New Guidelines for the Diagnosis of Paediatric Coeliac Disease

ESPGHAN

Coeliac Disease (CD) is underdiagnosed due to the varied presentation of clinical signs and symptoms. This advice guide provides new and updated summary guidance from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) on diagnosing children and adolescents with CD.

What's new in the 2020 guidelines?

- For initial testing, the combination of total IgA and IgA class antibodies against transglutaminase 2 (TGA-IgA) is recommended as this is most accurate and cost-effective. EMA-IgA or DGP-IgG need not be tested initially
- The no-biopsy approach for CD diagnosis is confirmed to be safe in children with high TGA-IgA values ≥10 times the upper limit of normal with accurate, appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample
- Children with positive TGA-IgA but lower titers (<10 times upper limit of normal) should undergo biopsies to decrease the risk of false positive diagnosis.
- HLA testing and presence of symptoms are not obligatory criteria for a serology based diagnosis without biopsies.

Consider testing for CD with the following symptoms, signs and conditions:

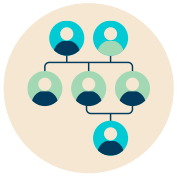
Gastrointestinal

- chronic or intermittent diarrhea/ constipation/abdominal pain
- distended abdomen
- recurrent nausea and/or vomiting

Extraintestinal symptoms

- weight loss/failure-to-thrive
- delayed puberty, amenorrhea
- irritability, chronic fatigue
- neuropathy
- arthritis/arthralgia
- chronic iron-deficiency anaemia
- decreased bone mineralization (osteopenia/osteoporosis), repetitive fractures
- recurrent aphthous stomatitis
- dermatitis herpetiformis–type rash
- dental enamel defects
- abnormal liver biochemistry

Specific conditions



- first-degree relatives with CD
- autoimmune conditions: T1DM, thyroid disease, liver disease
- Down syndrome
- Turner syndrome
- Williams-Beuren syndrome
- IgA deficiency

Abbreviations
IgA: Immunoglobulin type A
TGA-IgA: IgA against type-2 transglutaminase
EMA-IgA: IgA against endomysium
IgG: Immunoglobulin type G
DGP-IgG: IgG against Deamidated Gliadin Peptide
HLA: Human leukocyte antigen
ULN: Upper limit of normal

CD diagnosis can be accurately and safely established with or without duodenal biopsies if the following recommendations are observed:

Initial testing

Testing for total IgA and TGA-IgA should be used for children with suspected CD, after checking that the child is consuming normal quantities of gluten. In children with normal serum IgA values for age, TGA-IgA should be used, regardless of age. In children with low total IgA concentrations (low for age or <0.2 g/L above the age of 3 years), an IgG-based test (DGP, EMA or TGA) should be performed as a second step. If initial testing suggests coeliac disease, the child should be referred to a pediatric gastroenterologist/coeliac disease specialist.

Biopsy

A biopsy should be performed on children with positive TGA-IgA but lower titers (<10 times upper limit of normal). Patients should have ≥4 biopsies from the distal duodenum and ≥1 from the bulb, during a gluten-containing diet.

Evaluation of biopsies should be performed on optimally orientated biopsies. In cases of differing results between TGA-IgA-results and histopathology, re-cutting of biopsies and/or second opinion from an experienced pathologist should be requested.

No biopsy

A no-biopsy approach is appropriate for children with TGA-IgA values ≥10 times the upper limit of normal with appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample.

Asymptomatic children:
CD can eventually be diagnosed without duodenal biopsies in asymptomatic children, using the same criteria as in patients with symptoms.

TGA-IgA cut-off for diagnosis of CD with no biopsy
TGA- IgA serum concentration of ≥10xULN should be obligatory. Only antibody tests with calibrator curve-based calculation, and having the 10xULN value within their measurement range, should be used. All patients who are IgA deficient and who are positive for an IgG based serological test should be biopsied.

ESPGHAN recommends that the decision whether or not to perform duodenal biopsies in patients with high TGA-IgA should be made during a shared decision making process. This should be between the paediatric gastroenterologist/coeliac disease specialist, the parent(s)/ carer(s) and, if appropriate, the child.

HLA-testing

HLA-testing is not required in patients with positive TGA-IgA, if they qualify for CD diagnosis with biopsies or if they have high serum TGA-IgA ≥10xULN and EMA-IgA positivity. A negative test for HLA-DQ2 and/or -DQ8 indicates a very low risk of CD, while a positive result does not confirm the diagnosis. If no risk alleles are found, CD is unlikely.

Diagnosis

Coeliac Disease: A paediatric gastroenterologist/ coeliac disease specialist will determine the patient's treatment and follow-up.

Potential Coeliac Disease: Patients with positive TGA-IgA and EMA and no or minor small bowel histological changes are usually diagnosed as having 'potential' CD. However, such results may be due to low gluten intake prior to biopsies, sampling error or incorrect orientation of the biopsies for reading so these should be checked before diagnosing 'potential' vs 'true' CD. Once confirmed, potential CD requires clinical and laboratory surveillance (serology, further biopsies) to monitor possible evolution to villous atrophy and referral to a centre with expertise in CD for follow-up.

Full references for the advice within this guide can be found within the following paper, which this guide is based upon: Husby, Steffen, et al. "European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020." Journal of Pediatric Gastroenterology and Nutrition 70.1 (2020): 141-156.

A

CD serology positive for any reason[1]

Clinical suspicion of CD

CD risk group

Initial stage

Measure serum TGA-IgA and total IgA

TGA-IgA and total IgA

TGA-IgA negative → **See B**

TGA-IgA positive

Refer to paediatric GI (specialist in CD)

Specialist care

Review the results of the initial TGA-IgA antibodies[2]
Discuss diagnostic pathways with the family[3]

TGA-IgA

Discrepant serology → **See B**

TGA-IgA positive

Consider TGA-IgA concentration (xULN)

TGA-IgA <10xULN[4] → **Biopsy – See C**

TGA-IgA ≥10xULN

Test for EMA (separate blood sample)

EMA-IgA

EMA-IgA negative → **Biopsy – See C**

EMA-IgA positive

CD confirmed

B

TGA IgA negative

Initial stage

Review initial total IgA

Total IgA

Total IgA low[5] → Consult paediatric GI (specialist in CD)

Total IgA normal

Consider risk of false negative serology:
- low or short duration of gluten intake
- immunosuppressive medication
- extraintestinal manifestations[6]

Risk for false seronegativity

Risk for false seronegativity → Consult paediatric GI (specialist in CD)

No risk

No CD

Risk for false negative serology?

Consider HLA determination

HLA-DQ2/DQ8

HLA negative

CD unlikely, consider other diagnosis

HLA-DQ2/8 positive

Follow and retest on a normal gluten intake, consider biopsy

Risk possible

Total IgA low

Specialist care

Perform IgG test (TGA, EMA, DGP)

IgG TGA, EMA or DGP

IgG tests positive → **Biopsy – See C**

IgG tests negative

Consider risk of false negative serology

Risk of false seronegativity

No risk

No CD

C

Specialist care

Esophagogastroduodenoscopy

≥4 biopsies from distal duodenum and ≥1 from bulb

Histopathology[7]

Marsh 0-1 → Revise quality & orientation of the biopsy
Consult experienced pathologist

Revise histopathology

Marsh 2-3

CD confirmed

Marsh 0-1

Marsh 0 (normal) or Marsh 1 (only increased IEL) confirmed and positive serology. Options:
- Consider consultation with a CD expert center
- Consider false positive TGA result and test for EMA (if positive = potential CD)
- Consider additional tests (HLA, TGA deposits, etc.)
- Follow and retest on a normal gluten intake
- Consider relevance of symptoms

Footnotes

1. Other than TGA-IgA, including point-of-care tests and DGP. 2. Check the value also in relation to the cut-off and repeat the test if questionable or borderline. No need to retest if done with validated assay with calibration curve. Test with conventional TGA-IgA test if positive POCT and TGA has not been measured quantitatively. 3. Convey the message that the diagnosis of coeliac disease with or without biopsy confirms the need for a lifelong gluten-free diet and that re-evaluation after introduction of the diet would need prolonged re-exposure to gluten with a series of further investigations. 4. If TGA-IgA is only borderline positive confirm sufficient gluten intake and considerer re-testing of TGA-IgA and EMA. 5. Low for age or <0.2 g/L above the age of 3 years. 6. For example, dermatitis herpetiformis, in which serology is frequently negative. 7. The cut-off for normal numbers of IEL is >25 cells/100 enterocytes.