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Navigating the Pediatric Microbiome: Emerging Evidence and Clinical Implications

Zain Kassam · Thomas S. Murray

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Abstract There is emerging interest in the ability of the intestinal microbiome—the collective genome of resident microbes—to impact host function. Given the dynamics of development, the pediatric microbiome is of particular importance as alteration of microbial communities (microbiota) early in life may deeply influence long-term health and disease. This review explores the current understanding of the establishment and evolution of the microbiome in early life. It then discusses the evidence for three key spheres of microbiome-mediated disease in pediatrics: inflammatory bowel disease, obesity and atopic disease. The role of microbiota-derived therapeutics is also examined through the lens of future care for children. Probiotics and fecal microbiota transplant, a novel therapy to restore the microbiome, are explored and the rationale for caution outlined for infants and children. Ultimately, there is potential for research born out of the field to alter our paradigm of pediatric disease and its treatment.

Keywords Microbiome · Probiotics · Fecal transplant · Atopic dermatitis · Obesity · Inflammatory bowel disease

Glossary

Microbiota	Describes vast community of microbes that colonize the human body
Microbiome	Collective genetic repertoire (genome and gene products) of microbiota
Metagenomics	Field that serves to study the relationship between genomes within intricate microbial communities
Commensal	Non-pathological relationship between two organisms, traditionally where one organism benefits and the other is not significantly helped or harmed
Dysbiosis	Imbalance or disruption of a microbial community, which may lead to pathology
Enterotype	Core group of microbes, predominantly driven by a prominent bacterial genera
Phylotype	Relationships of one microorganism to another determined by comparing 16S rRNA gene sequences. A common threshold used to define species-level phylotype is 97 % sequence identity of the 16S rRNA gene sequence

Introduction

With the recent emergence of culture-independent sequencing techniques we are just beginning to understand the rich and diverse microbial landscape in both children and adults. The gastrointestinal (GI) system alone contains over 100 trillion microbes with complex diversity and heterogeneity across individuals [1, 2]. The perpetual interplay between microbial communities (microbiota), and human hosts has an impact on health and susceptibility to disease.

Z. Kassam
Harvard School of Public Health, Harvard University, Cambridge, MA, USA

T. S. Murray (✉)
Department of Medical Science, Frank H Netter MD School of Medicine, Quinnipiac University, 275 Mount Carmel Ave, Hamden, CT 06518, USA
e-mail: Thomas.murray2@quinnipiac.edu

Although the impact of the microbiota in GI disease has been robust, there is growing interest in the ability of the intestinal microbiota to influence host functions beyond the GI system. The microbiome appears to have a broad reaching impact on human health via modulation of immune homeostasis, metabolism, colonic colonization resistance and possibly alteration of neuro-active metabolic pathways that affect behavior [3, 4].

Given the dynamics of the microbiota in early life, it is speculated that infants and children are particularly sensitive to alternations in the microbiota and the associated downstream health consequences, suggesting a 'developmental window' in establishing a healthy microbiome.

Interestingly, host genetics may play a role in the establishment of the microbiome, as specific genetic loci appear to influence bacterial microbiome composition [5, 6]. In this vein, the 'early-life programming hypothesis' proposes that the energy metabolism of early life microbiota and the interaction of these microbes with the immune system help determine the risk for diseases later in life, possibly mediated by epigenetics [7]. Additionally, early commensal microbiota is also important in the establishment of a balanced helper T cell (Th1/Th2) immune response to antigenic stimuli more directly [8]. Accordingly, pediatricians and scientists must become familiar with this rapidly evolving field.

The prospect of harnessing the translational potential of this field has engaged funding agencies to invest in human microbiome consortiums. In 2007, the United States National Institutes of Health initiated the 171 million dollar Human Microbiome Project (HMP), and in 2008, the European Commission funded the 22 million euro Metagenomics of the Human Intestinal Tract (Meta-HIT) Consortium [3, 9, 10]. The HMP and Meta-HIT Consortium serve as beacons for the promise of a new era of personalized medicine.

Given the emerging importance of the microbiome in infants and children, the following review focuses on the current state of evidence on the establishment and evolution of the human microbiome, highlights the nexus of dysbiosis—pathologically deviated microbiota—in three representative pediatric disease examples, and provides insight into microbiota-derived therapeutics for infants and children.

Lessons from the Adult Microbiome Literature

The exploration of the microbiome in adults preceded evaluation of the pediatric population, and accordingly lessons can be learned about the direction of future research in children.

The progress of DNA-based, culture-independent techniques used to assess the microbiota in adults has primed pediatric-oriented researchers with the optimal tools to explore the microbiome in infants and children (Table 1) [11••]. The detail of the varied techniques are beyond the scope of this paper and well described elsewhere [11••]. Briefly, traditional in vitro culture methods used to grow bacteria cultivate less than 30 % of bacterial flora in the human GI system. Accordingly, researchers typically extract microbial DNA from stool and subject it to high throughput, next generation sequencing of the variable regions of the bacterial 16S rRNA gene [11••] (Table 1). The relationship between 16S rRNA gene sequences and comparison to a reference database of known bacteria allows for the phylogenic classification of the bacterial community.

Table 1 Examples of current genetic approaches to analyze the bacterial human microbiota [11••]

Methods	Targets	Comments
Next generation DNA sequencing	Variable region(s) of 16S rRNA gene	Bacteria grouped by 16S rRNA gene homology (phylotype, >97 % identical)
	Whole genome (shotgun approach)	Captures increased diversity in the gene pool; often produces sequences that are not highly homologous to DNA bacterial reference libraries used to classify bacteria
Fluorescent in situ hybridization	Phylotype specific bacterial genes, often 16S rRNA	Targets specific bacterial phylotypes, so bacteria not looked for are missed
Terminal restriction fragment length polymorphism	PCR amplified 16S rRNA genes	Different phylotypes produce fragments of different lengths after restriction enzyme digest of the 16S rRNA gene
DNA microarrays	Typically variable region of 16S rRNA genes	Probes hybridize to phylotype specific oligonucleotides

The definition of a 'normal' microbiome is complex in adults, as the commensal flora exhibit redundancy and diversity that continue to evolve as next generation sequencing better characterizes the microbial community. The complex field and its challenges are explored more thoroughly elsewhere [2, 12, 13]. Briefly, core functional clusters of bacteria, termed enterotypes, in adults are characterized by prominent microbial genera: *Bacteroides*, *Prevotella* and *Ruminococcus*, respectively. Assessing the proportions of the dominant genera that comprises a healthy microbiota is key in determining if alterations are associated with disease; however, distinct enterotypes have

yet to be clearly established in children and may differ depending on a child's age, in turn, making the definition of 'normal' GI microbiota in children challenging [10, 14]. The concept of dominant enterotypes, changes in microbial diversity, and a systems biology shift toward bacterial and possibly virome *groups* leading to pathology, rather than a single microbial agent as the cause of pathology, is emerging as the prevailing perspective [15]. Specifically, there is evidence to suggest that patients with recurrent *Clostridium difficile* infection (CDI) associated-diarrhea have a significant decrease in fecal microbiome diversity, whereas patients with celiac disease have higher diversity compared with controls [15–17]. Similarly, patients with inflammatory bowel disease (IBD) appear to have community microbial dysbiosis as compared to the presence of a single 'causative' organism, although speculation persists regarding the reduced abundance of *Faecalibacterium prausnitzii* in Crohn's disease and *Akkermansia muciniphila* in ulcerative colitis compared to controls [6, 15, 18]. In adults, irritable bowel syndrome, rheumatoid arthritis, obesity, metabolic syndrome, atopic disease, and neuropsychiatric illness appear to have meaningful differences in gut microbiota compared with controls; however, the pediatric microbial composition in these diseases has not been fully explored. Importantly, emerging animal models and human fecal microbiota studies are beginning to suggest the microbiome as part of the cause, as opposed to consequence of disease [4, 11••, 15, 18–20].

Establishment and Evolution of Human Microbiome

Recent molecular studies of meconium from small numbers of newborns suggest the fetal gut may not be sterile as previously thought, although the mechanism of colonization remains unclear [21, 22]. The composition of the newborn microbiome is determined in part by the birthing process when the baby is exposed to maternal microbiota [15]. As anticipated, babies born vaginally are colonized with maternal microbiota from the birth canal such as *Lactobacillus* sp., *Sneathia* sp. and *Prevotella* sp., whereas babies born by Cesarean section are colonized with common skin microbes such as *Staphylococcus* sp., *Propionibacterium* spp. and *Corynebacterium* sp. [15, 23]. During the first few months of life, GI bacterial diversity generally is low compared with adulthood. However, this changes rapidly and diversity dramatically increases by 3 months of life [15, 24]. By 11 months of life the initial colonizers are supplanted by individually unique infant-specific phylotypes, which are distinct from their mother [15, 25]. An adult-oriented microbiota begins to emerge at the end of the first year of life and is fully entrenched by 2.5 years of age, largely stable until old age [15].

In addition to the birthing delivery modality, many factors contribute to the composition of the pediatric microbiome, including maternal weight and early diet [15, 26]. Breast milk is not sterile, containing a variety of bacteria, and breast-fed infants are more likely to be initially colonized with *Bifidobacteria* sp. compared with formula-fed infants [15, 26, 27]. Breast milk also contains oligosaccharides that promote colonization with commensal organisms and antimicrobial factors such as lysozyme, lactoferrin and antibodies that prevent colonization with potential pathogens [7, 26, 27]. Other important factors that influence the evolution of the microbiota during early life include prolonged exposure to the healthcare setting (e.g. prematurity), antibiotic exposure (frequency, duration, type), the timing and type of solid food introduction, geographic location, and the local environment (e.g. farming, urban) [15, 27, 28]. For example, although methodologically limited, the introduction of solid food was associated with an increase in *Bacteroidetes* in an infant and whole genome analysis revealed an increase in bacterial genes associated with carbohydrate digestion compared with the time period prior to weaning [29]. Overall, the pediatric microbiome appears to undergo rapid early development and is sensitive to many external factors before long-term stability is established.

Microbial Dysbiosis and Pediatric Disease

Inflammatory Bowel Disease (IBD)

The intestinal microbiota is thought to play a role in the pathogenesis of IBD—a chronic inflammatory disorder of the GI tract—as opposed to the consequence of the disease [30–32]. Although the precise mechanism in which the microbiome interacts with host genetic, environmental factors, and the immune system is still under exploration, animal studies and clinical observations are promising. For example, mutations in NOD2 and ATG16L1, IBD risk alleles, are associated with a relative abundance of members of the *Faecalibacterium* and *Escherichia* genera compared to controls [33, 34]. Additionally, a large metagenomic sequencing study has highlighted a statistically significant difference comparing the bacterial microbiota in Crohn's disease, ulcerative colitis and healthy controls [35]. This concept was strengthened in the pediatrics literature with a recent prospective, multi-center study that highlighted the role of the microbiome in children with IBD [36]. The authors noted significantly less microbial species diversity in the gut microbiome of children with ulcerative colitis compared to controls. Most notably, steroid non-responders harbored less bacterial diversity compared with steroid-responsive children, signaling a potential prognostic marker [36]. Given the influence of the microbiome, there remains speculation regarding the role

of antimicrobial agents as a risk factor for the development of IBD in the pediatric population. A recent pediatric population-based cohort study has helped shed light on this association [37•]. Kronman et al. [37•] examined over one million children and noted an 84 % relative risk (RR) increase for IBD in children prescribed antibiotics such as clindamycin, that target anaerobic bacteria present in the gut (unexposed 0.83/10,000 person-years; exposed 1.52/10,000 person-years). A dose–response relationship between antibiotic use and IBD was found as each antibiotic course increased the IBD hazard by 6 %. Antibiotic therapy early in life (before 1 year of age) was associated with the highest adjusted hazard ratio for IBD (5.51, 95 % confidence interval, CI 1.66–18.28) but decreased significantly over the age span [37•]. Although, these findings are observational, it is another example of the importance of appropriate antibiotic stewardship, particularly early in infancy.

Obesity

The role of the intestinal microbiota is believed to extend beyond the GI tract. There is mounting evidence regarding the impact of microbes on obesity by modulation of host metabolism [19, 38, 39]. Most recently, Ridaura et al. [40••] demonstrated the impact of the microbiome in obesity in an elegant human–mouse model. Fecal microbiota were transplanted from adult human female twin pairs that were discordant for obesity into germ-free mice. Mice receiving the microbiota from the lean twin remained lean, while mice receiving microbiota from the obese twin had increased weight gain. Furthermore, cohousing the obese microbiota mice with lean microbiota mice prevented the development of obesity and the associated metabolic phenotype in the latter mice, as they acquired the lean microbiota including increased numbers of the phylum *Bacteroidetes* [40••].

Additional evidence supports a role for the gut microbiota in determining animal weight and metabolism. Traditionally raised mice have significantly more body fat compared to germ-free mice, and germ-free mice colonized with normal flora develop hepatic lipogenesis and decreased glucose tolerance [41, 42].

Although speculation remains on the precise mechanism, some have implicated the phylums of *Bacteroidetes* and *Firmicutes* in the pathogenesis of obesity, because obese mice have fewer *Bacteroidetes* and increased numbers of *Firmicutes* in their GI tract. Experimental evidence suggests that this predisposes animals to energy storage and obesity [18, 43]. A small ($n = 49$) Finnish study utilizing fluorescent in situ hybridization to characterize the fecal microbiome showed infants with lower *Bifidobacterium* and higher *Staphylococcus aureus* in their stool had an increased risk of obesity based on the International Obesity Task Force criteria [44]. A larger clinical study ($n = 175$) of Kazakh school children found a negative correlation between body mass index and *Bacteroidetes* number and *Bacteroidetes*/*Firmicutes* ratios, supporting the animal model evidence [45]. Interestingly, this association was only observed in females and the authors speculated that this was related to differential iron metabolism among genders that impacts the composition of the intestinal microbiota [45]. Although there is a need for ongoing research, the prospect of microbiota-driven therapeutics to help ameliorate the burden of childhood obesity is welcomed by all stakeholders.

Atopic Diseases

Several studies have looked at the relationship between the early microbiome and subsequent development of allergic disease with conflicting results. A recent study of 98 infants at risk for allergic disease found that decreased microbial diversity from fecal samples taken at 1 week of life was associated with increased risk for eczema, but not atopy, at 1 year of age compared with infants with a more diverse gut microbiota [46]. In contrast, a cohort study of 411 children born to mothers with asthma found that low microbial diversity at 1 month and at 1 year of age was associated with childhood atopy during the first 6 years as measured by immunoglobulin E (IgE) levels, skin testing, and eosinophilia [47]. Interestingly, no association was found for asthma or eczema with microbial diversity [47]. A third study of 47 infants with fecal samples for microbial diversity at 1 month and 1 year of age found an association between low diversity and asthma at 7 years of age but not other allergic diseases [48]. This study is limited by the small sample size with only eight children developing asthma. Collectively, these results demonstrate that the time-point chosen to examine both the diversity of the evolving microbiota and the clinical outcome in the developing child can profoundly impact the study results.

The hygiene hypothesis postulates that reduced exposure to microbes, including those in the GI tract, during the early programming period leads to an exaggerated Th2 allergic response [8]. This suggests that reductions or alterations in early microbiota from antibiotic utilization in infancy may predispose individuals to Th2 mediated atopic disease later in life. Again, there is conflicting evidence with prospective studies both in favor and against a role for early antibiotic use and risk for atopic disease [8]. However, a trend is emerging favoring an association between early antibiotic use, including during pregnancy, and allergy and asthma. A recent study of two cohorts, including over 30,000 children from the Danish National Birth Cohort followed for 5 years, found an increased risk

for asthma hospitalization (RR 1.17, 95 % CI 1.00–1.36) and the use of oral corticosteroids (RR 1.18, 95 % CI 1.10–1.27) for children born to mothers who took antibiotics during pregnancy [49]. A second longitudinal cohort study of 4,952 children found a striking dose-dependent response associating antibiotic use (before 2 years of age) with asthma, eczema and hay fever at age 7 years [50••]. The authors highlighted the odds ratio (OR) of having asthma with four or more courses of antibiotics was 2.82 (95 % CI 2.19–3.63) compared with a single antibiotic course (OR 1.11, 95 % CI 0.84–1.48) [50••].

Whether these associations are solely due to alterations in gut microbiota is unclear. Certain antibiotic classes such as the macrolides have immune-modulatory effects and may inherently promote a Th2 response independent of any direct bacterial killing [8]. Overall, the nature of the relationship between antibiotic therapy and atopy remains unresolved, and continues as an area of ongoing research.

Emerging Therapeutic Implications

Probiotics

Probiotics have been defined by the World Health Organization [51] as 'live microorganisms which, when administered in adequate amounts, confer a health benefit to the host'. A number of different bacteria are currently being used as probiotics, most commonly *Lactobacillus* and *Bifidobacteria* sp. Multiple studies have examined whether probiotic administration can prevent or treat atopic, inflammatory, and metabolic diseases. However, issues central to heterogeneity of probiotics have hampered precise evaluation in this field. Given immense variations in probiotics, doses, lengths and populations, there have been challenges in comparing outcomes across studies. Additionally, if one speculates on the association between microbial diversity in the gut and disease, 98 children given *L. rhamnosus GG* had no change in microbial diversity compared to controls, highlighting the uncertainty of a single microorganism shifting overall microbial diversity [52]. With these strong cautions in place, and despite heterogeneity in this research sphere, evidence is emerging that probiotics early in life *may* impact disease in later childhood.

Two recent meta-analyses concluded that early probiotic administration during pregnancy and/or in early childhood provides some protection against atopic disease [53, 54]. Elazab and colleagues identified 25 studies involving 4,031 children for analysis. Measured outcomes included total IgE levels, atopic sensitization as determined by skin prick test, and the presence of asthma or wheezing [53]. Early probiotics administered either during pregnancy or postnatally resulted in decreased IgE levels. There was also an association between probiotic administration and reduced atopy but only when the probiotics were given both pre- and postnatally (Table 2) [53]. No association was found between probiotics and asthma/wheezing. *L. rhamnosus GG* is an American Type Culture Collection strain of *L. rhamnosus* that commonly used for probiotic studies and was the most represented probiotic in studies included in this meta-analysis. However, a wide variety of probiotics were used and *L. acidophilus* was associated with increased atopic sensitization (Table 2) [53].

A second meta-analysis by Pelucchi et al. [54] examined the relationship between probiotic supplementation pre- and postnatally and atopic dermatitis (Table 2). The authors examined 18 publications from 14 study populations and concluded that probiotics offer moderate protection against atopic dermatitis regardless of whether the probiotics are administered prenatally, postnatally or both (Table 2) [54]. Overall, both meta-analyses must be interpreted with significant caution given methodological limitations that include the merging of estimates of studies that may not be similar. The pooling of different types of probiotics may underestimate or overestimate the true effect given the heterogeneity of the different studies. Accordingly, this highlights the need for more robust evidence regarding the effect of *individual* bacterial strains on the immune response and disease outcomes.

Bertelson et al. [55••] studied over 40,000 children examining the effects of probiotic milk consumption during pregnancy and childhood on atopic eczema, rhinoconjunctivitis, and asthma. Compared with babies born to mothers who did not consume probiotic milk, babies whose mothers did drink probiotic milk had reduced risk for eczema (adjusted RR 0.94, 95 % CI 0.89–0.99) at 6 months, although this link was not sustained at 18 months unless the child continued probiotic consumption (Table 2). Probiotics in pregnancy also reduced the risk for rhinoconjunctivitis (RR 0.87, 95 % CI 0.78–0.98) at 36 months of age, a risk further reduced if the infant also drank probiotic milk (Table 2) [49]. Consistent with the results of Elazab et al. [53] there was no association between probiotic milk consumption and asthma (Table 2) [55••]. It is worth highlighting that the probiotic milk products utilized in this study contained a mixture of organisms including *L. acidophilus* previously associated with increased risk for atopic sensitization [53].

While numerous studies associate differences in gut microbiota with weight, there is less evidence supporting the effects of early probiotics on obesity later in life [56]. In a small retrospective study ($n = 30$), children of normal weight at 10 years had higher numbers of fecal *Bifidobacteria* at age 3 months compared with children who were overweight at 10 years of age [57]. Normal weight children

Table 2 Examples of the effect of early probiotics to prevent pediatric disease

Disease (Study population age)	Studies	Interventions	Effects of probiotics (RR <1 favors disease prevention)
Atopic sensitization			
Birth-18 years	Elazab et al. [53] Meta-analysis of 21 studies	Multiple types of probiotics during pregnancy and infancy	RR = 0.88 (95 % CI 0.8–1.0)
Atopic dermatitis			
Birth-7 years	Pelucchi et al. [54]	Multiple types of probiotics either during pregnancy or infancy or both	RR = 0.79 (95 % CI 0.71–0.88)
6 months	Meta-analysis of 18 studies		RR = 0.94 (95 % CI 0.89–0.99)
18 months	Bertelson et al. [55••]	Probiotic mixture of different *Lactobacillus* sp. and *Bifidobacterium lactis* Bb12 during pregnancy only	RR = 1.00 (95 % CI 0.95–1.05)
18 months	Cohort study 40,614 mother–infant pairs	Probiotics during pregnancy and childhood	RR = 0.93 (95 % CI 0.86–1.00)
Rhinoconjunctivitis			
Between 18 and 36 months of age	Bertelson et al. [55••] Cohort study 40,614 mother–infant pairs	Probiotics during pregnancy only Probiotics during pregnancy and childhood	RR = 0.87 (95 % CI 0.78–0.98) RR = 0.80 (85 % CI 0.68–0.93)
Asthma/wheeze			
Birth-18 years	Elazab et al. [53]	Multiple types of probiotics during pregnancy or both pregnancy and infancy	RR = 0.96 (95 % CI 0.85–1.07)
36 months	Meta-analysis of 14 studies Bertelson et al. [55••] Cohort study 40,614 mother–infant pairs	Probiotic mixture during pregnancy	RR = 0.99 (CI 0.91–1.08)
Obesity			
Birth-10 years	Luoto et al. [58] Cohort study of 159 children (46 lost to follow up)	*Lactobacillus rhamnosus GG* during pregnancy and 6 weeks after delivery	Trend toward decreased weight in children receiving probiotics

also were exposed to increased adiponectin in maternal colostrum, so whether differences in gut microbiota cause differences in weight or only correlate with changes in metabolism remains unclear [57]. In another study, Luoto et al. [58] followed the weight of 113 children over 10 years whose mothers consumed *L. rhamnosus GG* 4 weeks before delivery and then who received probiotics during the first 6 weeks of life. When adjusted for birth weight, a trend emerged where children exposed to probiotics early weighed less than those in the placebo group. The effect was more pronounced for overweight children although the subgroup was small ($n = 25$) [58]. A meta-analysis of 17 randomized controlled human trials, 51 farm animal studies and 14 experimental models, examined the effect of different *Lactobacillus* sp. administration on weight [59]. The study found that *L. gasseri* was associated with weight loss in obese adults while *L. acidophilus* was associated with weight gain [59]. No consistent effect of *L. rhamnosus*, a common probiotic used in multiple pediatric studies, on weight was identified [59, 60]. However, this meta-analysis must be interpreted with caution given the pooling of human and animal data, a methodological limitation given aforementioned concerns about heterogeneity. Overall, whether there is a role for early probiotic administration in obesity prevention remains to be determined and will likely depend on the specific strain of microorganism consumed.

Fecal Microbiota Transplantation

Although there has been some promising probiotic research in children, there has been an understandable gap in research related to therapeutic modulation of the microbiota at the ecological scale in the pediatric population. Fecal microbiota transplant (FMT) is a treatment strategy that restores diversity to the intestinal microbiota and has been successful in conditions where probiotics have limited efficacy such as recurrent CDI. In adults, systematic review evidence supported a clinical cure rate of approximately 90 % in recurrent CDI with particular interest in FMT via enema [61•, 62]. Despite some methodological limitations,

Van Nood et al. [63••] reported robust success in the first randomized controlled study for recurrent CDI, which was stopped early for benefit. FMT via duodenal infusion yielded an 81 % (13/16 patients) clinical cure rate compared with only 31 % (4/13 patients) for vancomycin alone and 23 % (3/13 patients) for vancomycin with bowel lavage ($p < 0.001$ for both comparisons with the FMT group) [63••]. Similar success has been reported in a randomized controlled trial of 18 men with metabolic syndrome who underwent FMT from a lean donor or autologous FMT of their own stool [64]. These randomized studies highlight the promise of novel microbiota-directed therapies for both GI and non-GI disease in the future.

However, we must proceed with caution before applying FMT to the pediatric population. As outlined previously, there are dynamic fluctuations early in life with complex, linked microbial communities [65, 66]. Accordingly, disequilibrium early in life by microbiota-directed therapy may have downstream consequences, with the potential for adverse events. At this point, FMT must be navigated cautiously particularly in the pediatric population given the introduction of infectious disease or persistent phenotypic changes to the host [4, 61•]. Although there are various donor selection criteria reported [67, 68], there are noteworthy omissions regarding obesity and neuro-psychiatric metrics. Additionally, the literature is not consistently reporting long-term follow up for adverse events (3 weeks–8 years), which have been spontaneously reported rather than actively sought, increasing the risk for underreporting [61•]. Theoretical speculation exists regarding adverse events including peritonitis, enteritis and GI bleeding; however, these are linked to the mode of delivery and not FMT itself. More importantly, infectious, metabolic and neuro-psychiatric adverse events have not been routinely followed. Ultimately, long-term safety registries and extended follow up from emerging prospective randomized controlled trials are required before ubiquitous FMT application in the pediatric population. Despite these limitations, FMT remains promising as a potential novel therapeutic approach and warrants further exploration in this evolving field.

Conclusions

Although the field is still rapidly evolving and study outcomes are at times divergent, the composition and diversity of the gut microbiota in children is increasingly recognized as an integral component of health and disease. Evidence is also accumulating that the microbiota that colonize the GI tract in early childhood have a downstream impact on health later in life. Although exploring this intricate relationship remains in its infancy, it invites the exciting possibility that manipulating childhood gut microbiota may produce lasting health benefits. Pediatric microbiome research must continue to examine first the dynamic 'healthy' microbiome during childhood and changes in the microbiota that result in disease before meaningfully exploring microbiota-derived therapies. A focus on microbial–host interactions and metabolic properties of specific bacterial strains will be critical to identifying organisms most likely to have therapeutic benefit, or alternatively moving towards a systems biology solution with multiple microorganisms. The safety of children is also paramount in conducting clinical research trials so the long-term safety profile of these microbial interventions must be carefully monitored. Despite this caution, research into the pediatric microbiome remains promising and has the potential to offer novel therapies for certain pediatric diseases and, equally important, to prevent disease later in life.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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