



The Beat

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Inflammatory Bowel Disease and Blood Clots: What's the Connection?

Inflammatory bowel disease (IBD) affects more than 3 million adults in the U.S., and research shows that patients with IBD have a 3-4 times higher risk of developing thrombosis (blood clots) than people without IBD. Several factors may contribute to this heightened risk, including genetics. We recently

spoke to Dr. Dermot McGovern, Director of the Translational Research in IBD and Immunobiology Institute and Director of Precision Health at Cedars-Sinai in Los Angeles, CA, to learn more about the link between IBD and blood clots.

Q: Before we dive in, please tell us a little bit about yourself.

A: I'm a practicing gastroenterologist with an interest in IBD. I also run a lab, where we study how genetics influence the risk of developing IBD and the natural history of the disease – so how it behaves, what complications it can cause, how it responds to therapy, and so on. I oversee the Precision Health Initiative at my institution as well, which combines technology and research to personalize approaches to disease management. In other words, through precision health, we try to match the right treatment to each patient so we can improve outcomes.

Q: What is IBD is and what does it involve?

A: There are two main types of IBD: ulcerative colitis (UC) and Crohn's disease. Both conditions cause chronic inflammation and damage within the gastrointestinal (GI) tract. The GI tract typically helps us digest food, absorb nutrients, and get rid of waste, but the inflammation from IBD interferes with these functions. With Crohn's disease, the inflammation can affect any part of the gut from the mouth downwards. In UC, the inflammation is limited to the large intestine – the colon.

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Every Breath I Took Was More Excruciating Than the Last: Jared's Story

March 15, 2015 is a date that probably doesn't stand out to most of us – but Jared remembers that day clearly. It was the day he was hospitalized with a nearly fatal pulmonary embolism (PE).

Jared works in software sales and had been making round trips from Boston to Minnesota on a weekly

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Upcoming Support Groups

Upcoming Support Groups

Temporarily online due to COVID-19

April 20, 2021

May 18, 2021

All support groups are at 7:00 PM EST

Stay tuned for a date for our next quarterly *Ask the Expert* forum as well!

To register for a support group or submit topics for future *Ask the Expert* forums, please email events@natfonline.org or give us a call at 617-730-4120.



JARED'S STORY

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basis. "I'd leave Boston on a Monday morning and come back on a Thursday – that was my life for a long time," he recalls. One weekend, a mere two days after a return flight home, he had a bout of severe pain in his upper back near his left shoulder.

"I could barely move. I could barely breathe. I had no idea what was happening. I'd had a similar type of pain in the same area a few months prior but it went away after taking ibuprofen and applying heat. I was 29 years old and in relatively good health, so I didn't think anything too serious was going on at first."

Things worsened after 24 hours. "With every breath I took, it was like someone was stabbing me with a five-pronged knife and twisting it in my back. It was the worst pain I had ever experienced – and it was all localized to this one area. I couldn't sleep. I couldn't eat. I finally couldn't bear the pain any longer and told my wife that we had to go to urgent care. When we got there, I could barely even walk. Every breath I took was more excruciating than the last."

A CT scan identified a blood clot in Jared's lung. He was sent to the emergency room and admitted to the hospital shortly after arrival. "I was told that I had lung infarctions as a result of the clot, meaning that some of my lung tissue wasn't receiving enough blood flow or oxygen," he explains. He was started on high-dose blood thinners and discharged three

days later. "I'm so thankful that I caught the PE when I did. My doctor told me that if I had waited any longer, the clot could've killed me."

What Jared didn't know at the time is that there were a few risk factors at play that may have provoked his clot, including long-haul travel. "Before my PE, I don't think I ever considered my travel to be an issue. I didn't make a conscious effort to get up, walk around, or get the blood pumping through my legs. I was a typical sit-my-butt-in-the-seat traveler. I'd watch a movie, read a book, or do work from takeoff to landing."

Jared also has ulcerative colitis (UC), a chronic inflammatory bowel disease (IBD) that affects the large intestine (colon). Although his UC has been well controlled for years, it can triple or quadruple his risk for a blood clot compared to people without IBD.

A few weeks after his PE, Jared followed up with a hematologist and his workup further revealed a prothrombin gene mutation. Prothrombin—also called coagulation factor II—is a protein in the blood that helps the blood clot when the body is injured. With a prothrombin gene mutation, the body can produce too much prothrombin, causing abnormal blood clots to form.

"No one in my family has had a blood clot before, so my genetic screen was a bit of a surprise. My doctor surmised that the frequent plane travel along with



Jared R.

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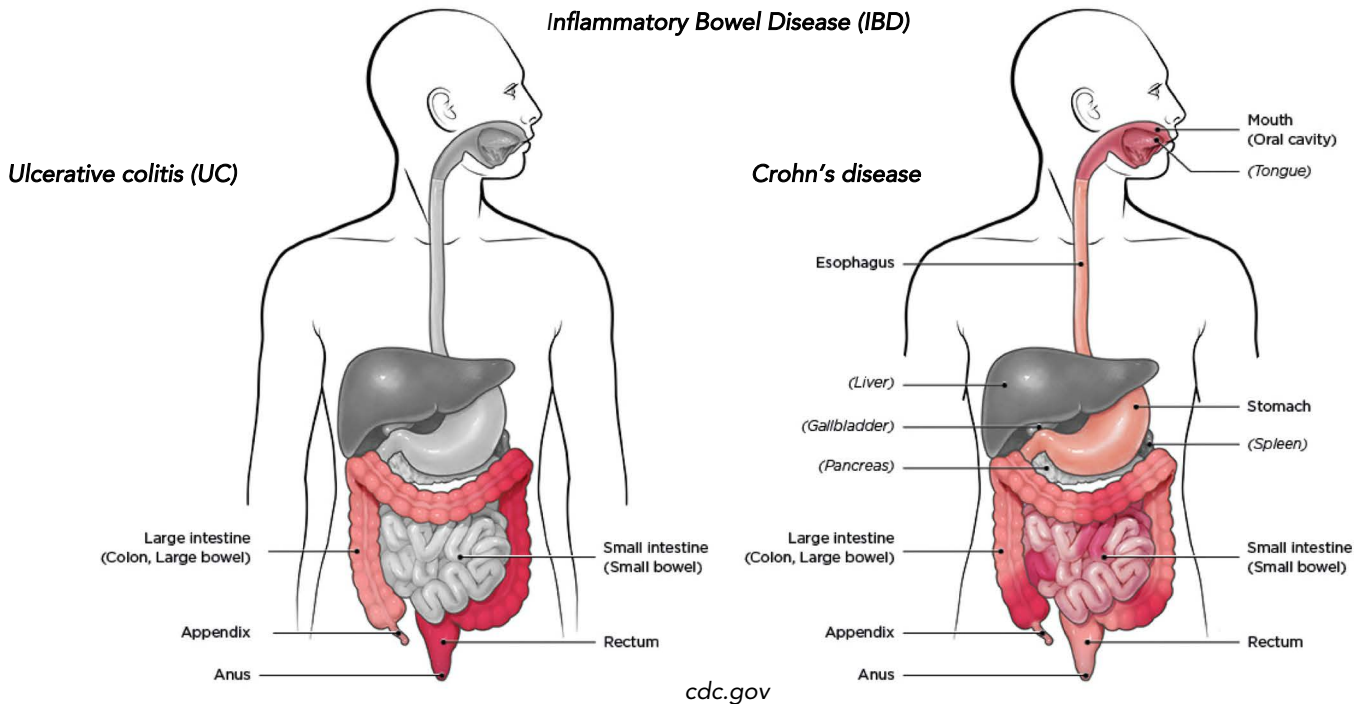


Historically, IBD was thought to mostly affect people of European ancestry, with the highest risk seen in the Ashkenazi Jewish population (Jews of Eastern European descent). Now we're seeing more IBD in African American, Hispanic, and Asian populations.

IBD can occur at any age but is most commonly diagnosed before age 35. At that time of life—the teenage years and early adulthood—people experience a lot of personal, social, and professional development, and IBD can be devastating. Symptoms can include stomach pain, diarrhea, rectal bleeding,

sometimes things go wrong, and IBD is an example of what can happen when our relationship with our microbiome is compromised.

We've made a lot of advances with new treatments, but we've still got a lot of work to do. The majority of our patients don't go into full remission, even with our best treatments. And, unfortunately, a lot of our patients suffer complications – one of which is venous thromboembolism (VTE), also known as blood clots. Blood clots are the #1 cause of death in patients with IBD.



and fatigue, to name a few – and a lot of our patients have symptoms outside the gut, too. We know that if we don't control the inflammation and get on top of these symptoms, patients can have a very poor quality of life.

Q: What causes IBD?

A: We don't understand the precise causes but do know that IBD occurs in individuals who are at genetic risk and who likely have an abnormal immune response to things in their environment, including their microbiome. The microbiome is a term used to describe the organisms that live in our body and have evolved with us over millions of years. There are trillions of bacteria that live in our gut, along with viruses, fungi, and other things. We normally have a very good relationship with these organisms – they can help keep us healthy. But

Q: Why does IBD increase the risk of blood clots?

A: Like most things in medicine, there's likely more than one factor – but there's no doubt that inflammation increases the risk. The surface area of the gut is huge by design, because it helps us absorb things as I mentioned. When that area is completely inflamed, the body is faced with a huge inflammatory load, which increases the risk of developing blood clots.

Dehydration may play a role as well. When people are really sick with IBD, they can quickly become dehydrated because they've got a lot of fluid loss through diarrhea, etc. They're probably not as mobile as usual, and many patients often require surgery – surgery in itself is a major risk factor for a blood clot.

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Some medications used to treat IBD, such as corticosteroids, may also increase blood clot risk. The U.S. Food and Drug Administration (FDA) actually put a black box warning on another medication that we use (called a JAK inhibitor) due to a significantly increased risk of VTE – although how significant the actual risk is from these drugs remains controversial.

Q: Is the risk for a blood clot the same across the spectrum of IBD, or is it higher when a person has a flare?

A: We think the risk is higher when people have a flare, which occurs when the immune system becomes overactive in the gut and causes damage to the lining of the bowel. Patients will notice some distinct IBD symptoms during a flare, like stomach pain, diarrhea, and rectal bleeding. In severe cases—particularly in Crohn's disease—the bowel can become so narrow that it forms what's called a stricture. A stricture causes an obstruction, and nothing can go through it. Surgery is often required at that point. So again, remember that both inflammation and surgery are risk factors for VTE, so a flare could certainly put a patient at higher risk of having a clot.

Q: Your research has identified specific genetic traits in patients with IBD that can more than double their risk of developing fatal blood clots. Tell us more about this study.

A: This research was spearheaded by a talented scientist in my group, Dr. Takeo Naito. We took two different genetic approaches; first we looked at existing genetic disorders that increase the risk of blood clots, such as factor V Leiden and prothrombin gene mutation. We call these *monogenic factors*, meaning that you have one single mutation that affects the function of that gene and heightens the risk for blood clotting.

But what's become increasingly clear from genetics—it's true in IBD, it's true in things like breast cancer, and so on—is that the rest of the genome also contributes, but likely in a different way. There are multiple genetic variants across the genome that increase your risk of developing a clot but that individually have a small effect, much smaller than factor V Leiden, for example. If you put all of these small genetic signals together, you can create a "score" of the number of genetic variants

that people carry called a *polygenic* risk score. It's all just a fancy way of saying that we looked at lots of different genetic variants – more than 250! It's also important to emphasize that these scores were originally generated in large population groups without IBD.

So, we found that people who had a high polygenic risk score and IBD had a high risk of developing clots. Patients who had both monogenic AND polygenic factors together had an 8-times higher risk of blood clots than people who didn't have either of those risk factors. In other words, rare genetic changes and more common genetic clotting traits together could greatly impact the risk of blood clots in patients with IBD.

Q: Based on the results of your study, do you believe that patients with IBD should be genetically screened to assess their blood clot risk?

A: We don't have the evidence to say that yet – but I hope our study will be a part of that discussion. For now, the most straightforward answer I have is that if you have IBD and develop a blood clot, you should have a conversation with your healthcare provider and decide together if screening would be appropriate.

Q: Are there any other take-home points from your research?

A: I think our study lays an important foundation for more research. My colleagues and I are focused on introducing more personalized approaches to healthcare in general, and understanding both the mono- and polygenic genetic components of risk is a big part of that.

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Naito T, et al. Prevalence and effect of genetic risk of thromboembolic disease in inflammatory bowel disease. *Gastroenterology*. 2021;160:771-780.

What is IBD? Crohn's & Colitis Foundation of America. <https://www.crohnscolitisfoundation.org/what-is-ibd>. ■



JARED'S STORY

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my colitis and gene mutation may have been the perfect storm for the blood clot. She made it clear that having a mutation didn't mean that I would *definitely* have another blood clot – but in light of my lifestyle and risk factors, I opted to start lifelong anticoagulation on Xarelto® (rivaroxaban). It gives me peace of mind and helps me feel protected.”

Fortunately, Jared hasn't had another blood clot in the last six years, but he's certainly become more in tune with his body. “I'm acutely aware of what that pain feels like. In hindsight, I wish I would've taken my first episode of pain more seriously. I just thought I had a muscle spasm, and since the pain went away after a few days, I was convinced that's what it was. Now I'm not so sure. Maybe it was a clot, maybe it wasn't. Either way, I pay closer attention now when I have pain,” he says.

On his last trip to Australia, for example, he felt some pain in his upper thigh and decided to go to an imaging center right away for a scan. “I had just

gotten off a very long flight and was concerned. I didn't end up having a clot, but my mantra now is that I'd rather be safe than sorry, and I'd advocate for anyone in my shoes to do the same thing. Get your pain checked out. Why not have peace of mind?”

Since his PE, Jared has also adopted simple techniques to prevent future clots. “I've changed my behavior when I travel. Before COVID grounded all of us, I made it a habit to get up, walk around, and stretch in the aisle, even on short flights. I also wear compression socks for long-haul flights. They're pretty comfortable, in my opinion! The way I look at it, these adjustments are easy to make. If they'll help mitigate a future clot, I'm all in.” ■

Do you have a blood clot story you'd like to share? If so, please contact Aviva Schwartz at aschwartz@natfonline.org.



Saving Lives, One Campaign at a Time

In 2014, Manu “Shaq” Williams passed away from a blood clot at age 36, leaving behind the love of his life, Christina Martin. Since Manu's passing, Christina has dedicated herself to educating people about thrombosis. She founded M.A.W. Charity Events in 2015, an organization that hosts events to raise money for blood clot awareness.

Last month, Christina led a robust online campaign for Blood Clot Awareness Month to raise money for NATF in Manu's memory. The NATF Board and Staff want to sincerely thank Christina for her efforts. We applaud the life-changing work that she's doing!

Please visit <https://www.mawcharityevents.com/> if you'd like to donate to Christina's campaign!



Christina and Manu



*Fighting blood clots
through education*

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