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The importance of the microbiome in pediatrics and pediatric infectious diseases

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Abstract

Purpose of Review—Emerging research on the pediatric microbiome implicates the importance of the microbiome on the development of the immune system, nervous system, and growth. Changes to the microbiome during infancy are associated with the development of chronic illnesses such as asthma and inflammatory bowel disease. Additionally, the microbiome provides protection against certain pathogens, affects vaccine responses and alters drug metabolism. This review highlights what is known about the microbiome, the establishment of a healthy microbiome and the significance that changes to the microbiome composition have on growth and health of children and adolescents.

Recent Findings—Vaginal delivery, breastfeeding, maternal health and nutrition help shape a healthy microbiome. Caesarian delivery, formula feeding and antibiotic use perturb the microbiome and are associated with the development of type II diabetes, asthma, allergic diseases and obesity later in life. Specific interventions using pre- and probiotics in multiple settings are under investigation with limited success.

Summary—A better understanding of the microbiome and the interaction with the immune system may help guide interventions to alter the microbiome towards a state of lifelong health.

Keywords

Microbiome; Gastrointestinal; Microbiota; Humans; Breastmilk; Antibiotic use; Immune response

Introduction

The human microbiome, composed of bacteria, viruses, fungi and archaea, is an active and emerging field of study. These microbial communities are particularly relevant to pediatrics since animal and human data suggest a critical role in immune development and growth (1, 2). Although it is not yet known what organisms compose a healthy microbiome, the composition of the microbiome varies by age and by body site and it appears that health is associated with greater bacterial diversity in most anatomical sites. Early alterations in the microbiome composition have been linked to the development of diseases later in life such

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Conflicts of interest

None.

as asthma, atopy, inflammatory bowel disease, obesity and type I diabetes (3–9) and may also impact neurodevelopment (10–12). Likewise, certain bacteria in the microbiome may confer protection against various pathogens or may make a child more susceptible to specific infections including upper respiratory infections, malaria, and campylobacter infections (12–15). Lastly, the microbiome may influence both vaccine responses (16) and drug metabolism (17–19).

To date, the vast majority of microbiome research has focused on bacterial populations inhabiting the intestines. However, viruses and fungi also contribute to the microbiome, as a complex dynamic exists in the populations of bacteria, viruses and fungi that colonize various anatomical sites in the gastrointestinal tract. These populations and dynamics may influence the healthy intestinal microbiome as well as the development of other disease states in ways that we are only beginning to understand (20–22). In this review, we focus on the immune effects of the intestinal microbiome discussing when the microbiome is established, what constitutes a healthy microbiome, the timing of a critical window for the establishment of a healthy microbiome and the impact that changes such as antibiotics, delivery mode, breastfeeding and nutrition have on the microbiome and on the future health and growth of a child.

Are we sterile at birth?

Given the significance of the microbiome on the developing neonate and the potential for therapeutic interventions, it is important to establish when the infant first becomes colonized with microbes. It has been widely assumed that infants are sterile at birth. However, this notion has recently been challenged by the *in utero* hypothesis, which proposes that the fetus is exposed to bacteria in the placenta and amniotic fluid (23). Findings to support the *in utero* hypothesis include the detection of bacteria in the placenta and amniotic fluid at the time of delivery (24, 25); the presence of bacteria cultured from cord blood; and the amplification of bacterial sequences in meconium (25, 26). Arguments in favor of the sterile womb paradigm include the difficulty of proving the significance of the bacteria detected in the amniotic fluid and placenta as these results were largely obtained by detection of nucleic acid and culturing bacteria from these sites has not been successful (27, 28). A careful study in which contamination controls were utilized and compared to placental samples found that there was no significant difference in detection of unique bacterial populations between the two groups. This indicates that the reported detection of microbes likely represents background contamination of the reagents (28) which plagues the analysis of all low biomass studies (29). To date, most infants have no bacteria at birth, though the definitive answer to this question remains unknown.

Factors Influencing Early Microbial Colonization and their Long-term Health Consequences

Regardless of whether there is some exposure in utero, it is clear that after birth infants are rapidly colonized with a complex mixture of microbes primarily derived from initial environmental exposures. Infants delivered vaginally have a microbiome composition more similar to the mother's vaginal flora containing *Lactobacillus*, *Prevotella*, *Atopobium* and/or

Sneathia species (30). In contrast, infants born via Caesarean-section (31) have a microbiome that is more similar to the maternal skin flora (30) and is less diverse (32). The changes in the microbiome, depending on the delivery mode persist, remaining until approximately one year of age (31, 33, 34) but appear to be mitigated by breastfeeding (35). The extent to which the effects of C-sections are due to prophylactic antibiotics is unclear since most, but not all studies, report this confounder (35). These changes can have important life-long consequences as children born via C-section have a greater risk of developing asthma and other allergic diseases (36, 37). A single, small study swabbing infants with maternal vaginal fluid at the time of C-section appeared to alter the infant's microbiome towards that of the vaginally-delivered infants, indicating that these changes in the microbiome may be reversible (38). Sample collection for this study ended at 30 days of life, so the persistence and full impact on future child and adolescent health is unknown.

Beyond delivery mode, breastfeeding is another important determinate in the establishment of the microbiome. Breast milk and the surrounding areolar skin are significant sources of bacteria for the infant's intestinal microbiome, contributing an estimated 28% (breast milk) and 10% (areolar skin) during the first 30 days of life (39). The contribution of breast milk is dose-dependent. The microbiome of breastfed infants is a distinct microbial population compared to those who are formula fed and these differences persist into adulthood (31, 32, 40, 41). Breastfeeding reduces both upper and lower respiratory tract infections and gastrointestinal infections in infants. Early breastfeeding, within the first hour of life, compared to 2–23 hours of life, or greater than 24 hours of life significantly reduces infant mortality (42, 43). The benefits of breastfeeding also extend to increased survival in HIV-infected infants both in developed and developing countries (44–49). Breastfeeding also reduces the development of atopic dermatitis, asthma in children with a family history of asthma and possibly the development of obesity and type II diabetes later on in life (50–53).

How much of these benefits are due to microbial transfer versus other protective components of breast milk remains unknown. Breast milk contains multiple components that protect the infant against infection such as caseins, lactoferrin, lysozyme, immunoglobulin A (35), and human milk oligosaccharides (HMOs) (54). HMOs are the third largest constituent of breast milk and have many putative functions including some antibacterial activity (55). Interestingly these substances are not digested by humans and appear to serve as prebiotics, promoting the growth of commensal bacteria such as *Bifidobacterium bifidum* (56). Therefore, breastmilk contains both important prebiotics and probiotics for the establishment of the infant's gut microbiome.

Maternal health is also important in the establishment of the infant microbiome. Perturbations of the infant's microbiome have been noted in preterm infants whose mothers are obese, term infants whose mothers are on antibiotics during pregnancy and infants whose mothers are HIV-infected (57–59). HIV-exposed, uninfected infants experience considerable morbidity and mortality and decreased growth compared to infants in the same setting born to HIV negative women (60–65). HIV-exposed, uninfected infants have more abundant populations of *Pseudomonadaceae* and *Thermaceae*, decreased bacterial diversity, and a less mature microbiome in their stool than HIV-unexposed, uninfected infants (59). These

perturbations may be one mechanism that accounts for the immunologic derangements and poor growth observed in these children.

The environment including race and ethnicity, geographical location, diet and exposure to pets has a significant effect on the microbiome (66). Genetic differences may also play an important role (67–72). Early exposure to pets correlates with an increase in *Ruminoccocus* and *Oscillospira* irrespective of delivery mode which may have implications towards decreased obesity and food allergies (73). Microbial differences are also observed in both infants and adults in specific ethnic groups and may explain the higher incidence of cardiovascular disease and diabetes amongst different ethnicities (74–76). This change begins early in life as differences are noted at one year of age in Canadian infants of South Asian descent and Caucasian descent (76). Race and ethnicity are significant determinants of the vaginal microbiome, and the microbial differences affect the risk of acquisition of sexually transmitted infections including HIV (77–79). Additionally, the vaginal microbiome alters the effectiveness of pre-exposure prophylaxis to prevent HIV transmission (17), so an understanding of racial and ethnic differences in microbiome composition has broad implications in health and disease.

The biogeography, or spatial organization, of bacteria along the gastrointestinal tract also plays a vital role in the establishment of the microbiome. The presence of naturally occurring antimicrobial peptides, secreted IgA, levels of oxygen, pH, and special anatomic constraints such as the appendix, colon crypts, and the mucous layer as well as other bacteria influence which bacteria inhabit specific areas of the gastrointestinal tract (80). Furthermore, certain bacteria present in the microbiome also modulate the immune system as *Bifidobacteria* and *Clostridia* species influence the development of T regulatory cells (81–83). Interactions with polysaccharides and short chain fatty acids also function as a stimulus for T regulatory cells (84–86).

Once established, the microbiome itself is very resilient and not easily changed (87–89). It has been noted that 60% of the bacteria sequences comprising the microbiome remain stable over the course of five years in an adult (88). Administered antibiotics can change the diversity initially, but the microbiome becomes more similar to the pre-antibiotic state within weeks to months after last administration of the antibiotic (90, 91). The reason why the healthy microbiome remains impervious to change over time may be the result of the abundance of microbial species present and increased diversity as decreased bacterial diversity has been associated with diseases such as type II diabetes, obesity, and inflammatory bowel disease (92). Resilience in unhealthy microbiomes may even be associated with chronicity of certain diseases such as inflammatory bowel disease and obesity (92).

The Developmental Window

Given the significant health consequences associated with microbial perturbations, it has been proposed that the first 1–24 months of life represents a critical developmental window for the establishment of the microbiome (93). The first few years of life is also a key period in immune system development (94). As certain bacteria are required for parts of the

immune system to develop or mature, these two processes are inextricably linked. For example, early infant colonization with *Bacteroides fragilis* is associated with B-cell maturation in the infant gut (95, 96).

Notable shift changes occur in the bacterial composition of the microbiome during the first few years of life. This microbial maturation can be assessed using an index developed by Subramanian et al (97). The index can be applied to compare communities, assess growth and assess severe acute malnutrition (97). Transition points have been recognized during the first month of life and with the introduction and expansion of solid foods. At two to three years of age, the microbiome becomes more similar to the diverse microbiome seen in adults (6, 40, 67) but this composition is still distinct even into adolescence (98).

While the microbiome changes more in the first few years of life, the composition in the first few months appears to be critical for allergic disease and imprinting. The Canadian Healthy Infant Longitudinal Development (35) study reported that the microbiome at three months of age, but not at one year, identified children who developed either atopy defined by skin testing or had clinical symptoms of wheezing (99). In this study, lower amounts of stool *Veillonella*, *Lachnospira*, *Rothia*, and *Faecalibacterium* was associated with atopy and wheezing (99). Moreover, in a murine model, administration of these bacteria attenuated airway inflammation (99). A US birth cohort also reported that the early stool microbiome was associated with atopy and asthma (3). In this study, stool profiles at one month but not six months of age were predictive (3). In this racially diverse group, risk was associated with lower bacterial levels of *Bifidobacteria*, *Lactobacillus*, *Faecalibacterium*, and *Akkermansia* and increased fungal levels of *Saccharomyces*, *Rhodotorula*, and *Candida* and decreased *Malassezia* (3). These studies are consistent with murine models in which early microbial colonization has life-long consequences on immune responsiveness (93).

At all ages, antibiotics can have a profound effect on the stool microbiome (40, 100, 101). Mouse models incorporating the use of a low dose antibiotic following weaning showed that changes in the microbiome correlated to more corpulence later on in life despite the microbiome normalizing (5, 102). However, the role of antibiotic exposure and current rates of childhood obesity is unclear as studies have been contradictory (103–107). Nevertheless, these concerns should prompt judicious use of antibiotics, especially as antibiotics are oftentimes overprescribed for treatment of viral illnesses.

Nutrition

The importance of proper nutrition in the developing child cannot be understated and an understanding of the complex interactions between the microbiome and nutritional status is starting to emerge. Undernutrition causes increased mortality in children under the age of five, has physical effects such as stunted growth, increased infections, decreased immunity, and impacts neurodevelopment (108, 109).

Malnourished children receiving ready-to-use therapeutic food (RUTF) do not gain the expected amount of weight compared to their healthy counterparts (97). Evidence suggests that microbes have an important role in the pathogenesis of malnutrition as highlighted by

the efficacy of antibiotics in improving nutritional recovery and decreasing mortality in children with severe acute malnutrition (110). Transfer of IgA-targeted bacteria from the gut microbiota of undernourished children into germ-free mice disrupts the small intestinal and colonic epithelial barrier and induces weight loss and sepsis (111, 112). Characterization of the IgA-targeted bacteria demonstrated that *Enterobacteriaceae* in combination with ten other microbes was sufficient to produce enteropathy (111). Furthermore, the enteropathy could be prevented by administering two IgA-targeted bacteria from a healthy microbiota (*Clostridium scindens* and *Akkermansia muciniphila*) (111).

Microbial diversity is decreased and microbiomes are immature in children with moderate and severe malnutrition (97, 113). Furthermore, lacking specific micronutrients can impact the microbiome by promoting growth of specific bacteria (114). Finally, environmental enteric dysfunction (EED) or tropical enteropathy may also play a role in malnutrition (115). EED is most commonly observed in developing countries and causes chronic inflammation in the small intestine and likely forms intestinal microerosions that impair the absorption of nutrients and promotes microbial translocation (115, 116). EED is thought to be caused by persistent exposure to microbes that promote chronic inflammation as a result of not having access to clean food and water, lack of access to toilets and lack of handwashing practices (115, 117). Improvement of child health from malnutrition will not only have to address macro and micronutrient deficiencies but may also need to develop strategies that also improve EED.

Therapeutic Potential

Given all the ways the microbiome impacts human health and disease, there is tremendous interest in manipulating the microbiome to improve health. However, data in humans is sparse. Fecal microbial transfers from healthy donors have been successful in manipulating the microbiome from a state of disease back to a state of health in the treatment of recurrent *Clostridium difficile* infections (118), but have not been as successful in other disease states (119, 120). It may be that treatment of *C. difficile* infection is uniquely successful because the disease has devastated the pre-existing communities creating an available niche for the microbiota from a healthy donor.

The use of prebiotics and probiotics has been another area of investigation with limited success. Prebiotics have shown some success in the desensitization of peanut allergies (121) as well as in reducing body weight and total body fat in obese children (122). Other studies have used a combination of pre-and probiotics, labelled symbiotics. One such study administered a symbiotic within the first 2–4 days after birth, for seven days, to healthy infants in a rural village in India and showed some success in reducing the combined primary outcome of death and sepsis as well as lowering the amount of lower respiratory tract infections (123). Partial success was also achieved with symbiotic administration in very low birth weight infants in reducing necrotizing enterocolitis (124). Other trials utilizing only a probiotic have had less success in reducing sepsis or necrotizing enterocolitis in pre-term infants (125–128). While therapeutic interventions to alter the microbiome show potential, more work needs to be done to understand the complex dynamics of the microbiome.

Finally, there is interest in using the knowledge gained about the microbiome and nutrition to improve health by improving available foods. This may be accomplished by finding foods that benefit microorganisms in the microbiome, by discovering nutritional components modified by microbes to benefit the human host, or by finding foods that benefit the human host (129). Once these components are identified, additional interventions may be done to alter crops in developing countries where specific nutrients essential for growth may be lacking in typical diets (129).

Conclusion

There is clear evidence that the microbiome has important long-term health implications for the growing child. The microbiome is established early and once established appears to be resilient to change (See Figure 1). A critical developmental window exists in the first one to three months of life, a window which decreases the risk of allergic diseases and establishes long-term health. Understanding all the factors that lead to a healthy microbiome is of critical importance and will likely include an understanding of the complex interactions between archea, viruses, bacteria and eukaryotes. In pediatrics, support of breastfeeding and good nutritional practices and avoiding procedures or interventions that alter the microbiome towards a state of dysbiosis are important for the health of a child. Avoiding medically unnecessary C-sections (36, 40, 130) and judicious use of antibiotics are critical, *primum non nocere.* More specific interventions, such as pre- and pro-biotics are as yet, of unproven benefit, but show potential and warrant further study.

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Key Points

- The microbiome has long-term ramifications for growing children.
- The microbiome is established early in life and appears to be resilient to change.
- A critical window for development exists during the first one to three months of life in which the healthy microbiome is established and the risk for asthma and allergies is decreased.
- The healthy microbiome is shaped by vaginal delivery, breastfeeding, maternal health and nutrition.
- Caesarian delivery, formula feeding and antibiotic use perturb the microbiome and are associated with the development of type II diabetes, asthma, allergic diseases and obesity later in life.

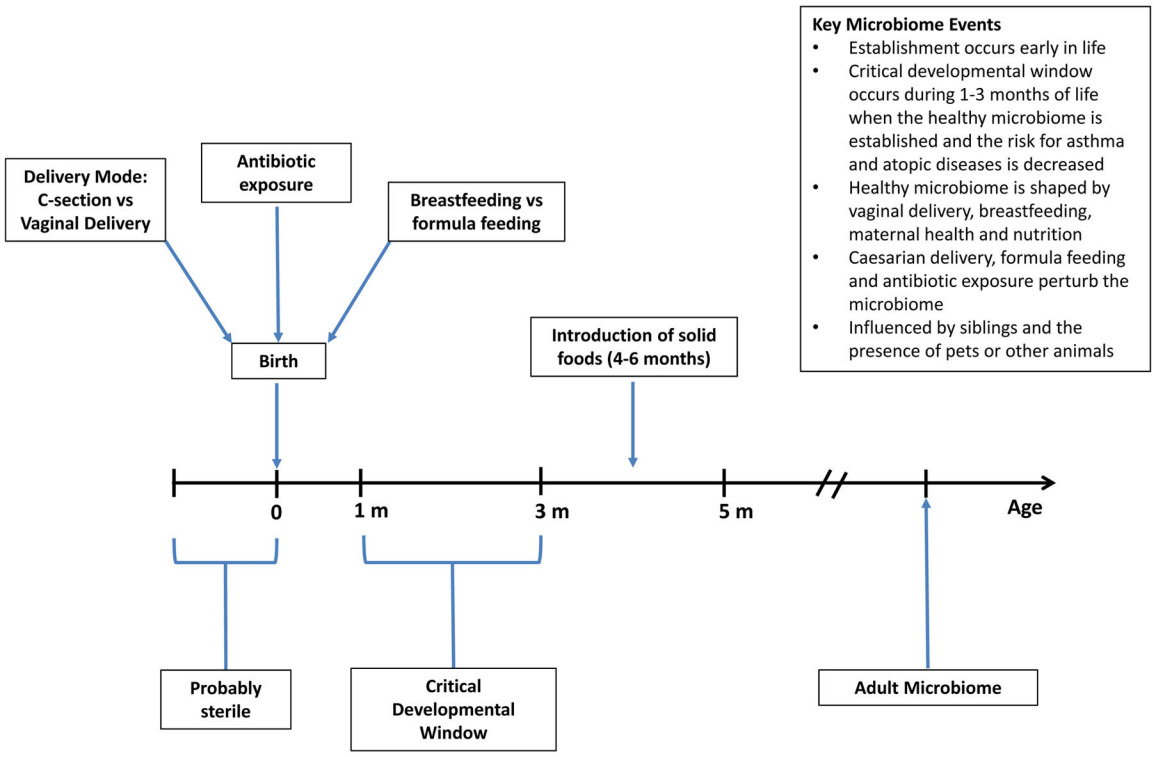

Figure 1.
Timeline of key events in the development of the microbiome.