

Necrotizing Enterocolitis and Neonatal Sepsis: Mechanisms, Biomarkers and Therapeutic Prospects

Jianping Xie^{1,2}, Zhaoran Zhang^{1,2}, Li Zhang^{2,*}

¹Department of Graduate Affairs, Xi'an Medical University, Xi'an 710000, Shaanxi, China

²Department of Neonatology, Northwest Women's and Children's Hospital, Xi'an 710061, Shaanxi, China

*Correspondence Author

Abstract: Necrotizing enterocolitis (NEC) and neonatal sepsis are two major causes of mortality and severe complications in preterm infants, which overlap significantly in timing, at-risk populations, and long-term outcomes. This review systematically examines the epidemiological, pathogenic, and biomarker overlaps between NEC and sepsis, and summarizes current treatment and prevention strategies. Additionally, NEC survivors face long-term complications including intestinal strictures, short bowel syndrome, and neurodevelopmental impairment—all significantly worsened by concurrent sepsis. Early clinical differentiation remains challenging. Future research should accelerate validation of multi-omics biomarkers, advance intelligent diagnostic tools, and explore targeted immunomodulatory interventions to improve long-term outcomes.

Keywords: Necrotizing enterocolitis, Neonatal sepsis, Preterm infants, Very low birth weight infants, TLR4 signaling pathway, Biomarkers.

1. Introduction

Necrotizing enterocolitis (NEC) is one of the most severe gastrointestinal emergencies in preterm infants, characterized by inflammation, ischemia, and necrosis of the small intestine and colon, with rapid progression to intestinal perforation, peritonitis, and sepsis [1,2]. The incidence of NEC in live births ranges from 0.5% to 5%, with an incidence of 7% to 10% in very low birth weight (VLBW) infants, and overall mortality rates of 23% to 30% [3]. The incidence of neonatal sepsis in the general population ranges from 2 to 202 per 100,000 live births, with mortality rates of 11% to 19%. As a leading cause of death and severe complications in preterm infants, sepsis is clinically closely intertwined with NEC [4].

The core clinical challenge lies in the substantial overlap of early manifestations between NEC and sepsis—including abdominal distension, apnea, and hemodynamic instability. Furthermore, NEC-induced intestinal barrier disruption can trigger bloodstream infections, while the systemic inflammatory response elicited by sepsis can exacerbate intestinal ischemic injury. 2025, a retrospective case-control study demonstrated that infants with sepsis had a significantly elevated risk of developing NEC (OR=3.02, P=0.002), with a sepsis incidence of 60.81% in the NEC group compared to 33.78% in the control group [5]. This association makes early differentiation extremely difficult and frequently delays precise intervention.

This review aims to delineate the intrinsic relationship between NEC and neonatal sepsis, covering epidemiological associations, pathogenic mechanisms, biomarkers, and clinical management strategies, with the goal of facilitating early recognition and tailored interventions.

2. Epidemiological Association Between NEC and Sepsis

2.1 Overlap in Incidence and Time Windows

NEC and neonatal sepsis exhibit significant epidemiological

overlap. Duess et al. reported that neonates with advanced or surgical NEC (Bell stage III) were twice as likely to develop culture-positive bacteremia compared to those with suspected or medical NEC [6]. Liu et al. further confirmed a sepsis incidence of 60.81% in the NEC group, significantly higher than the 33.78% in the control group [5].

Regarding timing, both conditions share a highly consistent window of onset. Perez et al. reported a late-onset sepsis (LOS) incidence of 20% in extremely preterm infants, while early-onset sepsis (EOS) occurred in 6% [7]. Adams and Bassler noted that the peak incidence of LOS occurs between postnatal days 10 and 22 [8], overlapping substantially with the peak onset of NEC, which typically occurs at 2 to 4 weeks of life. This temporal concordance suggests common pathological triggers.

2.2 Bidirectional Risk Factor Validation

Numerous studies confirm a bidirectional risk relationship between sepsis and NEC. Liu et al. found that neonatal sepsis significantly increased NEC risk (OR=3.02, P=0.002), with EOS accounting for a significantly higher proportion in the NEC group than in the non-NEC group (57.78% vs. 4.00%, P<0.001) [5]. Feng et al. further demonstrated that EOS is an independent risk factor for NEC-related surgical intervention (OR=3.853) and mortality (OR=5.017) [9].

Conversely, NEC itself serves as an important source of secondary bloodstream infections. Duess et al. noted that NEC-induced intestinal mucosal injury facilitates bacterial translocation into the bloodstream, triggering NEC-associated sepsis [6]. Su et al. confirmed in a meta-analysis that sepsis is a significant risk factor for NEC (OR=4.34) [10]. Zhao et al., in a Chinese preterm cohort, similarly identified sepsis as a risk factor for NEC (OR=3.91) [11].

2.3 Additive Impact on Prognosis

The prognostic impact of NEC complicated by sepsis far exceeds that of either disease alone. Feng et al. demonstrated that NEC infants with concurrent EOS had significantly

higher rates of surgery (67.35% vs. 22.45%) and mortality (29.59% vs. 8.16%) compared to those without EOS [9].

Regarding complications, Feng et al. found that NEC with concurrent EOS was associated with higher inflammatory marker levels, lower platelet counts, and increased incidence of hypoalbuminemia, shock, and coagulopathy [9]. These infants required more hemodynamic support, more frequent mechanical ventilation, and greater vasopressor use. Adams and Bassler noted that both LOS and NEC independently increase the risk of late death or survival with neurosensory impairment in extremely preterm infants [8]. Advanced NEC can precipitate sepsis, which in turn amplifies intestinal and remote organ injury through systemic inflammation, leading to massive inflammatory mediator release and multi-organ dysfunction, ultimately increasing mortality risk [6].

2.4 High-Risk Overlapping Populations

The high-risk populations for NEC and sepsis substantially overlap, primarily comprising:

1) Prematurity and very low birth weight: Adams and Bassler noted that the risk of LOS or NEC is inversely proportional to gestational age [8]. Perez et al. reported that approximately one-quarter of extremely preterm infants have at least one positive blood culture [7]. Balis et al., in a meta-analysis, found a 3.43-fold increased NEC risk with VLBW [12].

2) Severe NEC (Bell stage III): Duess et al. noted that infants with Bell stage III NEC were twice as likely to develop culture-positive bacteremia as those with early-stage NEC [6].

3) Invasive therapeutic exposure: Adams and Bassler systematically described how central venous catheters, mechanical ventilation, and other invasive procedures significantly increase infection risk [8]. Perez et al. also highlighted that extremely preterm infants face higher LOS risk due to immune immaturity, high central line utilization, and extensive invasive procedure requirements [7].

4) Broad-spectrum antibiotic exposure: Duess et al. identified prolonged antibiotic use as a NEC risk factor, potentially related to antibiotic-associated microbiome disruption [6]. Zhao et al.'s meta-analysis confirmed antibiotic exposure as a NEC risk factor (OR=2.12) [11].

5) Other clinical characteristics: Su et al. identified low birth weight (OR=3.00), small for gestational age (OR=1.85), congenital heart disease (OR=2.73), respiratory distress syndrome (OR=2.12), and pneumonia (OR=4.07) as NEC risk factors [10]. Zhao et al. further identified neonatal asphyxia (OR=2.46), respiratory failure (OR=7.51), and severe anemia (OR=2.86) [11].

3. Shared Pathogenic Mechanisms

3.1 Intestinal Barrier Disruption and the “Gut-Blood” Pathway

The integrity of the intestinal mucosal barrier depends on multiple defense layers, including the mucus layer, epithelial tight junctions, and antimicrobial peptides, as systematically

reviewed by Managlia et al. [13]. Bein et al. further demonstrated that in NEC preterm infants, mRNA expression of ZO-1, Occludin, Cingulin, and Claudin-4 is significantly downregulated in intestinal epithelium compared to controls, with ZO-1 and Occludin protein expression markedly reduced in jejunum and ileum, and the degree of downregulation positively correlated with the severity of intestinal injury [14]. Bergmann et al., in a neonatal NEC mouse model (formula feeding combined with hypoxia-cold stress), detected pathological increases in intestinal permeability prior to histological intestinal injury (12 hours after model induction). This early barrier dysfunction was closely associated with abnormal tight junction protein distribution, characterized by translocation of Claudin-4 and Occludin from cell membranes to cytoplasm, and increased tight junction length [15].

Barrier disruption opens the gateway for bacterial and product translocation. Duess et al. revealed that NEC-induced intestinal barrier disruption initiates the key step in transitioning from localized intestinal pathology to systemic infection—namely, bacterial translocation into the bloodstream. This process directly triggers bacteremia, induces systemic microcirculatory dysfunction, and promotes excessive inflammatory responses, establishing the pathological foundation for sepsis and multi-organ failure [6].

3.2 TLR4 Signaling: Central Hub, Amplification Cascade

Following intestinal barrier compromise and bacterial product entry, activation of the TLR4 signaling pathway serves as the central hub linking localized intestinal necrosis to systemic sepsis. Scheese et al. explicitly articulated this concept in their review [16], and Duess et al. also emphasized TLR4's critical role in NEC pathogenesis [6].

Scheese et al. found that TLR4 expression in preterm infant intestinal epithelium is significantly higher than in term infants [16]. Huang et al. reported that MD2 (a key TLR4 accessory protein) is markedly upregulated in intestinal tissue during acute NEC [17]. Huang et al. further demonstrated that upon binding of translocated lipopolysaccharide (LPS) to the MD2-TLR4 complex, a signaling cascade is initiated, recruiting MyD88 and activating NF- κ B [17]. Scheese et al. noted that this process simultaneously drives two pathological pathways: locally in the intestine, TLR4/NF- κ B activation induces inducible nitric oxide synthase and pro-apoptotic factors, leading to extensive intestinal epithelial cell death through apoptosis and necroptosis [16]; systemically, it releases large quantities of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β) [5,6,16]. Yazji et al. demonstrated that TLR4 activation in endothelial cells reduces endothelial nitric oxide synthase expression, leading to mesenteric vasoconstriction and intestinal ischemia [18]. Duess et al. concluded that this synergistic effect of “local tissue destruction plus systemic inflammatory storm” rapidly amplifies intestinal inflammation into systemic sepsis [6].

3.3 The Dual Dilemma of Hyperinflammation and Immunoparalysis

The immune system in NEC presents a complex state of disequilibrium—local intestinal hyperinflammation

coexisting with systemic immunosuppression. Duess et al. provided a detailed description of this phenomenon [6], and Ren et al. observed similar findings in a porcine model [19].

At the local intestinal level, Scheese and Duess et al. found that TLR4 signaling drives extensive infiltration of Th17 cells, while the proportion of regulatory T cells (Tregs) with anti-inflammatory functions in the intestinal lamina propria is significantly reduced. This Treg depletion weakens the restraint on excessive inflammation, further exacerbating local tissue injury [6,16]. Ma et al. demonstrated that in the NEC inflammatory microenvironment, IL-6 drives CCR9⁺ Treg polarization toward IL-17-producing Tregs (IL-17⁺ Tregs). Although these cells retain some Treg phenotypic characteristics, their immunosuppressive function is significantly impaired, and they acquire pro-inflammatory properties, further exacerbating the intestinal Treg/Th17 immune imbalance and promoting NEC progression. Blockade of IL-6 signaling reversed this transformation and attenuated intestinal injury [20].

Concurrently, Ren et al., in a preterm porcine model, found that NEC lesions (even subclinical lesions) induce systemic immunosuppression, characterized by increased peripheral Treg frequency, decreased neutrophil phagocytic function, downregulation of genes associated with innate immunity and Th1 polarization, and attenuated immune responses to LPS stimulation [19]. Ren et al. proposed that this paradoxical state of “local hyperinflammation and systemic immunoparalysis” may represent a key mechanism predisposing NEC infants to secondary infections and sepsis even before intestinal inflammation is fully controlled [19].

3.4 Gut Microbiome Dysbiosis: Driving Bidirectional Pathology

Gut microbiome dysbiosis serves both as a driver and a consequence of NEC, forming a bidirectional pathological cycle of “dysbiosis → inflammation → further dysbiosis.” Cuna et al. noted delayed colonization and reduced diversity of the preterm infant gut microbiome [21]. Shaw et al. referenced and supported Warner et al.’s findings on pre-NEC dysbiosis, but their own data revealed two distinct patterns of dysbiosis: one characterized by persistent high abundance of Enterobacteriaceae, and another characterized by low-CpG-content organisms such as *Clostridium perfringens* [22]. Based on these findings, Shaw et al. proposed a dual-pathway hypothesis for NEC pathogenesis—one pathway involving LPS-driven TLR4 overstimulation (corresponding to the Enterobacteriaceae-dominant pattern), and another involving insufficient CpG DNA leading to reduced TLR9-mediated inhibition of TLR4 (corresponding to the low-CpG microbial pattern). Both pathways converge to cause NEC through TLR signaling imbalance [22]. Inflammation-induced intestinal mucosal damage further promotes overgrowth of opportunistic pathogens, creating a self-reinforcing vicious cycle.

Furthermore, Kaplina et al. and Duess et al. reported that gut microbiome dysbiosis also involves reduction of short-chain fatty acid-producing anaerobes (e.g., butyrate producers), compromising energy support and immunomodulatory functions for the intestinal epithelium [6,23]. Collectively,

Duess et al. concluded that gut microbiome dysbiosis serves as an upstream event that triggers the TLR4 inflammatory cascade, while simultaneously being exacerbated by inflammation-induced barrier disruption and antibiotic use, continuously driving disease progression [6].

4. Diagnostic Biomarkers: Overlap and Differentiation

4.1 Limitations of Conventional Markers

C-reactive protein (CRP) and procalcitonin (PCT) show non-specific elevations in both NEC and sepsis, offering limited discriminatory value. Celik et al. noted in their review that CRP, as an acute-phase reactant, requires 10 to 12 hours to begin rising after infection and reaches peak levels at 36 to 48 hours, exhibiting significant response lag that hinders early diagnosis [24]. Although PCT responds more rapidly (rising within 2 to 4 hours), Celik et al. emphasized that a physiological elevation occurs at 2 to 4 days postnatally, interfering with EOS diagnosis [24]. Duess et al. also noted that early signs of both NEC and sepsis in preterm infants are subtle and non-specific, making clinical diagnosis extremely challenging [6].

4.2 Novel Markers with Differential Potential

1) Intestinal injury-specific markers: Coufal et al. found that urinary intestinal fatty acid-binding protein (I-FABP) within 12 hours of NEC onset distinguished NEC from sepsis with 81% sensitivity and 100% specificity, outperforming abdominal radiography (41%) [25]. Chen et al. further confirmed that serum I-FABP is significantly elevated in NEC infants, and proposed that combined I-FABP and IL-6 testing improves diagnostic accuracy compared to either marker alone [26]. Cheng et al. demonstrated that serum amyloid A (SAA) is significantly elevated in preterm infants with NEC secondary to LOS (median 145.8 mg/L vs. 54.3 mg/L) and is an independent risk factor [27]. Based on meta-analysis data, Song et al. concluded that SAA has superior diagnostic accuracy to CRP in early neonatal sepsis (0 hours), with a pooled sensitivity of 0.84 versus CRP’s delayed elevation and pooled specificity of 0.89 [28].

2) Infection-specific markers: IL-6 is recognized as an early sepsis biomarker. Kumar et al., in a prospective study of VLBW infants, found that IL-6 detected Gram-negative sepsis or NEC with 100% sensitivity and 78% specificity, but showed no significant elevation in coagulase-negative staphylococcal sepsis [29]. Additionally, Kumar et al. found that soluble tumor necrosis factor receptor-2 (sTNF-2), an IL-1 family receptor, is significantly elevated in NEC and Gram-negative sepsis, potentially reflecting intestinal inflammation and systemic inflammation induced by bacterial translocation [29].

4.3 Multi-Marker Combinations and Intelligent Models

Single markers cannot simultaneously achieve adequate sensitivity and specificity, making combined testing and intelligent modeling promising directions. Ghauri et al. emphasized that a dynamic rising CRP/albumin ratio predicted NEC surgery with an AUC of 0.959 [30]. Cheng et

al. demonstrated that the combination of gestational age, SAA, and hemoglobin decline (ΔHb) predicted NEC secondary to LOS in preterm infants with an AUC of 0.888 (95% CI: 0.810–0.953) [27]. Thibault et al. confirmed that combined fecal lipocalin-2 (LCN2) and calprotectin predicted NEC onset 7 to 10 days prior to diagnosis [31]. Regarding intelligent models, Huang et al., using machine learning, identified four shared immune genes (MAP2K6, CHKA, CA4, and ENTPD7) and constructed a NEC diagnostic model with an AUC of 1.000 and sepsis model with 0.864 [32]. Zhu et al. similarly employed machine learning to identify three necroinflammation-associated biomarkers (DAPK1, PARP1, and BIRC3) [33]. In conclusion, the diagnostic efficacy of single biomarkers is limited, while multi-marker combined testing integrated with machine learning algorithms holds promise for improving early differentiation between NEC and sepsis, thereby enhancing clinical decision-making efficiency.

5. Clinical Management and Therapeutic Strategies

5.1 Current Treatment Approaches

Medical management of NEC centers on intestinal decompression, fasting, fluid resuscitation, and antibiotic therapy. Roberts et al. noted that a unified antibiotic protocol guideline is currently lacking, with significant inter-institutional practice variation [1]. The Bell stage-based stratified antibiotic strategy proposed by Pace et al. represents a currently well-accepted management framework: Bell stage I receives ampicillin plus gentamicin for 48 hours; Bell stage II receives ampicillin plus gentamicin for 5 to 10 days; Bell stage IIIA adds metronidazole; and Bell stage IIIB receives piperacillin/tazobactam for 7 to 14 days [34]. Pace et al. further confirmed that this strategy significantly reduces broad-spectrum antibiotic use without increasing adverse outcomes [34].

5.2 Adjunctive and Emerging Therapies

Pentoxifylline, a phosphodiesterase inhibitor, exerts immunomodulatory effects by inhibiting TNF- α production. Pammi and Haque reported that pentoxifylline as an adjunct to antibiotic therapy reduced in-hospital mortality in neonatal sepsis (RR 0.57) and shortened hospital stays without reported significant adverse effects [35]. Regarding probiotics, Roberts et al., summarizing multiple RCTs, concluded that probiotics may reduce NEC incidence; however, strain selection, dosing, and safety require careful evaluation [1]. In terms of stem cells and growth factors, Mesfin et al. reported that mesenchymal stem cells attenuate intestinal injury and reduce NEC severity in various animal models [36]. Duess et al. also mentioned synthetic amniotic fluid and exosomes showing promise in preclinical studies [6].

5.3 Prevention as Priority

Prevention is the key strategy for reducing the combined burden of NEC and sepsis. Enhanced breastfeeding is the most effective preventive measure—Roberts et al. noted that breast milk inhibits TLR4 signaling through activation of the epidermal growth factor receptor, reducing NEC risk by approximately 4% [1]. Neumann et al., through multi-omics

analysis, demonstrated that supplementation with *Bifidobacterium infantis* requires concurrent breastfeeding (providing human milk oligosaccharides, HMOs) to achieve optimal colonization and protective effects [37]. Regarding standardized feeding protocols, Roberts et al. cited multiple studies indicating that early enteral feeding, breast milk priority, and gradual volume increments significantly reduce VLBW NEC incidence [1]. Pace et al. confirmed that the Bell stage-based management protocol reduces broad-spectrum antibiotic use without increasing adverse outcomes [34]. Additionally, Roberts et al. recommended avoiding unnecessary acid-suppressive medications (e.g., H_2 receptor antagonists and proton pump inhibitors) due to potential NEC risk increases [1]. The combination of these measures to create a protective microenvironment constitutes an important strategy for reducing NEC-sepsis comorbidity.

6. Long-Term Prognosis

Long-term prognosis in NEC survivors is primarily influenced by two categories of outcomes: gastrointestinal structural and functional outcomes, and neurodevelopmental outcomes.

Gastrointestinal outcomes: Intestinal stricture is one of the most common gastrointestinal complications during NEC recovery, with an incidence exceeding 30% (including both medical and surgical cases), predominantly affecting the colon (80%), typically manifesting clinically at 5 to 7 weeks post-NEC, and requiring contrast imaging for diagnosis (with distal loop contrast studies in ostomy patients) [38]. Only symptomatic infants (with obstruction, hematochezia, or growth failure) require surgical resection and anastomosis. Short bowel syndrome occurs in 10% to 30% of surgical patients and is the leading cause of parenteral nutrition dependence and liver disease [38]. However, Mutanen et al. demonstrated that infants with NEC-induced short bowel syndrome achieved earlier parenteral nutrition independence (84% vs. 59% at 5 years) and had lower liver disease rates (37% vs. 87% at 10 years), suggesting that early attainment of intestinal autonomy significantly improves hepatic outcomes [39].

Neurodevelopmental outcomes: NEC is significantly associated with cognitive, motor, and language developmental impairments. Berken et al., in a meta-analysis of 32 studies, confirmed a consistent association between NEC and developmental impairments across cognitive, motor, and language domains in infants and toddlers, with a pooled Bayley Scale effect size of moderate magnitude (SMD=0.43, 95% CI 0.34–0.52), although significant heterogeneity was noted across studies ($I^2=67\%$, $P<0.001$) [40]. Martin et al., in extremely preterm infants, demonstrated a graded relationship between NEC severity and neurodevelopmental risk: medical NEC (with or without bacteremia) showed no significant long-term risk; surgical NEC without bacteremia significantly increased the risk of psychomotor developmental delay ($\text{PDI}<70$, $\text{OR}=2.7$); while surgical NEC with late-onset bacteremia dramatically elevated the risk of spastic diplegia ($\text{OR}=8.4$) and microcephaly ($\text{OR}=9.3$), suggesting that systemic inflammation mediated by intestinal injury is the core driver of brain injury [41]. Ryu et al., using Korean national registry data for VLBW infants ($n=12,839$), further

revealed that single sepsis without NEC was not significantly associated with neurodevelopmental impairment (aOR=0.98), but multiple sepsis episodes (aOR=1.43) or sepsis combined with NEC (aOR=1.91) significantly increased neurodevelopmental impairment risk [42]. Jue et al., in a cohort of 236 preterm infants with stage II–III NEC followed to 1 year corrected age, reported a neurodevelopmental impairment rate of 10.5%, with birth weight <1000 g (OR=4.603), sepsis (OR=4.401), and intestinal perforation (OR=5.239) as independent risk factors [43].

In summary, NEC survivors require multidisciplinary long-term follow-up systems addressing both gastrointestinal functional recovery and neurodevelopmental surveillance to improve long-term quality of life.

7. Conclusions and Future Directions

NEC and neonatal sepsis interact bidirectionally, with combined occurrence significantly elevating surgical rates, mortality, and long-term neurodevelopmental impairment risk. The pathological core lies in intestinal barrier disruption triggering excessive TLR4 pathway activation, with local hyperinflammation coexisting with systemic immunosuppression, while gut microbiome dysbiosis perpetuates this vicious cycle. Current early clinical differentiation remains primarily dependent on conventional markers with limited capacity; novel markers including I-FABP, SAA, and IL-6, along with machine learning models, show promising adjunctive potential. Stratified antibiotic management, pentoxifylline adjunctive therapy, and enhanced breastfeeding are progressively optimizing current management pathways.

Regarding future research, subsequent studies should prioritize large-scale prospective validation of multi-omics biomarkers and intelligent models, further elucidate regulatory mechanisms of TLR4 signaling and immunoparalysis, and accelerate clinical translation of emerging therapies including stem cells and exosomes. Concurrently, standardized long-term follow-up systems covering gastrointestinal and neurodevelopmental outcomes should be established. Whether individualized microbiome modulation can effectively interrupt the comorbid disease cascade requires more robust evidence.

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