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Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes

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Abstract

Primary humoral immune deficiencies are characterized by limited antibody responses secondary to either impaired B-lymphocyte development or B-cell responses to T-lymphocyte signals. Given that the gastrointestinal tract is the largest lymphoid organ in the body, it is not surprising that intestinal diseases are common in immunodeficiency. These gastrointestinal diseases can be classified into one of 4 groups, infection, malignancy, inflammatory, and autoimmune, and can mimic other known disease processes, such as inflammatory bowel disease and celiac sprue. The exact pathogenesis of these gastrointestinal disorders in the setting of systemic immunodeficiency is still under investigation. However, studies suggest that defects in antibody deficiency alone do not result in gastrointestinal disease but rather that defects in cellular immunity are also involved. Treatment is difficult given an already immunocompromised state, and often therapy with immunomodulators is required for more severe processes.

Keywords

Immunodeficiency; gastrointestinal disease; humoral immunodeficiency; inflammatory intestinal disease

The mucosal immune system of the gastrointestinal tract faces distinct challenges in the form of commensal bacteria and dietary antigens daily. However, the system must maintain its integrity and be able to distinguish between harmful pathogens and normal intestinal flora. The intestine is the largest lymphoid organ in the body, housing more cells and being the site of greatest production of antibody (secretory IgA) in the body for protection against foreign antigens. T lymphocytes function to regulate the immune response toward viruses, intracellular bacteria, and parasites, whereas B lymphocytes function to protect against bacterial organisms and produce immunoglobulins. In addition, secreted factors, such as gastric acid, lysozyme, lactoferrin, and mucin, serve as innate defenses and further contribute to antimicrobial activities.

Unlike the systemic immune system, where foreign proteins, carbohydrates, and lipids are viewed as potential pathogens and eventually destroyed, the microenvironment and macroenvironment of the gastrointestinal tract is continuously exposed to bacteria, viruses, and parasites but maintains a balance between active immunity, tolerance, and immune suppression. Dysregulation of this controlled/physiologic inflammation in the gut can lead to mucosal injury and diseases such as inflammatory bowel disease (IBD), food allergy, or

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celiac sprue. Therefore it is not surprising that gastrointestinal disease is a common manifestation in patients with an underlying immunodeficiency in whom there is dysregulation in humoral immunity, cell-mediated immunity, or both.

GASTROINTESTINAL DISEASE IN THE SETTING OF SYSTEMIC IMMUNODEFICIENCY

Primary antibody deficiencies are the most common form of primary immunodeficiency diseases. The spectrum of immune deficiency is wide, ranging from a complete lack of B cells and absent serum immunoglobulins in X-linked agammaglobulinemia (XLA) to a reduction in only specific immunoglobulin isotypes, such as in selective IgA deficiency. Despite this broad difference in immunity, the antibody deficiency syndromes share clinical manifestations, such as recurrent sinopulmonary infections, autoimmunity, and gastrointestinal disease.

There are 4 major types of gastrointestinal manifestations associated with humoral immunodeficiencies: infection, malignancy, inflammatory, and autoimmunity (Table I). Treatment for antibody deficiency syndromes is the administration of immunoglobulin (intravenous or subcutaneous), which may reduce the frequency of infections and autoimmune disease, such as immune thrombocytopenic purpura. However, gastrointestinal diseases are not treated with immunoglobulin because preparations contain IgG, which cannot reach the lumen of the intact gut, and very little IgA or IgM. Treatment with oral immunoglobulin has not been successful because IgG is rapidly destroyed before reaching the small intestine. Currently, treatment for gastrointestinal manifestations in antibody deficiency syndromes is guided by successful therapy used for similar disorders in immunocompetent patients, with additional caution when immunosuppressive agents are administered. In this review we will discuss 3 major primary immunodeficiencies and highlight the gastrointestinal manifestations associated with these disorders. The incidence of these manifestations ranged from 20% to 60% in past reviews.[1–7] Our discussion is limited to antibody deficiency syndromes, although patients with combined T- and B-cell immunodeficiencies, such as severe combined immunodeficiency, or defects in innate immunity, such as chronic granulomatous disease, also have gastrointestinal disease. These immunodeficiency syndromes can be further reviewed in the literature; however, we have included them and their associated gastrointestinal manifestations in Table II [1,3–6,8–60] as a reference.

XLA

XLA is an intrinsic B-cell disorder resulting from a defect in Bruton tyrosine kinase, an intracellular kinase, which leads to the maturation arrest of pre-B cells and subsequent failure to generate mature B cells.[61] Laboratory findings include profound reductions in all classes of immunoglobulins and extremely low to absent circulating B cells. Serum IgG levels are usually less than 200 mg/dL, and IgM and IgA levels are less than 20 mg/dL. Peripheral blood $CD19^+$ B-cell counts are commonly less than 0.1%.[8,62] The diagnosis of XLA is usually made after 4 months of age, when maternal antibodies are degraded and the infant develops recurrent sinopulmonary and/or gastrointestinal infections.

Compared with other antibody deficiency syndromes, patients with XLA present with gastrointestinal symptoms less often, presumably because T-cell dysfunction present in other immunodeficiency syndromes drives intestinal disease, and in patients with XLA, T-cell function is generally preserved. Therefore disorders such as chronic malabsorption and villous atrophy are rare in patients with XLA when compared with those with common variable immunodeficiency (CVID), as described below. However, XLA patients who do

have gastrointestinal manifestations usually present with chronic diarrhea and may have malabsorption.[4,6,9] Cases of infectious diarrhea, most commonly caused by *Giardia lamblia*, followed by *Salmonella* species, *Campylobacter* species, and rotavirus, have been reported in patients with XLA and are likely caused by diminished antibody against gut flora. [4,9,10] Another type of infection that can often begin in the gut is an enteroviral infection, such as coxsackievirus and echovirus. Case reports of patients with XLA with enteroviral infections leading to severe neurologic defects have been reported, making this infection clinically important to recognize. [11,12,63] Rare cases of gastric adenocarcinoma, colorectal cancer, and Crohn-like disease occurring in the small bowel in patient with XLA have also been described.[13,64–66] Intestinal biopsy specimens demonstrate a normal morphology and a lack of plasma cells in the lamina propria. There are no germinal centers in the gut-associated lymphoid tissues, and nodular lymphoid hyperplasia (NLH) does not develop, which is in contrast to its common occurrence in other primary antibody deficiencies described below.

Selective IgA deficiency

Selective IgA deficiency is the most common primary immunodeficiency.[62] The majority of IgA-deficient patients are asymptomatic, although the absence of IgA has been associated with the development of recurrent infections and autoimmune diseases (possibly in association with IgG subclass deficiency).[67,68] Patients with concurrent IgG2 deficiency tend to be more symptomatic and present with frequent upper respiratory tract infections and diarrhea.[69,70] The serum IgA level is usually very low to absent (often <5 mg/dL), with normal IgG and IgM levels. Secretory IgA levels are often reduced as well. The pathogenesis of disease is defective terminal maturation of B cells into IgA-secreting plasma cells, causing reduced amounts of serum and mucosal IgA but normal serum IgG and IgM levels.[71] T-cell immunity, as well as natural killer cell activity, appears normal in patients with selective IgA deficiency.[72]

Secretory IgA plays a major role in excluding antigens entering through the mucosal route. Despite IgA being the major antibody in the intestinal mucosa, the prevalence of gastrointestinal disorders in patients with IgA deficiency is not as high as would be expected. It is thought that IgM, which can be transported from the mucosa into the intestinal lumen by the polymeric immunoglobulin receptor, might compensate for the lack of IgA, although several studies have challenged this idea because IgM is rapidly degraded in the intestine.[73–75] Asymptomatic patients with IgA deficiency are generally not treated.[62] If patients manifest gastrointestinal tract disease in the setting of IgA deficiency, they should be treated the same as a patient without this immunodeficiency.

Gastrointestinal infections leading to chronic diarrhea and steatorrhea occur with an increased frequency in patients with IgA deficiency commonly related to *G lamblia*.[1] *G lamblia* cysts, once ingested, excyst and give rise to trophozoites, which colonize the small intestine and cause abdominal cramping, bloating, excessive flatus, and watery diarrhea. Steatorrhea and villous flattening from chronic infection occur because of effacement of the mucosa and disruption of the absorptive capacity for lipids and carbohydrates. The extent of mucosal damage appears to be related to the duration of infection, and some epithelial damage might be irreversible. Luminal IgA might play a role in clearance of this parasite because studies have shown trophozoites on jejunal biopsy specimens from infected patients that stain positively with fluorescein-conjugated anti-human IgA. Presumably the lack of secretory IgA in these patients allows for attachment and proliferation of the organism on the intestinal epithelium, although mouse models have suggested that the actual clearance of this organism is T-cell mediated.[76] The diagnosis is made based on the results of stool examination for cysts or trophozoites of *G lamblia;* however, duodenal aspirates can yield

more positive findings. *Giardia* species infections can be treated with metronidazole but are often unremitting in IgA-deficient patients.

There is a 10- to 20-fold increased risk for celiac disease in patients with IgA deficiency, although the association of these 2 diseases might have a genetic basis because there is sharing of certain HLA-extended haplotypes. Genetic studies demonstrate that 1 important susceptibility locus between celiac disease with IgA deficiency is the ancestral haplotype HLA-A1, Cw7, B8, DR3, DQ2.[14–16,77] However, given the relatively high incidence of IgA deficiency and celiac disease independently, their co-occurrence might be purely coincidental. Secretory IgA can bind to wheat gluten and gliadin; thus in the absence of IgA, there might be abnormal handling of these antigens. IgA-deficient patients with celiac disease demonstrate villous flattening or atrophy on histopathology similar to that seen in nonimmunodeficient patients with celiac disease. Likewise, the gastrointestinal pathology in patients with IgA deficiency and celiac disease responds to a gluten-free diet.[78,79] In contrast, the specific IgA-class antibodies against gliadin, endomysium, and tissue transglutaminase are not produced in IgA-deficient patients, and IgA-secreting plasma cells are absent in intestinal biopsy specimens, [14,17,80–82] making detection of disease and monitoring of therapy challenging. However, serum IgG tissue transglutaminase levels are increased in IgA-deficient patients with coexisting celiac disease and can be used as a diagnostic marker.[83]

Another intestinal abnormality in patients with IgA deficiency is NLH. The diagnosis is made by means of small-bowel enteroscopy or contrast barium studies. These nodules can occur individually but are usually multiple in number and commonly 5 mm or greater in size. They are found largely in the lamina propria, superficial submucosa of the small intestine, or both but occasionally occur in the large intestine, rectum, or stomach. The lesions can be associated with mucosal flattening, leading to malabsorption, and if large enough, the nodules can cause obstruction. Immunohistochemical analyses have demonstrated that these nodules contain large amounts of IgM-bearing cells, suggesting but not proving that this represents an attempt by the intestine to compensate for the absent IgA.[18] NLH reported in patients with IgA deficiency can occur with or without giardiasis and leads to diarrhea and further malabsorption, which might be difficult to treat, although the nodules are exquisitely sensitive to oral steroids.[19] In the setting of IgA deficiency, NLH has been associated but not proved to be a source of the lymphomas (usually of B-cell origin) [84] and gastric carcinomas.[35]

Other associations between IgA deficiency and gastrointestinal diseases include lymphomas, pernicious anemia, [85,86] Crohn disease,[87,88] ulcerative colitis,[89] chronic hepatitis,[90] and biliary cirrhosis,[91] although the actual prevalence of each is not well defined in the literature.

CVID

CVID is the most common symptomatic primary immunodeficiency. The diagnosis of CVID is established based on reduced levels of 2 serum immunoglobulins (ie, IgG and IgA, IgM, or both) at least 2 standard deviations below the age-specific mean values in addition to impaired specific antibody production in response to vaccination *in vivo* or recent infections.[62] It is the failure of B cells to develop normally and differentiate into plasma cells that leads to diminished production of antibody in this disorder.

The molecular basis of CVID is complex, involving defects in both humoral and cell-mediated immunity. B-cell maturation is abnormal, and impaired somatic hypermutation and a lack of isotype-switched memory B cells have been demonstrated.[92–94] Several genes have

emerged in family studies, including mutations of the costimulatory molecule inducible costimulator (ICOS),[95] CD19,[96] and the receptor of B-cell activation factor (BAFF).[97] Mutations in the gene encoding TACI, a transmembrane activator and calcium-modulating ligand interactor, expressed on mature B cells are found in 7% to 10% of patients.[98,99] Impaired T-cell function (proliferation) and signaling have also been reported, including abnormalities in expression and function of the T-cell receptor.[100] Defective cytokine production in patients with CVID has been extensively studied; subgroups of patients with CVID have shown increased plasma TNF, IL-7, and IL-4 levels and reduced levels of IL-10, IL-2, and IEN-γ.[101–105]

Because of the complex proposed pathogenetic mechanisms for this disease, CVID is a heterogeneous disorder presenting with a variety of clinical manifestations. Most common are recurrent sinopulmonary infections, although autoimmunity and gastrointestinal disease are also quite prevalent and may be the initial presentation of CVID.[13,20] Unlike patients with XLA and IgA deficiency, gastrointestinal disease is more common in patients with CVID, further suggesting that T-cell dysfunction contributes to the pathogenesis of intestinal disease. Why some patients with CVID have gastrointestinal disease and others do not is still not well understood. Studies have demonstrated that although there are considerable numbers of early B cells found in the intestinal tract, there is an absence of plasma cells and a generalized lack of all immunoglobulin-staining cells, especially IgA.[106]

Similar to other primary immunodeficiencies, diarrhea is reported as a common gastrointestinal manifestation associated with CVID. A recent study found that gastrointestinal infections were more frequent in patients with undetectable serum IgA levels (47 [36%] of 131 patients) compared with patients with residual IgA production, further explaining why diarrhea does not improve in patients receiving treatment with intravenous immunoglobulin (IVIG; which does not replace IgA or IgM [107]). Hermans et al[108] reported that 60% of patients with CVID had chronic diarrhea with steatorrhea, giardiasis, or both; achlorhydria; an abnormal Schilling test result; or morphologic abnormalities on small intestinal biopsy. Hermaszewski and Webster[4] reported 40% of their patients with CVID having diarrhea with or without malabsorption. In another large study of 248 patients with CVID, 53 (21%) reported gastrointestinal disease.[3] A more recent study of Italian patients with CVID, found chronic diarrhea in 23% of patients at the time of diagnosis, and in a study reported from Iran, this was found in 56.6% of patients.[10,109]

G lamblia has been reported as a common cause of diarrhea associated with CVID. Treatment with metronidazole is generally effective but often requires a prolonged course, and patients exhibit a high relapse rate, reflecting the inability of the immunodeficient patient to eradicate this organism. Other pathogens, such as *Cryptosporidium parvum*, cytomegalovirus, *Salmonella* species, *Clostridium difficile*, and *Campylobacter jejuni* have also been implicated as a cause of diarrhea. Symptoms include watery diarrhea and abdominal cramping. The stool culture is not especially sensitive, but duodenal aspirates/ biopsy specimens reveal organisms attached to surface epithelium. Given the frequency of antibiotic use in these patients for upper respiratory tract infections, it is reasonable to suspect *C difficile* as a cause of intractable diarrhea. However, *C difficile* is not reported frequently in patients with CVID, possibly because of underreporting and symptomatic treatment. In addition, monthly infusions of IVIG containing high antibody titers against *C difficile* might reduce the incidence of this infection.[110,111]

Helicobacter pylori infection is commonly found in patients with CVID and might account for the incidence of chronic gastritis seen in approximately a third of patients.[109] Given the association between *H pylori* and gastric carcinoma and lymphoma,[112] routine screening and eradication is appropriate.

Another common manifestation observed in 24% to 50% of duodenal samples from patients with CVID is villous flattening in the small intestine. This appears to be an immune-mediated/ inflammatory phenomenon grossly resembling what is seen in celiac sprue.[13,21,22,108] Although bacterial overgrowth is reported in CVID, it does not appear to be associated with this villous flattening.[13] The villous atrophy can lead to malabsorption with weight loss, diarrhea, and associated findings, such as hypoalbuminemia, anemia, and low blood $CD4^+$ lymphocyte levels.[21] Despite its gross resemblance to celiac disease, several features distinguish the villous flattening of celiac disease from that seen in association with CVID. First, plasma cells are absent in intestinal biopsy specimens from patients with CVID, whereas in classic celiac disease, plasma cells are increased along with an increase in secreted IgA and IgMantibody. Second, in patients with CVID, serumantibodies against gliadin, reticulin, tissue transglutaminase, and endomysium are not detected secondary to poor antibody production. Third, gluten withdrawal is ineffective in patients with CVID and villous flattening, allowing for persistent malabsorption and weight loss. The poor response to gluten withdrawal supports an alternate pathogenesis for this disorder. Patients should have adequate replacement with water-soluble vitamins and antiresorptives for prevention of osteoporosis. In severe cases of malabsorption, an elemental diet or total parenteral nutrition may be required (although an indwelling catheter is a source for infection).[22] Given that this syndrome is not caused by bacterial overgrowth, treatment with antibiotics is often futile. Low-dose corticosteroids can be used with caution; however, higher doses can lead to a significant risk of opportunistic infections.

Inflammation of the small and large intestine is reported to be present in 2% to 13% of patients with CVID.[5,113] Hermaszweski and Webster[4] reported a prevalence of IBD in patients with CVID of 4%, with both Crohn-like and ulcerative colitis-like diseases observed. The IBD in patients with CVID is distinct from classic IBD and shares histologic features consistent with lymphocytic colitis,[114] collagenous colitis,[115] and colitis associated with graft-versus-host disease[13] Clinically, these inflammatory disorders present with diarrhea, rectal bleeding, and abdominal pain. It appears that patients with CVID may be predisposed to develop IBD-like disease because treatment with immunoglobulin does not reverse the colitis, suggesting that this predisposition toward inflammation is driven by T cells or other immunoregulatory defects.[3,23] This has been supported by several studies. Most recently, Mannon et al[23] demonstrated diffuse histologic inflammatory changes in duodenal and colonic mucosa, including villous flattening, increased lamina propria and intraepithelial lymphocytes, and epithelial apoptosis, in patients with CVID with gastrointestinal symptoms. In addition, lamina propriamononuclear cells from these symptomatic patients with CVID produced significantly higher levels of IFN-γ and IL-12. When this was compared to cytokines produced by lamina propria mononuclear cells from patients with Crohn disease, the patients with CVID did not produce the cytokines IL-23, IL-17, or TNF-α, as seen in patients with Crohn disease, suggesting an alternate pathway of inflammation. The management of IBD occurring in association with CVID is generally the same as for immunocompetent patients, although gut inflammation in patients with CVID might be more difficult to control. Antibiotics, such as metronidazole or ciprofloxacin; anti-inflammatory agents, such as 5-aminosalicylic acid; and rapidly metabolized steroids (budesonide)[116] or suppositories can be used. Immunomodulators, such as azathioprine/6-mercaptopurine, can be used safely given the fact that the doses used are too low to affect T- and B -cell function. Several groups have demonstrated improvement by using infliximab with careful monitoring for fungal infections in patients with severe T-cell defects.[105,117]

NLH, especially in the small intestine, has been observed in 8% of patients with CVID in a recent study.[109] The cause is still unknown, but it is thought that the lymphoid hyperplasia is a compensatory response to the antibody deficiency, although treatment with IVIG has not been shown to correct this. Immunofluorescence studies demonstrate an expanded

population of B lymphocytes but few or no plasma cells. In most cases, no treatment is required; however, hyperplasia can be associated with mucosal flattening, causing malabsorption, diarrhea, and weight loss, and large nodules can lead to intestinal obstruction. In the past, *Giardia* species infections were thought to be the cause of the lymphoid nodules, although Hermans et al[108] were not able to demonstrate the disappearance of the nodules despite treatment with metronidazole. NLH can persist unchanged for years, and whether this precedes the development of intestinal lymphoma in patients with CVID remains controversial.[5,114]

The cause of bacterial overgrowth in humoral immunodeficiency might be related to decreased luminal antibody (specifically IgA) in the small bowel. Overgrowth can be diagnosed based on breath tests and a clinical response to antibiotic therapy. Many patients have concurrent achlorhydria and atrophic gastritis with pernicious anemia. Pernicious anemia should be evaluated in patients with CVID reporting numbness in the extremities and signs of B12 deficiency. The diagnosis of pernicious anemia in patients with CVID is often made at an early age; 20 years earlier compared with a patient who is immunocompetent with classic pernicious anemia. [24] Because of the lack of antibody production in patients with CVID, no autoantibodies to intrinsic factor or parietal cells are detected in CVID-associated pernicious anemia, suggesting that a T cell–mediated process might be involved. On biopsy, there is gastric atrophy and lymphocytic infiltration in the mucosa with an absence of plasma cells in patients with CVID.[24] Treatment in patients with CVID, however, is similar to that in those with classic pernicious anemia, with monthly replacement of B12 and monitoring of the gastric mucosa for changes associated with malignancy.[25]

Previously, patients with CVID were identified to be at increased risk for viral hepatitis, possibly hepatitis C, acquired through blood-borne contamination of IVIG therapy.[3,4,118,119] Today, the risk for hepatitis C virus is reduced with improvements in the screening of blood products; however, patients with CVID and chronic hepatitis C virus appear to be at increased risk for the development of cirrhosis or acute liver failure.[26,27] Liver disease, including primary biliary cirrhosis and what appears to be autoimmune hepatitis, has been observed in patients with CVID with persistently increased liver enzyme levels.[3,4,120,121] In a recent histologic investigation of 10 patients with CVID with increased liver enzyme levels, hepatomegaly, and/or splenomegaly, biopsy specimens demonstrated mild portal and mild-to-moderate lobular chronic inflammation, and in all specimens plasma cells were absent. [28] Four patients had small numbers of scattered portal granulomas, lobular granulomas, or both, and 3 of these patients had a coexisting diagnosis of sarcoidosis. The cause of this “CVID hepatitis” is not clear, but the investigators speculate that it is a consequence of chronic inflammation of the gastrointestinal tract with excessive translocation of luminal antigens into the liver.

CONCLUSION

Patients with humoral immunodeficiency would benefit from routine evaluation of the gut given the frequency of gastrointestinal manifestations. Often these gastrointestinal disorders resemble classic forms of diseases, such as ulcerative colitis or celiac sprue, but they lack characteristic features typical of the classic disease, suggesting an alternate pathogenesis. These intestinal diseases do not necessarily correlate with the severity of underlying immunodeficiency, and treatment of the antibody deficiency with replacement immunoglobulin in most cases does not reverse progression of the gastrointestinal disease. Other immunodeficiency disorders, such as severe combined immunodeficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome, although not described here in detail, also present with gastrointestinal manifestations. Therefore patients presenting with

unusual or treatment-resistant intestinal disease should be evaluated for primary immunodeficiency. Prompt recognition and diagnosis of gastrointestinal disease in cases of immunodeficiency syndromes will improve the quality of life and prevent long-term sequelae, although further studies are needed to optimize therapy for this unique group of patients.

Abbreviations used

CVID	Common variable immunodeficiency
IBD	Inflammatory bowel disease
IVIG	Intravenous immunoglobulin
NLH	Nodular lymphoid hyperplasia
XLA	X-linked agammaglobulinemia

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TABLE I

Gastrointestinal diseases associated with humoral immunodeficiencies

Infectious	*Giardia* species, *Campylobacter* species, *Salmonella* species, rotavirus, enterovirus, bacterial overgrowth
Inflammatory	NLH, celiac disease, microscopic colitis, ulcerative colitis, Crohn disease, villous atrophy
Autoimmune	Pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, achlorhydria
Neoplastic	Adenocarcinoma of the stomach, lymphoma

TABLE II

Immunodeficiency syndromes and associated gastrointestinal disease

Immunodeficiency	Defect	Gastrointestinal manifestation
CVID	Multiple defects: TACI, inducible costimulator, T cell, cytokine; failure of B cells to differentiate into plasma cells	Chronic diarrhea, NLH, villous atrophy, IBD-like disease, pernicious anemia, hepatitis[3–5,13,20–34]
Selective IgA deficiency	Gene defect unknown; defective maturation of B cells into IgA-secreting plasma cells	Diarrhea, celiac sprue, NLH[1,14–19,35]
XLA	X-linked; defective Bruton tyrosine kinase → no mature B cells	Gastrointestinal disorders rare, chronic diarrhea, malabsorption [4,6,8–12,36]
Chronic granulomatous disease	Multiple defects: X-linked caused by defects in CYBB encoding the $gp91^{phox}$ component of NADPH oxidase; autosomal recessive caused by defects in NCF1, NCF2, or CYBA defects in components of NADPH oxidase	Granulomatous colitis, perianal fistulae, hepatic abscess, gastric outlet obstruction, small-bowel obstruction, granulomatous stomatitis, oral ulcers, esophageal dysmotility[37–41]
Wiskott-Aldrich syndrome	X-linked; defective WASP → poor cytoskeletal organization and defective signal transduction	Colitis, bloody diarrhea, malabsorption [42–44]
Severe combined immunodeficiency	Multiple defects: RAG1/2, JAK3, CD45, CD3 chain, ZAP70, Artemis, Ligase 4, IL2RG, IL-7Rα, ADA → defects in T and B cells	Chronic diarrhea, oral candidiasis, IBD[45–49]
Bare lymphocyte syndrome	Multiple defects: RFX5, RFXAP and CIITA defects lead to MHC class II deficiency; TAP defects lead to MHC class I deficiency	Diarrhea, progressive liver disease, sclerosing cholangitis[49–53]
X-linked hyper-IgM syndrome	X-linked; defective CD40 ligand on T cells → dysfunction in B-cell receptor for isotype switching	*Cryptosporidium* species enteropathy, sclerosing cholangitis, gastrointestinal carcinoma[54–59]
Immune dysregulation, polyendocrinopathy, enteropathy (IPEX) syndrome	Mutation in forkhead box P3 gene (*FOXP3*) → no FOXP3 protein or mutant protein with abnormal regulatory T-cell function	Severe enteropathy with watery, often bloody diarrhea associated with eosinophilic inflammation [60]

TACI, Transmembrane activator and calcium-modulating ligand interactor; *NADPH*, nicotinamide adenine dinucleotide phosphate; *NCF*, neutrophil cytosolic factor; *CYBB*, cytochrome b beta subunit; *WASP*, Wiskott-Aldrich syndrome protein; *RAG*, recombinase-activating gene; *JAK*, Janus kinase; *ZAP70*, zeta-chain–associated protein kinase 70; *IL2RG*, interleukin-2 receptor gamma; *ADA*, adenosine deaminase deficiency; *RFX5*, regulatory factor X, 5; *RFXAP*, regulatory factor X-associated protein; *CIITA*, class II transactivator; *TAP*, transporter associated with antigen processing; *FOXP3*, forkhead box protein 3.