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Necrotizing Enterocolitis in Newborns: Diagnosis, Etiology, Management, Prevention, Complications and their Relation to Future Sport Performance

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Summary

Necrotizing enterocolitis (NEC) is a serious gastrointestinal condition that primarily affects premature infants, although it can also occur in full-term infants. It is characterized by inflammation and injury of the intestinal tissue, which can progress to necrosis and

perforation of the bowel. NEC is a leading cause of morbidity and mortality in neonatal intensive care units (NICUs), particularly among very low birth weight infants.

Diagnosis of NEC is based on clinical signs and symptoms, radiographic findings, and laboratory tests. Management of NEC involves a multidisciplinary approach, including supportive care, medical therapy, and surgical intervention when necessary. Supportive care includes bowel rest, intravenous fluids, and nutritional support. Medical therapy may include antibiotics, gastric decompression, and parenteral nutrition. Surgical intervention may be required for infants with intestinal perforation, severe NEC, or complications such as intestinal stricture or short bowel syndrome. This condition and its complications may carry consequences for life and especially sport performance in the child's future.

Strategies for preventing NEC include promoting breastfeeding, avoiding unnecessary antibiotic exposure, minimizing enteral feeding interruptions, practicing strict infection control measures, and implementing protocols for gradual feeding advancement in premature infants.

Overall, NEC is a complex and multifactorial disease that poses significant challenges in neonatal care. Early recognition, prompt intervention, and comprehensive management are essential for optimizing outcomes for affected infants. Further research is needed to better understand the pathophysiology of NEC and to develop more effective prevention and treatment strategies.

Keywords: necrotizing enterocolitis, preterm infant, enteral feeding, hypoperfusion of bowel, neonatal intensive care, pediatric sport performance

Introduction

Necrotizing enterocolitis (NEC) is a serious gastrointestinal condition that primarily affects premature infants, although it can also occur in full-term infants. It is characterized by inflammation and injury of the intestinal tissue, which can progress to necrosis and perforation of the bowel. NEC is a leading cause of morbidity and mortality in neonatal intensive care units (NICUs), particularly among very low birth weight infants.

NEC primarily affects premature infants, with the highest incidence seen in infants born at less than 32 weeks gestational age. Low birth weight, formula feeding, enteral feeding, and other factors contribute to increased NEC risk. While the exact cause of NEC is unknown, it is believed to involve a combination of factors, including immaturity of the gastrointestinal tract, altered immune responses, intestinal ischemia, microbial colonization, and feeding-related factors. NEC typically presents with non-specific signs and symptoms, including feeding intolerance, abdominal distension, bloody stools, lethargy, temperature instability, and respiratory distress. The clinical presentation can vary from mild gastrointestinal symptoms to severe systemic illness with septic shock. Early recognition and diagnosis are critical for prompt intervention and improved outcomes [1].

Etiology of Necrotizing Enterocolitis

The etiology of necrotizing enterocolitis is multifactorial and not entirely understood, but several factors have been implicated in its development. Premature infants, particularly those born 32 weeks before gestation, have underdeveloped gastrointestinal systems, including immature mucosal barriers, reduced motility, and impaired immune responses. The introduction of enteral feeds, particularly in premature infants, has been strongly associated with the development of NEC. Immature gastrointestinal tracts may struggle to tolerate enteral feeding, leading to mucosal injury, inflammation, and subsequent NEC.

Also, reduced blood flow to the intestines can lead to ischemia (inadequate blood supply) and tissue hypoxia (low oxygen levels), which are key triggers for NEC development. Various factors can contribute to intestinal hypoperfusion, including hypotension, enteral feeding, sepsis, and circulatory compromise. Mucosal injury triggers an exaggerated inflammatory cascade, involving the release of cytokines, chemokines, and other inflammatory mediators. This inflammatory response contributes to tissue damage, necrosis, and systemic complications. Premature infants have impaired immune function, making them more susceptible to infections and inflammatory conditions. Dysfunction in both the innate and adaptive immune systems contribute to the pathogenesis of NEC [2].

The presence of umbilical catheters has been implicated in NEC development. Umbilical catheters are commonly used in neonatal intensive care units (NICUs) for vascular access and the delivery of fluids, medications, and parenteral nutrition to critically ill newborns, particularly premature infants. While umbilical catheters can be lifesaving in certain situations,

they are also associated with potential complications, including an increased risk of NEC in some cases. The improper placement or manipulation of umbilical catheters can cause mechanical trauma to the intestines, leading to mucosal injury and inflammation. The presence of foreign bodies within the umbilical vessels may also disrupt blood flow to the intestines, predisposing the infant to NEC. Umbilical catheters provide a direct route for microorganisms to enter the bloodstream, increasing the risk of bloodstream infections. Bacteremia or fungemia resulting from catheter-related infections can lead to systemic inflammation. The catheters may also lead to the formation of blood clots within the umbilical vessels or catheter lumen. Such thromboembolic events can impair blood flow to the intestines, predisposing the infant to intestinal ischemia [3].

Alterations in the gut microbiota (dysbiosis) play a role in NEC pathogenesis. Premature infants have a disrupted microbial balance, with an overgrowth of potentially harmful bacteria such as Enterobacteriaceae and a reduction in beneficial bacteria like Bifidobacterium. This imbalance can contribute to inflammation and tissue damage in the intestines. Innate immune responses play a central role in the host's initial defense against invading pathogens. Toll-like receptors (TLRs), pattern recognition receptors (PRRs), and other innate immune sensors recognize pathogen-associated molecular patterns (PAMPs) present on microbial pathogens. Activation of these receptors triggers downstream signaling pathways, such as the nuclear factor kappa B (NF-κB) pathway and the mitogen-activated protein kinase (MAPK) pathway, leading to the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides [4]. Dysregulation of innate immune activation and excessive production of pro-inflammatory mediators may contribute to intestinal inflammation and tissue damage in NEC. The intestinal epithelial barrier serves as a physical and immunological barrier against microbial invasion and maintains tissue homeostasis. Disruption of the intestinal barrier, characterized by alterations in tight junction integrity, mucin production, and epithelial cell turnover, is a hallmark of NEC pathogenesis. Molecular pathways involved in intestinal barrier dysfunction include the epithelial-to-mesenchymal transition (EMT) pathway, which regulates epithelial cell plasticity and migration, and the transforming growth factor-beta (TGF-β) signaling pathway, which modulates epithelial barrier integrity and immune responses [5]. Dysregulated inflammatory signaling cascades contribute to the pathogenesis of NEC by promoting intestinal inflammation, tissue injury, and systemic immune activation. Pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) are key mediators of inflammatory

responses in NEC. These cytokines activate downstream signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, and the extracellular signal-regulated kinase (ERK) pathway, leading to the recruitment of immune cells, the production of reactive oxygen species (ROS), and the induction of apoptosis and necrosis in intestinal epithelial cells [6]. Molecular pathways involved in microbial dysbiosis, and dysregulated host-microbiota interactions include alterations in microbial metabolism, disruption of microbial colonization patterns, and dysregulation of host immune responses to gut microbiota. Toll-like receptor signaling, nod-like receptor signaling, and inflammasome activation are among the molecular pathways implicated in host-microbiota interactions and immune regulation in NEC [7]. Also, excessive epithelial cell death, including apoptosis and necroptosis, contributes to intestinal injury and tissue remodeling in NEC. Molecular pathways involved in epithelial cell death and tissue remodeling include the caspase-dependent apoptotic pathway, the receptor-interacting protein kinase (RIPK)-dependent necroptotic pathway, and the Wnt/β-catenin signaling pathway, which regulates intestinal stem cell proliferation and differentiation [8]. Dysregulation of these pathways may lead to impaired epithelial regeneration and persistent mucosal injury in NEC.

Also, genetic polymorphisms, variations in DNA sequence among individuals within a population, may underly NEC etiology. Polymorphisms in genes involved in the regulation of immune responses may influence an infant's susceptibility to NEC. For example, variations in genes encoding toll-like receptors (TLRs), which play a key role in innate immune recognition of microbial pathogens, have been implicated in NEC risk. Polymorphisms in genes encoding cytokines, such as interleukins (ILs) and tumor necrosis factor-alpha (TNF-α), have also been studied for their potential association with NEC susceptibility and severity [9]. Also, genetic variants in genes involved in inflammatory signaling pathways may contribute to NEC pathogenesis. For example, polymorphisms in genes encoding components of the nuclear factor kappa B (NF-κB) pathway, which regulates the expression of pro-inflammatory genes, have been investigated. Variants in genes encoding inflammatory mediators, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), have also been studied for their potential role in NEC development [10]. Other genetic polymorphisms affecting the integrity of the intestinal mucosal barrier may predispose infants to NEC. Variants in genes encoding tight junction proteins, which regulate paracellular permeability, have been implicated in NEC susceptibility. Polymorphisms in genes encoding mucins, which

form the protective mucus layer in the gastrointestinal tract, are also undergoing further research. Possible genetic variants in genes involved in microbial recognition and host-microbe interactions may influence NEC susceptibility. For example, polymorphisms in genes encoding pattern recognition receptors (PRRs), such as nucleotide-binding oligomerization domain (NOD)-like receptors and retinoic acid-inducible gene-I (RIG-I)-like receptors, have been studied [11]. Some polymorphisms affecting the composition and function of the gut microbiota may influence NEC risk. Variants in genes involved in host-microbiota interactions, such as those encoding antimicrobial peptides, mucin glycoproteins, and microbial metabolite receptors, have been investigated for their association with NEC susceptibility and severity. Further research is needed to validate candidate genes and polymorphisms associated with NEC risk, elucidate the functional consequences of genetic variants, and identify potential therapeutic targets for NEC prevention and treatment [12].

Overall, NEC is a complex disease with multiple contributing factors, and its pathogenesis likely involves interactions between immaturity of the gastrointestinal tract, alterations in the gut microbiota, inflammatory responses, and other environmental and genetic factors. Understanding these factors is crucial for developing strategies for prevention, early detection, and management of NEC in vulnerable infants.

Diagnosing Necrotizing Enterocolitis

Diagnosing necrotizing enterocolitis (NEC) involves a combination of clinical assessment, laboratory tests, radiological imaging, and sometimes surgical intervention. Here's an overview of the diagnostic process:

Healthcare providers evaluate the infant's clinical presentation, including symptoms and signs suggestive of NEC. These may include feeding intolerance (such as increased residual gastric volumes or vomiting), abdominal distension, bloody stools (also known as "currant jelly" stools), lethargy, temperature instability (hypothermia or hyperthermia), apnea, bradycardia, and respiratory distress.

Blood tests are often performed to assess for signs of infection, metabolic abnormalities, and systemic inflammation, which are commonly associated with NEC. These tests may include complete blood count (CBC) to assess for leukocytosis (elevated white blood cell count) or leukopenia (decreased white blood cell count), blood culture to identify any bloodstream

infections, C-reactive protein (CRP) and/or procalcitonin levels to evaluate for systemic inflammation, and arterial blood gas analysis to assess for metabolic acidosis or respiratory alkalosis, which may indicate tissue hypoperfusion or respiratory compromise. [13]

Abdominal imaging studies are crucial for diagnosing NEC and assessing its severity. The most commonly used modalities include abdominal xrays and abdominal ultrasound. Abdominal X-rays may reveal signs suggestive of NEC, such as pneumatosis intestinalis (air within the bowel wall), portal venous gas (gas within the portal vein), bowel dilation, or free intra-abdominal air. Ultrasound may be used to assess bowel wall thickness, bowel perfusion, and the presence of intramural gas or fluid collections. [14]

Bell's staging criteria, also known as the modified Bell's criteria, are a widely used system for classifying the severity of NEC based on clinical and radiographic findings. The criteria were developed by Bell and colleagues in 1978 and have since been modified and refined for clinical use. The staging system helps clinicians stratify patients with NEC into different categories based on disease severity, which guides treatment decisions and prognostication. Here is an overview of Bell's staging criteria:

1. Stage I (Suspected NEC):

- Clinical Signs: Non-specific signs such as feeding intolerance, abdominal distension, lethargy, or temperature instability.

- Radiographic Findings: Mild or non-specific findings such as ileus, dilated bowel loops, or pneumatosis intestinalis not clearly associated with NEC.

2. Stage II (Definite NEC):

- Clinical Signs: Worsening clinical signs such as bilious gastric residuals, abdominal tenderness, or occult blood in stool.

- Radiographic Findings: Characteristic findings such as pneumatosis intestinalis (gas within the bowel wall) or portal venous gas.

3. Stage III (Advanced NEC):

- Clinical Signs: Severe clinical deterioration with systemic signs of sepsis, shock, metabolic acidosis, or disseminated intravascular coagulation (DIC).

- Radiographic Findings: Severe and extensive bowel necrosis, perforation, or pneumoperitoneum.

In addition to these stages, Bell's criteria may also include a designation for "NEC-NEC", which refers to infants with clinical and radiographic findings suggestive of NEC but without histologic confirmation. The staging system may be further modified or expanded to include additional criteria or subcategories based on institutional protocols or clinical judgment. It's important to note that while Bell's staging criteria provide a framework for assessing NEC severity, clinical decision-making should be individualized based on the patient's overall condition, response to treatment, and other factors such as gestational age, birth weight, and comorbidities. Close monitoring, multidisciplinary collaboration, and timely intervention are essential for optimizing outcomes in infants with NEC. [15]

In severe cases of NEC or when the diagnosis is uncertain, surgical exploration may be necessary. Surgical findings consistent with NEC include bowel necrosis, perforation, peritonitis, or pneumoperitoneum (air within the peritoneal cavity). [16]

The diagnosis of NEC is typically based on a combination of clinical findings, laboratory tests, and radiological imaging. Prompt recognition and diagnosis are essential for initiating appropriate treatment. Collaboration between neonatologists, pediatric surgeons, radiologists, and other healthcare professionals is crucial for the timely and accurate diagnosis of NEC and the implementation of appropriate management strategies.

Management Strategies for Necrotizing Enterocolitis

The goals of management include stabilizing the infant's condition, addressing gastrointestinal complications, and preventing further disease progression. Infants with suspected NEC require immediate assessment and stabilization. This includes ensuring adequate oxygenation, ventilation, and hemodynamic support. In severe cases, infants may require respiratory support, intravenous fluids, and inotropic agents to maintain hemodynamic stability.

The most important management involves discontinuing enteral feeding and providing bowel rest to reduce intestinal inflammation and allow the bowel to heal. Infants may receive total parenteral nutrition (TPN) to meet their nutritional needs during this period.

Broad-spectrum antibiotics are initiated promptly to cover likely pathogens associated with NEC, including Gram-negative bacteria such as Escherichia coli and Klebsiella species. Commonly used antibiotics include ampicillin, gentamicin, and metronidazole or clindamycin. Antibiotic therapy is adjusted based on culture results and clinical response [17].

Infants with NEC require frequent monitoring of vital signs, abdominal examination, and laboratory parameters (e.g., complete blood count, electrolytes, blood gases) to assess for disease progression, complications, and response to treatment. They are at risk of fluid and electrolyte imbalances due to gastrointestinal losses, third-spacing of fluids, and impaired renal function. Close monitoring and appropriate fluid resuscitation are essential to maintain hydration and electrolyte balance [18].

Once the infant's condition stabilizes, enteral feeding may be gradually reintroduced, starting with trophic feeds (small volumes of breast milk or formula) and advancing as tolerated. Human milk is preferred due to its protective effects against NEC. Dieticians play a crucial role in optimizing nutritional support and monitoring feeding tolerance.

Strategies to prevent complications associated with NEC include careful handling of umbilical catheters to minimize infection risk, judicious use of antibiotics to prevent antibiotic-associated complications, and early recognition and management of sepsis or thromboembolic events.

Preventing Necrotizing Enterocolitis in Infants

Preventing NEC in infants, particularly in those at high risk such as premature infants, is a multifaceted endeavor that involves a combination of strategies aimed at reducing predisposing factors, optimizing care practices, and promoting a supportive environment for infant health and development.

Breastfeeding is one of the most effective ways to prevent NEC. Human milk contains numerous bioactive components, including immunoglobulins, prebiotics, and growth factors, which help protect the immature gut and promote intestinal maturation. Encouraging and supporting breastfeeding, including providing lactation support and education for mothers of premature infants, is crucial. Providing an exclusive human milk diet (breast milk or donor human milk) to premature infants, rather than supplementing with formula, has been associated with a reduced risk of NEC. Hospitals and neonatal intensive care units (NICUs)

may implement protocols to prioritize human milk feeding and limit the use of cow's milk-based formula [19].

Another important preventative strategy is prenatal care aimed at optimizing maternal health and reducing risk factors for preterm birth can indirectly contribute to NEC prevention. This includes addressing maternal nutrition, avoiding tobacco and alcohol use, managing maternal medical conditions, and reducing exposure to environmental toxins [20].

Also, administration of antenatal corticosteroids to women at risk of preterm birth can help accelerate fetal lung maturation and reduce the incidence of respiratory distress syndrome, a risk factor for NEC. Antenatal steroids may also have beneficial effects on intestinal development and immune function [21].

There are also other feeding measures that reduce the risk of NEC. Probiotics (live microorganisms) and prebiotics (substances that promote the growth of beneficial bacteria) have been studied for their potential role in preventing NEC. Certain probiotic strains, such as Lactobacillus and Bifidobacterium species, have shown promise in reducing the incidence and severity of NEC in premature infants. However, the use of probiotics in NICU settings requires careful consideration of safety, strain selection, dosing, and monitoring. Also, gradual advancement of enteral feeds, particularly in premature infants, helps reduce the risk of NEC by allowing the immature gastrointestinal tract to adapt gradually. Close monitoring of feeding tolerance, abdominal examination, and signs of feeding intolerance is essential [22].

Additionally, implementing infection control practices, including hand hygiene, proper handling and storage of breast milk, and strict adherence to aseptic techniques during medical procedures, helps reduce the risk of NEC-associated infections and outbreaks in NICU settings. On the other hand, limiting the unnecessary use of antibiotics in newborns helps preserve the diversity of the gut microbiota and reduce the risk of antibiotic-associated complications, including dysbiosis and susceptibility to NEC [23].

Lastly, minimizing stressors and providing supportive care in the NICU environment can help reduce the risk of NEC. Strategies may include promoting skin-to-skin contact (kangaroo care), minimizing exposure to painful procedures, ensuring a quiet and calm environment, and supporting parental involvement in infant care [24].

Preventing NEC requires a comprehensive and multidisciplinary approach that addresses maternal, neonatal, and environmental factors influencing infant health and development. By implementing evidence-based preventive strategies and providing supportive care, healthcare providers can reduce the incidence and severity of NEC and improve outcomes for vulnerable infants.

Outcomes and Prognosis for Newborns with Necrotizing Enterocolitis

The outcomes and prognosis for newborns with necrotizing enterocolitis (NEC) can vary widely depending on factors such as the severity of the disease, gestational age, birth weight, presence of complications, and promptness of intervention. While some infants may have relatively mild cases with favorable outcomes, others may experience severe complications that can have long-lasting effects on health and development.

This pathology remains a significant cause of morbidity and mortality in premature and critically ill infants. Mortality rates vary depending on the severity of NEC and the population studied but can range from 10% to 30% or higher in severe cases, especially among extremely premature infants or those with extensive bowel necrosis and complications such as intestinal perforation or sepsis.

Infants who survive NEC may experience a range of outcomes depending on the extent of intestinal injury, presence of complications, and effectiveness of treatment. Some infants may recover fully with minimal long-term sequelae, while others may experience ongoing gastrointestinal dysfunction, nutritional challenges, or neurodevelopmental impairments.

NEC can cause localized or widespread necrosis of the intestines, leading to intestinal perforation. This allows the contents of the intestines to leak into the abdominal cavity, causing peritonitis and increasing the risk of sepsis. This perforation and bacterial translocation can lead to bloodstream infections (sepsis), which can be life-threatening if not promptly diagnosed and treated. Sepsis can lead to multi-organ dysfunction syndrome (MODS) and septic shock [25].

Severe NEC may necessitate surgical resection of necrotic bowel segments. Extensive bowel resection can result in short bowel syndrome (SBS), characterized by insufficient intestinal length to support adequate nutrient absorption. Infants with SBS may require long-term

parenteral nutrition and are at risk of nutritional deficiencies and complications such as liver disease [26].

Healing after NEC may result in the formation of fibrotic scar tissue, leading to bowel strictures or narrowing of the intestinal lumen. Bowel strictures can cause bowel obstruction, leading to symptoms such as abdominal distension, vomiting, and failure to thrive. Surgical intervention may be necessary to relieve obstructions. Complications of NEC can also include intestinal dysmotility, which results in disturbances in the coordinated movement of the intestines [27].

Some infants who survive NEC may experience long-term gastrointestinal dysfunction, including feeding intolerance, gastroesophageal reflux disease (GERD), and dysmotility disorders. Follow-up evaluations by pediatric gastroenterologists may include imaging studies (e.g., contrast studies, endoscopy) to assess structural abnormalities and functional testing (e.g., motility studies) to evaluate bowel function. Some infants with a history of NEC may require ongoing nutritional support due to compromised gastrointestinal function or malabsorption. Close monitoring by dieticians and healthcare providers is necessary to ensure adequate nutrient intake, optimize feeding regimens, and manage any feeding-related complications.

Premature infants, who are at increased risk of NEC, are also susceptible to neurodevelopmental impairments such as cognitive, motor, and sensory deficits. The combination of prematurity, NEC-related complications, and exposure to critical care interventions may contribute to long-term developmental delays and disabilities [28].

Ensuring that infants receive recommended immunizations and preventive healthcare services is essential to protect against infectious diseases and to promote overall health and well-being. Catch-up immunizations may be necessary for infants who missed doses or were immunocompromised during their illness.

Coordination of care between pediatricians, subspecialists, therapists, and other healthcare providers is crucial to ensure continuity of care for infants with a history of NEC. Care plans should be individualized based on the child's specific needs and should include regular follow-up appointments to monitor progress and adjust interventions as necessary.

Overall, long-term follow-up for infants who have experienced NEC aims to optimize growth and development, identify and address potential complications, and provide ongoing support to families as they navigate the challenges associated with their child's health condition. Regular monitoring, early intervention, and multidisciplinary collaboration are key components of comprehensive care for these infants.

Further Research

Researchers are investigating the role of the gut microbiome in NEC development and progression. Studies are exploring the composition, diversity, and function of the gut microbiota in infants at risk of NEC, as well as the impact of microbial dysbiosis on intestinal inflammation and injury.

Further research is needed to understand the complex interactions between host factors (e.g., immune function, genetic susceptibility) and microbial pathogens (e.g., Enterobacteriaceae, Clostridium species) in NEC pathogenesis. Identifying key molecular pathways involved in host-pathogen interactions may lead to targeted therapeutic interventions [29].

Biomarkers for NEC diagnosis, prognosis, and monitoring are under investigation. Research is focused on identifying blood, stool, urine, and imaging biomarkers that can reliably predict NEC development, assess disease severity, and guide clinical management decisions. Some examples of such biomarkers include C-reactive protein (CRP), whole elevated levels are associated with inflammation and infection, including NEC. Serial measurement of CRP levels may help monitor disease progression and response to treatment. Procalcitonin (PCT) is another sensitive marker of bacterial infection and systemic inflammation. Elevated PCT levels have been observed in infants with NEC and may aid in distinguishing NEC from other causes of abdominal symptoms. Various interleukins, such as IL-6, IL-8, and IL-10, have been reported in NEC and may serve as biomarkers of disease severity. Fecal calprotectin is a gut integrity marker of intestinal inflammation and mucosal injury. Elevated fecal calprotectin levels have been detected in infants with NEC and may help differentiate NEC from other gastrointestinal conditions. Intestinal Fatty Acid-Binding Protein (I-FABP), another gut integrity marker, is released into circulation upon intestinal epithelial cell damage. Elevated serum or stool I-FABP levels have been proposed as biomarkers for NEC diagnosis and prognosis. Elevated D-lactate levels, a metabolic marker, in blood or stool may indicate intestinal ischemia or bacterial overgrowth, both of which are associated with NEC. Other

metabolomic profiling of blood or urine samples may identify metabolic signatures associated with NEC development and progression. Dysbiosis of the gut microbiota is implicated in NEC pathogenesis. Analysis of stool samples using techniques such as 16S rRNA sequencing or metagenomic sequencing may reveal microbial signatures associated with NEC risk and severity. Detection of bacterial DNA in blood samples, using polymerase chain reaction (PCR) or other molecular methods, may indicate bacterial translocation and systemic infection, which are characteristic features of advanced NEC. Also, the Near-Infrared Spectroscopy (NIRS), a non-invasive imaging technique, measures regional tissue oxygenation. Monitoring splanchnic oxygenation using NIRS may help identify infants at risk of developing NEC and guide treatment decisions [30]. Integration of multiple biomarkers and clinical parameters into predictive models or algorithms may enhance the accuracy of NEC diagnosis and prognosis. However, further research is needed to validate the utility of biomarkers in clinical practice and to identify optimal biomarker panels for NEC management [31].

Studies are evaluating the role of exclusive human milk diets, fortification strategies, enteral feeding protocols, and supplementation with probiotics, prebiotics, and postbiotics in reducing NEC incidence and severity. Probiotics are an especially well researched nutritional intervention. They are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. They exert their effects through various mechanisms, including competitive exclusion of pathogenic bacteria, enhancement of mucosal barrier function, modulation of immune responses, and production of antimicrobial substances. By promoting a healthy balance of gut microbiota, probiotics may help prevent intestinal inflammation and reduce the risk of gastrointestinal disorders. Commonly used probiotic strains in newborns include species of Lactobacillus (e.g., Lactobacillus rhamnosus GG, Lactobacillus reuteri), Bifidobacterium (e.g., Bifidobacterium infantis, Bifidobacterium breve), and Saccharomyces (e.g., Saccharomyces boulardii) [32]. These strains have been studied for their safety, efficacy, and potential benefits in newborns. Numerous clinical trials and meta-analyses have evaluated the use of probiotics for NEC prevention in preterm infants [33]. While results have been generally promising, with reductions in NEC incidence and mortality observed in some studies, the optimal probiotic strain, dose, duration, and timing of administration remain areas of ongoing research and debate. They are generally considered safe for use in healthy terms and preterm infants when administered in appropriate doses and formulations. However, concerns have been raised regarding the potential risk of probiotic-associated sepsis, particularly in immunocompromised or critically ill infants. Close

monitoring for adverse effects is essential when using probiotics in newborns, and healthcare providers should weigh the potential benefits against the risks on a case-by-case basis. Further research is needed to establish optimal dosing regimens, identify the most effective strains, and clarify the long-term effects of probiotic supplementation in this vulnerable population [34].

Antibiotic exposure is associated with alterations in the gut microbiota and an increased risk of NEC. Research is exploring strategies for antibiotic stewardship in neonatal populations, including judicious antibiotic use, de-escalation of therapy, and alternative approaches to prevent infection-related complications [35].

Genetic and epigenetic factors may contribute to an infant's susceptibility to NEC. Genome-wide association studies (GWAS) and epigenome-wide association studies (EWAS) are being conducted to identify genetic polymorphisms and epigenetic modifications associated with NEC risk and severity [36].

In further research, animal models of NEC are valuable tools for studying disease pathogenesis, testing novel interventions, and translating findings to clinical practice. Translational research aims to bridge the gap between basic science discoveries and clinical applications in the prevention and treatment of NEC [37].

Quality improvement initiatives and standardized care protocols are being implemented in neonatal intensive care units (NICUs) to reduce NEC rates and improve outcomes. These initiatives may include auditing of clinical practices, staff education, interdisciplinary collaboration, and benchmarking against best practices [38].

Overall, further research into the pathophysiology, risk factors, prevention strategies, and management approaches for NEC is essential for reducing the burden of this devastating disease and improving outcomes for vulnerable infants. Collaborative efforts among researchers, clinicians, and healthcare organizations are crucial for advancing our understanding and addressing the challenges associated with NEC.

Acknowledging present medical condition and prevention of complications remains crucial in maintaining children’s gastrointestinal, thus athletic performance, and allows to assess future sport potential which helps in making future career choices.

Disclosure

Author's contribution

Conceptualization: Zofia Uszok and Michał Łepik; Methodology: Krzysztof Rosiak; Software: Kacper Płeska; Check: Kacper Reguła and Andrzej Czajka; Formal analysis: Zofia Uszok and Joanna Wojtania; Investigation: Kamil Waloch and Bartłomej Szymański; Resources: Szymon Piaszczyński; Data curation: Krzysztof Rosiak; Writing - rough preparation: Zofia Uszok and Kacper Reguła; Writing - review and editing: Michał Łepik and Kamil Waloch; Supervision: Joanna Wojtania; Project administration: Szymon Piaszczyński and Kacper Płeska; Receiving funding - no specific funding.

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The authors deny any conflict of interest.

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