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Management of celiac disease in daily clinical practice

Luca Elli[a,*,1], Francesca Ferretti[a,b,1], Stefania Orlando[a], Maurizio Vecchi[a,b], Erika Monguzzi[a,b,c], Leda Roncoroni[a,b,d], Detlef Schuppan[c,e]

[a] Center for Prevention and Diagnosis of Celiac Disease, Division of Gastroenterology and Endoscopy, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milano, Italy
[b] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Festa del Perdono, 20122 Milano, Italy
[c] Institute for Translational Immunology, Research Center for Immunotherapy (FZI), Johannes Gutenberg University (JGU) Medical Center, 55101 Mainz, Germany
[d] Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, Via Festa del Perdono, 20122 Milano, Italy
[e] Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

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ABSTRACT

Celiac disease (CD) is the most common autoimmune enteropathy worldwide. In CD, dietary gluten triggers a T cell driven small intestinal inflammation in a subset of genetically predisposed subjects, expressing the HLA DQ2 and/or DQ8 genes on their antigen presenting cells. HLA DQ2/DQ8 can bind gluten peptides after their prior modification by the CD autoantigen, tissue transglutaminase (TG2). This process leads to the activation of gluten reactive T cells, small bowel villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis, the histological hallmarks of CD. The clinical picture of CD is extremely heterogeneous including intestinal (especially diarrhea, abdominal pain, bloating) and extraintestinal (especially associated autoimmune diseases, anemia, osteoporosis) manifestations. The prevalence of CD in most parts of the world is estimated at 1:100–1:150 and its diagnosis is based on the presence of circulating autoantibodies (anti-TG2) and the histological detection of villous atrophy. Treatment is a lifelong gluten free diet but adjunctive therapies are in development. Although CD is a well-characterized disease, it is grossly underdiagnosed, despite the severe consequences of long-term gluten ingestion in CD, such as enhanced autoimmunity, refractory CD and intestinal T cell lymphoma. The aim of the presented review is to provide a clinical guide and to summarize the most recent clinical progress in CD research.

1. Introduction

Celiac disease (CD) is an immune-mediated enteropathy, triggered and maintained by dietary gluten in genetically susceptible individuals [1,2]. It is the most common enteropathy in Western countries, affecting about 1%, but mostly undiagnosed [3].

CD is triggered by dietary ingestion of wheat gluten and similar proteins contained in barley and rye. The presence of serological anti-type 2 transglutaminase (TG2) autoantibodies and the characteristic duodenal histology presenting increased intraepithelial lymphocytes (IELs), villous atrophy and crypt hyperplasia [4,5]. CD can present with a broad spectrum of manifestations and in the last decades a shift from classic malabsorptive symptoms to atypical manifestations occurred [6]. Moreover, CD can be present in overweight as much as underweight patients with clinical onset in older ages [7]. Using serological screening of at risk subjects, CD is often identified in superficially asymptomatic individuals, which are nonetheless at risk of complications [8]. Therefore, an increased knowledge is required in both primary and secondary/tertiary care to think of, identify and diagnose or rule out CD. Early diagnosis and the life-long strict gluten-free diet (GFD) secure a favorable outcome [9].

Aim of the presented review is to summarize the most recent clinical progresses in CD paying particular attention to the clinical point of view. A comprehensive PubMed search has been conducted for English written articles, without time limit. Celiac disease, gluten, gluten free diet, diagnosis, follow up, histology, transglutaminase, gliadin, antibodies have been the main terms used for research.

* Corresponding author at: Center for Prevention and Diagnosis of Celiac Disease, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milano, Italy.
E-mail address: luca.elli@policlinico.mi.it (L. Elli).
[1] Luca Elli and Francesca Ferretti equally participated to the manuscript preparation

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2. Pathogenesis

The inflammatory cascade leading to mucosal damage in CD is initiated by exposure to dietary gluten-derived peptides contained in wheat (gliadins and glutenins), rye (secalins) and barley (hordeins) [10–12]. These proteins are partly resistant to gastrointestinal digestion activating CD4 and CD8 T cells in the lamina propria and the epithelium of the SB [13]. The CD4 T cell activation (adaptive immune response) is pivotal, with at least 50 different immunogenic gluten peptides identified [14]. These peptides gain access to the antigen presenting cells (APCs) of the lamina propria, in part by paracellular passage through an "untight" tight junctions and mainly via active transepithelial transport [10,11,15]. Once in the lamina propria, the glutamine and proline residues can be deamidated by the type 2 transglutaminase (TG2) [16]; this deamidation increases their affinity for the human lymphocyte antigen molecules (HLA)-DQ2 and -DQ8 on the APCs [10–12]. This antigen presentation induces the activation of gluten specific T helper 1 (Th1) CD4 cells that release proinflammatory and promote antibody production to (deamidated) gluten peptides and to the TG2, mainly IgA (mucosal) type [17]. Thus, a proinflammatory cascade is activated with the release of interferon-γ (IFN-γ) and other cytokines, modifying intestinal permeability and remodeling the mucosa by matrix-metalloproteinses (MMPs) [18]. Moreover, IELs, a heterogeneous population composed primarily of T cell receptor (TCR) α/β + CD8+ cells but also of TCRγ/δ + and natural killer (NK)-like cells [19], promote intestinal epithelial cell damage via an innate immune response [20]. Notably, IELs are primarily responsible for processes leading to refractory CD type 2 and enteropathy-associated lymphoma (EATL) discussed below, where clonal expansion occurs [21].

In CD, Th1 cytokines promote increased cytotoxicity of IELs and NK cells, with apoptotic death of enterocytes by the Fas/Fas ligand system, or IL-15-induced perforin/granzyme and NKG2D-MICA mediated signaling pathways [22].

Additionally, CD4 Th2 cells drives the activation, clonal expansion and differentiation of B-cells into plasma cells secreting IgA and IgG anti-gliadin (AGA) and deamidated gliadin peptide (DGP) antibodies, as well as prominently IgA and to a minor degree IgG anti-TG2 antibodies [6].

While the main pathogenic factors of CD have been defined [23,24], the overall pathogenesis remains complex, with numerous additional immunologic, genetic and environmental factors.

An important genetic component is suggested by epidemiological studies [25,26]. The strongest genetic susceptibility factors in CD are HLA class II genes known as HLA-DQ2 and HLA-DQ8 residing on chromosome 6: nearly 25–30% individuals of European descent carry the HLA-DQ2 aplotype, but only about 3–4% of them will develop CD [12,27], therefore the presence of specific HLA-DQ alleles is necessary, although not sufficient.

Moreover, an important role of other environmental factors in the pathogenesis of CD was described [28], including gastrointestinal infections [29], exposure to heavy metals [30] drugs [31] and the intestinal microbiome [32].

3. Epidemiology

Once underestimated, CD it is now regarded one of the most common immune-mediated disorders in Western countries, with a prevalence around 1%. Globally the prevalence of CD is rising [33–35]; importantly, this is not only due to an increased awareness among clinicians and higher rates of diagnosis [36,37].

CD is more frequent among women compared to men, with a female:male ratio of up to 2.8:1 [6]. For a long time CD was considered a pediatric disease; actually, the incidence of CD by age shows a typical bimodal distribution, with incidence rates highest in people < 5 years of age and aged between 50 and 69 years [38].

The CD distribution seems to have followed the evolution of mankind, its migratory flows and the development of wheat harvesting and consumption [1,39], confirming the hypothesis that the genetic predisposition to CD is more common, but CD only occurs when there is a sufficient dietary exposure to gluten [40].

CD prevalence in North America and Europe is similar, but it seems to be higher in Northern Europe. The Scandinavian countries, UK, Italy and Germany show a higher prevalence of approximately 1–1.5%. CD is also becoming common in developing countries, particularly in North Africa [41], Middle East [41] and northwestern India [1,42].

There is an increased prevalence in some high risk groups [1] including first degree relatives of CD patients [8], type 1 diabetes [43], autoimmune diseases [44], Down's syndrome [45], Turner's syndrome [46] and IgA deficiency [47–49].

4. Clinical presentation

The natural history of CD is variable. The sequence of events includes the appearance of specific autoantibodies, the development of enteropathy, the onset of symptoms and eventually the development of complications. However, not all of the phases necessarily occur and each phase may range from weeks to decades. The clinical picture has recently changed: once considered a gastrointestinal disease of childhood affecting mainly whites, CD is now recognized as a systemic disease that may affect any age and different ethnic groups [1].

Although CD is a condition that primarily affects the small bowel, clinicians need to be aware that the onset with malabsorptive symptom or malnutrition in adults is now the exception rather than the rule [50]. Therefore, increased awareness is required in both primary and secondary care to recognize the shift of the common presenting features and the non-specific manifestations of CD in order to minimize the diagnostic delay.

Classic manifestations include diarrhea, weight loss and a failure to thrive. However, gastrointestinal symptoms comprise also non-specific manifestations such as anorexia, vomiting, abdominal pain, bloating and constipation [1]. Non classical (or atypical) manifestations include a broad spectrum of symptoms affecting different extra-intestinal organs (Table 1). Among them anemia, liver abnormalities (i.e. increased levels of transaminases), metabolic bone disease, neurologic symptoms and gynecologic disorders are the most common [51].

Anemia is a frequent manifestation in otherwise asymptomatic adults, occurring in about 10–20% of adult celiac patients. The etiology can be multifactorial: iron deficiency is the main cause, but also folate deficiency [52] as well as chronic inflammation and genetic polymorphisms can contribute [53,54]. Guidelines for gastroenterologists in the UK and USA suggest that all patients with iron-deficiency anemia should be tested for CD; in particular, the association with low total cholesterol or HDL levels as well as the failure to respond to oral iron supplementation should trigger in the clinician the suspect of CD [55–57].

Another common manifestation is reduced bone density which is due to the combination of nutritional deficiencies, inflammation and autoimmune mechanisms. Although screening of CD in osteoporotic women is still not recommended, experts suggest the evaluation of any patient with reduced bone mineral density which is not explained by age or other apparent medical conditions [58,59].

In recent years, different neurological manifestations of CD have been described. Peripheral neuropathy seems to be common (up to 49% prevalence including nonspecific symptoms such as asthenia, myalgia and muscle cramps). A small fiber neuropathy can be demonstrated in skin biopsy; rarer forms include cerebellar ataxia, epilepsy and migraine [60]. The association is often debated but the GFD appears to ameliorate symptoms suggesting utility of CD screening in these conditions [61].

In analogy, the relationship between CD and gynecologic disorders is still controversial. However, a recent meta-analysis suggested that women with unexplained infertility, recurrent miscarriage or

Table 1
Extraintestinal manifestations and CD-related diseases. *Gluten-dependent conditions.

	Extraintestinal manifestations	CD-associated diseases
Hematopoietic disorders	Anemia Hemorrhage due to K vitamin malabsorption Thrombocytopenia Thrombocytosis secondary to hyposplenism	Autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia.
Hepatic manifestations	Asymptomatic hypertransaminasemia	Autoimmune hepatitis Nonalcoholic steatohepatitis Primary biliary cirrhosis Primitive sclerosing cholangitis
Endocrinological manifestations	Hyperparathyroidism secondary to hypocalcemia	Autoimmune Hashimoto's thyroiditis Addison disease Primary hyperparathyroidism. Type 1 diabetes
Gynecological manifestations	Amenorrhea Delayed puberty Unexplained infertility in women Impotence due to hypothalamo-pituitary dysfunction Spontaneous and repeated abortions Preterm deliveries	
Skin/mucosal alterations	Glossitis Angular cheilitis Oral mouth sores (vitamin A and B deficit) Ecchymosis (vitamin K deficit) Aphthous ulcers Dental enamel defects	Psoriasis Vitiligo Alopecia areata Dermatitis herpetiformis*
Neurological manifestations	Headache Peripheral neuropathy Myopathy	Epilepsy Schizofrenia Depression Cerebral calcifications Leukoencephalopathy Multiple sclerosis Cerebellar ataxia*
Muscoloskeletal/rheumatological manifestations	Arthritis/arthralgia Osteopenia or osteoporosis Muscular hypotrophy Asthenia Tetany	Polymyositis Myasthenia gravis Connective tissue diseases (systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis)
Others		IgA deficiency Chromosomal disorders (Down syndrome, Turner syndrome, Williams syndrome) IgA nephropathy Cardiovascular diseases (ischemic heart disease, dilated cardiomyopathy, atherosclerosis and high LDL level) Inflammatory bowel diseases (ulcerative colitis, Crohn's disease, and microscopic colitis; either lymphocytic or collagenous) Pulmonary interstitial diseases (chronic fibrosing alveolitis, idiopathic pulmonary hemosiderosis, sarcoidosis)

intrauterine growth restriction have a 5-to-8 fold increased risk of undiagnosed CD, recommending serological screening in this subset of patients [62]. Besides the atypical presentation, clinicians should be aware that CD has been classically associated with other pathological conditions, including several autoimmune disorders [48]. This is important to correctly identify at-risk populations (Table 1). Among these conditions, dermatitis herpetiformis (DH) is a gluten-related condition characterized by intensely pruritic papules and vesicles, primarily on extensor surfaces such as elbows, knees and buttocks or the lower back that can be present only intermittently [63]. The diagnosis requires a skin biopsy showing granular IgA deposits and neutrophil infiltrates in the papillary dermis performed via direct immunofluorescence. Gluten free diet (GFD) and dapsone are considered the elective therapy [64]. Other conditions include glandular autoimmunity (autoimmune thyroid diseases, type 1 diabetes, Addison's disease) and rheumatoid diseases (the most frequent connective tissue disorder associated with CD is Sjögren syndrome, followed by systemic sclerosis and juvenile arthritis; the association with rheumatoid arthritis and systemic lupus erythematosus remains still debatable) [11,65–67].

5. Diagnosis and definitions

The diagnosis of CD is based on a combination of clinical manifestations, positive CD serological tests and histological findings at duodenal biopsies [68]. The suggested diagnostic algorithm in adults is presented in Fig. 1.

As mentioned above, serological screening for CD has to be considered in presence of potential symptoms of the disease and in high risk groups [69]. At present, mass screening of populations is not recommended.

Serology and duodenal histology should be performed in patients following a gluten containing diet, to confirm mucosal healing, which decreases the risk of complications.

Although there is no official and standardized terminology to describe CD, according to the combination of clinical presentation, serology and histology the so called “Oslo definition” of 2013 [70] included:

- Potential CD: Positive serological tests and normal intestinal biopsy
- Asymptomatic: Absence of symptoms despite specific questioning regarding symptoms

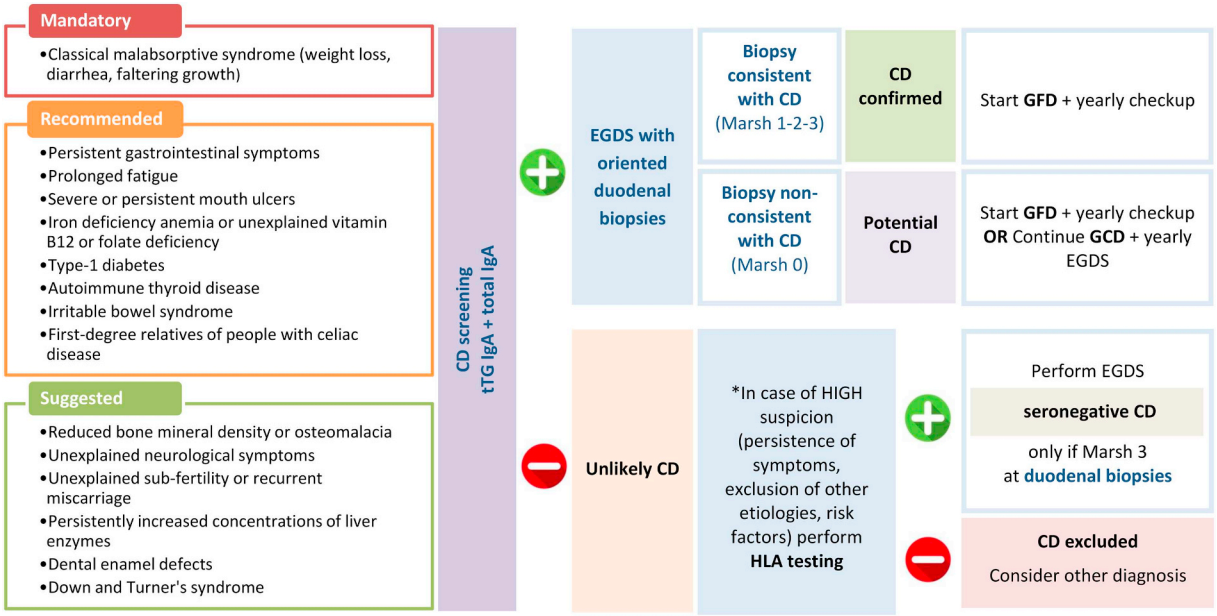

Fig. 1. Diagnostic flow-chart of suspected celiac disease.

- Symptomatic: Presence of either intestinal or extra-intestinal symptoms
  Classic: Diarrhea, signs and symptoms of malabsorption, or both
  Non-classic: Lack of malabsorption symptoms, but other symptoms present (eg, anemia, osteoporosis)
- Refractory: Persistent symptoms and villous atrophy despite adherence to a gluten-free diet

5.1. Serological tests

Anti-tissue (type 2) transglutaminase (TG2) IgA antibody (TG2-Ab) is the first line recommended serologic test for CD screening in individuals older than 2 years, with a high specificity and sensitivity (above 95%) [71]. Anti-endomysium antibody (EMA) testing has a higher specificity (around 99%), but is expensive, technically more difficult, with inter-observer and inter-site variability [72]. Therefore, EMA should not be tested routinely in screening (alone or with TG2-Ab), but only used as a confirmatory test in case of uncertain diagnosis (i.e. weak positivity of TG2-Ab) in high-risk populations [4]. IgA/IgG-anti native gliadin antibodies (AGA) have a low sensibility and specificity, making them an obsolete test that should not be performed [73].

Deamidated gliadin peptide (DGP) IgG should be used in children younger than 2 years of age, because in this age group DGP are more sensitive than TG2-Ab [74]. False negative serological tests can be due to a low-gluten diet or to primary IgA deficiency. Serological CD test screening is IgA based, indeed, total serum IgA should be initially assessed in conjunction with serology to avoid false negative tests. In patients with low IgA levels, IgG-based DGP and/or IgG anti-TG2 testing should be performed for serological assessment, even if IgG-DGP antibodies are the most sensitive [75]. Negative serological findings do not exclude CD with 100% accuracy, and histology confirmation is usually required. In the average, 2% of CD patients have a “seronegative” CD due to IgA deficiency or concomitant immunosuppressive therapy. It is important to underline the seronegative CD is very rare in children and almost always confined to subjects older than 50 years since the antibody reactivity decreases by age (i.e., antibody titers are significantly higher in infancy than in the elderly) [76,77]. However, there are several differential diagnoses of villous atrophy, as outlined below [78,79].

5.2. Histology

Histological examination of duodenal biopsy specimens is still a cornerstone for the diagnosis of CD [80]. Duodenal biopsy should be performed in all patients that undergo upper GI endoscopy with potential manifestation of CD. During endoscopic examination, markers of duodenal mucosal atrophy like mosaicism, scalloping or loss of duodenal folds can be observed but duodenum can also appear normal [81]. The histological signs of mucosal damage typical of CD include increased intraepithelial lymphocytes (IELs), in combination with crypt hyperplasia and villous atrophy [80]. Mucosal alteration in CD can be patchy, so it's important an adequate sampling with at least four endoscopic biopsies from the second part of the duodenum [82]. Recent evidence supports the usefulness of a duodenal bulb biopsy, even if in the setting of low pre-test probability of CD the diagnostic yield of bulb biopsy is limited [83]. Biopsy samples must be correctly oriented to avoid tangential artifacts and spurious shortening or absence of villi, for the correct evaluation of atrophic lesions and accurate count of IELs [68].

Histologic findings are usually classified according to the Marsh-Oberhuber system which includes different stages as defined in Fig. 2 [80,84]. Analogously, other less frequently used score systems to describe the CD histological damage are represented by the Corazza-Villanacci [85], Rostami [86] and Ensari [87] classifications.

These mucosal alterations are suggestive but not pathognomonic of CD [88]. An increase in the number of IELs in the absence of villous atrophy (Marsh 1 grade) is considered a non-specific finding, indicating CD in only 10–15% of cases [79]. Lymphocytic infiltration of the intestinal epithelium can be present in food allergy, gastrointestinal infection (including Helicobacter pylori infection), Crohn's disease, ulcerative colitis, common variable immunodeficiency (CVID) and autoimmune disorders [89]. Moreover, even villous atrophy can be present in other pathological conditions such as CVID, autoimmune enteropathy, Whipple disease, HIV, intestinal tuberculosis, giardiasis and eosinophilic gastroenteritis [79,89]. Recently, different cases of villous atrophy induced by olmesartan were reported and an analogous effect was suggested with telmisartan and ibersartan [90,91]. Therefore, in case of evidence of villous atrophy with negative serology (and genetic CD susceptibility), other causes of villous damage have to be excluded before hypothesizing a seronegative CD.

In case of uncertain diagnosis, some molecular analysis could be

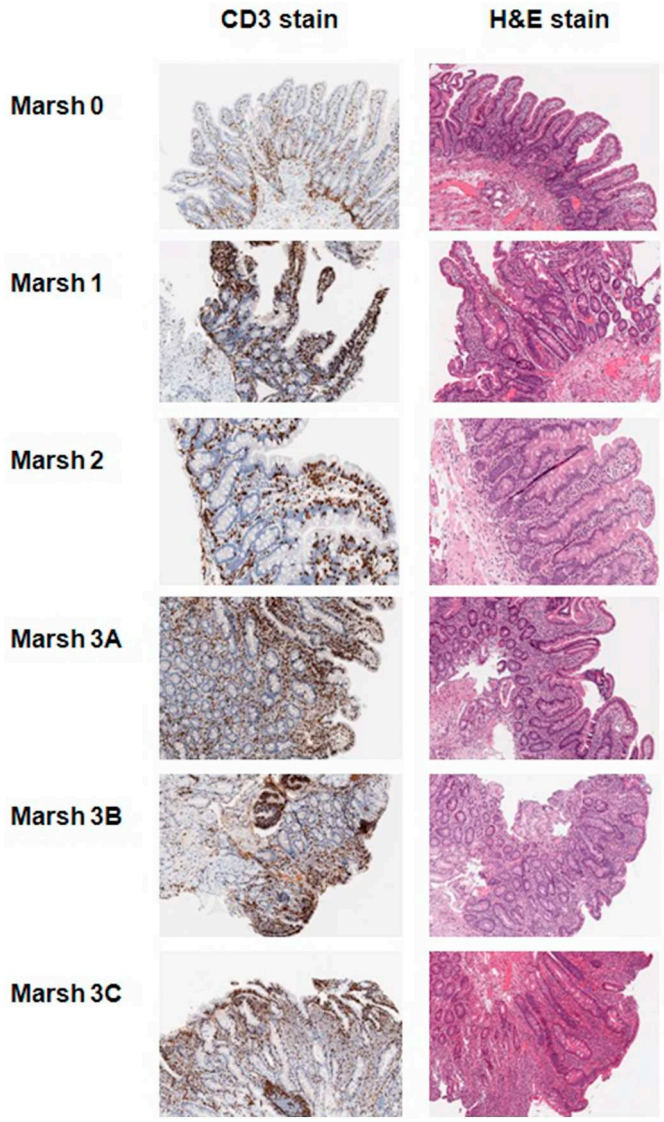

Fig. 2. Duodenal histological sections (Hematoxylin and eosin, H&E, and CD3 stainings) classified accordingly to the Marsh-Oberhuber classification. Marsh 0: normal duodenal mucosa, with villous-crypt ratio of 3:1 and scattered lymphocites in lamina propria and between enterocytes (< 20/100 enterocytes), Marsh 1: duodenal mucosa with normal architecture, showing nearly 40 intraepithelial lymphocytes, Marsh 2: duodenal mucosa characterized by focal crypt hyperplasia with crypts elongation and mitoses, and > 35 intraepithelial lymphocytes, Marsh 3 (a,b,c): duodenal mucosa with weak/mild/severe villous atrophy, charaterized also by crypt hyperplasia and marked intraepithelial lymphocytosis (> 50 lymphocytes/100 enterocytes).

used to support the CD diagnosis. The analysis of IELs by means of flow cytofluorometry (IEL lymphogram) may reveal an increased number of γδT cells, suggesting CD [92]. However, histologically, a mere increase of IEL in subjects consuming gluten (Marsh 1 lesion) predicts CD in only 15% of cases [79]. Similarly, the presence of TG2 IgA deposits in the duodenal mucosa seems specific for CD and thus, the detection od such deposits could be useful for diagnostic purposes [93].

Duodenal biopsy is necessary in adult patients but it can be avoided in selected symptomatic pediatric cases presenting specific characteristics (TG2-IgA > 10-fold above the upper limit, EMA positive test and HLA DQ2/DQ8 haplotype) [74]. In adults a similar strategy has been proposed only by the German CD guidelines [94].

5.3. Genetic testing

Genetic testing for the identification of HLA DQ2 and/or DQ8 has a high negative predictive value (> 99%) and can be used to rule out CD. In Western populations around 90–95% of celiac patients carry the HLA-DQ2 heterodimer and the remaining 5% are mostly HLA DQ8 carriers [95]. This test can be used in selected clinical settings, e.g., high risk patients to exclude a future onset of CD, patients already on GFD and equivocal diagnosis (*i.e* seronegative villous atrophy, discrepancy between serology and histology). The positive predictive value of the HLA for diagnosis of CD is very low, considering the HLA DQ2/DQ8 frequency in general population.

5.4. Gluten challenge

Patients already on a GFD should be tested for the presence of HLA DQ2/DQ8 and if positive, gluten should be reintroduced with a gluten challenge, before serologic and duodenal biopsies [96]. It is still not clear what an adequate daily intake of gluten is and for how long it should be applied, to ensure a correct diagnosis, mainly due to a high variability in sensitivity among patients. Classically, the gluten challenge consists in an oral intake of at least 10 g of gluten per day (approximately 4 slices of bread) for a period of 6–8 week, if tolerated well. The period has to be shortened if patients report significant complaints. A recent alternative is the ingestion of lower doses of gluten (> 3 g daily, equivalent to one-two slices of bread per day) for two weeks, followed by biopsy and serological testing at week 4, which has been suggested based on patients in remission challenged for 2 weeks and followed up by serology and biopsies [97].

5.5. Differentiation of celiac disease from other gluten(wheat) sensitivities

In the last decade a new classification of gluten (wheat) related disorders has been proposed, including a new entity, the so called non-celiac gluten sensitivity (NCGS; more correctly non-celiac wheat sensitivity, NCWS) [4,98]. NCGS is a syndrome characterized by the rapid onset of symptoms after the ingestion of gluten-containing food and symptom reliefon a GFD, while CD has been excluded [99]. The increasing number of patients adopting a GFD without medical prescription [100], made the differential diagnosis between CD and NCGS challenging. CD and NCGS clinical pictures can be similar; thus, the necessity to exclude the presence of CD serologically (TG2-Ab), genetically (especially when patienst are negative for HLA-DQ2 or –DQ8) and, if necessary, histologically represents the first step before embracing a GFD. It must be underlined that patients with NCGS do not present with circulating autoantibodies and characteristic (though often mild) histological alterations and its diagnosis remains based upon exclusion of other, classical intestinal diseases criteria and when possible a blind gluten challenge accordingly to the Salerno criteria [101].” Likely, the majority of these patients either suffers from an atypical wheat [102] allergy or ATI-sensitivity [103].

6. Therapy

6.1. Gluten free diet

The only effective treatment for CD is a life-long strict GFD, avoiding not only gluten-containing foods but also contaminations [104].

Among cereals, gluten is present in: durum wheat (*Triticum durum*), bread wheat (*Triticum aestivum*), barley (*Hordeum vulgare*), rye (*Secale cereale*), khorasan wheat (*Triticum turanicum*, Kamut®), the three species of spelt (einkorn, *Triticum monococcum*, emmer, *Triticum dicoccum* Schrank and spelta, *Triticum spelta*), triticale (Triticosecale Wittmack). Other gluten-containing wheat derivates are bulgur and seitan. Gluten is a protein of low nutritional value; however, it confers important

Table 2
Gluten free and gluten containing foods according "risk categories".

	Allowed	At risk (avoid unless labeled "Gluten free")	Avoid
Cereals and Pseudocereals	• Corn, millet, rice, fonio, cassava, sorghum, teff. • Buckwheat, quinoa, amaranth	• French fries, popcorn, polenta, risotto ready	• Barley, oats, rye, wheat, spelled, kamut, triticale, bulgur, cous cous
Fruit	• All kinds of fresh, dried, frozen, canned fruit	• Candied and glazed fruit. • Homogenized fruit	• Dried floured fruit (e.g dried figs)
Vegetable and Tubers	• All kinds of fresh, dried or frozen vegetables and legumes. • Tubers (potato, sweet potato etc.…)	• Pre-cooked and frozen ready meals. • Instant puree	• Vegetables (minestrone, soups) with prohibited cereals. • Breaded flour in batter with prohibited ingredients
Milk and Dairy product	• Fresh milk and UHT, milk for early childhood • Fresh and aged cheeses • Natural yogurt (light or whole), Greek yogurt with no added flavourings or other substances	• Fruit and soy yogurt • Melted, sliced, vegetable cheeses (eg tofu) • Creams, puddings, desserts • Vegetable drinks	• Ready-made breaded cheese dishes with prohibited flours
Meat, Fish and Eggs	• All kinds of fresh or frozen meat, fish and crustaceans. • Preserved fish: natural, in oil, smoked, free of additives, flavourings and other substances • Eggs • Raw ham	• Cured meats and sausages of pork, beef or poultry meat • Canned meat (eg canned meat, jelly) • Hamburger • Powdered eggs	• Meat or fish floured or mixed with breadcrumbs or cooked in sauces thickened with prohibited flours
Fat and Condiments	• Butter, lard • Vinegars (not flavored) • Yeast (of beer): fresh, freeze-dried, dry • Spices and aromatic herbs as they are	• Bechamel sauce with permitted grain flours • Light butter, margarine • Ready sauces • Sauces (mayonnaise, mustard, ketchup) • Tofu	• Natural yeast or mother yeast • Seitan • Béchamel sauce with prohibited grain flours
Desserts	• Honey • Raw licorice root • Pure fructose • Syrup of: agave, maple	• Candies, candies, chewing-gum • Cocoa powder • Chocolate, chocolate creams Sweeteners • Ice creams • Jams	• Chocolate with cereals • Cakes, biscuits and desserts prepared with prohibited flours
Beverages	• Nectars and fruit juices not added to preservatives, flavourings, colorings • Carbonated drinks not added to sweeteners • Coffee, tea, chamomile, herbal tea • Wine • Pure distillates	• Light drinks • Milk-shake (ready-made mixtures) • Ginseng coffee • Instant coffee • Alcoholic beverages with added flavourings or other substances • Allowed grain beer, Cider	• Soluble coffee, beverages and banned cereal preparations (eg barley)

qualities to foods, improving palatability and making it indispensable for the food industry [4]. Therefore, a major problem for celiac patients is the almost unbiquitous presence of gluten in refined foods that are not declared gluten free (GF), and that cannot be consumed by patients (Table 2).

Although the range of high quality GF products has increased in recent years and the GFD has gained broad acceptance, the compliance to a strict GFD depends on different individual and environmental factors [105]. Self-reported diet adherence among adult CD patients ranges from 36% to 96% [106–108].

One of the main pitfalls is meal sharing; in their social context patients are faced with the dilemma to risk consuming gluten or social isolation by having to eat their own or only declared GF food. Here, dietary requirements may still be perceived as rejection of hospitality and a problem for caregivers [109,110]. In particular, these problems reach their climax during adolescence and transition period [111,112]. Although many patients declare to follow a GFD, cross-contamination can occur both in the production lines or during preparation of gluten free foods at home or when eating out [104].

In this complicated setting, the counselling of a nutritionist and the use of food questionnaire is of great importance to provide patients with CD the knowledge and skills to adhere to a correct GFD and information about "how to read" food labels [113]. Moreover, the recent possibility to check the presence of gluten derived peptides in urine or feces could be useful in some cases to detect contaminations, although these tests are not yet inserted in any guideline [114].

In the last two decades different studies demonstrated that CD patients need to be evaluated for nutritional imbalances, highlighting that importance of "a balanced GFD". One of the main problem is the trend to overcome GFD restrictions by introducing foods with high sugars, fats and calories or to prefer foods rich in proteins as eggs and meat or snacks with a high content of lipids [115]. GFD is also often associated with a lower intake of dietary fibers [116]. Unfortunately, the majority of GF commercial grain-based products contain less fiber than their gluten-containing equivalents. In consequence, patients may report weight gain when on the GFD [115], making dietary advice about the alternatives to dietary gluten necessary [117].

6.2. *Other-than-gluten free diet therapies*

A strict life-long GFD, although safe and effective, is very restrictive and a challenge some patients, waiting for an other-than-GFD therapy [118,119]. Moreover, a certain degree of mucosal inflammation and symptoms may still persist despite a strict GFD in up to 5% of patients, classified as refractory celiac disease type 1. Therefore, there is a need for and a high interest in a (supportive) pharmacological treatment, which could at least alleviate the strictly GFD [118,120]. In the last years, new therapies have been tested in vitro or in in vivo models of CD with different potential therapeutic targets. These include the proteolytic degradation of gluten peptides, inhibition of intestinal permeability to prevent gluten uptake, the inhibition of TG2, or modulation of the immune response to gluten preventing T cells activation [11,121–123]. The most promising new therapy in CD is therapeutic vaccine, Nexvax2, an adjuvant-free mix of three peptides that include

immunodominant epitopes for gluten-specific CD4-positive T cells. Recent trials demonstrated a modified immune responsiveness to Nexvax2 peptides without deterioration in duodenal histology supporting the potential development of this techniques [124]. However, at present there are only preliminary studies and there are no pharmacological therapy in alternative to GFD; moreover, ethical concerns must be considered when dealing with pharmacological therapy in CD [125].

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7. Follow up

Patients should undergo regular follow-up, usually every six months in the first year after diagnosis and then on an annual basis, to evaluate persistent or new symptoms, adherence to the diet, nutritional status, the development of associated conditions such as osteoporosis and autoimmune thyroid disease and to assess the risk of complications. A transition program from pediatric to adult setting should be scheduled during adolescence [112]. Laboratory tests should be focused on anemia and micronutrient deficiency, liver and thyroid function test and serum IgA-TG2 levels. The GFD leads to regression of symptoms, normalization of IgA-TG2 level and mucosal healing. There is a progressive reduction of IgA-TG2 that usually normalizes in the first year after starting the GFD. The persistence or recurrence of abnormal levels of IgA TG2 usually indicates poor dietary compliance or unintended gluten exposure. Serum antibody titers are often used as a surrogate marker of intestinal healing, in order to avoid follow-up duodenal biopsy [68]. However, serological and histological findings do not correlate in a linear manner. Follow up biopsy is indicated with lack of clinical response or relapse of symptoms despite treatment, but not in asymptomatic patients [126] and it should be carefully evaluated and compared to the first biopsy using a specific score (Elli-Ferrero) [127].

In the setting of extra-intestinal manifestation, osteoporosis is important. The assessment of bone mineral density with dual-energy X-ray absorptiometry (DEXA) is recommended after 12–18 months of GFD not only in CD older than 55 years of age and in those with additional risk of osteoporosis, but in all adult CD patients after the age of 20 years. If DEXA results pathological, it should be repeated at regular intervals (e.g., after 18–24 months) [128].

During follow up of CD patients, clinicians should pay attention to early identification of complicate CD when new or persistent symptoms and alarm signs occur despite the GFD. In these patients, adequate assessment of the small bowel should be performed to early identify refractory celiac disease or malignancy [129–131].

8. Complications of celiac disease

8.1. Non responsive and refractory celiac disease

In a small proportion of patients, clinical symptoms and/or villous atrophy persist despite proven adherence to a strict GFD. Non-responsive CD is defined by the persistence of symptoms after at least one year of a strict GFD [132].

In symptomatic patients the first step is to review the diagnosis of CD and to evaluate the compliance to the GFD. The most common cause of persistent symptoms is poor compliance with the GFD or inadvertent gluten exposure. Other causes of persistent symptoms include other gastrointestinal condition, like concomitant irritable bowel syndrome. With persistent symptoms of active disease the second step is to evaluate the degree of mucosal damage by biopsy.

Refractory CD (RCD) is defined by the persistence of malabsorption and villous atrophy after 1 year of a strict GFD. Its estimated prevalence is around 1% among adult celiac patients and 2–3 times higher in women than in men [133]. Before confirming the diagnosis of RCD, poor compliance with the GFD and other causes of intestinal villous atrophy have to be ruled out [79]. RCD can be classified into two different variants, defined by the analysis of the phenotype and clonality of IELs. Type 1 RCD (RCD1) is characterized by a polyclonal pattern of the T cells receptor (TCRγ), absence of aberrant intraepithelial lymphocytes at flow cytometry (see below). RCD usually respond to treatment with steroids and budesonide or other mild immunosuppressants. Type 2 RCD (RCD2) is more aggressive and characterized by the presence of monoclonal and aberrant T cells (lack of surface CD8, CD3 expression, with expression of intracytoplasmatic CD3) and a high risk of development of EATL in the course of their disease. Up to 70% of RCD2 patients develop ulcerative lesions involving jejunum and ileum (ulcerative jejunoileitis) with clinical deterioration due to severe associated malabsorption and weight loss. Furthermore, RCD2 is considered a pre-neoplastic condition with 50% of cases developing EATL with 5–10 yers [133,134]. For this reason it has recently been proposed to consider RCD2 as a form of low-grade intraepithelial lymphoma (pre-EATL) [135]. In RCD2 steroid treatment is not effective and patients are eligible for therapy with cladribin, chemotherapy or autologous/allogenic bone marrow transplantation [136].

The workup of RCD requires an adequate assessment of (the whole) small bowel, often computer tomography, magnetic resonance enterography, or capsule endoscopy, depending on local resources and expertise [129].

8.2. Celiac disease and malignancies

Longterm untreated CD is associated with an increased risk of malignancies, with a > 100 fold increased risk for EATL and small bowel adenocarcinoma [137–139].

EATL usually develops in the setting of a known CD, or in some cases, CD and EATL are concomitantly diagnosed [140]. It usually occurs after 5 to 10 years from the diagnosis and it usually is preceded by clinical relapse after an initially good response to GFD or by a diagnosis of RCD2 [141]. EATL develops mostly in the jejunum, ileum, lymph nodes, stomach or colon. It is often disseminated at diagnosis and extra-intestinal localization is not uncommon. Immuno-histological characteristics of this lymphoma include the finding of a clonal proliferation of TCRα/β T cells.

Unfortunately, EATL is usually diagnosed at a late stage, commonly in presence of complications (intestinal perforation, bleeding or occlusion). Consequently, the prognosis is very poor compared to cases of EATL that evolve in the absence of prior CD (survival 11% at 5 years) [140].

Small bowel adenocarcinoma is a rare neoplasia in the general population (incidence 1/100,000) but the risk is 10–80 fold increased in CD patients according to different studies [142–145]. A diagnosis of CD was confirmed in 13% of a series of small bowel adenocarcinomas collected in United Kingdom [141]. It is mainly localized in the duodenum or jejunum and the diagnosis is made after an acute presentation with obstruction and/or hemorrhage, or when investigating anemia, abdominal pain, ileus or weight loss. Unlike EATL, small-intestinal adenocarcinoma is usually not associated with RCD. The prognosis after extensive resection, usually with adjuvant chemotherapy appears to be modest but better than for EATL.

9. Conclusions

CD is frequently faced in daily clinical practice by gastroenterologists all over the world. In spite of the presence of powerful diagnostic tools (anti transglutaminase antibodies) and a solid reference standard (duodenal histology), > 60% of CD patients remains undiagnosed [146] and up to 20% of CD diagnosis are erroneous when reevaluated in tertiary referral center [147]. Furthermore, the high prevalence of patients with a non-celiac gluten sensitivity or avoiding gluten without medical prescription, recently complicated the spectrum of gluten related disorders [148]. This scenario needs to be improved,

strengthening the knowledge about CD diagnosis and management.

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Conflict of interest

The authors have no conflict of interests to declare.

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