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SPEAKER 1: Today we have the great pleasure of welcoming Dr. Ari Grinspan as our Grand Round speaker. Dr. Grinspan received his medical degree from the Albert Einstein College of Medicine, and completed his internal medicine training at New York Presbyterian [INAUDIBLE] Cornell Medical Center.

He completed his fellowship in gastroenterology here at Mount Sinai, where he is now assistant professor in the Department of Medicine. Dr. Grinspan pioneered the Mt. Sinai Fecal Microbiota Transplant, FMT program to treat C. Dificile infection, which he has developed into a leading referral center for the tri-state area.

He has established himself as an expert in the field of FMT. His research focuses on the mechanism and clinical utility of FMT in C. Dif and IBD. He is a recipient of numerous awards, including the Solomon Silver Award in Clinical Medicine, and the beloved mentor to many fellows, residents, and medical students, including myself. Please join us in welcoming Dr. Grinspan.

[APPLAUSE]

ARI GRINSPAN: Thank you for having me. I titled this talk, *The Hitchhiker's Guide to Fecal Transplant* because I really loved that book growing up, and thought that there was a very good quote that Douglas Adams says. I just change it just ever so slightly. All you really need to know for the moment is that the microbiome, or my universe, is a lot more complicated than you might think even if you start from a position of thinking it's pretty damn complicated in the first place.

A lot of the things I'm going to tell you, there's a lot of basic science behind it that we don't even know if it's true, if it's real, or if it's meaningful. But I'll help sort of guide us through the process. So this is our microbiome. All that stuff that's floating around in our colons and how it interplays with our colonicytes, it's unbelievable the interactions and how important that is for our health, and, when it goes wrong, disease.

So the objectives and outline of our talk is to describe the role of the gut microbiome, to identify diseases associated with this meiosis, describe the

pathogenesis of C. diff. And that's what I'll be focusing the main portion of this talk. As well as assessing the role of FMT in the treatment of C. diff. And then discuss new potential targets on the horizon.

So our microbes matter. The 20th century was all about destroying these things, Cholera, Shigella, E. coli, Salmonella. You see a bacteria. We need to kill it because it's going to hurt us. And we got really, really good at doing that. Very few of us will die of an infection. We are very good at preventing that.

The problem is-- and this is our problem of the 21st century-- is the commensals, the good, the healthy bugs that populate our body. They provide the traits that genetics have not provided us. And it comes in sort of three main categories, if you will, of why these things matter. And one is metabolism.

And the most important thing-- and we'll get to this later in the talk-- is the importance of the commensals in deconjugating bile acids from primary bile acids to secondary bile acids. I ignored this for a long, long period of time. But as I'll show you, I think that for at least C. diff this is one of the most important things that our microbiome does.

They also create vitamins. They regulate all these different pathways that we need to live our lives and be healthy. They also help with our immunity. They help understanding, and help to develop the gut associated lymphoid tissue, when to fight, when to relax. What is something that we need to be concerned about? And one of the things that we don't need to rev up our immune system. Because when our immune system gets revved up because of a bad interaction with a bug, that's called Crohn's disease or ulcerative colitis.

And then there is the colonization resistance. So we have this set of microbes that colonize our gut. And they help keep foreign invaders out. These are the same bugs that we grew up with. So by the time we're about the age of three, the gut microbiome becomes an adult. It becomes essentially finalized. And the majority of those bugs remain in your gut until you leave this good, green Earth. And they help prevent other things from coming in.

So let's identify some diseases that are associated with this biosis. Well, you name it

and there is some association with the gut microbiome. The important thing to remember here is that just because there is an association does not mean that changes in the microbiome are causative. So association does not mean causation. We need to do a lot more work to figure out if changes in the microbiome are actually important for all of these different disease processes.

C. diff, not Clostridium difficile anymore. Now, it's Clostridioides difficile. But we can still call it C. diff. Somebody was going to change it to something with a P. diff. So it would have been P. diffi, or something like that, which I thought would've been pretty cool.

C. diff is a perfect example of when things go wrong in the microbiome that leads to a disease. C. diff, it's the most common cause of health care associated infection in US hospitals. In 2012 there was 450,000 cases and nearly 30,000 deaths that were attributed to C. diff. And it costs a lot of money. $5 billion plus in excess health care costs because of this infection.

Brief review of C. diff. Gram positive rod. It forms a spore. And it is toxin producing. And it's the toxin that leads to the colitis. It's the toxin that is toxic. The bug itself, the bacterium itself, not a big deal. But when it creates the toxin, that's the problem. And then we know the symptoms. Diarrhea, fever, abdominal pain. Pseudomembranous colitis, which I'll show you, and toxic megacolon are feared complications from this infection.

This is my favorite slide. If you guys don't have this laminated in your coat pocket, you should. I have a whole stack outside that I can hand out. The Bristol Stool Chart. We may know what diarrhea is, but our patients certainly do not. This is diarrhea. And another way to potentially explain that is if you should defecate into this cup, would your stool take the form of the cup, or would it have its own form within the cup?

[LAUGHTER]

Ah.

Risk factors for C. diff. We know about the exposures. We know about the host factors. Things to remember is gastric acid. It probably helps to prevent C. diff from

getting down further into our gut. So the unnecessary PPIs, we should be stopping those in our patients.

Clostridioides difficile is difficult to culture. Hence, difficile. And so how do we actually detect C. diff? Well, we have indirect measures of whether the C. diff is present or not. We use the GDH antigen. And this is not specific to any C. diff. It's everywhere, every single C. diff. The ones that produce toxin, the ones that don't produce toxin make this antigen. So if this GDH is positive, it just says the bacterium is present.

Again, the toxin is what causes the clinical scenario of a C. diff infection. You have to have toxin present in order for you to have all of those symptoms. The problem is that it can be sometimes difficult to detect whether it is there or not. It has a lower sensitivity than the other two, which I'll talk about in a moment. But it is the most specific for the infection which is C. diff.

And then there's this whole NAAT, Nucleic Acid Amplification Test, also known as PCR. This has the highest sensitivity for detection of the bacteria. But it's just looking for the gene that encodes for the toxin. By itself this cannot distinguish between colonization with a bacteria or infection with a bacteria.

In medical school we took nasal swabs, and we cultured them. And I had MRSA in my nose. So did half of my medical school class. Did you treat me for my MRSA infection of my nose? No. Just like you shouldn't treat colonization with C. diff.

So how do we distinguish that with these indirect measures? Well, we have this 2-step hypothesis, this 2-step algorithm. Step one is you send the GDH antigen. Again, sensitive. Does not distinguish between toxigenic and non-toxigenic strands. So a positive result by itself is not enough to really tell you that much.

You combine that with the toxin, which is, again, the most specific test for an infection of C. diff. The problem is that it degrades in a couple of hours if it's left out at room temperature. You've been to our emergency room. How long do you think those stool specimens stay in room temperature for? OK.

So if you get a concordant result, meaning both of these are positive, you're done. C. diff infection. If they're both negative, you're done. C. diff is negative. There is no

bacterium. There is no toxin.

The problem is that when you get a discordant result. And that is always going to be GDH positive, toxin negative. Then they reflex to the PCR. And this is what we do here at this institution. We reflex to the PCR. And we use the PCR as the tiebreaker. If the PCR is positive, you get a positive result in Epic.

The problem is is that that's all you get. You get a positive result. They do not provide us the information as to why was that test positive. Was it because the toxin was positive? And my take on this is that that is the most important thing. Or was the toxin negative? GDH was positive. So they reflexed to the PCR.

So what you can do is if you have a concern that I don't know if this patient has a real C. diff infection, you can call the micro lab and ask them to tell you what made that test positive? Because if the patient was toxin negative, that made it unlikely to be a true C. diff infection.

OK. Now, treatment for C. diff. These are the new guidelines from the ID Society of America. They classify that as non severe, severe, and fulminate. Severe is anyone who has a white count greater than 15, or a creatinine greater than 1.5 that is attributed to the C. diff. It turns out in terms of treatment, it doesn't make a difference if your patient has non severe or severe. You're going to treat it the same way.

And I want to highlight something that you'll see is missing from here. Metronidazole is out. We don't use that to treat C. diff anymore, except in the patients who have fulminant C. diff. And the reason why we add IV metronidazole in those who have fulminant C. diff is you've got to make sure that the antibiotic is getting to the colon. And in the fulminant patients, those patients are distended. They most likely have an ileus. You're giving them the oral vancomycin. It may not be getting to where it needs to go. So you add on the IV metronidazole, and then can consider adding vancomycin enemas in that scenario. Specifically, again, you gotta get the antibiotic to the colon.

Recurrent C. diff. This is a scourge to our patients, but it's great for business. C. diff recurs within eight weeks. That's the definition of recurrent C. diff, within eight weeks. Symptoms must resolve between episodes. And the meantime to recurrence

is about three weeks.

If you get C. diff once, there's a 20% chance it comes back. If you get C. diff twice, there's a 40% chance you get it another time. And if it comes back three times, there's about 2/3 chance that you're going to get that infection again.

So let's describe the pathogenesis of Clostridioides difficile. But first, let me just have a-- ah. OK. C. diff. Why does it come back? Well, we think it's because of the microbiome.

And what we think is that you get less diversity, less richness of the microbiome as you go further along with this recurrent C. diff infection, because how do we treat C. diff? Antibiotics. So we're reducing the diversity of that rich microbiome, which I showed you before, is what prevents C. diff from being there in the first place.

And so if you look at patients with recurrent C. diff over time, they have just low levels of C. diff. And so one way that I like to think about it, cause I love biochemistry in high school, you need activation energy to go from one stable state to another. You have to provide some energy to that system to change something. Well, the same thing can be said for the unhealthy state of recurrent C. diff.

So here's this healthy patient. At state R1 they have a good, healthy, rich microbiome. And they get some infection for which they get antibiotics. The antibiotics have enough activation energy to kill enough of that healthy microbiome to push you to state R2, disbiosis, where there is just lack of diversity, lack of richness in the system.

Well, how do we treat C. diff? Well, we give more antibiotics. And antibiotics, by themselves, do not have, most of the time, or some of the time, enough activation energy to push you back to state R1. So what? What do we have to do?

Well, we can do a fecal microbiota transplant. We could take stool from a healthy donor, infuse it into a patient with C. diff. And that has enough activation energy to push them to a healthy state. And it works 90% of the time.

From the 10,000 foot view, it appears that we are just putting all this healthy stuff in there. And it's staying. And it's doing the job. So I'm shocked. This is a 10-year-old

slide. This is what a patient looks like with disbiosis, this recurrent C. diff. This is what the patient's donor looks like.

This healthy swab of orange is bacterioides. So we've transferred this microbiome to this patient. And this is what the patient looks like two weeks later, very similar to what the donor looks like. The interesting thing is if you follow this now cured patient for about a month after the fecal transplant, this is what they look like now. They have similarities to the donor, but a little bit different.

What's interesting is that what we've shown here is that some of these bugs that were transferred to the donor can last up to five years in the patient, which is pretty wild. So I had a universal donor in 2013. And this donor cured 29 consecutive patients. I wrote her an unbelievable letter of recommendation. She is a star inside and out.

Her bacteria are still in about half of the patients that she delivered her stuff to. And they are all in medical school now, which is unbelievable. OK. So this is the 10,000 foot view. This is what we thought is going on.

We didn't know exactly what was happening. But we say, OK. Yeah. Sure. It's that we just put the healthy bugs in, and it does its stuff. And that cures C. diff. Well, over the past couple of years there has been a lot of challenges to that sort of global hypothesis. This study, which was published two years ago now shocked me, stunned me. It took five patients with recurrent C. diff. And they filtered out all the bacterium. Nothing grew. There was no bacteria. It was a sterile transplant. And they took that sterile stuff, and they gave it to five patients with really multiply, recurrent C. diff, four, five, six episodes. And after two weeks of every finished course of antibiotic, came right back. But after they got to sterile fecal transplant, all five were cured for more than six months.

What was the active ingredient in that sterile stuff that cured them? So the interesting thing about this is that to date I have not seen anybody replicate this study. So hm, OK. What they did show is that the virome changed in these patients dramatically post transplant.

So there was all this thing about bacteria phages. Bacteria phage is a virus that attacks not a human. It attacks a bacteria, and it kills a bacteria. Well, perhaps the

reason why these patients were cured is that we're transferring bacteria phages from the healthy donor to the recipient.

But then people started talking about, well, the virome. Well, what about the fungome? And it turns out that Candida, presence of Candida in the recipient can predict failure of FMT, suggesting, oh, maybe we should be looking for Candida. If it's there, destroy it. Kill it. Knock it down. And then give a fecal transplant. Interesting.

What's something that we've known for a long time is the importance of bile acids. So like I told you in one of the first couple slides, a major role, at least for C. diff, of the microbiome is it conjugates the primary bile acids that come down the intestinal tract into the colon. And it conjugates them from primary to secondary bile acids.

Well, if you look at patients with recurrent C. diff, if you look at their intestinal microbiome, or the milieu of the bile acids, they're all primary bile acids. Well, it turns out if you take a C. diff spore, and you drop it into a milieu of primary bile acids, the C. diff germinates. You get toxin production. You get more C. diff.

If you take the same C. diff and you drop into a milieu of secondary bile acids, the C. diff stays in spore form. You don't get toxin. You don't get mass production of C. diff. So if you look at patients prior to FMT and then after FMT, you can see a dramatic change in the bile acids. An interesting association.

This was just published in *Gut* just a couple of weeks ago. And I think that this is the mechanism of action of why FMT works. Bile salt hydrolases. These are the enzymes that conjugate bile acids from primary to secondary. And so bear with me as I try to explain the basic science here.

They took a milieu of C. diff. And they dropped in primary bile acids. And they looked to see how much C. diff grew. And sure enough, this is their control. If you take the C. diff, you put it into all these primary bile acids. Boom. You get C. diff growth. You get germination.

They took mice who had a successful fecal transplant. And they looked at the bacterium in the mice that made these bile salt hydrolases. And they took out these one, two, three, four bacterium. And they grew those four individual bacterium in

the milieu with the primary bile acids. And then they dropped in C. diff. And you got zero C. diff growth. It stayed in spore form.

So then they were like, OK. Well, maybe it's not the bile salt hydrolase. Maybe it's something to do with the bacterium themselves. So then they took the gene for the bile salt hydrolase. They took it out, and they put it into the genome of an E. coli. E. coli by itself has no effect on C. diff. And they showed that.

If you take E. coli and you put it into a milieu of primary bile acids, and then drop in C. diff, boom, you get C. diff germination and C. diff growth. But if you take the E. coli with high levels of the bile salt hydrolase, you do not get any C. diff germination.

And so what this suggests, and I think that this is true, cause we've seen it in other studies as well, is it's all about the bile acids for recurrent C. diff. So this suggests that maybe we don't have to do a full spectrum fecal transplant to cure C. diff. Maybe all we need to do is just find the right bacterium that create bile salt hydrolases, and just put that. So a more narrow spectrum approach.

Now, you could argue, well, why don't we just pump the colon full of secondary bile acids? That's called ursodiol. We've tried that. It does not work. Cause you have to take massive doses of ursodiol to affect the surface area of the colon. You just can't take that much.

So what do I tell my patients? Am I going to go into the bile salt hydrolase? No. That's crazy town. I paint a picture of a good, healthy, green lawn. And I say each one of these blades of grass is a healthy bacteria in your colon. Well, you got C. diff. You got some diarrhea.

Ah. You got weeds in your colon. And I've thrown vancomycin. I've thrown fidaxomicin. But those weeds keep coming back. So we need to resod your soil. We need to repoopulate your gut with healthy bacterium, get you back to that healthy, green lawn.

And it works. No matter how you deliver a fecal transplant, nasogastric tube, flex sig, colonoscopy, enema, crapsules, whatever it may be, it works. And it works about 90% of the time. It's been shown over, and over, and over again.

This was just published recently, comparing vancomycin versus fidaxomicin, versus a couple days of vancomycin, and then a fecal transplant. And, again, small numbers here. Fecal transplant dominated. It just worked the vast majority of the time, where our standard of care, vancomycin and fidaxomicin didn't do the trick.

Now, what about FMT in some special populations? Being here at Sinai, we have a lot of inflammatory bowel disease patients. We have a lot of patients who are immunocompromised.

So this was just put together. This was part of our group, along with at the Brigham, in Indiana, and at Brown, where we took a prospective study of 50 patients who had active IBD and C. diff. And we gave them a fecal transplant to cure their C. diff.

There's been some debate as to whether FMT works in this population, as well as does it actually worsen the IBD? Well, it turns out that you get a 92% cure rate by doing a single FMT in this population. And there was no worsening of the underlying IBD. In fact, the majority of the patients two to three months after fecal transplant had improvement in all of their scores, because you eliminated this recurrent C. diff issue.

What about immunocompromised patients? There's been a number of case series, cohorts talking about, well, is this safe? Is it effective? And this was a review that was published within the last year. And it took a look at 303 patients who were immunocompromised. The majority were on immunosuppressants. That's an anti-TNF. That's a steroid dose greater than 20 milligrams per day. That is calcineuron inhibitors, mTOR inhibitors, anything that can suppress the immune system, patients who had a solid organ transplant, an active malignancy, undergoing chemotherapy, bone marrow transplant, HIV, and they saw an 87% cure rate with a single FMT. 94% if they got a second FMT. And there was no significant safety signal seen in these patients.

Where is our chief? Ah. Chief. Our chief put together some interesting data, looking at patients who have had a single recurrent episode of C. diff. So let's say you got your C. diff. It came back. Now you have C. diff again. What do you do?

Well, here are the options. You could get vancomycin. You could get fidaxomycin.

You could combine vancomycin with bezlotuxumab, which is an anti C. diff toxin B antibody. The idea is that, well, if you combined the toxin, you might be able to prevent them from having a recurrent infection.

So those three options. Or FMT via capsules, or FMT via colonoscopy. And for a first recurrent episode-- this is now essentially their second episode of C. diff, FMT, whether it be a colonoscopy or capsules, was far superior in its cost effectiveness analysis compared to any of the other standard approaches. And not even close.

So what are the current indications for treatment or using FMT? Well, you need to have at least three episodes of non severe C. diff for current guidelines. An episode of severe C. diff that does not respond to standard therapy for at least three to five days, or those who have fulminant C. diff. Those are the ones in our ICUs. And we're going to talk about these patients, cause I think it's very important to know what we're supposed to be doing with them.

From an outpatient perspective, you continue the antibiotics until two days beforehand. We bring them in for a colonoscopy. And we give them the stuff. And this is the data that we have of 250 patients at Mount Sinai, overall an 87% success rate. And this is for all comers after a single fecal transplant. That number goes up if they need multiple.

So again now, let's talk about the severe C. diff cohort. Again, these are the patients who have a white count greater than 15, a creatinine greater than 1.5, or they're in the ICU on pressers, intubated, ileus shock, whatever it may be.

This is a healthy, beautiful colon. You could drink coffee off of this colon. This is pseudomembranous collitis. This is really bad C. diff. This is what causes them to be systemically ill.

This is a normal abdominal X-ray. This is the X-ray of a patient with toxic megacolon. And important to remember for the residents what toxic megacolon is. It's a colon that's more than six centimeters dilated on abdominal imaging, and the patient is toxic. The patient is systemically ill. That's what vital signs are for. Vital signs are vital. If they have abnormal vital signs and you see this, you need to act quickly. OK.

When you see these patients coming to the emergency room, or you get consulted

on them, or what do you do? You call the surgeons. All right? The surgeons are terrified of these patients because of this data. 30% to 60% of them die if they go for a standard of care, or what part of the guidelines, standard of care, total abdominal colectomy. All the guidelines say, if you have a fulminant C. diff patient. Yes. Start the antibiotics. But part of the guidance is call the surgeon.

When you look at it, at least in this retrospective systematic review, 41% of those patients who are brought to the OR died within 30 days of that surgery.

Well, they tried to improve that. That was with a total abdominal colectomy. You go in. You get source control. You take out the colon.

Well, there's another approach. This was innovated a couple years ago, 2011 in Pittsburgh. And what they did is instead of going in and doing a total colectomy, they went in and they gave a diverting ileostomy. So they took a loop of the ileum, and they pulled it out to the skin. So essentially diverting the fecal stream away from the colon. And then they put a Foley antegrade into the colon. And they flushed the colon with eight liters of PEG, essentially a bowel prep. Right?

And then they infused vancomycin directly into the colon for 10 consecutive days. And this is the data that they found. Historically, at the Pittsburgh VA where this was developed, 50% of patients who presented with this died within 30 days. When they did this procedure, this diverting loop ileostomy and colonic lavage, 19% of them died. There was a significant mortality benefit.

This was very slow to catch on with the surgeons, cause the surgeon said, well, if I'm going to open up the patient, I'm just going to take out the diseased colon. Over the past five years there has been a significant increase in the amount of patients undergoing this particular surgery. And the data has sort of been hit and miss. They still have a very high mortality rate.

So what else can we do? Well, there's emerging data that these are exactly the right patients to get a fecal transplant. This was a cohort of patients in France. They had begun to dabble with using FMT for any C. diff. And it turns out that in this small cohort of patients, wow. Look. FMT works for anybody with C. diff. So they had a protocol where at this small hospital in France in Marseilles, any patient admitted with C. diff automatically got a fecal transplant, either two to four days of

vancomycin, and then they got a fecal transplant. And that was followed by two to four days of vancomycin.

And when they looked at their data, they separated them, looking back, at those who had non severe C. diff, and those who had severe C. diff. Severe C. diff was classified as white counts greater than 15, albumin less than 3, abdominal tenderness or abnormal imaging.

And when they looked at their data it turns out as the patients who actually did not get a fecal transplant, 42% of them were dead at 30 days. Those who got a fecal transplant, 12% were dead at 30 days. A number needed to treat of three to save a life. Whoa. That's some good stuff.

So there is this whole algorithm that has been developed. Monica Fisher out of Indiana gets credit for this. She is the one that has been pioneering at least here in the States.

So those who come in with fulminant C. diff, you give them appropriate antibiotics. vancomycin, IV metronidazole. And then if they do not get better within a couple of days, they're still on pressers, they still have a white count of 40, they're still in renal failure, you do a bedside flex sig. And when I say you, I mean me. We do a bedside flex sig.

And we comment whether or not pseudo membranes are present or not. No matter what, we're there. We're going to give a fecal transplant. OK. If pseudo membranes are present, we restart vancomycin only for two to four days afterwards. And we repeat the flex sig. And we give another FMT. We commenting whether pseudo membranes are present or absent. If they are present, restart vancomycin, and we'll repeat this again two to four days later. We continue this until pseudo membranes are absent.

And that is the protocol that we have. So let me show you. This is April 3. This is the rectum of a patient with pseudo membranous colitis in an ICU on pressers, intubated. This is fulminant C. diff, pseudo membranous colitis.

Well, what did we do? I hope everyone had their breakfast this morning. This is an FMT in action. If you haven't seen it, you're going to see it in three, two, one. There

it is. Magic.

Fecal transplant. There's really not much to this. Don't tell anybody that. OK. So we give 250 CCs of this fecal slurry, and directly into the colon. We restarted vancomycin.

So this was April 3. This was April 7. Again, we do a flex sig. And again, you see pseudo membranous colitis. We gave another fecal transplant. I'll save you the video. We restarted vancomycin. And this is April 13.

AUDIENCE: Whoa.

ARI GRINSPAN: Whoa. Exactly. I showed this picture for two reasons. One, you can see that the mucosa is healed. You don't see pseudo membranes. And you see solid stool. OK.

This is our data from Mt. Sinai, patients who had severe or fulminant C. diff. And we looked back to see those who got FMT compared to those who got standard of care.

Now, we actually have more numbers than this. But an issue was is that we wanted to make sure that every single patient that we included got standard of care antibiotic therapy. They were not on any other antibiotics. And they had a real 48 hours of vancomycin and IV metronidazole for the fulminant cases, and at least standard of care vancomycin for those who had severe.

So our numbers were a little bit smaller, because some of the patients actually didn't get appropriate antibiotics. And we're going to talk about that a little bit. 16 patients got FMT. 32 patients got standard of care. And there was really no major difference between these two populations. And this is the Charleston Comorbidity Index, which was about seven for both of these groups. That is a very high number, which means that these patients are at a very high risk of having something bad happen to them. OK.

When we compared the primary outcome, which was mortality in the hospital stay, only three patients who received FMT died. So 18.8%. As opposed to half of the patients who got standard of care. This is a number needed to treat of three to save a life.

Here's the interesting thing. Well, what was going on with those 32 patients who got

standard of care? Well, I only knew about four of them. So of the 32 patients who got standard of care, GI was consulted on four.

Two of those patients got better. So we didn't do an FMT. One of the patients had an ongoing bacteremia, so we didn't do an FMT. And one of the patients when we went to see the patient had perfed prior to our doing anything for the intervention.

28 of those patients we were never even told. We didn't even know about them. So something that perhaps we should be working on at our institution. And not just our institution, but others.

If you look at what happened to those patients that got FMT as opposed to standard of care, only two of the patients in our group had a severe adverse event. One had a perforation. One developed Klebsiella pneumoniae. When you look at the 32 patients who got standard of care, two of them perforated, and 12 of them had bacteremia after their episode of C. diff.

Now, Monica Fisher at Indiana has been leading the charge when it comes to severe and fulminant C. diff and using FMT. She has started a program, an inpatient program, where any patient who has severe or fulminant C. diff automatically triggers a GI consultation for a potential FMT.

When she started this shortly after 2012, there was a dramatic reduction in the hospital of C. diff related mortality and C. diff related colectomy. Unbelievable results. And we publish them in a very big GI journal in just a couple of weeks, suggesting that having an inpatient program saves lives and saves colons.

I don't want you to dwell on this slide, but this is something that we will be initiating here. We already have guidelines that talk about this, but nobody even knows that they exist. They're hidden somewhere on the antibiotic stewardship website. But we're going to make an initiative here to try to improve this, a quality improvement project, so we can help emulate what they're doing at Indiana.

Now, what stuff are we putting into patients' colons? Quick sidebar. Yesterday I'm in the office. I get a frantic phone call from my secretary. She goes, Ari, you have a potential donor on the line. I'm like, oh. So I get ready. I'm like, Dr. Grinspan.

And the woman on the phone says, I would love to be a donor. I'm like, OK. Now, I'm

thinking like, how much should I ask? I don't want to ask for too much. I don't want to ask for too little. What's the number? And she goes, I want to donate my stool.

You want to donate your stool? So not money, it turns out. No. No. Nothing like that. Well, if this was a couple of years ago, I would have gone to her home. I would have tested her. And I would have taken her stool, just like the *South Park* episode that was just shown the other week. Did you guys see that? It's called *Turd Burglars.*

Anyways, back in the good old days I would ask the patient, well, who do you trust? Whose stuff do you want to use? And then I'd screen that patient. I'd make sure that they were as safe as I could possibly imagine. And I would take their stuff. They'd have to give it to me on the day of the fecal transplant. So you guys know about white coat phenomenon. And can you imagine that you have to poop for me right now so I can save your friend?

[LAUGHTER]

I take that sample across to Icon nine. I'd be in the micro lab. And I'd make the dirtiest martini. I'd bring her back across into endoscopy, do a colonoscopy, and flush it away.

Well, the question is is who is the right donor? Can it be anybody? Perhaps. Maybe this should be our donor. Perhaps. I don't know. Perhaps somebody a bit more pious. Perhaps some holy sh--

AUDIENCE: Yeah.

ARI GRINSPAN: It turns out, it does not matter who the donor is for C. diff. It can be anybody. Everyone's stuff is essentially the same when it comes to eradicating C. diff. And now there is a stool bank in Boston that does all this for us. And that's what we are exclusively using here at Mt. Sinai.

It is harder to be a donor for open biome than it is to get into MIT or Harvard. Less than 3% of potential donors can make it through. Is this safe?

New England Journal of Medicine published this just a couple of weeks ago. There was an FMT. This was at Mass General where they had a bank. And they made capsules, and they were using them for not only C. diff, but for clinical trials. There

were two patients who received FMT from the same healthy donor. And those two patients who were heavily immunocompromised-- one of them had cirrhosis and was in a trial for hepatic encephalopathy, for which that patient was receiving FMT. Another patient was getting a bone marrow transplant, and was part of a protocol for it to prevent GVHD. Those two patients after the FMT came down with an extended spectrum E. coli bacteremia, ESBL, [INAUDIBLE] E. coli One of those patients died from that infection.

So the FDA, appropriately, put a big warning out. This was in June. That essentially stopped every single FMT clinical trial in the country until they could figure out exactly what was going on.

Well, it turns out that in January of 2019 the FDA said every single FMT stool for any clinical trial must be screened for MRSA, VRE, and ESBL E. coli among other resistant organisms. They did not tell people who had banked things before then to go back to those samples and make sure that they didn't have any of these bad bugs. So this group at Mass General, they didn't do anything wrong, but hindsight being 2020, that's what happened.

So the AGA, which is the American Gastroentrological Association and NIH have already been doing this 10 year follow up study, and which we are doing here as well. We're enrolling all of our patients in a 10 year follow up after the FMT to see what happens to them.

Now, to date, we haven't seen anything happen. But as I showed you, change in the microbiome has been associated with so many different diseases and conditions that hopefully we don't see anything in the future, but that's what we're looking at.

The FDA is grappling with FMT. They're trying to figure out what to do with this. They've labeled FMT a drug. So that means that it has to go under all of the rules and regulations that all drugs have to. You can't prescribe a drug without a label. There is no label for fecal transplant.

The FDA allows us to perform FMT for C. diff and C. diff only. Every other indication has to go through an Investigational New Drug application, an IND. So let's talk about some of those things that we're looking at, some of the new targets on the

horizon. Can FMT, can manipulation of the microbiome be used in other conditions?

Well, as I showed you before, there's been an association between all these conditions. But is that real? Is that a cause? Is that an effect? The bottom line is we do not know. IBD, Inflammatory Bowel Disease, this is the next target.

When you look at IBD, at those patients, this is a normal person. They have 80% of the bugs in their gut are what we consider healthy bacteria, bacteroides for [INAUDIBLE], and only 20% come from the minor phylum.

Well, if you look at IBD patients sort of across the board, that ratio is flipped on its end. And 80% of the bugs come from the minor phylum, and only 20% from the healthy phylum. What's interesting is that in every single model of inflammatory bowel disease, specifically every model of colitis, you can knock out all the genes that should lead to inflammation, but if you do not have bacteria, so if you have a germ free model, you do not get the colitis. You have no inflammation without the bacteria present.

When you have all of those genetic knockouts, and this is the model colitis, and then you put the bacteria back in, boom, you get this massive colitis, suggesting that the commensals, that bacteria are very important in IBD.

But IBD is not just a disease of disbiosis and of the bugs. There's genetics. There is environment. There is an abnormal immune response. So it is complicated.

But there have been four randomized control trials of FMT in inducing remission in ulcerative colitis. These two were published in 2015. And they used single donors. This one that was in Europe was not significant. This one in Canada was. 24% of those who got FMT were in clinical remission at eight weeks, compared to only 5% who got a placebo.

The interesting thing here is that if you look at these patients, it was one donor that seemed to have that effect, donor B. One Toronto Canadian, maple leaf, Molson drinking, I don't know.

The two subsequent studies didn't want to have this issue. So they pooled donors. They had four to seven donors per patient to try to capture the right stuff. And when you pool it all together, 140 patients were randomized to fecal transplant. 137 got

placebo. Overall remission-- and this was a strict definition. That means they were off of steroids, and their colons had improvement compared to prior. 28% of the FMT group met this condition. And only 9% who got placebo.

And the Mayo score is the way we categorize how much inflammation is in the colon. It's a zero, one, two, or three. Zero is perfect, like that picture I showed you before. 14% who got FMT had that in their colon, and only 5% who got placebo.

And these are what the pictures look like. These are two patients with ulcerative colitis. And after FMT, this is what their colons looked like. As a gastroenterologist, pictures tell 1,000 words.

This is going to be the future of FMT. The problem is, we don't know exactly what we're supposed to put in there. And this is what we're going to be doing here at Mt. Sinai, hopefully in January. We're going to be emulating what the Australian study did. We're going to be giving fecal transport, but not via enemas. Via capsules. We're going to randomize patients who get antibiotics or no antibiotics, and then we're going to blast them with all of these capsules to see if we can get the same results, because enema therapy is much more difficult to do than taking a capsule. And that's hopefully what we'll be doing soon.

What about other conditions? There are currently 265 clinical trials across the world looking at FMT in you name it. There's an interesting trial coming out of Brazil looking at hang nails. OK. That's not true. But just about everything else.

And there has been some very interesting data in graphed versus host disease, hepatic encaphalopathy, PSC, immune checkpoint inhibitor colitis. So all these new agents that we're using for any number of oncologic conditions, doing FMT can reverse the colitis that we see in those patients. So in conclusion, don't panic. There is a paradigm shift in medicine. Bugs are good. For C. diff, FMT is a home run.

Do not wait to intervene in the fulminant patients. And we will be showing that. We have shown that. And hopefully with our quality improvement project, we can save even more lives. There is a promising role for microbial therapy in IBD. And again, there's much more on the horizon.

So thank you so much for your time. I want to thank Dr. [INAUDIBLE] for inviting me.

I'd like to thank my colleagues and my mentors, and everybody, and most importantly, the residents and the medical students who actually make all this research work for me. So thank you all very much.

[APPLAUSE]

SPEAKER 1: Questions? Down at the back.

AUDIENCE: Yeah. Hospital acquired infections, or hospital associated infections, health care associated infections include both hospital acquired, nursing home acquired when nurses transfer patients back and forth between these two kinds of facilities. And C. diff is rampant in one and less rampant in the other. So are there any preventative, prophylactic, or diagnostic studies that exist that can predict which patients will get it when they're moved from one setting to the other?

ARI GRINSPAN: That's a great question. The whole concept of prevention of C. diff, it's something that we all grapple with in hospitals and in nursing homes.

An interesting study. They looked at those who were colonized with C. diff when they entered a hospital. And it turns out that those patients were a little bit less likely than the surrounding patients to get a C. diff infection, suggesting that there was something about their own microbiome or something that prevented them from getting C. diff, but not the people who were around them.

So we don't do that at this point in time. We're not routinely checking for colonization as a marker of, oh, you are at increased risk. The bottom line, it's all going to come down to infection control, antibiotic stewardship, washing hands. But it turns out, of all of those things the most important thing we can do is antibiotic stewardship. It's not immediately throwing out the big guns. It's trying to avoid the Z Pack for the little sniffle. But it's an ongoing problem that every institution struggles with is how do you predict who is going to get the bad infection? And we don't do a good job.

SPEAKER 2: Any difference in-- you mentioned immunosuppressed patients, or transfer patients. Any difference in the response rate or complications with immunosuppressed patients? Or it's all the same?

ARI GRINSPAN: So there was an article published in I think the *American Journal of Transplant Medicine* or something like that.

SPEAKER 2: [INAUDIBLE]

ARI GRINSPAN: Exactly. That's the one. There was high rates of cure by using FMT. And we did not see bad things happening to those patients. We didn't see an increased rate of infections, perforations, or anything like that.

SPEAKER 2: Thank you.

AUDIENCE: Ari, your fifth front line on conclusions talks about microbial therapy. It doesn't say fecal microbial therapy. Is there a future for the microbes, with or without short chain fatty acids tossed in butyrate or something, as opposed to the whole stool?

ARI GRINSPAN: So absolutely. I mean, the idea is that right now we don't know the right bugs that we're supposed to be looking to at for really anything. So in C. diff there's this whole hypothesis about you looking at the bile, the ones who produce bile salt hydrolases. We don't know what we're supposed to be transplanting for IBD as of yet. Ideally, it would be some sort of narrow spectrum or something like that.

But the reason I wrote microbial therapy is that it's not just going to be fecal transplant. It's not just going to be bacteria. We're looking at bacteria phages for IBD that Rob Hurtons is running a study for here as well. So it's going to be using the microbes as a good thing as opposed to a bad thing. And we just need to learn a whole bunch more before we are gung ho about [INAUDIBLE].

AUDIENCE: And same thing for C. diff. Right? You can maybe just use microbes with some butyrate or something?

ARI GRINSPAN: Exactly. Over 10 years ago at Baylor, they had a small subset of bacteria that they used. And they got similar results. And that's what a lot of these companies are trying to do. They're trying to patent just a few collection of bacteria that they can put into a pill, and use that to treat C. diff. We'll wait to see what happens. [INAUDIBLE].

SPEAKER 2: Down the back.

AUDIENCE: One of the common diseases in mice at least has been treated with the fecal transplants. And that's obesity. Now, has there been work in humans yet?

ARI GRINSPAN: So the question was about using FMT for obesity, which is a trillion dollar idea. There has been two small studies that have looked at that. Jessica Allegretti at the most recent DDW over at the Brigham just presented her data on looking at obesity. But they didn't actually look at obesity as a primary outcome. What they were trying to do was to change levels of GLP1.

And it turns out that you can slightly change levels of GLP1 by giving a fecal transplant. But if you actually looked at what happened to the weight of those patients, not a drop of a difference.

So in any weight loss procedure or medication, if you do not invoke the lifestyle changes, it turns out that intervention is going to fail. So whatever may come up with FMT or manipulating the microbiome in obesity, it would have to have a large number of patients. And that has to include that lifestyle modification. Otherwise we're probably not going to see any differences. But we don't see the dramatic difference like they saw in the mouse.

SPEAKER 1: Thank you very much. Thanks very much, Ari.

[APPLAUSE]