ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Exploring the Early-Life Microbiome and Future Risk of Inflammatory Bowel Disease

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G&H What are the biggest early-life risk factors for inflammatory bowel disease overall?

SN Many studies have looked at risk factors for the development of inflammatory bowel disease (IBD) in early life. Antibiotic use, especially 3 or more courses, during the prenatal, perinatal, or postnatal period has been shown to be a risk factor for IBD. Other studies have shown that families that migrate from countries with low incidence of IBD to countries with high incidence of IBD are likely to have a higher risk of the disease in the second generation, possibly because of the influence of lifestyle, environment, and diet. Passive smoking (eg, maternal smoking) is also a risk factor. Studies have shown that a child with several infections in the gut has a 2- to 3-fold increased risk of developing IBD later in life. These factors have been consistently shown in studies to increase risk for the development of IBD.

Other factors are more controversial and have not consistently demonstrated an increased risk of IBD. Examples include hygienic factors and being born in more urbanized or Westernized areas.

On the other hand, some factors have been shown to be protective against IBD, such as exposure to furry animals/pets and being outdoors. One of the most consistent findings is that breastfeeding up to 12 months, or perhaps even longer, has been shown to be protective for the development of IBD.

Overall, it appears that the early-life period is very important in terms of the risk of developing IBD. There has been speculation that it may be possible to modulate some of these exposures or nonexposures in the hopes of preventing IBD.

G&H What early-life events have been shown to impact the gut microbiome?

SN Most of the work that has been performed on the gut microbiome in early life is from the healthy state or other immune-mediated diseases. The most important early-life event is likely the mode of delivery. Spontaneous vaginal delivery has been shown to be more advantageous than Cesarean section on the gut microbiome. Children born via vaginal delivery will acquire a lot of microbiome from their mother that is closely related to the gut. The features of this microbiome are important to prime the immune system to make children strong later in life. In contrast, the microbiome of children born by Cesarean section is more closely related to skin microbiota or even opportunistic pathogen colonization that may come from the operating room.

There are also other important early-life events. One is breastfeeding. Breast milk has been shown to be very beneficial in changing the gut microbiome of the infant by increasing short-chain fatty-acid bacteria, which are important to prime a good immune system. Certainly, intrapartum antibiotic use has been shown to be detrimental on the gut microbiome. Recovery of the microbiome following antibiotics exposure was inconsistent and varied across offspring, with some having persistent

perturbations at 12 months of age. Downstream effects of microbiome perturbations can include metabolic alterations. Further data are needed to understand the long-term outcomes.

G&H Could you discuss any recent studies showing that the maternal microbiome shapes the microbiome of the infant?

SN My colleagues and I recently examined a mother/infant cohort in which we analyzed the microbiome of the mother during pregnancy as well as the microbiome of the infant. We looked at the mother's stool microbiome during the 1st, 2nd, and 3rd trimesters of pregnancy; at the time of delivery; and after the infant was born (1, 6, and up to 12 months after birth). What was interesting was that in the third trimester, there was a sudden rise in certain bacterial species as well as in bacterial diversity and richness, which are likely beneficial. When we looked at the gut microbiome of the infant, we saw that the bacteria that were transferred from the mother to the infant were beneficial. Some of these microbes were butyrate-producers, which have been shown in animal models to increase the benefits of immune response. Thus, there is some evidence showing that the gut microbiome from the mother is transferred to the child.

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Another intriguing study showed the effect of mode of delivery on the infants' gut microbiome. The researchers examined the gut microbiome of infants delivered by Cesarean section and found differences in their gut microbiome compared with children born via vaginal delivery. The researchers then used fecal material from the mothers to perform fecal microbiota transplants through breast milk given to the infants. When the microbiome of the infants was checked again at approximately 6 months after delivery, its development in children born by Cesarean section caught up to that of children born by vaginal delivery. This is quite interesting and highlights the importance of the first days and how the microbiome can be modulated.

G&H How can bacterial diversity and composition of the gut microbiome differ between mothers with and without IBD?

SN My colleagues and I also performed a preliminary study with a group in New York and compared the microbiome and diversity of the bacteria in mothers with IBD vs healthy mothers. We found that mothers with IBD had reduced diversity of the gut microbiome during the first trimester of pregnancy all the way to the third trimester, compared with mothers without IBD. We also found that mothers with IBD had different bacterial composition from those without IBD. For example, those with IBD had an increase in Proteobacteria, which may result in inflammation. The question is whether this effect is caused by the drugs being taken by mothers with IBD or by the disease or inflammation in the gut. The answer is not clear yet. Interestingly, infants born to mothers with IBD also had reduced diversity and a different microbiome (eg, with increased proinflammatory bacteria) compared with infants born to mothers without IBD.

G&H Does the composition of breast milk also differ between IBD and non-IBD mothers?

SN There are very limited data on this issue. A future research direction should probably be to better understand what is inside the breast milk of IBD mothers. However, it is important to be careful about this issue. If IBD mothers are told that breast milk may have detrimental components in the microbiome, they might avoid breastfeeding, which might have uncertain effects on the infants' development. Therefore, more solid evidence is needed.

There has been some preliminary research conducted so far on breast milk components (eg, bacteria, metabolites), and the very early answer is that there does appear to be a difference in the breast milk microbiome of IBD mothers vs non-IBD mothers. In the breast milk of IBD mothers, bacterial diversity is lower and the composition of bacterial species is different. However, these findings are based on quite small numbers of patients, and research has only started on this issue. It is necessary to understand whether the difference in the breast milk microbiome has a long-term, clinical impact on the infant (eg, it causes more inflammation) or whether the difference does not matter because the infant can still develop a good microbiome from the breast milk and other things. There are plans to conduct animal research on this issue.

G&H What other evidence has shown a link between early-life exposures, the gut microbiome, and future risk of IBD?

SN Several groups have looked at exposure to antibiotics in early life. Certainly, these agents can change the gut microbiome. An animal study showed that receiving antibiotics during pregnancy or soon after infants were born resulted in some changes in the microbiome that were difficult to reverse, unlike if infants received antibiotics much later in life. The first 3 years of life are very important for priming the immune system. As children grow older, their gut microbiome becomes more static, whereas during the first several years of life, it can change with many factors such as the environment, diet, and breastfeeding.

There is also starting to be more research looking at maternal diet, not just well-known aspects such as eating more vegetables and less fat, but other issues such as emulsifiers. These are additives that are put in food to make it taste better and preserve it for a longer period of time. One common emulsifier is polysorbate 80. Some animal studies have shown that eating a lot of this emulsifier during pregnancy can cause disruption of the gut barrier and changes in the microbiome, which can then increase the risk of inflammation or IBD in adulthood in offspring.

Research is currently ongoing to try to determine whether it is possible to prevent the development of IBD by changing the gut microbiome ...

G&H How might these findings on the early-life microbiome impact clinical practice and intervention?

SN IBD is a lifelong disease; there is no cure. The disease is multifactorial and complex, and many patients have to take drugs. There are 3 ways to impact clinical practice: primary, secondary, and tertiary prevention. We are already doing tertiary prevention. When someone has the disease, whether they are young or old, they start to receive treatment. Some of these treatments may be used to change the gut microbiome. For example, fecal microbiota transplantation, the transferring of feces from healthy people to patients with IBD, has a remission rate of 30%. In other words, at 1 year, 3 out of 10 patients will remain well after fecal microbiota transplantation. Four or 5 studies have supported this notion, so microbiota modulation may work.

However, that is in patients who already have the disease. The holy grail of IBD treatment is primary prevention. In a high-risk family with a mother who has IBD, a major concern is whether the child will develop the disease as well. However, there is no single gold standard for prediction right now, so there is no way to know whether an infant born to a mother with IBD will develop the disease. Research is currently ongoing to try to determine whether it is possible to prevent the development of IBD by changing the gut microbiome, which would be a noninvasive intervention. There are a number of studies trying to accomplish this by using a certain diet, probiotic, fecal microbiota transplantation, or other noninvasive methods. Right now, these are key research interests, but the only way their effects can truly be understood is with longitudinal studies, which take a long time to conduct. Studies need to follow children from birth until they are 10 to 20 years old to see whether the modulation they use reduces the risk of developing IBD. Most of the current studies have been looking at one time point; longitudinal studies are what are needed next.

There was a Canadian study that attempted to look at this issue longitudinally. Researchers followed patients with IBD and their families over time in which there was a sibling who had not yet developed IBD. The researchers found that there was a window whereby the sibling's stool could reveal preclinical changes, for example, an increase in fecal calprotectin, which is a surrogate for inflammation, or changes in the gut microbiome. The bottom line is that there are some changes in the gut microbiome of people in high-risk families that may predispose them to IBD. These are initial insights, but I think they will impact clinical practice over time.

It is particularly important to prevent IBD development or lessen the severity of the disease because it is increasing globally. To reduce the incidence of IBD, it is necessary to start looking at the disease in children and how to prevent it from occurring in society.

G&H Are there any common myths or misconceptions in the medical community about this topic?

SN One is that many physicians think that if a mother has IBD, they should deliver the infant by Cesarean

section. Physicians often assume that a Cesarean section is safer because IBD is in the gut. However, as discussed previously, there are many beneficial effects of having the infant born by spontaneous vaginal delivery, not only in terms of the gut microbiome, but also because of other immune-mediated diseases (eg, asthma, allergies, eczema). A good deal of data have shown that vaginal delivery is protective for these conditions. Therefore, I recommend that mothers with IBD have a vaginal delivery unless there is a contraindication, such as the presence of many fistulas in the anal region.

Another issue involves antibiotic use. I think clinicians use antibiotics too liberally. Although these agents may work for IBD, I think we need to be more careful and conservative. I recommend using the shortest duration and smallest dose of antibiotics if they are absolutely necessary.

Finally, after the recent emphasis on sanitizing everything because of COVID-19, it is important to remember the hygiene hypothesis in which early childhood exposure to microorganisms can help stimulate good T-regulatory cell response and a strong immune system. Too much sanitizing can eliminate good bacteria and parasites in the gut microbiome that are needed to strengthen the immune system later on. Parents probably do not need to be so concerned about cleanliness (eg, making sure children do not pick up something from the floor). It is the natural evolution of a person's life to have different types of exposures so that their immune system can easily identify them again in the future and decide whether something is a bad bacterial pathogen or a good one. If the immune system has not encountered something before, it might react in a hyperactive manner, for an abnormal immune response.

Disclosures

Professor Ng has no relevant conflicts of interest to disclose.

Suggested Reading

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