

Ruth Adewuya, MD (host):

Hello. You're listening to Stanford Medcast, Stanford CME's podcast where we bring you insights from the world's leading physicians and scientists. This podcast is available on Apple Podcasts, Amazon Music, Spotify, Google Podcasts, and Stitcher. If you're new here, consider subscribing to listen to more free episodes coming your way.

I am your host, Dr. Ruth Adewuya. Welcome to season four of Stanford Medcast. This episode is part of our Hot Topics miniseries. Today, I will be chatting with Dr. Kian Keyashian on inflammatory bowel diseases.

Dr. Keyashian is a clinical associate professor at Stanford Medicine in the gastroenterology and hepatology department. He graduated medical school from UCSF in 2005 and continued to complete two fellowships in gastrointestinal and liver diseases, and inflammatory bowel disease. He is currently focused on improving patient outcomes and quality of life with inflammatory disease. Serving as director of IBD at Stanford, his research investigates new non-invasive diagnostic tests, finding factors early in the disease course that might predict a more aggressive disease course and need for different therapies, as well as investigating new promising, effective medications with fewer side effects.

Dr. Keyashian, thank you so much for chatting with me today.

Kian Keyashian, MD (guest speaker):

It's a real pleasure to join you.

Ruth Adewuya, MD (host):

A great place to start to center our conversation on IBD is definitions. What is inflammatory bowel disease, or IBD, and what are some of the differences between the two main types of IBD?

Kian Keyashian, MD (guest speaker):

Yeah, that is a good place to start. So the inflammatory bowel diseases include ulcerative colitis and Crohn's disease. These are chronic inflammatory conditions of the gastrointestinal tract and, typically, these are diagnosed in patient's teens and 20's, and they have what we call a relapsing and remitting course periods where symptoms are increased related to inflammation, what we call a flare, and then periods where there's absence of inflammation and oftentimes absence of symptoms. That's remission. This is a very classic characteristic of these inflammatory bowel diseases.

There are two types, ulcerative colitis and Crohn's disease. The management of them ends up being very similar. The only difference is surgical management if it's a more significant disease, but they're generally managed similarly, but there are some nuances that are worthwhile to review. Ulcerative colitis involves really the inner lining of the colon. It starts right at the rectum, the very last part of the colon, and moves up higher in about a third of patients. It's just the rectum that's involved in about a third. That inflammation extends all the way up to the left side, and then it's only about a third that have a little bit more involvement than that.

Ulcerative colitis really only involves the mucosa. The word colitis is in there, so it really only involves the colon, the inside layer. That's in contrast to Crohn's disease. Crohn's disease can involve really all layers of bowel. It's a transmural process, it's the term that we use, really anywhere from the mouth to the anus. The inflammation in Crohn's disease tends to be patchy. For example, if I were doing a colonoscopy on a patient with Crohn's disease, I might find that the rectum actually looks pretty healthy, and then I go up a bit, then I might see a patch of inflammation, go up further, again, normal, so there is this patchiness. The most common location for Crohn's disease tends to be the last part of the small

intestine called the ileum and the first part of the colon, so some subtle differences, but generally two main categories within the inflammatory bowel diseases.

Ruth Adewuya, MD (host):

As we think about these two diseases that we're putting in this large umbrella, do we know if there are any specific risk factors or predisposing factors that make certain individuals more likely to IBD?

Kian Keyashian, MD (guest speaker):

You know what? It's actually on a lot of patients' minds. It comes up with patients who I see that have inflammatory bowel disease and they're asking me more about, for example, their kids or siblings. The tough thing is looking at the individual patient and saying, "This was the reason that you have inflammatory bowel disease." I think, for the individual patient, the cause is not clear, but if you look at the entire population, it seems like most things to have a nature and a nurture component, a genetic component and an environmental component.

We know that about 10% of patients with inflammatory bowel disease have relatives with inflammatory bowel disease. There are specific genes that have been identified to be associated with IBD, and these genes actually code for the way the immune system interacts with the bacteria within the GI tract, and so I think of IBD as a hyperimmune disease where the immune system is really ramped up and is attacking things that it wouldn't normally attack. It's not necessarily attacking the bowel, and so I think the classic definition of an autoimmune disease is not how I would describe inflammatory bowel disease. It's just that the immune system for genetic causes potentially is really ramped up.

I do think bacteria is also important here. I think that, if you look at patients with inflammatory bowel disease, there's less diversity in the bacteria that live within the GI tract, the microbiome. There are different types of bacteria in patients with IBD. Then, of course, the environment, as I mentioned, plays a part in that, and so antibiotics, specific dietary components, tobacco exposure. These all seem to play a part in the risk of developing IBD, and so I tell patients that, in the patient with the right genetic predisposition with certain environmental triggers that result potentially a change in the microbiome, the bacteria that live within the GI tract, these are potentially the risk factors that bring about the diagnosis and their presentation.

Ruth Adewuya, MD (host):

How is the disease diagnosed especially since it sounds like there's a multifactorial origin of the disease? Then what are some of those key diagnostic tests?

Kian Keyashian, MD (guest speaker):

I'm a gastroenterologist, and I see patients who have had more advanced testing as well, but I do think that some of our audience may include providers with points of primary contact, primary care providers, and so I think there are some subtle clues that might clue one in to potentially a diagnosis of IBD. IBD may initially be suggested by simple lab tests, stool tests, blood tests. Blood tests may, for example, show an increase in inflammatory markers, something we call the C-reactive protein. You might see subtle anemia, iron deficiency anemia. You might see other nutritional deficiencies like vitamin D or B12 or other vitamins. Stool tests can also show this. There's actually a stool inflammatory test called the calprotectin which is typically within normal range, less than 50, but in patients with the inflammatory bowel disease, if it's checked and it's elevated, it could be a clue that this could be going on.

These initial tests are a great way for points of primary care, whether it's emergency department physicians or primary care providers, to at least start to explore whether IBD is a possibility in the patient sitting in front of them. Then, of course, the diagnosis requires more extensive testing. Colonoscopy could show ulcers, redness, what we call erythema, edema that could start in the rectum or move higher or skip areas and involve the small intestine like in Crohn's disease. There are ways to evaluate the small intestine, so capsule endoscopy where you swallow a pill-sized capsule, a video camera, a small video camera, pill-sized, and MRI and CT scans with both oral and IV contrast. All of these are also ways to explore whether small intestinal Crohn's disease is a possibility.

I do like to start with my non-invasive tests first and then, if there are clues there, then I think about more colonoscopy capsule and imaging. In the right patient, say, for example, with family history or unexplained anemia, I still think it's worthwhile to go ahead and move forward with some of those additional tests just to rule it out.

Ruth Adewuya, MD (host):

In the practical way, let's say a clinician is seeing a patient, what would this patient look like? What are some of the signs and symptoms that should trigger a clinician to consider IBD as a potential diagnoses?

Kian Keyashian, MD (guest speaker):

One should realize that there are some subtle differences in how patients present with UC and Crohn's. It's not the same necessarily for all patients with IBD. Patients with ulcerative colitis typically have symptoms that can be attributed to inflammation of the rectum, and so they're having multiple bowel movements, they have urgency, they might have accidents, not making it to the bathroom. They might pass blood into stools. They might feel uncomfortable passing gas without worrying about whether there's potentially stool there, and so they may actually go to the restroom to pass gas just in case they're stool. These are all signs of inflammation in the rectum.

Abdominal pain is a little bit less common in ulcerative colitis. Patients may describe cramping, say, before bowel movements, but as opposed to Crohn's disease where typically abdominal pain, whether it's on the right lower abdomen, perhaps the mid-abdomen, is a bit more common in addition to frequent stools, and then patients with Crohn's disease can have systemic symptoms otherwise. They can have fever. They can have unexplained weight loss. You see less passage of blood, less urgency in Crohn's disease, and then Crohn's disease we'll talk about in a little bit, but you can also get complications potentially, so areas of narrowing which can result in obstructive symptoms like nausea or vomiting, inability to pass gas.

The GI symptoms that make me even think about inflammatory bowel disease are increase in frequency, urgency, passage of blood, inability to distinguish gas from stool, belly pain, and then we also have to remember, Ruth, that interestingly there is a subset of patients that can have symptoms outside of the GI tract. Joint pain and swelling can happen, eye symptoms, either vision changes or redness or eye pain, rashes, kidney stones, gallstones, even jaundice as it relates to liver disease. Some of these gastrointestinal symptoms are our initial clues, but I do think then doing a broader look at symptoms within the GI tract and outside can really start to make the clinician really strongly consider inflammatory bowel disease especially if it's been going on for some time. I think that's the other piece is this chronicity of these symptoms.

Ruth Adewuya, MD (host):

Taking a step back, the reason why this is important, IBD affects millions of people. We're not talking about a rare disease or, when you talk about some of the symptoms of urgency and not being able to wait to go to the bathroom, you can see how it can impact one's quality of life and how significant that could be. Can you discuss some of the current challenges that are faced by patients with IBD, and what are the areas where you hope outcomes can be improved?

Kian Keyashian, MD (guest speaker):

You're hitting the nail right on the head here. The unpredictability of flares, not just when, but also how severe. The urgency, that's on a lot of my patient's mind. The need to rush and potentially having access to bathrooms is an important piece. A lot of my patients have memorized bathrooms that are on, say, a walking route or a hiking route or in stores and malls and those kinds of things. I do think that those pieces are there. Whether the patient is in remission or whether they're currently has some active symptoms, I think that those certainly impact the quality of life.

What we haven't even gotten into, Ruth, is that these acute issues are in patients' minds day-to-day, but remember that there are long-term risks as well that are in patients' minds, narrowings or strictures, nutritional deficiencies, even the risk of colon cancer, which seems to be slightly increased in patients, and so there are definitely short-term concerns and long-term concerns which all have significant impact on quality of life.

The good news is that we've already started to see some movement to address some of these important things. For example, the patient reported outcome of urgency are now incorporated into many clinical trials to make sure that that symptom is specifically addressed. Newer therapeutics are really working to reduce the frequency of flare so the disease becomes a bit more predictable, and certainly new causes of flare are being explored. It gets daunting to list all of these things that potentially could impact the patient's quality of life, but it is exciting to be part of this field and be working with patients to really see how far we've come from the descriptions in the '20s and '30s of this disorder and just how much we're moving in the right direction. I won't say we're all the way there, but I do think that there are steps to address all these different features that could impact the quality of life.

Ruth Adewuya, MD (host):

I want to move us along this patient journey and talk about treatment a little bit. What are some of the primary treatment methods that are currently available for IBD?

Kian Keyashian, MD (guest speaker):

It's important, when you're thinking about treatment, really first start off with what is the goal of treatment? In inflammatory bowel disease, the first goal is to improve symptoms and work towards remission. That is the primary goal. I think that you'll find that any sort of evaluation of the success of treatment initially starts with, okay, how are patients doing? Are they getting better, and do they get back to normal? I mean, those are kind of a spectrum of symptoms, get better and then get back to normal, what we call response and remission. Then secondary goals become normalizing those biomarkers that we talked about like the blood test, the C-reactive protein or the stool test, the calprotectin, and then healing. For example, if there was inflammation seen on a colonoscopy, really repeating the colonoscopy at some point and making sure the lining is healed because studies suggest that if you go beyond symptoms and actually heal the lining, it seems to be associated with better outcomes.

I think this is one of these things that I think health practitioners should know about IBD care is that it's important to certainly get patients' symptoms back to where they need to, but really going beyond symptoms and confirming healing has a long-term, improved prognosis for patients. It's important to keep those goals in mind and then realize that the treatment of IBD depends on the type of IBD, whether it's Crohn's disease or ulcerative colitis, the severity. Is it mild? Is it moderate? Is it severe? The relationship that a patient develops with their gastroenterologist or their primary care provider, that is what's going to help that patient in decision-making and what would be the best therapy for that patient at that time.

Ruth Adewuya, MD (host):

When you talk about healing and treatment, generally, are there averages of how long this takes place?

Kian Keyashian, MD (guest speaker):

Yeah. The first thing that any provider, any patient should look for is symptoms. That's where we focus. Initially symptoms improve and maybe even go into remission after a period of time where you're back to your baseline, and then the inflammatory markers improve, and then the healing. The different available therapies that we have have different times to achieve these goals, and the timing is also different in ulcerative colitis and Crohn's disease. In both diseases, some of these therapies can improve symptoms as fast as two to four weeks. Others can take two to three months to get fully working. Biomarkers like the C-reactive protein and the calprotectin, those can take one to two months to get better, but in others it could take three or so months, and then the healing is the last stage, looking with a colonoscopy or an MRI, and that's the third tier of benefit.

In Crohn's disease, that's sort of in the three to six-month window as far as healing. In ulcerative colitis, it's about three to five months, so it's similar. Again, it's important to shift goals as you achieve each and then look to the next goal. How are symptoms doing? Are they improved? How are symptoms doing? Are they resolved? How are the inflammatory markers? Are they markedly improved? Are they normalized? Then, finally, the healing that one might capture on a capsule endoscopy, colonoscopy, MRI or CT, that's more of a three to six-month process.

I think a good monitoring protocol to make sure that a medicine is working for the patient is to do timely checks of these things and, once they get to that state, then make sure that that's maintained, so some sort of tempo of once or twice a year stool tests or blood tests and then maybe a colonoscopy or MRI every few years to confirm that healing is maintained.

Ruth Adewuya, MD (host):

One of the things that I'm hearing from you is the need for this personalized treatment for each patient because, going back to where we started, it sounds like there are different factors that impact how the disease shows up in a patient, and so the clinician then in turn needs to recommend a course of treatment that is very personalized to the patient. One of the things that you talked about earlier in our conversation was the idea of nature versus nurture, and you talked about the environment and how people grow up and the diet that they eat. Most recently, the gut microbiome has been linked to various aspects of IBD. How does current research on the gut microbiome offer potential avenues for improving patient outcomes and quality of life?

Kian Keyashian, MD (guest speaker):

That's definitely going to be an area in the near future. It still is in its infancy, but I do think that we're really moving in the direction of being able to manipulate this. As I noted before, there are several aspects of the microbiome that suggest that there's clearly a role in the development of IBD and, perhaps, IBD flares. Antibiotics are a risk factor for the development of IBD. Multiple courses in our childhood, for example, could predispose to inflammatory bowel disease. The microbiome of patients with inflammatory bowel disease shows less diversity and some differences in composition compared to patients with IBD.

I do think that manipulating the microbiome may be a potential mechanism to treat inflammatory bowel disease as has been done in other conditions. For example, the FDA has approved stool transplant or fecal transplant for infectious colitis, *C. difficile* colitis from a donor to the patient, and that oftentimes results in cure of disease that's been recurrent or refractory. Interestingly, these microbiome studies have also been done in inflammatory bowel disease, and there are some studies that show quite good results. The problem is that IBD is a bit more complex and more heterogeneous if you look at the nuances of ulcerative colitis and Crohn's disease. You'll find a lot more variability in the early stool transplant studies, and I think a lot of that has to do with who were the donors for the stool? What were the recipients? Where was the location of their disease? There's a lot of this variability that makes it hard right now to give a general approach and say this is definitely going to be the way to do it in terms of the microbiome.

I think that currently available probiotics are unlikely to be the answer in the management of IBD. With probiotics, there's really no regulation by the FDA. There's some differences in formulation, but I do think that there are a number of microbiome-based therapies that are slowly moving forward towards the approval process in the management of IBD. They're already approved for *C. difficile* colitis, so I do think that that's the next step. We just have to understand that, when we do these studies targeting the microbiome, we have to have a very uniform population that's undergoing therapy so that we can generalize and say, "For a patient with ulcerative colitis of the left colon, giving the microbiome manipulation this way results in benefit."

I do think it's very exciting that, from early identification of the microbiome to now leveraging it and using it as therapy, I think we've come a long way, and I really think the next five years are going to be exciting to follow where this goes in IBD, and I do think we're going to have therapeutic options that are specifically targeting the microbiome.

Ruth Adewuya, MD (host):

That's very exciting, and it sounds like there's breakthrough on the way. We're in this age where every, once in a while, diet and lifestyle modifications in general, but they've garnered some attention in the management of IBD. Can you share any recent findings on how these approaches complement traditional therapies and could contribute to better patient outcomes?

Kian Keyashian, MD (guest speaker):

Ruth, yeah, it's a question that's on a lot of my patients' minds. One of the most common questions that I get is regarding diet. What should I be eating? What should I do with exercise? I do think there's an increasing body of literature that shows that, independent of being compliant with medications that are prescribed, patients could further improve their quality of life through these integrative approaches. Both diet and lifestyle changes have shown to potentially reduce symptoms attributed to IBD and, perhaps, reduce the frequency of flares, but we need a bit more evidence just in terms of healing. I think we're not there yet.

In terms of diet, diet studies, Ruth, are really hard to do. There's patient compliance issues with something that may not taste great and may not be able to be continued long-term. The funding for these studies is a bit more difficult for both ulcerative colitis and Crohn's disease. Diet should probably include a significant proportion of fresh fruits and vegetables, minimized servings of red meat. Crohn's disease tends to have a little bit more data when it comes to diet than ulcerative colitis. The Mediterranean Diet, for example, is a classic diet discussed by many providers where you avoid additives, emulsifiers, the processing, if you will, of food, all of which have been shown to worsen colitis in mouse models. Studies suggest that GI symptoms actually improve significantly as well through something like the Mediterranean Diet.

Then really outside of diet, studies suggest that exercise can actually reduce flares of the disease. During periods of remission, exercise could be beneficial in maintaining remission in addition to therapy that they're continuing. I already mentioned the importance of tobacco particularly in Crohn's disease, so avoiding tobacco in Crohn's disease is important. I do think that there are definitely these things that one should recognize probably will not take the price of medical therapy at least as of now, but really could be very nice adjuncts to really keep patients that are feeling well continuing to feel well and even, perhaps, better.

Ruth Adewuya, MD (host):

Up until this point, a lot of our conversation has really been focused on medication and diagnosis, treatment options, but I think it will be remiss of us if we didn't talk about the fact that psychological and emotional support can play a vital role in improving patient's quality of life. How do healthcare providers address these aspects in this comprehensive care of individuals with IBD?

Kian Keyashian, MD (guest speaker):

If you look at centers across the country that are centers that manage high volume of patients with inflammatory bowel disease, it's very clear that the management requires a team of professionals, a team headed by the gastroenterologist, but also including colorectal surgeons, including registered dietitians and psychologists amongst others. Studies consistently show that, when it comes to mental health, anxiety or depression can be seen in 25 to 30% of patients with IBD. Certainly, these symptoms studies have shown can affect long-term prognosis independent of how severe the disease is as it's going into remission. Independent of that 25 to 30%, there's an even larger proportion of patients where, I talked about this a bit earlier, in terms of some of the unpredictability and the fear of flares that really, unfortunately, significantly shapes quality of life even in periods of remission.

The degree to which this unpredictability affects patients depends on something that we have and we have varying degrees of, so resilience or the ability to be able to bounce back. A lot of movement across this country has been certainly to focus on the disease and the patient and talk about treating inflammation, but really to identify resilience, and so you're finding that, as far as psychological and emotional support, a lot of centers like Stanford are using triage tools to make sure that we're addressing this even if, for example, in a 20-minute visit or a 30-minute visit, we are busy with talking about GI symptoms that we don't get to delve into it, to at least to monitor patients this way, then the psychologist that's embedded in the clinic can basically cultivate these skills for improving resilience.

I think the goal of the psychologist that's embedded in IBD clinic is not necessarily to manage the concomitant depression or anxiety. That's more on a partnering psychologist or psychiatrist. I do think that, because it's been shown that stress and anxiety have such impact on the long-term course of IBD, I do think identifying that in patients that could use additional coaching and cultivation of skills is important, and that's where the IBD psychologist could be an important part of the care team.

Ruth Adewuya, MD (host):

It's encouraging to hear that there is that sense of whole healthcare, and I really like what you said about building resilience and how do we help patients build that resilience as they navigate a really challenging time in their life and potentially that will impact the rest of their life. As we wrap up our conversation today, what are some of the most promising areas of IBD research and treatment that give you hope and excitement for significantly improving patients' lives?

Kian Keyashian, MD (guest speaker):

I've already mentioned the treatments. I think, to me, it is really exciting where we are and where we're going in terms of the differences in just the specificity of these treatments, the improvement in the safety profiles and the side effects, and the ability to allow the patient to take that concern off their plate of, day-to-day, "Is this treatment going to do something to me," or something like that. I think that really is encouraging.

I've been in IBD certainly for the past 10, 15 years, and I can tell you that it's changed dramatically in that time. I think that that gets me excited.

As you know, these days, Ruth, you can't really look anywhere without some sort of discussion on AI and the incorporation of AI in different fields including medicine. I do think that AI and machine learning is going to be an important part of the future of IBD research and treatment. It's already being explored, and I think that there's some real promising use. In IBD, I think applications exist in early diagnosis in monitoring, protocolizing, monitoring, as we talked about those stages of improvement symptoms, then biomarkers, then healing.

I do think that it streamline the care of an IBD patient to make sure that things we're human and, in a busy practice, things could be missed, and I think that AI really could be helpful in that regard. AI may also help reduce the need for invasive diagnostics and potentially improve long-term outcomes. There are barriers that need to be overcome like good data sets to allow the machine learning and the leap to solid decision making.

I go to GI conferences and IBD conferences. It's an area that I do think that will truly change the field. Most people who deal with AI talk about you've got to either get on board or you're going to be left behind. To me, I think of it as that IBD is really going to benefit from some of this standardization and decision-making, and I'm hopeful that it'll really optimize and improve the care of the IBD patient.

Ruth Adewuya, MD (host):

Thank you so much for taking the time to share your insights with us on this topic.

Kian Keyashian, MD (guest speaker):

Really appreciate the opportunity.

Ruth Adewuya, MD (host):

Thanks for tuning in. This episode was brought to you by Stanford CME. To claim CME for listening to this episode, click on the Claim CME link below or visit medcast.stanford.edu. Check back for new episodes by subscribing to Stanford Medcast wherever you listen to podcasts.