# Necrotizing enterocolitis: an editorial

What is called necrotizing enterocolitis (NEC) in neonates is a highly ambiguous diagnosis and not a clearly defined or distinct disease (1-7). Although staging of intestinal dysfunction that has been diagnosed as NEC (Bell's Staging Criteria and subsequent adaptations) (8,9) has been a mainstay of neonatal intensive care since the 1970's, it is clear that infants diagnosed with 1 or 2 likely do not have intestinal necrosis. In fact, stage 1 is such a diffuse set of symptoms and signs that most extremely low birth weight infants exhibit these during their neonatal hospital course. Stage 2 has been highly dependent on radiographic signs such as pneumatosis intestinalis. This is often misdiagnosed and/or overread by radiologists and neonatologists (10,11). Such overreading frequently results in unnecessary measures such as prolonged antibiotics and disruption of enteral feedings, which are known to alter the intestinal microbial ecosystem and mucosal immune defenses (12,13). Stage 3 usually prompts surgical intervention, either laparotomy or peritoneal drain placement. When peritoneal drains are placed, lack of visualization of the bowel leads to confusion as to whether the bowel is necrotic. Over the past few decades, it has become clear that many of the cases diagnosed as NEC had spontaneous intestinal perforations (SIP), which do not involve extensive necrosis and represent a different pathophysiology (14).

Numerous other intestinal maladies in the preterm infant in addition to those mentioned in the previous paragraph, are also frequently diagnosed as "NEC" (1,6,15). Infants with Hirschsprung disease may exhibit "NEC" symptoms (16). Food protein induced enterocolitis syndrome (FPIES) frequently presents with bloody stools and may even exhibit pneumatosis intestinalis (15). There is no clear biomarker available for "NEC" that will distinguish it from these other maladies.

Progress in this field will be thwarted and biomarkers will likely not be found unless a clear definition of "NEC" becomes available or if we start over again and more clearly delineate the intestinal disorders that are now ambiguously termed "NEC". The lack of a clear definition and diffuse diagnostic criteria render the databases used for epidemiologic evaluations and observational studies of "NEC" inaccurate and misleading. Furthermore, use of such an ambiguous diagnosis leads to major difficulties in research for a clear pathophysiology. Without a distinct phenotype, a mechanistic pathophysiologic scheme putatively representing all phenotypic variations is likely to be misleading.

Studies evaluating inflammatory pathways, feedings, microbial exposures, metabolomics, proteomics and even studies in animals used as models of a highly diffuse problem are highly problematic. No wonder, little progress has been made in the past 60 years in terms of prevention, treatment and understanding of pathophysiology (1,3,17,18). A reevaluation of different forms of intestinal injury and dysfunction in neonates is clearly needed if progress is to be made in understanding their pathophysiology, prevention and treatment (1).

Newly developed technologies such as artificial intelligence (AI) and integrated multiomics offer such an opportunity (19). With newly developed AI, it is now possible to interrogate large datasets using unsupervised machine learning in an agnostic manner that can cluster phenotypes using a set of features derived from pre, peri and early postnatal life (20). These powerful and rapidly developing technologies are being applied in many fields of medicine (21-23). Our preliminary studies using supervised machine learning have utilized algorithms that show features highly predictive of SIP versus intestinal necrosis (24). However, since causes of intestinal injury and dysfunction that are currently being called "NEC" are numerous, the etiology of these remains unclear. If progress is to be made, we will need to begin with a fresh evaluation of the different forms of intestinal injuries and dysfunctions, many of which are currently referred to as NEC.

New technologies have been developed that will likely provide us with new insights. These include AI, with the capability of clustering large datasets of clinical and laboratory features into distinct entities. Newly developed multiomic integration technologies also provide the capability of interrogating individual newly derived individual cluster mechanistic changes over time that lead to pathology. Comparing these changes over time between the clusters will provide new insights into the pathophysiology of these distinct forms of intestinal injury and provide clearer understanding, improved prevention, and treatment. As we strive for this goal, several articles in this volume will provide some information as to the past, present and future understanding of these forms of intestinal injury currently collectively referred to as "necrotizing enterocolitis".

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