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Understanding the Use of Probiotics in Pediatric Populations

A discussion with probiotic experts
Dr. Allan Walker and Dr. Erika Isolauri

There has been a rather explosive interest in the topic of probiotics in the last few years. It is now well recognized that certain ingested microbes can modify the ecology of the intestinal lumen, and lead to beneficial structural and functional changes in the gut; particularly in relation to intestinal and systemic immunity. And we are understanding more of the complex mechanisms that govern these host-microbial interactions.

In this discussion we will review the importance of a “healthy” microflora, the effects of altered intestinal microflora, and how the intestinal microflora and probiotics can beneficially affect both local and systemic immune function. Finally, we will review the clinical benefits and safety aspects of those probiotics which are of particular relevance to pediatric clinicians.



Intestinal Microflora, Health and Immune Function

Question: A “healthy” intestinal flora is said to be important for health in general. Can you briefly describe how intestinal flora is relevant to host GI and systemic health?

Dr. Isolauri: Our thinking of gut microbiota indeed has changed much during the past decade. Today we know that the microbiota actually behave like an

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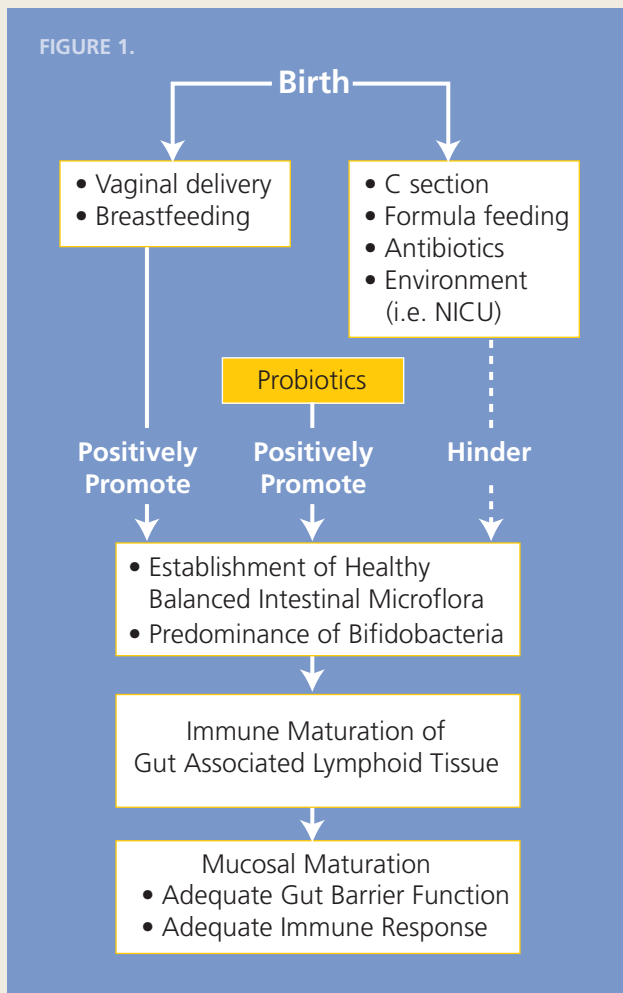
organ of the host – they are part of the host’s defense system. Intestinal microbiota play a role both in host defense, particularly preserving gut barrier function, as well as in modulating immune responses to prevent other immune related conditions.

A “balanced” microbiota appears critical for the gut barrier and mucosal maturation processes in infants. For example, the colonization patterns of infants born vaginally or delivered by caesarian-section are quite different, and lead to differences in immune system maturation as well in differences in gut barrier function. Compared to vaginally born infants, C-section infants have delayed colonization of *Bifidobacteria*, and also delayed maturation of humoral immunity. Earlier and better colonization with *Bifidobacteria*, as occurs in vaginally born infants and breast-fed infants, leads to better humoral defense and immune modulation mechanisms.(Figure 1)

This delay in C-section infants and non-breastfed infants is also associated with increased risk of diarrheal disease, particularly rotavirus diarrhea, as well as increased risk of atopic disease. These are the best studied conditions where probiotics may have a greater impact by improving the balance of intestinal microbiota. Therefore adequate intestinal colonization, and balancing the microbiota with specific organisms appears to prepare the host immunologically for adequate defense as well as minimize aberrant immune responses like allergic disease.

Question: The newborn is born with a relatively sterile gut and rapidly gets colonized. By what mechanisms do gut flora affect gut maturation and immune response of a newborn?

Dr. Walker: We can learn a great deal from studies in germ-free animals. In germ-free animals, the absence of bacteria leads to a gut epithelium that is atrophic, very thin, and with totally underdeveloped lymphoid tissues. There’s greater permeability, loss of barrier function, and abnormal peristalsis. When their gut is adequately colonized, all of these functions return to what you would see in a normally colonized infant. Similarly, in the human, the period of time from birth to about 18 months is absolutely critical for the development of microflora and for the



Lastly, colonization in the neonatal period is also critical with regard to what we call “oral tolerance”. If colonization doesn’t occur during the neonatal period, oral tolerance (immunologic tolerance to proteins) does not occur. This leads to inflammatory responses such as allergy and autoimmune disease which has increased worldwide in developed countries. A good example of this effect are babies who are born by C-section, that don’t get the microbial bolus coming through the birth canal. They take a long time to reach colonization (and having less *Bifidobacteria*) and are very susceptible to conditions such as allergy. It seems prudent that these babies in particular, are given a probiotic. Personally, I’ve had three grandchildren all born by C-section. I convinced their mothers to put them on probiotics right after birth, which can overcome a major deficit in the development of the immune system.

Determinants of Intestinal Microflora and Immune Response

Question: There appear to be significant differences in colonization in vaginally born vs. c-section and breastfed vs. formula fed infants particularly related to specific species of *Bifidobacteria*. What explains these differences and how does this impact the function of intestinal flora?

proper development of the mucosal protective immune system. A child in the womb is essentially in a germ-free environment and then rapidly becomes colonized after birth, particularly if they are born by vaginal delivery. An infant at birth is IgA deficient. With colonization, the infant begins to produce its own IgA antibodies and the epithelium develops tight junctions between cells, preventing large antigenic molecules and bacteria from crossing. There is also protection through a number of non-specific protective mechanisms, such as the release of mucus onto the surface, and an increase in peristalsis to get rid of any noxious substance within the intestine.

“...the period of time from birth to about 18 months is absolutely critical for the development of microflora and for the proper development of the mucosal protective immune system.”

DR. ALLAN WALKER

Dr. Isolauri: The new molecular techniques show that *Bifidobacteria* compose up to 80-90% of the microbiota of breastfed infants, while in formula fed infants the microbiota resembles more that of adults. There are several reasons for this. For example, we can detect *Bifidobacteria* in breastmilk, which to some degree may be important. There are also growth factors for specific *Bifidobacteria* in breastmilk (mostly oligosaccharides). In addition, there are data indicating there are some molecules in breastmilk which can mediate a host-microbe cross talk, which can facilitate the *Bifidobacteria* stimulation of the gut for immunologic maturation. Finally, in breastmilk we

have certain cytokines which promote a non-inflammatory environment in the gut like TGF beta which promotes IgA development.

Question: Breastfed infants receive human proteins in a non-sterile form, while formula fed infants typically receive non-human sterile proteins. In the last 100 years we have drastically changed (sterilized) our diet, and have decreased our environmental exposure to bacteria. It appears that this lack of host-microbe interaction may be associated with a number of inflammatory conditions, like allergy and autoimmune diseases, and this has led to the so-called “hygiene hypothesis”. What mechanisms explain these associations?

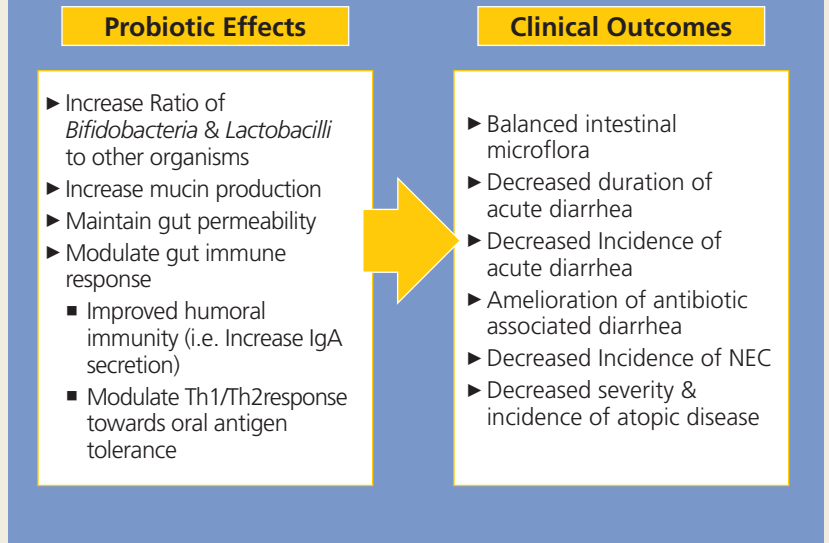
Dr. Walker: This explanation is a hypothesis which has evolved. Initially, it was postulated frequent infections helped the immune system to mature, and decreased the chances for immune related diseases. We now understand that it is the exposure to colonizing bacteria, particularly within the gut, that are critical in activating the immune system.

Dr. Isolauri: I agree. It is clear that it is the composition of microbiota, and its interaction with the infant in early life which is critical for healthy maturation of immunity—not infections per se. Interactions between bacteria and the infant immune system, happen early and independently of the occurrence of clinical infections that the infant may experience. It is a balanced gut microbiota that leads to immune maturation and regulation, and potential

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DR. ERIKA ISOLAURI

FIGURE 2.
Reported Effects of Various Probiotic Bacteria on Gut Microbiota, Immune Function, and Reported Clinical Outcomes



decreases in immune and allergic conditions.

Probiotics: Benefits and Mechanisms of Action

Question: The better documented effects of certain probiotics (ingested microbes with demonstrated health benefits) relate to viral diarrhea, and atopic disease. What are the

mechanisms by which probiotics can help prevent or manage these conditions?

Dr. Isolauri: There are two general ways by which these probiotic bacteria may help: One is increasing gut barrier function, and the other is modulating the immune response.

In diarrhea and allergy, an important target is gut barrier dysfunction. Certain probiotics have been shown to strengthen mucosal gut barrier function. They affect the tight junctions by decreasing gut

permeability, interact with fatty acids in the membrane, enhance IgA immunity in the intestine and control the generational pro-inflammatory cytokines. These mechanisms are important for preventing diarrheal disease and allergic reactions in atopic conditions, and the accumulated clinical data support this. Certain probiotics are increasingly showing benefits in atopic eczema, especially in patients who have food allergies. However, the effects have not been as clear in older children or adults with respiratory allergies where these mechanisms are not the same.

Dr. Walker: There's also evidence that probiotics actually stimulate genetic transcription of mucins and allow for increased release of mucus on the surface which provides a stronger physical barrier to microbial and antigen penetration. In addition, once the gut barrier is affected by any inflammatory process, further problems can develop. For example, for a long time we've known that infants who were allergic to cow milk would also develop allergies to soy and other proteins. I believe that what happens is that the initial process causing allergic reaction alters barrier function and allows other antigens or allergens which normally don't get across, to get across and create the same reaction.

In addition to improving gut barrier function, probiotics can modulate the host immune response. Often in a clinical allergy, there is a skewed helper cell response toward cytokines that mediate a Th2 response, which leads to IgE secretion and allergic symptoms. Some probiotics will specifically stimulate a counter-balance through Th1 cytokines, which then reduce the Th2 response, and thereby decrease the chances for allergic responses. But we are just hitting the tip of the iceberg of understanding. For example, we now know that certain bacteria can secrete a substance that can enter the cell and block inflammatory cytokines by actively down-regulating inflammatory processes.¹ (Figure 2)

“Given the seriousness of NEC, use of probiotics in this condition is considered one of the most exciting probiotic applications today.”

DR. ERIKA ISOLAURI

Question: There are inflammatory conditions that happen early in life, like necrotizing enterocolitis (NEC), which appear to have a microbial patho-physiologic component. How strong

is the evidence for use and/or mechanisms in these kinds of conditions?

Dr. Walker: There have been two large studies^{2,3} where premature infants of 1500 grams weight or less were started on the fourth or fifth day of life on a combination of *Bifidobacteria* and *Lactobacillus* and were shown to have a significantly decreased expression of NEC and in cases when NEC occurred, it was less severe. Now we've recently taken those same organisms, grown them in culture in the laboratory, and shown genetically that they stimulate genes that affect the down-regulation of inflammation.

Dr. Isolauri: I agree, the data so far show a reduction of risk. Given the seriousness of NEC, use of probiotics in this condition is considered one of the most exciting probiotic applications today. In our university hospital for more than 10 years, our premature babies have been given breastmilk, to which the milk bank adds probiotics.

Probiotics: Beneficial Species in Pediatrics

Question: “Probiotics” are a concept: to modify the intestinal flora in a way that ultimately leads to demonstrable benefits. But clearly not all non-pathogenic bacteria, or all those used as supplements or in the food supply, necessarily have a probiotic effect. Which would you consider the most appropriate agents for infants?

Dr. Isolauri: Surely, *Bifidobacteria* are useful, and I would generally recommend the *Bifidobacteria* species more commonly found in infants. Some may be more appropriate for adults (such as *Bifidobacterium adolescentis*) than for infants. In addition, *Bifidobacteria* are particularly safe. We have not had any reports on infections or any risks with these strains,

and we have seen similar benefits with Bifidobacteria as we have for certain *Lactobacilli*. Therefore incorporating *Bifidobacteria* for infant formulas and foods would be a good choice. *Lactobacilli*, like *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri*, although not typically in infant microbiota, have also shown to be efficacious for several applications. In choosing the right strains for current and future use preclinical testing for efficacy as well as safety is very important.

Dr. Walker: I agree, some Bifidobacteria species would be adequate. Amongst *Lactobacilli*, *Lactobacillus rhamnosus* (GG) is the better studied, and in most instances has been shown to be effective in diarrheal disease and allergy; however the results are mixed for Crohn's disease. I would reiterate that even within the genus *Lactobacillus* or *Bifidobacteria*, strains are different, so they should be individually investigated.

Safety of Probiotics

Question: Clearly not all bacteria have similar efficacy. Similarly, the safety profile of various microbes would be different. What should be the approach to assessment of safety of probiotics, particularly in vulnerable populations?

Dr. Isolauri: When speaking of very young infants, the best model is the breastfed baby who is up to 90% colonized by *Bifidobacteria*, with no documentation of sepsis from this, despite the large number of these organisms present in early life.

In addition, for *Bifidobacteria* taken orally, we have an excellent safety record, with no adverse effects documented. For several strains of *Lactobacillus*, particularly *L. rhamnosus* GG, we have also had very good experience. But use as probiotics of some strains from the genus *Lactobacilli* may not be applicable to millions of infants, given rare instances of infection in compromised infants.

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DR. ALLAN WALKER

Dr. Walker: As mentioned, *Bifidobacteria* do not seem to pose safety concerns in newborns, and they also have been used without apparent adverse effects in premature infants. The studies with *Lactobacillus* GG suggest that they're quite safe. However I would still have

some concern in conditions such as bone marrow transplantation with immune suppression, short bowel syndrome, and other clinical conditions, where although some suggest that probiotics may be effective, safety needs to be better assessed before use is recommended.

Looking Ahead

Question: How do you see the long-term use as we learn more of probiotics in terms of affecting public health?

Dr. Walker: The time from birth until 2 or 2½ years of age is very critical to the immune development of an infant. A baby's defenses aren't well established. In modern society, particularly when infants are not breastfed, they are more likely to have an imbalanced microbiota for a variety of reasons, and increased exposure to variety of infectious agents. It's important to stimulate an infant's own microbiota and their immune system through breastmilk or providing an appropriate probiotic, and I agree that use of *Bifidobacteria* in general, is probably the way to go. This should be very helpful in allowing the infant to get through that transitional period until they reach complete colonization and adequate defenses. During this vulnerable period of time and I feel strongly in a general sense, that we need to find ways to achieve this balance, so it favors the positive probiotic effect, and do it safely.

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