Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

A critical question for NEC researchers: Can we create a consensus definition of NEC that facilitates research progress?

Phillip V. Gordon, MD, PhD[a], *Jonathan R. Swanson, MD, MSc*[b,*], *Brianna C. MacQueen, MD*[c], *and Robert D. Christensen, MD*[c]

[a]*Department of Pediatrics, Sacred Heart Children's Hospital, Pensacola, FL*
[b]*Department of Pediatrics, University of Virginia Children's Hospital, Box 800386, Charlottesville, VA 22908*
[c]*Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT*

ARTICLE INFO

Keywords:
Necrotizing enterocolitis
Diagnosis
Gestational age
Thrombocytopenia
Pneumatosis

ABSTRACT

In the last decades the reported incidence of preterm necrotizing enterocolitis (NEC) has been declining in large part due to implementing comprehensive NEC prevention initiatives, including breast milk feeding, standardized feeding protocols, transfusion guidelines, and antibiotic stewardship and improving the rigor with which non-NEC cases are excluded from NEC data. However, after more than 60 years of NEC research in animal models, the promise of a "magic bullet" to prevent NEC has yet to materialize. There are also serious issues involving clinical NEC research. There is a lack of a common, comprehensive definition of NEC. National datasets have their own unique definition and staging definitions. Even within academia, randomized trials and single center studies have widely disparate definitions. This makes NEC metadata of very limited value. The world of neonatology needs a comprehensive, universal, consensus definition of NEC. It also needs a de-identified, international data warehouse.

Introduction

In the last decades the two most effective tools for reducing the reported incidence of preterm necrotizing enterocolitis (NEC) have been: (1) implementing comprehensive NEC prevention initiatives, including breast milk feeding, standardized feeding protocols, transfusion guidelines, and antibiotic stewardship[1–9] and (2) improving the rigor with which non-NEC cases, which frequently contaminated previous reports, are excluded from NEC data. In short, quality improvement and rigorous diagnostics have dropped the reported rates of NEC.

In contrast, after more than two-thirds of a century of NEC research in animal models, the promise of a "magic bullet" for NEC has yet to materialize. The origins of preterm NEC are increasingly understood to be diverse, spanning a spectrum of ontogenies.[10–12] These complexities cannot be accurately reflected in animal models that elicit intestinal necrosis through a single stereotypic insult.

There are also serious issues involving clinical NEC research. Some researchers still fail to achieve clean datasets in retrospective cohorts because there is a lack of a common, comprehensive definition of NEC. For example, each national dataset has its own unique definition of NEC. Administrative,

*Corresponding author.
E-mail address: jrs3yc@virginia.edu (J.R. Swanson).

http://dx.doi.org/10.1053/j.semperi.2016.09.013
0146-0005/

billing and diagnosis datasets also commonly have different NEC staging definitions. Perhaps the most difficult of all is that corporations increasingly see patient data as proprietary and profitable commodities. Even within academia, randomized trials, and single center studies have widely disparate definitions that reviewers and editors rarely challenge or try to standardize. This makes NEC metadata of very limited value. The world of neonatology needs a comprehensive, universal, and consensus definition of NEC. It also needs a de-identified, international data warehouse. This article provides a road map toward these goals; providing suggestions, data and logic to support these mandates.

A brief review of how NEC has been defined

NEC was first reported in the mid-20th century.[13–15] A hallmark of the disease has always been pneumatosis. In the late 1970s, Dr. Martin Bell proposed a staging system to help evaluate which NEC patients would best benefit from surgery.[16] During this early period there was substantial debate in the literature about the nature of NEC. In particular, it was suggested that NEC was not a single disease entity, but rather a spectrum of similar diseases.[17–19] At the same time, clinical research was evolving away from case series toward cohort studies as the dominant form of report in the literature. Researchers began to use Bell's staging as a tool to describe NEC cohorts. All of this occurred in the pre-surfactant era, when neonatal survivors were less preterm than they are today. Bell's staging system rapidly became the dominant methodology, essentially homogenizing all NEC cases of that era under one umbrella diagnosis.

By the late 1980s, after more than 2 decades of national research focus, surfactant appeared in NICUs around the world. There was a relatively rapid decrease in the gestational viability limit and a concomitant increase in NEC incidence. Through all of this, Bell's staging remained the dominant paradigm for describing NEC. However, with the expansion of NEC into the increasing preterm populations, modifications had to be made by the NEC research community. The first of these was to exclude Bell's stage I.[20] Essentially felt to be "pre-NEC" by many, stage I also commonly included ileus secondary to sepsis or obstruction, not true NEC.

A more recent modification, endorsed by Bell himself, is the recognition of spontaneous intestinal perforations (SIP) as a separate disease entity from surgical NEC.[11,21,22] There has been a gradual conversion of most national datasets to exclude SIP as a confounder of NEC. However, administrative datasets used for accounting remain especially vulnerable to this confounder. The predominant issue today is a lack of consistent SIP reporting and exclusion in NEC publications. Some editors and reviewers require SIP to be excluded in NEC studies, but many do not.

Recently, there has been an expansion of preterm NEC subset classification by looking at precedent associations. The limitation of this approach is that it is challenging to prove causality with a disease that originates through a multi-hit phenomena. Even with this limitation, a highly lethal subset of NEC following multiple packed red blood cell (pRBC) transfusions in anemic VLBW infants has been identified.[23–28] There have been clusters of pneumatosis around discharge in infants who received contaminated thickener.[29–30] There are a small subset of infants with relatively mild NEC-like disease, who tend to have high eosinophil counts and evidence of emerging cow's milk allergy/intolerance.[28,31,32] There are also countless reports of NEC clusters associated with viral or bacterial contagions.[12] Finally, it has become clear that infants who are term and develop NEC have a more classic hypoxic/ischemic mechanism of gut injury, when compared to preterm NEC.[32] The field of neonatology should not be utilizing a one-size-fits-all approach to NEC anymore. NEC is clearly more complicated than Bell originally envisioned with his staging and our current methods of clinical data gathering do not have sufficient granularity to carry us into the future.

What is the basis of modern preterm NEC?

The three hit model

Passive immune deficit

Most mammals give immunoglobulins and innate immune factors to their offspring through colostrum and/or breast milk. Primates give innate immune factors through milk but have evolved the ability to actively transport immunoglobulins across the placenta in the third trimester (Fig. 1).[33] For this reason, human infants born before 30 weeks universally

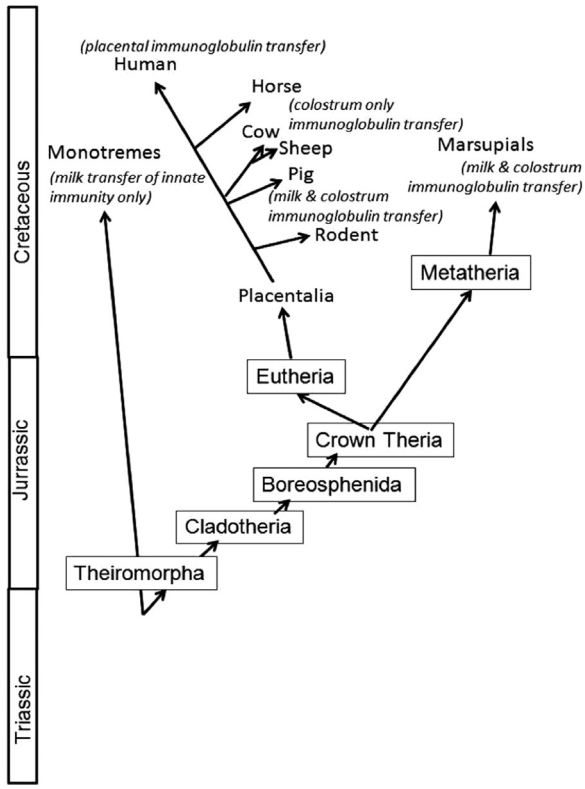

Fig. 1 – Schematic illustrating evolution of placenta and passive immunity transfer. All milk producing mammals transfer innate immunity and immune system modulation through milk. Schematic is not drawn to scale for precise determination of divergence.