

Lainey

Hi, I'm Lainey. So in August of 2019 I started having wild bowel movements. (laughs) That's about the only way that I can put it. I have celiac, I have irritable bowel, and these stools were nothing like I had ever encountered before. They were coming every hour to half an hour, seemed like I couldn't be more than 10 feet from my bathroom at any given time. I went to our little local first aid station kind of at my husband's job and they had medical staff and I said look, something's not right, it's not okay. I intentionally withheld the fact that I have celiac disease knowing that a lot of doctors actually like to just hang their hats on any GI symptom. And at the very end she had gone through everything, was gonna just basically say if it's still not okay in a couple of days, come back.

And somehow the word got out that I have celiac disease and she said, 'Oh, you must have just had gluten, that's all.' And even though I was sure she said, 'Have some bananas, drink lots of water, your stool should firm up and everything will be fine.' And all I really wanted to do was go to my normal GP but in rural Iowa he was over an hour away and I could not make that trip to save my life. No bathrooms on the way, no gas stations, it would have been me in a cornfield. So not an option. (laughs) Finally when I was having what I would consider a good day I called my doctor and I said, 'I'm on my way, I need to come see you.' And he submitted a test for C. diff, sure enough it came back positive. From there we went through basically the standard first steps and I was put on a course of metronidazole or Flagyl.

I saw a little improvement but once the course of antibiotics was finishes it was already back. So then he called in oral vancomycin. Thankfully that cleared it up. After the fact we were trying to do a little research on how I acquired my C. diff infection and it wasn't until it was a long thought afterthought that I had a bug bite before that and it had gotten infected and they had put me on ciprofloxacin about two months prior. Fast forwarding to March of 2021, I am a vet tech and it was my third week on the job. We were still doing curbside because of COVID, I went out to go get a dog to bring into the hospital. Somehow the dog's muzzle slipped off when the owner was placing its lead on. It lunged at me, tackled me into a snowbank, and I had puncture wounds in my arms and had to go seek medical attention where they put me on Clindamycin and ciprofloxacin.

I mentioned to urgent care I have a history of C. diff, please help me, that's not what we should be doing. And instead of her directions for having a yogurt everyday she suggested to have two yogurts everyday. That was a little insulting to say the least. A few days later my arm had abscessed, I went to my current doctor's emergency room. I went in and they said, 'We need to admit you to the hospital.' They started me in IV vancomycin, IV metronidazole, and IV aztreonam which is a pretty kind of novel antibiotic that they only use in real serious cases. From there my bite wound cleaned up, I was messaging my doctor every day at least a couple times a day freaking out about having C. diff again, sure that I was probably gonna have it again. And he agreed that I was probably gonna have C. diff again from all of these antibiotics.

Finally when I was discharged from the hospital three days later, they don't have an oral version of aztreonam so they out me on levofloxacin, another broad spectrum antibiotic. My heart kind of sank knowing what the future held. It was about 10 days after I was home from the hospital, had gone back to work, those urgent, loose stools that when you feel it you need to sprint to the bathroom but don't sprint too fast. (laughs) And I called my doctor and I said, 'Look, I think I've got C. diff.' He ordered the test, I came down, and I was positive for C. diff. So they started me on oral vancomycin right away and finally after it was a month on the vancomycin and doing a taper, things were starting to kind of finally feel normal.

I finished my antibiotics and it wasn't 30 days later before I was at work and I realized in the last hour and a half I'd gone to the bathroom three times. I messaged my doctor while I was at work, I said I need another test, I don't think it's gone. And sure enough I went over our lunch break, I took a longer lunch than we normally have and went down and by the time we were done that night at work I had my results that I had C. diff again, I had a recurrent C. diff infection. That meant my doctor was calling infectious disease specialists and I spoke to infectious disease specialists and they referred me immediately to a research trial for fecal transplant. They didn't even wanna see me, they just sent me straight there.

Then I get the phone call and I tell them my story, they said, 'You absolutely qualify for a fecal transplant with your recurrent infection, we'll schedule you for...' It was June 30th was my transplant date and I had it circled and starred on the calendar. But it was still a month out so it was exhilarating but also unnerving knowing that I had to deal with this infection. So we started another vancomycin taper. I stayed on the dose that basically kept my stool solid. From there I waited until my transplant date. My transplant was colonoscopy-guided so they did a colonoscopy and then they came in and applied the fecal transplant matter. I remember wheeling into the colonoscopy room and seeing a jar with brown liquid in it. I was so excited I screamed, 'That's my poop! That's my new poop!' And the doctors laughed at me. I was just so excited.

Thankfully post-transplant things are going well. I have post-infectious irritable bowel probably on top of normal irritable bowel but they're still calling it post-infection. So day to day life, things are going pretty well however every time I feel like a little gas bubble or I get a funny little cramp my heart sinks and I'm worried that the C. diff is back because the doctors did notify me that my infection was relatively severe and that I might have to kind of get what they call little tune-ups as far as just additional fecal transplants in the future. And so every time I get a funny little feeling I'm instantly worried.

My doctor even associates that with a little bit of PTSD honestly from the whole event. It's interesting to think that I have more trauma from the medical fallout from my dog bite than the actual dog bite itself. C. diff has really stuck with me. For anyone who's comparing it, as my mom was trying to put a label on it, she was saying it can't be worse than colonoscopy prep, it can't be worse than colonoscopy prep. (laughs) And I can officially say after doing both that C. diff is much worse.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Wow, thank you so much Lainey for taking the time to share your story with us, that's intense.

Erin Allmann Updyke

Yeah, wow. Thank you.

Erin Welsh

Hi, I'm Erin Welsh.

Erin Allmann Updyke

And I'm Erin Allmann Updyke.

Erin Welsh

And this is This Podcast Will Kill You.

Erin Allmann Updyke

Welcome everyone. We're excited about this episode.

Erin Welsh

As we are about all our episodes.

Erin Allmann Updyke

That's true.

Erin Welsh: But it's genuine excitement.

Erin Allmann Updyke: It always is. Today we're talking about Clostridium difficile, aka C. diff.

Erin Welsh: C. diff, that's how I'm gonna talk about it for the rest of the episode. But we're not talking just about this problematic pathogen, we're also talking about one of my favorite solutions to infection.

Erin Allmann Updyke: Yeah, one of my favorite solutions to a problem.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: I simply love it and of course we are talking about fecal microbiota transplantation.

Erin Allmann Updyke: Aka fecal transplant. We have talked about this, like we've dabbled in it in several other episodes and been like, 'Ooh, someday. Ooh, someday.' That day is finally here, everyone.

Erin Welsh: Yes. This is not gonna be a full take down of the microbiome and all the impact that it has on different conditions or whatever endless associations.

Erin Allmann Updyke: No.

Erin Welsh: But we are gonna do somewhat of a deep dive into fecal transplants or FMTs and we are very excited to bring on a special guest, an expert guest to help us out with that.

Erin Allmann Updyke: Yeah.

Erin Welsh: But that's jumping way ahead of ourselves.

Erin Allmann Updyke: It is because first it's quarantini time.

Erin Welsh: It is. What are we drinking this week?

Erin Allmann Updyke: This week Erin, we're drinking The Slurry.

Erin Welsh: We're sorry. (laughs)

Erin Allmann Updyke: Isn't that what everyone wants to drink?

Erin Welsh: Okay so the thing is it was either make a gross recipe or a gross name and not both.

Erin Allmann Updyke: One or the other had to happen.

Erin Welsh: Yeah, exactly. I mean we are but human. So what is in The Slurry?

Erin Allmann Updyke The Slurry contains mango, pineapple, lime, tamarind, and tequila. All delicious things. And of course you gotta blend it up.

Erin Welsh You got to. You gotta blend it up. But it tastes good, right.

Erin Allmann Updyke Yeah. I mean it's very fruity, it's a lot of flavors, we promise it's worth it.

Erin Welsh Yeah, yeah. And we will post the full recipe for The Slurry quarantini as well as the nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.

Erin Allmann Updyke Yes we will. Erin, what other business should we tell everyone about?

Erin Welsh Well how about our website? Okay, it's my turn to do the rundown of things on there, I'm nervous. (laughs)

Erin Allmann Updyke You can do it, I believe in you.

Erin Welsh Okay here we go. We have all of our references to all of our episodes on each episode page, we have transcripts, we have links to our bookshop.org affiliate page and our Goodreads list, we have links to music, Bloodmobile now on Spotify, we have links to our merch which we have very incredible merch, please check it out.

Erin Allmann Updyke We really do.

Erin Welsh And we have a promo code page. I mean I think that's gotta be most of the things on there.

Erin Allmann Updyke It's most of the things. Definitely check it out. [Thispodcastwillkillyou.com](http://thispodcastwillkillyou.com). So does that mean we're ready to talk about C. diff?

Erin Welsh Yeah, I think so. Thanks also to everyone who has requested this over the years.

Erin Allmann Updyke Yeah.

Erin Welsh And we hope you like the episode.

Erin Allmann Updyke Yeah. So let's get right into it after this break.

TPWKY (transition theme)

Erin Allmann Updyke So I don't know if anyone but me would notice this but I think it's funny. I'm gonna start this episode almost identically to anthrax I think, our anthrax episode.

Erin Welsh Oh. I don't remember this so this is good.

Erin Allmann Updyke Yeah that's fine. Nobody will but as I was typing it I was like this sounds familiar and then I opened my anthrax notes and I was like ah, okay. *Clostridium difficile* infection is caused by an anaerobic, gram-positive, rod-shaped, spore-forming, toxin-producing bacterium.

Erin Welsh Yeah. Hold on. Okay, quick question already.

Erin Allmann Updyke

Okay. Already! One sentence in.

Erin Welsh

Is that also how you started the botulism episode?

Erin Allmann Updyke

Ooh, probably, yeah! Probably.

Erin Welsh

Okay.

Erin Allmann Updyke

I genuinely forgot that we ever did botulism Erin, it was a long time ago.

Erin Welsh

I loved that, I loved that episode.

Erin Allmann Updyke

It was a good episode. I forgot. It'll also be probably the way that I start tetanus whenever we do that. So you know. So for the remainder of this episode like we said I'm probably just gonna refer to this as C. diff because it's easier and shorter and that's how we're gonna say it. So C. diff causes an infection that most of the time very commonly is what's called a nosocomial infection which means hospital or healthcare-acquired. So the way that I've tried to organize this biology section is to first focus on the disease that Clostridium difficile can cause, how it's transmitted, how it makes up sick, and then take kind of a bigger picture view and talk a little bit about the microbiome as it relates to C. diff infection because as a spoiler that Erin I know you probably already know and many listeners may know but C. diff doesn't always or necessarily cause infection.

Erin Welsh

Yeah, it's gotta be one of our first, besides MRSA maybe, super opportunistic pathogens.

Erin Allmann Updyke

Yeah, we haven't covered a lot of opportunistic pathogens on here. This is definitely one of them.

Erin Welsh

Yeah.

Erin Allmann Updyke

But we'll get there eventually. First of all. Transmission of C. diff at the most basic level, the way that anyone in the world gets exposed to C. diff in the first place in fecal-oral, so poop in mouth. It's a common mode of transmission especially for GI bacteria and C. diff, like mentioned, is a spore-forming bacterium like our friend Bacillus anthracis and Clostridium tetani.

Erin Welsh

And also botulinum.

Erin Allmann Updyke

And Clostridium botulinum. Anyways, C. diff is also an anaerobic bacterium like a lot of our gut bacteria are either entirely or facultatively anaerobic which means that they survive without oxygen. So what happens in the case of C. diff is that on contact with oxygen like when we poop out this bacterium, it forms spores. And these spores are very highly environmentally resistant, inactive forms of this bacteria. They really can't easily be killed by heat or cold or alcohol and they can persist in the environment not dying or desiccating, just hanging out until they're ingested by another human or animal because animals can also get infected. And then once we ingest them these spores can easily survive the acidic environment of our stomach, travel through our guts, and then these spores are activated in our small or large intestine when they come into contact with our bile acids. Isn't that fascinating?

Erin Welsh

Yeah. Okay, I have a question about how long these spores can last.

Erin Allmann Updyke: Ooh, good question. I don't have an exact timeline but definitely on the order of months, possibly years depending on the condition.

Erin Welsh: Ugh, I really hate that about these things.

Erin Allmann Updyke: I know.

Erin Welsh: It makes it very scary and it feels a bit challenging.

Erin Allmann Updyke: Oh very, very challenging.

Erin Welsh: Okay so the bile acids, what about them?

Erin Allmann Updyke: Yeah.

Erin Welsh: What is bile acid?

Erin Allmann Updyke: I'm so glad that you asked, Erin! Let me tell you. So bile acids are basically cholesterol derivatives. Our liver makes bile and secretes it into our gallbladder where it's stored and then whenever you eat something it sends signals to our gallbladder to contract, squeeze out the bile, and that goes into our small intestine. And these bile acids help support digestion, especially the digestion and eventual absorption of fats.

Erin Welsh: Okay.

Erin Allmann Updyke: And it's a little bit more complicated, there's like multiple kinds of bile acids and they're converted in our small intestine from primary into secondary. And it seems like when *C. diff* spores come into contact with some types of these bile acids especially in higher concentrations, that's when they very easily reactivate into a live, replicable, mobile *C. diff* bacteria which can then replicate and replicate and kind of beat out other bacteria in our guts and eventually cause infection.

Erin Welsh: Are there other bacteria that are activated or inactivated by bile? Like do the bile acids kill a lot of potentially food-borne bacteria or are other food-borne bacteria resistant to bile acids?

Erin Allmann Updyke: That's a good question I don't fully know the answer to. But I'm gonna put a pin in it cause I wanna kinda get back to bile acids in a minute.

Erin Welsh: Okay.

Erin Allmann Updyke: As it relates to our gut microbiome. Okay so now the spores are activated, *C. diff* is replicating, and then somehow this leads to disease. How you may ask, Erin, if you wanted to?

Erin Welsh: I do.

Erin Allmann Updyke: Okay, good. Some species of *C. Diff*, not only do they form these spores in adverse conditions but they also have ability to produce toxins. And it turns out that it's these toxins, not the bacteria themselves, that are capable of causing infection, aka *C. diff* colitis. So let's talk about what that actually looks like. Predominantly *C. diff*, the toxigenic strains, the strains that produce toxins, produce two major toxins very creatively named toxin A and toxin B.

Erin Welsh	Keeps it easy.
Erin Allmann Updyke	Mm-hmm. And essentially what these two toxins do is they work together to ultimately disrupt the membranes of the cells that line your gut and this results in little micro ulcerations of our gut wall, little, little holes. It also disrupts the junction between cells which are supposed to be a nice tight line of cells lining our gut. Basically these toxins get in there and kind of shred the lining between them leaving holes which increases permeability and that is what leads to watery, massive amounts of diarrhea. These toxins also then induce apoptosis and kill the cells that line our gut wall because of all of this disruption. And that leads to a lot of inflammation that can cause the formation of what are called pseudomembranes which sounds gross and it looks gross. Essentially just hordes of these dead cells mixed with bacteria and white blood cells and inflammatory gunk and it forms this kind of membrane that then lines your gut which even further prevents your colon from doing its job of absorbing water, etc, which then leads to even more diarrhea.
Erin Welsh	Okay so I'm assuming that the benefit that C. diff gets from these toxins is that it can sort of wipe out the competition even further and colonize as much as it wants to, your intestines.
Erin Allmann Updyke	Yeah that's a good question. Maybe, probably? I would guess so. I mean certainly it makes it hard for anything else to exist where the pseudomembranes exist.
Erin Welsh	Okay so it might not be necessarily helping with colonization but it helps clear the competition?
Erin Allmann Updyke	Yeah. It's interesting because C. diff is actually not a very good competitor to begin with.
Erin Welsh	Right.
Erin Allmann Updyke	Whether it's toxigenic or nontoxigenic. So maybe these toxins are helping a little bit in making it a little bit more competitive but I don't know for sure.
Erin Welsh	Okay. Toxins are costly to make.
Erin Allmann Updyke	Mm-hmm.
Erin Welsh	So you would think there would be some sort of benefit from the toxins.
Erin Allmann Updyke	Well kind of like we've talked about in a lot of our bacterial pathogens that cause diarrhea, people who are having massive watery diarrhea because of C. diff are spreading billions of spores.
Erin Welsh	Okay, so transmission.
Erin Allmann Updyke	And those spores are very environmentally hearty and so perhaps that's the major advantage is that you're able to spread.
Erin Welsh	Okay.

Erin Allmann Updyke

I don't know if it's that satisfying. But that's kind of the main end result. There's a lot more detail on these toxins, they're very interesting. There's also another toxin that is present in some strains that seems to when it's present cause even more severe disease. But I'm not gonna get into all of the specific biochemistry of it cause there's a lot more that I wanna talk about with C. diff. But the end result of these toxins and the disruption that they cause in the lining of our colon, the death that they cause of the cells that line our colon and all of this inflammation is what really causes the symptoms that we see.

Erin Welsh

Is it only the toxigenic strains that cause disease?

Erin Allmann Updyke

Yes.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. And there are a lot of studies looking at do you have to have both of these toxins because it's toxin A and toxin B or could you have just one of these toxins? There's still some question as to that, it seems like in some models or in some clinical studies they've seen that strains that only produce toxin B can still cause disease. So A might be kind of like a benefit but not necessary to cause disease. But then in other studies it looks like no, you really have to have both and if you only have one or the other you don't really see disease from C. diff even though you might have colonization. So it's still a little bit I think up in the air but it is really interesting the way that these two toxins kind of interact to then cause the actual symptoms that we see.

Okay so I've said the word 'symptoms' like a hundred times but I think the only thing I've said so far is diarrhea. And that is the hallmark symptom of a C. diff infection, massive watery maybe mucousy diarrhea. Generally it is not overtly bloody diarrhea like we see with dysentery and that's largely because C. diff doesn't invade through our cells and it's very rare that it causes disease outside of the intestine. But because it is causing all of this inflammation and this damage to the lining of our gut, you can see micro amounts of blood in the diarrhea but usually not what would look like bloody diarrhea.

And otherwise symptoms can really, really range. You can have very mild diarrhea with a C. diff infection to severe life-threatening colitis that is the inflammation of your colon, of your gut wall. And even though it doesn't usually go outside of our colon and cause actual infection anywhere else, it can generate such a strong inflammatory response in our body that you see a lot of other signs of infection and inflammation, a lot of abdominal pain with this infection, fevers, nausea, vomiting, generalized weakness because you are having diarrhea of anything you're trying to eat. And so in severe cases if this goes untreated it can lead to significant dehydration which can then lead to shock and death. It can also lead to something called toxic megacolon which sounds horrific and is horrific.

Erin Welsh

We talked about this, didn't we?

Erin Allmann Updyke

I think we have on-

Erin Welsh

Chagas.

Erin Allmann Updyke

Was it chagas? Okay. Essentially toxic megacolon is where your colon gets so inflamed, it's a very different mechanism here than in chagas disease but it becomes very, very distended and is unable to move any contents down your gut the way that it's supposed to so gas and fecal contents just keep building up and that can lead to perforation of your bowels which is of course a life-threatening emergency.

Erin Welsh: Yeah. I mean all of this sounds not only painful and really unpleasant but very life-threatening.

Erin Allmann Updyke: Very, yeah. So the mortality rate directly due to C. diff infection is estimated to be about 5% but that's just for death directly due to C. diff infection, so C. diff colitis causing death. If you look at overall mortality that's associated with C. diff infection which includes downstream complications but also just the fact that a large proportion of people who get C. diff infection are often already sick with underlying conditions.

Erin Welsh: Right.

Erin Allmann Updyke: And so the kind of associated mortality rate is often up to 15-25% or if you look at people who are already in the ICU, so already very sick, it's up to 30% which is horrific.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: Yeah. And scary.

Erin Allmann Updyke: It's really, really scary, yes. C. diff is the scourge of hospitals. But like I said at the top, as severe as the infection that C. diff causes can be it doesn't always make us sick, it's an opportunistic pathogen. And Erin, you'll probably talk more about this in the history section so I hope I'm not stepping on your toes but Clostridium difficile was actually first identified as just a normal component of the microbiome in healthy infants and neonates.

Erin Welsh: Mm-hmm.

Erin Allmann Updyke: What?!

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah. So this is a bacterium that might exist in me or you, Erin, or in quite a lot of you listening just as one of the I don't know how many hundreds of species happily coexist inside of our gut microbiome.

Erin Welsh: Right.

Erin Allmann Updyke: So then the question becomes who gets sick from C. diff and who lives with C. diff without ever getting sick and why? And the answer relates to two major things, one of which we've kind of already touched on. So first and most obviously is is this a toxin-producing strain or not? So not all strains of C. diff produce those toxins and because it's the toxins and not the bacterium that causes the damage. If you are colonized with a non toxigenic strain, you're very unlikely to get C. diff colitis or C. diff infection. And there's actually some interesting studies and I think this might be a little bit controversial because there just isn't a ton of data on it where they separate nontoxigenic from toxigenic strains. But the data that does exist suggests that if you're colonized with a nontoxigenic strain it might actually be protective against infection with a toxigenic strain. But what's interesting is it doesn't seem to be an immune-mediated response necessarily.

Erin Welsh: Oh so it's like competition?

Erin Allmann Updyke

Uh huh, let's talk about it a little more.

Erin Welsh

I mean does that just have to do with the fact that it's a bad competitor and it needs an open playing field?

Erin Allmann Updyke

Yeah. So the other major thing other than strain that affects whether somebody gets Clostridium difficile infection or just is colonized with C. diff or has neither, like doesn't get C. diff infection and isn't colonized with C. diff is their microbiome and the composition of their microbiome to begin with? So I'm gonna preface this by saying that all of the studies on human microbiome, at least the ones that I read in specific how it relates to C. diff, they're limited and have low sample sizes so keep that in mind. But there's still some really interesting things from some review articles. So let me tell you what I found. Studies that have looked at people colonized with C. diff vs not colonized with C. diff vs infected have found that people who test positive and have symptoms of infection with C. Diff, so people sick from C. diff with C. diff colitis have a significant reduction in their overall microbial diversity and species richness.

So for lots of people who don't know cause I even had to re-google this, species richness is just the actual number of different bacterial species that are present and diversity is a measure of both that richness, so the number of species, and the abundance of these different species. So people who get infected and get sick from C. diff have both low numbers of bacterial species in their gut and low diversity of those microbes. That's not surprising right, cause we already said that these are generally people who might be sick or that this is not a good competitor. But even people who are colonized with Clostridium difficile without any overt signs of infection also have decreased species richness and diversity. But the distribution of species is different in these two groups so it seems like there are certain species that are more protective against infection. And do you know what? It seems like the effect of this microbiome composition on the amount of bile acids that make it all the way to your gut likely play a role.

Erin Welsh

Interesting.

Erin Allmann Updyke

I know!

Erin Welsh

Okay.

Erin Allmann Updyke

Okay.

Erin Welsh

But I have questions about this. So this is what I think is difficult a lot about microbiome research is that there's still so much we don't know and so much is not necessarily about the species identity but the species role. So what's the functional role of those? Like you might have two different species but they might play a similar functional role.

Erin Allmann Updyke

Right. And so that's why they think that at least they've been able to identify some of that in that the functional role of some of these species might be to decrease the amount of bile acids that activate C. diff spores and therefore allow C. diff activation and colonization.

Erin Welsh

So then my second question is about the effect size. So when you say reduce the amount of bile, like how much?

Erin Allmann Updyke

Good question, I don't know.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah, yeah. It basically just shifts the ratio of primary bile acids to secondary bile acids but I don't know by what numbers.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

Interesting.

Erin Allmann Updyke

But it is really interesting.

Erin Welsh

Yeah, I agree. (laughs)

Erin Allmann Updyke

Even though I agree we really don't know and so it's also like how do we then translate that into something that can then prevent infection? It's still hard to do, right.

Erin Welsh

Right.

Erin Allmann Updyke

But what's important is that the biggest risk factor for C. diff colitis is antibiotic exposure, right. And it's not surprising when you look at studies that have looked at even very short course exposure to antibiotics rapidly reduces the diversity of your microbiome in your colon. And this diversity, this reduction in diversity rather, can persist for months and months leaving you potentially susceptible to something like an opportunistic pathogen.

Erin Welsh

Right. Because remember antibiotics, some are more targeted than others.

Erin Allmann Updyke

Right.

Erin Welsh

But none of them are like this will only kill this species. There are going to be bystanders that are wiped out just as a result of taking antibiotics.

Erin Allmann Updyke

Right and any antibiotics that you take through your mouth are going to make it to your gut so they're going to have some kind of an effect on your gut microbiome even if the antibiotics are for a kidney infection or a skin infection. It's going through your gut.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. The other risk factors for infection of course are things like exposure itself and so one of the reasons that C. diff infection is so pervasive in healthcare environments is because these spores exist in really, really high concentrations in the feces of people with C. diff infection which means that they exist in really high concentrations at healthcare facilities and they're so environmentally resistant that they're really hard to get rid of and so they're really easily transmitted throughout healthcare systems.

Erin Welsh

It's like a nightmare.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah, that's how my grandmother got sick from C. diff after having a knee replacement and it was horrible, I mean it was absolutely horrific, yeah.

Erin Allmann Updyke

Yeah. Older age is also a really big risk factor.

Erin Welsh

Yeah.

Erin Allmann Updyke

But it's not just healthcare, this just is getting more and more depressing. Because there are some studies that suggest like 30% of people who end up with a C. diff infection don't actually have any risk factors which also means that this isn't a problem only in hospitals or care facilities, this is also something that exists in the environment at large. And there are some studies in Europe in places like the Netherlands that suggests that this, what they call community-acquired C. diff aka not from a hospital, actually has a higher incidence than other causes of diarrhea that we might think are more common like campylobacter or salmonella. So it's a really important cause of diarrhea that not only can be fatal but also often causes recurrent infection. Yeah, so like 10-25% of people will get at least one recurrent infection after an initial infection and of those people who get it twice, something like 40-65% may go on to have another and another.

Erin Welsh

Just like MRSA again.

Erin Allmann Updyke

Yeah, exactly, right. I think with C. diff it's one of those infections that it had become so clear how important the gut microbiome is to the establishment and persistence of an infection like this or to the establishment and the susceptibility to an infection like this is.

Erin Welsh

Yeah. It's kind of like the perfect example of oh hey, this thing that we didn't really think all that much about, turns out that there's a very important balance and delicate balance and the disruption of that is deadly.

Erin Allmann Updyke

Right. Yeah, yeah. Or it can be.

Erin Welsh

Yeah.

Erin Allmann Updyke

That's all for the biology, Erin. I mean it is still a treatable infection a lot of the time but again because of the recurrence-

Erin Welsh

And the resistance.

Erin Allmann Updyke

And the resistance. Well the good news is that later in this episode we are gonna get to talk about fecal transplants. Fecal microbiota transplants aka FMT, putting healthy bacteria back into your colon. We'll talk more about it later as well as other novel treatments and prevention strategies. But first, Erin, tell me what's up with this. Where did it come from? Has it always been with us? Why is it making us so sick?

Erin Welsh

Good questions, good questions. I will try to answer them right after this break.

TPWKY

(transition theme)

Erin Welsh

The story that I wanna tell for this history section is really more like two stories, each with a central main character. To kind of origin stories, two rise of the villain or hero stories, and then only closer to the end do the two threads of the stories meet. And unlike most straightforward hero vs villain or good vs evil stories, the conflict doesn't drag on and on although there's still ample material for many sequels. But rather it resolves itself I think fairly quickly and in a satisfying way. So who are these two main characters?

Erin Allmann Updyke

Tell me.

Erin Welsh

Well the first is probably fairly obvious because it's the topic of today's episode and you've already gone in great detail about the biology of it, *Clostridium difficile*.

Erin Allmann Updyke

Oh okay.

Erin Welsh

And the second might be pretty obvious too since we've also already talked about it but I wanted to talk a bit about the history of fecal microbiota transplantations or FMT.

Erin Allmann Updyke

Yes!

Erin Welsh

Which are I think at least one of the obvious heroes in this story. And I also fully acknowledge that it's unfair and anthropomorphizing to cast *C. diff* in the villain role and that these bacteria might be more accurately described as pawns without motive or guile, allowed only to cause the damage they do because of a human invention, antibiotics. But I'm getting ahead of myself and also I don't know how much time we need to spend in this particular episode about anthropomorphizing of microbes and the symbolic language that we use like battle and war on microbes, whatever. It'd be interesting, I would like to read a paper about that.

Erin Allmann Updyke

That would be really interesting.

Erin Welsh

Yeah. What words do we use? Cause words matter. Anyway, *C. diff*. Where did it come from? The group *Clostridium* itself is incredibly ancient, it's estimated to have diverged from the bacterial domain about 2.34 billion years ago which is what I saw and that's right around the same time that the atmosphere began to contain more and more oxygen. And while I don't know the exact specific origin of *C. diff* itself, I would imagine that based on its genome and its ability to coexist with humans and many other animals, it's been a part of our gut microbiota and the microbiota of many other animals for quite some time. And genomic analyses of *C. diff* also support this.

The genome of a particular strain of *C. diff*, I think one of the most predominant ones, was fully sequenced and annotated around 2006 and this analysis, this genomic look told us a lot about the ecology of this bacterium and the type of relationship that it has with its host, like humans. So first it told us that *C. diff* is really well adapted to coexist with its host, not just to kill or pathogenically infect and cause disease which is in contrast to a relative of *C. diff* that we've talked about before, *Clostridium botulinum*. So *Clostridium botulinum* in contrast contains many unique genes that are involved with direct disease mortality which I think that's interesting cause that does speak to sort of the more multifaceted relationship that *C. diff* has to humans, it's not necessarily just a pathogen.

Erin Allmann Updyke

Right. Yeah and I mean it's not just a pathogen.

Erin Welsh

Right. It's a little bit deeper than that. Secondly and one of the things that I find super interesting is that the species itself like all the isolates and strains and whatever that make up *C. diff* that we know about, they are incredibly diverse even when compared to other bacterial species that have high genetic variability. So according to one paper I read by Knight et al from 2015, the amount of shared core genome of *C. diff*, so in my understanding that's the amount of genome shared across all isolates of *C. Diff*, like the core genome or whatever is as low as 16%.

Erin Allmann Updyke

What?

Erin Welsh

Which is lower than has been observed for any of the bacterial species so far. So what does that mean? So of course there's natural genomic variation across members of an individual species. Like Erin, you and I, we don't share the same exact genome.

Erin Allmann Updyke

Right.

Erin Welsh

But what this means is essentially that the amount of genomic variation across *C. diff* is more along what you might expect for members of a different genus rather than among strains within a species. And so this research and other research has called into question *C. diff*'s designation as one species with more researchers suggesting that we take a new approach to the taxonomy of *C. diff*. So for instance by recognizing certain strains as subspecies or separate species entirely.

Erin Allmann Updyke

Like the nontoxigenic vs toxigenic, that kind of...?

Erin Welsh

Something like that.

Erin Allmann Updyke

Okay.

Erin Welsh

Yeah. And so what does that mean in practice?

Erin Allmann Updyke

Right.

Erin Welsh

I don't know but I think it could have a lot to do with the evolution of this, trying to predict the evolution and the geographic spread, which ones to worry about.

Erin Allmann Updyke

Right.

Erin Welsh

I don't know. It's interesting to think about.

Erin Allmann Updyke

Well also it would really change the way that we've gotten estimates for things like *C. diff* colonization in the past.

Erin Welsh

Right.

Erin Allmann Updyke

Right? That it's been like all of these strains lumped together.

Erin Welsh

Yeah. So it would definitely change the disease burden or how we look at those numbers.

Erin Allmann Updyke

Yeah.

Erin Welsh

So let's go back to when our villain C. diff was first discovered or as it was first named, Bacillus difficilis. And so as you mentioned Erin, yes, this happened a long time ago back in 1935 specifically, the name was changed to Clostridium difficile in 1938. And it happened when these two researchers in Denver which I wanted to shout out because I don't think I've told everybody here on the podcast but I moved to Denver this year and I love it, it's incredible, it's the best. But these two researchers were named Ivan Hall and Elizabeth O'Toole and they collected the meconium and feces of 10 newborn infants at a hospital to see what microbes might be in there. And I thought that was interesting because I guess I didn't realize that the characterization of the microbiome or at least the recognition of endosymbiotic bacteria had started so early.

And it's true that a lot of the early germ theory days were focused on matching a disease to a pathogen, like oh we found a bacterium, it has to cause a disease, what does it cause? And so based on that when people were just hunting microbes, it does make sense that people would have encountered some over and over again that were not associated with any inherent or any apparent disease. But I think that also around this time there had been a growing recognition that not all bacteria were bad and that some might be helpful or at the very least neutral. And basically that's what it seems like Hall and O'Toole had set out to do with this study, just like find out what was there and especially the way that these microbe communities changed during the first 10 days after birth. And in their screening they found several species of bacteria that had already been described but they also found something new in several of the samples. Quote: "An actively motile, heavily-bodied rod with elongate subterminal or nearly terminal spores of about the same diameter of the rods." Man, what riveting reading. (laughs)

Erin Allmann Updyke

Riveting is right.

Erin Welsh

And they named this new species Bacillus difficilis because of how difficult it was to isolate and study under lab conditions. It's just like a finicky guy.

Erin Allmann Updyke

Finicky. It's anaerobic, you know.

Erin Welsh

Yeah, they're finicky. Then to see if they could figure out more about the role of this bacterium, they infected rabbits and guinea pigs with it to see what would happen. And they were surprised to find that it seemed quite pathogenic to them or at least that the bacterium produced a toxin that could lead to death or severe disease in these lab animals. Although the toxins wouldn't be described until 1974 when Green et al isolated it from the stools of guinea pigs treated with penicillin, although even then it was thought to be a virus and the connection to C. diff wouldn't be made until later. And that's all kind of part of the theme of C. diff. It's flying by under the radar, not really acting suspicious or earning any suspicion. That kind of makes up a lot of the history of C. diff.

And so this paper that I talked about, the Hall and O'Toole paper where C. diff was first described, that came out in 1935. And between the years 1940 and 1962, there were only two mentions of C. diff infections in humans in the medical literature and in both of these studies, C. diff was not suspected to be pathogenic to humans, it wasn't written about as a potential pathogen. And Hall and O'Toole did based on their rabbit and guinea pig studies, they did say, 'Oh maybe we wanna keep an eye out for this in infants as a possibility of causing disease.' But there didn't seem to be a whole lot of follow up and there didn't really seem to need to be a whole lot of follow up because it doesn't seem as though, at least from what I can tell, that there was a silent epidemic of C. diff during that time, so since Hall and O'Toole described it to, I don't know, the 1950s or something. And if anything I think I'll side with you in being surprised at how early C. diff was described.

Erin Allmann Updyke

Yeah.

Erin Welsh: Like 1935, at first I was like wow that's so recent and then I was like wait a second.

Erin Allmann Updyke: Yeah!

Erin Welsh: Based on it's biology, no that's very surprisingly early.

Erin Allmann Updyke: Right, especially cause it was not causing disease.

Erin Welsh: Yeah. And I definitely didn't find anything or read anything about historical infections of C. diff or ancient writings describing the disease. I mean of course there's plenty to choose from in terms of ancient writings of diarrhea, it's always been a part of human existence and I'm sure that C. diff took on the role of pathogen occasionally in human history. And the first description we have of pseudomembranous colitis for example which is that horrible-sounding condition caused by C. diff is from 1893, reported in a 22 year old woman who had recently undergone surgery for a gastric tumor. She later developed diarrhea and died.

Erin Allmann Updyke: Okay.

Erin Welsh: And so maybe that was caused by C. diff.

Erin Allmann Updyke: Right.

Erin Welsh: But we have no way of knowing for sure. But beyond cases like that, C. diff was probably just part of the background, minding its own business, popping up here and there. And it likely would have stayed that way just like a wallflower on your gut, gut-flower, but humans intervened. And of course I'm talking the rise of antibiotics. So the widespread use of antibiotics began in the 1940s with penicillin and it continued to grow and grow as more antibiotics such as vancomycin were discovered and then administered. By the 1950s antibiotics were readily available everywhere and frequently prescribed and the ones most commonly reached for we broad spectrum antibiotics, ones that would wipe out not only whatever was making you sick but a bunch of other species right along with it, casualties of the war on bacteria. And also it's still reasonable to prescribe broad spectrum antibiotics, especially when someone's sick and you don't know what it is and you need to try something.

Erin Allmann Updyke: Yeah, it's still very important that they exist and they save so many lives.

Erin Welsh: Yes. I am very-

Erin Allmann Updyke: Yeah, we are still pro-antibiotic.

Erin Welsh: Right. This isn't like, antibiotics are not part of the villain, they're just...yeah.

Erin Allmann Updyke: They're just a supporting character.

Erin Welsh: Yeah. But this is an inevitable consequence.

Erin Allmann Updyke: We are pro good antibiotic stewardship, Erin.

Erin Welsh: That is what we are pro.

Erin Allmann Updyke

Mm-hmm.

Erin Welsh

Mm-hmm. That's a very, very important-

Erin Allmann Updyke

Yeah, caveat there.

Erin Welsh

Yeah. Okay. So shortly after the rise of antibiotics in the 1950s and 1960s, doctors began to notice a rise in pseudomembranous colitis and a rise that seemed to be tied to antibiotic use. Surgeons had observed rates as high as 14-27% among people who had recently undergone surgery which is high.

Erin Allmann Updyke

That's very high.

Erin Welsh

Yeah. And of course the prescription of antibiotics after surgery was and continues to be a very common practice and it's important to prevent secondary infections. But even when people started to recognize the link between pseudomembranous colitis and antibiotics, *C. diff* wasn't really on the short or even long list of suspects. Most people actually thought that *Staph. aureus* was the likely culprit since it was often isolated in the patient's stool. And because of this vancomycin which was used to kill the *Staph* began to be given as the standard treatment for pseudomembranous colitis starting in the late 1950s. But over the next couple of decades *Staph. aureus* seemed less and less likely to be the cause since it wasn't really reliably found in the stool of many people with pseudomembranous colitis and the disease itself, like the rates of the disease, didn't really seem to go down at all.

A study in the 1970s firmly displaced *Staph. aureus* as the causative agent and threw suspicion on antibiotics themselves because they were like, 'Well if it's not *Staph*, what the heck is it?' And this study followed 200 patients at a hospital who had been given Clindamycin. 21% developed diarrhea and 10% developed pseudomembranous colitis but stool cultures were all negative for *Staph. aureus*. And so it was this study and another study from New Zealand that linked diarrhea and colitis with antibiotics that kind of caught the wider attention of the medical community including a Dr. John G. Bartlett who was then at Tufts University. So he had begun investigating antibiotic-induced diarrhea and pseudomembranous colitis in the mid 1970s and in 1978 he and his team published a series of papers in which they finally revealed the link between a toxin-producing *Clostridium* and pseudomembranous colitis.

And then he followed up this research by showing that he had found *C. diff* in the stool samples of several of the individuals in that first study of 200 patients that they could find no *Staph*, they were like, 'We don't know what it is.' And so he actually got some of the samples and was like, '*C. diff*'s here as well.' So that kind of was just like boom, this clearly made the link and he went on to uncover a great deal more about *C. diff* which also hugely opened up the field for other researchers to characterize its toxins, to examine strain diversity, and to understand transmission dynamics. From the late 1970s to now, we know an incredible amount about this bacterium. It's pretty amazing. I mean and that also speaks to the huge public health impact that it has. With these late 1970s studies from Bartlett and his group, the field of *C. diff* was blown wide open.

It seemed that once researchers started looking for the pathogen they found it everywhere and in increasingly high numbers. The continued use of antibiotics especially cephalosporins which C. diff is intrinsically resistant to during the 1980s and 1990s, it led to a huge rise in C. diff overall which of course led to a huge increase in the diversity of strains including the emergence of highly virulent strains. And over time the characterization of C. diff as a hospital-acquired pathogen and one that you have nothing to worry about if you aren't in the hospital or if you don't work in a hospital setting or if you aren't taking antibiotics, like you said Erin, that's become increasingly less accurate. Community-acquired infections have become more common, as I read have animal-associated infections either through direct contact as well as potentially food-borne which has led to many people calling for a one health approach for this pathogen.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

Oh I know, one health always.

Erin Allmann Updyke

Well yeah but the numbers that I saw on ground meats being contaminated was terrifying.

Erin Welsh

Are you gonna share them?

Erin Allmann Updyke

Oh I didn't write them down but I should pull them back up cause it is awful.

Erin Welsh

Okay. Yeah because also the other thing, and we touched on this in I think our antibiotics we had to have, maybe the second one, the overuse of antibiotics in both livestock and other animals has led to increasingly resistant and difficult to treat strains of C. diff. C. diff is now quite expectedly an enormous global problem which I know you'll get into more later.

Erin Allmann Updyke

Yeah.

Erin Welsh

It had this dramatic rise from zero to villain that was made possible only by antibiotics. So maybe it's time we looked for an out of the box solution or out of the bowl solution. I don't know.

Erin Allmann Updyke

Ew, no. (laughs)

Erin Welsh

(laughs) No? Okay.

Erin Allmann Updyke

Oh goodness.

Erin Welsh

So you know the saying fight fire with fire.

Erin Allmann Updyke

Oh sure.

Erin Welsh

What about fighting poop with poop?

Erin Allmann Updyke

Oh Erin.

Erin Welsh

You know I can't resist, come on.

Erin Allmann Updyke

I love it, I do.

Erin Welsh

Introducing fecal microbiota transplants. So at the end of this episode you'll get to hear a whole lot more about the how and the why of fecal microbiota transplants and I can't wait to get into it. But I wanted to first provide a bit of context, a bit of the 'where did this come from and how did we get to where we are today' type of thing. Essentially like you said Erin, the idea behind fecal microbiota transplants is that you take the fecal material from a healthy donor and put it in the intestinal tract of someone who has some sort of GI disorder, often because their microbiota is disrupted. And you do this in order to change the gut microbiota, the composition of the microbes in the gut with the hope that this infusion acts like a hard reset and can take out the disease, kind of get things back to normal.

Erin Allmann Updyke

Yeah, like unplug it and plug it back in again.

Erin Welsh

Exactly. And it works in many cases, like remarkably well. It's beautiful. It's a beautiful thing, I love it, I get chills when I think about FMTs, they're just so satisfyingly wonderful.

Erin Allmann Updyke

It's so elegant.

Erin Welsh

Yeah, it is.

Erin Allmann Updyke

It's weird to say because it's poop but it is.

Erin Welsh

I think it's the simplicity of it and the logic of it is so...of course.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. So who first came up with this idea that healthy poop could cure someone's bad poop.

Erin Allmann Updyke

Yeah. I don't know, tell me.

Erin Welsh

It actually goes way, way back, all the way back to the 4th century in China, CE. Yeah, 4th century CE.

Erin Allmann Updyke

Oh! I love that Erin and it is somehow shocking and also not surprising at all if you've ever listened to this podcast I feel like.

Erin Welsh

Exactly, yeah. Yeah so it was described in the first Chinese handbook of emergency medicine and in this book it was recommended that if you had food poisoning or severe diarrhea, you should ingest fecal suspension by mouth.

Erin Allmann Updyke

Wow!

Erin Welsh

And it was described as not just being somewhat successful like oh try this and it might work but like miraculous, bringing back patients from the brink of death.

Erin Allmann Updyke

Wow.

Erin Welsh

And this isn't the only reference to early fecal transplants either. In the traditional Chinese medicine book 'Compendium of Materia Medica' a series of prescriptions are described that are essentially various preparations of human fecal material. You've got your fermented fecal solution, fresh fecal suspension, dry feces, infant feces, take your pick. All for the effective treatment of abdominal diseases with severe diarrhea, fever, pain, vomiting, and constipation. Just various things. And so reading about this got me thinking about all of the times that we have laughed and laughed and laughed about ancient or medieval cures and how ridiculous they are.

Erin Allmann Updyke

I know, I know.

Erin Welsh

And it struck me that if we had done this podcast, this episode 20 or 30 years ago, we may have similarly laughed at yellow soup, at actually eating poop. But we're not laughing now. Except at ourselves, maybe.

Erin Allmann Updyke

Yeah that's hard, Erin.

Erin Welsh

I know. And that's not to say... I'm not saying that hey, maybe we should look into how effective saying 'my wart be with you' is for treating HPV or mice tails for rabies or something but it is a good reminder that every generation thinks of themselves as being so advanced and looks down on past generations with scorn. Like how on earth could they have believed something like that? And so maybe we shouldn't be so quick to dismiss the ideas of the past. And I am super guilty of this.

Erin Allmann Updyke

Same.

Erin Welsh

Of like haha, look at these cures, these are ridiculous.

Erin Allmann Updyke

I know, we all need to be more open-minded, don't we?

Erin Welsh

We do, I think so.

Erin Allmann Updyke

Yeah.

Erin Welsh

And even if they are clearly not based in any sort of medicine or clearly they would not be effective, I think it also is still useful to at the very least try to understand the logic or reasoning behind them. Why mice tails ground with wine or pigeon heart and beer or something like that?

Erin Allmann Updyke

Right.

Erin Welsh

What about that? Because if there's one thing that an absolute certainty it's that future generations will look back on us now and our medical practices or scientific knowledge that's widely accepted today and they'll think how on earth could they have thought that? Or oh my god, did they not realize that they were only making things worse?

Erin Allmann Updyke

Right. I think that almost everyday, Erin.

Erin Welsh

Yeah. And the examples of this I think are endless, like our limited understanding of autoimmune disorders or the mechanisms behind different mental health issues or some of the ways that we treat cancer or how we overuse antibiotics. There's a lot there.

Erin Allmann Updyke

Yeah.

Erin Welsh

There's ample material for people to laugh at us in the future. But we think we know it all now.

Erin Allmann Updyke

We're all just doing our best!

Erin Welsh

We're all just doing our best. But my point is I think that we can look back and see how far we've come with these things, with our knowledge and technology and maybe feel okay laughing a bit about 'my wart be with you' just because it's such a great saying. But I think we also need to recognize that there is still so far to go and that scientific or medical advancements are rarely if ever done in leaps and bounds but rather the accumulation of years and years and centuries sometimes of shared knowledge being built. All right so soapbox moment over.

Beyond those early descriptions of yellow soup and poop as treatment from China, there are a couple of other examples of what is essentially fecal microbiota transplants from other parts of the world. In the 17th century there was an Italian anatomist who wrote, quote: "I have heard of animals which lose the capacity to ruminate which when one puts into their mouth a portion of the materials from the mouth of another ruminant which that animal has already chewed, they immediately start chewing and recover their former health. And he called that process transfaunation. And also I just wanna point out that many animals regularly consume feces for probably a variety of reasons.

Erin Allmann Updyke

Oh, my dog loves it.

Erin Welsh

Yeah. Dogs love poop. And then later on in the 17th century also a German physician recommended fecal transplant for humans in a book whose title translates to either 'Healing Mud Pharmacy' or 'Salutary Filth Pharmacy' depending on the source.

Erin Allmann Updyke

Okay.

Erin Welsh

I found it translated both ways so I don't know. I also saw it mentioned that bedouin groups historically consumed camel stools as treatment for bacterial dysentery, something that seems to have been picked up during WWII when German soldiers were dying of dysentery in Africa. Nazi scientists observed that locals would consume fresh camel stools at the first sign of disease and it seemed to prevent them from getting sick and so the scientists cultured what they could find in the stools and they isolated *Bacillus subtilis* which they cultured and administered to decent success, like it seemed to work to a certain extent. So that's kind of cool. This all goes way back further than I thought.

Erin Allmann Updyke

Yeah.

Erin Welsh

But from then as far as I can tell, the concept of fecal microbiota transplantation, it really only remained mostly in practice or even in experimentation in veterinary medicine until 1958 when Eiseman and colleagues successfully used fecal microbiota transplants to treat four people with pseudomembranous colitis associated with antibiotic use. This time fortunately using an enema rather than oral application.

Erin Allmann Updyke

1958?

Erin Welsh

Yeah!

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. And this kind of just goes to further show that developments are not made in isolation, there's a lot of background to things. Because in this study he wrote that, quote: "Most of the recently reported cases of pseudomembranous colitis have followed the use of oral broad spectrum antibiotics, suggesting that the intestinal flora was thus altered to permit the overgrowth of antibiotic-resistant *Micrococcus pyogenes* within the gut." And so yeah, he didn't get the bacterial species right necessarily.

Erin Allmann Updyke

Sure.

Erin Welsh

But all you have to do is swap out *Micrococcus pyogenes* for *C. diff* and he's absolutely right in this mechanism of how broad spectrum antibiotics perfectly set up the gut for something to take over.

Erin Allmann Updyke

Yeah.

Erin Welsh

But decades would pass before the idea of the fecal microbiota transplant would gain any real traction in human medicine especially as more antibiotic classes were discovered, being like oh well we can fix that, we can fix that this way, you know. It kind of reminds me a bit of how phage therapy dropped out.

Erin Allmann Updyke

Yes, yeah.

Erin Welsh

And it was used again, fecal microbiota transplants were used again in 1989 to treat someone with refractory ulcerative colitis and it was remarkably successful with lasting recovery. But for the most part reports of people successfully using fecal microbiota transplants were kind of one-offs, like these case studies of people trying out fecal microbiota transplants for a variety of infectious and noninfectious conditions on one patient, on a handful of patients, but not large scale. It wasn't until 2013 that the first randomized clinical trial was conducted in the Netherlands to look at fecal microbiota transplant as a treatment for *C. diff* infections. Here's where our villain and our hero meet. Took a while but hey.

And you'll see that it soon is resolved because in this study the participants all had recurrent *C. diff* and they were all randomly assigned to one of three groups, either receiving vancomycin alone, vancomycin with bowel lavage, or bowel lavage and then fecal microbiota transplant as treatment. And although this study was initially supposed to include 120 people with 40 people in each group, it was stopped early with only 43 participants. Why was it stopped? Because it was so incredibly successful that it wasn't ethical to keep going with the other control groups when fecal microbiota transplant showed such incredible cure rates.

Erin Allmann Updyke

Wow!

Erin Welsh

Yeah. So of the 19 people in the fecal microbiota transplant group, 94% were cured of *C. diff* infection.

Erin Allmann Updyke

Wow.

Erin Welsh

After a couple rounds of treatment, like 80-something were cured after one. 94% cured. Cured.

Erin Allmann Updyke

Yeah, right. And that means no more recurrences.

Erin Welsh No more recurrences. Compared to 31% of those in vancomycin-only groups and 23% of those in the vancomycin plus bowel lavage groups. So yeah, I mean leaps and bounds beyond the ability of antibiotics.

Erin Allmann Updyke Yeah.

Erin Welsh I love that, what a clear indication of hey, there's real promise here.

Erin Allmann Updyke Yeah.

Erin Welsh And after the study was stopped, the people who were in the vancomycin groups were treated with fecal transplants and they also showed high rates of cure. But how exactly do they work? How do fecal microbiota transplants work? What diseases or conditions do they seem to be effective against? How does one become a stool donor? What makes someone a good candidate for fecal microbiota transplants? Are there long-term consequences? We have so many questions about fecal microbiota transplantation and thank goodness we have an actual expert to help us answer them. But before we get to that I think that Erin, I want you to tell me just how much the world needs creative solutions like fecal microbiota transplants for this incredibly enormous global C. diff problem.

Erin Allmann Updyke I would love to right after this break.

TPWKY (transition theme)

Erin Allmann Updyke So we're starting off this season two episodes in a row with not great numbers when it comes to... We didn't know. Listen.

Erin Welsh Of all the diseases I would have expected C. diff to have good numbers.

Erin Allmann Updyke Yeah. I would have. Let me tell you what I've got. Estimates in the US and from what I can tell these numbers that get thrown around seem to be from 2011 is where they're getting these estimates-

Erin Welsh That's a long time ago in C. diff.

Erin Allmann Updyke It is 10 years ago.

Erin Welsh Yeah.

Erin Allmann Updyke Yeah. But that's what we're working with here, Erin. The US estimates about 500,000, half a million cases a year and 29,000 deaths due to C. diff infection. Now that number in the studies that I read was thought to be a huge underestimation but that's still the number that the CDC cites on their website for example today here in 2021.

Erin Welsh I was gonna say that sounds lower than I would have thought.

Erin Allmann Updyke Yep. The European Center for Disease Prevention and Control in the same year 2011 was estimating 124,000 cases a year and didn't have a real estimate on deaths that I found.

Erin Welsh Wait, all across Europe?

Erin Allmann Updyke

That was yeah, the European Center for Disease Prevention and Control. Now I obviously wanted to get better numbers than that so I was trying to find global estimates. I found a paper that was a meta analysis from a couple of years ago that looked at a whole bunch of different papers and calculated an average number of C. diff infections for every 1000 hospital admissions worldwide. And they calculated a global average of 2.25 cases of C. diff infection for every 1000 hospital admissions worldwide. And I was like wait a second, that number doesn't make a lot of sense. And if you look in that paper at the ranges with which they calculated this average, the ranges are bananas. They're anywhere from one case per 1000 to 37 cases per 1000 hospital admissions depending on which geographic region you look at. North America by far has the greatest number of cases reported compared to other places and even though this study looked at 41 different countries, there was no data whatsoever from South America or from Africa or from a lot of countries in Asia.

Erin Welsh

So still we don't have great numbers.

Erin Allmann Updyke

We still don't have great numbers.

Erin Welsh

Okay but the 29,000 deaths and half a million cases in the US in 2011 was an underestimation then and likely continues to be an underestimation.

Erin Allmann Updyke

Yes.

Erin Welsh

Okay.

Erin Allmann Updyke

I did a little bit of Erin math, you know, my trademark.

Erin Welsh

I love Erin math.

Erin Allmann Updyke

Me too. Trademarked Erin math, don't trust these numbers. So according to the American Hospital Association, and that's just in the US, there are over 36 million hospital admissions every year in the US alone. So if you look at those estimates of maybe it's as low as 2.5 - it isn't - cases of C. diff per 1000 hospitalization or has high as 37 per 1000, that's anywhere from 80,000 to over 1.2 billion cases in US hospitals alone each year.

Erin Welsh

It's quite a range.

Erin Allmann Updyke

Right.

Erin Welsh

Plus it's not just hospitals, what about long term care facilities?

Erin Allmann Updyke

Exactly, exactly. That's the problem. And we just with a lack of surveillance in a lot of places and sometimes even a lack of definitions on how are you testing or screening for C. diff infection vs colonization, how are you even defining a C. diff infection? It makes global estimates really, really difficult.

Erin Welsh

Well I think we can come up with a qualitative metric based on the biology of the disease as well as our medical practices of using a lot of antibiotics for good reason.

Erin Allmann Updyke

Right.

Erin Welsh: And that it's probably been only increasing since it was very first seen, I mean skyrocketed in terms of numbers and now it's everywhere and it's a huge problem.

Erin Allmann Updyke: It really is. So because of that there are a lot of areas of research ongoing when it comes to C. diff. Even though it seems like future areas, a lot of this research is promising enough that there are things that are not future future directions of research, they're present. The very first thing is probiotics. Probiotics are an area of research that I think is really fascinating, it all goes back to the whole microbiome which again we don't know a lot about. But there was a Cochrane Review from the team that showed with moderate certainty evidence - which is pretty good for a Cochrane Review - that probiotics can reduce the risk of C. diff infection by as much as 60% in people who are inpatient in the hospital on antibiotics.

Erin Welsh: Wow.

Erin Allmann Updyke: So giving probiotics concurrently with antibiotics might be significantly protective.

Erin Welsh: This is like opening a huge can of worms.

Erin Allmann Updyke: I know, I know.

Erin Welsh: Probiotics, what does that mean?

Erin Allmann Updyke: And it was a Cochrane Review. Exactly. I don't have data on what that actually means in practice because yeah, probiotics, they're not exactly regulated, we don't know enough about the human microbiome to know what are the specific bacteria and which probiotics do you take and how much money are you supposed to spend on these things, etc?

Erin Welsh: Right. And things that are claiming to be probiotics but are they actually probiotics?

Erin Allmann Updyke: Exactly.

Erin Welsh: What do you need to do to have 'probiotic' on your label?

Erin Allmann Updyke: That I don't have an answer to.

Erin Welsh: Things to think about.

Erin Allmann Updyke: Things to think about. And they did mention yogurt specifically multiple times in this.

Erin Welsh: That makes sense, yeah.

Erin Allmann Updyke: I know.

Erin Welsh: And I'm also all for probiotics.

Erin Allmann Updyke: Me too.

Erin Welsh: But we gotta ask questions.

Erin Allmann Updyke

But yeah, so that's kind of one thing now that seems to be really promising. And I don't think that it's really talked about enough and it's likely because of all the problems that are inherent like we already said with the idea of probiotics, that we just don't have good regulation on them, we don't know a lot about them. But that doesn't mean you can't find places that have live cultures of bacteria and help yourself. I don't know. Other things, there are even though antibiotics are still used very commonly for treatment of C. diff, we know that antibiotic resistance is a huge problem. There are a number of different monoclonal antibodies that have been shown to be beneficial for the treatment of especially recurrent C. diff infection, that would be something that's only available in the case where you're already really, really sick, it's not necessarily preventing you. There are also a lot of different vaccine candidates that have been studied, generally these are toxoid vaccines so vaccines against just the toxins A and B to help prevent infection from C. diff rather than just colonization. But yeah, there's a lot of promise both in terms of how we can potentially deal with especially severe C. diff infections today but going forward how we might be able to prevent them even more down the line. But here on TPWKY we all have our biases and one of ours is how amazing fecal microbiota transplantation is.

Erin Welsh

Yeah, I don't think we've been enthusiastic enough about it this episode.

Erin Allmann Updyke

No, it is truly... Like the first time that I heard about it I was just so enthused, I wanna be a donor and/or I want a transplant just because I think it's amazing.

Erin Welsh

I think it is like you said, it's just chef's kiss beautiful.

Erin Allmann Updyke

Yes! I love it.

Erin Welsh

Yeah.

Erin Allmann Updyke

So we were absolutely thrilled to speak with a true expert from OpenBiome which is a nonprofit organization that is all about expanding safe access to fecal microbiota transplant and increasing research into the human microbiome. We'll let them introduce themselves right now.

Majdi Osman

I'm Majdi, I am the Chief Medical Officer at OpenBiome and I'm a physician trained in infectious diseases, as you can probably tell by the accent trained in the UK. And my first encounter with FMT was about 10 years ago now and a patient, an elderly woman who had C. difficile infection after a hip operation and we'd run out of options for her. The sort of next thing on the treatment ladder was surgery which for a frail patient like this was going to come with a lot of risks. And so this was before stool banks, we had to do the FMT ourselves from a related donor of the patient and within three days the patient had fully recovered from their C. diff and was eating and ready to go home. So that was sort of my first encounter with this treatment, it wasn't until I came to the US and met the team at OpenBiome just as things were getting started there and ended up embarking on this adventure.

Erin Welsh

That's amazing. So talking now about OpenBiome, can you tell us a bit about the project and sort of what a nonprofit stool bank is? How did it get started and what are some of its missions?

Majdi Osman

Yeah, yeah. So OpenBiome, we're a nonprofit stool bank as you said. Our first mission is to enable safe access to this treatment, fecal microbiota transplants of FMT. And the second half of our mission is to capitalize research in the human gut microbiome using FMT but also other tools in our toolkit to support new ways of understanding and treating diseases, especially those in areas of unmet need. And we started really because of our Executive Director, Carolyn, she had a relative, a young guy in his early 20s just out of college had a gallbladder infection, had surgery and then some antibiotics after that and developed C. diff infection.

And eventually having found out that he would have to wait several months for an FMT, he would have had to drive hours to one of the hospitals in New York to get this treatment, decided to take matters into his own hands and ended up doing an FMT himself. And so that's sort of the motivating patient in a way for us to establish OpenBiome, really to make sure that patients who had C. difficile infection who had failed antibiotic therapy didn't have to go through that process again of having to source their own donor and getting their own treatment arranged and to make this as straightforward as getting a blood transfusion. And so we set ourselves up really to serve that need. And yeah, we've grown to the point now where we work with over 1000 hospitals across the US and 99% of the US population is within a 4 hour drive of a hospital using OpenBiome FMT.

Erin Welsh

That is amazing. What an origin story, I can't believe that. But it's clear that over the years the need for FMTs is more and more pressing and so it's an incredible thing that you guys are doing. And so before we get further into the transplant aspect of this, I wanna talk about donation. What is a stool bank? And also how does one become a donor, what are the criteria for acceptance? I have a lot of questions but we'll start there.

Majdi Osman

Yeah, sure thing. So a stool bank is a bit like a blood bank really. So what we do is we screen our donors, we're based in Boston and so all of our donors come from around this area. A bit like with a blood transfusion, we would screen our donors to make sure that they aren't potentially passing on any risk of either infection to a recipient or potentially some of these other diseases that we seem to see in association with the gut microbiome, these are things like asthma, diabetes, obesity, even mood disorders like depression or anxiety. And so we put these donors through a pretty comprehensive screening process which starts off initially with an online form that if anyone is interested in becoming a donor they go to our website, fill out a short form that excludes the common reasons that folks are ineligible to become a donor.

And so then if a prospective donor completes that form and it's all clear then they would be invited for an in-person clinical assessment led by one of our clinical team. That includes a clinical assessment where they run through nearly 200 questions related to their health, physical assessment, then if they pass that they go through a blood and a stool test. And yeah, it doesn't stop there though. If a donor passes all of that then they have an assessment each time they drop off a stool sample and then every 60 days they undergo the same three step screens, so the clinical, the blood, and the stool. The pass rate for becoming a donor is less than 3% so we often say that it's harder to become a donor at OpenBiome than it is to say get into MIT or Harvard because we are sort of screening these folks really rigorously.

Erin Welsh

Wow, that is very interesting. What a thorough process, I mean it completely make sense. So now I wanna switch to transplants. What are FMTs, fecal microbiota transplants, and how do they work? Could you walk us through the entire process from the patient's perspective?

Majdi Osman

Sure. So a fecal microbiota transplant or an FMT is a very simple treatment in a lot of ways. It's essentially taking stool from a healthy donor and transferring it to a patient who's got a disease, in this case *C. difficile* infection. And when a donor who's been screened and gone through that very rigorous process provides a sample, that sample is inspected and tested and then simply we add a saline glycerol buffer so that it stays stable once it's frozen, we homogenize it or blend it and then filter it to remove anything like food debris or other things that aren't relevant for the treatment. And so then that treatment gets frozen either as a liquid preparation that is instilled by a colonoscopy or via upper endoscopy when they use a gastric tube or alternatively we prepare it into capsules and these capsules can be taken by the patient at their doctor's office. And the patients are observed for several hours afterwards and then they can usually start eating 4-6 hours afterwards as well. And then in many cases patients are discharged on the same day, so they're able to go home.

And one thing we are really keen on emphasizing at OpenBiome is prevention of *C. diff* and so when patients go home, making sure that their home is clean, making sure that high touch surfaces are clean so that they're not re-exposing themselves to *C. diff* and where possible avoiding antibiotics as well or having a conversation with their physician that they've had an FMT and might be at risk of *C. diff*. So yeah the treatment itself is surprisingly straightforward in many ways but I think the complexity is around the donor screening and making sure that the patient is appropriately selected for an FMT and that the risks and benefits are clearly communicated to them as well before performing the treatment.

Erin Welsh

Gotcha, yeah. That is fascinating. I love the idea of pills, just like a little capsule and here's a new microbiome for your gut. It just feels like the future. And so actually your last comment there leads me to my next question which is about eligibility. As you mentioned unfortunately not everyone who has a *C. diff* infection is eligible for an FMT. So I wanted to ask what are the criteria for eligibility and who decides it?

Majdi Osman

So FMT is recommended for patients with *C. diff* that haven't responded to antibiotic therapy and that's the only patient group that this treatment is recommended for at the moment. And so 460,000 Americans experience *C. diff* every year, of those about 20-35% will experience a recurrence of that infection and then potentially from that population about 40-60% will experience a second recurrence and it's on that second recurrence of the *C. diff* infection that they are eligible for an FMT. The other consideration is FMT is still an investigational drug and what that means is that it has not gone through the FDA approval process and there remains some unknowns about the treatment itself.

And so at this stage in a relatively early time in the field it's important to make sure that patients, especially those who are immunocompromised for example, children or those in pregnancy perhaps, are carefully considered for FMT and in some patients they may not be eligible because of perhaps one of those reasons that mean the risk-benefit of that FMT treatment doesn't make sense in their case. So those are the main criteria really for FMT and I think over time we'll be refining those hopefully both to enhance the safety of the treatment and also to improve the efficacy as well of each treatment that's administered.

Erin Welsh

Yeah. And so you mentioned that there are some risks associated with FMTs both short term and potentially long term, for instance there's a lot that we still don't know about how our gut microbiota affects our risk of developing some chronic conditions right, like cancer, diabetes, heart disease, many studies have shown a link but what that link actually means, is it correlative? Is it causative? It's unclear. And so could you walk us through some of the risks of FMT both short and long term or maybe what you see as the biggest gaps in knowledge regarding risk?

Majdi Osman

Yeah, absolutely. So I think when it comes to risk of FMT it's always quite context-specific. In the case of C. difficile infection especially severe disease which carries a very high mortality rate and where even surgery carries a significant rate of morbidity and poor outcomes following the surgery, that profile, the risk-benefit profile in that patient may be very different to someone who is very early in their C. diff and perhaps has more options left on the table such as antibiotics or bezlotoxumab or other interventions. So I think the first thing to emphasize is that it's very context-specific and it depends on the patient but more generally speaking this is a treatment that relies instilling bacteria into a patient and we do all we can just like a blood transfusion to screen out pathogens and bacteria, viruses.

But there is always the potential risk that an infection might be transmitted. And COVID has taught us that we have to continuously be evolving our criteria for screening for infections to assess for new infections that might be on the horizon, especially antibiotic-resistant ones and also continuously enhancing the tests that we use to screen out pathogens that might be potentially transmitted in stool. The second sort of category of risks I'd say are as you said the potential association with noninfectious diseases. Today we haven't seen any evidence to suggest that FMT transmits any of those conditions or increases the risk of those, however I think it's something that we have to be very mindful of that we don't have much evidence on the long term effects of FMT.

And so it's really important with the patient that the clinician is having a meaningful conversation around the risks and the unknowns of some of these long term consequences of FMT. But for a patient who has run out of all other treatment options and faces potentially resection of their bowel or long term antibiotics or even worse development of really severe disease, that sort of risk-benefit needs to be taken into consideration. There are sort of efforts being made to set up registries, so the American College of Gastroenterology has set up a patient registry to follow up recipients of FMT for up to 10 years and I think that's going to be really helpful in understanding the risk profile of FMT and also the long term cure rates as well.

Erin Welsh

Yes, absolutely. And so you mentioned that this is still pretty new and those early studies, like when I talk about the early studies of FMT we're talking less than 10 years ago and those did show incredible effectiveness in curing C. difficile infection. Has that success been maintained since those early studies and as the number of FMTs performed has increased over the years?

Majdi Osman

Yeah that's been a really interesting thing. So at OpenBiome we follow the clinical outcomes of each patient that receives an FMT. A few years ago we presented data on over 2000 patients who had received an OpenBiome treatment and observed a clinical cure rate of 82% which is pretty consistent with the findings and clinical trials. But also the American College of Gastroenterology or ACG have been running a patient registry as well that I mentioned and they've to date followed up 259 patients and observed clinical cure rates of 90%. And so we're seeing these findings from these randomized control trials being replicated in the real world setting which is very reassuring of the treatment and its use in clinical practice.

But I think what we are going to hopefully learn more about in the coming years is how to improve that efficacy, how to select patients so that we are using this in the right context and the patient's microbiome perhaps is suited to this treatment. I think also simple questions like dosing for example could be potentially optimized. And so we're still learning so much about what it is that leads to clinical cure, why is it that some patients don't respond, and hopefully we're gonna be gathering more data on the real world evidence over time.

Erin Welsh

Yeah. Yeah that's really interesting. Those are incredibly high cure rates, it's just an amazing thing. And for this amazing, potentially amazing life-saving treatment there have got to be I assume some barriers in terms of cost or access. So what are some of those barriers?

Majdi Osman

So yeah, at OpenBiome our goal is to reduce the costs of treatment so that patients can access this at their nearest hospital. And so we've got over 1000 hospitals now that are able to provide OpenBiome treatments and the way that we've reduced the cost of the treatment is by centralizing all of that donor screening. If only 3% of donors pass the clinical screening you can imagine that 97% of that for a clinician to be able to screen donors who may not be eligible is really expensive. And so for a clinician to do this themselves can range from \$4000 to up to \$20,000 per single treatment. And at OpenBiome we charge just over \$2000 for our treatments. And so that hopefully makes the treatment itself more accessible but FMT today is still an investigational drug so it hasn't received an approval from the FDA, it's being provided to patients under a framework called enforcement discretion.

What does that mean to this question? It means that the treatment itself at the moment isn't covered by insurance and so patients are having to pay out of pocket for it or alternatively the clinicians are having to eat up the costs themselves. And so that obviously creates a barrier to access especially if we're thinking about coverage in some of the more rural areas or centers that might not be near a large gastroenterologist or infectious disease practice. But I think an interesting other lens on this is that given we are still quite early in the field, is there some justification for potentially building up centers of excellence that can provide this treatment at their centers, do all of the really sort of rigorous screening and assessment of the patient and follow up and really gathering the data to understand how effective this treatment is?

Erin Welsh

Right, yeah. So in this episode so far we've largely been focusing on FMTs in the context of *Clostridium difficile*. But they have been found to be an effective treatment for a number of other conditions or at least there's been early explorative research looking at FMTs for other conditions. So can you take us through some of the research that OpenBiome is working on in terms of other applications of FMT beyond *C. diff* infections?

Majdi Osman

Yeah, sure thing. So I think one example that's really interesting and potentially points us to how the field might move in the future is a clinical trial that we did looking at fecal transplants in hepatic encephalopathy. So hepatic encephalopathy is a condition that is associated with late stage liver disease, so liver cirrhosis and it is characterized by confusion and agitation, drowsiness, loss of consciousness and can be putting patients into the intensive care unit and is typically quite a challenging condition to treat, especially to maintain clinical cure. But it's caused by a build up of nitrogenous waste products that accumulate in the systemic circulation and part of the role of the gut bacteria is to break down some of those waste products.

And so working with a colleague of ours, Dr. Jasmohan Bajaj at the University of Virginia, we conducted a randomized control trial that showed that FMT was able to effectively treat this. Basically in this trial of about 20 patients, so a small study, half of the patients in standard of care group were cured and all of the patients in the FMT arm had clinical cure. And so that's just a really interesting sort of example of we talk about the gut-brain axis and this is sort of an early example of how potentially FMT and the gut microbiome may play a role in that.

The other piece of the study that I think is really interesting is Dr. Bajaj characterized the gut microbiomes of these patients before the study to see whether there were some common microbial signatures in the composition of function of the microbiomes in these patients. And we observed that these patients were particularly depleted in bacteria that play a role in the production of short chain fatty acids. And so what we did was to go back to our donors and we characterized the microbiomes of our donors and selected a donor that had a particularly high abundance of these microbes that these patients were depleted in. And so that sort of rational donor selection or personalized medicine approach to this may be something that we see more and more in the future with the sort of falling costs of genomics and the introduction of that into clinical practice. So I think that's a really interesting one.

The other diseases like inflammatory bowel disease, there've been a number of trials now that have shown promise in that especially in ulcerative colitis where we're seeing in patients with the very difficult disease about 37% of patients are in clinical remission after FMT which compared to about 18-20% of the standard of care is really exciting. And then as a nonprofit we are also exploring the role of this in disease areas that are perhaps neglected by pharma companies in the US and Europe to support clinical trials in low and middle income countries. And so we're actually working with the University of Cape Town at the moment looking at the role of fecal transplants in children with severe acute malnutrition who failed to respond to a nutritional therapy which is surprisingly the case in about 1/3 of kids with malnutrition. So yeah, really broad disease areas that we're working on.

Erin Welsh

That is so incredible though. I mean yeah, like you said very broad but promising and it just seems like such an incredible potential solution. So what do you see as the future of FMT? What hopes do you have for FMT in the future?

Majdi Osman

Yeah so I think we are at such an early stage of our understanding of the microbiome and the potential and the way that we should be using FMT and what I hope is a few things, I think. Firstly that we accumulated more and more data on patient outcomes in a more systematic way across the world for all patients that are receiving this treatment. I think the second piece is that aspect of personalization and can we do more to potentially increase the cure rates for patients who are receiving FMT for conditions like C. diff.

And perhaps in the future we're treating patients who have failed multiple rounds of antibiotics, is there potentially more we can do in prevention? Is there a world perhaps in a few years time where you bank your stool prior to receiving antibiotics and then you receive your own stool back to restore your gut microbiome after a course of antibiotics. And this is already being explored in some patient populations who are receiving lots of antibiotics like stem cell transplant patients. But we i think at OpenBiome are really interested in the public health approach to FMT and the microbiome and can we prevent diseases as much as treating them when patients are really sick.

And I'd say sort of the last thing really is we started OpenBiome to enable access to this treatment for patients when they need it, we know that there's still much more to do for that in the US but I think globally C. diff is likely to become more and more of a burden as we see wider antibiotic use and wider occurrence of risk factors that are associated with C. diff like inflammatory bowel disease. And so I think we're gonna have to be really mindful of making sure that people who may not necessarily have access to the same health systems as we do in the US can still access this treatment when they need it. I think COVID has highlighted more than ever the importance of sort of health equity and technologies and access to them as quickly as possible. And so I think yeah, hopefully that's the other piece that gets resolved and we're all working towards overtime.

TPWKY

(transition theme)

Erin Welsh

Thank you so much Dr. Osman, that was just so enlightening and I think I somehow, I didn't know it was possible, love fecal microbiota transplants that much more.

Erin Allmann Updyke

Even more, even more. Oh Erin, what a fun episode this was.

Erin Welsh

This was very interesting. I mean it did have its frustrating moments.

Erin Allmann Updyke

Oh yeah. Yeah like I really wish that we had better numbers and yeah, there's a lot of frustrations.

Erin Welsh: But I think *C. diff* is a very remarkable pathogen in that it's not necessarily a pathogen and its recent emergence and how much our existing medical structures kind of facilitate the growth of this bacterium and the spread of it is terrifying.

Erin Allmann Updyke: Absolutely, yeah.

Erin Welsh: Well okay, should we do sources?

Erin Allmann Updyke: Yeah, let's.

Erin Welsh: Okay. So I'm just gonna shout out a few, I have a bunch of papers but a couple that were key for the history and genomic aspects of *C. diff*. One if by Bartlett from 2008 and the other is the one that I already mentioned by Knight et al from 2015. And then in terms of the fecal microbiota transplant stuff, 'I Contain Multitudes' by Ed Yong, a very fun book about the human microbiome, check it out. And by De Groot et al from 2017 and I have to shout this out also because it doesn't just have great information but it also contains an amazing figure, one of my favorite that I've seen, of the most important developments in the timeline of fecal microbiota transplants but it's marked along intestines.

Erin Allmann Updyke: Ooh!

Erin Welsh: It's like starting in one part of the intestine and going into the other. It's beautiful.

Erin Allmann Updyke: Oh that's so cool.

Erin Welsh: I loved it. Yeah.

Erin Allmann Updyke: One of my favorite papers that I read was actually by Crobach et al 2018 called 'Understanding *Clostridium difficile* colonization'. I found that one just really, really interesting. But there was a number of other review papers on sort of *C. diff* infection and a couple at least including the 'Global burden of *Clostridium difficile* infections: a systematic review and meta analysis' that were trying to get at the global distribution. Yeah, so we'll post a list of all of those source son our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh: Thanks again Lainey so much for providing the firsthand account, we really appreciate you taking the time to chat with us.

Erin Allmann Updyke: Yeah, thank you. Thank you also to Bloodmobile who provides the music for this episode and all of our episodes.

Erin Welsh: And thank you to Exactly Right of whom we are a very proud part.

Erin Allmann Updyke: Mm-hmm. And thank you to you, listeners! You make this podcast possible and we love you for it.

Erin Welsh: We really do. Especially thanks also to our patrons, you guys are absolutely amazing. We love you, we appreciate you, it's just incredible.

Erin Allmann Updyke: A joy.

Erin Welsh

It is. Okay well this feels quite relevant but-

Erin Allmann Updyke

It does.

Erin Welsh

Until next time, wash your hands!

Erin Allmann Updyke

You filthy animals. With soap and water and not just an alcohol-based hand sanitizer. (laughs)

Erin Welsh

(laughs) I like that.