



Immune Dysregulation and Malabsorption

Patients with many types of primary immunodeficiencies suffer from malabsorption caused by GI disorders, which can be treated through diet, supplements and medications.

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THE LUNGS, GASTROINTESTINAL (GI) tract and skin are the organs most affected in patients with primary immune deficiencies (PIs). Because these organs are in direct contact with the outside world, they are constantly exposed to foreign material that must be fended off with resident immune cells. Therefore, when the immune system doesn't work correctly, both disordered inflammation and chronic infection are seen.

GI disorders are one of the most common disorders in PIs. The GI tract houses the most lymphocytes of any organ in the body and is the source of large amounts of immunoglobulins. Indeed, the GI tract is exposed to many pathogenic and nonpathogenic microbes, many of which are part of the important normal flora of the intestines. As such, the immune system of the GI tract has to be tightly regulated to allow the "good" microbes in and keep the "bad" microbes out.

Frequently, PI patients affected by GI disorders suffer from malabsorption. Following is a discussion of the signs and symptoms of malabsorption, PIs most associated with malabsorption and some approaches to therapy.

What Is Malabsorption?

Malabsorption occurs when nutrients are not properly absorbed from the diet by the gut. In most instances of malabsorption, fat is not absorbed normally. Fat malabsorption is also associated with improper absorption of other nutrients, including vitamins A, D, E and K. Certain types of infections, gut surgeries, inflammatory bowel diseases/disorders and some medications can cause malabsorption. In PIs, malabsorption is seen most frequently in the setting of inflammatory bowel disease, small bowel enteropathy and chronic infection. Symptoms of malabsorption include bloating, cramping, gas, diarrhea, fatty stools, malnutrition and weight loss. To diagnose malabsorption, tests such as stool cultures, endoscopy and blood tests are conducted.

PI Conditions That May Result in Malabsorption

Following are some of the main PIs associated with GI disease, which can lead to malabsorption.

X-linked agammaglobulinemia (XLA) or related conditions with absence of immunoglobulins. Diarrhea occurs in about 10 percent to 20 percent of individuals due to chronic infection and/or inflammation. The infections can be from bacteria such as Salmonella, viruses such as enterovirus, or parasites such as giardia, and are difficult to clear due to the absence of secreted antibody. There is an increase in GI cancers as well in XLA.

CD40 ligand deficiency/hyper IgM syndrome. Similar to XLA, there is an absence of many antibodies, including very low levels

of secretory IgA and low levels of IgG. This can lead to chronic infection. Compared with XLA, individuals with CD40 ligand deficiency can have chronic cryptosporidia infection, which is a parasitic infection that can be very difficult to treat and can cause chronic diarrhea. This can also lead to liver disease.

Common variable immunodeficiency (CVID). GI disease is common with CVID, presenting frequently as celiac-like disease with malabsorption or as inflammatory bowel disease. An inflammatory hepatitis (liver inflammation) may be present as well.

Severe combined immunodeficiency (SCID). SCID often presents with diarrhea and failure to gain weight or grow. Because this is a very severe combined (T and B lymphocyte) immunodeficiency, these complications are frequently due to infections.

Chronic granulomatous disease (CGD). GI disease is fairly common in CGD, a neutrophil defect PI, and typically presents as an inflammatory bowel disease similar to Crohn's disease, but with more inflammation in the colon. Because the small intestine is not usually as affected, there often is not as much malabsorption; however, a protein-losing enteropathy may be present, which causes low levels of albumin protein.

IN PIs, MALABSORPTION IS SEEN MOST FREQUENTLY IN THE SETTING OF INFLAMMATORY BOWEL DISEASE, SMALL BOWEL ENTEROPATHY AND CHRONIC INFECTION.

Wiskott-Aldrich syndrome (WAS). Bloody diarrhea from inflammatory bowel disease may be one of the presenting signs in WAS due to the combination of a lymphocyte immunodeficiency and thrombocytopenia.

Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX). With IPEX, the lack of regulatory T cells, the lymphocytes that help prevent autoimmunity, leads frequently to an early onset (frequently infancy) of inflammatory bowel disease that may be severe and require intravenous nutrition. Some presentations of other PIs such as gain-of-function STAT1 can look like IPEX and cause early onset inflammatory bowel disease as well.



Tricho-hepato-enteric syndrome (THE). THE is an extremely rare syndrome that presents in early infancy with severe diarrhea. There is immune deficiency present as well, usually affecting the lymphocytes and sometimes antibody production. These children frequently require intravenous nutrition.

How Is Malabsorption Treated?

Diet. In general, eating a small meal or snack every three to four hours is recommended for malabsorption. Meals and snacks should be low in fiber, fat, lactose and other sugars to help minimize symptoms and promote good nutrition. Since fluid is lost in diarrhea, consuming adequate fluids is also important. The following suggestions meet the needs of most people. However, if patients experience worsening symptoms after eating a recommended food, they should avoid that food until they recover.

To stay adequately hydrated, beverages should be chosen that are low in added sugars and caffeine-free. Recommended choices include water, rehydration beverages (Pedialyte, Gatorade), lactose-free liquid supplements (Boost, Ensure), sugar-free beverages and caffeine-free coffee and tea. Since fruit juices are high in sugar, juice can be diluted with equal parts water. Alcoholic beverages should be avoided.

Lactose is a type of sugar found in milk and other dairy products. Even if patients are not normally lactose-intolerant, they may temporarily be unable to digest lactose during periods of malabsorption. Therefore, lactose-free milk is recommended (Lactaid). Lactose-free milk alternatives such as soy, rice and almond milk are also appropriate. Yogurt is naturally low in lactose and should be well-tolerated. Yogurts containing nuts or dried fruits should be avoided as they are hard to digest. Cheese is also a low-lactose food and can be consumed in moderate amounts. All dairy products consumed should be low-fat or nonfat.

Grains can be a rich source of fiber in the diet so it is important that they are chosen carefully when experiencing malabsorption. Foods made from enriched or refined grains tend to be lower in fiber. Good choices include white bread, white rice and white pasta. When looking at nutrition labels, patients should choose grains that have less than 2 grams of fiber per serving. Whole wheat bread, whole wheat pasta and brown rice should be avoided.

Similar to grains, fruits and vegetables may also be high in fiber. Following a low-fiber diet does not mean avoiding these foods entirely. Low-fiber fruit options include ripe bananas, melons, fruits canned in water or 100% fruit juice and fruit juice

without pulp. All other raw fruits (besides ripe bananas and melons) should be avoided along with dried fruit and fruits canned in heavy syrup. Most well-cooked vegetables without peels or skins are tolerated. However, it is recommended to avoid broccoli, Brussels sprouts, cabbage, corn, cauliflower and greens. All raw and fried vegetables should be avoided as well.

Protein-rich foods are generally well-tolerated as long as they are lean and prepared without added fat. Good choices include tender, well-cooked beef, pork, skinless poultry, fish and eggs. If nut butters are preferred, they should be the smooth kind. High-fat meats, including fried options, sausage, bacon and hot dogs should be avoided.

Foods high in fat may increase diarrhea. Therefore, foods such as butter, margarine, oils, cream, mayonnaise, gravies, heavy sauces, salad dressings and rich baked goods/desserts should be limited. Fats should be limited to no more than 8 teaspoons per day.

Many patients find it helpful to keep a food and symptom diary to help identify well-tolerated foods and foods that make symptoms worse.

Supplements. If malabsorption is prolonged, individuals may require supplemental vitamins, especially the fat-soluble vitamins A, D, E and K. These vitamins are essential for proper health and are involved in vision, immune function, bone health and blood clotting. Vitamins may be provided in an alternative, water-soluble form or provided intravenously.

Malabsorption may result in weight loss because some of the calories consumed are not absorbed by the gut. To provide calories without making symptoms worse, dietitians and doctors may recommend an alternative type of fat called medium chain triglyceride oil (MCT oil). This type of fat is easily absorbed and well-tolerated.

Medications. Medications to treat malabsorption in PI depend on the etiology of the GI disease. It is important to initially confirm the absence of an infection causing the diarrhea. For some infectious causes of persistent diarrhea such as giardia or Clostridium difficile, there are specific antibiotic-type therapies. However, for some infections, treatment is difficult. Norovirus, which is a common cause of stomach flu vomiting and diarrhea can cause persistent diarrhea and lead to malabsorption with some PIs such as with CVID. Therapy is difficult as antiviral medications do not have much activity against Norovirus. There are reports of some people responding to therapies such as oral immune globulin or antibiotics with some activity.

If an infection causing the malabsorption is excluded, then upper or lower endoscopy with biopsies performed by

a gastroenterologist can determine if there is inflammatory bowel disease. In this setting, immune-suppressant medications may need to be given. In CGD, for instance, prednisone and medications such as 6-mercaptopurine (6-MP) may help to reduce the diarrhea. Because these medications weaken the immune system in individuals with already weak immune systems, it is important that a multidisciplinary team is involved, including immunology or infectious diseases, gastroenterology and nutrition specialists.

IF MALABSORPTION IS PROLONGED, INDIVIDUALS MAY REQUIRE SUPPLEMENTAL VITAMINS, ESPECIALLY THE FAT-SOLUBLE VITAMINS A, D, E AND K.

A Multidisciplinary Approach

GI disease and malabsorption are common in PIs and can be caused by disordered inflammation such as autoimmunity or by chronic infection. A multidisciplinary approach with treatment of the underlying causes of the inflammation or infection, along with dietary measures and vitamin/nutrient supplementation, can improve general health, as well as growth and development in children. ■

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