

Gluten-Sensitive Enteropathy

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KEY CONCEPTS

- Celiac disease (CD) is a permanent intolerance to ingested gluten with damage to the small intestine that resolves with the removal of gluten from the diet.
- CD is a global health problem, affecting Western and Eastern populations.
- CD is strongly associated with the HLA class II genes located in chromosome 6 that encode the molecules DQ2 and DQ8.
- CD is defined according to the clinical presentation and has been likened to an iceberg, “the celiac iceberg.”
- The mainstay of treatment of CD is lifelong adherence to a diet that excludes foods containing gluten.

Introduction

Celiac disease (CD), also known as gluten-sensitive enteropathy, is the end result of collision between the human immune system and the widespread cultivation of wheat (the major food source that fueled Western civilization). The point of contact is the lining of the small intestine. The collision results in inflammation and architectural changes of the absorptive mucosa in those susceptible to CD. The inflammation leads to destruction and eventual loss of absorptive surface (villi), increased net secretion, and potentially a multitude of consequences of malabsorption (Fig. 17.1).

CD is defined as a permanent intolerance to ingested gluten that damages the small intestine and that resolves with the removal of gluten from the diet [1].

Classically, CD causes increased loss of ingested fat and fatty acids in the stool, malnutrition, and deficiency of micronutrients (iron, folate, and the fat-soluble vitamins) that may result in a syndrome of severe malabsorption. However, the disorder frequently presents with only the vaguest symptoms or, indeed, may remain entirely silent for many years despite much damage to the intestine [2]. The disease is a global health problem, and cases have been described in Western and Eastern populations [3]. The disorder usually completely resolves with exclusion of gluten from the diet, but reoccurs when gluten is reintroduced.

Although it was once thought to be a rare disease, it is now recognized as a common chronic disorder affecting as much as 1% of the general population in Western countries [4].

Other forms of intolerance to wheat/gluten

Although CD is the best-recognized pathologic consequence of gluten ingestion, wheat and gluten may be implicated in other syndromes that partly resemble CD. Clinical syndromes of chronic diarrhea that respond to gluten exclusion have been described in people who lack the architectural changes of CD in the small intestine.

Wheat may be subject to incomplete digestion in adults. Gluten has been implicated in autism and schizophrenia; however, these have remained in the realm of uncontrolled observations. Despite the lack of scientific rigor supporting these conclusions, the prescription of a gluten-free diet (GFD) has found favor among many practitioners of alternative medicine. CD, with its many complications and implications, should be diagnosed before commencing the GFD, because subsequent confirmation may be difficult.

Wheat may, of course, induce a more classic allergic response that is characterized by IgE or eosinophil-mediated responses; its diagnosis is made by eliciting a history of an immediate reaction to wheat including urticaria, wheezing, and angioedema. While skin prick testing would support suspect food items, ultimately double-blind food challenge may be needed as proof [5].

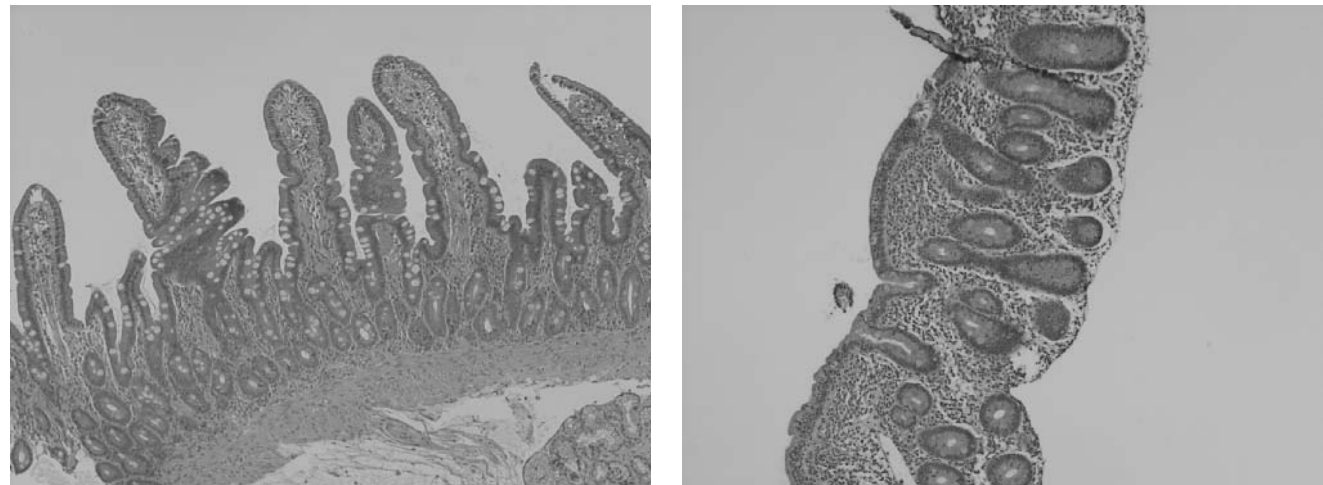


Figure 17.1 A normal mucosa on the left in contrast with the typical changes of the mucosal lesion of CD on the right. There is loss of the villous structures and hyperplasia of the crypts. Lymphocytes and plasma cells predominate in the inflamed lamina propria. Intra-epithelial lymphocytes increase in density (magnification 200×).

Etiology

The intestinal lesion in CD is characterized by architectural and inflammatory changes in the mucosa of the small intestine. The inflammatory response consists of increased numbers of lymphocytes, plasma cells, and macrophages in the lamina propria, and increased lymphocytes in the surface layer of the epithelium (intra-epithelial lymphocytes). The normally tall thin villi are shortened and flattened, and crypt layer is increased in depth. These changes may be patchy or continuous, and may affect a variable length of the small intestine [6].

All these changes may result in substantial loss of the absorptive function of the small intestine.

The combination of genetic predisposition, environmental insults, and the intestinal immune system culminates in the intestinal mucosal damage of CD (Fig. 17.2).

Genetics

The genetic basis of the disease comes of the recognition that CD occurs more commonly in families or relatives of probands (Table 17.1).

CD is a complex trait with several genes involved in disease susceptibility. CD is strongly associated with the human leukocyte antigen (HLA) class II genes located in chromosome 6 that encode the molecule DQ2, and less often DQ8. Thus, the majority (95%) of patients carry genes that encode the haplotype DQ2 (DQA1*05/DQB1*01), and the remaining patients express DQ8 (DQA1*03/DQB1*0302) [7]. Such is the strength of the association that the carriage of one of these HLA haplotypes is virtually essential for the disease to occur. Even more, there is a gene dosage effect in which homozygosity increases the risk of the disease, and may influence in severity or age of onset.

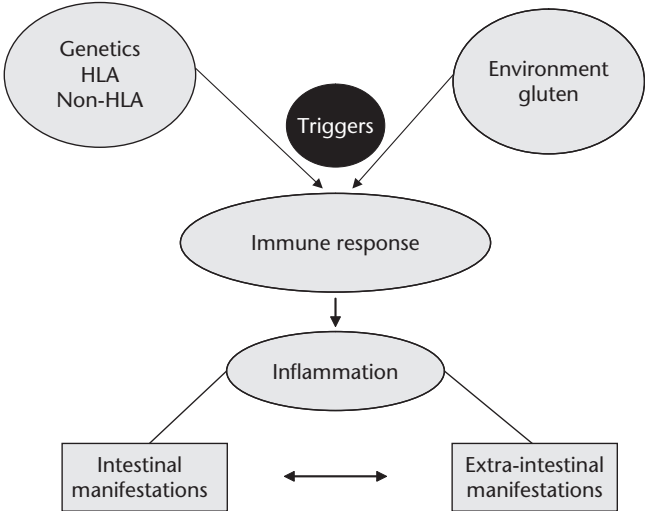


Figure 17.2 Schematic representation of the pathogenesis of CD.

Table 17.1 Risk of CD in relatives of known celiacs

Likelihood of a second case	50%
Sibling	10–20%
Parent	5–10%
Sibling sharing at-risk HLA	40%
Child	5–10%
Niece/nephew	5% or less
Grandchild	5%

There are several possible reasons that explain how these HLA genotypes increase the risk of CD. First, these HLA haplotypes are associated with an increased risk of autoimmune diseases in general due to the escape of autoreactive T-cells from thymic selection. People with these HLA genotypes develop a larger repertoire of T-cells that are potentially

self-reactive. Second, a unique binding affinity exists between DQ2 or DQ8 and certain peptide fragments of wheat (especially if they have undergone modification) that may occur in the gut.

HLA haplotypes confer at least 40–50% of genetic predisposition [8]. Thus, there are other genes involved in the susceptibility for CD. Genome-wide linkage analyses have identified a number of putative “celiac loci.” A locus on the 5q31-33 (CELIAC2) [9] region contains a number of cytokine genes and has been implicated in other autoimmune diseases. A loci on chromosome 2q33 (CELIAC3) encompassing the CTLA4 gene have been associated in several studies but is considered to confer only a very modest risk for CD [10]. A locus on chromosome 19 (CELIAC4) has been demonstrated to confer risk for CD in certain populations [11]. A locus on chromosome 7q was reported recently in a large set of North American families (ethnically homogeneous sample) with a minimum of two cases of CD [12].

In summary, there are several promising linkage regions to investigate further for true CD pathogenesis-related genes, but often lack replication in independent populations.

Environmental factors

It has long been known that CD is triggered by the cereal proteins, collectively known as “gluten,” that are derived from wheat, barley, and rye. These cultivated grain plants (plant tribe Triticeae) are closely related grasses from the family (Poaceae). The storage proteins of these grains are needed for seed germination. The proteins most harmful to those susceptible to CD are gliadins and glutenins in wheat, hordeins in barley, and secalins in rye [13]. The avidins in oats, although long suspected as harmful, are probably not toxic to the vast majority of celiacs [14,15].

These toxic proteins are large and complex, and they contain many separate amino acid sequences (epitopes) that can elicit vigorous responses in CD. These proteins consist of remarkably large proportions of glutamine (35%) and proline (20%) residues [16]. *Proline* residues are especially important, because they confer to proteins a high resistance to proteolysis in the intestine. This incomplete digestion favors the persistence of a large 33-mer gliadin peptide which contains several immunogenic peptide epitopes [17]. Additionally, proline residues favor immunologic reaction to gluten by enhancing (1) recognition and presentation of peptides by HLA-DQ2-containing cells and (2) selective deamidation of glutamine by tissue transglutaminase (tTG) that enhances the immunogenic properties of the gluten.

Intestinal permeability modulation

Gluten-induced increased intestinal permeability is an early phenomenon in CD pathogenesis [18]. Increased intestinal permeability allows the entry of gliadin peptides and enhances the immune response in the lamina propria [19].

The responsible mechanisms are complex, and include tight-junction (intercellular) dysfunction, transepithelial translocation, and epithelial apoptosis [20,21]. The molecular details of these processes are beyond the scope of this chapter, but are potential targets for emerging non-dietary therapies for CD.

Immunologic factors

The intestinal mucosa responds constantly to myriad foreign antigens in the gut lumen including food, bacteria, viruses, and toxins. It must do so in a way that protects the host from pathogens and toxins but allows the controlled entry of nutrients. The gut immune system is a delicately balanced milieu in which both the innate and adaptive arms of the immune system are in a controlled state of chronic inflammation. In CD, the consumption of gluten disturbs this homeostasis, resulting in unchecked inflammation in the intestinal mucosa.

Mucosal immune response

Cellular immunity

Cellular immunity seems to play the major role in the intestinal damage of CD [22]. The pathogenic sequence of events has been elucidated primarily through *in vivo* challenge studies in treated patients with CD and *in vitro* challenge studies on biopsies from treated and untreated patients [23]. The accumulation and activation of gluten-reactive memory T-cells in the duodenal mucosa play a crucial role in the immunopathogenesis of CD. Activated T-cells increase in the small intestine, and many of them respond specifically to gluten [24]. The response is dominated by an HLA-restricted Th1 type cytokine response characterized by IFN- γ , tumor necrosis factor (TNF), and others pro-inflammatory cytokines. These cytokines induce a migration of lymphocytes into the surface epithelium, subsequent recruitment of activated lymphocytes, macrophages, and plasma cells into the lamina propria, and deposition of complement in the subepithelial layer [25].

The surface epithelial layer is infiltrated with an increased number of predominantly CD8 T-lymphocytes [26]. These cells predominantly express the $\alpha\beta$ receptor, but an increased proportion of cells express the $\gamma\delta$ receptor. The intra-epithelial cells in the surface layer also express the natural killer (NK) cell surface marker CD94 [27]. These cells migrate into the intra-epithelial compartment in response to gliadin, an effect that may be mediated by interleukin (IL)-15, expressed on the surface of enterocytes [28]. These cells may be affected by innate response to gluten or other noxious stimuli. The innate response provides the costimulatory signals needed to expand the initial adaptive response [29]. Enterocytes, monocytes, and dendritic cells (DCs) may also play a crucial role in amplifying the initial adaptive response. Indeed, CD11c+ cells (a unique subset

of DCs) are responsible for antigen presentation of gluten to T-cells in the celiac lesion. Even more, a DC–T cell interaction at the mucosal site is an early event in the inflammatory response to gluten exposure [30].

The complex interrelationship between the surface enterocytes and the supporting fibroblasts is disrupted, leading to loss of the orderly migration and differentiation of the villous surface. The thickening of the crypt is not so much a response to loss of surface enterocytes as it is the result of inflammation and remodeling of the mucosa. The inflammatory response likely also damages the structural support and the microcirculation of the villi, causing the villous atrophy. This damage is most intense in the proximal small intestine, and it decreases caudally [31]. Surface lymphocytic infiltration of the stomach and colon may also be seen. The rectal mucosa of untreated CD responds to rectal exposure to gluten [32] (Fig. 17.3).

Humoral response

A potent humoral response occurs in untreated CD. The intestinal mucosa in CD contains increased numbers of

plasma cells secreting IgA, IgG, and IgM directed against gluten peptides, and antibodies against connective tissue autoantigens. Those antibodies are found in the intestinal juice and the serum. The dynamics of the humoral response seem to parallel those of cellular injury, although antibodies may arise before mucosal relapse and disappear before healing. Secreted IgA against gliadin may be a vain attempt to exclude a harmful antigen, while anti-connective tissue antibodies may target host antigen(s) in the connective tissue of the jejunum, umbilical cord, and endomysium. The main autoantigen target is the enzyme tTG [33].

The role of antibodies in the pathogenic process has been discounted because of the predominant role of the cellular immune response in the small intestinal lesion, and case reports that CD can occur in the setting of hypogammaglobulinemia [34]. However, the coincidence of tTG as the autoantigen, its release in CD, and a unique interaction with gliadin have renewed the interest in the humoral response in CD pathogenesis [35]. Gliadin antibodies can be seen in other intestinal conditions, but the connective tissue antibodies are highly specific to CD. The humoral response may have a role

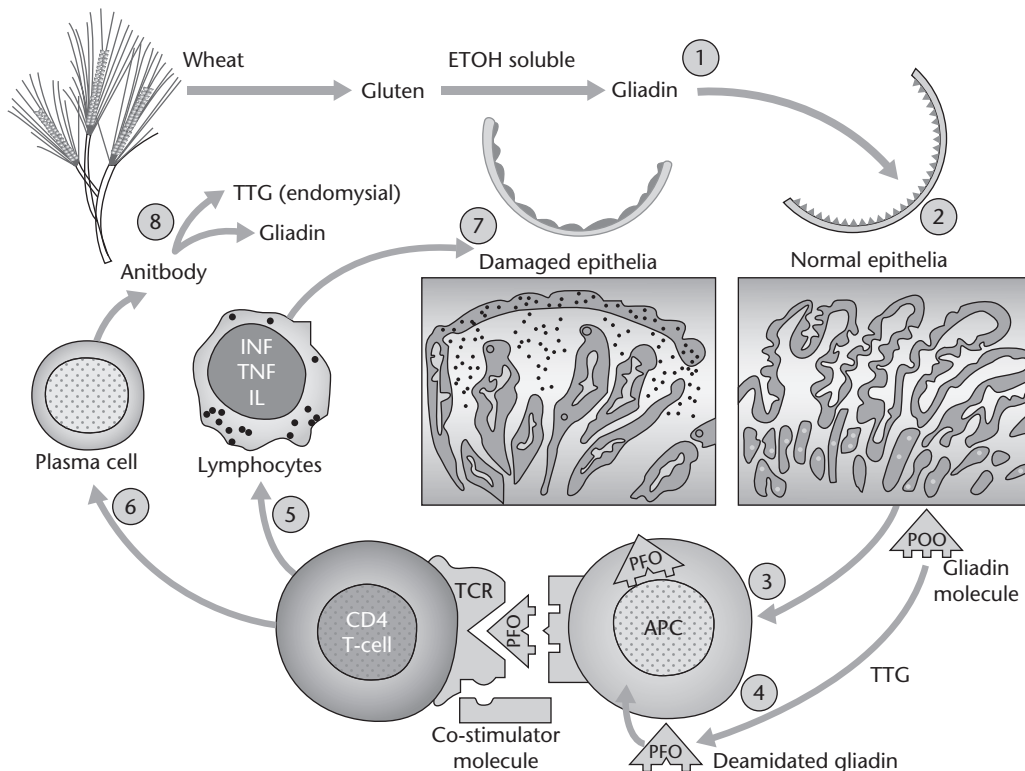


Figure 17.3 The steps that lead to CD are shown in this illustration. (1) Gliadin, the alcohol-soluble fraction of wheat, and similar proteins from rye and barley, undergo partial digestion in the gut. (2) The resulting peptides cross the gut epithelial barrier. (3) Native gliadin molecules are taken up by antigen-presenting cells (APCs) as is, or (4) they undergo deamidation (glutamine (Q) is changed to glutamic acid (E)), after which they are presented to activated T-cells. These activated T-cells in turn activate the (5) cellular and (6) humoral pathways. (7) The T-cells cause

production of more cytokines and recruitment of other inflammatory markers that lead to epithelial damage. (8) The plasma cells produce antibodies directed against both gliadin and autoantibodies. It is not clear how these antibodies cause disease in the gut, but cross-reactive antibodies may cause DH. Both environmental (predominantly gluten) and genetic factors give rise to the inflammation that leads to the destruction of the absorptive surface of the intestine. (Adapted from *Encyclopedia of Gastroenterology*, copyright The Mayo Foundation.)

in some of the extra-intestinal manifestations seen in CD, including dermatitis herpetiformis (DH), hyposplenism, IgA nephropathy, liver disease, and hypoparathyroidism [36].

Host modification of gluten by tissue transglutaminase

An intriguing feature of tTG is that its substrate is glutamine, which constitutes 35% of α -gliadin's amino acids. tTG itself may complex with gliadin thereby providing gliadin-responsive T-cell to help tTG-responsive but inactive B-cells to generate a potent self-directed antibody response [37]. It seems likely that tTG modifies the gliadin peptides, increasing the binding affinity for the antigen-presenting site of the two HLA molecules [38]. Interestingly, the deamidated peptides are not recognized in the context of DQ types that are not involved in CD [39]. This host modification of the external antigen may be a crucial step in expanding the immune response to the exogenous gliadin molecule once tTG has been released.

Epidemiology

CD has raised considerable interest in the past few years with the demonstration of its high prevalence (up to 1% in almost every studied country). This new insight in prevalence has been possible, in part, due to the use and availability of celiac serologic tests.

CD has been described in all the continents of the world, in developed and developing countries, and in a diversity of racial groups [3].

In Latin-American and Middle-East countries, CD appears to be at least as frequent as in Europe or the United States. Thus, the old concept of CD as a "rare and predominantly European disease" is completely incorrect. CD must be approached as a global health problem (Fig. 17.4).

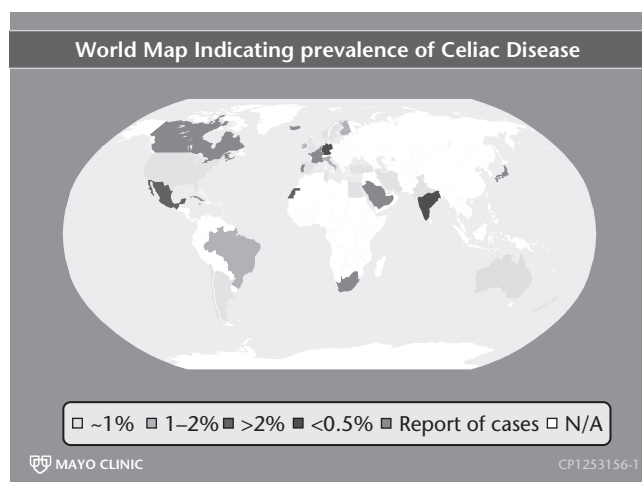


Figure 17.4 World map indicating prevalence of CD (copyright The Mayo Foundation).

However, CD remains an under-diagnosed disorder with less than 1:10 affected being diagnosed.

CD probably starts in the first decade, though the majority of patients are not diagnosed until later. The increased number of cases detected by serology from the Denver studies, in which a birth cohort of subjects that share the HLA haplotypes for CD has been followed up serologically on an annual basis, supports the concept of delayed detection [40].

The incidence of CD varies internationally but appears to be a trend to increasing incidence in many countries [41,42].

The explanation for the increasing incidence is not clear. However, there has been an increase in wheat consumption globally, but especially in North America over the last 20 years, with a 70% increase in per capita wheat consumption, largely reflecting an increase in the use of pre-packaged convenience foods. The increased exposure to gluten can result in a major number of symptomatic subjects. This explanation is not enough because a high percentage of the new detected cases has mild symptoms or are completely symptomless.

The role of modification of wheat to enhance production cannot be ruled out as a possible contributory factor for the increasing incidence of CD but it is not proven to date. Even more, the use of new technologies to improve agriculture has increased the production and distribution of wheat worldwide.

Natural history of celiac disease

CD is a chronic disease and one that will persist unless treated. It may be asymptomatic despite being otherwise fully evolved in terms of villous atrophy and positive serology. Many patients may remain untreated and the ultimate outcome of untreated CD is really unknown.

The conditions required for CD to start exist from early life with a combination of genetic predisposition and the consumption of the inciting grains.

There are four possible outcomes to CD once it develops. Some patients will be symptomatic and obtain diagnosis and treatment. Others will be symptomatic but not receive the diagnosis and will go untreated. Yet more patients will remain asymptomatic and never be diagnosed, and a few patients who would have remained asymptomatic are diagnosed by some type of screening detection.

Clinical presentation

The classic constellation of symptoms and signs characterizing the malabsorptive syndrome of CD includes diarrhea, steatorrhea, weight loss or failure to thrive, bloating, and flatulence with multiple deficiency states [43] (Table 17.2). More common and difficult to recognize are the other ways in which CD presents, the so-called "atypical" presentations [44]. It can mimic many common clinical entities

Table 17.2 Presentations of CD (partial list)

Gastrointestinal	Non-gastrointestinal
Steatorrhea	Dermatitis herpetiformis
Chronic diarrhea	Infertility
Weight loss	Anemia
Elevated transaminases	Dementia
Recurrent pancreatitis	Osteoporosis
Bloating, abdominal pain	Neuropathy
Failure to thrive	Dental enamel defects
Enteropathy-associated T-cell lymphoma	Ataxia
Vomiting	Osteomalacia
Duodenal obstruction	Tetany

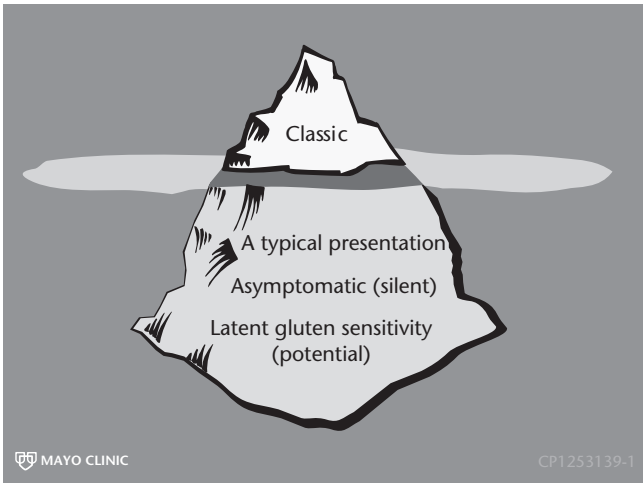


Figure 17.5 The celiac iceberg (see text) (copyright The Mayo Foundation).

(CD is considered the “modern impostor”) including irritable bowel syndrome, deficiencies of single micronutrients, especially iron, folate, B12, and the fat-soluble vitamins. Other “atypical” presentations are secondary osteoporosis, osteomalacia, ataxia, dementia, fatigue, neuropathy, and chorea.

The presentation of CD in children similarly can result in stunting of growth and intellectual development, epilepsy, and dental abnormalities as single symptoms without the more classic malabsorption symptoms of malnourished pot-bellied infant with steatorrhea [45].

CD is defined according to the clinical presentation and has been likened to an iceberg, “the celiac iceberg” (Fig. 17.5).

The tip of the iceberg represents the most obvious part of the clinical spectra (classic malabsorption). If the patient’s symptoms are characteristic of the malabsorption syndrome (diarrhea, steatorrhea, weight loss, fatigue); then the adjective “classical” is used. Then there is the “non-classical” CD, adjective applied when patients have non-specific symptoms such as abdominal discomfort, bloating, indigestion, or non-gastrointestinal (GI) symptoms (microcytic anemia).

Thus, this group of patients had minimal symptoms but can be detected clinically if there is a high suspicion for the diagnosis. Paradoxically, the “non-classical” is now the most frequent presentation of CD in the United States. Finally, there is the submerged part of the iceberg where patients have histologic evidence of CD but remain undetected. Some of that portion consists of identifiable at-risk groups such as families of people with CD and subjects with CD-associated diseases. In “silent” CD, intestinal biopsies show the characteristic morphologic changes in an asymptomatic patient. Autoantibodies may or may not be present. “Latent” disease refers to genetically susceptible persons, without symptoms or histologic evidence of CD who will ultimately go on to develop CD. These cases are found by following up persistently positive autoantibodies such as endomysial or tTG antibodies, in patients with DH who initially have an apparently normal small intestine who then develop CD while on a gluten-containing diet, or occasionally in asymptomatic family members of an index case.

Diagnostic tests for celiac disease

An important consideration is whether the patient has been on a GFD prior to the testing. All of the tests, including the intestinal biopsies, may have returned to normal, making confirmation difficult without reintroducing gluten into the diet.

The pre-modern diagnosis of CD was based on the constellation of features, especially steatorrhea and weight loss or failure to thrive, that are hallmarks of frank malabsorption. Almost simultaneously in the 1950s, advances in understanding of the specific pathologic lesion in the small intestinal mucosa and its gluten-induced etiology enhanced the precision with which the disease could be diagnosed; diagnosis included the response to therapy (GFD). Current guidelines require histologic evidence of enteropathy and a positive response of symptoms or signs to a GFD. The earlier requirement for three sets of biopsies (one at diagnosis, after treatment with GFD, and after gluten challenge) was both cumbersome and, in most cases, unnecessary to establish and confirm a diagnosis of CD. Three biopsies may be needed in individuals diagnosed at less than 3 years of age, when the population from which the individual comes is subject to common alternative diagnoses, and when the original diagnosis is uncertain or is challenged later [46].

Serologic testing has greatly facilitated the identification of CD in people with clinical presentations too mild to justify the invasiveness of a biopsy as the initial diagnostic test. The ready availability of serology has made detection accessible to primary-care doctors and their patients in primary care. Not only are more people being diagnosed, but many other issues have arisen about the accuracy of the diagnosis and how to incorporate serologic testing into the diagnostic approach (Fig. 17.6).

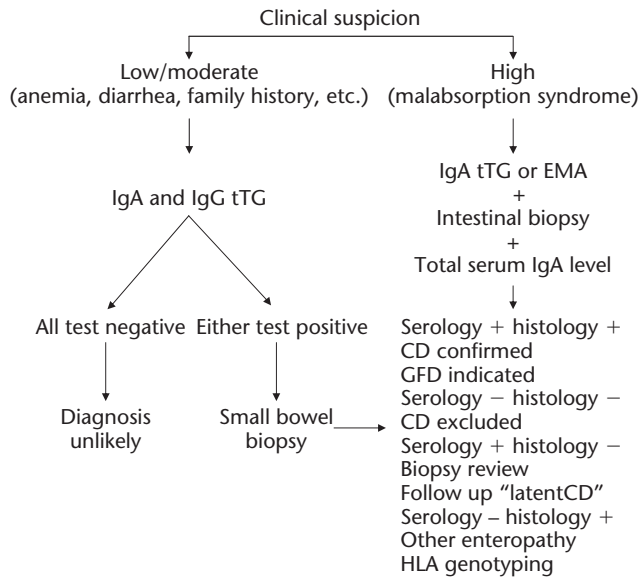


Figure 17.6 Approach to the diagnosis of CD. EMA, endomysial antibodies; positive +; negative –.

Table 17.3 Serologic tests for CD

Substrate/antigen	Antibody isotype	Test type	Sensitivity (%)	Specificity (%)
Gliadin	IgA	ELISA	31–100	85–100
Gliadin	IgG	ELISA	46–100	67–100
Endomysium	IgA	IFA	57–100	95–100
Tissue transglutaminase	IgA	ELISA	92–98	98

IFA, immunofluorescence assay.

Serology

A summary of serologic tests available for CD diagnosis is shown in Table 17.3.

Intestinal biopsies

Intestinal biopsy is always necessary to confirm the diagnosis of CD, except in the case of patients with biopsy-proven DH and positive celiac serology. The biopsy must be interpreted by an expert pathologist with recognition of the whole spectrum of the histologic lesion in CD. The most used histologic classification is that described by Marsh [47]. Briefly, Marsh type 0 is a normal mucosa. Marsh type I or “infiltrative” lesion is characterized by intra-epithelial lymphocytosis in the absence of other abnormality but is not specific for CD. Marsh type II or “hyperplastic” lesion is characterized by intra-epithelial lymphocytosis with crypt hyperplasia. Marsh type III or “atrophic” lesion is characterized by partial atrophy (3a), sub-total atrophy (3b), and total atrophy (3c) [48]. Marsh type IV refers to the most severe “hypoplastic” lesion.

Gluten challenge

It is no longer necessary to re-challenge most patients who have a well-established diagnosis of CD. However, in patients first diagnosed under the age of 3 years or those who have already embarked on a GFD and are seeking a confirmation of the diagnosis, a formal gluten challenge may be desirable [49]. This is not usually needed if the patient had a biopsy while on gluten-containing diet. Review of the original histology slides, if available, may suffice to confirm the diagnosis.

The length of time it takes to relapse with gluten challenge is quite variable [50]. The gluten in three to four slices of whole wheat bread daily should be sufficient to produce damage in 2–4 weeks, although it can take longer for the full pattern of injury to occur. Some very sensitive patients may need a reduction of this dose to prevent severe symptoms. Most patients relapse within 6 months although, in rare cases, it may take years to relapse.

Celiac crisis

A life-threatening presentation of CD has been reported in children and less frequently in adults [51,52]. Profuse acute diarrhea, dehydration, hypokalemia, and severe metabolic acidosis, the so-called “celiac crisis,” need emergent life-saving therapy. This dramatic clinical scenario can be a spontaneous clinical presentation or precipitated by the gluten challenge in patients very sensitive to the gluten.

Dermatitis herpetiformis

DH is characterized by chronic, intensely pruritic, polymorphic rash that causes vesicles–bullae on extensor surfaces of the elbows, knees, buttocks, and scalp [53]. There is a slight male preponderance of DH [54]. It is a skin manifestation of the intestinal immune response to ingested gluten that is characterized by the deposition of IgA granules at the dermo-epidermal junction. The source of these IgA deposits in the skin is unknown, but they may be produced in the intestinal mucosa and are likely cross-reactive with the closely related skin-based autoantigen epidermal transglutaminase, which is similar to tTG (the primary autoantigen in the gut) [55]. The intestinal damage may be asymptomatic at the time of presentation of the skin rash, but it is indistinguishable from that seen in CD. A positive serologic test strengthens the certainty of the skin diagnosis, and would also mandate examination of the patient for consequences of malabsorption. However, it is not necessary to perform these antibody tests or even an intestinal biopsy to establish the etiologic role of intestinal gluten exposure in DH. That can be reliably inferred by the demonstration of the granular IgA deposits in the skin (Fig. 17.4). The serology test may be useful in cases in which there remains some doubt, for example, in distinguishing it from bullous linear IgA disease, which is not a gluten-sensitive disorder. Gliadin antibodies may be seen in other bullous skin disorders and are not particularly helpful in this setting [56].

Many patients in the United States with DH have not been treated with GFD, but rather with dapsone, which suppresses only the skin rash. The usual starting dose is 100mg/day; however, dapsone does not prevent intestinal damage, but its benefit on the rash may delay or divert the patient from taking the appropriate dietary measures. Many of these patients may present years later with GI symptoms, anemia, and severe metabolic bone disease or even malignancies. Additionally, dapsone side effects include methemoglobinemia, hemolytic anemia, and a severe idiosyncratic reaction called dapsone hypersensitivity syndrome [57]. Thus, lifelong GFD must be recommended as the mainstay of the long-term treatment of DH.

Treatment

Dietary therapy

The mainstay of treatment of CD is lifelong adherence to a diet that excludes foods containing gluten [58] (Table 17.4). Patients may have difficulty accepting that something as fundamental to their diet as wheat can injure them.

Table 17.4 Sources of gluten in the diet

<i>Gluten-containing grains and flours</i>	<i>Commonly overlooked sources of gluten (continued)</i>
Wheat	Cheese spreads
Rye	Chip and dip mixes
Malt	“Cornflour” in Europe
Barley	Hot chocolate mixes or cocoa
Triticale (wheat–rye hybrid)	Imitation bacon or seafood
Couscous	marinades
Kamut	Instant coffee and tea, salad
Spelt	dressings
Semolina	Modified food starch
<i>Gluten-containing foods</i>	Natural flavorings
Bread	Non-dairy creamer
Breaded foods	Non-fat processed food
Cakes	Malt or malt flavoring
Cookies	Processed meats and poultry
Crackers	Some brands of ice cream
Croutons	Sausage products
Pasta	Sauces
Pizza	Soup bases
Stuffing	Soy sauce
Toast	Stuffings
<i>Commonly overlooked sources of gluten</i>	Thickeners
Beer	Tomato sauce
Broth	<i>Unexpected sources of gluten</i>
Brown rice syrup	Medications (both prescription and OTC)
Coating mixes	Tooth paste, denture fixatives
Caramel color	Glues, pastes, and dry wall filler
Cereal products	Airborne flour
Catsup and mustard	Communion wafers
Candy bars	Cross-contamination

The patient can be motivated with the expectation of what can often be a dramatic improvement in general well-being in addition to improvement of GI symptoms [59]. A GFD should result in a prompt and even dramatic improvement in symptoms [60]. The recovery is more rapid and complete in children than adults. Resolution of symptoms may take 3–6 months, and complete healing of the intestine may take longer, especially in adults.

Detailed instruction from an experienced, well-informed dietitian is invaluable for most patients. In the absence of dietary instruction, many patients unfortunately resort to books or the Internet for information and may not fully understand important details. Inadvertent gluten intake or an overly restricted diet deficient in essential nutrients may be adopted. A CD support group can provide local information and emotional support to newly diagnosed patients.

Oats were once thought to be toxic for most CD patients, but recent controlled studies have shown that a moderate amount of a pure oat product did not impair healing of the intestine or cause a relapse. However, contamination of commercial oat products with other grains may occur. Vigilance is needed on the part of the patient and physician if a decision is made to incorporate oats in the diet.

Hidden sources of gluten are frequently present in what seem to be safe foods. Ingredient lists of gluten-free foods must be reviewed regularly for changes. It may be difficult to ascertain the exact grain source of ingredients because of production outsourcing. Even non-food items may be sources of trace gluten and can cause symptoms in more sensitive patients. Contamination of supposedly gluten-free products can also occur.

Lactose intolerance affects one-half of celiacs at diagnosis but usually resolves with mucosal restoration. Temporarily limiting lactose ingestion or using lactase may be necessary.

Vitamin or mineral supplements are given to correct deficiencies of iron, folate, B12, calcium, and fat-soluble vitamins as needed. Marked osteopenia and osteoporosis are common in both men and women. Patients with decreased axial bone density should be advised to obtain at least 1200mg of calcium and replacement doses of vitamin D. Secondary hyperparathyroidism may occur but tetany is rare. Pancreatic enzyme supplementation may be useful in very malnourished patients, and this may accelerate weight return.

All patients should be followed up to ensure compliance with, and a response to, the GFD [61]. Adolescents seem especially likely to be non-compliant with the dietary restrictions [62]. All antibody levels diminish with the institution of a GFD, often within weeks; by 6 months both tTG-IgA and endomysial antibody (EMA)-IgA may be undetectable. The gliadin antibody titers, however, often persist for a year or more into the GFD. Repeat testing is used to monitor the diet. However, a negative test is not entirely reliable as an indicator of low-level gluten ingestion. Improved absorption may cause patients to gain excess

weight, increase absorption of medications such as thyroid replacement, or develop increased cholesterol.

Non-dietary therapies

The better knowledge of CD pathogenesis may make possible the development of non-dietary therapies. The current explored approaches include: (1) pre-digestion of dangerous wheat epitopes (oral enzyme therapy); (2) intestinal permeability pathways blockade (zonulin receptor antagonist); and (3) induction of immune tolerance.

Prevention

Breast-feeding and gradual introduction of gluten

Protective factors, such as breast-feeding and delayed introduction of large quantities of gluten into the infant diet, seem to reduce the likelihood of developing CD in early age. This practical knowledge derives from the experience and analysis of the “Swedish epidemic of CD” [63]. In Sweden, a high incidence of CD was observed after national infant-feeding policies were changed to favor the introduction of larger quantities of gluten at the age of 6 months, after weaning was complete.

The prevalence of symptomatic CD (clinically detected) returned to “pre-epidemic” values after a national change in infant-feeding recommendations was proposed in 1996: a slow introduction to gluten during weaning was stressed, the recommendation being the introduction of smaller quantities of gluten at the age of 4 months and continuation of breast-feeding instead of larger quantities at the age of 6 months at the time of weaning [64]. However, no difference was found in undiagnosed CD between the screened children born before and after 1996. Thus, a slow introduction of gluten in infancy could protect some children from developing symptomatic CD, but it might not protect them from subclinical or silent forms of this disease in childhood.

Vaccines

Currently, there is not a useful vaccine for CD. However, as the gluten is clearly identified as the most important environmental factor, and the autoantigen (tTG) is known, the development of a vaccine is hypothetically possible (mainly through induction of oral tolerance to the gluten epitopes). Prophylactic vaccination against pneumococcal infections may be appropriate in the context of CD-associated hyposplenism [65]. Patients with CD have a good immune response to the polyvalent pneumococcal vaccine [66]. On the other hand, a lack of response to hepatitis B vaccine has been reported in CD [67].

Persistent or recurring symptoms

Patients with previously diagnosed CD who have persistent or recurrent diarrhea should undergo a careful dietary review and a check of their serology [68]. If both are negative

and it is less than 6 months since diagnosis, treatment with lactose-restricted diet, pancreatic supplements (especially if there are features of malabsorption and low fecal elastase 1) should be started. Colonic biopsies may identify microscopic colitis. If it has been longer than 6 months since diagnosis, it may be prudent to re-biopsy the small intestine to assess for improvement. Other causes of recurrent symptoms are small intestinal bacterial overgrowth, other food allergies, and parasitic infections [69].

Refractory sprue

Refractory sprue (RS) is a combination of continued or recurrent severe malabsorption (“functional intestinal failure”), progressive malnutrition, intestinal villous atrophy on repeat biopsy, and increased mortality despite compliance with a GFD for more than 6 months [70]. This condition affects approximately 5% of CD patients. Usually tTG and EMA antibodies are negative. Patients may have extensive small intestinal ulcerations extending beyond the distal duodenum (ulcerative jejunoileitis) with a high risk of perforation, obstruction, and transformation to lymphoma [71]. Other uncommon complications are mesenteric lymph node cavitation, and collagenous sprue (subepithelial collagen band thicker than 10 μ m). Enteric protein loss may be marked. The clinical presentation includes profound malnutrition, weight loss, abdominal pain, and fever.

Enteropathy-associated T-cell lymphoma should be carefully sought. CT scanning, small bowel radiography, capsule endoscopy, and more recently double-balloon enteroscopy have been used to establish the diagnosis. The presence of T-cell clones on molecular analysis of the intestinal mucosa may indicate “cryptic” lymphoma or RS type II [72]. The abnormal clone of intra-epithelial lymphocyte express cytoplasmic CD3 but loose the surface CD8 marker (and other T-cell markers), and demonstrate clonal T-cell receptor (TCR) gamma gene rearrangement. The absence of a T-cell clone (RS type I) has a much better prognosis, with responses to steroids or immunosuppression likely. Parenteral nutrition support allows correction of the nutritional problems, but some patients require home total parenteral nutrition for survival. Prognosis of RS type II is poor, with 50% of patients suffering a fatal outcome. Currently, there is not an effective treatment for RS type II. Steroids and immunosuppressive drugs should be used with caution and frequently are ineffective. A third of the patients with RS type II were clinically and histologically improved with the use of 2-chlorodeoxyadenosine, or cladribine; however, the T-cell abnormal clone persisted in all the patients and in 40% the disease progressed to overt lymphoma [73]. The use of alemtuzumab (anti-CD52 monoclonal antibody) [74] or autologous hematopoietic stem cell transplantation has been reported as a successful treatment for overt T-cell lymphoma [75]. IL-15 blockade represents one promising option for the future treatment of RS type II [76].

Mortality in celiac disease

Patients with untreated or partially treated symptomatic CD are at high risk of complications and mortality associated with the disease.

Malignancies are a common cause of death in patients with CD [77]. The risk of malignancy is highest during the first 3 years after diagnosis, and remains higher if CD is left untreated [78]. The development of hypoalbuminemia, anemia, recurrent steatorrhea, weight loss, lymphadenopathy, fever, and malaise in a previous stable patient should prompt a search for neoplasm.

Patients with untreated CD have a particularly high risk of enteropathy-associated T-cell lymphoma [79], an otherwise rare form of high-grade and frequently lethal lymphoma. Adenocarcinoma of the small intestine, nasopharyngeal, melanoma, and esophageal cancer are also more common in CD [80]. On the other hand, a lower incidence of breast cancer has been reported in women with CD.

Non-malignant complications also play a role in mortality in CD. Infections as a consequence of immunodeficiency associated with malnutrition could be a major cause of death. Also, in the setting of severe malnutrition and/or functional intestinal failure, total parenteral nutrition complications or central venous catheter-related sepsis could be major issues. Fatal pneumococcal septicemia (the so-called OPSI syndrome) has been reported in celiacs with hyposplenism [81].

Screening family members

Consider active screening of at-risk family members, including siblings, children, and possibly parents, because at least 50% of patients have an undiagnosed family member with CD [82]. Serologic screening test could be used for asymptomatic relatives, but those with specific symptoms suggestive of CD should undergo intestinal biopsy. Of course, the family members must be ingesting gluten-containing foods to maximize the accuracy of the testing.

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References

- Green PH, Jabri B. Celiac disease. *Annu Rev Med* 2006;57:207–21.
- Lee SK, Green PH. Celiac sprue (the great modern-day imposter). *Curr Opin Rheumatol* 2006;18:101–7.
- Catassi C. The world map of celiac disease. *Acta Gastroenterol Latinoam* 2005;35:37–55.
- 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;163:286–92.
- Palosuo K. Update on wheat hypersensitivity. *Curr Opin Allergy Clin Immunol* 2003;3:185–8.
- 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;102:330–54.
- Tollefsen S, Arentz-Hansen H, Fleckenstein B, *et al.* HLA-DQ2 and -DQ8 signatures of gluten T cell epitopes in celiac disease. *J Clin Invest* 2006;116:2226–36.
- van Heel DA, Hunt K, Greco L, Wijmenga C. Genetics in celiac disease. *Best Pract Res Clin Gastroenterol* 2005;19:323–39.
- Greco L, Corazza G, Babron MC, *et al.* Genome search in celiac disease. *Am J Hum Genet* 1998;62:669–75.
- Holopainen P, Naluai AT, Moodie S, *et al.* Candidate gene region 2q33 in European families with celiac disease. *Tissue Antigens* 2004;63:212–22.
- Van Belzen MJ, Meijer JW, Sandkuijl LA, *et al.* A major non-HLA locus in celiac disease maps to chromosome 19. *Gastroenterology* 2003;125:1032–41.
- Garner CP, Ding YC, Steele L, *et al.* Genome-wide linkage analysis of 160 North American families with celiac disease. *Genes Immun* 2007;8(2):108–14.
- Molberg O, Uhlen AK, Jensen T, *et al.* Mapping of gluten T-cell epitopes in the bread wheat ancestors: implications for celiac disease. *Gastroenterology* 2005;128:393–401.
- Holm K, Maki M, Vuolteenaho N, *et al.* Oats in the treatment of childhood celiac disease: a 2-year controlled trial and a long-term follow-up study. *Aliment Pharmacol Ther* 2006;23:1463–72.
- Haboubi NY, Taylor S, Jones S. Celiac disease and oats: systematic review. *Postgrad Med J* 2006;82:672–8.
- Vader LW, Stepniak DT, Bunnik EM, *et al.* Characterization of cereal toxicity for celiac disease patients based on protein homology in grains. *Gastroenterology* 2003;125:1105–13.
- Qiao SW, Bergseng E, Molberg O, *et al.* Antigen presentation to celiac lesion-derived T cells of a 33-mer gliadin peptide naturally formed by gastrointestinal digestion. *J Immunol* 2004;173:1757–62.
- Clemente MG, De Virgiliis S, Kang JS, *et al.* Early effects of gliadin on enterocyte intracellular signaling involved in intestinal barrier function. *Gut* 2003;52:218–23.
- Drago S, El Asmar R, Di Pierro M, *et al.* Gliadin, zonulin and gut permeability: effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. *Scand J Gastroenterol* 2006;41:408–19.
- Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. *Science* 2005;307:1920–5.
- Duerksen DR, Wilhelm-Boyles C, Parry DM. Intestinal permeability in long-term follow-up of patients with celiac disease on a gluten-free diet. *Dig Dis Sci* 2005;50:785–90.
- Jabri B, Kasarda DD, Green PH. Innate and adaptive immunity: the yin and yang of celiac disease. *Immunol Rev* 2005;206:219–31.
- Jabri B, Sollid LM. Mechanisms of disease: immunopathogenesis of celiac disease. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:516–25.

- 24 Molberg O, Solheim Flaete N, Jensen T, *et al.* Intestinal T-cell responses to high-molecular-weight glutenins in celiac disease. *Gastroenterology* 2003;125:337–44.
- 25 Sollid LM. Celiac disease as a model of gastrointestinal inflammation. *J Pediatr Gastroenterol Nutr* 2005;40:S41–2.
- 26 Kakar S, Nehra V, Murray JA, *et al.* Significance of intraepithelial lymphocytosis in small bowel biopsy samples with normal mucosal architecture. *Am J Gastroenterol* 2003;98:2027–33.
- 27 Collin P, Wahab PJ, Murray JA. Intraepithelial lymphocytes and celiac disease. *Best Pract Res Clin Gastroenterol* 2005;19:341–50.
- 28 DiSabatino A, Ciccocioppo R, Cupelli F, *et al.* Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in celiac disease. *Gut* 2006;55:469–77.
- 29 Stepniak D, Koning F. Celiac disease-sandwiched between innate and adaptive immunity. *Hum Immunol* 2006;67:460–8.
- 30 Raki M, Tollefsen S, Molberg O, *et al.* A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells. *Gastroenterology* 2006;131:428–38.
- 31 Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. *Baillieres Clin Gastroenterol* 1995;9:273–93.
- 32 Ensari A, Marsh MN, Morgan S, *et al.* Diagnosing celiac disease by rectal gluten challenge: a prospective study based on immunopathology, computerized image analysis and logistic regression analysis. *Clin Sci* 2001;101:199–207.
- 33 Dieterich W, Ehnis T, Bauer M, *et al.* Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med* 1997;3:797–801.
- 34 Rubio-Tapia A, Hernandez-Calleros J, Trinidad-Hernandez S, Uscanga L. Clinical characteristics of a group of adults with nodular lymphoid hyperplasia: a single center experience. *World J Gastroenterol* 2006;12:1945–8.
- 35 Biagi F, Campanella J, Laforenza U, *et al.* Transglutaminase 2 in the enterocytes is celiac specific and gluten dependent. *Dig Liver Dis* 2006;38:652–8.
- 36 Hernandez L, Green PH. Extraintestinal manifestations of celiac disease. *Curr Gastroenterol Rep* 2006;8:383–9.
- 37 Skovbjerg H, Noren O, Anthonsen D, *et al.* Gliadin is a good substrate of several transglutaminases: possible implication in the pathogenesis of celiac disease. *Scand J Gastroenterol* 2002;37:812–17.
- 38 Aremtz-Hansen H, McAdam SN, Molberg O, *et al.* Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues. *Gastroenterology* 2002;123:803–9.
- 39 Kim CY, Quarsten H, Bergseng E, *et al.* Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease. *Proc Natl Acad Sci USA* 2004;101:4175–9.
- 40 Hoffenberg EJ, MacKenzie T, Barriga KJ, *et al.* A prospective study of the incidence of childhood celiac disease. *J Pediatr* 2003;143:308–14.
- 41 Steens RF, Csizmadia CG, George EK, *et al.* A national prospective study on childhood celiac disease in the Netherlands 1993–2000: and increasing recognition and a changing clinical picture. *J Pediatr* 2005;142:239–43.
- 42 Murray JA, VanDyke C, Plevak MF, *et al.* Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. *Clin Gastroenterol Hepatol* 2003;1:19–27.
- 43 Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) institute technical review on the diagnosis and management of celiac disease. *Gastroenterology* 2006;131:1981–2002.
- 44 Rampertab SD, Pooran N, Brar P, *et al.* Trends in the presentation of celiac disease. *Am J Med* 2006;119:355.e9–14.
- 45 Fasano A. Clinical presentation of celiac disease in the pediatric population. *Gastroenterology* 2005;128:S68–73.
- 46 Hill ID, Dirks MH, Liptak GS, *et al.* North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:1–19.
- 47 Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. *Baillieres Clin Gastroenterol* 1995;9:273–93.
- 48 Oberhuber G. Histopathology of celiac disease. *Biomed Pharmacother* 200;54:368–72.
- 49 NIH consensus statement on celiac disease. *NIH Consens State Sci Statements* 2004;21:1–22.
- 50 Laurin P, Wolving M, Falth-Magnusson K. Even small amounts of gluten cause relapse in children with celiac disease. *J Pediatr Gastroenterol Nutr* 2002;34:26–30.
- 51 Baranwal AK, Singhi SC, Thapa BR, Kakkar N. Celiac crisis. *Indian J Pediatr* 2003;70:433–5.
- 52 Wolf I, Mouallem M, Farfel Z. Adult celiac disease presented with celiac crisis: severe diarrhea, hypokalemia, and acidosis. *J Clin Gastroenterol* 2000;30:324–6.
- 53 Oxentenko AS, Murray JA. Celiac disease and dermatitis herpetiformis: the spectrum of gluten-sensitive enteropathy. *Int J Dermatol* 2003;42:585–7.
- 54 Turchin I, Barankin B. Dermatitis herpetiformis and gluten-free diet. *Dermatol Online J* 2005;11:6.
- 55 Sardy M, Karpati S, Merkl B, *et al.* Epidermal transglutaminase (Tgase3) is the autoantigen of dermatitis herpetiformis. *J Exp Med* 2002;195:747–57.
- 56 Karpati S. Dermatitis herpetiformis: close to unraveling a disease. *J Dermatol Sci* 2004;34:83–90.
- 57 Sener O, Doganci L, Safali M, *et al.* Severe dapsone hypersensitivity syndrome. *J Investig Allergol Clin Immunol* 2006;16:268–70.
- 58 See J, Murray JA. Gluten-free diet: the medical and nutrition management of celiac disease. *Nutr Clin Pract* 2006;21:1–15.
- 59 Case S. The gluten-free diet: how to provide effective education and resources. *Gastroenterology* 2005;128:S128–34.
- 60 Murray JA, Watson T, Clearman B, Mitros F. Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. *Am J Clin Nutr* 2004;79:669–73.
- 61 Schuppan D, Dennis MD, Kelly CP. Celiac disease: epidemiology, pathogenesis, diagnosis, and nutritional management. *Nutr Clin Care* 2005;8:54–69.

- 62 Pietzak MM. Follow-up of patients with celiac disease: achieving compliance with treatment. *Gastroenterology* 2005;128:S135–41.
- 63 Ivarsson A, Persson LA, Nystrom L, *et al.* Epidemic of celiac disease in Swedish children. *Acta Paediatr* 2000;89:165–71.
- 64 Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. *Am J Clin Nutr* 2002;75:914–21.
- 65 Johnston SD, Robinson J. Fatal pneumococcal septicemia in a celiac patient. *Eur J Gastroenterol Hepatol* 1998;10:353–4.
- 66 McKinley M, Leibowitz S, Bronzo R, *et al.* Appropriate response to pneumococcal vaccine in celiac sprue. *J Clin Gastroenterol* 1995;20:113–16.
- 67 Noh KW, Poland GA, Murray JA. Hepatitis B vaccine nonresponse and celiac disease. *Am J Gastroenterol* 2003;98:2289–92.
- 68 Krauss N, Schuppan D. Monitoring nonresponsive patients who have celiac disease. *Gastrointest Endosc Clin North Am* 2006;16:317–27.
- 69 Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of non-responsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002;97:2016–21.
- 70 Trier JS, Falchuk Z, Carey M, Schreiber D. Celiac sprue and refractory sprue. *Gastroenterology* 1978;75:307–16.
- 71 Elsing C, Placke J, Gross-Weege W. Ulcerative jejunoileitis and enteropathy-associated T-cell lymphoma. *Eur J Gastroenterol Hepatol* 2005;17:1401–5.
- 72 Cellier C, Delabesse E, Helmer C, *et al.* Refractory sprue, celiac disease, and enteropathy-associated T-cell lymphoma. *Lancet* 2000;356:203–8.
- 73 Al-Toma A, Goerres MS, Meijer JW, *et al.* Cladribine therapy in refractory celiac disease with aberrant T cells. *Clin Gastroenterol Hepatol* 2006;4:1322–7.
- 74 Vivas S, Ruiz de Morales JM, Ramos F, Suarez-Vilela D. Alemtuzumab for refractory celiac disease in a patient at risk for enteropathy-associated T-cell lymphoma. *N Engl J Med* 2006;354:2514–15.
- 75 Rongey C, Micallef I, Smyrik T, Murray J. Successful treatment of enteropathy-associated T cell lymphoma with autologous stem cell transplant. *Dig Dis Sci* 2006;51:1082–6.
- 76 Cellier C, Cerf-Bensussan N. Treatment of clonal refractory celiac disease or cryptic intraepithelial lymphoma: a long road from bench to bedside. *Clin Gastroenterol Hepatol* 2006;4:1320–1.
- 77 Viljamaa M, Kaukinen K, Pukkala E, *et al.* Malignancies and mortality in patients with celiac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis* 2006;38:374–80.
- 78 West J, Logan RF, Smith CJ, *et al.* Malignancy and mortality in people with celiac disease: population based cohort study. *BMJ* 2004;329:716–9.
- 79 Halfdanarson TR, Litzow MR, Murray JA. Hematologic manifestations of celiac disease. *Blood* 2007;109:412–21.
- 80 Green PH, Fleischauer AT, Bhagat G, *et al.* Risk of malignancy in patients with celiac disease. *Am J Med* 2003;115:191–5.
- 81 Parnell N, Thomas P. Fatal pneumococcal septicemia in a celiac patient. *Eur J Gastroenterol Hepatol* 1998;10:899–900.
- 82 Fraser JS, King AL, Ellis HJ, *et al.* An algorithm for family screening for celiac disease. *World J Gastroenterol* 2006;12:7805–9.