Celiac disease is a unique autoimmune disease affecting approximately 1% of the population worldwide. The treatment is a gluten-free diet, and adherence to the diet improves symptoms in the majority of patients. However, approximately 7% to 30% of patients experience persistent symptoms while being treated with a gluten-free diet, commonly because of continued gluten ingestion. Individuals who are nonresponsive to treatment present a challenge to the clinician and are frequently encountered at tertiary-care referral centers.

Symptoms may fail to improve initially or may recur after an extended period of treatment with a gluten-free diet. A systemic approach in evaluating these patients is helpful for excluding causes such as persistent gluten exposure, microscopic colitis, small-intestinal bacterial overgrowth, lactose or fructose intolerance, pancreatic exocrine insufficiency, and autoimmune enteropathy. Consultation with a skilled dietician is crucial, but availability is limited in many areas.

Other reasons for persistent symptoms include refractory celiac disease (RCD). RCD, defined as persistent diarrhea and villous atrophy despite adherence to a gluten-free diet for at least 12 months, is divided into two types, depending on the population of intraepithelial T lymphocytes. In type I RCD, the intraepithelial lymphocytes have normal surface CD3 and CD8 expression as well as a polyclonal T-cell receptor arrangement, similar to uncomplicated celiac disease. In type II RCD, an aberrant lymphocyte population is expanded with loss of surface CD3 and CD8 expression, retention of CD3 expression within the cell, and a monoclonal T-cell receptor arrangement. Type II RCD has a poor prognosis with increased mortality, often because of the development of enteropathy-associated T-cell lymphoma, an unfortunate complication occurring in over 50% of patients. Luckily, in the United States, RCD type II appears rare compared with European populations, although the reasons for this are unclear. For patients with unresponsive celiac disease or suspicion of refractory disease, conventional upper endoscopy is needed to obtain biopsy specimens for immunohistochemistry, flow cytometry, and T-cell receptor polymerase chain reaction studies.

Capsule endoscopy is a useful, noninvasive method for examining the entire small intestine, not only in patients with obscure bleeding but also in celiac disease. The role of capsule endoscopy in the initial evaluation and subsequent monitoring of patients with celiac disease is evolving. Features of celiac disease on capsule endoscopy include scallop ing of folds, villous atrophy, layering of folds, and a mosaic pattern. In an initial multicenter trial, capsule endoscopy had an excellent reported sensitivity and specificity of 87.5% and 90.9%, respectively, for the detection of villous atrophy as compared with the criterion standard of duodenal histology. Capsule endoscopy may be considered in those with suspected celiac disease with positive celiac serology results (tissue transglutaminase or anti-endomysial antibody) who are unable or unwilling to have an upper endoscopy. Also, according to an international consensus conference, capsule endoscopy can be considered for evaluating the distal small intestine in those with positive celiac serology results and normal duodenal histology. Capsule endoscopy was not shown, however, to have any added benefit for detecting villous atrophy in patients with positive celiac serology results and normal duodenal histology in a recent study by Lidums et al. Finally, capsule endoscopy can be performed if there is suspicion of refractory or complicated disease, such as malignancy or ulcerative jejunitis. When there are warning signs, such as weight loss and abdominal pain, capsule endoscopy combined with imaging via CT enterography or magnetic resonance enterography is indicated. If findings are suspicious for a malignancy, deep endoscopy by using a balloon or spiral-assisted approach can be performed to obtain biopsy specimens. There are few studies in the literature on capsule endoscopy in refractory disease. In RCD type II, capsule endoscopy and small-bowel radiologic imaging may detect abnormalities such as malignancy or ulcerative jejunitis, but the yield appears low in individuals with RCD type I.

The recent study by Atlas et al in this issue contributes to the limited literature on capsule endoscopy in patients with nonresponsive celiac disease. The investigators examined the accuracy of capsule endoscopy for detecting mucosal abnormalities in celiac disease. The same investigators had previously demonstrated that the severity of clinical presentation in celiac disease is not associated with the extent of small-bowel involvement. In their current study, capsule
endoscopy studies of 42 patients with nonresponsive celiac disease were compared with studies of 84 age-matched and sex-matched controls without celiac disease. A retrospective evaluation of capsule studies of 30 patients with uncomplicated celiac disease on a gluten-free diet also was performed. The sensitivity and specificity for detecting villous atrophy via capsule endoscopy was disappointingly low at 56% and 85%, respectively. There was weak agreement of capsule endoscopy and histology in the patients with nonresponsive celiac disease ($k = 0.44$). Small-bowel erosions and ulcerations also were found in equal numbers in those with and without celiac disease. Not all small-bowel ulcerations represent refractory disease, ulcerative jejunitis, or significant pathology. Those interpreting capsule endoscopy studies must recognize that small-bowel erosions may be present in healthy individuals. A detailed medication history is warranted in evaluating patients with nonresponsive disease to exclude the use of nonsteroidal anti-inflammatory medications or aspirin. Importantly, cases of lymphoma and adenocarcinoma were detected in this series via capsule endoscopy. This is consistent with reports of prior studies performed at our center. Notably, celiac antibodies were found subsequently to be positive in 51% of patients with nonresponsive disease, suggesting persistent gluten exposure as a cause of symptoms. Before patients undergo expensive endoscopic evaluation, consultation with an expert dietician should first be performed. Thirty-one percent of patients with nonresponsive celiac disease were found to have features of villous atrophy on capsule endoscopy. Failure to normalize the mucosal inflammation and villous atrophy in celiac disease is in fact not uncommon, even in patients who are clinically doing well.

Limitations of the study by Atlas et al include the use of older-generation capsule technology (Given M2A; Given Imaging Ltd, Yoqneam, Israel). It is not clear, however, whether use of the newer generation of capsule endoscopes (Given PillCam SB2; Given Imaging Ltd, Yoqneam, Israel, and Olympus Endocapsule; Olympus America Inc, Center Valley, Pa) with improved optics and field of view would increase the sensitivity and specificity of detecting villous atrophy. The study was retrospective and interpreted by a single reviewer with expertise in capsule endoscopy studies of celiac patients. Nonsteroidal anti-inflammatory medication use was assessed retrospectively, but the assessment was performed by using a mandatory preprocedure medication reconciliation process.

Capsule endoscopy does have limitations in the evaluation of celiac disease. Interpretation is subjective, examination of the intestine may be incomplete, partial villous atrophy may not be appreciated, and biopsy specimens cannot be obtained. Techniques that provide a standardized, computer-based, non-subjective assessment of villous atrophy are being developed. No standardized scoring system has been applied to capsule imaging in celiac disease. The Lewis score provides a common language for assessing inflammatory changes in the small intestine based on villous appearance, ulcerations, and stenosis, but it has mainly been applied to Crohn's disease.

Although capsule endoscopy has promise in the diagnosis and monitoring of patients with celiac disease, conventional upper endoscopy still remains the criterion standard for obtaining biopsies for histology in both the diagnosis of celiac disease and in the assessment of patients with nonresponsive celiac disease. Capsule endoscopy does not appear necessary in the evaluation of nonresponsive celiac disease without alarm symptoms or without type II RCD.

**DISCLOSURE**

All authors disclosed no financial relationships relevant to this publication.

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**Abbreviation:** RCD, refractory celiac disease.

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