KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Gut Pathology - Part Five

Okay, now we're going to move on to bacterial infections. A number of bacteria can cause disease in the gut. I've put a few examples on the slide …

… including aeromonas, bacillus species, campylobacter, clostridium, e. coli, h. pylori, klebsiella, salmonella, shigella, staphylococcus, and Yersinia. Bacteria can be classified in different ways according to location in the intestine, small versus large, how the disease was acquired, by a food, water, person-to-person contact, or if it's a commensal bacteria, its effect on the host, intoxication versus gastroenteritis versus inflammatory diarrhea, et cetera. So real bacterial infections like campylobacter, for example, are foodborne and tend to be self-limiting and don't require treatment, whereas others can become chronic and definitely do require treatment. And the symptoms can range from mild GI discomfort with food poisoning to really severe, intractable, and even fatal in the case of antibiotic-resistant C. diff.

Bacterial infections can also interact with the host genotype to cause serious complications and chronic disease. One example of this is Klebsiella pneumoniae. Klebsiella pneumoniae is a gram-negative aerobic bacterium found in the mouth, skin, and gut. It can cause pneumonia and infection in the GI tract, as well as in the urinary and biliary tract. But in people with HLA-B27, a specific genetic trait inherited on the sixth chromosome that affects antigen presentation, the presence of klebsiella can trigger autoimmune disease, especially reactive and rheumatoid arthritis, ankylosing spondylitis and Crohn's disease. This occurs via a phenomenon known as molecular mimicry: HLA-B27 is expressed in lymphocytes and synovial cells and other tissues,

so the immune system produces antibodies to klebsiella, and then those antibodies cross-react with HLA-B27 in the tissue.

Studies have also found that transient, self-limiting infections can have chronic consequences, for example campylobacter, which causes food poisoning, has been associated with subsequent reactive arthritis, irritable bowel syndrome, delayed gastric emptying, which is a risk factor for SIBO, dyspepsia, chronic constipation, and diarrhea. I also just this morning was reading a study that showed that people with giardia infection are far more likely to be diagnosed with irritable bowel syndrome three years later, so this is even after the giardia gas been cleared, so this is a chronic consequence of that initial infection. There's actually even a term for this, which is post-infectious irritable bowel syndrome, and as I mentioned earlier, Dr. Pimentel and others believe that pretty much all irritable bowel syndrome is post-infectious; it's just that the initial infection may not always be something as clear as a giardia infection, and not to say that that's always clear, but it could be something as simple as a viral gastroenteritis, stomach flu. It's also possible that some infections that are currently considered to be self-limiting have chronic expressions, so, for example, I've found campylobacter and Yersinia in patients several months after they experienced the symptoms of food poisoning, so of course it's possible that they were food poisoned again and didn't have any symptoms, but it's also possible that those bacteria can cause chronic problems and take up residence in the GI tract despite the conventional wisdom that suggests they're self-limiting infections.

And of course, it's well established that some bacteria can colonize the GI tract and stick around for a long time, and h. pylori is a good example of this. It's associated with high risk of gastric and duodenal ulcer, gastric cancer, which is the second-most lethal form of cancer, and mucosa-associated lymphoid tissue lymphoma, or MALT lymphoma. On the other hand, some studies have shown that h. pylori rates are lower in people with GERD and Barrett's esophagus, and Dr. Marty Blaser, who wrote a fantastic book called *Missing Microbes*, and others have shown that if h. pylori is acquired early on in life, it can lower the risk of asthma and allergies, and even diabetes, and this is part of the old friends hypothesis that we were discussing earlier, and we're going to talk about it more when we dive into more detail with h. pylori, but in short, we co-evolved with h. pylori for 58,000 years at least, and it may very well be one of these old friends that has a beneficial immune-regulating effect if we're exposed to it early on in life.

Having said all that, on balance I think the evidence does suggest that the risk of not treating h. pylori at all may be greater than the risk of treating it, especially for adults as we get older, or people with a family history of cancer, especially gastric cancer. That doesn't necessarily mean full eradication is necessary, but some treatment may be, and again we're going to talk about this in more detail later.

The next pathology we're going to talk about is dysbiosis and fungal overgrowth. Dysbiosis is a term indicating an imbalance of microbes in the gastrointestinal tract, and it's an older term, it's being replaced by phrases like disrupted gut microbiome. I don't know how much that distinction matters, but if you're talking with researchers and clinicians, it's a more typical way of referring to it now. And the important thing to understand about this is of course as you know we all have

microbes in our gastrointestinal tract, a hundred trillion of them in fact, which outnumber human cells by ten to one, so the key question is, what is the relative state of that ecosystem? We all have some harmful or potentially harmful commensal bacteria in yeast in our system, like candida, which we're going to talk about shortly, and that in itself is not a problem if we have plenty of beneficial microbes whose job it is, among many other functions, to keep those potentially harmful commensal organisms in check.

So when we talk about dysbiosis or disrupted gut microbiome, what we're typically talking about is a situation where there's an underrepresentation of beneficial microbes and there's an overrepresentation of harmful microbes. So I mentioned yeast and candida, and that's a perfect example because candida and other yeasts are normal residents of the human gastrointestinal tract, and their presence is typically benign, but both human and animal studies suggest that candida can become overrepresented when levels of beneficial microbes that protect against that colonization are low. Candida colonization has been shown to promote low-level inflammation and delay healing of inflammatory lesions, which of course can lead to a vicious cycle. Candida colonization is also associated with elevated levels of pro-inflammatory cytokines like interleukin 17. Other factors that can determine the potential for candida overgrowth or overgrowth of other fungi include the host immune status, what our overall, not only our beneficial microbes, but our overall immune function and ability to protect against that kind of overgrowth, and fungal gene expression, so differences in how the genes of the fungi express themselves, and make them more or less invasive. In studies which are limited, candida has been associated with inflammatory bowel disease. When I say "candida," I mean excessive candida colonization. Inflammatory bowel disease is like ulcerative colitis and gastric ulcers.

Before we move on, I just want to mention that I think that candida became a real fad diagnosis, particularly in the 90s, where people were self-identifying with candida just based on a symptom questionnaire that they read about online, and alternative medicine practitioners were diagnosing people with candida, with no real lab results or no understanding of its nature as a commensal organism, and it led to some really extreme anti-candida diets that had never been shown to be effective in scientific literature, and actually there's some reason to believe that they could encourage the growth of candida, because they could be ketogenic, and candida actually thrives on ketones. We'll talk more about this later, but my point here is just that you'll see a lot of patients that come in and tell you they have a candida problem, and don't take that at face value. I mean, of course you want to listen to them and respect their opinion, but since there was so much misdiagnosis of this in the 90s and the early 21st century, I think it's really important to be clear about what we're seeing and use the proper diagnostic methods and techniques to figure it out instead of just diagnosing someone empirically with something like candida.