THE STANDARD

ROAD MAP SERIES

Functional Strategies for the Management of Gastrointestinal Disorders:

Principles and Protocols for Healthcare Professionals

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POINT INSTITUTE

STEVENS POINT, WI

The Point Institute was founded by Thomas Guilliams, Ph.D. as an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease. Along with therapies generally defined as lifestyle interventions, the Point Institute specializes in the evidence and application of nutraceuticals (dietary supplements, herbs, vitamins, minerals, etc.) as therapeutic and preventative agents in clinical practice.

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Table of Contents

Table of Contents

Table of Contents

Table of Contents

Preface

The fundamental role of the gastrointestinal tract in health and disease has been appreciated since ancient times, as it has played a vital role in the diagnostic and therapeutic schemes of most traditional forms of medicine. But what those ancients could only have speculated, that the GI tract is in some way involved in nearly every facet of human physiology, is now being uncovered in the very latest scientific discoveries. The information on the role of the gut microbiome alone has radically altered our understanding of the pathophysiology of metabolic, immune and psychiatric disorders in ways that could not have been predicted even a few decades ago. For us, these discoveries are even more exciting, as they reinforce the notion that the vast majority of gastrointestinal dysfunctions, whether organic or functional in origin, can often be managed through lifestyle and nutrient support of the core functions of the GI tract.

However, the exhilaration of hearing one new revelation after another is soon replaced by the daunting task of making sense of this avalanche of new information, not to mention forming a balanced and evidence-based approach for clinical application. After all, when does this new information merely confirm what we have already known (with better mechanisms to explain what is seen clinically), and when does it change diagnostic and therapeutic paradigms? This publication seeks to help answer those questions.

Like our previous Road maps, this project is limited in scope. Our goal is not to replace modern textbooks on gastroenterology, but to introduce a framework that allows the clinician to form coherent functional strategies to manage chronic gastrointestinal dysfunctions through the support of core gastrointestinal functions. We summarize these core functions in a manner accessible to the functional and integrative medical practitioner, while also evaluating the evidence for the commonly used diagnostic and therapeutic strategies within these communities. In addition, we hope to introduce these ideas to practitioners and students outside the functional and integrative communities.

In today's world, scientific research and the interpretation and application of that research is constantly changing. For instance, the Rome IV publications were just being published as we finalized our manuscripts, and we were only able to incorporate some of this new information for the reader, especially as it pertains to irritable bowel syndrome. Plans for a second edition to expand on this work are already being discussed to fill in the inevitable gaps a project such as this creates.

We welcome your input. If you know of reputable scientific information that would challenge or modify our recommendations, we ask that you communicate with us via email at info@pointinstitute.org so that we can evaluate the information and consider revising our recommendations. Before sharing your insights, please be sure you have the most recent edition of this guidebook, or have read any updates or addendums posted on our website (www.pointinstitute.org) or through the retailer of this guidebook.

the gut first." This idea reminds clinicians of the front-line role the GI system plays in nearly every facet of health. It is rare to find an individual with any chronic condition without some related GI system dysfunction. Conversely, patients with major GI disorders will manifest symptoms that are systemic. On top of this, all other recommended therapies involving foods, beverages, supplements or drugs require a predictable interface with the GI system and related detoxification pathways. Therapies that may work in a healthy GI environment may be neutralized or even exacerbate the condition for which they are intended to help when GI function is disrupted. "Heal the gut first" is a reminder that GI dysfunction can lead to many, seemingly unrelated, chronic conditions that may be best addressed after (or along with) known GI dysfunctions.

Core Functions of the GI System

Within this Road map, GI functions will be grouped into five core areas based on function: **Digestion, Elimination, Protective Barrier, Microbial Ecosystem,** and **Neuroendocrine.** These core functions are discrete and different, though most are interrelated and highly dependent upon one another. We will briefly define these core functions here, though each will be expanded greatly throughout this text.

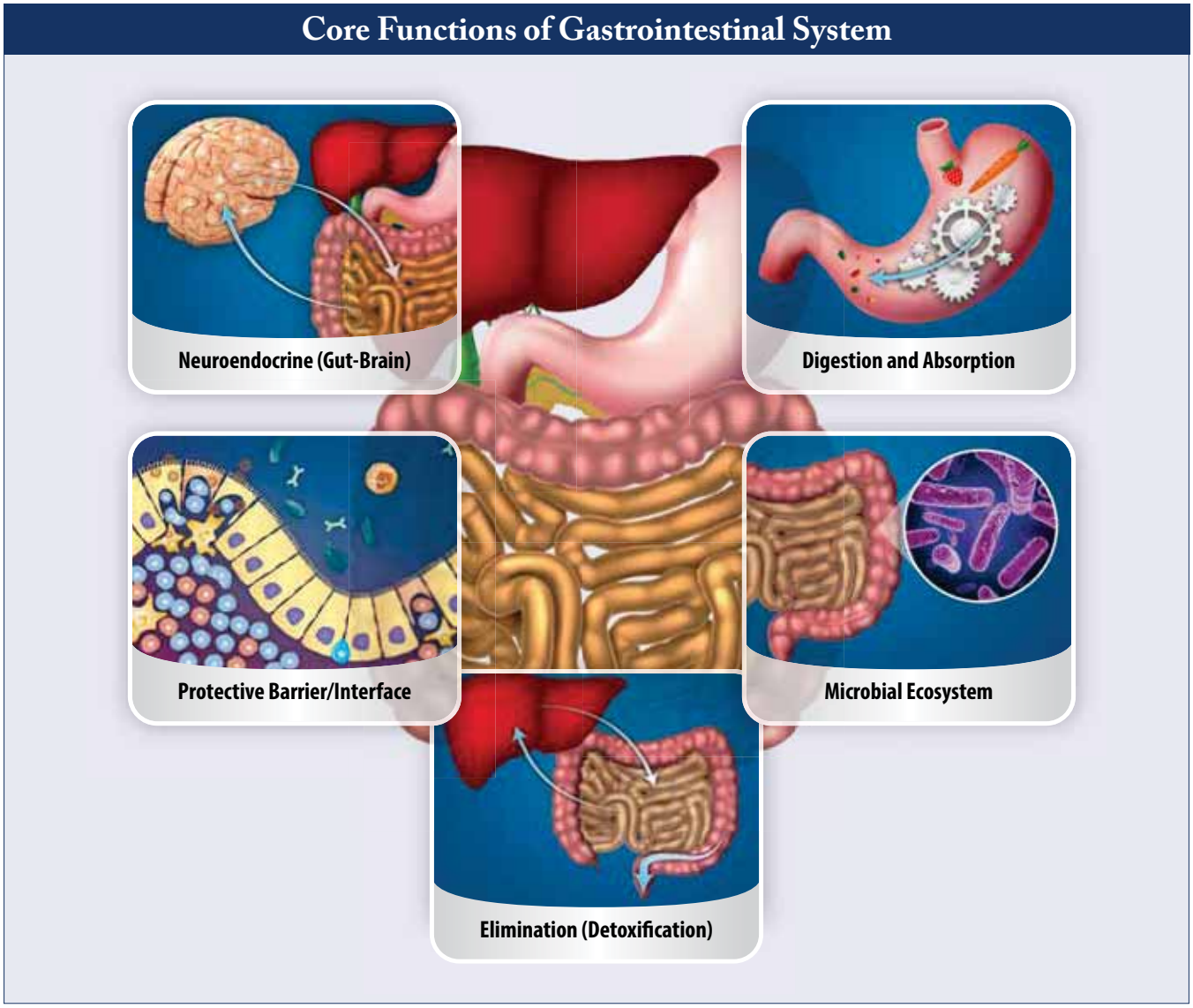


Figure 4: The five categories of core gastrointestinal functions used within this Road map. See text for more details.

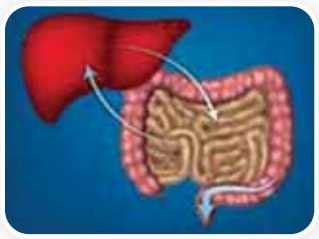
Digestion (and Absorption)

Perhaps the most obvious of all its functions, the GI tract is tasked with digesting and absorbing the nutrients within the food and beverages we consume. Through a complex coordination of enzymes, acids, bile salts, peristaltic action, transporters, and microbial biotransformation, our GI tract must take complex foodstuffs and deconstruct them into macronutrients (protein, carbohydrate, fat) and micronutrients (vitamins, minerals, phytonutrients, etc.) that can be transported into the body. Each step in the processes of digestion is important, as it only requires a deficiency in one or a few micronutrients to lead to a metabolic dysfunction.

Since the GI tract is exposed to 30-50 tons of food in the average lifetime, the types of food we eat are extremely important in maintaining proper GI health. The Standard American Diet, or SAD (sometimes called MUD, the Modern Urban Diet), is associated with nearly every chronic illness discovered, including most chronic GI complaints. Highly processed foods with high amounts of refined carbohydrates, hydrogenated fatty acids, food additives and preservatives, and low in fiber, natural colors and phytonutrients are typical of this dietary pattern. These poor dietary patterns are pro-inflammatory, place a significant burden upon the detoxification reserve capacity, and reduce bowel transit time, all of which can generate a downward spiral of gastrointestinal complaints and dysfunction. On top of this, many individuals have undiagnosed food allergies that continue to mediate ongoing immunological reactivity, further weakening the barrier function of the gut.

We will outline the types of diets and eating patterns known to be beneficial for the prevention and treatment of a range of digestive disorders, including discussions of a variety of ways to specifically improve digestion and absorption of nutrients. In addition, several ways clinicians can test a patient for poor digestive function will be listed.

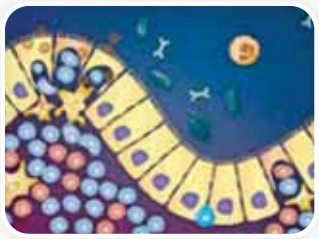
Elimination



The process of elimination can be nearly as important as digestion. Ridding the body of the unusable portions of foods as well as the toxic metabolites stored and produced in the body is a critical function of the GI system. Healthy liver detoxification (biotransformation), bile production and regular bowel movements are hallmarks of a healthy GI tract. Proper elimination also helps regulate bowel transit time, which has an effect on proper digestion and absorption, water and electrolyte balance, and healthy microbial function. Constipation is one of the most common GI symptoms for which people seek a remedy. Stool frequency and morphology have been used to define overall health for millennia.

Details will be given about healthy detoxification and ways in which clinicians can encourage patients to avoid unhealthy toxins and allergens encountered in their diets, as well as nutritional and supplementary strategies to increase detoxification efficiency. We will also review the efficacy and safety of lifestyle and non-pharmacological approaches for preventing and treating constipation.

Protective Barrier

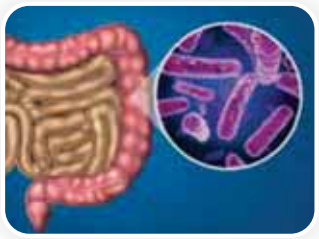


While we think of the GI tract as a digestive and absorptive organ, maintaining proper mucosal barrier function is vital for both GI and system-wide health. The GI tract is specifically equipped to balance the need for massive absorption of nutrients, while preventing the passage of unwanted particles or organisms into the body. The lumen of the gut contains numerous entities that should never reach the blood stream or lymphatic system, such as large antigenic/allergenic food particles, toxins, harmful microorganisms and their metabolites. The integrity of the mucosal barrier is maintained by a single layer of tightly fitted columnar epithelial cells that comprise a surface area the size of a doubles tennis court. As we shall outline later, greater than 70% of the immune system is closely associated with the GI tract in specialized lymphatic compartments within the mucosa

and in the intercellular space along the epithelium. The barrier protection can be compromised by a number of factors such as dysbiosis, inflammation, food allergies and immune system dysregulation.

We will outline the consequences of barrier disruption that leads to gastrointestinal permeability (i.e., leaky gut), discussing both the common causes and ways to prevent and treat barrier disruptions. We will also describe the role of the gut-associated lymphoid tissue in maintaining the barrier function, describing ways to improve gut-immune function (and overall immune function), a role closely tied to both the microbiome and the neuroendocrine functions of the GI system.

Ecosystem for Gut Microbiome



The human GI tract is host to at least 100 trillion individual microorganisms, from at least 1,000 different identified subspecies of bacterial and yeast alone. Over the past decade, research has been uncovering the interrelationship between proper human metabolism and the signals and metabolites that are generated from this internal microbial ecosystem. In fact, by some measures these microorganisms represent one of the most metabolically active systems within the human body— affecting glycemic control, cholesterol and amino acid metabolism, short-chain fatty acid production (e.g., butyrate for colon cell energy), and vitamin synthesis. Proper microbial balance helps regulate immune function and maturation, prevent overgrowth of harmful organisms, and regulate bowel motility.

Dysbiosis, the generic name given to any number of potential imbalances within the gut microbial environment, can lead to a wide range of GI pathologies and create vulnerabilities within the immune and detoxification systems, resulting in system-wide effects. This guidebook will overview the current scientific understanding of the human gut microbiome as it pertains to human metabolism, health and disease, while reviewing the known lifestyle, diet and non-pharmacological approaches (e.g., probiotics and prebiotics) for modulating the gut microbiome in the prevention and treatment of GI-related outcomes.

Neuroendocrine

Since the GI system maintains a critical interface with the external environment, there are a number of signaling mechanisms designed to coordinate its function with the rest of the body. The enteric nervous system of the gut interacts in a coordinated fashion with the central nervous system to control a number of gastrointestinal functions. Beyond these basic neuronal connections, a number of endocrine signaling processes occur within the gastrointestinal tract to modulate gastric secretions, mucosal immune functions, microbial signaling, and a collection of functions usually labeled as "gut-brain" interactions. For instance, the strong connection between HPA axis stress and GI function is primarily mediated through the neuroendocrine functions within the GI tract.

As with all the other core functions of the GI system, the neuroendocrine functions of the gut are integrally entwined with the other core functions described above. Throughout the text, we will explain various aspects of the cells and functions which coordinate the neuroendocrine functions of the GI system within the other core functions already mentioned.

Functional Testing and GI Function

Within the functional and integrative medical community, a wide variety of laboratory tests are performed to help the clinician assess basic GI function within patients and to decipher complex gastrointestinal dysfunctions. Some of these tests are commonly used by a wide range of physicians or GI specialists, while others are more commonly used by clinicians trained within functional or integrative clinical models. Throughout various sections of the text, we will include a discussion of the available laboratory tests that may help a clinician confirm (or rule out) a particular GI dysfunction.

The Human Gut Microbiome: The Basics

As most are now aware, the human GI tract is a host to countless microbes (some estimate 100 trillion bacteria alone) that have a powerful impact on human health. This impact extends well beyond the gut lumen, and has been implicated in nearly every facet of human physiology and metabolism.[1,2,3] In fact, the gut microbiome is now commonly viewed by many as a semi-autonomous symbiotic organ or organ-like system within the GI tract. However, while our knowledge of the microbiome within the human gut has greatly expanded in just the past few years, there is much we still do not know about this complex ecosystem, especially as it pertains to modifying its structure and metabolic functions to favor a healthy outcome for the host.

Our knowledge of the commensal gut microbiota is heavily weighted toward bacterial species, though there is a growing base of knowledge on GI-resident viruses, bacteriophages (viruses that infect bacteria), fungi, and protozoa. Recent technological advances that allow for the recovery, amplification and sequencing of genetic material from the gut have given us exponentially more information than the plating/growth technologies of the past, allowing for the identification of more than 1,300 different bacterial species in humans worldwide (identified primarily by ribosomal RNA sequences).†[4,5]

Acknowledging that the human GI tract is a highly complex network of microbes is one thing, understanding the important features within this complexity has been much more daunting. This is partly due to the fact that the primary tool used to study the gut microbiome in humans is the analysis of fecal microbiota (from stool samples), which we now know is only a rough approximation of the many microbial niches found within the GI tract. However, since this is how most of the data is generated, we will start our discussion there.

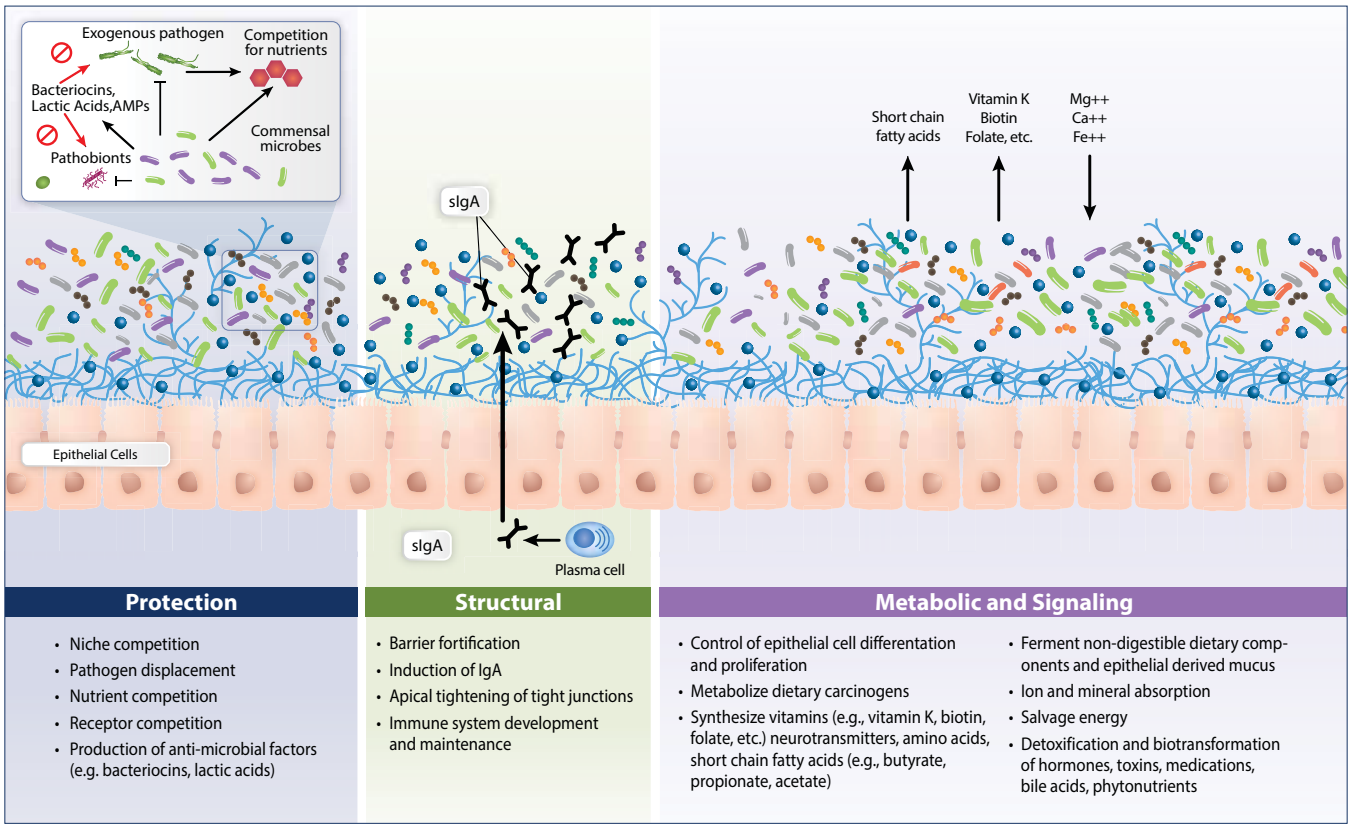


Figure 16: Basic Function of the Commensal Gut Microbiota. From the perspective of the host, this figure illustrates the three basic functional categories performed by the commensal gut microbiota. Some of these activities are also provided by certain probiotic organisms. See text for more details.

† There is some debate about the number of species identified with the global human microbiome based on the definition of a species and the techniques used to identify genetic differences. This number continues to expand as better genetic tools become available and larger populations are sampled.

compounds called polyphenols, many of which have been studied for their health-related benefits when part of the diet (or via supplementation). Since many of these compounds are known to have poor gastrointestinal absorption, their higher concentrations throughout the GI tract allow for microbial metabolism and signaling.

Ironically, much of the early studies on polyphenolic compounds (e.g., flavonoids, catechins, anthocyanins, isoflavones, lignans, stilbenoids, curcuminoids, tannins, etc.) were related to their potential antimicrobial activities.[78] In fact, while many are still commonly used as antimicrobial agents, today researchers are realizing that many of these dietary plant compounds have a diverse range of specific influences on the microbiome that can help explain their health-promoting outcomes. In addition to these findings, it is now appreciated that many of these polyphenolic compounds would be of little health benefit to the host without first being metabolized by the gut microbiota, either to produce the "active" compound or to alter the compound to improve its bioavailability. Therefore, the relative efficacy of certain plant phytonutrients (either from dietary intervention or supplementation) may greatly depend upon the metabolic activities expressed by an individual's gut microbiota.[79]

There are numerous well-studied examples of microbial metabolism altering the biological effect of dietary phytonutrients. One of the most well studied is the conversion of the soy isoflavone compounds daidzin and genistin into the more absorbable daidzein and genistein, along with the deconjugation of their liver metabolites and the creation of secondary metabolites with specific estrogen-like effects (e.g., equol; see Figure 22).[80] Therefore, the ability for these compounds to generate a biological effect in those consuming soy is partly (perhaps mainly) influenced by the availability of certain bacterial species, which are themselves influenced by the diet and genetics of the host.[81,82] This may explain many of the differences between certain epidemiological disease risk in populations that regularly consume soy from early life and intervention trials using concentrated soy isoflavones in populations with little history of soy consumption.

Another example of this back and forth relationship between the microbiota and a well-known phytonutrient is with the alkaloid berberine, known to possess "antimicrobial" activity and used in a variety of

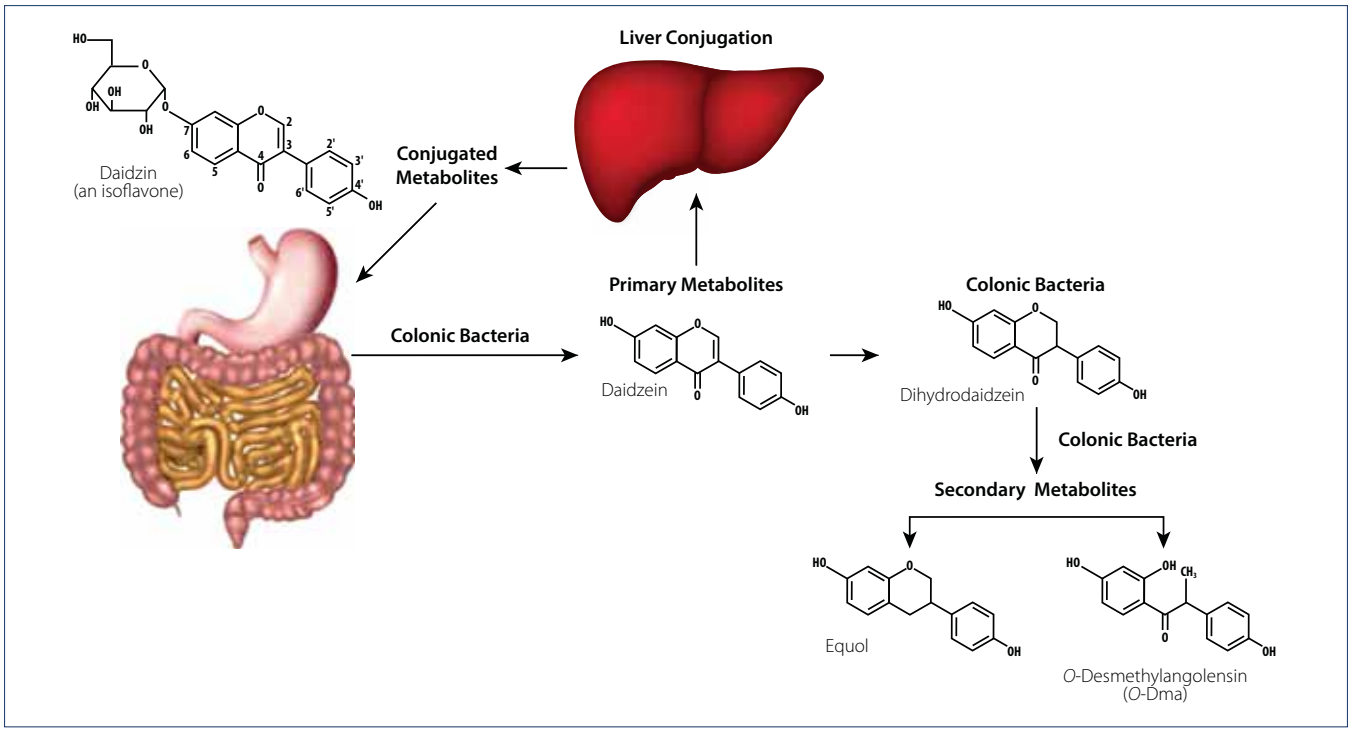


Figure 22: Bio-activation of Soy Isoflavone by Gut Microbiota. This figure illustrates how commensal organisms within the colon convert the biologically inactive soy isoflavone daidzin by converting it to the aglycone daidzein and then further metabolizing that compound to biologically active secondary metabolites, like equol. Conjugated isoflavone metabolites from the liver are also modified by the gut microbiota into bioactive compounds.

Multi-Strain vs. Single-Strain vs. Rotating Strains

Since there are many purposes for which a probiotic may be recommended, and the published literature includes a wide range of probiotic formulas, strains and doses, many different theories of proper probiotic recommendations have emerged. Two, in particular, are the multi-strain and rotation of single-strain approaches. We advocate for using a multi-strain approach for the vast majority of applications within the clinical setting. First, since a diverse blend of commensal species appears to be one of the most important factors in maintaining a healthy gut microbiome, using a range of different strains has the best chance of promoting a wider array of commensal organisms. In addition, because of individual differences in strain survival, compatibility and metabolic potential, a multi-strain approach allows for a more diverse benefit in a wider range of individuals. Finally, recall that probiotics represent a part of the transient microbiome (see page 102), which is normally encountered as a range of organisms ingested in the diet, and through contact with the soil and air. A multi-strain approach is therefore more consistent with this natural encounter with ingested microorganisms.

There are several ways to define a multi-strain approach. In general, we define this as a product with five or more proven probiotic strains containing at least two Lactobacilli and two Bifidobacterium strains. One way to enhance the potential for diversity using this multi-strain approach is to choose products that contain species (or sub-species) with a range of genetic variability (see phylogenetic relationship of common probiotic strains in Figure 27). By combining strains that are more genetically diverse, rather than clustering the diversity with closely related sub-species, a greater potential for diversity may be achieved. Inclusion of *Streptococci*, *Saccharomyces boulardii*, or other non-LAB strains will expand this diversity even further.

The other popular means of attempting to achieve diversity is to rotate single-strain probiotics, consuming a different strain for a few months and then switching to a different strain and so on. The difficultly in recommending this approach is that there is virtually no information available to evaluate this strategy and, in comparison to the multi-strain approach above, does not mimic the way we encounter transient microbes from our food or environment. Also, since many probiotics require several weeks or months of continuous use to achieve noticeable benefit, the subject might be planning to rotate to a new strain just as tangible benefits may be realized from the current product, and switching may not be in the best interest of the patient. While switching from one product to another may be necessary to find a product more suited for an individual or a therapeutic purpose, rotating single-strain products in an attempt to increase overall microbiota diversity is likely a hold-over from the days when only single-strain products were available and is accomplished more efficiently by the use of multi-strain products. As a final note, rotating different multi-strain products is not discouraged, provided they are equally diverse, though research investigating this approach is also lacking.

Changes in Commensal Population from Probiotic Intake

Compared to the changes detected in commensal populations that occur after radical dietary changes, bariatric surgery or antibiotic use (or fecal microbiota transplants), detectible changes in the commensal microbiota after probiotic consumption are much more limited.[16,17] This should come as little surprise since the strains used as probiotics are generally limited to just a few genera, are almost exclusively transient in nature (because of their species and/or commercial domestication), and are usually given in doses that are difficult to detect in fecal samples (by culture or genetic methods). However, there are several important points that need to be considered before determining such subtle changes are unimportant.

First, as we shall show in subsequent sections, even when no major changes are detectible in commensal microbiota after ingestion of certain probiotics, there is often still a demonstrable improvement in GI or other health outcomes. This suggests that subtle changes in commensal species abundance or function, along with the direct metabolic contributions of the transient probiotic species, can have profound and important health benefits for the host. Second, the dose of most probiotics is likely to alter the immediate

layer is very compact and difficult to penetrate, forming a nearly sterile environment next to the epithelium. Both layers of mucus are formed within the stomach and large intestinal mucosa, while only the loose mucus layer is present in the small intestines. Interestingly, the thickness of this loose layer is extremely thin or absent where immune system Peyer's patches interface with M cells for immune surveillance of the gut lumen contents.

In order to form these different types of mucus, there are two basic types of mucin proteins: secretory mucin (mostly composed of MUC2, but include MUC5 and MUC6) and transmembrane mucins (e.g., MUC1, MUC3, MUC4, MUC13, MUC17). The transmembrane mucins are secreted by goblet cells or other epithelial cells and are embedded into the apical membrane to form a network into which secretory mucins also incorporate. The density of this mucus network is dependent on the types, glycosylation and amounts of the various transmembrane mucins secreted. Research investigating the role of mucins has shown genetic polymorphisms within mucin genes are associated with increased risk of gut-related outcomes such as IBD, colorectal and gastric cancers and susceptibility for certain gastrointestinal infection such as *H.pylori*., further demonstrating the importance of the specific matrix created by these different mucins.[5,6,7] In addition, chemical, enzymatic or microbial disturbance of the mucus layers from the lumen, or cell signals that cause changes in mucin gene expression, can create a vulnerability that leads to barrier disruption. We will discuss some of these factors as they pertain to barrier function outcomes in this chapter, while also covering some specifics in other chapters as well.

Tight Junctions: Managing Paracellular Permeability

The paracellular space between each gastrointestinal epithelial cell is connected to the adjacent cells with three different transmembrane protein complexes: desmosomes, adherent junctions and tight junctions. Of the three, the tight junction is tasked with regulating paracellular transport of small ions while acting as a barrier to larger macromolecules. Tight junctions should not be viewed as static barriers between epithelial cells, but as a dynamic complex of proteins forming a fence to large particles and a network of pores (gates) for small ions (~3.5 kDa and smaller) and water. As Figure 31 shows, tight junctions form several tightly sealed layers around the entire cell between the apical and basolateral sides (tight junctions form mostly near the apical side).

Tight junctions (TJs) are composed of several different transmembrane proteins consisting mostly of occludin, claudins (at least 24 different kinds), and junctional adhesion molecule (JAM) proteins.[8] The extracellular portions of these proteins interact with similar proteins expressed on adjacent cells to form the interlocking junction (see Figures 31 and 32). The intracellular portions of these transmembrane proteins are tethered to intracellular actin/myosin filaments by linker or scaffolding proteins, most commonly zonula occludens (ZO) proteins. The TJ can be modulated by the expression pattern of the various proteins involved (some claudins form pores while others form tight barriers), as well as the phosphorylation pattern of these

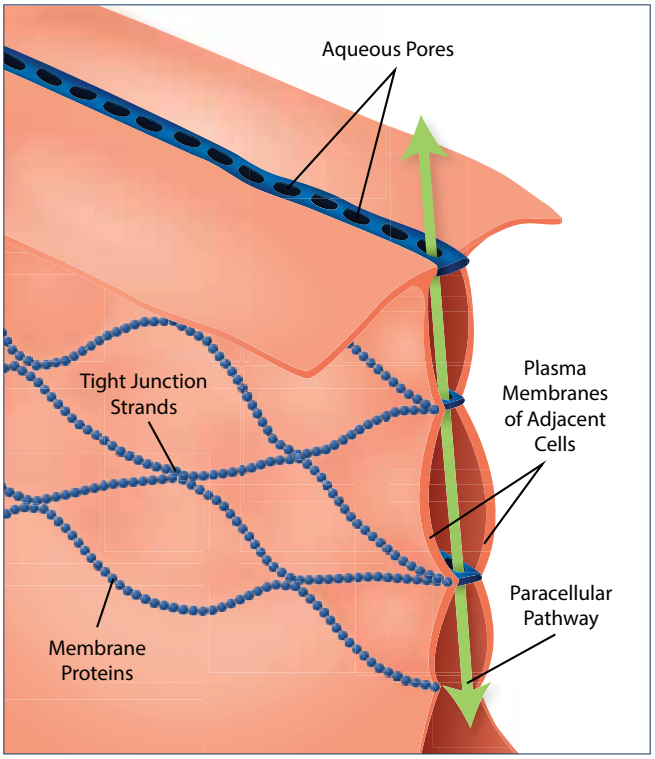


Figure 31: Tight Junctions and Paracellular Transport: As this image shows, tight junctions form a zipper-like network of proteins that link adjacent enterocytes at their apical ends (other types of junctions not shown here). The amounts and types of each protein that forms the tight junction allows for the formation of tiny pores to allow very small molecules to pass through the paracellular space.

Etiology and Risk Factors for the Development of IBD

Genetics

The exact etiology of IBD is unknown, but it is mostly categorized as an altered immune response (sometimes viewed as an autoimmune response) resulting from a combination of a subject's genetic susceptibility, environmental triggers, intestinal barrier status and gut microbiota.[8] Evidence shows a major genetic basis for IBD risk, including family clustering and racial and ethnic differences. Studies suggest that 10 to 20% of individuals diagnosed with IBD have a family history of IBD, with the highest risk among first-degree relatives. This familial link is a key risk factor for IBD; having a close relative with IBD increases a person's risk tenfold.[9] Large genome-wide association studies (GWAS) using data from 75,000 IBD patients have identified 163 different potential risk loci (~300 genes), 110 of which were associated with both CD and UC.[10] Mutations of the *CARD15* gene (also known as the *NOD2* gene) on chromosome 16 appear to have the most significant impact on the risk for developing CD. Specific polymorphisms in this gene lead to alterations in NF-κB signaling, which drives increased inflammatory cytokines, dysregulation of gut barrier function, a decreased production of antimicrobial peptides—resulting in decreased clearance of invasive luminal bacteria.[11,12]

Immune/Barrier Dysfunction[13]

Other genetic links have also confirmed alterations in both innate and adaptive immune function as part of the pathophysiology of IBD.[14] Normally, the mucosal immune system is responsible for the balance between pro- and anti-inflammatory mediators. This system helps to defend against luminal pathogens, as well as prevent an immune over-reaction against harmless luminal antigens (such as beneficial bacteria or food). In IBD, this immunological balance is impaired and shifted toward a more pro-inflammatory state, driven by the increased activation of effector immune cells through up-regulation of the NF-κB pathway. These immune cells produce high levels of pro-inflammatory cytokines (such as TNF-α, IL-6 and interferon-γ), resulting in mucosal inflammation and tissue damage.[15] While mucosal inflammation explains some of the intestinal permeability issues in IBD patients, other factors that affect gut barrier function have also been reported in these subjects. The mucin glycoprotein MUC2, and related genes in the synthesis and post-translational modification of mucins, are known to be affected in subjects with IBD, altering the thickness/viscosity of this important part of the mucosal barrier, though these alterations are different in UC compared to CD.[16] Not surprisingly, tight junction regulation is

	CROHN'S DISEASE	ULCERATIVE COLITIS
Location of lesions	Mostly affects the terminal ileum and colon, but can affect any portion of GI tract	Colon exclusively; from the rectum and extending proximally
Depth of pathology	Entire bowel wall	Mucosa and submucosa
Blood in stool	Usually absent	Frequently present
Weight loss/anorexia	Weight loss and anorexia are common	Weight loss in more severe cases
Diarrhea	Moderate	Present
Immune response	Th1 and Th17 pathways predominate	Th2 and Th17 pathways predominate
Complications	• Small bowel abscesses, obstruction, and fistulas • Perianal disease • Malabsorption • Toxic megacolon • Colon cancer	• Perforation • Hemorrhage • Toxic megacolon • Colon cancer

Table 7: General Differences between Crohn's Disease and Ulcerative Colitis

Assessing and Treating Predisposing Factors and Root Causes of IBS

Since IBS is defined by the lack of specific organic disease on the one hand and the presence of dysfunctions leading to symptoms that persist on the other hand, defining a cause for IBS is obviously difficult. As Figure 37 illustrates, IBS is considered to be the convergence of numerous physiological and psychological disturbances mediated through pathways that are generally referred to as "Gut/Brain Signaling". Therapies designed to address these underlying dysfunctions will have more long-term success than those designed to limit the symptoms of diarrhea or constipation alone.

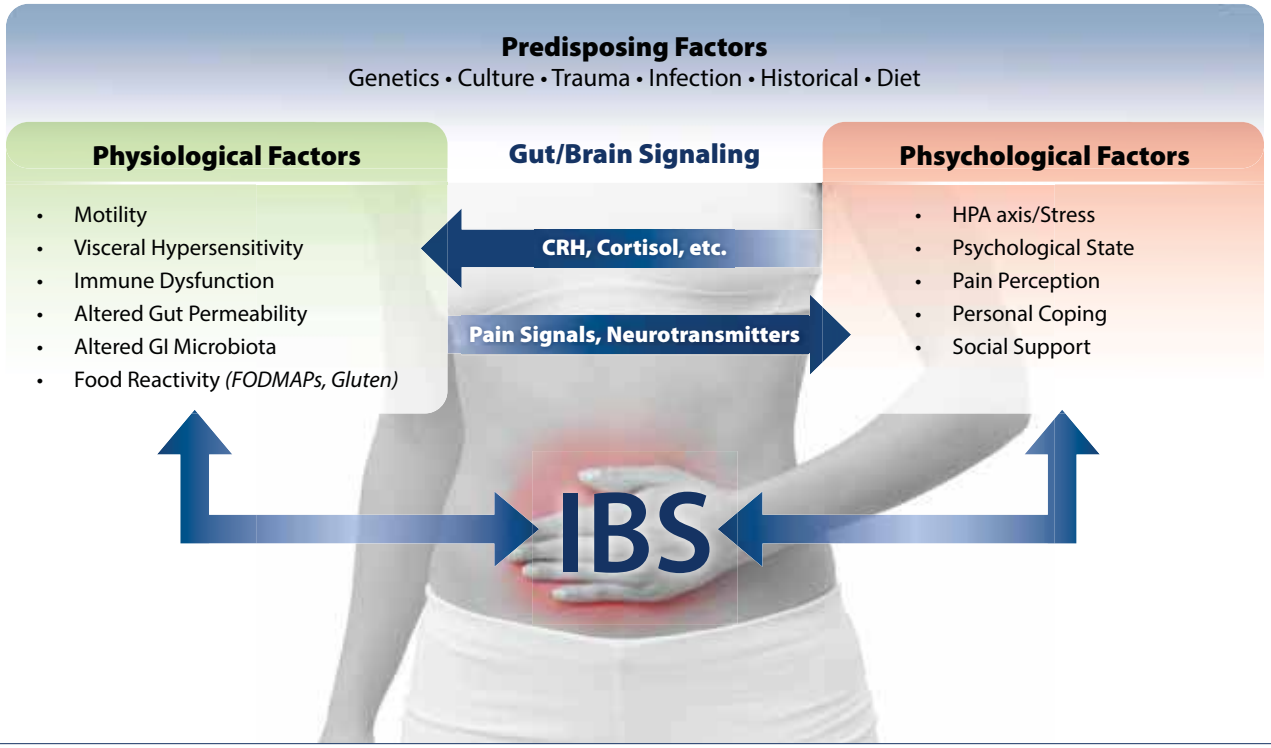
Genetics

Large national surveys of IBS patients and their relatives indicate a genetic component related to this dysfunction. However, compared to other gastrointestinal conditions, and most other chronic diseases, there is limited evidence linking specific genetic loci with the increased risk for IBS.[14] More than 60 candidate genes have been studied, many involved with serotonin synthesis, mucosal immunity, neuropeptide signaling (including CRH; see below in HPA axis), pain signaling, bile acid synthesis and a variety of intestinal secretions. While many of these have helped researchers investigate the complex pathophysiology related to IBS (or a rare loss-of-function mutation), there is currently no specific gene (allele or polymorphism) that, if identified, is likely to help a clinician diagnose or manage a patient who fits the diagnostic criteria for IBS.[15]

Psychological Factors

It does not take a trained scientist to realize there is a connection between the functions of the GI tract (especially motility) and the feelings of anxiety, fear and stress. There is a strong interaction between the way we perceive the world around us and the function of the gastrointestinal tract, mediated by what is often called the gut-brain axis. IBS specifically, and the majority of other functional gastrointestinal disorders according to Rome IV, are now referred to as "Disorders of Gut-Brain Interaction."[16]

Figure 37: Underlying Dysfunction in IBS



showed a statistical difference between these groups (6.2% and 0.66% positive breath test, respectively).[14] These differences also highlight the wide variability of the association between SIBO and IBS reported in the literature (see IBS and SIBO on page 197).

Breath Testing, Our Recommendation

Whether a positive breath test is diagnostic for SIBO or merely the evidence of elevated and early production of gas due to the fermentation of undigested carbohydrates may be an unimportant distinction, since both scenarios may contribute equally to the patient's signs and symptoms (gas, bloating, diarrhea, abdominal pain). And, with the exception of the use of antibiotics, which some clinicians may consider appropriate for a diagnosis of SIBO, the therapies for these are similar (see below). Clinicians should consider testing for SIBO when such a diagnosis is likely to alter their therapeutic strategy. Check with existing labs for their available test methods, substrates and cut-off points. One final note: Since breath testing is highly dependent on proper test methods, including pre-testing dietary restrictions, clinicians should be careful to ensure the patient understands these restrictions and is capable of performing the test as instructed.

PPI Use and SIBO

Low stomach acid (hypochlorhydria or achlorhydria) is thought to create an environment that allows for increase overgrowth of bacteria in the small intestines, especially when this condition is induced by drugs.[15,16] Therefore, the relationship between the use (or overuse) of proton-pump inhibitors (PPIs) as a contributing risk factor for SIBO is of concern to many. A recent systematic review and meta-analysis was conducted to evaluate the association between PPI use and SIBO, and found when SIBO was defined by duodenal or jujunal aspirate overgrowth, there was a strong association showing PPI users had a sevenfold higher incidence of SIBO.[17] However, while the risk for a positive breath test as a measure of SIBO in PPI users was nearly double (OR 1.93), this association did not reach statistical significance.

While some studies show no difference in the incidence of SIBO in those who use PPIs compared to subjects who do not, on balance, the majority of studies confirm this association, as does the physiology of an altered gastric and duodenal pH. In a study of 70 children (mean age 13.5 years) given 20 mg of omeprazole for four weeks who were glucose breath-test negative for SIBO at baseline, 21 of the 70 (30%) became breath-test positive after PPI use and an additional five more developed symptoms of SIBO while remaining breath-test negative.[18] The use of a probiotic (2 billion CFU/day of *L. rhamnosus* and *L. acidophilus*) in these children was not able to mitigate the PPI-induced SIBO. Therefore, unless their use is strongly indicated, there are many reasons to limit the use of PPIs in patients; the increased risk of small intestinal dysbiosis is merely one more. When possible, clinicians should help patients taper the use of PPIs and use therapies addressing the root cause of the condition for which the PPI was prescribed in the first place (see the negative consequences of PPI use and ways to taper patients off PPIs on page 219).

Prevention and Intervention Strategies for SIBO

Since the difference between a "normal" small intestinal microbiome and one defined as "SIBO" is difficult to define, it is not surprising that the majority of prevention and intervention strategies are also difficult to assess. The primary goal of most therapies is to eradicate the overgrowth (or at least the harmful and out-of-place organisms) while allowing the appropriate growth of the commensal organisms to thrive. This is typically attempted by limiting the environmental conditions for SIBO (avoiding PPIs and certain carbohydrates), directly altering the microbiota (antibiotics, probiotics) or by stimulating changes in bowel transit (laxatives, prokinetics, fiber supplementation).

Dietary Restriction

Since SIBO is characterized by altered fermentation of carbohydrates, many clinicians, nutritionists and dietitians recommend restriction of certain carbohydrates (fructose, lactose, FODMAPs, etc.). Surprisingly, we are not aware of any studies looking into the efficacy of these dietary approaches for non-IBS, SIBO-specific outcomes. One retrospective study suggests that in obese subjects, carbohydrate intake may influence their risk for SIBO.[19] Comparing 60 obese subjects with normal lean controls, 23.3% of the obese subjects had a positive glucose breath test, while only 6.6% of lean subjects had a positive breath test. Using diet recall, obese subjects with SIBO consumed statistically higher amounts of carbohydrates, refined sugars and less total and insoluble

Candida Overgrowth in the GI Tract and Beyond

Candidiasis is the term used to describe overgrowth of the yeast *Candida albicans* and similar species (*C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) in the GI tract or other mucosal tissues.[1,2] *Candida* is a normal inhabitant of the GI tract in humans, as well as the mucus membranes of other orifices, such as the mouth, nose and vagina, where it is often deemed a commensal organism.[3] In fact, *Candida* species are the dominant genera within the human mycobiome.[4] When *Candida* grows as a single-celled "yeast" organism, it is generally not considered to be a pathogen. However, when *Candida* undergoes a phenotypic switch to its sessile, biofilm-forming hyphae form, it is considered a pathogen and difficult to remove.[5,6] Though these features are not necessary for invasive behavior, and *Candida* biofilm have not yet been demonstrated in the GI tract, agents that inhibit this phenotypic switch are considered important for inhibiting *Candida* overgrowth outside the GI tract (e.g., mouth, vagina) and especially on implanted devices.[7,8]

During times of immune suppression/compromise, critical illness or GI microbiota disruption (i.e., antibiotic use) *Candida* can become an opportunistic pathogen as the yeast alters its invasive characteristics and migrates from the GI tract to colonize other tissues.[9,10] The oldest description of a *Candida* infection is oral thrush, which is common in immune-compromised individuals.[11] Recurrent vulvovaginal candidiasis is experienced by millions of women worldwide, and along with thrush, is the most common form of extra-gastrointestinal candidiasis seen by the clinician.[12] Candidemia, the invasion of live *Candida* in the blood or other tissue, is rare, severe and should result in immediate hospitalization (although the patient is likely to already be hospitalized as this is frequently a nosocomial infection).[13] Finally, *Candida* is often found on dental devices (e.g., dentures, implants) or other implants within the gastrointestinal, genitourinary tract or elsewhere, often resulting in continued re-infections in individuals treated for *Candida* overgrowth (some of these can be serious candidemia when involving cardiovascular implants).[14,15]

Candida overgrowth is commonly related to the following:

- Antibiotic use, either long-term use (acne, otitis media, sinusitis, etc.) or short-term, high-dose use (surgery, UTI, etc.).[16,17,18,19]
- High consumption of sugars, white flour, pastries, etc., are assumed to increase the growth of *Candida* in the GI tract and mouth. These assumptions are based on *Candida*'s use of simple sugars as an energy source, though studies examining the effect of *Candida* growth following increased sugar intake have had equivocal results.[20,21]
- Compromised immune system (HIV/AIDS, organ transplant, chemotherapy).[22]
- Chronic HPA axis activation/stress (which suppresses the immune system)[23,24]
- *Clostridium difficile* infection[25]
- Inflammatory bowel disease[26,27,28]

Diagnosing GI Overgrowth of *Candida*

While oral or vaginal *Candida* overgrowth is common and easily diagnosed, overgrowth within the GI tract often goes unrecognized or is attributed to other causes. Such causes may be concomitant with *Candida* overgrowth, including dyspepsia (gas, bloating), bacterial dysbiosis, SIBO or IBD symptoms. Other non-GI symptoms often related to *Candida* overgrowth may include mental fog, muscle/joint weakness or pain, general fatigue, and skin irritations. These symptoms are a result of yeast growth (and their metabolites), as well as the death of yeast organisms. These processes put additional burden on the detoxification capacity of the liver, which is responsible for transforming yeast metabolites into harmless substances for elimination.