Review Article

Update on the management of neonatal sepsis based on evidence and international guidelines

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Abstract

Neonatal sepsis remains a major cause of morbidity and mortality worldwide, particularly among preterm and low birth weight infants. Its pathophysiology is closely linked to immune immaturity, characterized by functional neutrophil deficits, reduced opsonization and complement activity, and a limited adaptive immune response. Once infection is established, an exaggerated inflammatory cascade involving proinflammatory cytokines contributes to endothelial dysfunction, capillary leak, microcirculatory impairment, metabolic acidosis, and ultimately multi-organ failure. These mechanisms are especially severe in premature infants due to their physiological vulnerability. Globally, the incidence of neonatal sepsis has increased over recent decades, although mortality has declined, reflecting advances in clinical care. However, the burden remains disproportionately high in low- and middle-income countries. The epidemiology varies according to timing of onset, with early-onset sepsis commonly caused by Group B *Streptococcus* and *Escherichia coli*, and late-onset sepsis more frequently associated with coagulase-negative staphylococci and Gram-negative organisms. Rising antimicrobial resistance, exacerbated during the coronavirus disease pandemic, further complicates empirical treatment strategies. Clinical presentation is often non-specific, including thermal instability, lethargy, and respiratory distress, which may progress to hypotension, oliguria, and neurological impairment. Diagnosis relies on blood cultures as the gold standard, complemented by laboratory markers such as C-reactive protein and procalcitonin, although limitations in sensitivity persist. Management requires timely empirical antibiotics tailored to gestational age and onset timing, followed by culture-guided adjustment and de-escalation. Comprehensive care includes fluid resuscitation, vasoactive support, respiratory management, metabolic stabilization, and continuous monitoring. Prevention strategies, antimicrobial stewardship, and emerging molecular diagnostics are essential to improve outcomes and address ongoing challenges.

Key words

Immune dysregulation, inflammatory cascade, bacteremia, antimicrobial stewardship, microcirculatory dysfunction, prematurity.

Introduction

The modern conceptualization of neonatal sepsis differs significantly from the definitions applied in pediatric and adult populations. In contrast to older children and adults, where sepsis is primarily defined by the presence of infection associated with organ dysfunction, neonatal sepsis definitions are mainly based on microbiological cultures and clinical signs. This distinction reflects the particular characteristics of the neonatal period, in which the immaturity of the immune system and the frequently non-specific clinical presentation of infection require diagnostic approaches that differ from those used in other age groups [1].

Within this context, the classical criteria based on the systemic inflammatory response syndrome present important limitations when applied to neonates. Although these criteria are commonly used in older populations, they are not directly applicable in the neonatal setting due to the unique physiological responses of newborns and the non-specific nature of sepsis manifestations in this age group. The distinct baseline physiological parameters of neonates and the variability in their inflammatory responses reduce the reliability of systemic inflammatory response syndrome thresholds, reinforcing the need for neonatal-specific considerations [2].

Clinically, neonatal sepsis is classified according to the timing of symptom onset. Early neonatal sepsis, defined as occurring within the first seventy-two hours of life, is typically associated with pathogens acquired during birth, most commonly Group B *Streptococcus* and *Escherichia coli*. However, epidemiological patterns are evolving, and an increasing prevalence of pathogens such as Klebsiella species has been observed in low- and middle-income countries. In contrast, late neonatal sepsis, defined as occurring after seventy-two hours of life, is more frequently linked to hospital-acquired infections, with Coagulase-negative Staphylococcus representing a common etiological agent. Health-care-associated sepsis encompasses infections acquired in medical settings and highlights the importance of infection control measures within healthcare environments [3, 4].

The global burden of neonatal sepsis remains substantial and continues to represent a leading cause of neonatal mortality, particularly in low- and middle-income countries where healthcare resources are limited. The global mortality rate attributable to neonatal sepsis is estimated at approximately 17.6 percent, with higher mortality observed in early-onset cases [5]. Preterm infants and those with low birth weight are at increased risk due to their underdeveloped immune systems, contributing significantly to neonatal morbidity and mortality [2]. Furthermore, both the incidence and outcomes of neonatal sepsis vary significantly according to the level of available healthcare resources, with low- and middle-income countries experiencing a disproportionately higher burden because of limited access to advanced medical care and diagnostic capabilities [5, 6].

The aim of this review is to critically analyze and synthesize the most recent scientific evidence and international clinical guidelines on neonatal sepsis to update its conceptual framework, diagnostic approach, classification, and management strategies, with particular emphasis on epidemiological patterns, antimicrobial therapy, supportive care, and variability across healthcare settings.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of neonatal sepsis based on contemporary evidence and major international clinical guidelines. The review was designed to reconstruct the evolving conceptual framework of neonatal sepsis, integrating advances in immunopathophysiology, epidemiology, microbiological variability, diagnostic strategies, and current therapeutic approaches. Emphasis was placed on the interaction between neonatal immune immaturity, non-specific clinical presentation, limitations of available diagnostic tools, and the need to adapt international recommendations to diverse healthcare settings. Stratification according to gestational age, birth weight, and resource availability was incorporated to enhance clinical applicability. This study was not conducted as a systematic review; therefore, PRISMA flow diagrams and meta-analytic techniques were not applied. Instead, the methodological approach prioritized interpretative synthesis, pathophysiological integration, and clinical relevance.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed publications in English or Spanish published between January 2021 and December 2026. The selected timeframe reflects recent updates in international neonatal sepsis guidelines, advances in molecular diagnostics, antimicrobial stewardship strategies, and evolving definitions of neonatal sepsis. Foundational publications predating this period were included when essential for historical or conceptual context. The search strategy combined Medical Subject Headings and free-text terms using Boolean operators, including: (“neonatal sepsis” OR “early-onset sepsis” OR “late-onset sepsis”) AND (“diagnosis” OR “biomarkers” OR “blood culture” OR “molecular diagnostics”) AND (“management” OR “antibiotic therapy” OR “hemodynamic support” OR “international guidelines”). The initial search identified 214 records. After removal of duplicates and title–abstract screening, 96 articles underwent full-text review. A total of 58 studies met eligibility criteria and were included in the final qualitative synthesis. Study selection and content evaluation were performed independently by two authors, with discrepancies resolved by consensus.

Eligible sources included clinical studies, randomized controlled trials when available, large observational cohorts, meta-analyses, expert consensus statements, and contemporary international guidelines from organizations such as WHO, AAP, and other neonatal societies. Studies were excluded if they were non–peer-reviewed, methodologically insufficient, duplicated, or not directly related to the definition, diagnosis, prognostic assessment, or management of neonatal sepsis. Priority was given to multicenter studies, investigations with robust microbiological confirmation, updated guideline documents, and research addressing resource-limited settings. Extracted variables included study design, population characteristics (gestational age and birth weight), diagnostic criteria, biomarkers evaluated, antimicrobial regimens, supportive care strategies, and reported outcomes such as mortality, treatment response, and complications. Methodological quality and internal validity were assessed narratively, considering study design robustness, risk of bias, consistency of findings, and applicability to diverse clinical environments. Artificial intelligence–based tools were employed exclusively to assist in literature organization, thematic clustering, and structural coherence during manuscript preparation. Critical appraisal of the evidence, verification of sources, and final interpretation were conducted independently by the authors to ensure academic rigor and methodological oversight throughout the development of the review.

Pathophysiological basis and immune response

Neonatal immune immaturity constitutes a central element in the pathophysiology of neonatal sepsis and explains, to a large extent, the increased susceptibility of this population to invasive infections. Neonates, and particularly preterm infants, exhibit a functional deficit in neutrophils, which play a crucial role in the initial immune response to pathogens. This deficit is not limited to reduced circulating numbers but also involves impaired neutrophil function, thereby compromising effective pathogen recognition, phagocytosis, and microbial killing [7, 8].

In addition to neutrophil dysfunction, the neonatal immune system is characterized by decreased opsonization capacity and reduced complement activity, both of which are essential for marking pathogens for destruction and facilitating their clearance. This deficiency is partly attributable to hypogammaglobulinemia, since immunoglobulin A and immunoglobulin M are not transferred across the placenta, and immunoglobulin G transfer occurs predominantly during late gestation [7]. Moreover, the adaptive immune response in neonates remains underdeveloped and relies heavily on innate immune mechanisms. This immaturity results in a limited capacity to mount a robust and coordinated adaptive response to invading pathogens, thereby increasing susceptibility to sepsis and reducing the efficiency of immunological memory formation [8, 9].

Once infection is established, the inflammatory cascade becomes a critical determinant of disease severity. Neonatal sepsis is characterized by overactivation of proinflammatory cytokines, including interleukin-6, interleukin-1 beta, and tumor necrosis factor alpha, which serve as central mediators of the inflammatory response. This excessive cytokine release can culminate in a systemic inflammatory state and contribute to the development of multi-organ dysfunction [10, 11]. Thus, the very mechanisms intended to control infection may paradoxically drive tissue injury when dysregulated. In parallel, endothelial dysfunction plays a pivotal role in the progression of neonatal sepsis. The endothelial glycocalyx, a protective layer lining the interior surface of blood vessels, becomes disrupted during sepsis, leading to structural and functional endothelial impairment. This disruption contributes to increased vascular permeability, which in turn facilitates fluid extravasation and promotes organ dysfunction. The inflammatory response further alters capillary permeability, exacerbating tissue edema and impairing effective oxygen delivery to tissues [12].

Microcirculatory disorders represent another critical component of the septic process. Sepsis-induced alterations in the microcirculation result in tissue hypoperfusion, thereby compromising oxygen and nutrient delivery to vital organs [12]. Impaired perfusion and oxygenation subsequently lead to metabolic acidosis, a frequent complication in septic neonates that further aggravates organ dysfunction and hemodynamic instability. In addition, mitochondrial dysfunction emerges as a downstream consequence of the septic insult, contributing to cellular energy failure and structural damage in affected tissues [11]. These metabolic and cellular disturbances reinforce the progression toward multi-organ failure. The particular vulnerabilities of preterm infants further intensify these pathophysiological mechanisms. Preterm neonates are especially susceptible to bacteremia due to the combined effect of immune immaturity and the high prevalence of invasive procedures in neonatal intensive care units [7]. Furthermore, the immaturity of the cardiovascular system in preterm infants increases the risk of refractory shock, a severe and difficult-to-manage complication of sepsis that is frequently associated with poor outcomes [11].

Epidemiology, risk factors and microbiology

The global incidence of neonatal sepsis has shown a significant increase over recent decades. Between 1990 and 2019, the worldwide incidence rose by 12.79 percent, reaching an estimated 6.31 million cases in 2019. Despite this rise in case numbers, mortality decreased by 12.93 percent during the same period, suggesting meaningful improvements in healthcare interventions and clinical management [13]. Nevertheless, the burden of disease remains unevenly distributed. The incidence is markedly higher in low- and middle-income countries, where rates have reached 3,930 cases per 100,000 live births in the last decade [5].

Recent epidemiological trends further illustrate the dynamic nature of neonatal sepsis. Although mortality rates have declined overall, particularly in regions with a high universal health coverage index, the increase in incidence reflects persistent vulnerability and evolving challenges [3]. The coronavirus disease pandemic has also influenced sepsis patterns, contributing to a shift toward increased late-onset sepsis and heightened antimicrobial resistance. These changes highlight the interplay between global health crises and infection control dynamics within neonatal populations [14].

Maternal and neonatal risk factors play a crucial role in shaping the epidemiology of neonatal sepsis. Conditions such as chorioamnionitis and prolonged rupture of membranes significantly increase the risk of early-onset sepsis. Chorioamnionitis has been associated with an odds ratio of 8.99 for early-onset sepsis, while premature rupture of membranes carries an odds ratio of 1.69 [13]. In addition, prematurity represents a major determinant of vulnerability. Infants born before 37 weeks of gestation exhibit higher mortality rates, particularly when invasive devices are required during neonatal intensive care [14]. Other maternal factors, including infections during pregnancy, cesarean delivery, and maternal antibiotic exposure, have also been associated with an increased risk of early-onset sepsis [15].

The microbiological landscape of neonatal sepsis varies according to the timing of onset. In early-onset sepsis, Group B *Streptococcus* and *Escherichia col*i remain the most commonly identified pathogens. In contrast, late-onset sepsis is more frequently associated with Coagulase-negative Staphylococcus and Gram-negative bacteria, including Klebsiella pneumoniae. These differences reflect distinct transmission pathways and environmental exposures in the perinatal and postnatal periods [16, 17].

Antimicrobial resistance has emerged as a growing and complex concern in the management of neonatal sepsis. Increased resistance to commonly used antibiotics, such as ampicillin and piperacillin, has been reported during the coronavirus disease pandemic, further complicating empirical treatment strategies. Resistance patterns vary significantly according to geographic region and pathogen distribution, necessitating continuous epidemiological surveillance and local data integration into clinical decision-making. The rise of multidrug-resistant organisms within neonatal intensive care units limits therapeutic options and complicates management strategies, particularly in critically ill infants. In this context, effective antimicrobial stewardship programs are essential to contain resistance and improve outcomes. Empirical treatment protocols must be regularly updated in accordance with local resistance profiles to ensure both efficacy and rational antibiotic use [14, 18].

Clinical manifestations and initial assessment

Neonatal sepsis is frequently characterized by a non-specific clinical presentation, which complicates early recognition and timely intervention. One of the most common manifestations is thermal instability, as affected neonates may exhibit either hypothermia or hyperthermia. This abnormal temperature regulation is related to the systemic inflammatory response syndrome, which disrupts autonomic nervous system control and alters physiological homeostasis [11, 19].

In addition to thermal instability, lethargy is a frequent but non-specific symptom of neonatal sepsis. Although it may appear subtle, decreased activity or reduced responsiveness often represents one of the earliest observable signs of systemic infection in clinical practice [6]. Given its non-specific nature, lethargy must be evaluated in conjunction with other clinical findings to avoid delayed diagnosis. Respiratory distress is also commonly observed in septic neonates and is frequently linked to the inflammatory response affecting pulmonary function. This inflammatory involvement may lead to conditions such as pneumonia, thereby contributing to breathing difficulty and compromised oxygenation [11, 20].

As the condition progresses, signs of systemic involvement may become evident. Cardiovascular dysfunction, particularly hypotension, represents a hallmark of systemic commitment in neonatal sepsis. Hypotension often results from the complex interaction between inflammatory mediators and the intrinsic immaturity of neonatal cardiovascular physiology, leading to impaired vascular tone and reduced perfusion [20]. Concurrently, oliguria may develop, reflecting renal involvement and serving as an indicator of evolving multi-organ dysfunction in severe cases. Neurological manifestations, including irritability or seizures, can also occur due to the effects of systemic inflammation on the central nervous system [11].

Given the variability in presentation and the potential for rapid deterioration, risk stratification plays a central role in neonatal sepsis management. Various clinical algorithms and risk assessment tools have been developed to categorize the likelihood of infection by integrating factors such as gestational age, birth weight, and clinical signs [21]. These structured approaches aim to support clinical decision-making and reduce both missed diagnoses and unnecessary treatment. In addition to static risk models, dynamic evaluation through continuous monitoring of vital signs and laboratory markers enhances early detection. Serial assessment of biomarkers such as C-reactive protein and interleukin-6 contributes to a more responsive and individualized management strategy, facilitating timely therapeutic adjustments [19, 22].

Evidence-based diagnosis

Blood cultures remain the gold standard for the diagnosis of neonatal sepsis, as they provide definitive microbiological confirmation of infection. However, their diagnostic performance is frequently limited by the small volume of blood that can be safely obtained from neonates. Because culture sensitivity is directly related to sample volume, increasing the amount of blood collected can improve diagnostic yield, yet practical and ethical considerations often restrict this approach in the neonatal population [23]. In addition to volume constraints, the standard incubation period for blood cultures, typically up to five days, may delay diagnostic confirmation and therapeutic adjustments. This limitation has prompted the exploration of rapid diagnostic methods aimed at shortening time to detection and facilitating earlier clinical decision-making [24].

Alongside microbiological testing, laboratory studies play a complementary role in the diagnostic evaluation of suspected neonatal sepsis. A complete blood count with differential may reveal findings suggestive of infection, such as leukocytosis or a left shift; however, these alterations lack specificity and may be influenced by non-infectious conditions, thereby limiting their standalone diagnostic value. Biomarkers have therefore gained increasing relevance. C-reactive protein is widely used in clinical practice and demonstrates a high negative predictive value, particularly when measured serially within the first thirty-six hours following suspicion of sepsis [25]. Similarly, procalcitonin has shown high sensitivity for neonatal sepsis, with a suggested cut-off value of 0.5 ng/mL to optimize sensitivity, although specificity remains variable. Procalcitonin measurements are especially useful in guiding decisions regarding the discontinuation of antibiotic therapy [26, 27]. Serum lactate levels may also provide clinically relevant information, as elevated concentrations can indicate tissue hypoperfusion and are associated with sepsis; nevertheless, lactate elevation is not specific and may occur in other pathological conditions [23].

In response to the limitations of conventional methods, molecular techniques have been increasingly investigated to enhance diagnostic accuracy and timeliness. Multiplex polymerase chain reaction assays targeting specific pathogens, such as Group B *Streptococcus* and *Escherichia coli*, can be applied to blood culture media to identify infections even in cases with negative culture results, thereby enabling more rapid diagnosis [24]. Furthermore, metagenomic next-generation sequencing offers comprehensive pathogen detection by simultaneously identifying bacteria, viruses, fungi, and parasites in a single test. Despite its broad diagnostic potential, this technology is not yet widely implemented in routine clinical practice [28].

Despite these advances, important diagnostic limitations persist. Traditional methods, including blood cultures, exhibit low sensitivity, particularly in the early stages of infection, which may contribute to delayed diagnosis and treatment initiation. Interpretation of diagnostic markers is also more complex in premature infants. For example, procalcitonin levels have different reference ranges in preterm neonates and are physiologically higher shortly after birth, requiring age-specific reference standards to avoid misinterpretation [29].

Updated antimicrobial management

Initial empirical therapy in neonatal sepsis is primarily guided by gestational age and the timing of symptom onset, as these factors are closely linked to the likely spectrum of pathogens. In early-onset sepsis, which commonly involves organisms such as Group B *Streptococcus* and *Escherichia coli*, empirical regimens frequently include ampicillin combined with gentamicin, as these pathogens are generally susceptible to this standard approach. In contrast, late-onset sepsis is more often associated with coagulase-negative staphylococci and other nosocomial organisms, which require broader antimicrobial coverage. In these cases, antibiotics such as vancomycin and cefotaxime are commonly considered to address the higher likelihood of resistant hospital-acquired pathogens [4, 18].

The distinction between early- and late-onset sepsis is therefore not merely chronological but also microbiological and epidemiological. Early-onset sepsis typically occurs within the first seventy-two hours of life and is frequently linked to maternal transmission, whereas late-onset sepsis develops after seventy-two hours and is more strongly associated with healthcare-related exposures. Because the pathogen spectrum and resistance profiles differ significantly between these two entities, the choice of empirical therapy must reflect these variations to ensure adequate initial coverage [4, 30].

Once microbiological identification and antimicrobial susceptibility results become available, therapeutic adjustment is essential. Culture-based modifications allow clinicians to tailor treatment to the specific pathogen, thereby reducing unnecessary exposure to broad-spectrum agents. This process is closely linked to antibiotic de-escalation strategies, which involve narrowing the antimicrobial spectrum according to culture findings. De-escalation is a key component in minimizing the development of antimicrobial resistance and reducing the risk of adverse drug effects, while maintaining effective infection control [18, 23].

The duration of antibiotic therapy varies depending on microbiological confirmation and clinical evolution. In confirmed sepsis, treatment typically ranges from seven to fourteen days, with the exact duration influenced by the causative pathogen and the neonate's clinical response. In contrast, when sepsis is suspected but blood cultures remain negative, a shorter course of therapy, often five to seven days, may be considered to limit unnecessary antibiotic exposure and reduce the risk of antimicrobial resistance and other complications [31].

Within this framework, antimicrobial optimization programs play a fundamental role in improving outcomes and preserving antibiotic efficacy. Antimicrobial stewardship initiatives aim to prevent resistance by promoting judicious antibiotic use and reinforcing infection control practices [18, 30]. Furthermore, therapeutic individualization based on patient-specific risk factors and local resistance patterns allows for more precise and effective management. Personalized regimens help optimize treatment outcomes while minimizing unnecessary antibiotic exposure, thereby balancing efficacy with long-term sustainability in neonatal care settings [23].

Hemodynamic support and comprehensive management

Fluid resuscitation in neonatal sepsis requires a carefully balanced approach to restore adequate perfusion while avoiding fluid overload, which may exacerbate capillary leak and worsen clinical outcomes. Crystalloids are preferred for initial resuscitation, and the use of balanced solutions is recommended to minimize the risk of hyperchloremia and metabolic acidosis [32, 33].

Particular caution is necessary in premature infants, whose immature renal function and fragile cerebral vasculature increase the risk of complications such as intraventricular hemorrhage. In this population, fluid therapy should be individualized and guided by hemodynamic parameters to avoid both under-resuscitation and excessive volume administration. Tailoring fluid management according to the infant's physiological status is essential to optimize outcomes while minimizing iatrogenic harm [34, 35].

When fluid resuscitation alone is insufficient to maintain adequate perfusion, vasopressors and inotropics become necessary. These agents are indicated in cases of septic shock and play a critical role in stabilizing hemodynamics and improving microcirculatory function [32, 36]. The choice of pharmacological agent depends on the underlying hemodynamic profile. Norepinephrine is frequently used in dopamine-resistant shock and has demonstrated efficacy in improving hemodynamic parameters in preterm neonates [37]. Other inotropes, such as dobutamine and dopamine, are selected based on the specific cardiovascular characteristics of the infant, including myocardial function and systemic vascular resistance [33, 36].

Respiratory support constitutes another fundamental component of comprehensive management. Oxygen therapy is essential to ensure adequate tissue oxygenation and should be titrated carefully to maintain appropriate oxygen saturation levels. In more severe cases characterized by respiratory distress or failure, mechanical ventilation may be required. Ventilatory strategies must be individualized to provide sufficient gas exchange while minimizing the risk of ventilator-induced lung injury [21].

Metabolic management is equally important in neonatal sepsis. Maintaining normoglycemia is critical, as both hyperglycemia and hypoglycemia have been associated with adverse outcomes. Continuous glucose monitoring and, when necessary, insulin therapy may be required to achieve stable glycemic control. In addition, electrolyte disturbances are common in septic neonates and should be promptly corrected. Regular monitoring and timely adjustment of electrolyte levels are necessary to prevent further complications and maintain physiological stability [21].

Continuous monitoring underpins all aspects of supportive care. The infusion of fluids and medications must be closely supervised to ensure accurate dosing and to prevent complications such as fluid overload. Careful assessment of water balance is particularly important in premature infants, who are especially vulnerable to fluid imbalances [35]. Furthermore, biomarkers and clinical parameters, including lactate clearance and capillary refill time, provide valuable information to guide therapy and assess response to treatment, allowing for dynamic adjustment of management strategies [33].

Prevention, guideline recommendations and future perspectives

Intrapartum prophylaxis and the prevention of Group B *Streptococcus* infection represent key strategies in reducing the incidence of early-onset sepsis. Universal maternal screening for Group B Streptococcus combined with intrapartum antibiotic prophylaxis has been shown to decrease the incidence of early-onset sepsis in neonates born at or after 34 weeks of gestation, although its effectiveness is reduced in those born before 34 weeks. Following the widespread implementation of screening programs, the pathogen profile of early-onset sepsis has shifted, with a relative decrease in Group B *Streptococcus* cases and an increased proportion of infections caused by other organisms such as *Escherichia coli* and *Streptococcus bovis* (38). In this context, strict adherence to screening protocols and appropriate timing of antibiotic administration are essential to maximize preventive efficacy and further reduce neonatal sepsis incidence [39].

Within neonatal intensive care units, infection prevention measures are fundamental to limiting the occurrence of late-onset and healthcare-associated sepsis. Hand hygiene and the implementation of structured prevention bundles constitute essential components of infection control strategies in these settings. In addition to preventive measures, efforts are ongoing to improve early diagnosis and management through the use of sepsis risk assessment tools and biomarkers, which may help reduce unnecessary antibiotic exposure while maintaining patient safety [21, 23].

Despite advances in prevention and management, notable variations persist among international guidelines for neonatal sepsis. Differences are observed particularly in recommendations regarding antibiotic selection and duration of therapy [40, 41]. The implementation of structured risk assessment tools, such as the Kaiser Permanente Sepsis Risk Calculator, has demonstrated a significant reduction in antibiotic use when applied alongside established guidelines, including those from NICE [42]. However, guideline adaptation to local epidemiological data and resource availability remains essential to optimize clinical outcomes and ensure context-appropriate care [40].

Several controversies continue to shape the current discourse on neonatal sepsis management. The routine use of biomarkers remains debated due to the absence of a single reliable diagnostic marker capable of accurately distinguishing infected from non-infected neonates [23]. Similarly, the optimal duration of antibiotic therapy remains uncertain, with concerns regarding both overtreatment and the risks associated with insufficient therapy [41]. Fluid therapy strategies also remain under discussion, as no clear consensus has been reached regarding the most effective approach in neonatal sepsis [21].

Looking forward, emerging diagnostic and therapeutic strategies offer promising avenues for improvement. Early molecular diagnostic techniques and precision medicine approaches are being explored to enhance the accuracy and timeliness of diagnosis. At the same time, new antimicrobial strategies, including the development of targeted therapies, are under investigation to address the growing challenge of antibiotic resistance and to improve treatment outcomes in neonatal sepsis [43].

Conclusions

Neonatal sepsis arises from the interplay between immune immaturity and a dysregulated inflammatory response, leading to endothelial dysfunction, microcirculatory impairment, and multi-organ failure, with preterm infants being particularly vulnerable.

Although global mortality has declined, the incidence of neonatal sepsis remains high and unevenly distributed, especially in low- and middle-income countries, where evolving pathogen profiles and increasing antimicrobial resistance pose significant challenges.

Optimal management requires an integrated approach that combines evidence-based diagnosis, timely and individualized antimicrobial therapy, careful hemodynamic support, and strong prevention and stewardship strategies to improve outcomes and address emerging resistance.

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