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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Management of Refractory Celiac Disease: Expert Review

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DESCRIPTION: The purpose of this expert review is to summarize the diagnosis and management of refractory celiac disease. It will review evaluation of patients with celiac disease who have persistent or recurrent symptoms, differential diagnosis, nutritional support, potential therapeutic options, and surveillance for complications of this condition. **METHODS:** This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the CPUC and external peer review through standard procedures of *Gastroenterology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Since systematic reviews were not performed, these BPA statements do not carry formal ratings of the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: In patients believed to have celiac disease who have persistent or recurrent symptoms or signs, the initial diagnosis of celiac disease should be confirmed by review of prior diagnostic testing, including serologies, endoscopies, and histologic findings. **BEST PRACTICE ADVICE 2:** In patients with confirmed celiac disease with persistent or recurrent symptoms or signs (nonresponsive celiac disease), ongoing gluten ingestion should be excluded as a cause of these symptoms with serologic testing, dietitian review, and detection of immunogenic peptides in stool or urine. Esophagogastroduodenoscopy with small bowel biopsies should be performed to look for villous atrophy. If villous atrophy persists or the initial diagnosis of celiac disease was not confirmed, consider other causes of villous atrophy, including common variable immunodeficiency, autoimmune enteropathy, tropical sprue, and medication-induced enteropathy. **BEST PRACTICE ADVICE 3:** For patients with nonresponsive celiac disease, after exclusion of gluten ingestion, perform a systematic evaluation for other potential causes of symptoms, including functional bowel disorders, microscopic colitis, pancreatic insufficiency, inflammatory bowel disease, lactose or fructose intolerance, and small intestinal bacterial overgrowth. **BEST PRACTICE ADVICE 4:** Use flow cytometry, immunohistochemistry, and T-cell receptor rearrangement studies to distinguish between subtypes of refractory celiac disease and to exclude enteropathy-associated T-cell lymphoma. Type 1 refractory celiac disease is characterized by a normal intraepithelial lymphocyte population and type 2 is defined by the presence of an aberrant, clonal intraepithelial lymphocyte population. Consultation with an expert hematopathologist is necessary to interpret these studies. **BEST PRACTICE ADVICE 5:** Perform small bowel imaging with capsule endoscopy and computed tomography or magnetic resonance enterography to exclude enteropathy-associated T-cell lymphoma and ulcerative jejunoileitis at initial diagnosis of type 2 refractory celiac disease. **BEST PRACTICE ADVICE 6:** Complete a detailed nutritional assessment with investigation of micronutrient and macronutrient deficiencies in patients diagnosed with refractory celiac disease. Check albumin as an independent prognostic factor. **BEST PRACTICE ADVICE 7:** Correct deficiencies in macro- and micronutrients using oral supplements and/or enteral support. Consider parenteral nutrition for patients with severe malnutrition due to malabsorption. **BEST PRACTICE ADVICE 8:** Corticosteroids, most commonly open-capsule budesonide or, if unavailable, prednisone, are the medication of choice and should be used as first-line therapy in either type 1 or type 2 refractory celiac disease. **BEST PRACTICE ADVICE 9:** Patients with refractory celiac disease require regular follow-up by a multidisciplinary team, including gastroenterologists and dietitians, to assess clinical and histologic response to therapy. Identify local experts with expertise in celiac disease to assist with management. **BEST PRACTICE ADVICE 10:** Patients with refractory celiac disease without response to steroids may benefit from referral to a center with expertise for management or evaluation for inclusion in clinical trials.

Keywords: Celiac Disease; Enteropathy-Associated T-Cell Lymphoma; Tissue Transglutaminase Antibody; Gluten.

Celiac disease is present in 1% of the US population and causes a myriad of symptoms and manifestations. Its diagnosis rests on a combination of serologic testing for anti-tissue transglutaminase, anti-endomysial, and/or anti-deamidated gliadin peptide antibodies, as well as characteristic findings of villous atrophy and

Abbreviations used in this paper: **AGA, American Gastroenterological Association; cyt, cytoplasmic; EATL, enteropathy-associated T-cell lymphoma; FODMAP, fermentable oligo-, di-, and monosaccharides and polyols; IEL, intraepithelial lymphocyte; IHC, immunohistochemistry; RCD, refractory celiac disease; s, surface; TCR, T-cell receptor.**

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intraepithelial lymphocytosis on duodenal biopsies. The mainstay of treatment is strict life-long adherence to a gluten-free diet, which in most cases results in symptom improvement, normalization of associated serum antibody levels, and reversal of small bowel villous atrophy. However, persistent or recurrent symptoms or signs and elevated celiac antibodies, either alone or in combination, are not uncommon, and their presence raises the possibility of nonresponsive celiac disease with a broad differential, including refractory celiac disease (RCD). RCD is defined as celiac disease with persistent symptoms of malabsorption and villous atrophy despite at least 12 months of strict adherence to a gluten-free diet. Persistent or recurrent symptoms and signs that could raise suspicion of RCD include diarrhea, weight loss, anemia, and malabsorption with persistent nutritional deficiencies. Patients with complications of RCD may also present with symptoms of gastrointestinal bleeding, fever, night sweats, and bowel obstruction. Although elevated celiac antibodies may occur in RCD, they do indicate ongoing gluten ingestion. RCD is believed to occur in only approximately 1% of patients with celiac disease, although this may be an overestimate, as data are obtained from referral centers. RCD can be classified into 2 subtypes, with differing diagnostic criteria, prognosis, and response to therapy. Type 1 (RCD1) is characterized by villous atrophy, but a population of intraepithelial lymphocytes (IELs) similar to that seen in conventional celiac disease. Type 2 (RCD2) is characterized by aberrant clonal T-cell expansion in the gastrointestinal tract and other organs, has an overall poorer prognosis than RCD1, and implies risk for development of ulcerative jejunoileitis or enteropathy-associated T-cell lymphoma (EATL). The goal of this Clinical Practice Update is to review optimal practices for diagnosis and management of refractory celiac disease.

Best Practice Advice 1: In patients believed to have celiac disease who have persistent or recurrent symptoms or signs, the initial diagnosis of celiac disease should be confirmed by review of prior diagnostic testing, including serologies, endoscopies, and histologic findings.

Celiac disease can be associated with and overlap with multiple other gastrointestinal conditions, including functional bowel disorders, lactose or fructose intolerance, microscopic colitis, pancreatic insufficiency, and inflammatory bowel disease. Patients with nonceliac gluten sensitivity may also have been diagnosed with celiac disease. Therefore, when considering the possibility of RCD, the initial diagnosis of celiac disease should first be confirmed with review of the prior diagnostic workup (Figure 1).[1] Most frequently, a clinical condition prompts serologic testing that leads to endoscopy and duodenal biopsy showing villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia.[2–5] However, these pathologic findings are not specific for celiac disease. If the biopsy is performed first, celiac serologic testing with tissue transglutaminase IgA, deamidated gliadin peptide IgA and IgG, and possibly endomysial antibodies should be performed. IgG tissue transglutaminase or/and deamidated gliadin peptide should be considered in patients with IgA deficiency. If the prior diagnostic workup was equivocal or discrepant, testing for the celiac disease–associated HLA haplotypes DQ2 or DQ8 can be considered. Seronegative celiac disease can occur.[6] In this case, the diagnosis of celiac disease can be established by a clinical and histologic response to the gluten-free diet in patients with consistent pathology and compatible HLA haplotypes.

Best Practice Advice 2: In patients with confirmed celiac disease with persistent or recurrent symptoms or signs (nonresponsive celiac disease), ongoing gluten ingestion should be excluded as a cause of these symptoms with serologic testing, dietitian review, and detection of immunogenic peptides in stool or urine. Esophagogastroduodenoscopy with small bowel biopsies should be performed to look for villous atrophy. If villous atrophy persists or the initial diagnosis of celiac disease was not confirmed, consider other causes of villous atrophy, including common variable immunodeficiency, autoimmune enteropathy, tropical sprue, and medication-induced enteropathy.

If celiac disease has been confirmed, ongoing gluten ingestion, whether intentional or inadvertent, should be excluded in patients with recurrent or persistent symptoms. Persistent gluten ingestion accounts for 40%–50% of patients with poorly or nonresponsive celiac disease.[7,8] Review with a dietitian experienced in celiac disease is essential to uncover potential sources of inadvertent gluten ingestion. Elevated celiac antibodies suggest persistent gluten ingestion, although the rate of decline of antibody levels after beginning a gluten-free diet is variable.[9] Negative serologies do not completely exclude intermittent or low-level gluten ingestion, and celiac antibody levels are often normal in patients with RCD.[10] Stool and urinary biomarkers of persistent gluten ingestion are available commercially (gluten immunodominant peptides) and may be helpful to evaluate for persistent gluten ingestion.[11] These biomarkers are not validated or widely available in Europe.

Esophagogastroduodenoscopy and small bowel biopsies are essential in the evaluation of persistent or recurrent symptoms in patients with confirmed celiac disease. Although at least 1–2 biopsies from the duodenal bulb and at least 4 biopsies from the distal duodenum are recommended for initial diagnosis, the optimal biopsy protocol for follow-up and evaluation of potential RCD is not well-defined.[12,13] The primary objective of the biopsies is to identify persistent villous atrophy, which is necessary but not sufficient for diagnosis of RCD. Persistent villous atrophy in patients with confirmed celiac disease may be caused by gluten ingestion, slowly responsive celiac disease, or RCD.[14,15] Patients with minimal or no histologic changes on duodenal biopsy should be evaluated for other potential causes of their symptoms, as outlined below. If the suspicion for RCD is strong, such as in patients with weight loss, anemia, gastrointestinal bleeding, or persistent nutritional deficiencies, the endoscopist should also consider obtaining up to 6 additional biopsies from the distal duodenum for flow cytometry (usually 2–3 biopsies to be placed in normal saline or RPMI medium), immunohistochemistry (IHC), and

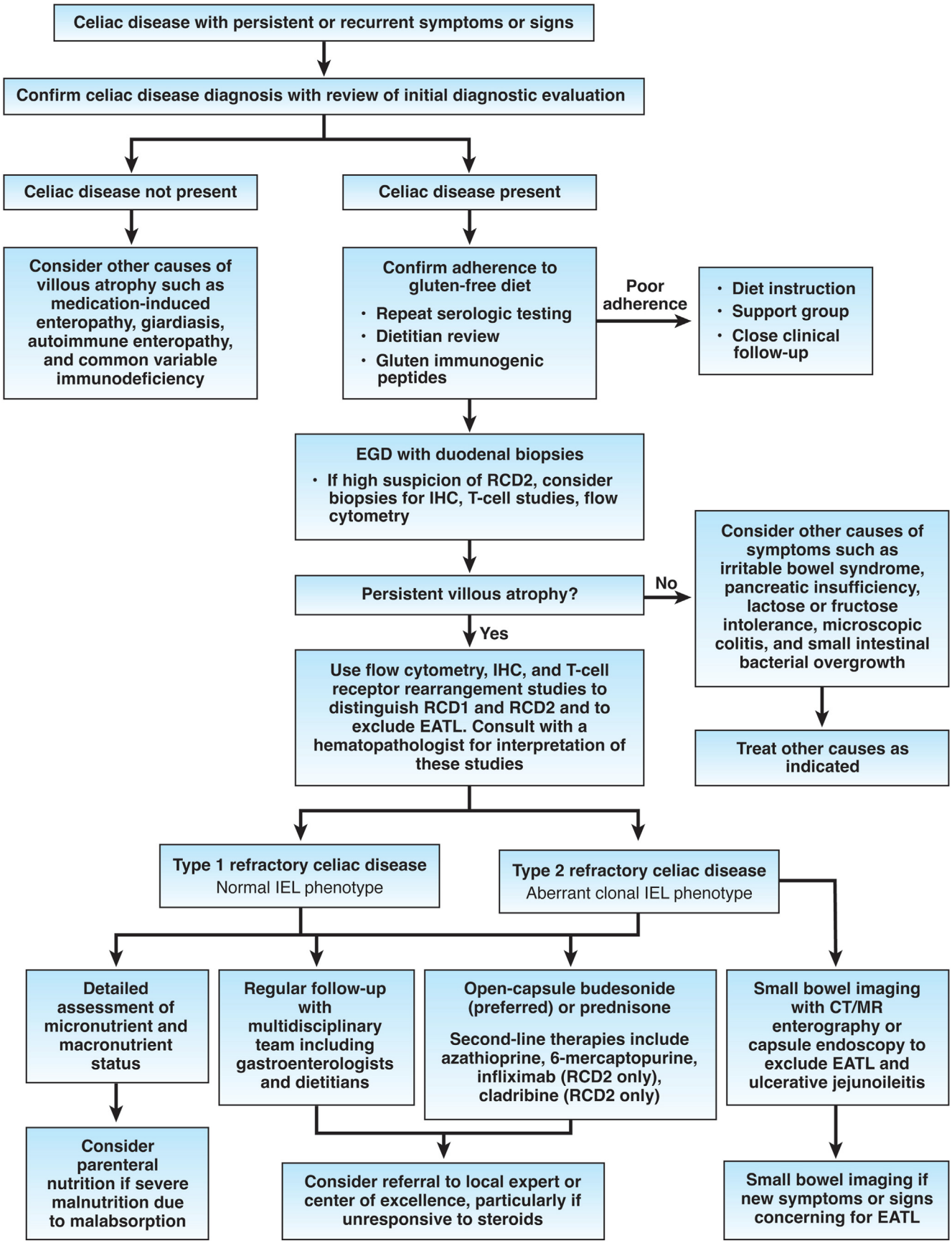

Figure 1. Algorithm for diagnosis and management of refractory celiac disease.

T-cell receptor (TCR) rearrangement studies at this time to help distinguish between RCD1 and RCD2. Targeted biopsies from any areas of abnormal mucosa should also be taken.

A frequent misstep is labeling any patient with consistent pathology as having celiac disease and commencing the gluten-free diet without performing celiac serologic testing. Patients with villous atrophy due to causes other than celiac disease will not respond to the gluten-free diet. If the celiac disease diagnosis is not confirmed and villous atrophy persists, other causes of villous atrophy should be considered. Medication-induced villous atrophy can be confused with celiac disease. Olmesartan enteropathy can cause severe illness, but responds rapidly to drug cessation.[16] Other angiotensin receptor blocker drugs have been reported to cause a similar enteropathy and may aggravate celiac disease symptoms and slow mucosal healing.[17,18] Mycophenolate, methotrexate, and azathioprine can also cause an enteropathy.[19] Common variable immunodeficiency disease can also cause similar symptoms and pathology.[20]

Autoimmune enteropathy can be diagnosed in individuals with a sprue-like biopsy appearance, other autoimmune diseases, and anti-enterocyte and/or anti-goblet cell antibodies. Pathologically, absence of Paneth or goblet cells and increased crypt apoptotic bodies may be recognized. Features of autoimmune enteropathy may coexist with celiac disease.[21,22] The diagnosis of tropical sprue requires travel or residence in tropical countries. Folate and/or vitamin B12 deficiency is characteristic. Typically, biopsies demonstrate partial villous atrophy, which may be patchy, and less intraepithelial lymphocytosis.[23] Tropical sprue responds rapidly to treatment with folic acid and tetracycline. Some patients with a sprue-like histology lack evidence of other etiologies and can be labeled as "unclassified sprue" or idiopathic villous atrophy. Whether this is a form of autoimmune enteropathy is unclear.

Re-examination of the biopsy by an experienced gastrointestinal pathologist may reveal evidence of an alternative diagnosis, such as EATL, low-grade $CD4^+$ lymphoma,[24] tuberculosis, *Mycobacterium avium* complex, giardiasis, or Whipple's disease. HIV enteropathy should be excluded.

Best Practice Advice 3: For patients with nonresponsive celiac disease, after exclusion of gluten ingestion, perform a systematic evaluation for other potential causes of symptoms, including functional bowel disorders, microscopic colitis, pancreatic insufficiency, inflammatory bowel disease, lactose or fructose intolerance, and small intestinal bacterial overgrowth.

Persistent or recurrent symptoms may reflect the development of nonresponsive celiac disease and are a frequent reason for seeking care. Although gluten ingestion is the most common cause, both lactose and fructose intolerance can cause similar symptoms and can be diagnosed with appropriate breath tests.[7,25,26] Irritable bowel syndrome may contribute to persistent symptoms[7] and respond to fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) restriction.[27] If a low-FODMAP diet is being considered for patients thought to have irritable bowel syndrome, referral to a dietitian with expertise in managing gastrointestinal disorders can be helpful. The low FODMAP diet is not indicated in all patients with nonresponsive celiac disease.[28] Pancreatic insufficiency is common in this setting and can be treated with gluten-free pancreatic enzyme supplements.[29]

Small intestinal bacterial overgrowth can be detected by means of breath testing.[30,31] Colonoscopy is indicated in patients with celiac disease and persistent or recurrent diarrhea because of the increased risk of microscopic colitis[32] and inflammatory bowel disease.[33] These conditions can occur in those with celiac disease who are refractory to diet, as well as those with healed small intestinal mucosa.

RCD should be strongly considered in patients with persistent or recurrent symptoms or signs of malabsorption after exclusion of other more common causes and malignancy.

Best Practice Advice 4: Use flow cytometry, immunohistochemistry, and T-cell receptor rearrangement studies to distinguish between subtypes of refractory celiac disease and to exclude enteropathy-associated T-cell lymphoma. Type 1 refractory celiac disease is characterized by a normal intraepithelial lymphocyte population and type 2 is defined by the presence of an aberrant, clonal intraepithelial lymphocyte population. Consultation with an expert hematopathologist is necessary to interpret these studies.

A diagnosis of RCD requires symptoms of malabsorption and villous atrophy in duodenal biopsies. Subclassification into RCD1 and RCD2 is based on immunophenotypic and molecular characteristics of IELs. RCD1 is characterized by a normal IEL population and RCD2 is defined by the presence of an aberrant, clonal IEL population.[34] The IEL immunophenotype is determined by IHC and flow cytometry, and TCR γ or β gene rearrangement is determined by polymerase chain reaction. Flow cytometry requires fresh, unfixed specimens placed in RPMI medium or normal saline. IHC and polymerase chain reaction can be performed on formalin-fixed or fresh unfixed tissue. Close collaboration with gastrointestinal pathologists and experienced hematopathologists is needed to interpret these studies.[35]

The IELs in RCD1 are similar to those seen in healthy individuals and patients with active celiac disease and are characterized by polyclonal expansion with a normal phenotype. These IELS are surface (s)$CD3^+$, cytoplasmic (cyt)$CD3^+$, $CD8^+$, and $sTCR^+$, with polyclonal TCR β or γ gene rearrangements.[36]

The diagnosis of RCD2 depends on interpretation of histopathology and flow cytometry. In contrast to RCD1, RCD2 is characterized by clonal proliferation of aberrant IELs most frequently characterized as $CD7^+$, $sCD3^-$, $cytCD3^+$, $sCD4^-$, $CD103^+$, $CD8^-$, and $sTCR^-$[37,38] which make up 20% or more of the total IEL population. IHC allows detection of the approximate number of $CD3^+$ lymphocytes, but does not distinguish between sCD3 and cytCD3. IHC in RCD2 is typically $CD8^-$, although unusually may be $CD8^+$. Polymerase chain reaction detection of TCR clonal or monoclonal TCR β or γ gene rearrangements supports the diagnosis of RCD2. However, RCD2 can occur without clonal TCR rearrangements,[39] and their absence does not preclude

a poor prognosis in patients with RCD.[40] Research is ongoing to identify novel diagnostic biomarkers of gastrointestinal T-cell neoplasms, such as NKp46.[41] In addition, the diagnosis of RCD2 cannot be made on the basis of detection of TCR β or γ clonal rearrangements alone because clones can be detected with newly diagnosed celiac disease, celiac disease on a gluten-free diet, and RCD1. Clonal TCR rearrangement detection is not infrequent in cases lacking features of RCD2. Therefore, TCR rearrangement results should be assessed in conjunction with immunophenotypic, histologic, and clinical findings for appropriate diagnosis and classification of RCD.[42] Prominent clonal peaks can persist without evidence of progression to RCD2.[42,43]

This classification of RCD2 as a single entity does not completely reflect the atypical RCD2 variants that are encountered.[44] Although RCD2 is regarded as a low-grade or intraepithelial malignancy, progression to full-blown EATL is manifested by the presence of large or atypical lymphocytes, as well as discrete tumors.

Best Practice Advice 5: Perform small bowel imaging with capsule endoscopy and computed tomography or magnetic resonance enterography to exclude enteropathy-associated T-cell lymphoma and ulcerative jejunoileitis at initial diagnosis of type 2 refractory celiac disease.

After RCD2 is diagnosed, complications, such as EATL or ulcerative jejunoileitis should be excluded due to their management implications with capsule endoscopy and either computed tomography (CT) or magnetic resonance (MR) enterography. Risk of lymphoma in RCD1 is extremely low, and imaging is indicated in these patients only if they are not doing well on therapy. Capsule endoscopy can help quantify the extent and severity of villous atrophy, as well as look for these complications.[45] In general, the extent and severity of villous atrophy is greater in patients with RCD2 compared with RCD1.[46–48] CT or MR enterography are complementary to capsule endoscopy, and may show findings such as bowel wall thickening, mesenteric adenopathy, small bowel masses, or ulcerative jejunoileitis.[49] Repeat imaging should be obtained in patients with RCD2 who are clinically worsening due to the increased risk of lymphoma. The presence of strictures, inflammation, erosions, ulcers, or mass lesions on capsule endoscopy or cross-sectional imaging should prompt further evaluation with small bowel enteroscopy to secure a pathologic diagnosis.

Best Practice Advice 6: Complete a detailed nutritional assessment with investigation of micronutrient and macronutrient deficiencies in patients diagnosed with refractory celiac disease. Check albumin as an independent prognostic factor.

Best Practice Advice 7: Correct deficiencies in macro- and micronutrients using oral supplements and/or enteral support. Consider parenteral nutrition for patients with severe malnutrition due to malabsorption.

Celiac disease may be associated with both micronutrient and macronutrient deficiencies. The presence and severity of malnutrition should be evaluated on the basis of history of nonvolitional weight loss; low body mass index; and physical examination or test showing loss of muscle mass/strength, presence of ascites/edema, and/or physical manifestations of micronutrient deficiencies. Micronutrient status should also be evaluated objectively by testing for deficiency of fat-soluble vitamins (A, D, E, and prothrombin time for potential vitamin K deficiency), folate, vitamin B12, iron, copper, and zinc. Measurement of thiamine, magnesium, selenium, and vitamin B6 levels should be considered, particularly with chronic or severe diarrhea. As hypoalbuminemia is an independent predictor of mortality, albumin should be routinely monitored.[50]

In most patients, diet optimization guided by a registered dietitian and oral supplements can be used initially to correct nutrient deficiencies. Patients with more significant malnutrition may require enteral support, and patients with severe malnutrition due to malabsorption may need parenteral support.

Best Practice Advice 8: Corticosteroids, most commonly open-capsule budesonide or, if unavailable, prednisone, are the medication of choice and should be used as first-line therapy in either type 1 or type 2 refractory celiac disease.

At present, we have minimal prospective data on the management of RCD. Therefore, management suggestions are based on small retrospective studies and expert opinion, with no US Food and Drug Administration–approved therapies.[51–53] The goals with therapy are improvement or resolution of symptoms and duodenal mucosal abnormalities, management of malnutrition, and prevention of development of lymphoma.[34]

Glucocorticoids are considered first-line therapy; open-capsule budesonide is generally accepted as initial treatment of choice (Table 1).[45,52,54] Most patients (92%) had clinical response and histologic improvement (89%) with open-capsule budesonide in an open-label study.[55] Open-capsule budesonide is given as 3 mg 3 times daily with the first capsule opened and placed into applesauce, the second capsule opened and swallowed with water, and the third capsule swallowed intact. One alternative with proven efficacy but likely higher risk for adverse effects is prednisone.[45] Intravenous methylprednisolone is an alternative for severe disease, followed by oral prednisone or open-capsule budesonide. Unfortunately, initial doses and taper recommendations for steroids have not been examined rigorously. Overall, 80%–90% of RCD patients have an adequate clinical response to open-capsule budesonide or prednisone with higher clinical response in RCD1.[45,55] Resolution of the molecular and genetic abnormalities in patients with RCD2 has been reported with steroid therapy, but remains controversial. Reduction in risk of lymphoma development remains uncertain.[56] Patients who do not respond, have an incomplete response, or have recurrent symptoms during the steroid taper may require second-line therapy.

The optimal choice for second-line therapy is presently unknown, but addition of an immunosuppressant agent, such as azathioprine,[57] mercaptopurine, and tioguanine,[58] to steroids appears to be effective in RCD1. Azathioprine is the immunosuppressant of choice for long-term treatment

Table 1. Potential Therapies for Refractory Celiac Disease

Variable	Dose	Response	Other comments
Oral therapies			
Open-capsule budesonide[55]	3 mg 3 times daily	92% clinical response 89% histologic improvement	—
Prednisone[45]	40–60 mg daily with slow taper over several months	90% clinical response in RCD1 77% clinical response in RCD2	—
Small intestinal release mesalamine[61]	2–4 g/d	75% clinical response with mesalamine alone 33% complete response in patients treated with mesalamine and budesonide	—
Azathioprine[57] Mercaptopurine	2–2.5 mg/kg/d 1 mg/kg/d	71% clinical response	Potential risk of accelerated lymphoma development Use with caution in RCD2
Tioguanine[58]	0.3 mg/kg/d	83% clinical response 78% histologic response	Not available in United States
Dietary therapies			
Elemental diet[60]		67% clinical response 89% histologic improvement	—
Parenteral therapies			
Cladribine[63,64]	0.1 mg/kg/day IV × 5 d 1–3 courses every 6 mo	35% clinical improvement[63] 59% histologic improvement[63] 81% clinical response rate[64] 47% histologic response rate[64]	Only for RCD2
Infliximab[62]	5 mg/kg IV	Case report	Only for RCD2
Autologous stem cell transplantation[65,66]		85% clinical response 66% 4-y survival	Only for RCD2
Anti-interleukin 15 monoclonal antibody 714[37]	8 mg/kg IV on d0, d7, and every 2 wk thereafter through wk 10	Improvement in symptoms but no reduction of aberrant intraepithelial lymphocytes	Only for RCD2

of RCD1, although it has also been linked to villous atrophy in case reports.[59] Tioguanine is not available in the United States.[58] Low-dose steroids as monotherapy or in combination with immunosuppressants have been used with clinical success to maintain response in small case series, but prospective data are lacking. Immunosuppressant agents are not advised in patients with RCD2 due to concern for accelerated lymphoma development, although data are scarce and not definitive. Alternative therapies such as elemental diet,[60] cladribine (only suggested for RCD2), small intestinal release mesalamine,[61] and biologics[62] should be considered in life-threatening disease on a case-by-case basis, as current evidence is limited to small case series or even case reports with risk of publication bias.

The best treatment for RCD2 is unknown. Clinical response has been reported with steroids (as discussed above). However, risk of lymphomagenesis is a concern, and reduction of risk has not been proven in prospective studies. Cladribine was well tolerated in 17 patients with RCD2; 58% had histologic improvement and 35% had a decrease of aberrant IELs.[63] Unfortunately, 41% were diagnosed with EATL and died. A subsequent study of 32 patients treated with cladribine showed 5-year survival rate of 63% among responders and risk of EATL of 16%.[64] Thus, cladribine could be a safe and effective alternative in patients with RCD2 that is unresponsive to steroids. Autologous stem cell transplantation showed promising results in a small number of patients with RCD2, but its role in clinical practice has not been defined.[65,66] Clinical response rate after transplantation was 85%, with a 4-year survival rate of 66%.[66] Anti-interleukin 15 monoclonal antibody 714 showed improvement in symptoms but failed the primary end point of reduction of aberrant IELs in 28 patients with RCD2 compared with placebo.[37]

Surgery is rarely needed for patients with RCD, but is an option for rare patients with acute abdomen due to bowel perforation or RCD2 and localized ulcerative jejunitis with bowel obstruction or recurrent gastrointestinal bleeding.[45]

Best Practice Advice 9: Patients with refractory celiac disease require regular follow-up by a multidisciplinary team, including gastroenterologists and dietitians, to assess clinical and histologic response to therapy. Identify local experts with expertise in celiac disease to assist with management.

Best Practice Advice 10: Patients with refractory celiac disease without response to steroids may benefit from referral to a center with expertise for management or evaluation for inclusion in clinical trials.

Medical follow-up for patients with RCD is based on expert opinion.[67] A multidisciplinary approach is advised, including gastroenterologists and dietitians. Medical visits every 3 months are reasonable until disease is well controlled; after that, visits every 6 months may be appropriate. Clinical and laboratory parameters should be assessed during each visit, with aggressive correction of nutritional deficiencies. Dietitian follow-up includes malnutrition management (if present), assessment of adherence, and recommendation of continuation of strict gluten-free diet. The use of emerging biomarkers for gluten ingestion may be helpful in RCD1 to rule out low-degree, inadvertent gluten ingestion.[11,68] Hypoalbuminemia is a strong independent predictor of mortality, and monitoring during follow-up visits is advised.[50]

The optimal frequency of intestinal biopsy during follow-up is not well defined. A repeat intestinal biopsy 3–6 months after starting therapy is advised to assess response to treatment, including mucosal recovery and resolution of molecular and genetic abnormalities in the IEL. Evaluation of the intestinal biopsies by an expert gastrointestinal pathologist and molecular studies by a hematopathologist is invaluable.[35] Mucosal recovery has been demonstrated in RCD1, but is less likely in RCD2.[54] It is the authors' practice to repeat intestinal biopsy within 12 months after second intestinal biopsy in patients with RCD and good clinical response. In patients with lack of response to initial therapy, a repeat intestinal biopsy is considered after at least 3–6 months of therapy with an alternative medication or intervention. Small bowel imaging including capsule endoscopy,[46–48] MR imaging or CT enterography,[49] and 18F-fluorodeoxyglucose positron-emission tomography scan[69] should be strongly considered on a case-by-case basis anytime during follow-up when suspicion for overt lymphoma arises, particularly with RCD2.[70] The role of small bowel imaging during routine follow-up of patients with good clinical response is currently unknown.[71]

Conclusions

Celiac disease is a common disorder, and patients often have an incomplete clinical response to a gluten-free diet. Diagnosis and management of RCD remains challenging due to the rarity of the condition and the absence of a reference standard diagnostic marker. Ongoing prospective and comparative studies are needed to define proper diagnostic criteria for well-classified RCD patients and to identify optimal management strategies for this rare condition.

References

1. Husby S, Murray JA, Katzka DA. AGA Clinical Practice Update on diagnosis and monitoring of celiac disease-changing utility of serology and histologic measures: expert review. Gastroenterology 2019;156:885–889.
2. Corazza GR, Villanacci V, Zambelli C, et al. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. Clin Gastroenterol Hepatol 2007;5:838–843.
3. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330–354.
4. Oberhuber G. Histopathology of celiac disease. Biomed Pharmacother 2000;54:368–372.
5. Robert ME, Crowe SE, Burgart L, et al. Statement on best practices in the use of pathology as a diagnostic tool for celiac disease: a guide for clinicians and pathologists. Am J Surg Pathol 2018;42:e44–e58.
6. Leonard MM, Lebwohl B, Rubio-Tapia A, et al. AGA Clinical Practice Update on the evaluation and management of seronegative enteropathies: expert review. Gastroenterology 2021;160:437–444.
7. Leffler DA, Dennis M, Hyett B, et al. Etiologies and predictors of diagnosis in nonresponsive celiac disease. Clin Gastroenterol Hepatol 2007;5:445–450.
8. Stasi E, Marafini I, Caruso R, et al. Frequency and cause of persistent symptoms in celiac disease patients on a long-term gluten-free diet. J Clin Gastroenterol 2016; 50:239–243.
9. Nachman F, Sugai E, Vazquez H, et al. Serological tests for celiac disease as indicators of long-term compliance with the gluten-free diet. Eur J Gastroenterol Hepatol 2011;23:473–480.
10. Al-Toma A, Verbeek WH, Hadithi M, et al. Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut 2007;56:1373–1378.
11. Stefanolo JP, Talamo M, Dodds S, et al. Real-world gluten exposure in patients with celiac disease on gluten-free diets, determined from gliadin immunogenic peptides in urine and fecal samples. Clin Gastroenterol Hepatol 2021;19:484–491.e1.
12. Evans KE, Aziz I, Cross SS, et al. A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. Am J Gastroenterol 2011; 106. 1837–1742.
13. Gonzalez S, Gupta A, Cheng J, et al. Prospective study of the role of duodenal bulb biopsies in the diagnosis of celiac disease. Gastrointest Endosc 2010;72:758–765.
14. Rubio-Tapia A, Rahim MW, See JA, et al. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. Am J Gastroenterol 2010;105:1412–1420.
15. Fernandez-Banares F, Beltran B, Salas A, et al. Persistent villous atrophy in de novo adult patients with celiac disease and strict control of gluten-free diet adherence: a multicenter prospective study (CADER Study). Am J Gastroenterol 2021;116:1036–1043.
16. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012;87:732–738.
17. O'Morain N, Shannon E, McManus J, et al. Coeliac disease enteropathy and symptoms may be aggravated by angiotensin receptor blockers in patients on a

gluten-free diet. United European Gastroenterol J 2021;9:973–979.
18. Cartee AK, Reyes Genere JP, Oxentenko AS. New onset villous atrophy in a patient with celiac disease. Gastroenterology 2018;155:988–989.
19. DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. Am J Gastroenterol 2013; 108:647–653.
20. Malamut G, Verkarre V, Suarez F, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol 2010;105:2262–2275.
21. Sharma A, Choung RS, Wang XJ, et al. Features of adult autoimmune enteropathy compared with refractory celiac disease. Clin Gastroenterol Hepatol 2018; 16:877–883.e1.
22. van Wanrooij RLJ, Neefjes-Borst EA, Bontkes HJ, et al. Adult-onset autoimmune enteropathy in an european tertiary referral center. Clin Transl Gastroenterol 2021;12: e00387.
23. Sharma P, Baloda V, Gahlot GP, et al. Clinical, endoscopic, and histological differentiation between celiac disease and tropical sprue: a systematic review. J Gastroenterol Hepatol 2019;34:74–83.
24. Margolskee E, Jobanputra V, Lewis SK, et al. Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. PLoS One 2013;8:e68343.
25. Dewar DH, Donnelly SC, McLaughlin SD, et al. Celiac disease: management of persistent symptoms in patients on a gluten-free diet. World J Gastroenterol 2012; 18:1348–1356.
26. Abdulkarim AS, Burgart LJ, See J, et al. Etiology of nonresponsive celiac disease: results of a systematic approach. Am J Gastroenterol 2002;97:2016–2021.
27. Trott N, Rej A, Coleman SH, et al. Adult celiac disease with persistent IBS-type symptoms: a pilot study of an adjuvant FODMAP diet. Gastroenterol Hepatol Bed Bench 2021;14:304–310.
28. van Megen F, Skodje GI, Lergenmuller S, et al. A low FODMAP diet reduces symptoms in treated celiac patients with ongoing symptoms-a randomized controlled trial [published online ahead of print January 17, 2022]. Clin Gastroenterol Hepatol doi:10.1016/j.cgh.2022.01.011.
29. Leeds JS, Hopper AD, Hurlstone DP, et al. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? Aliment Pharmacol Ther 2007; 25:265–271.
30. Rubio-Tapia A, Barton SH, Rosenblatt JE, et al. Prevalence of small intestine bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. J Clin Gastroenterol 2009;43:157–161.
31. Tursi A, Brandimarte G, Giorgetti G. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. Am J Gastroenterol 2003;98:839–843.
32. Green PH, Yang J, Cheng J, et al. An association between microscopic colitis and celiac disease. Clin Gastroenterol Hepatol 2009;7:1210–1216.
33. Pinto-Sanchez MI, Seiler CL, Santesso N, et al. Association between inflammatory bowel diseases and celiac disease: a systematic review and meta-analysis. Gastroenterology 2020;159:884–903.e31.
34. Hujoel IA, Murray JA. Refractory celiac disease. Curr Gastroenterol Rep 2020;22:18.
35. Soderquist CR, Bhagat G. Cellular and molecular bases of refractory celiac disease. Int Rev Cell Mol Biol 2021; 358:207–240.
36. Cellier C, Patey N, Mauvieux L, et al. Abnormal intestinal intraepithelial lymphocytes in refractory sprue. Gastroenterology 1998;114:471–481.
37. Cellier C, Bouma G, van Gils T, et al. Safety and efficacy of AMG 714 in patients with type 2 refractory coeliac disease: a phase 2a, randomised, double-blind, placebo-controlled, parallel-group study. Lancet Gastroenterol Hepatol 2019;4:960–970.
38. Daum S, Cellier C, Mulder CJ. Refractory coeliac disease. Best Pract Res Clin Gastroenterol 2005;19:413–424.
39. Soderquist CR, Hsiao S, Mansukhani MM, et al. Refractory celiac disease type II: an atypical case highlighting limitations of the current classification system. Hematol Oncol 2020;38:399–405.
40. Arguelles-Grande C, Brar P, Green PH, et al. Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease. J Clin Gastroenterol 2013; 47:593–601.
41. Cheminant M, Bruneau J, Malamut G, et al. NKp46 is a diagnostic biomarker and may be a therapeutic target in gastrointestinal T-cell lymphoproliferative diseases: a CELAC study. Gut 2019;68:1396–1405.
42. Hussein S, Gindin T, Lagana SM, et al. Clonal T cell receptor gene rearrangements in coeliac disease: implications for diagnosing refractory coeliac disease. J Clin Pathol 2018;71:825–831.
43. Celli R, Hui P, Triscott H, et al. Clinical insignficance of monoclonal T-Cell populations and duodenal intraepithelial T-cell phenotypes in celiac and nonceliac patients. Am J Surg Pathol 2019;43:151–160.
44. de Mascarel A, Belleannee G, Stanislas S, et al. Mucosal intraepithelial T-lymphocytes in refractory celiac disease: a neoplastic population with a variable CD8 phenotype. Am J Surg Pathol 2008;32:744–751.
45. Malamut G, Afchain P, Verkarre V, et al. Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. Gastroenterology 2009; 136:81–90.
46. Barret M, Malamut G, Rahmi G, et al. Diagnostic yield of capsule endoscopy in refractory celiac disease. Am J Gastroenterol 2012;107:1546–1553.
47. Daum S, Wahnschaffe U, Glasenapp R, et al. Capsule endoscopy in refractory celiac disease. Endoscopy 2007;39:455–458.
48. Atlas DS, Rubio-Tapia A, Van Dyke CT, et al. Capsule endoscopy in nonresponsive celiac disease. Gastrointest Endosc 2011;74:1315–1322.
49. Al-Bawardy B, Barlow JM, Vasconcelos RN, et al. Cross-sectional imaging in refractory celiac disease. Abdom Radiol (N Y) 2017;42:389–395.

50. Rubio-Tapia A, Malamut G, Verbeek WH, et al. Creation of a model to predict survival in patients with refractory coeliac disease using a multinational registry. Aliment Pharmacol Ther 2016;44:704–714.
51. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. Gut 2010;59:547–557.
52. Rubio-Tapia A, Kelly DG, Lahr BD, et al. Clinical staging and survival in refractory celiac disease: a single center experience. Gastroenterology 2009;136:99–107; quiz 352–353.
53. Malamut G, Cellier C. Refractory celiac disease. Gastroenterol Clin North Am 2019;48:137–144.
54. Brar P, Lee S, Lewis S, et al. Budesonide in the treatment of refractory celiac disease. Am J Gastroenterol 2007; 102:2265–2269.
55. Mukewar SS, Sharma A, Rubio-Tapia A, et al. Open-capsule budesonide for refractory celiac disease. Am J Gastroenterol 2017;112:959–967.
56. Cording S, Lhermitte L, Malamut G, et al. Oncogenetic landscape of lymphomagenesis in coeliac disease. Gut 2021;71:497–508.
57. Maurino E, Niveloni S, Chernavsky A, et al. Azathioprine in refractory sprue: results from a prospective, open-label study. Am J Gastroenterol 2002;97:2595–2602.
58. Tack GJ, van Asseldonk DP, van Wanrooij RL, et al. Tioguanine in the treatment of refractory coeliac disease—a single centre experience. Aliment Pharmacol Ther 2012;36:274–281.
59. Ziegler TR, Fernandez-Estivariz C, Gu LH, et al. Severe villus atrophy and chronic malabsorption induced by azathioprine. Gastroenterology 2003;124:1950–1957.
60. Olaussen RW, Lovik A, Tollefsen S, et al. Effect of elemental diet on mucosal immunopathology and clinical symptoms in type 1 refractory celiac disease. Clin Gastroenterol Hepatol 2005;3:875–885.
61. Jamma S, Leffler DA, Dennis M, et al. Small intestinal release mesalamine for the treatment of refractory celiac disease type I. J Clin Gastroenterol 2011;45:30–33.
62. Gillett HR, Arnott ID, McIntyre M, et al. Successful infliximab treatment for steroid-refractory celiac disease: a case report. Gastroenterology 2002;122:800–805.
63. Al-Toma A, Goerres MS, Meijer JW, et al. Cladribine therapy in refractory celiac disease with aberrant T cells. Clin Gastroenterol Hepatol 2006;4:1322–1327; quiz 1300.
64. Tack GJ, Verbeek WH, Al-Toma A, et al. Evaluation of cladribine treatment in refractory celiac disease type II. World J Gastroenterol 2011;17:506–513.
65. Al-Toma A, Visser OJ, van Roessel HM, et al. Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. Blood 2007; 109:2243–2249.
66. Tack GJ, Wondergem MJ, Al-Toma A, et al. Auto-SCT in refractory celiac disease type II patients unresponsive to cladribine therapy. Bone Marrow Transplant 2011; 46:840–846.
67. Malamut G, Cellier C. Complications of coeliac disease. Best Pract Res Clin Gastroenterol 2015;29:451–458.
68. Moreno ML, Cebolla A, Munoz-Suano A, et al. Detection of gluten immunogenic peptides in the urine of patients with coeliac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing. Gut 2017; 66:250–257.
69. Hadithi M, Mallant M, Oudejans J, et al. 18F-FDG PET versus CT for the detection of enteropathy-associated T-cell lymphoma in refractory celiac disease. J Nucl Med 2006;47:1622–1627.
70. Chandesris MO, Malamut G, Verkarre V, et al. Enteropathy-associated T-cell lymphoma: a review on clinical presentation, diagnosis, therapeutic strategies and perspectives. Gastroenterol Clin Biol 2010;34:590–605.
71. Chetcuti Zammit S, Sanders DS, Cross SS, et al. Capsule endoscopy in the management of refractory coeliac disease. J Gastrointestin Liver Dis 2019; 28:15–22.

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Conflicts of interest
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