Celiac Center

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

Non Responsive Celiac Disease

Key Points

- Currently, the only treatment for celiac disease (CD) is strict life-long adherence to a gluten-free diet (GFD). A minority of cases, however, will fail to completely improve or may relapse while on the diet.[1]

- Non responsive Celiac Disease (NRCD) affects 7-30% of patients on a GFD.[2] It may be defined as continued signs and symptoms that suggest CD despite dietary gluten avoidance for 6-12 months.[3]

- NRCD can be further classified as primary or secondary. Primary refers to an initial failure to achieve symptomatic response on a GFD. Secondary NRCD occurs when symptoms return while on a GFD.[2]

- When the symptoms fail to improve or recur, proper evaluation should be followed to identify and treat the specific cause (See Figure 1).[4] It is important to review and carefully examine the initial diagnosis of CD based on the history of symptoms, signs, lab tests, and biopsy results at the time of diagnosis.

- An endoscopy should be considered if the diagnosis was done based only on blood tests. This will also help the doctor assess intestinal healing and other conditions that can cause similar biopsy findings (See Blood Tests and Endoscopy).

- The most common cause of NRCD is accidental gluten ingestion. Gluten exposure accounts for 35-50% of ongoing symptoms in patients with CD.[3] For this reason, it is very important to obtain sound dietary advice from an expert celiac dietitian.[1] It will also help you identify if the cause of ongoing symptoms could be due to lactose intolerance or fructose malabsorption. These two conditions can occur as a result of intestinal damage caused by CD.

- A positive blood test for CD could be helpful to assess cross-contact with gluten and adherence to the GFD. It is important to remember, however, that a normal blood test does not exclude cross contact with gluten as a possibility.

- After a dietitian carefully excludes gluten as a cause of the symptoms, a small intestinal biopsy may be repeated and compared with the initial biopsy. A normal or near normal biopsy will lead the doctor to consider other possible causes (See Table 1).[5]

- It is widely accepted that small intestinal villous atrophy (decrease in size, or wasting) is required for the diagnosis of CD.[1] Biopsies of the small intestine are obtained with the help of a safe and

quick procedure called an esophago-gastro-duodenoscopy (EGD) or endoscopy.

- An endoscopy is routinely used to evaluate gastrointestinal symptoms and allows direct visualization of the upper gastrointestinal tract (esophagus, stomach, beginning portion of the small intestine called the duodenum) through a flexible, narrow tube with a camera attached at the end called an endoscope. The endoscope is inserted through the mouth and moved through the stomach into the duodenum.

Other causes for NRCD include but are not limited to:

1. **Small intestinal bacterial overgrowth syndrome (SIBO):**
   - Small intestinal bacterial overgrowth syndrome (SIBO) is caused by abnormal intestinal motion, lowered immune defenses, or damage to the intestinal mucosa. These factors create imbalance in the gut flora that results in overgrowth of the harmful bacteria.
   - This condition can be challenging but is often assessed with a hydrogen and methane breath test and treated with a course of antibiotics. The use of prebiotics and probiotics may also be useful.

2. **Microscopic colitis:**
   - Microscopic colitis is a common cause of long standing diarrhea caused by inflammation of the large intestine (colon).
   - It generally presents with episodes of watery, non-bloody diarrhea of long standing, intermittent, or recurrent course.[6]
   - The diagnosis is made by colonoscopy and confirmed by assessment of biopsies under a microscope (thus the name microscopic).
   - Treatment varies depending on the persistence and severity of symptoms.

3. **Pancreatic insufficiency:**
   - Pancreatic insufficiency is caused by insufficient production of digestive enzymes by the pancreas. This low production leads to malabsorption of nutrients and fatty diarrhea (pale, bulky and foul smelling stools, often with oil droplets).
   - Diagnosis is made by measuring the amount of enzymes (usually elastase) and/or fat in the stool.
   - Treatment is based primarily on pancreatic enzyme replacement therapy. It may also include lifestyle modifications and vitamin supplementation.

4. **Irritable bowel syndrome (IBS):**
   - IBS is a functional disorder of the intestine that commonly presents with abdominal pain or discomfort, is associated with bowel changes and is usually relieved by bowel movements. Other symptoms such as bloating, diarrhea and/or constipation are required to establish a diagnosis.
   - No damage is seen in the intestine compared to CD.
   - In many cases, this condition can be controlled by changes in lifestyle including diet and stress management.

5. **Refractory Celiac Disease (RCD):**[3,7,8]
    - RCD is a severe form of CD that belongs to a subset of NRCD.
    - This is a rare condition affecting 1-2% of patients with CD and up to 10% of those with NRCD. Damage to the small intestine continues despite a strict GFD and no evidence of another disease, including cancer (lymphoma).
    - RCD can be further subdivided into type I and type II. This distinction is based on a special type of white blood cells seen on the biopsy of the small intestine.
    - RCD type I has a better clinical course and survival than RCD type II.

Other diagnoses that may be associated with CD include inflammatory bowel disease and lactose or fructose intolerance (caused by mucosal damage from CD). These conditions should be excluded and treated correctly.[1]

Take Home Messages:

- In the majority of people with CD, a GFD is sufficient to allow for clinical improvement and improved biopsy results.
- A minority of patients will still have symptoms 6-12 months after starting a GFD.
- The most common cause of ongoing symptoms and abnormal lab values is cross contact with gluten.
- GFD adherence should be supported by the guidance of an expert dietitian, advocacy groups, and regular clinic visits.
- Treatment of other causes of NRCD depends on the cause.

Table 1:

Causes of Nonresponsive Celiac Disease

Cause	Typical Features/Tests	How Common
Gluten exposure (see Chapter 20)	Evaluation by dietitian skilled in celiac disease	Very common
Irritable bowel syndrome (see Chapter 38)	None	Very common
Lactose intolerance or fructose malabsorption (see Chapter 37)	Trial of lactose or fructose restriction; lactose or fructose breath testing	Somewhat common
Microscopic colitis (see Chapter 39)	Biopsy of colon	Somewhat common
Small intestinal bacterial overgrowth (see Chapter 40)	Breath testing and or a response to antibiotic therapy	Somewhat common
Refractory celiac disease (see Chapter 43)	Biopsy of small intestine	Rare
Eating disorder (see Chapter 30)	None	Rare
Inflammatory bowel disease	Biopsy of small or large intestine, imaging studies of intestine	Rare
Pancreatic exocrine insufficiency	Stool levels of chymotrypsin or elastase	Rare
Motility disturbances (too slow or too fast movement of food through the intestine)	Gastric emptying study, intestinal transit testing	Rare
Food allergy (see Chapter 35)	Allergy testing (skin or blood)	Very rare
Cancer	Endoscopy, imaging studies of intestine	Very rare

From Shailaja Jamma, MD, and Daniel A. Leffler, MD: Nonresponsive Celiac Disease. In *Real Life with Celiac Disease: Troubleshooting and Thriving Gluten Free* by Melinda Dennis, MS, RD, LDN, and Daniel A. Leffler, MD.

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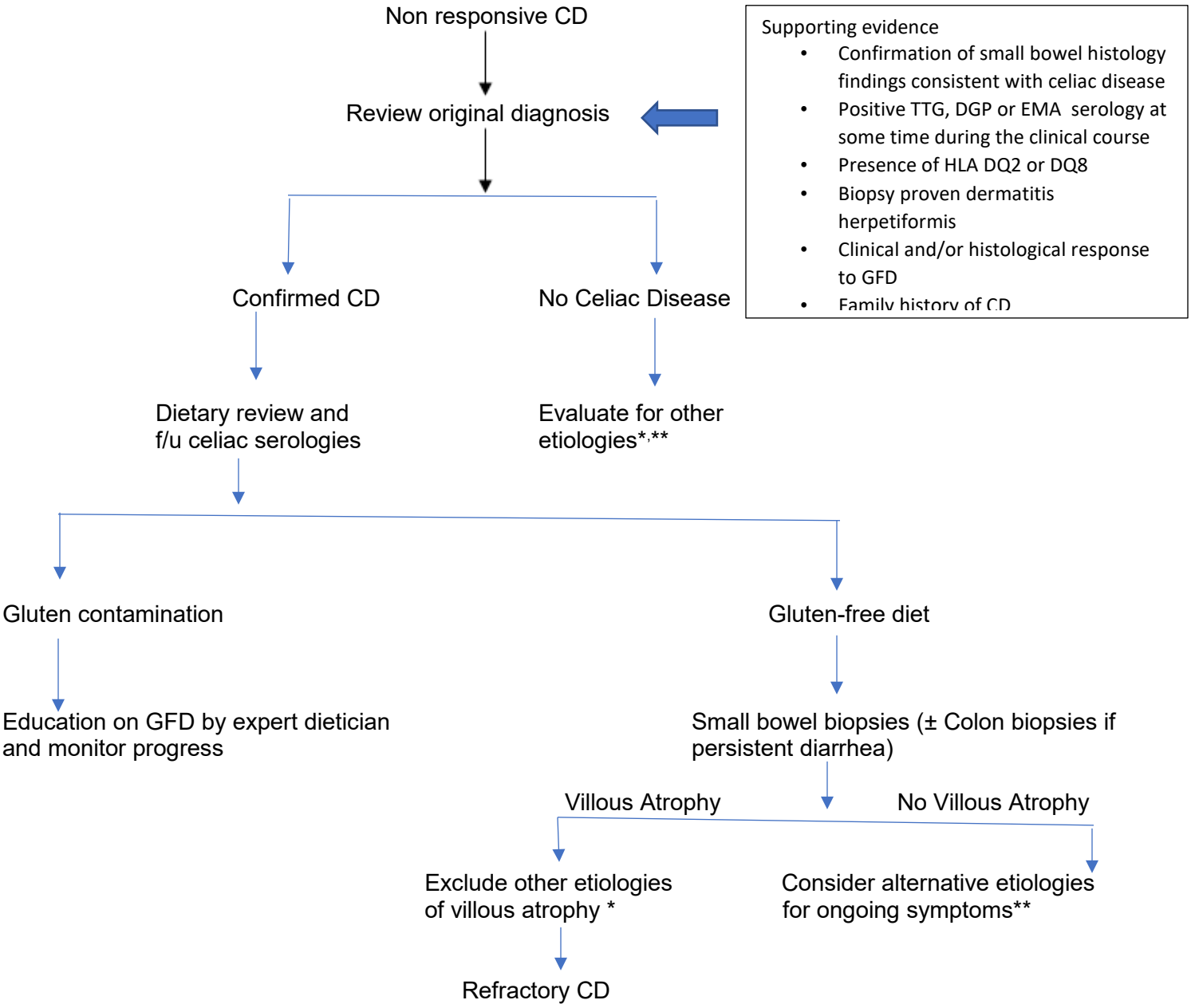
Figure 1: An approach to the investigation of Nonresponsive celiac disease



* Autoimmune enteropathy, combined variable immunodeficiency, collagenous sprue, small intestinal bacterial overgrowth (SIBO), Crohn's disease, tropical sprue, eosinophilic enteritis, and peptic duodenitis
** Irritable bowel syndrome, SIBO, food intolerances, eosinophilic enteritis, microscopic colitis, and Crohn's disease

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