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What blood tests help diagnose celiac disease?

EVIDENCE-BASED ANSWER

Histological confirmation of infiltrative lesions via small bowel biopsy is the gold standard for diagnosing celiac disease. Four serum antibody assays may serve as a first-step diagnostic tool to identify biopsy candidates: immunoglobulin A tissue transglutaminase (IgA tTG), IgA endomysial antibody (IgA EMA), IgA antigliadin antibody (IgA AGA), and IgG antigliadin antibody (IgG AGA). IgA tTG and IgA EMA offer the best diagnostic accuracy. Patients with selective IgA deficiency may have falsely negative IgA assays (strength of recommendation [SOR]: **B**, based on a systematic review, multiple small cross-sectional studies, and expert opinion).

CLINICAL COMMENTARY

The most reliable testing option is also the most cost-effective

When faced with a cryptic array of available serologic tests for celiac disease, and often pressed for time to look up which one is best, we are often quite tempted to simply check "Celiac Panel" on the lab order sheet and just order them all. However, the authors present us with an evidence-based rationale for limiting our lab testing to just one of the available serologic tests.

What a delight to find that the most reliable testing option is also the most cost-effective. At our university hospital, the billable cost of each serologic marker for celiac disease is approximately $50, and the entire panel—which includes IgA tTG, IgG tTG, IgA EMA, and IgA/G AGA—is $250. Rather than ordering the redundant panel (why include anti-AGA at all?), it is far better to start with IgA tTG or IgA EMA, and follow-up with IgG levels if necessary.

When ordering these tests, it is worth noting that some physicians recommend patients be on a gluten-containing diet for 2 to 4 weeks before serologic testing, to minimize the possibility of insufficient antibody titers.

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Evidence summary

Celiac disease (also called celiac sprue, nontropical sprue, or gluten-sensitive enteropathy) is an autoimmune disorder classified by intestinal inflammation and malabsorption in response to dietary gluten—a storage protein component of wheat gliadins. Celiac disease patients—0.5% to 1.0% of the US population[1]—are often sensitive to other closely related grain proteins found in oats, barley, and rye.

Celiac disease's classic histological finding is an infiltrative small intestine lesion characterized by villous flattening, crypt hyperplasia, and lymphocyte accumulation in the lamina propria.[2] The American Gastroenterological Association's (AGA) diagnostic criteria include

TABLE

Diagnostic accuracy of serologic tests for celiac disease patients with normal IgA levels

SEROLOGIC TEST	SN	SP	LR+	LR–
IgA tTG	95%–98% .95	94%–95% .94	16	0.05
IgA EMA	>90% .91	>95% .96	23	0.09
IgA AGA	80%–90% .85	85%–95% .90	8.5	0.17
IgG tTG	40%	95%	8	0.63
IgG EMA	40%	95%	8	0.63
IgG AGA	80%	80%	4	0.25

Sn, sensitivity; Sp, specificity; LR+, likelihood ratio of a positive test result; LR–, likelihood ratio of a negative test result.

FAST TRACK

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confirmation of this abnormal mucosa and unequivocal improvement on repeat biopsy following a gluten-free diet.[3] However, either clinical improvement or biopsy of dermatitis herpetiformis skin lesions (common occurrences in celiac disease) are often considered adequate for diagnosis without repeat intestinal biopsies.

Its reversible nature makes prompt diagnosis of celiac disease important. Three antibodies commonly appear in celiac disease patients: antibodies to tTG, antiendomysial antibodies, and antigliadin antibodies.[4–6] AGA binds dietary gluten and EMA binds the enzyme tTG, which is found in connective tissue surrounding the smooth muscle cells in the intestinal wall.

The gluten-autoantibody interaction in the small intestinal lumen has IgA as its major component; IgG represents a longer-term immune response. Serum assays of the IgA and IgG forms of AGA and tTG are enzyme-linked immunosorbent assays (ELISA); EMA is measured by indirect immunofluorescence.[5,6]

In 2 studies of the diagnostic accuracy of IgA tTG, 95% to 98% of biopsy-proven celiac disease patients had positive tests, while only 5% to 6% of controls were positive.[4,5] In a systematic review, there was no statistically significant difference between IgA EMA and IgA tTG—both had sensitivities greater than 90% and specificities greater than 95%.[7] IgA AGA did not perform as well (sensitivity 80%–90%, specificity 85%–95%). The **TABLE** summarizes the diagnostic accuracy of the various tests.

Two to 3% of patients with celiac disease have selective IgA deficiency.[2] These patients often have falsely negative serum IgA assays (for EMA, tTG, and AGA), so IgG is a diagnostic alternative.[8,9] In a cross-sectional study, 100% of 20 untreated celiac disease patients with IgA deficiency had positive IgG tests for tTG, AGA, and EMA despite negative IgA tests for the same antibodies.[9] Eleven patients with celiac disease and no IgA deficiency all had positive tTG, AGA, and EMA tests, whether testing for the IgA or IgG forms.

Despite the performance of the IgG assays in this study, only IgG AGA has performed well in larger studies. In a systematic review, IgG tTG and IgG EMA had specificities of 95% but sensitivities of only 40%.[7] IgG AGA has similar sensitivity to the IgA assay—approximately 80%—with a slightly lower specificity of 80%. The discrepancy in the sensitivity of IgG tTG and IgG EMA between studies occurs because of differing antibody levels with variations in dietary gluten.[9,10] Therefore, testing for IgG tTG and IgG EMA should be reserved for patients with selective IgA deficiency.

Another notable limitation of using serologic markers to diagnose celiac disease is poor sensitivity in patients with mild disease.[11] Diagnosis in these patients may be particularly challenging. Patients with karyotype abnormalities and those with diabetes are also more likely to have false-negative serologic tests.[2]

Recommendations from others

The AGA recommends using serologic markers to screen patients with either nonspecific symptoms or medical conditions that increase the risk of celiac disease.[3]

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Patients whose clinical profile causes a high index of suspicion and negative IgA serologic markers should be tested for selective IgA deficiency. The AGA recommends relying on small intestinal biopsy for the final diagnosis.

Both the AGA and the North American Pediatric Society for Pediatric Gastroenterology state that tissue transglutaminase and endomysial antibodies are the most useful serologic tests. Antigliadin antibody tests are considered inferior in terms of diagnostic accuracy. ■

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FAST TRACK

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