Impact of Feeding and Medical Practices on the Development of Necrotizing Enterocolitis

Brian L. Montenegro · Camilia R. Martin

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Abstract A single, unifying mechanism explaining the cause of necrotizing enterocolitis has remained elusive. It is unlikely that one precipitating cause will be found. However, it is increasingly evident that common risk factors do exist such as intestinal immaturity, dysbiosis, and feeding (including type of feeding). Modifying these risk factors to facilitate optimal postnatal intestinal development may lessen the vulnerability to intestinal injury in the preterm infant. Understanding the feeding and medical practices employed in the neonatal intensive care unit and their potential effects on postnatal intestinal development will begin to inform bedside strategies to reduce maladaptive intestinal responses in the preterm infant and the risk of this devastating disease.

Keywords Necrotizing enterocolitis · Immunonutrients · Fatty acids · Microbiome · Digestion · Feeding practices

Introduction

Prematurity and enteral feeding are universally accepted risk factors for neonatal necrotizing enterocolitis (NEC) [1•]. Despite an appreciation of these associations, the precise mechanisms by which these factors contribute to

the pathogenesis of NEC have remained elusive. As a result, there has been little change in the prevalence of NEC, which varies among centers, affecting anywhere from 5 to 15 % of very low birth weight infants [2]. Advances in neonatal care have nonetheless been plentiful including a growing understanding of the importance of breast milk in supporting development and lowering disease incidence [3•]. In theory then, increasing rates of breast milk utilization in neonatal intensive care units (NICUs) should have resulted in decreasing rates of NEC; however, the change in incidence has been minimal to date [2, 4]. It is likely that the prevention of adverse neonatal outcomes, like necrotizing enterocolitis, will not be realized by applying a single theory or by discovering a silver bullet, but rather from a deeper understanding of the interplay between prematurity, intestinal development, immunity, and nutritional support.

Normal Intestinal Development and Immune Ontogeny

During in utero development, the fetus swallows a complex matrix of immunomodulating biologic factors that are present in the amniotic fluid. These factors interact with the developing gut and its associated immune effectors to prepare the fetus for ex utero life. When fully mature, the gut is primarily responsible for nutrient digestion and absorption, and is an active participant in the immune system. Exposure to antigens in utero, via interface with the amniotic fluid, activates already present antigen-presenting cells. This ongoing sensitization during fetal life leads to processes of immunotolerance and immunodeviation that collectively can be referred as immunomodulation [5]. By this process, the fetal gut begins to learn to discriminate between pathogenic antigens, to which an

B. L. Montenegro
Division of Newborn Medicine, Boston Children's Hospital,
300 Longwood Avenue, Mail Stop BCH 3146, Boston, MA
02115, USA
e-mail: brian.montenegro@childrens.harvard.edu

C. R. Martin (✉)
Department of Neonatology, Beth Israel Deaconess Medical
Center, 330 Brookline Avenue, Rose-318, Boston, MA 02215,
USA
e-mail: cmartin1@bidmc.harvard.edu

inflammatory response is warranted, and beneficial antigens that should be tolerated.

The interface between the immature gut and the environment is immediately challenged following birth. Modulators of postnatal intestinal health predominantly involve a complex interaction between nutrient exposure and microbial colonization. The effect of breast milk, the preferred enteral substrate for infants, on gut development serves as a prime example of this interaction. Although breast milk is a primary source of macro- and micro-nutrients to support growth, it is also a complex biologic system with direct influences on structure and function of the gastrointestinal tract, the intestinal microbiome, and consequently downstream intestinal gene expression [6•]. Cytokines such as transforming growth factor beta (TGFβ) present in breast milk modulate the inflammatory response, while secretory IgA protects against pathogenic bacteria. Additionally, oligosaccharides, which can behave as pre-biotics, influence the composition of the gut microbiome by providing substrate for the production of short-chain fatty acids with resulting proliferation of *Bifidobacteria* and *Lactobacillus* [7•]. When fully mature, the gastrointestinal tract and its associated lymphoid tissue (GALT) accounts for 70 % of the entire immune system [5].

Disrupted Intestinal Development with Premature Delivery

Premature delivery results in altered organ development—the arrest of normal developmental processes that would have continued if the premature infant had remained in utero and in abnormal adaptive processes in response to their NICU environment (e.g., feeding/nutritional practices; medication exposures; altered biochemical homeostasis such as hypoglycemia, acidosis, hypoxia; and

exposure to the hospital's indigenous pathogenic organisms). While the importance of human milk delivery and the intestinal microbiome on gut development are discussed elsewhere, other factors that are also influential to gut development and can be potentially addressed through modified bedside practices include: (1) inadequate postnatal provision of immunonutrients after premature delivery; (2) absent or minimal enteral substrate delivery early in the postnatal period; (3) exposure to medications that influence gut development; and (4) delivery of nutritional ingredients that may be inadequately processed by the immature, developing gut (Fig. 1). An understanding of these premises may begin to form the basis to modify clinical bedside practices and develop a “package of care” that optimizes postnatal intestinal development and minimizes the vulnerability to NEC.

Cessation of Immunonutrient Transfer with Premature Delivery and Inadequate Postnatal Provision

Prior to birth, nutrients are primarily provided to the fetus by way of the placenta and by swallowed amniotic fluid that additionally accounts for approximately 10–20 % of fetal energy demands [8]. Proteomic analysis of amniotic fluid revealed the presence of a complex mixture of biologic molecules including immunoglobulins, complement C3, fibronectin, vasoactive endothelial growth factor, vitamin D-binding protein, and antithrombin [9]. Thus, while in utero, the fetal gut is continuously exposed to a dynamic fluid mixture, the components of which play important roles in immunity, growth, nutrition, and organ development. An abrupt cessation of exposure to this milieu in the setting of preterm birth has critical implications on continued development, including overall gastrointestinal health and the risk of local (NEC) and systemic disease.

Fig. 1 Maladaptive gut development in the preterm infant

Ideally parenteral and enteral nutrition should mimic in utero exposure to nutrients previously provided by amniotic fluid and the placenta; however, current nutritional practices fall short of this ideal for many critical biologic factors. Barriers to adequate postnatal provision include a limited understanding of the fetal accretion rates or exposure levels in utero; definitions of clinically meaningful endpoints whether it is a final disease state, modification of a specific mechanistic pathway, or promotion of optimal organogenesis or immune ontogeny; and finally the biologically significant levels after early birth to achieve those endpoints. A brief review of a few of these nutrients illustrates these principles.

Glutamine and Arginine

Glutamine is essential for energy production within intestinal tissue and also enhances the functional parameters of immune cells including macrophages, T cell proliferation, and B-lymphocyte differentiation [10]. In a study of premature infants who went on to develop NEC, lower serum levels of glutamine and arginine were found 7 days prior to disease onset compared to the control group [11]. Whether these changes can be ascribed to inadequate exogenous provision or absorption, low endogenous production, or increased utilization in the setting of intestinal pathology could not be answered, but the importance of these amino acids are nonetheless highlighted especially when considering their role in the pathways of health and disease. A Cochrane review of glutamine supplementation in preterm infants cited a lack of sufficient evidence to recommend supplementation. However, the data on enteral administration did result in a decreased rate of invasive infection and decreased time to attain full enteral feedings [12], both clinically meaningful outcomes and possibly along the causal pathway to NEC. As a result, further exploration of glutamine is warranted as route, dosing and desirable target levels all remain undefined.

Arginine also plays an essential role in immune function as a precursor to nitric oxide production. Inhibition of nitric oxide synthesis in a feline model of ischemia–reperfusion increased intestinal damage, while infusion of the precursor arginine attenuated injury in a piglet model of NEC [13, 14]. In a double-blind placebo-controlled study done by Amin et al., 152 premature infants <1,250 g and <32 weeks gestational age were randomized to arginine supplementation or placebo. NEC (Bell Stage II or greater) developed in 6.7 % of the supplemented group versus 16.9 % in the placebo group. However, this reduction in NEC incidence did not reach statistical significance ($p = 0.077$) likely given the small sample size [15]. More importantly, arginine supplementation significantly reduced all stages of NEC, including suspected but not

confirmed NEC—a clinically meaning outcome given the high rates of feeding intolerance in this population and the medical interventions associated with suspected NEC (suspension of feeding, radiographs, and antibiotic exposure). Thus, an outcome of improving overall health may be just as important as attenuating the disease itself.

Long-Chain Polyunsaturated Fatty Acids (LCPUFAs)

Long-chain polyunsaturated fatty acids are some of the most studied immunonutrients in neonatology. LCPUFAs are biomagnified from mother to fetus to enhance maturation and growth of mainly the brain and eye. Largely due to a lack of appropriate postnatal delivery of LCPUFAs, the preterm infant rapidly undergoes changes in the absolute level and ratios of these critical fatty acids. In a retrospective cohort study of 88 infants born <30 weeks of gestation, decreased levels of the LCPUFAs docosahexaenoic (DHA) and arachidonic acids (AA) were demonstrated within the first postnatal week. Additionally, there was an almost threefold increase in the absolute level of linoleic acid and concomitantly the n6:n3 LCPUFA ratio. The changes in fatty acid levels were associated with an increased risk of chronic lung disease and late-onset sepsis [16•].

Despite the known importance of LCPUFAs on fetal development, postnatal enteral supplementation either as DHA alone or DHA and AA in formula has had somewhat disappointing results with no to minimal benefit in health status and long-term neurodevelopment [17].

An understanding of the postnatal transition of these fatty acids as described above in context of the common feeding practices in the extremely preterm infant may explain the limited response to supplemental DHA and AA. Studied supplemental strategies began with the attainment of a certain volume of enteral feedings. By this time, a deficit of LCPUFAs is already established, and the amount supplemented is below the estimated fetal accretion rates such that an ongoing, chronic deficit of these fatty acids is inevitable [18].

As with glutamine, arginine and many other immunonutrients, the precise means for delivery, timing and dosing of LCPUFAs need to be explored further to identify the potential benefits in attenuating disease as well as promoting health. The pleiotropic effects of fatty acids in organogenesis, immune ontogeny, angiogenesis, and regulation of inflammation [19–21, 22•] underscore why we must understand how to best prevent the postnatal alterations of these fatty acids early after premature delivery. An understanding of the fetal to postnatal changes in exposure to important biologic factors, such as LCPUFAs, in the preterm infant has important implications on normal development as well as disease pathogenesis.

Minimal Enteral Substrate in the Early Postnatal Period

A concern over potential deleterious side effects of enteral feedings in the critically ill preterm infant often results in delayed initiation of enteral feedings, especially among very low birth weight infants. A web-based survey in 2010 of 127 tertiary NICUs in Australia, Canada, Denmark, Ireland, New Zealand, Norway, Sweden, and the UK revealed that the proportion of units initiating enteral feeding within the first 24 h of life was 35 % for infants born at less than 25 weeks gestation and 43 % for those born between 25 and 27 weeks gestation [23]. Commonly stated clinical concerns that form the rationale to withhold feedings are often not evidence based. According to a survey of 24 Australian neonatal intensive unit directors of tertiary perinatal centers, reasons stated for withholding feedings included intrauterine growth restriction, absent or reversed end diastolic flow, inotropes, umbilical artery catheters, a significant patent ductus arteriosus and bile-stained aspirates [24]. Gastric residuals, for example, are not associated with an increased risk of NEC in extremely low birth weight infants [25]. Although retrospective studies have reported an association between a PDA and NEC, a large multicenter trial by the NICHD failed to show an association between PDAs and NEC in extremely low birth weight infants [26, 27]. Furthermore, many clinicians are hesitant to feed infants during the treatment of a PDA with cyclooxygenase (COX) inhibitors such as indomethacin and ibuprofen given concerns over decreased intestinal blood flow. However, a prospective randomized study including 177 very low birth weight infants treated with COX inhibitors failed to show an increased incidence of NEC in those fed trophic feedings. Rather, a decreased time to attain full feedings was found in those infants receiving trophic feedings while receiving indomethacin or ibuprofen compared to infants who were made NPO [28]. Review of available literature highlights the paucity of data that exists to justify withholding of feedings for the other aforementioned reasons of intrauterine growth restriction, absent or reversed diastolic flow, inotropes, and the presence of umbilical artery catheters [29–33]. Taken together and in the setting of what is now known about the ramifications of withholding enteral feedings, the current level of evidence favors a more liberal approach to feeding.

A delay in enteral feeding may potentiate undesirable consequences in postnatal gut development. In newborn animal models, significant mucosal atrophy is observed within 3 days of TPN and no enteral substrate in rats, [34] with similar findings in a piglet model. In neonatal piglets, nutritional support with TPN alone with no enteral substrate led to decreased jejunal mass, villus height, and crypt depth within 1–2 days of TPN. Concurrently, increased

rates of villous and crypt epithelial cell apoptosis was demonstrated [35]. Conversely, the provision of minimal enteral feedings in neonatal dog and pig models has been associated with improved gut motility and activity of digestive enzymes [36, 37]. The preterm infant's response to enteral food intake also demonstrates an adaptive physiological response such as improved intestinal blood flow and increased production of gut regulatory peptides (e.g., motilin, gastrin, neurotensin, and enteroglucagon) that promote continued gastrointestinal development that would otherwise be disturbed in the absence of an enteral substrate [38].

Delayed Provision of Enteral Feeding

There is very likely a beneficial adaptive gut response to enteral feedings in the preterm infant. A delay in feeding could disrupt this process and lead to maladaptive intestinal consequences. A key component in maximizing the benefit of enteral feedings is to provide the exposure early. As stated above, a delay of only 2–3 days results in morphological changes in the gut in neonatal animal models and is accompanied by physiological modification in blood flow, enzyme production, and nutrient metabolism. In addition, the full benefit of immunonutrients in the neonatal diet may be optimal when given earlier, before other maladaptive processes dominate. An example of this interplay is illustrated in a recent study examining the protective effect of human milk oligosaccharides (HMO) for NEC. HMOs behave as prebiotics and antimicrobials in addition to possibly modulating immune function [39, 40]. In a rodent model of NEC, formula feedings with an HMO protected against NEC demonstrating intestinal pathology scores no different from those observed from the dam-fed group. If the introduction of the HMO was delayed to after the first 24 h or was truncated to only the first 24 h the protective effect of the HMO was lost. Thus, early and continuous exposure was necessary for the full protective effect to be realized [41]. This underscores the importance of both early initiation and continuous exposure of immunonutrients for optimal physiological benefit.

The Practice of Enteral Feeding

The safety of early initiation of feedings is supported by several Cochrane-based reviews that address relevant issues of early trophic feeding, delayed (≥ 5 –7 days) versus early (≤ 4 days) feeding, and slow (15–20 ml/kg/day) versus fast (30–35 ml/kg/day) advancement [42–44]. In summary, early feeding and fast advancement of enteral feedings were not associated with an increased risk of NEC and instead resulted in decreased time to attain full feedings [45] (Table 1). The generalizability of this data to

Table 1 Feeding strategy and neonatal outcomes

Feeding strategy	Increased risk of NEC	Time to full feedings
Early trophic feeding “small volumes of milk (typically 12–24 mL/kg/day) without advancing the feed volumes during the first five to seven postnatal days”	No	No difference
Delayed (≥ 5 –7 days) versus early (≤ 4 days) introduction and progressive	No	Longer in delayed group
Slow (15–20 mL/kg/day) versus fast (30–35 mL/kg/day) advancement	No	Longer to regain birth weight and attain full feedings in slow group

Adapted from SIFT Investigators Group. Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews [45]

extremely lower birth weight infants is limited given a relatively small number of such infants included in these studies. Additional studies are ongoing that will help answer these questions in the extremely low birth weight cohort. However, early retrospective data do suggest that early initiation and fast advancement are safe for the smaller, more immature infant. In a recently published retrospective study of very low birth weight infants conducted after an unit policy change to promote early enteral feeding, infants who were fed at a median age of 14 h of life demonstrated a trend toward a decreased NEC incidence compared to infants fed at a median age of 33 h of life [46]. Furthermore, standardized feeding protocols that highlight the importance of early initiation of enteral feedings are likely to provide benefit even to the most extreme of premature infants [47].

Exposure to Gut-Altering Medications

Undeniably the care of the very low birth weight infant necessitates the use of medications for preventative or treatment purposes. Nevertheless, it is also well known that the use of medications in the NICU may result in known and unknown side effects. There has been an increasing appreciation of how medications may have specific gastrointestinal implications that interfere with gut development. A specific look at the potential consequences of antibiotics and acid blockers in the establishment of the gut microbiome and subsequent risk of intestinal injury illustrates this concept well.

The intestinal microbiome of the preterm infant is altered significantly from the term breast-fed infant due to multiple unique biologically inherent and environmental exposures [49]. The establishment of an intestinal microbiome after birth is critical for the continued development of the intestinal tract and the immune system. It has been hypothesized that this dysbiosis in the intestinal microbiome is a major contributor to the risk of NEC [50]. Recent work has identified altered proportions of Firmicutes, *Bacteroides*, and Proteobacteria in the GI tract of

premature infants. In patients with NEC, a “blooming of Proteobacteria” and reduced microbial diversity have been observed [51–53].

Few infants, especially those of very low birth weight, reside in the NICU without a course of antibiotics. In fact, antibiotics are the most commonly prescribed medication in the NICU [48]. Concerns over impaired immunity in the premature infant and high a rate of mortality among premature infants with invasive bacterial infections are potential reasons for this practice. Antibiotics play a role in contributing to the increased risk of NEC possibly by exacerbating the postnatal dysbiosis in the preterm infant. A large review of empiric antibiotic exposure within the first 48 h among extremely low birth weight infants demonstrated a trend toward an increased risk of NEC with prolonged antibiotic exposure ≥ 5 days (OR: 1.21 [95 % CI: 0.98–1.51]) [54]. This trend was even more pronounced when prolonged antibiotic exposure was defined as ≥ 4 days (OR: 1.34 [95 % CI: 1.04–1.73]). Multivariate logistic regression analysis attempted to correct for identifiable risk factors associated with sicker infants and prolonged antibiotic exposure; however, the increased risk of NEC after a prolonged course of antibiotics remained increased compared to infants who did not receive a prolonged course of antibiotics.

Of additional concern is the lack of rationale in providing a prolonged course of antibiotics that will lead to difficulty in modifying this potential harmful practice. Cordero and Ayers investigated the determinants that defined the duration of empiric antibiotic use for suspected early onset sepsis in extremely low birth weight infants utilizing the Clinical Risk Index for Babies (CRIB). They found no difference in CRIB scores for infants with sterile cultures who received <3 days versus >7 days of antibiotics [55]. This suggests that the length of an antibiotic course may be provider and/or institutional dependent rather than related to illness severity. The practice of frequently indiscriminate antibiotic administration is concerning given an incidence of less than 2 % of early onset sepsis in very low birth weight infants [56]. The use of a predictive model for neonatal sepsis might serve to guide

antibiotic utilization via a targeted approach that maximizes benefit while minimizing potential unintended consequences [57].

Similar to antibiotic exposure, the use of acid blockers also plays a role in increasing the risk of NEC presumably by altering the intestinal microbiome. Several case control studies have found H2-blocker use to be associated with higher rates of NEC in very low birth weight infants [58, 59]. Terrin et al. found a 6.6-fold higher rate of NEC in ranitidine-treated very low birth weight infants in addition to significantly higher rates of mortality and prolonged hospitalization [58]. The indication for antacid use is an important potential confounding factor as H2-blockers may be more utilized in sicker infants; however, even after adjustment for these factors, the relationship between the use of H2-blockers and NEC persists.

Available data support the role of gastrointestinal pH in the development of NEC. For example, a prospective double-blind study comparing infants supplemented with 0.01–0.02 ml of 1 N HCl/ml of milk versus a similar volume with water found a significantly reduced incidence of NEC [60]. Additionally, comparative stool analysis of preterm infants on H2-blocker therapy noted a shift toward lower microbial diversity and an abundance of *Proteobacteria* [61], a shift that has been implicated in the development of NEC. Lastly, part of the protective effect of breast milk in the development of NEC may be explained by its poor buffering capacity relative to formula. This results in a lower colonic pH in breast-fed infants and a microbial flora with relatively increased quantities of *Lactobacilli* and *Bifidobacterium*. Gastrointestinal acidity and disturbances to gastric pH via H2-blocker therapy or formula feeding likely play critical roles in host defense, dysbiosis, and pathogenesis of NEC. Of general concern is the absence of evidence for use of antacids in NICUs. A clear benefit to antacid use in the preterm population has not been established. In fact, the literature has supported the lack of improvement or benefit for neonates receiving H2-blockers [62–65].

Nutritional Ingredients Inadequately Processed by the Immature Gut

The digestive capabilities of the premature gut are limited due to the reduced production of important digestive enzymes. In one example, the immature pancreas produces limited amounts of lipase at birth with levels still below adult levels until at least 6 months of age [66]. However, lactating maternal mammary glands secrete bile salt-stimulated lipase (BSSL) that allows for proper fat hydrolysis and absorption by the breast-fed infant [67]. On the other hand, pasteurization of human milk destroys heat-labile

BSSL and formula lacks digestive enzymes all together. This is of clinical importance, as infants fed formula will demonstrate fat malabsorption. Fat absorption, quantified as coefficient of fat absorption (CFA), in formula or pasteurized human milk-fed preterm infants is 70–80 % [22•] in contrast to 90 % in preterm infants fed mother's own milk. Casper et al. demonstrated that preterm infants fed formula or pasteurized human milk supplemented with recombinant human BSSL showed improved growth velocity and fat absorption [68].

The consequences of fat malabsorption extend beyond potential impaired growth. Neonatal mouse pups with lipase deficiency (induced with a BSSL inhibitor or as a product of BSSL knockout mice) fed artificial formula or dam milk were noted to have lipid accumulation within the intestinal epithelium of the ileum and lower jejunum with associated villus damage and loss of epithelial integrity [69]. Interestingly, the site of injury was predominantly in the distal ileum—a location that activates the “ileal brake” in the presence of undigested fats and is the predominant region involved in the majority of NEC cases.

Fat absorption and delivery of structurally appropriate feedings also have implications for gut motility and feeding tolerance. The phenomenon of an ileal brake has been observed when partially digested triglycerides are delivered to the ileum with ensuing impaired jejunal motility [70]. Gut motility may also be affected by protein content as demonstrated by Mihatsch et al. Very low birth weight infants fed preterm formula with hydrolyzed protein established full enteral feedings significantly faster than those fed standard preterm formula [71]. Postulated mechanisms include higher induction of motilin levels and reduced activity of opioid receptor agonists with hydrolyzed protein [72, 73].

Intestinal Health as a Gateway to Systemic Disease

Optimizing postnatal gut development is not only important in mitigating the risk of NEC, but may also play a role in mitigating the risk of common systemic morbidities observed in the preterm infant. Clustering of disorders such as retinopathy of prematurity (ROP), periventricular leukomalacia, and bronchopulmonary dysplasia (BPD) with NEC is observed among extremely low gestational age newborns [74]. A heightened vulnerability to diseases secondary to prematurity could easily explain disease clustering in very low birth weight infants. However, even after controlling for gestational age, infants with severe NEC (Bell stage IIIB) remained at significantly increased risk of BPD, ROP, and white matter injury. With the explanatory variable of extreme prematurity removed, the clustering of these disorders must share an alternate etiology.

Altered postnatal gut development including microbial dysbiosis, impaired innate defenses, and dysregulated inflammation allows for bacterial translocation and a transition from a local to systemic neonatal inflammatory response. The systemic inflammatory response associated with NEC results in the release of mediators that have been implicated in distal organ injury including the brain, lungs, and retina [75–77]. In a study of infants born at 23–27 weeks' gestation, children followed at 24 months post-term equivalent who had a history of surgical NEC without late-onset bacteremia were at an increased risk of Psychomotor Developmental Indices <70 [OR = 2.7 (1.2, 6.4)] [78]. This observation suggests that bowel injury, at least in its most severe form, contributes to a systemic inflammatory response with both short-term multi organ and long-term developmental consequences.

Conclusions

Immediate practice changes as well as future pursuits may serve to optimize early intestinal development (Table 2). Following birth, NPO status should be limited and early feeding with progressive advancement should be carried forward in an attempt to avoid disruption of intestinal development and to promote continued growth. Additionally, the importance of human milk delivery is self-evident in the context of a growing understanding of the nutritional and non-nutritional benefits of human milk. An appreciation of the impact of gut-altering medications, such as antibiotics and antacids, may furthermore help to limit their pathologic impact on bacterial colonization and intestinal physiology. Variability in feeding practices should finally

Table 2 Nutritional strategies to optimize early intestinal development

What can be implemented now?
Limit duration of NPO status
Practice early and progressive enteral feedings
Encourage delivery of human milk
Limit medication exposures that are known to alter bacterial colonization patterns, disrupt intestinal epithelium
Establish a feeding policy to help minimize variability in nutritional delivery
What can we pursue?
Prebiotics (nucleotides, oligosaccharides)
Probiotics
Human milk derived fortifiers
Immunonutrients (specific amino acids, LCPUFAs)
Personalized medicine with metabolomic phenotypic signatures (nutrigenomics)
Other?

be addressed via establishment of evidence-based feeding protocols. Moving forward, further research is required in the use of prebiotics, probiotics, human milk-derived fortifiers, and immunonutrients. Nutritional and developmental support may also be individualized in the future with advancements in the field of nutrigenomics. An unveiling of the developmental pathways of the gut that are altered with premature delivery and manipulated by nutritional and non-nutritional NICU interventions can further identify additional bedside strategies that can incrementally improve upon the care and optimize postnatal gut development in the preterm infant.

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