubators or radiant warmers [2][130]. These interventions should be individualized according to gestational age, disease severity, cardiovascular status, and ongoing fluid and nutritional requirements. Intravenous immunoglobulin (IVIG) has been considered because of its potential to enhance neonatal humoral immunity and provide additional volume support. However, its transient effects, potential adverse events, cost, limited availability, and lack of convincing evidence for mortality reduction have limited its routine use in neonatal sepsis [131][132]. Overall, effective management requires a balance between rapid treatment of genuine infection, prevention of healthcare-associated transmission, antimicrobial stewardship, appropriate supportive care, and timely reassessment based on clinical and microbiological findings.

Conclusion:

Neonatal sepsis requires rapid recognition and coordinated management because clinical manifestations can be subtle and disease progression can occur rapidly. EOS and LOS differ in their epidemiology, risk factors, causative organisms, and prevention strategies. Maternal Group B Streptococcus screening, appropriate intrapartum prophylaxis, prenatal care, infection prevention, and reduction of avoidable invasive exposure remain central preventive measures. Diagnosis should integrate maternal and neonatal risk factors, serial

clinical assessment, blood culture, and supportive biomarkers rather than relying on a single clinical or laboratory finding. Suspected EOS requires timely microbiological investigation and empiric antimicrobial therapy, followed by treatment modification according to culture results, clinical response, and local resistance patterns. LOS management requires attention to healthcare-associated pathogens and infection-control practices. Supportive respiratory, cardiovascular, metabolic, and nutritional care is essential throughout treatment. Antimicrobial stewardship should guide decisions on initiation, continuation, narrowing, and discontinuation of therapy. Routine intravenous immunoglobulin has no established mortality benefit and should not replace evidence-based antimicrobial and supportive care. A multidisciplinary, risk-based pathway can improve recognition, reduce unnecessary antibiotic exposure, and support better neonatal outcomes.

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