SPEAKER 1: We are lucky to have with us today Dr. Robert Hirten for his grand rounds on the assessment and management of penetrating Crohn's disease. If you don't mind taking a moment to silence your cell phones and pagers. Dr. Hirten completed his internal medicine residency and chief residency at Montefiore Medical Center. He completed a GI Fellowship at Northwell Health followed by an Inflammatory Bowel Disease Fellowship here at Mount Sinai, where he is now an assistant professor of medicine and gastroenterology.

Dr. Hirten and also is also the secretary to the New York Crohn's and Colitis Organization, a research consortium comprised of all major medical centers in the New York metropolitan area. His research currently focuses on the role of stress in IBD as well as the application of wearable device technology to IBD research join me in welcoming Dr. Hirten.

[APPLAUSE]

ROBERT HIRTEN: Thank you very much. I really appreciate the invitation to come and speak with you all today. Over the next 45 or 50 minutes, we're going to speak about the assessment of management of Penetrating Crohn's disease. So in general, we're going to be speaking about today and some of our learning objectives is to understand the epidemiology and characteristics of Penetrating Crohn's disease. Learn about how we assess fistulas in inflammatory masses. Discuss the medical, interventional, as well as surgical treatment options that we have for fistulas, phlegmons, and abscesses. And in general, really just get a good understanding of how we approach this unfortunate complication of IBD.

So why do we care about IBD? But particularly, why do we care about Crohn's disease and its penetrating complications? In general, inflammatory bowel disease tends to affect about 1% of the US population. So about 3 million people are affected by it. At Mount Sinai, though, we actually see a significant higher percentage of patients with IBD than perhaps you would see in a general medical practice or practice outside of Sinai. And that's really because we have one of the busiest IBD centers in the world.

So we see around 3,200 patients a year with IBD, which means that a lot of you, whether you're in general medicine or various specialties, are going to see a large percentage of IBD patients in your practices. Which makes it important to not only have a good understanding of the disease, but particularly, the complications that might come up for some of your patients. The main reason though we're worrying about penetrating disease is for the patients in general. So this represents one of the worst complications for patients to particularly associated with high rates of disability, morbidity, and even mortality, as we'll talk about in a little bit.

So it's quite important that we have an understanding of this. And in fact, I'm on the IBD service right now. And just yesterday for example we had two consults that were admitted to medicine relating to penetrating complications. So it's something we're going to be seeing. So just a little bit of background on Crohn's disease. And this is a very general sense. So what is Crohn's disease?

Well, it's an inflammatory condition of your GI tract. It's going to affect anywhere from the mouth to the anus. And it's manifested primarily by ulcerations in your intestinal tract. These ulcers can result in symptoms, which is how your patients will present. You can have diarrhea, abdominal pain, bleeding with bowel movements. And we treat these patients aggressively to try to heal these ulcers and improve their symptoms.

One of the main goals of treatment though is actually to reduce the rate the chance that these patients are going to develop complications. From retrospective studies, it's been shown that if we treat these patients aggressively, can get mucosal healing and heal the ulcers that are present, we can hopefully reduce the chance the complications will develop from their IBD. What are these complications?

Well you can see here in this picture fibrotic strictures. So one of the complications that can develop from ongoing inflammation is a narrowing of the intestinal tract. You have deposition of collagen, thickening of the muscles. And this can result in potentially obstructions that can require surgery. So that's one complication we worry about. The other, which is what we're speaking about today, is penetrating complications.

So Crohn's disease is a transmural disease. It's not just causing inflammation in the mucosa, the lining of the intestine. It's causing it in the entire bowel wall. So what this can result in is the development of small sinus tracts that can pierce the lining of the intestine. And if they pierce through the serosa and link to another epithelial ice surface, forms of fistula, which you can see here in the picture. A small little tract between two components of bowel or whatever other surface that it ends up linking on.

If these sinus tracts though don't link to another epithelialized surface-- so they just sort of go out through the bowel wall, you can get a walled off inflammatory mass. Essentially, it's a sealed off perforation. And this inflammatory mass we call phlegmons. And this is what we'll be talking about as well today. If this flegmon gets super infected, we then term it an abscess. So those are the three big penetrating complications we'll discuss, fistulas, flegmons, and abscesses.

So when we think about penetrating complications in general, we kind of divide it up into two large groups. One, perianal fistula. So all the fistulas abscesses in plague mines that develop around the anal area or around the rectal area. The other group is essentially lumping together all these penetrating complications outside of the perianal region. And you can see in this picture kind of representations of where they primarily are. So rectovaginal fistulas for example, between the rectum and the posterior wall of the vagina.

You can have links between the bowl ball and the colon, small bowl and small bowel, intestine and bladder, and the intestinal tract and the skin. Any of these fistulas can be complicated by abscesses or infections and you can get inflammatory masses therefore. So as we go through this talk, we're going to be really dividing it into two groups through each part, perianal fistulizing disease and non-perianal fistulizing-- or penetrating disease.

Oh, just a little bit of a plug too. If anyone is interested-- so this is from Jill Gregory, this picture in our library. And they have a phenomenal group that can actually draw any diagrams you might want for potential manuscripts that you're submitting free of charge. And she actually drew it for us, this one, which is kind of a very nice service that they provide.

So we're first going to start talking about the epidemiology classification and assessment of penetrating disease. So we're going to go through fistulas, flegmons, and abscesses for both the perinatal and nonperishable locations. So we're seeing a patient with Crohn's disease, what's the chance that this patient has a potential penetrating complication like a fistula for example? When we look at referral studies, we see that there's probably on average around a 20% to 40% lifetime chance that a patient is going to develop a penetrating complication.

But we know there's inherent bias in some of these referral-based studies, as well as there's some biases in themselves in population-based studies. So we can get maybe a little bit of a better idea of the risk of this by looking at some inception cohorts that have been published. And there's two large ones, one in adults and one in children that have been published. And we kind of can see what percentage of these patients are developing fistulas. And we see in the adults around 35% will develop a fistula in any place over about 25 years. 45% being non-perianal in location.

In children, it's much lower, 2.6% with 83% being non-perianal in location. So when we kind of do the math here what we can end up seeing in adults, which is we're primarily going to speak about today, around 19% of adults in these inception cohorts can develop perianal fistulizing disease, versus 16% of adults with non-perianal fistulizing disease in these inception cohorts as well. So the perianal location is slightly more prevalent based on these studies.

So we've gone arbitrarily sort of divided our fistulas perianal and non-perianal in location. Well, people have asked, what's the chance if someone has it in the perianal region? What's the chance that they have it in the other portions of their bowel as well? One of the largest studies that looked at this actually found that while 14% of patients have isolated perianal disease, 10% will have internal disease alone. About 8%, so you could really think in your head maybe one in 10 people will have both internal and external fistulizing disease at the same time.

People have also asked, well, if you are seeing a patient with Crohn's disease, which can affect anywhere in the GI tract, what's the chance that they'll have fistulizing disease in the perianal region based upon their disease location? And this is from a large study of over 800 patients, who around a quarter had fistulizing disease. And they looked at the Crohn's disease based upon location. And what you can see it's not unexpected. That most people who have colonic but particularly rectal involvement or their Crohn's are more likely to have penetrating disease around the anal area, fistulas. And it's going to be most likely in people with just isolated small bowel disease.

What about for fistulas throughout the rest of the GI tract? And you can see here, this is sort of a relative frequency chart for where you're most likely to have fistulas if they're not in your perianal region. You can see here, the most common location is small bowel to colon, particularly actually ilia to sigmoid being the most common. And the least common is cologastric fistulas. So ones that are connecting the stomach to the colon.

So how do fistulas in general-- a nice way for us to discuss how they might be presenting in most patients? Well, perianal fistulas-- usually patients will report leakage around the perianal region, not only of liquid stool, but maybe perianal drainage. For these other fistulas though, generally most are asymptomatic. Particularly, the ones linking one part of the intestine to another. In general, though if some of them are linking very high up in the small intestine to either lower down in the small intestine or to the colon, large segments of bowel might be bypassed. And in those cases, patients will be manifesting diarrhea or can even have malabsorption of different nutrients.

Enterocutaneous fistulas, this will present with leakage of fecal material onto the skin with some surrounding inflammatory changes. Rectovaginal fistulas will present for example, with stool through the vaginal canal or painful intercourse. Enterovesical fistulas, the most common presenting symptom of this is pneumaturia in 75% of patients. Interestingly, studies have shown that patients won't generally report this to you. And actually, you have to ask them, are you noticing for example, air when you're urinating coming out?

These entrovestical fistulas are much more common in men than women because the uterus drapes over the bladder dome sort of protecting the bladder. So we see this more commonly in men. More often on the right side where the ilium is sort of close to the bladder as well. And then these other fistulas that are linking the small intestine to the colon, as I had mentioned earlier, if they're large enough, you're bypassing large segments of the bowel. So you can get diarrhea or malabsorption.

So if we're going to talk about fistulael as we all have to sort of be speaking the same language about them. Like, how do we classify it? And this is important when one doctor is talking to another. So you're calling the surgeon and saying this is what we found on our MRI, for example, or we saw in our patient. But it's also important when you're speaking with your patients about this, because a key thing in dealing with patients with IBD is you want tc make sure that they have a very good understanding of their disease. And this is important not only so that if they understand it, they're willing to get treatments, but then they can also relay the character six of their disease to other doctors that they're seeing.

So we'll first start with perianal fistula classifications, how we're talking about them. And you can see heree-- so this is the anal and rectal anatomy. And when we're going to discuss the different classification schemes, a lot of them really rely on their proximity or relationship to the external and internal anal sphincter. Potentially, the dentate line and the levator ani muscle. There have been several classification schemes that have been developed over the years. Some as simple as just saying a fistula is high or low, meaning it comes from above or below the dentate line. But others that are significantly more intricate.

And you can see here, this is the Park's Classification. And you might notice this when your getting an MRI report for a patient who you're admitting in the ER and they mentioned there's a transsphincteric fistula for example. This is the most anatomically precise classification scheme that we have. And it really is characterizing the primary tract that we're seeing. And you can see here on this diagram, each of the fistulas as they correlate. For example, a superficial fistulas here really doesn't involve any of the sphinters at all or the muscular structures.

You have the intersphinteric tracts which go between the internal and external anal sphincter and the interspenteric space. You have the transsphinteric fistulas here, they cross through the external anal sphincter and then come out. Supersphincteric tracts, these penetrate the intersphincteric space, go over the puborectalis muscle, and then come out through the levator ani muscle to the skin. And then of course, you have extra sphincteric ones, which are sort of bypassing going outside the sphincter complex.

Now, this is a very nice classification system. It really is very anatomically precise, but it doesn't have much clinical relevance. And it also doesn't mention other complications we can have like abscesses, which is a concern we have. So what is really trying to incorporate those other components is the AGA Classification System. So the AGA, it's the American Gastroenterology Association. And they said, you know what? We have some great classification symptoms that are trying to say where fistulas are originating, where they're going. But is this really clinically relevant for our patients? And doesn't have any prognostic value?

So to kind of answer those questions and address these issues, they come up with a general classification system. Simple fistulas and complex fistulas, that's it. They just dividing it between these two. Simple fistulas are any fistula that is low, so below the dentate line, has only a single external opening, there's no pain or fluctuation to suggest an abscess. There's no rectovaginal fistula or no anal rectal stricture. A complex fistula is essentially the opposite of this. So having the opposite properties.

And this is very important as we start talking about the treatments of fistulas since this differentiation between a simple and complex fistula will start coming into play. I included over here the St. James Hospital Classification. This is often, you'll see, included in MRI reports for example. And radiologists use this a lot, where they'll grade fistulas based upon a scale of 1 through 5 really based on what anatomy that they're involving. But we're going to, for the most part, discuss the AGA classification system.

So that's perianal disease. What about the other fistulas that we were talking about? How do we classify these? Well, in a broad sense, if we're not looking in the period region and we have fistulaly another portion of the GI tract, we can think of them first into two large categories, internal and external fistulas. External ones, which link to the skin-- or really enterocutaneous or colocutaneous fistulas. And it can be further differentiated based on their output. With greater than 500 milliliters or half a liter coming out onto the skin a day being high output fistulas.

Internal ones, which are ones that are all contained within the abdomen, so not reaching the skin. We classify these just based upon their origin and termination. So enterocolic, enteroentero, rectovaginal based upon the organs involved. So now, let's talk a little bit about the epidemiology of anal rectal abscesses. So we discussed fistula and this is an unfortunate complication that can develop from perianal fistulas.

How often do we see anal rectal abscesses in our patients? Well, from the studies, it seems about 50% to 60% of patients with perianal disease-- perianal and fistulas will end up developing an abscess at some point. Where are these abscesses located? And you can see on this diagram, the four main regions where they can occur. The most common being perianal in location. So this is very superficial on the skin. The next most common is the ischiorectal area, so this penetrates through the external sphincter into the ischiorectal space.

You can have then superlevator abscesses here, which are often complications of pelvic Crohn's disease and the inflammation that occurs. And then you can have intersphenteric fistula abscesses, which develop between the internal and external sphincters. All of these abscesses generally present as abscesses do. People will get pain in the anal erectile area, fevers, you can get purulent rectal drainage if they linking in and draining into the rectal or anal canal. And you can also see in duration or fluctuates on the physical exam.

What about inflammatory masses or abscesses in the remainder of the GI tract and not in the perinatal region? Well, about 28% of patients with Crohn's disease can develop these. Cross-sectional imaging studies, where they've looked at all their patients with Crohn's disease who have had cross-sectional studies and said, well, how often are we seeing these inflammatory masses? It's probably around 3% to 4% of patients on these imaging studies will have it. And it represents around 3% of all Crohn's disease related admissions.

And you can see here two pictures of patients actually that we've seen in the IBD center. You can see a flegmon mount here. And this is a sub hepatic abscess is developed from their IBD. These complications commonly develop adjacent to disease bowel, often in the right abdomen, because that's where your ilium, which is a very common site of involvement in Crohn's. And usually near a site of prior resection. These present with abdominal pain, fevers. And up to a third of your patients you'll actually be able to feel it. You'll feel a palpable mass in the abdomen.

One important point to know is about psoas abscesses. So if you're having an abscess that's involving the psoas muscle, which can be a complication from penetrating disease in the ilium, your patient will report to you but they're having perhaps flank or back pain. But particularly, they're having pain when they walk or they're noticing that they're limping. So if you're ever seeing a Crohn's patient who's talking about this flank pain or pain with walking or limp, right away this should sort of pop into your mind that this could potentially represent a penetrating complication like psoas muscle abscess, which we do see fairly often.

All right, so we've talked about how to classify these diseases. A little bit of their epidemiology. Well, let's get into the assessment of how we assess them. So let's start again, as we've been doing as we've been going through the talk. Perianal disease first. How do we assess anal rectal or perianal disease? You can see here, there are three studies-- different imaging studies or exams we can do. And you'll notice that CAT scans aren't listed here. And CAT scans are great. We use them for a lot of things and GI.

But for one thing they're not very good at is looking at the pelvis. And that's really because the structures of the pelvis are very difficult to differentiate. So the sphincter itself looks very similar, for example, to the other soft tissue of the pelvis. And in fact, in studies being able to pick up an abscess actually is quite difficult with CAT scan in the pelvis. It's only about 77% sensitive. So we end up relying on other studies. In particular, MRI pelvis. And we use this very frequently to assess perianal disease.

In general, when you're assessing anything-- any kind of imaging study you need a gold standard. And in this case, most studies consider gold standards to be their exam under anesthesia. Where a surgeon put you to sleep and they do a detailed rectal exam, an endoscopy looking in, and try to explore all the shows that could be present or abscess. So when we're looking at these other studies, a lot of them have been compared to exam under anesthesia as a gold standard.

When we do that, we find that our MRIs have about an 85% concordance with surgery, which is pretty good. Some studies though, actually, three large studies have been published that said, you know what? Maybe an exam under anesthesia isn't our gold standard. Let's MRI patients, and then follow them over time. And let's see truly what develops in these patients to say what our MRI picked up or missed.

And those studies have found that the sensitivity is as high as 95% for picking up perinatal complications, which is pretty good. It's generally recommended as our first evaluation. It's easy to do, it gives you a nice three dimensional representation of the rectal and anal area. And some studies have shown it actually can add up to 21% information in up to 21% of patients who are then going to be going for an exam under anesthesia. So it can provide extra information that might have been missed.

An EUS is another possible test we can use. So an endoscopic ultrasound, it's a small endoscopy. It has an ultrasound probe on the end. It's inserted into the rectal canal and gives you a nice three-dimensional view of the rectal and anal. Area one important thing with this is you need to have operators or people that are using it who know how to use it in the rectal area itself. It's very commonly used in other areas of the GI tract. But when you have this expertise, its accuracy is quite high, up to 100% in some studies. And it's been shown to change your surgical approach up to 15% of patients.

And then of course, the gold standard, which is exam under anesthesia. In the hands of an experienced colorectal surgeon, it's got an accuracy of around 90%. It also allows real time interventions to take place. So abscesses to be drained, setons to be placed, anything else that might need to be done. There is one study that was published by a gastroenterologist who's done a lot of research into perianal disease, David Schwartz. And he looked at all three of these.

And he said, well, what's the diagnostic accuracy of each of them? And he got around 90%. Then he did show though, if we combined any two of them are diagnostic accuracy approaches 100%, based on an arbitrary gold standard that they sort of came up with by looking at each individual patient. So we kind of apply this in our general practice when we're seeing patients. We usually get an MRI of the pelvis, and very often we work very closely with our colorectal surgeons for consideration of an exam under anesthesia.

So this has allowed us to now look very closely in the perianal region, the perirectal area for any complications that are going on. We often link this with an endoscopy, a flexible sigmoidoscopy. And we'll see as we get to the treatments, why that's important. So in addition to characterizing the fistulas or abscesses that are present, it's important that we also know if there's perirectal-- so inflammation in the lining of the rectum as well, because that can influence some of our treatments.

How do we assess non-perianal an fistula housing disease? This is a table that's sort of a compendium of the sensitivity and specificities of our three main imaging tests, ultrasound, CT enterography, or MR enterography. This is based on a meta analysis of six different studies that had looked at this. You'll see actually, ultrasound is quite good. But most of these studies actually were out of Europe, where the radiologist had to have a little bit better training in the use of ultrasounds to a assess the intestine. And also they're using contrast agents to increase this-- increase the resolution.

In the US in general, we tend to rely on CT enterography and MR enterography. And what an interrogative is, is the patient's going to drink contrast, it's a negative contrast agent that lets it lets the radiologist look very finely at the mucosal lining of the small intestine. And you can see the sensitivity and specificity are quite good for fistulas and inflammatory masses. And these tests also allow us to get a nice 3D representation of the GI tract as a whole so you can see where any of these complications are in the abdomen and what structures they're involving.

So now we talked about how to assess our patients with penetrating disease. So you've seen your patients say in the office, you're seeing them in the hospital. We thought about how we should be classifying the patients. How we should be assessing their disease. And now we have to start thinking about treatment. So any patient that you're seeing with fistulas is already sort of a high risk patient. We know that penetrating disease is a poor prognostic sign regarding outcomes in Crohn's disease. So it deserves aggressive treatment in particular.

The goal of our treatment is to try to achieve complete closure of all of their fistulas. But like with many things in life, we can't achieve our goals. So we try to do sometimes the best we can if we're unable to fully close the fistula tracts. And that would be primarily characterized by decreasing any output from the fistulas, any drainage. Or perhaps, closing or partially closing some of the tracts if possible. We'll talk about that a little bit more.

When we're treating any penetrating complication, it needs to be a multidisciplinary approach. So it needs to involve a medical and a surgical approach. This has been shown in different studies to be superior than any one alone, which I'll show on the next slide. This concept was also highlighted in the studies that looked at for example, infliximab and adalimumab, so Remicade, Humira. When you look at these studies where patients were getting these agents to heal their fistulas, up to 15% of patients could actually form an abscess if they perhaps didn't have a surgical intervention accompanying it.

And the reason this is felt is that you have a tract for example, say around the anal area with or without an abscess. And when you give them a medicine to start healing this tract, often, what can happen is the external orifice may close first. Now, you have a little bit of a blind kind of-- a pouch that's formed. Of course, then you have fecal material coming in, and that's just a recipe for getting an infection and an abscess. So what often will happen-- and we'll talk about this in more detail in a second, surgeons will do an exam and they'll place setons.

And for those of you haven't seen a seton, it's essentially just a little rubber band that goes through the fistula tract, out to the skin, and then back into the anal canal and into the rectum. And the goal of this is it just keeps the tract open, lets it continue to drain as we're treating it medically. Hopefully, allowing the tract to dry up with the medical therapies. And then at some point, we can remove the seton to let the tract fully heal.

And this slide is just highlighting again that benefit of the combination medical and surgical approaches. This is from a study looking at patients who are perianal renal disease who are either given Remicade in the blue boxes, or Remicade plus an exam under anesthesia with a seton. And 100% response rate was seen here as we kind of use a combination approach. And you can see the recurrence rate is also significantly lower when we're having a medical and surgical approach together. So really highlighting that.

All right, so how are we going to treat these patients? When you look in the literature, there are various treatment algorithms you can look at. So the European Crohn's and Colitis Society has one. The AGA has one. But I'm actually going to focus on the Crohn's and Colitis Foundation, formerly the Crohn's and Colitis Foundation of America's treatment algorithm that they put out. Because it's fairly simple and straightforward and it sort of gets a lot of these major points across about how we should be evaluating these patients.

So first, we're going to do the assessment we talked about. You're going to get your flexible sigmoidoscopy, you're going to get your MRI. You're going to have your surgeon maybe do their exam under anesthesia. And then we're going to divide our patients into two groups. Essentially, two large groups. Those with complex fistulas, which we talked about earlier. The AGA made this nice classification scheme between complex and simple ones. And the other being simple fistulas, either with or without rectal inflammation.

So let's talk about these first, the simple fistulas. These in general, as we said before, don't have any abscesses involving them, are just a simple tract that's not really involving any of the anal sphincter complex, the muscles, anything like that. These can in general, be treated either medically or surgery. There's no studies necessarily comparing which is better. Usually, we do things jointly together. So we get a first usually think of these simple fistulas as being treated medically, which is what we'll often do.

One of the key treatments that we use when we're treating perinatal fistulizing disease is use of antibiotics. There's no prospective placebo controlled studies using antibiotics. But they significantly reduce the drainage from fistulas, which is quite important, not only for patients just because of the symptom that they're experiencing, but it actually might help with healing. And you can see, when studies have combined it with infliximab adalimumad-- so Remicade or Humira, would be the name brands-- you can see that the combination group has a significantly higher response if the antibiotics are given as well. So in general, when we're seeing these patients with fistulas, antibiotics are an important thing to start as an adjuvant therapy along with whatever other medical therapies you're going to pick.

So now, antibiotics are good and one way that they're going to decrease that drainage. But we need to have something stronger of sorts to kind of get meaningful healing to take place. And what should that be? Well, if you put 10 gastroenterologists in front of a room and these IBD conferences and you ask them anything about treatments, everybody says different answers.

But one thing that people tend to agree on is that with perianal disease in particular, it's a bad prognostic sign as far as how their course of disease will be, how aggressive it will be. So most people treated fairly aggressively. Oftentimes, with combination agents. So combining multiple drugs together. The drugs we often will combine together are anti-TNF agents. So the anti-tumor necrosis factor agents like infliximab or adalimumab. And also temporarily perhaps, with our thiopurines, like azathioprine or mercaptopurine.

Let's talk about these individually first so. The thiopurines, like azathioprine or mercaptopurine, there's no prospective randomized trials evaluating them for fistulizing disease-- dedicate fistula disease in the study. Meta analysis though from subgroups looking at the clinical trials that have just applied mercaptopurine or azathioprine to Crohn's have shown that in general, you have superior healing rates compared to placebo. So they seem to work. There is also an open-label study where it was combined with antibiotics.

And again, significantly increased number of patients had improved drainage compared to those that were on antibiotics alone. So these agents do seem to work from some of the data that we have. The mainstay of our treatment though relies on our anti-TNF agents. So the anti-tumor necrosis factor agents. When we look at the literature, there's actually been a few randomized controlled studies that have actually been dedicated just to healing fistuliing disease, particularly with infliximab.

So there was one study of 94 adults with either abdominal-- so enteric cutaneous or an fistulas, most 90% with perianal fistulas, and they gave them Remicade-- or infliximab. And you can see significant higher healing rates in the inlifiximab group. 68% versus 26% in the placebo group. And this was a 50% reduction in draining. So these seem to work very well. The next logical question of course, then is well how well does this work long-term?

The ACCENT II Study looked at patients with infliximab going out almost for a year-- a little over a year to see how well it worked in healing these fistulas. And what we end up seeing is that 46% versus 23% had a response still at one year. And also, a complete response was noted in 36% versus 19% of patients. So this seems to work very well. As far as evidence dedicated only to fistulizing disease with these randomized controlled studies, that's the extent of it.

The other anti-TNF for example, Humira-- or adalimumab, we're looking at some of the other studies that were really dedicated to just see how effective it was in treating Crohn's disease to extrapolate its effects on fistulas. The CLASSIC-I trial was our induction trial. It included 299 patients, 11% of patients had fistulizing disease and actually showed no difference between the two groups. But it only looked at patients for about four weeks. It was for induction.

So maybe if we look a little bit longer out, we'll see some effects. To the CHARM Study-- a CHARM Trial, which was the maintenance study for Humira, or adalimumab, took almost 800 patients, randomized them after induction. And it actually showed that 33% compared to 13% had closure of their fistulas at one year. Again, these are subgroups that are being analyzed. I didn't include certolizamab, which is the third anti-TNF approved for Crohn's disease. Its generally viewed as being the least effective of the anti-TNFs.

And the data is even a little bit small-- a little bit worse as far as it's efficacy in fistulizing disease. There's two main studies, the PRECISE-I and the PRECISE-II Study that looked at certolizamab and include a subgroup with fistulas. And it didn't meet the primary endpoint for increasing drainage-- for decades enclosure rates, actually, looking out at almost half of a year. So we tend to try to favor infliximab or adalmumab if we can. The evidence is a little bit better for them.

So we've gone through our algorithm, so we've decided, all right, we have simple fistulas. We're giving everyone antibiotics. We're going to treat them very often with both azathioprine and 6-MP, and then anti-TNF together. And we're going to see what happens. If we have a treatment success-- so fistulas are closing, that's great. We've been very successful, we're going to continue our therapy because we've improved at least the quality of life hopefully for our patient.

If it doesn't work what are we going to do? Well, if you had rectal inflammation present, which is why it was important to look at it initially, we're going to say, all right, let's treat this like a complex fistula. Which we'll get to that part of the algorithm in a second. Otherwise, you can consider some general surgical interventions, fistulotomy, fibrin glue, or endorectal advancement flaps. What are these? So this is what your colorectal surgeon will do.

A fistulotomy is where they take a probe, they put it through the fistula. You can see the anal canal here. They cut along the tract. And then they sew it up to marsupialize it. They kind of extroverts the tract allowing healing to take place. Its success rate can be up to 100% in some studies. There was one observational study followed people for as long as 76 months showing that it was only a 7% reoccurrence rate.

One thing you worry about is incontinence that can happen. And this really depends upon your selection of the fistula. You really don't want to do this if the fistula is involving your anal-- the internal or external anal sphincter. In some studies though, incontinence can be reported quite highly depending, again, how you're selecting your fistula. But again, we really want to reserve this for very simple fistulas not involving the internal or external sphincter.

What other options do we have? Fibrin glue. So in this case, you take fibrinogen and thrombin, you inject it into the fistula tract. It forms a little bit of a fibrin clot. And this acts as a matrix essentially for healing. There was one prospective randomized open-label study looking at this, which showed it was successful compared to just observation alone. In general though, we don't really use this as a long-term fix. It hasn't been shown to be as successful. So it's taken of a backseat to some of our other surgical options. But it could be used, for example, if you have a patient who's really suffering with increased drainages at least a way to maybe decrease the drainage, potentially temporarily.

And this brings us to our third main surgical intervention we could have performed, a mucosal advancement flap. And in this case, you take a probe, you debride the fistula to remove the epithelialized surface. You then cut along the lower part of the rectal mucosa. And then you make a little flap that you can cover the internal opening of the fistula with to sort of block it. And hopefully, get healing that occurs from that. One systematic review of 35 studies at 29 months of follow up show there's a 64% success rate. Not bad.

Some people did developing continence, which could occur if you damage the sphincter in some way. But a large percentage of people, up to 50% needed re-operation. These are at least things you could consider. So now, we're going to speak about our complex fistulas. So any of our simple fistulas that responded well to treatment, that's great. If our simple fistula had rectal inflammation, we're going to now think of it in the same way we're going to talk about complex fistula at this point. Or if our simple fistula without rectal inflammation as we said, didn't respond to medical or surgical therapy, we're sort of going into this arm of our algorithm now, the complex fistulas.

So how do we approach this? Well, all of our complex fistulas should get setons placed. So you're colorectal surgeon places little rubber band through the fistula tract to keep it open as we're, again, trying to induce healing with our medical therapy. We're going to give our patients antibiotics. We're going to probably give them together an anti-TNF with either azathiprine or 6-MP, our best medical options there. And we're going to see what happens.

If they get a treatment success-- so we've healed the fistula, which is great. We've decreased the output from the fistula, you can remove the setons and then continue your medical therapy. The problem is if you don't achieve healing-- it's a treatment failure, what are you going to do? I didn't talk about some of the other biologic agents we have, like ustekinumab or Entyvio or betalizamab.

We don't have as good of evidence for perianal fistulizing disease from those medications, at least published yet. There have been abstracts looking at it. But we often will then try some of these other biologic agents. You could also then consider other maybe older medicines like, tacrolimus, which is a calcium urine inhibitor. There was one small randomized controlled study that showed tacrolimus improved healing at four weeks of the fistulas, but didn't result in significant induction of remission compared to placebo.

But unfortunately, for these people with very complex period fistulizing disease, we're oftentimes not able to medically induce healing. So sometimes we're unfortunately, forced with taking a little bit more drastic options, such as fecal diversion. And this is really reserved for people with really severe perianal disease, perianal sepsis that's hard to control. Really active fistulizing disease that's not responsive to our medical therapies or the placement of setons. And in this case, what they do is you often will make a stoma.

So you'll bring the colon or the bowel up to the skin wall and you'll have a bag essentially, where the stool is going into. Diverting all the stool from around from the rectal area. And this is based on the idea that if you divert the fecal stream, Crohn's disease gets better. And the problem with this, though, is that when you re-anastamose the person and you reconnect their bowel, the fecal stream again goes through the rectal area. And you can very often have reoccurrence of their fistulizing disease.

There was a large meta analysis that looked at a lot of studies. 16 studies that kind of evaluated this kind of surgical approach. A lot of patients had an early response. 64% got better with a diversion. 35% of the people in these studies attempted to restore continuity, to read put the ballot together. But this was only successful in 17% of patients. Most of these patients ended up needing to have be rediverted. And overall, 42% just didn't work and they ended up having to have a proctectomy, to actually take out the rectum, take out the anus to remove the whole [INAUDIBLE] of where this fistulizing disease is happening.

So it's unfortunate, but when we're talking about diversions with our patients, know the patients are very hopeful that we can induce healing while the bowel is kind of diverted. But we do tell them you have to be very realistic that oftentimes, when we put it back together, the intestinal tract-- this disease can reoccur. And this is just the overall treatment algorithm that sort of there. And this is, again, from that Crohn's and Colitis Foundation.

So over the next and last like 15 or 20 minutes, we're just going to talk about non-perianal fistulas. So these are, again, fistulas involving the rest of the GI tract. So if we're going to be trying to treat these fistulas, one thing you should always have in mind when you're treating anything is, what factors are going to be associated with my inability to treat this? Or what is going to be associated with my reduced rate of fistula closure? And you can see from the literature, these are all the factors that have been associated with reduced rates of fistula closure.

Again, this is not perianal fistulas, this is everywhere else in the GI tract. You can see things like surgical etiology, high output through the fistula, short fistula tract. So kind of doesn't know almost makes sense you would think. You would think a very long tract would be harder to heal. But short tracts, when the two surfaces are so closely together-- so the two organs are essentially touching, can be very hard to close that connection. [INAUDIBLE] deficits, poor nutritional status, multiple tracts. You can sort of see the various things that are going to affect our treatment.

So we're sort of lumping together how we're going to treat all of these various fistulas. And we'll see why in a second. But there's very little evidence that's dedicated specifically to one of these vicious subtypes, which makes it very difficult for us to treat patients. In general, as a general medical management, if the patient has a high output fistula-- so a lot of stool and secretions coming through the fistula tract, first, you want to give them obviously, IV hydration, correct electrolytes.

Octreotide can be very helpful. It's been shown in a meta analysis to have significant decreases in time to closure and reducing the length of time you're going to be in the hospital. So it can be quite effective as an adjunct therapy. And of course, anti-diarrheal agents. Anything to decrease the output. Malnutrition can be a significant problem. So you have ongoing inflammation in these patients. There might be mal absorbing as large amounts of either bowel is being bypassed either going to the skin or to other sections of bowel. So correction a malnutrition is key.

And this we do see a lot in the hospital as well for patients that are malnourished from fistulas. We're kind of asking ourselves do we give them TPN and or Exclusive Enteral Nutrition. So TPN, obviously, you get a line placed. You're going to get the food through the line. And you're not going to eat anything by mouth. And the goal with this is to try to decrease stool output and the amount of stool that's going through the bowel that's also going to be going through these fistula tracts.

Exclusive Enteral Nutrision, you're giving them nutrition like short peptide-based nutrients that are already highly broken down. So they're absorbing very high up in the small bowel. So you're really decreasing the overall stool burden. In general, we try to favor enteral nutrition because it's safer. It has trophic effects on the mucosa of the bowel, which can hopefully reduce some of the other complications you can see with TPN, like bacterial translocation and the GI tract or line infections. It's been shown in one study to actually be quite effective.

So these were 48 patients with enterocutaneous fistulas to their skin not responsive to other therapies. They were all put on exclusive enteral nutrition. So they couldn't eat anything but kind of these mixes they were given for three months. 14 patients had very high output fistulas. And in the end, almost 63% actually had complete closure of their fistulas with the addition of ventral nutrition in an average of a month. So it can be quite effective.

What medical management do we have for these other fistulas? And you'll note actually this slide is-- this slide and our next slide are essentially the same. And that unfortunately, is because we do not really have any trials that are dedicated to non-perianal fistulas regarding medical therapies. There's this large meta analysis I talked about earlier showing thiopurine healing from all of the studies. The vast majority of these patients were all suffering from perianal and fistulizing disease. It worked but they were all perianal fistulas.

The one randomized controlled study that was published in the*New England Journal* looking fistula healing from mercaptopurine, they didn't specify the breakdown of fistula types. But again, they say the majority-- vast majority are all perianal fistulas. Which makes it very difficult, because we end up extrapolating a lot of the data from perishing fistula are rising disease to these other fistulas. And they're not the same. If you have a fistula around the anal area, that's certainly not the same as having a fistula connecting your small ball to your bladder or to your skin.

This is the slide I showed earlier looking at infliximab and Humira for example. And we looked at the studies specifically dedicated to fistula and infliximab. And I highlighted here, you could see 90% were perianal were fistulas, which makes it a little bit difficult to extrapolate this information. The ACCENT II Trial, which is our maintenance study-- which was by Dr. Sands actually-- 80% around where perianal fistulas. Only 20% non-perianal and fistulizing disease.

Humira, with the Humira studies, same thing. Maybe 10%. Here, only four patients had non-perianal fistulas. So it's very difficult when we're speaking with our patients to say, what should we do from an evidence based perspective? Because a lot of the clinical trials that were performed really excluded these non-perianal fistulas, which can make it a little bit more difficult. One area, we do have a little bit more information though from is from the ACCENT II Study, which Dr. Sands had performed. They did actually a very nice post hoc analysis, looking specifically at the patients who had non perianal fistulizing disease. Specifically, rectovaginas fistulaas.

So we mentioned this study has 80% perianal disease. The other 20%- a sizable percentage, had rectovaginal fistulas. So Dr. Sands looked to see really how effective oral treatments in this subgroup, which is a very common penetrating complication that we're seeing. In general, they found that 64% had closure at some point after induction. At week 54, so approximately a year out, 44% fistulas were closed among responders, which is great. And the duration of response in those receiving inflicts that was much higher-- significantly higher than those receiving placebo. So at least we have a little bit more information in that subgroup.

Otherwise, what we're really relying on some retrospective studies that have been performed. There's your [INAUDIBLE] Group, which is a consortium in Europe. They looked at 48 enterocutaneous fistulas who are receiving biologic therapy, anti-TNFs. They found complete closure occurred in a third of patients. Otherwise, you're looking at some meta analyzes that are trying to put together a small retrospective studies to get some meaningful outcomes at least for some of these other subtypes.

For example, in rectovaginal fistulas, complete response was seen in 41% of patients with anti-TAF therapies. Enterovesical fistulas, you had a 50 57% complete response rate. But these have all the caveats that you're seeing for retrospective studies, case series, things like that. Other medical options-- I'm just including this to really show again the lack of true data we have. Methotrexate, we really have the largest amount of data from a case series of 16 patients. Procalcitonin inhibitors, like tacrolimus and cyclosporine.

I mentioned this randomized controlled study. Essentially, all of the patients were perianal disease. Only four patients didn't have perinatal disease in this. So, again, were very limited in extrapolating these results. So we sort of take the medical knowledge that we have from perianal fistulizing disease and try to apply it to this very diverse group often relying on infliximab, which is most effective in the perinatal fistulizing disease. Humira being-- or adalimumab being our secondary agent. But it can be frustrating and a little bit difficult.

For the fistulas that don't get better, sometimes patients do need surgery. Indications would be diarrhea, malabsorption, recurrent infections, or sepsis. It's very important to optimize nutritional status first. And obviously, maximize medical therapy to try to get healing in those cases. Oftentimes, if resection is needed, you should always think of fistulas-- they are starting from an area of disease bowel, and then involving another healthy area of battle. So we want to completely resect the disease about where the fistula is originating from. And then usually, you can just remove or the tract is penetrating or entering the other healthy bowel.

Sometimes, if there's very extensive disease or you're concerned about short bowel syndrome, you can try to do wedge sections and over of the tracts. But there's always a concern that they'll reoccur. And just for about five more minutes, I just want to talk about non-perianal flegmons and abscesses. So earlier, when we were talking about perianal disease, the fistulas, really any abscess that is found in the perianal region, your colorectal surgeon will have to take care of that by doing usually an incision and drainage. Can be a little bit more complicated, though, for these inflammatory masses involving the rest of the GI tract.

So first, flegmons. So these are inflammatory masses we talked about. So you're having a tract that's going through the wall of the small intestine or colon, doesn't link to another surface, and you get inflammatory mass. How do we treat these? Usually, the mainstays of therapy have been antibiotics and possibly resection of the collection. But in some ways, we should be thinking perhaps of these flegmons-- these inflammatory masses as just complications of the inflammation in Crohn's disease. So often, at times what we'll think about is trying to suppress the inflammation in the GI tract to improve this inflammation and these inflammatory masses.

One question we often get, especially in patients in the hospital is, can you start steroids or can you start an anti-TNF like Remicade in a patient with an inflammatory mass? When we look at the evidence, there's not many studies to support whether that's safe or not. I listed the two here. One by Felder and Colleagues. They took 24 patients with Crohn's disease and masses in the abdomen. They gave them all IV steroids. 16 of the patients, the majority antibiotics.

And they actually show that these inflammatory masses got better in 15 of the subjects. And decreased by 50% in the rest of the subjects. Only four patients required surgery actually during the hospitalization. And that was because wtih tapering of steroids, the masses again increased in size. This study was from the early '90s so we didn't have medicines like infliximab or adalimumab, other things to kind of maintain remission as well in the Crohn's disease.

Cullen and Colleagues, this was published in the anti-TNF era, looked at 13 subjects receiving anti-TNF therapy with flegmons in place. Actually, 12 of them also had abscesses. All were given antibiotics, a median of a little over a month. Usually, they were given it for a few weeks. And then started on anti-TNF therapy. Two of the patients actually required surgery only out of the 13. And in fact, these two surgical causes were-- two to surgical indications weren't even from the mass. It was actually for other complications like structures that were present.

So these studies, well, they're supporting the concept of combining anti-inflammatory medications with say, antibiotics to treat the mass. They're not advocating for it. But at least it lends some evidence to say, we should maybe be approaching these flegmons or inflammatory complications as extensions of their Crohn's disease. But of course, always linking-- if we're giving immunosuppressive suppresses, linking it with antibiotics.

And this brings us now to abscesses. So the mainstay of treatment for abscesses in many cases, is at least initiation of antibiotics. We should always be thinking if we're treating an internal abscess with antibiotics, what are the risks that the antibiotics are going to fail? Generally, these antibiotics are successful in about 2/3 of patients at treating the abscesses. But we do know there are some risk factors that have been associated with failure of antibiotics.

And if you're seeing a patient with an abdominal abscess, if they have any of these factors, you should already be thinking that the antibiotics might not be enough. So that's anyone with a large abscess greater than three centimeters. If they'd needed, obviously, drainage before, they're already on immunosuppression, they have fistula tract associated with the abscess, your antibiotics might not work. And in that case, you should already be thinking about, should we drain the abscess or send the patient to surgery?

Really, you can go with either of these approaches. And it often depends on where the abscess is located if it's actually amendable to drainage or not. But percutaneous drainage by interventional radiology can be very important. And it actually can be quite successful in up to 95% of patients who undergo drainage. Although, up to half may require surgery at some point. Up to 85% of those subjects may be able to avoid surgery after drainage.

But in any case, drainage shouldn't necessarily be only looked at as the only treatment for this. Very often we'll be combining it with surgery. Because studies have actually shown, if you perform a drainage first before going to surgery, you'll actually have lower complication rates. You can probably perform a primary reanastomosis, and they'll be in the hospital shorter. You can see here, three factors in the literature that associated with failure of drainage. So a multi-loculated related abscess, which makes sense. Associated fistulas, or if it's related to underlying Crohn's progression.

And this is just the last slide. This is an algorithm that we had come up with on how you should approach intrabdominal abscesses or inflammatory collections. In general, if you see these abscesses, you start antibiotics. You want to look for the factors we talked about where it means antibiotics are likely to not be successful. Otherwise, if they don't have these, you continue antibiotics. You could then consider re-imaging in three to five days if they're not getting better. And of course, if they're worsening, you're going to want to do a drainage of some type.

But if they're getting bad are you going to continue antibiotics. And then of course, assess their Crohn's disease treatment. Because this is a complication of the Crohn's disease, so it means we need to be a little bit more aggressive in its treatment. And that, hopefully-- I know it was a lot of information but, hopefully, with comprehensive about all the different penetrating complications.

[APPLAUSE]

SPEAKER 2: [INAUDIBLE] questions, please.

SPEAKER 3: Yeah, I see you used the TNF inhibitors in the phase of [INAUDIBLE]. Is that a big problem? Because in rheumatology, when we have someone who has an infection, we stay away from the TNF inhibitors.

ROBERT HIRTEN: Yeah.

SPEAKER 3: [INAUDIBLE] have a lot of problems.

ROBERT HIRTEN: That's a good point. So before you're going to initiate a TNF inhibitor, if you have say someone with an abscess, you want to gain control of the infection first. So if you have intraabdominal abscess for example, and you're going to want to start steroids or an anti-TNF-- both immunosuppressives-- for their underlying IBD, you want to be able to assure that you gain control of the infection. So not only have started antibiotics, but initiated drainage of the collection.

So I'll often have IR drain it first or surgery drain it. And then once we are kind of confident that we kind of control it, we can then consider initiation of it. It might not be within those few days, but it might be in the short term, within a week or two weeks for example, after that. That's a very good point. You really want to control the infection first, and then you can think about initiating therapy.

SPEAKER 4: Thanks for a very good presentation. And I guess if there's a section in heaven where there are GI expert experts sitting, I suppose the Doctors Crohn, Ginsburg, Oppenheimer are a [INAUDIBLE]. I do have a research question, though. Two-part question.

Number one, do we know why fistulas occur? And second part of that question is, your slide indicated that when young people get this bad disease there's a big difference between 15-year-olds and five-year-olds in the frequency. Do you know anything about why that difference occurs?

ROBERT HIRTEN: That's a good-- particularly, your second question is very interesting. Why are we seeing this difference in the location in particular, as well as the frequency of the penetrating complications in adults versus kids? My best guess of why that could be is perhaps-- I don't know if this is true, all of IBD isn't the same. We're linking a group of diseases together that we're calling Crohn's and ulcerative colitis, but Crohn's that can develop later in life might be phenotypically different than those that are developing very early in childhood.

And, also the spectrum of disease is quite different. So not everybody has the same aggressive phenotypes with it. So I just think it's something about the presentation of the phenotypes of kids that are getting Crohn's, which tends to be more aggressive in some ways-- in some ways, but it doesn't seem to be in the penetrating realm. I don't have a great answer for that. I don't know if someone else-- maybe Dr. Sands can say why they're different.

BRUCE SANDS: There's at least one other factor, which is that children of course, have a lesser follow up time in their less than 18 years from--

ROBERT HIRTEN: That's a good point.

BRUCE SANDS: [INAUDIBLE] the analysis that's compared to 18 plus the entire lifespan. So of course, you have to adjust for the time of observation.

ROBERT HIRTEN: That's a good point, yeah.

SPEAKER 2: Dr. [INAUDIBLE]?

SPEAKER 5: Yeah, are there are obvious differences in the infiltrating cell types in fistulizing versus non-fistulizing IBD?

ROBERT HIRTEN: You mean the infiltrating cell types into tracts that are [INAUDIBLE].

SPEAKER 5: Yeah. Presumably, some cell types are able to actually destroy the wall, and others are not. And I'm wondering if having this huge population of pathological specimens, it's possible to phenotype which cell types are able to actually create the full penetration.

ROBERT HIRTEN: Yeah, and it gets to the question-- this is one of the main questions we have is, why do some patients develop fistulas and others don't? You're asking, does one patient have a specific cell type that's there? I don't know why certain cases develop it versus others phenotypically. I'm not-- Dr. Sands, [INAUDIBLE]

[LAUGHTER]

BRUCE SANDS: Great answer on that. I don't know that either. But the [INAUDIBLE] Study that you cited, which was an observational cohort-- conception cohort of children who developed complicated behaviors, either stricture or fistula. They are biologically different diseases. So you find a gene expression related to extracellular matrix type of genes in the stricture formers. Who also respond differently to TNF treatment early in their disease as compared to the fistulizers, who have the other-- I can't remember exactly what, but other genetic markers.

And also the microbiome are different in those two manifestations. But the cellular biology is not well understood.

SPEAKER 5: I know there's one animal study in which there's a claim that inhibiting one of the integrands, alpha-v beta-3, actually has an impact on unfibrotic type subscriptions. So just understanding the cell biology and the matrix interactions may offer a way of ultimately predicting which patients in trying to look for potential targets types.

ROBERT HIRTEN: I mean that whole idea, that concept of personalized medicine is something I'd be very interested in. So the disease is so varied in presentations with strictures to penetrating complications, predicting who is going to have what complications is really key. Because everyone doesn't need to be treated the same way. But we haven't really come up with the best way to do that yet and to individualize our approaches. I mean, that's the goal-- the ultimate goal of therapies.

SPEAKER 2: We'll take one last question [INAUDIBLE].

SPEAKER 6: There have been some patients who inflammatory bowel disease who responded to changing their microbiome with fecal transplantation. Have any of those patients, as far as you know, had fistulas? And did it make any difference?

ROBERT HIRTEN: So the main study that was done looking at that was the FOCUS Trial, which was in patients with ulcerative colitis. Where they were giving the fecal enemas like five days a week on average. And they got improvement of their disease while they were on the enams during the fecal transplants. But invariably, once the fecal transplants were stopped, a lot of it reoccured-- their disease.

But we don't really have studies like that in Crohn's disease as far as I know. At least large clinical trials seeing its effects on fistulas. It's an interesting idea though, because you're right, the microbiome drives a lot of it. But we don't have the data on that at this point.

SPEAKER 6: Great and thank you very much.

[APPLAUSE]