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Defining Necrotizing Enterocolitis: Current Difficulties and Future Opportunities

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Abstract

Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in hospitalized infants. First classified through Bell staging in 1978, a number of additional definitions of NEC have been proposed in the subsequent decades. In this review, we summarize 8 current definitions of NEC, and explore similarities and differences in clinical signs and radiographic features included within these definitions, as well as their limitations. We highlight the importance of a global consensus on defining NEC to improve NEC research and outcomes, incorporating input from participants at an international NEC conference. We also highlight the important role of patient-families in helping to redefine NEC.

Defining a disease or condition has important implications. Meeting a set of criteria for a disease or condition can influence how a patient or family perceives their condition, what kind of prognostic information they receive, and how they are monitored, evaluated and treated. A disease definition may influence the feasibility and generalizability of studies, how outcomes are compared across centers and countries, how biomarkers or other tools are developed and used for diagnosis or prognosis, how treatment is approached and research funded. In this review, we summarize how the definition of NEC has evolved over time, compare NEC definitions and highlight the urgent need to develop an accurate, reliable, and reproducible definition of NEC that can garner global consensus.

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THE FIRST CRITERIA FOR NECROTIZING ENTEROCOLITIS (NEC): BELL STAGING

In 1978, Bell and colleagues proposed the first classification system for NEC(1). At the time, the etiology and pathophysiology of NEC were unclear, there were no proven preventative measures, and studies of the treatment for NEC were limited by the lack of uniformly accepted diagnostic criteria. Bell staging system included a set of characteristics used to classify infants into 1 of 3 stages of NEC (Figures 1 and 2), which were used to stratify infants by illness severity, guide treatment, and support valid comparisons of the management of NEC. In this report, NEC varied in progression and evolution across the disease stages. Over four decades later, Bell staging remains the most commonly utilized case definition of NEC worldwide(2).

EXPANDING BELL STAGING: MODIFIED BELL STAGING

In 1986, Modified Bell staging criteria were introduced, updated Bell staging by increasing the number of stages from 3 to 6 (Figures 1 and 2) to guide therapeutic decisions based on differences in severity of illness across the expanded stages (3). The newer staging system differentiated infants with Bell stage I by the criteria of bright red blood from the rectum (Stage IB), to those without this finding (Stage IA). In addition, Stage IIA and IIB allowed differentiation of severity of illness, from infants who were mildly ill (Stage IIA) to moderately ill (Stage IIB) with ascites or portal venous gas. Finally, stage IIIB identified infants with pneumoperitoneum, contrasting stage IIIA. Modified Bell staging was adopted as the diagnostic criteria in some large cohorts, such as the National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network(4), although most studies continued to use Bell staging(2). These authors later demonstrated that the stage of NEC correlated with long-term outcomes among survivors(5).

LIMITATIONS OF BELL AND MODIFIED BELL STAGING

Despite wide use of Bell staging to define NEC, there are several limitations as discussed below.

Bell staging is not an explicit case-definition

Although Bell staging provides criteria to stage the severity of disease once an infant had been diagnosed with NEC(1), the staging has been adapted as diagnostic criteria. The challenge is that the criteria include a number of characteristics with varying sensitivity and specificity that are not weighed by the importance to the diagnosis of NEC (e.g. feeding intolerance and blood in stool). This can lead to over- or underestimation of NEC as was reported in a recent Swedish cohort study(6). Some newer definitions, as discussed below, have focused on only some of the characteristics described in the Bell staging.

Non-specific findings in Bell stage I

Among very low birth weight infants (VLBW), symptoms of Bell stage I, including feeding intolerance and abdominal distention (Figures 1 and 2), are common and may be normal

findings or caused by separate diseases such as sepsis. To address this, the majority of reports of NEC incidence from cohorts in high-income countries as well as trials of therapies to prevent NEC, such as probiotics, use the definition of Bell Stage II or greater as the case-definition(2).

Inclusion of infants with spontaneous intestinal perforation

Spontaneous intestinal perforation (SIP) is a focal gastrointestinal perforation that typically occurs in the distal ileum in the first 1–2 weeks of life(7). SIP has been recognized for several decades as an entity distinct from NEC(8). In addition to an earlier timing of onset than NEC, SIP often occurs in an infant receiving no or minimal feeding. Development of SIP has been associated with concomitant exposure to indomethacin for PDA closure and systemic corticosteroids(9, 10). Radiographically, there is absence of pneumatosis, and histologic findings do not demonstrate inflammation and necrosis that is typically observed in NEC(9), while microRNA features are distinctly different when compared to NEC infants(11). However, based on the Bell staging criteria, many infants with SIP could be classified as Bell Stage III (or modified Bell stage IIIB). This has led to concerns regarding significant contamination of data reported in studies of NEC, with infants with SIP misclassified as NEC(12). To address these limitations, some studies describe exclusion of infants with SIP. Although there are not widely accepted diagnostic criteria for SIP, most definitions of SIP include infants with pneumoperitoneum without other radiographic features of NEC (pneumatosis, portal venous gas) or differentiate SIP and NEC by direct visualization of affected bowel, when possible. A recent study comparing signs and symptoms of NEC or SIP highlight some of the challenges in differentiating SIP and NEC, given the overlap in clinical characteristics(13). Postnatal age may be a simple, albeit imperfect criterion, to differentiate SIP from NEC, as infants with SIP tend to develop disease at an earlier age than those with NEC(7).

Other concerns

Neither Bell nor modified Bell staging accounts for baseline risk, particularly gestational age, which is a major risk factor that influences the baseline risk of NEC. Additionally, Bell staging uses criteria that may be subjective (e.g. abdominal distention) or be an unreliable diagnostic radiographic finding(14, 15), as discussed in later sections.

NEWER SCORING CRITERIA OR DIAGNOSTIC DEFINITIONS FOR NEC

Vermont Oxford Network (VON) definition

The VON is a collaborative, currently including more than 1200 hospitals around the world, that supports benchmarking of outcomes and quality improvement(16). The VON criteria define NEC as a diagnosis at surgery or on post-mortem examination or based on clinical and radiographic criteria (comprised of features from Bell staging)(17). Infants must have at least 1 of the following clinical signs: bilious gastric aspirate or emesis, abdominal distension or occult/gross blood in stool (no fissure). In addition, infants must have at least 1 of the following radiographic findings: pneumatosis intestinalis, hepato-biliary gas (portal venous gas) or pneumoperitoneum. Infants found at surgery or post-mortem examination to have a focal intestinal perforation (spontaneous intestinal perforation) are coded as having

that disease and not NEC. Recent reports have noted a declining incidence of NEC in the US, from 7.1% in 2005 to 5.2% in 2014, using this definition(18).

Centers for Disease Control and Prevention (CDC) definition

The CDC is a US health agency that performs infectious disease surveillance through the National Health Safety Network (NHSN). The CDC surveillance definition for NEC is similar to the VON definition, with some modifications(19). Infants must have at least 1 of the following clinical findings: “bilious aspirate (excluding aspirate obtained from a transpyloric tube), vomiting, abdominal distention or occult/gross blood in stools (with no rectal fissure).” In addition, infants must have at least 1 of the following imaging findings: “pneumatosis intestinalis, portal venous gas (hepatobiliary gas) or pneumoperitoneum.” If at least one imaging test finding is equivocal, then clinical correlation with physician documentation of antimicrobial treatment for NEC is needed. Surgical NEC is defined as meeting one of the following findings: “surgical evidence of extensive bowel necrosis (>2 cm of bowel affected)” or “surgical evidence of pneumatosis intestinalis with or without intestinal perforation.” Infants with SIP are not explicitly excluded in this definition.

Gestational Age-Specific Case Definition of NEC (UK)

The UK Neonatal Collaborative Necrotising Enterocolitis (UKNC-NEC) Study Group, referred to as UK in Figures 1 and 2, developed a point-based gestational age-specific case definition using a population-based cohort of infants(20). The NEC score ranged from 1–9 and included 1 point for the presence of abdominal discoloration, tenderness, increased or bilious aspirations and abdominal distention, or one or more radiographic signs of pneumoperitoneum, fixed loop or portal venous gas. Two points were assigned for blood in the stool and 3 points for pneumatosis. Based on the gestational age group (<30 weeks, 30 to <37 weeks’ or ≥37 weeks), infants would have score cut-points to meet the case definition, ranging from 2 or more points at <30 weeks to 4 or more points required at ≥ 37 weeks. These cut points were chosen as the predicted probability of NEC exceeded 40% once this threshold was met. In the study, the authors reported a lower error rate in classifying infants with NEC when compared to the VON definition.

In addition to this definition, a more restrictive definition of NEC has been used for population-based surveillance in the UK that is limited to infants with the most severe disease(21). In this definition, severe NEC was defined as NEC confirmed by laparotomy, histology, or autopsy, or, if no tissue evidence was available, the reported primary cause of death on the death certificate. Infants with a diagnosis of SIP at time of laparotomy were excluded.

Two of 3 rule

The 2 of 3 rule is a scoring system that diagnoses preterm NEC if an infant has abdominal distention, ileus and/or bloody stools and meets at least 2 of the following criteria: pneumatosis and/or portal air by x-ray or ultrasound at presentation, persistent platelet consumption (platelet count <150,000 × 3 days after diagnosis) and postmenstrual age at disease onset more consistent with NEC than SIP(22). Patients known to have SIP, complex congenital anomalies, being fed < 80 ml/kg/d or ≥ 36 weeks’ gestation would be excluded

from a diagnosis of preterm NEC. The authors who proposed this rule have also highlighted defining NEC subsets based on possible etiology or risk factors(23). One potential limitation of using disease subsets is defining NEC by a postulated risk factor, which may or may not be causal and could lead clinicians and families to assign a single cause of NEC (e.g. transfusion-associated NEC) that has uncertain supporting evidence or that may not adequately reflect the multifactorial pathophysiology of NEC.

Stanford NEC score

This Stanford NEC score was developed using a 6-center cohort of 520 infants with suspicion of NEC(24). The tool included a number of characteristics (Figure 1 and 2), including baseline characteristics (e.g. postnatal age, gender, ethnicity), clinical/historic factors (e.g. feeding intolerance, ventilation on day of NEC), clinical exam findings (e.g. abdominal wall discoloration), laboratory findings (platelet count, pH value) and radiographic findings (e.g. pneumatosis intestinalis or portal venous gas). These inputs generate a score, which can be used to classify the severity of disease and also determine the risk of progression of disease.

International Neonatal Consortium (INC) NEC workgroup definition

A workgroup of stakeholders was assembled by the International Neonatal Consortium to guide the development of a new definition of NEC(25). The proposed criteria provide an emphasis on the timing of onset and clinical and radiographic evidence of NEC. Infants would require 1 of 2 clinical signs (abdominal distention or hematochezia), onset between the 10th postnatal day and 36 weeks' postmenstrual age, and at least one of the following: intestinal necrosis at laparotomy, either pneumatosis intestinalis or portal venous air (by radiograph or ultrasound), or evidence of vasculitis, coagulopathy or inflammation in the absence of bacterial, fungal or viral infection. This definition differentiates infants with "preterm NEC", excluding those with intestinal perforation in the first 10 days without evidence of pneumatosis intestinalis, portal venous air, or tissue necrosis noted at surgery or autopsy or infants with NEC that are >36 weeks' gestation, have isolated feeding intolerance, congenital cyanotic heart disease or gastroschisis. The report recommends infants with NEC that do not meet the criteria for "preterm NEC" should be classified as either "atypical NEC" or "term NEC" for reporting in clinical research.

DEFINING NEC: CURRENT BARRIERS AND FUTURE OPPORTUNITIES

Comparisons of definitions

Limited studies have compared the diagnostic validity of definitions against a gold-standard diagnosis of NEC. A critical part of the challenge is that there is not a generally agreed upon method to determine the gold-standard for NEC. The recent gestational-age based UK NEC definition, which also assessed the VON definition, assessed the ability of the case-definition to classify infants with and without NEC, with a sensitivity of 64% and specificity of 97% using the NEC score and gestational age thresholds, when compared to the clinically determined "gold standard" that was determined by visual inspection of the bowel, tissue histology or autopsy for infants undergoing a laparotomy, or by an unequivocal diagnosis of NEC by an attending clinician for infants managed medically.

One challenge is the staging and clinical criteria across definitions are highly variable, as highlighted in Figures 1 and 2. The only consistent characteristic we observed across all staging criteria or definitions of NEC was the presence of radiologic findings of pneumatosis intestinalis or portal venous gas. Few reports on NEC provide data on the characteristics of individual components of the definition used to ascertain NEC. Reporting such data could allow for better comparison of studies and pooling of NEC outcomes and results across studies. This information could also help researchers refine and improve on current NEC definition(s).

Ascertainment of pneumatosis intestinalis

Given the importance of pneumatosis to the diagnosis of NEC, how pneumatosis is ascertained is critical. Most trials and studies have not reported on how uncertainty regarding the presence of pneumatosis was determined. One observational study noted differences in the characterization of pneumatosis as “definite”, “possible”, “questionable” or “difficult to exclude” and this differed across assigned modified Bell stages of NEC(26). The use of ultrasound may help with ascertainment of pneumatosis(27), although systematic-reviews report low sensitivity for the diagnosis of NEC(28, 29). In addition, a skilled operator may not be available when needed for evaluation of an infant with possible NEC.

Use of biomarkers

A number of studies have examined the use of biomarkers to aid in the diagnosis or prognosis for NEC(22, 30). However, given the relatively low incidence of NEC, and the non-specific clinical findings that may lead to an evaluation for NEC, the performance of biomarkers (e.g. sensitivity, specificity, likelihood ratio) needs to be good enough to be useful without leading to unintended consequences from false-positives or missed cases of true NEC. The major barrier in the study of biomarkers is having a standard, well-agreed upon definition of NEC to assess a biomarker. Reports of biomarkers in neonatal sepsis (complete blood count, C-reactive protein) have shown these biomarkers are not sufficiently accurate to help early diagnosis of sepsis, despite their widespread use(31, 32). The topic of biomarkers will be addressed in detail in another review in this series.

Use of machine learning and artificial intelligence

Machine learning and artificial intelligence offer promise to guide the prognosis, diagnosis and treatment of disease(33). Machine learning could be used to guide the diagnosis of NEC and classify infants based on many factors, although studies to date have been limited(34). However, a central challenge to machine learning is having a high-quality, and representative dataset that includes data available to clinicians in routine electronic health records to support validation and implementation of derived tools. As with prior disease definitions, determining the gold standard definition of NEC with which a large dataset of input variables can be evaluated remains a challenge. The use of machine learning in specific aspects of the diagnosis of NEC, such as the interpretation of abdominal radiographs is an exciting potential area for future research.

INPUT FROM A NEC DEFINITION WORKSHOP HELD AT AN INTERNATIONAL NEC CONFERENCE

In 2018, a workshop at the Special Interest Group NEC (SIGNEC) Conference (signec.org) stimulated discussion on redefining NEC towards a global consensus definition for evaluation (35). This meeting included neonatologists, surgeons, researchers, epidemiologists, radiologists and patient-families. The workshop was led by some of the authors of this review. Attendees were queried using an audience response system regarding questions relevant to defining NEC (Table 1). This was an initial step in assessing the "readiness" of clinicians and researchers to adopt changes to certain aspects of newer definitions of NEC, such as the use of ultrasound, inclusion of platelet count or C-reactive protein or approaches to exclusion of infants with SIP. Participants emphasized collaboration in overcoming current barriers to redefining NEC and the urgent need to work towards a global consensus definition. However, these data may not be generalizable or representative of the broader neonatal community.

Engaging patient-families

Patient-families describe experiences highlighting the variability in the diagnosis and treatment of NEC. Some patient-families have observed in online forums(36) that accounts they have read are remarkable for their lack of consistency. Efforts by the research community to define NEC are evolving at the same time as the amount of information accessible by patient-families is rapidly increasing. However, without a reliable definition patients and families risk suboptimal diagnosis, treatment and prognostication. Researchers partnering with patient-families can improve communication regarding the diagnosis and prognosis for NEC to families. In addition, patient-families are essential in determining outcomes important in comparing NEC definitions, as discussed in the next section.

Assessing the performance of current NEC definitions

As many of the current NEC definitions include subjectively chosen criteria, as opposed to the use of a data-driven approach, additional studies are needed to better understand how current NEC definitions perform. One approach could involve applying the various definitions to a large cohort of infants undergoing possible evaluation for NEC to assess their ability to predict which infants will develop short and long-term complications of NEC, such as the need for surgery, prolonged parental nutrition and neurodevelopmental impairment. However, before this can be done, it is critical for parents and clinicians to identify the most important and relevant outcomes of NEC. Once a case definition and relevant outcomes have been agreed upon, NEC definitions could be compared (e.g. sensitivity, specificity, AUROC). In addition, components of each NEC definition (e.g. abdominal tenderness) could be individually assessed. Such an approach has recently been used to compare various case definitions of bronchopulmonary dysplasia, and can serve as a model for how to assess existing definitions of NEC and help refine future iterations of these definitions(37). Improving the definition of SIP could also help ensure better differentiation from this distinct disease when ascertaining NEC.

To achieve this, multicenter prospective studies, ideally on a global scale, could compare NEC definitions, supporting the use or development of a consensus definition. Alternatively, existing study data or routinely collected health record data could be used, following on the approach used in the UK(20), but with limitations regarding retrospective ascertainment of characteristics important in defining NEC. As definitions are being evaluated, the intent of the definition should be considered. A diagnostic definition using detailed clinical data may not be pragmatic for population-based disease surveillance. Similarly, a very narrow set of diagnostic criteria in a case-definition may be useful for clinical trials and observational studies but be less useful to families of infants with atypical presentations of NEC.

CONCLUSION

We believe a consensus definition of NEC is critical to improving NEC outcomes by advancing research and supporting the development of an accurate, reliable, and reproducible definition of NEC. This will require a concerted effort of collaboration among a wide range of stakeholders and the involvement of patient-families.

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Conflicts of Interest:

RMP has received honoraria and travel support from Mednax, Inc, partial travel support from Danone Nutricia to attend a meeting, and consulted for Shipman & Goodwin, LLP and serves on the data-monitoring committee of the Connection Study conducted by Premier Research/Infant Bacterial Therapeutics. None of these entities had any role in this manuscript. SJM received lecture fees from Abbott, grant support from Evolve Biosystems and the Carver College of Medicine at the University of Iowa for unrelated work. MK received an educational grant from Danone Nutricia to organize a conference on NEC. Michael Caplan received consulting fees from Sigma Tau Pharmaceuticals and lecture fees from Mead Johnson Nutrition. The remaining authors declared no competing interests.

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Variable category	Bell staging			Modified Bell staging						UK	VON	CDC	2 of 3	ST	INC
	I	II	III	IA	IB	IIA	IIB	IIIA	IIIB						
Reference	1			3						20	17	19	22	24	25
Risk grouping															
GA										+			+		+
Postnatal or PMA													+	+	+
Gender														+	
Ethnicity														+	
Exclusion															
SIP										+	+		+		+
Congenital anomaly													+		+
Fed <80 ml/kg/day													+		
GA ≥ 36 weeks													+		+
Systemic Signs															
Temp. instability	+	+	+	+	+	+	+	+	+						
Apnea	+	+	+	+	+	+	+	+	+						
Bradycardia	+	+	+	+	+	+	+	+	+						
Lethargy	+	+	+	+	+	+	+	+	+						
Acidosis (mild)[a]							+	+	+					+	
Thrombocytopenia							+	+	+				+	+	+
Hypotension / shock			+					+	+						
Acidosis[a]								+	+					+	
DIC								+	+						+
Neutropenia								+	+						
Ventilated														+	

Figure 1. Comparison of risk group, exclusion criteria and systemic signs across NEC definitions

Abbreviations: UK, United Kingdom; VON, Vermont Oxford Network; CDC, Centers for Disease Control and Prevention; ST, Stanford; INC, International Neonatal Consortium; GA, gestational age; PMA, postmenstrual age; SIP, spontaneous intestinal perforation; DIC, disseminated intravascular coagulation

[a] Modified Bell staging criteria did not specify a specific definition of “mild” acidosis, to differentiate from “acidosis”. In the ST NEC score, pH value was the most weighted predictor.

Variable category	Bell staging			Modified Bell staging						UK	VON	CDC	2 of 3	ST	INC
	1	II	III	IA	IB	IIA	IIB	IIIA	IIIB						
Intestinal signs															
Poor feeding (intolerance)	+	+	+											+	
Emesis	+	+	+	+	+	+	+	+	+		+	+			
Pre-gavage residuals	+	+	+	+	+	+	+	+	+	+					
Bilious aspirates	+	+	+							+	+	+			
Abdominal distention (mild)	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Marked distention		+	+					+	+						
Guaiac-positive stool	+	+	+	+	+	+	+	+	+						
Rectal bleeding (occult)[a]	+	+	+		+	+	+	+	+	+	+	+	+		+
Marked hemorrhage			+												
Absent bowel sounds						+	+	+	+						
Abdominal tenderness						±	+	+	+	+					
Marked tenderness								+	+						
Generalized peritonitis								+	+						
Abdominal cellulitis							±	+	+						
Right low quadrant mass							+	+	+						
Abdominal discoloration										+				+	
Radiologic findings															
Normal				+	+										
Ileus[b]	+	+	+	+	+	+	+	+	+				+		
Pneumatosis		+	+			+	+	+	+	+	+	+	+	+	+
Portal venous gas		+	+				+	+	+	+	+	+	+	+	+
Ascites							±	+	+						
Pneumoperitoneum			+						+	+	+	+			
Fixed loop[c]		+	+							+					
Small bowel separation[d]		+	+												

Figure 2. Comparison of intestinal signs and radiologic findings across NEC definitions

Abbreviations: UK, United Kingdom; VON, Vermont Oxford Network; CDC, Centers for Disease Control and Prevention; ST, Stanford; INC, International Neonatal Consortium; GI, gastrointestinal.

[a] Includes descriptions of bright blood from rectum, hematochezia or occult bleeding (without specific mention of testing for blood such as guaiac testing).

[b] Includes descriptions of intestinal dilitation or distention

[c] Also characterized as unchanged “rigid” loops of bowel

[d] Caused by edema in bowel wall

Tables 1:

Responses from an international NEC meeting workshop on defining NEC

Question (number of respondents)	%
What current definitions do you use to decide on a diagnosis of NEC (clinical or research)? (n=44)	
-Bell staging	5%
-Modified Bell staging	57%
-VON definition	20%
-2 out of 3 rule	7%
-UK NEC definition	2%
-None of above / other	18%
How best can we exclude spontaneous intestinal perforation? (n=45)	
-Exclude cases based on postnatal age criteria	6%
-Case-by-case review for any case before 14 days of age	24%
-Case-by-case review for any case at any postnatal age	69%
Should volume of feeding be incorporated into differentiating spontaneous intestinal perforation vs. NEC (n=46)	
-Yes	17%
-No	83%
Can NEC be determined only based on clinical signs and symptoms without presence of definite pneumatosis, portal venous gas or pneumoperitoneum (e.g. using the United Kingdom gestational-age based NEC definition) (n=46)	
-Yes	28%
-No	72%
Should platelet count be part of a NEC definition? (n=45)	
-Yes	53%
-No	47%
Should C-reactive protein be part of a NEC definition (n=45)	
-Yes	27%
-No	73%
Do you use ultrasound for diagnosis of NEC (n=45)	
-Never	44%
-As part of research	4%
-Clinically, occasionally	42%
-Clinically, regularly	9%
Should ultrasound findings be incorporated into a NEC definition (n=43)	
-Yes	14%
-No	35%
-Maybe	51%
Would you include Bell Stage 1 NEC in outcomes? (n=46)	
-Yes	9%
-No	91%

Audience responses at a workgroup session on defining NEC conducted at the 2018 Special Interest Group Necrotizing Enterocolitis (SIGNEC) UK meeting (31), with permission. Some response categories were combined, which may lead to category percentages that exceed 100% due to rounding.