How COVID-19 impacts gut health with Ken Cadwell, PhD & Jonas Schluter, PhD [Podcast]

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AMA Update

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In today’s AMA Update, Jonas Schluter, PhD, assistant professor at the Institute for Systems Genetics and Department for Microbiology, along side Ken Cadwell, PhD, the Recanati Family Professor of Microbiology at NYU Langone Health in New York, share findings from their study on the impacts of COVID infection on gut health. AMA Chief Experience Officer Todd Unger hosts.

Speakers

- Jonas Schluter, PhD, assistant professor, Institute for Systems Genetics and Department for Microbiology, NYU Langone Health
- Ken Cadwell, PhD, Recanati Family Professor of Microbiology, NYU Langone Health

Transcript

Unger: Hello and welcome to the AMA Update video and podcast series. Today's topic is our gut's microbiome and its connection to COVID. I'm joined by Dr. Ken Cadwell, the Recanati Family Professor of Microbiology, and Dr. Jonas Schluter, assistant professor at the Institute for Systems Genetics and Department for Microbiology. Both are calling in from NYU Langone Health in New York. I'm Todd Unger, AMA's chief experience office in Chicago. Dr. Cadwell, Dr. Schluter welcome.

Dr. Cadwell: Good to join you.

Dr. Schluter: Yeah, thanks for having us.

Unger: Well, this topic, you see it everywhere in the papers these days. And I didn't actually hear the term "microbiome" until about four years ago. But now it has a great deal of interest as we read about the gut's effect on overall health.
But this issue around COVID is new. We're going to get into that. But, Dr. Cadwell, let's start with you. Why don't you give us just a little bit of background about the connection between our gut's microbiome and our overall well-being?

**Dr. Cadwell:** Yeah, so the gut microbiome refers to these trillions of microbes, many of which are bacteria that colonize and live in our gastrointestinal tract. And these are not only abundant, there's many of them. But they're pretty diverse and they have different types of activities. So they're constantly communicating with us and releasing things and taking up nutrients, right?

And so that has a couple consequences for our physiology. Most of it is good, actually, in a healthy person. So one of them is digesting food. They help us get nutrients out of our diet.

And the other one, which is most relevant to what we're talking about today, is their role in promoting immunity. And so they not only communicate directly with our immune system and the cells of our bodies but they also communicate with and block infection by disease-causing microbes, like nasty bacteria.

**Unger:** Dr. Cadwell, maybe I'm imagining it. But I am reading a lot and seeing a lot more about the microbiome and its impact on health. Why am I seeing so much more today?

**Dr. Cadwell:** I think a large part of that is that it's a relatively new field. And, well, we first had to do is to figure out what's there. And that took a lot of effort and a lot of technological innovation.

So, first, you have to make the dictionary or encyclopedia. And then you can start figuring out what these bacteria and other microbes are actually doing there. And we're now seeing a lot of these studies really take off that are making progress and, thus, more molecular understanding of the microbiome.

**Unger:** Dr. Schluter, what happens when the microbiome gets out of balance? How does that happen in the first place? And how would you even know if your gut was unhealthy in the first place?

**Dr. Schluter:** Yeah, that's a very good question. And, of course, the factors that lead to what we call dysbiosis, which is when, as you said, the bacterial populations are out of balance. Those factors are still subject to ongoing research.

But there is a recurrent pattern that we observe. Many factors associated with our industrialized lifestyle do contribute to changes in the microbial populations. That includes, of course, first and foremost, also dietary changes that lead to shifts relative to other populations.

But the most striking signal comes repeatedly, of course, from antibiotics. When we take oral antibiotics, these medications are targeting bacteria. They kill bacteria and they also kill these bacteria...
that are normal residents of our flora.

**Unger:** Well, both of you were recently part of a study that examined how COVID infection affects our gut. That was a kind of a new thing to read—or vice versa, of course. I want to talk about that.

How did you first become interested in studying that connection between gut health and the microbiome? And what were the kind of key questions that you were looking to answer? Dr. Schluter, why don't you lead off?

**Dr. Schluter:** Yeah, so my lab has focused largely on studying cancer patients and the relationship between the microbiome and their immune system. But one thing that we've learned from cancer patients is that dysbiosis, when the bacterial populations are very different from what we see in healthy individuals, can lead to detrimental effects downstream. And one of the most striking ones is when gut bacteria translocate from the microbiome into the bloodstream and cause a secondary infection.

Now, this is possible in cancer patients because their microbiome is very disturbed, the gut epithelium is leaky and the immune cell populations in the blood are very low. So they have very little to fight a bacterium that translates into the blood. And then in learning that during COVID, in severe cases, early on, we see a decline in immune cell populations circulating in the blood.

And knowing that, of course, these patients are also severely sick and have dysbiotic microbiomes, we were wondering if a similar thing could be observed, if there exist a similar risk to COVID patients that gut bacteria could translocate into the bloodstream.

**Unger:** Let's say there are other kind of pre-existing conditions that have affected someone's response to COVID. Is it the case that COVID is causing these disturbances in the microbiome or somebody susceptible because there is an issue already pre-existing with the microbiome?

**Dr. Schluter:** In part, of course, that is a very good question. You're asking a chicken and egg problem here. Is it that the disease leads to a dysbiotic microbiome? Or is it that the dysbiotic microbiome favors more severe disease course? And that is exactly what we try to address also with our study.

**Unger:** Dr. Cadwell, let's talk about the study. How did you go about doing this research? And what did you find?

**Dr. Cadwell:** So we took a two-pronged approach that allowed us to both demonstrate the relevance to humans and the actual COVID patients but also try to address this exact question that you were asking, Jonas, about the chicken and then the egg, what's causing what. So we took both an approach using animal models and also direct sampling of human specimens from patients who were
hospitalized with COVID-19.

And with the animal studies, what we're able to do is to restrict our analysis to just the effect of SARS-CoV-2 infection. So we take these mice. We infect them with the virus. We don't give them antibiotics or they don't get the cafeteria food from the hospital. All they see is the virus.

And when we did that, we saw these big changes in the composition of the microbiome, this dysbiosis that Jonas mentioned earlier. So because that's the only manipulation we did to the mice, we know that the virus, in principle, can affect the microbiome without other factors being involved.

**Unger:** So, Dr. Schluter, when you switched to looking at patients where maybe you don't have that same level of control, what did you see there?

**Dr. Schluter:** Yeah, exactly. So Ken's mouse model has shown that the virus alone can lead to changes in the microbial populations. And when we then went and studied the microbiome in patients, we saw a similar shift in the microbiome. We went to two hospital sites and collected stool samples from patients that are diagnosed with COVID-19, and then we sequenced those stool samples and profiled the bacterial populations.

And then we see sometimes usually rare bacteria expand in these samples. So bacteria that are normally in low abundance or perhaps not there at all expand in these populations, in these samples from these patients. And that is reminiscent of the same patterns that we saw in the mouse model but perhaps even stronger in these patients.

So some patients have really entirely depleted microbiomes, where there are single species, perhaps the only ones left over, in their microbiome. And that is likely due to a combination of effects, where both the viral infection and the antibiotic treatments that these patients received contribute to this dysbiosis.

**Unger:** Dr. Schluter, translate then what you've found. What is most significant in your mind about that outcome?

**Dr. Schluter:** Exactly. So going back to our original hypothesis that similar to what we have learned from other hospitalized patient populations, in particular cancer patients, that the microbiome, when dysbiotic, can be the source of secondary infections. We went and looked for that in these patients.

Now, it's important to know—and that's why the study is significant—the leading cause of death among hospitalized COVID patients right now is nosocomial infections, hospital-acquired bloodstream infections with bacteria. And what we did then is to identify that the gut can, indeed, be a source of these infections. And we did that by identifying the similar DNA sequences in the bloodstream from bacteria isolated from the bloodstream with the DNA sequence sequenced in the stool sample from


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the patient.

**Unger:** Well, now that you've made that kind of connection, looking forward, what do you think you want to investigate more? What are those key questions that still need to be answered?

**Dr. Schluter:** Yeah, absolutely. In my lab, we are very interested in understanding the ecological interactions between these bacteria to understand and predict perhaps, when does dysbiosis happen? How does that happen? And can we stop it from happening?

You can think of it really as a garden almost. We try to be gardeners of that ecosystem, understanding who eats whom, who benefits from whom and then perhaps exert some form of control. And one of those measures which we have, one of those means by which we could perhaps exert control would, of course, be dietary interventions.

And we're studying in collaboration with Memorial Sloan Kettering, for example, the effect of dietary contributions to the development of dysbiosis during antibiotic courses. And we see in unpublished data but hopefully out soon that dietary intake of sugars, simple sugars can actually exacerbate the damage that antibiotics cause.

**Unger:** Well, that certainly will give, I guess, new meaning to gardening. And we think about the potential for that, Dr. Cadwell, as we think about this and just hearing that factoid there about the effect of sugar, for instance. When you think about trying to give a patient who's had COVID advice about how to heal their guts, is there anything that physicians should be telling patients like that?

**Dr. Cadwell:** So that's a really good question. The microbiome field is exciting but it's relatively young. We've known quite a lot about other organs in our body, like the liver. But our understanding, at least at the molecular level of the microbiome, has really come to fruition most recently. So our ability to manipulate the microbiome and the microbiome-targeted therapies is quite rudimentary at the moment.

However, what we can do—and this is by far the most effective thing to do—is to prevent injury to the microbiome. And I think that's one of the things that our study really reveals. If you take yourself back to early 2020 at the height of the pandemic, especially in New York City when the hospitals were overwhelmed and we didn't know too much about COVID-19, the doctors and the nurses were pretty desperate and doing everything they can to try to prevent illness. And that included using a lot of antibiotics.

Now, we actually know a little better. And we're hoping that we could target the patients with the right antibiotics or maybe even not give antibiotics when there's no danger of a bacterial infection. And that will prevent a lot of the downward spiral that Jonas just described to you.
**Unger:** Dr. Schluter, any additional kind of perspective, whether it's in relation to COVID, either the prevention around damage to the microbiome or the healing part of that that you have?

**Dr. Schluter:** Yeah, I would like to echo what Ken has said that there is a level of humbleness that is required with respect to the microbiome. It is a young science. And we need much more causality to really turn the microbiome into a therapeutic target, which is the hope and a huge promise on the horizon. And I'm personally convinced that there will be a future of microbiome-focused medicine. But we are still in the early stages.

Now, where do we have certainty? We do have certainty exactly in what Ken said that antibiotics do harm. And unless there is a specific need to change the microbiome, you probably want to keep it as is.

And with that in mind, I think an important message that our study contributes to as well is that antibiotic treatments do not come for free. They do cause collateral damage. And it's an important public health message to limit the usage of it as much as that is possible.

**Unger:** Do you think, at least according to my Instagram feed—and I may be peculiar. I see a lot of stuff going through there about probiotics, prebiotics, postbiotics—are we kind of over our skis on that relative to the research? Or do you think there's a lot more forthcoming? Dr. Schluter.

**Dr. Schluter:** Well, I would say that this demand shows that there's a real need to fill this need. People know intuitively that the gut matters a lot for their health and they are somewhat desperate. Now, whenever there is a huge need and desperation, opportunity arises for, more or less, honest contributors to this need. And I would leave it at that.

I think there's a lot of very good science happening. And then there is some stuff happening that is exploiting this need. I think there is hope on the horizon.

**Dr. Cadwell:** And if I may add just one thing, I completely agree with what Jonah has said. We know from the limited success of therapies like fecal microbiome transplants that are used to treat C. diff colitis, that targeting the microbiome can improve health. And the elements are there but we're still trying to figure out the rules.

And I think a lot more research needs to be done in order to make the microbiome accessible to the type of surgical precision that you need to really treat these very complex diseases. There are no low-hanging fruits. And it's going to just take some very inquisitive minds and hard research in order to figure it out.

**Unger:** Well, we'll look forward to seeing that research as it develops. And I want to thank both of you for joining us today and giving us your perspective, Dr. Cadwell, Dr. Schluter. Thank you again.
we'll be back soon with another AMA Update.

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