# Not All That Flattens Villi Is Celiac Disease: A Review of Enteropathies

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## Abstract

Enteropathies can be overwhelming for clinicians. There is a wide spectrum of diseases involved; their effect on patients can be severe; and their underlying cause can be obscure. In this article, we outline a practical approach to enteropathies that are most common and not to be missed and is applicable to general and specialist physicians.

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Diseases of the small intestine, termed *enteropathies*, are a common cause of diarrhea.[1] The small intestine functions as both an absorptive and a secretory organ. When damaged, both absorptive failure and secretion excess can occur.[1] Features of clinically significant enteropathy include diarrhea and malabsorption, leading to weight loss. Oily, pale, foul-smelling, or bulky stools; postprandial bowel movements; and bloating are suggestive of steatorrhea.[1] Enteropathies are of particular interest to internists and

gastroenterologists alike because the differential diagnosis is challenging and extensive. Thus, a thorough systemic evaluation is required to identify both the cause and direct therapy.

Numerous patients present with diarrhea, but not all have an enteropathy. We must identify the more serious cases because of the potentially significant effect on morbidity and mortality. The malabsorption associated with enteropathies can be severe, and at times it can require parenteral nutrition. In certain cases, namely, collagenous sprue and Whipple disease, enteropathy can be fatal. It is important to determine the cause of enteropathy because although certain principles of management, such as corticosteroids, are similar in different etiologies, there are also unique therapeutic options that depend on the underlying diagnosis.

Although there are myriad causes of enteropathy, we will limit the scope of this article to those that cause villous atrophy, thereby creating an environment of malabsorption resulting in clinically significant weight loss and possible nutritional deficiencies in addition to diarrhea. We will focus on the high-yield etiologies that are the most common (celiac disease [CD], medications, collagenous sprue, and common variable immune deficiency) and on the not to miss diagnoses (human immunodeficiency virus [HIV], tropical sprue, giardiasis, Whipple disease, and viral infection). As such, this article will not address small-bowel ischemia, food allergies, Crohn disease, abetalipoproteinemia, amyloidosis, eosinophilic enteritis, tuberculosis, Zollinger-Ellison syndrome, gastric metaplasia, lymphoproliferative diseases, autoimmune enteropathy, small intestinal bacterial overgrowth, and others.[2] Items from this list will be briefly highlighted in our comprehensive table (Table), but not discussed. Relative frequencies of causes of villous atrophy not including CD are shown in Figure 1.

## COMMON CAUSES OF VILLOUS ATROPHY

We begin by addressing some of the most common causes of enteropathy.

### Celiac Disease Including Seronegative

Celiac disease (CD) is an autoimmune disorder involving chronic inflammation of the small intestine due to an immune reaction against ingested gluten. Seropositive and seronegative CD are the most common causes of enteropathy causing villous atrophy. Celiac disease affects roughly 1% of the population and is largely undiagnosed.[1] The broad range of presentations may partially explain this deficit in diagnosis. Although classical CD presents with malabsorption, it can also present with atypical symptoms, such as elevated liver enzymes and infertility, or with no symptoms. These nonclassical presentations are increasing in frequency, particularly in the undiagnosed cohort.

Current guidelines recommend case finding for detection of CD, which involves testing individuals with either classical or nonclassical symptoms, or associated at-risk conditions such as autoimmune diseases or Down syndrome.[6] A family history of CD is a significant risk factor and should be sought in the history and prompt evaluation. An initial screening test for CD includes tissue transglutaminase antibodies.[6] Gliadin antibodies are no longer recommended, although deamidated gliadin antibodies can be helpful in indeterminate cases. Routinely, IgA isotype antibodies are used; all individuals should be screened for IgA deficiency and, if present, should be tested with IgG isotype antibodies. In cases of positive serology or negative serology with high clinical suspicion for CD, the criterion standard diagnostic test, upper endoscopy with multiple bulb and distal duodenum biopsies should be performed.[6] Histologic changes consistent with CD range from inflammation to villous atrophy and are stratified using the Marsh-Oberhuber classification.[6]

Once diagnosed, the recommended treatment is a lifelong gluten-free diet after receiving instructions and education from a dietitian with expertise.[6] Generally, patients respond well to this, and if they do not, detailed investigation into inadvertent gluten contamination should be performed before evaluating for alternative diagnoses.

Most cases of CD will have positive serology, but there is a minority in which serology will be negative (5%-10%), termed *seronegative CD*. This is defined by negative celiac serology, positive histologic findings, and permissive human leukocyte antigen DQ2 and DQ8 haplotypes[7] and is suggested to be the most common cause of villous atrophy in the setting of negative celiac serology.[8]


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Although the reason for seronegativity is unknown, one hypothesis is that antibodies are trapped in the small intestinal mucosa and do not pass into the bloodstream, in which they could be detected by serological tests. In addition, those who are already limiting gluten in their diets or those who are IgA deficient may inadvertently be grouped into this category. Management of seronegative CD is similar to that of seropositive CD with a strict gluten-free diet.[7]

## Medications

Diarrhea is a common adverse effect of several medications, and certain drugs damage the small intestine itself, resulting in medication-induced enteropathy. Mycophenolate mofetil, azathioprine, methotrexate, and nonsteroidal anti-inflammatory drugs are well-recognized culprits.[9]

More recently, olmesartan-associated enteropathy has been identified.[10] It is typically classified by severe malabsorptive symptoms commonly leading to nutritional deficiencies and electrolyte abnormalities.[11] Most cases have either human leukocyte antigen DQ2 or DQ8 haplotype. Histologic features, including villous atrophy and a subepithelial collagenous layer consistent with collagenous sprue, can be found in the small bowel, gastric, and colonic mucosa.[11] Diagnosis requires these histologic findings, negative celiac serology, lack of response to a gluten-free diet, and improvement after discontinuing olmesartan.[10] Treatment involves withdrawal of the drug, and in severe cases topical or systemic corticosteroids. Although controversial, some evidence, including a case report on valsartan, suggests that enteropathy may be a class-related drug effect.[11]

## Collagenous Sprue

Collagenous sprue is a rare condition that is part of a family of collagenous gastroenteritides that includes collagenous gastritis and colitis, the latter being the most common.[12] Classically this is a disease of older women, and although the etiology of the collagen deposits is not known, in some cases it is felt to be the pathological consequence of another disease process, such as CD, tropical sprue, or medication-associated enteropathy.[12,13] Collagenous sprue is characterized by histologic findings of villous atrophy and a distinct layer of the subepithelial collagen in the small bowel mucosa (usually >20 μm). The presentation can be severe with significant malnutrition. Treatment is targeted at the associated condition (if known) and often also includes topical corticosteroids or immunosuppressants. It is uncommon to have treatment lead to resolution, and previous case reports detail a high risk of mortality, but resolution can potentially be seen in those cases in which the underlying etiology is reversible, such as in the case of comorbid CD or medication-associated enteropathies.[12,13]

## Common Variable Immune Deficiency

Common variable immune deficiency (CVID) is a rare disorder that can be either congenital or acquired and can therefore occur at any age. This disease involves deficient production of immunoglobulins and is characterized by low levels of at least 2 serum isotypes (other isotypes are IgG, IgE, IgA, IgM, and IgD), frequently IgA.[14] Typically, individuals present with frequent respiratory tract infections and poor response to vaccinations. Diarrhea and malabsorption are common symptoms, and individuals are at risk for intestinal infections (eg, recurrent giardiasis) and small intestinal bacterial overgrowth. In one-third to one-half of cases of CVID, gastrointestinal symptoms are associated with villous atrophy (more commonly partial as opposed to severe), felt to be secondary to dysregulation of the intestinal immune system.[14] Common variable immune deficiency is diagnosed by measuring serum immunoglobulins, and CVID enteropathy is characterized by villous atrophy on histologic examination with little to no plasma cells.[14] Nodular lymphoid hyperplasia is a common finding. Management of the underlying CVID involves intravenous immunoglobulin therapy in certain cases, although this does not help the gastrointestinal involvement and resultant symptoms.[14] Aggressive treatment of associated gastrointestinal tract infections is recommended. Budesonide may be effective for gastrointestinal symptoms after infection has been ruled out.[14]

**TABLE. Causes of Villous Atrophy**

| Category | Diagnosis | Historical clues | Study results | Treatment |
|---|---|---|---|---|
| Autoimmune | Celiac disease | Worsens with dietary gluten (wheat, barley, rye) | Positive TTG, EMA, range from inflammation to villous atrophy on biopsy | Gluten-free diet |
| | Crohn disease | Other areas of the gastrointestinal tract involved | Elevated ESR, CRP levels, characteristic biopsy | Immunosuppression, steroids, immunotherapy |
| | Autoimmune or immune-mediated enteropathy | Other autoimmune disease, mesenteric lymphadenopathy | Positive anti-enterocyte antibody | Immunosuppression, steroids—budesonide |
| Medication-related | Angiotensin receptor blocker | Hypertension, medication list | Lack of autoantibodies, HLA DQ2 or DQ8 present | Discontinue the offending agent |
| Neoplastic | Immunoproliferative small intestinal lymphoma | Young men, Middle Eastern or Mediterranean populations, low socioeconomic status, previous enteric infections | Immunostains on biopsy | Hematologist consult for consideration of chemotherapy |
| | Enteropathy-associated T-cell lymphoma | History of celiac disease, resurgence of symptoms despite a gluten-free diet | Immunostains on biopsy | Hematologist consult for consideration of chemotherapy |
| | Diffuse large B-cell lymphoma | Weight loss, fevers, night sweats, older adults, history of IBD or Epstein-Barr virus | Immunostains on biopsy | Hematologist consult for consideration of chemotherapy |
| Infiltrative | Amyloidosis | Pseudo-obstruction, diarrhea or constipation, macroglossia, neuropathy, periorbital purpura after proctoscopy | Congo red stain on biopsy or subcutaneous fat pad aspirate | Limited options, experimental therapies |
| | Eosinophilic enteritis | Allergies, food intolerances | Elevated IgE levels, infiltration of eosinophils, eosinophilia | Corticosteroids |
| | Collagenous sprue | Older women, can be secondary product of other primary disease | Thick band of the subepithelial collagen on histopathology | Gluten-free diet, corticosteroids—budesonide |

*Continued on next page*

**TABLE. Continued**

| Category | Diagnosis | Historical clues | Study results | Treatment |
|---|---|---|---|---|
| Infectious | HIV | Weight loss, changes in fat distribution | Low CD4 count, positive HIV test | Antiretroviral therapy |
| | Tropical sprue | Travel to the tropics (especially Cuba, Haiti, Puerto Rico, the Dominican Republic, India, Vietnam, Burma, Malaysia, and Indonesia, but not China, Africa, the Middle East, the Bahamas, or Jamaica) | Low folate and/or vitamin $B_{12}$ | Tetracyclines and folic acid (3-6 mo) |
| | Giardiasis | Camping, sick contacts, day care center exposure | Giardia antigen in stool, O&P stool microscopy | Metronidazole or similar tinidazole medications |
| | Whipple disease | Eye involvement, fevers, arthralgias, ataxia, cognitive impairment | Intracellular organisms on periodic acid–Schiff stain, PCR | Ceftriaxone or penicillin G and then TMP/SMX or doxycycline and hydroxychloroquine |
| | Tuberculosis | Endemic area, fever, night sweats | Tuberculin skin test, QuantiFERON Gold test, acid-fast stain | RIPE therapy—rifampin, isoniazid, pyrazinamide, ethambutol |
| | Viral infection/post-viral syndrome | Recent self-limiting illness | Other negative studies | Supportive care |
| | Small intestinal bacterial overgrowth | Abnormal structure or function (motility) of small bowel, no weight loss | Elevated hydrogen or methane on breath test | Antibiotics—rifaximin and others |
| | *Helicobacter pylori* (can rarely lead to celiac-like changes, usually lymphocytic enteritis) | Residence in a developing country | *H pylori* stool antigen detected, CO2 detected on urea breath test, positive serology, biopsy with presence of urease, culture and histology consistent with *H pylori* | Quadruple therapy—bismuth, metronidazole, tetracycline, proton pump inhibitor |
| Inflammatory | Peptic duodenitis | Peptic ulcer disease | Ulcer visible on endoscopy or positive *H pylori* test | Proton pump inhibitor |
| Diet-related | Malnutrition | Weight loss, failure to thrive | Low albumin, prealbumin, hemoglobin, vitamin and mineral, sodium, BUN, creatinine levels | Supportive care, nutritional support |
| | Food allergy | Atopy, numerous allergies | Reaction on skin test, elevated IgE levels, trial elimination diets | Allergen avoidance |
| Ischemic | Small bowel ischemia | Cardiovascular disease history, thrombotic conditions, hypovolemia, dialysis | Ischemia or occlusion seen on CT angiography | Pain control, hemodynamic support, anticoagulation, antibiotics, surgical exploration |
| Other | Common variable immune deficiency | Recurrent sinopulmonary infections, autoimmune cytopenias | Low IgG, IgA, or IgM levels, lack of response to pneumococcal vaccine, absence of plasma cells on biopsy | Intravenous immunoglobulin (for recurrent infections) and corticosteroids (for enteropathy) |
| | Radiation enteritis | Previous cancer therapy with radiation | Pallor, friability, telangiectasias on endoscopy | Dietary modification, antidiarrheal agents, bile acid resins, surgical resection |
| | Idiopathic or unclassified sprue | No response to a gluten-free diet | Other negative studies | Steroids and/or immunosuppression |

BUN = blood urea nitrogen; CRP = C-reactive protein; CT = computed tomography; EMA = endomysial antibody; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IBD = inflammatory bowel disease; O&P = ova and parasite; PCR = polymerase chain reaction; TMP/SMX = trimethoprim/sulfamethoxazole; TTG = tissue transglutaminase.
Information from *Am J Gastroenterol*,[3] *Gut*,[4] and *Aliment Pharmacol Ther*.[5]

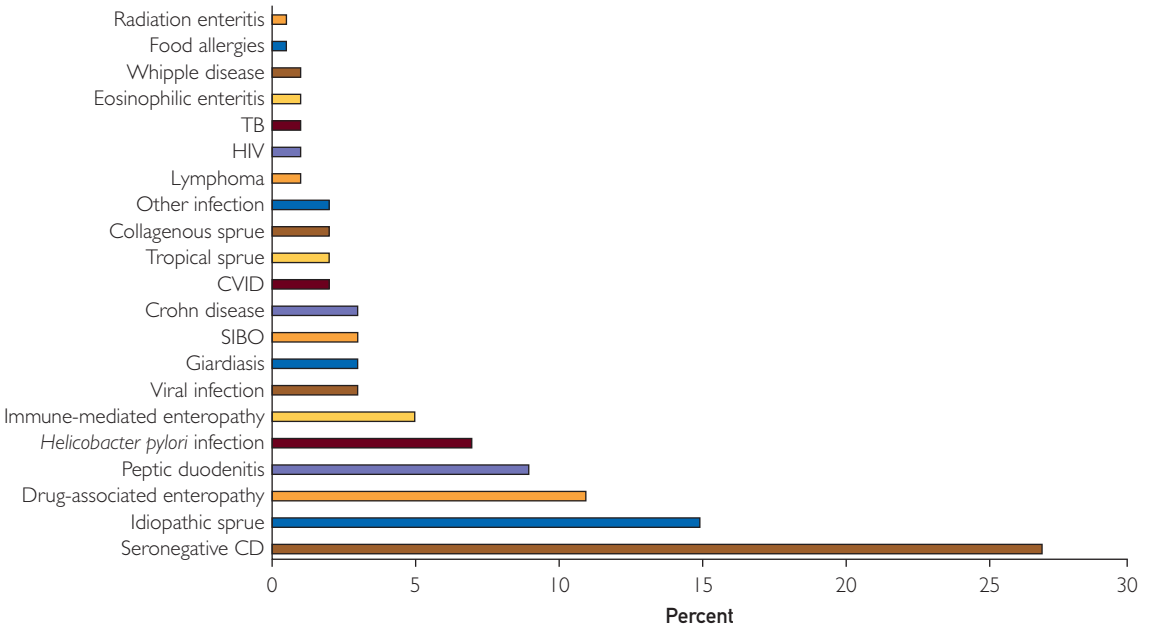


**FIGURE 1.** Frequencies of causes of villous atrophy other than CD. CD = celiac disease; CVID = common variable immune deficiency; HIV = human immunodeficiency virus; SIBO = small intestinal bacterial overgrowth; TB = tuberculosis. Adapted from *Am J Gastroenterol*,[3] *Gut*,[4] and *Aliment Pharmacol Ther*.[5]

## NOT TO MISS DIAGNOSES OF VILLOUS ATROPHY

Next we shift our discussion to diagnoses that should not be missed.

### Human Immunodeficiency Virus

Wasting syndrome—manifested as weight loss, malnutrition, and diarrhea—and opportunistic enteric infections are well-known complications of HIV. A lesser known consequence, although common in HIV, is dysfunction of the small intestine in the absence of microorganism infection—termed *HIV enteropathy*. It is debatable whether this enteropathy results from direct damage to the mucosa by the virus or immunological disturbances such as the markedly low level of $CD4^+$ T cells in the intestinal mucosa.[15] Human immunodeficiency virus enteropathy results in partial villous atrophy, epithelial hypoproliferation, and enterocyte dysfunction leading to decreased brush border enzyme activity causing malabsorption.[15] This entity improves with antiretroviral therapy. It is important to search for HIV as a cause of enteropathy because the infection has devastating consequences and potential for spread if undetected and untreated.

### Tropical Sprue

Tropical sprue is an enteropathy that affects travelers to and residents of certain tropical regions. Endemic areas include locations between 30° north and south of the equator, but all nations are not affected equally.[16] It is uncommon in travelers with visits of less than 2 weeks; typically afflicted travelers have stayed for a month or longer. The pathogenesis of tropical sprue is unclear but thought to be infectious (exact pathogen unknown) in nature, with subsequent bacterial overgrowth attacking the structure of the small bowel.[17] The resultant intestinal injury affects absorption, particularly of carbohydrates, fat, vitamin $B_{12}$, and especially folate. It presents with malabsorption, borborygmi, and sequelae of nutritional deficiencies. Intestinal biopsies reveal villous atrophy to a lesser degree than in CD, which supports the diagnosis, but ultimately, response to treatment confirms it.[17] Treatment is with antibiotics (commonly tetracycline) and folate supplementation for a


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duration of 3 to 6 months.[18] This condition is not to be missed because it can be detected from the history of travel and requires a long course of treatment. In addition, if not managed with behavior change or improved precautions, it can recur, as reexposure to the pathogen is not only possible but likely for those living in the tropics.

### Giardiasis

Another infection to be mindful of is *Giardia intestinalis* (also called *giardia lamblia* or *duodenalis*). It is a food- and waterborne parasite with broad geographic reach; it is the leading parasite responsible for enteric infections in the United States.[19] It is frequently found in areas with limited water treatment capacity and poor sanitary conditions.[19] It can also be transmitted fecal-orally.[17] The parasite has 2 forms: cysts and trophozoites. Cysts are infectious and can be ingested and excreted.[19] Trophozoites are pear-shaped multi-flagellated forms and localize to the small intestine in which they attach to the surface but do not invade.[17] Illness is characterized by bloating, flatulence, abdominal cramping, watery diarrhea, malabsorption, and weight loss. Diagnosis is made by stool examination (detection of giardia antigen) or detection of the characteristically shaped organisms by the pathologist. Villous atrophy can be present on small intestinal biopsy.[3] This diagnosis is not to be overlooked, as it is a frequent occurrence in the United States and readily treatable with nitroimidazoles.

### Whipple Disease

The gram-positive bacteria *Tropheryma whipplei* cause this rare multisystem infection. It predominantly affects middle-aged white men.[18] The most common presenting symptom is steatorrhea or diarrhea, resulting in weight loss. This gastrointestinal disturbance is due to impaired lymphatic transport caused by bacteria and can be present years before other areas of the body are attacked.[17] Beyond the small bowel, it can involve essentially any organ system. Its variable systemic presentation can include arthritis, fever, cardiac valve issues, and central nervous system disease such as myoclonus, dementia, oculomasticatory myorhythmia that is pathognomonic of Whipple disease (jaw contractions accompanied by synchronous pendulum-like vergence oscillations in the eyes).[18] It is diagnosed by endoscopy with intestinal biopsy, revealing characteristic periodic acid—Schiff stain—positive *T whipplei* bacteria within macrophages and/or polymerase chain reaction.[18] Slides will also reveal disrupted villous architecture usually affecting the duodenum and jejunum.[17] The optimal treatment is uncertain. The initial phase requires intravenous antibiotics for several weeks (ceftriaxone or penicillin G) followed by a long oral maintenance phase (trimethoprim/sulfamethoxazole or doxycycline plus hydroxychloroquine).[20] This diagnosis is not to be missed, because the prognosis is poor and it can be fatal.

### Viral Infection

Perhaps both the most common and overlooked causes of enteropathy are an active viral infection or a post-viral syndrome. Viruses are the main culprit for acute infectious gastroenteritis. Norovirus, rotavirus, adenovirus, and astrovirus are some of the pathogens responsible for outbreaks.[17] Diarrhea can be accompanied by nausea, vomiting, fevers, and abdominal pain. Although the incubation, infectious, and symptomatic (2-8 days) periods are short, with the illness being self-limited, effects to the gastrointestinal system can sometimes be lasting.[17] Viral gastroenteritis can cause abnormal villous shortening, loss of the brush border, compensatory crypt hyperplasia, and lymphocyte infiltration.[17] These changes are temporary and rarely documented because of the short course of illness. Bacterial illnesses such as salmonella, cholera, shigella, typhoid, yersinia, and others also affect the small intestine, but not as often as viral infections. This category is a reminder not to overdiagnose, because viral enteritis is an exceedingly common cause of self-limited diarrhea, which can be elicited through the history and presence of sick contacts.

## GENERAL APPROACH TO ENTEROPATHY

When a patient presents with an enteropathy causing clinically significant diarrhea, malabsorption, and weight loss and is found to have villous atrophy, it is reasonable to begin by assessing for CD. Celiac disease is by far the most common cause of villous atrophy (79%-93% of cases) in the United States.[4] If CD is deemed unlikely, we recommend revisiting the history and considering further

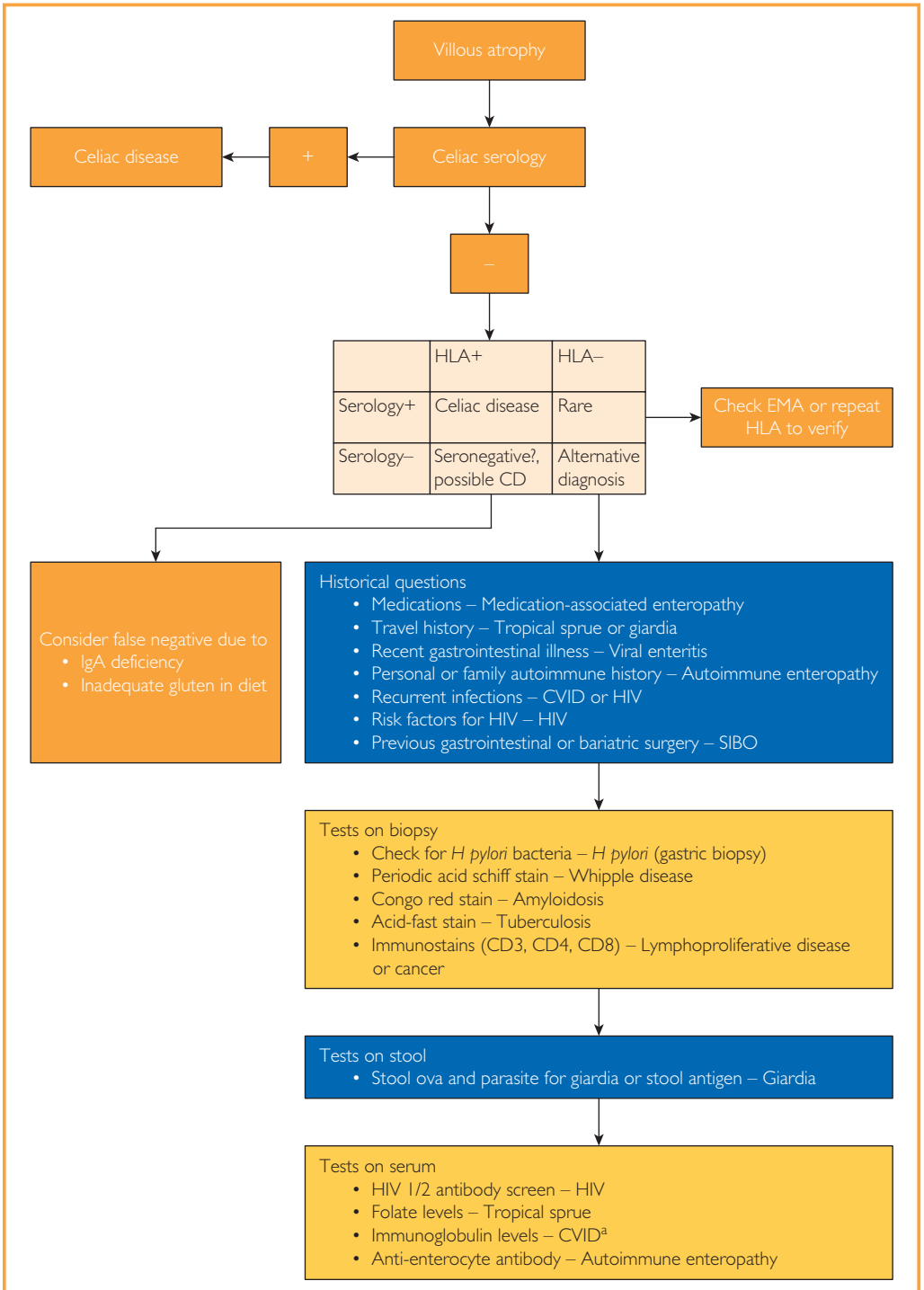


**FIGURE 2.** Villous atrophy algorithm. CD = celiac disease; CVID = common variable immune deficiency; EMA = endomysial antibody; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; *H pylori* = *Helicobacter pylori*; SIBO = small intestinal bacterial overgrowth. [a]Rituximab has been associated with a form of CVID.



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testing as outlined in Figure 2. Also examine the biopsy specimen to rule out artifact such as a wholly flattened slide due to operator error during preparation. If just the villi are flat, check the report or ask the pathologist to review the slide for clues. Special stains can also be requested. Many diseases seen by staining are rare or suggested by the history; these studies should be reserved for the appropriate clinical scenario. The biopsy of tropical sprue and medication-associated enteropathy mimic CD. Working in a stepwise fashion by evaluating for CD and if negative, performing tests on serum and biopsy, as guided by clinical suspicion, is our suggested approach to working up an enteropathy.

## TREATMENT

After an etiology is uncovered, treatment is dictated by the underlying cause. Corticosteroids are frequently useful, as they help subdue inflammation. Guidelines are often practical sources for current clinical information.[6] The Table references treatment options.

## CONCLUSION

Enteropathies encompass a wide spectrum of illness; they cause diarrhea, nutritional deficiencies, and weight loss. A detailed and careful approach can often reveal the underlying cause. An example of such a work-up is described in this article, featuring the most common and not to miss enteropathies. We hope that it is of particular use in scenarios in which CD is not the final diagnosis and so it may broaden the differential diagnosis and awareness of other illnesses, because not all that flattens is CD.

**Abbreviations and Acronyms:** **CD** = celiac disease; **CVID** = common variable immune deficiency; **HIV** = human immunodeficiency virus

**Potential Competing Interests:** Dr Murray is a board member of Celimmune. He is a consultant for Boehringer Ingelheim, Inova Diagnostics, BioLineRx, GlaxoSmithKline, ImmusanT, Institute for Protein Design (PvP Biologics), Takeda Pharmaceutical, Innovate Biopharmaceuticals, Intrexon, MediBeacon, UCB (Atlanta), Allakos, and Rockwell Medical. He has received research grant from the Broad Medical Research Program at the Crohn's and Colitis Foundation of America, the National Institutes of Health, and the Oberkotter Foundation. He has received money for patents from Miomics. He has received royalties from Torax.

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