Review

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Diagnosis and Staging of Necrotizing Enterocolitis: Current Controversies and a Phenotype-Based Framework

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Abstract

Necrotizing enterocolitis (NEC) remains one of the most devastating gastrointestinal emergencies in neonates and also presents major diagnostic challenges. Despite extensive research, NEC still lacks a practical definition and relies on a set of nonspecific clinical, laboratory, and radiological findings rather than a single pathognomonic presentation or test. The modified Bell staging system remains the most widely used framework in clinical practice and research, but it was originally developed to base the treatment decisions rather than helping in diagnosis and has important limitations when applied as a diagnostic aid. Clinical and radiological criteria used for early stages of NEC are nonspecific, progression of the disease is not always linear, radiographic signs are inconsistently present, and histopathological confirmation is unavailable in most of the cases as surgery is not undertaken in all the cases. These limitations have led to the opinion that even the modified Bell staging is "broken" when it is used to define the disease itself. At the same time, increased understanding about gut immunity and microbiome progression, and neonatal hemodynamics have made it increasingly clear that NEC is not a single uniform disease. It is now regarded as a heterogeneous syndrome comprising multiple phenotypes that share a final common pathway of intestinal injury and necrosis but differ in timing, predisposing factors, mechanisms involved, and clinical course. These presentations overlap with several neonatal conditions including spontaneous intestinal perforation, septic ileus, cow's milk protein allergy, congenital heart disease-related intestinal hypoperfusion, viral enterocolitis, malrotation with volvulus, and intussusception. This review discusses controversies in the definition and staging of NEC, consolidates alternative diagnostic criteria proposed beyond Bell's system, and elaborates a phenotype-based framework for clinical distinction. Also, the review throws light on the clinical mimickers, practical bedside diagnosis using serial clinical assessment and imaging, consequences of NEC, and emerging precision medicine approaches. A shift from stage-based labeling toward a practical, phenotype-informed framework may improve diagnostic precision, reduce misclassification, and enhance both clinical care and research.

Keywords: enterocolitis; necrotizing; diagnostic criteria; phenotypes; infant; premature; dysbiosis; intestinal ischemia

Introduction

Necrotizing enterocolitis is a multifactorial inflammatory disease resulting in necrosis of the neonatal intestine. It primarily affects preterm and very low birth weight infants and remains one of

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the devastating diseases in neonatal intensive care [1,2]. Although survival of extremely preterm infants has improved globally, NEC continues to contribute to substantial mortality, surgical burden, and long-term morbidity. Though population incidence varies with the definition used and population studied, among very low birth weight infants it is commonly between 5% and 10%, with highest burden among those born at the lowest gestations [2,3]. Mortality is high around 30-50%, especially when surgical intervention is needed or when disease is fulminant [3,4].

The impact of NEC on the survivors extends beyond the acute episode. Survivors may develop intestinal strictures, short bowel syndrome, intestinal failure, prolonged need for parenteral nutrition, cholestatic liver disease, postnatal growth failure, repeated rehospitalization, and adverse neurodevelopmental outcomes [5–8]. Severe NEC also imposes a major emotional and financial burden on families and health systems. These consequences make the diagnosis important not only from academic point of view: but the definition used would influence bedside decisions, epidemiology, trial design, and long-term counseling.

Defining and diagnosing NEC with precision is very difficult. There is no single biomarker or universally reliable imaging finding, and no single clinical feature that is present in all cases. Instead, diagnosis is made from combinations of abdominal signs, systemic instability, laboratory abnormalities, and imaging findings. Many of these findings are common in premature infants with other illnesses such as septic ileus, feeding intolerance, or spontaneous intestinal perforation [9–11]. Due to the overlapping features between these conditions, both overdiagnosis and underdiagnosis of NEC can occur.

The modified Bell staging system is mostly commonly used for NEC diagnosis and staging both in clinical and research setting [12,13]. Bell's original work offers a practical framework linking the severity of illness to treatment decisions. However, over time, this staging system was increasingly used as a surrogate diagnostic definition, even though it had not been designed for that purpose. In particular, "Stage I NEC" often includes neonates with nonspecific gastrointestinal and systemic abnormalities who would neither develop nor progress to have intestinal necrosis [9,10]. Moreover, progression is not in the orderly stage-wise manner as given in Bell staging. Some present abruptly with fulminant disease, while others improve without progression.

Our biological understanding of NEC has evolved dramatically. NEC is now recognized as a multifactorial syndrome arising from interactions among intestinal immaturity, microbial dysbiosis, exaggerated inflammation, epithelial injury, impaired barrier function, and in some infants, mesenteric hypoperfusion or ischemia-reperfusion injury [14–20]. This evolving understanding necessitates disease paradigm that accommodates heterogeneity.

Accordingly, there has been many alternative definitions, consensus case criteria, and phenotype-based approaches that separate "suspected intestinal disease" from "definite NEC," and also distinguish NEC from its mimickers. It also recognizes that different clinical phenotypes may represent biologically distinct forms of intestinal injury [10,11,21]. In this review, we will discuss why Bell staging is inadequate as a diagnostic framework. We then discuss alternative definitions and the rationale for treating NEC as a syndrome composed of overlapping phenotypes. We expand these phenotypes in detail, discuss differential diagnoses and mimickers, and propose a dynamic, integrative approach to diagnosis that is more clinically actionable.

The "Broken Bell": Rethinking Traditional Bell Staging

The modified Bell staging system is universally employed because of the simplicity, but several of its core assumptions limit its usefulness as a diagnostic framework today [9,10,12,13]. There are major limitations while using the same for diagnosis. The first major problem is the nonspecificity of early-stage criteria. Bell Stage I includes increased gastric residuals, abdominal distension, vomiting, occult or gross blood in stool, apnea, bradycardia, temperature instability, and intestinal dilatation or ileus [13]. All these features can occur in premature infants for reasons other than NEC. Infection, noninvasive ventilation-related abdominal distension, feed intolerance, postoperative ileus or viral

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infection can produce a similar picture. Thus, labelling an infant as having Stage I NEC often reflects diagnostic uncertainty.

The next problem is the staging suggestive of linear progression. Bell staging suggests that the disease progresses from suspected NEC to definite NEC to advanced disease. In day-to-day practice, however, NEC progression is not reliably linear. Some infants are first recognized in advanced disease when pneumoperitoneum or profound shock is already present. Few infants oscillate between mild and moderate signs; still others are treated for "possible NEC" and later labelled as not having NEC at all [9,10].

A third major limitation relates to imaging findings. The pathognomonic radiographic sign of NEC, pneumatosis intestinalis, is highly useful when clearly present, but it is not always seen [22,23]. It may be transient, absent in some severe cases, or difficult to distinguish from stool or intraluminal gas. Portal venous gas may also be fleeting. In extremely premature infants, radiographs may show only nonspecific bowel dilatation, fixed loops, or a gasless abdomen. Inter-observer variability in interpretation is well documented, and agreement is often poorest especially in the cases where there is diagnostic dilemma [22]. Consequently, criteria that rely heavily on classical radiographic signs may lack sensitivity, whereas those that do not consider imaging requirements lose specificity.

The fourth limitation is that Bell staging is often used in a manner that mixes up diagnosis and severity stratification. A diagnostic definition should identify whether the disease is present; a severity system should estimate how advanced or dangerous it is. Both are attempted simultaneously using the Bell staging. This can be problematic because a child can be severely ill due to volvulus or spontaneous intestinal perforation and not NEC, while another may have genuine NEC without characteristic signs [11,24]. The conceptual mixing of diagnosis and severity contributes to inconsistent case classification.

The fifth limitation is the rarity of histopathological confirmation. In NEC, pathological diagnosis is generally available only in infants who undergo surgical resection bowel or occasionally at autopsy. The findings can vary from patchy mucosal necrosis to diffuse transmural necrosis with perforation. Some surgical conditions initially labeled as NEC may later appear more consistent with isolated perforation or another etiology [4,24]. Thus, the pathological "gold standard" is not always available for most cases and findings are also not uniform.

Finally, Bell staging was however devised before deeper insights was achieved regarding intestinal epithelial signaling, Toll-like receptor 4 activation, microbiome disruption, human milk protection, inflammatory priming, and hemodynamic vulnerability in growth-restricted or cardiac infants [14–20]. Because the staging system is based on severity rather than mechanism involved, it is not useful in distinguishing distinct biological pathways that presents with similar bedside signs.

These concerns have led some authors to describe Bell's framework as "broken" when used as a disease definition [9]. A revised framework should ideally accomplish several things: separate certainty of diagnosis from severity, improve distinction from NEC and its mimickers, acknowledge gestational-age-specific variable presentations, incorporate newer imaging modalities, and accommodate clinical phenotypes rather than attributing all presentations to a single linear pathway.

Alternative Diagnostic Criteria

Recognition of the limitations of Bell staging has led to repeated attempts to define NEC more rigorously so as to improve comparability across studies and reduce the erroneous inclusion of infants who do not actually have NEC [9–11,21,25].

The development of consensus-based definitions is intended for research use as well. They are based on a combination of clinical deterioration and other evidence of intestinal disease, such as characteristic imaging, surgical findings, or pathology, and attempt to exclude NEC mimickers like isolated spontaneous intestinal perforation [11,21]. Another important development has been gestational-age-specific case definitions. Battersby and colleagues argued that NEC does not present similarly across different gestational ages and proposed a gestational age specific case definition intended to improve diagnostic consistency, particularly in very preterm infants [10]. This work highlighted that highly

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immature infants may show less classical radiographic appearance and more systemic instability, whereas more mature infants may exhibit classic features on imaging or more localized intestinal pathology. A "one size fits all" definition may therefore perform poorly at the edges of prematurity.

Some proposed frameworks also distinguish between "suspected," "probable," and "definite" NEC. This takes into account how diagnosis changes at the bedside. The clinician's diagnostic certainty changes over time as serial examinations, radiographs, ultrasound, laboratory trends, and response to treatment evolves. Instead of only a binary label, probabilistic models acknowledge uncertainty while also clearly expressing the clinical concern.

The Vermont Oxford Network and other registries have also employed operational definitions for reporting and benchmarking [25]. Although these definitions increase standardization, they still have challenges like heavy dependence on documentation and imaging interpretation. Apparent differences in NEC rates between units not only reflects the care practices and outcomes but also depends on the case definition used.

The trade-off between sensitivity and specificity lies at the heart of NEC diagnosis. If the threshold for diagnosis is lowered, more infants are treated and research cohorts become diluted. If it is raised, some early disease may be missed.

Another critical area requiring attention is the separation of NEC from spontaneous intestinal perforation (SIP). SIP differs in timing, pathogenesis, pathology, radiology, and risk factor profile. It usually presents earlier, often without diffuse bowel inflammation or classical pneumatosis, and may be linked to steroid or indomethacin exposure, extreme prematurity, and focal intestinal weakness rather than the diffuse inflammatory cascade associated with classical NEC [24]. Newer case definitions increasingly regard SIP as a distinct entity that should be excluded from NEC cohorts.

Despite these advances, no single alternative definition has achieved universal adoption. This is because NEC pathogenesis and clinical presentation itself is very heterogeneous and is further compounded by the limitations of the currently available diagnostic tools. A highly specific definition may be desirable for trials but less useful at the bedside where early diagnosis and management is important. Conversely, a more sensitive clinical definition may be acceptable for management decisions but suboptimal for research purpose. NEC may not be a single disease that can be captured completely by one fixed set of criteria.

This highlights the importance of a phenotype-based approach. This can explain the clinico-biological patterns leading to the disease and give guidance for diagnosis and management. Such a phenotype-based approach provides a stronger framework along with the operational definitions.

NEC Pathophysiology

NEC is multifactorial and is caused by interaction between inherent developmental vulnerability and environmental exposures **(Figure 1)** [14–20,26]. The gastrointestinal tract of preterm infants is anatomically and functionally immature, contributing significantly to their susceptibility to NEC. The **epithelial barrier**, composed of tight junctions, mucus layer, and immunological defences, is underdeveloped [27], making it more permeable to luminal bacteria and toxins.

- Tight junction proteins (e.g., claudins, occludins) are poorly expressed in preterm intestines, allowing microbial translocation into the lamina propria.
- Goblet cells and Paneth cells, critical for mucus and antimicrobial peptide production respectively, are fewer and functionally immature, limiting mucosal defense.
- Impaired **gut motility** leads to stasis, promoting bacterial overgrowth.

A major mechanism in NEC pathogenesis is inappropriate activation of innate immune pathways, particularly Toll-like receptor 4 (TLR4) signaling in the immature intestinal epithelium [18,19]. Evidence suggests that excessive TLR4 activation can impair epithelial restitution, promote enterocyte apoptosis, weaken barrier function, and exaggerates the inflammatory injury. In the preterm gut, where counter-regulatory pathways are underdeveloped, this inflammatory cascade may produce a vicious cycle of bacterial translocation, cytokine amplification, mucosal injury, and necrosis.

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Microbial dysbiosis is another key component. Longitudinal studies of the preterm microbiome have identified patterns preceding NEC that include reduced microbial diversity and relative overrepresentation of Proteobacteria [20,27,28]. The unstable microbial ecosystem by itself does not cause NEC but it interacts with the immature mucosa and immune system and thus increases inflammatory susceptibility. Human milk plays a crucial role in enhancing epithelial maturation. Components such as epidermal growth factor (EGF), glutamine, and short-chain fatty acids (SCFAs) derived from microbial fermentation promote enterocyte proliferation and tight junction integrity [17,29,30].

Hypoxia and ischemia add significantly to the pathogenesis. Even mature neonates develop intestinal injury in the settings of low systemic flow, mesenteric hypoperfusion, congenital heart disease, significant patent ductus arteriosus, severe anemia, or fetal growth restriction with antenatal Doppler abnormalities [31–35]. In such infants, ischemia-reperfusion injury may be a major driver, perhaps interacting with feeding and inflammation. The clinical presentation can resemble classical NEC yet may differ in timing, imaging, and distribution of injury.

Inflammatory priming before or shortly after birth may also be relevant in certain infants. Exposure to chorioamnionitis, fetal inflammatory response, perinatal hypoxia, or early sepsis may sensitize the intestine and worsens subsequent intestinal injury [36,37]. This could explain atypical early presentation, even before substantial feed advancement, and prominent systemic inflammation but relatively subtle abdominal signs at presentation.

Overall, these mechanisms suggest that NEC is a final common pathway of intestinal injury produced by varying contributions from immaturity, microbial disruption, inflammatory dysregulation, and perfusion failure. The proportions of these contributions differ from case to case. A phenotype-based approach is therefore a clinically useful way of linking bedside patterns to dominant mechanisms.

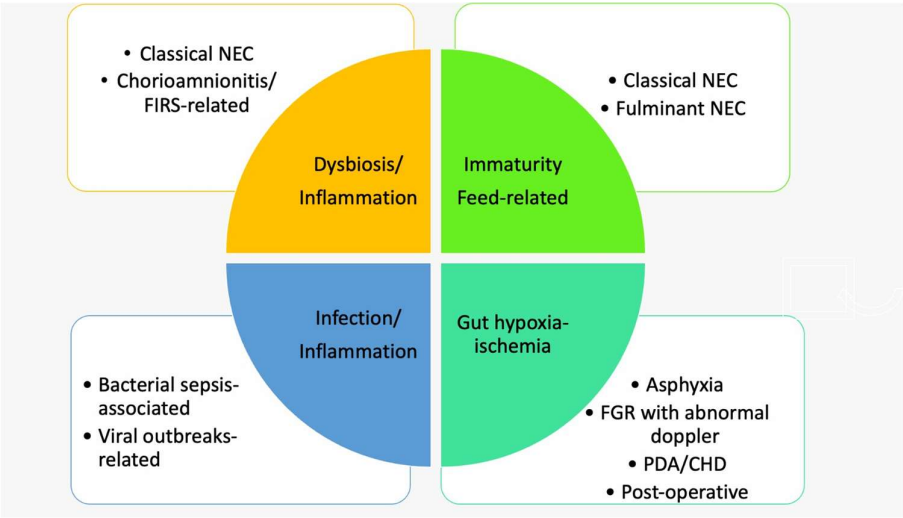

Figure 1. Classification of NEC into distinct phenotypes based on predominant pathophysiological mechanisms.

NEC-Clinical Phenotypes

A phenotype-based framework recognizes that infants diagnosed with NEC do not all present in the same way, at the same time, or secondary to same pathophysiology.

a) Classical NEC

The classical type usually occurs in very preterm infants after initiation and advancement of enteral feeding, commonly in the second or third postnatal week, although timing varies by gestational age and ICU practices [3,38]. This occurs as a result of interaction between intestinal immaturity, dysbiosis, and exaggerated inflammatory signaling.

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Typical risk factors include extreme prematurity, formula exposure or limited access to human milk, recent feed advancement, microbial dysbiosis, and episodes of systemic instability. Clinically, infants often present with emesis, abdominal distension, tenderness, or visible bowel loops, followed by bloody stools or features of systemic illness. Radiographs in this phenotype usually show pneumatosis intestinalis and portal venous gas [22,23].

Formula feeding, altered colonization, and immature mucosal barrier creates an inflammatory cascade and TLR4-mediated inflammation becomes destructive [18,19]. It is also the phenotype in which protection from human milk is especially emphasized [17,29,30]. Even in this "classical" phenotype there is wide variability with some having localized disease and recovery, whereas others progress rapidly to necrosis and perforation.

b. Early-Onset or Inflammation-Associated NEC

A subset of infants develops NEC unusually early, sometimes within the first week of life and occasionally even before significant enteral feeding is established [36,37]. In such infants, inflammation may play a more dominant role than feed-microbiome interaction alone. Maternal chorioamnionitis, fetal inflammatory response syndrome, early-onset sepsis, severe perinatal stress, or profound respiratory instability may lead to this phenotype.

Clinically, these infants often present with systemic features out of proportion to abdominal signs and imaging findings: worsening acidosis, apnea, hypotension, escalating ventilatory need, thrombocytopenia, or poor perfusion, with only mild distension or subtle bowel gas abnormalities initially. Because pneumatosis may be absent in such phenotype, the clinical presentation is easily confused with septic ileus. Some may later develop radiographic findings compatible with NEC, while others continue to pose diagnostic challenge.

This phenotype does not follow the usual teaching that NEC is a post-feeding disease of the second or third week. Thus, a very immature infant with inflammatory priming may develop intestinal injury without the classical sequence assumed in Bell staging. This highlights the importance of the role played by antenatal inflammation, perinatal adaptation, and early sepsis in causing the intestinal injury.

c. Perfusion-Related NEC

In some infants with NEC, the dominant inciting factor is mesenteric hypoperfusion rather than dysbiosis or inflammation. This phenotype is seen in neonates with hemodynamically significant patent ductus arteriosus, congenital heart disease, systemic hypotension requiring inotropes, fetal growth restriction with abnormal antenatal Dopplers, or severe anemia [14,31–35]. The intestine in these conditions is already compromised and chronically under-perfused making it more susceptible to injury.

Infants may show feeding intolerance, abdominal distension, acidosis, rising lactate, and poor peripheral perfusion. Pneumatosis may be absent or limited, and radiographs may show nonspecific dilated loops or a gasless abdomen. Ultrasound might show poor intestinal perfusion before radiographs become definitive [23].

i) Cardiac-associated NEC: Infants with congenital heart disease, especially those with duct-dependent systemic circulation may develop intestinal injury with NEC-like features [14,33]. The term "cardiac NEC" is often used clinically and intestinal involvement is different from that of classical NEC with colon involved predominantly.

ii) Fetal growth restriction (FGR)-associated intestinal injury: Growth-restricted infants exposed to abnormal antenatal Dopplers may have chronic redistribution of fetal blood flow and impaired intestinal vascular development. After birth, when enteral feeding is initiated, the immature gut exposed to chronic hypoperfusion may struggle to adapt to increased metabolic demand representing a "reperfusion injury". This can lead to mucosal damage, impaired motility, barrier dysfunction, and an exaggerated inflammatory response, all of which increase susceptibility to NEC [34,35].

iii) Transfusion-associated intestinal injury: The concept of transfusion-associated NEC remains debated. Studies attribute NEC causation to the preceding anemia or clinical instability rather than a

 doi:10.20944/preprints202604.0221.v1

direct transfusion effect [39]. Regardless of causality, this phenotype highlights the role of oxygen delivery and hemodynamic instability in causing intestinal injury.

iv) Fulminant NEC

Fulminant NEC is characterized by rapid progression over few hours [2–4,40]. These infants deteriorate rapidly with severe metabolic acidosis, coagulopathy, refractory hypotension, thrombocytopenia, abdominal wall erythema or discoloration, and multiorgan dysfunction. Imaging may show extensive pneumatosis, portal venous gas, or alternatively a gasless abdomen with little warning. Surgical exploration often reveals widespread necrosis, pan-intestinal involvement, or multiple areas of ischemic injury.

This phenotype highlights the limitations of progression of disease through stages, because there may be little or no clinically observed interval between "suspected" and "advanced" disease.

v) NEC in Term Infants

Although NEC is primarily a disease of prematurity, term infants can also develop this intestinal injury when they have other morbidities like congenital heart disease, perinatal asphyxia, polycythemia, sepsis, or other stressors [33,41]. Compared with classical preterm NEC, term disease more often has identifiable precipitating conditions.

vi) Postoperative or Anomaly-Associated NEC

Postoperative ileus, bowel edema, altered perfusion, stoma-related complications, and impaired motility can make diagnosis challenging in NEC that develops after surgery or in congenital anomalies. Likewise, intestinal compromise in the setting of gastroschisis, omphalocele, or other anomalies may resemble NEC clinically but arise through distinct pathways.

Phenotypes matter because they have variable pretest probability, expected clinical and imaging findings, and mimics differ (Table 1). A 25-week infant on advancing feeds with bloody stools and pneumatosis suggests classical feeding-associated NEC. A 24-week infant on minimal feeds in the first days of life with sudden pneumoperitoneum but no pneumatosis raises concern for spontaneous intestinal perforation. A duct-dependent cardiac infant with acidosis and abdominal distension but nonspecific radiographs suggest perfusion-related intestinal injury.

Table 1. Clinical and Pathophysiological Features of Necrotizing Enterocolitis (NEC) Phenotypes in Neonates.

Endotype	Etiology	Gestation	Median postnatal age of onset	Clinical features	Radiological findings	Histopathological findings	Additional testing	Outcome
Classical NEC	Dysbiosis + Immature immune response	<32 weeks	2nd–3rd week	Abdominal distension, feeding intolerance, bloody stools	Pneumatosis, portal venous gas	Transmural necrosis, inflammation, bacteria	CRP, CBC, blood culture	Variable, ~70–80% survive
Atypical presentations in preterm neonates- Early or non-nutrition associated NEC								
NEC associated with infections								
NEC and Bacterial Sepsis	Hematogenous seeding of gut	<32 weeks	Often earlier (Day 5–10)	Septic signs predominate	Similar to classical NEC	Focal/multifocal necrosis, neutrophilic infiltrate	Positive cultures, inflammatory markers	Higher mortality, Increased risk of perforation
Viral Outbreaks Triggering NEC	Enteric viruses (e.g., Norovirus, Rotavirus)	<34 weeks	1st–2nd week	Diarrhoea, vomiting, apnea	Pneumatosis ± atypical pattern	Milder necrosis, lymphoid aggregates	PCR/viral panels	Variable
CMV-Associated NEC	Congenital/Perinatal CMV	Any GA, esp. <30 weeks	~1st week	NEC-like symptoms, hepatosplenomegaly	Bowel wall thickening, atypical gas pattern	CMV inclusions, necrosis	Blood CMV PCR, urine/saliva CMV PCR	Often surgical NEC

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Fulminant NEC	Severe systemic inflammatory response	<28 weeks	<Day 7	Rapid progression to shock	Diffuse pneumatosis, gasless abdomen	Pan-intestinal necrosis	Blood gas, coagulation profile, cultures	High mortality (~50–80%)
NEC related to compromised gut perfusion								
NEC associated with PDA	Reduced mesenteric perfusion	<32 weeks	~2nd week	NEC + murmur, bounding pulses	Typical or right-sided NEC (involving predominantly the ascending colon and terminal ileum: supplied by watershed zones of the superior mesenteric artery)	Patchy ischemic necrosis	Echo for PDA	Slightly worse outcomes
NEC associated with abnormal antenatal Dopplers	Antenatal placental insufficiency	IUGR, <32 wks	Early onset (Day 3–7)	Feed intolerance, distension	Diffuse NEC	Mucosal sloughing, ischemic changes	Antenatal doppler	Moderate survival
Atypical presentations (Term neonates)								
NEC associated with perinatal asphyxia	Hypoxic-ischemic injury	Term or late preterm	Day 1–3	Rapid deterioration, lactic acidosis	Free air, bowel wall edema	Ischemic necrosis without inflammation	Blood gas, Lactate, MRI brain	Often poor prognosis, Multisystem sequelae
NEC associated with congenital heart disease (CHD-NEC)	Mesenteric hypoperfusion in CHD	Term infants	Variable (Day 3–10)	Signs of NEC + cardiac symptoms	Right-sided NEC, portal gas	Ischemia-dominant	Echo, lactate	High surgical rate
NEC associated with congenital intestinal anomalies and surgery (post-operative NEC)	Post-surgical gut stress/inflammation	Term or preterm	Variable, post-op	Lethargy, ileus, fever	Difficult to detect early	Patchy necrosis, inflammation	Surgical history, cultures	Depends on underlying disease

Differential Diagnoses and Close Mimickers

The diagnosis of NEC is further complicated by other disorders that can mimic it [11,14,24,33,42–47]. Distinguishing these from NEC is essential because management and prognosis may differ across these conditions.

a) Spontaneous intestinal perforation: It is among the most important mimics, particularly in very immature infants [24]. It usually presents earlier than classical NEC, often within the first week of life. It results in a focal perforation rather than diffuse necrosis. Classical radiological signs of NEC like pneumatosis or portal venous gas are absent and it presents with free air and clinically presents as abrupt abdominal distension. Histologically also, there is only focal muscularis disruption with

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lesser inflammation than in NEC. Risk factors include extreme prematurity, postnatal steroid exposure, and exposure to indomethacin or ibuprofen.

b) Septic ileus: Late-onset sepsis can present with feed intolerance, abdominal distension, apnea, lethargy, thrombocytopenia, and acidosis, all of which overlap with NEC. Dilated bowel loops can be seen in radiography but classical features like pneumatosis or pneumobilia are not seen. In day today clinical practice, infants with suspected NEC are treated for sepsis until serial clinical evolution and imaging findings help to narrow down the diagnosis. The distinction can be particularly difficult in very early or inflammation-associated NEC.

c) Cow's milk or food protein allergy: This condition also presents with bloody stools and abdominal signs in otherwise relatively stable infants [43]. Severe acidosis, thrombocytopenia, and classical radiographic findings of NEC are usually absent. The timing is often later, and improvement follows elimination of the offending protein.

d) Viral enterocolitis: Viruses like cytomegalovirus, rotavirus, norovirus, and enterovirus also can cause enterocolitis mimicking NEC [45]. This condition also can present with distension, bloody stools, and even pneumatosis. A history of exposure and an atypical course may suggest an infectious mimic. CMV enterocolitis should be considered especially in very preterm infants with prolonged illness, cytopenia and transfusion exposure.

e) Surgical emergencies: Malrotation with midgut volvulus presents with bilious vomiting, distension, bloody stools, shock, and metabolic acidosis and may be misdiagnosed as fulminant NEC [45]. Incarcerated hernia, obstructive bands, Hirschsprung-associated enterocolitis, and colonic perforation are other surgical conditions that may present similarly. Bilious vomiting, rapid hemodynamic collapse without typical imaging, and abnormal upper gastrointestinal contrast study findings can help in identifying these differentials.

f) Others: Opioids for analgesia, anticholinergic exposure, severe respiratory disease, high continuous positive airway pressure, and electrolyte disturbances may all impair gut motility. These conditions can result in large gastric residuals and distension without intestinal inflammation. Labelling as NEC in these situations can unnecessarily interrupt feeds and prolong central line exposure.

Because no single sign distinguishes NEC from all mimics, the differential diagnosis must remain active over time. Diagnostic accuracy improves when clinicians repeatedly reassess not just "how sick is the baby?" but "what process best explains the evolving findings?"

A Dynamic Diagnostic Framework for NEC

The most practical way to diagnose NEC is not as a one-time label but as a dynamic clinical process that integrates antenatal and perinatal history, serial examination, imaging, laboratory tests, and delineation of the phenotype [10,11,21,23,46].

Step 1: Assess the Clinical Context

Gestational age, day of life, feed exposure, type of milk, antenatal history, recent hemodynamic events, risk of infection, transfusion exposure, and congenital disease all shape diagnostic probability. A 26-week infant in week 3 on advancing feeds has a different profile from a 24-week infant on minimal feeds on day 4, or a term infant with congenital heart disease after surgery. Phenotyping begins at this point.

Step 2: Assess the Pattern of Systemic and Abdominal Findings

The next question is whether there is evidence of evolving intestinal disease rather than isolated feeding intolerance. Progressive abdominal distension, tenderness, discoloration, visible bowel loops, abdominal wall edema, or gross blood in stool usually suggest progressive intestinal disease. Systemic signs such as recurrent apnea, increasing oxygen requirement, hypotension, temperature instability, lethargy, rising lactate, thrombocytopenia, or metabolic acidosis strongly suggest a

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inflammatory process. No individual sign is specific, but the combination of all these signs point towards NEC.

Step 3: Use Serial Imaging, Not a Single Radiograph

Abdominal radiography remains the backbone of initial imaging, but its limitations must be acknowledged [22,23]. A normal or nonspecific first radiograph does not exclude NEC. Serial films may reveal evolving bowel wall gas, fixed dilated loops, portal venous gas, ascites, or free air. Serial imaging and pattern recognition is important.

Abdominal ultrasound has become an valuable adjunct [23,46]. It can assess bowel wall thickness, echogenicity, perfusion with Doppler, peristalsis, free fluid, focal collections, and bowel wall integrity. Complex ascites, absent mural perfusion, bowel wall thinning, or pneumoperitoneum may suggest advanced disease or impending perforation. Its limitations include operator dependence but when expertise exists, it adds meaningful information and aids in diagnostic confirmation.

Step 4: Interpret Laboratory Tests

Common laboratory abnormalities in NEC include thrombocytopenia, metabolic acidosis, elevated lactate, neutropenia or neutrophilia, hyponatremia, coagulopathy, and increased inflammatory markers [47]. These findings help in assessing severity and offer supportive care, but none are specific to NEC. Trend interpretation is more important rather than confirming the diagnosis based on a single value. A falling platelet count, worsening acidosis, or increasing lactate in an infant with concerning abdominal findings suggests progression and would warrant surgical consultation.

Step 5: Reassess the Differential at Each Stage

A dynamic framework deliberately revisits alternative diagnoses. If pneumatosis never appears, cultures become positive for bloodstream infection, and the abdomen improves rapidly with sepsis treatment, septic ileus may be more likely. If the infant is extremely premature, minimally fed, and develops isolated free air early, SIP should be considered. If the infant is term with sudden onset bilious vomiting and shock, volvulus must be considered.

Step 6: Use Biomarkers with Caution

A large number of biomarkers have been studied in NEC, including intestinal fatty acid-binding protein (I-FABP), fecal calprotectin, serum amyloid A, cytokine panels, claudins, and urine peptide signatures [48–51]. These are biologically appealing because they indicate enterocyte injury, barrier disruption, or inflammatory activation before overt clinical or radiological findings. However, most remain limited by variable thresholds, lack of routine availability, cost, and positivity in multiple conditions. At present, biomarkers are just adjuncts rather than replacements for clinical and imaging assessment.

Step 7: Characterize the Clinical Phenotype (Figure 2)

Currently, one of the most useful strategies is to stop asking the complex question of whether the child has NEC or not. Instead, we need to focus on "Among neonatal intestinal diseases, what process most likely explains this infant's presentation right now, how certain are we, and what phenotype or mimic best fits the pattern?"

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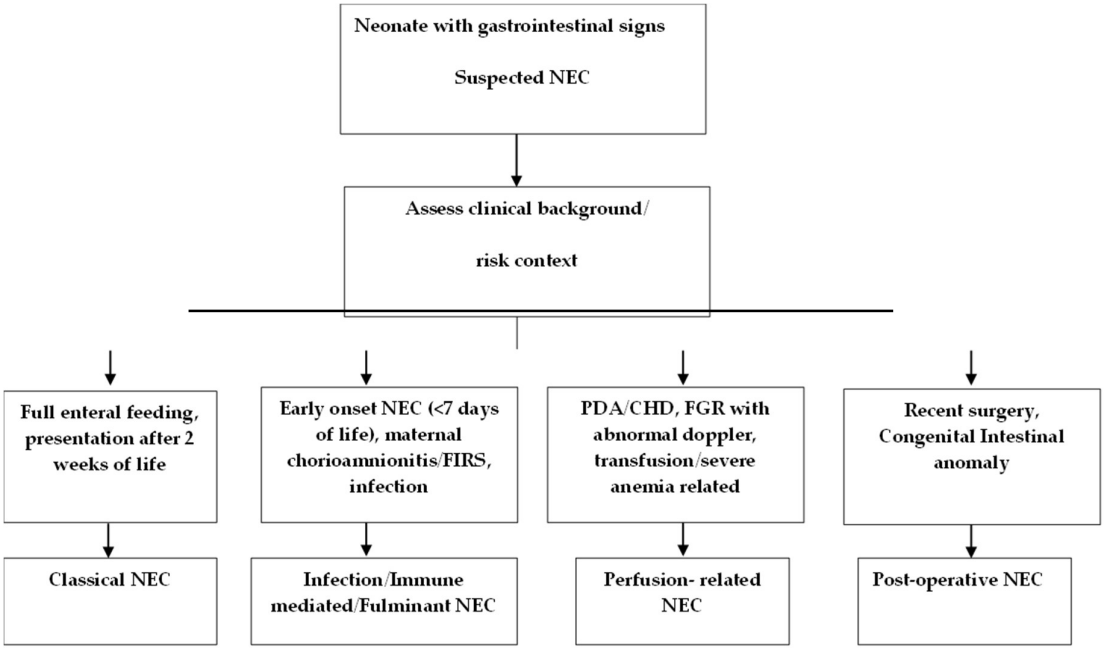

Figure 2. Algorithm for phenotype-based approach to suspected NEC in neonates.

Aftermath and Consequences of NEC

Even after the acute episode resolves, the consequences of NEC can continue for a long time [5–8]. Intestinal strictures, short bowel syndrome, intestinal failure, prolonged dependence on parenteral nutrition, central line associated blood stream infection, and intestinal failure-associated liver disease can occur after surviving from NEC. Nutritional rehabilitation would be required for a prolonged period.

All these complications contribute to growth failure compounded by increased metabolic demands. Neurodevelopmental impairment is also more frequent after NEC, especially after surgical disease, following exposure to systemic inflammation, prolonged illness, infection, impaired nutrition, and prolonged hospitalization [6–8].

Future Directions

Future progress in NEC will likely come from combining improved phenotyping with biological stratification [14–16,20,48–51]. Multi-omics approaches integrating microbiome profiles, metabolomics, transcriptomics, and host inflammatory signatures may help to identify the dominant mechanism involved. Rather than a single NEC biomarker, the future may involve a panel.

Artificial intelligence and machine learning may also contribute by analyzing the following trends continuously: cardiorespiratory instability, feeding patterns, lab trends, medication exposure, and imaging features [52]. Predictive systems will however need careful external validation. Their role is specifically important for earlier recognition of fulminant disease.

Equally important is refinement of case definitions for research. Trials should explicitly state whether they target suspected NEC, definite NEC, surgical NEC, or particular phenotypes. Without this clarity, effective interventions may be missed because different biological phenotypes are grouped together.

Conclusion

NEC remains a complex, heterogeneous condition rather than a single uniform disease. The traditional Bell staging system, though valuable for grading severity, is inadequate as a standalone diagnostic framework because early criteria are nonspecific, disease progression is not reliably linear, imaging is imperfect, and important mimics such as spontaneous intestinal perforation may be

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misclassified. Alternative definitions might have improved the research accuracy discussion but still not able to demarcate multiple biological pathways causing NEC.

A phenotype-based framework offers a more clinically useful way forward. By recognizing classical feeding-associated inflammatory NEC, inflammation-associated NEC, perfusion-related NEC, fulminant NEC, term NEC, and postoperative or anomaly-associated intestinal injury, clinicians can better integrate clinical course and, anticipate diagnostic challenges. The most effective diagnostic strategy is dynamic and integrative: serial clinical assessment, repeated imaging including ultrasound where available, supportive laboratory trends, and persistent reassessment of alternative diagnoses.

Better alternate definitions are essential for improving bedside decisions, surgical timing, epidemiology, trial design, and long-term outcomes. The future of NEC diagnosis lies in moving beyond the broken Bell toward a phenotype-informed, and biologically grounded framework.

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