Management of celiac disease in adults

AUTHOR: Paul J Ciclitira, MBBS, MD, PhD, FRCP, AGAF
SECTION EDITOR: J Thomas Lamont, MD
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Feb 01, 2023.**

INTRODUCTION

Celiac disease can be defined as a condition in which there is an abnormal small intestinal mucosa that improves morphologically when treated with a gluten-free diet and relapses when gluten is reintroduced. The disorder is commonly referred to as "celiac sprue" or "gluten-sensitive enteropathy" in the United States. It was first described by Samuel Gee in 1887, although a similar description of a chronic malabsorptive disorder was recorded as far back as the second century AD [1].

As a general rule, there are six key elements in the management of patients with celiac disease, which can be summarized with the following acronym [2]:

- Consultation with a skilled dietitian
- Education about the disease
- Lifelong adherence to a gluten-free diet
- Identification and treatment of nutritional deficiencies
- Access to an advocacy group
- Continuous long-term follow-up by a multidisciplinary team

The recommendations made in this topic are generally consistent with guidelines from the British National Institute for Health and Clinical Excellence, the American Gastroenterological Association, the American College of Gastroenterology, and a consensus statement issued by the National Institutes of Health [2-4].

The management of celiac disease and its complications will be reviewed here. Its pathogenesis, clinical manifestations, and diagnosis are discussed separately. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults" and "Diagnosis of celiac disease in adults".)

DIETARY COUNSELING

The cornerstone of treatment of celiac disease is the elimination of gluten in the diet. Treatment of the patient with celiac disease begins with dietary counseling.

Indications — A gluten-free diet is recommended in patients with celiac disease (classic disease, atypical celiac disease, and asymptomatic or silent celiac disease). Patients with celiac disease should be referred to a registered dietitian who is knowledgeable about celiac disease. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Terminology'.)

Patients with latent celiac disease (positive IgA endomysial antibody, but normal small bowel biopsy) are not advised to be on a gluten-free diet but should continue to be monitored and rebiopsied if symptoms develop. However, it is important that such patients are adequately evaluated with multiple intestinal biopsies since histologic abnormalities can be patchy [5]. (See "Diagnosis of celiac disease in adults", section on 'Endoscopy with small bowel biopsy'.)

Components of the gluten-free diet — The principal sources of dietary gluten are wheat, rye, and barley. Consumption of a gluten-free diet requires a major lifestyle change since gluten is contained in a variety of foods that are commonly consumed in a Western diet. Thus, it is usually helpful to provide written information and dietary counselling to improve compliance. A number of resources are available for patients with celiac disease. (See "Patient education: Celiac disease in adults (Beyond the Basics)".)

As general rules, the following dietary advice can be given to all patients:

- Foods containing wheat, rye, and barley should be avoided.
- Soybean or tapioca flours, rice, corn, buckwheat, and potatoes are safe.
- Read labels on prepared foods and condiments carefully, paying particular attention to additives such as stabilizers or emulsifiers that may contain gluten.
- Distilled alcoholic beverages and vinegars, as well as wine, are gluten free. However, beers, ales, lagers, and malt vinegars should be avoided because they are often made

from gluten-containing grains and are not distilled. However, in Europe gluten-free beers are now marketed and can be obtained worldwide.

- Dairy products may not be well tolerated initially, since many patients with celiac disease can have secondary lactose intolerance. (See "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management".) As a result, lactose-containing products should initially be avoided in patients whose symptoms appear to be worsened by them.

- Oats should be introduced into the diet with caution given the variety of oats with variable toxicity and uncertainty as to whether oats stripped of gluten contamination during harvesting are considered safe for all people with celiac disease. Patients require monitoring for clinical or serologic evidence of disease recurrence when pure/uncontaminated oats are added to a gluten-free diet.

In a meta-analysis of 28 studies (661 patients, six randomized control trials, and two nonrandomized control trials) that evaluated the safety of oats in patients with celiac disease, oat consumption in a gluten-free diet for 12 months showed no effect on symptoms, histologic scores, or serologic test results [6]. Limitations of the study included the lack of information on the type of origin and quantity of oats, variation in study design and time, small number of randomized controlled trials, and lack of information on compliance with gluten-free diet.

In a large, cross-sectional study of 869 patients with celiac disease on a gluten-free diet for 10 years, of whom 82 percent consumed oats, there were no differences in symptoms, positive EMA, histologic recovery after one year, malignancy, bone disease, or fractures between those who consumed oats and those who did not [7]. Those who consumed oats had better health scores.

There are a few reasons why oats may be better tolerated.

- First, even though oats contain a sequence homology (ie, QQQPF) with gliadin peptides, which have been shown to be disease activating, this homology may not be relevant since T-cell activation requires larger epitopes [8,9].

- Second, oats contain a relatively smaller proportion of this toxic prolamin moiety compared with other gluten-containing cereals. This hypothesis is supported by studies on oat challenge in patients with celiac disease, which suggest that tolerance to oats depends at least in part upon the total amount consumed [10]. Daily oats consumption less than 40 to 60 g/day by patients whose celiac disease is in remission appears to be well tolerated,

while larger daily intake is associated with disease recurrence [10]. However, studies using these larger quantities were performed before the advent of small bowel biopsy.

- Finally, there may be variability in the immunogenicity of different oat cultivars, which may explain some of the disparate results when it comes to oat tolerability in patients with celiac disease [11].

Is strict gluten avoidance necessary? — As gluten elimination poses several lifestyle restrictions, compliance with a strict gluten-free diet is limited [12]. This is in part because the ability to tolerate gluten in the diet is highly variable among patients. While some patients are exquisitely sensitive to even small amounts of gluten, other patients can tolerate the reintroduction of small amounts in their diet after achieving remission.

Despite this variable response, several arguments favor encouraging strict adherence to a gluten-free diet in most patients with established celiac disease regardless of clinical symptoms:

- Despite feeling clinically well, patients may have a variety of micronutrient deficiencies that may ultimately have clinical sequelae such as bone loss due to vitamin D deficiency. These can be partially reversed with a gluten-free diet [13]. (See 'Prevention of bone loss' below.)

- Multiple reports have suggested increased overall mortality and risk of malignancy (lymphoproliferative disease and gastrointestinal cancer) in patients with celiac disease compared to the general population [14]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

  Although, in one study, the increased risk of non-Hodgkin lymphoma persisted for five years after diagnosis despite adherence to a gluten-free diet [15], several other studies have suggested that the risk is decreased in patients adhering to a gluten-free diet [16-19].

- At least two studies found that the likelihood that patients with celiac disease will develop other autoimmune disorders associated with celiac disease (eg, type 1 diabetes mellitus, connective tissue diseases, Hashimoto's thyroiditis, and Graves' disease) appeared to be related to the duration of exposure to gluten [20,21], although discordant data have been reported [22].

- Mothers with undiagnosed celiac disease appear to be at increased risk for having low birth weight newborns and preterm births compared to those whose disease has been diagnosed (and presumably treated) [23,24].

Trace amounts of gluten may be contained in products that are labeled as gluten-free. However, the small amount of gluten contained in these products does not necessarily cause treatment failure. A study evaluating occult gluten intake (from grain contaminants) among 76 patients on a gluten-free diet estimated that gluten contamination of up to 100 parts per million (up to a total of 30 mg per day) did not result in histologic injury [25]. Interestingly, 13 of 59 naturally gluten-free products and 11 of 24 wheat starch-based gluten-free products contained gluten ranging from 20 to 200 mg/kg. Medications (pills) generally contain minimal gluten and do not need to be avoided.

MONITORING THE RESPONSE TO A GLUTEN-FREE DIET

The rapidity of the response to a gluten-free diet is variable. Approximately 70 percent of patients have noticeable clinical improvement within two weeks [26]. As a general rule, symptoms improve faster than histology, especially when biopsies are obtained in the proximal intestine. The reason is incompletely understood; however, a possible explanation is that the less severely damaged distal small intestine recovers faster than the proximal intestine, which is typically more severely affected due to relatively increased exposure to gluten [27].

We suggest that patients be evaluated in three to six months following the initiation of a gluten-free diet at which time a complete blood count, folate, B12, iron studies, liver chemistries, and serologic testing should be performed [4]. It is important to note that females often experience breast tenderness for three months after starting a gluten-free diet and reassurance should be provided.

Patients with celiac disease should continue to be monitored at regular intervals for residual or new symptoms, assessed for adherence to gluten-free diet, by both history and serological testing, and for complications of celiac disease. Periodic medical follow-up should be performed by a clinician with knowledge of celiac disease (algorithm 1) [28-30].

Serologic testing — IgA anti tissue transglutaminase (tTG) or IgA (or IgG) deamidated gliadin peptide (DGP) should be used to monitor the response to gluten-free diet [31]. We perform serologic testing 6 and 12 months after the initial diagnosis of celiac disease and annually thereafter [3].

For whichever assay that will be used, a pretreatment antibody level should be determined at the time of diagnosis. Exclusion of gluten from the diet results in a gradual decline in serum IgA anti-gliadin and IgA tTG levels (half-life of six to eight weeks). A normal baseline value is typically reached within 3 to 12 months depending upon the pre-treatment concentrations. Normal IgA

tTG levels do not reliably indicate recovery from villous atrophy [32]. Conversely, if the levels do not fall as anticipated, the patient is usually continuing to ingest gluten either intentionally or inadvertently [33].

Although the general patterns above can be helpful, the accuracy of these tests in establishing compliance with a gluten-free diet is unsettled [32,34]. The value of these tests in monitoring adherence to a gluten-free diet is particularly limited in three respects:

- The test is useless if antibody levels are not elevated prior to therapy.
- Inter-assay variations in test results may be substantial and make interpretation difficult. Serial samples should ideally be sent to one laboratory for testing to keep inter-assay variation to a minimum. Minor fluctuations in IgA anti-gliadin or IgA TTG levels are the norm and their importance should not be over interpreted.
- Persistently high antibody levels usually reflect continued exposure to substantial amounts of dietary gluten. Antibody levels will fall when dietary gluten intake is reduced, however, they are not a sensitive indicator of occasional or minor dietary transgressions [35]. Negative serology in a treated patient is also not a reliable indicator of mucosal healing.

Serum IgG anti-gliadin and IgA endomysial antibody levels also fall when patients with celiac disease adhere to a strict gluten-free diet [36-38]. However, the decline in IgG anti-gliadin is more gradual than for IgA anti-gliadin [39,40], making it less useful in monitoring recent dietary adherence. IgA endomysial antibody levels are more costly and results are more difficult to quantify than IgA antigliadin or IgA tTG.

Small bowel biopsy — The need for a follow-up biopsy in patients with clinical improvement has been debated, especially since serologic testing can be used to monitor recovery and compliance with the diet. We perform a follow-up biopsy in adults after two years of starting a gluten-free diet to assess for mucosal healing [4].

The consensus is that re-biopsy should be undertaken four to six months after commencing a gluten-free diet to confirm the diagnosis and a satisfactory response to the diet. In patients with persistent Marsh 2 or more severe histologic lesions on re-biopsy, a follow-up upper endoscopy with biopsy should be performed in 12 months [3]. An upper endoscopy with biopsy should also be performed in patients with established celiac disease who fail to respond to a gluten-free diet or with relapse of symptoms despite a gluten-free diet [31]. (See "Diagnosis of celiac disease in adults".)

Gluten re-challenge — Gluten re-challenge is unnecessary according to a consensus statement issued by the National Institutes of Health [2]. Guidelines issued by the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) suggested that gluten re-challenge is not mandatory in patients with good improvement in symptoms, histology, and a decline in the titer of anti-endomysial antibodies (which usually return to normal in three to six months) [41]. According to the ESPGAN guidelines, gluten re-challenge should only be used in equivocal cases such as when no initial biopsy was performed, biopsies were inadequate or atypical, in communities with high rates of other enteropathies, or in situations when patients plan to abandon a gluten-free diet in an uncontrolled way. Gluten re-challenge should be performed after obtaining a control biopsy on a gluten-free diet and repeat biopsies should be obtained two weeks to six months later with the recognition that relapse can take five to seven years or more.

A rare hazard in giving a gluten re-challenge is the development of fulminant diarrhea, with resulting dehydration, acidosis, and other metabolic disturbances (a condition known as "gliadin shock") [42]. Such patients should be treated with glucocorticoids. There is a suggestion that use of gluten challenge in young children may be associated with an increased likelihood of development of autoimmune disorders such as insulin dependent diabetes mellitus [20].

NON-RESPONDERS

Non-responders are individuals who have persistent symptoms or serologic and/or histologic abnormalities after two years on a gluten-free diet. The majority of patients with celiac disease respond to a gluten-free diet but approximately 5 percent of individuals do not.

In patients who are incomplete responders or non-responders, it is important to consider that not all clinical features of celiac disease respond at the same rate. (See 'Dermatitis herpetiformis' below.) Furthermore, bone loss due to secondary hyperparathyroidism and peripheral neuropathy may only improve partially despite a gluten-free diet [43]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

Patients who do not respond to a gluten-free diet fall into five main categories:

- Patients with poor compliance or inadvertent gluten ingestion (>90 percent)
- Patients with clinical or histologic features that overlap with celiac disease but are caused by other disorders
- Patients with concurrent disorders
- Patients with refractory sprue

- Patients with ulcerative jejunitis or intestinal lymphoma

Poor compliance or inadvertent gluten ingestion — The most common reasons for a lack of response are poor compliance or inadvertent gluten ingestion (table 1) [44-46]. In patients who continue to have symptoms or persistent histologic abnormalities, or in those in whom serum antibody titers have not declined, a meticulous dietary history should be obtained, and dietary counselling pursued with a dietitian specifically trained and experienced in celiac disease.

One group proposed a short survey that on initial evaluation was a more accurate predictor of compliance with a gluten-free diet than serologic testing compared with a formal nutritional assessment as the reference standard [47]. Additional validation studies are needed. (See 'Monitoring the response to a gluten-free diet' above.)

Larazotide acetate, a novel oral peptide that modulates intestinal tight junctions, may reduce symptoms in patients with inadvertent gluten exposure. However, further studies are needed to determine if it is safe and effective for patients with persistent symptoms despite a gluten-free diet, and to determine the optimal dose [48]. In a randomized trial, 342 adults with celiac disease who had been on a gluten-free diet for 12 months or longer were assigned to larazotide 0.5, 1, or 2 mg or placebo three times daily for 12 weeks to relieve ongoing symptoms while continuing their gluten-free diet during the study [49]. The primary endpoint was the difference in average on-treatment Celiac Disease Gastrointestinal Symptom Rating Scale score. The primary endpoint was met with the 0.5 mg dose of larazotide acetate but not the 1 and 2 mg doses. Treatment with larazotide (0.5 mg dose) also resulted in an increase in the number of improved symptom days and a reduction in the number of symptomatic days, severity of abdominal pain, and non-gastrointestinal symptoms of tiredness and headache. The safety of larazotide was comparable with placebo. While the reason for the lack of efficacy of higher doses is unclear, it may be due to peptide aggregation at higher doses.

Other diagnoses — An erroneous diagnosis of celiac sprue may result from false positive serology, specifically IgA anti-gliadin antibodies as raised titre occurs in 5 percent of normal subjects. Diseases associated with small bowel villous atrophy should be excluded in patients with persistent symptoms who do not show histologic improvement (algorithm 2) [50]. (See "Approach to the adult patient with suspected malabsorption".)

Concurrent disorders — Other concurrent diagnoses should be considered in patients who, despite apparent compliance, continue to have symptoms or do not have histologic improvement [44,51]. In a series of 78 patients with celiac disease treated with a gluten-free

diet for at least 12 months, persistent diarrhea was observed in 13 patients (17 percent) due to other concurrent diagnoses, including human immunodeficiency virus [51].

- Concomitant or secondary lactose intolerance is a possible cause of continued diarrhea and flatulence. (See "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management".)
- Patients with celiac disease may have concurrent bowel disturbances such as irritable bowel syndrome, which affects a large proportion of the general population. (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults".)
- Small bowel bacterial overgrowth, which may respond to antibiotics, develops in a small percentage of patients with celiac disease [52,53]. (See "Small intestinal bacterial overgrowth: Management".)
- Some patients have coexisting pancreatic insufficiency [54]. (See "Overview of the treatment of malabsorption in adults".)
- Microscopic colitis is found in 4 percent of patients with celiac disease, which represents a 70-fold increase in risk [55]. These patients had more severe villous atrophy and frequently required glucocorticoids or immunosuppressive drugs to treat the diarrhea. (See "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management".)

Refractory sprue — Patients with refractory sprue (also referred to as "unclassified sprue") fall into two clinical categories [56,57]:

- Patients who have no initial response to a gluten-free diet.
- Patients who experience initial clinical improvement on a gluten-free diet, but, after a period of remission, develop disease refractory to gluten abstinence.

Refractory sprue has also been subdivided into two immunologic categories [58-62]:

- Type 1 in which there is a normal population of intraepithelial lymphocytes.
- Type 2 in which there is an aberrant or premalignant population of intraepithelial lymphocytes based upon clonality analysis of T-cell receptors and immunophenotyping. Type 2 can progress to enteropathy-associated T-cell lymphoma, which may present clinically as ulcerative jejunitis [59]. The diagnosis can be established on biopsy, possibly

requiring a surgical full thickness biopsy; CT, MRI, and 18F-FDG PET scans can help identify suspicious areas [63,64]. (See 'Ulcerative jejunitis and intestinal lymphoma' below.)

Differentiation between types 1 and 2 refractory sprue is important for both management and prognosis [31]. Patients with type 1 disease have a less severe presentation and a much better prognosis than patients with type 2 disease [65-68]. Furthermore, type 1 does not appear to evolve into type 2. An illustrative study compared outcomes in 41 patients with type 1 disease to 50 patients with type 2 disease [65]. Five-year survival was higher in the type 1 group (96 versus 58 percent). Most deaths were due to development of T-cell lymphoma (which developed in one-half of patients during follow-up). No patient with type 1 disease developed type 2 disease during an average five years follow-up. A staging system (based upon age, hemoglobin, albumin, the presence of T-cell clones, and total villous atrophy) has been proposed and awaits further validation [68].

Refractory sprue (particularly type 2) can be severe and associated with progressive malabsorption and death in 55 percent of untreated cases. A subset of patients develops subepithelial collagen deposition, a condition referred to as "collagenous sprue" [69].

The cause of refractory sprue is unknown. It is possible that some patients with this condition develop sensitivity to a dietary constituent other than gluten [70]. However, identification of the responsible antigens in most patients is difficult and unrewarding. Patients with refractory sprue should be monitored closely and receive aggressive nutritional support, including parenteral nutrition if needed. Treatment has focused on immunosuppression, which has traditionally relied upon glucocorticoids.

The dose of glucocorticoids required varies among patients, and not all patients respond. In severely ill patients, we usually begin with hydrocortisone (100 mg IV Q6H). Oral dosing (such as 40 to 60 mg of prednisolone daily) can be used in patients who are tolerating an oral diet. After a few weeks, the dose can be reduced by 5 to 10 mg per day in responding patients and subsequently tapered to the lowest dose that keeps the patient in remission.

In patients with type 2 refractory sprue, we begin with prednisolone (15 to 20 mg daily) and an immunomodulator. We treat patients with normal thiopurine methyl transferase genotype and phenotype with azathioprine or 6-mercaptopurine (2 mg/kg/day). We treat patients who cannot tolerate azathioprine or mercaptopurine with mycophenolate mofetil commencing at 500 mg twice daily to avoid side effects, then increasing the dose to 1 g twice daily with careful monitoring. In patients who respond to treatment, we gradually taper prednisolone over eight weeks and continue azathioprine/6-MP/mycophenolate mofetil as maintenance therapy [71].

(See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

However, experience with alternative immunosuppressant therapy in patients who require high doses of glucocorticoids is limited to case reports and clinical experience. Azathioprine, 6-mercaptopurine, and thiopurine derivative thioguanine (TG) appear to be effective steroid-sparing agents [72-75]. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease".)

- Oral budesonide (9 mg, range 6 to 12 mg) has been effective in case series [76,77].
- A case series described clinical and histologic improvement following treatment with an elemental diet in patients with type 1 refractory sprue [62].
- In a small pilot study of 10 patients with type 1 refractory sprue treated with small intestinal release mesalamine, 5 of 10 patients had a complete response and one had a partial response. Subgroup analysis showed that response did not significantly vary by concurrent budesonide use [78].
- Another report described remission in a patient with type 2 disease following treatment with alemtuzumab, an anti-CD52 monoclonal antibody used to treat chronic lymphocytic leukemia [79]. However, the drug was not effective in other reports [80].
- Cladribine (a synthetic purine nucleoside with cytotoxic activity) was associated with clinical and histologic improvement in 6 of 17 patients with type 2 refractory sprue [81].

Ulcerative jejunitis and intestinal lymphoma — Ulcerative jejunitis and lymphoma should be considered in patients with refractory sprue unresponsive to glucocorticoids. The conditions are thought to share a similar pathogenesis, since both have aberrant T-cell monoclonality [17,82].

Patients with ulcerative jejunitis have multiple chronic, benign-appearing ulcers, most frequently in the jejunum. Clinical manifestations are similar to severe celiac disease; patients may present with new or recurrent symptoms of malabsorption, lassitude, anorexia, weight loss, abdominal pain, diarrhea, and fever despite being on a gluten-free diet [83]. Intestinal stricturing can develop with resulting small bowel obstruction. The disease most commonly presents in middle-aged patients with underlying celiac disease. Evaluation should begin with an abdominal computed tomography (CT) enterography or magnetic resonance (MR) enterography scan and upper endoscopy, which, if negative, should be followed by a capsule endoscopy. Ulcerative jejunitis responds poorly to a gluten-free diet and is associated with an

unfavorable prognosis. Up to one-third of patients die from complications. The prognosis can be improved if the ulcerated or strictured segment can be resected.

Lymphoma should be suspected in patients with celiac disease presenting with the clinical features described above for ulcerative jejunitis. Among patients who initially responded to a gluten-free diet, the diagnostic dilemma is whether the return of symptoms is due to dietary lapses or the development of lymphoma. Clinical manifestations more suggestive of lymphoma, such as fever, hepatomegaly, splenomegaly, duodenal mass(es), or ascites, may help the diagnostic conundrum, but their presence implies more advanced disease. Other presentations of lymphoma include acute perforation, gastrointestinal obstruction, or, less commonly, gastrointestinal hemorrhage.

The evaluation should begin with an abdominal CT enterography or a magnetic resonance (MR) enterography scan, upper endoscopy and capsule endoscopy. In patients with lymphoma, the histology of adjacent intestine is often indistinguishable from untreated celiac disease. However, it remains uncertain whether these patients had occult celiac disease that became evident only after lymphoma developed, or whether the lymphoma caused the development of celiac-like histology [84]. A full-thickness surgical intestinal biopsy may be required to establish the diagnosis in patients in whom clinical suspicion is high, but radiographic and endoscopic testing is inconclusive. These lymphomas are almost always of high-grade histology and the prognosis is poor.

Five-year survival can be approximately 10 percent, with the worst outcomes in patients with previously diagnosed celiac disease [85]. Favorable outcomes with multidrug therapy occur only in patients who have minimal gastrointestinal symptoms prior to the diagnosis of lymphoma, and can tolerate therapy [85]. Patients should also be maintained on a gluten-free diet.

OTHER ASPECTS OF MANAGEMENT

Repletion of nutritional deficiencies — Patients should be tested for deficiency of vitamins (A, D, E, B12), copper, zinc, carotene, folic acid, ferritin, iron, and prothrombin time (PT) measured for potential vitamin K deficiency. Deficiency in thiamine, vitamin B6, magnesium, and selenium may also occur depending on the disease severity and dietary intake and should be tested for in the presence of clinical signs or symptoms of a deficiency [31]. (See "Overview of water-soluble vitamins" and "Hypomagnesemia: Clinical manifestations of magnesium depletion".)

A gluten-free diet may induce troublesome constipation since it is low in roughage. This usually responds to fiber supplementation with psyllium seed husks.

Medication absorption — There may be incomplete absorption of medication in untreated, partially treated, or refractory celiac disease. This is important for females of childbearing age who take oral contraceptive pills, where there may be incomplete absorption of the medication such that they should be advised to use alternative contraception. (See "Contraception: Counseling and selection", section on 'How to do contraceptive counseling'.)

Prevention of bone loss — Bone loss (principally osteopenia and less often osteoporosis) is common in celiac disease, and can occur in patients without gastrointestinal symptoms [13,86-88]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".). Much of the bone loss is related to secondary hyperparathyroidism, which is probably due to vitamin D deficiency. Patients with advanced disease may have bone pain, pseudofractures, or deformity, but the majority of patients are asymptomatic or have only raised serum levels of alkaline phosphatase or hypocalcemia [13,89]. It can only be partially reversed with a gluten-free diet; loss of bone density in the peripheral skeleton may persist despite apparent normalization at axial skeletal sites [43].

Patients diagnosed with celiac disease should be evaluated for bone loss using a DXA (dual energy x-ray absorptiometry) scan. Monitoring by repeat DXA scan after one year is useful in patients with osteopenia since it permits estimation of the rate of change of bone mineral density [90]. Treatment of osteoporosis and osteopenia is discussed in detail separately. (See "Overview of the management of osteoporosis in postmenopausal women" and "Treatment of osteoporosis in men".)

Pneumococcal vaccination — Celiac disease is associated with hyposplenism. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".) Therefore, prophylactic administration of pneumococcal vaccine is recommended [4]. (See "Pneumococcal vaccination in adults".)

Dermatitis herpetiformis — Celiac disease is associated with a number of skin disorders of which dermatitis herpetiformis is the most common (table 2) [91]. (See "Dermatitis herpetiformis".)

Improvement in dermatitis herpetiformis following withdrawal of gluten may be considerably delayed (6 to 12 months) compared to the response of the intestinal manifestations of the disease [92]. As a result, treatment with sulfones (such as dapsone 100 mg/day) in addition to gluten avoidance may be necessary to achieve rapid control [91].

Investigational approaches

- **Transglutaminase 2 inhibitor** – Inhibition of transglutaminase 2 has been evaluated in patients with celiac disease. In a randomized trial, 159 adults with well-controlled celiac disease were assigned to one of three dose levels (10 mg, 50 mg, 100 mg) of a selective oral transglutaminase 2 inhibitor or placebo for six weeks while on a daily gluten challenge (3 grams/day) [93]. Treatment with the oral transglutaminase 2 inhibitor at all three dose levels significantly attenuated gluten-induced duodenal mucosal damage, as measured by the ratio of villus height to crypt depth, as compared with placebo. Symptoms while on a gluten challenge, as measured by the celiac disease symptom index, increased in all groups over the study period, but the increase was significantly smaller in the highest dose group as compared with placebo. It is important to note that an amount of gluten employed in this study is significantly lower than the standard dietary intake of 12 g/d. Further studies conducted with higher doses of gluten are needed to validate the results before it can be considered an alternative to a gluten-free diet.

- **Other potential approaches** – Naturally occurring wheat gluten proteins that do not contain celiac disease-toxic motifs could be used to develop novel variants of wheat, employing wheat grain radiation mutants, mutagenesis, and standard wheat breeding techniques to develop novel strains of wheat that generate flour that is non-toxic to subjects with celiac disease [94].

SCREENING FAMILY MEMBERS

Relatives of patients with celiac disease are at increased risk for having celiac disease [95-98]. The risk is highest among monozygotic twins (approximately 75 percent) [97], HLA-identical siblings (approximately 40 percent) [97], and among first-degree relatives of families with at least two affected siblings (17 percent) [95]. Among first-degree relatives, the risk has varied from 5 to 11 percent in various reports [98,99]. In one report, the risk was highest among male siblings, almost one-half of whom had clinically silent celiac disease despite severe intestinal villous atrophy [98]. Thus, screening of first-degree relatives (particularly siblings) should be considered, particularly when symptomatic. (See "Diagnosis of celiac disease in adults", section on 'Individuals with high celiac disease probability'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Celiac disease" and "Society guideline links: Dermatitis herpetiformis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Celiac disease (The Basics)" and "Patient education: Gluten-free diet (The Basics)")
- Beyond the Basics topic (see "Patient education: Celiac disease in adults (Beyond the Basics)")

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: Celiac disease".)

SUMMARY AND RECOMMENDATIONS

- **Dietary counseling** – Celiac disease can be defined as a condition in which there is an abnormal small intestinal mucosa that improves morphologically when treated with a gluten-free diet and relapses when gluten is reintroduced. We recommend that patients with serologically and histologically confirmed celiac disease and compatible clinical or laboratory manifestations adhere to a gluten-free diet (**Grade 1A**). (See 'Indications' above.)

We refer patients with celiac disease to a dietitian who is familiar with counselling patients on a gluten-free diet. Providing written information and referral to a support group can also be helpful. Periodic medical follow-up should be performed by a clinician with knowledge of celiac disease (algorithm 1). (See "Patient education: Celiac disease in adults (Beyond the Basics)".)

- **Repletion of nutritional deficiencies** – Patients should be tested for deficiency of vitamins (A, D, E, B12), copper, zinc, carotene, folic acid, ferritin, and iron. Deficiency in thiamine, vitamin B6, magnesium, and selenium may also occur depending on the disease severity and dietary intake and should be tested for in the presence of clinical signs or symptoms of a deficiency. A gluten-free diet may induce troublesome constipation since it is low in roughage. This usually responds to the addition of psyllium seed husks. (See "Overview of the treatment of malabsorption in adults" and 'Repletion of nutritional deficiencies' above.)

- **Prevention of bone loss** – Bone loss (principally osteopenia and less often osteoporosis) is common in celiac disease and can occur in patients without gastrointestinal symptoms. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

  Much of the bone loss is related to secondary hyperparathyroidism, which is probably due to vitamin D deficiency. It can only be partially reversed with a gluten-free diet. Patients diagnosed with celiac disease should be evaluated for bone loss using a DXA (dual energy x-ray absorptiometry) scan and appropriate therapy instituted based upon the results. (See 'Prevention of bone loss' above.)

- **Pneumococcal vaccination** – Pneumococcal vaccination is suggested since celiac disease is associated with hyposplenism. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults" and "Pneumococcal vaccination in adults".)

- **Monitoring** – Patients should be followed clinically and with serologic testing to determine response to dietary therapy. An upper endoscopy with biopsy should be performed in patients with established celiac disease who fail to respond to a gluten-free diet or with relapse of symptoms despite a gluten-free diet. (See 'Monitoring the response to a gluten-free diet' above.)

- **Evaluation of non-responders** – The majority of patients with celiac disease respond to a gluten-free diet. The most common reasons for a lack of response are poor compliance or inadvertent gluten ingestion (table 1). Thus, we suggest a meticulous dietary history should be obtained, and dietary counselling pursued with an experienced dietitian in

patients who continue to have symptoms or persistent histologic abnormalities, or in those in whom serum antibody titers have not declined. (See 'Non-responders' above.)

Patients who do not respond despite adherence to a gluten-free diet fall into four main categories: those with clinical or histologic features that are caused by other disorders; those with concurrent conditions such as refractory sprue; and those with ulcerative jejunitis or intestinal lymphoma (algorithm 2). (See 'Non-responders' above.)

REFERENCES

1. Adams F. The extant works of Aretaeus the Cappadocian, London Sydenham Society, 1856.
2. National Institutes of Health Consensus Development Conference Statement. Celiac Diseas e 2004. Available at: http://consensus.nih.gov/ (Accessed on March 11, 2011).
3. 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.
4. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. Am J Gastroenterol 2023; 118:59.
5. Ravelli A, Bolognini S, Gambarotti M, Villanacci V. Variability of histologic lesions in relation to biopsy site in gluten-sensitive enteropathy. Am J Gastroenterol 2005; 100:177.
6. Pinto-Sánchez MI, Causada-Calo N, Bercik P, et al. Safety of Adding Oats to a Gluten-Free Diet for Patients With Celiac Disease: Systematic Review and Meta-analysis of Clinical and Observational Studies. Gastroenterology 2017; 153:395.
7. Aaltonen K, Laurikka P, Huhtala H, et al. The Long-Term Consumption of Oats in Celiac Disease Patients Is Safe: A Large Cross-Sectional Study. Nutrients 2017; 9.
8. Sturgess R, Day P, Ellis HJ, et al. Wheat peptide challenge in coeliac disease. Lancet 1994; 343:758.
9. Shidrawi RG, Day P, Przemioslo R, et al. In vitro toxicity of gluten peptides in coeliac disease assessed by organ culture. Scand J Gastroenterol 1995; 30:758.
10. Schmitz J. Lack of oats toxicity in coeliac disease. BMJ 1997; 314:159.
11. Comino I, Real A, de Lorenzo L, et al. Diversity in oat potential immunogenicity: basis for the selection of oat varieties with no toxicity in coeliac disease. Gut 2011; 60:915.

12. Hall NJ, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther 2009; 30:315.
13. Shaker JL, Brickner RC, Findling JW, et al. Hypocalcemia and skeletal disease as presenting features of celiac disease. Arch Intern Med 1997; 157:1013.
14. West J, Logan RF, Smith CJ, et al. Malignancy and mortality in people with coeliac disease: population based cohort study. BMJ 2004; 329:716.
15. Green PH, Fleischauer AT, Bhagat G, et al. Risk of malignancy in patients with celiac disease. Am J Med 2003; 115:191.
16. Holmes GK, Prior P, Lane MR, et al. Malignancy in coeliac disease--effect of a gluten free diet. Gut 1989; 30:333.
17. Corrao G, Corazza GR, Bagnardi V, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001; 358:356.
18. Askling J, Linet M, Gridley G, et al. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology 2002; 123:1428.
19. Collin P, Reunala T, Pukkala E, et al. Coeliac disease--associated disorders and survival. Gut 1994; 35:1215.
20. Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999; 117:297.
21. Cosnes J, Cellier C, Viola S, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. Clin Gastroenterol Hepatol 2008; 6:753.
22. Sategna Guidetti C, Solerio E, Scaglione N, et al. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. Gut 2001; 49:502.
23. Nørgård B, Fonager K, Sørensen HT, Olsen J. Birth outcomes of women with celiac disease: a nationwide historical cohort study. Am J Gastroenterol 1999; 94:2435.
24. Ludvigsson JF, Montgomery SM, Ekbom A. Celiac disease and risk of adverse fetal outcome: a population-based cohort study. Gastroenterology 2005; 129:454.
25. Collin P, Thorell L, Kaukinen K, Mäki M. The safe threshold for gluten contamination in gluten-free products. Can trace amounts be accepted in the treatment of coeliac disease? Aliment Pharmacol Ther 2004; 19:1277.
26. Pink IJ, Creamer B. Response to a gluten-free diet of patients with the coeliac syndrome. Lancet 1967; 1:300.

27. MACDONALD WC, BRANDBORG LL, FLICK AL, et al. STUDIES OF CELIAC SPRUE. IV. THE RESPONSE OF THE WHOLE LENGTH OF THE SMALL BOWEL TO A GLUTEN-FREE DIET. Gastroenterology 1964; 47:573.
28. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology 2006; 131:1981.
29. Herman ML, Rubio-Tapia A, Lahr BD, et al. Patients with celiac disease are not followed up adequately. Clin Gastroenterol Hepatol 2012; 10:893.
30. Vahdani K, Rose GE. The Presentation and Surgical Treatment of Peribulbar Dermolipomas. Ophthalmic Plast Reconstr Surg 2021; 37:226.
31. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013; 108:656.
32. Hopper AD, Hadjivassiliou M, Hurlstone DP, et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clin Gastroenterol Hepatol 2008; 6:314.
33. Kelly CP. Coeliac disease: Non-invasive tests to screen for gluten sensitive enteropathy and to monitor response to dietary therapy, Dublin University, Trinity College, Dublin 1995.
34. Leffler DA, Edwards George JB, Dennis M, et al. A prospective comparative study of five measures of gluten-free diet adherence in adults with coeliac disease. Aliment Pharmacol Ther 2007; 26:1227.
35. Vahedi K, Mascart F, Mary JY, et al. Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. Am J Gastroenterol 2003; 98:1079.
36. Bürgin-Wolff A, Gaze H, Hadziselimovic F, et al. Antigliadin and antiendomysium antibody determination for coeliac disease. Arch Dis Child 1991; 66:941.
37. Kapuscinska A, Zalewski T, Chorzelski TP, et al. Disease specificity and dynamics of changes in IgA class anti-endomysial antibodies in celiac disease. J Pediatr Gastroenterol Nutr 1987; 6:529.
38. Kumar V, Lerner A, Valeski JE, et al. Endomysial antibodies in the diagnosis of celiac disease and the effect of gluten on antibody titers. Immunol Invest 1989; 18:533.
39. Kelly CP, Feighery CF, Gallagher RB, et al. Mucosal and systemic IgA anti-gliadin antibody in celiac disease. Contrasting patterns of response in serum, saliva, and intestinal secretions. Dig Dis Sci 1991; 36:743.

40. Kilander AF, Nilsson LA, Gillberg R. Serum antibodies to gliadin in coeliac disease after gluten withdrawal. Scand J Gastroenterol 1987; 22:29.
41. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990; 65:909.
42. KRAINICK HG, DEBATIN F, GAUTIER E, et al. [Additional research on the injurious effect of wheat flour in celiac disease.I. Acute gliadin reaction (gliadin shock)]. Helv Paediatr Acta 1958; 13:432.
43. Selby PL, Davies M, Adams JE, Mawer EB. Bone loss in celiac disease is related to secondary hyperparathyroidism. J Bone Miner Res 1999; 14:652.
44. Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. Am J Gastroenterol 2002; 97:2016.
45. Leffler DA, Dennis M, Hyett B, et al. Etiologies and predictors of diagnosis in nonresponsive celiac disease. Clin Gastroenterol Hepatol 2007; 5:445.
46. 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.
47. Leffler DA, Dennis M, Edwards George JB, et al. A simple validated gluten-free diet adherence survey for adults with celiac disease. Clin Gastroenterol Hepatol 2009; 7:530.
48. Kelly CP, Green PH, Murray JA, et al. Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study. Aliment Pharmacol Ther 2013; 37:252.
49. Leffler DA, Kelly CP, Green PH, et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. Gastroenterology 2015; 148:1311.
50. Shah VH, Rotterdam H, Kotler DP, et al. All that scallops is not celiac disease. Gastrointest Endosc 2000; 51:717.
51. Fine KD, Meyer RL, Lee EL. The prevalence and causes of chronic diarrhea in patients with celiac sprue treated with a gluten-free diet. Gastroenterology 1997; 112:1830.
52. Rubio-Tapia A, Barton SH, Rosenblatt JE, Murray JA. Prevalence of small intestine bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. J Clin Gastroenterol 2009; 43:157.
53. 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.

54. Carroccio A, Iacono G, Lerro P, et al. Role of pancreatic impairment in growth recovery during gluten-free diet in childhood celiac disease. Gastroenterology 1997; 112:1839.

55. Green PH, Yang J, Cheng J, et al. An association between microscopic colitis and celiac disease. Clin Gastroenterol Hepatol 2009; 7:1210.

56. Trier JS, Falchuk ZM, Carey MC, Schreiber DS. Celiac sprue and refractory sprue. Gastroenterology 1978; 75:307.

57. Ryan BM, Kelleher D. Refractory celiac disease. Gastroenterology 2000; 119:243.

58. Mulder CJ, Wahab PJ, Moshaver B, Meijer JW. Refractory coeliac disease: a window between coeliac disease and enteropathy associated T cell lymphoma. Scand J Gastroenterol Suppl 2000; :32.

59. Cellier C, Delabesse E, Helmer C, et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. Lancet 2000; 356:203.

60. Cellier C, Patey N, Mauvieux L, et al. Abnormal intestinal intraepithelial lymphocytes in refractory sprue. Gastroenterology 1998; 114:471.

61. Bagdi E, Diss TC, Munson P, Isaacson PG. Mucosal intra-epithelial lymphocytes in enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and refractory celiac disease constitute a neoplastic population. Blood 1999; 94:260.

62. Olaussen RW, Løvik 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.

63. 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.

64. Van Weyenberg SJ, Meijerink MR, Jacobs MA, et al. MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system. Radiology 2011; 259:151.

65. 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.

66. 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.

67. Gao Y, Kristinsson SY, Goldin LR, et al. Increased risk for non-Hodgkin lymphoma in individuals with celiac disease and a potential familial association. Gastroenterology 2009; 136:91.

68. 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.
69. McCashland TM, Donovan JP, Strobach RS, et al. Collagenous enterocolitis: a manifestation of gluten-sensitive enteropathy. J Clin Gastroenterol 1992; 15:45.
70. Baker AL, Rosenberg IH. Refractory sprue: recovery after removal of nongluten dietary proteins. Ann Intern Med 1978; 89:505.
71. Nasr I, Nasr I, Beyers C, et al. Recognising and Managing Refractory Coeliac Disease: A Tertiary Centre Experience. Nutrients 2015; 7:9896.
72. Rolny P, Sigurjonsdottir HA, Remotti H, et al. Role of immunosuppressive therapy in refractory sprue-like disease. Am J Gastroenterol 1999; 94:219.
73. Vaidya A, Bolanos J, Berkelhammer C. Azathioprine in refractory sprue. Am J Gastroenterol 1999; 94:1967.
74. Mauriño E, Niveloni S, Cherñavsky A, et al. Azathioprine in refractory sprue: results from a prospective, open-label study. Am J Gastroenterol 2002; 97:2595.
75. 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.
76. Daum S, Ipczynski R, Heine B, et al. Therapy with budesonide in patients with refractory sprue. Digestion 2006; 73:60.
77. Brar P, Lee S, Lewis S, et al. Budesonide in the treatment of refractory celiac disease. Am J Gastroenterol 2007; 102:2265.
78. 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.
79. Vivas S, Ruiz de Morales JM, Ramos F, Suárez-Vilela D. Alemtuzumab for refractory celiac disease in a patient at risk for enteropathy-associated T-cell lymphoma. N Engl J Med 2006; 354:2514.
80. Verbeek WH, Mulder CJ, Zweegman S. Alemtuzumab for refractory celiac disease. N Engl J Med 2006; 355:1396.
81. 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.
82. Ashton-Key M, Diss TC, Pan L, et al. Molecular analysis of T-cell clonality in ulcerative jejunitis and enteropathy-associated T-cell lymphoma. Am J Pathol 1997; 151:493.
83. Bayless TM, Kapelowitz RF, Shelley WM, et al. Intestinal ulceration--a complication of celiac disease. N Engl J Med 1967; 276:996.

84. Isaacson PG. Intestinal lymphoma and enteropathy. J Pathol 1995; 177:111.

85. Egan LJ, Walsh SV, Stevens FM, et al. Celiac-associated lymphoma. A single institution experience of 30 cases in the combination chemotherapy era. J Clin Gastroenterol 1995; 21:123.

86. Walters JR, Banks LM, Butcher GP, Fowler CR. Detection of low bone mineral density by dual energy x ray absorptiometry in unsuspected suboptimally treated coeliac disease. Gut 1995; 37:220.

87. Mustalahti K, Collin P, Sievänen H, et al. Osteopenia in patients with clinically silent coeliac disease warrants screening. Lancet 1999; 354:744.

88. Meyer D, Stavropolous S, Diamond B, et al. Osteoporosis in a north american adult population with celiac disease. Am J Gastroenterol 2001; 96:112.

89. Cooke WT, Holmes GK. Clinical presentation. In: Coeliac Disease, Cooke WT, Holmes GK (Ed s), Churchill Livingston, London 1984. p.90.

90. Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. British Society of Gastroenterology. Gut 2000; 46 Suppl 1:i1.

91. Fry L. Dermatitis herpetiformis. Baillieres Clin Gastroenterol 1995; 9:371.

92. Garioch JJ, Lewis HM, Sargent SA, et al. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. Br J Dermatol 1994; 131:541.

93. Schuppan D, Mäki M, Lundin KEA, et al. A Randomized Trial of a Transglutaminase 2 Inhibitor for Celiac Disease. N Engl J Med 2021; 385:35.

94. Japelj N, Suligoj T, Zhang W, et al. Natural variants of α-gliadin peptides within wheat proteins with reduced toxicity in coeliac disease. Br J Nutr 2020; 123:1382.

95. Book L, Zone JJ, Neuhausen SL. Prevalence of celiac disease among relatives of sib pairs with celiac disease in U.S. families. Am J Gastroenterol 2003; 98:377.

96. Gudjónsdóttir AH, Nilsson S, Ek J, et al. The risk of celiac disease in 107 families with at least two affected siblings. J Pediatr Gastroenterol Nutr 2004; 38:338.

97. Greco L, Romino R, Coto I, et al. The first large population based twin study of coeliac disease. Gut 2002; 50:624.

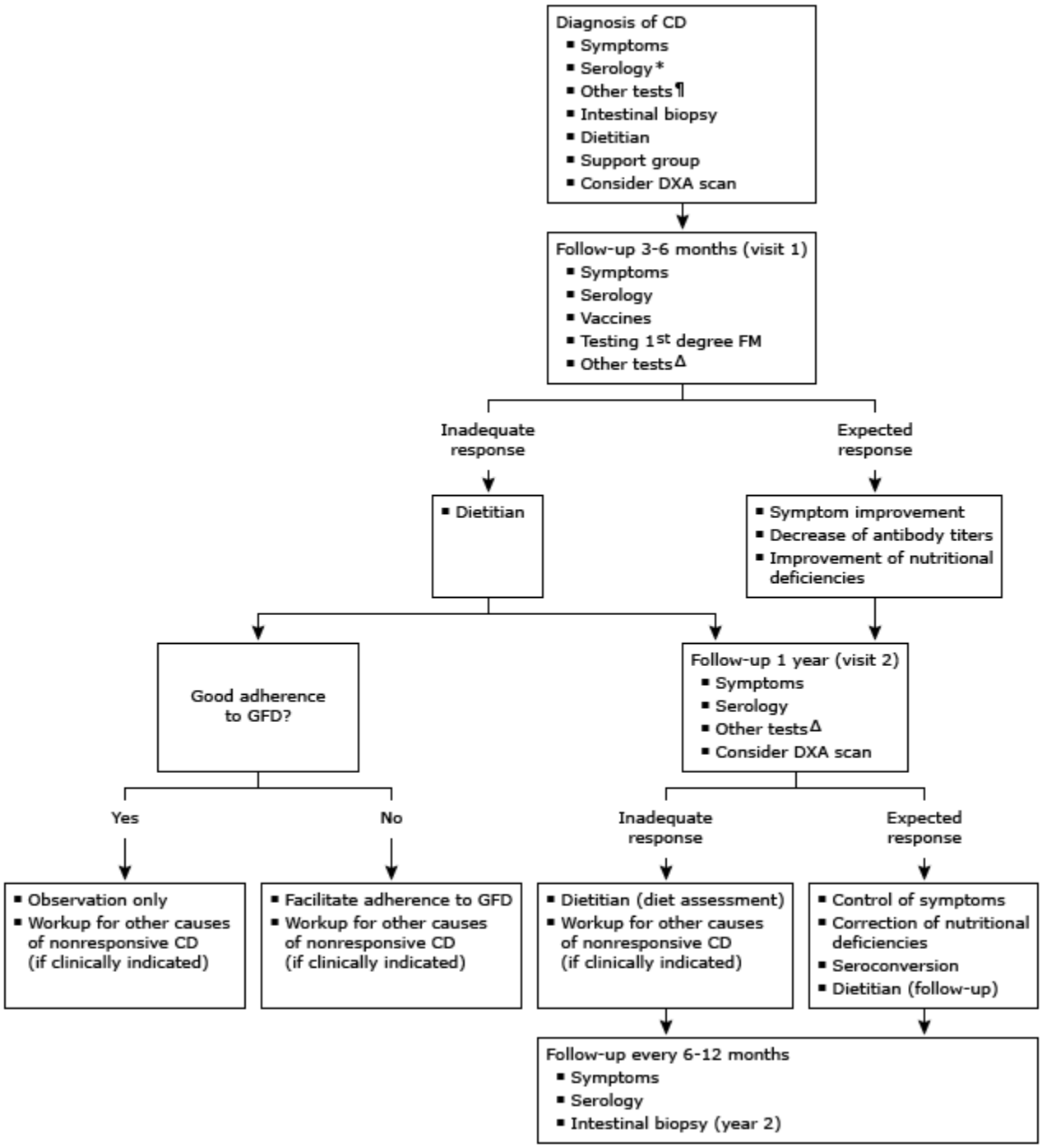
98. Rubio-Tapia A, Van Dyke CT, Lahr BD, et al. Predictors of family risk for celiac disease: a population-based study. Clin Gastroenterol Hepatol 2008; 6:983.

99. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163:286.

Topic 4777 Version 43.0

GRAPHICS

Approach to monitoring celiac disease



DGP: deamidated gliadin peptide; DXA: dual-energy x-ray absorptiometry; GFD: gluten-free diet; TTG: tissue transglutaminase.

* TTG and DGP can be used for monitoring celiac disease considering the availability of test at baseline before initiation of the GFD.

¶ Other tests may include complete blood count, alanine aminotransferase, aspartate aminotransferase, vitamins (A, D, E, B12), copper, zinc, folic acid, ferritin, and iron.

Δ Blood tests at follow-up should be individualized to verify correction of laboratory tests that were abnormal at baseline.

Graphic 140675 Version 1.0

Foods and products that may contain gluten

Frequently overlooked foods that may contain gluten and need to be verified:
Brown rice syrup
Breading and coating mixes
Croutons
Energy bars
Flour or cereal products
Imitation bacon
Imitation seafood
Marinades
Panko (Japanese bread crumbs)
Pastas
Processed luncheon meats
Sauces, gravies
Self-basting poultry
Soy sauce or soy sauce solids
Soup bases
Stuffings, dressing
Thickeners (roux)
Communion wafers
Herbal supplements
Probiotic products*
Drugs and over-the-counter medications
Nutritional supplements
Vitamins and mineral supplements
Play-Doh, crayons, paint, glue, paper mache – A potential problem if the child puts their hands on or in the mouth while playing; wash hands after using these products

NOT ALLOWED in any form:
Wheat (einkorn, durum, faro, graham, kamut, semolina, spelt)
Rye
Barley
Triticale
Malt, malt flavoring, malt vinegar (are generally made from barley; verify the source)

* In 2015, a study of 22 commonly used probiotics revealed that 12 (55%) contained gluten, including 2 that were labeled gluten-free despite containing gluten levels higher than the 20 parts

per million required for gluten-free labeling.[1]

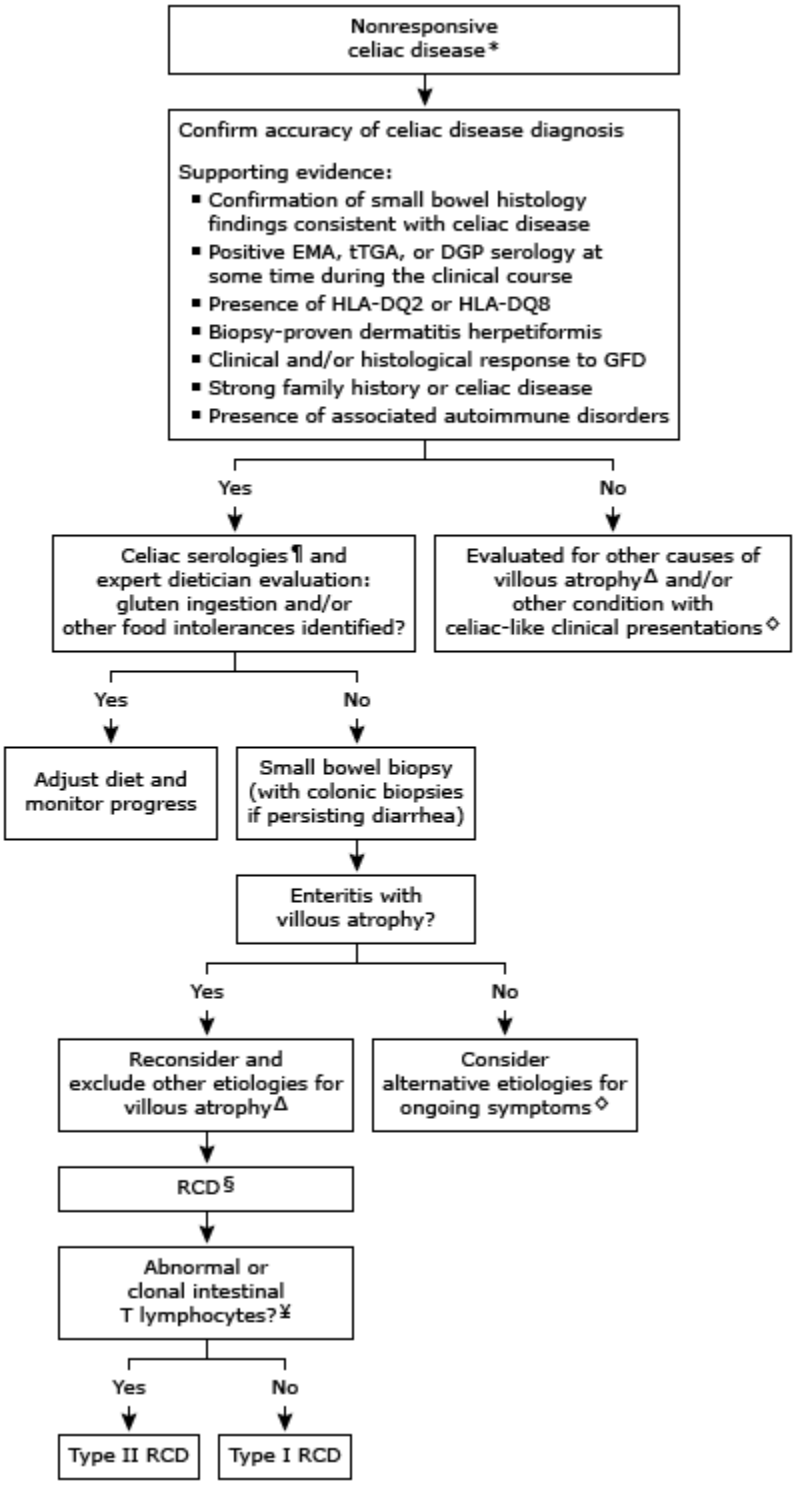
---

1. *Nazareth S, Lebwohl B, Voyksner JS, Green PH. Widespread Contamination of Probiotics With Gluten, Detected by Liquid Chromatography-Mass Spectrometry. Gastroenterology 2015; 148:S28.*

Modified with permission: "Frequently overlooked foods that may contain gluten and need to be verified." From Quick Start Diet Guide for Celiac Disease © 2009. Celiac Disease Foundation. www.celiac.org.

Graphic 79790 Version 6.0

An approach to the investigation of nonresponsive celiac disease and refractory celiac disease



NRCD: nonresponsive celiac disease; RCD: refractory celiac disease; DGP: deamidated gliadin peptide; EMA: endomysium antibodies; HLA: human leukocyte antigen; GFD: gluten-free diet; IELs: intraepithelial lymphocytes; TTGA: tissue transglutaminase antibody.

* NRCD may be defined as persistent symptoms, signs, or laboratory abnormalities typical of celiac disease despite 6 to 12 months of dietary gluten avoidance.

¶ Positive celiac serologies despite 12 months of treatment with a gluten-free diet suggest that there may be ongoing gluten ingestion.

Δ Causes of nonceliac, small intestinal villous atrophy that may be misdiagnosed as celiac disease include autoimmune enteropathy, tropical sprue, small intestinal bacterial overgrowth, hypogammaglobulinemia and combined variable immunodeficiency, collagenous sprue, eosinophilic enteritis, Crohn disease, and peptic duodenitis.

◇ Conditions that present clinically in a similar fashion to celiac disease but where villous atrophy is not evident include irritable bowel syndrome, food intolerances, small intestinal bacterial overgrowth, eosinophilic enteritis, Crohn disease, and microscopic colitis.

§ RCD may be defined as persistent or recurrent malabsorptive symptoms and signs with small intestinal villous atrophy despite a strict GFD for more than 12 months and in the absence of other disorders, including overt lymphoma.

¥ Abnormal intestinal lymphocytes may be identified by immunohistochemistry of IELs or by flow cytometry showing an increased number of CD3-positive cells lacking CD8, or by the identification of clonal T-cell receptor gene rearrangement by molecular analysis.

Graphic 89800 Version 2.0

Skin disorders associated with celiac disease

Dermatitis herpetiformis
Vitiligo
Alopecia areata
Psoriasis
Eczema

Urticaria
Acne

The risk for dermatitis herpetiformis is increased by more than 100-fold among patients with celiac disease. For the other dermatologic disorders listed, patients with celiac disease have only a small increased risk (odds ratio between 1.5 and 2)[1].

Reference:

1. *Lebwohl B, Söderling J, Roelstraete B, et al. Risk of skin disorders in patients with celiac disease: A population-based cohort study. J Am Acad Dermatol 2021; 85:1456.*

Graphic 71271 Version 4.0

Contributor Disclosures

Paul J Ciclitira, MBBS, MD, PhD, FRCP, AGAF Grant/Research/Clinical Trial Support: Celiac Foundation [Celiac disease]. All of the relevant financial relationships listed have been mitigated. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→