Necrotizing Enterocolitis and Neurodevelopmental Outcome

Ira Adams-Chapman, MD, MPH

KEYWORDS

• Necrotizing enterocolitis • Neurodevelopment • Sepsis • Follow-up

KEY POINTS

- Surgical necrotizing enterocolitis (NEC) is associated with adverse neurodevelopmental outcome.
- Morbidities associated with NEC increase the risk for central nervous system injury in preterm infants.
- Additional data are needed to determine whether surgical drain or laparotomy is associated with the best neurocognitive outcome in preterm infants.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a devastating complication of prematurity affecting 3% to 9% of prematurely born infants.[1–3] Although the etiology is poorly understood, it is most likely multifactorial, including a combination of factors, such as immaturity of the developing gastrointestinal (GI) tract, imbalance of immune mediators in the GI tract, inflammatory response to tissue injury, and bacterial invasion. This diseases manifests clinically on a spectrum from mild clinical disease associated with feeding intolerance to bowel perforation and tissue necrosis. The risk for NEC is clearly inversely associated with gestational age, but neonates of all gestational ages can be affected, including term infants. Those who require surgical intervention are known to have an increased risk for adverse neurodevelopmental (ND) outcome, including an increased risk for cerebral palsy and cognitive impairment. Limited data are available on the ND outcome of affected term infants. In this review, we highlight various factors that are likely contributors to the increased risk for adverse ND outcome in preterm infants with a history of NEC.

Disclosure Statement: The author has no commercial or financial conflicts of interests or any funding sources.
Department of Pediatrics, Division of Neonatology, Emory University School of Medicine, Children's Healthcare of Atlanta, 2015 Uppergate Drive, Atlanta, GA 30303, USA
E-mail address: iadamsc@emory.edu

Clin Perinatol 45 (2018) 453–466
https://doi.org/10.1016/j.clp.2018.05.014
perinatology.theclinics.com

PATHOGENESIS OF NECROTIZING ENTEROCOLITIS

Despite decades of research and prevention strategies to prevent NEC, the etiology of this disease remains elusive. Limited understanding has been learned from animal studies, but these models are considered by many to be poorly representative of neonatal disease.[4] NEC is a disease that primarily affects preterm infants. Thus, the immaturity of the preterm GI tract has long been considered a contributing factor. Researchers have identified various factors in the immature GI tract that may predispose to the development of this disease, including innate gut immaturity, immature immune response, bacterial colonization patterns in the preterm infant, and regulation of blood flow to the GI tract.[2,3] It is beyond the scope of this review to discuss these factors in detail. However, they have been outlined by other investigators[3,5] and the schematic in **Fig. 1** provides an overview of the possible mechanisms involved (see **Fig. 1**).[5]

The risk for both disease and the need for surgical intervention varies inversely with gestational age.[6,7] In a review by Stoll and colleagues[7] in the Neonatal Research Network (NRN) evaluating trends in neonatal morbidity over the past 20 years for

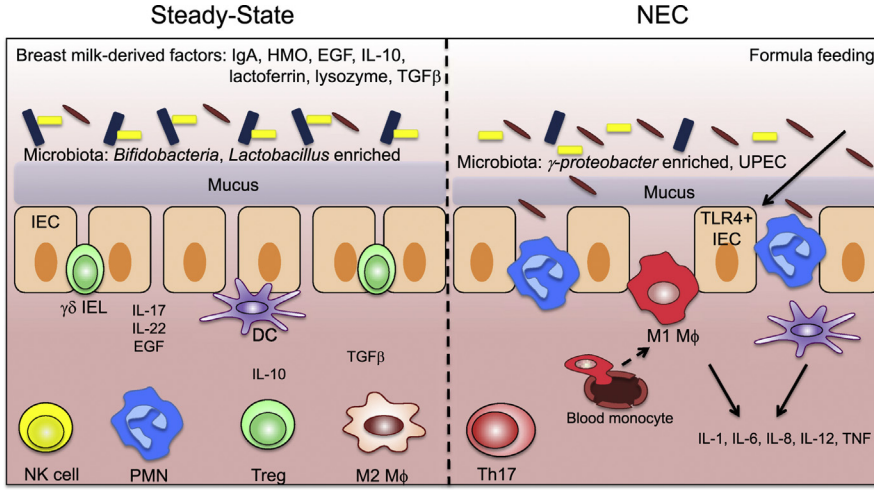

Fig. 1. Premature infant gut in the steady state and during NEC. In the steady state, homeostasis is promoted by beneficial bacteria (*Bifidobacteria* and *Lactobacillus*) and breast milk components (immunoglobulin A, human milk oligosaccharides [HMO], epidermal growth factor [EGF], IL-10, lactoferrin, lysozyme, TGF-β). In the preterm gut, γδ intraepithelial lymphocytes (IELs) are among the first intestinal-resident immune cells contributing to the maintenance of epithelial integrity via IL-17A and EGF. Natural killer (NK) cells also protect against and repair barrier damage. Neutrophils (PMN) may be important during initial colonization in the neonatal gut, providing transient barrier protection in response to threats from potentially pathogenic bacteria, via IL-22 production. Resident macrophages (Mϕ) and dendritic cells (DCs) maintain tolerance toward the intestinal microbiota via the production of IL-10, which, in combination with TGF-β, induce regulatory T (Treg) cells. During NEC, lack of breast milk protective components and dysbiotic flora (eg, Gammaproteobacter) may allow barrier breakdown and bacterial translocation. This leads to innate signaling via Toll-like receptor 4 (TLR-4) (in response to PAF and LPS), which in turn causes recruitment of neutrophils and monocytes into the intestine, where they, along with resident DCs, drive proinflammatory cytokine production, including IL-1β, TNF, IL-8, and IL-12, which can promote pathogenic Th1 and Th17 responses. UPEC, uropathogenic E. Coli. (*From* Denning TL, Bhatia AM, Kane AF, et al. Pathogenesis of NEC: role of the innate and adaptive immune response. Semin Perinatol 2017;41(1):22; with permission.)