KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Gut Pathology Review

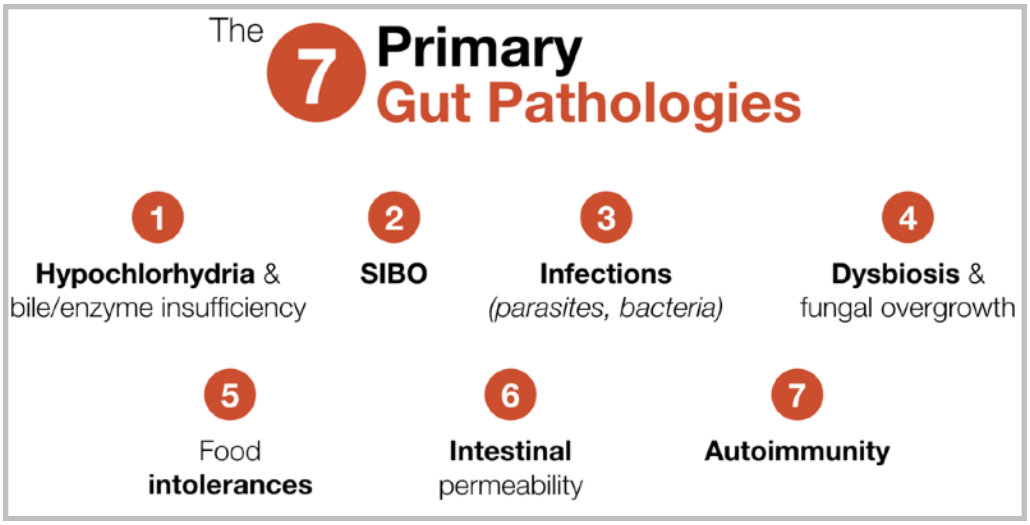
"All disease begins in the gut."
—Hippocrates

"Syndrome" is a label that we give to a collection of signs and symptoms. Syndromes are helpful in allowing us to refer to a condition when we're talking to other clinicians or patients, but they do not necessarily shed light on the cause of the problem.

The term "disease" is more specific than syndrome because it refers to a specific ideology or pathology. Diseases are mediated by underlying pathologies. These underlying pathologies are mechanisms of physiological dysfunction. If we want to address the root cause of illness, we need to focus on these pathologies.

Main Risk Factors for Developing Digestive Pathology

Family history	Antibiotics	Hypothyroidism
Cesarean birth	Other medications	HPA axis dysfunction
Formula-fed	Chronic stress	Excess alcohol
Standard American Diet	Sleep deprivation	Cigarette smoking
Food poisoning	Physical inactivity	Environmental toxins



The Seven Primary Gut Pathologies:

1. Hypochlorhydria & bile/enzyme insufficiency

The stomach produces hydrochloric acid, which aids the chemical breakdown of food and the absorption of nutrients and protects against pathogens. Research shows four primary consequences of low stomach acid:

1. Increased bacterial overgrowth in the small intestine, or SIBO
2. Impaired nutrient absorption
3. Decreased resistance to infection
4. Increased risk of cancer and other diseases

Problems in the stomach will often lead to problems further down the GI tract. For example, secretion of pancreatic enzymes requires chyme from the stomach to be at a certain pH when it enters the small intestine. If the stomach acid is low, the pH of the chyme will be too high, and the pancreas won't secrete digestive enzymes. This will lead to undigested food, especially carbohydrates, which can lead to SIBO.

GERD – low stomach acid leads to bacterial overgrowth, which in turn causes production of gases that put pressure on the lower esophageal sphincter and cause it to open inappropriately, which then allows acid from the stomach to reflux into the esophagus.

RISK FACTORS FOR HYPOCHLORHYDRIA INCLUDE:

PPIs or any acid-suppressing drugs, chronic stress, bacterial overgrowth, vegetarian diets (which are low in protein and reduce acid production), H. pylori infection, genetic factors such as polymorphisms and interleukin 1 that promote inflammation associated with hypochlorhydria, food poisoning, and food intolerances. Another risk factor is pernicious anemia, which is an autoimmune attack against the parietal cells in the stomach and/or an intrinsic factor, which is produced by the parietal cells. These cells are also involved in acid production.

TESTING FOR HYPOCHLORHYDRIA:

Heidelberg radiotelemetry test is the most accurate, but it is not commonly used.
Another option is an HCl challenge, where we give the patient hydrochloric acid supplements, gradually increasing the dose until he or she feels a burning sensation, and then ask the patient to reduce the dose to the dosage he or she was taking just prior to that burning sensation.

Impaired production of **pancreatic enzymes and bile** leads to malabsorption of protein, fat, and carbohydrates.

Causes of problems with enzyme secretion include low stomach acid, celiac disease, chronic pancreatitis, and excess alcohol intake.

Causes of problems with bile production or metabolism include impaired liver function, which is where bile is produced; gall bladder problems, where gluten can be a major factor; intestinal dysbiosis; and GI pathology.

Diagnosis of bile and pancreatic enzyme production issues are mostly based on **symptoms**.
Symptoms of bile insufficiency include: poor fat digestion; bitter, metallic taste in the mouth; itchy skin; clay-colored stools; stools that float; and a history of gallstones.
A useful marker for poor enzyme production is **fecal elastase**.

2. SIBO

RISK FACTORS:

Poor diet, low stomach acid, antibiotic use, acid-suppressing drugs, impaired function of the migrating motor complex (MMC), constipation, gut infections, structural abnormalities of the GI tract, and immune dysfunction.

SIBO is more likely in people with IBS, metabolic disorders, the elderly, celiac disease, chronic constipation and diarrhea, long-term antibiotic use, and other organ dysfunction, particularly liver disease and pancreatitis, both of which can alter the function of the MMC.

CONSEQUENCES OF SIBO

Decreased vitamin/mineral absorption and related conditions *(anemia, neuropathy, etc.)*

Decreased fat absorption *(from bacterial deconjugation of bile salts)*

Carbohydrate malabsorption *(leading to vicious cycle)*

Protein malabsorption *(some bacteria may digest protein)*

Gas production leading to bloating, pain, constipation, diarrhea *(or both)*

Intestinal permeability and damage to lining of small intestine mucosa

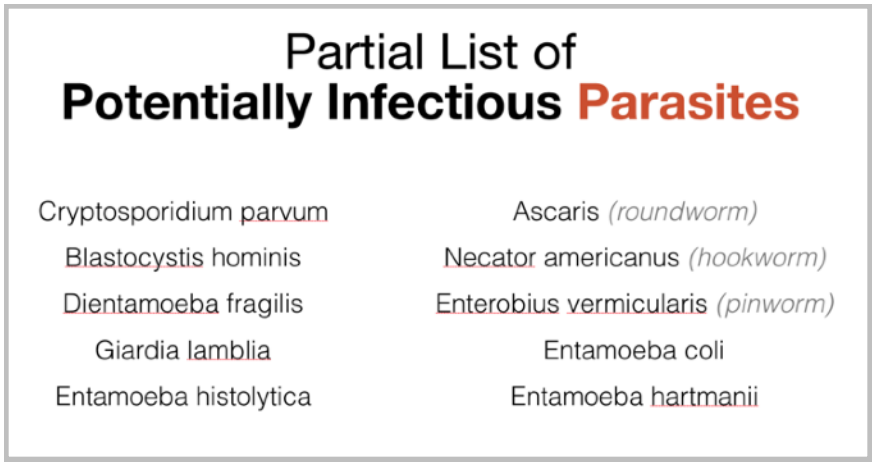
Autoimmunity *(from increased permeability and efflux of bacteria/LPS)*

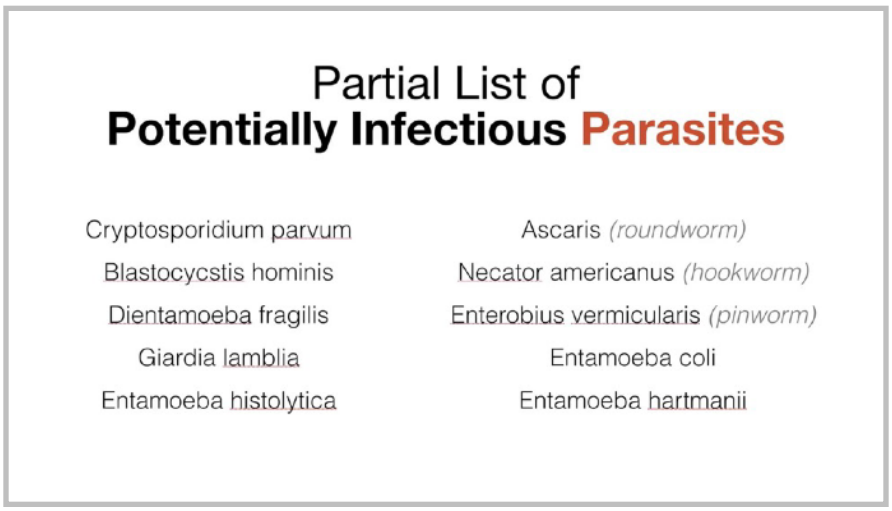
Neurological symptoms *(from toxins produced by bacteria)*

DISEASES AND HEALTH PROBLEMS ASSOCIATED WITH SIBO

- Acne vulgaris/rosacea
- Anemia
- Atrophic gastritis
- Celiac disease
- Cystic fibrosis
- Diabetes
- Diverticulitis
- Fibromyalgia
- Gastroparesis
- GERD
- Hepatic encephalopathy
- Inflammatory bowel disease
- Irritable bowel syndrome
- Intestinal permeability
- Liver cirrhosis
- Muscular dystrophy
- Non-alcoholic fatty liver disease
- Parkinson's
- Restless leg syndrome

3. Infections (parasites, bacteria)





PARASITIC INFECTIONS:
Some of these parasites are considered by most researchers and physicians to be non-pathogenic commensals, meaning they can be normal residents of the digestive tract.

- Unequivocally pathogenic: Giardia and Cryptosporidium.
- "Old friends" that may provide some benefit to the host: Necator americanus, or hookworm.

Risk factors for parasites include: Consuming contaminated food and water, increased use of daycare centers, travel to developing countries, household pets, consumption of uncooked foods, antibiotic use, insect vectors, and sexual contact.

Symptoms associated with parasitosis are **often general and nonspecific**. They vary from fatigue and malaise to GI distress, diarrhea, and constipation to things like brain fog, sleep disturbance, or skin issues.

Patients may present with cyclical symptoms because parasites have lifecycles that can influence their pathogenicity in the host. So one red flag for parasitic infection is if someone feels relatively normal and then they feel really kind of rotten and then they feel normal again, and that alternates in a consistent way. Patients may have **NO GI symptoms**.

PATHOLOGY:

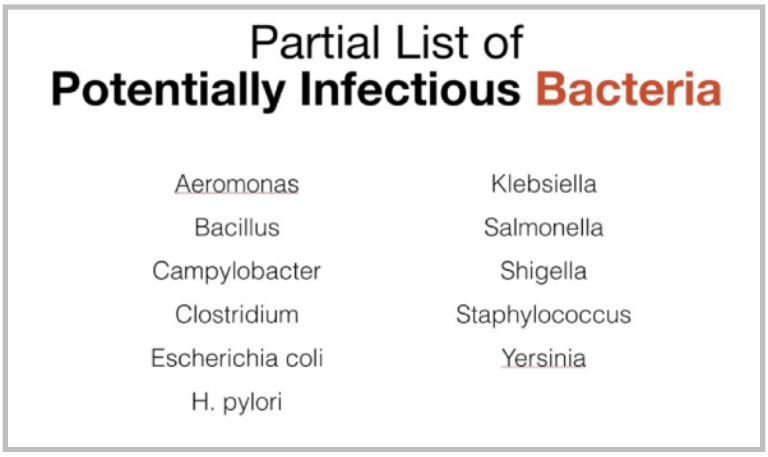
Parasites can cause pathology in a number of ways, depending on the organism. For example, Cryptosporidium damages the topography of the small intestine by invading intestinal epithelial cells. It damages the microvilli, which hurts the absorption of nutrients and compromises the gut barrier integrity. It further weakens the body's defense against opportunistic infections, and in acute, severe cases, it can cause high fever, severe diarrhea, and even death in people that are malnourished. In chronic cases it can cause fatigue, gas, bloating, changes in stool frequency, and all the other symptoms previously stated. Like some other parasites, Crypto can migrate to extraintestinal sites like the lungs and the conjunctiva of the eyes.

DIAGNOSIS:

Parasites are notoriously difficult to detect. One reason is that they can assume different forms, like the cystic form that is dormant in tissue and not shed in the stool.

Use labs that specialize in parasite detection, and use different methods like stool microscopy, proteomic analysis, and immunological essays like fecal antigen together because you increase the likelihood of catching something that would be missed using only one methodology.

BACTERIA:



Bacterial infections can be self-limiting and require no treatment, whereas others can become chronic, requiring treatment.

Symptoms can range from mild GI discomfort to severe pain.

Bacterial infections can also interact with the **host genotype** to cause serious complications and chronic disease. One example of this is Klebsiella pneumoniae. In people with HLA-B27, 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, ovial 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 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, dyspepsia, chronic constipation, and diarrhea.

Another is post-infectious IBS caused by Giardia infection. It's also possible that some infections that are currently considered to be self-limiting have chronic expressions.

Finally, some bacteria can colonize the GI tract for extended periods of time, such as H. pylori. In adults, this is associated with high risk of gastric and duodenal ulcer, gastric cancer, and MALT lymphoma. Alternatively, research has shown that H. pylori maybe an "old friend" because if it is acquired early on in life, it can lower the risk of asthma and allergies, and even diabetes.

4. Dysbiosis & fungal overgrowth

Dysbiosis is a situation where there's an **underrepresentation of beneficial microbes** and an **overrepresentation of harmful microbes.**

For example, Candida is a normal resident of the human gastrointestinal tract. However, 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, delay healing of inflammatory lesions, and potentially elevate levels of pro-inflammatory cytokines like interleukin 17.

Overall host immune status and the body's own ability to protect against unfavorable overgrowth also influence gut dysbiosis and fungal overgrowth.

Symptoms range from obvious things like gastrointestinal discomfort to less obvious symptoms like depression, anxiety, brain fog, ADHD, autism spectrum disorder, skin disease, neurological problems, etc.

Disrupted gut microbiota can lead to production of compounds that have a neurotoxic effect and to inflammatory cytokine production, which can suppress activity of the frontal cortex and cause all kinds of other problems.

DIAGNOSIS:

- Stool tests
- Some markers on urine organic acids tests, like d-arabinitol for fungal overgrowth.

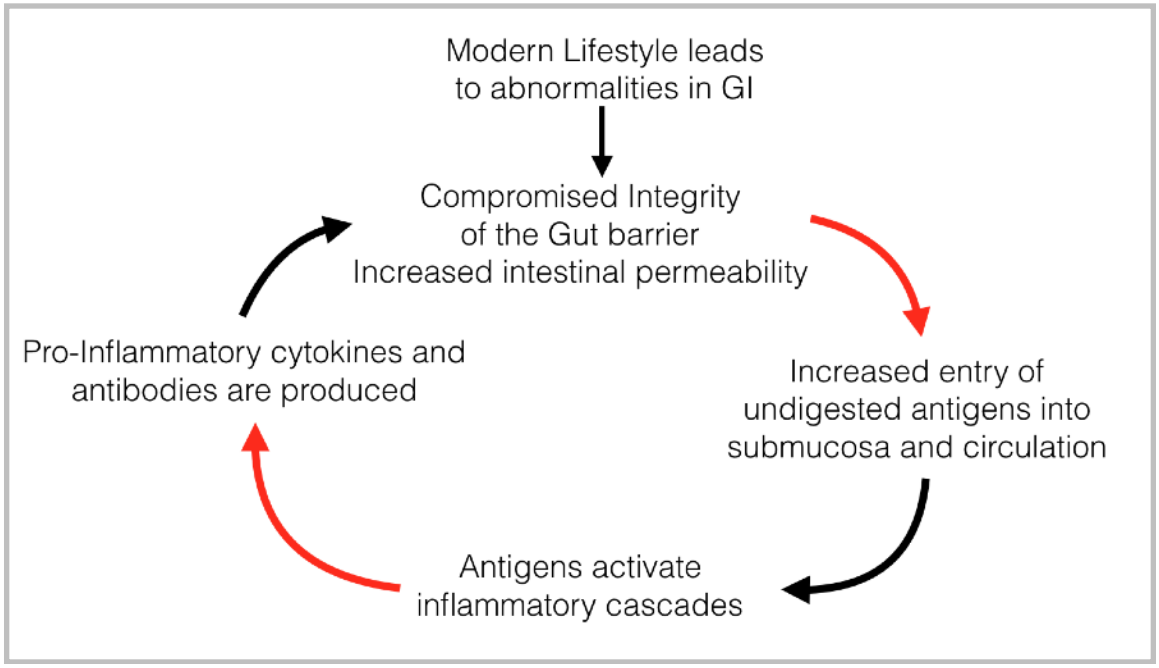
5. Food intolerances

In many cases, food intolerances are a consequence of other pathologies, such as disrupted gut microbiome, SIBO, or intestinal permeability. However, food intolerances can also cause problems like intestinal permeability. Thus, the food intolerance needs to be addressed independently.

Individual food intolerances can be severe. Others may be less severe but cause chronic low-grade inflammation and intestinal permeability, which can then lead to antibody production to everything from the joints to the myelin sheath in the brain, and certainly
over time can lead to more serious pathologies and disease.

6. Intestinal permeability

Formerly known as leaky gut.



Respected researcher Dr. Alessio Fasano, who is well known for his discovery of zonulin, a protein that regulates tight junction permeability, believes that leaky gut is actually a precondition to developing autoimmunity, along with genetic vulnerability and environmental triggers. He has argued that increased permeability of the intestinal barrier to macromolecules is associated with local and systemic inflammatory conditions, including, of course, celiac and non-celiac gluten sensitivity, food intolerances, IBD, numerous autoimmune diseases, neurological conditions like MS, cognitive dysfunction, behavioral disorders, skin conditions, and new connections that we're discovering.

TESTING FOR INTESTINAL PERMEABILITY:

The two primary methods that are used are the lactulose-mannitol test and the antigenic intestinal permeability screen.

7. Autoimmunity

Inflammatory bowel disease, primarily **Crohn's disease** and **ulcerative colitis**.
Ulcerative colitis is restricted to the colon or rectum and affects only the superficial layer of the mucosa.

Crohn's disease can occur anywhere in the gastrointestinal tract and can affect all layers of the GI tract.

Risk factors for IBD include:
Genetics, cigarette smoking, diet, physical inactivity, obesity, infections, antibiotics, NSAIDs, oral contraceptives, chronic stress, and sleep deprivation.

Symptoms are consistent with other gut dysfunction. Some additional symptoms more specific to IBD include bleeding, abscess, fistulas, B12 deficiency, and 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:

- IBD is often diagnosed by colonoscopy, endoscopy, or capsule endoscopy.
- Basic blood markers include erythrocyte sedimentation rate (ESR) and C-reactive protein.
- Newer antibodies include ASCA, ANCA, anti-OMPC, and anti-CBIR.
- Stool markers for IBD include calprotectin, lactoferrin, and lysozyme.