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# ETIOPATHOGENETIC FEATURES OF NEONATAL SEPSIS: CONTEMPORARY EVIDENCE ON MICROBIAL ETIOLOGY, HOST RESPONSE, AND DIAGNOSTIC STRATEGIES

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## ABSTRACT

Neonatal sepsis remains a major cause of preventable morbidity and mortality, particularly among preterm and very-low-birth-weight infants. This narrative review critically examines contemporary microbial epidemiology, the immature neonatal immune response, endothelial and microcirculatory injury, diagnostic uncertainty, and antimicrobial resistance. Selected systematic reviews and international guidance were synthesized without an exhaustive systematic search or original patient-level analysis. A population-based meta-analysis estimated 28.24 neonatal sepsis cases per 1,000 live births (95% confidence interval [CI] 18.92–41.94), with substantial between-study heterogeneity. A more recent pathogen meta-analysis reported that Gram-negative organisms represented 53% of early-onset and 71% of late-onset isolates in the analyzed samples, challenging overly rigid pathogen assumptions based on timing alone. Blood culture remains essential but is limited by sampling volume and previous antibiotic exposure; inflammatory biomarkers require serial, context-sensitive interpretation. An integrated approach combining clinical surveillance, microbiological evidence, antimicrobial stewardship, and infection prevention is therefore essential. These figures describe published cohorts and must not be interpreted as locally measured data.

**Keywords:** neonatal sepsis; early-onset sepsis; late-onset sepsis; Gram-negative bacteria; innate immunity; antimicrobial resistance; blood culture; inflammatory biomarkers.

## INTRODUCTION

Neonatal sepsis is a life-threatening syndrome in which suspected or confirmed infection is accompanied by systemic illness and potentially progressive organ dysfunction. Its recognition is complicated by nonspecific manifestations, including temperature instability, apnea, respiratory distress, feeding intolerance, lethargy, impaired perfusion, and abnormal glucose homeostasis. Unlike adults, newborn infants have gestation-dependent innate and adaptive immune function, and premature infants frequently require invasive devices and prolonged intensive care. Consequently, sepsis risk reflects interactions between maternal and perinatal exposure, microbial virulence, host developmental biology, and healthcare-associated factors [1–4]. Traditional classification distinguishes early-onset sepsis (EOS), often occurring during the first 72 hours of life, from late-onset sepsis (LOS), usually developing thereafter; some epidemiological definitions use a seven-day EOS boundary. This classification remains operationally useful, but timing is not an adequate surrogate for

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microbiological etiology across all regions. Emerging evidence from lower-resource settings points to substantial Gram-negative involvement even in EOS, requiring empiric prescribing to consider local susceptibility data and the clinical context [2,5].

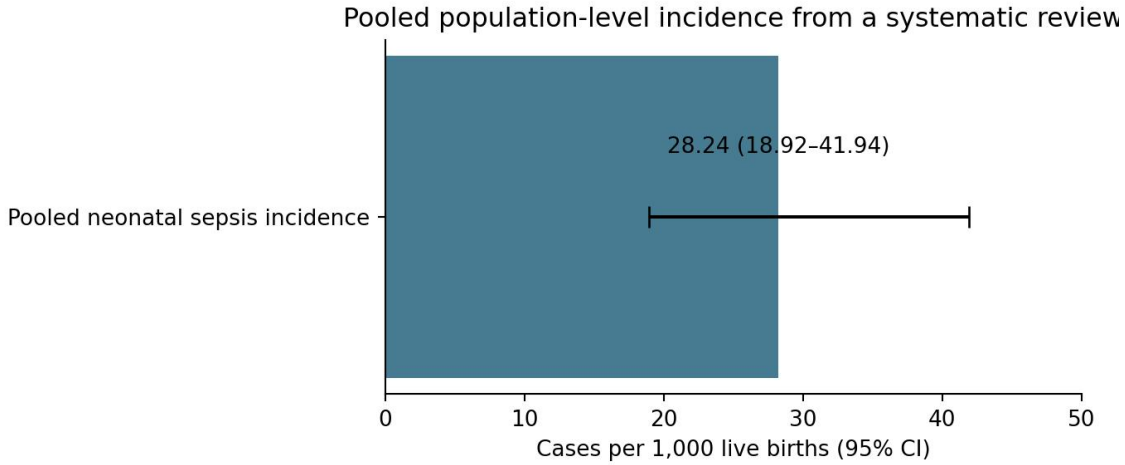
A central conceptual difficulty is the absence of a universally accepted neonatal-specific sepsis definition that integrates microbiological confirmation, systemic inflammatory manifestations, and organ dysfunction. Culture-confirmed infection is more specific but excludes clinically significant culture-negative episodes; conversely, broad clinical definitions risk misclassifying noninfectious instability. For this reason, interpretation of reported incidence and mortality must account for whether investigators used culture-confirmed, clinically suspected, or treatment-based case definitions [1–3].

## MATERIALS AND METHODS

A focused narrative synthesis was prepared from international clinical guidelines, systematic reviews, major neonatal infection studies, and mechanistic literature. Priority was given to sources addressing pathogen distribution, neonatal immune dysregulation, clinical diagnostics, prevention, and antimicrobial resistance. This is not a PRISMA systematic review: no exhaustive database retrieval, risk-of-bias scoring, pooled reanalysis, or original neonatal cohort was performed. Numerical estimates reproduced below are explicitly attributed to the respective published investigations.

## RESULTS

The systematic review by Fleischmann and colleagues, drawing on 26 studies and nearly 2.8 million live births, estimated a pooled neonatal sepsis incidence of 2,824 per 100,000 live births (28.24 per 1,000; 95% CI 18.92–41.94) and case fatality of 17.6% (95% CI 10.3–28.6%). These estimates are affected by differences in case definitions, surveillance quality, health-system setting, and the inclusion of clinical rather than exclusively culture-confirmed sepsis. They should not be directly generalized to individual neonatal intensive care units or to Uzbekistan without local surveillance [1].



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Figure 1. Published pooled neonatal sepsis incidence with 95% CI, converted from cases per 100,000 to cases per 1,000 live births. Source: Fleischmann et al. [1]. Not original study data.

EOS may follow ascending maternal infection or intrapartum transmission, while LOS may arise from the postnatal environment, central vascular access, respiratory support, or prolonged hospitalization. Group B Streptococcus and Escherichia coli remain important in many high-income settings, whereas Klebsiella spp., E. coli, and other Gram-negative organisms have prominent roles in several low- and middle-income settings. Coagulase-negative staphylococci are frequently isolated in neonatal units but require careful discrimination between true bloodstream infection and specimen contamination [2,5–8].

A 2024 systematic review of 48 articles, incorporating 757,427 blood and cerebrospinal fluid samples from 311,359 neonates in 25 countries, reported Gram-negative organisms among 53% of EOS and 71% of LOS isolates in its analyzed datasets. These proportions reflect the reviewed samples and study inclusion criteria; they are not population-level incidence estimates and do not imply identical distributions across hospitals [5].

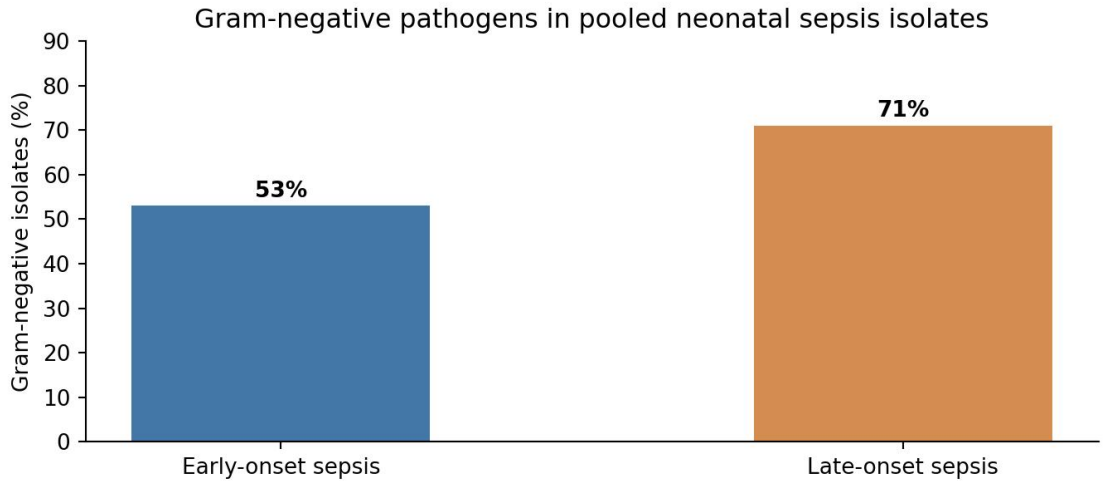



Figure 2. Proportion of Gram-negative isolates in early- and late-onset neonatal sepsis reported in a 2024 systematic review [5]. Literature-derived proportions, not measurements from the present author.

Table 1. Etiological and clinical contrasts relevant to neonatal sepsis

| Domain | Early-onset sepsis | Late-onset sepsis |
|---|---|---|
| Typical onset | First 72 h (definitions vary) | After 72 h to day 28 |
| Major exposures | Maternal colonization, intra-amniotic infection, intrapartum exposure | Neonatal unit environment, devices, postnatal exposure |
| Potential pathogens | GBS, E. coli, Klebsiella spp. and others depending on setting | Gram-negative bacilli, S. aureus, coagulase-negative staphylococci, fungi in |

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|---|---|---|
| | | selected high-risk infants |
| Interpretive caution | Timing alone cannot determine pathogen | Positive skin-commensal culture requires clinical correlation |

The distinction between vertically acquired and healthcare-associated infection has direct implications for prevention and surveillance. Maternal fever, suspected intra-amniotic infection, prolonged rupture of membranes, prematurity, and inadequate intrapartum prophylaxis may modify EOS probability, whereas duration of central venous catheterization, parenteral nutrition, prolonged ventilation, and antibiotic selection pressure can influence LOS risk. These exposures should be analyzed as potential confounders rather than treated as interchangeable causal determinants [2,7,8,14].

Neonatal susceptibility arises from immature epithelial and mucosal barriers, reduced complement activity, limited neutrophil reserve and chemotaxis, developmentally distinct monocyte signaling, and variable maternal antibody transfer. Preterm birth further reduces passive immunoglobulin acquisition and exposes the infant to interventions that disrupt protective barriers. Pathogen-associated molecular patterns stimulate pattern-recognition receptors, including Toll-like receptors, activating inflammatory mediators such as IL-1β, IL-6, and TNF-α. Although these pathways are required for pathogen clearance, an excessive or poorly regulated response can contribute to endothelial activation, capillary leak, impaired microcirculation, and organ injury [3,4,9–11]. The pathophysiology is not limited to a simplistic "cytokine storm." Neonates may display simultaneous inflammatory activation and immune hyporesponsiveness, influenced by gestational age, microbial burden, antecedent antibiotic exposure, and underlying illness. Microvascular dysfunction, altered coagulation, mitochondrial stress, and tissue hypoxia may contribute to shock and multi-organ impairment. Distinguishing infection-driven systemic inflammation from respiratory distress syndrome, hypoxic-ischemic injury, or noninfectious neonatal conditions is therefore crucial [4,9–11].

At the tissue level, pathogen recognition activates interconnected innate immune pathways and may disturb the balance between protective antimicrobial responses and collateral host injury. Endothelial glycocalyx disruption, vascular permeability, dysregulated leukocyte trafficking, and coagulation activation can contribute to circulatory instability. In premature neonates, baseline physiological immaturity complicates interpretation of these responses; therefore, biomarkers measured at a single time point cannot reliably distinguish a transient inflammatory signal from evolving systemic infection [3,4,9].

Blood culture obtained before antibiotics, when this does not delay urgent treatment, remains a cornerstone of etiological confirmation and susceptibility testing. Adequate blood volume and meticulous aseptic technique improve yield. A negative culture does not invariably exclude infection, especially after maternal or neonatal antibiotic exposure. Serial clinical examination is indispensable; C-reactive protein and procalcitonin can support reassessment but are not sufficiently specific to establish neonatal sepsis independently. Procalcitonin is also affected by physiological postnatal changes, while leukocyte indices have limited standalone discriminatory value [2,6,7,12].

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Table 2. Diagnostic methods and interpretation limitations

| Assessment | Clinical contribution | Major limitation |
|---|---|---|
| Blood culture | Identifies pathogen and susceptibility | Low volume, prior antibiotics, contamination |
| CRP (serial) | Supports trend assessment and stopping decisions | Delayed rise; noninfectious elevation |
| Procalcitonin | May aid serial evaluation | Physiological neonatal rise; contextual cutoffs |
| CBC / neutrophil indices | Adds hematological context | Low sensitivity or specificity alone |
| Molecular assays | Potentially faster pathogen identification | Cost, contamination, lack of full susceptibility information |
| Clinical reassessment | Detects deterioration and response | Symptoms may overlap with noninfectious disease |

A rigorous diagnostic strategy should document the time of symptom onset, gestational and postnatal age, maternal antimicrobial exposure, prior neonatal antibiotics, blood volume cultured, number of positive specimens, and time to culture positivity. The decision to obtain cerebrospinal fluid or other specimens depends on clinical stability, suspected meningitis, and local neonatal protocols. Where biomarkers are used, repeated values should be interpreted alongside the trajectory of respiratory support, hemodynamics, perfusion, and feeding tolerance rather than through isolated universal thresholds [2,6,7,12].

Increasing resistance among Enterobacterales and other hospital-associated pathogens threatens the reliability of standard empiric regimens. Antimicrobial choice must reflect the infant's severity, infection timing, suspected source, regional epidemiology, and available susceptibility profiles rather than a universal regimen. The 2024 WHO guidance for serious bacterial infections in infants aged 0–59 days and NICE neonatal infection guideline provide evidence-based frameworks, but local adaptation and neonatal specialist oversight remain necessary [6,12,13]. The central stewardship challenge is balancing the potentially catastrophic consequences of delayed treatment in a genuinely infected neonate against the harms of unnecessary broad-spectrum antibiotic exposure. Appropriate strategies include timely cultures, prompt therapy when clinically indicated, regular reassessment, narrowing according to organism identification and susceptibility, and discontinuation when infection becomes unlikely in accordance with local protocols. Infection-prevention measures—hand hygiene, aseptic vascular-access care, maternal infection prevention, and appropriate device removal—are equally central [6,12–15].

Table 3. Practical priorities for clinical and research programs

| Priority | Rationale | Suggested measurable endpoint |
|---|---|---|
| Local microbiological surveillance | Empiric regimens require site-specific evidence | Pathogen and resistance distribution by EOS/LOS |

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| Standardized blood culture sampling | Reduces false-negative and contaminated results | Culture volume, contamination rate |
| Serial assessment protocol | Limits prolonged unnecessary antibiotic use | Antibiotic days per 1,000 patient-days |
| Device-related infection prevention | Reduces healthcare-associated transmission | Central-line-associated bloodstream infection rate |
| Prospective outcome tracking | Clarifies burden and case-mix differences | Culture-confirmed sepsis, mortality, length of stay |

An additional challenge is the ecological relationship between antibiotic consumption and resistance. Broad-spectrum exposure can alter neonatal intestinal microbial communities and select resistant organisms, particularly in units with sustained antimicrobial pressure. Nevertheless, immediate adequate treatment remains essential when severe infection is suspected. This tension supports protocolized reassessment at predefined intervals and multidisciplinary stewardship involving neonatologists, microbiologists, infection-prevention personnel, and pharmacists [6,12,14,15].

## DISCUSSION

The combined literature suggests that neonatal sepsis should be conceptualized as an interaction among microbial ecology, immune development, and healthcare exposure rather than a single homogeneous disease. The 2024 pathogen meta-analysis challenges assumptions that Gram-positive bacteria necessarily dominate EOS or that timing alone can dictate empirical treatment. Conversely, the large heterogeneity in pooled incidence and mortality indicates that global summaries must be interpreted cautiously when designing local protocols. Neither culture positivity nor inflammatory biomarkers alone can substitute for integrated bedside judgment [1,2,5,12]. Future studies in regional neonatal units should prospectively record gestational age, birth weight, maternal risk factors, timing of infection, prior antibiotic use, culture sampling volumes, organism identity, susceptibility, organ dysfunction, and short-term outcomes. Harmonized definitions and stratification by prematurity are essential to distinguish true epidemiological variation from diagnostic artifacts. Studies of IL-6, procalcitonin, and emerging molecular biomarkers may be valuable, but their incremental predictive performance should be validated against clinically meaningful outcomes rather than assessed solely through case-control discrimination [3,4,9].

The principal limitations of the present review are its narrative, non-systematic design and reliance on heterogeneous international datasets. The included incidence and pathogen proportions are not directly comparable because they arise from different denominators, geographic distributions, case definitions, and sampling strategies. The figures and tables are intended to clarify published evidence and diagnostic priorities; they do not constitute a local epidemiological survey or proof of the effectiveness of any specific intervention. Prospective multicenter neonatal surveillance in Uzbekistan would be necessary to estimate setting-specific etiological patterns and antimicrobial susceptibility.

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## CONCLUSION

Contemporary neonatal sepsis is characterized by heterogeneous microbial causes, developmentally specific host responses, and substantial diagnostic uncertainty. Recent international evidence highlights the importance of Gram-negative pathogens in both early- and late-onset infection and the growing relevance of antimicrobial resistance. Accurate microbiological sampling, repeated clinical evaluation, locally informed antimicrobial decisions, and robust infection prevention are the foundations of rational care. Further prospective, setting-specific research is needed to establish reliable etiological profiles and to evaluate whether integrated clinical and laboratory algorithms improve neonatal outcomes.

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