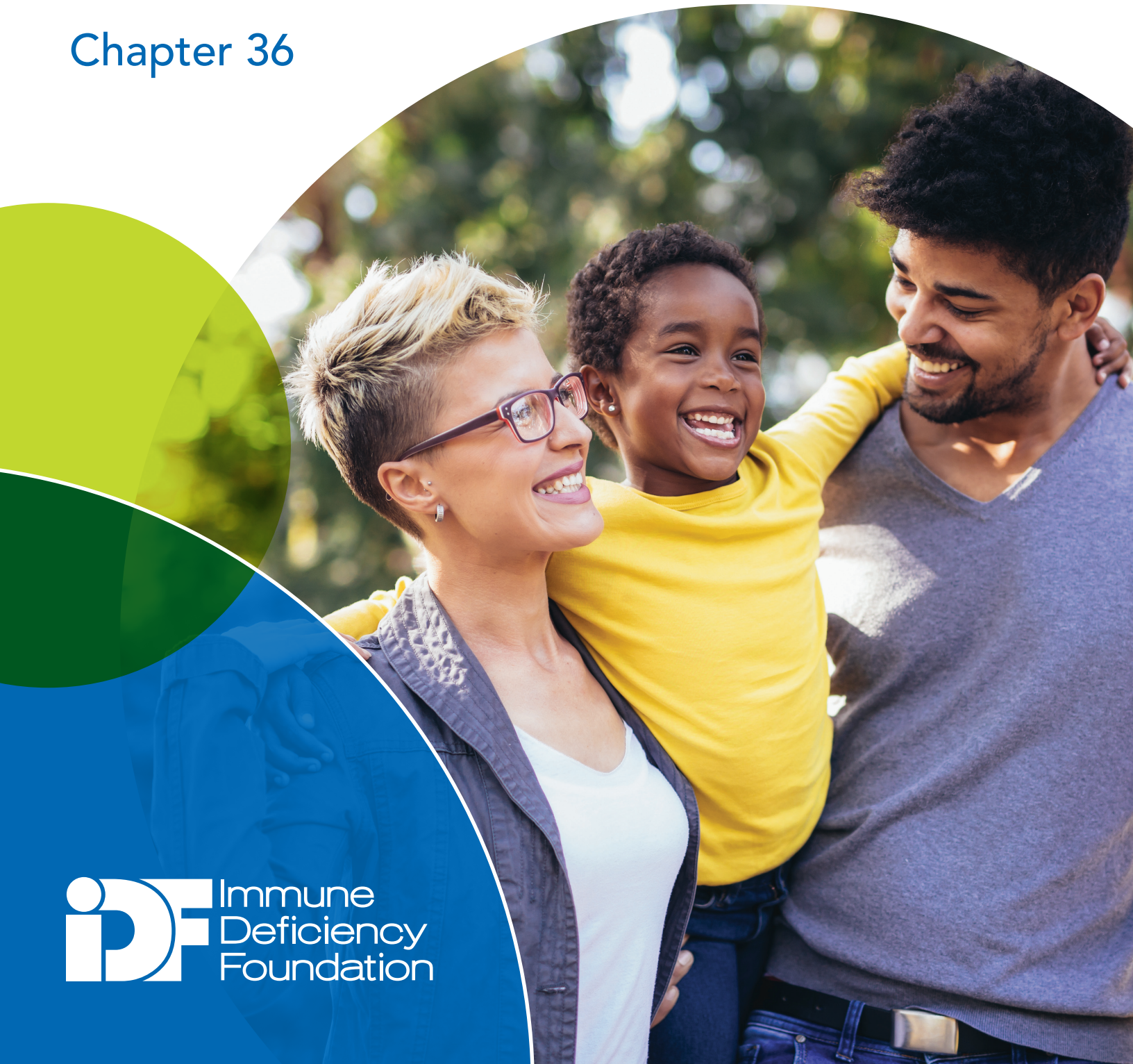
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 36



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Chapter 36

Gastrointestinal (GI) Complications in Primary Immunodeficiency Diseases

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Introduction

The gastrointestinal (GI) tract includes all the organs from the mouth to the anus. This tract is responsible for the intake of nutrients, their digestion, absorption, and final elimination. Understanding the structure and function of the gut can help explain the symptoms and signs of GI complications of primary immunodeficiency diseases (PI).

For instance, the mouth provides for the first processing (chewing, macerating) and digesting (salivary enzymes) of food and the esophagus is a muscular tube that efficiently transfers the swallowed food to the stomach. The stomach further grinds down the food and also continues the process of digestion. The food passes to the small intestine where it mixes with bile (from the liver) and digestive enzymes (from the pancreas) to undergo the most thorough digestion and prepares the digested food for absorption across the bowel wall into the bloodstream. Finally, the remnants of the digested food are passed into the colon where fluid is absorbed back into the body and stool is prepared for elimination.

In the past decade, the rich collection of bacteria and other microbes (the gut microbiome) that live in the colon at the highest concentrations, but is found throughout the GI tract, have been of great interest to researchers who are defining the roles of these organisms in human health and disease. Given the fact that these communities of gut microbes can be affected by the immune deficient state itself (seen in animal models) as well as by repeated exposure to antibiotics (common in individuals with PI), the state of the gut microbiome may also be necessary to consider when evaluating GI complications of PI.

Evaluating GI Symptoms

The types of GI problems that can occur can be quickly linked to the organ involved or sometimes be harder to pinpoint by questioning alone. For instance, trouble swallowing, like food getting stuck, etc., heartburn, and even chest pain can come from the esophagus. Upper abdominal pain and vomiting poorly digested food can come from the stomach. Unexplained weight loss and diarrhea can come from disturbances in small bowel digestion and/or absorption of food while slower bowel pattern with pain and even vomiting after meals could come from small bowel obstruction. Lastly diarrhea and lower abdominal pain along with a sense of stool urgency and pain on elimination can come from the colon. However, many symptoms and signs including abdominal pain, changes in bowel habits, bloating and upset stomach as well as all types of GI bleeding from the upper or lower gut, most often cannot be diagnosed just by asking questions. Often special tests are needed to make an accurate diagnosis.

The most common tests that a GI specialist (gastroenterologist) relies upon include upper endoscopy (where a scope is introduced through the mouth into the GI tract to look at the esophagus, stomach, and upper small bowel) and colonoscopy (where a scope is introduced into the anus to look at the anus to the beginning of the colon and even into the end of the small intestine. Beyond just looking at the lining of the gut for abnormalities, these procedures allow for samples of gut contents to be taken as well as tissue samples (biopsies) for inspection under the microscope. In addition, special x-rays of the intestines and abdomen are used (often to examine the rest of the small bowel that is beyond the reach of the usual scopes) to detect an abnormal appearance. Unfortunately, biopsies cannot be obtained from these radiographic procedures.

There are other studies that can be used to assess the GI tract:

- Stool can be cultured for infectious organisms.
- The upper small intestine can be checked for inappropriate growth of bacteria (called small intestinal bacterial overgrowth) by using a hydrogen breath test.
- The small intestine checked for normal absorption (using d-xylose).
- Special endoscopy studies can be done using a much longer scope (double balloon endoscopy).
- Video endoscopy is done with a pill-sized camera that is swallowed. As it travels through the bowel, pictures are taken.
- Manometry (pressure monitoring) can be done to assess the function of the esophagus. This measures the strength and coordination of muscular contractions.
- Monitoring of pH can be done to assess for abnormal acid exposure that could cause damage to the esophagus and gut mucosa.

Major Types of GI Complications in PI

The major GI complications fall into three main categories: infectious, idiopathic inflammatory/autoimmune, and neoplastic (cancer). Certain types of PI seem to increase the risk for gastrointestinal complications (from mild to severe). Individuals with Common Variable Immune Deficiency (CVID) and Chronic Granulomatous Disease (CGD) have some of the most frequent and significant gut manifestations, and these are discussed in more detail below. It should be appreciated, however, that not every individual with PI will necessarily have GI complications, and if GI disease develops, it may not always be a direct result of the PI.

GI Complications by Specific PI Diagnosis

Selective IgA Deficiency

Selective IgA Deficiency (SIgAD) is generally asymptomatic and without GI complications. However, SIgAD is associated with a higher frequency of celiac disease. Special attention to proper screening tests is needed (use of genetic testing as well as IgG-based serum antibodies) for these people. People with SIgAD can also be affected by increased infections with gut pathogens as in CVID. Individuals with SIgAD may acquire infections with a protozoa called Giardia lamblia when swimming in lakes and streams, so they should be avoided. Chlorinated pools and oceans are usually fine. SIgAD is also associated with enlargement of the lymph nodes in the gut (nodular lymphoid hyperplasia) that can be associated with malabsorption. Associations between SIgAD and autoimmune intestinal disease occurs including chronic hepatitis, biliary cirrhosis, ulcerative colitis and regional enteritis.

Common Variable Immune Deficiency

Individuals with Common Variable Immune Deficiency (CVID) can have high rates of gut infections (up to 60% of individuals might experience at least one) despite the use of IgG replacement. Among the infectious agents, Giardia lamblia, non-typhoidal Salmonella, and Campylobacter jejuni are mostly seen, but Cryptosporiudium may also be found. People with CVID, like those with SIgAD, can also be affected by increased infections with gut pathogens and may acquire infections with a protozoa called Giardia lamblia when swimming in lakes and streams. Individuals with CVID should avoid lakes and streams because of this potential infection, but chlorinated pools and oceans are usually fine.

Clostridium difficile and viruses (cytomegalovirus) may be encountered in people with CVID. C. difficile usually occurs when people are taking antibiotics that kill good bacteria as well as bad pathogenic bacteria. Because of the wide use of antibiotics in individuals with CVID, one would think that the occurrence of C. difficile infections would be higher compared to the normal population; however, this has not been found to be true.

People with PI do have a higher rate of gastric Helicobacter pylori infection than do people with normal immune systems. Infection with H. pylori is important to detect as it is a World Health Organization (WHO) Class 1 carcinogen with chronic infection associated with gastric cancer.

Another GI infection that can lead to persistent diarrhea is Norovirus that can be very difficult to treat; individuals need to be very vigilant on cruise ships where Norovirus infections have been commonly reported.

Finally, small intestinal bacterial overgrowth (SIBO), a condition where collections of bacteria normally found in the lower GI tract are growing at high concentrations in the upper GI tract (where they interfere with nutrient digestion and absorption causing diarrhea and weight loss) is present in up to 30% of individuals with CVID with chronic GI symptoms.

The autoimmune/inflammatory GI complications of CVID include an idiopathic enteropathy that is an intestinal disease of unknown cause that affects the small bowel. The bowel looks normal to the eye but appears inflamed and damaged when looked at through the microscope. This condition typically causes symptoms of very chronic diarrhea combined with inability to absorb nutrients leading to severe weight loss. Much less frequently, obvious ulceration resembling Crohn's disease might occur. CVID-associated autoimmune disease involving the GI tract also includes type II gastritis that can lead to loss of acid production and vitamin B12 deficiency (pernicious anemia).

Nodular lymphoid hyperplasia also occurs in CVID and can lead to chronic diarrhea. Lastly, cancer complications of intestinal lymphoma and gastric adenocarcinoma (related to autoimmune gastritis) have been reported.

Chronic Granulomatous Disease (CGD)

The most common gastrointestinal complaints in individuals with CGD are abdominal pain and diarrhea (with or without rectal bleeding). GI symptoms usually begin before age 10, sometimes preceding the diagnosis of CGD.

While infectious diarrhea (especially Salmonella and C. difficile) occur in CGD, an inflammatory bowel disease also develops:

- In the mouth, ulcers and dental abscesses cause pain and difficulty eating; in the esophagus, feeding difficulties can result from narrowing by strictures (scarring) and altered muscle function related to granulomatous inflammation and fibrosis;
- In the stomach, loss of function and volume due to thickened wall leads to vomiting, pain, and weight loss;
- In the small and large intestine, diarrhea, bowel obstruction (large granulomata block the gut), rectal bleeding and rectal pain can result from ulcers, anal fissures and abscesses.

Feeding difficulties and the chronic inflammatory state itself predispose to growth delay that often affects children with CGD.

Liver abscesses also can complicate CGD in up to 45% of individuals. These individuals often have fever, abdominal pain, fatigue, and, less often, abdominal tenderness and liver enlargement. A high level of suspicion, especially in the setting of fever with or without abdominal pain, should instigate a search for a hepatic abscess.

Types of PI with Less Frequent GI Complications

Individuals with the rare X-linked recessive Wiskott-Aldrich Syndrome (WAS) can develop a non-infectious colitis resembling ulcerative colitis with rectal bleeding increased by the accompanying low platelet counts. Successful hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, for WAS can also be a curative treatment for colitis.

Rare mutations that affect IL-10 activity lead to early onset inflammatory bowel disease (EOIBD). Individuals present with colitis within weeks of birth that has features of Crohn's disease. HSCT can be a curative therapy for this condition.

Individuals with X-linked hyper-IgM syndrome (type 1) can have Cryptosporidia infectious diarrhea, inflammation of the bile ducts (sclerosing cholangitis), cirrhosis and cancer of the hepatobiliary system. Rarely non-infectious colon inflammation has been reported. HSCT, preferably done before chronic complications occur, is the only potential for curative treatment.

X-linked lymphoproliferative syndrome 2 (XIAP deficiency) can present with very early-onset anal skin inflammation in up to 20% of individuals.

Lastly, the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) has the gut lining as a major site affected by inflammation, and this complication produces a watery, sometimes bloody, diarrhea and inability to absorb nutrients. Treatment requires HSCT, but the gut disease may be managed temporarily with corticosteroids and immunosuppressants.

Summary

The GI tract is a major site of symptoms related to PI including increased infections, inflammation, and rarely cancer. Individuals and caregivers with their healthcare providers need to be aware of the potential for the development of GI disorders associated with PI. Early diagnosis and appropriate treatment can be effective in preventing long-term complications of these conditions.

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