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Gastrointestinal Manifestations and Complications of Primary Immunodeficiency Disorders

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SUMMARY

Although the hallmark of PIDs is increased susceptibility to infection, many are associated with and initially present with GI diseases, making routine evaluation of the gut necessary. A history of recurrent infections, clinical and/or histologic features atypical of the usual pattern of GI disease, or a poor response to conventional therapy should prompt further immunologic evaluation. Early diagnosis and treatment may prevent irreversible tissue damage and mortality. In most cases, treatment with replacement immunoglobulin and antibiotics does not reverse or prevent the development of GI disease; therefore, additional immunomodulatory therapies, including, in some cases, organ transplantation, are indicated.

Keywords

Primary immunodeficiency disorder; Gastrointestinal tract; Inflammatory bowel disease; Intestinal disease; Chronic enteropathy; Diarrhea

INTRODUCTION

Primary immunodeficiency disorders (PIDs) comprise more than 300 diseases characterized by defects across humoral, cellular, and phagocytic immunity.^{1,2} Most PIDs share an increased susceptibility to infection, autoimmunity, and organ-specific disease. The gut-associated lymphoid tissue is the largest lymphoid organ in the body, with varying mechanisms for immune regulation; thus, dysregulation of immunity can manifest in a wide array of gastrointestinal (GI) diseases. Because of the complex relationship between antigen tolerance and active immunity, GI disease in PIDs is often intractable and associated with significant morbidity and mortality.

Depending on the nature of the immune defect, GI disease ranges from 5% to 50% in PIDs. Diarrhea and malabsorption are common across many PIDs; whereas enteropathy may be more specific to PIDs with defects in more than 1 component of the immune system. This review highlights GI manifestations of common PIDs, focusing on symptom recognition, appropriate diagnostic studies, and therapies.

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Selective IgA Deficiency

The most common primary immunodeficiency is selective IgA deficiency (sIgAD), defined as the absence of IgA (IgA <7 mg/dL) with normal or elevated levels of other immunoglobulins.² The prevalence varies among ethnicities from 1:100 to 1:1000.³ Though the exact pathogenesis is not well-defined, decreased IgA production results from defects regulating terminal maturation of B-cells into IgA-secreting plasma cells.² Most sIgAD patients are asymptomatic, however, some individuals, more commonly those with concomitant IgG2 subclass deficiency, develop recurrent upper respiratory infections, autoimmune disorders, and allergic diseases.² IgA deficiency is associated with various autoimmune and inflammatory disorders of the gut. A 10- to 20- fold increase risk for celiac in sIgAD has been reported. The link between these diseases may be genetic through shared HLA haplotypes.⁴ The histopathology and symptoms of celiac disease includes crypt hyperplasia, increased numbers of intraepithelial lymphocytes, villous flattening or shortening, and infiltration of the lamina propria with lymphoid cells resulting in malabsorption, diarrhea, steatorrhea, and weight loss. The absence of IgA-secreting plasma cells in intestinal biopsy specimens is characteristic of sIgAD. Thus, traditional screening tests using antiendomysial-IgA, antigliadin-IgA, and anti-tissue transglutaminase (tTG)-IgA antibodies are not reliable for diagnosis. Instead, IgG to deamidated gliadin peptides and tTG-IgG has been reported to be highly specific for diagnosing celiac disease in sIgAD.^{4,5} Treatment includes elimination of gluten-containing foods, resulting in resolution of mucosal lesions and symptoms within a few weeks to months.⁶

Infections causing chronic diarrhea, commonly related to *Giardia lamblia*, occur with increased frequency⁴ because lack of secretory IgA in sIgAD allows for attachment and proliferation of organisms on the intestinal epithelium.⁷ *G lamblia* cysts give rise to trophozoites that colonize the small intestine and trigger bloating, cramping, excessive flatus, and watery diarrhea. Chronic infection can lead to steatorrhea and villusflattening, and disruption of the absorption of lipids and carbohydrates. The degree of mucosal damage is associated with chronicity of infection and can cause irreversible epithelial damage. Diagnosis is made by examination of the stool for cysts or trophozoites of *G lamblia*, though duodenal aspirates may be more conclusive. Giardiasis is treated with amebicides; however, the parasitic burden can be unrelenting, requiring longer courses and/or alternative antimicrobials with more adverse profiles.

Nodular lymphoid hyperplasia (NLH) is characterized by numerous small nodules (usually 5 mm or larger) diffusely distributed along the GI tract in the lamina propria, superficial submucosa of the small intestine, or both. It is occasionally found in the stomach, large intestine, or rectum. NLH tends to have a benign course and usually regresses spontaneously in children. However, in adults, it is often associated with immunodeficiency with unclear prognosis.⁸ Lesions can be associated with mucosal flattening, causing malabsorption, intussusception, and obstruction. Many patients are asymptomatic but may develop abdominal pain, chronic diarrhea, and bleeding. Diagnosis is made via endoscopy or barium study and confirmed by histologic findings, including hyperplastic, mitotically active germinal centers with well-defined lymphocyte mantles and lymphoid follicles. Immunohistochemical staining of sIgAD-associated NLH demonstrates large numbers of

IgM-bearing cells, suggesting compensation for absent IgA.⁹ Although there is no specific treatment, when discovered in the setting of *G lamblia* or *Helicobacter pylori*, eradication of the infection leads to regression of lymphoid nodules. Persistent NLH necessitates small bowel endoscopy with biopsy because NLH has been linked to lymphomas, usually B-cell tumors,¹⁰ and gastric carcinomas.¹¹

Other GI manifestations reported in sIgAD include chronic hepatitis, biliary cirrhosis, pernicious anemia, Crohn disease, and ulcerative colitis, although the prevalence of each is not well-defined.⁴

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA), occurring in approximately 1 in 379,000 live births,¹² is an intrinsic B-cell disorder resulting from a defect in Bruton tyrosine kinase, causing arrest of pre-B cells and failure to generate mature B-cells. Peripheral CD191 B cells are typically less than 2%, leading to a profound reduction in all immunoglobulin classes and depressed or absent humoral responses to specific antigens.²

GI manifestations are less common in XLA than other antibody deficiencies; however, in recent registry surveys, GI manifestations were reported in 35% of XLA patients.¹³ Inflammatory bowel disease or enteritis in up to 10%, suggesting an effect of B cells on regulatory T cells (Tregs).¹⁴ Chronic diarrhea that causes malabsorption is the most common manifestation, along with infectious diarrhea from *G lamblia*, *Salmonella*, *Campylobacter*, *Cryptosporidium*, and rotavirus.^{15–17} Enteroviral infections, namely coxsackievirus and echovirus, can also cause meningoencephalitis.¹⁸ Diagnosis can be made by cultures and/or polymerase chain reaction (PCR) assays. GI infections are treated based on cultures or PCR, and may require longer treatment courses and parenteral nutrition. Rare cases of gastric adenocarcinoma and colorectal cancer have been described.^{19,20}

Hyper-IgM Syndromes

Hyper-IgM (HIGM) syndromes are a group of disorders leading to loss of T-cell-driven immunoglobulin class-switch recombination and/or defective somatic hypermutation with impaired T-cell activation.^{2,21} The most common cause are mutations in the gene-encoding CD40 ligand (CD40L), leading to X-linked disease; less frequent are autosomal recessive mutations in CD40, activation-induced cytidine deaminase, and uracil-DNA glycosylase. An autosomal dominant gain of function mutation in phosphoinositide 3-kinase catalytic delta component²² and mutations in the IKBKG gene nuclear factor-kappa beta (NF- κ B) essential modulator (NEMO),²³ both of which demonstrate elevated serum IgM levels, have also been identified. The estimated frequency of CD40L deficiency is 2 per 1,000,000 male patients, and autosomal mutations are even rarer.²⁴ T-lymphocyte numbers are typically normal and B-cell numbers are normal or slightly reduced. Patients have significantly low or absent levels of IgG and IgA, and normal or elevated levels of IgM. IgG response to vaccinations is poor or nonprotective. Patients with HIGM present early in life with recurrent sinopulmonary bacterial infections due to *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*; however, opportunistic infections are more likely to occur with X-linked HIGM and CD40 defects due to impairment in macrophage and T-cell activation.²⁵

Infectious diarrhea and noninfectious diarrhea are the most frequent GI diseases reported.^{24,26} Infectious diarrhea has been associated with *Cryptosporidium*, *Giardia*, *Salmonella*, or *Entamoeba* infection.^{26,27} CD40L defects are suspected to increase risk of chronic *Cryptosporidium* infection and hepatic complications, including sclerosing cholangitis, cirrhosis, and cholangiocarcinoma requiring liver transplantation.^{21,28,29} Boiling or filtering drinking water can reduce the risk of *Cryptosporidium* infection. One HIGM cohort study found that liver disease with persistent infection at diagnosis was a statistically significant predictor of mortality for patients treated with hematopoietic stem cell transplantation (HSCT).³⁰

Aphthous ulcers, gingivitis, and rectal ulcers can be associated with chronic or intermittent neutropenia.²¹ Malignancies of the liver and GI tract, including biliary duct, hepatocellular carcinomas, carcinoid of the pancreas, glucagonoma of the pancreas, and adenocarcinomas of the liver and gall bladder, have been reported in HIGM.^{24,31}

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID), a heterogeneous PID characterized by the loss of B-cell function, has an estimated prevalence of 1 in 25,000 to 50,000 in whites.^{1,32} The pathogenesis for CVID has not been clearly delineated; however, mutations in an increasing number of genes associated with B-cell development, including BAFF, TACI, ICOS, CD20, CD19, CD81, and CD21, as well as, more recently, NFKB1, CTLA4, LRBA, PI3KCD, STAT3, and IKAROS have been identified.^{1,32} In CVID there are significantly low levels of IgG associated with low IgA and/or IgM, and poor or absent specific antibody responses, with the exclusion of other genetic or medical causes of hypogammaglobulinemia. Decreased numbers of isotype-switched memory B-cells (CD27⁺IgD-IgM⁺), increased numbers of CD21^{low} B cells, and loss of plasma cells in bone marrow and tissue are characteristic. T-cell defects, including excess numbers of memory T cells, loss of T-cell proliferation, and T-cell-associated cytokine defects, can contribute to clinical phenotypes. Patients typically present with recurrent bacterial infections of the respiratory tract, autoimmune disease, granulomatous or lymphoid infiltrative disease, and increased incidence of malignancy.³³ Most patients are diagnosed between the ages of 20 and 40 years, although the diagnosis of CVID may be delayed by 6 to 8 years even after the onset of characteristic symptoms.

Various reviews have noted a higher incidence of both infectious and noninfectious GI diseases in CVID as compared with other antibody deficiencies, perhaps due to more global impairments in cellular function.^{33–36}

Acute or chronic infectious diarrhea is the most common GI symptom associated with CVID (20%–60%), leading to weight loss and malnutrition. Prolonged courses of treatment for eradication may be required.^{36,37} Newly available PCR testing can rapidly detect many bacteria, viruses, and parasites. *G lamblia* is the most common organism; however, *Campylobacter jejuni*, *Salmonella* spp, cytomegalovirus, and (more recently) norovirus have been reported.^{16,35,38,39} Giardiasis can cause villous blunting, increased intraepithelial lymphocytes, and NLH. Despite the frequent use of antibiotics in CVID, there does not seem to be a higher incidence of *Clostridium difficile* infection, possibly due to high titers of anti-*C difficile* antibodies in immunoglobulin preparations that may leak into the gut.⁴⁰ In

contrast, small intestine bacterial overgrowth is common. Diagnosis may be challenging due to intermittent or chronic antibiotic exposure; it requires a hydrogen breath test.

The *H pylori* infection rate in CVID is equivalent to the general population; however, has been associated with gastritis, gastric dysplasia, and gastric cancer in CVID.⁴¹ Previous studies reported a 10-fold increased risk of gastric cancer in CVID compared with the general population; however, recent studies suggest the risk may be lower.^{33,41,42} In 1 cohort; 6 of 8 CVID subjects with *H pylori* infection had gastric intestinal metaplasia and pathologic factors that did not resolve with treatment.³⁸ Therefore, patients who do not respond clinically to treatment should have regular endoscopic surveillance. In another study, CVID-associated adenocarcinomas were found to be diagnosed at a younger age, were of intestinal type, and associated with increased numbers of intratumoral lymphocytes.⁴³

Small bowel villous atrophy is frequent in CVID patients and is frequently associated with severe malabsorption, as well as bloating, diarrhea, and weight loss. Histopathology demonstrates short villi, crypt hyperplasia, intraepithelial lymphocytosis, and (in some cases), an increase in apoptotic bodies in crypt epithelial cells.^{35,38,44} Plasma cells in the lamina propria are absent or reduced and patients do not produce antibodies to tTG, endomysium, or gliadin. Most patients do not respond to a gluten-free diet or bear the HLA genes associated with celiac disease, suggesting alternative dysregulation in disease pathogenesis.^{38,45} Inflammation and symptoms respond to corticosteroid therapy, and immunomodulators such as 6-mercaptopurine (6MP) or azathioprine (AZA) can be used. In cases of severe malabsorption, significant loss of the essential nutrients calcium and zinc, and vitamins A, D, and E, may lead to bone loss and neurologic deficits. Limited use of total parenteral nutrition may be required, with risk of central venous catheter-related infections.

Approximately 10% of CVID patients present with evidence of liver damage, including chronic hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and cirrhosis, most commonly due to nodular regenerative hyperplasia, which can lead to chronic cholestasis and portal hypertension that is difficult to manage.^{32,33,46,47} These patients may be asymptomatic or have fatigue, nausea, vomiting, jaundice, ascites, hepatosplenomegaly, and esophageal varices.^{46,48} Laboratory tests, and other liver function tests, show elevated alkaline phosphatase, with or without significant increases in bilirubin. In CVID, imaging to evaluate structural changes and liver biopsy are required for diagnosis. Biopsy demonstrates nonspecific portal and lobular inflammation, interface hepatitis, lymphocyte infiltration without plasma cells, granulomas, fibrosis, macrovesicular steatosis, and neogenesis of biliary ducts.^{47,48} Current therapies for autoimmune liver disease in CVID include corticosteroids or immunomodulators^{49–51}; ursodeoxycholic acid can be used if biliary damage is evident.⁵² Liver transplant for cirrhosis has been reported⁵³; however, a recent study demonstrated a statistically significant decrease in survival after liver transplantation for CVID-related liver disease (55% at 3 and 5 years).⁵⁴

Malignancies are more frequent in patients with CVID compared with the general population, with lymphomas most commonly reported.^{32,33,42} Non-Hodgkin B-cell lymphomas, Epstein-Barr virus–negative, predominate and often involve extra nodal sites, including the GI tract. CVID patients may develop NLH distributed diffusely throughout the

stomach, ileum, and colon, which can result in intestinal obstruction and intussusception, as well as malabsorption. Immunohistochemical and gene rearrangement studies can be helpful in evaluating cases of atypical lymphoid hyperplasia; however, identification of clonal B-cell expansion may not be diagnostic.⁵⁵ Treatment of CVID-associated lymphoma is similar to that of other lymphomas and may include rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Approximately 10% to 20% of patients develop granulomatous disease. Most are noncaseating granulomas found in the lung, lymph node, or liver; however, they have also been reported in the GI tract, causing diarrhea and weight loss. Granulomatous disease in CVID is difficult to treat but biological therapies such as infliximab and rituximab have been used.⁴⁹

Inflammatory bowel disease (IBD) resembling Crohn or ulcerative colitis has been reported in CVID cohorts^{33–35,44,56} with weight loss, chronic diarrhea, rectal bleeding, abdominal pain, and malabsorption. IBD-like disease is typically diagnosed after the diagnosis of CVID but can be the presenting condition. Endoscopic features include longitudinal ulcers and cobblestone appearance. Histologically, it can mimic lymphocytic colitis, collagenous colitis, and colitis associated with graft-versus-host disease.^{44,57} Tissue pathologic assessment reveals increased numbers of CD81 T-cell infiltrates in the lamina propria, with a paucity of plasma cells. Furthermore, lamina propria mononuclear cells of CVID patients may produce more interleukin (IL)-12 and interferon- γ but not IL-23 and IL-17 compared with controls, suggesting an alternative pathway of inflammation.⁵⁶

Immunoglobulin replacement does not ameliorate IBD-like disease, and use of corticosteroids increases infectious susceptibility. Treatment of CVID-associated colitis includes antibiotics to eliminate bacterial overgrowth, oral budesonide, 5-aminosalicylate agents, 6MP, and AZA.⁵⁸ These medications do not significantly compromise immune function and immunoglobulin replacement helps protect patients from infectious complications to some degree. Gut inflammation in CVID is often difficult to control and unresponsive to standard IBD therapies. Targeted biological therapies, such as infliximab, adalimumab, and ustekinumab, have been used with some benefit in cases of severe enteropathy; however, patients with significant T-cell defects require monitoring for fungal infections,^{59–61} and the duration of treatment is not established. There is some concern that the use of the anti- $\alpha 4\beta 7$ integrin vedolizumab could potentially worsen enteropathy by blocking extravasation of Tregs into the gut mucosa⁶⁰ but this therapy has been used with some success.⁶²

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD), affecting 1 in 200,000 US births, is caused by the inability of phagocytes to produce adequate reactive oxygen metabolites to kill ingested microorganisms owing to abnormalities in components of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, with the most common form being X-linked (gp91^{phox}) and others being autosomal recessive.² Most individuals present with recurrent infections by catalase-positive organisms, such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Aspergillus* sp, *Chromobacterium violaceu*, and *Nocardia* sp, at epithelial

surfaces (skin, gut, lungs), as well as in organs with a large numbers of reticuloendothelial cells, such as the liver.⁶³ Diagnosis is established by flow cytometry demonstrating defective oxidation of dihydrorhodamine by neutrophils and genetics to confirm the inheritance pattern.²

GI involvement occurs in approximately 80% of patients with CGD, ranging from noninfectious diarrhea, oral aphthae, anal fistula, and abdominal pain. The rate of gut involvement has been reported to be higher in X-linked gp91^{phox} deficiency compared with autosomal recessive forms. Intestinal dysmotility, obstruction, and ulcerations can occur along the entire length of the GI tract, with the colon being most frequently involved.⁶³ The presence of perianal disease and rectal abscesses in infancy are clinically suggestive of CGD. Granulomas, giant cells, and macrophages laden with brown-yellow fine pigment are present in gastric biopsies. It is speculated that chronic antigenic stimulation from organisms persisting within phagocytes results in granuloma formation and bowel wall thickening.⁶⁴ These may resolve after treatment with corticosteroids and antibiotics but in many cases require surgery.

An IBD phenotype with gut inflammation is frequently chronic and relapsing.⁶⁴ Patients present with recurrent diarrhea, anal fissures, perirectal abscesses, and GI tract obstruction.⁶⁵ Endoscopy can reveal colonic narrowing, cobblestone pattern, thickened bowel wall, fistulization, pancolitis, patchy friability, pseudopolyps, and/or hemorrhage.^{65,66} Inflammation is typically discontinuous and the perianal area is frequently involved. Histopathologic findings include acute and chronic inflammatory infiltrates, granulomas (usually in the muscularis), submucosal edema, and crypt abscesses. CGD-unique elements include lack of neutrophils, increased eosinophils, eosinophilic cryptitis, and pigment-laden macrophages in the lamina propria.^{66,67} A high rate of antimicrobial antibodies are present in CGD-associated colitis, with 1 study sequencing *Acetobacteraceae* from patient granulomas.⁶⁸

Treatment is not well-defined; however, infectious causes should be excluded and treated with agents targeting bacterial and fungal pathogens. Systemic steroids or ileal-release budesonide has been initiated after biopsy confirmation of granuloma but relapses are common on discontinuation.^{66,69} Steroid-sparing agents, including 5-aminosalicylates, thiopurines, methotrexate, cyclosporine, and antitumor necrosis factor- α , are other options, though reports of infectious complications may preclude their use in CGD.^{66,70} Treatment with granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor have also been investigated.^{71,72} Surgery may be considered in patients with refractory colitis. Bone marrow transplantation can be offered to those with complicated disease and a suitable stem cell match.⁷³

Liver involvement in CGD is common, frequently as abscesses; however, nodular regenerative hyperplasia, portal hypertension, and hepatosplenomegaly also occur. Hepatic abscesses, reported in up to 32% of patients, may be recurrent, numerous, and prolonged.^{69,74} Patients may present with elevated transaminases, fever, abdominal pain, weight loss, and night sweats. *Staphylococcus aureus* is the most common organism identified in liver abscesses. A low threshold for imaging is required for diagnosis. Treatment requires

extensive surgical drainage and debridement with appropriate antimicrobial agents. More recently, the combination of extensive antibiotic therapy with prolonged corticosteroids has been used with success, demonstrating the excessive inflammatory nature of these lesions.⁷⁴ A small portion of CGD patients develop progressive noncirrhotic portal hypertension due to microvasculature damage from repeated liver abscesses. Diminishing platelet counts may be used as a clinical indicator of disease progression.

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) is a group of congenital disorders characterized by severe impairment in T-cell, B-cell, and natural killer (NK) cell function. It is classified as T-B 1 NK1, T-B 1 NK-, T-B-NK1, or T-B-NK- based on the presence or absence of defects affecting these cells. Several molecular defects, including but not limited to mutations in adenosine deaminase, purine nucleoside phosphorylase, Zeta-chain-associated protein kinase 70 (ZAP 70), Janus kinase 3 (JAK3), recombination-activating genes (RAG ½), IL-7 receptor- α, and IL2-Rγ chain have been reported to result in the SCID phenotype.¹ SCID prevalence is estimated at 1 in 50,000 live births, but may be more frequent in cultures with consanguineous marriages. The diagnosis is suspected when the absolute lymphocyte count is less than 2500 cells/mm,³ CD3+ T cells are less than 20%, and proliferative responses to mitogens are less than 10% of the control. Serum levels of immunoglobulins are usually very low and specific antibody responses are impaired. In the absence of bone marrow transplantation, SCID is fatal. Newborn screening using dried blood spots to measure T-cell receptor excision circles has been instituted in almost all states, leading to early recognition of these infants.²

Before newborn screening, infants with SCID presented in the first year of life with severe bacterial, viral, and opportunistic infections, usually of the lung and GI tract; eczematous rashes; and failure to thrive. Oral, esophageal, and perianal candidiasis is common, often affecting nutritional status. Affected children develop severe, chronic diarrhea, malabsorption, and growth impairment early in life. Cultures for bacterial, fungal, and viral pathogens are essential, and identification may require PCR and histopathological examination of the tissue. GI infections with cytomegalovirus and rotavirus are common and may cause persistent diarrhea and malabsorption. Picornavirus, parvovirus, adenovirus, *Salmonella*, *G lamblia*, *Escherichia coli*, and *Cryptosporidium* have also been isolated.⁷⁵ Intestinal biopsies demonstrate hypocellular lamina propria without plasma cells or lymphocytes and villous atrophy occurs in some infants owing to infection-related intestinal damage.⁴⁴ SCID patients receiving blood transfusions or allogeneic bone marrow transplant are susceptible to graft-versus-host disease, which may affect the colon and small intestine.

Immune Dysfunction, Polyendocrinopathy, Enteropathy, X-Linked Syndrome

Immune dysfunction, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is due to the loss of function mutations in the FOXP3 gene, a transcriptional regulator required for Tregs and maintenance of peripheral tolerance.^{76,77} The exact prevalence is unknown. IPEX patients present within the first few months of life with multiple autoimmune manifestations, diabetes mellitus, eczematous dermatitis, thyroiditis, thrombocytopenia, and severe enteropathy.⁷⁸ Serum IgG, IgA, and IgM levels are usually normal; however, IgG can be

reduced from enteric protein loss. Total and antigen-specific IgE are usually elevated and eosinophilia may also be present. Affected patients typically have decreased numbers of Tregs and are unable to suppress T-cell proliferation.⁷⁹ Diagnosis is made by demonstrating decreased FOXP3 protein expression and reduced numbers of Tregs; definitive diagnosis requires gene sequencing to identify FOXP3 gene mutations.⁸⁰

The most consistent feature of IPEX is chronic intractable diarrhea, usually watery but also mucoid or bloody, with failure to thrive due to enteropathy and malabsorption.⁸¹ Histopathologic findings include destruction of small bowel mucosa due to total or partial villous atrophy, ulcerations, and hyperemic mucosa. Involvement of the large intestine can occur with lymphocytic and plasma cell infiltrates in the lamina propria and presence of eosinophils.

Patients are often severely ill due to malnutrition, electrolyte imbalance, or infection by the time IPEX is diagnosed. In the absence of aggressive therapy and HSCT, IPEX can be fatal before 2 years of age.⁸² HSCT has resulted in gut immune reconstitution and improved colitis.^{83,84} Symptomatic treatment of GI disease includes bowel rest with total parenteral nutrition. Immunosuppressive agents, such as cyclosporine A, tacrolimus (FK506), sirolimus, and corticosteroids have been used with some success; however, long-term treatment may be challenging due to toxicity and underlying immune suppression,^{85–87} and may facilitate opportunistic infections.^{88,89}

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KEY POINTS

- The gastrointestinal tract mucosa is the largest immune system organ containing the majority of lymphocytes and immunoglobulins synthesized in the body.
- There is a wide range of infectious and noninfectious GI disease associated with primary immunodeficiency that can be the presenting symptom of immunodeficiency.
- Although symptoms of GI disease in immunodeficiency patients mimic those in immunocompetent patients, the pathologic factors and mechanism of disease are unique.
- Failure of GI diseases to respond to conventional treatment should prompt an evaluation for possible immunodeficiency.
- Further cellular and molecular understanding of the cause of GI involvement may provide more specific therapeutic options.