New Guidelines for the Diagnosis of Paediatric Coeliac Disease

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
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 $\geq 10 \times $ULN 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.

Disclaimer
ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment are at the discretion of physicians. This advice guide is produced and published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and authored by members of the society’s Coeliac Disease Working Group.

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.
**Initial stage**

- **CD serology positive for any reason**
  - Measure serum TGA-IgA and total IgA
  - TGA-IgA and total IgA
  - TGA-IgA positive
  - Refer to paediatric GI (specialist in CD)

  *Specialist care*

  **Discuss diagnostic pathways with the family**

  **Test for EMA (separate blood sample)**

  **EMA-IgA negative**

  **EMA-IgA positive**

  **CD confirmed**

**Footnotes**

- Other than TGA-IgA, including point-of-care tests and DGP.*
- 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.
- 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.
- If TGA-IgA is only borderline positive confirm sufficient gluten intake and consider re-testing of TGA-IgA and EMA.
- Low for age or <0.2 g/L above the age of 3 years.
- For example, dermatitis herpetiformis, in which serology is frequently negative.
- The cut-off for normal numbers of IEL is >25 cells/100 enterocytes.

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**B**

- **TGA IgA negative**
  - Review initial total IgA
  - Total IgA normal

  **Consider risk of false negative serology**

  - Low or short duration of gluten intake
  - Immunosuppressive medication
  - Extraintestinal manifestations

  **No risk**

  **No CD**

- **Risk for false seronegativity**

  **Total IgA low**

  **TGA IgA negative**

  **TGA IgA positive**

  **Conduct serology with IgG tests (TGA, EMA, DGP)**

  **IgG tests negative**

  **Risk possible**

  **HLA-DQ2/DQB positive**

  **HLA-DQ2/DQB negative**

  **IgG tests negative**

  **Risk of false seronegativity**

  **No risk**

  **No CD**

  **Risk for false negative serology?**

  **Consider HLA determination**

  **CD unlikely, consider other diagnosis**

  **Follow and retest on a normal gluten intake, consider biopsy**

  **Biopsy – See C**

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**C**

- **Esophagogastroduodenoscopy**
  - 4x biopsies from distal duodenum and 2x from bulb

  **Histopathology**

  - 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

  **Marsh 0-1**

  **Marsh 2-3**

  **CD confirmed**

  **Revise quality & orientation of the biopsy**

  **Consult experienced pathologist**

  **Revise histopathology**

  **Marsh 0-1**

  **Marsh 0 (normal) or Marsh 1 (only increased IEL) confirmed and positive serology. Options**

  1. Other than TGA-IgA, including point-of-care tests and DGP. 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. 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. If TGA-IgA is only borderline positive confirm sufficient gluten intake and consider re-testing of TGA-IgA and EMA. Low for age or <0.2 g/L above the age of 3 years. For example, dermatitis herpetiformis, in which serology is frequently negative. The cut-off for normal numbers of IEL is >25 cells/100 enterocytes.