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Gastrointestinal Disorders Associated with Primary Immunodeficiency Diseases

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Abstract

There are now 354 inborn errors of immunity (primary immunodeficiency diseases (PIDDs)) with 344 distinct molecular etiologies reported according to the International Union of Immunological Sciences (IUIS) (Clin Gastroenterol Hepatol 11: p. 1050-63, 2013, Semin Gastrointest Dis 8: p. 22-32, 1997, J Clin Immunol 38: p. 96-128, 2018). Using the IUIS document as a reference and cross-checking PubMed (www.ncbi.nlm.nih.pubmed.gov), we found that approximately one third of the 354 diseases of impaired immunity have a gastrointestinal component [J Clin Immunol 38: p. 96-128, 2018]. Often, the gastrointestinal symptomatology and pathology is the heralding sign of a PIDD; therefore, it is important to recognize patterns of disease which may manifest along the gastrointestinal tract as a more global derangement of immune function. As such, holistic consideration of immunity is warranted in patients with clinically significant gastrointestinal disease. Here, we discuss the manifold presentations and GI-specific complications of PIDDs which could lead patients to seek advice from a variety of clinician specialists. Often, patients with these medical problems will engage general pediatricians, surgeons, gastroenterologists, rheumatologists, and clinical immunologists among others. Following delineation of the presenting concern, accurate and often molecular diagnosis is imperative and a multi-disciplinary approach warranted for optimal management. In this review, we will summarize the current state of understanding of PIDD gastrointestinal disease involvement. We will do so by focusing upon gastrointestinal disease categories (i.e., inflammatory, diarrhea, nodular lymphoid hyperplasia, liver/biliary tract, structural disease, and oncologic disease) with an intent to aid the healthcare provider who may encounter a patient with an as-yet undiagnosed PIDD who presents initially with a gastrointestinal symptom, sign, or problem.

Keywords Primary immunodeficiency diseases · Gastrointestinal disease · Inflammatory bowel disease · Very early onset IBD · Molecular diagnosis · Immunogenetics

Introduction: Bowel Disease Epidemiology in PIDD

Gastrointestinal (GI) manifestations in primary immunodeficiency diseases (PIDDs) run the gamut of inflammatory disease, infectious complications, chronic diarrhea, and structural/oncologic disease (Table 1). Inflammatory manifestations alone are a principal finding of 28 molecularly described PIDDs [1]. The treatment of the underlying disease, for example, hematopoietic stem cell transplantation in IL10/IL10 receptor deficiency, may completely reverse the inflammatory bowel disease (IBD) manifestations [2].

The prevalence of individuals presenting with gastrointestinal disease can approach or exceed 50% depending upon the distinct PIDD classification. In one large series of patients with antibody deficiency, for example, over 40% of the patients were affected in some way along the gut [3]. A thorough literature review suggests that the International Union of Immunological Sciences (IUIS) category "combined immunodeficiencies associated with syndromic features" has the greatest number of disorders

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Table 1 Reported GI disease—PIDD associations by IUIS category

Immunodeficiencies affecting cellular and humoral immunity		GI manifestation
T-B+ SCID	X-linked SCID (IL2RG deficiency)	IBD, autoimmune hepatitis, diarrhea, celiac disease
T-B-SCID	RAG1 deficiency	Hepatomegaly, diarrhea, IBD
	RAG2 deficiency	IBD, diarrhea, malignancy
	Artemis (DCLRE1C) deficiency	IBD, diarrhea, Liver Dz
	DNA PKCs deficiency	Colon cancer
	DNA ligase IV deficiency	Hepatomegaly, diarrhea
	ADA deficiency	IBD, diarrhea
Combined immunodeficiencies	DOCK2 deficiency	EOE
	X-linked hyper IgM (CD40L def.)	Hepatitis, cirrhosis, cholangiocarcinoma
	CD40 deficiency	Diarrhea, cholangiocarcinoma
	ICOS deficiency	IBD, autoimmume pancreatitis, hepatitis
	CD3γ deficiency	IBD, diarrhea
	MHC class I deficiency (TAP1/TAP2)	Colon cancer, hepatocellular carcinoma
	DOCK8 deficiency	IPEX-like disease, sclerosing cholangitis, diarrhea
	MST1 deficiency	Hepatocellular carcinoma
	TCRα deficiency	Diarrhea, hepatomegaly
	MALT1 deficiency	IPEX-like disease
	IL21/IL21R deficiency	Early onset IBD, intestinal cancer, chronic cholangitis, diarrhea, biliar fibrosis
Combined immunodeficiencies with associated or syndromic features		**GI manifestation**
Immunodeficiency with congenital thrombocytopenia	Wiskott-Aldrich syndrome	Enteropathy, Hematochezia
	WIP deficiency	IBD
DNA repair defects	Ataxia-telangiectasia	GI malignancies, hepatic steatosis
	Nijmegan breakage syndrome	Celiac-like disease
	Bloom syndrome	Colorectal cancer
	ICF1-4	Infectious diarrhea
	PMS2 deficiency	Colorectal cancer
Thymic defects with additional anomalies	DiGeorge syndrome	Esophageal atresia
	CHARGE a/w *CHD7* mutations	Esophageal fistula
	CHARGE a/w *SEMA3E* mutations	Tracheoesophageal fistula
Immuno-osseous dyplasias	Cartilage-hair hypoplasia	Hirschsprung's disease, small bowel lymphoma
	Schimke immuno-osseous dysplasia	Enteropathy, chronic diarrhea
Hyper IgE syndromes	AD-HIES/STAT3 deficiency	IBD, esophageal dysfunction
	Comel-Netherton syndrome	Enteropathy
Dyskeratosis congenita, myelodysplasias	TERC deficiency	Liver cirrhosis
	TERT deficiency	Liver fibrosis
	Coats Ppus a/w STN1 deficiency	GI telangiectasias—hematochezia
	Coats plus a/w CTC1 Deficiency	Liver cirrhosis, liver failure, esophageal varices
Defects of vitamin B12 and folate	Transcobalamin 2 deficiency	Glossitis, protein losing enteropathy (PLE)
Anhidrotic ectodermaldysplasia w PIDD	NEMO/IKBKG deficiency	IBD, enterocolitis, chronic diarrhea
	IKBA gain of function mutation	Recurrent *Salmonella typhimurium* infection
Calcium channel defects	ORAI-1 deficiency	Enteritis, GI candidiasis
	STIM1 deficiency	Chronic diarrhea
Other defects a/w syndromic features	PIDD w multiple intestinal atresia (TTC7A deficiency)	Multiple intestinal atresia
	HOIP deficiency	GI telangiectasis, chronic diarrhea
	Lymphangiectasia-lymphedemia syndrome (CCBE1 deficiency)	Intestinal lymphangiectasia, PLE, cholestasis

Table 1 (continued)

	Kabuki syndrome (KMT2D deficiency)	Extrahepatic biliary atresia, pyloric stenosis
Predominantly antibody deficiencies		GI manifestation
Severe reduction in immunoglobulins with decreased or absent B cells	X-linked agammaglobulinemia	IBD, chronic diarrhea, NHL
	μ heavy chain deficiency	Recurrent enteroviral induced vomiting/diarrhea
	Igα deficiency	Chronic/recurrent diarrhea
	BLNK deficiency	Recurrent enteroviral induced vomiting/diarrhea
Severe reduction in ≥ 2 IgG subtypes/CVID phenotype	*PIK3CD* mutation (GOF)	Primary sclerosing cholangitis
	PIK3RI deficiency (LOF)	Chronic diarrhea
	PTEN deficiency (LOF)	Hepatomegaly, hamartomatous polyps
	Trichohepatoenteric syndrome (TTC37)	Chronic diarrhea
	ATP6AP1 deficiency	Hepatic dysfunction
Severe reduction in IgG and IgA with normal/elevated IgM and normal B cells (hyper IgM)	AID deficiency	IBD, autoimmune hepatitis
	MSH6	Lynch syndrome, GI malignancies
Functional IgG deficiency w normal B cells	Selective IgA deficiency	NLH, celiac disease, chronic diarrhea
Diseases of immune dysregulation		GI manifestation
Familial hemophagocytic lymphohistiocytosis (FHL syndromes)	FHL5 (STXBP2 deficiency)	Chronic intractable diarrhea
FHL syndromes w hypopigmentation	Chediak-Higashi syndrome	IBD, hepatomegaly
	Griscelli syndrome, type 2	Recurrent diarrhea, hepatomegaly
Regulatory T cell defects	IPEX	Enteropathy, intractable Diarrhea, PLE
	CD25 deficiency	Phenocopy of IPEX
	CTLA4 haploinsufficiency	Enteropathy, gastritis, atrophic gastritis
	LRBA deficiency	Enteropathy, gastritis, atrophic gastritis
	STAT3 GOF	IBD
	BACH2 deficiency	IBD, “Lymphocytic Colitis”
Autoimmunity with/without lymphoproliferation	APECED	IPEX-like phenotype
	ITCH deficiency	Enteritis, autoimmune hepatitis
	JAK1 GOF	Eosinophilic enteritis
	Prolidase deficiency	IBD, hepatomegaly
Immune dysregulation with colitis	IL10/IL10Ra/IL10Rb deficiency	IBD/VEOIBD
	NFAT haploinsufficiency	IBD
Susceptibility to EBV and lymphoproliferation	XIAP deficiency	IBD, VEOIBD
Congenital defects of phagocyte number or function		GI manifestation
Congenital neutropenias	Glucose-6-phosphate catalytic subunit 3 (G6PC3) deficiency	IBD
	Glycogen storage disease type 1b	IBD, candidal esophageal strictures
Neutrophil motility disorders	LAD type 1	IBD, hirschsprung’s disease, necrotizing enterocolitis
	LAD type 3	GI bleeding
	Specific granule deficiency	Intractable diarrhea
	Schwachman-Diamond syndrome	Exocrine pancreatic insufficiency, autoimmune hepatitis
	Cystic fibrosis	Intestinal obstruction, exocrine pancreatic insufficiency, biliary tract cancer
Defects of respiratory burst	Chronic granulomatous Disdase (X-linked, autosomal recessive)	IBD, dysmotility, fistula formation, granulomatous GI disease
Defects in Intrinsic and innate immunity		GI manifestations
Mendelian susceptibility to mycobacterial disease	IL12 and IL23β1 chain deficiency	Salmonellosis
	IFN-γ receptor 1 and 2 deficiency	EBV associated lymphoma, intestinal pseudotuberculosis

Table 1 (continued)

Epidermodysplasia verruciformis (HPV)	EVER1 deficiency	Gastric adenocarcinoma
Herpes simplex encephalitis	TRAF3 deficiency	NLH
Predisposition to mucocutanous candidiasis	STAT1 GOF	IPEX-like disease, enteropathy, esophageal candidiasis and stenosis, esophageal squamous cell carcinoma
TLR signaling pathway defect w bacterial susceptibility	MyD88 deficiency	Yersinia enterocolitica associated mesenteric adenitis and terminal ileitis
Other inborn errors of immunity w non-hematopoietic Issues	NBAS deficiency	Acute febrile-illness induced liver failure
Autoinflammatory disorders		GI manifestations
Type 1 interferonopathies	X-linked reticulate pigmentary disorder	IBD, chronic diarrhea
	CANDLE	Hepatomegaly, steatosis
Inflammasome defects	Familial Mediterranean fever	IBD, hepatomegaly, infantile NEC
	Mevalonate kinase deficiency	Diarrhea, vomiting
	Familial cold autoinflammatory synd. 2	Episodic abdominal pain
	NLRC4-macrophage activation synd.	IBD, infantile enterocolitis, diarrhea
Non-inflammasome-related conditions	TRAPS	Recurrent vomiting and diarrhea, IBS
	PAPA syndrome	IBS
	ADAM17 deficiency	Chronic diarrhea, plasma cell duodenitis
	Majeed syndrome	Hepatomegaly
	DIRA	Hepatomegaly
	IL36 receptor antag. def. (DITRA)	Cholangitis
	SLC29A3 mutation	Pancreatic exocrine insufficiency, hepatomegaly
	Otulipenia	Chronic diarrhea
	A20 deficiency	GI mucosal ulceration
	ADA2 deficiency	Mesenteric polyarteritis nodosa
Complement deficiencies		GI manifestations
	C1s deficiency	Autoimmune hepatitis
	Ficolin 3 deficiency	NEC
	C1 inhibitor deficiency	Hereditary angioedema—bowel wall edema

CANDLE chronic atypical neutrophilic dermatitis with lipodystrophy, *CGD* chronic granulomatous disease, *DIRA* deficiency of the interleukin-1 receptor antagonist, *GOF* gain of function, *IBD* inflammatory bowel disease, *IBS* irritable bowel syndrome, *LAD* leukocyte adhesion deficiency, *LOF* loss of function, *PLE* protein losing enteropathy, *NEC* necrotizing enterocolitis, *NLH* nodular lymphoid hyperplasia, *PAPA* pyogenic sterile arthritis, pyoderma gangrenosum, acne, *TLR* Toll-like receptor, *TRAPS* TNF receptor associated periodic syndrome, *VEOIBD* very-early onset inflammatory bowel disease

associated with GI disease (Fig. 1). However, the category "diseases of immune dysregulation" has the most disorders where GI pathology is a consistent part of the phenotype (Table 2).

There is now a precedent to consider IBD as a distinct PIDD [4]. In general, the incidence of pediatric IBD appears to be on the rise with a more rapid increase among young children noted in some studies [5, 6]. While distinct monogenic IBD-like disease is more common in younger individuals and the preponderance of IBD is considered to be polygenic, Mendelian diseases affecting immunity represent a subsection of those with severe disease in early life. Among patients with PIDD, IBD-like disease may present along a spectrum of age from neonatal onset to the teenage years and be clinically indistinguishable from classic IBD [7–9]. A modified Montreal Classification of IBD suggests the following age-based categories, beginning with neonatal (0–28 days) onset and followed by infantile (1–24 months), very-early (< 6 years), early (< 10 years), and pediatric onset IBD (< 17 years) [7, 10–12].

Because the immune system is inextricably linked to normal function of most organ systems, and PIDDs present with variable expressivity, it is not surprising that diverse GI tract pathology can be noted in the same PIDD. For example, common variable immunodeficiency (CVID), the most common symptomatic PIDD has at least four clinically distinct gastrointestinal manifestations [13, 14]. Patients with CVID may suffer from recurrent diarrhea with GI infections such as *Giardia* have inflammatory disease such as villous atrophy, malignancy such as gastric cancer, and present with autoimmune GI-spectrum disease such as autoimmune hepatitis [14]. In the context of PIDD GI disease in general, infections and inflammatory/autoimmune disease may present with diarrhea, malignancy may present with obstruction, or protean manifestations of cancer such as weight loss, anemia, and overwhelming fatigue. Because of the disruption of normal GI function in many PIDDs and the manifold ways that GI pathology may be present in PIDDs, it is important to consider an underlying defect in normal host response for patients presenting with severe, unusual, and/or recurrent gastrointestinal pathologies.

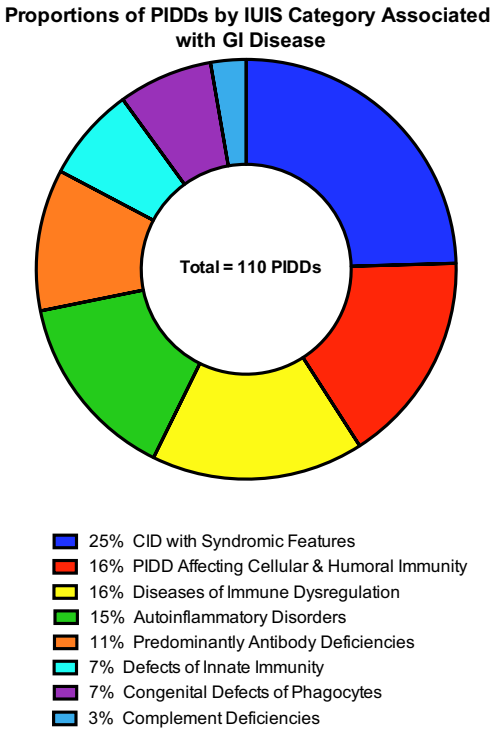

Fig. 1 Proportions of PIDDs by IUIS category associated with GI disease

Primary Immunodeficiency Diseases Associated with Inflammatory GI Pathology:

Of the major associations, inflammatory GI disease is the most prominent among the 354 IUIS classified PIDDs (Table 2) [15]. Patients may present with early life inflammatory bowel disease signs, adult onset IBD-like symptoms, or with involvement of gastrointestinal structures such as hepatobiliary disease [16–18].

T Cell Disorders

Immune Dysregulation, Polyendocrinopathy, X-Linked Syndrome

The immune dysregulation, polyendocrinopathy, X-linked syndrome (IPEX) is associated with mutations in the *FOXP3* gene, concomitant reductions in number and function of T-regulatory cells, and severe, inflammatory enteritis [19–21]. These patients often present with early life failure to thrive and chronic diarrhea. Histopathological evidence of enteritis may be evidenced by villous blunting and inflammatory infiltrates on biopsy of the small intestine [21–24]. While IPEX is considered a primary immunodeficiency owing to the central defect in T-regulatory cells (CD3+CD25+FOXP3+), routine immune testing may be normal or minimally affected. Blood counts, lymphocyte phenotyping, proliferation studies, and immunoglobulin quantity may be normal. Often, serum IgE and eosinophils are elevated and the gastrointestinal manifestations are present within the first months of life [25–27]. In addition to the intractable diarrhea, even with bowel rest, patients may also present with severe food allergy [27]. Treatment is aimed at control of enteritis with immune suppression, management of endocrinopathies such as thyroid disease and diabetes, and eventual hematopoietic stem cell transplantation with a suitably matched HLA donor [28].

CD25 Deficiency

Disorders presenting like IPEX ("IPEX-like") but with normal *FOXP3* gene sequencing exist and may present with early life, severe enteritis, and diarrhea. Caudy et al. described a patient with typical IPEX presentation (severe diarrhea and insulin-dependent diabetes mellitus at 6 weeks of age) but *FOXP3* gene sequencing was normal [29]. That patient also suffered infections which were suspicious for a T cell immunodeficiency (CMV pneumonitis, CMV enteritis, EBV lymphadenitis) and ultimately developed severe eczema, hepato-splenomegaly, and chronic diarrhea with protein-losing enteropathy. The patient was treated with immunomodulation (glucocorticoids, rituximab, IgG replacement, cyclosporine, and antimicrobials) and ultimately required hematopoietic stem cell transplantation (HSCT) (J. Verbsky, personal communication, January 31, 2018). The molecular diagnosis was suspected when CD25 was notably absent on T cells by flow cytometry. Subsequent sequencing of the *CD25* gene revealed a likely pathogenic variant.

Combined Immunodeficiencies

Severe Combined Immunodeficiency

Human severe combined immunodeficiency (SCID) patients suffer from susceptibility to nearly all pathogens and may present with infections of any organ system, including the gastrointestinal tract. Given the advent of newborn screening for SCID, most patients are now detected prior to onset of severe disease [30]. However, it is possible for patients with SCID to present with bowel disease as a complication of immune dysregulation with hypomorphic mutations or "leaky SCID." For example, a case of CD3 deficiency SCID has been reported to include inflammatory bowel disease with intractable diarrhea as the initial presentation. This infant had marked improvement in his gastrointestinal disease symptoms after HLA-identical sibling transplantation [31].

Other Combined Immunodeficiencies

Patients with combined immunodeficiency that do not meet criteria for SCID, but have significant impairment of the T and B cell compartments, may present with inflammatory

Table 2 Major primary immunodeficiency—gastrointestinal disease associations

PIDD associated with inflammatory GI pathology	
T cell disorders	CD25 deficiency
	IPEX
Combined immunodeficiencies	DOCK8 immunodeficiency syndrome (DIDS)
	NEMO deficiency
	SCID (e.g., CD3 deficiency)
B cell disorders	Common variable immunodeficiencies (CVID)
	X-linked agammaglobulinemia (XLA)
Neutrophil disorders	Chronic granulomatous disease (CGD)
	Glucose-6-phosphate catalytic subunit 3 (G6PC3) deficiency
	Leukocyte adhesion deficiency type 1 (LAD-1)
Diseases of immune dysregulation	CTLA4 haploinsufficiency
	Hemophagocytic lymphohistiocytosis (HLH)
	IL10/IL10R deficiency
	IL21/IL21R deficiency
	LRBA deficiency
	STAT3 loss of function (autosomal dominant hyper-IgE)
	STAT3 gain of function
	STAT1 gain of function
	Wiskott-Aldrich syndrome
	X-linked lymphoproliferative disease type 2 (XLP2; XIAP)
Other diseases	APECED
	BACH2 deficiency
	ICF/ZBTB24 deficiency
	ITCH deficiency
	NFAT5 deficiency
	NLRC4-macrophage activation syndrome
PIDDs commonly associated with diarrhea	
	Chronic granulomatous disease
	CVID
	Familial HLH type 5 (STXBP2 deficiency)
	Tricohepatoenteric syndrome (THES)
	X-linked agammaglobulinemia
	X-linked hyper IgM syndrome (CD40/CD40L deficiency)
PIDDs associated with nodular lymphoid hyperplasia	
	CVID
	Selective IgA deficiency
PIDDs associated with liver and biliary tract disease	
	AID deficiency
	APECED
	Chronic granulomatous disease
	CVID
	ITCH deficiency
	X-linked hyper IgM syndrome
PIDDs Associated with Structural Bowel Disease	
	Cartilage-hair Hypoplasia (CHH)
	DiGeorge syndrome/22q11.2 deletion syndromes
	STAT3 loss of function/hyper IgE syndrome
	TTC7A deficiency
PIDDs associated with malignancy of the GI tract	
	CVID
	X-linked agammaglobulinemia
	X-linked hyper IgM syndrome

gastrointestinal symptoms. For this reason, complete immune phenotyping should be undertaken in the patient with non-classical IBD, early or very-early onset IBD, or inflammatory gastrointestinal symptoms which are severe, unusual, or non-responsive to typical first-line therapies. For example, the dedicator of cytokinesis 8 (DOCK8) immunodeficiency syndrome (DIDS), an autosomal recessive hyper IgE syndrome, has been associated with an IPEX-like phenotype including

severe enteritis [32]. This atypical presentation of a rare inborn error of immunity underscores the utility of unbiased genetic evaluation (i.e., whole exome/whole genome sequencing) when the highest priority molecular etiology is ruled out or where the candidate gene list is very large [33].

Other combined immunodeficiencies such as ectodermal dysplasia with immunodeficiency (i.e., NEMO/IKBKG deficiency) may present with an element of gastrointestinal disease such as colitis [34–36]. In this scenario, the patient's constellation of symptoms is recognizable as part of a larger syndrome potentially before onset of GI disease. In NEMO deficiency, inflammatory colitis can be severe and immune modulation is important as hematopoietic stem cell transplantation may not cure the bowel disease [37]. Published case reports describes IBD in a fraction of NEMO deficiency patients which involves the small and large intestines and is associated with severe intestinal ulcerations, villus blunting, and cell tufting [38–40]. Biopsies show edema, mucosal ulceration, and superficial crypts with abundance of neutrophils within the lamina propria, consistent with acute inflammation. This enterocolitis is unresponsive to antimicrobials and may only improve with anti-inflammatory therapy [39].

B Cell Disorders

X-Linked Agamaglobulinemia

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency where mutations in Bruton's tyrosine kinase (BTK) result in defective pre-BCR signaling, impaired B cell survival, and arrest in maturation at the pre-B cell stage. Although the classical clinical presentation is agammaglobulinemia with recurrent bacterial infections, some patients may present with symptoms of abdominal pain, diarrhea, weight loss, failure to thrive, nausea, vomiting, and varying degrees of gastrointestinal inflammation. Among patients in one large XLA patient cohort ($n = 200$), 71 (35%) patients had gastrointestinal manifestations, with the most common being diarrhea, abdominal pain, GERD, and gastroenteritis [41]. A spectrum of histologic changes among XLA patients includes chronic-atrophic gastritis, atrophied villi with increased mucosal lymphocytes resembling celiac disease, nodular lymphoid hyperplasia, and inflammatory bowel disease [42, 43]. Interestingly, the prevalence of inflammatory bowel disease in the USIDNET (United States Immunodeficiency Network) XLA patient cohort was found to be 8 times higher than the reported prevalence in the general population and up to 20 times higher in another study [41, 44]. There were no significant differences between T cell subsets and immunoglobulin levels of XLA patients with IBD/enteritis compared to those without GI manifestations [41]. Given the lack of a clear biomarker, all XLA patients require longitudinal monitoring for the development of inflammatory GI complications.

Common Variable Immunodeficiencies

CVID patients typically suffer recurrent sino-pulmonary infections such as otitis media, sinusitis, and pneumonia. In addition, gastrointestinal diseases are prevalent and may be the initial presentation of disease [42, 45]. Gastrointestinal complications are reported in 20–60% of the patients with CVID, and infectious diarrhea is the most common problem, occurring in 27–50% of the patients [42, 45–49]. Other GI diseases observed in CVID patients include inflammation of the small or large intestine resembling Crohn's disease or ulcerative colitis, villous flattening resembling celiac disease, pernicious anemia, nodular lymphoid hyperplasia, lymphoma or gastric adenocarcinoma, and collagenous enterocolitis [42, 47, 50–60].

Like XLA, the incidence of IBD in CVID patients exceeds that of the general population, ranging from 2 to 13% [54, 58]. Histopathology analysis of CVID patients with inflammatory colon disease shows endoscopic and histopathological features that overlap considerably with Crohn's disease or ulcerative colitis. [54, 61, 62]. Additionally, CVID-related enteritis can exhibit features similar to those of untreated or refractory celiac disease. Villous atrophy is identified in 24 to 50% of the duodenal samples from patients with CVID compared to 0.5–1% typically found in the general population [42, 53–55]. These confounders sometimes lead to misdiagnosis of IBD or celiac disease prior to CVID diagnosis. One difference that can help recognition of patients with CVID is the paucity of plasma cells in their biopsy (shown in 68% of the patients) [54]. The current understanding about GI disease in CVID patients underscores importance of considering a broad immunologic disease in patients with IBD and/or celiac disease and concomitant extragastrointestinal manifestations.

Neutrophil Disorders

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is an inherited immunodeficiency disorder associated with dysfunction of the nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase (NOX)) system [63, 64]. In CGD, NOX deficiency impairs microbial killing in the phago-lysosome related to deficient reactive oxygen species (ROS) and hydrogen peroxide generation [65–67]. In particular, CGD patients are susceptible to catalase positive organisms [68]. Two thirds of the patients have an X-linked form of CGD stemming from mutations in the gene *CYBB*, which encodes gp91phox subunits

of NOX and is associated with an early disease presentation, a severe clinical course, and the development of inflammatory disorders [69, 70]. In contrast, bi-allelic mutations of the other NOX subunit genes (*CYBA*/p22phox, *NCF1*/p47phox, *NCF2*/p67phox, *NCF4*/p40phox) generally present with less-severe phenotypes [71, 72]. Appropriate antibiotic prophylaxis and the advent of using azole-class antifungal drugs for *Aspergillus* species prophylaxis have greatly reduced the frequency of bacterial and fungal infections. Now inflammatory GI disorders are the most prominent complications among CGD patients older than 10 years, affecting over 80% of such patients [69, 72].

Gastrointestinal involvement is a common initial feature of CGD and often precedes the diagnosis in up to 17% of the patients [73]. Intestinal dysmotility, obstruction, and ulceration may also occur along the entire length of the GI tract, with the colon being the most frequently affected site (in 15–44% of the cases) [72–75]. Almost all CGD colitis patients are predisposed to perianal disease such as fistula-in-ano and rectal abscesses [75–77]. Similar to XLA and CVID, GI involvement in CGD can mimic Crohn's disease and lead to misdiagnosis, especially in the absence of a suggestive history of recurrent infections [74]. Endoscopic and histopathologic appearance of IBD in CGD is similar to Crohn's disease, ranging from mild erythema to deep ulcers with discontinuous inflammation, granulomas, and transmural inflammatory infiltrate [75, 76, 78]. In contrast, micro-granulomas, lack of neutrophils, increased eosinophils, and the presence of pigment-laden macrophages in the lamina propria are more indicative of CGD-specific histopathology [75, 76, 78–80]. Patients with X-linked CGD are more than twice as likely to develop IBD compared to patients with AR CGD [69]. Chronic unresolved microbial infections and ensuing dysregulated inflammatory response are thought to underlie CGD-gut inflammation; however, the complete etiology of GI inflammation in CGD remains unclear [81–83].

Leukocyte Adhesion Deficiency Type 1

Leukocyte adhesion deficiency type 1 (LAD-1) is an autosomal recessive defect in neutrophil vascular adhesion and migration stemming from mutations in the *ITGB2* (beta2 integrin family receptor beta-chain; CD18) gene [84]. Impaired integrin function results in deficient neutrophil chemotaxis, inability to extravasate into tissue sites and form pus resulting in sneutrophilia within the vascular compartment [85]. Classically, patients present with omphalitis and delayed separation of the umbilical cord; however, this is an infrequent finding and the development of non-purulent infections of the skin and mucous membranes is more commonly noted in LAD-1 patients [86, 87].

Gastrointestinal findings such as diarrhea, organomegaly, and inflammatory disease of the rectum with perirectal abscess formation are reported in LAD-1 patients [87]. Adding to the IBD phenotype in LAD-1, Jain et al. reported a patient with co-existent Crohn's disease who underwent HSCT with resolution of infections and IBD complications [88]. Others have also reported on clinical presentations of LAD-1 patients who appear to have Crohn's disease [89–91]. Importantly, Uzel et al. pointed out that while the Crohn's-like inflammation in LAD-1 is transmural with fat-wrapping and stricture formation, it is distinct from classical IBD histologically in that neutrophilic inflammation is absent [91]. These descriptions of inflammatory gastrointestinal disease among LAD-1 patients suggest that IBD is a noteworthy component of the phenotype in this PIDD.

Glucose-6-Phosphate Catalytic Subunit 3 Deficiency

Severe congenital neutropenia (SCN) due to bi-allelic mutations in the *G6PC3* (glucose-6-phosphatase catalytic subunit 3) gene was originally reported to be associated with structural heart disease, urogenital anomalies, and prominent superficial veins [92]. Subsequently, patients with IBD have been reported further expanding the phenotype of this variant of SCN [93].

A report of longitudinal care in a French cohort of 14 G6PC3 deficient patients revealed three patients with biopsy proven Crohn's disease and several with steatorrhea [94]. The IBD patients in this report responded to steroid mono-therapy, and onset of inflammatory bowel symptoms began between 6 and 10 years of age. In another report, Begin et al. described a patient with G6PC3 deficiency associated with T cell lymphopenia who presented with SCN early in life and development of oral and genital aphthous ulcers at the age of 6 years [95]. At 10 years of age, she underwent colonoscopy which revealed a hepatic angle colonic stricture. This patient's IBD progressed with development of enterocutaneous fistulae necessitating hemi-colectomy. Initiation of infliximab therapy allowed for complete remission of inflammatory bowel disease. Given current understanding about this form of SCN, it is possible that subsequent patients will prove IBD to be an important phenotypic component of the G6PC3 deficiency syndrome.

Diseases of Immune Dysregulation

The largest subgroup of the PIDD's associated with gastrointestinal inflammatory pathology involves diseases of immune dysregulation [15]. These disorders include hemophagocytic lymphohistiocytosis (HLH), autoimmune polyendocrinopathies, "CVID-plus" diseases, cytokine disorders, and aberrations in signal transduction which cause lymphoproliferative disease among others.[15]

Hemophagocytic Lymphohistiocytosis

The collection of multi-organ involved diseases with pathological inflammation referred to as HLH often involves the gastrointestinal system. In HLH, immune cells hyperproliferate as a result of an underlying genetic defect in cytotoxicity (i.e., primary HLH), a precipitating infection such as Epstein-Barr virus (EBV), or due to a medication or other underlying inflammatory state (i.e., secondary HLH) [96–99]. Patients often come to medical attention with prolonged fever, organomegaly, and cytopenias along with a markedly elevated serum ferritin [100].

In HLH, gastrointestinal disease may arise secondarily from the immunologically dysregulated state or it may be the principal driver of HLH. Because underlying viral infections may trigger secondary HLH in patients with primary IBD, identification of the basis for HLH is critically important [101, 102]. In primary HLH, treatment of the underlying pathological inflammation is expected to improve global inflammatory disease; whereas, eradication of the secondary cause of HLH could improve the clinical state. Therefore, a rigorous genetic evaluation is warranted in a patient with clinical and laboratory findings of HLH so that precise treatment can be employed and genetic counseling provided.

In primary/familial HLH, most forms of disease known to date involve disruption of normal cellular mechanisms related to cytotoxic granule transport, membrane fusion, and exocytosis or function of lytic contents. In particular, Familial HLH Type 5 (FHL5) involves intractable diarrhea without inflammation (see as follows in the section on "Primary Immunodeficiency Disease-Associated Diarrhea"); while, other primary genetic forms of HLH such as the X-linked lymphoproliferative disease with susceptibility to EBV (XLP2; XIAP/BIRC4 deficiency) involve a Crohn's-like bowel disease which may be indistinguishable from typical Crohn's disease (CD) [99, 100, 103].

In XIAP (X-linked inactivator of apoptosis) deficiency (XLP2), multisystem autoinflammation is a consistent phenotypic feature which includes late-onset severe Crohn's-like disease; it is also in the differential diagnosis for infants presenting with neonatal IBD [104, 105]. Patients with XLP2 may present with classical Crohn's disease and other inflammatory disease without evidence of EBV exposure. In contrast to XLP1/SAP deficiency, the characteristic features of fulminant EBV-driven disease, dysgammaglobulinemia (typically hypogammaglobulinemia), and susceptibility to lymphomas are part of the clinical phenotype but are less consistently noted in XLP2 [99]. Patients with XLP2 also differ from those with XLP1 in that while EBV-driven HLH is the most common cause of death in early life, it is not always encountered [106]. In XIAP deficiency/XLP-2, diagnosis is often made by sequencing *XIAP* and/or copy number assessment of the gene. Treatment of XLP-2 requires allogeneic HSCT which cures the underlying inflammatory bowel disease due to autoinflammation; whereas traditional Crohn's disease therapies are ineffective [107].

CTLA4 Haploinsufficiency

Disruption of the important T cell negative regulator CTLA-4 causes multisystem autoimmune disease with autoimmunity [108]. In part, abnormal CTLA-4 function relates to its important role in controlling T-regulatory cell effector functions which results in defective suppressor activity of immune responses [109, 110]. Additionally, CTLA-4 is important for depletion of the CD80 and CD86 critical co-stimulatory molecules required for normal antigen-presenting cell activation of T cells [111].

In humans, heterozygous damaging variants in the *CTLA4* gene may present with Evan's syndrome, inflammatory joint disease, vitiligo, and enteritis with recurrent infections [112, 113]. While enteropathy is a common feature of CTLA-4 haploinsufficiency (also termed "CHAI" or CTLA-4 haploinsufficiency with autoimmune infiltration), these patients present with signs of lymphoproliferation (organomegaly and lymphadenopathy) as well as cytopenias and CNS inflammation among other systemic immune dysregulation findings [113]. Current treatment of CHAI has included abatacept (CTLA-4-immunoglobulin fusion protein) and sirolimus for mitigation of autoimmune complications [113, 114]. Hematopoietic stem cell transplantation has also proven successful in CHAI with GVHD complications noted in a significant number of patients curbing enthusiasm for transplantation except in the most severe cases [115].

LRBA Deficiency

Patients with mutations in the lipopolysaccharide-responsive vesicle trafficking, beach, and anchor containing (LRBA) deficiency have clinical findings which are largely indistinguishable from CHAI patients but arise from an autosomal recessive inheritance pattern [115]. They also display organomegaly, cytopenias, organ-specific autoimmunity, and hypogammaglobulinemia. The clinical link between CHAI and LRBA deficiency (also referred to as "LATAIE" LRBA deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration, and enteropathy) is connected at the molecular level. Lo et al. showed that LRBA deficiency results in a secondary loss of CTLA-4 stemming from impaired trafficking and substantial reduction in surface expression of the CTLA-4 protein on T-regulatory cells and activated T cells [116].

Clinically, patients with LATAIE often present with symptoms earlier in life compared to those with CHAI [115]. Features of lymphoproliferation and cytopenia are reminiscent of autoimmune lymphoproliferative syndrome (ALPS);

whereas, patients presenting with hypogammaglobulinemia are often diagnosed with CVID. In particular, immune dysregulation (lymphoid cell encroachment upon non-lymphoid organs) is a prominent feature. Enteropathy, which can be indistinguishable from that seen in IPEX patients, was a significant finding in 62% of a recently described cohort [117]. Additionally, chronic autoimmune hepatitis was noted in 14% of this cohort.

From an immunological phenotype perspective, LATAIE patients often display leukopenia and neutropenia. Lymphocyte subpopulations (CD4, CD8, etc.) and mitogen-induced proliferation were often normal; however, the double negative T cell counts were elevated in 38%. Mild reductions in the T-regulatory and NK compartments were noted, but most significant abnormalities were noted in the B cell compartment where total CD19+ cells, switched memory B cells (CD27+IgD−), and plasmablasts ($CD21^{low}CD38^{low}$) were low in the majority of patients. Most LATAIE patients display abnormalities in immunoglobulin quantity and/or quality [117].

Treatment of LATAIE patients is often aimed at reducing immune dysregulation with immunomodulating medications such as glucocorticoids, cyclosporine, mycophenolate mofetil, sirolimus, and abatacept [117]. Abatacept, in particular, has shown promise in controlling the systemic immune dysregulation in LATAIE patients [116]. Immunoglobulin replacement is often needed, and HSCT has been performed with variable success [117].

Disorders of JAK-STAT Signaling

The signal transducer and activator of transcription (STAT) and Janus kinase-associated proteins (JAKs) are ubiquitous and important signaling proteins which mediate critical cellular processes such as proliferation, apoptosis, and the development/differentiation in immune and non-immune cells [118]. Human diseases associated with JAK-STAT dysfunction include the autosomal dominant loss of function STAT3 hyper-IgE syndrome and STAT3 gain of function associated with lymphoproliferation and inflammatory bowel disease among other immunological perturbations [119–122]. In patients with *STAT1* gain of function mutations, chronic mucocutaneous candidiasis may result; additionally, patients with an IPEX-like phenotype associated with enteropathy have been reported [123].

Inflammatory gastrointestinal disease is a prominent component of the clinical phenotype in patients with activating/gain of function variants in *STAT3*. In two recent reports, Milner et al. and Haapaniemi et al. described several patients with lymphoproliferation and a wide range of gastrointestinal disease [119, 121]. Among these individuals, enteropathy, hepatitis, achalasia, small bowel wall thickening, celiac disease, and lymphocytic colitis were found. Patients from these cohorts also suffered severe and unusual infections with mycobacteria, herpes viridae, and bacteria [119, 121]. Treatment with biological agents (anti IL-6, JAK inhibitors) and HSCT has shown promise in these cohorts.

IL-10 and IL-10 Receptor Deficiency

Patients with IL-10 and IL-10 receptor deficiency often present within the first few months of life with severe inflammatory bowel disease (neonatal IBD); in particular, perianal disease is often severe [2]. These individuals are prone to enterocutaneous and recto-vaginal fistulas. They form abscesses, and the robust inflammatory state is frustratingly unresponsive to anti-inflammatory therapies [124, 125]. Due to the severe nature of the bowel and rectal disease, some patients have required partial or complete colectomy. Hematopoietic stem cell transplantation should be considered due to the severe inflammatory bowel disease, susceptibility to bacterial and mycobacterial infections, recalcitrant folliculitis, and inflammatory joint disease seen in these patients [2, 125, 126].

The IL-10 axis disorders are inherited in autosomal recessive fashion and display bi-allelic variants in either the *IL10* gene or one of the IL10-receptor subunits (*IL10RA* or *IL10RB*) [124]. This is a very rare disorder with only a handful of cases reported [2, 124, 127]. Laboratory findings in these patients may reveal hypogammaglobulinemia, decreased CD4+/CD8+ ratio, increased serum IgA, increased T cell counts, or even normal findings [124]. Some patients have required IgG replacement therapy prior to HSCT. Transplant outcomes are favorable with both HLA-identical and mismatched related donors; importantly, pre-transplant IBD and rectal disease were corrected by transplantation [124]. For patients managed with medical therapy, immunosuppression with glucocorticoids, infliximab, azathioprine, adalimumab, methotrexate, and cyclosporine has been used.

IL-21 and IL-21 Receptor Deficiency

Salzer et al. described a patient with B cell defects and IBD in a consanguineous Turkish family who had two siblings that died of intractable diarrhea in the first year of life [128]. He presented with recurrent aphthous ulcers and persistent mucoid diarrhea at 2 months of age prompting endoscopy with findings suggestive of Crohn's disease. Additional findings, included recurrent sino-pulmonary infections and immunological studies, revealed hypogammaglobulinemia with reduced numbers of total B cells, naive and class switched memory B cells. Sequencing of the *IL21* gene revealed rare homozygous variants in a conserved region of the gene. At the time of the report, the patient failed to respond clinically to mesalamine, omega-3 fatty acid supplementation, enteral feeding, IgG replacement, and trimethoprim-sulfamethoxazole prophylaxis.

Wiskott-Aldrich Syndrome

The Wiskott-Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency characterized by the triad of eczema, micro-thrombocytopenia, and susceptibility to infections due to combined immunodeficiency [129]. The WAS protein is an important regulator of cytoskeletal arrangement in hematopoietic cells, and mutations in the *WASP* gene cause Wiskott-Aldrich syndrome [130, 131]. Interestingly, mutations in *WASP* may cause a milder phenotype of X-linked thrombocytopenia (XLT), X-linked neutropenia, partial WAS, or the severe, full syndrome of WAS with autoimmune disease [132, 133].

Patients with WAS display a wide range of autoimmune complications such as hemolytic anemia, vasculitis, inflammatory arthritis, neutropenia, and inflammatory bowel disease which may present as Crohn's disease or ulcerative colitis [134, 135]. For inflammatory bowel disease in the setting of WAS, a combination of steroids and cyclosporine has been used with efficacy [134]. In severe WAS, the most effective treatment providing lasting improvements in immunological function is HSCT. In one recent series of 12 patients, Ngwube et al. reported generally good outcomes following fully ablative transplant. Several of the patients had mixed-donor chimerism which seemed to affect platelet reconstitution [136]. For autoimmune hemolytic anemia, steroids, cyclophosphamide IVIG, rituximab, and azathioprine have been successfully used [134, 137].

Other Immunodeficiencies Associated with Inflammatory GI Disease

BACH2 Deficiency

BACH2 deficiency is associated with CVID and early onset large or small bowel lymphocytic-predominant inflammatory disease [138]. Patients may also display organomegaly, bronchiectasis, and pulmonary fibrosis. Afzali et al. reported three patients from two unrelated families with chronic diarrhea and evidence of either Crohn's disease or ulcerative colitis. In at least one patient, inflammatory bowel disease began during infancy. The patients were noted to have marked reduction in Foxp3 protein expression, low memory, and class-switched B cells with impaired plasmablast generation in addition to dysfunctional class switch recombination.

Immunodeficiency Centromeric Instability and Abnormal Facies (ICF; ZBZB24 Deficiency)

Conrad et al. reported a patient with syndromic facial features, developmental delay, a perianal fistula, and very-early onset inflammatory bowel disease [139]. Immunological investigations were significant for hypogammaglobulinemia, impaired pneumococcal vaccine responses, and reductions in the levels of memory B cells and natural killer cells. Gross endoscopic examination of the colon revealed ulcerative disease, and histopathological examination was notable for disruption of the crypt architecture. Chromosomal changes significant for centromere instability were found on karyotype analysis. Whole exome sequencing uncovered homozygous frameshift mutations in a gene associated with the B cell development and ICF2 (*ZBTB24*) which segregated appropriately in the family.

NFAT5 Deficiency

Onset of abdominal pain, intermittent fevers, non-bloody diarrhea, and eczema at 7 years in association with mono-allelic mutation in *NFAT5* was described by Boland et al. [140]. In this report, the proband was given a diagnosis of IBD and treated with glucocorticoids, azathioprine, and 6-mercaptopurine. Endoscopy was notable for nodularity of the terminal ileum and rectum. Histopathological examination of bowel biopsy material revealed intraepithelial lymphocytosis with impaired goblet cell architecture suggestive of autoimmune enterocolopathy. An assessment of immune function showed reduction in NK cells, impaired proliferation due to antigens, and impaired CD8+ T cell degranulation following stimulation with IFN-g and TNF-a.

Autoimmune Polyendocrinopathy Candidiasis with Ectodermal Dystrophy

Since IPEX is a clinical syndrome, several IPEX-like conditions have been described including autoimmune polyendocrinopathy candidiasis with ectodermal dystrophy (APECED). In APECED, individuals suffer from chronic mucocutaneous candidiasis (CMC), autoimmune endocrinopathy such as Addison's disease, autoimmune parathyroid disease, and multisystem inflammatory disease stemming from mutation of the *AIRE* (autoimmune regulator element) gene [141]. These patients may display enteropathy with antibody formation against tryptophan hydroxylase (anti-TPH1) and histidine decarboxylase [142]. Severe diarrhea and failure to thrive may be early signs of disease in APECED. Histopathological examination from endoscopy may reveal small intestine villous atrophy. Distinguishing APECED patients from those with true IPEX is challenging. However, mutation in the *FOXP3* gene and formation of anti-AIE-75 autoantibodies are characteristic of IPEX; whereas, mutation in

the *AIRE* gene and formation of anti-TPH1 lead to the diagnosis of APECED.[143]

ITCH Deficiency

Lohr et al. reported on a group of 10 Amish patients from 3 distinct demes who presented with dysmorphic facial features, developmental delay, failure to thrive, and multisystem autoimmune disease [144]. The patients were found to have homozygous frameshift mutations in the *ITCH* gene which codes for an E3 ubiquitin ligase and has a role in maintenance of immune tolerance by designating certain proteins for degradation through the proteasome [145]. Among patients with ITCH deficiency, enteropathy was a notable feature (20%) and was exhibited by chronic diarrhea and biopsy evidence of lymphocytic infiltration of the small bowel lamina propria. The patients with enteropathy were treated with either low-dose steroids or a combination of immunomodulators such as sirolimus, azathioprine, tacrolimus, and glucocorticoids.

NLRC4-Macrophage Activation Syndrome

Romberg et al. described a striking case of neonatal onset of secretory diarrhea, fever with underlying pathological inflammation beginning at 1 week of life, ultimately resulting in death at 23 days without findings of infection [146]. Evidence for an underlying inflammatory disease included autopsy findings of diffuse small and large bowel immune-cell infiltrate and invasion of the central nervous system by activated macrophages. Family history of the index case became prominent when his father presented 2 days later with fever, respiratory distress, subarachnoid hemorrhage, disseminated intravascular coagulation, and cytopenias. The father's childhood history was notable for episodes of recurrent fevers, diarrhea, and failure to thrive. Given the shared familial syndrome of neonatal onset enterocolitis, periodic fevers, and pathological inflammation, a genetic etiology was explored. Ultimately, informatics analysis of trio-whole exome sequencing led to the consideration of a likely pathological variant in the *NLRC4* gene (V341A substitution) among 34 other shared protein altering changes. Biological impact was proven following pedigree analysis of segregation for the morbid monoallelic gain of function variant arising as a de novo change in the index case's father. This report identified a new inflammasomeopathy related to overproduction of IL-1 family cytokines and resulting in pathological inflammation.

Subsequently a report of NLRC4-related disease suggested that IL-18 was a prominent biomarker and markedly elevated in the plasma [147]. Canna et al. reported a case of a 6-week-old female with protracted fevers and macrophage activation syndrome following a parainfluenza illness. She was ultimately diagnosed with NLRC4-associated hyperinflammation and treated successfully with a recombinant IL-18 binding protein. Interestingly, this case arose from a de novo variant in *NLRC4* which was identical to the one causing disease in the family described by Romberg et al. Importantly, the case established a precedent for successfully treating a life-threatening inflammatory disease.

Primary Immunodeficiency Disease-Associated Diarrhea

Patients with PIDD may have multiple etiologies which could contribute to diarrhea. These include inflammatory disease as discussed previously, infectious diarrhea related to the underlying host-defense impairment, genetic factors which relate to the primary defect, and motility defects. Additionally, there is evidence that the gut microbiome is less diverse in PIDD patients and unrelated to antibiotic use [148]. These and other data raise the concern that the underlying defect in immune function alter the gut microbiota in harmful ways to the host and could predispose to diarrhea.

In CVID, up to 60% of the patients are reported to present with diarrhea which is often of infectious etiology and associated with malabsorption [149]. Therefore, it is important to consider an underlying PIDD in patients who present with protracted and recalcitrant diarrhea. Commonly implicated infectious causes of diarrhea in XLA include *Giardia lamblia*, *Salmonella*, *Campylobacter*, *Cryptosporidium*, *Mycoplasma*, and enterovirus infections [10]. However, infectious organisms are unable to be identified in most cases.

Similar to XLA, the most common causes of infectious diarrhea in CVID include *Giardia lamblia*, *Campylobacter jejuni*, *Salmonella,* CMV, and *Clostridium difficile* [49, 54, 150–152]. It is interesting to note that despite frequent exposure to antibiotics, CVID patients do not have a higher incidence of *C. difficile* infections compared to the general population [152]. Norovirus infection may also cause severe chronic enteropathy and villous atrophy in CVID patients. Its clearance has been associated with improved GI histopathology and resolution of villous atrophy [153, 154]. Interestingly, some studies suggested that GI infections are more common in patients with low or undetectable serum IgA [49]. Also, GI infections are more common in CVID compared to XLA or IgA deficiency, and symptoms often persist despite immunoglobulin replacement therapy. This suggests the role of T cell or other immune factor dysfunction in the susceptibility of CVID patients to GI infections which is not correctable by IgG replacement alone [58].

Chronic granulomatous disease patients with diarrhea warrant careful consideration about the underlying etiology. Although non-typhoid *Salmonella* gastroenteritis had been reported, many organisms could cause diarrhea in CGD patients who often present with non-specific GI complaints such as diarrhea, constipation, abdominal pain, weight loss, and

failure to thrive [69, 70, 72, 73]. Given the extent of GI disease among patients with CGD, a thorough workup is warranted in patients with abdominal pain, failure to thrive, or hypoalbuminemia [73].

In some disorders of immune dysfunction, diarrhea is a consistent finding and unrelated to infection. For example, in trichohepatoenteric syndrome (THES), early-onset, intractable diarrhea is a cardinal feature [155]. These patients present with diarrhea, wooly hair, facial dysmorphism, and short stature arising from bi-allelic mutations in the *TTC37* or *SKIV2L* genes [156–158]. In familial HLH5 (FHL5) with Muc18-2 deficiency caused by mutations in *STXBP2*, patients present with chronic diarrhea with enteropathy [103]. These patients have criterion-defined HLH with pathological inflammation which may be corrected by HSCT; however, the diarrhea in FHL5 often persists despite transplantation [159, 160]. In X-linked CD40 ligand deficiency (X-linked hyper-IgM syndrome), chronic diarrhea with or without *Cryptosporidium* was a common clinical finding noted in a recent, large, retrospective study conducted by de la Morena et al. [161].

Diarrhea is a common sign among patients with primary immunodeficiency. However, it is a non-specific finding with varied etiology. Timing of onset, degree of chronicity, and severity coupled with microbiological data may provide insight into the cause for diarrhea. Additionally, extreme features and unusual findings may suggest a host-defense impairment and raise the specter of PIDD.

Nodular Lymphoid Hyperplasia

Gastrointestinal nodular lymphoid hyperplasia (NLH) is a non-specific finding of unclear etiology characterized by multiple small (2- to 10-mm diameter) nodules [162]. It may be found in the stomach and distal gut, but is most commonly noted in the small intestine in adults; whereas, in children, NLH is most commonly found in the rectum, colon, and terminal ileum [163, 164]. Histologically, NLH is typified by hyperplastic lymphoid follicles located within the mucosa and/or submucosa [165]. It can be mistaken for lymphoma or celiac disease histologically [162, 166]. In most patients, NHL is an asymptomatic, incidental finding on endoscopy; however, in some patients, it is associated with abdominal pain, diarrhea, bleeding, intussusception, or intestinal obstruction [162, 167]. An association between infection due to *Giardia lamblia* and *Helicobacter pylori* has also been made with NLH [168–170].

Some associations between immunodeficiency diseases and NLH are reported. In particular, patients with primary antibody deficiency syndromes are often found to have NLH [162]. In IgA deficiency, patients have presented with abdominal pain, diarrhea, and even concomitant Burkitt lymphoma in association with NLH [166, 171]. Interestingly, IgA deficiency also has a 10- to 20-fold increased risk of celiac disease which can be a challenging diagnosis to make given the histologic similarities [166, 172]. Hypogammaglobulinemia and CVID are also frequently associated with NLH [173–175]. In one study of NLH in CVID patients, follicles were characterized by a core of IgM-bearing B cells surrounded by many CD8+ T cells suggesting a link to immune dysregulation [176].

Liver and Biliary Tract Disease in Primary Immunodeficiency Diseases

Liver disease is common in the setting of PIDD [23, 177]. In one study of 147 PIDD patients, Rodrigues et al. noted that liver disease occurred with a prevalence of nearly 24% [177]. Among that subgroup of 35 patients, 63% had hepatomegaly and 60% had sclerosing cholangitis. In CVID, the most common symptomatic PIDD, patients may develop hepatomegaly which can be the initial presenting sign in 6–17% [47, 57]. Additionally, among CVID patients, hepatitis may develop which is non-specific, lobular hepatitis, or granulomatous hepatitis and primary-biliary cirrhosis can be a complication [47]. It is important to highlight that CVID appears to be the most common primary immunodeficiency to present initially to the gastroenterologist without a diagnosis; therefore, GI disease across the spectrum could herald a diagnosis of CVID [23].

The liver is a focus of disease activity in chronic granulomatous disease. The formation of liver abscesses is common and affects 30–42% of the patients [73, 178, 179]. Liver function abnormalities in CGD are also very common and noted in upwards of 60% of the patients. These derangements are most often related to liver abscess or drug hepato-toxicity [23, 179]. Additionally, in one study of 88 liver biopsy specimens from 38 CGD patients, 95% of the specimens showed portal and lobular chronic hepatitis [179]. Thus, all patients with CGD should undergo routine surveillance for liver disease and care providers should remain vigilant for indolent liver disease in the setting of CGD.

In the X-linked hyper-IgM syndrome (XHIGM; CD40L deficiency), liver disease is an important predictor of overall outcome and mortality [161, 180]. In the large multi-center study reported by de la Morena et al., liver disease was the only statistically significant negative predictor of mortality [161]. Among this cohort, 20% (36/176 patients) had liver disease which was the initial presenting clinical sign in 40% (16/36 liver disease patients). Interestingly, while *Cryptosporidium* was only noted in 7% of the group, it was found in 25% of the XHIGM patients with liver disease.

Among other PIDDs with significant liver disease, AID deficiency, APECED, and ITCH deficiency have all been associated with autoimmune hepatitis [142, 144, 181]. Durandy

et al. reported on two AID-deficient patients with biopsy proven autoimmune hepatitis. One patient had anti-hepatocyte and anti-liver-kidney-microsome antibodies [181]. In patients with ITCH deficiency, Lohr et al. described intermittent hepatomegaly without elevation of serum transaminases. Among the ITCH-deficient patients in this report, 30% (3/10) had hepatitis. Liver biopsy done on one patient showed accumulation of pink inclusions in the cytoplasm of periportal hepatocytes and electron microscopy revealed cytoplasmic accumulation of smooth endoplasmic reticulum [144].

Structural Gastrointestinal Defects in Primary Immunodeficiency Diseases

Structural bowel disease is not common in PIDDs; however, certain associations are worth mentioning. In cartilage-hair hypoplasia (CHH), Hirschsprung's disease (HD) is a noted complication [182, 183, 209]. Among a relatively large Amish CHH cohort, Rider NL et al. described three patients with HD all of whom did well following surgical correction [209]. In another series of CHH patients, HD has been found to portend a suboptimal prognosis [183]. Outcome among this series of 13 CHH patients with HD was poor if postoperative enterocolitis developed. The DiGeorge syndrome and other 22q11.2 deletion spectrum disorders are also associated with structural GI disease. In particular, esophageal atresia and anal atresia are reported [184]. Furthermore, among patients with the STAT3 mono-allelic loss of function hyper-IgE syndrome, esophageal disease, particularly diffuse wall thickening, and esophageal tortuosity were noted [185]. Given these associations, it is important to consider structural bowel disease among patients with syndromic immunodeficiency syndromes if GI complaints arise.

In addition to syndromic immunodeficiencies, the association of combined immunodeficiency (CID) and multiple intestinal atresia (MIA) was noted decades ago and only recently found to arise from bi-allelic mutations in *TTC7A* [186–192]. These patients often present very early in life with bowel obstruction or bowel perforation. Intrauterine death or polyhydramnios is also seen. The combined immunodeficiency is typified by profound T and B cell cytopenias with impaired mitogen-induced proliferation and clinically significant hypogammaglobulinemia. Patients may be identified by TREC-based newborn screening as suggested by Chen et al. [186]. Severe infection in patients with *TTC7A* mutations differs from SCID patients in that sepsis due to enteric pathogens is more common than viral disease. As noted by Samuels et al., not all patients have CID; however, many patients have died prior to immunologic assessment so the true prevalence of CID is not known [187]. Surgical correction of bowel atresia is often needed and HSCT is noted to correct the CID but not the bowel disease.

Malignancy of the Gastrointestinal Tract Associated with Primary Immunodeficiency Diseases

Primary immunodeficiency diseases are associated with an increased incidence of malignancy in general [193–195]. Infection mortality aside, malignancies are the leading cause of death in patients with PIDD [195]. In terms of gastrointestinal malignancy, primary antibody deficiency syndromes appear to have the highest reported risk [193, 196, 197]. For example, patients with CVID and X-linked agammaglobulinemia are reported to have gastric and colon adenocarcinoma [193, 198]. Leven et al. reported on a large cohort of hyper-IgM patients where liver adenocarcinoma, pancreatic carcinoid, and colon adenocarcinoma were noted in a small number of individuals [199]. In this cohort, one of the five patients with *Cryptosporidium* infection died of a hepatoma and two others underwent liver transplantation [199]. In the report by de la Morena et al., six patients developed biliary tract carcinoma (bile duct (one), gallbladder (one), metastatic hepatic neuroendocrine (one), choangiocarcinoma (one), neuroendocrine carcinoma of liver/biliary system (2)) [200] all of whom died. [161]. Finally, lymphomas of the gastrointestinal tract are also reported in the context of PIDDs [201, 202]. These associations call out the importance of considering malignancy as a part of the care plan during longitudinal monitoring of patients with PIDD.

Conclusions

The interplay between gastrointestinal host immunity and the microbiota is a crucial symbiotic and dynamic relationship. Microbial bio-diversity and population density increase with progression through the gut with a maximum burden in the colon [200, 203]. The host depends upon the microbiome for health and metabolic activity of gut microbiota has local as well as distant effects. For example, studies indicate that undigested complex carbohydrates are fermented by gut bacteria into short-chain fatty acids (SCFAs) among other products [204]. These SCFAs epigenetically modulate local colonic FOXP3+ regulatory T cells and promote immune homeostasis [205–207]. The effect of SCFAs extends to peripheral T cell function, and murine models show attenuation of airway inflammation and disease when dietary modifications are made by enriching SCFA intake which improves individual health and is even passed on to offspring [208].

Given the importance of host immunity in maintaining health by combatting pathogens and interacting with the microbiome, it is not surprising that gastrointestinal health and function are broadly impaired by primary defects of immunity. As we continue to unravel the pathobiology of currently known PIDDs and uncover new PIDDs, further insight

into balance between host-immunity, the microbiome, and gut function will likely emerge. Gastrointestinal disease may be wholly penetrant with severe defects of immunity; therefore, consideration of an underlying PIDD is warranted when caring for patients with GI problems. At the same time, it is possible that we can leverage host-microbe interactions to augment immune function in patients with PIDD and other disease states arising from immune dysregulation. Lastly, the importance of accurate and definitive genetic diagnosis cannot be understated. Phenotypic expansion of rare diseases is expected as more cases are studied and reported. Understanding the natural history, risk factors, and options for effective therapy for patients with these conditions depend upon genomic methodologies and robust associated informatics.

Compliance with ethical standards

Ethical Statement This article is in compliance with the *Journa's* ethical standards. Due to the nature of the review article, no patients were involved, and thus, informed consent was not applicable.

Conflict of Interest The authors declare that they have no conflict of interest.

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