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From UPMC Children's Hospital of Pittsburgh, welcome to, That's Pediatrics. I'm Brian Martin. I'm the vice-president of medical affairs here at Children's Hospital of Pittsburgh.

Carolyn Coyne: I'm Carolyn Coyne. I'm a scientist in the Division of Pediatric Infectious Diseases. Joining us today is Dr. Mike Horowitz, who's an associate professor of surgery at the University of Pittsburgh School of Medicine. He's Also an attending physician in the Division of Pediatric General and Thoracic Surgery. His lab is dedicated to setting changes in the microbiome in critically ill patients. Much of his work is actually focused on necrotizing enterocolitis in premature infants, but he has also actually broadened his studies into studies of the microbiome in older children within the pediatric ICU. Welcome to, That's Pediatrics, Mike.

Mike Morowitz: Thank you for having me.

Carolyn Coyne: I sort of mentioned necrotizing enterocolitis. Why don't you tell us a little bit about that?

Mike Morowitz: Sure. Well, as you mentioned I'm a general pediatric surgeon, and one of the great unsolved problems in neonatology is a condition called necrotizing enterocolitis and it's actually one of the few conditions, I would say, that over the past 50 years has not seen an improvement in outcomes. What it is, is a disorder of intestinal inflammation in premature newborn infants, typically within the first month of life. It's characterized by severe intestinal inflammation that often comes on quite suddenly. Shockingly in 2018, we have very low little understanding of why some infants and not others develop this problem, which can be life-threatening.

Carolyn Coyne: How common is it, Mike?

Mike Morowitz: This diagnosis of NEC affects about 7% of premature infants, but the significance of it actually extends beyond that, because I always say that in NICUs, people tend to be walking on eggshells sort of afraid that any one infant is going to develop this problem at any time. What that means in real terms is that a neonatologist are uncertain how to begin feeding infants, how to and when to administer antibiotics to infants, because there's been thought for quite a long time that some of these factors impact whether or not the problem will develop. Blood transfusions is another one.

My interest in this came about in my training, which finished longer ago than I'd like to admit, but I was very frustrated by the number of infants that would

develop this problem in a very common situation was that parents would ask how this problem happened or why it happened, and very commonly would say, "The baby was doing so well two days ago," and then developed this problem requiring surgery and that's what led to my interest in the problem.

Carolyn Coyne: Sorry. How soon after birth does something like this presents itself?

Mike Morowitz: The most common time period is three weeks after being born.

Carolyn Coyne: Oh, okay. Is that sort of regardless of when the baby is born in terms of gestational age?

Mike Morowitz: That's a good question. There is some relationship, and so older infants that are maybe late preterm tend to have the problem earlier, maybe around 10 to 14 days of life, but the smallest, quote on quote micro premies tend to develop the problem around three to four weeks of life. But it's always in that first four to six weeks of life, which is kind of an amazing situation that babies aren't born with the problem, it didn't start before they were born, and once they go home it never happens, but it's a peculiar problem to the first few months of life while they're in the hospital.

Brian Martin: Mike, can you tell us a little bit about briefly some of the surgical management challenges and then some of the long-term consequences of the situation for your patients?

Mike Morowitz: When necrotizing enterocolitis begins, it can begin as a low grade, mild inflammation of the intestine, and that can be out of the smaller large intestine. In about two thirds of infants, that can be treated with antibiotics and by withholding formula or breast milk for a few days, but in one third of patients surgery is required to remove necrotic or dead intestine that makes children sick. In that one third of infants requiring surgery, unfortunately, 40 to 50% do not survive. Of those that do, it's now well-documented that long-term disability is quite significant, either because intestines had been removed and so they can't eat later in childhood or because of a neurologic disability. Even though I am a surgeon, and would like to say that I can cure this problem in the operating room, I think everybody realizes that we need to figure out how this happens and how to prevent it before surgery is required.

Brian Martin: Segueing over to your work with a micro bio, is there a hypothesis you mentioned, or as part of the hypothesis, such that this environment here in the hospital somehow inhibits or has an effect on the microbiome that's different, for example, then when we send a very young infant to a home environment?

Mike Morowitz: Well, necrotizing enterocolitis is one of several diseases, and I would include Crohn's disease, asthma, diabetes. It's one of the diseases in this category where for 40 or 50 years it had been thought that bacteria or viruses play a role in the development of the disease. I would say that probably 20 to 30 years ago,

many people gave up on, quote, figuring it out because their studies of the bacteria that the babies had were hitting a dead end. About 15 years ago, a really integral advance took place in medical research which involved a 21st century study of what's referred to as the microbiome. That term is not known to everybody, but what it refers to is the groups of organisms that we all have on the body, in the body, and over the past 15 to 20 years, the techniques you use to study this topic have improved dramatically, just like they have for studying the human genome itself.

What's been very cool is that during this time, a lot of these diseases where, as I said, people had sort of given up studying the role of of bacteria and other organisms, has been reinvigorated. And so when I finished training, it just so happened to be around the same time that the NIH was launching what they call the human microbiome project in 2007 to really dive deep into studying which organisms colonize our bodies when we're healthy and then which do the same in people that are not healthy. In the case of babies, it's kind of a fascinating topic, because when babies are born, there's essentially no germs, but it's important for people to understand that we want bacteria and other organisms to coat the body, because many of them do really important things.

To get back to your question, we don't really know why, but it is safe to say that the organisms that you see coating the body of premature infants is very different from that of full term healthy infants. Why is that? Well, they're exposed to antibiotics. Because they're born prematurely, the surface of the intestinal tract on the inside is not as developed in their immune system's not as developed, and that probably has a role too, so it's multifactorial, but there is the opportunity to make some advances in I'm distinguishing babies with and without the problem.

Carolyn Coyne: You brought up sort of an interesting point that that earlier when you were introducing the problem of NEC was one of the first things that popped into my head, which is, you think of an infant being born in the NICU, and it being a very sterile environment, and of course knowing that infants are born sterile, and so where does that initial microbiome come from? Is it from the mother? Is it from breast milk? Is it dependent upon mode of delivery? What are the sort of things that are involved in exposing the infant to the microbiome?

Mike Morowitz: Yeah, the baby's first exposure to microbes, some would call germs, but I don't like to use that term because it has a bad connotation.

The baby's first exposure to microorganisms is a really, really important time of life that we're just beginning to understand. The way that a baby's born for example, has a huge impact. Vaginal delivery is referred to as a natural delivery and one of the reasons that it is that the mother, during the process of childbirth, provides her infant with organisms that will help the child, and during a Cesarean section, that same exposure does not take place. I have two children that were born by Cesarean section and they're fortunately doing pretty well, so

it's not as though that's a in and of itself a deal breaker to not have that exposure, but it's one exposure that does adversely impact the microbiome.

Then if you look at antibiotic exposure on top of that, that's probably another exposure that's better to avoid if possible. Then like you mentioned, breast milk has been studied quite a bit in the last couple of years and it really does contain a surprisingly high amount of bacteria and that's no coincidence. It's there to help the infant, again, to fight infection and to develop the immune system.

Carolyn Coyne: And so, is your research looking at just profiling the microbiome in premature infants with and without NEC and what have you found?

Mike Morowitz: Right. From our standpoint, the first step is to take what I said was a deep dive to distinguish babies with and without the problem. I think we're getting to the point now where we can confidently say that babies that develop the problem have a slightly altered set of bacteria from infants that don't develop the disease. And so, the next question will be what to do about it, and that's something that has motivated a lot of research in my lab, not just in neonates that are critically ill, but older children as well, because older children in the pediatric ICU, for example, after a severe trauma or a real bad infection, will similarly develop massive changes in the colonization of their body by bacteria. In the last few years, we've been able to show how severe these changes are.

But the next questions are to first determine if they matter in terms of do they impact outcomes, and assuming that they do, which I think they do, what can we do about it? There are a number of very inexpensive ways to, quote, optimize the bacteria on the body and as well there's enormous amount of interest from the pharmaceutical sector to develop agents either to provide organisms or to eradicate others. There's quite a bit of interest in manipulating the microbiome right now.

Brian Martin: Can you speak a little bit, Mike, about your colleagues across the country that are also doing this work? Are you part of a national ... is there a national consortium of pediatric surgery that the that's working on NEC? Can you speak about any inter-institutional work or insights that you've shared with your other colleagues?

Mike Morowitz: Just in the few years a consortium dedicated to necrotizing enterocolitis has been initiated and it's really working on a shoe string budget at the moment, but we are very passionate about the fact that this is a disorder that doesn't tend to get the exposure that some other equally important conditions do. We do think that it would benefit children by bringing attention to it ultimately so that more research can be conducted, some of which is really amazing molecular 21st century research, but other aspects are really sort of low costs, common sense interventions such as providing hospitals with support for lactating mothers so that they can develop the supply of breast milk that's

needed to feed infants, which is really quite an understudied problem in the setting of preterm birth.

Brian Martin: Yeah. I've had some exposure to the milk as medicine concept and the importance of building that type of infrastructure at this hospital and other hospitals to encourage breastfeeding wherever appropriate or possible for at-risk children.

Mike Morowitz: UPMC and Children's Hospital have been very supportive in an initiative to support the use of donor human milk, as well. That they deserve a lot of credit in that regard because milk donated from healthy lactating mothers is also effective in reducing the incidents of this problem and probably has other understudied benefits as well.

Carolyn Coyne: Yeah, so you mentioned that the sort of bacteria that comprise the microbiome in infants with NEC, as well as much older and children that are in the ICU, you see the similar shifts sort of in species. Why is that? Is it treatment related? Is it sort of the body's response to some sort of trauma, infection as you mentioned before? What do you think actually causes that?

Mike Morowitz: Yeah, well this is the topic that motivates me the most and it might be a little bit of a cop out, but it is multifactorial to say that. I think that's one reason why this particular problem has been harder to study. Specifically what I mean by that is there are so many reasons why the microbiome becomes altered during critical illness, ranging from just obvious factors like the fact that care providers are touching the patient, and you're not used to being a necessarily touched by these people, and that there will be a transfer of organisms.

Also, you can't necessarily eat. Eating is probably the single most important determinant of the microbiome, and when you can't eat and you're receiving intravenous nutrition, that'll be a major change there. Antibiotics, we mentioned, and as well there are other medications that might be needed to suppress the immune system, for example, and that will have unintended consequences on the bacteria. I think it's, as I mentioned, becoming clear that these changes take place and I think what jazzes me up is thinking about how to develop treatment plans to rescue the microbiome, so to speak. It's a good chance that what's effective for person won't be effective for another person.

Carolyn Coyne: It sort of answers a bit of a naive question, of course, that popped into my head as you were discussing this as well. You know, you see microbes or probiotics on the shelf in lots of different supplements. Why can't you just give them the bacteria that they're lacking, let's say, and is that something that you see as a potential future therapeutic, or what are sort of some of the technical limitations perhaps if that?

Mike Morowitz: Yeah, so probiotics is one of my least favorite things to talk about, so thank you Carolyn for bringing that up.

Carolyn Coyne: I assumed as someone whose studied the microbiome, that it might be.

Brian Martin: Thanks for going there, Carolyn.

Mike Morowitz: That's the third rail of microbiome science.

Carolyn Coyne: Exactly, right.

Mike Morowitz: Probiotics is a really interesting topic and what the term means is the administration of live organisms that have health benefits. A very interesting fact is that the probiotic industry hasn't been very well or tightly regulated over the past 100 years or so since the concept was first originated. At the moment, just about any company can say that they have a probiotic formulation with health benefits, but it's very, very clear that some do have benefits and some don't. I think another great challenge for the next 10 years is identifying, really with some rigor, which organisms, what dose to use, again, whether one formulation of probiotics might be helpful in one group of people but another would be better for another.

It's somewhat complicated, because when you ask somebody to swallow a pill with some probiotics, much of it may not even survive the stomach, which is a harsh, acidic environment. It really needs to be studied better. I will say that the safety profile of probiotics is quite good, very, very few adverse events in published studies, but at least in children's hospitals and especially in neonatal ICUs in the United States, there has been great reluctance because of potential safety problems to administer live organisms to a very fragile infant. But in other parts of the world, in Asia and Europe, a number of places have studied large studies of probiotics in newborns and the results have been mixed.

Brian Martin: One other question about the, the diet-based interventions, how receptive have your ICU colleagues in the pediatric ICU world, been to these to your investigation and changing conversation in regards to nutritional management? You know, longstanding probably as your role as a pediatric surgeon, the knowledge about nutrition and wound healing, but specifically in the concept of evolving, positively evolving a microbiome. Can you tell us a little bit about how interdisciplinary work is there?

Mike Morowitz: It's going really well, but it's definitely an in, in its early stages. This is something else that I'm trying to draw attention to and specifically, I mean, I happen to know that both of you host enjoy eating nice food and trying interesting types of meals. One thing that has bothered me for quite a long time is that when we have patients in the hospital that arguably are in the greatest need for a well-balanced nutritious meal, the options for providing them nutrition are unacceptably poor.

Typically, various hospitals have had contracts with companies that provide formulas for nutrition, and those contracts have been in place for decades, and

those formulas have done a lot of good for people of all ages, but it's my feeling that it's time to modernize our approach to nutrition. Specifically, I think that it's becoming increasingly possible to provide real food, whether blenderized or pureed, to patients that can't eat. Now, this doesn't necessarily apply to newborn infants, of course, but but to older people in the hospital. That's something that we'd like to develop over the next couple of years. That too has a major microbiome angle, because when you provide a real foods such as plants and vegetables, you promote the growth of the body's own probiotics, for example, without actually administering exogenous organisms.

Carolyn Coyne: Well, this was really interesting, Mike. Thank you for joining us.

Mike Morowitz: Thanks for having me.

Brian Martin: Thanks very much for your time, Mike.