Evidence-Informed Expert Recommendations for the Management of Celiac Disease in Children

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Although the need for effective long-term follow-up for patients with celiac disease (CD) has been recognized by many expert groups, published practice guidelines have not provided a clear approach for the optimal management of these patients. In an attempt to provide a thoughtful and practical approach for managing these patients, a group of experts in pediatric CD performed a critical review of the available literature in 6 categories associated with CD to develop a set of best practices by using evidence-based data and expert opinion. The 6 categories included the following: bone health, hematologic issues, endocrine problems, liver disease, nutritional issues, and testing. Evidence was assessed by using standardized criteria for evaluating the quality of the data, grade of evidence, and strength of conclusions. Over 600 publications were reviewed, and 172 were chosen for inclusion. The thorough review of the results demonstrated that the quality of the data available was often insufficient to provide unequivocal best practices. However, using the available data and the clinical experience of the panel, a practical framework for the management of children with CD was created. These recommendations were developed by our expert panel and do not necessarily reflect the policy of the American Academy of Pediatrics. The potential usefulness of these best practices is underscored by the fact that consensus, measured by the outcome of anonymous voting, was reached by the panel for 24 of the 25 questions. We hope that these best practices may be useful to the pediatric gastroenterology and larger general pediatric communities.

Celiac disease (CD) is a systemic immune-mediated illness triggered by gluten in genetically susceptible persons and affects ∼1% of the world's population.[1–4] Although great progress has been made in the diagnosis and management of CD in recent years,[1–6] important problems still exist. One of the most pressing is the lack of effective long-term management programs to optimize the treatment of CD and the diagnosis and management of associated disease states.[7,8] The need for effective long-term follow-up to improve compliance and outcomes for patients with CD has been recognized by many expert groups for several reasons.[3–6] Patients with CD who do not carefully adhere to the gluten-free diet (GFD) appear to have an increased risk of mortality and lower quality of life assessments.[9–11] In addition, patients with CD often have important nutritional deficiencies and are at increased risk for a variety of associated diseases.[1–4]

Despite this clearly recognized need for effective follow-up for CD,

abstract

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recent reports indicate that such optimal follow-up care is not being provided.[7,8] Although many practice guidelines have been published in North America and Europe,[3–6,12] they have not generated a consensus on when and how to provide effective management of these patients. This is likely due to the fact that few evidence-based data were available to support such management guidelines. The absence of clear recommendations on management may also have been influenced by the extremely dynamic nature of the field of gluten-related disorders in general, and of CD in particular. To help address these issues, a best practices conference was convened to review the available evidence and to provide recommendations about how to follow-up these patients. These recommendations were developed by our expert panel and do not necessarily reflect the policy of the American Academy of Pediatrics.

METHODS

Six acknowledged experts in pediatric CD were chosen to provide a thorough assessment of the data and to develop best practices in 6 topic areas: bone disease, endocrine problems, hematologic issues, liver issues, nutritional problems, and testing to monitor CD activity. The assignment of 1 panel member to each topic area was made by the organizer and moderator (Dr Snyder) based on that person's recognized knowledge of the topic and was made in consultation with North American senior experts in pediatric gastroenterology who were not part of the panel. Each panel member researched and summarized their topic area. The panel met and thoroughly reviewed each topic before evaluating and voting on each best practice. In addition to their expertise, the panel members were chosen to provide a geographic representation of the major pediatric CD programs in the United States and Canada. The number of experts chosen was also influenced by logistic and financial considerations because the project was funded by a nonrestricted grant from a nonprofit organization, the Celiac Disease Program of Children's National Health System. The meeting was convened at Children's National Health Center in Washington, DC, on January 25 and 26, 2013. The goal was to provide a critical review of the management of pediatric CD in North America and to develop a practical set of best practices for the Children's National Health System Celiac Program by using evidence-based data and expert opinion.

Literature Search and Grading the Articles for Quality of Evidence

Each expert completed a thorough literature search combining the term "celiac disease" with multiple terms specific to their section using accessible databases including PubMed, Medline, Embase, Cochrane Library, BioSciences Information Services Previews, EBM Reviews, ISI Web of Science, and Scopus. The search included publications from 1973 to January 2013 and included publications of all types that presented or reviewed data on CD in patients younger than 20 years old. Publications were assessed by using criteria including study design, sample size, data analysis, synthesis of results, potential bias, and limitations.

The search identified over 600 unique publications. Of these 600 articles, 172 were included after exclusion of publications that did not present relevant evidence, that did not present sufficient evidence for pediatric patients, or were commentaries, case reports, abstracts, or nonsystematic reviews. Reviews of the literature were used to find additional primary research references and to provide summaries of data, references for pathophysiology, and to point our team to more extensive background reading. Reviews were also used to support introductory statements. The review articles and guidelines are identified in the References. Only original clinical studies were used to develop the "Best Practice" management questions.

Voting on Best Practice Statements and Grading the Statements for Quality of Evidence

Details about mechanism for anonymous voting, assessment of quality of data, use of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system to evaluate the available evidence, and strength of recommendation are included in the Supplemental Information, Part 1.[13]

BEST PRACTICES

A. Bone Health

Background

CD can affect the bone health of children in several ways with a variety of signs and symptoms including bone pain, rickets, tetany, osteomalacia, osteopenia, osteoporosis, fractures associated with minimal trauma, or growth failure with or without symptoms of malabsorption.[14–16] With the exception of osteopenia or osteoporosis identified by the evaluation of bone mineral density, these are now rarely the presenting signs and symptoms of CD in children because of the widespread use of CD serological testing to assist in diagnosis.[14–16] Initiation of a GFD rapidly restores bone mass to normal levels in almost all children and some adolescents.[17–27] Instruction on age-appropriate intake of calcium, vitamin D, and the need for exercise to promote bone health should be provided during nutritional counseling at the time of diagnosis.[23,28,29]

Detailed information on the mechanisms of bone injury, bone mineral density, fracture risk, effect of the GFD, and calcium and vitamin D intake are included in the Supplemental Information, Part 2A.[14–49]

Best Practice 1

Should routine screening for bone health by using calcium, PO4, alkaline phosphatase, ± parathyroid hormone (excluding vitamin D) be done routinely for all children being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: C

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS: DISAGREE

Agree, 2 (29%). 2A

Disagree, 5 (71%). 1D-, 3D, 1D+

STRENGTH OF RECOMMENDATION: WEAK

Comment

With the advent of serological testing, children now present with a variety of milder symptoms and associated conditions.[1,5,6] Abnormalities of the above tests most often occur with presentations that are associated with severe malabsorption, prolonged delay in diagnosis, or clinical presentations suggestive of bone disease including bone pain, rickets, osteomalacia, tetany, or fractures caused by minimal trauma.[21–28,30,33–35] With these presentations, screening with the tests listed above should be conducted. If abnormalities are detected, patients should be treated with dietary calcium and vitamin D including supplements if necessary.[26–30] Annual serial follow-up should be conducted until results normalize.[28,33,48]

Best Practice 2

Should screening for vitamin D status be done routinely for all children being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: C

GRADE OF EVIDENCE: LOW

VOTING: CONSENSUS: AGREE

Agree, 5 (71%). 1A+, 3A, 1A-

Disagree, 2 (29%). 2D

STRENGTH OF RECOMMENDATION: WEAK

Comment

Small case-control studies exist that differ in patient age, geographic location, time of year of measurement, clinical presentation, and results. Some demonstrate vitamin D deficiency.[18,25,27,30,35] Furthermore, many children and adolescents do not receive adequate dietary calcium or vitamin D.[26,28–30] Additional data on vitamin D status for children and adolescents with CD from multiple geographic areas across North America that control for sunlight exposure are needed to further define which children require vitamin D testing.

Best Practice 3

Should screening using imaging studies (bone density) evaluating bone health be done routinely for all children and adolescents with CD when they are seen at 1-year follow-up?

QUALITY OF DATA: C

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS: DISAGREE

Agree, 1 (14%). 1A+

Disagree, 6 (86%). 5D-, 1D+

STRENGTH OF RECOMMENDATION: WEAK

Comment

When CD is diagnosed at a young age with a short duration of symptoms, bone density recovers rapidly and completely to normal values for age and size.[17–21,23–27] Routine follow-up bone density testing is not required or cost-effective. More data about bone density recovery in adolescents with various presentations of CD on a strict GFD are required. Abnormalities of bone density are likely to occur with presentations that are associated with severe malabsorption, prolonged delay in diagnosis, or clinical presentations suggestive of bone disease, including bone pain, rickets, osteomalacia, tetany, or fractures caused by minimal trauma. With these presentations, bone mineral density is the test of choice to obtain at diagnosis. If abnormalities are detected, serial follow-up every 1 to 2 years should be conducted until results normalize.[28,33,48] This is especially true for adolescents where recovery may be slower and dietary compliance may be more problematic.

Best Practice 4

Should instructions on age-appropriate intake of calcium and vitamin D, including information on the impact of geographic region and season of the year, be provided during the initial GFD counseling?

QUALITY OF DATA: B

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS: AGREE

Agree, 7. 4A+, 2A, 1A-

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

Data from multiple geographic regions demonstrate that children and adolescents consume diets deficient in vitamin D and calcium.[26,28,29,35,36] Additional studies have revealed that recovery of bone mineral density will occur in children if a GFD with adequate nutrition is provided.[17–21,23–27] In some geographic areas, this can be accomplished by GFD alone. However, in other areas, vitamin D supplementation will likely be required.[23,28,29]

Best Practice 5

Should screening using imaging studies (bone density) to evaluate bone health be done routinely for selected patients with CD who do not adhere to a GFD?

QUALITY OF DATA: B

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS: AGREE

Agree, 7 (100%). 4A+, 3A

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

Maximum bone density is accrued in adolescence, late teens, and early 20s, the ages when adherence to a GFD is most difficult.[25,28,48] At these ages, symptoms may not develop with poor dietary control and a reduction in bone density may occur that increases fracture risk and can result in early onset osteoporosis. If abnormalities in bone mineral density are identified, caregivers should provide an explanation of increased risk of bone disease, as well as dietary counseling, which includes instructions about calcium and vitamin D intake and supplementation.

B. Hematologic Problems

Background

CD has been associated with a variety of hematologic disorders, of which anemia is by far the most common. In fact, anemia may be the only clinical abnormality identified in many patients and can be the presenting feature of CD, especially in older children and adults.[50–54] Anemia in children with CD can be the end result of several different, and sometimes interrelated causes; however, the single most common type of anemia is iron deficiency.[50]

Detailed information on anemia, folate deficiency, vitamin B_{12} deficiency, anemia of chronic disease, platelet abnormalities, thromboembolic problems, coagulation abnormalities, immunoglobulin (Ig)A deficiency, and splenic dysfunction are included in the Supplemental Information, Part 2B.[50–72]

Best Practice 6

Should screening for anemia using a combination of tests including a complete blood cell (CBC) count (CBC plus evaluation of mean cell volume), ferritin, iron, and total iron-binding capacity be done routinely for all children being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: B+

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS: AGREE

Agree, 7. 2A+, 3A, 2A-

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

There is abundant evidence in the literature about the prevalence of anemia, especially iron-deficient, in children with CD at the time of diagnosis.[50–53,58] This group unanimously supports the measurement of "iron studies" as reported above as an appropriate screening tool, in light of the possible need for replacement.

Best Practice 7

Should a CBC count be obtained routinely for all children undergoing follow-up evaluation for CD?

QUALITY OF DATA: C+

GRADE OF EVIDENCE: LOW

VOTING: CONSENSUS: AGREE

Agree, 6 (86%). 1A+, 3A, 2A-

Disagree, 1 (14%). 1D+

STRENGTH OF RECOMMENDATION: WEAK

Comment

Although a consensus was reached by our group on the question, the evidence to support this position comes from studies of small populations, comprising a variety of ages and clinical presentations.[50–53]

Best Practice 8

Should screening for folate deficiency be done routinely for all children being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: C

GRADE OF EVIDENCE: VERY LOW

VOTING: CONSENSUS DISAGREE

Agree, 2 (29%). 2A-

Disagree, 5 (71%). 1D+, 1D, 3D-

STRENGTH OF RECOMMENDATION: WEAK

Comment

A consensus was reached by our group on the lack of need to routinely test for folate deficiency. However, again the available data come from small, case report studies addressing various ages and clinical presentations.[58–60]

C. Endocrine-associated Disorders in CD

Background

Endocrine disorders frequently cooccur with CD, primarily due to their shared HLA predisposition, but the association is also affected by shared non-HLA variants.[73] Autoimmune thyroid disease and type 1 diabetes mellitus (T1DM) are the most common autoimmune diseases that occur with CD but Addison disease, parathyroid disorders, and growth hormone deficiency have also been reported[74–76]; however, they are much less common.

The frequency at which CD is diagnosed in individuals with type 1 diabetes and autoimmune thyroid disorders ranges from 3% to 12% for type 1 diabetes and up to 7% for autoimmune thyroid diseases; this has led expert panels from the 2 largest pediatric gastroenterology

societies, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), to recommend that CD be routinely screened for in patients with these disorders.[5,6] However, the reverse recommendation has not been made because there are insufficient data to support screening for associated endocrine disorders in individuals with an existing diagnosis of CD.

Nine sets of recent reviews and guidelines, all published since 2005, mention screening for CD in individuals with endocrine disorders such as T1DM and thyroid disease.[3–6,77–81] Three also mention screening in individuals with Addison disease.[3,78,80] All of these guidelines also recommended additional screening for CD for children with short stature or delayed puberty.

Detailed information on autoimmune thyroid disease and T1DM are included in the Supplemental Information, Part 2C.[73–80,82–98]

Best Practice 9

Should individuals with CD be screened for T1DM or prediabetes with tests including islet autoantibodies?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS DISAGREE

Agree, 0

Disagree, 7 (100%). 5 D+, 2D

STRENGTH OF RECOMMENDATION: STRONG

Comment

Insufficient data exist to establish the risk of diabetes in this population. Furthermore, because no preventative strategies exist, it is not recommended to screen for a prediabetic state outside of the research setting.[95–98]

Best Practice 10

Given the slightly increased risk of diabetes in individuals with CD, should counseling for signs and symptoms of diabetes be recommended?

QUALITY OF DATA: D

GRADE OF EVIDENCE: LOW

VOTING: MAJORITY AGREE

Agree, 4 (57%). 2A+, 2A

Disagree, 3 (43%). 3D

STRENGTH OF RECOMMENDATION: WEAK

Comment

The recommendation was based on panel's judgment of the limited risk of counseling. However, evidence for the effectiveness of counseling on preventing morbidity or mortality is not available.

Best Practice 11

Should thyroid disease be screened at the time of diagnosis in children with CD?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 7 (100%). 4A+, 3A

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

A significantly elevated overall risk of autoimmune thyroid disease, especially Hashimoto's disease, exists in those with CD.[84–88,90] Screening with thyrotropin is recommended in those with type 1 diabetes, and should be used also in CD.[80] The serum thyrotropin assay is accurate and widely available to screen for all common forms of hypothyroidism and hyperthyroidism. In addition, effective therapies for thyroid disease are available.

Best Practice 12

Should thyroid disease be screened for at the time of follow-up evaluation for children with CD?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 6 (86%). 1A+, 4A, 1A-

Disagree, 1 (14%). 1D-

STRENGTH OF RECOMMENDATION: INTERMEDIATE

Comment

Although thyroid disease has been determined to be a coexisting condition, the actual prevalence of thyroid disease in established CD has not been determined.[84–88]

Best Practice 13

Should screening for thyroid disease be performed in children with CD by using antithyroid antibodies?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS DISAGREE

Agree, 0

Disagree, 7 (100%). 5D+, 1D, 1D-

STRENGTH OF RECOMMENDATION: STRONG

Comment

The natural history of thyroid autoimmunity and its relationship with the development of clinical thyroid disease has not been determined.[89,90]

D. The Liver and CD

Background

The liver can be 1 of the major sites for extraintestinal manifestations of CD. A spectrum of liver abnormalities has been described, ranging from elevated aminotransferases (cryptogenic hypertransaminasemia) to celiac hepatitis to autoimmune liver disease.[99–109] Detailed information on celiac hepatitis and response to

hepatitis B vaccine are included in the Supplemental Information, Part 2D.[99–120]

Best Practice 14

Should screening for liver disease using tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) be done routinely for all children being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: A

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS AGREE

Agree, 5 (71%). 2A+, 1A, 2A-

Disagree, 2 (29%). 1D-, 1D

STRENGTH OF RECOMMENDATION: MODERATE

Comment

Many studies identify celiac hepatitis as a possible presenting sign of CD.[99–109] The hepatitis usually resolves with a GFD.

Best Practice 15

Should routine screening for hepatitis B immunization status be done for all children being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 6 (86%). 2A, 4A-

Disagree, 1 (14%). 1D

STRENGTH OF RECOMMENDATION: MODERATE

Comment

The current literature estimates that 30% to 70% of patients with CD are nonresponsive to hepatitis B vaccine before treatment.[112–120] If this is accurate, a serious public health concern exists. More large-scale studies are needed to validate this estimate.

E. Nutritional Problems and CD

Background

Nutritional problems in CD can occur as a result of intestinal inflammation from the disease process itself and as a consequence of medical nutritional therapy (MNT) with the GFD. It is important to consider this dynamic situation, as nutritional issues at the time of diagnosis may change after implementation of the GFD. Detailed information on anthropometric impact, micronutrient impact, and medical nutrition therapy are included in the Supplemental Information, Part 2E.[121–155]

Best Practice 16

Should assessment of height, weight, and BMI or weight for height ratio in children younger than 3 years old be done routinely for all children being evaluated for CD at the time of diagnosis and follow-up?

QUALITY OF DATA: B

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS AGREE

Agree, 7 (100%). 7A+

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

The assessment of anthropometric parameters is important in all children, but particularly important in children with CD who often have a suboptimal nutritional status at the time of diagnosis.[121,123,126–129,131,132] Monitoring response in growth on the GFD is essential to assure normal growth and development.

Best Practice 17

Should all children being evaluated and treated for CD have access to an experienced dietitian who is knowledgeable about CD?

QUALITY OF DATA: B

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS AGREE

Agree, 7 (100%). 7A+

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

The only treatment of CD is MNT with a strict GFD. Therefore, referral to an experienced registered dietitian, knowledgeable about CD, is the optimal way to provide thorough nutritional assessment and education related to the GFD.[149,151,155]

Best Practice 18

Should screening for zinc and other trace elements (besides iron) be routinely obtained for all patients being evaluated for CD at the time of diagnosis?

QUALITY OF DATA: C

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS DISAGREE

Agree, 0

Disagree, 7 (100%). 3D-, 1D, 3D+

STRENGTH OF RECOMMENDATION: WEAK

Comment

The evidence to support or refute the practice of routine screening for Zn and trace elements is weak, as it comes from studies of small populations, comprising a variety of ages and clinical presentations.[139–142] More research is needed.

Best Practice 19

Should multivitamin supplementation be offered routinely to all children with CD at the time of diagnosis?

QUALITY OF DATA: D

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 7 (100%). 1A+, 2A, 4A-

Disagree, 0

STRENGTH OF RECOMMENDATION: WEAK

Comment

Although a consensus was reached by our group on the basis of expert opinion and practice, there are no well-designed studies evaluating the clinical benefit of providing a gluten-free multivitamin to children newly diagnosed with CD.[155]

F. Testing and Monitoring

Diagnostic Tests and Monitoring

Several tests are used to diagnose and monitor CD, including serologic tests, genetic testing, and histology.[1–6] The current diagnostic algorithm for CD includes initial screening serological tests, followed by a confirmatory small intestinal biopsy revealing the autoimmune insult typical of CD in children and adults.[3–6] The relative merits of these tests in various situations, including detailed information on initial diagnosis: serology, serology in IgA deficient patients, histology, use of HLA testing, monitoring successful compliance to the GFD, and current guidelines are included

TABLE 1 Summary of Consensus Best Practices

Best Practices	Initial Evaluation	Follow-up Evaluation	Grade of Evidence	Strength of Statement
Bone				
1. Routine screening for bone health (biochemical studies and imaging)	No	At 1 y if previously abnormal[a]	Moderate	Weak
2. Measure 25-OH vitamin D level	Yes	Only if previously abnormal	Low	Weak
3. Measure bone density at 1 y	No	Only if previously abnormal	Moderate	Weak
4. Provide counseling on age-appropriate intake of calcium and vitamin D supplementation by a dietitian	Yes	Yes	High	Strong
5. Measure bone density in patients not adhering to GFD despite dietary counseling	—	Yes	High	Strong
Hematology				
6. Routine screening for anemia (CBC, evaluation of mean cell volume, ferritin, iron, total iron-binding capacity)	Yes	—	High	Strong
7. Routinely obtain CBC at follow-up evaluation	—	Yes	Low	Weak
8. Routine initial screening for folate deficiency (serum folate)	No	—	Very low	Weak
Endocrine				
9. Routine screening for type 1 diabetes	No	No	Moderate	Strong
10. Routine counseling about signs and symptoms of diabetes	Yes	—	Low	Weak
11. Routine screening for thyroid disease at time of diagnosis (thyrotropin)	Yes	—	Moderate	Strong
12. Routine screening for thyroid disease at follow-up (thyrotropin)	—	Yes	Moderate	Intermediate
13. Screening for thyroid disease using antithyroid antibodies	No	No	Moderate	Strong
Liver				
14. Routine screening for ALT and AST	Yes	Only if previously abnormal	High	Moderate
15. Screening for hepatitis B virus immunization status	Yes	Only if previously abnormal	Moderate	Moderate
Nutrition				
16. Routine assessment of anthropometric measures	Yes	Yes	High	Strong
17. Access to an experienced dietitian	Yes	Yes	High	Strong
18. Routine screening for Zn and other trace elements at time of diagnosis	No	Only if previously abnormal	Moderate	Weak
Exception: severe malabsorption, prolonged delay in diagnosis				
19. Routine vitamin supplementation	Yes	—	Moderate	Weak
Testing				
20. Routine initial testing with quantitative IgA and IgA anti-tTG antibody	Yes	—	High	Strong
21. Routine testing with IgA anti-tTG Ab at periodic intervals to help monitor compliance with GFD	—	Yes	Moderate	Strong
22. Use of IgA antiendomysial antibody limited to patients with comorbidities that increase the chance of false-positive tTG antibodies	Yes	Yes	Moderate	Strong
23. Negative serologic evaluation cannot rule out CD	Yes	—	High	Strong
24. Consider use of HLA typing for children at risk for CD who have negative serology	Yes	—	Moderate	Strong
25. Consider use of HLA typing for patients considered as diagnostic dilemmas	Yes	—	Moderate	Strong

[a] Exception: severe malabsorption, prolonged delay in diagnosis, or bone disease symptoms at diagnosis.

in the Supplemental Information, Part 2F.[156–172]

Best Practice 20

Should quantitative IgA and IgA anti-tissue transglutaminase (tTG) antibody be obtained routinely as the initial screening tests for all children being evaluated for CD?

QUALITY OF DATA: B

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS AGREE

Agree, 7 (100%). 7A+

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

Most of the studies published, including population studies and studies specifically focused at comparing commercially available assays, report extremely high specificity.[156–160] However, well-designed studies to assess sensitivity have not been performed. These studies should be based on the use of endoscopy and histologic analysis as primary standard to validate the sensitivity of these tests.

Best Practice 21

Should IgA anti-tTG antibody be obtained for all children diagnosed with CD at periodic intervals after diagnosis to help monitor compliance with the GFD?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 7 (100%). 7A+

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

There have been several reports with variable data revealing that tTG IgA antibody titers tend to decrease or completely return within normal limits after 6 to 12 months after the implementation of a GFD.[171,172] However, while tTG IgA ELISA is a validated assay for the diagnosis of CD, this assay has not been validated for monitoring.[164]

Best Practice 22

Should the use of the antiendomysial antibody be limited to patients with comorbidities that increase the chance of false-positive tTG antibodies?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 6 (100%). 1A+, 1A, 4A-

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

There are several reports in the literature revealing that low tTG IgA titers are often detected in patients affected by autoimmune diseases other than CD, including type 1 diabetes and autoimmune liver disease.[160,163]

Best Practice 23

A negative serologic evaluation cannot rule out CD.

QUALITY OF DATA: A

GRADE OF EVIDENCE: HIGH

VOTING: CONSENSUS AGREE

Agree, 6 (100%). 5A+, 1A

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

There is strong evidence in the literature that ~10% of celiac cases can test falsely negative to the tTG IgA test.[160]

Best Practice 24

Should HLA typing be considered in the evaluation of children at risk for CD who have negative serology?

QUALITY OF DATA: B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 5 (83%). 3A+, 2A

Disagree, 1 (17%). 1D-

STRENGTH OF RECOMMENDATION: STRONG

Comment

Several studies suggested that screening for HLA DQ2/8 in at-risk children, who test negative for tTG IgA antibodies, can be cost-effective in deciding whether to continue (HLA compatible) or not continue (HLA not compatible) monitoring for CD in these children over time.[169,170]

Best Practice 25

Should the use of HLA typing be considered for use in patients regarded as diagnostic dilemmas, including children who have already been placed on a GFD?

QUALITY OF DATA: LEVEL B

GRADE OF EVIDENCE: MODERATE

VOTING: CONSENSUS AGREE

Agree, 6 (100%). 4A+, 2A-

Disagree, 0

STRENGTH OF RECOMMENDATION: STRONG

Comment

In the ever growing situation in which children have been placed on a GFD before confirming the diagnosis of CD, the assessment of HLA status can be of great assistance in deciding whether to perform a gluten challenge.[1,172]

SUMMARY

Serious concerns have been raised about the lack of effective long-term management programs to optimize the treatment of CD and the diagnosis and management of associated disease states.[7,8] Recent reports indicate that optimal follow-up care is not being provided.[7,8] In an attempt

to provide thoughtful and effective best practices for managing CD and associated disorders in children, a group of experts in the field were convened to critically review and discuss the available data to provide an evidenced-based approach to optimal care. When the quality of evidence was not sufficient, expert opinion was used.

The thorough review of the data in these 6 categories of care demonstrated that the quality of the data available is insufficient to provide unequivocal best practices in most areas. However, using the available data and the clinical experience of the panel, we have attempted to provide a practical framework and useful approach to the management of children with CD. The potential usefulness of these best practices is underscored by the fact that consensus, measured by anonymous voting, was reached by the panel for 24 of the 25 questions and that unanimous agreement was found for 15 of the questions. These recommendations, which were developed by our expert panel, do not necessarily reflect the policy of the American Academy of Pediatrics. We hope that these best practices may be useful to the pediatric gastroenterology and larger general pediatric communities.

A condensed summary of the best practices is found in Table 1.

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ABBREVIATIONS

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CBC: complete blood cell
CD: celiac disease
ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition
GFD: gluten-free diet
Ig: immunoglobulin
MNT: medical nutritional therapy
NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
T1DM: type 1 diabetes mellitus
tTG: tissue transglutaminase

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