Dr. Troy Cline: Alright. Good afternoon everybody. I'm going to go ahead and start. Thanks for showing up. I know you're all anxious to start your Halloween festivities. But, this is too much thing in topic to miss, so I'm glad you're here. We are welcoming a local gastroenterologist, he's from San Jose, Dr. Peter Bangsund. He got his MD at the University of Missouri in Columbia. He did a residency and fellowship in Iowa, at The University of Iowa or The University of Iowa and he returned to California to set up a practice in Chico about two years ago. Two to three years ago and he's going to talk about fecal microbiota transplants as a treatment option for treating clostridium difficile infections. So, let's welcome Dr. Bangsund.

Dr. Peter Bangsund: Alright, well thank you. Thank you everybody for coming. I know 4 o'clock on a Friday, right before Halloween is a tough time to be here, so I do appreciate you all being here. My name is Peter Bangsund, gastroenterologist here in Enloe Medical Center. And, I'll be talking about fecal microbiota transplantation. Specifically, in the treatment of clostridium difficile or C. diff infections but will, maybe touch on some other applications here if we get some time. This is actually a procedure that's been around for some time but just over the past five or 10 years has been gaining acceptance by the medical community, my patients. So, it's something that we are starting to use more and more. Right now it's only been used for the treatment of C. diff infections but we're, like I said we're looking at other applications as well. Inflammatory bowel disease and some other things and so I think over time we're going to be seeing this more and more. I do have a lot of slides to get through, so I'm going to get started and hopefully we'll get through these and get you out of here in a timely manner. See if this works.
Oops, there we go. So, a lot of you may have heard of us C. diff already, so I apologize if some of this is old news for you but that is kind of an introduction. C. diff is a gram-positive spore forming anaerobic bacillus. Actually, fairly common pathogen, we used to see it mainly in patients who have been recently hospitalized or patients who were in some kind of a long-term care facility. But, increasingly we're seeing it more and more commonly, not only in those locations but also in the in the community as well. Because, antibiotics have been the main treatment for this, we're also starting to see a lot of antibiotic resistance. Which means, it's becoming more difficult to treat and we're also seeing a lot of recurrences of this infection as well. C. diff is responsible for up to a quarter of antibiotic associated diarrhea infections in the hospital. Which it's responsible for half million infections a year. Up to 29,000 deaths within 30 days of diagnosis, where it can be a fatal disease.
The economic cost is quite high as well, hospitalization just for a C. diff infection, that's not including any other comorbidities just the C. diff infection itself can run anywhere from 9 to $30,000 per hostile admission. In the 2008 that cost almost $5 billion, so it's a huge cost to the healthcare community. One of the major risk factors for C. diff infection is recent antibiotic use and the idea is that a lot of us are carriers of C. diff, even if we don't have the symptoms. A lot of us have it in our colons but it kept at bay by that the protective microbiota, the normal gut flora that we have. As soon as somebody gets put on some kind of broad-spectrum antibiotic, that antibiotic and then change that microbiome and allow the C. diff to flourish. And, so traditionally the treatment has been additional antibiotic, even though antibiotics where, what got us into this mess in the first place. The treatment has been additional antibiotics at us, specifically to kill off the C. diff to metronidazole and vancomycin have been the antibiotics that we use the most. There's additional kind of newer antibiotics, fidaxomicin example
we'll talk about that in little bit but the result is that we see more, more antibiotic resistance as I mentioned before. And, additionally since antibiotics were, what started the problem in the first place, the additional antibiotic, even though they kill off the C. diff, they are not fixing the underlying problem, which is the, the dysbiosis. We do have newer antibiotics, fidaxomicin, which is mentioned in the last slide. That's an attempt to get around the problems of the current antibiotic resistance. Problem with fidaxomicin is that, it's very expensive 3 to $4000 for a 10 day course. Obviously most patients can't afford that. Most insurance companies won't cover it but it can be effective. if the insurance company will cover it. So clearly there's a need for different modality of a treatment for C. diff.
And, that's where fecal microbiota transplantation or FNT comes into play. The idea here is that somebody who has dysbiosis from recent antibiotic use can be treated by taking a healthy population we put that in quotes. A healthy population of bacteria from a healthy donor and that bacteria then repopulates the colon and hopefully suppresses of the C. diff. hopefully eradicates the C. diff, although that's not always the case. Sometimes the patient remain C. diff positive, the goal is just to make them a symptomatic. I say healthy population in quotations because it's not entirely clear exactly which bacteria we need, so we take all of them in a stool transplant of course. In that way you can think of a stool transplant as being in ultimate probiotic.
The first FNT's, where actually performed a long time ago, fourth century China. What they would do, would take stool samples from a human or camel sometimes, mixing with water to create a yellow soup or a golden syrup. Which may sound a little more appetizing than the yellow soup maybe not, I don't know. And, then the patient would simply drink it and sometimes they would get better. Other times they wouldn't but apparently it worked often enough that this became a treatment for diarrhea. The first FNT's the United States were before the 1958 and those were, for patients who had C. diff infections. Right now FNT is only being used for C. diff, like I said were looking at other applications as well. The efficacy rate is really good. About 90% or more and this isn't a population of people who already failed multiple course of antibiotics. 90% is very, very good.
So, here’s the outline in want I’m going to talk about, I'm going to spend a little bit of time talking about the gut microbiome, the role of that in human health. I'm going to spend actually a little bit of time talking about that because it's kind of interesting field and it's kind of a hot area of research right now. I'll spend some time talking a little bit more about Clostridium difficile or C. diff. I'll talk about the FNT procedure itself. Then, if we have time, we'll talk about some of the future indications for FNT.
So, talking about the role
of the gut microbiome, it say, reviewing the literature that came across this quote and I thought it was too good to pass up, so I stole. It does go across to slides, so bear with me. I'm going to read it out loud. Imagine this scenario. The scientists at a conference claims to have found a new organ in the human body. It is comparable to the immune system, in as much as it is made up of a collection of cells. It contains 100 times more genes than the host. It is host-specific, contains heritable components, can be modified by diet, surgery or antibiotics, and in its absence nearly all aspects of host physiology are affected. While this may seem far-fetched, it is the current situation in which we find ourselves.
which we find ourselves. We now realize of the hug... the human microbiota, is an overlooked system that makes a significant contribution to human biology and development. Moreover, there is good evidence that humans co-evolved a requirement for their microbiota.
So, like I said, it has been a hot air of research over the past 10 to 15 years. The human body actually contain several different microbiomes. I'm going to be talking about the gut microbiome but there's also the microbiome of the mouth, the vagina, the nose. The intestinal microbiome, is actually kind of challenging to study for several reasons. Part of the reason
is that the... Let's get rid of that...
Here we go. Is that the microbiome actually changes as you go through the intestinal system. The small intestinal microbiome is different than the colonic microbiome. If you want to study the colonic microbiome that's a little bit easier to do. You just take a stool sample and culture it and see what you grow. The small intestinal microbiome isn't quite as accessible yet to go in with the scope. It take some small bowel biopsies and then culture those. It's a little bit more difficult to get. Beyond that, the microbiome is dynamic. It changes even in one person and it can change based on your close contacts, so intimate partners will very often have microbiomes. They don't become the same but they kind of, they become more similar to each other over time. Obviously, they can change and response to antibiotics or probiotics that can respond to, to diets. Even to, the health of the host can change the microbiome as well. Then, on top of that we have an in complete data set. Most of the data that we have on a microbiome, is from studies that were done in the United States and Western Europe and so we don't have good data on patients from Asian and African and other places. And, it's a, I think it's safe to say that their microbiomes are going to be different than ours, so we don't have, we have kind of a skewed data set.
So, the gut microbiome is largely divided into two different phyla. They're as many as 10 different phyla that have been identified in the human gut but most of those bacteria fall into two. That consists of firmicutes which are mainly gram-positive clostridium and bacteroidetes, which are gram-negative species including bacteroidetes fragilis, which is a common bacterium. And, the microbiome varies widely from one individual to another. We've identified as many as 1100 species of bacteria in the whole collection of people that we looked at. I've seen estimates, even as high as 2000 but in a single individual on average, a personal have 160 species of bacteria represented in their testenal system. So, you can imagine from that huge pool of diversity, there's going to be a lot of variation for one person to the next and the question comes up very frequently. You know, which bacteria are the important ones? Which ones are the ones that are conferring health benefits to us? And, more and more we started to think that it's not so much the species of bacteria that's important but more the functions of those bacteria are performing. In other words, it doesn't matter whether you have species A, B and C, it's more the functions that A, B and C are providing and maybe D, E and F provide the same functions. As, okay to have those as well, so it's more the function rather than the actual species. There are some caveats to that. One example would be, (oficiala bacterium prosidency) which is a bacteria that is, either absent or in very low levels in patients who have inflammatory bowel disease. Like ulcerative colitis as or Crohn's and maybe one of the positive factors in patients who have that diseases, they don't have the right bacterium in there.
So, talking about the functions of the gut microbiome, a lot of what the bacteria do is carbohydrate malabsorption or carbohydrate metabolism, I'm sorry. So, when we eat something like a complex plant-based polysaccharides, some bacteria help to break that up into smaller oligosaccharides. Other bacteria help to break that up into smaller, short chain fatty acids and other gases. Those short chain fatty acids end up being very important for human health. They are very important source of energy, especially for the colonic cells. And in fact in patients who have undergone some kind of a diversion surgery, so that's where part of the intestinal system is disease for whatever reason. Maybe they have an obstruction from the colonic tumor that is preventing stool from going through or maybe they have a very bad inflammatory bowel disease and for whatever reason that part of the colon has to be bypassed. We can do it diversion, which is where you either have an ileostomy where the small bowel hooks up to the bowel wall. The small bowel hooks up the abdominal wall and stool drains into a bag from that or colostomy where the colon is hooked up to the bowel that the abdominal wall. And, what we find is that downstream from there in the part of the colon that has been bypassed, those colon cells can get very inflamed and irritated. And, the reason for that is that are not getting their usual energy supply from the short chain fatty acids. Which are actually coming from bacterial metabolism and one of the treatments for that is to provide short chain fatty acids often in the form of an enema. You just give them a short chain fatty acid enemas and overtime you'll see the, the health of the colonic cells increase. Actually up to 10% of our daily energy requirement, probably comes from colonic fermentation of food stuffs that we wouldn't be able to metabolize ourselves. To be on the source of energy, the byproducts of bacterial metabolism also include small organic compounds that can help regulate the peripheral immune system or tolerance of the resolution of inflammation and then also act as substrates for lipogenesis and gluconeogenesis.
Not only does the microbiome help maintain a normal human health and physiology, some of those byproducts can cause disease as well. And, what we find is that often when you provide the bacteria with a substrate that consists of animal protein and fats are very often the byproducts will include things like ammonia and hydrogen sulfide and other molecules that can actually play a role in causing disease. They can cause inflammation, they can break down the tight junctions between neighboring corn walls cells. Which leads to a leaky gut. Which can lead to translocation of bacteria into the bloodstream and bacterial toxins, like endotoxin, lipopolysaccharide. What we're finding is that a diet that's higher in fiber and plant-based carbohydrates may inhibit some of those actions and in addition to that certain byproducts like polyphenols, which we find in alkalis red wine and various other sources, can actually change the composition of the microbiomes as well and produce a more health promoting microbiome. Microbiome that has more bifida bacteria lactobacillus for example. There is an interesting interplay that's going on here, not only do we provide a substrate that the bacteria metabolize and the byproducts affect our health but also the substrate that we provide the bacteria can actually affect the microbiome itself.
So, this is an interesting study. It's very small, so you're only looking at 18 patients. This is done in 2012 and this is looking at the role of the microbiomes on insulin resistance, so insulin resistance is part of the path of physiology of type II diabetes. And, it kind of goes along with the whole metabolic syndrome. The metabolic syndrome is a cluster of different disease processes, which include, again, insulin resistance but also cardiovascular disease, fatty liver disease, dyslipidemia like high cholesterol and high triglycerides. They took 18 patients who have metabolic syndrome and for each of them, they gave them a FNT. They did it through a duodenal tube, which is a tube that goes through one of your nostrils, down into your stomach, into your small bowel and then they infused stool through there. So, that's a lot of fun for them I guess. I don't know how they got those guys to volunteer but they did apparently. So, nine of them received a stool transplant from a lean donor. A donor who had a BMI of less than 23. The other nine received an FNT, where they used themselves as the donors, so they used their own fecal material that went back into the duodenal tube into their small bowel. They measured their insulin resistance both at baseline prior to the FNT and also six weeks later and in addition they looked at the microbiota composition. Both of the colon as well as the small bowel they ended up with stool sample and then small bowel biopsies and they looked at the production of short chain fatty acids.
Here's the data, in this case it's a little messy swimming kind of, run through this. So, there's two panels here, A and B. A, they're looking at peripheral insulin resistance, which has to do with how well insulin is driving glucose into the cells in the periphery. B is looking at hepatic insulin resistance or sensitivity, which is where they're looking at how well insulin suppresses gluconeogenesis in the liver. And, what they found was that in the patients who had the allogenic transplant, which is, where they gotten, it was the lean donor, what they found was that there was a significant improvement in insulin sensitivity and that was significantly with a p of less than .05. They did not see the same one in the autologous transplant and by the way this is a type O way thing from the author that should be autologous. With the hepatic insulin resistance they saw similar trend but it didn't quite reach a statistical significance and remember this is a small sample size. So, in other word the stool transplant did cause a change in the host physiology.
They also, so this is a representation of the microbiome of the colon, so on the left you have the lean donor group. On the right you have the self-donor group and so each column represents each patient. So, they’re represented by random numbers here. Each row represents a bacterium, bacterial species and in the color represents whether that bacterium increase or decrease, so the more red it gets, the more increase, the more blue it gets, the more decreased between baseline and the six-week time period. And, what they found was that over that period of time there were 16 species of bacteria that increased and between the allogenic in the autologous groups there were six that differ significantly between those groups. And, those are the ones that are outlined in red and interestingly all six of those are butyrate producers.
Likewise, this is the small bowel, microbiota. They found that at the end of the six weeks there was seven species of bacteria that it increased and between the allogenic and the autologous groups there were three species that increase significantly. And, again those are butyrate producers as well.
And, so to summarize the results in more word format I guess. Again. They found a significant improvement in peripheral insulin resistance, in the allogenic transplant of lean donor group but no change in the self-donor group. There was a trend towards improvements in hepatic insulin resistance in the lean donor group but not in the self-donor group. Interestingly the obese patients had a much lower diversity of colonic bacteria before the transplant, higher amounts of bacteroidetes and decreased amount of firmicutes compared with lean donors. Six weeks after the transplant we talked about the increase in 16 groups of bacteria including many of which were butyrate producers.
Same with the small bowel and the conclusion that they reached was that the data suggest a role of bacterial functions, especially butyrate production in improving insulin resistance. And, this may be partially due to an effective butyrate on decreasing translocation of endotoxin, which is been shown on a passive driving resistance. It's unclear whether that's due to the difference in diversity because again remember the obese patient had a much lower diversity of the bacteria to begin with. Or whether they had to do with specific strains, if they were inoculated with, with the transplant but at some point in the future this this may provide another therapeutic modality for treatment of insulin resistance. The metabolic syndrome and maybe even type II diabetes.
So, I might skip through some of these next slides a little bit quicker just because of time but the punch line here is that the microbiome has an effect on several different areas of human disease. Liver disease would be one. Just quickly looking at the, the normal blood flow through the gut,
Inflammatory bowel disease

- Inflammatory bowel disease (IBD)
  - Crohn’s disease (CD)
  - Ulcerative colitis (UC)
- Complex interaction between host factors and microbiome
  - Strong genetic component in IBD, but not complete penetrance
- Bacterial etiology suspected for over a century. *Mycobacterium avium* suspected in 1913. Other potential culprits have included *Helicobacter*, *Campylobacter*, pathogenic strains of *E. coli* and others
  - With the vast number of bacteria in the gut, identifying the culprit was like finding a needle in a haystack
  - Over past decade, focus has shifted to the haystack itself

(Hold CIL, et al. WGO 2014; 205): 1102-1210.)
after the blood leaves the intestinal system and travels through the veins. Into the hepatic portal vein, where then hits the liver. So the liver is the first stop for blood coming out of the intestinal system and you can, should be easy to see that the liver can be easily influenced by the gut microbiome and by metabolites, endotoxin and so that's coming from the gut microbiome. So there is a role in liver disease.
There's a role in inflammatory bowel disease as well
and I'm going to skip through most of this
but um,
we are starting to look at the FNT is a treatment modality for inflammatory bowel diseases as well.

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<th>Role of probiotics in IBD:</th>
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<tr>
<td>- May be used in conjunction with standard meds (5-ASA compounds, immunomodulators, immunosuppressants)</td>
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<tr>
<td>- <em>Lactobacillus</em> sp, <em>Bifidobacterium</em> sp, <em>Saccharomyces boulardii</em>, <em>E. coli</em> Nissle 1917</td>
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<td>- VSL#3: commercially available probiotic which contains 8 strains of bacteria: <em>Bifidobacterium breve</em>, <em>Bifidobacterium longum</em>, <em>Bifidobacterium infantis</em>, <em>Lactobacillus acidophilus</em>, <em>Lactobacillus plantarum</em>, <em>Lactobacillus paracasei</em>, <em>Lactobacillus bulgaricus</em>, <em>Streptococcus thermophilus</em></td>
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<td>- Increase microbial diversity, compete with pathogenic bacteria, increase mucosal barrier function through production of SCFAs, decrease inflammation through interaction with intestinal dendritic cells.</td>
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Role of FMT in IBD

- To date, few studies have been done with inconsistent results. In one small series, 6 adults with chronic active UC, unresponsive to medical therapy, were given FMT. At 2 weeks, all had some symptomatic improvement, but none experienced clinical remission: 3 patients had demonstrable alterations to their microbiome (decreased *Proteobacteria* and increased *Bacteroidetes*), but this did not correlate with long-term improvement.  

- In another series, 6 adults with UC were treated with FMT daily for 5 days. All were in remission at 4 months. 1-13 years later, no clinical, colonoscopic, or histologic evidence of UC in any patient.  

There's a role in colorectal cancer, the data is a real good yet but it does appear that a certain bacterial species are linked with adenomas in colorectal cancer.
I might talk about this study real quick just because it's, it's pretty interesting. It's known that in the United States, African-Americans have a much higher rates of colorectal cancer than general population. It's also known that in Africa the rate of colorectal cancer is much lower, there's probably many reasons for that. Part of being less, less diagnosis but one of the reasons is wiser such a huge difference it's probably more than just the fact there were not diagnosing a lot of it in Africa. It's hypothesized that a lot of it may have to do with diet changes and also with changes in the microbiome and so in this study what they did was they took a group of African-Americans in the place them on kind of an African diet. That is very high in fiber, low in animal fat and protein and a measured the mucosal expression of Chi 67 which is a biomarker for colorectal cancer risk. So not a marker for cancer but for cancer risk. It's actually a marker of cell proliferation and what they found was that Chi 67 decrease within two weeks of starting the diet. It's pretty quick and likewise when they put rural South Africans on a westernized diet, which was much lower in fiber, higher in plant, I'm sorry animal protein and fat. Again, they found an increased expression Chi 67 within two weeks. Suggesting that diet has a very important role in colorectal cancer risk. They also found that there was differences in the microbiome between after changing the diet suggesting that perhaps the diet was affecting the microbiome, which is in turn affecting colon cancer risk. Obviously, this is a correlational data, so it's hard to find a causal link specifically but it was interesting none of the less.
I think I'll stop there as far as the gut microbiome. The bottom line is that the gut microbiome does appear to have an effect on host, a health over a broad range of, of organ systems and FNT may become useful for at least some of these in the future as well. To talk a little bit more...
about C. diff, I've mentioned before it's a gram-positive spore forming bacillus. It's actually present in up to 13% of a symptomatic people, so some of you sitting here maybe sit next to somebody was C. diff right now or may have it yourselves. The spores are very resistant to antibiotics, dehydration, and temperature. Obviously, this is spread to the fecal oral route, so if somebody doesn't wash their hands very well and they touch a doorknob, somebody else touches that same doorknob eventually touches their mouth and that's how it gets spread. And, the spores can last on doorknobs and counter-tops and that kind of things, for a long time. Also, because they're resistant to antibiotics, that's one of the reasons why people can have recurrent C. diff because the antibiotic will kill the fully developed C. diff but the spores that remain behind can avoid that and then develop it C. diff later. The toxin genetic streams produce two toxins which we called toxin A and toxin B because we didn't have a better imagination I supposed. And, the way those toxins work they can affect the tight junctions between and recites, which can again lead to more leaky gut. They can infect, they can affect the cell cytoskeleton, which leads to deformation of the cells and the overall effect is that there is a leakage of bacteria and bacterial contents into the blood supply, which can lead to inflammation chemotaxis of neutrophils and other inflammatory cells. That area, which in turn release more of pro-inflammatory cytokines and the overall increase permeability of the gut wall, secretion of fluid into the intestinal lumen, the inflammation mucosal damage is what leads to the profuse watery diarrhea and mucosal bleeding that we see with C. diff.
There's also a hyper virulent strain, which is called NAP-1027. Which is alarmingly becoming more and more common. Not only in the hospital but also in the community and the significant thing about this is that, number one it has increased resistance to fluoroquinolones. A fluoroquinolones aren’t usually used to treat C. diff, so the reason that's significant is that fluoroquinolones are very broad spectrum antibiotic that we used for a variety of other infections including pulmonary infection, sinus infections, skin infections and various other things and the more resistant C. diff is to that the more likely the antibiotic is to select for the C. diff. So, in other words, you're more likely to get a C. diff infection, if you're already colonized and they use one of these antibiotics. The hypervigilant strain also has an increased expression of Botox A and B. In fact, the expression can be 20 to 30 times higher than, the than the regulant strains, through the regulant strains. And, it's a significant risk factor for a more severe disease, which I'll define in a little bit. The need for colectomy, which is the surgical removal of the colon and 14 day mortality. So, it's a nasty strain of C. diff.
This is a gram stain of C. diff, so you can see the purple rods.
This is a biopsy of the colon of somebody who has C. diff. And, so the usual architecture that you would see, these things here are called the crypt. So, you normally see that in the colon, the area between us is called the lamina propria. What you're seeing here, it's going to be a little bit difficult to, low magnification but there's inflammatory cells are coming into the epithelial lining of the crypt. We call that crypt Titus. You're starting to see that in a lamina propria there's an increased density of inflammatory cells as well, so right here it looks a lot more dense than, for example in this area here. There's a lot of inflammation going on in there. This pinker, kind of eosinophilic area right here, is cell necrosis. And, then the interesting part and the part I wanted to show in this particular biopsy, is this area right here. If you use your imagination this looks like a little bit like a volcano exploding. And, that's actually called a volcano lesion. This stuff up here is all fibrin and cell debris and bacteria. And, this finding here is almost pathognomonic for C. diff infection, if you see this on a biopsy is almost always C. diff.
If you did a colonoscopy, this is what you would see. This is what a normal colon should look like. You can see this nice, pale, pink mucosa with this well demarcated blood vessels in there. That's what you want to see, that's normal. This would be a colon that's infected with C. diff, so you can see that the mucosa is much more inflamed. You've lost that nice of vascular structure, you can't see that anymore and then all this [exit date] here, again, is fibrin and cell debris. It can be very tenacious and difficult to wash off the wall and we called those pseudomembrane. You can see that in this picture as well. These are all called pseudomembrane, again that's pathognomonic for clostridium difficile. In fact, one of the other names for C. diff is pseudomembranous colitis because of the way the colon looks when it's affected.
The risk factors, again, includes a recent antibiotic use. Especially, broad-spectrum antibiotics because they’re going to kill off more of the normal gut, microbiome. In fact, 90% of patients with C. diff, have had antibiotics in the past two weeks. Increasing age is a risk factor. A recent hospital admission, use of acid suppressing medications, so these are medications like proton pump inhibitors and H2 blockers. Which are very commonly used, in fact they’re some of the most prescribed medications in the country. They’re used for acid reflux and goertzen, you may actually be on them. It’s a risk factor for C. diff and the reason for that, is that, since C. diff is spread through the fecal oral route normally the acid in your stomach, which pH run one is very acidic. Would kill whatever bacteria's coming through but if you suppressing that acid and the pH comes up to run four, which we typically see with this kind of therapy. The C, diff could get through more effectively. If the patient is using some kind of an anti-motility agent, like Imodium and a lot of them are because it got diarrhea. That's not necessarily risk factor for C. diff but that is a risk factor for severe C. diff. A more severe form of the infection because the bacteria can move and get out of the colon as quite as quickly, kind of fester in the colon and causes more of a problem. Mechanical ventilation and hypo almunia, that's just a low albumin level in your blood. These last two are just markers of, just overall illness, so patients who are in the intensive care unit or maybe malnourished or have chronic liver disease or something like that. Those can be risk factors as well.
The clinical presentation of the most common thing, of course, is going to be profuse diarrhea. It's usually watery, it can be bloody as well, up to 10 or 20 times per day sometimes. Patients can also have abdominal pain, fever, fatigue, nausea, vomiting and weight loss. Not every patient is going to have all those symptoms but any of those symptoms can occur in a patient with C. diff and of course, the diarrhea is going to be the main one.
I mentioned severe C. diff before, there's actually a specific definition for severe C. diff. And, that's where, not only do they have C. diff but they also develop an increase of white blood cell count greater than 15,000. If you’re following a patient in the hospital and they suddenly bumped their white count, and it's time to start getting nervous. If they develop acute kidney injury and that's defined by a serum creatinine, increasing by one and a half times their normal baseline. The creatinine, is a lab that we follow, which looks like kidney function, is actually inversely proportional to the function of the kidneys. So, as the creatinine goes up, it means the kidney function is going down. So, again if you see the creatinine bump, it's time to get nervous. It can lead to sepsis and shock, which is manifested by low blood pressure, high heart rate and fevers. And, the dreaded complication is something called toxic megacolon, which is where is, it's exactly what it sounds like. The colon become severely dilated, enlarged. It loses its usual peristalsis where it doesn't move things through the way it is supposed to. It's in a very high risk for perforation and peritonitis and, so if the patient develops toxic megacolon, that usually requires a surgical resection and usually pretty quickly.
So, here's toxic megacolon, so this is an x-ray. It's a plain film, pretty obvious where the colon is in there. Shouldn't be that dilated, that should make you very, very nervous. And, here's a surgical resection of the colon and you can see just how dilated and enlarged and unhappy that it looks. Either that or just a really small surgeon, I don't know.
So, as far as diagnosis goes, the first step anytime you're diagnosing is good history and physical exams. So, on history you're looking for the major risk factors, which would be, you know, recent antibiotic use, reason infections, and recent hospitalizations that sort of thing. On physical exam there's not a lot that you're going to see. Specifically, that makes you think of C. diff but you're going to be, of course, paying attention to the abdominal exam, if they're getting very distended. If they have decreased bowel sounds and you start thinking about toxic megacolon. On a laboratory examination, the main things you're going to be looking at are there blood counts. You want to make sure that they're not becoming anemic from blood loss, again, they can't have a lot of bloody diarrhea with this. And, you want to make sure they don't have a leukocytosis, which is a high white count, again, that just means they are becoming a more sick with a more severe form of C. diff. You'll be paying attention to electrolytes, specifically, kidney function but if anytime that somebody is having a lot of profuse diarrhea, they can develop all manner of other electrolytes abnormalities as well. The treatments or the diagnosis of choices is going to be a C. diff PCR, polymerase chain reaction. You take a stool sample, you're looking for C. diff DNA. That's actually quite sensitive and specific, 90% sensitive, 96% specific. Actually, I think the sensitivity is probably higher than that. That's the number I came across, when I was reviewing the literature but I think it's actually higher. And, it got a very quick turnaround time, which is very nice, so you can send in the stool sample within an hour. So, you have a positive or negative result. Imaging is usually not needed unless you're concerned about toxic megacolon or perforation. The x-rays usually kind nonspecific but it can show free era of the diaphragm, if there's been a perforation. CT scan is going to be a little bit more specific for inflammation, not necessarily C. diff but you'll see colon wall thickening, which usually means inflammation. Mucosal enhancement, which just means that the bowel wall is kind of lighting up because there's increased blood flow there from the irritation.
Mesenteric fat stranding is just an appearance of the mesenteric fat. It kind of gets kind of hazy and, and smoky looking on the CT. All of those just mean inflammation, so that's what you would see on, on a CT scan. Colonoscopy is usually not needed but if a colonoscopy was done, of course, you'll see the changes that we saw on the slides if you slide back, pseudomembrane in a very inflamed colon. You can get a stool sample during a colonoscopy, so you can actually go up and ask for a stool sample. Again, that's usually not necessary, if you're having 20 stools per day. Is readily available.
The treatments, the first thing you want to do is try to stop the offending antibiotic as soon as you can. That's not always possible, they're put on the antibiotic for a reason. For some other infection, a dental infection or something, but, as soon as you're able to safely stop it, you want to do that. You may be able to narrow down the spectrum of the antibiotic, a little bit. Which, which can be helpful but the main treatment, of course, is going to be to start additional antibiotics. So, we talked about before metronidazole and vancomycin being the two that we use the most. Metronidazole is usually used for mild and moderate disease, although, we're starting to see a lot more resistance to that. So, a lot of us are just starting off with vancomycin, even for more mild infections. The interesting thing about vancomycin, when vancomycin is used for any other disease process, any other infection, is always given IV. If you take metro, vancomycin by mouth it doesn't get absorbed into the bloodstream, so it has to be given IV. But, if you get IV it doesn't get into the intestinal lumen and so the treatment of C. diff, this is the only treatment where you would use vancomycin orally. If the patient is very sick, oftentimes they'll have decreased intestinal motility. Things aren't moving through their intestinal system the way they're supposed. They'll have an ileus or if they're developing toxic megacolon, taking the vancomycin by mouth, the vancomycin may not need, may not go where it needs to go, if they have decreased the intestinal motility. So, in those cases it can also be given directly via enema. That's how you'll treat the initial infection, once that's been treated there's a 30% chance that you'll get a recurrence. If you have one recurrence there's a 40% chance that you'll get another recurrence. If you get that recurrence there's a 50% chance to get another one, so it becomes more and more likely. So, the first recurrence we typically treat the same as before, again, metronidazole or vancomycin, sometimes you'll get lucky and it works a second time and the infection is gone. My experience is more likely, that's not the case. Alternatively, you could use fidaxomicin, again, it's incredibly expensive.
Patients can't pay for it, most insurance companies don't pay for it. I've actually stopped, even trying to use it. It's a great antibiotic, it's just, and it's too expensive to be used.
For the second recurrence, so if they fail that second course of antibiotics, the third course typically involves a prolonged and tapered course of oral vancomycin and the idea behind this, we have talked about the spores before. Now the spores can be very resistant to antibiotics. While the idea here is that you want to keep antibiotics in the intestinal system for a prolonged period of time, so as the spores start to develop into mature C. diff and then they'll get hit by the antibiotic and die. And, this actually does work from time to time. I've actually been able to, to hold off on doing an FNT on somebody because of, of this sort of thing but that, that the typical course would be vancomycin four times a day for two weeks. Then, twice a day for a week and then once a day for a week and every other day for a week and every third day for a week and then stop. And, then by the time you're done you're
kind of feeling like,
like this guy here, made out of pills. A lot of medications to be taken.
There is a role for probiotics, in the treatment of C. diff. really the only probiotic that shown any promises is saccharomyces boulardii. The brand name is florastor, its effect is modest at best. You would never use it as the only treatment, it would always go alongside with antibiotics. And I use it from time to time as well. Usually, there's no evidence for using any of the other probiotics, other than saccharomyces.
So, that's it for C. diff in the treatments. Next I'll talk a little bit about the FMT procedure itself.
The first thing you need to do is find somebody to provide the stool. There's a couple ways that you can do this. The first is that the patient needs to bring their donor with them to the clinic. It's either going to be a spouse or family member or close friend. The other way is that we're now starting to get stool banks. Popping up around the country kind of like a blood bank there are now stool banks. Where you can get a pre-processed stool that you can use this kind of thing. When I first started doing this at the University of Iowa, we always used a donor that was brought in by the patient. Obviously, the main risk that you want to think about is the transmission of some kind of infectious disease. Same with blood transfusion, where you can get HIV or viral hepatitis or something else. You can also get an infection from a stool donation and so most of the exclusion criteria are going to include infectious disease risks. So, no high-risk sexual behavior, no tattoos in the last six months, no incarceration in prison within the last 12 months and so on. No recent travel to areas of the world
where a high risk...
Infectious diseases are endemic. Including India, Southern Africa and Great Britain. Does anybody know why Great Britain would be on that list? It's not their food. Actually, it is their food, it's because of mad cow disease. They had an outbreak of mad cow disease, 15 or 20 years ago. And, so we don’t want their stool, I guess. One thing that people often don’t think about is this last one. That if you, if somebody has eaten something like peanuts or shellfish and the recipient has a life-threatening allergy to that. They could go into anaphylaxis and so the donor can't have eaten any allergens that the recipient might be allergic to. People don't often think about that. And, the other thing that makes this quite difficult is that we want to make sure that the donor doesn't have a whole variety of other diseases. They need to have they, they can't have constipation. They can't have chronic diarrhea, they can't have fibromyalgia chronic fatigue syndrome. A whole host of other diseases because we're learning more and more of the microbiome might play a role in some of these disease processes. And, it's theoretically possible you might give somebody fibromyalgia through the treatment for their C. diff.
So, not only do they go through this rigorous medical history, of course, they get tested as well. So, the stools are tested for other infections, their cultured, microscopy looking for various parasites to check for C. diff. The blood is checked for a viral appetite, HIV, syphilis and various other things.
We have talked a little bit about kind of a related donor, versus a non-related donor. Initially there is some data that was shown, it might be a difference in efficacy. Where the related donor might be a little bit more efficacious than getting a transplant from a non-related donor. I don't think the difference is as dramatic as what we're seeing here because the data that we're getting from stool banks is close to
90% for the,
for the treatment. Which is, so I don't think this different is quite as big. But, that's at least something to think about when you're talking to patients about efficacy rates of this. Again, if you're using a known acquaintance of the patient and you're not using up a pre-processed sample from stool bank. The stool sample has to be fresh, it has to be less than six hours old at the time of the procedure and that can be very difficult to do it. We found this out when we were doing this at the University of Iowa, it turns out that not everybody can poop on command and so if you have six hours to poop and then get that to the place for the, the colonoscopy and it's a two-hour drive to get there and you have a four hour window now. Not everybody can do that within that four hours and so we would have people showing up for their procedure without a donated sample. And, that's a big, big problem of course. It can be very difficult finding a donor who fits those criteria. Those criteria are very strict, if the spouse has chronic constipation or chronic diarrhea, right there they can be used. If they have any of these other illnesses like chronic fatigue and fibromyalgia, which are very common, they can't be used for this process. So, finding a donor can be very difficult and then there's a lot of psychosocial barriers as well. A lot of patients have difficulty asking somebody, if they can provide stool for a transplant. This is very difficult thing to ask a family member or a friend and so this is been very difficult and that's where the...
stool banks have come in handy and really streamline the process. Open biome is the one that we use at Enloe. They get the stool, is pre-processed, it comes frozen. Soon as you need it, you thought it's good to go, it's really made this lot easier.
They used professional donors, so these are people who have been screened. They meet all the selection criteria, of course. They, they're very closely monitored, so after they provide a stool sample, that stool sample is processed and then is held in the freezer until they past their next set of screenings. Before its release for clinical use. They typically use about 50 g or more stool is mu, homogenized into a sample size of 250 cc. Filtered to remove the particulate matter and then kept frozen, it can remain frozen for up to six months. Then you can thaw in a 37° water bath for an hour or so prior to the procedure and use it. It's a very, very easy, very convenient.
There's several different ways, that you can give it. One way is through in a nasal digital tube, so again that's a tube that goes through into a nostril, down into the stomach and goes through, this is the duodenum right here, this loop. And, then be on the ligament of treitz into the jejunum and you just infuse it straight through into their small bowel. The nice thing about that is that you don't have to prep somebody for colonoscopy and sedate them and then go through that whole process. The problem with it is a couple things, number one, if again and if somebody has decreased motility because of their illness it may not get to where it needs to go in a timely manner. And, the second problem is that most patients just are not agreeable to having someone stool in fusing to their upper GI tract. You don't want to have that in fusing and verve afterwards, it's not fun. So, I've actually never had a single patient who wanted to have this done but it's possible.
Generally, it's given via colonoscopy and so what we do as we advance the colonoscopy all the way to the very first part of the colon. You're looking at the patients, so this is the right side and this is the left side. I generally, even go into the very end of the small bowel the terminal ileum and then you can infuse the stool into this area, generally, the ileum and the right colon. It can also be given as an enema, in that case the stool only gets to about here and so looking at the efficacy rates based on where it's infused, you can see that it's going into the sink and the ascending colon has the highest efficacy rate. It's less than the other places, I don't know who's putting it into the stomach. That's a horrible, gastric acid by itself. That's probably why the efficacy rate is lower but, I guess the fourth century Chinese, where doing that.
If the initial transplant is ineffective there is some benefit to repeating it using a different donor? And, overall as far as the safety and side effects go, infection of course, is the greatest theoretical concern so far in the literature. There hasn't been a single case of infection and that's because of how closely the, the donors are being screened. Sometimes people can have us impose procedural abdominal pain, that's typically minor and short-lived and actually you can get that with the standard colonoscopy as well. There was one report of weight gain after getting a donation from an obese patient. That's one of the exclusion criteria that open biome uses, you have to be within a certain range of, of a BMI but overall it's very, very well-tolerated.
So, there's some FDA issues, which are kind of interesting. FNT is actually not approved by the FDA right now. FDA considers it an investigational new drug. Typically, if you're going to use an investigational new drug, you have to file an IND application with them but because of the very high rate of efficacy, the very low complication rate and the mortality and morbidity of untreated C. diff, they finally did loosen their restrictions. And, as of July 2013 the FDA states, that it would exercise enforcement discretion, which allows physicians to perform FNT's without an IND. Again, we can only do that for C. diff infections, if you want to treat inflammatory bowel disease or something else, then you still do need to go through the FDA with an IND application. So, right now it's only for a, for C. diff that we can use it for. Interestingly I've actually had patients show up in my clinic. Specifically, asking for an FNT because they're obese, so this information is out there in the publican and people are asking for it. Maybe, it's been on Dr. Oz show or something like that.
And, finally just a few minutes on the future indications for FNT.
It is becoming the standard of care for treatment C. diff, we're going to be seeing it more and more. Right now Enloe is the only place in Northern California, north of Sacramento where it's being done. But, I think as we as people become more comfortable with it, as patients become more comfortable with it, we're going to see it more. There's ongoing research into its role in the treatment of a variety of different illnesses. Inflammatory bowel disease being the main one right now but IVS, various metabolic disorders. Even neuropsychiatric conditions, all kinds of things that people are looking at FNT right now.
This, I know you can't read this but this was a table that I got from one of the review articles I was looking at and it’s just a summary of extra intestinal disorders associated with gut microbiota, so it includes diabetes and cardiovascular disease, Parkinson’s disease, multiple sclerosis, Lupus hashimoto's, asthma, all kinds of things.

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Biological Sciences Forum

Fecal Matter Transplant

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The next step, is we're going to move beyond doing colonoscopies for FNT's and we're going to start using stool capsules. Where we're able to isolate the bacteria and then re-suspended in glycerol and saline and put them into little capsules or crapsules, perhaps. And, then just give them to the patient by mouth and the study so far actually looked pretty good. So, this studied that was done this earlier, this year in 19 patients. They got and 89% success rate, six of them failed to respond with the first transplant. Then out of those 6, 4 of them did respond after the second transplant. That gave the total of 89% for success rate.
And, that's it. Any questions?

Audience Member: [inaudible]

Dr. Bangsund: It took me a couple of days, 48 hours or so. Sometimes, even sooner than that.
**Audience Member:** I have a question in terms of possible prevention [inaudible] so if somebody is going on antibiotics or therapy [inaudible]

**Dr. Bangsund:** So, the main thing would be trying to select an antibiotic that's going to have the least risk. So, and that's not always possible to do but if, if you happen to know what the sensitivities are of the bacteria, you're treating sometimes you can select something that's a lot more narrow.
Certain antibiotics are known to have a much higher risk for C. diff like, clindamycin for example, has that, probably the highest risk for C. diff. So, trying to avoid the ones you know can cause it. Sometimes, I have seen some people who will recommend a stopping after acid suppressing medications.
Although, if you think about the pathophysiology doesn't make a lot of sense because if they get C. diff from the antibiotic that means they already had it anyways, so preventing it from going to the stomach probably doesn't do much but I have seen some people make that recommendation. Good antibiotic stewardship, so when somebody shows up in the doctor’s office with a sore throat, that's usually viral and not antibiotics, which is not using antibiotics for that. There isn't very good evidence for using probiotics to help prevent it. So, most of it would just be selecting antibiotics would be really the main thing. Staying out of the hospital, if you can. Hospitals are the last place you want to be, if you're sick.

**Audience Member:** Yeah, can I, what do you know about physical arenas and like german [inaudible] and their role in the gut flora and how possible you can use this transplant to kind of, you know deal with those illness like eukaryotes symptoms.

**Dr. Bangsund:** So, that's get a little bit outside of my area as a gastroenterologist. I'm not dealing with a lot of these immunologic things. That is something that they're looking at, as far is, the microbiome, certainly seems to have an effect on various allergic disorders but beyond that I don't have a great answer. It's kind of outside of my area it's, it is not a field of literature that I follow.

**Audience Member:** But it, it's, it is being worked on?

**Dr. Bangsund:** I don't think they're specifically looking at it as, as a, something that an FNT would treat but, but they're looking at it as far as the role of, of the microbiome. So, the intestinal system has a very strong immune component.
You know, the inside of your intestinal system is still part of the outside of your body, things that you consume still have to pass across the cell barrier to get into your body and the surface area of your gut is a lot greater the surface area of your skin. So, most of your outside is actually on your inside and so as you can imagine there the immune system is very active in the gut and, so there's a lot of interplay between the gut, microbiome and the immune system. But, beyond that as far as the treatment of allergic condition it's kind of outside of my area. I don't have an intelligent answer.

**Audience Member:** Like over-the-counter and [inaudible] like in that group of like acid lowering [inaudible]

**Dr. Bangsund:** They, those tend not to be as effective at lowering the acid as the prescription ones are. Something like Nexium is really going to lower the amount of, I should say raise the pH of your stomach a lot more. You can actually get omeprazole over-the-counter, so but, but tums and that kind of things would not, not be quite as much of a risk factor because that would will increase the pH of your stomach but it's a pretty transient effect. Yes.

**Audience Member:** I have a two-part question. One is that, do they capsules, extend the time [inaudible] you said the [inaudible] only for six months. I'm wondering if the capsules extend beyond that. The second part of the question is, if it can get extended, have them consider [inaudible] in the future.

**Dr. Bangsund:** So, yea that's a good question. As far, as the first part goes, the study that I, my last slide of the study that I had a reference, was sort of a proof of concept study. And, basically what they did was after they had isolated the bacteria and then re-suspended it in glycerol and, and saline, they froze it for no longer than six weeks. And, so they were using it within six weeks. Well, no but, but you're correct. That the stool samples that we're using from open biome that we're putting through the colonoscope, we can hold it for six months. But, these capsules, at least in that study, they were holding them from six weeks at the most. So, you know once these start to get created, it's like a standard process. Whether, they'll find some way to have them last longer. I don't know, hopefully, it will be nice if you can go to the drugstore and take some off the shelf and, and use them but it may be something it has to be frozen, handled very specifically, in that sort of thing. And, the second, I think that maybe addresses the second part of your questions as well. Yeah. Yes.

**Audience Member:** Isn't there like a significant decrease in the diversity of microbes? Just by exiting the colon and the intestinal. Like do you lose a lot of the natural floral that you within the gut, just like environment.

**Dr. Bangsund:** You mean just by, like having a bowel movement for example?
Does that decrease your gut flora, is that what you're asking?

**Audience Member:** Well, the flora that you're trying to put back in, so you know, by putting it in line more aerobic environment and freezing it and temperature.

**Dr. Bangsund:** Yes, that's actually a really good question. So, one thing that I didn’t mention, when talking about using a known acquaintance as, as the donor, they do have to handle the stool in very specific way. So, one of the things they have to do is as soon as they get a stool sample they have to put underwater to help protect it from oxygen. You can't use tap water because that has chlorine in all kinds of other stuff in it, so we would give them bottle of sterile saline and they have to keep it under the sterile saline. It doesn't seem like freezing it seems to kill off the bacteria but, but you're right that if it stayed out at room temperature or the wrong temperature for too long, like for example, a very high temperature the yes that would probably kill it off. Yeah.

**Audience Member:** Question.

**Dr. Bangsund:** Yes, you and then you.

**Audience Member:** Because, of the nephrotoxicity [inaudible] even though, you're giving it orally because of the renal failure and in some patients and then [inaudible] or what do you do for that renal compromise patient when you can't use [inaudible]

**Dr. Bangsund:** Well, that's actually the thing about using it orally is that it doesn't get absorbed in the bloodstream at all and so it never gets the kidneys, so there's really no risk for nephrotoxicity when you use it orally. The, and really I don't run into any toxicity problems at all when you use it orally but you are correct, if you were to use an IV then those are definitely some things you need watch out for. Absolutely. I think there another question over here maybe. Somewhere.

**Audience Member:** [inaudible] bacteria is a lot more sensitive to the [inaudible]

**Dr. Bangsund:** You mean where the preserving procedures select for some bacteria maybe kill off others.

**Audience Member:** Yeah, so like some not will be able to last as long as others [inaudible] environment, you know stuff like that.

**Dr. Bangsund:** Probably, having said that the 90+% efficacy rate of using those samples demonstrate that at least the right bacteria with the right functions are getting to where they need to be, even if that microbiome is changing somewhat to the preservation process. Does that makes since?
Audience Member: Yeah.

Dr. Bangsund: Yeah. Yes?

Audience Member: Yea I understood the first step of [inaudible]

Dr. Bangsund: So, we’ve done about 12 or so. A couple them I read transplanted because the first didn't take. Out those 12, only one hasn’t taken. So, that actually goes along with the, what we see in literature as well. Yes.

Audience Member: [Inaudible] only allowing FNT's for C diff. What would be the next [inaudible]

Dr. Bangsund: Probably in flat inflammatory bowel disease, ulcerative and Crohn's. Those are the ones that are being looked at the most right now.

Audience Member: Are there any others that maybe be in the near future, they might.

Dr. Bangsund: Yeah, I would, knowing the way the FDA works I would, I wouldn't say near future for any of this stuff but probably something, your bowels or something. I, I guess I couldn't predict beyond inflammatory bowel diseases, that seems to be the one, they're looking at the most.

Audience Member: I was wondering if there were others [inaudible]
Dr. Bangsund: Yeah, so this one,
table, so these are things that at least there is an effect of the microbiome on these disease processes. I don't know if autism is on there. I didn't see autism but is it.

**Audience Member:** Yea. [Inaudible]

**Dr. Bangsund:** Yea. There it is. Yup. So, I don't know that they specifically tried FNT's for all of these but there are at least looking at the, the role of the gut microbiota on them. I thought I saw a hand over here, somewhere, maybe. Yes.

**Audience Member:** [inaudible]

**Dr. Bangsund:** This is from a World Journal Gastroenterologist 2015. That's the citation right at the bottom.

**Audience Member:** Oh, okay. Thank You.

**Dr. Bangsund:** Yup.

**Audience Member:** One more question, right here.

**Dr. Bangsund:** Yes.

**Audience Member:** [inaudible] my question is, when the doctor [inaudible]

**Dr. Bangsund:** I didn’t quite catch that, I'm sorry.

**Audience Member:** Like when the [inaudible] does it smell stinky?
**Dr. Bangsund:** Oh, yes. Yes, there's no question about it. Yea, I mean a lot of that comes from the bacteria itself of course, so yea it's stinky. Yeah.

[Audience laughter]

**Audience Member:** [inaudible]

**Dr. Bangsund:** Yes. On that note. Thank you.