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

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The Emoroid Digest
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Celiac Disease

- Affects 1% of the US population
- **Dx:** serologic testing (**anti-tissue transglutaminase**, anti-deamidated gliadin peptide, and anti-endomysial antibodies) & duodenal biopsies (villous atrophy and intraepithelial lymphocytosis (IELs))
- **Txt:** strict gluten free diet (GFD)

Refractory Celiac Disease (RCD)

- **RCD:** Persistent signs of malabsorption (diarrhea, weight loss, anemia) and villous atrophy despite 12 months of strict GFD (seen in ~1% of those with CD)

Type 1 (RCD1):
- villous atrophy
- IELs similar to conventional celiac disease

Type 2 (RCD2):
- aberrant clonal T-cell expansion in the GI tract and other organs
- **poorer prognosis** than Type 1
- ↑ ulcerative jejunoileitis and enteropathy-associated T-cell lymphoma (EATL)

Diagnosis of RCD

- If there is Celiac disease with persistent or recurrent symptoms or signs, confirm celiac disease diagnosis w/ review of prior endoscopies, histology, & serology

Not Celiac Disease

Consider other causes of villous atrophy (med-induced or autoimmune enteropathy, tropical sprue, giardiasis, CVID, etc.)

Celiac Disease

Confirm adherence to GFD w/ serologic testing (↑ celiac Abs), dietitian review, & detection of immunogenic peptides in stool or urine

If poor adherence: dietary instruction, support groups, & close clinical f/u are recommended

EGD w/ duodenal bx
- Recommend at least **1–2 biopsies** from the duodenal bulb and **4** from the distal duodenum
- Goal is to identify if there is persistent villous atrophy (necessary but not sufficient to dx RCD)
- If strong suspicion for RCD (in pts w/ wt loss, anemia, GI bleeding, persistent nutritional deficiencies), **consider 6 additional biopsies** from the distal duodenum for flow cytometry, IHC, and T cell receptor rearrangement studies to distinguish between RCD1 and RCD2

If persistent villous atrophy → flow cytometry, IHC, & T cell receptor rearrangement studies to distinguish RCD1 & 2, exclude EATL
- IEL phenotype is determined by IHC and flow cytometry
- T cell receptor γ or β gene rearrangement is determined by PCR

RCD1 - Polyclonal expansion of IELs with normal phenotype
- Surface (s) CD3þ, cytoplasmic(cyt) CD3+, CD8+, and sTCR+, with polyclonal TCR β or γ gene rearrangements

RCD2 - Clonal proliferation of aberrant IELs
- Most frequently CD7+, sCD3–, cytCD3+, sCD4–, CD103+, CD8–, and sTCR+

If no persistent villous atrophy consider:
- Irritable Bowel Syndrome
- Exocrine Pancreatic Insufficiency
- Lactose/fructose intolerance
- Microscopic colitis
- Small Intestinal Bacterial Overgrowth

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Management of RCD

RCD1 and RCD2

- Assess **micro/macro nutrient status**
  - Test for Vitamin A, D, E, and prothrombin time for vitamin K deficiency, folate, vitamin B12, iron, copper, and zinc
  - Assess thiamine, Mg, Se, and vitamin B6, particularly with chronic or severe diarrhea
- Consider **parenteral nutrition** if severe malnutrition
- **Check albumin** as an independent prognostic factor

Open capsule budesonide (preferred) or prednisone
Second line therapies include azathioprine, 6MP

RCD2

Small bowel imaging w/ CTE/MRE or VCE to exclude EATL and ulcerative jejunoileitis

VCE- can quantify the extent and severity of villous atrophy

CT/MRE- can note bowel wall thickening, mesenteric adenopathy, small bowel masses
Repeat imaging if clinically worsening as ↑ lymphoma risk

Second line therapies include infliximab and cladribine

First Line Oral Medication Options

Open Capsule Budesonide
- Administer 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
- 92% w/ clinical response and 89% w/ histologic improvement

Oral Prednisone
- Administer 40–60 mg daily with slow taper over several months

Second Line Oral Medication Options

Add an **immunosuppressant** to steroids
- Azathioprine: 2-2.5 mg/kg/d
- Mercaptopurine: 1 mg/kg/d
- Tioguanine .3 mg/kg/d (not available in the US)

Not advised in those w/ RCD2 given increased risk of lymphoma development

Alternative Therapies for RCD 2

Elemental Diet - 67% see clinical response, 89% w/ histologic remission

Cladribine - 0.1 mg/kg/day IV x 5 d, 1-3 courses every 6 months

Infliximab - 5 mg/kg IV

Small intestine release mesalamine- 2-4 g PO/day

Autologous Stem Cell Transplant- 85% clinical response

Anti-IL 15 monoclonal Ab 714- 8 mg/kg IV on d0, d7, and every 2 wk thereafter through wk 10
- Improvement in symptoms but no decrease in aberrant IELs

Long Term Care

Patients w/ RCD **require regular follow**-up by a multidisciplinary team, including gastroenterologists and dietitians, to assess clinical and histologic response to therapy
- Clinic visits every 3 months until disease is well controlled, then every 6 months

Identify local experts in celiac disease to help w/ management or if no response to steroids, refer to a center with expertise for management and evaluation for inclusion in clinical trials

Repeat intestinal biopsy 3–6 months after starting therapy to assess response to treatment, including mucosal recovery and resolution of molecular/ genetic abnormalities in the IEL.
- Mucosal recovery is seen in RCD1 but less likely in RCD2

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