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Changing the paradigm of defining, detecting, and diagnosing NEC: Perspectives on Bell's stages and biomarkers for NEC

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ABSTRACT

Better means to diagnose and define necrotizing enterocolitis are needed to guide clinical practice and research. Adequacy of Bell's staging system for clinical practice and clarity of cases used in NEC clinical datasets has been a topic of controversy for some time. This article provides reasons why a better global definition for NEC is needed and offers a simple alternative bedside definition for preterm NEC called the "Two out of Three" rule. Some argue that biomarkers may fill knowledge gaps and provide greater precision in defining relevant features of a clinical disease like NEC. NEC biomarkers include markers of inflammation, intestinal dysfunction, hematologic changes, and clinical features. Development and reporting of NEC biomarkers should be guided by the FDA's BEST Consensus resource, "Biomarkers, EndpointS, & other Tools" and consistently report metrics so that studies can be compared and results pooled. Current practice in the NICU would be enhanced by clinical tools that effectively inform the clinical team that a baby is at increasing risk of NEC. Ideally, these tools will incorporate both clinical information about the baby as well as molecular signals that are indicative of NEC. While meaningful biomarkers for NEC and clinical tools exist, translation into practice is mediocre.

Introduction

The field of necrotizing enterocolitis (NEC) research and the diagnosis of NEC itself has existed for more than 60 years.[1,2] It has preceded and transcended all the different forms of continuous positive ventilation, and it has been transformed in the era of surfactants.[3] The field has also seen the emergence of clinical cohort studies (versus case-series), randomized controlled trials, long-term outcome studies and meta-analytics. In short, the field of NEC is older than neonatology itself. For much of that time, the field has relied on the opinion of the surgeon who created Bell's criteria to characterize the severity of disease in the pre-surfactant era.[4] Bell's three stages were originally designed to help the bedside clinician determine when surgery was prudent. However, during the age when cohort studies were emerging, Bell's staging became popular as the means to define NEC cohorts. It has been refined successfully only once[5] yet still informs many of the dataset definitions that are in use for billing[6] and quality improvement.[7] After the advent of surfactant and improved survival of premature newborns, it was determined that the lowest stage contained too many patients with confounding, non-NEC diagnoses.

The challenge today lies in the evolution of neonatal patient populations and our ability to refine large datasets, such that these

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populations now represent distinct and often novel patient groups.[8,9] Term infants versus preterm infants experience different NEC outcomes and precedent risk factors.[10,11] Infants with severe congenital anomalies, even if they have a common endpoint disease like NEC, also have dramatically different presentations and outcomes compared to gestational age-matched cohorts with NEC. Finally, there are non-NEC diseases that lurk within our datasets and literature (such as spontaneous intestinal perforations; SIP), which can fatally sabotage our understanding of NEC.[8] Recent success in NEC prevention[12] and recognition of NEC subsets (where more stringent definitions are being used),[13] demonstrate that we must refine our global NEC definition if we are to progress in our understanding of the disease.[14]

The success and clinical utility of emerging biomarkers, applied diagnostics like ultrasound and quality initiatives (e.g., bundles and checklists) that aim to reduce NEC are highly dependent on a refined and more precise definition. Each modality promises improved capacity to pinpoint the timing, accuracy, and potentially the sub-cohort categorization of NEC. New technologies and approaches make it imperative that we create a more adaptive definition. Finally, it remains crucial that any new definition be operative at the bedside. Whether in London or Kampala, a clinician must have the ability to make the diagnosis of NEC with reasonable accuracy every time. Promising preventive strategies are emerging, including breast milk feeding, antibiotic stewardship, and probiotics whose success will only be fully realized through dissemination and adoption of more rigorous risk assessment and diagnostic definitions.[15–17] As NEC decreases globally we must have the ability to capture confirmed cases in our datasets, correctly, or risk an ever greater pool of non-NEC versus true cases of NEC.[14] The purpose of this review is to (1) offer a better definition of NEC based on newer and novel markers and radiographic imaging, and (2) define adequate biomarkers which may be used to help guide clinical decision-making.

Defining NEC

Survey of experts about adequacy of current NEC definitions

During the 2017 NEC Symposium, participants at a "Defining NEC" workshop were asked questions about the adequacy of current definitions used to define NEC. Prior to the conference, a waiver of consent was obtained from the University of Virginia Social and Behavioral Sciences Institutional Review Board (project #2017-0125-00). Workshop participants were self-selected stakeholders in NEC so initial survey questions were used to identify bias. Respondents to the survey included 20 physicians (4 of whom were surgeons), 18 non-physician clinicians (nurses, neonatal nurse practitioners, dietitians, etc.), 9 non-physician researchers, and 5 others (including one parent). Participants were asked to rank their agreement on a scale of 1–5 (with 5 being strong agreement and 1 being strong disagreement) with statements about ease of NEC diagnosis and reliability of Bell's staging for creating preterm NEC datasets. Responses are shown in Figure 1. Responses suggest that workshop participants came in with a relatively strong bias against Bell's staging as a reliable definition and many felt that NEC is not easy to diagnose correctly.

Additionally, respondents were asked to relate NEC definition to 17 potential biomarkers, clinical findings, or demographic variables. The participants ranked the order of importance in "forming a correct diagnosis of NEC." Too few complete responses were available for statistical analysis, potentially signaling a lack of deep understanding and/or a lack of clarity in the evidence about each variable which can be used consistently and reliably to define NEC clinically.

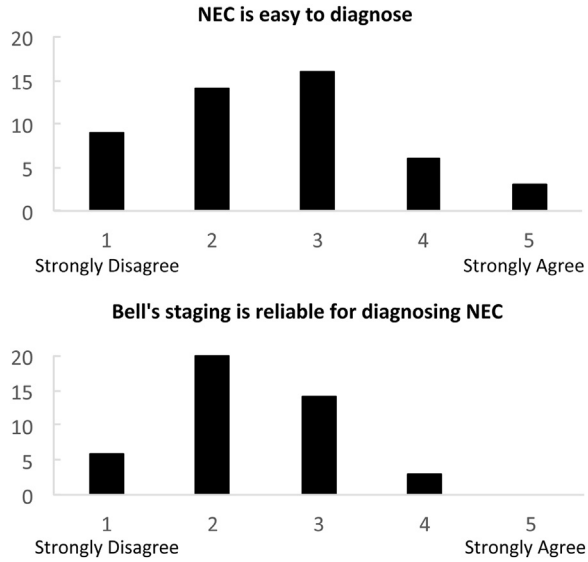

Fig. 1. Pre-workshop perspectives on Bell's reliability. Responses to two pre-workship survey questions. *Y*-axis = number of respondents.

In the post-workshop survey, participants were asked five questions, with the first four allowing only a single answer choice. Respondents were asked to pick the statement that "best reflects your opinion" regarding the definition of NEC. Results are shown in Figure 2. The majority of participants thought Bell's staging to be poorly reliable for the diagnosis of preterm NEC. Likewise, the vast majority thought that a new definition of NEC was necessary and that we needed to either abandon or modify Bell's in order to improve data quality. Finally, the overwhelming majority felt preterm and term NEC were either different diseases entirely or similar but with different preceding events and risks. No survey respondent felt the two entities to be the same disease.

A fifth question allowed the participant to check any or all of the responses. It asked, "Which of the following statements best reflects your opinion" on variables used to define NEC. The responses are represented in Figure 3. Respondents picked histopathology and a final common pathway of disease as the two most important variables for defining NEC. Use of subgroups that respond to quality improvement was a respectable third choice. Use of an inclusive definition was not picked often.

After workgroups met, leaders presented a summary to all NEC symposium attendees. Dr. Gordon presented a brief synopsis, described the post-workshop responses indicating that we needed to abandon or modify Bell's staging to improve our data, and led the discussion. There was surprising agreement across a large audience of researchers and clinicians, many with long careers devoted to NEC. When asked to recommend a definition to replace Bell's staging, Dr. Gordon described the Two out of Three rule, as a place to start for a new bedside definition (see Table 1), which incorporates timing of medical NEC versus SIP onset described elsewhere.[18] (Conference attendees suggested that ultrasound-identified pneumatosis and portal air be considered alternatives to the same radiographic findings and the definition has been modified accordingly.)

Biomarkers for NEC

Assessing risk for NEC and diagnostic uncertainty

To address the unmet need of reducing or eliminating NEC will require both the development of new tools to assist in defining NEC objectively and a deeper understanding of NEC-associated