Review Article

Introduction and historical aspects and where may we be going in the future: getting rid of necrotizing enterocolitis

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Abstract: The precise pathophysiology, prevention and treatment of what is commonly diagnosed as necrotizing enterocolitis (NEC) disease has been elusive. This bears at least partial responsibility for lack of progress in preventative strategies. A clear unambiguous definition that represents a discrete disease is not currently available and likely is a major component of difficulties with understanding a discrete pathophysiology. It is thus becoming increasingly clear that our current paradigm of NEC as a distinct disease is incorrect and the ambiguity in what is being referred to as NEC may be a reason for our lack of progress in prevention. Because of this, we need to critically review our current concepts, how they have evolved in the past several decades and determine how we can best re-evaluate intestinal injuries and dysfunctions that are currently being called NEC. In this review, we discuss historical aspects of NEC as well as our current concepts and a potential pathway using newly developed artificial intelligence/machine learning (AI/ML) and multiomic integrations for a paradigm shift that will alter our strategies for early prediction, diagnostics, prevention, and treatment of the various forms of intestinal injury and dysfunction currently referred to as NEC. This will represent a major challenge but is critical if we are to make progress.

Keywords: Necrotizing enterocolitis (NEC); artificial intelligence (AI); multiomic integration; biomarker development; pathophysiology

Received: 26 April 2023; Accepted: 11 July 2023; Published online: 21 July 2023.

doi: 10.21037/pm-23-30

View this article at: https://dx.doi.org/10.21037/pm-23-30

Introduction

Neonatal intensive care as a formal discipline in the US began in the 1960s. At that time, an emphasis was placed on respiratory support of critically ill neonates. Other areas of emphasis included infections, fluid and electrolyte management and thermoregulation. As smaller, more immature infants survived, another major cause of mortality and morbidity, necrotizing enterocolitis (NEC) emerged (1,2). Since that time, considerable research efforts have been placed to better understand NEC as well as to provide better strategies for diagnosis, prevention and treatment.

Background

The classic paradigm has been to consider NEC as a specific disease. However, it has never had a clear definition (3-5) and the specific etiology remains unclear. The pathophysiology of NEC is considered "multifactorial" (2,6). Although staging criteria have been developed that provide information about severity of intestinal injury (7), these stages, despite being placed under the diagnosis that includes intestinal necrosis in its name, do not clearly represent a necrotic intestine and likely should be abandoned (8). Furthermore, the phenotype is broad and likely represents not one but several distinct entities, like the paradigm for diabetes, where type 2 clearly has a different pathophysiology compared to type 1 (9).

Unfortunately, there is not a precise definition for NEC (4). There are several entities wherein intestinal injury and/or dysfunction are major components, all of which are referred to as NEC. Can we even aim to accurately predict these forms of intestinal injury if what is currently

called "NEC" represents more than one disease? (1). Thus, trying to define NEC might be futile.

Knowledge gap

If NEC represents several different entities, it will be important to delineate them phenotypically as well as from a pathophysiologic perspective so that they can be prevented. What are some of the entities currently referred to as NEC?

Objective

In this chapter, we wish provide examples of a few entities that are currently termed NEC in the newborn infant and to discuss how this has led to a lack of progress in the field and consider pathways for making progress in the future.

Past, present and future

Stages 1 and 3 "NEC"

In the late 1970s, a pediatric surgeon, Dr. Martin Bell proposed clinical staging criteria for neonatal intestinal illnesses referred to as NEC (7). These criteria are becoming increasingly outdated (10). Stage 1 signs and symptoms occur in most extremely preterm infants and does not represent intestinal necrosis. Most of the infants with stage 1 NEC exhibit feeding intolerance, which is largely based on their intestinal nervous system immaturity, lack of motility, and common use of opiates, which decrease intestinal motility.

In order to provide a clearer focus on more specific intestinal pathology that is not provided when including patients with stage 1 NEC, large neonatal research networks have limited the criteria for NEC diagnosis to Bell's stages 2 and 3. Stage 2 is based on clinical signs and radiographic criteria. The clinical signs include absent or decreased bowel sounds, abdominal distention and the radiographic images include h pneumatosis intestinalis or portal venous gas. A bubbly appearance may be secondary to stool in the bowel lumen. This is often misinterpreted as gas in the bowel wall and is diagnosed differently by different radiologists and neonatologists as pneumatosis intestinalis or as commonly seen in the radiographic reports—"cannot rule out necrotizing enterocolits" (11,12). The use of ultrasound may be very helpful in determining intestinal injury in neonates, but this is still in progress.

The finding of pneumoperitoneum on radiograph could is frequently diagnosed as stage 3 (surgical) NEC and when it occurs, is often recorded as a case of NEC. However, lack of direct visualization by the surgeon with a laparotomy will not provide definite determination of whether this was caused by erosion of necrotic bowl with subsequent extension or a simple spontaneous intestinal perforation (SIP) (13).

Ischemic bowel due to congenital heart disease (CHD)

CHD is a risk factor for the development intestinal injury and this is often referred to as "NEC" (14). Univentricular heart disease associated intestinal injuries are most often called NEC. Decreased or absent mesenteric blood flow may cause ischemic intestinal necrosis in neonates with these forms of CHD.

A change in nomenclature for infants with this presentation to cardiogenic ischemic intestinal disease would be much more apt than the general term NEC applied to this problem.

Food component sensitivity

A distinct intestinal problem related to the composition of feeds has also been described (15). Vomiting, bloody stools, a septic appearance and abdominal distension are commonly seen with this syndrome, called food protein intolerance enterocolitis syndrome (FPIES). One identifying factor is that the symptoms will improve after cow's milk protein is excluded, but relapses after re-challenge with the same protein. Antigens that cause FPIES may cross through breast milk (16). Very similar presentations have been described in preterm infants and raises the question of whether FPIES occurs in preterm neonates (17). If so, this likely causes confusion with other forms of NEC.

A clear diagnosis of FPIES differentiating it from other forms of intestinal dysfunction is challenging. There are currently no biomarkers or other laboratory findings that are confirmative for the diagnosis (18).

SIP

SIP was first commonly reported as NEC but manifests as a perforation found in the ileum that is not associated with significant necrosis (19). Pathologic specimens often show focal thinning or absence of the intestinal muscularis propria (20). SIP mainly affects extremely low-birthweight

(ELBW) infants at an early postnatal age (21). Despite these differences, NEC and SIP are often treated in a similar manner, with placement of peritoneal drains. They are often both recorded in medical records as NEC, which is a problem when used in retrospective or observational studies. A recent study by our group that used supervised machine learning (ML) was able to determine a set of features that discerned intestinal necrosis from SIP with a high degree of accuracy (22).

Transfusion-related NEC

Packed red blood cell transfusions are one the most common therapies in the neonatal intensive care unit. A temporal association between packed red blood cell transfusions and NEC has been suggested (23), but causality of NEC from transfusions has not been supported by randomized controlled trials. In fact, pre-existing anemia appeared to be highly associated with the development of subsequent intestinal necrosis (24).

So, our current concept of NEC involves a poorly defined diagnosis that describes several seemingly more discrete entities. If we are to make progress in the prevention and treatment of the entities, we are currently calling NEC a better description of the various intestinal injury phenotypes needs to be better categorized and their individual pathophysiologies delineated. How do we go about doing this?

The future

There are numerous reasons underlying our lack of progress with NEC, but the fact that it is clearly not a homogeneous entity, but with different pathways contributing to its development, has not previously been taken into serious account (25). Similar to diabetes, NEC should not be considered as a single entity, but several more discrete problems that require better delineation in terms of both phenotype and pathophysiology (25,26). Once we have this understanding, we can develop more personalized approaches for prevention and treatment.

Conclusions

To make progress in the understanding of causality, therapy, and prevention of the entities that we call NEC, we need to take a major step in no longer labelling the large number of heterogeneous intestinal dysfunctions by this term. Newly developed technologies such as AI/ML with unsupervised clustering should be used to better delineate phenotypes of intestinal injury and dysfunction in the neonate. These phenotypes can be interrogated for mechanisms using multiomic integration and systems biology (26). This can lead to development of biomarkers distinct for the individual clusters that can be used for early detection and prevention, goals that are unlikely to be achieved if we do not shift the paradigm. Although the technologies are currently available, highly skilled teams of clinician scientists, bioinformaticians, and experts in AI will need to collaborate to attain these goals.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Pediatric Medicine* for the series "Necrotizing Enterocolitis". The article has undergone external peer review.

Peer Review File: Available at https://pm.amegroups.org/article/view/10.21037/pm-23-30/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://pm.amegroups.org/article/view/10.21037/pm-23-30/coif). The series "Necrotizing Enterocolitis" was commissioned by the editorial office without any funding or sponsorship. J.N. served as the unpaid Guest Editor of the series. J.N. received grants from Infant Bacterial Therapeutics, and consulting fees from Glycome Siolta Therapeutics. J.N. also gave serval unpaid lectures with IPOKRaTES Foundation, Global Scientific Council of the Nestle Nutrition Institute, and Scientific Advisory Board for Astarte and Medela. J.N. involved as expert witness in serval cases, participated in several meetings with reimbursement of travel expenses, and has several patents. J.N. declared that none of the relationships with industry, grants or contracts, consulting, etc. have any direct relationship to this review. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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doi: 10.21037/pm-23-30
Cite this article as: Neu J. Introduction and historical aspects and where may we be going in the future: getting rid of necrotizing enterocolitis. Pediatr Med 2024;7:15.