SPEAKER 1: Today, we're very pleased to have Dr. Ryan Ungaro join us for a discussion on ulcerative colitis. Dr. Ungaro is an Assistant Professor of Medicine in the Division of Gastroenterology in the Susan and Leonard Feinstein Inflammatory Bowel Disease Center. He received a medical degree from the Icahn School of Medicine at Mount Sinai, where he subsequently completed his internal medicine residency, his chief residency, and his fellowship training in gastroenterology.

Dr. Ungaro then received training in translational IBD research as a Howard Hughes Medical Institute Research Fellow. And he's a recent recipient of the Career Development Award from the Crohn's and Colitis Foundation. His research includes such areas as the role of toll-like receptors in intestinal inflammation, and environmental factors in IBD.

He's been published in numerous peer reviewed journals and presented nationally. His current research interests are risk stratification and optimization of therapy and early intervention in IBD. Please join me in welcoming Dr. Ungaro.

[APPLAUSE]

RYAN UNGARO: Thanks, [INAUDIBLE]

Good Morning, everyone. Thank you for having me. It's a real honor and pleasure to be back here, and getting introduced. I used to do the introductions myself, like you, being the Chief Resident before. So, I was asked to give an overview talk of ulcerative colitis. So, not too big of a topic, but enough that I want to give you guys a flavor of some of the things that we see every day. These are my disclosures.

So, I'm going to could talk a little about the clinical presentation and diagnosis of ulcerative colitis, talk a little about the epidemiology and the burden that these diseases have on our patients, a little bit about the pathophysiology and risk factors for all ulcerative colitis, and then give you an overview of our approach to medical management in these cases. And then hit on a couple of key scenarios, where we have complications or special populations of patients that we encounter. And finish on some future directions and lingering questions in the field.

But first, I think any IBD lecturer at Mount Sinai, you have to recognize the history and historic impact that our institutions had on IBD. And just to go through, this is a few of the contributions. First report linking colitis and ulcerative colitis and colorectal cancer was here in the 1920s. The first description of Crohn's disease, as you're all very well aware-- and here's Dr. Crohn down here. The earliest descriptions radiologically of Crohn's disease.

Many IBD surgeries were pioneered here, many of them by the late Dr. Greenstein. Chromoendoscopy for dysplasia and cancer surveillance in these patients, as well, was pioneered here-- Dr. Marion and others involved in that research. And many of the therapies that have really revolutionized the care of ulcerative colitis were either innovated here, or were major contributions made here, including the use of thiopurines, which Dan Present, who is one of the giants in the field really pushed and pioneered, the use of cyclosporine in acute ulcerative colitis, and the use of anti tumor necrosis factor agents.

Many of these research endeavors were involved also with our former Chair, Dr. Lloyd Mayer. So, anyone who's doing research or clinical care in IBD at Mount Sinai is really standing on the shoulders of giants. And I just wanted to quickly acknowledge that.

So first, what's the clinical presentation? How do we diagnose ulcerative colitis? So, just very briefly, what is all ulcerative colitis? The kind of textbook description, it's a chronic disease that causes a relapsing or remitting inflammation in the colon. It starts in the rectum and then progresses proximally throughout the colon. And this is in contrast to Crohn's disease, which is kind of its sister or cousin diagnosis, where it can affect-- in Crohn's disease, you can have inflammation anywhere from the mouth to the anus, and you have skip lesions. And so this is a major contrast, in terms of the disease location as a distinguishing feature.

So, how do these patients present in the clinic? Well, oftentimes the prominent symptoms are diarrhea and rectal bleeding. These patients can also have cramping. And if they have more extensive or severe disease, you can have more systemic symptoms, like fevers, fatigue, decreased appetite. But really, the clinical presentation varies a lot on the phenotype of ulcerative colitis and where the disease is located.

So, we think of ulcerative colitis in three phenotypes, based on the Montreal classification. The first is proctitis, or disease limited to the rectum. The second is left-sided colitis, or disease that goes up to the splenic flexure. And the third is pancolitis, where you have disease going beyond this splenic flexure and involving the entire colon. And these classifications impact both the way patients present, as well as our treatment strategies.

So, for example, proctitis patients, oftentimes their major symptom will be just urgency, having to rush to the bathroom or tenesmus, the sensation of incomplete evacuation. Whereas patients with left-sided colitis or pancolitis are more likely to have diarrhea, abdominal cramping, or more systemic symptoms. And also, depending on how much of the colon is involved, this may impact our treatment selection, which I'll hit on a little bit later on.

So, what does ulcerative colitis look like when we do an endoscopy? So this is a beautiful normal looking colon. You can see the pink mucosa, the nice vascular pattern, and all the folds of the colon here. So, in ulcerative colitis what do we see? Well, as I mentioned, you have continuous inflammation from the rectum proximally. You have edematous mucosa. You can have friability, so easily bleeding, erosions and ulcerations.

And we use various endoscopic scores. The most commonly used is the Mayo score, to grade the severity of the colitis. And so here, you can see a more mild case. We have a little bit of erythema and some normal appearing mucosa here as well. Here's a more moderate case. We have some erosions. And you lose all your vascular pattern. You also lose the folds that you can see so nicely in a regular colon. And then you can have very, very severe disease, where you have deep ulcerations and spontaneous bleeding in our sickest patients.

And on histology, you also see changes that are characteristic as well. So this is a normal colon on histology, where we have the nice crypts all aligned and a relatively thin lamina propria. But when you have ulcerative colitis, you see chronic changes in inflammatory infiltrates. So some of the characteristic findings you would see are these crypt branching phenomena, where the crypts start to this sort of crypto form pattern.

You then could also have infiltration within the lamina propria of various inflammatory cells, neutrophils. And becoming more chronic, lymphoplasmacytic infiltrate over time. And in the most severe cases, you actually have a loss of the epithelium, where it's completely denuded with a massive inflammatory infiltrate. So these are some of the changes that our pathologists look for on our biopsies.

So, how do we diagnose ulcerative colitis? Well, it's a combination of the things I just showed you. Classic endoscopic findings, as well as histologic findings that are all suggestive of ulcerative colitis. And this is all in the presence of a negative evaluation for alternative diagnoses. So, what are some of the common things we are considering when we see a patient who may have ulcerative colitis?

One is infectious colitis. So part of the workup for these patients are stool studies to rule out any bacterial, fungal, mycobacterial infections. Ischemic colitis is another consideration. Segmental colitis associated with diverticulitis, radiation induced colitis, medication induced colitis, particularly NSAIDS can sometimes appear as IBD. Obviously, Crohn's disease is one of the major distinctions we're trying to make in the clinic.

And something that I think is sometimes overlooked, particularly in proctitis patients, in patients who engage in anal intercourse, or sexually transmitted diseases, like chlamydia or gonorrhea, so this is something to also keep in the back of your mind, if you're seeing patients with bloody diarrhea. And this is a little pearl for primary care. If you have someone that you're seeing with diarrhea, abdominal pain, who you're thinking, well, maybe this is IBS, or maybe it's something inflammatory, faecal calprotectin, which is a stool test that's a protein shed by neutrophils in the gut, if it's very low, there's a less than 1% chance the patient has IBD. So, it's a quick screening for inflammatory causes of diarrhea in the clinic.

So, what about the epidemiology and disease burden of ulcerative colitis? So, ulcerative colitis, unfortunately, impacts patients really at the peak of their youth. And I'm sort of extending that into the 40s. As I'm getting older, I kind of view 40s as youth, as well as the 20s. And it also affects both men and women equally. And the highest prevalence rates are in really Western countries-- so Europe, Canada, the United States.

And very recently there was a CDC survey, a national survey, where they estimated that actually three million Americans have IBD. And about half of those are ulcerative colitis. So, about one to one and a half million people have ulcerative colitis. And you can see here, this is actually some recent data from an inception cohort, the OSCCAR cohort in Rhode Island, where the line with these little triangles is the incidence rate by age in the state of Rhode Island. And you can see that the incidence rate is highest in the 20s, 30s, 40s, but there are still cases out even into the 70s. So even though it does drop off a little bit, in older populations, there are incident cases in older patients.

So what impact does ulcerative colitis have on our patients? Well, if you look at patients who have chronic diseases-- asthma, migraine, rheumatoid arthritis, and compare them to UC, ulcerative colitis patients actually are more likely to say that their disease controls their life. And it can have major psychological impact on our patients, where they're worrying about the long-term effects of their disease, they feel embarrassed about their disease. They're worrying about where they're going to find the bathroom if they have to go. And oftentimes, they're saying they feel depressed. So it can have a major impact on our patients' lives.

And what about the economic impact? Well, ulcerative colitis is a very expensive, burdensome disease, where it's estimated that there's $8-$15 billion a year that are spent on indirect and direct costs in the United States alone. This is a study. It's not from the US, but from Norway. But they found that ulcerative colitis patients are twice as likely to not be able to work. So, that's contributing to the loss of productivity.

And another study from Europe, called the COIN study, looked at what were the main drivers of these costs. And actually, a huge driver is the cost of our medications, which we'll talk about in a minute, but they're very expensive, our biologic agents, about a third of the costs. Another quarter of the costs due to hospitalizations. But then nearly 40% is due to lost productivity and these indirect costs that I mentioned before.

Now, an interesting phenomena that we've been seeing is that the incidence and prevalence of ulcerative colitis has been rising over time. So you can see both the United States, as well as worldwide, the rates of ulcerative colitis have been going up ever since it was first described in the 1850s by Sir Walter Wilks.

And this I thought was an interesting paper that recently came out, where they showed how the prevalence and incidence is rising in the Western world-- so, the US, and Europe, and Canada-- but something that's been happening more recently is that the developing world, and particularly in Asia, in places like China and India, increasing rates of IBD or being noticed. And since the 1950s, these have been increasing in prevalence as well. So, the burden of these diseases is growing, not just in the United States, but also worldwide. And this also hints at potential contributors to the pathophysiology, which I'm going to get to now.

So what causes UC? Well, the short answer is that we don't really know. But with research over years, we have a better idea of what are the major factors that contribute to patients developing UC. So this is the current dogma of why people get IBD. You have to have a genetic predisposition. So there's some genetic component. You have a deregulated immune system, so some sort of immune system disturbance. And the setting of some sort of environmental factors or environmental triggers that increase the risk or maybe potentially precipitate the disease.

So, first genetics. Genetic play an important role in IBD. 8 to 14% of patients have a family history. It's more common in certain ethnic populations, and particularly Jewish populations. And there's been over 200 IBD susceptibility genes identified over the past 15, 20 years. A lot of this is the work by Dr. Judy Cho, who's here. And about 27 of those genes are UC specific. So a lot of the genes actually overlap between Crohn's and ulcerative colitis. And many of the genes that have been implicated for UC are involved in barrier function and immune mediated pathways.

However, genes are not the whole story. There's only a 19% concordance rate for monozygotic twins. And the ability of genetics to predict phenotype or predict disease has been very limited. So although they're important, it's only one piece of the puzzle.

So, the second piece of the puzzle is a deregulated immune response. And I'd just like to briefly say, give a little plug for our medical illustrators here at Sinai. This was a figure that Jill Gregory did for us, who's one of our medical illustrators, for a review we did on ulcerative colitis. And if you're doing any papers or grants, and you're looking to have a really beautiful figure, beyond what you're making in PowerPoint, I would highly recommend going to see her.

So, this disregulated immune response, on the left-hand side here-- or I guess on your-- yes, you're left-- on the left-hand side, we have the gut in a healthy state. So, we have a microbiome that's very diverse and well-balanced, an intact epithelial border, with the mucous barrier intact. And an immune function that is tolerogenic.

So, the immune cells in your gut are tolerant of the bacteria and the antigens that it's seeing from the gut and are not causing any inflammation. However, in contrast, in ulcerative colitis, you have multiple things that are perturbed. So, you have an abnormal microbiome, which is unclear if this is causative, or if it's in reaction to the altered immune response, but you have decreased diversity, decreased abundance of bacteria in ulcerative colitis.

And then, you also have a disrupted epithelial barrier with decreased mucus and increased permeability of the epithelium. And then, what happens is you have an activation of the immune system. So, you have increased influx of inflammatory cells that are recruited through the bloodstream, through increased expression of integrins. And then those inflammatory cells, both T cells, NK cells, start to produce cytokines, such as TNF-Alpha, IL-13, IL-9, that are mediators of inflammation. And this process becomes a chronic one that perpetuates over time.

So, what triggers this or predisposes patients to this, in addition to the genetics? There's an increasing appreciation that environmental factors likely play a role. And the evidence that suggests this is the rising incidence over time, both in the US and worldwide. And so, there's multiple factors that have been implicated in UC pathogenesis, or increasing or decreasing the risk. So, just a few here of note.

Interestingly, cigarette smoking, while it worsens and increases your risk of Crohn's disease, actually decreases your risk of ulcerative colitis. It's probably one of the only diseases where cigarette smoking has a positive effect. But it decreases the risk fairly dramatically. Patients who have a prior bacterial gastroenteritis are more likely to later on go on to develop IBD. Perhaps this is a perturbation of the microbiome that's triggered, or an antigen that the lamina propria, the immune cells, are exposed to, that sets off this cascade of inflammation. It's not entirely clear.

There's various medications that have been suggested to play a role in the risk for IBD. One are NSAIDs and hormone replacement therapy, which appear to increase the risk of ulcerative colitis. Antibiotics were initially thought to increase the risk of ulcerative colitis. They probably increase the risk of Crohn's disease. It's not as clear that they increase the risk of UC.

Statins appear to decrease your risk of ulcerative colitis. And surgeries, actually, in particular appendectomy, appears to decrease your risk of ulcerative colitis. It's not entirely clear why that is. Potentially something about altering the microbiome afterwards, or it's also thought to be a reservoir of NK cells, which may play a role in ulcerative colitis, but it's not entirely clear. And also, other things have been associated with the risk of ulcerative colitis are breastfeeding and sleep disturbance.

And of course, we can't not mention the microbiome and diet. Our patients always ask us about diet-- did my diet cause me to have ulcerative colitis? What role is it playing? I always tell them that we're just not smart enough yet to know exactly what how diet is playing a role. We're getting more and more information about this, but we're still not entirely clear on which dietary factors may play a role.

But one thing that is clear is that your diet drastically impacts your microbiome. And the microbiome is altered in ulcerative colitis patients. So, there may be something about dietary changes in Westernizing countries, for example, that lead to altered microbiome that could potentially trigger an immune response.

And then this is one piece-- just an interesting study that recently came out. It's in mice, so take it with a grain of salt. But they gave-- this group gave mice emulsifiers, which are common in preservatives in foods. That make peanut butter look much more pleasing to the eye, instead of being separated, make it everything all altogether in the peanut butter jar. They took two common emulsifiers and they gave them to mice.

And what they saw is that in a healthy mouse, you have this mucus layer here, between the epithelium, and the red dots are bacteria. And as you give these emulsifiers, the mucus layer decreased and the bacteria were more likely to come in contact with the epithelium. So, perhaps this could be playing a role in a dietary-- in the way the diet may be contributing to ulcerative colitis. But obviously, this is not entirely clear yet, but intriguing data.

OK, so how do we approach our medical management to ulcerative colitis? So, I'm going to give a bit of an overview, with some details, not too much inside baseball, but enough to give you guys a sense of how we approach these patients. So, the first step when we see an ulcerative colitis patient is to assess their disease severity. And the first step is a clinical assessment.

And there's multiple clinical disease activity indices. The most commonly used ones are the Montreal classification and the Truelove and Witt's criteria, which basically classify patients based on the number of stools they're having, how much blood is in their stool, and if they have more systemic symptoms. Basically, you can pick whichever one you like and you can use that to help you classify clinically.

But more recently, there's been a push to, in addition to these clinical indices, to engage more objective markers of inflammation in our disease assessments, and in particular, endoscopy. And why endoscopy? Well, we found that endoscopic healing leads to better outcomes. And in particular, this is a landmark paper where they did a post-hoc analysis of one of the trials with ulcerative colitis where infliximab was tested.

And if you look here, patients who had endoscopic healing, which are these top two lines, were significantly less likely to need a colectomy, have their current removed, out to a year, whereas patients who did not have endoscopic healing. And this was also recapitulated in a meta analysis that one of our Fellows did. Where if you had endoscopic healing, you were four times less likely to not need a colectomy, compared to patients who did not have endoscopic healing.

So, with this data, there was a expert international consensus guideline that was derived, the STRIDE guidelines, where a group met to decide what should be our target or our goal when treating ulcerative colitis patients. It was a combination of both symptomatic resolution-- we want our patients to feel better. But we also want to couple that with an endoscopic resolution of inflammation as well. So, it's a two-tiered goal where we're treating our patients, resolution of symptoms, as well as endoscopic remission.

Something to mention is that our patients are at increased risk for outcomes over time, in particular colectomy, with medically refractory disease or patients developing cancer. And it's probably as high as 15% out of 10 years. So, there's been a push now to, in addition to these clinical endoscopic indices, which are really snapshots in time, to incorporate factors that can tell us-- help us predict who's going to have a more aggressive disease course and be at higher risk for a colectomy, and try to incorporate those factors into our treatment decisions.

And this has been actually highlighted in the recent AGA guidelines, where treatment decisions should take into account if patents are at low risk or high risk for colectomy. So patients who are considered low risk for colectomy are patients who have limited endoscopic disease, so proctitis or left-sided colitis, or a mild endoscopic disease.

And in contrast, patients who are higher risk for colectomy are patients who have pancolitis, patients with deep ulcerations on endoscopy, younger patients, high inflammatory burden with high CRP, ESR. Patients who need steroids and more likely to have a colectomy, and history of C diff, CMV infection, or hospitalization. So, if patients have one of these factors, we take their-- we would step up their care more aggressively.

So, what are the medications that we have at our disposal to treat ulcerative colitis? So, this is a slide where I have all the major medications on this table. And I'll just quickly walk you through some of them. So, we have 5-ASAs, 5-aminosalicylates, which are oral and topical agents, that we use in more mild disease. We also have steroids, both prednisone as well as a relatively newer formulation called budesonide MMX, which has a high first pass metabolism, so less systemic side effects.

We use thiopurines as well, which are oral medications that inhibit DNA and purine synthesis. And of course, we have our biologic agents, which I showed before are major drivers of the cost of care in ulcerative colitis, but are also our most effective agents. The two classes of these are anti-TNF, which really revolutionized the care of IBD. We have IV formulations, which are infliximab, and subcutaneous formulations, adalimumab and golimumab.

And the newest kid on the block are the anti-integrins-- so vedolizumab. This is a biologic that actually targets the interaction between white blood cells in the circulation, between integrins, that then allow them to egress from the circulation into the gut. So it's a gut specific mechanism. And it has been increasing in its use, I'd say, as a favored biologic in IBD, mostly because of its side effect profile. And then lastly, is cyclosporine, which is really limited to the-- in patients with severe UC cases.

So, just to give you guys a little flavor of how we think about instituting these therapies, when we see a patient with ulcerative colitis, we're thinking of their care in two phases. One is to induce remission, get the inflammation under control quickly, and get them feeling better quickly. And then the second is to maintain that remission. And this is a classic step up diagram here, where the solid line are inductive therapies that as the disease is increasing in severity, we use more and more potent medications. And the dotted lines are medications that are used for maintenance.

Many of these are used both for induction and maintenance, although just a couple of notable exceptions. Steroids, we only use for induction. And thiopurines are only used for maintenance. And everything else we can use both as an inducing as well as a maintaining agent. And so just to point out here, more mild disease, we would favor using the 5-ASA drugs, the 5-aminosalicylates.

When you get into the moderate to severe diseases is when we start to use steroids to induce. And we may then use our biologics as well. And then we would, once we get patients into remission, we would then maintain them on one of these drugs.

This is a busy slide where it's an algorithm that we put together for a review paper that incorporates the US, European, and Canadian guidelines. But I'll just quickly hit on some highlights. So, you have a patient that you've classified as mild to moderate UC. And the first thing that we look at is the disease extent. So, patients with proctitis versus left-sided or extensive disease, if you just have proctitis, oftentimes these patients can get away just with some topical 5-ASAs, just some 5-ASA suppositories. Whereas, if you have more extensive disease, we combine oral and topical agents.

And then we would assess them for response. And if they respond, continuing them on these agents. And they're not responding, then we would make sure we optimize our 5-ASAs. And if they do respond after optimization, then you can continue on the same medication. However, if patients aren't responding to our 5-ASA drug, then this is where then you start to think about using steroids, either prednisone or budesonide MMX.

And if patients respond, because they required steroids, most people would go probably to step up their therapy, either with thiopurine or a biologic. Although, depending on how severe the disease was, it's not unreasonable to continue them on a 5-ASA as a maintenance drug. However, if patients in this category are still not responding to steroids, and are still flaring, then you have to step up to the next degree of severity.

So, from moderate to severe UC, this is where you're using steroids. And if patients respond to steroids, this is where you then can transition them. Again, as I mentioned before, either to 5-ASA, thiopurine or a biologic. Typically, if patients are requiring a high dose of steroids, and depending on the disease severity, we're less likely to put them on a 5-ASA and more likely to step up their treatment. But like I said, there's certain-- case by case basis.

And if patients go into remission one of these therapies, then you can continue on them as a maintenance. But if patients don't respond, particularly if they're on a biologic agent, one of the things we do is we make sure we optimize the drug by checking drug levels. And if they have low drug levels, we would increase the dose of their biologic. And if they do have an adequate drug level, and they're still not responding, then we may change classes of drugs.

What if patients don't respond to oral corticosteroids? This is oftentimes where patients may need to get hospitalized, which I'll talk about it in a minute. But oftentimes, they may need IV steroids and then get transition to a thiopurine or a biologic. And if they don't respond to steroids, this is where you're going straight to one of our biologics, either vedolizumab or an anti-TNF. And once they respond, you can continue on those agents as a maintenance.

And similarly to before, if they're not responding, then you would make sure that your biologic is optimized. And if it is optimizing, you may need to change class. And if patients are not getting better, despite our best medications, our biologics, this is where you need to then talk about surgery.

So, surgery in these patients, the preferred surgery is a subtotal colectomy. And then creation of a J-pouch. So this is a little picture of a J-pouch. This is where basically the patient's small intestine is brought down to the anus and is made into this little pouch, this little reservoir, kind of like a fake rectum. And they're directly reconnected to be able to have bowel movements without an ostomy. Although, in some cases, we may use a permanent ostomy, particularly if someone's sphincter tone is very poor.

So, we're using surgery as a preferred therapy if patients obviously are failing medical therapy or if they're coming with massive, unrelenting hemorrhage, which is very rare, but can happen. Patients who have toxic megacolon, which you may see in the hospital, these patients need surgery. Patients with high grade dysplasia, or multi focal dysplasia, or cancer, would need surgery. And then long-term intractability.

So what are some of the complications that we're worried about in ulcerative colitis and special situations? So, first is acute severe UC, which is probably what the house staff see most often. We'll have patients admitted to the hospital with severe flares. And these are the patients when you look at the Truelove and Witt's criteria that are having multiple bowel movements a day-- 10-plus bowel movements. They have a low grade fever or are tachycardic, and have elevated inflammatory markers.

So, these patients need to be hospitalized for further care. And the workup I've outlined here very briefly includes preparing them for potential anti-TNF therapies by checking for hepatitis B and tuberculosis, getting a plain abdominal film to check for colonic distension, and checking for any concomitant infections, C diff or other bacterial infections.

And all these patients should get a sigmoidoscopy, with biopsies, both to assess their disease severity, as well as to biopsy potentially for CMV. And in these patients, we want to avoid narcotics. And we don't routinely use antibiotics. And we allow these patients to eat. So, this is somewhat in contrast to Crohn's disease, where we may give them bowel rest and sometimes we'll use antibiotics. But in general, for severe UC cases, they can eat as much as they're tolerating and we don't use antibiotics.

And I think the most important take-home point here is that these patients are at markedly increased risk for venous thromboembolism. So, if you look at all hospitalized patients, and you look just at the patients with UC flareup, compared to other hospitalized patients, all hospitalized patients obviously are at increased risk for VTE, or most hospitalized patients, but ulcerative colitis flare patients are probably about eight times as likely to develop a VTE. So, it's extremely important that these patients are on subq heparin, or whatever your prophylaxis is, to decrease the risk of them developing VTE.

And the reason why we take these patients so seriously is that, this was a study from the National Inpatient survey in the US. And if you see here, over time, the patients that are hospitalized, once you're hospitalized for a week or more, there actually is a mortality rate that develops. And these patients actually have a life threatening condition. So we watch them very closely and take them very seriously.

So, this is a proposed algorithm for the management of acute UC, just because the house staff probably see these patients a lot with us, and how we're thinking sequentially, what are the next steps. So, after our initial workup, or a concomitant of our initial workup, the real first line treatment is IV steroids. And within three days, you should know if the patient's going to respond or not to IV steroids.

And if they're not responding to IV steroids in three days, then you need to make a decision about what's the next treatment. And at that point, the next treatment would be either cyclosporine, or remicade, or infliximab. And typically, now we've been using more infliximab, just because of its side effect profile. And also you can continue them on this medication.

And after they get their dose of infliximab, then you're going to assess response within five days. And if they're not responding, then they would need to go to colectomy. But if patients do respond, then we continue on these medications and follow them very closely as an outpatient.

So, other types of complications that we see commonly in ulcerative colitis are extra intestinal manifestations. And this happens in up to a third of ulcerative colitis patients. And there's a numerous number of complications that can develop, intestinal manifestations that can develop, that I have listed here. Most common is peripheral arthritis. PSC and pyoderma gangrenosum are two of the extra intestinal manifestations that are more common in UC than in Crohn's disease.

And I think, interestingly, about 25% of patients will develop one of these complications-- one of these extra intestinal manifestations before they develop their ulcerative colitis. And these complications, these extra intestinal manifestations may or may not mirror the bowel activity of the UC. And it really takes a multidisciplinary approach to these patients, where we're relying on our dermatology, rheumatology colleagues, and hepatology colleagues as well.

So, the last complication I want to mention is probably our most feared complication of ulcerative colitis, is colon cancer. This is a meta analysis that was published back in 2001, where it's looking at the risk of colon cancer over time in patients with ulcerative colitis. And it used to be thought that there was this exponential increase over time, where patients were-- 20% to 25% of them were going to get colon cancer.

Well, recent data has suggested that it's probably not as high of a risk. This may be due to better screening, or medications, or the way the studies were done. And it appears that UC patients are at increased risk for colon cancer, but it's probably more like 1.5 to 2 times the general population. So, what do we do to survey these patients and monitor these patients?

Well, based on the AGA recommendations, after eight years of the disease is when we would begin to survey. And this is a common question on your boards, for the medicine residents. After eight years of the disease, we would begin to survey with colonoscopy with random biopsies and/or chromoendoscopy, which is its own talk altogether. But we would be repeating this every once to two years.

I think it's important to note that depending on what country or what society, the recommendations about surveillance do vary. But in general, the take-home point, after eight years, we're doing annual or colonoscopies every one to two years. And patients that are at higher risk are patients who obviously have a history of colorectal cancer, who have longer staying disease, or a higher inflammatory burden.

And I think a special population to take note of are the PSC patients. So Primary Sclerosing Cholangitis patients, who also have UC are at markedly increased risk for colon cancer. So PSC, UC patients are nine times as likely to develop colorectal cancer. In those patients, we don't wait eight years to start surveying. As soon as they're diagnosed, we do annual colonoscopies on those patients, because they're such high risk.

All right, so for the last section here, I just want to talk a little about some future directions and touch a little on some research we've been doing. So one of the major things that's confronting us now in IBD care, it's a very exciting time, because we have multiple agents that are in the pipeline or newly approved. As you can see here, this is-- these are all the different mechanisms of action. Some of them are a little bit like "Me Too" drugs, TNF inhibitors. But there's a lot of new mechanisms of action that are being tested or are in the pipeline. And actually, for UC, there's at least 27 new drugs that either recently completed a trial or are currently undergoing trials.

So, this kind of presents us with both opportunity, but it's also a bit of a conundrum, of how are we going to position these medicines and when are we going to use them, in which patient. So just briefly, two of the medicines that you're going to be seeing coming out soon, that'll closest to being ready for release, are Tofacitinib, which is already being used by the rheumatologists. And I think, as a general theme, the GI doctors usually steal the drugs from the rheumatologists, with the exception of our gut specific adalimumab.

And, so Tofacitinib is an oral medication that's a janus kinase inhibitor. So, it blocks cytokine signaling through multiple-- multiple different cytokine pathways get blocked through this oral agent. And there's phase 3 trial that was recently completed in the *New England Journal* that showed that these patients were more likely to reach clinical remission, more likely to have mucosal healing, both in induction and in maintenance phases. So, this is potentially a very useful drug, especially in that it's an oral agent. So, our patients, instead of injecting themselves, or having to do infusions, this is going to potentially help in that aspect.

Another drug is Ozanimod. That's in the pipeline. This has completed phase two studies. This is an oral S1-P1, S1-P5 receptor agonist. Basically, what that means is, in lymph nodes, if you agonize these receptors, it sequesters the lymphocytes within the lymph nodes and prevents them from going into circulation and going to the gut. So, this is also another oral agent that has had some promising results in phase two. And phase three trials are underway. And so, we eagerly await the results of that.

So, you can't have a GI talk and not talk about poop. And so, what role does fecal transplantation have here? So, there's been really three major studies that have come out about fecal transplantation for ulcerative colitis. These are the first two. One was positive, where it showed increased rates of clinical remission, and the other one was negative. And so, these were conflicting results. They were relatively smaller studies. And so, it left the jury out.

And the most recent study, though, that was published in*The Lancet,* was the largest study to date, looking at fecal transplant for ulcerative colitis. And what they did is they randomized patients to FMT through a colonoscopy, followed by enemas, stool enemas, five days a week, for eight weeks. So, it's very intensive therapy That. Patients have to be very motivated to do, to give themselves stool enemas five days a week.

But the results were promising. We had 27% of patients in clinical and endoscopic remission at the end of week eight. This is very short-term follow up. So, there's lingering questions about the sustainability of these results. Longer term, can you use it as a maintenance? And so, I think the jury's still out. But I think anti-microbial or some sort of microbial therapy is going to likely play a role at some point in ulcerative colitis. Is just kind of still in the development. We're not sure exactly where it's going to fit in our treatment algorithms.

So, as I mentioned, all of these treatments that are in the pipeline or recently available, it's a great opportunity, and it's really great for our patients, but it's also presenting us with the challenge of how are we going to select treatments for patients? How are we going to select the right drug for the right patient at the right time?

And so, what we think is going to play a role here are biomarkers, clinical prediction tools, and head to head trials, to really help us decide how we're going to position these medications. And just one paper that came out very recently that's very exciting, in *Nature of Medicine,* looked at patients with ulcerative colitis. If you took a biopsy before they started a TNF-- so either infliximab or adalimumab, and you looked at the gene expression in the mucosa of the rectum, can you predict who's going to respond or not respond?

And they found that this molecule, called OSM, and its receptor, OSMR, it's a cytokine, if you had a high expression of this, you were significantly less likely to respond to anti-TNF therapy, about five times more likely to not respond. So, this potentially, if this is replicated, could help us guide therapy. It tells us who's not going to respond. So, we also would like things that will tell us who's going to respond to which medications, but this is a nice step forward.

And just as the last thing I wanted to talk about, is a clinical question and research question that I've been working with one of my mentors, Dr. Colombel. And it's based on this clinical observation that in ulcerative colitis, you have this very, very stark, in many patients, stark line where you go from disease mucosa to normal mucosa. And we have no idea why is it that all of a sudden, you have disease, and then it just stops, just stops right in his tracks, like this. You have this sharp demarcation.

And the other question that we have is, how do we know which of these patients who have limited disease are then going to go on to extend their disease and involve more of the colon? And we know, based on some work that we did, that patients who have proctitis and left-side colitis, about 30% of those, about one in three, are going to go on to more extensive disease. And when you go on to more extensive disease, this event of having this extension is actually very, very poor outcome for patients, and is associated with increased immunosuppression, needing to have colectomy, hospitalizations, many poor outcomes.

And so, related to this, we collaborated with a group in Denmark to look at a perspective inception cohort of ulcerative colitis patients to see are there any clinical predictors of extension and what happens to these patients when they extend. And basically, what we found is that we only found one clinical predictor of extension. And that was if patients had E2 disease-- so, if they had left-sided colitis as opposed to proctitis, they are more likely to extend their disease by about a hazard ratio of two. But there were no other clinical factors that seem to predict extension.

And then the other thing that we saw was, in this bottom line here, the red is patients who had extensive disease-- sorry, limited disease, from diagnosis and their risk of colectomy. And you can see, if you have limited disease, your risk of colectomy is fairly low. This blue line are the patients who had extensive disease since diagnosis. And you can see that their risk is markedly higher than patients with limited disease, and sort of levels out around five, six years.

However, this line, the green line are patients who extended their disease. So, they went from limited disease, and then at some point, went to that pancolitis. And you can see that they were at numerically higher risk of having a colectomy. And this played out when we looked at our Cox modeling as well, where patients who extended from E1 or E2 limited disease to pancolitis were 22 times more likely to need a colectomy, So, this event of extension is a very, very dramatic one and leads to very poor outcomes.

And so, if we can understand one, why that happens, and two, can we predict who it's going to happen to, it may help us personalize our treatments and our management approaches. And so, since we weren't able to find any clinical predictors, we've been starting various research projects, looking at histological predictors of extension and molecular predictors of extension.

And this is just some preliminary data from the Mount Sinai Crohn's and Colitis registry that we're working with, where we took patients who had biopsies and inflamed mucosa, and then had a biopsy in the adjacent normal. And then further, normal biopsies as well. And this first column here is gene expression in the inflamed area. And then the second column here is gene expression in the immediately adjacent area, that's normal on endoscopy.

And you can see that there's a set of genes that dramatically drop and a set of genes that dramatically increase as you can make that transition and then stay that way. And so, this is an analysis that's obviously very preliminary, but we're looking to see if any of these genetic changes here may predict extension. And that's our next step, is to look at which of these patients who had these drastic changes went on to extend their disease.

So, just in closing, I'd like to just plug our IBD Center, which we're actually located on the fifth floor of the CAM building. This makes the CAM building look beautiful, this picture. It's probably the most beautiful picture of IMA you've ever seen. And we're on the fifth floor there. You guys are on the seventh, I believe, so not too far away. And really, we have a-- it's a really world class multidisciplinary care team that we have there, that's really a privilege to be a part of.

And you can see, this is just-- this is only some of the people that are involved. And we have a whole team of adult gastroenterologists, a whole team of pediatric gastroenterologists, who are IBD specialists, who are able to take care of people from childhood all the way through adulthood. We have a whole team of IBD surgeons-- there's just three of them here-- that we work with very closely.

Coupled with that, we have a fantastic ostomy nurse for patients have ostomies. We have world experts in IBD, in particular Noam Harpaz here, that we partner with. And IBD radiology experts, as well, because we really rely on our colleagues in radiology and pathology to help us guide diagnosis and treatment.

What's really I think a unique aspect to our IBD Center is we have a clinical psychologist, who specializes in the mental health of patients with GI disorders, in particular IBD patients. And so she's involved in various different research studies, as well as clinical care, providing hypnotherapy, providing resilience counseling, anxiety, stress counseling. And so, we couple this with our patient care.

And we have a full nutrition team as well, both nutritionists and a MD that specializes in nutrition. And I think the people that aren't here, that really help the center go, are all our staff, and nurses, and nurse practitioners, who every day are really helping our patients get the care they need.

And so, like I said, we really provide a multidisciplinary approach to patients. I'm starting to call this IBD 360. We have the patient in the middle. And we have all these different services that we provide for them. And we really pride ourselves in being able to care for patients at all these different stages, because IBD is a lifetime disease. And so being able to care for patients at different stages of their life with their disease, we feel like we can do that all in one location at our IBD Center.

And then just one last plug. We're going to have a recently diagnosed IBD patient rapid access program that is going to be rolling out this summer. Where we believe that the care you receive in the first year can really help set the trajectory for the rest of your disease course. And patients in the first year of disease are also very vulnerable, have a lot of questions, and it's a very uncertain time for them. And so, providing this multidisciplinary care very early on in the disease course, and very rapidly, we think can really improve outcomes and increase patient satisfaction.

So, I'd just like to thank my mentors, and collaborators, and current and past funding, and thank all of you for your attention, inviting me to be here today.

[APPLAUSE]

[INAUDIBLE]

AUDIENCE: Thank you, great talk.

RYAN UNGARO: Thank you.

AUDIENCE: As far as more of an indicator, what is the algorithms, since now they're reporting vedolizumab [INAUDIBLE]

RYAN UNGARO: So co-Infected patients, it's a minority group, but we do see them here. They did-- actually Saurabh Mehandru with a resident looked at patients with HIV and IBD, both Crohn's and UC, and it seemed that they were less likely to need more aggressive therapies. And there is, as you mentioned, with HIV, there is the intigrin that is blocked by vedolizumab. It seems to play a role in development of the reservoir of HIV in the gut.

And so, there is a lot of interest and research coming out, in terms of potentially repurposing vedolizumab for treatment of HIV. But in general, it's a rare patient population, but they tend to have a little bit more mild course. But that's not, obviously, there will be UC patients who are more severe with HIV as well.

AUDIENCE: I've seen a video of a surgeon who injects-- an oncologic surgeon who injects the intestine at the time of surgery with a dye taken up by lymphatics and it demarcates just like that. And I wonder whether that's the answer as to what the demarcation is.

RYAN UNGARO: Yeah, that's a fascinating observation, that we actually-- I didn't mention it, but we are taking surgical specimens and doing that kind of work. We're trying to see the vasculature, the nervous system, the lymphatics, all around the margin, if there's stark contrast. What we-- well, not me, but Dr. Colombel has done research in Crohn's disease, looking just at that, taking surgical specimens.

And there are definitely marked differences in Crohn's disease in the lymphatics. It's not entirely clear yet in UC, but we're looking at that right now. And it may very well may be that the lymphatic and the distribution play a key role there. I think that's a really interesting observation that we're still trying to learn more about.

AUDIENCE: Thanks very much for a fine presentation.

RYAN UNGARO: Thanks.

AUDIENCE: It is a mystery, I think, about the age presentation of this disease. Maybe you could comment on whether you're aware of any research about age. Why does this strike people who are younger, and beginning, middle aged, and rarely, but, of course, occasionally assault older people. Yes

RYAN UNGARO: It's not entirely clear. What we do know is that patients, particularly pedia-- if you look at the extremes of age, pediatric patients have a higher-- seem to have a higher genetic burden, and it's more driven by genetic predisposition. And as you get more into older patient populations, it seems that the genetic burden is probably less. And it's more driven by environmental factors.

And it's started to be appreciated that there are increasing rates, probably about 10% or so of IBD cases are now being diagnosed in the elderly. And IBD elderly is defined as age greater than 60. And that those cases seem to be more driven by environmental factors. Some may be medication exposures, maybe ischemia. Maybe there's something about microvasculature.

And why it hits in that 20 to 30-year-old range, like as the highest peak, is not entirely clear, to be 100% honest with you, but it may just be that it takes time for the combination of the genetic, environmental factors, and insults to accumulate. And that sort of just seems to be the amount of time that it takes.

SPEAKER 1: We'll take a last question.

AUDIENCE: In mice, it has been noted that a decreased amount of IL-10 or a decreased IL-10 receptor, or a defect in either one of those, leads to macrophage induced inflammation of mucosa, including intestinal mucosa. Has this been looked at in humans?

RYAN UNGARO: Yes, so, IL-10 plays a regulatory role, for sure. And there's been some extreme-- there was a case series in the *New England Journal* like six years ago, where they looked at extreme phenotypes of IBD. And some of them were actually patients who seemed to have defects in IL-10. And there are some agents in the pipeline where the pharmaceutical companies are trying to actually give IL-10, either a synthetic IL-10 or IL-10 agonist.

And those studies, so far, have been just early phases. There's been sort of mixed results. But it certainly is a pathway that seems to be important. But I'm not sure it's going to end up being an end-all, be-all kind of target for us.

[APPLAUSE]