

# Gastrointestinal Problems in Immunodeficiencies:

Common among PI patients, leaky gut has many underlying causes that, when identified, can determine the best course of treatment.

By Terry O. Harville, MD, PhD

# What Is Leaky Gut?

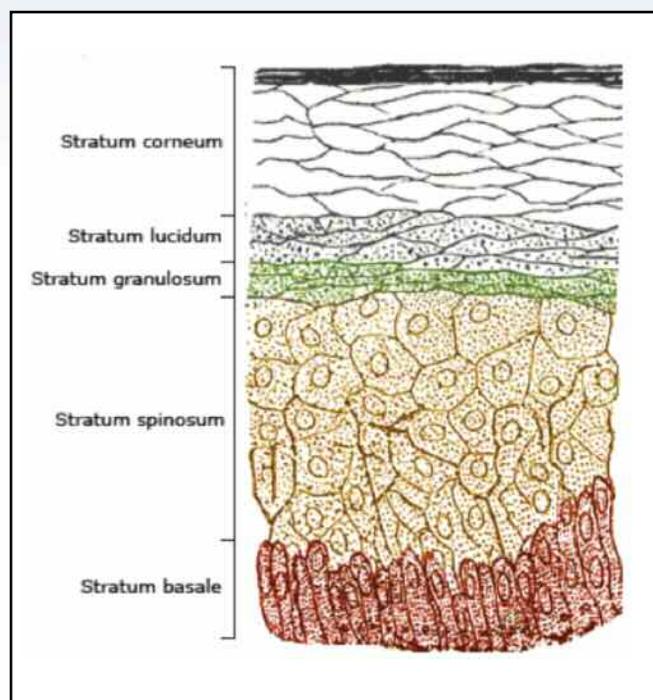
**ALONG WITH THE** skin, the gastrointestinal (GI) tract interfaces our bodies with the world. While we think of the GI tract as being “inside of us,” it is actually connected to the world “outside of us.” In simple terms, our bodies are a “tube,” with the mouth at one end and the anus at the other. Anything in the world can potentially enter the mouth (or anus), migrate through the GI tract and exit from the anus (or mouth). Thus, the GI tract is always in direct contact with the outside world.

The skin covers the outer portion of our bodies (the tube), and the mucosal cells of the GI tract cover the inner portion. Together, these two coverings protect all the cells, tissues and organs inside of our bodies. Like the skin, the mucosal cells of the GI tract come into contact with a myriad of microorganisms, acting as a barrier to keep them out of our bodies. It is estimated there are 10 times more microorganism cells in our GI tract than the total number of cells that make up our bodies. Thus, we are only about 10 percent of a community of organisms with which we must live in harmony or suffer some form of adverse consequence.

Under normal circumstances, the immune system becomes tolerized to the microorganisms that are present in the GI tract. Collectively, this is known as our microbiome. As long as the microorganisms remain outside the body in the open space of the intestines (the lumen), they are not perceived as a threat, and the immune system does not attack them. The relationship is commensal (neither is trying to hurt the other) and symbiotic (we provide them with food and a place to live, and the microorganisms provide certain nutrients we need). Additionally, some of the microorganisms may have important roles in the development of our immune system, as well as roles to help prevent conditions such as allergic diseases and autoimmune disorders from developing. Therefore, when our GI tract remains functionally intact, we have the correct microbiome present, and our immune system is functioning normally; we are healthy, and all is remaining well.

Unfortunately, things break down when immunodeficiencies are present or autoimmunity occurs. Further, antibiotics and some medications may alter the microenvironment of the GI tract resulting in problems with the microbiome.

**Figure 1. Layers of Skin Cells**



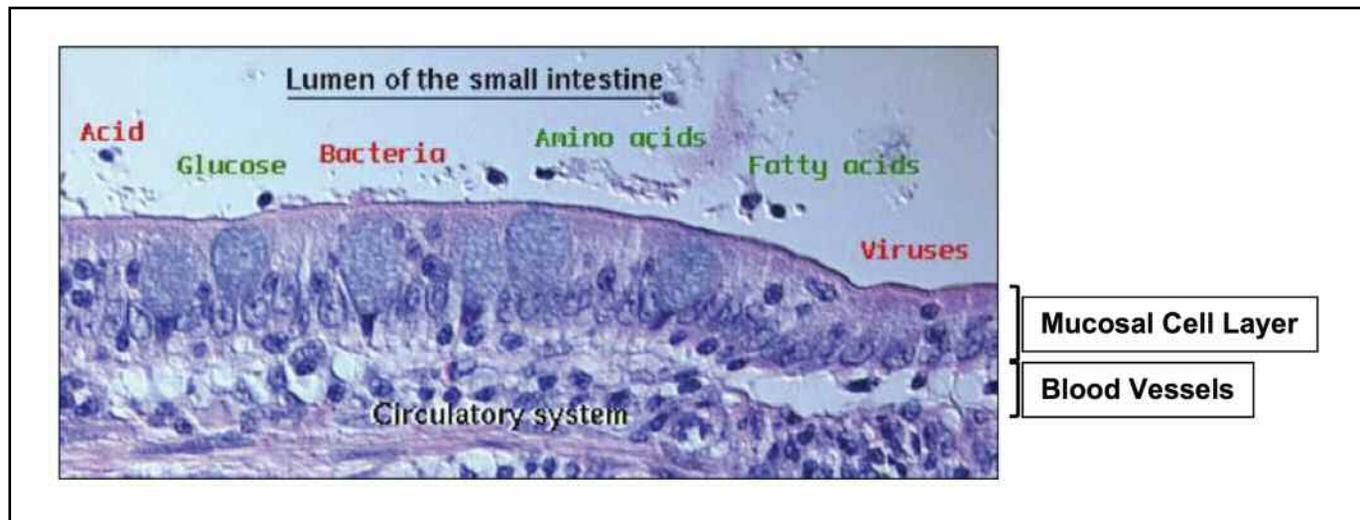
*The skin, as a barrier, has multiple layers of cells to keep water and other molecules inside, while simultaneously keeping unwanted things out. (Modified from the original Grey's diagram: [en.wikipedia.org/wiki/Image:Gray941.png](http://en.wikipedia.org/wiki/Image:Gray941.png); public domain: [commons.wikimedia.org/w/index.php?curid=1374564](http://commons.wikimedia.org/w/index.php?curid=1374564))*

## Functions of Skin and GI Mucosal Cells

Skin acts as a barrier with multiple layers of cells and blood vessels to prevent loss of water and other molecules, as well as unwanted entities entering from the outside world (Figure 1).

In contrast, GI mucosal cells are typically one cell layer thick, which suggests it may be somewhat easier to lose the layer's integrity and keep what should remain outside from what is inside. The relative thinness is by design, though. When food is digested and water is ingested, the mucosal cell

**Figure 2. GI Mucosal Cells**



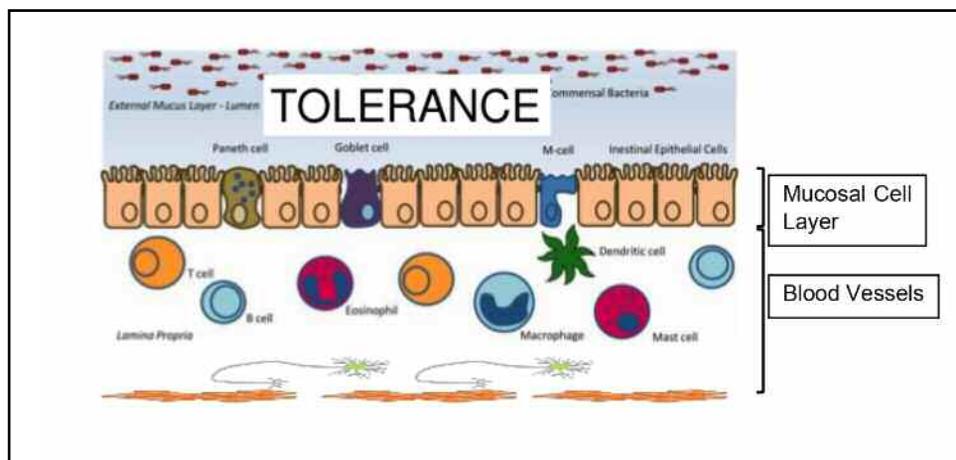
GI mucosal cells are essentially a single cell layer lining the intestines from the mouth to the anus. The inside of the intestines, where food transits, is known as the lumen. This is also where the microorganisms reside. Food is digested into the individual components: amino acids from proteins, glucose and simple sugars from carbohydrates and fatty acids from fats. There are specific transporters located on the luminal side of the intestines that transport these nutrients, minerals (e.g., calcium, iron, etc.) and water into the GI mucosal cells. Then, there are specific transporters on the back side of the cells to transport these items into the blood vessels for distribution to the rest of the body. ([www.vivo.colostate.edu/hbooks/pathophys/digestion/stomach/gibARRIER.html](http://www.vivo.colostate.edu/hbooks/pathophys/digestion/stomach/gibARRIER.html))

layer can more readily transport the nutrients directly into the blood system just below the cell layer (Figures 2 and 3).

To maintain mucosal cell layer integrity, a specific mechanism creates a tight adherence between the cells. By analogy, the GI mucosal cell layer is a brick wall (each brick is a cell) with a front and back side. The front is the intestinal luminal side to the outside world, and the back is the side to the body. The other four sides interact with the adjacent cells. Using this analogy, the mortar (desmosomes) between the bricks (cells) maintain tight integrity to keep things out or in (Figure 4).

Because the wall is only one cell thick, the GI mucosal cell layer is somewhat tenuous. Damage to the cells or breaks in the adhesion between the cells could readily allow for a leaky gut.

**Figure 3. Diagram of GI Mucosal Cells**



In the diagram of the GI mucosal cell layer, the individual cells and blood vessels below them (which transport the various immune cells) are more readily seen. It is also obvious that this barrier is very meager when compared with the skin. ([image.slidesharecdn.com/probioticsandgastrointestineffects-160517184732/95/probiotics-and-gastrointestinal-effects-17-638.jpg?cb=1463512760](http://image.slidesharecdn.com/probioticsandgastrointestineffects-160517184732/95/probiotics-and-gastrointestinal-effects-17-638.jpg?cb=1463512760))

### Is It Always “Abnormal” for the Gut to Become Leaky?

Throughout life, there is a need for cells to grow and divide to replace old, dying or injured cells. From infancy into adulthood, a tremendous amount of growth and cell division must occur.

And, during this process in the GI mucosal cell layer, adhesion between cells is temporarily lost in order to complete the division cycle. As such, early in life, excess normal leakiness of the gut naturally occurs as the cells grow and divide. When the normal and intact immune system and the correct microbiome of the intestines are in place, appropriate immune maturation occurs, despite the occasional normal leakiness. Therefore, evolutionary growth from infancy to adulthood results in some normal, extra leakiness of the intestines. It's part of normal maturation of the immune system and for tolerance induction to allow symbiotic and commensal microorganisms to live in harmony.

### Causes and Consequences of the Gut Becoming “Abnormally” Leaky

Unfortunately, the tenuous mucosal cell layer can undergo pathologic processes and become abnormally leaky due to a number of causes.

In some individuals (most typically children), some food item (e.g., peanuts) exposures early in life, when the GI tract is more normally leaky, or some alteration of the microbiome (e.g., antibiotic treatment) may enhance abnormal leakiness or alter the tolerization. When this happens, the food item can be mistaken by the immune system as a parasitic attack, and allergic disease may result. In the mistaken response to rid the GI tract of parasites, this reaction compounds itself in cycles of increased leakiness due to mediators released by the immune

cells. Typically, avoidance of the offending food item allows the GI mucosa to heal and the immune system to retolerize and return to a less leaky state.

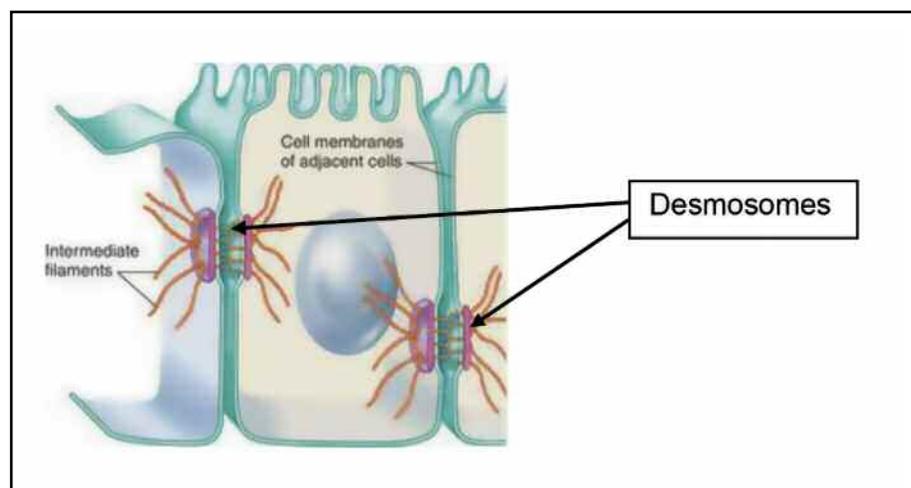
On another front, inflammatory bowel disease (IBD) is a major cause of a leaky gut. While this is not fully understood, it is believed that tolerization against certain microorganisms is lost early in the process. It's not clearly understood, but possibly some microorganisms with a greater pathogenic potential became present and invaded the GI mucosa, initiating an immune system inflammatory response. Inflammation worsens the leakiness, which then compounds the effects of the microorganisms' exposure to the immune system, perpetuating cycles of continuous leakiness and inflammation. The breakdown in tolerance to the microbiome of the intestines could also be due to the influence of specific genes, beginning with malfunction of the immune system, causing it to initiate inflammation in the mucosa and the leakiness, which again results in seemingly endless cycles perpetuating leakiness. Diarrhea typically occurs when tolerization against microorganisms is lost. Several useful treatment options can downregulate the immune system's activation state, which can reduce the extent of inflammation and, in turn, reduce leakiness.

At least 10 percent of patients with common variable immunodeficiency (CVID) report symptoms of the GI tract. But, endoscopy and biopsy analyses indicate 50 percent or more have alterations suggestive of infectious or inflammatory diseases.

Approximately 2 percent of patients with CVID may develop granulomatous disease, which can involve the GI tract. In granulomatous disease, nodules of immune cells aggregate into clusters in the tissues and disrupt the normal function of the specific tissue. Finding granulomas is one of the histopathologic criteria for the diagnosis of Crohn's disease (one specific IBD found in approximately 0.2 percent of the population), but other conditions (e.g., sarcoidosis) may also present with granulomas. Use of IBD treatments may be beneficial for treating granulomatous disease.

Unfortunately, patients with primary immunodeficiency (PI) seem destined to develop some extent of an increased leaky gut. With an immune system

**Figure 4. Desmosomes Forming Tight Junctions Between Cells**



*Desmosomes act like mortar between cells to form a tight junction to prevent things from leaking out of the body into the lumen of the intestines and prevent unwanted things, including microorganisms, from leaking between the cells into the body. (medical-dictionary.thefreedictionary.com/desmosome)*

that is not intact, tolerization to the microbiome may not occur. As stated previously, tolerization should occur early in life, when normal, excess leakiness may be present. Due to lack of tolerization, the symbiotic and commensal microorganisms may be perceived as trying to invade the body, or in some cases, may actually invade (opportunistic infections). At this point, most patients require antibiotics to treat respiratory infections. The antibiotics alter the normal microbiome, which may allow for potentially pathogenic organisms to become present (e.g., *C. difficile*). Indeed, antibiotic usage since the middle of the 20th century has altered the microbiome in such a way that we are not totally sure what is truly normal.

Additionally, parasites may become chronically present. For example, giardia (a microscopic parasite that causes diarrhea) can be commonly found in the normal water supply, or brought into the home by pets. Other bacteria and parasites may also take up residence in the GI tract (e.g., *Isospora*, *Coccidia*, *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, *Cryptosporidium*, etc.), each of which can result in continuous inflammation and leakiness.

## CHRONIC DIARRHEA INDICATES THE GI TRACT IS LEAKING PROTEINS AND FLUIDS FROM INSIDE THE BODY.

Another way microorganisms cause increased GI tract leakiness is through the release of toxic compounds, known as enterotoxins. Perhaps one of the best known is the cause of shigellosis through Shiga toxin from *Shigella*. Enterotoxins tend to produce extensive diarrhea by adversely affecting the mechanisms mucosal cells normally use to transport nutrients and electrolytes into cells, and then into the body. Some enterotoxins actually cause essentially a reversal of the transport process so that water, electrolytes and nutrients are pumped out of the body into the GI tract. When this happens, massive amounts of diarrhea may occur, resulting in extensive loss of nutrients and proteins from the body.

Viruses can also compound leakiness. Enteroviruses make up a large category of viruses that may enter the body and result in respiratory, GI and central nervous system symptoms (e.g., meningoencephalitis). Some are commonly called the “24-hour

bug” or the stomach flu (not influenza). Norovirus is now more recognized as a cause of chronic diarrhea in patients with immunodeficiencies. Other viruses such as cytomegalovirus may also plague patients with immunodeficiencies. These viruses may directly infect intestinal cells, resulting in cells losing tight adherence, causing them to die and activating the immune system to kill the infected cells. In short, loss of the mucosal cell integrity occurs, which can cause extensive leakiness. Viruses may be difficult to treat, but for some, antiviral agents are available. An increase in replacement immune globulin (IG) may also be helpful.

Chronic diarrhea indicates the GI tract is leaking proteins and fluids from inside the body. This can result in loss of nutrients and specific proteins such as albumin, but in particular, loss of IgG. This can further impair immunodeficiency since the level of circulating IgG may not be able to be maintained at a sufficient level for good immune protection.

In addition, there is evidence of oxidative stress, which occurs in cells undergoing inflammation, in patients with leaky gut. Exposure of the immune system to microorganisms in the wrong manner (i.e., a break in tolerization), alterations of organisms’ molecular components due to oxidative damage (the generation of new antigens to which the immune system may respond) and alterations of one’s own tissues due to oxidative damage (likewise, possibly generating new auto-antigens to which the immune system may adversely respond) may continue a cycle of inflammatory responses with intestinal leakiness that can be difficult to break. In this case, antioxidative therapy is commonly recommended, which is unlikely to cause harm. Yet, even though it may be beneficial, it is unlikely to completely resolve the problem in all persons.

Also, gluten sensitivity may result in the diagnosis of celiac disease (CD), which has been shown to occur in approximately 1 percent of people and can be a major source of GI leak. In patients with CVID who had endoscopic and biopsy features similar to those found in patients with CD, only 20 percent had improvement with a gluten-free diet. Therefore, merely trying a gluten-free diet may not be beneficial for most patients with a leaky gut. However, those with the specific risk factors for CD may benefit. Specific testing for CD and its risk factors should be considered and discussed with a physician.

In summary, there are numerous causes of a leaky gut. Some may be attributed to normal circumstances during normal cell growth and division, as well as during normal growth from infancy to adulthood. There are abnormal circumstances due to the development of allergic disease, alterations in the microbiome due to antibiotic treatment, inflammation arising from IBD, altered tolerance to the microbiome due to immunodeficiencies,

opportunistic infections due to immunodeficiencies, toxins produced by microorganisms, viral infections, oxidative stress and conditions such as gluten sensitivity. Mutations may be present in the immune system, affecting how it responds to the microbiome interface. And, there may be mutations affecting the way mucosal cells function, further compounding the issues.

### What Can Be Done for a Leaky Gut?

Unfortunately, due to the nature of the onset of a leaky gut and the inflammation that precedes and/or follows, endless cycles of the condition may occur that can be difficult to break. For those treated with IG replacement therapy, sometimes higher dosing may ease symptoms by helping to control the infectious processes and reduce inflammation, which in turn reduces leakiness.

Corticosteroids can be useful since they reduce inflammation and tend to reestablish the tight junctions between mucosal cells. Chronic corticosteroid use, though, can result in numerous adverse side effects. Therefore, a corticosteroid such as budesonide, which is poorly absorbed systemically, may be better to use.

If there are known mutations that are further promoting leakiness, specific therapies associated with these may be helpful. For example, specific genes upon activation can result in autophagy (damaging and killing of cells, and production of much inflammation), which is responsible for some IBD. Specific inhibitors of these pathways can be very useful in ameliorating a leaky gut in patients with specific mutations.

In some instances, probiotics can be useful, especially in those treated with antibiotics. The goal is to try to reestablish a normal microbiome. When parasites are present (e.g., giardia), the typically recommended course of treatment may be woefully inadequate; sometimes months of treatment are required to prevent relapses.

Gluten avoidance can be useful in some, but the specific risks for CD should be evaluated (since these are the patients likely to benefit) and fully discussed with a physician before attempting it to prevent further nutritional deficiency. Glutamine supplementation is generally accepted as providing some benefit, but its use should be well planned and discussed.

Antioxidative supplements (e.g., omega-3 fatty acids) may provide some benefit, but use should be thoroughly discussed.

EnteraGam, derived from bovine serum immunoglobulin, is an oral product indicated for chronic diarrhea. It puts antibodies into the GI tract where they are needed, and some have used it successfully to improve leaky GI tracts. This product must be prescribed by a physician.

Fecal transplants, also known as fecal microbiota transplants, collect normal microorganisms from the GI tracts of nondiseased

persons to treat patients with GI tract problems. This is a U.S. Food and Drug Administration-approved treatment for *C. difficile*. Use of fecal transplants in PI patients has not been widely studied, but many consider it relatively safe and likely beneficial. There is concern, though, that opportunistic pathogens could be present and create significant problems for those with PI. Once again, this approach requires very careful discussion of the pros and cons.

Helminthic therapy uses rat tapeworms introduced into the human GI tract to induce specific immune responses for down-regulating autoimmune disorders, asthma and allergic diseases. It has also been reported to benefit some neurologic disorders and autism. While it could benefit some forms of GI tract inflammation such as IBD in PI patients, it has not been studied fully. There are concerns that an immune system that cannot respond normally will not generate the desired beneficial effect of a decrease in inflammation, followed by a decrease in GI tract leakiness. Unfortunately, there is also potential for the opposite to occur: worsening of the leakiness.

Some specific diets (e.g., specific carbohydrate diet) have been touted as bringing remarkable changes in a leaky gut, but they have not been tested in a rigorous fashion. Major dietary changes should be undertaken with guidelines from a nutritionist and a physician.

Any therapeutic intervention should be carefully considered and thoroughly discussed with a physician before attempting.

### A Major PI Disorder Complication

Leaky gut is a major complication in PI patients. There are multiple reasons for it to present, as well as causes for worsening symptoms. Identifying a treatable underlying cause or exacerbator is currently the best approach for improvement. Careful and thorough evaluations should be performed to determine how best to treat the condition. Full discussion with a physician is necessary to make sure individuals receive the correct treatment approach. ■

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### Resources

1. Agarwal, S, and Mayer, L. Diagnosis and Treatment of Gastrointestinal Disorders in Patients with Primary Immunodeficiency. *Clinical Gastroenterology and Hepatology*, Volume 11, Issue 9, September 2013, Pages 1050-1063, ISSN 1542-3565. doi:10.1016/j.cgh.2013.02.024.
2. Fasano, A. Leaky Gut and Autoimmune Diseases. *Clinical Reviews in Allergy and Immunology*, February 2012, 42(1):71–78. doi:10.1007/s12016-011-8291-x. PMID 22109896.
3. Uzzan, M, Ko, HM, Mehandru, S, and Cunningham-Rundles, C. Gastrointestinal Disorders Associated with Common Variable Immune Deficiency (CVID) and Chronic Granulomatous Disease (CGD). *Current Gastroenterology Reports*, April 2016, 18(4):17. doi:10.1007/s11894-016-0491-3.