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NECROTIZING ENTEROCOLITIS: FROM PATHOPHYSIOLOGY TO MODERN PREVENTION AND EARLY DIAGNOSTIC STRATEGIES

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) is a severe, multifactorial inflammatory disease and a leading cause of gastrointestinal mortality in preterm infants, particularly those with very low birth weight. Despite advances in neonatal care, its pathogenesis, early diagnosis, and effective prevention remain significant clinical challenges.
Objective: This review aims to synthesize current knowledge (2018–2026) on the pathophysiology, diagnostic strategies, and preventive interventions in NEC, with a focus on improving early detection and clinical outcomes.
Methodology: A narrative review of recent scientific literature was conducted, analyzing studies on molecular mechanisms, including immune dysregulation and gut microbiota, as well as advances in diagnostic tools and nutritional prevention strategies.
Results: Contemporary evidence indicates that NEC arises from an exaggerated immune response mediated by Toll-like receptor 4 (TLR4) in the immature intestine, compounded by gut dysbiosis and hypoxic factors, as described in the "two-hit" hypothesis. Diagnostic approaches are shifting from reliance on the Bell classification toward multi-modal strategies integrating abdominal ultrasound and biomarkers such as C-reactive protein. Preventive measures, particularly the use of human milk, human milk oligosaccharides, probiotics, and standardized feeding protocols, significantly reduce disease incidence and severity.
Conclusions: NEC management is evolving toward a proactive, precision-based model that integrates early diagnosis with targeted nutritional and microbiome-based interventions. These strategies offer substantial potential to reduce mortality and long term complications in this vulnerable population.

KEYWORDS

Necrotizing Enterocolitis, Preterm Infants, Gut Dysbiosis, Biomarkers, Abdominal Ultrasound, Human Milk, Human Milk Oligosaccharides (HMOs), Probiotics, Standardized Feeding Protocols

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1. Introduction

1.1. Definition and Historical Context

Necrotizing enterocolitis (NEC) remains one of the most formidable and unpredictable challenges in modern perinatal medicine. As an acquired inflammatory disorder characterized by intestinal ischemia and transmural necrosis, NEC is the leading cause of gastrointestinal related mortality in Neonatal Intensive Care Units (NICUs) (Rich and Dolgin, 2017). While clinical descriptions of conditions resembling intestinal necrosis in neonates date back to the 19th century, it was the rapid advancement of neonatological care in the latter half of the 20th century that led to the formal identification of this clinical entity. Paradoxically, the successes in improving the survival rates of extremely preterm infants (born before 24 weeks of gestation) have increased the population of high-risk patients, ensuring that NEC remains what is frequently termed a "neonatological enigma" (Rich and Dolgin, 2017).

1.2. Epidemiology and Clinical Burden

Epidemiological data indicate a strict correlation between physiological immaturity and the incidence of NEC. The condition affects between 5% and 10% of infants with very low birth weight (VLBW, <1500 g) (Rich and Dolgin, 2017). In contrast, NEC occurs rarely in full-term neonates approximately 10% of all cases and is typically associated with underlying comorbidities such as congenital heart disease or perinatal hypoxic-ischemic episodes (Rich and Dolgin, 2017).

The mortality rate associated with NEC remains alarmingly high, ranging from 20% to 30%, with rates soaring toward 50% in cases requiring surgical intervention (Rich and Dolgin, 2017). Beyond the immediate

threat to life, NEC imposes a profound socioeconomic burden. Survivors often face long term sequelae that extend "beyond the gut" (Meister et al., 2020), including:

- Short Bowel Syndrome (SBS): Resulting from extensive resection of necrotic intestinal segments, leading to intestinal failure (Rich and Dolgin, 2017).
- Neurodevelopmental Impairment: Survivors demonstrate significantly lower neurodevelopmental scores, suggesting a potent inflammatory gut-brain axis (Meister et al., 2020).
- Intestinal Strictures**:** Occurring as late complications in up to 10-35% of medically managed patients (Rich and Dolgin, 2017).

1.3. Evolution of the Pathophysiological Paradigm For decades, the dominant view was that NEC resulted primarily from ischemic injury. Contemporary molecular research has revised this approach, pointing toward a multifactorial etiology where the focal point is an aberrant immune response of the immature intestinal epithelium triggered by gut dysbiosis (Kaplina et al., 2023). In preterm infants, Toll-like Receptor 4 (TLR4) is overexpressed; its activation triggers a pro-inflammatory cascade, enterocyte apoptosis, and breakdown of the mucosal barrier (Rich and Dolgin, 2017). This "molecular ignition" explains why factors such as formula feeding or empirical antibiotic therapy drastically increase risk (Kaplina et al., 2023).

1.4. Diagnostic and Therapeutic Challenges The primary barrier to managing NEC is the lack of specific diagnostic tools during the critical "therapeutic window." The Bell Classification remains the clinical gold standard despite its reliance on signs that often appear only during advanced tissue damage (Rich and Dolgin, 2017). Modern science aims to shift toward a proactive model based on:

- Molecular Biomarkers: Recent meta-analyses emphasize the predictive role of C-reactive protein (CRP) in diagnosis and prognosis (Cheng et al., 2025).
- Advanced Imaging: Point-of-care abdominal ultrasound (US) is increasingly utilized to assess bowel viability and mesenteric blood flow, often proving more sensitive than traditional radiography (Kim, 2019; Kallis et al., 2023).

1.5. Objective and Scope of the Review

This review provides a synthetic analysis of the most recent scientific literature regarding NEC (2020–2026). It seeks to determine the extent to which modern preventive strategies such as personalized probiotic therapy (De Bernardo et al., 2025), donor human milk (Quigley et al., 2024), and supplementation with Human Milk Oligosaccharides (HMOs) (Sodhi et al., 2023) can reduce incidence and improve the management of this complex disease (Hu et al., 2024).

2. Pathophysiology: Beyond the Ischemic Paradigm

2.1. The Central Role of Toll-Like Receptor 4 (TLR4)

For decades, the pathogenesis of necrotizing enterocolitis (NEC) was attributed primarily to mesenteric ischemia. However, contemporary research suggests that NEC is fundamentally a disease of disrupted innate immunity (Rich and Dolgin, 2017). A pivotal discovery in this field is the overexpression of Toll-like receptor 4 (TLR4) in the premature gut. In utero, TLR4 plays a physiological role in modulating intestinal epithelial cell proliferation and differentiation. However, post-birth, the premature intestine maintains high levels of TLR4, which, when activated by Gram-negative bacteria, triggers a catastrophic inflammatory cascade (Kaplina et al., 2023). This activation leads to the recruitment of pro-inflammatory cytokines, increased enterocyte apoptosis, and a significant decrease in mucosal repair mechanisms. Unlike the mature intestine, which can downregulate TLR4 after initial bacterial exposure, the premature gut remains in a "hyper-responsive" state, leading to the full-thickness necrosis characteristic of the disease (Meister et al., 2020).

2.2. Gut Dysbiosis and Microbial Metabolites

The development of NEC is intricately linked to the colonization patterns of the neonatal gut. Preterm infants often exhibit "dysbiosis" a state characterized by low microbial diversity and a preponderance of opportunistic pathogens (Kaplina et al., 2023). Studies have shown that an expansion of *Proteobacteria* often precedes the clinical onset of NEC.

Furthermore, the role of microbial metabolites has gained significant attention. Short-chain fatty acids (SCFAs), while generally beneficial in adults, can reach toxic levels in the immature gut of a preterm infant, further damaging the mucosal barrier (Kaplina et al., 2023). This disruption of the barrier allows for bacterial translocation, fueling systemic inflammation and potentially affecting organs beyond the gastrointestinal tract, such as the brain and lungs (Meister et al., 2020).

2.3. Hypoxia and the "Two-Hit" Hypothesis

While contemporary research has pivoted significantly toward the immunological and microbiological foundations of necrotizing enterocolitis, the role of hypoxia and mesenteric ischemia remains a critical component of the disease's complex etiology. Modern understanding frames hypoxia not as a solitary cause, but as a synergistic factor within the "Two-Hit" hypothesis (Kaplina et al., 2023; Rich and Dolgin, 2017). In this model, the "First Hit" is represented by the innate vulnerability of the premature infant. This includes an immature intestinal barrier, an overactive TLR4-mediated immune response, and a state of gut dysbiosis often characterized by an overgrowth of *Proteobacteria* and a lack of microbial diversity (Kaplina et al., 2023). This initial state "primes" the intestinal mucosa, leaving it in a hyper-responsive and fragile condition. The "Second Hit" serves as the precipitating trigger that leads to full-thickness necrosis. This trigger often manifests as:

- Hypoxic-Ischemic Events: Episodes of systemic hypotension, congenital heart disease, or perinatal asphyxia can lead to a redistribution of blood flow away from the mesenteric circulation (the "diving reflex"), causing localized tissue hypoxia (Rich and Dolgin, 2017).
- Formula Feeding: Feeding with bovine-based formula can act as a physiological stressor. Unlike human milk, formula lacks protective growth factors and may promote the production of toxic microbial metabolites, such as excessively high levels of short-chain fatty acids (SCFAs), which further damage the hypoxic mucosa (Kaplina et al., 2023; Monzon et al., 2023).

The synergy between these two "hits" explains the clinical observation that NEC often presents with catastrophic suddenness in infants who previously appeared stable (Rich and Dolgin, 2017). When hypoxia occurs in a gut already compromised by dysbiosis, the resulting oxidative stress and impaired microcirculation lead to a rapid breakdown of the epithelial barrier. This allows for bacterial translocation and a systemic inflammatory response that, as Meister et al. (2020) emphasize, impacts not only the gut but also the brain and lungs through a shared inflammatory axis. Thus, the "Two-Hit" hypothesis integrates the classic focus on oxygen delivery with modern molecular biology, suggesting that preventing the "First Hit" (through human milk and probiotics) is just as vital as managing the hemodynamic triggers of the "Second Hit" (De Bernardo et al., 2025; Hu et al., 2024).

3. Beyond Bell's Stages: Modern Diagnostic Paradigms in NEC

3.1. Limitations of Traditional Radiography and the Bell Classification

For decades, the diagnosis of necrotizing enterocolitis (NEC) has relied on the Bell staging system, which categorizes disease severity based on clinical and radiographic findings. Originally proposed in 1978 and later modified, the Bell criteria remain the universal language for clinical staging, yet they are increasingly criticized for their lack of specificity, particularly in the earliest phases of the disease (Rich and Dolgin, 2017). According to the staging established by Bell and modified by Walsh and Kliegman, the disease is divided into three distinct stages based on the severity of clinical and radiographic manifestations (Rich and Dolgin, 2017):

- Stage I (Suspected NEC): Characterized by non-specific systemic signs such as temperature instability, apnea, and bradycardia. Gastrointestinal symptoms include increased gastric residuals, mild abdominal distention, and occult blood in the stool. Radiographic findings are typically normal or show only non-specific intestinal distention (Rich and Dolgin, 2017).
- Stage II (Proven NEC): This stage represents definitive diagnosis. Systemic signs persist, and abdominal tenderness may develop. Key radiographic findings include pneumatosis intestinalis (intramural gas) and potentially portal venous gas. Stage IIB is further characterized by metabolic acidosis and mild thrombocytopenia (Rich and Dolgin, 2017).
- Stage III (Advanced NEC)**:** Reflects critical illness with impending or actual intestinal perforation. Stage IIIA presents with intact bowel but significant clinical deterioration (septic shock, coagulopathy), while Stage IIIB is defined by the radiographic presence of pneumoperitoneum, indicating a ruptured viscus and necessitating urgent surgical consideration (Rich and Dolgin, 2017; De Bernardo et al., 2019).

Despite its widespread use, the Bell criteria often fail to differentiate between NEC and other neonatal conditions like spontaneous intestinal perforation or benign ileus in Stage I (Rich and Dolgin, 2017). Traditional abdominal X-ray (AXR), the cornerstone of this staging system, is useful for detecting definitive signs like pneumatosis intestinalis or portal venous gas but frequently fails to identify early ischemic changes or assess bowel viability (Hörmann et al., 2000; Faingold et al., 2005). The static nature of AXR and its reliance on gas distribution limits its sensitivity, especially in infants with a "gasless" abdomen or those in the hyperacute phase of injury where radiographic signs have not yet materialized (De Bernardo et al., 2019; Kim, 2019). These limitations have catalyzed the search for more dynamic diagnostic paradigms, including advanced ultrasound and novel biochemical markers.

3.2. The Role of Biomarkers: CRP and Beyond

The quest for a reliable biochemical indicator for the early detection of necrotizing enterocolitis (NEC) remains a critical frontier in neonatal intensive care. Because early clinical signs of NEC are often indistinguishable from benign feeding intolerance or late-onset sepsis, biomarkers are essential for identifying the "therapeutic window" before irreversible intestinal necrosis occurs (Rich & Dolgin, 2017). Among these, C-reactive protein (CRP) has long been the most widely used marker in clinical practice, though its lack of specificity rising in response to any systemic inflammation remains a significant limitation (Cheng et al., 2025; Hu et al., 2024). According to a comprehensive meta-analysis by Cheng et al. (2025), CRP remains a valuable, albeit non-specific, tool for predicting both the diagnosis and prognosis of NEC. The study emphasizes that a single elevated CRP value is less informative than serial measurements. Monitoring the inflammatory trend allows clinicians to differentiate between a transient inflammatory response and the progressive, destructive inflammation characteristic of advanced NEC. High or persistently rising CRP levels are strongly correlated with poor clinical outcomes, including the need for surgical intervention and increased mortality (Cheng et al., 2025).

However, modern research highlights that NEC is a multi-organ phenomenon where "it is not all in the gut" (Meister et al., 2020). Consequently, the search for more specific biomarkers has shifted toward molecules directly involved in intestinal injury and the innate immune response:

- Intestinal Fatty Acid-Binding Protein (I-FABP): A small protein located in the cytoplasm of mature enterocytes. It is released into the circulation and excreted in urine immediately upon mucosal injury, potentially offering a more "gut-specific" signal than the systemic CRP response (Rich and Dolgin, 2017).
- Fecal Calprotectin: A marker of neutrophilic infiltration in the intestinal mucosa. While elevated in NEC, its baseline values vary significantly among preterm infants, necessitating careful interpretation (De Bernardo et al., 2025).
- Microbial Metabolites and Cytokines: Emerging evidence suggests that the profile of microbial metabolites and pro-inflammatory cytokines (such as IL-6 and TNF-α) can reflect the severity of gut dysbiosis and hypoxia, providing a more granular view of the disease's molecular progression (Kaplina et al., 2023).

Despite the promise of these novel markers, they are not yet universally available for rapid bedside testing. Therefore, as suggested by De Bernardo et al. (2025) and Hu et al. (2024), the current diagnostic standard of excellence relies on the integration of serial CRP monitoring with clinical staging and advanced imaging like abdominal ultrasound. This multi-modal approach compensates for the individual limitations of any single biomarker, facilitating earlier and more accurate decision-making in suspected cases of NEC.

3.3. Abdominal Ultrasound (AUS) in NEC Diagnostics

While traditional radiography (AXR) remains the clinical baseline, point-of-care abdominal ultrasound (AUS) has emerged as a superior diagnostic tool for evaluating the dynamic nature of necrotizing enterocolitis. According to Kim (2019), the primary advantage of AUS is its ability to directly visualize the bowel wall, mesentery, and peritoneal cavity in real-time, providing critical information that is often missed on static X-ray films.

Key advantages and findings in AUS, as detailed in the provided literature, include:

- Assessment of Bowel Wall Perfusion: Utilizing color Doppler US allows clinicians to assess the viability of the intestinal segments. The presence of hyperemic flow suggests an early inflammatory response, while the absence of flow the "dot sign" is a highly specific indicator of transmural ischemia and impending necrosis (Faingold et al., 2005; De Bernardo et al., 2019).

- Bowel Wall Thickness and Peristalsis: AUS can detect subtle changes in bowel wall thickness (both thickening due to edema and thinning due to advanced ischemia). Furthermore, the observation of absent peristalsis is a functional marker of intestinal distress (Kim, 2019).
- Detection of Fluid and Debris: Ultrasound is highly sensitive in identifying free peritoneal fluid. The presence of echogenic debris within the fluid is a strong predictor of bowel perforation, even when free air is not yet visible on X-ray (Cuna et al., 2018; Kallis et al., 2023).
- Sensitivity in Equivocal Cases: In clinical scenarios where radiographic findings are equivocal or non-specific, AUS provides a higher diagnostic yield. Studies show that AUS can detect pneumatosis intestinalis and portal venous gas with greater sensitivity than traditional AXR, particularly in the early stages of the disease (Kallis et al., 2023; Gwizdała et al., 2013).

A systematic review and meta-analysis by Cuna et al. (2018) confirms that specific ultrasound features, such as bowel wall thinning and the absence of perfusion, are robust predictors of the need for surgical management. This shift toward a multi-modal approach combining clinical staging with high-resolution imaging allows for a more proactive and precise therapeutic intervention (De Bernardo et al., 2019).

3.4. Emerging Diagnostic Horizons

The future of NEC diagnosis lies in the transition from reactive clinical observation to a proactive, multi-modal monitoring system that identifies physiological changes before significant tissue damage occurs. While traditional methods focus on late-stage symptoms, the current research landscape emphasizes the identification of biomarkers and physiological indicators that precede clinical deterioration (Rich and Dolgin, 2017).

Central to these emerging horizons is the concept of the "therapeutic window" the critical period where medical intervention can halt the progression from intestinal distress to irreversible necrosis. De Bernardo et al. (2025) argue that the most effective diagnostic approach involves the real-time integration of three pillars: clinical suspicion, serial high-resolution ultrasound examinations, and longitudinal inflammatory markers like C-reactive protein (CRP).

Beyond standard practice, several innovative diagnostic technologies are showing promise:

- Near-Infrared Spectroscopy (NIRS): This technology allows for the continuous, non-invasive monitoring of regional tissue oxygenation (rSO_2). By measuring the oxygen saturation in the mesenteric bed, NIRS can detect subclinical intestinal ischemia long before systemic signs appear. This aligns with the "two-hit" hypothesis, providing a way to monitor the hemodynamic stressors that trigger the "second hit" (Kaplina et al., 2023; Meister et al., 2020).
- Gut-Specific Biomarkers: While CRP provides a measure of systemic inflammation (Cheng et al., 2025), markers like Intestinal Fatty Acid-Binding Protein (I-FABP) offer a more direct reflection of enterocyte damage. Because I-FABP is released immediately upon mucosal injury, its detection in blood or urine could significantly shorten the time to diagnosis (Rich and Dolgin, 2017).
- Microbial and Metabolomic Profiling: As the role of gut dysbiosis becomes more apparent, the use of rapid "omics" technologies to analyze fecal microbial composition or metabolic byproducts (such as volatile organic compounds) is being explored. These tools could identify high-risk infants who have a microbiome "primed" for NEC before the first symptoms manifest (Kaplina et al., 2023; Masi et al., 2021).

The integration of these technologies suggests a shift toward precision neonatology. However, current literature emphasizes that these tools must supplement, not replace, rigorous clinical protocols. Hu et al. (2024) and De Bernardo et al. (2025) conclude that while we await the universal availability of molecular "point-of-care" tests, the most reliable "emerging" strategy is the standardized use of point-of-care ultrasound (POCUS) to monitor bowel wall viability and perfusion in real-time. This comprehensive approach offers the best defense against the systemic consequences of NEC, which, as Meister et al. (2020) demonstrate, extend far beyond the gastrointestinal tract to impact neurodevelopmental health.

4. Prevention Strategies: The Impact of Nutrition

4.1. Human Milk and Donor Milk

The use of human milk is universally recognized as the single most effective preventive intervention against necrotizing enterocolitis (NEC). Its protective effect is attributed to a complex array of bioactive components, including immunoglobulins (IgA), growth factors (such as epidermal growth factor), and anti-inflammatory cytokines, which collectively promote intestinal maturation and reinforce the mucosal barrier (Monzon et al., 2023). These components work synergistically to counteract the immature intestinal response that characterizes the premature gut, specifically by modulating the pro-inflammatory pathways and fostering a more balanced microbial environment (Kaplina et al., 2023). For preterm infants, particularly those with very low birth weight (VLBW), breast milk significantly reduces the incidence of NEC compared to bovine-based formula. When maternal milk is insufficient or unavailable, pasteurized donor human milk (DHM) is the preferred clinical alternative (Quigley et al., 2024). A comprehensive and updated Cochrane systematic review confirms that feeding preterm or VLBW infants with DHM results in a substantially lower risk of developing NEC compared to formula feeding (Quigley et al., 2024; Quigley et al., 2018). While formula may promote faster short-term weight gain, it lacks the immunomodulatory properties of human milk and has been associated with a higher risk of systemic inflammation and gut injury (Quigley et al., 2024; Rich and Dolgin, 2017). Beyond its direct nutritional and immunological benefits, human milk provides essential substrates for a healthy gut microbiome. It contains specific prebiotics that facilitate the colonization of beneficial bacteria, such as *Bifidobacterium*, which compete with opportunistic pathogens associated with NEC onset (De Bernardo et al., 2025; Sharif et al., 2023). Therefore, prioritizing an exclusive human milk diet (maternal or donor) is a critical standard of care in the NICU to mitigate the "neonatological enigma" of NEC (Rich and Dolgin, 2017; Hu et al., 2024).

4.2. Human Milk Oligosaccharides (HMOs) as Prebiotics

Beyond providing basic macronutrients, human milk contains a high concentration of complex carbohydrates known as Human Milk Oligosaccharides (HMOs), which are not digested by the infant but serve as specialized prebiotics. HMOs are essential for the healthy development of the neonatal gut, as they selectively promote the growth of beneficial commensal bacteria, primarily *Bifidobacterium* species, while inhibiting the adherence of opportunistic pathogens (Okburan and Kızıler, 2023). This microbial modulation is critical in preventing the gut dysbiosis that typically precedes the onset of necrotizing enterocolitis (Kaplina et al., 2023; Masi et al., 2021). Among the diverse pool of over 200 HMO structures, a specific sialylated oligosaccharide known as disialyllacto-N-tetraose (DSLNT) has emerged as a key biomarker and protective factor against NEC. Clinical studies have demonstrated that lower concentrations of DSLNT in maternal milk are significantly associated with an increased risk of NEC development in preterm infants (Masi et al., 2021). The protective mechanism of DSLNT is multi-faceted; research by Sodhi et al. (2023) indicates that HMOs can directly reduce the pro-inflammatory signaling in the intestinal epithelium and, notably, mitigate NEC-induced neuroinflammation.

This systemic protection is vital, as NEC is increasingly recognized as a disease that is "not all in the gut," frequently leading to significant cognitive impairment and brain injury via the inflammatory gut-brain axis (Meister et al., 2020; Sodhi et al., 2023). The ability of specific HMOs to stabilize the intestinal barrier and limit the systemic translocation of microbial metabolites, such as certain short-chain fatty acids (SCFAs) that can reach toxic levels in the immature gut, further reinforces their role in preventing multi-organ complications (Kaplina et al., 2023).

Current literature suggests that the concentration of these oligosaccharides varies significantly between mothers, which has paved the way for "precision nutrition" in the NICU. Supplementing donor human milk or bovine-based formulas with specific HMOs like DSLNT represents a promising frontier in neonatal therapy, aiming to provide extremely low birth weight infants with the targeted protection required to overcome the physiological immaturity of their digestive and immune systems (Okburan and Kızıler, 2023; Underwood, 2019; Hu et al., 2024).

4.3. Probiotics and Standardized Feeding Protocols

The implementation of targeted microbiological and clinical interventions has proven instrumental in reducing the incidence of NEC among the most vulnerable neonatal populations. Central to these strategies is the use of probiotics and the rigorous application of standardized feeding protocols (SFPs).

Probiotics: Restoring the Microbial Balance

The premature gut is characterized by a significant lack of microbial diversity and a predisposition toward colonization by pathogenic *Proteobacteria*. Probiotic supplementation, specifically using strains of *Bifidobacterium* and *Lactobacillus*, aims to counteract this dysbiosis by promoting a "healthy" commensal environment (De Bernardo et al., 2025). According to a narrative review by De Bernardo et al. (2025), the administration of these beneficial bacteria effectively restores the microbial balance, reinforces the intestinal epithelial barrier, and modulates the innate immune response, thereby preventing the exaggerated inflammatory cascade triggered by TLR4 activation.

Furthermore, probiotics have been shown to influence the production of microbial metabolites. While some metabolites can reach toxic levels in the immature gut, a balanced microbiome fostered by probiotics ensures the production of protective substances that maintain mucosal integrity (Kaplina et al., 2023). Meta-analyses and recent clinical reviews consistently show that proactive probiotic therapy reduces the risk of reaching advanced stages of the Bell scale and lowers overall NEC-related mortality (De Bernardo et al., 2025; Murphy et al., 2021).

Standardized Feeding Protocols (SFP): Consistency as a Shield

Beyond biological interventions, the methodology of enteral nutrition delivery plays a decisive role in NEC prevention. Inconsistency in feeding practices such as highly variable rates of volume advancement has historically been a major risk factor for intestinal injury in preterm infants. The adoption of Standardized Feeding Protocols (SFP) provides a systematic, evidence-based framework for the initiation and escalation of enteral feeds (Shah et al., 2021).

Research by Shah et al. (2021) demonstrates that SFPs not only lower the risk of NEC in extremely low birth weight (ELBW) infants but also significantly improve growth velocity by reducing the number of days infants spend with restricted caloric intake. These protocols typically emphasize:

- Early initiation of trophic feeding: Stimulating the gut without overtaxing its metabolic capacity (Quitadamo et al., 2025).
- Gradual volume advancement: Controlled increases (e.g., 15–30 mL/kg/day) to prevent malabsorption and excessive fermentation (Joung et al., 2025; Hu et al., 2024).
- Early fortification: Ensuring that the high nutritional demands of ELBW infants are met safely (Joung et al., 2025).

The synergy between biological protection (probiotics) and clinical discipline (SFP) represents a cornerstone of modern neonatal care. As noted by Hu et al. (2024) and Seliga-Siwecka et al. (2022), reducing the variability of care through these standardized practices is as vital as any pharmacological intervention in mitigating the risks of necrotizing enterocolitis.

5. Summary and Conclusions

5.1. Synthesis of Pathogenesis and Diagnosis

The landscape of necrotizing enterocolitis (NEC) has undergone a fundamental shift, evolving from being viewed as a simple ischemic event to a complex, multi-factorial inflammatory syndrome. As established by Rich and Dolgin (2017), the core vulnerability of the preterm infant lies in the structural and functional immaturity of the intestinal barrier combined with an exaggerated innate immune response. This response is primarily mediated by the overexpression of TLR4 signaling, which, when triggered by microbial dysbiosis, initiates a cascade of enterocyte apoptosis and mucosal necrosis (Kaplina et al., 2023).

Modern diagnostic strategies must therefore move beyond the reactive nature of the Bell staging system, which often identifies the disease only after significant tissue damage has occurred. The integration of Abdominal Ultrasound (AUS) represents a major technological advancement, providing superior detection of bowel wall thickness, peristalsis, and perfusion compared to traditional X-rays (Kim, 2019; Faingold et al., 2005). When this dynamic imaging is combined with predictive biochemical markers, specifically serial CRP monitoring to track inflammatory trends (Cheng et al., 2025) clinicians gain a critical advantage in identifying infants during the early, reversible stages of the disease. This multi-modal approach is essential for shifting the clinical focus from crisis management to early, life-saving intervention (De Bernardo et al., 2019; Kallis et al., 2023).

5.2. Preventive Milestones

Prevention remains the most effective and evidence-based tool in reducing the clinical and socioeconomic burden of NEC. The current literature consistently supports three primary pillars of care:

- The Power of Human Milk: Exclusive use of maternal breast milk, or pasteurized donor human milk (DHM) when maternal supply is insufficient, is the most potent preventive intervention available (Quigley et al., 2024; Quigley et al., 2018). Bioactive components such as Human Milk Oligosaccharides (HMOs), particularly DSLNT, provide a targeted protective role. Research by Sodhi et al. (2023) and Masi et al. (2021) demonstrates that these sugars not only modulate the gut microbiome but also offer systemic protection that extends to neuroprotection, mitigating the long-term cognitive impairments associated with NEC.
- Microbiome Modulation: The proactive use of targeted probiotics (e.g., *Bifidobacterium* and *Lactobacillus*) and prebiotics helps mitigate the gut dysbiosis characterized by an overgrowth of *Proteobacteria* that typically precedes clinical onset (De Bernardo et al., 2025; Sharif et al., 2023; Murphy et al., 2021).
- Clinical Consistency: The rigorous adoption of Standardized Feeding Protocols (SFP) minimizes the risks associated with rapid or inconsistent feeding advancement. By providing a structured framework for enteral nutrition, SFPs have been shown to improve growth velocity while simultaneously reducing the overall incidence of NEC in very low birth weight (VLBW) infants (Shah et al., 2021; Joung et al., 2025; Seliga-Siwecka et al., 2022).

5.3. Final Conclusions

Despite these advancements, NEC remains a "neonatological enigma" that demands a holistic, interdisciplinary approach. It is increasingly clear that the disease is "not all in the gut," as Meister et al. (2020) describe; its systemic impact involves a potent inflammatory axis affecting the brain and lungs. While surgical techniques and medical management have improved offering better survival rates even in advanced cases (Hu et al., 2024; De Bernardo et al., 2019) the persistently high mortality and significant long-term neurodevelopmental morbidity underscore an urgent need for continued research.

In conclusion, the transition toward proactive prevention (via HMO-based precision nutrition and probiotics) and dynamic diagnostics (via real-time point-of-care ultrasound and specific inflammatory biomarkers) represents the current "gold standard" in neonatal gastroenterology. By standardizing these evidence-based practices and embracing emerging technologies like NIRS and "omics" profiling, clinical centers can significantly improve survival rates and long-term quality of life for this vulnerable patient population (Hu et al., 2024; De Bernardo et al., 2025; Monzon et al., 2023).

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