The Human Microbiome and Its Potential Importance to Pediatrics

abstract

The human body is home to more than 1 trillion microbes, with the gastrointestinal tract alone harboring a diverse array of commensal microbes that are believed to contribute to host nutrition, developmental regulation of intestinal angiogenesis, protection from pathogens, and development of the immune response. Recent advances in genome sequencing technologies and metagenomic analysis are providing a broader understanding of these resident microbes and highlighting differences between healthy and disease states. The aim of this review is to provide a detailed summary of current pediatric microbiome studies in the literature, in addition to highlighting recent findings and advancements in studies of the adult microbiome. This review also seeks to elucidate the development of, and factors that could lead to changes in, the composition and function of the human microbiome. *Pediatrics* 2012;129:950–960

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KEY WORDS

human microbiome, metagenome, microbiota, pediatric diseases, dysbiosis, probiotic

ABBREVIATIONS

FISH—fluorescence in situ hybridization
GI—gastrointestinal
HMO—human milk oligosaccharide
IBD—inflammatory bowel disease
IBS—irritable bowel syndrome
NEC—necrotizing enterocolitis
TNBS—2,4,6-trinitrobenzene sulfonic acid

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The growing recognition that our resident microbes may contribute fundamentally to infant and childhood development and immunity is creating an impetus to understand the importance of the human microbiome in pediatrics.[1–5] Global health efforts focused on the first 1000 days of life and developmental origins of disease highlight the potential significance of the human microbiome for human health.[6] Bacterial cells outnumber human cells in the body by an estimated factor of 10, with ~10 to 100 trillion microbes living in the gastrointestinal (GI) tract alone.[7,8] The collective genomes and gene products of these resident microbes living within and on humans are referred to as the human microbiome.[7,9] In 2007, the National Institutes of Health–sponsored Human Microbiome Project was formed to gain insights into the evolution and composition of the human microbiome, factors that may influence or affect its composition, and whether the human microbiome affects health and tendencies toward particular diseases.[7] The advent of new molecular technologies has been useful in the detection of uncultured microbes and may enable more microbes to be cultured in the future.[10,11] These culture-independent methods include fluorescence in situ hybridization (FISH), DNA pyrosequencing, microarrays (PhyloChip), and quantitative polymerase chain reaction assays[12,13] (Table 1). Advances in DNA sequencing technologies and computational methods have been used to analyze bacterial communities by using the conserved 16S rRNA gene for phylogenetic analysis,[7] resulting in a deeper understanding of our commensal residents, beneficial microbes, and their contribution to human health.

TABLE 1 Glossary of Terms

Microbiome: Collective genomes and gene products of resident microbes living within and on humans
Microbiota: Microbial community
Metagenome: Collection of genomes within complex microbial communities and human DNA
Culture-independent techniques: Techniques that do not require the growth of bacteria on defined media under controlled laboratory conditions; they include techniques like PhyloChip, FISH, and 16S rRNA gene pyrosequencing
PhyloChip: DNA microarray that is unique in its ability to identify multiple bacterial and archaeal organisms from complex microbial samples[13]
FISH: Technique that uses fluorescent probes designed to bind to specific complementary sequences of DNA, thereby allowing for detection of specific DNA sequences by fluorescence microscopy[148]
16S ribosomal RNA gene: 16S ribosomal RNA is a component of prokaryotic ribosomes that is highly conserved between different species of bacteria and is used for phylogenetic studies
Pyrosequencing: Method of DNA sequencing that detects the release of pyrophosphate upon nucleotide incorporation rather than chain termination by deoxynucleotides with Sanger sequencing[149]
UniFrac: β-Diversity measure that is phylogeny based; microbial communities are more similar if they are composed of members that are more closely related, phylogenetically, as this implies a shared evolutionary history[15,147]
Principal coordinates analysis: Standard multivariate statistic used to analyze and visualize individual or group similarities

COMPOSITION OF THE HUMAN MICROBIOME

This review discusses the development and composition of the human microbiome at different body sites and illustrates how changes in composition may have important consequences for human pathophysiology and disease susceptibilities. Human-associated bacterial communities likely play a central role in host nutrition, development of immunity, and protection from diverse pathogens.[9,14] The human body contains many different sites that are colonized by microbial communities during neonatal and childhood development and throughout the lifetime of individuals in health and disease states. Predominant bacterial phyla (composed of hundreds of bacterial genera and species) in the human body, regardless of body site, include Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria (Table 2).[15] Bacterial species populations vary significantly between individuals, and bacterial community composition appears to be driven primarily by body habitat.[16] To highlight the heterogeneity of human microbiome composition, the human skin differs dramatically in terms of predominant bacterial phyla (Actinobacteria, Firmicutes, or Proteobacteria) by virtue of the location of the skin site on the human body and its relative humidity.[17] The phylum Bacteroidetes is a minor component of the human microbiome on many different skin sites[17] while Firmicutes comprise the major phylum in the vagina.[18] Studies of the GI tract, by contrast, have consistently demonstrated the predominance of the same phyla, Bacteroidetes and Firmicutes, in children and adults.[16,19] In addition to body habitat, different bacteria may serve as "anchor microbes" in particular individuals. For example, a recent study found 3 distinct identifiable enterotypes in the intestinal microbiome among adults from multiple countries, which were characterized by prominent genera including *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2), and *Ruminococcus* (enterotype 3).[20] These enterotypes also appear to be driven by species composition and relative functional capacities of gut bacterial communities. Distinct intestinal enterotypes are yet to be described in the pediatric population.

The intestinal microbiome undergoes dynamic change during development, with the most dramatic changes in composition believed to occur throughout infancy and childhood.[21,22] The diversity and flux of microbes observed during this time are believed to be important for the normal functional development of the immune system and its impact on health later in life.[21,23]

TABLE 2 Predominant Bacterial Phyla in the Human Body

Phylum	Class	Characteristics	Examples
Firmicutes	Bacilli; Clostridia	Gram-positive; diverse in their morphology (rod, coccoid, spiral), physiology (anaerobic, aerobic); include commensal and beneficial bacteria	*Lactobacillus*; *Ruminococcus*; *Clostridium*; *Staphylococcus*; *Enterococcus*; *Faecalibacterium*
Bacteroidetes	Bacteroidetes	Gram-negative; composed of 3 large classes widely distributed in the environment, including soil, seawater, and guts of animals	*Bacteroides*; *Prevotella*
Proteobacteria	Gammaproteobacteria; Betaproteobacteria	Gram-negative; include a wide variety of pathogens	*Escherichia*; *Pseudomonas*
Actinobacteria	Actinobacteria	Gram-positive; diverse morphology; major antibiotic producers in the pharmaceutical industry	*Bifidobacterium*; *Streptomyces*; *Nocardia*

The predominantly colonizing phyla found in the infant GI tract belong to Firmicutes, Bacteroidetes, and Proteobacteria.[10,21] However, the composition of gut-associated bacterial communities was found to be highly variable in individual infants in terms of timing of acquisition and colonization by individual bacterial species.[21] A recent study observed significant changes in genomic divergence and relative abundance of 2 *Citrobacter* strains in a premature infant during a 3-week period, suggesting that fluctuations in strains of a single species may contribute to differences in the "fine" or detailed functional capacity of the microbiome.[24] Facultative bacteria like *Escherichia coli*, *Enterococcus* spp, α-hemolytic streptococci, and *Staphylococcus* spp colonize the sterile, aerobic newborn GI tract in the first few days of life.[21,25–28] After the first weeks of life, anaerobic conditions have been created in the gut due to the consumption of oxygen by these facultative bacteria.[29,30] This environment coupled with the presence of human milk oligosaccharides (HMOs) in breast milk leads to a shift in composition to predominantly anaerobic bacteria such as *Bacteroides*, *Bifidobacterium*, and *Clostridium* spp.[21,25,31] Development of a core microbiome, which can refer to a set of microbes or a set of metabolic functions, may occur by the end of infancy.[21,32,33] However, recent metagenomic studies suggest that the gut microbiota of school-age and adolescent children differ significantly from that of adults,[34,35] indicating that the human microbiome may be evolving during childhood and adolescence.

ENVIRONMENTAL FACTORS AFFECTING THE COMPOSITION OF THE HUMAN MICROBIOME

Mode of Birth Delivery

Mode of birth delivery, hospitalization, diet, and nature of feeding are environmental factors that may impact the composition and diversity of the infant microbiota.[36] Early microbial colonization of a newborn begins at birth.[21,37] The microbiota of vaginally delivered newborns represented the maternal vaginal and intestinal microbiota, while newborns delivered via cesarean delivery exhibited a microbiome representative of the maternal skin microbiota including *Staphylococcus* spp (Fig 1).[38] Vaginally delivered newborns exhibited bacterial communities composed of several prominent genera including *Lactobacillus*, *Prevotella*, *Escherichia*, *Bacteroides*, *Bifidobacterium*, and *Streptococcus* spp.[38,39] Different molecular methods confirmed a reduced proportion of *Bifidobacterium* or *Bacteroides* spp in the GI tract of infants delivered via cesarean delivery.[29,40] Regardless of delivery mode and in contrast to their mothers, bacterial communities among newborns exhibited a uniform distribution across different body sites, including the skin, nasopharynx, intestine, and oral cavity.[38] Presumably, it takes weeks or longer for the human microbiome to differentiate into body site–specific microbial communities. A recent study by Capone et al corroborates this argument as site-specific bacterial communities were found on the skin of infants ranging from 1 to 3 months of life.[41] As such, the birth process and mode of delivery may have a profound impact on microbial composition early in life, and these factors may help explain 1 aspect of the developmental origins of human microbiomes at different body sites.

First Foods: Breast Milk and Infant Formula

Beneficial factors in breast milk are widely acknowledged and include immunoglobulins, cytokines, growth factors, lysozyme, lactoferrin, and HMOs.[42–44] HMOs are an abundant carbohydrate component in breast milk and function similarly to prebiotics, stimulating the growth of *Bifidobacterium* sp and thereby selectively altering microbial composition in the infant intestine.[45] More than 200 different HMO structures have been characterized in human milk, and HMOs contain a lactose core with diversity generated by covalent modifications such as extensive fucosylation and/or sialylation.[46] Particular HMOs also share similar glycan structural motifs, which are believed to protect infants from disease by acting as decoys in preventing pathogens from binding to epithelial cells.[47]

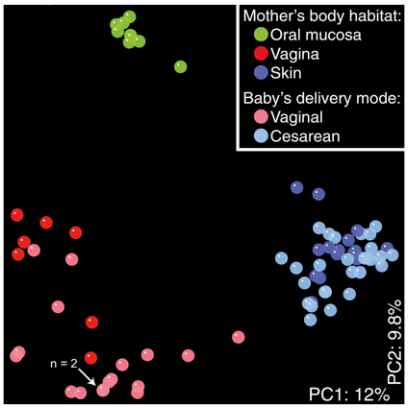

FIGURE 1
16S bacterial rRNA analysis reveals influence of delivery mode on the neonatal microbiome. UniFrac analysis revealed similarities and clustering of bacterial communities based on the mother's body habitat or the delivery mode of the newborn. Each colored point represents a similar community in specific body sites of the mother and all newborn body habitats.[147] The percentage of variation of the principal coordinates analysis is indicated in white text on both axes. (Reproduced with permission from Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA.* 2010;107[26]:11973.)

Anaerobes such as *Bifidobacterium* appear during the first weeks of life, and species of this genus are well adapted to HMOs.[48] While numerous studies reported a higher relative abundance of *Bifidobacterium* and *Lactobacillus* in the microbiomes of breastfed infants,[21,44,49,50] others have reported no difference in abundance between these 2 genera in breastfed and formula-fed infants.[29,51,52] Increased colonization by *Clostridium* spp and particularly *C difficile* in formula-fed infants compared with breastfed infants has been reported in several studies.[23,29] The greater abundance of *C difficile* in the intestinal microbiota of formula-fed infants has also been associated with eczema in infants.[29,52,53] Breastfed, vaginally delivered term infants exhibited reduced colonization by *C difficile* and *E coli* and enhanced colonization by beneficial microbes, like *Bifidobacterium* spp.[29] The proliferation of beneficial microbes supported by breastfeeding may provide protection from disorders such as allergies, neonatal diarrhea,[54] necrotizing enterocolitis (NEC),[55] obesity,[56] and type 2 diabetes.[57]

Hospitalization and Gestational Age

Hospitalization and gestational age may impact the composition and development of the intestinal microbiota. Preterm infants, exhibiting diverse bacterial communities after birth, acquired similar intestinal bacterial composition during the first weeks of life as a result of cross-transmission during hospitalization.[58] Correspondingly, increased hospital stays have been associated with delays in colonization and development of the infant intestinal microbiota, which could result from exposure to different microbes or antibiotic treatment.[59,60] For example, increased colonization by *C difficile* was observed in both preterm infants and infants hospitalized after birth, which could be attributed to a high carriage rate and the persistence of *C difficile* spores in the environment.[29] Furthermore, the intestinal microbiota of preterm infants with a gestational age of <33 weeks exhibited significantly reduced bacterial diversity.[61,62] In particular, recurrent *C difficile* infection and other disease states have been associated with reduced bacterial diversity in the intestine.[63]

Effects of Diet

Major shifts of taxonomic groups in the microbiome have been observed with major life events including changes in diet, such as weaning to solid foods.[31] In fact, diet may be a primary factor involved in generating compositional change and diversity in the microbiome.[64] Studies performed in germ-free mice colonized with human microbial communities revealed that the initial colonizing bacterial communities can be rapidly altered by diet.[65] Alterations of fiber and fat/protein content in the diets of a small cohort of children and adults also yielded changes in the composition of the microbiome within a 24-hour period, which then remained stable over the duration of the study.[66] Longer-term changes in diet may be necessary to effect more substantial changes. Moreover, the *Bacteroides* enterotype was associated with consumption of animal protein and saturated fat, whereas the *Prevotella* enterotype was associated with a carbohydrate-rich diet.[66] Comparisons of intestinal microbiota from children in rural Africa and Europe exhibited similar patterns with a greater abundance of Bacteroidetes and lower abundance of Firmicutes in the Africa cohort compared with the European cohort.[67] *Bacteroides* spp produce beneficial molecules like polysaccharide A and short-chain fatty acids.[65,68] Polysaccharide A yielded a protective effect in a mouse colitis model,[69] while short-chain fatty acids have demonstrated beneficial effects for the host including the maintenance of the colonic epithelium, provision of energy for host metabolism, and regulation of immunity[14] (Fig 2). *Bacteroides* spp may affect the maturation of humoral immunity in early infancy and the balance of the Th1 and Th2 cell immunity.[2,70–73] A study also reported an abundance of 2 genera, *Prevotella* and *Xylanibacter*, which contain genes involved in the hydrolysis of cellulose and xylan. These findings support the hypothesis that the intestinal microbiota is altered by differences in diet, allowing for enhanced energy extraction from a polysaccharide-rich diet and anti-inflammatory effects.[67] Microbial communities in the intestinal microbiota were first shown to influence host energy homeostasis and fat storage by Backhed et al.[74] Subsequent studies revealed the ability of intestinal microbiota to suppress the expression of fasting-induced adipose factor,

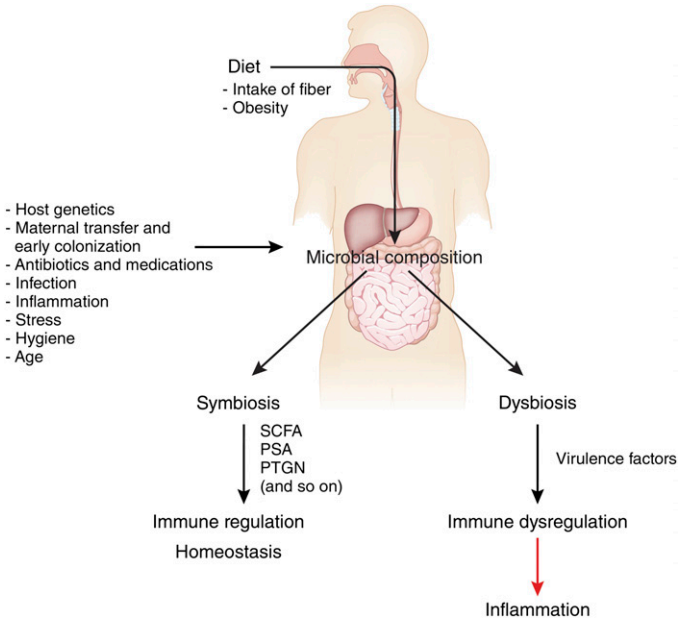

FIGURE 2
Effects of diet, host, and environmental factors on the microbiome. Antibiotic use, diet, host, and environmental factors can affect the composition of the microbiota. In this model, balanced microbial composition may result in symbiosis among resident microbes, production of immunomodulatory compounds, and subsequent regulation of the immune response. Disruption or alteration of the microbiota by environmental factors such as diet and antibiotic use could result in dysbiosis and dysregulation of the immune response. (Reproduced with permission from Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. *Nat Immunol.* 2011;12[1]:6.)

resulting in the increased storage of triglycerides in adipocytes.[74] A humanized gnotobiotic mouse model supported this observation with mice developing more adiposity within 2 weeks of being fed a typical Western diet, high in fat and sugar and low in plant polysaccharides, compared with control mice.[65] Together, these studies suggest that the human diet may impact the phylogenetic diversity and functional capacity of the human microbiome with downstream effects on disease risk and disease penetrance.

Effects of Antibiotics

Antimicrobial agents can drastically alter the composition of the intestinal and oral microbiota contingent on the spectrum and dosage, route of administration, and treatment duration.[75–77] Reduction in microbial diversity is often observed within days of ingestion of antibiotics, and complete recovery of initial bacterial community composition is rarely achieved.[75,77] Moreover, profound alterations of microbial communities have been shown within days of treatment with the fluoroquinolone ciprofloxacin. The lack of recovery from this perturbation by several organisms emphasizes the potential impact of excessive antimicrobial therapy.[75] The impact on the native gut microbiota is pronounced in infants <1 year of age, with significant reductions in *Bifidobacterium* and *Bacteroides* as well as overall reductions of bacterial community diversity.[29,78] Additional risks associated with antimicrobial treatment include the selection of antibiotic-resistant strains of bacteria and the development of *C difficile*–associated diarrhea.[76,77,79–81] Several studies have shown the persistent increase of erythromycin B (*erm*B) gene levels in fecal samples after antibiotic treatment with macrolides like clarithromycin.[77,82] The occurrence of *C difficile* infections is increasing in the United States, and this disease pattern may be due to the expansion of preexisting *C difficile* populations after antibiotic treatment or the acquisition of spores from a hospital environment.[83,84] Additionally, reduced diversity of the intestinal microbiome due to widespread use of antibiotics may be placing more children at risk for *C difficile* infections and other causes of antibiotic-associated diarrhea/colitis.[63] These reports demonstrate the importance of judicious application of antibiotics to minimize potentially deleterious effects on the composition and function of the human microbiome.

ALTERED STATES OF THE HUMAN MICROBIOME AND PEDIATRIC DISEASES

Skin Microbiome, Dermatologic, and Immune-Mediated Disorders

Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes represent the predominant phyla colonizing the adult human skin, and considerable bacterial diversity was observed at the species level.[17] Metagenomic sequencing also revealed significant interpersonal variation among individuals and temporal variation dependent on the specific body site.[17] The phylum Firmicutes predominates at specific skin sites in the infant microbiome, possibly as a result of differences in the structure and composition of infant skin compared with adult skin.[41,85] Changes in the microbiota linked to skin diseases have been found in children, including psoriasis, atopic dermatitis, and acne.[17,86–90] A study of psoriatic lesions on adult skin revealed significantly overrepresented Firmicutes, while the Proteobacteria and Actinobacteria phyla were significantly underrepresented compared with healthy skin.[86] Furthermore, sequence-based analysis identified the presence of several species not previously associated with atopic dermatitis, such as *Stenotrophomonas maltophilia*.[89]

The frequency of atopic diseases such as eczema, asthma, and food allergies is rising in incidence and linked to alterations of the intestinal microbiota.[53] The hygiene hypothesis, proposed by Strachan in 1989, suggested that the lack of infections in early infancy led to this observed rise in atopic disease.[91] As the interaction of immune cells with microbial antigens is fundamental to the function and development of the adaptive immune response, the lack of immune stimulation during early life in developed countries could account for increased immune dysregulation observed in asthma and atopic diseases.[2,42,51] Delays or changes in the core microbiome could also potentially affect the development of the immune response.[70] Epidemiologic data provide further evidence that infants delivered via cesarean delivery have higher incidences of atopic diseases such as asthma and type 1 diabetes and food allergies compared with vaginally delivered infants.[92–94]

Pulmonary Microbiome and Diseases of the Respiratory Tract

Few metagenomic studies in the literature have described the microbiome of the human respiratory tract. While some studies have reported stable oral microbial communities in adults and children,[16,95] others have found highly variable and diverse bacterial communities in the nasopharynx of children that were independent of antibiotic use.[96] Bacterial communities in the respiratory tract of intubated patients with ventilator-associated pneumonia demonstrated infection by the pathogen *Pseudomonas aeruginosa* associated with concomitant loss of microbial diversity after antibiotic administration.[97] Compared with culture-based studies, pyrosequencing studies identified a more diverse and comprehensive set of microbes in cystic fibrosis.[98] Pyrosequencing also revealed greater interpersonal variability of bacterial community compositions in the lungs of patients with cystic fibrosis, which may be influenced by colonization of bacterial communities in the oral cavity.[99,100] Sequencing-based studies are expanding our appreciation of diverse and abundant microbial communities in the respiratory tracts of healthy patients and those with cystic fibrosis.[100,101]

GI Microbiome and Intestinal Disorders

The pathophysiology of NEC appears to be multifactorial, with premature birth being the most pronounced risk factor.[102] Other factors in the development of NEC include intestinal immaturity, an excessive intestinal inflammatory response to microbial stimuli, and colonization by disease-predisposing microbial populations in the GI tract.[103] Several studies using metagenomic comparisons of fecal microbiota reported a reduction in microbial diversity in preterm infants with NEC compared with healthy preterm infants.[15,104] However, other studies reported similar overall microbial profiles between infants with NEC and control infants.[105,106] Recent studies of infants with NEC found increased abundances of Proteobacteria (Fig 3) including *Citrobacter* sp in fecal microbiota.[15,105] Furthermore, Neu et al recently described a greater proportion of Gammaproteobacteria in fecal microbiota prior to the diagnosis of NEC in infants.[107] Treatment regimens for NEC currently include the prolonged use of parenteral antibiotics, which may reduce intestinal microbial diversity and preclude colonization by a diverse community of microbes.[104,108,109] Human-associated microbial communities with reduced microbial diversity may be supplemented by probiotics or expressed breast milk, as several studies have shown a reduced incidence of NEC in preterm infants after breast milk and probiotic consumption.[110–113]

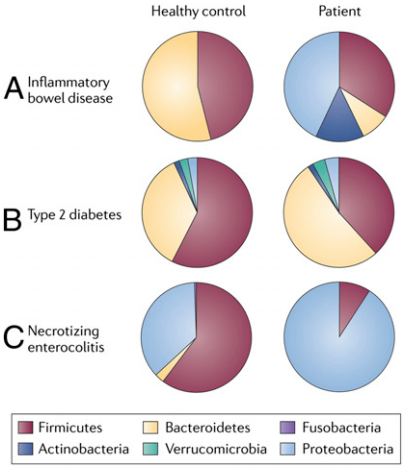

FIGURE 3
Disease states reveal phylum-level differences compared with healthy controls. Comparisons of the relative abundances of predominant bacterial phyla in IBD, type 2 diabetes, and NEC compared with healthy controls. Fecal samples from infants with NEC and patients with type 2 diabetes were compared with healthy controls revealing a predominance of Proteobacteria in patients with NEC. Cecal samples from patients with IBD were compared with healthy controls, and relative abundances were assessed. (Reproduced with permission from Spor A, Koren O, Ley R. Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat Rev Microbiol.* 2011;9[4]:281.)

The composition of the intestinal microbiome differs between healthy individuals and individuals with inflammatory bowel disease (IBD) with respect to phylogenetic diversity and relative abundances of microbial taxa.[114–116] This imbalance or disruption of the host microbiota, termed dysbiosis, can induce an inflammatory response by the host as evidenced in Crohn disease.[117,118] Studies have shown that the gut microbiota of individuals with IBD exhibited reduced proportions of Firmicutes and Bacteroidetes and an increased proportion of Proteobacteria compared with healthy individuals (Fig 3).[115,119] Present evidence suggests that IBD may result from abnormal interactions between indigenous microbiota and the host immune system.[120–122] A reduced abundance of *Faecalibacterium prausnitzii*, a member of the Firmicutes phyla, has been associated with Crohn disease activity.[115] Anti-inflammatory effects of

F prausnitzii were demonstrated by cytokine studies in vitro and a murine TNBS-induced colitis model.[115] In addition, metabolomic studies yielded signature microbial metabolites possibly involved in the pathogenesis of Crohn disease.[123]

Irritable bowel syndrome (IBS) is a functional GI disorder that includes recurrent abdominal pain and changes in defecation patterns ranging from hard to watery stool.[124] Although the pathogenesis of IBS is also not well understood, dysbiosis has been associated with diarrhea-predominant IBS and constipation-predominant IBS. The intestinal microbiota of patients with diarrhea-predominant IBS differs from that of healthy subjects with respect to the relative prevalence of genera, including *Lactobacillus*, *Streptococcus*, *Ruminococcus*, and *Veillonella*.[125,126] Specific microbial signatures in school-age, preadolescent children with IBS compared with healthy controls were recently described and included a greater abundance of Gammaproteobacteria and an association of *Alistipes* with greater pain frequency. Pediatric IBS subtypes were distinguished by using microbial feature selection and compositional differences of the human intestinal microbiome.[34]

Treatment and Manipulation of the Human Microbiome

Manipulation of the human microbiome may include microbial supplements (probiotics or synbiotics), foods or substrates (diet or prebiotics), and microbial suppression or elimination (antibiotics) strategies. Beneficial microbes such as *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* are commonly used as probiotics, which are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[127] Probiotics are believed to assist the resident microbiota in preventing pathogen adherence,[128,129] downregulating proinflammatory cytokines,[130] inducing immunoglobulin A production,[131] and enhancing intestinal mucosal barrier function and epithelial integrity.[129] Recent studies have demonstrated that probiotic *L reuteri* targets sensory nerves in the enteric nervous system, thereby affecting pain perception and gut motility.[132] Probiotic formulations are generally believed to be safe, and the American Academy of Pediatrics has supported the administration of probiotics for the treatment of acute gastroenteritis and the prevention of antibiotic-associated diarrhea.[108,133] Prebiotics, which are nondigestible food ingredients that stimulate the growth and activity of designated species of beneficial bacteria, may enhance the treatment efficacy of other anti-inflammatory medications by stimulating butyrate production in humans and suppressing production of proinflammatory cytokines.[134,135] Synbiotics, a combination of both probiotics and prebiotics, have also been used to treat inflammatory diseases.[136] Probiotics and prebiotics may be applied in the regulation and homeostasis of intestinal microbial composition and as a therapeutic strategy for various disorders.[137,138] Other therapies have been effective in restoring normal bacterial communities including the transplantation of fecal microbiota from a healthy donor to a patient. Fecal transplantation has been increasingly used in the last 2 decades for *C difficile* infection, with a success rate of >90%.[139–141] Analysis of the microbiota could result in the development of naturally derived drugs to treat chronic inflammation, and additional evidence suggests that enteric bacteria produce immunomodulatory molecules that have anti-inflammatory properties.[142–144] For example, a recent study demonstrated that a polysaccharide of *Bacteroides fragilis* had immunomodulatory properties and prevented intestinal inflammation in mice.[69] More examples of these naturally derived substances include bacteriocins, which are antimicrobial peptides produced by bacteria that inhibit the growth of other bacteria in the microbial community. Broad- and narrow-spectrum bacteriocins have been effective against *C difficile*.[145,146] In addition to bacteriocins, antibiotics may selectively target classes of organisms in the human microbiome. Combinations of antibiotics, probiotics, and diet may yield potent strategies to manipulate and reshape disease-prone microbiomes.

CONCLUSIONS

The importance of the microbiota to many aspects of human health and the realization that its foundation is established in early infancy are becoming increasingly recognized. The rapidly advancing knowledge of the human microbiome, through metagenomic analysis, has yielded information regarding the differences observed between healthy and disease states and factors that influence the composition and diversity of the microbiome. Future studies may lead to improved health benefits for pediatric patients through the manipulation of the intestinal microbiota.

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