THE SIGNIFICANCE OF THE MICROBIOME: ITS ROLE IN INFANT DEVELOPMENT AND LONG-TERM HEALTH

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Abstract

Humans enjoy a beneficial symbiotic relationship with bacteria. Although commonly thought to be the cause of illness, bacteria aid in food digestion along with creating resistance to disease. The microbiome refers to the aggregate of bacteria that reside in our intestinal track. There has been an effort over the past decade to map the human microbiome in order to identify this relationship. Given this crucial role of microbiota in human health, it is important to know how the microbiome is formed in infancy as it may impact one's future ability to obtain wellness. A review of the literature was done to examine what is known of the microbiome at the earliest stage of life and the relationship to issues later in life. The articles were identified using the databases CINAHL, PubMed, and MEDLINE. Five themes were identified across the articles studied. The microbiome: (a) of preterm infants differs from full-term infants; (b) at birth is found in both the lungs and intestines; (c) development is affected by an infant's intake of formula vs. breastmilk; (d) present and its amount present during infancy may influence the risk of developing behavioral issues; (e) development is altered when antibiotics are administered to newborns/infants. The choices of how a child will be fed is decided during pregnancy and consideration of the microbiome and its effect on future health has serious implications. Knowledge of the microbiome's role in healthy growth and development should be considered when working with expectant mothers, parents and families of newborns.

Table of Contents

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The Significance of the Microbiome: It's Role in Infant Development and Long-Term Health

In an effort to understand and ensure a healthier human body, scientists have spent decades trying to discover and comprehend what factors influence health. The human body has a symbiotic relationship with the microbes that reside within us and play a role in our health. In recent years, there has been a project to map the human microbiome (Gritz & Bhandari, 2015). With the discoveries made thus far, there has been a clear correlation with the early gut microbiome composition and future health problems such as asthma, atopic eczema, irritable bowel syndrome, and many metabolic disorders (Ventura, Milani, Lugli & Sinderen, 2019). It becomes apparent that these metabolic disorders correlated with alterations in the composition of the microbiome, pose a threat to the future health of infants.

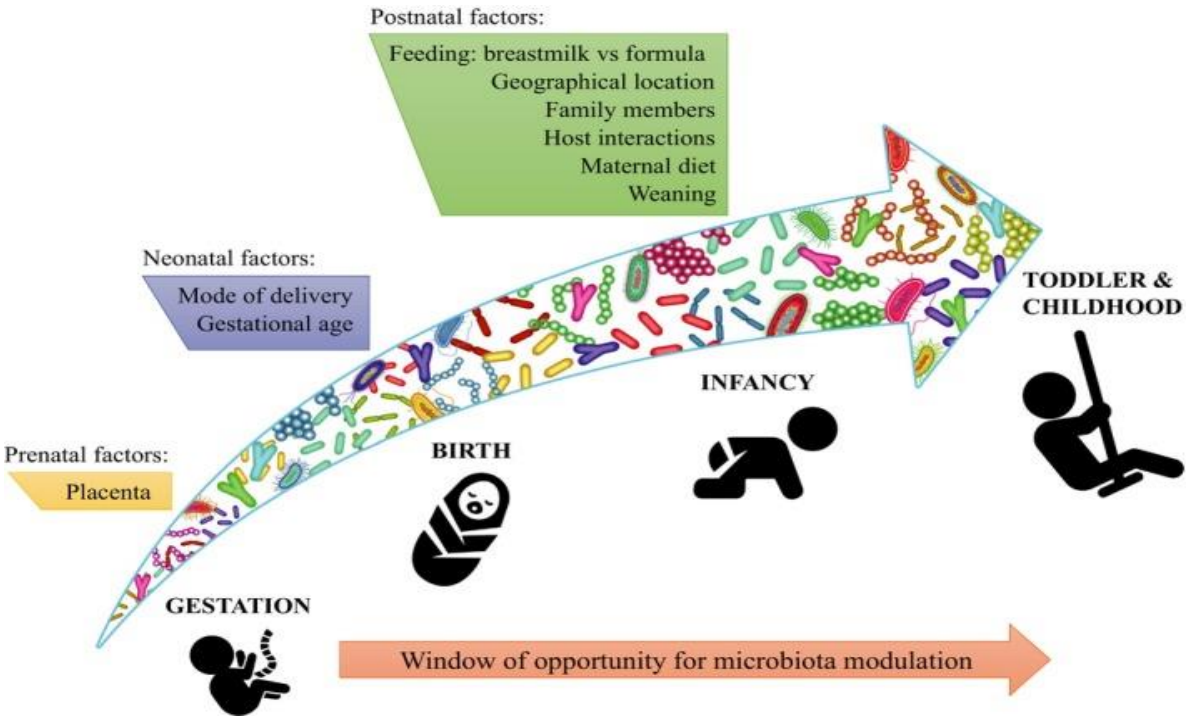

Figure 1: Microbiome Development from Gestation to Childhood. (Ventura et al., 2019).

Being able to comprehend the exact composition necessary to establish this foundation for the microbiota would guide us in developing a plan to ensure that infants are exposed to the needed microbes in order to be healthy in the future and aid in fighting disease. As healthcare providers always aiming to improve patient care, we must ensure we are doing all that we can to promote healthy microbiome development for long term health and wellness. With this research, it can provide us with guidelines to share with expecting mother and their families. This will allow for informed choices when it comes to feeding and other forms of care for the infant.

Background

An essential term to define is the microbiome. This term, often interchangeable with microbiota, intestinal flora, and gut bacteria, refers to the array of microbes/strains of bacteria found within the gastrointestinal track of the human body (Gritz et al., 2015). These microbes come from exposures in the environment such as being vaginally born, exposures to different foods, owning/interacting with animals such as pets, and even living in different parts of a country. One of the more well-known sources of these microbes are yogurts which contain probiotics which are deemed as beneficial microorganisms. The microbiota serves a number of roles such as absorption of nutrients, digestion of certain foods, and synthesis of vitamins (Kane, Dinh, & Ward, 2015). One specific example is the digestion of cellulose found in the vegetables we eat. Humans do not have the enzyme to digest cellulose and fibers. The bacteria within our G.I tract have this capacity and thus break these foods down for us providing both ourselves and themselves with nutrients needed for growth (Senior, 2019).

It comes to our understanding that the colonization of the microbiome and the final composition will help predict what health issues can arise in the future and thus what characteristics we can alter to prevent illness. This bears the need to pay closer attention to the development of the microbiome from the moment of birth and well along the infancy stage since different factors will alter the microbiome. The colonization and maturation of the microbiota begin in utero but is mostly impacted after birth. The mode of birth is one of the initial factors; a child born vaginally will have a very different microbial composition versus a child who was born via cesarean. The child born vaginally will more likely experience less illness/health issues later in life versus the child who was born by c-section. This is due to the microbes found on the mothers vagina that the infant is exposed to upon vaginal delivery thus giving the infant more microbial exposure versus their cesarean counterpart.

As previously mentioned, the development of the microbiota for newborns begin with the type of birth and is further affected by the types of feeding the infant receives and the skin to skin contact with a mother. Some of these benefits include better infant temperature maintenance, higher blood oxygen levels, improved weight gain and for the mothers it helps with breast milk production and child bonding (Seitz, 2017). Full-term infants who are breastfed receive the nutrients and compounds to develop a sturdy microbiome. Preemies on the other hand are often taken to the NICU and already have an underdeveloped microbiota due to not being exposed to the vaginal microbes of the mother. These preemies in the NICU develop their microbiome through feedings obtained through a tube placed in the stomach through the nose or mouth. Due to the conditions of infants in the NICU, breastfeeding is not always possible and so through

these feeding tubes infants receive breastmilk, formula and other nutrients. The components of these feedings greatly influence the growth of bacteria in the gastrointestinal tract which emphasizes the need to care for the nutrition of the preterm infant (Gritz et al., 2015). Breastfed infants obtain more of the natural and essential nutrients required for establishing a healthier microbiota and immune system since breastmilk contains components such as antimicrobials that help the immune system mature. Formula fed infants develop an altered microbiome from breastfed infants because of the differing nutrients and lack of antimicrobials in formula (Groer, Luciano, & Dishaw, 2014). It is found that formula-fed infants have lower levels of the bacterial strain *Bifidobacterium* and breast-fed infants have an increased abundance in intestinal bacteria (Groer et al., 2014).

When teaching new mothers about providing nutrition to their infants, breastfeeding is routinely emphasized as the best form to feed an infant given the numerous benefits. These benefits include providing immune protection, reduces the permeability of the intestine in a neonate, meaning certain molecules can pass the cellular barrier of intestines to be absorbed, and provides growth factors to help the neonate develop (Dieterich, Felice, O'Sullivan & Rasmussen, 2013). Breastfeeding is encouraged because not only does it provide skin-to-skin contact to promote bonding but also because certain immune components are passed along. This last piece is taught to mother but the microbiome may not be explicitly referenced. Instead the information tells us that it is often easier for the newborn to digest breastmilk, and that the immune system is boosted this way, including the fact that it is more cost effective and overall provides all the necessary nutrients. Feeding education for newborn mothers is addressed with the

primary care provider and/or an OB/GYN after delivery and further include the nurses and even a lactation consultant. The decision to breastfeed or bottle feed is influenced by a number of factors including financial resources, cultural practices, maternal attitudes/feelings, and education on the subject. Sometimes it may be a physical barrier such as the inability to produce breastmilk that would prevent someone from breastfeeding.

The aim of this literature review is to identifying what we know about the microbiome from birth, how the microbiome affects future health and wellness and what can we do to ensure a healthy microbiome to reduce the risk of illness across a lifespan. The research question is: What is the importance and effects in the early diet choices of an infant to promote the development of the child's microbiome and reduce the risk of illness across the lifespan?

Methods

A systematic review of the literature was utilized in order to identify the necessary components needed in early microbiomes and which factors play a role in altering it. When sorting through and identifying articles, the advanced search settings were adjusted to narrow down the results. The databases referenced in this systematic review included the Cumulative Index of Nursing and Allied Health Literature (CINAHL) Plus, PubMed, and MEDLINE.

Utilizing a Boolean search, the following keywords were inserted in the search engine: newborn, neonate, infant, microbiome, microbiota and intestinal flora. Boolean operators such as "or" and "and" were utilized between the key words to ensure that articles with those terms that might be deemed important were not excluded.

The age restrictions within the studies included: birth-1 month, infant 1-23 months, and all infants from birth to 23 months. The term “probiotic intervention” was also included in the search bar to narrow down the results for articles. The time frame for the articles fell within the last five to ten years. This decision was based on how significant the results were in the studies. The time frame for the findings for five to ten years was the most recent studies performed therefore held the most current significance. Full text articles were included in addition to clinical studies, essentially primary sources were included in order to analyze and synthesize the findings of each study.

Exclusions from the results included those children over the age of five if it was not a longitudinal study or did not provide any concrete findings or something of importance that could be further analyzed to aid in the guide to help establish a healthy intestinal flora. Inclusion of specifically named bacterial strains were necessary in the articles found along with the use of PCR testing and other tests to obtain bacterial samples. The narrowed down articles were further studied to identify the major themes. See Figure 2 below.

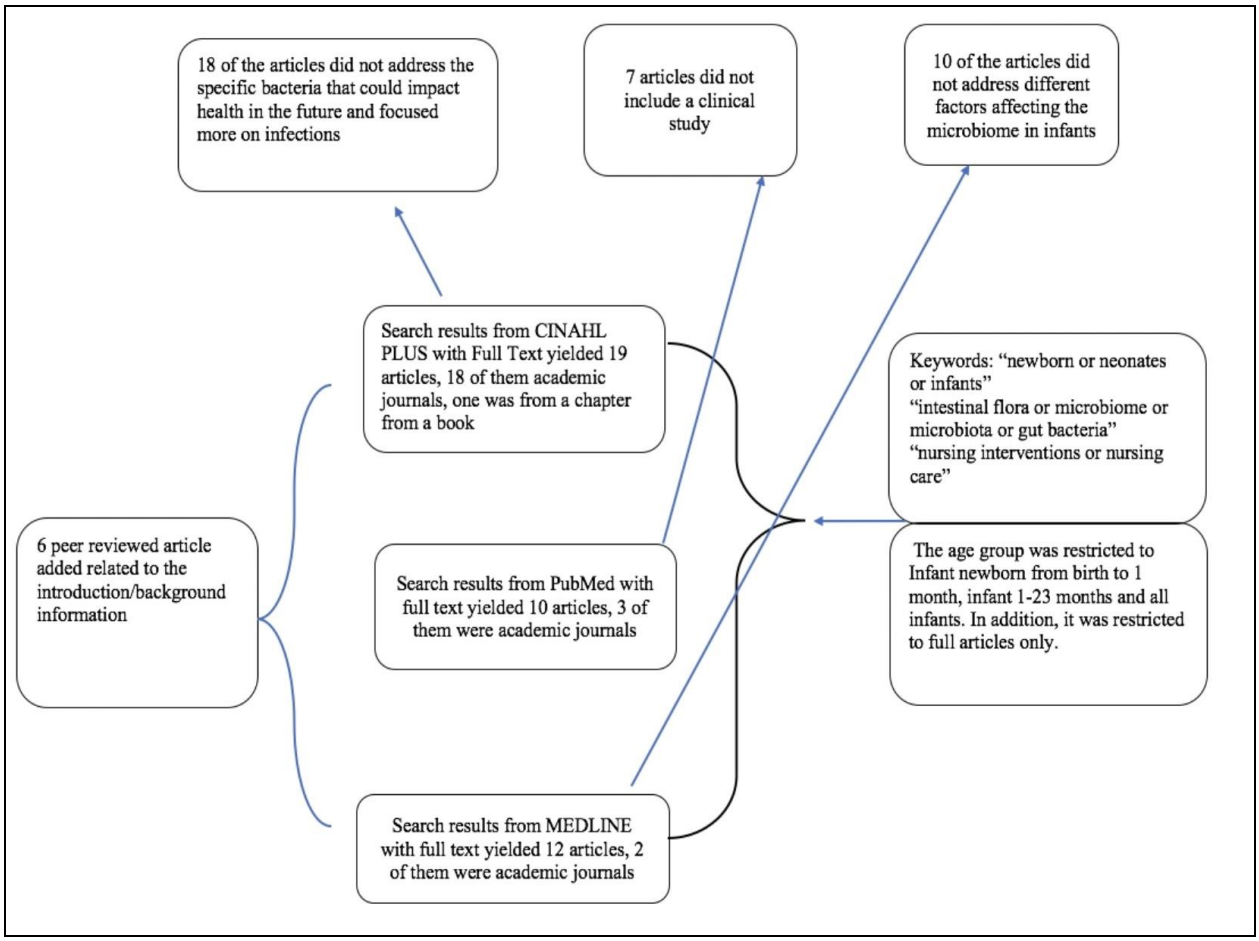

Figure 2; Keyword Article Search Process.

Results

The results of this systemic review of the literature found that a number of factors do influence the composition of the intestinal flora at an early stage in life. Five themes were identified across the articles selected. The themes were identified based on multiple authors referring to the significance of the factors impacting the infant microbiome and results later in life. The themes are as follows: The microbiome: (a) of preterm infants differs from full-term infants; (b) at birth is found in both the lungs and intestines; (c) development is affected by an infant's intake of formula vs. breastmilk; (d) present and

its amount present during infancy may influence the risk of developing behavioral issues; (e) development is altered when antibiotics are administered to newborns/infants.

The Microbiome of a Preterm Infant Differs from Full-term Infants

The microbiome is not the same in preterm infants as it is if these infants were delivered at full-term (Korpela, 2018; Forsgren, 2017). Preterm infants are not only physically underdeveloped but also experience a delay in their microbiota development. *Bifidobacterium* is one of the main bacterial strains that is necessary in abundance to develop a microbiome effectively. Bacterial strains, such as *Bifidobacterium*, develop in a pattern (Korpela et al., 2018) and when the infant is delivered prior to 40 weeks gestation, the pattern of development is delayed (Forsgren et al., 2017). It is the microbiome of full-term infants that is compared to that of a premature infant's, to identify how delayed the development is (Korpela et al., 2018). Narrowing the gap of the microbiome in these two infant groups can take as long as 6 months (Forsgren et al., 2017). Over the course of the first few months of life, it is evident in preterm infants that care directed towards the infant microbiome is vital to catch up with full term infants. There must be a balance in place for the healthy growth of the intestinal flora which is not present in preterm infants.

The Microbiome at Birth Is Found in Both the Lungs and Intestines

Development of the microbiome is determined not only by gestational age, but also is impacted by strains of microbes within the body and where they are found (Hoen, 2015; Korpela, 2018). The microbes in our bodies are not limited to just the gastrointestinal tract, but are also located in the lungs of the respiratory tract (Hoen et al., 2015). The microbes across these two locations communicate and influence our health even at birth. The incidence of cystic fibrosis and exacerbations early in life, are

associated with the presence of bacterium that are found in the gastrointestinal tract but not found in the respiratory tract (Hoen et al., 2015). This indicates that despite differences in the microbial composition of the lungs and intestines, it is not always correlated with diseases such as cystic fibrosis. Additionally, preterm infants experience an imbalance of normal flora vs. bacterium normally present in small numbers that are not enough to cause illness or disease meaning subtle imbalances will not negatively impact the infant (Korpela et al., 2018). If the imbalances grow greater however, it can then lead to health issues later in life.

This indicates that physical maturity can determine microbiota development. The main microbes necessary in adequate microbiota development include *Bifidobacterium, Enterobacter,* and *Staphylococcus.* The composition of the preterm infant was found to have overgrowth of *Enterococcus* which was an obstacle for microbiota development causing the inhibition of growth of the normal bacteria (Korpela et al., 2018).

The Microbiome Development Is Affected by an Infant's Intake of Formula vs. Breastmilk

A factor in both infant development as well as microbiome development is the means by which the child is fed. An important determinant of a healthy microbiome is breastfeeding of the child rather than being formula fed (Hoen, 2015; Korpela, 2018; Loughman, 2020). Breastfeeding promotes healthy microbiome development (Korpela et al., 2018), and is an important determinant of micro diversity in the respiratory tract (Loughman et al., 2020). The gut microbiota develops rapidly during infancy and changes as the child transitions to solid food (Loughman et al., 2020). Providing an infant with the proper diet will help foster a healthy intestinal flora.

The Microbiome Present and Its Amount Present During Infancy May Influence the Risk of Developing Physical and Behavioral Issues

The microbiome's influence on a child's growth and development is shown not only in how the microbiome changes, but also in the levels when compared to children with a normal microbiome (Hoen, 2015; Loughman, 2020). In the incidence of children with cystic fibrosis, the gut microbiome is more relevant than that of the respiratory tract (Hoen et al., 2015) whereas for children with behavioral issues, the lower the microbiome levels, the higher the incidence (Loughman et al., 2020).

It is important to highlight exact diseases that have the potential to arise later in life with correlation to the microbiome. One study highlights that a decrease in the diversity of the microbiota is associated with disorders such as asthma, inflammatory bowel disease, and cystic fibrosis. This study further states that prior to CF onset, there is a change in the microbiome supporting the importance of the role the microbiome plays (Hoen et al., 2015).

> One major finding during research was a study conducted that pointed out the correlation between microbiome composition, emphasizing the bacterial strain *Prevotella*, and behavioral issues. The study found the following:
>
> In an unselected birth cohort, we found a clear association between decreased normalized abundance of *Prevotella* in faecal samples collected at 12 months of age and increased behavioural problems at 2 years, in particular Internalizing Problem scores. This association appeared independent of multiple potentially confounding variables, including maternal mental health. Recent exposure to

antibiotics was the best predictor of decreased *Prevotella*. (Loughman et al., 2020).

The finding displays a clear association between reduced abundance of microbiomes and increased risk of showing behavioral issues at 2 years of age. Intervention of providing *Prevotella* in the infants diet would decrease the risk of behavioral issues. According to the author, the prevalence of *Prevotella* has been correlated to autism in which many behavioral issues are common (Loughman et al., 2020). Behavioral issues can be seen in individuals who suffer from genetic or physiological disorders, the latter which can be influenced by microbiome composition as mentioned before. Preventing an altered microbiota composition from developing would help prevent the risk of behavioral issues seen later on.

The Microbiome Development Is Altered When Antibiotics Are Administered to Newborns/Infants

The use of antibiotics to treat illness also results in a change in the microbiome (Huda, 2019; Loughman, 2020). The earlier antibiotics are used in treatment, the greater the risk of an altered microbiome (Loughlan et al., 2020). For infants delivered by cesarean section and those who have lengthy hospitalizations, the need for antibiotics is higher and this can result in lower levels of microbiota (Huda et al., 2020).

Previously mentioned was the impact that preterm birth has on the microbiota growth and development but that is not the only factor altering the development. Administering antibiotics can drastically reshape the microbiome in newborns. One author pointed out that in the study the findings were “consistent with evidence…demonstrating that antibiotic exposure in early life influences gut microbiota, and alters brain cytokines and behavior” (Loughman et al., 2020). Connecting back to the

behavioral issues later in life associated with microbiome composition alteration, changes in the brain cytokines is a possible factor in causing the behavioral issues. These cytokines are small proteins that help in controlling the activity and growth of immune system cells.

Neonatal antibiotic exposure is associated with lower levels of microbiota. This is evident given that the purpose of an antibiotic is to reduce/eliminate unwanted bacteria but in the process also reduces/eliminates necessary strains such as "B.bifidum, B. breve, B. lactis and B. longum" (Forsgen et al., 2017). The detrimental effects and benefits of antibiotic administration have to be carefully evaluated and must be utilized as a last resort. In the case that its use is deemed absolutely necessary, interventions must be put in place to help restore the microbiome or at least deter the microbial effects on the microbiota. Preterm infants not exposed to numerous microbiota due to modifying practices such as: C section vs. vaginal delivery and early antibiotic exposure. The more frequent these practices are, the longer hospitalization for the infant.

Discussion

The literature provides a clearer picture on the effects that different factors have on the microbiota. The difference in microbiome composition between full term and preterm infants highlights the need to provide interventions for preemies in order for them to reach the same microbiome development as that of full term infants. Early diet planning can help advance the delayed development since feeding full-term infants can be more of a choice at birth, whereas the healthcare needs of a preemie may not allow for the same choice.

Difference in diversity found within the microbiota in the lungs and the GI tract may not necessarily lead to health issues but the GI tract microbiota composition was the one to have the most effect on an infant's health. However, should these differences become more distinct it can lead to health disorders since there must be a degree of balance within these microbiome compositions.

Intake of breast milk has proven to be of the utmost importance to establishing a healthy microbiota despite formula trying to mimic its affects and impacts. The more exposure to the necessary microbes in early life, the better development of the microbiota becomes and in turn enhances a healthier life. Breastfeeding was one of the most important findings in the role of the microbiome development. Thus far it is known that there are numerous benefits to breastfeeding which includes helping them build a better immune system, bonding with the mother and overall nutritional needs are met with breastfeeding. The findings of the literature review add to the benefits because breast milk provides some of the fundamental components needed to establish a good microbiome for the infant. Those who were breastfeed had a different composition from those who were not. It is important to point this out because infants who may not be able to be breast fed can suffer the consequences on their health later on due to the fact that they will lack certain bacterial strains to. Some of the consequences include being more susceptible to disease such as allergies, catching a cold often, or even conditions like cystic fibrosis.

There is a necessity for well-informed breastfeeding counseling and diet education for parents of newborns. A diverse and abundant microbial composition is wanted in order to mitigate the risks of behavioral issues down the line and healthcare workers should work

with families to ensure this. Ensuring bacterial strain abundance would help in the risk reduction of behavioral issues that can often be seen in individuals with physiological disorders. While microbes can be found all over the body, they work together in communicating and ensuring microbial abundance that can help mitigate both disease and behavioral issues later on in life. This would further insinuate and beg the question is there a relationship between certain bacteria and brain development. It would not be far-fetched given the microbes ability to communicate with the human body and the plasticity of the brain.

Antibiotic use is a concern for full-term infants however the risk of infection is often lower than that of preemies who require longer hospitalizations and possibly invasive procedures. This is a further indication to closely examine the need for antibiotic administration. Reducing, when possible, the administration of antibiotics will help prevent delays and alterations in the intestinal flora development to ensure a healthy future for the child.

This type of information needs to be taught to expecting families so they are equipped with the necessary education to provide the infant with the necessary nutrients needed or to plan with their health care provider as to what foods can help the child attain all the necessary bacteria to help the microbiome grow healthily.

Limitations

This systematic review of the literature has some limitations. In this specific area of interest, the articles available were very few. Given such limited search results indicates a need for the authors to continue their studies and for others to work in this area as well.

Conclusion

The non-focused care of the infant microbiome must be changed. The role that the microbiome plays in an infant's immediate and long term health is something that must be emphasized not only to pediatric and delivery nurses, but expecting mothers and families as well. More focused interventions aimed at the microbiome should be performed by nurses on a unit to ensure that the child is receiving the necessary microbes to establish their healthy microbiome. In addition, more dietary guidelines should be put forth in patient education and in patient care for infants so as to provide the needed nutrients and at the same time ensuring bacterial exposure for the microbiome. Not only are we concerned with immediate health, but long term concerns such as behavioral issues and developing illnesses such as asthma. As healthcare providers, ensuring health continuity is one of the objectives in client care. We can provide this through microbiome-focused care to ensure adequate bacterial strains and a healthy microbiota composition in an effort to avoid issues like cystic fibrosis, behavioral issues, and even allergies.

These results are crucial because of the huge role that the microbiome plays in health contrary to past beliefs. So little was known before about the role that the microbiome played in previous decades and health was believed to be influenced by external factors apart from our immune system. Instead, it has dawned upon us that our internal microbes may be the biggest players in affecting our health.

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