Chapter 11

Celiac Disease in Children

Isabel Polanco Allué

Full Professor of Pediatrics, School of Medicine, Autonomous University of Madrid

Head of Gastroenterology and Pediatric Nutrition Service, La Paz University Children's Hospital, Madrid, España.

ipolanco.hulp@salud.madrid.org

Doi: http://dx.doi.org/10.3926/oms.227

How to cite this chapter

Polanco I. *Celiac Disease in Children.* In Rodrigo L and Peña AS, editors. *Celiac Disease and Non-Celiac Gluten Sensitivity.* Barcelona, Spain: OmniaScience; 2014. p. 221-233.

Abstract

Celiac Disease (CD) is an immune-mediated systemic disorder caused by gluten and related prolamins in genetically susceptible individuals, characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy. CD-specific antibodies comprise autoantibodies against TGt2, including endomysial antibodies (EMA) and antibodies against deamidated forms of gliadin peptides (DGP).

To diagnose children and adolescents without intestinal biopsy, the following conditions are imperative: signs or symptoms suggestive of CD, high anti-TG2 levels (>10 times UNL), verified by EMA and positive HLA-DQ2 and/or DQ8. Only then the intestinal biopsy can be avoided, the CD diagnosis made and the child started on a gluten-free diet (GFD).

In childhood and adolescence, intestinal biopsy can be omitted in symptomatic subjects with high anti-TG2-IgA levels (>10 times normal values), verified by EMA and positive HLA-DQ2 and/or HLA-DQ8. In these cases, a GFD can be started. In all other cases, intestinal biopsies should be perform first before starting a GFD to avoid misdiagnosis.

1. Introduction

Celiac disease (CD) is a systemic disorder with an immunological basis, caused by the ingestion of gluten and similar proteins (gliadins, secalins, hordeins and possibly avenines), which affects people with genetic predisposition. It is characterized by a variety of clinical manifestations dependent on gluten ingestion: CD-specific antibodies, HLA-DQ2 and/or HLA-DQ8 haplotypes and enteropathy. Specific antibodies are tissue transglutaminase (AAtTG) autoantibodies, endomysial antibodies (EMA) and deamidated gliadin peptide antibodies (DGP).[1]

It appears that the absence of breastfeeding, ingestion of excessive amounts of gluten and the early introduction of these cereals in the diet of susceptible people are risk factors for its development. A strict gluten-free diet, leads to the disappearance of clinical symptoms, as well as to the normalization of the intestinal mucosa and prevents complications.

The contact of the intestinal mucosa with gluten leads to the appearance of mucosal damage, whose spectrum ranges from cases where there is only a slight increase in the population of intraepithelial lymphocytes (lymphocytic enteritis) to advanced forms of villous atrophy.[1-3] Any of the histological forms of the disease, even milder forms, may run their course with various states of deficiency, including anemia, osteopenia or osteoporosis and a wide range of digestive and extradigestive symptoms.[4] All these manifestations and serological and histological alterations disappear when gluten is removed from the diet and reappear when it is reintroduced in the diet. The only effective treatment for celiac disease is a strict, indefinite gluten-free diet.

CD affects both children and adults and the female/male ratio is 2:1. It is present in both in Europe and in countries populated by people of European descent, as well as in the Middle East, Asia, South America and North Africa. It may affect up to 1% of the population in Western countries and up to 5% of the native population of sub-Saharan Africa.[5] However, it is considered that CD epidemiology can be likened to an iceberg, and that its prevalence may be much higher, since a significant percentage of the cases remains undetected.[6] Today it is thought that subclinical forms are more frequent than symptomatic forms; their diagnosis constitutes a challenge for the general health system.

2. Symptoms

Clinical history and physical examination are the diagnostic cornerstones in the primary care field[7,8] and should be based on knowledge of different patterns of disease presentation, including atypical, paucisymptomatic or monosymptomatic forms, certainly the most prevalent today (Table 1).

2.1. Classic Forms

Classic symptoms include chronic diarrhea, vomiting, mood swings, poor appetite, failure to thrive and growth retardation. Prominent abdomen and flattened buttocks complete the distinctive appearance of these patients and can easily lead to suspect the diagnosis.

Children	Adolescents	Adults
Symptoms		
Diarrhea	Frequently asymptomatic	Dyspepsia
Anorexia	Abdominal pain	Chronic diarrhea
Vomiting	Headache	Abdominal pain
Abdominal pain	Arthralgia	Irritable intestine syndrome
Irritability	Delayed menarche	Bone and articular pain
Apathy	Menstrual irregularities	Infertility, recurrent abortions
Introversion	Constipation	Paresthesia, tetany
Sadness	Irregular bowel habit	Anxiety, depression, epilepsy, ataxia
Signs		
Malnutrition	Canker sores	Malnutrition with/without weight loss
Abdominal bloating	Enamel hypoplasia	Peripheral edemas
Muscular hypotrophy	Abdominal bloating	Short stature
Failure to thrive	Muscular weakness	Peripheral neuropathy
Iron deficiency anemia	Low stature	Proximal Myopathy
	Arthritis, osteopenia	Iron deficiency anemia
	Follicular keratosis	Hypertransaminasemia
	Iron deficiency anemia	Hyposplenism

Table 1. Clinical manifestations according to age of presentation

When the disease is left untreated, serious manifestations may appear (celiac crisis), comprising dermic or gastrointestinal hemorrhages (due to a defect in default vitamin K synthesis and other intestinal-dependent factors), hypocalcaemic tetany and edema due to hypoalbuminemia. There may be severe hypotonic dehydration along with great abdominal distention marked hypokalemia; extreme malnutrition may also occur. A state of celiac crisis arises if no proper diagnosis or treatment have been made.

2.2. Nonclassical Forms

Digestive symptoms may be absent or in the background (Table 1). Sometimes, in older children, it takes the form of constipation, associated or not with abdominal cramping, bloating or sudden onset of edema, usually coinciding with a precipitating factor (infection, surgery, etc.). Delayed puberty or height increase can also be evocative data. Another isolated manifestation occurs through iron deficiency anemia caused by iron and folate malabsorption in the jejunum. In untreated celiac disease, enamel hypoplasia has been described.

The epileptic triad has also been described as well as bilateral occipital intracranial calcifications and celiac disease, which responds to treatment with gluten-free diet.

2.3. Subclinical Forms

The disease may be asymptomatic for several years, even with high levels of specific antibodies, compatible HLA and enteropathy, as it has been proved in first-degree relatives of celiac patients. Therefore, careful clinical follow-up of these relatives is necessary, including serological markers (transglutaminase IgA antibodies) and even intestinal biopsy, if necessary.

2.4. Potential Forms

The term “potential celiac disease” should be reserved for those individuals who, while consuming gluten, with or without symptoms, have a normal jejunal biopsy, or else just increased intraepithelial lymphocytes, but positive celiac serology. As it progresses, it could include intestinal villi atrophy with anatomic normalization after withdrawing dietary gluten from the diet and reappearance of injuries after its reintroduction. These patients are usually first-degree relatives of celiac patients and, given their high risk of developing the disease, should be monitored regularly.

3. Risks Groups

3.1. First-Degree Relatives

They are a high-risk group in which celiac disease prevalence of wavers between 10 and 20%. They may remain clinically asymptomatic or exhibit mild clinical forms.

3.2. Associated Diseases

They usually precede celiac disease, but may also occur simultaneously with it and even its after diagnosis (Table 2). Patients who suffer from them are considered risk groups since their association occurs with a frequency higher than expected. The following are the most representative:

Dermatitis herpetiformis. It occurs in older children, adolescents and young adults in the form of pruritic vesicular lesions in normal skin, or macular plaques located symmetrically head, elbows, knees and thighs. Diagnosis is made by means of direct immunofluorescence demonstration of the granular IgA deposits in the dermal-epidermal junction in healthy skin; it means, in most cases, severe damage to the intestinal mucosa.

Diabetes mellitus type 1. Approximately 8% of patients with type 1 diabetes are associated with celiac disease.

Selective IgA deficiency. Approximately 4% of celiac patients also have selective IgA deficiency.

Down's syndrome. The association with celiac disease is higher than 15%.

Thyroid diseases. The association of celiac disease with autoimmune thyroiditis is frequent, about 4%, both in children and in adults.

Liver disease. Elevated transaminase is a common finding in up to 10% of active celiac patients. Its gradual normalization should be monitored after starting a gluten-free diet.

First-Degree relatives	
Patients with associated diseases	
Autoimmune diseases	Neurological and psychiatric disorders
Dermatitis herpetiformis	Progressive encephalopathy
Type I diabetes	Cerebellar syndromes
Selective IgA deficit	Dementia with cerebral atrophy
Thyroiditis	Leucoencephalopathy
Inflammatory bowel disease	Epilepsy and calcifications
Sjögren's syndrome	Other associations:
Systemic lupus erythematous	Down's syndrome
Addison's disease	Cystic fibrosis
IgA nephropathy	Turner's syndrome
Chronic hepatitis	Williams' syndrome
Primary biliary cirrhosis	Hartnup's disease
Rheumatoid arthritis	Cystinuria
Psoriasis, vitiligo and alopecia areata	

Table 2. Risk groups.

4. Diagnosis

4.1. Serum Markers

Serum markers are quite useful as indicators of CD, provided that their interpretation is correct (age, gluten intake, immunosuppressive drug treatment, etc.). They aid in selecting the individuals most likely to develop it, being particularly useful in patients without gastrointestinal symptoms, in patients with diseases associated with CD and in searching for first-degree relatives of diagnosed CD patients.[9-11] It ought to be considered, however, that the negativity of these markers does not definitively exclude diagnosis, being sometimes necessary to resort to more complex tests[12] (genetic study) when clinical suspicion is high.

Human tissue transglutaminase IgA antibodies (AAtTG) have proven to be most useful, cheap and cost-effective in screening for the disease; they must be systematically indicated, along with total serum IgA plasma levels of when faced with clinical suspicion of CD. It is not unusual to find IgA deficit in the celiac population, which could lead to a "false negative" while testing for antibodies. In such a situation, AAtTG IgG can be analyzed and only if they yield negative results can serology be considered to be negative.

Recently, an interesting study of 5,000 Italian schoolchildren has been published, suggesting that that celiac disease could be detected by the determination of tissue transglutaminase IgA antibodies in saliva.[13] Although this is a simple and safe screening test that could allow early diagnosis of the disease, with the undoubted benefits that its application could entail, further studies are needed to confirm the sensitivity and specificity of salivary antibodies.[14] In any case, they also have the limitation of not being detectable in patients with isolated IgA deficiency.

Gliadin antibodies (AGA) were the first to be used. Those belonging to IgA class are preferred and their effectiveness in CD screening is higher in children than in adults. They are sensitive but very nonspecific, so at present they are not indicated for use in CD screening. Determination of deamidated gliadin peptide antibodies (DGP) could be of more interest, although their specificity is no higher than that of AAtTG or EMA.[15]

The detection of IgA endomysial antibodies (EMA) is also used. Its sensitivity and specificity vary according to age. They have the disadvantages of being difficult to determine, of their subjective interpretation and their high cost. However, levels greater than 10 times the normal limit value can be regarded as highly specific for CD even when AAtTG are negative.[1]

In practice, serology results determine what course to take, making it necessary to consider the following situations:[1, 9-11]

- Serology sensitivity is very high (close to 100%), especially in people with advanced histological lesions (villous atrophy). Therefore, only in very specific cases and under specialized care, when faced with the presence of very suggestive symptoms, clearly positive serology (levels higher than 100 U, 10 times the normal limit, validated by EMA) and demonstrated genetic susceptibility (HLA DQ2 or DQ8 positive individuals), could gluten be removed from the diet without performing bowel biopsy. Favorable clinical response would definitely confirm the diagnosis.[1]
- In the remaining cases, that is to say, whenever there is any degree of diagnostic uncertainty, intestinal biopsy performed in a specialized environment is still the

definitive diagnostic criterion. If morphological alterations are compatible, gluten must be removed from the diet.

- Recent evidence suggests that negative serology does not definitely exclude celiac disease. This is particularly true for patients with mild histological lesions (Marsh 1 and 2). On the other hand, low-relevance morphological alterations (lymphocytic enteritis without villous atrophy) do not preclude the patient from having clinically evident symptoms and signs of disease (asthenia, flatulence, anemia, osteopenia, etc.). For this reason, when faced with suspicious symptoms and negative serology, especially in risk groups, the possibility of evaluating the case in a specialized environment must be considered.

4.2. Genetic Studies

Genetic studies (HLA-DQ2/DQ8) are useful in the management of celiac disease[12], since almost all celiac patients are HLA-DQ2 or DQ8 positive. 90% of CD patients are HLA-DQ2 positive while only 20-30% of individuals in the general population express it. The rest of celiac patients have allelic variants encoding HLA-DQ8 without HLA-DQ2 (6%) or a single HLA-DQ2 allele. Therefore, the absence of HLA-DQ2 and HLA-DQ8 makes the diagnosis of CD is highly unlikely. Genetic testing has therefore, a high negative predictive value, allowing the exclusion of CD with 99% certainty.

Genetic testing has clinical utility in some of the following situations:

- Excluding genetic susceptibility in first-degree relatives of celiac patients.
- Excluding CD in symptomatic patients with negative serology and a normal biopsy.
- Selecting high-risk individuals among relatives of celiac patients, patients with CD-associated diseases (type I diabetes, Down's syndrome, autoimmune thyroid disease, etc.), with positive autoantibodies and normal biopsies.
- In patients with intestinal biopsy consistent with CD and doubtful or negative serology.
- Latent celiac disease.
- Asymptomatic patients for whom gluten has been withdrawn and with no intestinal biopsy.
- People with positive antibodies who reject having a biopsy made.

4.3. Intestinal Biopsy

The gold standard for definitive diagnosis is making a biopsy of the proximal duodenum or jejunum (a more habitual procedure in children), although the need to perform it in every case is being reviewed.[1,15,16] It ought to be conducted prior to the removal of gluten from the diet. It is necessary to have a prior coagulation study, since some patients may have a prothrombin deficiency secondary to vitamin K malabsorption.

In the Marsh[17] classification of small bowel lesions (Figure 1) the pathologic criteria are: Marsh 0 (preinfiltrative mucosa); Marsh 1 (an increase in the number of intraepithelial lymphocytes); Marsh 2 (crypt hyperplasia); Marsh 3 (partial villous atrophy 3a, subtotal 3b, total 3c) and Marsh 4 (hypoplasia).

Since histological lesions may be patchy, it is advised that, at least, four samples be taken for histological analysis.[2] Anatomopathologic study allows confirmation of compatible lesions and establishing the lesion type (Marsh classification).[17] The spectrum of histological lesions in these patients is broad and ranges from varieties with lymphocytic enteritis, in which there is only an increase of the population of intraepithelial lymphocytes (>25%, Marsh 1) to severe forms of mucosal atrophy (Marsh 3). Since hematoxylin-eosin staining could not be conclusive, it is important to have anti-CD3 monoclonal antibody immunostaining in order to count intraepithelial lymphocytes. Only in this way can lymphocytic enteritis be diagnosed with any reasonable certainty (>25 lymphocytes/100 epithelial cells).

Any of the abovementioned histological forms is compatible with the disease, but none of them is specific. Hence the importance of serology and genetic studies (should there be negative serology and high clinical suspicion), in order to enhance the diagnosis and to verify clinical improvement following the removal of gluten from the diet. Regarding the gluten challenge, it ought to be done when there is doubt about the accuracy of the diagnosis.

In the Marsh[17] classification of small bowel lesions (Figure 1) the pathologic criteria are: Marsh 0 (preinfiltrative mucosa); Marsh 1 (an increase in the number of intraepithelial lymphocytes); Marsh 2 (crypt hyperplasia); Marsh 3 (partial villous atrophy 3a, subtotal 3b, total 3c) and Marsh 4 (hypoplasia).

The diversity and different sensitivity and specificity of the methods used in the diagnosis of CD has led to their being comprehensively appraised, especially while looking for new, noninvasive diagnostic strategies.

It is necessary to clinically monitor patients in order to observe the progression of symptoms and monitor growth in children and diet compliance. Determining AAtTG is useful for assessing proper adherence to the diet when serology is positive. In those patients who continue having symptoms or relapses despite the gluten-free regime, a deliberate search for hidden sources of dietary gluten or minimal transgressions must to be conducted. Both situations account for most cases which remain symptomatic or have maintained high serum marker levels.

5. Treatment

There are no pharmacological treatments for CD. The only effective treatment for this disease is a strict, lifelong gluten-free diet.[18-19] Improvement of symptoms is achieved after approximately two weeks, serological standardization between takes between 6 and 12 months and recovery of the intestinal villi around 2 years after starting treatment.

In recent years, other possible therapeutic strategies have been studied, other than the gluten-free diet.[20] However, before their clinical application, their efficacy and safety compared to the gluten-free diet should be demonstrated.

Dietary suppression of all gluten-bearing products includes flour made from barley, rye, wheat and possibly oats, as well as their derivatives. Although the toxicity of oats has been questioned, there are no conclusive studies on the subject.

After excluding gluten from the diet, complete histological recovery does not occur immediately; in adults it may even take more than 2 years and it does not occur in children before one year after the beginning of dietary treatment. Therefore, it may be necessary to temporarily exclude dietary lactose, until the intestinal wall enzymes have recovered, especially lactase. Also, depending on the malabsorption and/or malnutrition degree in the patient's initial dietary treatment, it may be necessary to recommend a high-calorie or low-fiber diet. Iron supplements and/or other minerals are usually not necessary, except in situations of significant nutritional deterioration.

Table 3 shows food that is either unsuitable or suitable for celiac patients. Keep in mind that flours are widely used in the food industry.

Gluten-free food	Gluten-bearing food	Food which may contain gluten
Milk and dairy products: cheese, curd, cream, natural yoghurt and whey All sorts of meat and fresh entrails, frozen, naturally preserved, or dried; ham, high-quality cooked ham Fresh and frozen fish, fresh seafood, preserved or in oil Eggs Vegetables, tubers Fruit Rice, corn (maize) and tapioca as well as their derivates Sugar and honey Oil and butter Coffee (grains or ground), tea and fruit juice All kinds of wine and bubbly drinks Raw dried fruit Salt, wine vinegar, all natural, fresh spices (fresh leaves or grains)	Bread and wheat, rye, barley, oats and triticale flour Industrial products which include any of the abovementioned flours in any form; starches, modified starches, and their proteins Pastries, cakes, cookies, pies and all sweet and salty baked products Pasta (macaroni, noodles, etc.) and wheat meal Milk shakes Distilled or fermented drinks made from cereals: beer, barley water, some liquors, etc.	All kinds of sausages, black pudding, etc. Delicatessen food Flavored yoghurt with pieces of fruit Melted and flavored cheeses Pâté Canned meat Canned fish with sauce Candy (all types) Coffee substitutes and other machine-dispensed drinks Dried, fried and toasted fruit with salt Ice cream Chocolate substitutes Food coloring

Table 3. Food that is either unsuitable or suitable for celiac patients.

The Official Journal of the European Union has recently the Regulations for the composition and labeling of foodstuffs suitable for people intolerant to gluten[21], whose contents are summarized below:

5.1 Composition and Labeling of Foodstuffs for People Intolerant To Gluten

1- Foodstuffs for people intolerant to gluten, consisting of one or more ingredients from wheat, rye, barley, oats or their crossbred varieties, which have been especially processed to reduce gluten, shall not contain a gluten level exceeding 100 mg/kg in foods as sold to the final consumer.

2- The labeling, advertising and presentation of the products referred to in paragraph 1 shall bear the words very low gluten content. They may bear the term "gluten-free" if the gluten content does not exceed 20 mg/kg, based on the food as sold to the final consumer.

3- Oats contained in food for people intolerant to gluten must be produced, prepared or treated specially in order to avoid contamination by wheat, rye, barley, or their crossbred varieties and the gluten content shall not exceed 20 mg/kg.

4- Foodstuffs for people intolerant to gluten, consisting of one or more ingredients that substitute wheat, rye, barley, oats or their crossbred varieties shall not contain a gluten level exceeding 20 mg/kg in the food as sold to the final consumer. The labeling, presentation and advertising of these products must include the phrase "gluten-free".

5- In the case of foodstuffs for people intolerant to gluten that contain ingredients which substitute wheat, rye, barley, oats or their crossbred varieties as well as ingredients from wheat, rye varieties, barley, oats or their crossbred varieties which have been especially processed to reduce gluten, paragraphs 1, 2 and 3 shall apply and paragraph 4 shall not apply.

6- The terms "very low gluten content" or "gluten-free" referred to in paragraphs 2 and 4 shall appear in proximity to the product's commercial name.

References

1. Husby S, Koletzko S, Korponay-Szabo IR, et al. E*uropean Society for Paediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease*. J Ped Gastroenterol Nutr. 2012; 54: 136-60. http://dx.doi.org/10.1097/MPG.0b013e31821a23d0
2. Polanco I, Grupo de Trabajo sobre "Diagnóstico precoz de la enfermedad celíaca". *Diagnóstico precoz de la enfermedad celíaca*. Madrid: Ministerio de Sanidad y Consumo; 2008.
3. Polanco I, Ribes C. *Enfermedad celíaca*. En: SEGHNP-AEP, ed. Protocolos diagnóstico-terapéuticos de gastroenterología, hepatología y nutrición pediátrica. Madrid: Ergon; 2010: 37-46.
4. Polanco I, Mearin ML. *Enfermedad celíaca*. En: Argüelles F, et al, eds. Tratado de gastroenterología, hepatología y nutrición pediátrica aplicada de la SEGHNP. Madrid: Ergon; 2011: 284-91.
5. Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, et al. *Increasing prevalence of coeliac disease over time*. Aliment Pharmacol Ther. 2007; 26: 1217-25. http://dx.doi.org/10.1111/j.1365-2036.2007.03502.x
6. West J, Logan RFA, Hill PG, Lloyd A, Lewis S, Hubbard R et al. *Seroprevalence, correlates, and characteristics of undetected coeliac disease in England*. Gut. 2003; 52: 960-5. http://dx.doi.org/10.1136/gut.52.7.960
7. Polanco I, Roldán B, Arranz M. *Documento técnico protocolo de prevención secundaria de la enfermedad celíaca*. Madrid: Dirección General Salud Pública y Alimentación; 2006.
8. Catassi C,, Kryszak D, Louis-Jacques O, Duerksen DR, et al. *Detection of Celiac Disease in Primary Care: A Multicenter Case-Finding Study in North America*. Am J Gastroenterol. 2007; 102: 1454-60. http://dx.doi.org/10.1111/j.1572-0241.2007.01173.x
9. 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. http://dx.doi.org/10.1053/j.gastro.2006.10.004
10. Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garritty C, et al. T*he diagnostic accuracy of serologic tests for celiac disease: a systematic review*. Gastroenterology. 2005; 128 (4 Suppl 1): S38-46. http://dx.doi.org/10.1053/j.gastro.2005.02.028
11. Polanco I, Román E. *Marcadores serológicos en la Enfermedad Celíaca*. An Pediatr Contin. 2006; 4:176-9. http://dx.doi.org/10.1016/S1696-2818(06)73607-1
12. Wolters VM, Wijmenga C. *Genetic background of celiac disease and its clinical implications*. Am J Gastroenterol. 2008; 103: 190-5. http://dx.doi.org/10.1111/j.1572-0241.2007.01471.x
13. Bonamico M, Nenna R, Montuori M, Luparia RP, Turchetti A, Mennini M, et al. *First salivary screening of celiac disease by detection of ant-transglutaminase autoantobody radioimmunoassay in 5000 Italian primary schoolchildren*. J Pediat Gastroenterol Nutr. 2011; 52: 17-20. http://dx.doi.org/10.1097/MPG.0b013e3181e6f2d0
14. Green PHR, Cellier C. *Celiac Disease*. N Eng J Med. 2007; 357: 1731-43. http://dx.doi.org/10.1056/NEJMra071600

15. Lindfors K, Koskinen O, Kaukinen K. *An update on the diagnostics of celiac disease*. Int Rev Immunol. 2011; 30: 185-96. http://dx.doi.org/10.3109/08830185.2011.595854
16. *Guideline for the Diagnosis and Treatment of Celiac Disease in Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition*. J Pediat Gastroenterology Nutr. 2005; 40: 1-19. http://dx.doi.org/10.1097/00005176-200501000-00001
17. 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.
18. Case S. *The gluten-free diet: How to provide effective education and resources*. Gastroenterology. 2005; 128: S128-S134. http://dx.doi.org/10.1053/j.gastro.2005.02.020
19. Polanco I. *Libro Blanco de la Enfermedad Celíaca*. Ed: ICM. Madrid: Consejería de Sanidad de la Comunidad de Madrid; 2008.
20. Polanco I, Arranz E. *Nuevos avances en el tratamiento de la Enfermedad Celíaca*. An Pediatr Contin. 2006; 4: 46-9. http://dx.doi.org/10.1016/S1696-2818(06)73587-9
21. *Reglamento (CE) No 41/2009 de la Comisión de 20 de enero de 2009 sobre la composición y etiquetado de productos alimenticios apropiados para personas con intolerancia al gluten. Diario Oficial de la Unión Europea 21.1.2009.* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:016:0003:0005:ES:PDF