Title:

AGA Institute Guideline on the Laboratory Evaluation of Functional Diarrhea and Diarrhea Predominant Irritable Bowel Syndrome in adults (IBS-D)

Expiration: These Guidelines should expire in five years.

Authors

Walter Smalley MD MPH [a]

Corinna Falck-Ytter MD [b]

Alonso Carrasco-Labra DDS [c]

Sachin Wani MD [d]

Yngve Falck-Ytter MD, AGAF [b]

a – Vanderbilt University School of Medicine (Medicine -Gastroenterology) and VA- Tennessee Valley Health Care System, Nashville, TN

b – Case Western Reserve University (Medicine – Gastroenterology) and VA Northeast Ohio Health System, Cleveland, OH

c – Universidad de Chile (Dentistry) and Center for Evidence-Based Dentistry for the American Dental Association (ADA)

d – University of Colorado Anschutz Medical Campus, Aurora, CO

Address for Correspondence

Chair, Clinical Guidelines Committee,

American Gastroenterological Association

National Office, 4930 Del Ray Avenue,

Bethesda, Maryland 20814

Telephone: (301) 941-2618.

Terms and abbreviations:

IBS-D	Diarrhea-predominant irritable bowel syndrome
IBD	Inflammatory bowel disease
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein

Introduction

The focus of this guideline is to aid clinicians in choosing appropriate laboratory tests to exclude other diagnoses in the setting of suspected functional diarrhea or diarrhea-predominant irritable bowel syndrome (IBS-D). These guidelines apply to the evaluation of the immunocompetent patient with "watery" diarrhea of at least six weeks duration. This would exclude those patients with bloody diarrhea; diarrhea with signs of fat malabsorption; presentations with alarm features such as weight loss, anemia, and hypoalbuminemia; those patients with a family history of inflammatory bowel disease (IBD), colon cancer, or celiac disease; and those with a travel history to regions with recognized specific diarrhea-related pathogens.

This guideline was developed using a process outlined elsewhere. [1] Briefly, the American Gastroenterological Association Institute (AGA) process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [2] and best practices as outlined by the Institute of Medicine. [3] GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it. [4] Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met face-to-face on September 08, 2017 to discuss the quality of evidence (Tables 1 and 2) and consider other factors relevant for the risk-benefit assessment of the recommendations. The guideline panel included two members of the AGA Clinical Practice Guidelines Committee (WS, SW, YFY) a GRADE methodologist (AC-L) and a primary care physician (CFY). The members of the guidelines panel subsequently formulated the recommendations by consensus. Although quality of evidence was a key factor in determining

the strength of each recommendation (Table 2), the panel also considered the balance between

the benefit and harm of interventions, patients' values and preferences, and resource utilization.

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Table 1. GRADE Definitions on Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate The true effect is likely to be substantially different from the estimate of effect

Table 2. GRADE Definitions on Strength of Recommendation

	For the patient	For the clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not	Most individuals should receive the recommended course of action Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not	Different choices will be appropriate for different patients Decision aids may well be useful in helping individuals making decisions consistent with their values and preferences Clinicians should expect to spend more time with patients when working toward a decision

Table 3

Recommendation 1: In patients presenting with chronic diarrhea, the AGA suggests the use of stool tests, either fecal calprotectin or fecal lactoferrin to screen for inflammatory bowel disease.	*Conditional recommendation*	*Low quality evidence.*
Recommendation 2: In patients presenting with chronic diarrhea, the AGA suggests against the use of blood tests ESR or CRP to screen for inflammatory bowel disease.	*Conditional recommendation*	*Low quality evidence.*
Recommendation 3: In patients presenting with chronic diarrhea, the AGA recommends stool testing for giardia.	*Strong recommendation*	*High quality evidence.*
Recommendation 4: In patients presenting with chronic diarrhea with no travel history to or recent immigration from high risk areas, the AGA suggests against testing stools for ova and parasites (other than giardia.)	*Conditional recommendation*	*Low quality evidence*
Recommendation 5: In patients presenting with chronic diarrhea, the AGA recommends testing for celiac disease with IgA tTG and a second test to detect celiac disease in the setting of IgA deficiency	*Strong recommendation*	*Moderate quality evidence.*
Recommendation 6: In patients presenting with chronic diarrhea, the AGA suggests testing for bile acid diarrhea.	*Conditional recommendation*	*Low quality evidence.*
Recommendation 7: In patients presenting with chronic diarrhea, the AGA makes no recommendation for the use of currently available serologic tests for diagnosis of IBS	*No Recommendation*	*Knowledge gap*

Recommendation 1: In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for inflammatory bowel disease, *Conditional recommendation; low quality evidence.*

Comment: A threshold value of 50 ug/g for fecal calprotectin is recommended to optimize sensitivity for inflammatory bowel disease. Threshold values in the range of 4.0-7.25 ug/g for fecal lactoferrin are recommended to optimize sensitivity.

Calprotectin and fecal lactoferrin have been proposed as markers for inflammatory conditions such as IBD. There are several studies using fecal calprotectin with different threshold values to identify persons with IBD. Based on a review of the available data it appears that using fecal calprotectin with a threshold of 50ug/g yields the optimal performance. Among studies using this threshold the pooled sensitivity for IBD was 0.81 (95% CI: 0.75 to 0.86) and the pooled specificity was 0.87 (95% CI: 0.78 to 0.92). Risk of bias and statistical imprecision influenced the determination that evidence supporting the use of fecal calprotectin was of low quality. Use of a higher threshold value (100-164 ug/g) is associated with a markedly decreased sensitivity without a marked increase in specificity.

In a similar fashion fecal lactoferrin has been studied as a marker for IBD. Utilizing data from the available studies using a threshold value from 4.0-7.25ug/g the pooled sensitivity for IBD was 0.79 (95% CI: 0.73 to 0.84) and the pooled specificity was 0.93 (95% CI: 0.63 to 0.99). Risk of bias, significant heterogeneity and statistical imprecision influenced the determination that evidence supporting the use of fecal lactoferrin was of low quality.

The low quality of evidence supporting the use of these tests is compounded by the small likelihood that a positive test would initiate further confirmatory evaluation leading to an earlier diagnosis of IBD compared to the 10% likelihood that persons without IBD might be needlessly exposed to further confirmatory testing.

Recommendation 2: In patients presenting with chronic diarrhea, the AGA suggests against the use of ESR or CRP to screen for inflammatory bowel disease. *Conditional recommendation: low evidence.*

Both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been tested in populations with diarrhea to identify patient with IBD. In studies using a value of 5-6 mg/L as a threshold for CRP level the pooled sensitivity was 0.73 (95% CI: 0.64 to 0.80) and the pooled specificity was 0.78 (95% CI: 0.58 to 0.91). Studies of similar design utilizing threshold values of 10-15 mm/hr for ESR resulted in lower estimates of diagnostic accuracy for IBD.

While there are few settings where ESR should be considered as an appropriate screening test for IBD there are some settings where the use of CRP might be a rational option. For example, if testing for fecal lactoferrin or calprotectin are either not available or not covered by insurance the use of CRP might be considered to be a reasonable option to screen for IBD.

Recommendation 3: In patients presenting with chronic diarrhea, the AGA recommends testing for giardia.

Strong recommendation: high quality evidence.

Comments: Use of a giardia antigen test or PCR for giardia test is recommended

Throughout the United States, giardia is a common cause of watery diarrhea which can be readily treated. Modern diagnostic tests for giardia have excellent performance characteristics with many studies demonstrating sensitivity and specificity of over 95%. The best available tests utilize either detection of giardia antigens or polymerase chain reaction (PCR) for the giardia small ribosomal unit RNA (SSU rRNA). Because treatments are straightforward there is little risk in utilizing these tests in evaluation of chronic watery diarrhea.

Recommendation 4: In patients presenting with chronic diarrhea with no travel history to or recent immigration from high risk areas, the AGA suggests against testing for ova and parasites (other than giardia). *Conditional recommendation: low quality evidence.*

In the absence of travel or immigration from high risk areas the practice of routinely testing the stool for ova and parasites is highly unlikely to identify important causes of chronic watery diarrhea. Guidance on testing and treating diarrhea among those who have been in a high-risk area can come from several sources. [5]

Recommendation 5: In patients presenting with chronic diarrhea, the AGA recommends testing for celiac disease with IgA tTG and a second test to detect celiac disease in the setting of IgA deficiency. *Strong recommendation: moderate quality evidence.*

Comments: Testing options for IgA deficient subjects include IgGtTG, and IgG or IgA DGP

Celiac disease is an important cause of chronic diarrhea and other manifestations. Among patients with chronic diarrhea who do not have IgA deficiency use of serum IgA tissue transglutaminase (tTG) is a highly efficient strategy for determining the presence of celiac disease. In these patients the sensitivities of serum IgA tTG using thresholds in the 7 – 15 AU/ml range for are typically greater than 90% and the specificities are typically slightly higher. A positive test would warrant confirmation by duodenal biopsy. [6]

Because IgA deficiency can lead to a false negative result there are two strategies to use among those tested who have a negative IgA tTG. A quantitative IgA level if normal confirms the accuracy of a negative IgG tTG. The use of either the IgG tTG or a test for IgG deaminated gliadin peptides (IgG DGP) might be considered for use in IgA deficient patients or combined as an initial strategy combined with IgA tTG when IgA levels are not available.

In adults, small bowel biopsy should be used to confirm a serological diagnosis of celiac disease prior to committing a patient to a strict gluten free diet. [6]

Recommendation 6: In patients presenting with chronic diarrhea, the AGA suggests testing for bile acid diarrhea. *Conditional recommendation: low quality evidence.*

Comments: In settings with limited availability of commercial assays, an empiric trial of a bile acid binder could be considered.

Bile acid diarrhea may be due to excess production or decreased absorption of bile acids which then reach the colon and can cause watery diarrhea. There are several tests that have been proposed to identify those persons who have bile acid diarrhea. [5]Selenium HomotauroCholic Acid Test (SeHCAT), is a nuclear medicine test used to identify those whose diarrhea is due to bile acid malabsorption and has moderate diagnostic efficiency. This test is used in Europe but is not available in North America. In the US, other tests for bile acid diarrhea are measurement of total bile acids in a 48 hour stool collection (which would document increased fecal bile acids) and serum fibroblast growth factor 19 (FGF19) which measures defective feedback of bile acid synthesis. A test thatis not yet available is measurement of serum levels of the marker 7α-hydroxy-4-cholesten-3-one (C4) — a measure of bile acid synthesis. Because these tests are not widely available, it is reasonable in patients in whom bile acid diarrhea is considered to use an empiric trial of bile acid binders with clinical response suggesting excess bile acids as cause for the diarrhea.

Recommendation 7. In patients presenting with chronic diarrhea, the AGA makes no recommendation for the use of currently available serologic tests for diagnosis of IBS.

No recommendation; knowledge gap.

Irritable bowel syndrome with diarrhea (IBS-D) is a major cause of chronic watery diarrhea. Several tests have been proposed to identify those with IBS-D and who might thus benefit from

IBS-D specific therapy. Specifically, it has been postulated that a strategy of measuring antibodies to cytolethal distending toxin B (CdtB) and the gut mucosal protein, vinculin, might be used to identify persons who have post infectious IBS-D.

The available data is sparse but suggest that the contemporary tests lack the diagnostic accuracy needed for routine use. The specificity in the two studies available for the technical review was in the 90% range meaning a positive test would indicate a high likelihood of IBS-D. However, the low sensitivity (20-40%) would not be sufficient to employ these tests in routine use. More data will be helpful in determining the proper roles of these and similar tests.

Summary

These practice guideline recommendations for the evaluation of functional diarrhea and IBS-D with the intent of excluding other diagnoses in adults were developed using the GRADE framework and in adherence with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines. These guidelines are intended to reduce practice variation and promote high-quality and high-value care for this patient population. Current evidence supports the use of fecal calprotectin or fecal lactoferrin and stool testing for giardia in patients presenting with chronic diarrhea. The panel suggests against the use of blood tests ESR or CRP to screen for IBD. Our evidence profiles also strongly recommend testing for celiac disease with IgA tTG and a second test to detect celiac disease in the setting of IgA deficiency. In addition, testing for bile acid diarrhea is suggested. The AGA makes no recommendation for the use of currently available serologic tests for the diagnosis of IBS and should be the focus of future research. A clinical decision support tool is included to guide the evaluation of patients with chronic watery diarrhea (>6 weeks) (Figure).

References

1. American Gastroenterological Association. AGA Institute clinical practice guideline development process. Available from: http://www.gastro.org/guidelines-policies. Accessed: July 19, 2016.

2. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.

3. Institute of Medicine. Clinical practice guidelines we can trust. Washington, DC: Institute of Medicine, 2011.

4. Carrasco-Labra A, Lytvyn, L, Falck-Ytter Y, Surawicz CM, Chey W. AGA Institute Guideline on the Laboratory Evaluation of functional diarrhea and Diarrhea Predominant Irritable Bowel Disease in adults (IBS-D). Gastroenterology (In press)

5. https://wwwnc.cdc.gov/travel/yellowbook/2018/the-pre-travel-consultation/travelers-diarrhea#4955
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6. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology* 2006;**131**:1981–2002.

7. Riddle MS, Connor BA, Beeching NJ et al, Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. Adva J Travel Med. 2017 Apr 1;24(suppl_1):S57-S74.