Guideline for the Diagnosis and Treatment of Celiac Disease in Children:

Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

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CONTENTS

Abstract
Synopsis
1. Introduction
2. Methods
3. Diagnosis
3.1. Who to Test?
3.2. How to Test?
3.2.1. Serological Tests
3.2.2. HLA DQ2 and DQ8
3.2.3. IgA deficiency
3.2.4. Intestinal biopsy and histopathology
4. Treatment
4.1. Who to Treat?
4.2. How to Treat?
4.3. How to Monitor?
5. Algorithms for the Evaluation and Management of Infants and Children with Suspected Celiac Disease
5.1. Evaluation of the symptomatic child (Figure 1)
5.2. Evaluation of the asymptomatic child in groups at risk (Figure 2)
5.3. Treatment and monitoring of patients with celiac disease (Figure 3)

ABSTRACT

Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It occurs in children and adolescents with gastrointestinal symptoms, dermatitis herpetiformis, dental enamel defects, osteoporosis, short stature, delayed puberty, persistent iron deficiency anemia and in asymptomatic individuals with type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency and first degree relatives of individuals with celiac disease. The Celiac Disease Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition has formulated a clinical practice guideline for the diagnosis and treatment of pediatric celiac disease based on an integration of a systematic review of the medical literature combined with expert opinion.

The Committee examined the indications for testing; the value of serological tests, HLA typing and histopathology; and the treatment and monitoring of children with celiac disease. It is recommended that children and adolescents with symptoms of celiac disease or an increased risk for celiac disease have a blood test for antibody to tissue transglutaminase (TTG); that those with an elevated TTG be referred to a pediatric gastroenterologist for an intestinal biopsy; and that those with the characteristics of celiac disease on intestinal histopathology be treated with a strict gluten free diet. This document represents the official recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition on the diagnosis and treatment of celiac disease in children and adolescents.

SYNOPSIS

Who to Test?

Celiac disease (CD) is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It occurs in symptomatic children and adolescents with gastrointestinal and non-gastrointestinal symptoms. It also occurs in some asymptomatic individuals who have conditions that are associated with CD. Based on a number of studies in Europe and the USA, the prevalence of CD in children between 2.5 and 15 years of age in the general population is 3 to 13 per 1000 children, or approximately 1:300 to 1:80 children.

Numerous studies demonstrate that children with CD frequently have gastrointestinal (GI) symptoms such as diarrhea with failure to thrive (FTT), abdominal pain, vomiting, constipation and abdominal distension. However, there is little information currently available about the precise prevalence of CD in children with these specific types of GI symptoms. There is strong evidence for an increased occurrence of CD in children with dermatitis herpetiformis, dental enamel defects, type 1 diabetes, IgA deficiency, Down syndrome, Turner syndrome, Williams syndrome, and first degree relatives of patients with CD. There is moderate evidence for an increased prevalence of CD in children with short stature and some evidence for an increased prevalence of CD in children with autoimmune thyroiditis. There is evidence that anemia is common in children with CD, and an increased prevalence of unexplained anemia as a presenting feature is well described in adults with CD. Other conditions that have been described in association with CD include a variety of neurological disorders; however, the evidence for these associations in children is poor.

It is recommended that CD be an early consideration in the differential diagnosis of children with FTT and persistent diarrhea. In addition, it is recommended that CD be considered in the differential diagnosis of children with other persisting GI symptoms, including recurrent abdominal pain, constipation and vomiting. Testing is recommended for children with non-gastrointestinal symptoms of CD (dermatitis herpetiformis, dental enamel hypoplasia of permanent teeth, osteoporosis, short stature, delayed puberty and iron-deficient anemia resistant to oral iron). Testing is also recommended for asymptomatic children who have conditions associated with CD (type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency and first degree relatives of celiac patients). It is recommended that testing of asymptomatic children who belong to groups at risk begin around 3 years of age provided they have had an adequate gluten containing diet for at least one year prior to testing.

There is good evidence that in certain groups (type 1 diabetes, first degree relatives of affected individuals and Down syndrome) some individuals who initially have a negative serological test may subsequently develop a positive test on repeat testing over a period of years, and have biopsies compatible with CD. Therefore, it is recommended that asymptomatic individuals with negative serological tests who belong to groups at risk be considered for repeat testing at intervals. As there is no good evidence that CD is more common in children with autism, there is no indication to routinely test patients with autism for CD.

How to Test?

Based on the current evidence and practical considerations, including accuracy, reliability and cost, measurement of IgA antibody to human recombinant tissue transglutaminase (TTG) is recommended for initial testing for CD. Although as accurate as TTG, measurement of IgA antibody to endomysium (EMA) is observer dependent and is therefore more subject to interpretation error and added cost.

Because of the inferior accuracy of the antigliadin antibody tests (AGA), the use of AGA IgA and AGA IgG tests is no longer recommended for detecting CD.

Individuals with CD who are also IgA deficient will not have abnormally elevated levels of TTG IgA or EMA IgA. The occurrence of both CD and IgA deficiency in the same individual appears to be rare in asymptomatic individuals (approximately 1:8500 of the general population) but is more likely in symptomatic children with CD (approximately 2%). Therefore, when testing for CD in children with symptoms suspicious for CD, measurement of quantitative serum IgA can facilitate interpretation when the TTG IgA is low. In individuals with known selective IgA deficiency and symptoms suggestive of CD, testing with TTG IgG is recommended. Even when serological tests for CD are negative, in children with chronic diarrhea and/or FTT, and in those belonging to a group at risk (e.g., selective IgA deficiency or a positive family history of CD) who have symptoms compatible with CD, an intestinal biopsy can be helpful to identify the unusual case of seronegative CD, or to detect other mucosal disorders accounting for the symptoms.

It is recommended that confirmation of the diagnosis of CD requires an intestinal biopsy in all cases. Because the histologic changes in CD may be patchy, it is recommended that multiple biopsy specimens be obtained from the second or more distal part of the duodenum. There is good evidence that villous atrophy (Marsh type 3) is a characteristic histopathological feature of CD. The presence of infiltrative changes with crypt hyperplasia (Marsh type 2) on intestinal biopsy is compatible with CD, but with less clear evidence. Diagnosis in these cases is strengthened by the presence of positive serological tests (TTG or EMA) for CD. In the event the serological tests are negative, other conditions for the intestinal changes are to be considered and, if excluded, the diagnosis of CD is reconsidered. The presence of infiltrative changes alone (Marsh type 1) on intestinal biopsy is not specific for CD in children. Concomitant positive serological tests for CD (TTG or EMA) increases the likelihood such an individual has CD. In circumstances where the diagnosis is uncertain additional strategies can be considered, including determination of the HLA type, repeat biopsy or a trial of treatment with a gluten free diet (GFD) and repeat serology and biopsy.

The diagnosis of CD is considered definitive when there is complete symptom resolution following treatment with a strict GFD in a previously symptomatic individual with characteristic histological changes on small intestinal biopsy. A positive serological test that reverts to negative following treatment with a strict GFD in such cases is further supportive evidence for the diagnosis of CD.

Who to Treat?

Treatment with a GFD is recommended for all symptomatic children with intestinal histopathological abnormalities that are characteristic of CD. Clinical experience has demonstrated that children with persistent diarrhea and poor weight gain due to CD have complete resolution of symptoms on treatment with a GFD. There is good evidence that treatment with a GFD reverses the reduced bone mineralization in children with CD, and decreases the rate of spontaneous abortions and frequency of low birth weight infants in adult women with CD. Epidemiological evidence suggests treatment of CD can decrease the risk for some intestinal cancers and lower mortality rates to that of the general population. The evidence that early treatment of CD prevents the onset of other autoimmune diseases is weak.

Treatment with a GFD is also recommended for asymptomatic children who have a condition associated with CD and characteristic histological findings on small intestinal biopsy. In patients with type 1 diabetes, who otherwise have no symptoms associated with CD, there is little evidence to demonstrate that a GFD improves their diabetes in the short term. The intermediate and long-term

benefits to diabetes care of treating such patients with a GFD are not known. There are no studies on the benefits of treating asymptomatic CD in individuals with other associated conditions.

How to Treat?

A GFD for life remains the only scientifically proven treatment available for symptomatic individuals with CD. It is recommended that treatment be started only after the diagnosis has been confirmed by intestinal biopsy according to the diagnostic algorithms presented in this guideline.

The Celiac Disease Guideline Committee endorses the recently published American Dietetic Association guidelines (a document produced by members of the Canadian and USA dietetic societies) for the treatment of CD. However, given the dynamics of this field, these recommendations require periodic review and modification in light of new scientific evidence.

There is evidence to demonstrate that even small amounts of gluten ingested on a regular basis by individuals with CD can lead to mucosal changes on intestinal biopsy. Previously, products containing less than 200 ppm were regarded as gluten free. Currently, a limit of 20 ppm is being considered in the proposed Codex Alimentarius as defining gluten free. Controversy surrounding what constitutes a GFD is due to inaccurate techniques for detecting gluten and the lack of solid scientific evidence for a threshold of gluten consumption below which no harm occurs. Management of a GFD is facilitated by ongoing collaboration between patients, health care professionals and dieticians.

Most newly diagnosed children will tolerate ingestion of lactose, particularly in moderate amounts; therefore dietary lactose restriction is not usually necessary. Young children with more severe disease may benefit from a lactose free diet initially.

How to Monitor?

It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination and adherence to a GFD. There is little evidence on the most effective means of monitoring patients with CD. The Celiac Disease Guideline Committee recommends measurement of TTG after 6 months of treatment with a GFD to demonstrate a decrease in antibody titer as an indirect indicator of dietary adherence and recovery. Measurement of TTG is also recommended in individuals with persistent or recurrent symptoms at any time after starting a GFD, as a rise in antibody levels suggests dietary non-adherence. In the asymptomatic patient measurement of TTG at intervals of one year or longer may serve as a monitor of adherence to the GFD.

Studies in children have shown that adherence to a GFD is reported by 45% to 81% of patients. These may be overestimates, as some patients reporting strict adherence have abnormal small intestinal histology. A complete lack of adherence is reported by 6% to 37% of patients. These may be underestimates as patients are reluctant to admit that they are not following medical advice. Based on limited data, the rate of adherence in asymptomatic patients who were detected as part of a population screening is similar to the rate of adherence in patients who had symptoms that led to the detection of CD.

Evidence demonstrates that about 95% of children with symptoms of CD, a biopsy characteristic (Marsh type 3) of CD and resolution of symptoms on a GFD do in fact have CD. Therefore, additional biopsies for confirmation of the diagnosis are not recommended in such cases.

1. INTRODUCTION

Celiac disease (CD) is defined as a permanent sensitivity to gluten in wheat and related proteins found in barley and rye. It occurs in genetically susceptible individuals and is manifest as an immune mediated enteropathy as defined by characteristic changes seen on intestinal histology. Although epidemiologic studies in Europe and the United States of America (USA) indicate that CD is common, and may occur in 0.5% - 1% of the general population [1-5], long delays between onset of symptoms and diagnosis often occur [6] and the condition remains under-diagnosed. One reason for this is failure by health care professionals to recognize the variable clinical manifestations of CD and to perform the appropriate tests to make the diagnosis. Currently the only available treatment is lifelong adherence to a gluten free diet (GFD).

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition has published criteria for the diagnosis of CD, but there are no current evidence based guidelines for the evaluation and treatment of CD in children. Therefore, the CD Guideline Committee was formed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) to develop a clinical practice guideline for the diagnosis and treatment of CD in children. The Committee consists of a primary care pediatrician, a clinical epidemiologist who is also a primary care pediatrician, eight pediatric gastroenterologists and an internist gastroenterologist. This clinical practice guideline is designed to help all health care professionals who take care of children in both inpatient and outpatient settings, including pediatricians, family practice physicians, pediatric gastroenterologists, pediatric endocrinologists, medical geneticists, physician assistants and nurse practitioners. The desirable outcome of the guideline was defined as the complete resolution of symptoms and the prevention of complications of CD through implementation of a lifelong GFD at an early stage of the disease utilizing the most effective strategy available.

This document represents the official recommendations of NASPGHAN on the diagnosis and treatment of celiac disease in children.

2. METHODS

In order to develop evidence based guidelines the following search strategy was used. Articles written from 1966 to February 2003 were identified using the medical subject heading (MESH) “Celiac Disease” through searches in PubMed [http://www.ncbi.nih.gov/entrez/query.fcgi], the Database of Abstracts of Reviews of Effects (DARE) [http://nhscrd.york.ac.uk/darehp.htm], and the Cochrane Database of Systematic Reviews [through OVID (Ovid Technologies, Inc. www.ovid.com)]. Letters to the editors, editorials, case reports, and non-systematic reviews were not included.

No articles were identified in the Cochrane database, and four were identified through DARE. The first subcategory used in PubMed was diagnosis. A total of 317 articles was found, 285 limited to English and 167 of those limited to children. In the subcategory of prognosis, 117 articles were found, with 86 limited to English and 38 of those limited to children. In the subcategory of therapy, a total of 1503 articles were found, with 1143 limited to English and 486 limited to children. Thirty articles were duplicated in more than one category. A second search was performed in September 2003, and an additional 73 articles were identified.

Articles were evaluated by two committee members using written criteria developed by Sackett and colleagues [7-9] [http://www.cebm.net/levels_of_evidence.asp; accessed on 2/3/2004]. Twenty-nine randomly chosen articles were independently reviewed by two members of the committee with expertise

in clinical epidemiology (GL, MD). Concordance using the criteria was 82%. The Committee based its recommendations on integration of the literature review combined with expert opinion when evidence was insufficient. Consensus was achieved through the Nominal Group Technique, a structured, quantitative method [10]. Using the methods of the Canadian Preventive Services Task Force [11], the quality of evidence of each of the recommendations made by the Celiac Disease Guideline Committee was determined and is summarized.

3. DIAGNOSIS

Based on a number of studies in Europe and the USA, the prevalence of CD in children between 2.5 and 15 years of age in the general population is 3 to 13 per 1000 children, or approximately 1:300 to 1:80 children [1-3,5,12,13]. Therefore, in a pediatric practice of 1500 children there are probably between 5 and 20 children with CD, either diagnosed or undiagnosed.

3.1 WHO TO TEST?

Because CD is characterized by intestinal damage, clinical manifestations of disease are often related to the gastrointestinal tract. However, many patients first present with a variety of signs and symptoms not related to the gastrointestinal tract. Furthermore, some individuals with characteristic changes on small intestinal biopsy may remain asymptomatic, or oligo-symptomatic, for many years and possibly even for life. Failure to appreciate the variable clinical manifestations of CD can lead to delays in diagnosis.

3.1.1 Gastrointestinal manifestations.

There are numerous studies demonstrating that children with CD have gastrointestinal (GI) symptoms such as diarrhea with failure to thrive (FTT), abdominal pain, vomiting, constipation and abdominal distension, but there is little information currently available about the prevalence of CD in children with these specific types of GI symptoms. Limited data suggest the prevalence of CD may be increased 2-10 times in children with some of these GI symptoms, or occur in up to 5% of cases [12].

The classic form of CD in children consists of gastrointestinal symptoms starting between 6 and 24 months of age, after the introduction of gluten in the diet. Infants and young children typically present with chronic diarrhea, anorexia, abdominal distension, abdominal pain, poor weight gain or weight loss, and vomiting. Severe malnutrition, and even cachexia, can occur if the diagnosis is delayed. Behavioral changes such as irritability are common. Rarely, severely affected infants present with a celiac crisis characterized by explosive watery diarrhea, marked abdominal distension, dehydration, hypotension and lethargy, often with profound electrolyte abnormalities including severe hypokalemia. Older children with CD presenting with gastrointestinal manifestations may have onset of symptoms at any age. The variability in the age of onset of symptoms may be dependent on the amount of gluten in the diet and other environmental factors such as duration of breast feeding. Gastrointestinal symptoms in older children include diarrhea, nausea and vomiting, abdominal pain, bloating, weight loss and constipation.

3.1.2 Non-gastrointestinal manifestations.

Many symptomatic patients with newly diagnosed CD initially present with non-gastrointestinal manifestations. Table 1 lists the main non-gastrointestinal manifestations of CD.

There is strong evidence that dermatitis herpetiformis is a skin manifestation of CD [14]. Most patients with dermatitis herpetiformis have concomitant intestinal mucosal changes of CD on biopsy, even in the absence of gastrointestinal symptoms. Both the rash and intestinal mucosal morphology improve on a GFD [15]. There is strong evidence for an increased prevalence of CD in children with dental enamel defects involving the secondary dentition [16]. These changes may be the only initial presenting manifestation of CD. There is strong evidence that patients with untreated CD are at risk for developing low bone mineral density and osteoporosis [17,18].This has also been found in asymptomatic individuals with CD detected during screening studies [19]. Reduced bone mineral density in adults improves on a GFD, but CD patients may be at increased risk for bone fractures [20]. Studies in children with CD have shown complete reversal of low bone mineral density following introduction of a GFD [21,22].

There is moderate evidence for an increased prevalence of CD in children with short stature. Serological testing of children with idiopathic short stature identified between 8% to10% with CD [23]. There is moderate evidence that adolescent females with untreated CD may have delayed onset of menarche [24]. Iron deficiency anemia, resistant to oral iron supplementation, is the most common non-gastrointestinal manifestation of CD reported in some studies, and is often the primary clinical manifestation in adults [25,26]. Between 5% and 8.5% of adults with unexplained iron deficiency anemia have CD [27]. This figure increases to 11% when those with either iron deficient or folate deficient anemia are included [28]. While anemia is a common finding in children with newly diagnosed CD, there is little evidence to demonstrate that CD is common in children presenting with anemia.

There is some evidence for elevated serum transaminases (ALT, AST) in untreated adults with CD. Up to 9% of adults with elevated transaminase levels of unclear etiology may have silent celiac disease [29]. Liver biopsies in these adults showed non-specific reactive hepatitis and liver enzymes appeared to normalize on a GFD [30]. There is little information on this association in children. Arthritis is fairly common in adults with CD, including those on a GFD [31]. Up to 3% of children with juvenile chronic arthritis have been reported to have celiac disease [32]. A number of neurological problems, including the syndrome of epilepsy with intracranial calcifications [33,34], have been reported in patients with CD but the evidence for this association in children with CD is weak.

3.1.3 Associated Conditions.

CD is associated with a number of autoimmune and non-autoimmune conditions (Table 2). There is strong evidence for the association between type 1 diabetes and CD [35-46]. Up to 8% of patients with type 1 diabetes have the characteristic features of CD on small intestinal biopsy. This figure may be an underestimate as serial screening of individuals with type 1 diabetes over a period of years has identified additional cases who initially had negative serological tests [41,42,47]. Type 1 diabetes usually manifests years before symptoms related to CD become evident [48]. There is moderate evidence for an association between autoimmune thyroiditis and CD in adults. The evidence for this association in children is weak [49,50].

There is strong evidence for an association between Down syndrome and CD. The prevalence of CD in individuals with Down syndrome is between 5% and 12% [1,51-55]. Those with Down syndrome and symptomatic CD usually have gastrointestinal manifestations such as abdominal bloating, intermittent diarrhea, anorexia or failure to thrive. However, about one third of all Down patients with CD have no gastrointestinal symptoms [53]. Compared to those without CD, individuals with Down syndrome who have CD more often have anemia, low serum iron and calcium, and lower weight and height percentiles [53]. The youngest child diagnosed with both Down syndrome and CD through screening was 3.2 years. Older cohorts of Down syndrome patients screened for CD have a higher prevalence of CD than

childhood cohorts, suggesting an increase with time. An increased prevalence of CD has also been reported in individuals with Turner syndrome and Williams syndrome [56-59]. The point prevalence of CD in children with Turner syndrome ranges from 4.1%-8.1%. The prevalence of CD in children with Williams syndrome (microdeletion 7q11.23) was 8.2% in an Italian study [60].

Strong evidence exists for an association between selective IgA deficiency and CD. Based on studies involving over 3200 adults and children in Italy and Ireland, the frequency of selective IgA deficiency in CD is about 2% [61-63]. Based on retrospective studies, 1.7 to7.7% of individuals of European origin with selective IgA deficiency also have CD [61,62,64]. The prevalence of selective IgA deficiency in celiac patients who are asymptomatic or oligo-symptomatic is unknown. There is also strong evidence demonstrating that first degree relatives of a confirmed case of CD are at increased risk for CD, with a prevalence of 4% to 5% [1].

In summary, it is recommended that CD be an early consideration in the differential diagnosis of children with a combination of persistent diarrhea and poor weight gain, weight loss or FTT. In children with other persisting GI symptoms, including recurrent abdominal pain, anorexia, constipation and vomiting, and those with non-gastrointestinal symptoms associated with CD (Table 1, Figure 1), it is recommended that CD be included in the differential diagnosis.

It is also recommended to test asymptomatic children who belong to specific groups at risk, and advise treatment for those proven to have intestinal changes of CD. The groups at risk recommended for screening are type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, individuals with selective IgA deficiency, first degree relatives of a confirmed case of CD and patients with autoimmune thyroiditis (Table 2, Figure 2).

It is recommended that routine testing of asymptomatic children belonging to these groups at risk begin after age 3 years provided they have been receiving an adequate gluten containing diet for at least one year. There is good evidence that some children with type 1 diabetes, Down syndrome and first degree relatives who initially have negative serological tests, may subsequently over a period of some years become positive on repeat testing and have biopsies compatible with CD [41,42,47,65]. Therefore, it is recommended that individuals who fall into these categories undergo later testing (Figure 2). There is no good evidence that CD is more common in children with autism, and for this reason there is no indication to routinely test patients with autism for CD.

3.2 HOW TO TEST?

3.2.1 Serological Tests

Although an intestinal biopsy is still considered necessary to confirm the diagnosis of CD, serological tests are frequently used to identify individuals for whom the procedure is indicated. Commercially available tests include anti-gliadin IgA and IgG (AGA IgA and AGA IgG), anti-reticulin IgA (ARA), anti-endomysium IgA (EMA) and anti-tissue transglutaminase IgA (TTG) antibodies. These tests are particularly helpful in individuals without gastrointestinal symptoms, those with conditions associated with CD, and for screening asymptomatic first-degree relatives of known cases. They have also been widely used in epidemiological studies to determine the prevalence of CD.

Numerous studies have evaluated the accuracy of these tests in diverse populations from many countries. Study designs have included population screening studies (e.g., general population or groups at risk); studies of groups pre-selected to go undergo endoscopy and biopsy; retrospective studies comparing

the performance of new tests on stored serum samples from clinically characterized subjects; and prospective studies of consecutive patients with symptoms.

Interpretation of the results from these studies in the clinical setting may be problematic for a number of reasons. The technical aspects and performance of the tests have improved over time (e.g., use of more purified antigen). The population selected for study may differ from that in the clinical setting, thus giving unrepresentative results. The definition of a true positive may vary. The number, size, and site of biopsies obtained, the processing (e.g., orientation) of the sample, and the interpretation of the histology in a research setting (blinded interpretation, use of celiac experts, and different scoring systems) are seldom applicable to the clinical setting. In addition, there is limited data on serologic testing of children less than 5 years of age. For all these reasons, the accuracy of the serologic tests in the clinical setting may not be as good as that reported in the research setting.

In the clinical setting, where children have been identified on the basis of symptoms, the serological tests have been evaluated as a single test, a combination of tests or sequential use of two or more tests. The sensitivity of AGA IgA among reported studies ranges between 0.52-1.00 in children [66-72] and between 0.65-1.00 in adults [73-75]. The specificity of AGA IgA in children ranges between 0.92-0.97 [66,70-72] and in adults between 0.71-0.97 [73,74]. The AGA IgG is similar in sensitivity to the AGA IgA, but the specificity is much lower, in the range of 0.5. This indicates that many individuals without CD express AGA IgG antibody [70]. False positive tests have been recorded in individuals with a variety of other gastrointestinal disorders including esophagitis, gastritis, gastroenteritis, inflammatory bowel disease, cystic fibrosis and cow milk protein intolerance.

The EMA test is based on an immunofluorescent technique using either monkey esophagus or human umbilical cord as substrate, with the accuracy of the test being similar for either substrate. The nature of this test renders it more time consuming to perform, generally more expensive and, because the interpretation is operator dependent, potentially more prone to errors. The sensitivity of the EMA in children ranges from 0.88-1.00 [66,68,70-72,76-79] and in adults is reported to be 0.87-0.89[74,75,77] The specificity of the EMA in children ranges from 0.91-1.00 [66,70-72,78,79] and in adults is reported to be 0.99 [74]. The EMA test may be less accurate in children under 2 years of age [68].

When first introduced, the TTG assays used guinea pig protein. Subsequent cloning of the human TTG gene led to the development of assays based on the human TTG protein. The sensitivity of TTG in both children and adults ranges from 0.92-1.00 [66,76-80]. The specificity of TTG in both children and adults ranges from 0.91-1.00 [66,76-80]. There is evidence that TTG assays using human recombinant protein and human derived red cell tissue transglutaminase, have a higher sensitivity (0.96-1.00 vs. 0.89-0.94) and specificity (0.84-1.00 vs. 0.74-0.98) when compared to assays using guinea pig protein [81-83].

Most individuals with CD identified as part of routine screening are asymptomatic or have only mild symptoms. In such studies the positive predictive value for biopsy evidence of CD is lower than that reported for clinically identified subjects. In young asymptomatic children with a genetic risk for CD, a positive TTG by RIA had a positive predictive value of 0.70-0.83 for biopsy evidence of CD [5]. In studies of adults in the United States [1], and children in Hungary [3], a positive EMA had a positive predictive value of 1.00. A number of other studies have combined AGA plus EMA testing with positive predictive values ranging from 0.62 to 0.90 [3,13,84].

A comparison between several commercially available serological tests using standardized serum demonstrated that EMA and TTG are superior to AGA, with EMA being more reproducible than TTG [85]. However, human derived TTG was not used in this study. Tests on selected adult stored sera using commercially available human TTG ELISA kits demonstrated the human TTG based kits performed

better (improved specificity) than guinea pig-TTG based kits [82,86]. There are insufficient data on the accuracy of currently available commercial panels of tests compared to individual tests.

In summary, there is good evidence that EMA and TTG are highly sensitive and specific tests for identifying individuals with CD. In symptomatic individuals, the positive predictive value of EMA and TTG assays for finding biopsy evidence of CD approaches 1.00. In screening-identified individuals, AGA+EMA, EMA alone, and TTG alone, have positive predictive values for biopsy evidence of CD ranging from 0.6-1.00. A positive serological test in an individual with normal small intestinal histology may represent a false positive serological test, milder disease, or a more sensitive test that identifies latent CD prior to mucosal injury. Based on the available evidence and practical considerations, including relative low cost, ease of test performance and reliability, the TTG assay is recommended for the initial testing for CD. Even if serological tests for CD are negative, in symptomatic children with chronic diarrhea and/or FTT, and those with IgA deficiency or a positive family history of CD, an intestinal biopsy may be useful to identify the unusual case of seronegative CD, or to detect other intestinal mucosal disorders to account for the symptoms. Because of the variable and generally inferior accuracy of the antigliadin antibody tests (AGA), the use of AGA IgA and AGA IgG tests is no longer recommended for identifying individuals with CD.

3.2.2 HLA DQ2 and DQ8

Susceptibility to CD is determined in part by a common HLA association: specifically, the major histocompatibility complex class II antigens HLA-DQA1*0501-DQB1*02(DQ2) and HLA-DQA1*0301-DQB1*0302(DQ8). These genes (located on chromosome 6p21.3) code for glycoproteins which bind to peptides, forming an HLA-antigen complex that can be recognized by CD4+ T cell receptors in the intestinal mucosa. DQ2, present in 86-100% of patients, is in strong linkage disequilibrium with DR3 and DR5/7 [87-96]. Homozygosity for DQ2 alleles may be associated with the early onset, classic form of disease [97], and confer the highest concordance in twins [98]. Almost all CD patients without HLA DQ2 (~5%) have a DQ8 molecule, encoded by DQB1*0302 and DQA1*0301, in linkage disequilibrium with DR4. Although DQ2 genes form a basis for the genetic susceptibility to CD, approximately 30% of the general population in North America is DQ2 positive [5]. Other genetic loci possibly associated with CD have been reported, including loci on chromosome 15q11-13 [99], and chromosomes 5 and 11 [100]. The development of CD is clearly multigenic, with the presence of DQ2 or DQ8 being an essential component. Thus, probes for DQ2 and DQ8 have high sensitivity but poor specificity, indicating a low positive predictive value but a very high negative predictive value for CD.

In type 1 diabetics, a positive EMA and/or TTG is found predominantly in those with the HLA DQ2 or DQ8 genotype [101,102]. Up to one third of diabetics with HLA DQ2 have positive TTG, compared to less than 2% of diabetics without HLA DQ2 or DQ8 [101]. Some diabetics who were TTG positive were EMA negative and had normal histology on intestinal biopsy [101]; therefore some investigators recommend a positive TTG be followed by a positive EMA prior to biopsy in patients with type 1 diabetes, but the evidence supporting this approach is limited, and the management of those with a positive TTG but a negative EMA remains unclear. Others have found HLA DQ2 is present in about 80% of type I diabetics with CD, compared to 49% of diabetics without CD [103]. In first degree relatives of type I diabetics, CD mainly occurs in those who are HLA DQ2 positive (80%). HLA DQ2 is also found in 28% of siblings who do not have CD [104]. Those with CD in the absence of DQ2 had the DQ8 genotype [104]. Thus, type 1 diabetics who are DQ2 or DQ8 positive are at risk for CD.

CD in individuals with Down syndrome is mainly linked to the presence of the DQ2 heterodimer, with the carriage rate of DQ2 among Down syndrome persons who also have CD approaching 100% [54,65105]. An additional allele (DQB1*0301) is also implicated in 20% of Down syndrome individuals

in some series [54,105], and the DQA*0101 allele in one [106]. A few Down syndrome individuals with DQ8 and CD have been identified [105,107]. All children with Turner syndrome and CD were positive for HLA DQ2, while the frequency of this heterodimer was not elevated in Turner syndrome without CD compared to the general population [59,108]. HLA DQ2 or DQ8 heterodimer identification has not been specifically studied in Williams syndrome. HLA DQ2 correlates strongly with EMA and TTG positivity in first degree relatives of individuals with CD (97%). In a study of healthy members of multiple case celiac disease families the positive predictive value of the EMA was 67% [109]. Whether some of these family members developed small intestinal histopathological abnormalities of CD at a later stage remains to be determined as follow-up was short. For relatives without DQ2 the risk of having CD was minimal.

No studies have been designed to evaluate whether determining HLA DQ2/DQ8 status is of value in screening children. However, given the strong association between HLADQ2/DQ8 and CD, it may have a role as part of the screening strategy for asymptomatic individuals who belong to groups at risk for CD. These include first degree relatives of a confirmed case, type 1 diabetics, and those with Down syndrome, Turner syndrome and possibly Williams syndrome (Figure 2). A negative result for HLA DQ2/DQ8 renders CD highly unlikely, and hence there is no need for subsequent serological testing of such individuals.

3.2.3 IgA deficiency

The definition of selective IgA deficiency for purposes of CD evaluation has been inconsistent. Assays employed for quantitating IgA are not always adjusted to accurately measure lower levels. Furthermore, cut-off values used by various laboratories vary and have included < 5mg/dL [64,110] in children and < 5-7 mg/dl in adults [111,112], age-adjusted values [113], <15% of mean population values and age-specific values [114]. When defined by a serum IgA <5mg/dL, selective IgA deficiency occurs in 1:163 –1:965 healthy blood donors in Europe, the United States and Brazil [115-117].

Although CD occurs with increased frequency in those with selective IgA deficiency, screening studies of the general population suggest that very few cases will be missed by not routinely measuring IgA levels as part of the screening regimen [110]. In one such study involving more than 17,000 children, the prevalence of CD occurring together with IgA deficiency was only 1 in 8500 [2]. Nor is the frequency of selective IgA deficiency increased in those with type 1 diabetes [118]. In addition, very few asymptomatic cases of CD with selective IgA deficiency have been identified on the basis of a positive test for AGA IgG [84,119]. Thus the strategy of routinely determining serum IgA levels or adding IgG-based serology as part of a panel to screen asymptomatic individuals in the general population is not warranted. However, in symptomatic patients with a clinical suspicion for CD, a test for IgA deficiency during the screening process is a consideration so as to more accurately evaluate the significance of a negative serological test. This strategy is also a consideration when screening asymptomatic individuals who belong to a group at risk for CD although based on the available evidence only a few cases of CD in IgA deficient individuals will be identified in this manner.

IgG antibody tests have been used in individuals with known selective IgA deficiency to identify those requiring an intestinal biopsy for the diagnosis of CD. AGA IgG tests are more frequently used for this purpose than EMA IgG or TTG IgG [120]. However, in individuals with selective IgA deficiency and symptoms suggestive of CD, the positive predictive value of a high titer AGA IgG for biopsy confirmation of CD is poor, and in one study was only 0.31 [110,114]. Based on these findings the use of AGA IgG tests is considered a poor option for identifying individuals with CD who have selective IgA deficiency.

There is some evidence that EMA IgG and TTG IgG tests are more accurate than AGA IgG for identifying individuals with CD. Testing with TTG IgG in a small number of subjects has shown promise [120-122]. TTG IgG or EMA IgG1 had almost 100% sensitivity in selected series of symptomatic individuals with known selective IgA deficiency [123,124], and there was near perfect concordance between TTG IgG and EMA IgG1 in adults with symptoms of malabsorption [122]. The sensitivity and specificity of TTG IgG ranges from 0.84-0.97 and 0.91-0.93 respectively in the symptomatic population, with a positive predictive value of 0.63 [121-123,125] for small intestinal histological features of CD. However, if those with total villous atrophy are excluded, accuracy decreases significantly, suggesting that TTG IgG may fail to identify individuals with less severe histological changes. EMA IgG in selective IgA deficient individuals has a sensitivity of 0.83, a specificity of 0.80 and a positive predictive value of 0.925 [120]. Based on these studies, EMA IgG and TTG IgG are considered better tests than AGA IgG for identifying individuals with selective IgA deficiency that require a biopsy to confirm the diagnosis of CD. However, these tests have not been prospectively evaluated in a large cohort of selective IgA deficient subjects, and there is no good data on their accuracy for identifying CD in asymptomatic individuals with selective IgA deficiency.

On the balance of evidence, for those individuals with known selective IgA deficiency and symptoms or signs strongly suggestive of CD (e.g., chronic diarrhea with failure to thrive) serological testing offers little advantage over directly proceeding to intestinal biopsy to establish the diagnosis. For individuals known to have IgA deficiency but with a lower clinical index of suspicion for CD, TTG IgG, which is commercially available, may be of value to identify those who need an intestinal biopsy. For those individuals with known selective IgA deficiency who are truly asymptomatic but at high risk for CD (e.g., first degree relatives, type 1 diabetics), TTG IgG is a consideration. Determination of the HLA DQ2/DQ8 heterodimer status is an additional consideration in some of these cases. However, IgA deficient individuals have a higher prevalence of the HLA DQ2 genotype than the general population [126], and thus the proportion of individuals who will be reassured by having neither DQ2 nor DQ8 may be smaller than for some other high risk groups.

3.2.4 Intestinal Biopsy and Histopathology

It is currently recommended that confirmation of the diagnosis of CD requires an intestinal biopsy in all cases. A clinical diagnosis in children on the basis of gastrointestinal symptoms alone was incorrect in over 50% of cases [127,128]. Radiological and other non-serological laboratory tests are also unable to separate those with or without villous atrophy [129]. Serological tests for CD have enhanced the ability to identify individuals who may have CD, but are still not sufficiently reliable to confidently diagnose a condition requiring lifelong adherence to a strict GFD [130-132].

The initial biopsy based criteria for the diagnosis of CD were published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition in 1970 [133]. These criteria required 3 biopsies over a period exceeding one year. Retrospective analysis of over 3,000 patients who had multiple biopsies demonstrated the diagnosis of CD was correct in over 95% of those who had symptoms suggestive of CD, the characteristic findings on small intestinal mucosal histology while on a gluten containing diet and complete symptom resolution on a GFD [134]. Most of the remaining 5% who did not have CD were less than 18 months of age and had a final diagnosis of cow milk protein enteropathy. Based on these findings, revised criteria for the diagnosis of CD were published in 1990 [135]. These state that for children over 2 years of age who have symptoms suggestive of CD, the characteristic histological findings on small intestinal biopsy and unequivocal clinical resolution following institution of a GFD, the diagnosis can be considered definitive for lifelong CD without need for additional biopsies. The addition of positive serological tests for CD, that revert to negative following a period on a GFD, is considered supportive evidence for the diagnosis in these cases.

Small intestinal biopsies are now generally obtained by grasp biopsy forceps during an endoscopic procedure. Endoscopic biopsies appear comparable to suction capsule biopsies for the purposes of making a definitive diagnosis in children and adults [136-140]. With either technique the biopsy specimen was considered satisfactory in about 90% of cases. Both suction and endoscopic biopsies are considered relatively safe [141-147]. Potential advantages to use of the endoscopic procedure include the ability to inspect the mucosa and obtain multiple samples, a shorter procedure time and absence of radiation. The main disadvantage is the higher cost involved. Suction biopsies are generally obtained from the region of the ligament of Treitz. The number of biopsies taken has varied from 2 to 4 specimens at the same level [135,137,140,145,148] to three specimens at different levels [149]. Comparison of biopsies from the second, third and fourth parts of the duodenum, the ligament of Treitz and the proximal jejunum has demonstrated each site is suitable for diagnosing CD [150]. However, the presence of Brunner glands in the duodenal bulb and the second part of the duodenum can adversely affect interpretation of the histology, rendering assessment of the villous:crypt ratio difficult [150-152]. For this reason it may be preferable to obtain biopsies from the more distal segments of the duodenum.

Endoscopic features of duodenal villous atrophy described in CD include the absence of folds, scalloped folds, visible submucosal blood vessels and a mosaic-pattern of the mucosa between the folds. These features may only be reliable in cases with subtotal and total villous atrophy (Marsh 3b and 3c) [153]. Inter-observer agreement in the interpretation of these endoscopic findings was good for the mosaic pattern and the scalloped folds, but judged to be only fair for reduction in number or loss of duodenal folds [149,154,155]. Furthermore, with partial villous atrophy the endoscopic appearance can be normal.

There is good evidence that the mucosal changes in CD may be patchy in nature and vary in severity [156]. In some cases a biopsy from one site had total villous atrophy while that from an adjacent site was normal or showed only mild lymphocyte and plasma cell infiltration of the lamina propria [157]. The coexistence of villous atrophy with relatively normal adjacent mucosa on histology has been reported in children with newly diagnosed CD [158], and is also frequently found in cow milk protein intolerance and in post infectious enteritis [159,160]. Patchy lesions have been described in 35% of children with CD after 1 to 4 months of a gluten challenge [160]. Milder changes and patchy lesions may be more likely when CD is diagnosed in patients with minimal or no symptoms.

It is recommended that multiple endoscopic biopsies be obtained from the more distal segments of the duodenum. Areas with a mucosal mosaic pattern or scalloping of the duodenal folds, when present, are preferred sites for obtaining a biopsy [161]. Correct orientation of the biopsy specimens will greatly facilitate identification of the histological features of CD [136,139,140,149,162]. Evaluation of the biopsy specimens includes an assessment of the characteristic histological changes seen with CD and a grading of severity. There is a recognized spectrum of histological features varying from mild to severe as described by Marsh and others [153,163,164]. None of the individual features is pathognomonic for CD as each may be seen in other disease states. However, the combination of histopathological features in a compatible clinical setting is sufficient evidence for a diagnosis of CD.

The characteristic changes described in CD include an increased number of intraepithelial lymphocytes (>30 lymphocytes per 100 enterocytes), an intraepithelial lymphocyte mitotic index above 0.2%, a decreased height of the epithelial cells (changes from columnar to cuboid to flat epithelium), a loss of nuclear polarity with pseudostratification of the epithelial cells, a decrease in the number of goblet cells, and brush border abnormalities. Structural changes include elongation of the crypts (increased crypt length), partial to total villous atrophy, and a decreased villous:crypt ratio. Lamina propria changes include an increased crypt mitotic index and infiltration of plasma cells, lymphocytes, mast cells and

eosinophils. An increase in the intraepithelial lymphocytes may be a more sensitive index of gluten sensitivity than the changes in villous structure as they are found early in the course of the disease and disappear before other features of structural recovery can be detected [165,166]. Marsh and Miller proposed that a mitotic index >0.2% of intraepithelial lymphocytes is useful to differentiate CD from other childhood enteropathies [167]. A decrease in the height of the villi and enterocytes is the most readily recognized change in CD and occurs in the more advanced stages of the disease [153]. Less well recognized and reported by pathologists are an increase in the mitotic cells in the epithelial crypts, a reduction in the number of goblet cells and an altered ratio of gamma/delta cells. Most pathologists subjectively grade the degree of cell infiltrate and the increase in the ratio of intraepithelial lymphocytes to enterocytes. Morphometric techniques have been employed in an attempt to generate more objective data but are not widely used in clinical practice [159,168,169].

Histological grading systems used include the conventional, and that introduced by Marsh [153]. The conventional system grades the mucosal findings as normal, slight partial villous atrophy, marked partial villous atrophy, subtotal and total villous atrophy. Marsh classified the histological changes of CD as Type 0 or pre-infiltrative stage (normal), Type 1 or infiltrative lesion (increased intraepithelial lymphocytes), Type 2 or hyperplastic lesion (type 1+ hyperplastic crypts), Type 3 or destructive lesion (Type 2 + variable degree of villous atrophy) and Type 4 or hypoplastic lesion (total villous atrophy with crypt hypoplasia). Type 3 has been modified to include Type 3a partial villous atrophy, Type 3b subtotal villous atrophy and Type 3c total villous atrophy [170]. There is good evidence that villous atrophy (Marsh type 3) is clearly a feature of CD. The evidence that hyperplastic changes (Marsh type 2) are distinctive features of CD is not as clear. The presence of Marsh type 2 changes on intestinal biopsy is suggestive of CD. In these cases the diagnosis is strengthened by the presence of positive serological tests for CD. In the event the serological tests are negative, other conditions for the intestinal changes are to be considered and, if excluded, reconsideration of the diagnosis of CD is warranted. The presence of only infiltrative changes (Marsh type 1) on intestinal biopsy is nonspecific in children. The presence of positive serological tests for CD (TTG or EMA) in children with Marsh I changes increases the likelihood the individual has CD. Under such circumstances additional strategies to confirm the diagnosis can be considered. These include determination of the HLA type, repeat biopsies or a trial of treatment with a GFD and repeat serology and biopsy.

4. TREATMENT

The only treatment currently available for CD is strict adherence to a GFD for life. There is evidence that diagnosed but untreated CD is associated with a significant increase in morbidity and mortality. Prolonged adherence to a GFD may reduce this risk for both morbidity and mortality to the levels found in the general population. For these reasons prompt diagnosis and treatment with a GFD as early as possible is desirable. The GFD has both lifestyle and financial implications for the individual and thus has potential for impacting adversely on their quality of life. Hence, it is strongly recommended that an intestinal biopsy be performed to establish the diagnosis of CD prior to instituting treatment. A trial of a GFD prior to biopsy is not recommended as this has potential to promote mucosal healing and to normalize serological tests for CD, thus rendering it impossible to make a positive diagnosis without first challenging the individual with gluten.

4.1 WHO TO TREAT?

Clinical experience has demonstrated that treatment of children with FTT and persistent diarrhea due to CD results in resolution of symptoms. When children with symptomatic CD adhere to a gluten free diet, it will generally result in resolution of gastrointestinal symptoms, normalization of nutritional measures, improved growth in height and weight with resultant normal or expected stature, and

normalization of hematological and biochemical parameters [171-174]. There is good evidence demonstrating that treatment with a GFD reverses the decrease in bone mineralization in children with CD [175]. In adults with CD and established osteoporosis, treatment appears effective in restoring bone mineralization, but it is uncertain whether it has an effect on reducing the risk for fractures [176]. Studies in symptomatic children with CD treated with a GFD demonstrate improvement in their sense of physical and psychological well being. The quality of life of children on a GFD who were symptomatic at the time of diagnosis is similar to that of children without CD [177]. Improved physical and psychological well being can occur after starting a GFD in screening-detected celiac disease patients who were apparently asymptomatic at the time of diagnosis [178].

There are data suggesting that treatment can decrease the occurrence of spontaneous abortions in fertile females, lower the incidence of low birth weight infants, decrease the risk of some cancers and avoid other consequences of late or delayed diagnosis [179-183]. Compared to those on a GFD, women with untreated CD have an increased relative risk for spontaneous abortion (8.9:1), for delivery of a low birth weight infant (5.8:1) and for a shortened duration of breast feeding (2.5:1) [182]. In longitudinal studies, institution of a GFD reverses these effects [183]. There is little evidence that treating CD in patients with type 1 diabetes, who have no symptoms associated with CD, affects the course of the diabetes in the short term. The intermediate and long-term benefits of treating such patients with a GFD are not known. There are no studies on the benefits of treating asymptomatic CD in individuals with other associated conditions. It has been suggested that untreated CD may lead to the onset of other autoimmune disorders in genetically susceptible individuals, but the evidence supporting this hypothesis is conflicting [184-189].

Although CD is associated with an overall increase in mortality in adults, primarily due to malignancy, there is good evidence that treatment of symptomatic individuals with CD decreases the mortality rate compared to those who remain untreated [179-181]. When CD is diagnosed in childhood or adolescence there appears to be no increased cancer risk, presumably due to early initiation of a GFD [190].

Thus treatment with a GFD is recommended for all symptomatic children with intestinal histopathological abnormalities that are characteristic of CD. Treatment with a GFD is also recommended for asymptomatic children who have a condition associated with CD and characteristic histological findings on small intestinal biopsy.

4.2 HOW TO TREAT?

The only treatment available for CD is a GFD for life. It is recommended that treatment for CD be started only after the diagnosis has been confirmed by intestinal biopsy according to the diagnostic algorithms presented in this guideline. Wheat, rye and barley are the predominant grains containing the peptides known to cause CD. Triticale (a combination of wheat and rye), kamut, and spelt (sometimes called farro) are also known to be harmful. Other forms of wheat are semolina (durum wheat), farina, einkorn, bulgur and couscous. The harmful potential of rendered gluten-reduced wheat starch is controversial**.** Many celiac societies in Southern Europe exclude wheat starch; however, there is some evidence that it does not cause villous damage [191]. Additional data about this issue are necessary before definitive conclusions can be made. Malt is also harmful because it is a partial hydrolysate of barley prolamins. It may contain 100-200 mg of barley prolamins /100 g of malt [192]. In general, any ingredient with malt in its name (barley malt, malt syrup, malt extract, malt flavorings) is made from barley.

Previously, oats were implicated in the development of the villous damage in CD. More recently this has been questioned as both *in vivo* and *in vitro* immunological studies suggest oats are safe [193-199]. Despite the accumulating evidence that oats are safe for individuals with CD, there remains some concern about recommending consumption of this grain to CD patients. Contamination of oats with gluten during the harvesting and milling process is known to occur, so unless the purity of the oats can be guaranteed, their safety remains questionable.

There is evidence to demonstrate that even small amounts of gluten ingested on a regular basis can lead to mucosal changes on intestinal biopsy. However, the strict definition of a GFD remains contentious. Products containing less than 200 ppm (<200 mg/kg) were previously regarded as effectively gluten free. Currently, <20 ppm (<20 mg/kg) is being considered in the proposed Codex Alimentarius Guidelines to define gluten free. The National Food Authority has recently re-defined their term for gluten-free. By their definition gluten-free now refers to no gluten and <200 ppm is regarded as low gluten. Controversies surrounding what constitutes a GFD are in part due to inaccurate gluten detecting techniques and lack of solid scientific evidence for a threshold of gluten consumption below which no harm occurs.

The American Dietetic Association (ADA) recently published guidelines for the dietary treatment of CD [200]. This document was produced by members of the Canadian and USA dietetic societies and the recommendations were based on the best available evidence. The CD Guideline Committee recommends acceptance of the ADA recommendations for treatment of CD. However, given the dynamics of this field, the diet requires ongoing collaboration between patients, health care professionals and dieticians, and the recommendations require periodic review and modification in light of new scientific evidence. At this time, a GFD for life remains the only scientifically proven treatment available for symptomatic individuals with CD.

Most children with newly diagnosed CD will tolerate ingestion of lactose, particularly in moderate amounts; therefore dietary lactose restriction is not usually necessary. Young children with more severe disease may benefit from a lactose free diet initially [201].

4.3 HOW TO MONITOR?

It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination and adherence to the GFD (Figure 3). The range of adherence to a strict GFD as reported by patients is 45% to 81%. These may be overestimates, as some patients reporting strict adherence have abnormal intestinal histopathology [171,173,174,202-206]. The range of reported complete lack of adherence is 6% to 37%. These may be underestimates as patients are reluctant to admit they are not following the physician's advice. The rate of adherence in patients who were detected as part of a population screening may be comparable to patients who had symptoms that led to detection of celiac disease [178,207].

There is little evidence on the most effective means of monitoring patients with CD. The Celiac Disease Guideline Committee recommends measurement of TTG after 6 months of treatment with a GFD to demonstrate a decrease in antibody titer as an indirect indicator of dietary adherence and recovery. Measurement of TTG is also recommended in individuals with persistent or recurrent symptoms at any time after starting a GFD, as a rise in antibody levels suggests dietary non-adherence. In the asymptomatic patient measurement of TTG at intervals of one year or longer may serve as a monitor of adherence to the GFD.

5. Algorithms for the Evaluation and Management of Infants and Children with Suspected Celiac Disease.

5.1 Evaluation of the symptomatic child (Figure 1).

Identification of children with symptoms who need an intestinal biopsy to diagnose CD requires that health care professionals appreciate the variable clinical manifestations of the disorder. This includes recognition of both gastrointestinal and non-gastrointestinal manifestations (Figure 1, Box 1; Table 1). Following a detailed history and physical examination (Box 2), if CD is a consideration in the differential diagnosis, serological testing with TTG is recommended (Box 3). If TTG is normal, it is unlikely the child has CD and other conditions are considered (Boxes 4 and 5). Symptomatic children with a positive TTG are referred to a pediatric gastroenterologist for small intestinal biopsy (Boxes 5 and 6). Those with histological features of CD on biopsy are treated with a strict GFD (Boxes 8 and 9). If there is complete symptom resolution on a GFD the diagnosis of CD can be considered definitive for life.

Children with symptoms who are TTG positive but without characteristic changes of CD on small intestinal histology present a diagnostic challenge (Boxes 7 and 8). Possibilities in these cases include the child does not have CD and the TTG was false positive, the child has CD but the histological changes were either not detected by the pathologist or were missed on biopsy due to the patchy nature of the disease, or a positive TTG with a truly normal biopsy represents an early stage of the disease that is manifest by seropositivity only. Under such circumstances several strategies are available that may help establish a diagnosis (Box 7). These include a careful review of the original biopsy specimens by an experienced pathologist, measurement of EMA, repeating an endoscopy to obtain multiple small intestinal biopsy samples and determination of the HLA DQ2 and DQ8 genotypes. In the event the child is negative for both HLA DQ2 and DQ8, it is highly unlikely that CD is the cause of the symptoms and other conditions would be considered.

5.2 Evaluation of the asymptomatic child in an at-risk group (Figure 2).

It is recommended that asymptomatic children, who are first degree relatives of an individual with confirmed CD, and those with autoimmune and non-autoimmune conditions known to be associated with CD, undergo testing for CD beginning in childhood (Figure 2, Box 1; Table 2). It is recommended that testing occur after age 3 years, after the child has been on an adequate gluten containing diet for at least one year prior to testing. The initial test of choice for this purpose is the TTG (Box 2). For those individuals who are selective IgA deficient, measurement of TTG IgG is recommended. If the TTG is negative it is unlikely the child has CD at that time. However, as demonstrated on interval testing in some patients with type 1 diabetes and Down syndrome, an initial negative serological test for CD does not entirely exclude the possibility the individual will develop CD later in life. Strategies for addressing this possibility include repeat TTG testing at intervals over a period of some years, and at any time that the child develops symptoms compatible with CD, or determining whether the child has the HLA DQ2 or DQ8 genotype (Boxes 3 and 4). Those who have neither of these genotypes may be reassured they are at minimal risk for CD and need no further testing. Conversely, those who are either HLA DQ2 or DQ8 positive are considered potentially at risk and may warrant later testing.

In the event the initial TTG is positive the child is referred to a pediatric gastroenterologist for an intestinal biopsy (Boxes 4 and 5). If the histology is compatible with CD the child is treated with a GFD for life (Boxes 7 and 8). Those with a positive TTG but without characteristic changes of CD on histology require additional strategies to clarify the situation (Boxes 6 and 7). These include reviewing the

pathology with an experienced pathologist, repeating the endoscopy and obtaining multiple biopsies to exclude a patchy lesion, testing for EMA and determining whether the individual has either the HLA DQ2 or DQ8 genotype (Box 6). In the event the child is neither HLA DQ2 nor DQ8 positive, the likelihood of having CD is extremely small and no further testing is warranted. (For type 1 diabetics, see section 3.2.2.)

5.3 Treatment and monitoring of patients with CD (Figure 3).

The treatment of CD is a GFD for life. Untreated CD carries a significant increased risk for both morbidity and mortality. Following histologic identification of intestinal mucosal features compatible with CD (Figure 3, Box 1), it is recommended education be provided about CD and the potential adverse health consequences associated with continued ingestion of gluten and related products. It is recommended the patient be referred to a nutritionist for education about a GFD (Box 2). Referral to a CD support group is also considered beneficial to provide the opportunity for emotional and psychological support as well as being a source of information for gluten free products available locally.

Periodic assessment by the physician and nutritionist is recommended to monitor for symptom resolution, maintenance of continued growth and development, dietary review and repeat serological testing (Box 3). During these assessments health care professionals can reinforce the benefits of compliance with a strict GFD for life. Failure of the TTG level to decline over a period of 6 months after starting the GFD suggests continued ingestion of gluten or related products. In these cases there is need for careful dietary review looking for sources of gluten, and reinforcement of the need to remain on a strict GFD (Boxes 4 and 5). Normalization of TTG on repeat testing suggests compliance with the GFD. The complete resolution of symptoms in the previously symptomatic child is further supportive evidence that the patient is adhering to treatment (Boxes 5 and 6). These patients then receive annual assessment providing they remain asymptomatic (Boxes 3 and 6).

Children whose symptoms persist, or who develop symptoms again after a period of symptom resolution, may either be not adhering to treatment or have an additional problem not related to CD (Boxes 6 and 7). Repeat serological testing in these cases is recommended. A positive test suggests non-adherence and requires dietary review and reinforcement of the need for compliance (Box 4). A negative test suggests the symptoms are not related to CD but does not entirely exclude this possibility (Box 7). If after evaluation for other conditions no alternative cause for the symptoms is identified, it is reasonable to consider repeating the intestinal biopsy to determine whether there are still changes compatible with CD.

Disclaimer

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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Table 1. Non-gastrointestinal manifestations of celiac disease
A) Manifestations for which there is strong to moderate evidence
Dermatitis herpetiformis Dental enamel hypoplasia of permanent teeth Osteopenia/Osteoporosis Short stature Delayed puberty Iron-deficient anemia unresponsive to treatment with oral iron (*well documented in adults only*)
B) Manifestations for which the evidence is less strong
Hepatitis (elevated liver enzymes) Arthritis Epilepsy with occipital calcifications

Table 2. - Conditions associated with an increased prevalence of celiac disease
Type 1 diabetes
Autoimmune thyroiditis
Down Syndrome
Turner Syndrome
Williams Syndrome
Selective IgA deficiency
First degree relatives of celiac patients

FIGURE LEGENDS

Figure 1. Algorithm for the evaluation for celiac disease in a child with symptoms.

Figure 2. Algorithm for the evaluation of an asymptomatic child belonging to a group at-risk for celiac disease. *For patients with selective IgA deficiency measurement of TTG-IgG is recommended.

Figure 3. Algorithm for the treatment and monitoring of a child with celiac disease.

1436 Appendix. Quality of the Evidence
1437

Section	Evidence and Recommendations	Grade
3	Based on a number of studies in Europe and the USA, the prevalence of CD in children between 2.5 and 15 years of age in the general population is 3 to 13 per 1000 children.	A
3.1	Numerous studies demonstrate that children with CD frequently have gastrointestinal (GI) symptoms such as diarrhea, failure to thrive (FTT), abdominal pain, vomiting, constipation and abdominal distension, although there is little information currently available about the exact prevalence of CD in children with these specific types of GI symptoms.	B
3.1	There is strong evidence for an increased prevalence of CD in children with type 1 diabetes, IgA deficiency, Down syndrome, Turner syndrome, William's syndrome, dental enamel defects and first degree relatives of patients with CD.	A
3.1	There is moderate evidence for an increased prevalence of CD in children with short stature.	B
3.1	There is weak evidence for an increased prevalence of CD in individuals with autoimmune thyroiditis.	C
3.1	There is evidence that anemia is a common finding in adults with CD, and that CD is more prevalent in adults presenting with unexplained anemia.	A
3.1	Other conditions that have been described in association with CD include a variety of neurological disorders; however, the evidence for this association in children is poor.	D
3.1	Based on clinical experience, it is recommended that CD be an early consideration in the differential diagnosis of children with FTT and persistent diarrhea. In addition, it is recommended that in children with other persisting GI symptoms, including recurrent abdominal pain, constipation and vomiting, CD be considered in the differential diagnosis.	D
3.1	It is recommended to test asymptomatic children who belong to high risk groups, and advise treatment for those proven to have intestinal changes of CD, as there are epidemiological data that suggest treatment can reverse osteoporosis in children, decrease incidence of spontaneous abortions in fertile females, lower the incidence of low birth weight infants, decrease the risk of cancer and avoid other consequences of delayed diagnosis. The high risk groups recommended for screening are type 1 diabetes, selective IgA deficiency, Down syndrome, Turner syndrome, William's syndrome, unexplained dental enamel defects, autoimmune thyroiditis and first degree relatives.	C
3.1	It is recommended that routine testing of asymptomatic children who have a first degree relative with proven CD begin at age 3 years of age provided they have been receiving an adequate gluten containing diet for at least one year.	D

3.1	There is good evidence that in certain groups (type 1 diabetes, HLA compatible siblings and Down syndrome) some individuals who initially have negative serological tests may subsequently become positive on repeat testing over a period of some years and have biopsies compatible with CD. It is recommended that individuals who fall into these categories be considered for repeat testing.	C
3.1	There is no good evidence that CD is more common in children with autism, and for this reason there is no indication to routinely test patients with autism for CD.	B
3.2.1	Based on available evidence and practical considerations, measurement of IgA antibody to human tissue transglutaminase (TTG) is recommended for initial screening for CD.	B
3.2.1	Because of the poor accuracy of antigliadin antibody (AGA), the use of these IgA and IgG tests is not recommended to detect CD.	A
3.2.1	Individuals with CD who are also IgA deficient will not have abnormally elevated levels of TTG IgA or EMA IgA. The occurrence of both CD and IgA deficiency in the same individual appears to be rare in asymptomatic individuals (approximately 1:8500 of the general population) but is more likely in symptomatic children with CD (approximately 2%). Therefore, when testing for CD in children with symptoms suspicious for CD, measurement of quantitative serum IgA can facilitate interpretation when the TTG IgA is low. In individuals with known selective IgA deficiency and symptoms suggestive of CD, testing with TTG IgG is recommended.	B
3.2.1	Even if serological tests for CD are negative, a small intestinal biopsy may be useful in symptomatic children with chronic diarrhea, FTT, a positive family history of CD or IgA deficiency to identify the unusual case of serology negative CD or other intestinal mucosal disorders.	C
3.2.2	Based on expert opinion it is currently recommended that confirmation of the diagnosis of CD requires an intestinal biopsy in all cases.	D
3.2.2	Because the intestinal lesions in CD may be patchy it is recommended that multiple biopsy specimens be obtained from the second or more distal part of the duodenum or jejunum by either endoscopic or suction capsule technique.	C
3.2.2	There is good evidence that villous atrophy (Marsh type 3) is a characteristic feature of CD. The evidence that hyperplastic changes (Marsh type 2) are distinctive features of CD is not as clear. The presence of Marsh type 2 changes on intestinal biopsy is suggestive of CD. The diagnosis is strengthened by the presence of positive serological tests for CD. In the event the serological tests are negative, other conditions for the intestinal changes are to be considered and, if excluded, the diagnosis of CD is reconsidered. Serological tests recommended for this purpose are the TTG and EMA, or the IgG TTG and IgG EMA in those who are known to have selective IgA deficiency. The presence of infiltrative changes (Marsh type 1) on intestinal	B

	biopsy is not specific for CD in children. The presence of positive serological tests for CD (TTG or EMA) increases the likelihood the individual with Marsh type 1 changes has CD. Under such circumstances additional strategies to confirm the diagnosis can be considered. These include determination of the HLA type, repeat biopsies or a trial of treatment with a gluten free diet and repeat serology and biopsy.	
4.1	Clinical experience has demonstrated that treatment of children with FTT and persistent diarrhea due to CD results in resolution of symptoms.	B
4.1	There is good evidence that treatment of symptomatic individuals with CD decreases the mortality rate compared to those who remain untreated.	B
4.1	There is good evidence demonstrating that treatment with a gluten free diet reverses the decrease in bone mineralization in children with CD.	B
4.1	In adult women with CD, treatment decreases the frequency of spontaneous abortions and low birth weight infants and is associated with prolongation of breast feeding.	B
4.1	The evidence that early treatment of CD prevents onset of other autoimmune diseases is weak.	C
4.1	It is recommended to treat asymptomatic children with proven intestinal changes of CD who have type 1 diabetes, selective IgA deficiency, Down syndrome, Turner syndrome, William's syndrome, autoimmune thyroiditis or a first degree relative with CD. There are epidemiological data that suggest treatment can prevent the onset of osteoporosis, decrease the incidence of spontaneous abortions in fertile females, lower the incidence of low birth weight infants, decrease the risk of cancer and avoid other consequences of delayed diagnosis.	D
4.1	In patients with type 1 diabetes who otherwise have no symptoms associated with CD, there is little evidence to demonstrate that a gluten free diet improves their diabetic control in the short term. Treatment with a GFD in these cases is aimed at reducing morbidity and mortality associated with untreated CD in the long term.	B
4.2	The treatment of celiac disease is a gluten free diet. At this time, a GFD for life remains the only scientifically proven treatment available for symptomatic individuals with CD.	B
4.2	It is recommended that treatment for CD with a GFD be started only after the diagnosis has been confirmed by intestinal biopsy according to the diagnostic algorithms presented in this guideline.	D
4.2	The Celiac Guideline Committee endorses the recently published guidelines of the American Dietetic Association guidelines for the treatment of CD.	D
4.2	There is evidence to demonstrate that even small amounts of gluten ingested on a regular basis can lead to mucosal changes on intestinal biopsy.	B

4.2	Management of a gluten free diet is facilitated by ongoing collaboration between patients, health care professionals and dieticians.	C
4.2	Most newly diagnosed children will tolerate ingestion of lactose, particularly in moderate amounts. Dietary lactose restriction is not necessary in most children, although young children with more severe disease may benefit from a lactose free diet initially.	D
4.3	It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, signs and growth and measurement of TTG.	C
4.3	It is recommended that initial serological monitoring with TTG begin 6 months after treatment with a GFD is instituted, and this be repeated at yearly intervals in the asymptomatic individual, or more often if symptoms develop.	C
4.3	Based on limited data, the rate of adherence to a GFD in individuals who were detected as part of a population screening may be comparable to patients who had symptoms that led to detection of CD.	C
4.3	Over 95% of children with symptoms of CD, characteristic changes of CD on intestinal biopsy and complete resolution of symptoms on a gluten free diet do in fact have CD. Therefore additional biopsies for confirmation of the diagnosis is not recommended in such cases.	B

Grades of Evidence and Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level