Complete Summary

GUIDELINE TITLE

AGA Institute medical position statement on the diagnosis and management of celiac disease.

BIBLIOGRAPHIC SOURCE(S)

AGA Institute. AGA Institute medical position statement on the diagnosis and management of celiac disease. Gastroenterology 2006 Dec;131(6):1977-80. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Celiac disease

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine
Nutrition
Pathology

INTENDED USERS

Dietitians
Physicians

GUIDELINE OBJECTIVE(S)

- To provide recommendations to gastroenterologists and primary care practitioners on the diagnosis and management of celiac disease
- To suggest preferred approaches to specific medical issues or problems

TARGET POPULATION

Adult patients with suspected celiac disease

Note: The major focus is on adults, although some data from studies on children are also included for completeness.

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Serologic tests, particularly:
    - Immunoglobulin A (IgA) antiendomysial antibody (EMA)
    - IgA tissue transglutaminase antibodies (tTGA)
2. Intestinal biopsy
3. HLA-DQ2 and DG8 testing to exclude the diagnosis of celiac disease

Treatment/Management

1. Lifelong gluten-free diet (GFD)
2. Education about celiac disease and gluten-containing products
3. Consultation with dietitians and referral to a support group
4. Follow up
    - Monitoring adherence to GFD
    - Treatment of nutritional deficiencies (e.g., iron, folate, vitamin B_{12})
    - Assessment of bone mineral density
5. Immunosuppression in cases of refractory sprue

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic tests
- Effectiveness of gluten-free diet
- Risk of mortality and lymphoma

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search is current and includes outcomes not covered in a prior report. Citations identified by the search strategy underwent multilevel screening by 2 independent reviewers using predetermined forms detailing the inclusion and exclusion criteria.

The reference list for this review is extensive and has been shortened to meet length requirements. The guideline developers reference sections of the Agency for Healthcare Research and Quality report, and the updated list in its entirety is available online (http://www.ahrq.gov/downloads/pub/evidence/pdf/celiac/celiac.pdf and (http://www.ahrq.gov/clinic).

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Included articles were assessed for quality using a design-specific instrument. The obtained data were extracted and statistically pooled if clinically and statistically appropriate. If statistical pooling was not possible, a qualitative description of the studies is presented.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible the use of experts' consensus may occur.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Medical Position Statements developed under the aegis of the American Gastroenterological Association (AGA) Institute and its Clinical Practice and Economics Committee (CPEC) were approved by the AGA Institute Governing Board on September 25, 2006.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Epidemiology

It is the position of the American Gastroenterological Association (AGA) Institute that testing for celiac disease should be considered in symptomatic individuals who are at particularly high risk. These include those with unexplained iron deficiency anemia (IDA), a premature onset of osteoporosis, Down syndrome, unexplained elevations in liver transaminase levels, primary biliary cirrhosis, and autoimmune hepatitis. Situations in which testing for celiac disease should be selectively considered during the medical evaluation, especially if symptoms that could be the result of celiac disease are present, include type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome, unexplained recurrent fetal loss, unexplained delayed puberty, selective immunoglobulin (Ig) A deficiency, irritable bowel syndrome, Turner's syndrome, peripheral neuropathy, cerebellar

ataxia, and recurrent migraine, as well as children with short stature and first- and second-degree relatives of patients with celiac disease.

Refer to the original guideline document for detailed information on epidemiology.

Diagnosis

Diagnostic tests should be performed before the initiation of gluten restriction begins. Positive serologic test results may resolve and histologic findings may improve with the removal of gluten from the diet. The initial detection of possible celiac disease is probably best obtained by the use of a simple and accurate serologic test: the IgA tissue transglutaminase antibodies (tTGA).

Serologic Testing

The diagnostic approach to detecting celiac disease has undergone important changes in recent years. Serologic tests, particularly the IgA antiendomysial antibody (EMA) and the IgA tTGA, have become a relatively sensitive and specific way to initially detect celiac disease. The IgA tTGA is both sensitive and specific for celiac disease and supplants the use of gliadin antibody testing as the preferred means of serologic detection. Overall, many studies demonstrate a specificity of IgA tTGA greater than 95% and a sensitivity in the range of 90% to 96%. The EMA detected by an indirect immunofluorescence assay is more time consuming and operator dependent than the tTGA. It has a slightly lower and variable sensitivity but an excellent specificity (99.6%). IgA antigliadin antibody by enzyme-linked immunosorbent assay predates the previously described serologic tests, but its diagnostic performance compared with IgA tTGA and IgA EMA is not attractive.

The prevalence of IgA deficiency in celiac disease is sufficiently low, such that the routine measurement of serum IgA levels along with IgA EMA or tTGA is not warranted as a first step toward diagnosis unless IgA deficiency is strongly suspected. In cases of selective IgA deficiency, either the IgG EMA and/or IgG tTGA have excellent sensitivity and specificity, although those IgG-based tests are markedly less sensitive and specific than the IgA-based tests in those with normal levels of IgA. Measurement of the serum IgA level is an appropriate next step in individuals with a negative IgA EMA or IgA tTGA in whom celiac disease is still suspected. If celiac disease is strongly suspected despite negative serologic test results, one can test for the presence of the disease-associated HLA alleles and, if present, proceed to small intestinal mucosal biopsy. Alternatively, it is reasonable to proceed directly to upper intestinal endoscopy and small bowel biopsy if the signs and symptoms that suggested celiac disease would otherwise warrant those procedures.

Conclusion

In the primary care setting, the IgA tTGA is the most efficient single serologic test for the detection of celiac disease. Evidence indicates that the additional inclusion of IgG antigliadin antibody and IgA antigliadin antibody is not warranted.

Intestinal Biopsy

Positive serologic test results are supportive of the diagnosis of celiac disease. Distal duodenal biopsy specimens demonstrating characteristic histologic changes in the small intestinal mucosa, which includes a spectrum of change from total to partial villous atrophy, and crypt lengthening with an increase in lamina propria and intraepithelial lymphocytes, remain the gold standard for establishing the diagnosis of celiac disease. An increase in intraepithelial lymphocytes without other mucosal changes may represent latent celiac disease or a part of the spectrum of gluten-sensitive enteropathy but should not be considered diagnostic of celiac disease. It is important to take multiple (ideally 6) biopsy specimens and best to obtain these from the second part of the duodenum or beyond because mucosal changes can be patchy or Brunner's glands or peptic changes may hamper histopathologic examination if biopsy specimens are obtained from the more proximal duodenum. Gluten challenge and a repeat biopsy are no longer required to establish the diagnosis of celiac disease in patients whose initial small intestinal biopsy specimen has the characteristic histologic appearance and in whom an objective response to a gluten-free diet (GFD) is obtained. However, a gluten challenge with a subsequent biopsy does have a role in establishing the diagnosis in select clinical settings (e.g., in those with a high suspicion for celiac disease and a negative serologic test result and who started on a GFD without biopsy confirmation of the disease). It is crucial that the dietary status of the patient at the time of biopsy be taken into account. Patients should undergo biopsy promptly after obtaining a positive serologic test result and should be instructed not to avoid gluten until after biopsy specimens are obtained. A gluten-reduced diet may reduce the severity of the lesion and impact pathologic interpretation. How long gluten must be reintroduced before biopsy specimens are taken can vary among individuals already on a GFD. A 4-week challenge with sufficient gluten to reproduce the symptoms is adequate in most. However, some patients may have very delayed responses, and it can take up to several years for relapse to occur.

Reaching a definitive diagnosis can be difficult in those with minimal histologic findings, in those with a negative serologic test result, or if the disease is patchy or an insufficient number or poorly oriented biopsy specimens were taken. There are other disease entities that can resemble celiac disease histologically. Most of these entities are either rare in the developed world, are suggested by the clinical history, or have distinguishing histologic findings on careful review of the biopsy samples.

Endoscopy provides a ready opportunity to examine the duodenal mucosa visually and to obtain a sufficient number of biopsy specimens. However, the visual examination of the small bowel mucosa is not entirely sensitive for identifying villous atrophy, although endoscopists should be aware of the visual appearance of villous atrophy. Endoscopists should not regard the absence of visual endoscopic features of celiac disease as sufficient to rule out the diagnosis.

Use of HLA-DQ2 and –DQ8 to Exclude the Diagnosis of Celiac Disease

Approximately 40% of the general population in the United States have either the HLA class II heterodimer HLA-DQ2 or HLA-DQ8, which reflects the presence of the DQ alleles DQA1*05 and DQB1*02 (DQ2) or DQA1*03 and DQB1*0302 (DQ8). However, almost all patients with celiac disease have either DQ2 (approximately 95% of patients with celiac disease) or DQ8 (approximately 5% of patients with

celiac disease). A very small number of patients with celiac disease have been noted to have only DQA1*O5 or DQB1*02, the latter usually being associated with HLA-DR7 heterozygosity or homozygosity.

Because virtually all patients with celiac disease have the celiac disease–associated alleles mentioned previously at the DQA1 and DQB1 loci, the absence of these alleles provides a negative predictive value for the disease of close to 100% (i.e., if individuals lack the relevant disease-associated alleles, celiac disease is virtually excluded). HLA testing for the relevant DQ alleles can be a useful adjunct in an exclusionary sense when the diagnosis based on other tests is not clear. When using HLA testing in the context of disease susceptibility in families, one must have the resources available to provide genetic counseling.

Treatment

Treatment of celiac disease requires a strict, lifelong adherence to a GFD. This is also the case for patients with dermatitis herpetiformis. Clinicians need to ensure that patients have adequate education, motivation, and support to achieve this diet. Consultation with an experienced dietician, referral to a support group, and clinical follow-ups for compliance are recommended. Treatment of nutritional deficiency states (e.g., iron, folate, vitamin B_{12}) is essential, and a determination of bone mineral density to assess for osteoporosis is recommended.

Promoting Adherence to a GFD

Changes in dietary habits are difficult to maintain, and there are many barriers to continued compliance with a GFD. Improved knowledge of celiac disease, the GFD, gluten-containing food products, and outcomes of untreated celiac disease would likely improve compliance. Membership in a local celiac society provides patients with celiac disease with improved knowledge regarding their disease, the intricacies of the GFD, and also emotional and social support opportunities.

Follow-up is necessary to confirm the diagnosis by an objective response to a GFD and to detect and manage noncompliance. Patients with celiac disease should be evaluated at regular intervals by a health care team including a physician and a dietician. These visits can be used to assess, by history, a patient's compliance with a GFD and to reinforce the importance of such compliance. Beyond this, there are no clear guidelines as to the optimal means to monitor adherence to a GFD. In general, monitoring adherence to a GFD with serologies (i.e., tTGA or EMA) is sensitive for major but not for minor transient dietary indiscretions. In children, histologic improvement on a GFD appears to occur quickly, while in adults the small intestinal mucosa heals more slowly and less completely. Monitoring adherence by clinic visits and serologic testing appears to be a reasonable approach in children. In adults, this approach is also reasonable with the understanding that a negative serologic test result does not necessarily mean improvement beyond severe subtotal or total villous atrophy.

Expected Benefits of a GFD

Compliance with a GFD is likely protective against the development of non-Hodgkin's lymphoma in celiac disease and dermatitis herpetiformis. There is compelling evidence that treatment of symptomatic celiac disease results in

substantial improvement in nutritional parameters. The treatment of celiac disease with a GFD can result in improvements in bone mineral density, with the greatest improvements appearing in the first years of the GFD. Treatment with a GFD for at least 12 months can result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional and biochemical status including iron absorption. Patients adhering to a strict GFD usually consume fewer calories than noncompliers but show a trend toward greater improvements in measurements of body composition. The benefits of a GFD on short-term outcomes in diabetic patients with celiac disease are inconclusive. They suggest that nutritional parameters can improve but no convincing change in diabetic control has been demonstrated, although insulin requirements often increase.

Nonresponsive Celiac Disease

Patients with known celiac disease can continue to have or can redevelop symptoms despite being on a GFD. These symptoms may be due to incompletely healed celiac disease, an associated condition, a complication, or a second unrelated diagnosis. Persistent or intermittent symptoms due to known or inadvertent ingestion of gluten are commonly reported. If gluten ingestion is not suggested by direct review of the dietary history or positive serologic test result, then a careful search should be undertaken for other entities such as microscopic colitis, pancreatic exocrine insufficiency, bacterial overgrowth, and disaccharidase deficiency. Intestinal lymphoma, small bowel strictures, or true refractory sprue should be considered in the absence of these and in persistently febrile or very ill patients.

Refractory sprue is a rare entity with a high morbidity and mortality and is defined as continued or recurrent malabsorption and diarrhea associated with persisting moderate or severe villous atrophy despite adherence to a strict GFD. The evaluation of these patients should include a careful evaluation for coexistent T-cell lymphomas. The optimal therapy for celiac sprue is not known but frequently includes immunosuppression.

In summary, serologic testing for tTG and EMA antibodies can detect and histologic examination of endoscopically directed duodenal biopsy specimens can confirm the diagnosis of celiac disease.

Minimizing the delay in diagnosis appears to have a variety of health benefits for patients with celiac disease. Educating patients and parents, utilizing a multidisciplinary approach to patient management, and follow-up would also be expected to improve compliance and patient outcomes. A strict lifelong GFD is still the mainstay therapy, although alternative therapies are contemplated.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefits

Appropriate diagnosis and management of celiac disease

Specific Benefits

- Compliance with a gluten-free diet (GFD) is likely protective against the development of non-Hodgkin's lymphoma in celiac disease and dermatitis herpetiformis. There is compelling evidence that treatment of symptomatic celiac disease results in substantial improvement in nutritional parameters. The treatment of celiac disease with a GFD can result in improvements in bone mineral density, with the greatest improvements appearing in the first years of the GFD. Treatment with a GFD for at least 12 months can result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional and biochemical status including iron absorption. Patients adhering to a strict GFD usually consume fewer calories than noncompliers but show a trend toward greater improvements in measurements of body composition.
- Making the diagnosis at a young age, educating patients and parents, and utilizing a multidisciplinary approach to patient management and follow-up would be expected to improve compliance and patient outcomes.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The Medical Position Statements developed under the aegis of the American Gastroenterological Association (AGA) Institute and its Clinical Practice and Economics Committee were approved by the AGA Institute Governing Board. The data used to formulate these recommendations are derived from the data available at the time of their creation and may be supplemented and updated as new information is assimilated. These recommendations are intended for adult patients, with the intent of suggesting preferred approaches to specific medical issues or problems. They are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible the use of experts' consensus may occur. The recommendations are intended to apply to healthcare providers of all specialties. It is important to stress that these recommendations should not be construed as a standard of care. The AGA

Institute stresses that the final decision regarding the care of the patient should be made by the physician with a focus on all aspects of the patient's current medical situation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

AGA Institute. AGA Institute medical position statement on the diagnosis and management of celiac disease. Gastroenterology 2006 Dec;131(6):1977-80. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Dec

GUIDELINE DEVELOPER(S)

American Gastroenterological Association Institute - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association Institute

GUIDELINE COMMITTEE

American Gastroenterological Association Institute Clinical Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Martin F. Kagnoff

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Martin F. Kagnoff is supported by National Institutes of Health grants DK35108 and DK58960 and a grant from the William K. Warren Foundation.

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology 2006 July;131(6);1981-2002.

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 6, 2007. The information was verified by the guideline developer on April 10, 2007.

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