

Clinical Communication

Gastrointestinal manifestations in common variable immunodeficiency (CVID) are associated with an altered immunophenotype including B- and T-cell dysregulation

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Clinical Implications

- Gastrointestinal manifestations occur in most patients with common variable immunodeficiency (71%) and include both infectious and noninfectious etiologies. Gastrointestinal manifestations in common variable immunodeficiency have been shown to significantly affect morbidity and mortality and can be difficult to treat. Increased awareness of these issues will encourage early targeted intervention.

TO THE EDITOR:

Common variable immunodeficiency (CVID) is a heterogeneous collection of disorders characterized by impaired B-cell differentiation and defective immunoglobulin production. It is the most common symptomatic primary immunodeficiency worldwide, with an estimated incidence of 1 in 25,000 to 30,000 people.¹

Most commonly, CVID is associated with loss of humoral immune defense, predisposing patients to recurrent infections in the sinopulmonary tract. However, a subset of patients with CVID suffers from noninfectious complications including inflammatory, lymphoproliferative, and autoimmune conditions.² Among these, inflammatory and autoimmune gastrointestinal (GI) disease is a major cause of morbidity and mortality in CVID; the mortality risk among patients with CVID with GI complications has been reported as 2.8 times higher than among those without GI complications.³

The major etiology of inflammatory and autoimmune GI disease identified in patients with CVID historically includes a form of autoimmune enteropathy, and to a lesser extent inflammatory bowel disease (IBD).⁴ Histopathologically, CVID-associated autoimmune enteropathy is characterized by a depletion or absence of plasma cells, villous blunting, follicular lymphoid hyperplasia, and prominent intraepithelial lymphocytosis.⁵ Clinically, CVID-associated autoimmune enteropathy can result in protein wasting or malabsorption. The enteropathy associated with CVID is not responsive to immunoglobulin replacement therapy, and has no standardized targeted therapeutics to date.⁴ Previous studies have reported a high prevalence of GI manifestations in CVID, with a potential link between GI pathology, systemic inflammation, and immune activation, given the finding of elevated levels of soluble CD25, soluble CD14, and fecal calprotectin levels in patients with GI inflammation.^{6,7}

Historically, CVID has been considered to be primarily an antibody deficiency syndrome. However, there is growing evidence that a more global dysregulation of the adaptive immune response occurs in a subset of patients with CVID, with abnormalities identified in both the B- and T-cell compartments, suggestive of a combined immune defect.^{8,9} The T-cell receptor (TCR) repertoire in patients with CVID is more clonally restricted than in healthy controls, and is characterized by both reduced junctional diversity and a reduction in shared clonotypic sequences.⁸ This suggests that the restriction of the TCR repertoire in CVID may be related to an intrinsic defect rather than to an extrinsic chronic antigenic driver. The intrinsic contraction of the naive T-cell pool appears to be the major driver for TCR oligoclonality in CVID. Furthermore, the reduction in TCR repertoire diversity is predominantly restricted to those patients who also exhibit severely reduced class-switched memory B cells and an elevated level of CD21 (lo) B cells (Freiburg 1a).⁹ GI inflammation in patients with CVID has been associated with lower CD19⁺CD27⁺ memory B cells and CD19⁺ B cells.^{6,7}

We sought to understand and evaluate the prevalence and type of GI manifestations, treatments, and correlation with T-cell immunophenotyping for patients with CVID with GI manifestations because these are currently not well characterized. Our hypothesis was that differences in T-cell immunophenotype, specifically loss of naive CD4⁺ T cells, may underlie or reflect a predisposition to developing autoimmune and lymphoproliferative complications in a subset of patients with CVID.

We performed a retrospective analysis of patients with CVID in the Partners HealthCare CVID cohort. The assembly of this institutional review board–approved cohort was previously described.² The diagnosis of CVID was verified by immunologist chart review of patients with low IgG and low IgA and/or IgG with poor or absent response to immunization and without another defined immunodeficiency state. We evaluated GI symptoms, infectious and noninfectious GI manifestations, treatments received, and T-cell immunophenotype (as determined by flow cytometry, and compared against age-matched reference ranges) by review of the electronic medical record and using a queryable language processing tool (Queryable Patient Interference Dossier). The association of GI manifestations with T-cell abnormalities was evaluated using logistic regression, where 2-tailed *P* value of less than .05 was considered statistically significant.

We identified 207 patients with CVID in the cohort, with 146 female (70%) and 61 male (30%) patients. The mean age was 55 ± 17 years. The median cohort IgG level was 422 mg/dL, IgA 43 mg/dL, and IgM 42 mg/dL. In this cohort, 147 (71%) had documented GI symptoms, either acute or chronic, most commonly diarrhea (*n* = 114), abdominal pain (*n* = 72), and weight loss/malabsorption/protein wasting (*n* = 33) (Figure 1, A). GI infectious workup was performed in 123 of 207 (59%) patients. An infectious etiology was identified in 57 of 147 (39%) patients, with the most commonly identified infections being those caused by *Helicobacter pylori* (*n* = 20), *Clostridium difficile* (*n* = 13), and *Giardia* (*n* = 8) (Figure 1, B). Infectious complications occurred despite all patients with GI

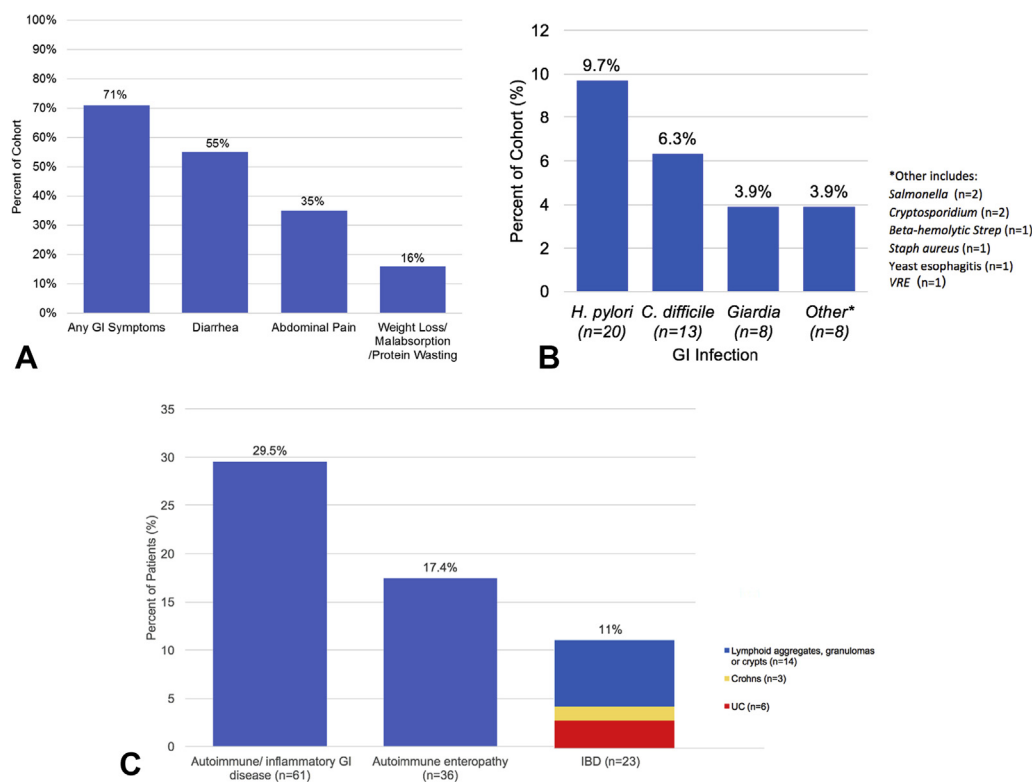


FIGURE 1. GI manifestations in CVID (n = 207). **(A)** Overall GI symptoms and most commonly reported GI symptoms. **(B)** Infectious GI complications. **(C)** Autoimmune and inflammatory GI disease. EGD, Esophagogastroduodenoscopy; UC, ulcerative colitis; VRE, vancomycin-resistant enterococci.

disease (n = 147) being treated with immunoglobulin replacement. Chronic inflammatory hepatitis was identified in 27 of 207 (13%) patients; most hepatitis was noninfectious (n = 21 [68%]), including nodular regenerative hyperplasia and autoimmune hepatitis, followed by infectious hepatitis (n = 6).

Autoimmune/inflammatory GI disease was reported in 61 of 207 (29%) patients, with 36 of 207 (17%) diagnosed with autoimmune gastropathy or enteropathy, and 23 of 207 (11%) diagnosed with IBD (Figure 1, C). Of the patients with a diagnosis of IBD, this included ulcerative colitis (n = 6), Crohn disease (n = 3), or pathology consistent with IBD based on the presence of lymphoid aggregates, granulomas, or crypts on biopsy (n = 14). Celiac disease was diagnosed in 6 of 207 (3%) based on autoantibodies (n = 1), biopsy with villous blunting (n = 5), and biopsy with villous blunting in addition to HLA typing (n = 1).

Diagnostic modalities included infectious GI workup including serology and/or stool studies (59%), endoscopy (42%), and colonoscopy (51%).

Of the patients receiving immunomodulators, 15 of 61 (25%) patients received immunomodulators/biologics for an indication of GI disease. These immunomodulators included prednisone, rituximab, azathioprine, methotrexate, hydroxychloroquine, and mycophenolate mofetil, with mixed effectiveness (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). There was overlap in that some patients received multiple immunomodulators because of the refractory nature of their disease. Notably, these treatments were most often used for multiple autoimmune and lymphoproliferative complications such as

granulomatous-lymphocytic interstitial lung disease, and not solely for the GI indication.

Consistent with previous reports,^{6,7} low B cells (CD19⁺) and low switched memory B cells (IgM⁺IgD⁺CD27⁺CD19⁺), defined as less than 2% of CD19⁺ cells, were associated with autoimmune/inflammatory GI manifestations (odds ratio [OR], 3.36; 95% CI, 1.32-8.90; *P* = .01 and OR, 5.8; 95% CI, 1.6-24.2; *P* = .01, respectively). Autoimmune/inflammatory GI manifestations were associated with T-cell abnormalities. Specifically, lower total CD3⁺ T-cell count (OR, 2.6; 95% CI, 1.1-6.3; *P* = .03), lower CD4⁺ (OR, 2.7; 95% CI, 1.2-6.2; *P* = .02), and lower CD8⁺ T cells (OR, 2.6; 95% CI, 1.1-6.3; *P* = .03) were observed among patients with CVID with autoimmune/inflammatory GI manifestations compared with those without (Table I). In addition, autoimmune/inflammatory GI manifestations were associated with skewing toward a low naive T-cell immunophenotype (OR, 5.0; 95% CI, 1.03-24.3; *P* = .04). These data demonstrate an association between combined B- and T-cell dysfunction and the occurrence of autoimmune/inflammatory GI disease in CVID. Abnormalities in complement levels were not associated with GI manifestations.

This analysis has major strengths, including an in-depth analysis of GI manifestations in CVID, and the findings of an association of these GI complications with contraction of the naive T-cell compartment in addition to the B-cell immunophenotypic changes. Potential limitations include the retrospective review, which raises potential concerns about information bias. In addition, incomplete ascertainment bias was likely

TABLE 1. Immunophenotypic abnormalities associated with autoimmune/inflammatory GI manifestations in CVID patient cohort (N = 207)

Cell type	GI (n = 61)		No GI (n = 146)		OR (95% CI)	P value
	Total tested	Lab abnormality present (%) [*]	Total tested	Lab abnormality present (%)		
Low total T cells (CD3 ⁺)	37	15 (40.5)	68	14 (20.6)	2.63 (1.09-6.43)	.03
Low T _H cells (CD4 ⁺)	43	17 (39.5)	77	15 (19.5)	2.70 (1.18-6.29)	.02
Low T killer cells (CD8 ⁺)	38	15 (39.5)	68	11 (16.2)	3.38 (1.36-8.64)	.009
Low naive T cells (CD45 ⁺ RA)	15	10 (66.7)	14	4 (28.6)	5.00 (1.09-27.0)	.046
Low CD45 ⁺ RO	15	0	10	1 (10.0)	NA	NA
High total T cells (CD3 ⁺)	37	0	68	4 (5.9)	NA	NA
High T _H cells (CD4 ⁺)	43	0	77	5 (6.5)	NA	NA
High T killer cells (CD8 ⁺)	38	1 (2.6)	68	2 (2.9)	0.89 (0.04-9.61)	.93
High CD45 ⁺ RA	15	0	14	0	NA	NA
High CD45 ⁺ RO	15	9 (60.0)	10	2 (20.0)	6.00 (1.06-50.0)	.059
Low B cells (CD19 ⁺)	31	17 (54.8)	49	13 (26.5)	3.36 (1.32-8.90)	.01
Low switched memory B cells (IgM ⁻ IgD ⁻ CD27 ⁺ CD19 ⁺)	20	14 (70.0)	21	6 (28.6)	5.83 (1.60-24.2)	.01

Lab, Laboratory; NA, not available/applicable.

^{*}Percentage of patients tested with the lab abnormality present.

present, in that patients went for certain procedures or diagnostic testing only if there was an indication that raised clinical suspicion and prompted the clinician to order testing. The data are also limited by varying length of follow-up because this was a retrospective chart review. The analysis was performed using data from a large, but single, health care system, so these findings may not be generalizable to other settings. This study was cross-sectional, so longitudinal studies will be necessary to elucidate whether the T- and B-cell pathology (including contraction in the naive T-cell compartment, and T- and B-cell lymphopenia) predates or coincides with the pathological GI findings in this subset of patients. The altered immunophenotype, including B- and T-cell abnormalities, may be due to several factors including that these changes may be driven by the underlying immune dysregulation, loss of lymphocytes through the GI tract, or decreased bone marrow output. Given the heterogeneous nature of CVID, insights regarding molecular mechanisms may uncover specific genetic predispositions to GI manifestations. Many of the patients in this cohort are undergoing genetic testing to further evaluate this hypothesis.

In conclusion, GI manifestations occur in most patients with CVID (71%) and include both infectious and noninfectious complications. GI complications range in severity, but are often refractory to treatment, and may contribute substantially to morbidity and mortality. Additional research is needed to evaluate the TCR repertoire in patients with CVID-associated enteropathy, as well as to identify viable treatment options in patients suffering from GI complications. GI manifestations in primary immunodeficiencies such as CVID are often underreported and underrecognized, and it is important for clinicians to be aware of these potential complications to increase screening and early targeted intervention.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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TABLE E1. Immunomodulators/biologics used in GI cohort and effectiveness

Immunomodulator/biologic name	No. of patients	% of GI cohort (n = 147)	% Effective
Prednisone	43	29.3%	83.7%
Rituximab	17	11.6%	76.5%
Azathioprine	15	10.2%	40.0%
Methotrexate	13	8.8%	38.5%
Hydroxychloroquine	12	8.2%	66.7%
Mycophenolate mofetil	6	4.1%	83.3%
Cyclophosphamide	4	2.7%	25%
Infliximab	2	1.4%	0%
Adalimumab	2	1.4%	100%
Abatacept	2	1.4%	100%
Tacrolimus	1	0.7%	100%
Sirolimus	1	0.7%	0%
Alemtuzumab	1	0.7%	0%
Colchicine	1	0.7%	0%
Etanercept	1	0.7%	0%
Leflunomide	1	0.7%	100%

Effectiveness was scored by physician-documented response to treatment. If effectiveness was unknown, this was not scored as effective.