

Gut Pathology - Part Seven

Risk Factors for **Intestinal Permeability**

Genetic susceptibility	NSAIDs
Gender (<i>M</i>)	Gut pathogens
Inflammation	Nutrient deficiency
SIBO/dysbiosis	Stress
Alcohol consumption	

Risk factors for intestinal permeability are listed on this slide. Genetic susceptibility is certainly one, we know that 10 to 25 percent of first-degree relatives of inflammatory bowel disease patients have intestinal permeability, even in the absence of any other symptoms. Gender is a risk factor, estradiol regulates the epithelium formation, and occludin expression, which in turn affects the tight junctions. So females who tend to have higher levels of estradiol, these female rats in studies are more resistant to tissue injury that's induced by acidosis, so it's thought that being male is actually one of the risk factors for intestinal permeability. Inflammation is another; inflammatory cytokines disrupt the tight junctions. SIBO, or dysbiosis, is a risk factor, SIBO has been associated with intestinal permeability in studies, and probiotics have been shown to decrease intestinal permeability by improving tight junction function and decreasing inflammation. It's well established that alcohol consumption, particularly significant alcohol consumption in a short period of time, disrupts the function of the tight junctions, a little bit of a tongue twister there, and increases permeability. We know that NSAIDs like ibuprofen directly damage epithelial surfaces and lead to gut permeability. Gut pathogens such as clostridium difficile, e.coli, et cetera, activate an inflammatory cascade that can modify or impair the function of the tight junctions. We know that several different nutrient deficiencies like vitamin A, zinc, long-chain omega-3 fats, vitamin D, and magnesium can increase barrier permeability, and we know that stress can affect occludin and zonulin levels, which would impact tight junctions.

Testing for intestinal permeability as with SIBO is definitely not perfect, and there's really no gold standard test yet. The two primary methods that are used are lactulose mannitols and the antigenic intestinal permeability screen. There are new markers currently under investigation, like urinary delectate or serum zonulin or fecal butyrate, and the best approach is probably to use some combination of all of them, but that may not always be practical, for example zonulin, at least at the time of this recording, it's not possible to order a serum zonulin test outside of a

research setting. And I'm again going to discuss the ins and outs of the various testing methods for these pathologies when we review the tests and get further into that later.

The final pathology we'll discuss is autoimmunity. So I've touched on this already throughout the presentation, but specifically now with gut pathology we're referring to inflammatory bowel disease, and that is primarily Crohn's and ulcerative colitis. The difference between these two is that ulcerative colitis is restricted to the colon or rectum and affects only the superficial layer of the mucosa, whereas Crohn's can occur anywhere in the gastrointestinal tract and can affect all layers of the GI tract. These conditions are still not well understood, it's not for lack of effort, they've been studied extensively, and there are a lot of different competing theories about what causes them. There's a school of thought that they're caused by a mycobacterium that infects the intestine and leads to this kind of chronic inflammation. There is the more prevailing theory that they're caused by an autoimmune response to commensal gut bacteria, so anyone who has an IBD condition, it essentially attacks their own beneficial commensal gut bacteria, and then this causes persistent inflammation and tissue damage. In the old friends hypothesis, one of the theories is that commensal organisms that we co-evolve with, like hookworm, typically tune and regulate our immune system, that are no longer present in these highly sanitized environments that we live in, have actually predisposed us to this kind of autoimmune response, and that's one of the main causes of IBD. As I mentioned before, Alessio Fasano and others believe that intestinal permeability is a pre-condition to developing inflammatory bowel disease and other autoimmune disease, in which case that would be one of the major pathological mechanisms.

The risk factors for IBD are numerous, and include genetics, cigarette smoking, diet, physical inactivity, obesity, infections, antibiotics, NSAIDs, oral contraceptives, chronic stress, and sleep deprivation. Symptoms are pretty consistent with other gut dysfunction, but some that are less common in functional gut problems like IBS would be bleeding, abscess, fistulas, B-12 deficiency because B-12 is absorbed in the terminal ileum, and that's often the area that's affected in Crohn's disease, and then extra-intestinal symptoms like skin conditions, arthritis, kidney stones, osteoporosis, macrocytic anemia, pulmonary involvement and eye disease, many of which are related to nutrient deficiencies that can be caused by IBD.

Testing for IBD is actually more straightforward and conclusive typically than testing for things like intestinal permeability and SIBO. IBD is often diagnosed by colonoscopy or endoscopy or capsule endoscopy, which is where you swallow a camera and it goes all the way through the intestinal tract taking pictures. It's a really expensive test, insurance doesn't typically cover it, and it's usually not used unless the suspicion is that the inflammation is in an area that can't be reached by an endoscope or colonoscope. There are new markers for serum testing that can help to identify likelihood of IBD, and these include things ... well, there's the basic blood markers that have been used for a long time like erythrocyte sedimentation rate, ESR, c-reactive protein, and then there are newer antibodies like ASCA and ANCA and anti-OMPC and anti-CBIR1, and you can get these as a panel together from labs like LabCorp or Quest, and they can be helpful in identifying people that are more likely to have this that you might be then likely to refer to a colonoscopy. We're going to talk more about diagnostic algorithm for IBD later, when we talk in detail about that condition. There are also some really good stool markers for

IBD that are on the doctor's data stool tests that I'm going to be teaching, and those include calprotectin, lactoferrin and lysozyme, and significant elevations in the fecal versions of these markers can indicate IBD and can be helpful in differentiating between IBD and functional gut disorders like IBS.

Okay, that's it for now. Next we're going to dive much further into diagnosis and treatment of food intolerances and start looking at some labs and cases, which is so much fun. See you soon.