REVIEW ARTICLE

Neonatal intestinal dysbiosis

Mark A. Underwood [ID]¹ · Sagori Mukhopadhyay [ID]² · Satyan Lakshminrusimha [ID]¹ · Charles L. Bevins³

Abstract
The initial colonization of the neonatal intestinal tract is influenced by delivery mode, feeding, the maternal microbiota, and a host of environmental factors. After birth, the composition of the infant's microbiota undergoes a series of significant changes particularly in the first weeks and months of life ultimately developing into a more stable and diverse adult-like population in childhood. Intestinal dysbiosis is an alteration in the intestinal microbiota associated with disease and appears to be common in neonates. The consequences of intestinal dysbiosis are uncertain, but strong circumstantial evidence and limited confirmations of causality suggest that dysbiosis early in life can influence the health of the infant acutely, as well as contribute to disease susceptibility later in life.

Introduction

The intestinal microbiota consists of trillions of living microbes that co-exist with the host. Bacteria represent the most abundant colonizers, but archaea, fungi, and viruses are also abundant in healthy individuals. The complexity of interactions between the triad of microbiota, environmental factors, and the host is underscored by evidence that this massive microbial community (1) competes for and generates nutrients, (2) influences and is shaped by the host innate and adaptive systems, and (3) protects against and triggers acute and chronic disease. Mounting evidence further suggests that the intestinal microbiota influences mucus production, maturation and continuity of the epithelial monolayer separating the intestinal lumen from the submucosa, essential qualities of inflammatory responses, and physiological homeostasis [1]. Interactions between gut microbes and the developing immune system appear to be particularly important early in life [2].

The paradigm that intestinal microbes easily fit into circumscribed categories such as symbionts or mutualists (both the host and the microbe benefit from this co-existence), commensals (the microbe benefits and the host is unharmed), and pathogens (the microbe benefits and the host is harmed) is being replaced because of an understanding that cooperative factors that allow nonpathogenic microbes to colonize and benefit the host share essential qualities similar to virulence factors that can drive pathogenicity [3, 4]. Thus, many intestinal microbes are more precisely characterized as pathobionts, capable of causing harm in some situations while being tolerated (or even beneficial) in others.

Intestinal dysbiosis describes alterations in the intestinal microbiota associated with disease. In some cases, the compositional shift and associated phenotype can be ascribed to changes in a small collection of microbes. Disease causality for such changes can be tested in model systems by demonstrating transmissibility of host disease phenotype with microbiota transfer [5, 6]. In other cases, an association is more nuanced. Measures of dysbiosis often cannot confirm a causal role of the specific microbiome pattern in a specific disease [7–9]. Dysbiosis may be the result of disease, or merely coincident, rather than causative. In addition, in newborns the converse maybe true. Alterations that are not immediately associated with pathology may potentially have far reaching consequences later in childhood via microbiome–immune interactions. Herein, we review the importance of the intestinal microbiota in neonatal development and the consequences of alterations in this complex microbial community in newborns.

✉ Mark A. Underwood
munderwood@ucdavis.edu

1 Department of Pediatrics, UC Davis School of Medicine, Sacramento, CA, USA

2 Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

3 Department of Medical Microbiology and Immunology, UC Davis School of Medicine, Davis, CA, USA

Dysbiosis and development

Injury to an organ during its morphogenesis can have consequences for both organ recovery and development, as well as on function of downstream systems reliant on that organ. Formative years for the microbiome include the first 3 years of life with age-dependent shifts in dominant taxa driven by environment, diet, and medication [10–12]. The intestinal immune system develops in parallel with the child's microbiome and is affected by both structural components of microbes and products of microbial metabolism [12–14]. The importance of this early period is demonstrated in animal models where microbiome disruption during the early life window causes specific immune/health alterations that are not elicited when the disruption is triggered at a mature age [15, 16].

Animal models have been helpful in analyzing the impact of the intestinal microbiota on development, particularly experiments in animals raised in germ-free conditions. The impact of the microbiota begins in utero as evidenced by the observation that offspring of germ-free dams are at high risk for metabolic syndrome even if raised in conventional conditions [17]. Mice raised in germ-free conditions have poor growth, decreased weight and mucosal surface area of the small intestine, decreased intestinal motility, increased mucus production, increased size of the cecum and mild diarrhea [18]. Germ-free mice also demonstrate altered neurodevelopment with deficiencies in stress responsivity, anxiety-like behaviors, sociability, and cognition [19]. The elegance of this approach is fully evident with colonization of germ-free animals with single microbes or specific microbial communities (gnotobiotic or "known microbiota") and analysis of the resulting phenotype. Comparisons of germ-free, gnotobiotic, and wild-type animals demonstrate the importance of the intestinal microbiota in intestinal development [20] and an essential causal role of intestinal dysbiosis in severe acute malnutrition [21], obesity [22], nonalcoholic liver disease [23], Alzheimer's disease [24], and colitis-associated colorectal cancer [25], to name a few.

Prevalence of neonatal intestinal dysbiosis

To address the question of how commonly intestinal dysbiosis occurs in early life presumes an understanding of the "normal" microbiota of the infant which unfortunately is lacking. The following assumptions seem reasonable: (1) microbial communities are dynamic and shaped by host factors, environmental factors, and available nutrients, (2) the composition of the intestinal microbiota of our ancestors' neonates was shaped by the maternal vaginal, fecal, oral, and milk microbiota, by nutrients available in human milk, and by horizontal transmission within families and small communities that shared food, eating utensils and toileting facilities, and (3) the introduction of modern hygiene practices, antibiotics, antiseptics, and other medications, modern diets such as the so-called "Western" high fat/high sugar diet, and infant formula has fundamentally changed the intestinal microbiota of humans from that of our ancestors.

The earliest attempts to describe the fecal microbiota of the breast-fed infant were published by Tissier [26] and Logan [27]. Both described a predominance of Gram-positive, anaerobic, Y-shaped, nonmotile bacteria in healthy infants. These bacteria were characterized as a single species, *Lactobacillus bifidus*, until the 1960s when the multiple species were grouped in a single genus *Bifidobacterium* (family Bifidobacteriaceae, order Bifidobacteriales, phylum Actinobacteria). *Bifidobacterium* species selectively ferment carbohydrates; some produce the glycosidases necessary to digest plant oligosaccharides (e.g., *Bifidobacterium adolescentis*, *B. longum* subsp *longum*) and others the glycosidases necessary to digest milk oligosaccharides (e.g., *B. longum* subsp *infantis*, *B. bifidum* and some strains of *B. breve*). These differences are encoded in the bacterial genome and have been confirmed by biochemical and molecular characterization of bacterial glycosidases and transport proteins [28–30]. Microbes capable of consuming milk components have a competitive advantage in the infant gut. Given the abundance of oligosaccharides in human milk, the relatively few species of bacteria capable of consuming these glycans, such as those mentioned from the *Bifidobacterium* genus, can multiply and their abundance "blooms." The observation that mothers produce large quantities of human milk oligosaccharides with vast structural diversity that do not serve as a direct nutrition source for the infant, given their lack of the necessary glycosidases, suggests either co-evolution of human milk and a limited number of bacterial species millions of years ago, or a very clever design, or perhaps some of both. The end result is that the mother is shaping the microbiota of her infant through selective nutrients and antimicrobials in her milk (Fig. 1).

However, this ancient mechanism of maternal influence on infant microbiota via breastmilk, may be weakened by modern practices. A recent review of 14 studies published between 1926 and 2017, which included more than 300 healthy breastfed infants, documented over that time period an increase in fecal pH from 5.0 to 6.5 [31]. This change in pH is consistent with a decrease in Bifidobacteriaceae (which produce lactic acid and lower fecal pH) and increases in Clostridiaceae and Enterobacteriaceae (both associated with increased fecal pH).

Such changes could have immediate health consequences (Figs. 1, 2). For example, the mentioned Enterobacteriaceae

Fig. 1 Neonatal intestinal dysbiosis and disease risk. a Normal colonization of the infant gut is shaped by environmental factors, maternal microbes and breast milk (human milk oligosaccharides). Colonizing microbes influence development of the intestinal innate and adaptive immune systems. **b** Several factors result in dysbiosis increasing risk for neonatal conditions such as necrotizing enterocolitis and long-term health issues such as autoimmune diseases, atopy and obesity. Copyright Satyan Lakshminrusimha.
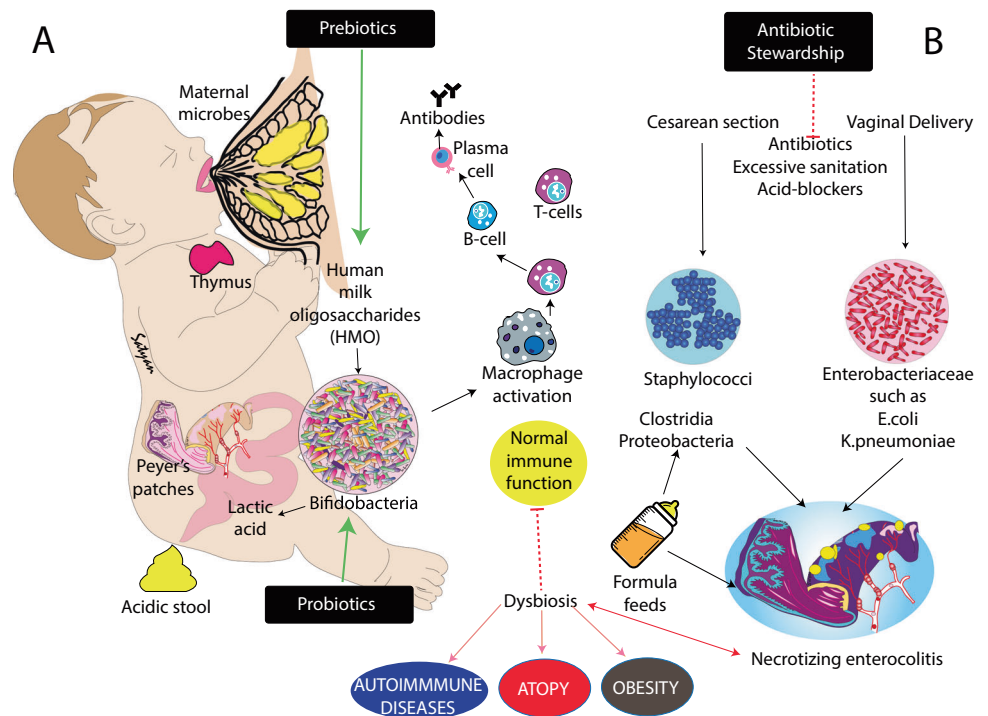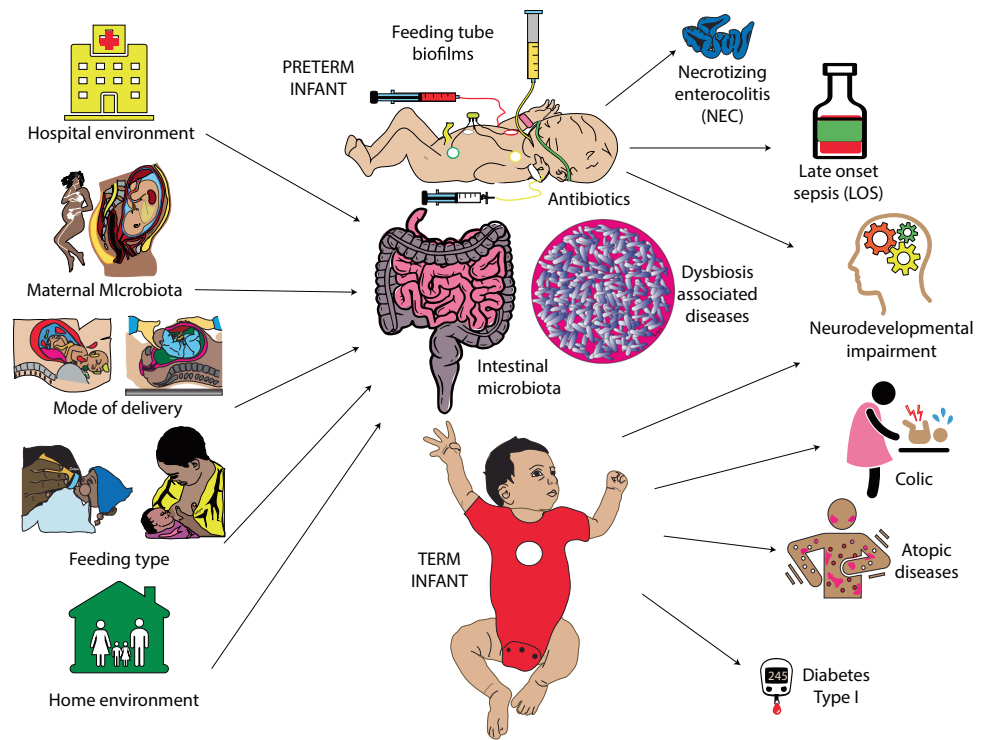

Fig. 2 Contributors and consequences of intestinal dybiosis. Factors influencing the intestinal microbiota in preterm and term infants are presented at the left and top of the figure with diseases associated with intestinal dybiosis to the right.

(phylum Proteobacteria) are Gram-negative facultative anaerobes that include two species well known to neonatologists: *Escherichia coli* and *Klebsiella pneumoniae*. Virulence factors include flagella that provide motility, fimbriae that allow attachment to the host cell surface, and toxins that interfere with homeostasis. Many Enterobacteriaceae trigger a host immune response through recognition of microbial patterns such as lipopolysaccharide in the cell wall or flagella. *E. coli* and *K. pneumoniae*, in particular, can cause devastating overt disease in neonates. An abundance of Enterobacteriaceae has been described as one hallmark of dysbiosis [32].

Studies of the fecal microbiota of the healthy term infant have shown recognizable patterns although with a high degree of individual variation. The broad patterns now emerging suggest a first wave of bacterial colonists influenced by mode of delivery (Enterobacteriaceae in babies born vaginally and Staphylococcaceae in babies born by cesarean section) and a second wave influenced by feeding type (Bifidobacteriaceae in breast-fed infants and a more diverse population in formula-fed infants including Staphylococcaceae, Clostridiaceae, Enterococcaceae, Bifidobacteriaceae, and Bacteroidaceae) [33]. In the very preterm infant, the pattern is more complex (again with a high degree of individual variation): initial colonization with Staphylococcaceae followed by Enterobacteriaceae and then Clostrideaceae with Bifidobacteriaceae and Lactobacillaceae characteristically delayed or absent [34, 35]. In both term and preterm infants, cessation of breastfeeding and introduction of complementary foods begin a steady increase in microbial diversity resulting in a more complex microbiota, ultimately resulting in stable communities characteristic of adults.

In broad terms, the presence of low numbers of Bifidobacteriaceae and high numbers of Enterobacteriaceae and Clostridiaceae can serve as a reasonable starting place to define dysbiosis in the first months of life. This pattern is common in several settings, including very preterm infants, term infants requiring prolonged hospitalization or antibiotics, and in well-appearing infants in some geographic areas with increased risk for dysbiosis-associated diseases [36]. Microbiota composition "immaturity" is a term coined for a delay of the patterned progression of the microbiota. It is characteristic of severe acute malnutrition in children [37] and may be another useful definition of dysbiosis in the infant [38–40].

Causes of neonatal intestinal dysbiosis

As noted above, in term infants, both mode of delivery and feeding type (human milk vs. formula vs. a combination) significantly influence the composition of the infant microbiota [41, 42]. Differences in the infant microbiota with home delivery vs. hospital delivery have been reported [43]. The mother's diet and the microbes in her milk (generally similar to the microbiota of maternal skin and feces) also influence the infant fecal microbiota though generally to a modest extent [44–46]. Many other factors can influence the microbiota and some can cause dysbiosis. Exposure to intrapartum antibiotics for prevention of Group B streptococcal sepsis and/or due to cesarean section is extremely common and impacts the neonatal intestinal microbiota [47, 48]. In addition to antibiotics [49], other medications commonly administered to mothers and/or infants that alter the intestinal microbiota include acid blocking agents [50, 51], selective serotonin reuptake inhibitors, metformin and laxatives [52, 53]. Recent demonstrations of altered infant microbiota with exposure to environmental toxins [54, 55], maternal smoking [56], and proximity to furry animals [42, 57] underscore the many factors affecting this community.

Very preterm infants are a unique population in that they are "new" from an evolutionary standpoint, have prolonged hospital stays (with multiple environmental exposures), are frequently exposed to antibiotics, and have immature innate and adaptive immune systems. In very preterm infants, the primary determinants of the composition of the intestinal microbiota are the postmenstrual age and age in weeks [34, 35], however, multiple other factors are also influential including antenatal corticosteroids, mode of delivery, antibiotic exposure, feeding type, feeding tube dwell time and biofilms, gender, and stress [58–61]. Table 1 presents several examples of alterations in the infant fecal microbiota related to perinatal exposures [43, 47–49, 56, 57, 60, 62–67].

A dysbiosis index

A "dysbiosis index" has been described for new onset pediatric Crohn's disease (CD) based on the ratio of bacteria increased in patients with CD (Enterobacteriaceae, Pasteurellacaea, Veillonellaceae, Fusobacteriaceae, Neisseriaceae, and Gemellaceae) to the bacteria decreased in patients with CD (Erysipelotrichales, Bacteroidales, Clostridiales, and Bifidobacteriaceae) [7, 68]. This index has diagnostic validity and correlated with symptom severity but did not predict response to treatment. Gastrointestinal dysbiosis indices have subsequently been described with varying diagnostic and prognostic value for stroke [69] and *Helicobacter pylori* infection [70]. A commercially available GA-map™ Dysbiosis Test (Genetic Analysis, Oslo, Norway) determines the degree of deviation of the microbiota composition of a patient sample compared with a healthy control adult population and generates a dysbiosis index score that correlates with fecal calprotectin (a marker of intestinal inflammation) [8]. An elevated dysbiosis index with this product has been demonstrated in adults with ankylosing spondylitis [8], irritable bowel syndrome, inflammatory bowel disease [71], and Sjogren's syndrome [72]. A dysbiosis index has not yet been described for diseases affecting the term or preterm infant. Given the discussion above of patterned progression of the microbiota, a dysbiosis index for neonates would need to incorporate gestational age and age at the time of stool collection.

Table 1 Alterations in the infant fecal microbiota related to perinatal exposures.

Intervention	Change in the neonatal intestinal microbiota and metabolites
Intrapartum antibiotics [47, 48, 62]	↓ Bacteroides and Bacteroidetes
	↓ Parabacteroides
	↓ Bifidobacterium and Actinobacteria
	↑ Proteobacteria
	↑ Veillonella, Enterococcus and Firmicutes
	↑ Clostridia
	↓ Alpha diversity
	↓ Fecal acetate
	↑ Antibiotic resistance genes
Postnatal antibiotics (term infant) [49]	↓ Bacteroidetes
Postnatal antibiotics (preterm) [63, 64]	↓ Alpha diversity
	↑ Antibiotic resistance genes
Cesarean delivery [65]	↓ Actinobacteria
	↓ Bacteroidetes
	↑ Firmicutes
Home birth [43]	↑ Bifidobacterium
	↑ Bacteroides
	↑ Streptococcus
	↑ Lactobacillus
	↓ Clostridium
	↓ Enterobacteriaceae
Very preterm birth [66]	↑ Proteobacteria
	↓ Firmicutes
	↓ Bifidobacterium
	↓ Short chain fatty acids
Mother's own milk [60]	↑ Bifidobacteriaceae
	↓ Staphylococcaceae
	↓ Clostridiaceae
	↓ Pasteurellaceae
Maternal smoking [56]	↑ Ruminococcus
	↑ Akkermansia
	↑ Bacteroides
	↑ Staphylococcus
Furry pet in the home [57]	↓ Streptococcaceae
	↑ Oscillospira and Ruminococcus
Disinfectant [67]	↑ Lachnospiraceae
	↓ Haemophilus
Eco-friendly disinfectant [67]	↓ Enterobacteriaceae

Table 2 Disease processes associated with intestinal dysbiosis.

Acute/subacute	Chronic
Necrotizing enterocolitis in preterm infants	Type 1 diabetes
Late onset neonatal sepsis	Type 2 diabetes
Antibiotic associated diarrhea	Chronic kidney disease
Clostridium difficile colitis	Inflammatory bowel disease
Infant colic	Dyslipidemia
Severe acute malnutrition	Coronary artery disease
	Breast cancer
	Colon cancer
	Atopic dermatitis
	Non-alcoholic fatty liver
	Parkinson's disease
	Alzheimer's disease
	Obesity
	Depression
	Schizophrenia

Consequences of neonatal intestinal dysbiosis

The list of disease processes associated with intestinal dysbiosis is long and diverse (Table 2 provides several examples). For the majority, a causal link between intestinal dysbiosis and the dysbiosis-associated disease has not been established, however, for some causality and underlying mechanisms have been demonstrated. Examples of the latter include type 1 diabetes [73, 74] and atopic disease/asthma [75, 76]. Studies of associations between antibiotic exposure in utero or in the perinatal period and the diseases of childhood obesity and the triad of atopic dermatitis, asthma and allergic rhinitis have been mixed [77–80]. Among diseases of infants, compelling data for an association with intestinal dysbiosis come from studies of NEC, late onset sepsis (LOS) and infant colic (Fig. 2).

For NEC, careful studies of the fecal microbiota prior to disease onset demonstrated a pattern at the phylum level of increased Proteobacteria and decreased Firmicutes and Bacteroidetes [81]. Delving deeper, increased Enterobacteriaceae at the family level [82], and *Klebsiella* at the genus level were reported as well as increased fimbriae-expressing bacteria [82]. Several studies have demonstrated that empiric treatment of the preterm infant with antibiotics for more than 4 days increased risk of later development of NEC [83, 84]. Administration of acid-blocking agents to preterm infants is also associated with both fecal dysbiosis [50] and increased risk of NEC [85]. It is likely that dysbiosis in hospitalized infants is influenced by the microbes on NICU surfaces [86, 87] and may explain some of the wide variation in NEC incidence between hospitals. A recent careful analysis demonstrated a NICU "room specific microbiota" that is shaped by the infant gut microbes [88].

For LOS, the case for intestinal dysbiosis in disease pathogenesis is less clear. Most LOS in the NICU has been attributed to infections involving skin microbes and central

Table 3 Bacteria that produce short chain fatty acids and lactate.

Genus (phylum)	SFCA
Bifidobacterium (Actinobacteria)	Acetate, lactate
Akkermansia (Verrucomicrobia)	Acetate, propionate
Faecalibacterium (Firmicutes)	Butyrate
Clostridium (Firmicutes)	Butyrate
Eubacterium (Firmicutes)	Butyrate
Roseburia (Firmicutes)	Butyrate
Bacteroides (Bacteroidetes)	Acetate, propionate
Lactobacillus (Firmicutes)	Lactate

catheters. However, recent investigation of LOS identified identical organisms in the feces and blood cultures of infants with LOS, which suggests that translocation of gut microbes could be a common cause of LOS [89]. In rodent models, an abundance of specific intestinal microbes is protective against induced sepsis, while their absence is associated with increased disease severity [90]. In preterm infants, an abundance of *Bifidobacterium* species appears to be protective, or a marker of protection, against LOS [89, 91].

Lastly, infant colic is common and associated with increased risk of long term learning and behavioral challenges [92]. Several studies have demonstrated an association between intestinal dysbiosis and infant colic, including association of specific taxa with severity [93].

Mechanisms

A detailed discussion of mechanisms by which intestinal dysbiosis triggers local and systemic disease is beyond the scope of this review and has been reviewed by others [94–102]. Rather, we will touch briefly on well-established mechanisms and some promising novel proposed mechanisms and then consider in more detail the role of short chain fatty acids produced by probiotic and commensal bacteria. Key well-established mechanistic demonstrations, include (1) alteration of intestinal permeability by gut microbes [103], (2) alteration of local and systemic inflammation by gut microbes (e.g., through stimulation of Toll-like receptors and related cytokines and through alteration of T cell and neutrophil responses) [13, 104], and (3) alteration of intestinal maturation by gut microbes and their metabolites [105, 106]. More recent discoveries that shed light on mechanisms by which gut microbes impact host disease susceptibility, include (1) the alteration by gut microbes of passage of antigens from the intestinal lumen to the lamina propria through goblet cell-associated passages [107], (2) the induction by early life gut microbes of erythroid differentiation regulator-1 (Erdr1) a regulator of cellular differentiation and survival that is not detected in mice raised

in germ-free conditions or in germ-free mice colonized with fecal microbiota from control mice at weaning, suggesting that there is a window of development early in life in which the microbiota (directly or via metabolites) can induce Erdr1 to alter intestinal development and capacity for regenerative repair [108], and (3) the stimulation by gut microbes of production by the host enterochromaffin cells of serotonin, the primary neurotransmitter of the enteric nervous system [109].

Short chain fatty acids (SCFAs, most commonly acetate, propionate, and butyrate) are the products of fermentation of dietary fiber by several gut bacteria (Table 3). SCFAs are an important energy source for colonocytes [32] and modulate insulin sensitivity, glucose and lipid homeostasis, and systemic inflammation [110, 111]. A recent large scale analysis of genotype, fecal microbiota, and fecal SCFA analysis in adults demonstrated causal associations between increased fecal butyrate and improved insulin response after oral glucose tolerance testing and between decreased fecal propionate and increased risk of type 2 diabetes [112]. SCFAs impact glucose metabolism through induction of intestinal gluconeogenesis [113], however, the role of SCFAs in energy metabolism appears to be even broader with reported effects of SCFAs on appetite regulation and the gut–brain axis [114]. In mice, SCFAs produced by maternal gut microbes influence differentiation of the neural, intestinal, and pancreatic cells of the embryo through activation of embryonic G protein-coupled receptors [17]. In rabbits, the cecal microbiota is altered early in the transition from suckling to weaning resulting in increased production of butyrate which impacts intestinal permeability [105].

Patients with CD and ulcerative colitis have low numbers of SCFA-producing bacteria and low levels of fecal SCFAs. Mechanisms by which SCFAs protect the host against inflammatory bowel disease include support of enterocyte proliferation, induction of tight junction proteins to increase barrier function, induction of antimicrobial peptides, and a range of anti-inflammatory effects [115].

SCFAs and lactic acid are produced in abundance when human milk is combined with a microbe that can consume human milk oligosaccharides, such as *B. longum* ssp *infantis* which results in decreased fecal pH and suppression of facultative anaerobes such as Enterobacteriaceae [116]. The immature intestine may respond differently to SCFAs than the mature intestine. While SCFAs have demonstrated anti-inflammatory effects on human fetal organoids and fetal mouse intestine [117], butyrate appears to trigger NEC-like lesions in germ-free lactose-fed quails [118] and in a piglet NEC model, formula containing fermented *E. coli* had high levels of acetate and propionate and was associated with NEC-like lesions [119]. Tryptophan in human milk is metabolized by gut microbes, including *B. longum* ssp *infantis*, into indole-3-lactic acid, which binds

to the aryl-hydrocarbon receptor in immature intestinal tissue and inhibits the pro-inflammatory cytokine IL8 [120].

Attempts to attenuate neonatal intestinal dysbiosis

Antibiotic stewardship

In the United States, 30–35% of term infants are exposed to antibiotics in the immediate perinatal period, either for Group B *Streptococcus* prophylaxis or concerns for maternal intra-amniotic infection (Fig. 1) [121]. This approach has decreased infant mortality, however, the long-term consequences of the resultant intestinal dysbiosis are uncertain. Unfortunately, a much-anticipated maternal vaccination against Group B *Streptococcus* and key strains of *E. coli* [122] does not appear imminent but would potentially lead to decreased antibiotic exposure. Minimizing unnecessary antibiotic exposure in the first months of life may have value in decreasing risk for dysbiosis and its associated disease processes as well as decreasing costs and emergence of antibiotic resistant bacteria [123]. A review of 127 California NICUs showed a wide range of antibiotic usage (from 2.4 to 97.1% of patient-days) with a median of 24% of patient days. NICUs with high antibiotic usage had similar rates of documented infection to NICUs with low antibiotic usage [124] suggesting an opportunity to decrease antibiotic administration. A follow-up study by the same group showed a 22% decline in NICU antibiotic use from 2013 to 2016 (42,960 fewer antibiotic days) with a greater decline in NICUs with an established antibiotic stewardship program [125]. This and other studies suggest that further benefits may be gained by antibiotic stewardship [123].

Prebiotics

Prebiotic glycans are dietary supplements that provide a nutrient substrate to stimulate growth of commensal bacteria. Human milk oligosaccharides, discussed above, are highly selective in that only a limited number of bacteria can utilize them as a source of nutrition (predominantly *Bifidobacterium* and *Bacteroides* species). In contrast, many other commercial prebiotics are consumed by a variety of gut microbes and thus may stimulate the growth of both commensals and pathogens. Human milk oligosaccharides are highly tolerant of heat and therefore resistant to pasteurization (and abundant in donor human milk). While the benefits of human milk are related to multiple bioactive components, it is likely that the prebiotic effects of the complex carbohydrates are at least partly responsible for observed decreases in NEC with human milk feeding. A recent meta-analysis of 18 randomized placebo controlled trials showed a decrease in the incidence of sepsis and death and length of hospital stay with administration of prebiotic supplements, but no difference in the incidence of NEC [126].

Probiotics

Probiotics are dietary supplements that contain live microbes. The evidence for benefit from probiotic administration is perhaps most compelling for reduction of NEC and death in preterm infants. A large number of randomized placebo-controlled clinical trials of probiotics in preterm infants have been performed. Several meta-analyses of these trials have demonstrated a significant decrease in NEC, death and/or length of hospital stay in preterm infants with probiotic administration [127, 128]. In addition, meta-analyses of observational cohort studies of probiotic administration to preterm infants have shown similar reductions in NEC and death to those seen in the clinical trials [129, 130]. A recent meta-analysis of randomized controlled trials of probiotic administration to mothers during pregnancy demonstrated a reduction in atopic eczema, preterm delivery, NEC, and death in the offspring [131]. A meta-analysis of randomized controlled trials in term infants with colic demonstrated a significant decrease in crying time with probiotic administration. The probability of a >50% reduction in crying time was close to 2-fold higher [132]. The European Society for Paediatric Gastroenterology and Hepatology recently released a conditional recommendation for probiotic use in preterm infants for the prevention of NEC [133] based on a strain-specific network analysis of clinical trials [134]. The recent recommendations of the American Gastroenterological Association summarized the limited evidence for benefits of probiotic administration in adults and the compelling evidence for benefits in prevention of NEC in preterm infants [135]. Risks associated with probiotics include contamination of the probiotic product [136] and sepsis from the probiotic microbes [137]. It appears that harm from probiotic administration to infants is an uncommon complication given that NEC, sepsis and death are either equal or lower in infants receiving probiotics compared to those receiving placebo or no probiotic in most studies. Those advocating against routine administration of probiotics to preterm infants note that regulatory oversight of probiotic manufacture is inadequate and that questions remain regarding the preferred probiotic strain or combination of strains and the optimum dose [138].

Conclusion

In the last two decades there has been a virtual explosion of knowledge gained on the role played by the colonizing

microbiota in mediating host physiology and maintaining homeostasis. Unfavorable changes in the composition of the microbiota, dysbiosis, can in some cases lead to overt disease, but often has more subtle and insidious consequences. In well-appearing term infants in developed countries, intestinal dysbiosis is common and is likely due to diversion from exclusive breast-feeding, cesarean sections, antibiotics and other medications, a "Western" diet and modern sanitation practices. In preterm infants cared for in modern NICUs, intestinal dysbiosis appears to be almost universal. The consequences of intestinal dysbiosis in infants are uncertain, but strong circumstantial evidence and limited confirmations of causality suggest that many acute and chronic diseases that are increasing over time are related to intestinal dysbiosis. Interventions to limit or reverse maternal and early infant intestinal dysbiosis including antibiotic stewardship, increased breastfeeding support, vaccine development to reduce use of prophylactic antibiotics and informed use of probiotic microbes and prebiotic glycans offer promise in reversing these trends.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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