HHS Public Access

Author manuscript

Curr Opin Clin Nutr Metab Care. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2015 May ; 18(3): 285–288. doi:10.1097/MCO.0000000000000169.

Preterm infant nutrition, gut bacteria, and necrotizing enterocolitis

Josef Neu

Department of Pediatrics, University of Florida, Gainesville, Florida, USA

Abstract

Purpose of review—Provide research that relates the developing intestinal microbiome, nutrition, and the subsequent host response to the development of necrotizing enterocolitis (NEC), one of the most common and deadliest diseases seen in newborn infants. After nearly 50 years of little to no progress in this area, we are finally beginning to obtain evidence that is likely to lead to better understanding of both pathophysiology and prevention of the disease.

Recent findings—We will discuss new discoveries related to the development of the microbiome from prenatal to postnatal life, as well as new findings of microbes and human milk oligosaccharides in human milk as they relate to pathogenesis of NEC. The effect of antibiotics and acid blocking agents as they may increase the odds of development of NEC will also be discussed.

Summary—The implications of these findings are that improved understanding of the developing microbiome, the factors that affect the microbiome including nutrition such as donor milk versus baby's own mother's milk, and certain drugs, will help clinicians to adjust their current feeding and drug utilization to potentially prevent this disease.

Keywords

antibiotics; microbiome; necrotizing enterocolitis; nutrition

INTRODUCTION

Necrotizing enterocolitis (NEC) is an all too common and deadly disease affecting primarily preterm neonates. This review will focus on recent developments pertaining to nutrition and the developing microbiota as they affect the development of NEC in preterm infants. There are probably several pathways leading to different forms of what is termed 'NEC'. Due to this, as well as the lack of good animal models to evaluate the disease, understanding of pathophysiology, prevention, and treatment have been very elusive. Although the pathophysiology of NEC remains poorly understood, it is likely that a relationship between

Correspondence to Josef Neu, MD, Department of Pediatrics, Division of Neonatology, Room HD 112 Human Development Building, University of Florida, 1600 S.W. Archer Road, Gainesville, FL 32610, USA. Tel: +1 319 273 8985; fax: +1 352 273 9054; neuj@peds.ufl.edu.

Conflicts of interest

The author is a scientific advisory board member for Medela and has consulted for Infant Microbial Therapeutics.

nutrition, the intestinal microbes, and the interaction of the host with these microbes and nutrition plays a major role in the pathogenesis of this disease. The more common form of NEC that is seen primarily in preterm infants, that occurs usually after the first couple weeks after birth, has a major inflammatory component, and is not related to primary ischemic disease. This is done in order to differentiate this entity from primary intestinal ischemic bowel disease as seen in babies with congenital cardiac disease, babies with isolated intestinal perforations, or other 'mimickers' of NEC.

PRENATAL, PERINATAL AND IMMEDIATE POSTNATAL MICROBIOME

At this juncture, is not clear whether there is a predisposition to NEC that may have its roots even before birth, but recent evidence suggests that events that transpire during very early intestinal development could play a role. There is a common notion that the fetus emerges from a sterile environment at the time of birth, and after emerging from the womb begins to associate with environmental microbes. However, a convincing body of evidence is beginning to suggest otherwise. Studies of the placenta [1■] and meconium [2■,3■■] from babies delivering at various gestational ages show a high prevalence of microbes. The site of origin of these microbes is still not fully understood but possibilities include the maternal gastrointestinal tract, mouth, and vagina. Although it was originally thought that the most likely site of the microbes found in amniotic fluid and placenta originated from the vagina via ascending spread and translocation of the microbes through choriodecidual membranes, recent studies suggest that this relationship may not be as strong as previously believed [4]. Of interest is the fact that prematurely delivered infants show different microbes in their amniotic fluid, placenta, and meconium than those babies delivered at term [1■,3■■]. Whether this relates causally to preterm delivery is not fully understood and requires additional study.

The fetal gastrointestinal tract is not an inert organ. On the contrary, it is developing rapidly and is also exposed to large quantities of antigens present in swallowed amniotic fluid as well as through hematogenous entry. The fetus swallows large quantities of amniotic fluid, especially during the last trimester of the pregnancy, and this volume may reach up to 150 ml/kg/day. Microbes in the mother' s gastrointestinal tract have a significant capability of producing large quantities of metabolites that are found in her bloodstream [5] that may subsequently affect the fetus. Interrelationship of the microbes and the mother's gastrointestinal tract may also lead to the production of the various inflammatory mediators that are derived from the mother. In addition, these microbes may actually translocate from the mother's gastrointestinal tract and reach the developing fetus hematogenously and harbor in the fetal gastrointestinal tract. A fascinating potential for speculation is that the mother's diet may play a large role in the microbiota that she harbors and the consequences of her diet on her intestinal microbial population and the consequent production of the various metabolites and inflammatory mediators that may affect the highly susceptible fetus.

Thus, factors that affect the maternal gastrointestinal tract microbial ecology may result in distal effects on the fetus. For example, depending on the maternal diet, drugs, or other environmental factors, a shift of her intestinal microbes may commonly occur during pregnancy. This shift in microbes is associated with the mother's weight gain as well as the

pregnant mother's propensity to develop insulin resistance. Studies using transfaunation of microbes from early versus late stages of pregnancy into germ-free mice have shown fascinating effects [6]. If the microbes are provided early in pregnancy, no effects are seen in terms of obesity or insulin resistance. However, when germ-free mice are transfaunated with microbes from pregnant mother's stools during late pregnancy, they do develop obesity and insulin resistance [6]. This strongly supports a role for the maternal intestinal microbes' metabolic effects on the mother, which could in turn significantly affect her developing fetus.

At this juncture, little is known about the effects of certain drugs on the developing gastrointestinal microbiota in the pregnant mother and the consequences on the fetus but these could be very significant. Antibiotic treatment could result in major shifts in the microbiota of the mother. Other common treatments that are thought to be benign, such as H2 blockers or proton pump inhibitors may have significant effects on the microbiome [7]. Gastric acid blockers used in the treatment of gastroesophageal reflux may thus alter the gastrointestinal microbiota of the mother. These could all potentially have major effects on metabolite production, inflammatory mediator production, and presentation of microbes to the developing fetus.

Well known phenomena exists in which priming of the gastrointestinal tissues with inflammatory mediators such as flagellin or lipopolysaccharide may serve to prime the intestinal epithelia as well as other intestinal cells and induce a tolerance to subsequent exposures to these proinflammatory agents. Whether such phenomenon occurs in the human fetus has not been thoroughly investigated and remains a fertile field for investigation, especially as it pertains to the development of various neonatal inflammatory conditions, which include respiratory distress syndrome, chronic lung disease, white matter disease of the brain, and of course NEC.

POSTNATAL FACTORS AFFECTING THE NEONATAL MICROBIOME

There are several postnatal factors that may affect the intestinal microbiota of the newborn. However, for the sake of brevity, here will be discussed the early use of the antibiotics, H2 acid blockers, and the use of human milk versus formula versus donor milk. Studies of these factors as they relate to the intestinal microbiome are in their very early phases. Current evidence suggests that they all play a role in altering the intestinal microbiota of the infant, which in turn interacts with the gastrointestinal mucosal immune system. Here, evidence will be provided that links these interventions with the prevention or development of NEC.

The microbial ecology of the neonate who develops NEC differs from that of control infants [8■■,9,10■■]. These studies demonstrate that a dysbiosis occurs with the phylum Proteobacteria highly represented before the development of NEC. Of interest, this particular phylum contains numerous gram-negative pathogens with high levels of cell wall lipopolysaccharide. Furthermore, these microbes are also highly present in other disease entities such as inflammatory bowel disease, in which blooms are seen prior to exacerbations of the inflammation [11].

Human milk feeding in preterm infants protects against the development of NEC. Studies in the past few years have shown that human milk contains a wide variety of microbes. More recently, human breast tissue was evaluated for the presence of bacteria, using both culture and nonculture-based techniques [12■]. These investigations detected a diverse population of bacteria within the tissue, even if the women never lactated. None of the individuals had signs of infection, although 8 different strains were able to be cultured using a limited culture assay. The function of these microbes in maintenance of breast health or microbes present in human milk remains to be clarified. Whatever the mechanism, fresh breast milk provides a variety of bacteria that colonize the newborn gastrointestinal tract, where they have the capability to interact with the developing mucosal immune system. Whether content of lactose and oligosaccharides along with the microbes in human milk contributes to a healthy infant microbial ecosystem is an area of recent interest. De Leoz *et al.* [13] obtained serial fecal specimens from two healthy breast-fed infants and sequenced their bacterial DNA to characterize the microbiota; they used mass spectrometry to determine the abundances of human milk oligosaccharides (HMOs) in the intestinal tract. Over the first few weeks, the microbial population shifted to HMO-consuming bacteria. This was accompanied with decreases in fecal HMOs. These results are consistent with a 'prebiotic' effect of the HMOs, which shapes the microbial ecology of the intestinal tract within the first few weeks after birth. This is also highly relevant to the fact that many preterm infants are now receiving banked donor milk. This milk is pasteurized and contains very low levels of live bacteria. Thus, even if the HMOs are not significantly affected by the pasteurization process, the question remains whether loss of the indigenous milk microbiome results in loss of the early microbial HMO interaction that may potentially be beneficial.

It is common practice to provide antibiotics to preterm infants shortly after birth. In fact, the majority of very low birth weight infants receive antibiotics immediately after birth, the putative rationale being that many babies have respiratory distress, which is difficult to discern from pneumonia. Another reason for routine antibiotic treatment is the possibility of maternal infection-induced preterm labor. The prolonged use of antibiotics has been associated with an increased odds ratio of the development of NEC [14■]. It is not to clear whether it was simply degree of illness that caused the greater use of antibiotics in these infants and that greater degree of illness also predisposed these babies to the development of NEC. Nevertheless, this association is highly intriguing. It is clear that antibiotics can lead to an intestinal dysbiosis in early life. A better understanding of the interplay between antibiotics, the developing intestinal microbiota, and the host responses will be very important to better understand this phenomenon and possibly for a more cautious use of antibiotics in these infants.

Another interesting relationship exists between the development of NEC and the use of H2 blockers in premature infants. H2 blockers have commonly been used as many preterm babies have episodes of apnea and bradycardia related either to developmental immaturity of the central nervous system, or to gastroesophageal reflux. However, a relationship was found between increased sepsis as well as NEC in babies receiving H2 blockers. Nevertheless, these agents have recently been found to affect the intestinal microbiota [7]. The mechanism of this remains poorly understood, but the aforementioned relationship

between intestinal pH and ability of the intestine to support the growth of potentially pathogenic Proteobacteria is intriguing.

CONCLUSION

Recent studies show that a predisposition to the development of NEC may actually begin before birth. The role of the microbes and microbial products from the mother's gastrointestinal tract may be very important in this regard. If the maternal intestinal microbes actually predispose to NEC in the fetus, it allows the intriguing opportunity for microbial manipulation in the mother's gastrointestinal tract by diet or other microbial therapeutic measures. It also underlines the need for cautious care in antibiotic usage in the pregnant mother as well as other medication such as H2 blockers. Similarly, diet as well as medications affects the neonates' gastrointestinal microbial ecology, which in turn may play a role in the pathogenesis of NEC. At this juncture, data remain sparse, and there is a strong need for studies that will rigorously evaluate NEC causality from dietary factors and the maternal and neonatal microbiome.

Acknowledgements

None.

Financial support and sponsorship

This study is supported by the grant NIH RO1 HD 059143.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1■. Aagaard K, et al. The placenta harbors a unique microbiome. Sci Transl Med. 2014; 6:237ra265. Provides important information about the developing microbiome in the placenta during late pregnancy and relates taxonomy to different levels of prematurity and the use of antibiotics early during pregnancy.

2■. Moles L, et al. Bacterial diversity in meconium of preterm neonates and evolution of their fecal microbiota during the first month of life. PLoS One. 2013; 8:e66986. [PubMed: 23840569] Evaluates microbes in meconium at different gestational ages using both culture-based and nonculture-based techniques.

3■■. Ardissone AN, et al. Meconium microbiome analysis identifies bacteria correlated with premature birth. PLoS One. 2014; 9:e90784. [PubMed: 24614698] Provides the first information relating microbes in meconium as a reflection of the in-utero environment including swallowed amniotic fluid. Suggests a testable hypothesis that swallowed microbes may incite an inflammatory response in the fetal intestine that triggers preterm labor.

4. Romero R, et al. The vaginal microbiota of pregnant women who subsequently have spontaneous preterm labor and delivery and those with a normal delivery at term. Microbiome. 2014; 2:18. [PubMed: 24987521]

5. McFall-Ngai M, et al. Animals in a bacterial world, a new imperative for the life sciences. Proc Natl Acad Sci U S A. 2013; 110:3229–3236. [PubMed: 23391737]

6. Koren O, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell. 2012; 150:470–480. [PubMed: 22863002]

7. Freedberg DE, Lebwohl B, Abrams JA. The impact of proton pump inhibitors on the human gastrointestinal microbiome. Clin Lab Med. 2014; 34:771–785. [PubMed: 25439276] Shows that proton pump inhibitors can alter the intestinal microbial environment and thus brings up the hypothesis that acid reduction may actually lead to an altered microbial environment that causes the increase in NEC in babies receiving such agents.

8■■. Torrazza RM, Ukhanova M, Waln X, et al. Intestinal microbial ecology and environmental factors affecting necrotizing enterocolitis. PLoS One. 2013; 8:e83304. [PubMed: 24386174] Shows the dysbiosis that occurs prior to development of NEC in preterm infants as well as nutritional (human milk versus formula and antibiotic usage).

9. Mai V, et al. Fecal microbiota in premature infants prior to necrotizing enterocolitis. PLoS One. 2011; 6:e20647. [PubMed: 21674011]

10■■. Claud EC, et al. Bacterial community structure and functional contributions to emergence of health or necrotizing enterocolitis in preterm infants. Microbiome. 2013; 1:20. [PubMed: 24450928] Shows the intestinal microbial ecology prior to the development of NEC in preterm infants using both 16S and metagenomic technologies.

11. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. Semin Immunopathol. 2015; 37:47–55. [PubMed: 25420450]

12■. Urbaniak C, et al. Microbiota of human breast tissue. Appl Environ Microbiol. 2014; 80:3007–3014. [PubMed: 24610844] Supports the previous studies that show microbial presence in human milk, but shows that microbes are present in the breast tissue, suggesting the presence of a breast microbiome.

13. De Leoz ML, et al. Human milk glycomics and gut microbial genomics in infant feces show a correlation between human milk oligosaccharides and gut microbiota: a proof-of-concept study. J Proteome Res. 2015; 14:491–502. [PubMed: 25300177]

14■. Greenwood C, et al. Early empiric antibiotic use in preterm infants is associated with lower bacterial diversity and higher relative abundance of Enterobacter. J Pediatr. 2014; 165:23–29. [PubMed: 24529620] Largely supportive of previous studies that also show a relationship between the use of antibiotics and the subsequent development of NEC, again supporting the need for careful antibiotic stewardship in this population.

KEY POINTS

- The early intestinal microbial environment is likely to play a significant role in the pathogenesis of NEC.
- The intestinal microbial environment can be perturbed by the use of antibiotics, diet, various drugs, and other environmental conditions, thus predisposing to NEC.
- Although associations between microbes and NEC have been found, proof of causality will require additional studies.