European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020


ABSTRACT

Objectives: The ESPGHAN 2012 coeliac disease (CD) diagnostic guidelines aimed to guide physicians in accurately diagnosing CD and permit omission of duodenal biopsies in selected cases. Here, an updated and expanded evidence-based guideline is presented.

Methods: Literature databases and other sources of information were searched for studies that could inform on 10 formulated questions on symptoms, serology, HLA genetics, and histopathology. Eligible articles were assessed using QUADAS2. GRADE provided a basis for statements and recommendations.

Results: Various symptoms are suggested for case finding, with limited contribution to diagnostic accuracy. If CD is suspected, measurement of total serum IgA and IgA-antibodies against transglutaminase 2 (TGA-IgA) is superior to other combinations. We recommend against deamidated gliadin peptide antibodies (DGP-IgG/IgA) for initial testing. Only if total IgA is low/undetectable, an IgG-based test is indicated. Patients with positive results should be referred to a paediatric gastroenterologist/specialist. If TGA-IgA is ≥10 times the upper limit of normal (10×ULN) and the family agrees, the no-biopsy diagnosis may be applied, provided endomysial antibodies (EMA-IgA) will test positive in a second blood sample. HLA-DQ2/DQ8 determination and symptoms are not obligatory criteria. In children with positive TGA-IgA <10×ULN at least 4 biopsies from the distal duodenum and at least 1 from the bulb should be taken. Discordant results between TGA-IgA and histopathology may require re-evaluation of biopsies. Patients with no/mild histological changes (Marsh 0/1) but confirmed autoimmunity (TGA-IgA/EMA-IgA+) should be followed closely.

Conclusions: CD diagnosis can be accurately established with or without duodenal biopsies if given recommendations are followed.

Key Words: children and adolescents, coeliac disease, diagnostic tests, meta-analysis

What Is Known

- Coeliac disease is underdiagnosed because of the heterogeneous presentation of clinical signs and symptoms.
- To diagnose coeliac disease, different approaches are applied (history, clinical examination, serology, HLA testing, histopathology), but neither 1 of them has been considered sufficient alone to make a reliable diagnosis.
- For the first time, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines allowed serology-based diagnosis, omitting the necessity of histopathology in selected cases, but the evidence came mainly from retrospective studies.

What Is New

- For initial testing, the combination of total IgA and IgA class antibodies against transglutaminase 2 is more accurate than other test combinations.
- The no-biopsy approach for coeliac disease diagnosis is safe in children with high serum IgA class antibody concentration against transglutaminase 2 values (≥10 times the upper limit of normal) with appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample.
- Children with positive IgA class antibodies against transglutaminase 2 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.
The recognition of the broad clinical spectrum of coeliac disease (CD) has evolved during the last decades. It became evident that CD is a common disease occurring at all ages and with a variety of signs and symptoms. In 2012, the CD working group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) revised their diagnostic guidelines for CD (1). One main message of these guidelines was that the diagnosis of CD can be made without biopsies in a subgroup of paediatric patients because coeliac enteropathy (with Marsh 2 or 3 changes) was nearly invariably present in patients with very high coeliac auto-antibody levels in serum. For this so-called no-biopsy approach, all of the following criteria had to be fulfilled:

1. Symptoms suggestive of CD (particularly malabsorption)
2. Serum levels of ≥10 times the upper limit of normal (ULN) of IgA antibodies against type-2 (tissue) transglutaminase (TGA-IgA)
3. Positive endomysial antibodies (EMA-IgA) in a second serum sample
4. Positive coeliac HLA risk alleles DQ2 and/or DQ8
5. Omitting duodenal biopsies should only be considered in patients/parents who understand the diagnosis and are committed to a gluten-free diet. The diagnosis and follow-up of CD should be made by a paediatric gastroenterologist or paediatrician with extensive knowledge of CD.

Although later published guidelines intended for adults (2,3) did not give the option for the no-biopsy approach, the 2012 ESPGHAN guidelines attracted considerable interest. Several recent prospective studies have favourably evaluated their performance (4,5) and on this basis, it is timely to update and expand the 2012 guidelines.

METHODS

Guideline Development Process

In 2016, ESPGHAN established a working group to develop an updated evidence-based clinical guideline for the diagnosis of CD. Ten focused clinical questions were formulated according to PICO format: Population, Indicator, Comparator, and Outcome. For each question, a bibliographic search was conducted; informative studies, systematically assessed for the risk of bias and clinical applicability, were included in the evidence base; meta-analysed study results were summarized and graded for certainty of evidence; and the implications for clinical practice were discussed and recommendations formulated and graded for strength.

The working group consisted of paediatric gastroenterologists, a GRADE methodologist (AH), biostatisticians and a member of the Association of European Coeliac Societies (AOECS). Smaller working groups focused on each clinical question and all questions were discussed jointly at 4 face-to-face meetings and 12 telephone conferences.

Population, Indicator, Comparator, and Outcomes

The 10 questions addressed in this guideline reflect the 2016 NICE guidelines on CD (6), and the resulting recommendations are listed in Table 1. Histological analysis of duodenal biopsies was considered as the reference standard in diagnostic accuracy and the predefined outcomes of most interest were sensitivity, specificity, and positive-/negative-predictive values (PPV/NPV).

Search for and Inclusion of Studies

Eligibility criteria: For each question, study characteristics (limited to children and adolescents whenever appropriate, setting, index test, reference standards, target conditions and study design) were specified.

In collaboration with an information specialist, the following databases were searched for eligible studies published from 2000 to 2016: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, EMBASE (Ovid), MEDLINE (Ovid), and MEDLINE In-Process (Ovid).

Studies were screened and, for potentially eligible studies, full texts were assessed. The final choice of studies was agreed by subgroup discussion and consensus. Covidence (www.covidence.co.org) was used to organize the flow of references and studies.

Assessment of Risk of Bias and Clinical Applicability

All included studies were risk-assessed, using the QUADAS-2 tool (7) and data extraction and assessment was conducted by 2 independent reviewers.

Evidence Synthesis Process

Methods and results of studies were summarized according to the question posed. For questions 3 to 6, a meta-analysis for sensitivity and specificity and/or PPV was performed. For questions 1 and 2 and 7 to 10, results were summarized qualitatively (Table 1). A clear distinction was made between prospective and retrospective studies, and for diagnostic accuracy, between cross-sectional (cohort) studies and case-control studies. All figures and tables with “S” are supplementary materials, which are available online.

Diagnostic Accuracy Measures and Synthesis of Results

For a test to be useful at ruling out a disease, it must have high sensitivity and to be useful at confirming a disease it must have high...
### Table 1. Questions for the 2019 European Society Paediatric Gastroenterology, Hepatology and Nutrition criteria for the diagnosis of coeliac disease

<table>
<thead>
<tr>
<th>Question</th>
<th>Text</th>
<th>Recommendation</th>
<th>Grading (strength)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is there a difference in the prevalence of CD in children with constipation, abdominal pain, signs of irritable bowel syndrome (IBS), dyspepsia, malabsorption, iron deficiency anaemia, oral aphthae as compared with the general population?</td>
<td>We recommend considering testing for CD in children and adolescents with symptoms, signs and conditions shown in Table 2.</td>
<td>—</td>
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<tr>
<td>2</td>
<td>What will HLA-DQ2 and DQ8 determination add to the diagnostic certainty of CD-diagnosis?</td>
<td>We recommend that HLA-DQ2 and DQ8 typing is not required in patients with positive TGA-IgA, if they qualify for CD diagnosis with biopsies or have high-serum TGA-IgA (≥10× ULN) and EMA-IgA positivity. If a patient tests negative for HLA DQ2 and DQ8, the risk of CD is very low, whereas a positive result does not confirm the diagnosis</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>How does the algorithm proposed to avoid biopsies in symptomatic patients work in asymptomatic subjects?</td>
<td>We recommend that in subjects with normal serum IgA values for age, TGA-IgA should be used as the initial serological test regardless of age</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Which serological test is the most appropriate to diagnose CD?</td>
<td>We recommend that HLA-DQ2 and DQ8 typing is not required in patients with positive TGA-IgA, if they qualify for CD diagnosis with biopsies or have high-serum TGA-IgA (≥10× ULN) and EMA-IgA positivity. If a patient tests negative for HLA DQ2 and DQ8, the risk of CD is very low, whereas a positive result does not confirm the diagnosis</td>
<td>—</td>
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<tr>
<td>5</td>
<td>Should more than 1 serological test be used and, if so, what should be the sequence of testing?</td>
<td>We recommend considering testing for CD in children and adolescents with symptoms, signs and conditions shown in Table 2.</td>
<td>—</td>
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<tr>
<td>6</td>
<td>A diagnosis of CD may be safely done (positive-predictive value &gt;95%) with omission of biopsy, at which cutoff for TGA-IgA (ULN ×10, ×7, ×5)?</td>
<td>We recommend that for CD diagnosis without biopsies, TGA-IgA serum concentration of at least 10× ULN should be obligatory. Only antibody tests with proper calibrator curve-based calculation, and having the 10× ULN value within their measurement range, should be used. Omitting biopsies in IgA-deficient cases with positive IgG-based serological tests is not recommended</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Is endomysial antibody test (EMA) testing necessary in every case to diagnose CD with omission of biopsy?</td>
<td>We recommend that in children with TGA ≥10× ULN, and parents/patient agreement to the no-biopsy approach, the CD diagnosis should be confirmed by a positive EMA-IgA test in a second blood sample</td>
<td>—</td>
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<tr>
<td>8</td>
<td>What is the inter- and intra-observer variability regarding CD diagnosis of histopathology results of duodenal and bulb biopsies? What degree of lesion is considered to be untreated CD? Do duodenal bulb biopsies increase the detection rate of CD? Is a reference pathologist needed in clinical practice?</td>
<td>At least 4 biopsies from the distal duodenum and at least 1 from the duodenal bulb should be taken for histology assessment during a gluten-containing diet. Reading of biopsies should be performed on optimally orientated biopsies. A villous to crypt ratio of &lt;2 indicates mucosal lesions. In cases of discordant results between TGA-results and histopathology, re-cutting of biopsies and/or second opinion from an experienced pathologist should be requested</td>
<td>—</td>
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<tr>
<td>9</td>
<td>Does Marsh 0 or 1 (increased IEL counts only) compared with Marsh 0 have a different long-term outcome regarding diagnosis of CD in children with coeliac autoimmunity (positive TGA or EMA)?</td>
<td>We recommend before diagnosing potential CD to check the gluten content of the diet and the correct orientation of biopsies. Once confirmed, potential CD requires clinical and laboratory surveillance (serology, further biopsies) to monitor possible evolution to villous atrophy. For follow-up, it is important to refer the patient to tertiary care centres with expertise in CD</td>
<td>—</td>
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<tr>
<td>10</td>
<td>How often are other clinically relevant diagnoses missed if upper (oesophageal-gastroduodenal) endoscopy is not performed in patients diagnosed by the no-biopsy approach?</td>
<td>We recommend that the decision to omit upper endoscopy with biopsies can be taken without the consideration of missing other pathologies or diagnoses</td>
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</table>

Two arrows (††) indicate a strong recommendation in favour, 1 arrow (†) indicates a weak conditional recommendation; and similarly for strong and weak conditional recommendations against (‖) as suggested by the GRADE Working Group (11). Statements and recommendations from the 2012 Guidelines not investigated in the frame of these 10 questions remain in force (see supplementary file S 23, http://links.lww.com/MPG/B719). CD = coeliac disease.
specificity. As most seronegative patients do not get a biopsy, and thus true negatives are often missing, no study could provide valid data on sensitivity for case finding. Additionally, a high positive predictive value (PPV) was more appropriate for some questions, such as determining the TGA-IgA level for the no-biopsy approach.

For summarizing sensitivity and specificity for different groups, bivariate binomial meta-regressions were used together with investigation of statistically significant differences between the different groups [by following the method suggested by the Cochrane Diagnostic Test Accuracy Working Group (8)]. For each group, Youden index was calculated as J = sensitivity + specificity – 1 (9). A Forest Plot showing sensitivity and specificity was constructed for each group and summary receiver operating characteristics curves (ROC) were plotted for each group based on the models.

For selecting the optimal cut-off point for sensitivity and specificity, a multiple cut-offs model was used based on a restricted maximum likelihood (REML)-based multi-level random effects model (10). Computations were carried out in R version 3.3.3 (www.r-project.org/) using the packages “lme4,” “meta,” and “diagmeta” (https://CRAN.R-project.org/package=diagmeta), as well as Review Manager version 5.3.

Quality of the Evidence

GRADE was used to rate the overall quality of evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect (11). The GRADE ratings of very low-, low-, moderate-, or high-quality evidence reflect the extent of confidence that the diagnostic measures obtained are correct. Although the formal GRADE approach focused on a quantitative estimate (typically from a meta-analysis) whenever possible, similar principles were applied to assess the certainty of a qualitative summary, recognising the increased uncertainty in this procedure. Also, though standard outcomes of accuracy studies, such as sensitivity and specificity, can be regarded as surrogate outcomes, the correct diagnosis of CD is clearly linked to a well-established and effective intervention (gluten-free diet). Thus, studies were not downgraded for indirectness or lack of directly patient-relevant important outcomes.

Strength of Recommendations

The recommendation included a grading of strength, according to the GRADE approach and as suggested by the GRADE Working Group.

The implications of a strong recommendation for patients would be: “most parents and children in your situation would want the recommended diagnostic test and only a small proportion would not.” For clinicians, the implications would be that most patients should receive the recommended diagnostic test. For a conditional recommendation, clinicians should realise that different diagnostic tests will be appropriate for different children with suspected CD; that is, the clinician must help each suspected patient (and parents) to arrive at a decision consistent with their values and preferences.

Ethics and Regulations

All guideline members’ conflicts of interest have been noted and registered on the ESPGHAN website. The guideline was funded by ESPGHAN and was developed in collaboration with AOECS.

RESULTS

Symptoms and Signs

Question 1: Is there a difference in the prevalence of CD in children with constipation, abdominal pain, signs of irritable bowel syndrome (IBS), dyspepsia, malabsorption, iron deficiency anaemia, or oral aphthae compared with the general population?

On the basis of results from the literature search (Fig. S1), Supplemental Digital Content, http://links.lww.com/MPG/B719, 13 relevant studies were selected and evaluated (Table S1, Table S11, Supplemental Digital Content, http://links.lww.com/MPG/B719).

Prospective Studies

Two studies addressed the issue of functional gastrointestinal disorders (FGID) but without healthy controls [n = 78 (12) and n = 1047 (13)]. They found a prevalence of CD in children with IBS of 4.4% and 2.2%, respectively; whilst functional abdominal pain and dyspepsia prevalence in CD ranged from 0.3% to 1%. In 101 children with functional constipation lasting >2 months (14), 4 cases had positive TGA-IgA, 3 were biopsied, and 1 had CD, resulting in a prevalence of 1%. In a large prospective birth cohort (n = 6.706) with 3 monthly testing for TGA-IgA in serum symptoms were assessed by parental questionnaire without their knowledge of TGA-IgA results (15). At 3 and 4 years of age constipation and abdominal discomfort were more frequently reported in those with confirmed TGA-IgA positivity compared with age- and sex-matched participants remaining TGA-IgA-negative. In the ProCeDE study (4), stool consistency was prospectively assessed by the Bristol stool scale in 653 children and adolescents with newly diagnosed CD: 13% documented hard stool (type 1 or 2) compared with 17% reporting soft/liquid stool (type 6 or 7). Although there was no control group, the data indicate that constipation is almost as frequent as diarrhea in children with CD. Chronic diarrhoea was investigated in 825 cases and 825 controls (16) with a 9% CD prevalence in the diarrhoea cases as compared with 0.6% in controls. In another study, 24 cases of CD (23%) were diagnosed in 103 children with chronic diarrhoea compared with 18 (19%) of 97 disease controls (17).

Oral aphthae were assessed in 50 CD cases and 50 controls and the prevalence was 62% and 13% respectively (18). Similarly, delayed dental eruption was observed in 38% and 11% and specific enamel defects in 48% and 0%, respectively. The prevalence of CD in Iranian teenagers and adults (n = 247, age range 13–40 years) reporting recurrent oral aphthae, was 2.8%, the youngest CD patient being 13 years old. This prevalence was significantly higher than the 0.9% found in the general population (19).

In 302 patients positive for antithyroid antibodies (age range 3.1–24.9 years), the prevalence of biopsy-confirmed CD disease was 2.3%. However, when patients with type 1 diabetes or Down syndrome were excluded, the prevalence decreased to 1.3% (20).

Iron deficiency anaemia (IDA) is a typical complication of malabsorption in CD. In the large ProCeDE cohort of children diagnosed based on symptoms, iron deficiency anaemia was reported in 17% (4). When CD children were identified by TGA-IgA screening in a large paediatric population-based cohort in Germany, no significant differences were found between 97 TGA-IgA seropositive children compared with 12,509 seronegatives; however, serum ferritin was significantly lower in seropositives indicating lower iron stores (21). When 135 iron deficient anaemia patients without gastrointestinal symptoms were screened,
Retrospective Studies

A chart review (23), including 165 paediatric CD patients, concluded that abdominal pain (in 52.7%) and constipation (in 38.9%) were the most frequent presenting features for CD. One additional case-control study, found a positive serology in 1.1% of abdominal pain cases and in 1.2% of controls (24). No duodenal biopsies were performed.

Statement

A broad spectrum of symptoms and signs have been reported in patients at the time of CD diagnosis. Classical symptoms of malabsorption seem to be more specific and include failure to thrive, weight loss, and chronic diarrhoea. For less specific symptoms, there is evidence that patients with diarrhoea-predominant IBS-like symptoms, iron deficiency anaemia, chronic constipation, and enamel defects have increased risk for CD. For other nonspecific gastrointestinal symptoms like abdominal pain, dyspepsia, and bloating, there is insufficient evidence.

Recommendation

We recommend considering testing for CD in children and adolescents with symptoms, signs and conditions shown in Table 2 [1].

### TABLE 2. Symptoms and signs suggesting coeliac disease

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Chronic or intermittent diarrhea*</th>
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<tbody>
<tr>
<td></td>
<td>Chronic constipation not responding to usual treatment</td>
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<tr>
<td></td>
<td>Chronic abdominal pain</td>
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<td></td>
<td>Distended abdomen*</td>
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<tr>
<td></td>
<td>Recurrent nausea, recurrent vomiting</td>
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<tr>
<td></td>
<td>Weight loss, failure-to-thrive*, stunted growth/’short stature’*</td>
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<tr>
<td></td>
<td>Delayed puberty, amenorrhea</td>
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<td></td>
<td>Irritability, chronic fatigue</td>
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<tr>
<td></td>
<td>Neuropathy</td>
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<td></td>
<td>Arthritis/arthritis</td>
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<td></td>
<td>Chronic iron-deficiency anaemia</td>
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<tr>
<td></td>
<td>Decreased bone mineralization (osteopenia/osteoporosis), repetitive fractures</td>
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<tr>
<td></td>
<td>Recurrent aphthous stomatitis, Dermatitis herpetiformis—type rash</td>
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<tr>
<td></td>
<td>Dental enamel defects</td>
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<tr>
<td></td>
<td>Abnormal liver biochemistry</td>
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<tr>
<td>Extraintestinal symptoms</td>
<td>First-degree relatives with CD</td>
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<td></td>
<td>Autoimmune conditions: T1DM, thyroid disease, liver disease</td>
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<tr>
<td></td>
<td>Down syndrome, Turner syndrome</td>
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<tr>
<td></td>
<td>William’s-Beuren syndrome</td>
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<td></td>
<td>IgA deficiency</td>
</tr>
</tbody>
</table>

CD = coeliac disease; T1DM = type-1 diabetes mellitus. *Common symptoms.

Voting

Statement and Recommendation: Agree: 18 Disagree: 0 Abstain: 0

HLA Aspects

Question 2: What will HLA-DQ2 and DQ8 determination add to the diagnostic certainty of CD-diagnosis?

ESPGHAN 2012 recommendations for a no-biopsy approach included testing for HLA-DQ2 and DQ8 in individuals with very high TGA-IgA titres and EMA-IgA positivity, often described as a “triple test” (TGA/EMA and DQ) in several publications. This term, however, may imply that all 3 tests can be performed from 1 blood sample, which does not conform to the guidelines. The recommendation presumed that DQ typing added further accuracy to the diagnosis, given that this is unlikely among DQ2/DQ8 negative individuals. HLA testing, however, is not universally available and quite costly in some countries, and if it does not improve the no-biopsy diagnosis, it should be omitted. In an Australasian coeliac population (n = 356), 99.6% were DQ2/DQ8-positive (25) and the production of TGA-IgA and/or EMA was shown to be HLA-DQ-dependent. It may be concluded that the higher percentage of HLA DQ2/DQ8-negative CD patients (up to 5%) in earlier publications had several causes, with 1 of these being the HLA testing method. SNP-based tests are cheap to perform and recognize the common variants (DQ2.5, DQ8, DQ2.2, DQ7.5), whereas in depth allele typing is required to identify rare variant alleles. Therefore, the accuracy to exclude CD by HLA testing still depends on the method used. Other causes for so called ‘‘HLA DQ2/DQ8 negative CD patients’’ are the inclusion of a more heterogeneous group of patients with CD-compatible symptoms, and in some cases, false-positive histopathology considering an interobserver-variability of 5–7% regarding CD diagnosis (see Question 8 below).

A QUADAS-2 analysis was performed based on 8 papers (Table S2, Supplemental Digital Content, http://links.lww.com/MPG/B719) and the evidence for the value of HLA-testing as a criterion of the no-biopsy approach was graded (Table S12, Supplemental Digital Content, http://links.lww.com/MPG/B719).

Prospective Studies

Two prospective studies were of high quality in relation to this question (4,5). Werkstetter et al (4) analysed 645 paediatric patients with positive TGA-IgA and biopsy-proven CD where high TGA-IgA titres (>10× ULN), positive EMA and Marsh 2 or 3 lesions were found in 399 patients, compatible with the no-biopsy strategy. All 399 were positive for DQ2 and/or DQ8, and it was concluded that HLA typing did not add to the certainty of CD diagnosis in these patients. Wolff et al (5) reported 409 CD patients with TGA-IgA titres higher than 10× ULN, positive EMA and biopsy-proven CD. HLA testing was available in 227 and all typed positive for HLA-DQ2 or DQ8.

In another study (26), 82 CD patients had villous atrophy, 81 were positive for HLA-DQ2/DQ8 (98.8%) and for TGA and/or EMA. The single case negative for both genetics and serology tests was later found to have noncoeliac enteropathy.

In a Finnish study (27) including relatives of CD patients, all 114 with biopsy-proven CD and TGA-IgA and EMA-IgA positivity had a coeliac-type HLA. In a screening study in 7208 12-year olds in Sweden (28), 153 children had biopsy-proven CD, and all were HLA-DQ2 and/or DQ8 positive.
Retrospective Studies

Of the three retrospective studies (29–31), 1 (29) reported 401 DQ2 and/or DQ8-positive (99%) patients among 405 with a TGA-IgA titre $\geq 10 \times$ ULN. One centre had previously reported all cases undergoing duodenal biopsy because of suspicion of CD (31). Of 150 with complete data, 116 were positive for TGA-IgA, EMA and HLA and were all diagnosed with CD. Four patients (2.7%) were initially considered to have neither DQ2 nor DQ8 heterodimers, but were heterozygous for *0202 HLA-DQB1 allele, so actually all carried a permissibility gene. In a further multicentre study, 368 of 749 CD cases were genotyped, with 98.1% positive for DQ2/DQ8 and 1.9% negative for those haplotypes (30).

Statement

HLA-typing does not add to the certainty of the diagnosis if the other criteria for CD diagnosis are fulfilled. Testing for HLA DQ2 and DQ8 may be useful in other circumstances. If no risk alleles are found, CD is unlikely.

Recommendation

We recommend that HLA typing is not required in patients with positive TGA-IgA, if they qualify for CD diagnosis with biopsies or if they have high TGA-IgA ($\geq 10 \times$ ULN) and EMA-IgA positivity. If a patient tests negative for HLA DQ2 and DQ8, the risk of CD is very low, while a positive result does not confirm the diagnosis.

Voting

Statement: agree: 17 Disagree: 0 Abstain: 1
Recommendation: agree: 15 Disagree: 2 Abstain: 1

Antibodies

Question 3: Does the algorithm proposed to avoid biopsies in symptomatic patients work in asymptomatic subjects?

Eleven articles were considered suitable and underwent QUA-DAS-2 analysis (Table S3 and S13, Supplemental Digital Content, http://links.lww.com/MPG/B719). Even in these selected articles, however, limitations were present, as different populations with diverse study designs, reference standards and varying sample size and assays applied. In addition to the data presented in the publications, the original data of the asymptomatic children were included from 4 of the 6 prospective studies (4,5,32,33). The majority of asymptomatic individuals were screened as they belonged to at-risk groups. Three of the 6 prospective studies concerned patients suspected for CD (4,5,34), whereas the other 3 were birth cohorts with genetic susceptibility for CD (HLA-DQ2/DQ8 positive) (32,33,35). The 2 cross-sectional studies were mass-screening studies in the general population, not seeking medical attention for any complaint or risk (36,37). The 3 retrospective studies included patients who were at risk of CD (29,38,39). As studies with a large number of CD cases with coexisting type 1 diabetes have not been included in our literature search, this specific group of patients has not been addressed in this question.

In an analysis of data from 555 asymptomatic children with TGA-IgA titres $\geq 10 \times$ ULN (Table S21, http://links.lww.com/MPG/B719), 552 had diagnostic small bowel biopsies, with 520 (94.2%) having Marsh class 2 or 3 duodenal lesion. The Forest plot (Fig. 1) shows a considerable variation with PPV from as low as 0.69, therefore, pooling of results is statistically not appropriate. The 3 studies with the smallest sample size had the lowest PPV, whereas the rest had values above 0.90, but with 95% confidence intervals including values down to 0.79. The outcome is further described in the supplementary material (S21, Supplemental Digital Content, http://links.lww.com/MPG/B719).

Statement

Recent studies suggest that the no-biopsy approach to diagnose CD can be applied in asymptomatic children. In asymptomatic children, however, the PPV of high TGA-IgA $\geq 10 \times$ ULN may be lower than in symptomatic children, which needs to be considered during the decision-making process.

Recommendation

We give a conditional recommendation that, taking available evidence into account, CD can be diagnosed without duodenal biopsies in asymptomatic children, using the same criteria as in patients with symptoms. We recommend that the decision whether or not to perform diagnostic duodenal biopsies should be made during a shared decision-making process together with the parent(s) and, if appropriate, with the child.

![Figure 1. Forest plot for positive-predictive values for Question 3.](http://links.lww.com/MPG/B719)
**Question 4: Which serological test is the most appropriate to diagnose CD?**

Eighteen articles were selected for a detailed QUADAS-2 analysis (Table S4, Supplemental Digital Content, http://links.lww.com/MPG/B719), along with 5 prospective and 13 retrospective studies. Three tests were thoroughly evaluated: TGA-IgA, DGP-IgG, and EMA-IgA.

**Prospective Studies**

The prospective studies (5,40–43) were in general large ones with a low risk of bias and of high quality (Table S14, Supplemental Digital Content, http://links.lww.com/MPG/B719). The largest study (5) found EMA-IgA to have excellent accuracy. Three out of 5 recent articles showed surprisingly low specificity for EMA-IgA (41,42,44), with 2 of them coming from the same centre. As the 3 articles provided insufficient information about the technical aspects of serology and histology assessment with an allowed time gap up to 6 months between serology and biopsies (allowing time for the effect of gluten-restriction before biopsies), it was not possible to decipher the reasons for the discrepant results.

**Retrospective Studies**

The retrospective studies had higher degrees of bias, in particular as to patient selection, and were judged to be of lower quality. Overall, the Forest plot for TGA-IgA, DGP-IgG, and EMA-IgA (Fig. 2) showed considerable heterogeneity.

A bivariate binomial meta-regression meta-analysis disclosed similar accuracies for the three antibody species (Fig. S2, Supplemental Digital Content, http://links.lww.com/MPG/B719) that showed overall significant differences between the tests for both sensitivity ($P = 0.005$) and specificity ($P = 0.016$), with summary ROC curves showing summary points and 95% confidence intervals for TGA-IgA, DGP-IgG, and EMA (Fig. S2, Supplemental Digital Content, http://links.lww.com/MPG/B719). The highest value obtained was for EMA that had the highest sensitivity but specificity.

**Statement**

The three specific coeliac antibodies (TGA-IgA, EMA-IgA, DGP-IgG) show different performance. TGA-IgA scored highest by a comparison of assay accuracy and is therefore regarded as the most appropriate primary test for CD in the diagnostic work up of children with suspected CD.

**Recommendation**

We recommend that in subjects with normal serum IgA values for age, TGA-IgA should be used as the initial test regardless of age [11].

**Voting**


**Question 5: Should more than one serological test be used and, if so, what should be the sequence of testing?**

We searched the literature to find whether any combination of tests (either 2 separate tests or a blended test kit for both IgA and IgG detection) is better for initial testing than TGA-IgA plus total IgA. Evidence from studies restricted to young children below 2 or 3 years of age was downgraded, if the diagnosis of CD in cases with negative autoantibodies was not confirmed by a gluten challenge, as recommended in the current guidelines. Of 107 studies identified, 10 were of sufficient quality to be considered for the final analysis (Table S5 and Table S15, Supplemental Digital Content, http://links.lww.com/MPG/B719), and further described in more detail (supplementary material S22, Supplemental Digital Content, http://links.lww.com/MPG/B719).

**Prospective Studies**

**TGA-IgA plus DGP-IgG With or Without DGP-IgA**

The only unbiased prospective study was performed in adults (45), in which 2297 unslected adults were screened with TGA-IgA, DGP-IgG, and DGP-IgA. A total of 56 were positive on at least 1 antibody test and duodenal biopsies were performed in 40. Of 8 biopsy-confirmed CD cases, 7 were positive for TGA-IgA, 5 for DGP-IgG and 5 for DGP-IgA, with 4 positive in all 3 tests. False-positive results were found in 2 for TGA-IgA, in 5 for DGP-IgG, and in 28 for DGP-IgA. In order to find the only CD-case with negative TGA-IgA, almost 2300 tests for DGP-IgG had to be performed plus 4 unneeded endoscopies. Wolf et al (5) prospectively included children below 18 years of age, referred because of either a positive serology for CD and/or symptoms. A total of 989 children were centrally tested for total IgA, TGA-IgA, DGP-IgG, and EMA-IgA. When TGA-IgA plus total IgA was compared with TGA-IgA and DGP-IgG (TGA-DGP procedure) for initial testing, 592 were diagnosed with CD, 245 as no CD, and 24 had no final diagnosis. The TGA-DGP procedure detected 6 additional CD patients, 5 of which were also negative for EMA IgA, whereas the remaining child was positive for EMA-IgG and TGA-IgA. The TGA-DGP compared with the TG2-IgA procedure resulted in 16 unnecessary endoscopies (negative TGA-IgA but false positive DGP-IgG).

**DGP-IgA With Total IgA and AGA-IgA**

Vriezinga et al (32) reported a European multi-centre placebo-controlled intervention trial in infants at genetic risk for CD (all HLA DQ2 or DQ8 positive family history positive). Participants were regularly tested from age 4 months for TGA-IgA and AGA-IgA, and with an IgG-based test in case of low total IgA. Biopsies were offered to those with persistent positive TGA-IgA levels, high or increasing AGA-IgA, and symptoms strongly suggesting CD regardless of serology results. All IgA-competent children with biopsy-proven CD were positive for TGA-IgA, whilst all 17 TGA-IgA negative children biopsied, based on symptoms or AGA-IgA positive results, had either a normal mucosa or a transient enteropathy. Transient positivity of AGA-IgA occurred in a third of infants randomized to early gluten exposure and was not predictive for later CD.

**Retrospective Studies**

**TGA-IgA and DGP-IgG With or Without DGP-IgA**

Of 5 retrospective studies, 4 were performed in young children only (42,46–48), whilst 1 included children and adults (49). A further description is included in the supplementary material (S22, Supplemental Digital Content, http://links.lww.com/MPG/B719). These studies, however, have major limitations:
the biopsy rate of patients with a positive test result in either TGA-IgA or DPG was low, there was no reference pathologist and no gluten challenge in children below 2 years of age with villous atrophy but negative autoantibodies. In summary, these studies do not support to add DGP to TGA-IgA testing for initial screening.

**TGA-IgA and TGA-IgG**

Of 2911 persons (age range 1–80 years) with a positive coeliac serology during a 17-year period, 233 individuals with an isolated positivity for TGA-IgG were identified (50). Biopsies were performed in 178/233 (78%), with a normal histology in 160 (90%), Marsh 1 in 9 (4.5%), villous atrophy because of other diagnosis than CD in 3 (1.5%) and the remaining 6 patients (3%) having histopathology as CD. The authors concluded that TGA-IgG did not add to the accuracy.

**TGA-IgA With Total IgA and AGA-IgA**

One study (46) evaluated whether AGA-IgA testing in addition to TGA-IgA testing improves case finding in children below 2 years of age. Of 4122 children tested, 312 (8%) were TGA-IgA or EMA positive, whilst 85 were only AGA-IgA positive. Clinical data was available in 62 and duodenal biopsy results in 33 of them, leading to CD in 5 children. The remaining 57 children

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**FIGURE 2.** (A) Forest plots for sensitivity and specificity for Question 4. (B) Meta-analysis for Question 4. Meta-regressions showed that there is statistical evidence (chi-square = 10.4, $P = 0.005$) that the expected sensitivity differs between the assays, as well as statistical evidence (chi-square = 8.3, $P = 0.016$) that the expected specificity differs between the assays.
with isolated AGA positivity, including 4 with villous lesions, received a diagnosis other than CD.

Statement

Current evidence indicates that adding DGP-IgG, DGP-IgA, or AGA-IgA testing to TGA-IgA testing seldom improves sensitivity after excluding patients with low total IgA. Specificity markedly decreases, especially in children below 4 years of age, in which isolated DGP or AGA positivity is a common transient phenomenon.

Recommendation

We recommend testing for total IgA and TGA-IgA as initial screening in children with suspected CD. In patients with low total IgA concentrations, an IgG-based test (DGP, EMA, or TGA) should be performed as a second step. Testing for EMA, DGP or AGA antibodies (IgG and IgA) as initial screening in clinical practice is not recommended [11].

Voting

Statement and recommendation: Agree: 18 Disagree: 0 Abstain: 0

Question 6: At which cut-off for TGA-IgA (ULN 10×, 7X, 5X) may a diagnosis of CD safely be done (positive predictive value > 95%) with omission of biopsies?

Higher serum levels of TGA-IgA are strongly associated with higher degree of villous atrophy if TGA-IgA is measured by a calibration curve-based immunoassay. ESPGHAN 2012 guidelines (1) suggested that the no-biopsy approach can be considered when TGA-IgA values ≥10× ULN but this guideline evaluates the evidence for ≥10× ULN and possibly lower cut-offs to predict Marsh 2 to 3 lesions and CD.

A search yielded 44 studies where PPV of high TGA-IgA levels were compared with the histopathological outcome. Of these, only 36 utilised antibody tests suitable for calculating multiples of ULN. After narrowing the scope to those paediatric studies, where exact numbers of true positives and false positives could be extracted, 19 retrospective (29, 31, 38 – 40, 42, 43, 46, 51 – 60, 94) and 3 prospective studies (4, 5, 41) remained for QUADAS-2 and further analysis (Table S6 and Table S16, Supplemental Digital Content, http://links.lww.com/MPG/B719). These 49 datasets constituted 9 conventional ELISA assays (Biosystems, DiaSorin, Euroimmun, Eurospital, Immco, Inova, Organetec, Phadia, R-Biopharm), 2 fluorescent immunoassays (Phadia), and 2 chemiluminescence tests (Immulite, Inova).

From the 30 datasets evaluating the TGA IgA cut-off at ≥10× ULN, 28 reported >95% PPV and 2 reported >99% PPV (Fig. 3). The PPVs were higher in studies where both Marsh 2 and 3 were accepted as CD (all >97% PPV) compared with studies, which required strictly Marsh 3 for CD diagnosis. At cut-off levels 5 to 7.5× ULN PPV values varied between 92.3% and 100%, still 4/7 datasets showing PPV >99%. At cut-off levels 2 to 4× ULN PPV values varied between 86 and 100%, again with 4/7 datasets still showing PPV >99% (Fig. 3). The study of Werkstetter et al (4), included 8 TGA-IgA assays in the central head-to-head analysis, which showed a PPV of 99% even at lower cut-offs than 10× ULN (presented only as graphs), but the same study also demonstrated high inter-test and inter-laboratory variability at these lower ranges. Notably, in local laboratories, a PPV >99% was only reached at 10× ULN. At the cut-off levels between 3 and 10× ULN, the test kit and the diagnostic approach (Marsh 3 only or Marsh 2–3 as CD) influenced the clinical outcome. In most retrospective studies, no reference pathologists were involved and the histology evaluation was not blinded. Interestingly, all three prospective studies providing a blinded reference pathologist yielded excellent PPV values (100%, 99.1%, and 98.9%) suggesting that high TGA IgA levels strongly support the CD diagnosis and discrepant results occur more likely because of technical difficulties with the histology.

TGA-IgG cut-off levels reliably predicting CD in IgA-deficient persons could not be derived from the literature. Therefore, the 10× ULN cut-off is not validated for TGA-IgG. Differences in calibrators and slow IgG antibody kinetics warrant special caution with IgA-deficient subjects where levels of EMA and TGA-IgG may remain high for several years after starting a gluten-free diet (61).

Statement

High serum TGA IgA levels ≥10× ULN predict enteropathy (Marsh 2/3) and should be used as a criterion for CD diagnosis without biopsies. Due to inter-laboratory and inter-test variability, the reliability of positive TGA IgA levels <10× ULN and that of TGA-IgG are prone to technical error and not sufficient for the no-biopsy approach.

Recommendation

We recommend that for CD diagnosis without biopsies, TGA- IgA serum concentration of at least 10× ULN should be obligatory. Only antibody tests with proper calibrator curve-based calculation, and having the 10× ULN value within their measurement range, should be used. We recommend against omitting biopsies in IgA-deficient cases with positive IgG-based serological tests [11].

Voting

Statement: Agree: 17 Disagree: 1 Abstain: 0
Recommendation: Agree: 17 Disagree: 0 Abstain: 0

Question 7: Is endomysial antibody (EMA-IgA) testing necessary in every case to diagnose CD without biopsy?

The recommendations for a no-biopsy approach in patients with high TGA-IgA levels rests on a second serum sample taken for EMA-IgA on a separate occasion on a gluten-containing diet (62). This consideration aims at avoiding mislabelling of samples or technical errors and confirming coeliac auto-immunity using another test assay with high specificity.

EMAs are directed against the transglutaminase 2 (TG2) antigen present in the anatomical endomysium in a tissue section and the EMA test is based on indirect immunofluorescence performed on primate oesophageal or human umbilical cord substrate. The test is considered positive if a serum dilution of 1:5 or higher gives a visible binding pattern. The EMA-IgA test performance, however, depends on a subjective interpretation of the results, which may be critical at low titres. The inter-lab variability of EMA titers is highly dependent on lab condition. In addition, the test is more time-consuming and expensive than measurement of TGA-IgA. Ten studies were identified for QUADAS2 analysis (Table S7, Supplemental Digital Content, http://links.lww.com/MPG/B719) and further evaluation (Table S17, Supplemental Digital Content, http://links.lww.com/MPG/B719).
Prospective Studies

In three prospective studies, a total of 1788 symptomatic children were included of whom 1357 had a final diagnosis of CD (4,5,41) (Table S17, Supplemental Digital Content, http://links.lww.com/MPG/B719). In total, 895 out of 1357 had TGA-IgA levels of $\geq 10$ ULN qualifying for the no-biopsy approach, 4 of which had a negative EMA; 1 of these 4 had a final diagnosis of no CD and 3 remained unclear. Thus, 1 to 4 of 895 patients qualifying for the no-biopsy approach (symptoms with TGA-IgA $\geq 10$ ULN) need to be tested with EMA-IgA to find 1 case with a final diagnosis of no CD. This yields a "number needed to test" of 224 to 895 to identify a non-CD case among those with TGA-IgA $\geq 10$ ULN.

In the study by Wolf, 5 patients considered not to have CD (n = 2) or unclear diagnosis (n = 3) out of 405 patients with TGA-IgA $\geq 10$ ULN also had a positive EMA-IgA (6). Four out of 5 had $< 10$ ULN for TGA-IgA at the first sample assayed locally, suggesting transient high levels and a need for 2 separate samples to apply the no-biopsy criteria, or alternatively uncertain histology. In the study by Werkstetter (4), 4 cases regarded as possible false positives also had TGA-IgA $< 10$x ULN or were negative in the second sample.

The studies have not formally assessed whether a second TGA-IgA test could serve as an alternative approach to cater for the possibility of transient increases or technical errors.

Retrospective Studies

Seven retrospective studies did not report symptoms ((31,38,43,44,56,63,64). Only 1 of these presented stratified tables in categories of TGA-IgA levels and with EMA-IgA for the group with TGA-IgA $\geq 10$ ULN. Two of the papers presented data suitable to answer the question. In total, 4 out of 565 individuals with TGA-IgA $\geq 10$ ULN were considered as false positives for a diagnosis of CD based on biopsy. These appeared in the same study and all had a negative EMA-IgA. The authors reported that in 3 of those children, the TGA-IgA result was normal after 2–5 months.
whilst still on a gluten-containing diet. Thus, these cases could be
due to a transient antibody increase, sample mixing or technical
errors. The numbers needed to test with EMA-IgA to avoid a false
positive diagnosis was 141.

**Statement**

Although high TGA-IgA (>10xULN) results are rare in
children with normal histopathology, a positive EMA-IgA result
will further decrease the rate of false positive results.

**Recommendation**

We recommend that in children with TGA >10X ULN, and
parents/patient agreement to the no-biopsy approach, the CD
diagnosis should be confirmed by a positive EMA-IgA test in a

**Biopsy**

**Question 8:** What is the inter- and intra-observer vari-
ability regarding CD diagnosis of histopathology results of
duodenal and bulb biopsies? What degree of lesion is considered
to be untreated CD? Do duodenal bulb biopsies increase the
detection rate of CD? Is a reference pathologist needed in
clinical practice?

Currently, the histological lesions in CD are graded using
grouped classifications, mostly based on Marsh-Oberhuber (65,66)
and literature shows unsatisfactory inter-observer agreement
between evaluators (67–69). The use of validated standard operat-
ing procedures (SOPs) with correct orientation and cutting of the
duodenal specimen is considered critical for an accurate interpre-
tation of the mucosal architectural changes (69–71). Villous height-
crypt depth ratio of less than 2 in some parts of at least 1 duodenal
biopsy is considered to be in agreement with CD. Marsh-Oberhuber
grading can only be given with proper tissue orientation, as is the
case for villus height crypt depth morphometry. In a recent inter-
observer agreement study in paediatric patients, only approximately
half of the biopsies were considered optimally oriented and satis-
factory results were obtained with respect to CD with a Kappa value
of 0.84. When specific Marsh-Oberhuber gradings were, however,
compared by different evaluators, poor agreement in grading the
injury was observed. In the study by Werkstetter et al (4), there was
disagreement between the local and the central pathologist regard-
ing the diagnoses of no-CD (Marsh 0 or 1) or CD (Marsh 2 or 3a–c)
in 7%, whereas discordant judgement considering all classes
(Marsh 0, 1, 2, 3a, 3b, or 3c) was reported in 58%. Some pathol-
ogists tended to give a suggestive or clear diagnosis, even in cases
with very poor quality of biopsies, instead of requesting adequate
samples (4).

The traditional histological evaluation of CD has undergone
marked changes in recent years, as bulb biopsies have been
recommended (1). These new recommendations came as a conse-
quence of reported cases showing histologic lesions only in the
duodenal bulb. The literature search identified 3 relevant paediatric
studies for the inter-observer agreement of the histopathology
results and 13 studies relevant for the duodenal bulb histopathology
evaluation in children, 3 of them of high quality (67,72) (Table S8,
Table S18, Supplemental Digital Content, http://links.lww.com/MPG/B719). A recent finding from a large multi-centre study
confirms that sometimes the mucosal injury is found only in the
bulb (4). Some studies have, however, questioned the added value
of intestinal bulb biopsies in improving CD diagnosis, especially in
children (73–75).

**Statement**

The inter-observer variability of the grading of small-bowel
histopathology lesions is high, indicating that histopathology can-
not serve as the sole reference standard. A higher detection rate for
CD may be achieved with more duodenal samples, including at least
1 from the bulb. Histopathology reading can be improved by
validated standard operating procedures (SOPs). Biopsies of low
quality or lacking correct orientation are not suitable for
CD diagnosis.

**Recommendation**

At least 4 biopsies from the distal duodenum and at least 1
from the duodenal bulb should be taken for histology assessment
during a gluten-containing diet. Reading of biopsies should be
performed on optimally oriented biopsies. A villous to crypt ratio
of <2 indicates mucosal lesions. In cases of discordant results
between TGA-IgA results and histopathology, re-cutting of biopsies
and/or second opinion from an experienced pathologist should be

**Question 9:** Does Marsh 1 (increased IEL counts only)
compared to Marsh 0 have a different long-term outcome
regarding diagnosis of CD in children with coeliac autoimmu-
nity (positive TGA or EMA)?

The Marsh classification is based on stages identifiable
during mucosal remodelling (76). Marsh 1 lesions are in most
cases not associated with TGA-IgA or EMA autoimmunity and
in these cases not related to CD. If Marsh 1 lesions are found in
seropositive persons (“potential CD”), particularly in those with
moderately high titres of TGA-IgA, the question arises whether this
is sufficient to diagnose CD. Six articles were identified as being
suitable for QUADAS-2 analysis (Table S9, Supplemental Digital
Content, http://links.lww.com/MPG/B719) and for further GRADE
evaluation (Table S19, Supplemental Digital Content, http://
l Links.lww.com/MPG/B719)

In 18 out of 20 subjects with potential CD, a higher than
normal number of γδ IELs were found versus 11 of 13 active CD
patients and 20 out of 42 controls (77). In the end 38%, potential CD
patients were classified as CD (55% of those Marsh 1 and 14% of
those Marsh 0) on the basis of a discriminating equation taking into
account CD3 IELs, γδ IELs, and lamina propria CD25+ cells (78).
Presence of TGA-IgA in the mucosa is found by immunofluores-
cence in the majority of patients with potential CD [see Tables S9
and S19, Supplemental Digital Content, http://links.lww.com/MPG/
B719, and (79,80)].

In children, evolvement of potential CD to CD has been
reported to occur in 33% (81) to 100% of cases. Other possible
outcomes are persistent seropositivity in the presence of normal
mucosa, fluctuation or permanent seroconversion to negative auto-
antibodies (81). There are no specific studies addressing the out-
come of Marsh 0 versus Marsh 1 histology in biopsies but the
increase of γ/δ IELs contribute to a discriminating equation pre-
dicting the evolution to villous atrophy.

Children with potential CD may already present with symp-
toms (82) and or signs, like iron deficient anaemia (83). Symptom-
atic patients range from 27% (81) to 100% (84). The rate of
responders to GFD is variable from 54% (85) to 100% (84),
although a placebo effect for subjective symptoms cannot be
excluded. Depending on the severity of symptoms and after exclu-
sion of other causing diseases, a GFD may be recommended for a
symptomatic child, based upon a decision shared with the parents.
Care must be given to follow-up with clinical evaluation for
improvement and serological testing.

Statement

The term potential CD identifies subjects with positive TGA-
IgA and EMA and no or minor small bowel histological changes.
Reasons for this situation, however, may also be low gluten intake
before biopsies, sampling error or incorrect orientation of the
biopsies for reading, leading to misdiagnosis of potential instead of
true CD. Marsh 1 is not considered sufficient to diagnose CD but
some observations suggest that potential CD cases with Marsh 1
small bowel lesions have a higher chance to evolve to villous
atrophy in comparison to Marsh 0.

Recommendation

We recommend before diagnosing potential CD to check the
gluten content of the diet and the correct orientation of biopsies.
Once confirmed, potential CD requires clinical and laboratory
surveillance (serology, further biopsies) to monitor possible evo-
lution to villous atrophy. For follow-up, it is important to refer the
patient to tertiary care centres with expertise in CD [1].

Voting

Statement and recommendation: Agree: 18 Disagree: 0 Abstain: 0

Question 10: How often are other clinically relevant
diagnoses missed if upper (oesophageal-gastro-duodenal)
endoscopy is not performed in patients diagnosed by the non-
bioy approach?

When CD is diagnosed by endoscopy, other conditions may be
detected, which may remain undetected in children diagnosed with-
out biopsies. Concern has been expressed that these conditions will be
missed in children diagnosed with CD based on the nonbioy
approach (86). These may be coincidental findings, occurring with
similar prevalence in individuals with and without suspected CD.
Alternatively, other conditions detected could be truly associated and
occur more frequently in individuals with CD but may resolve with a
GFD (87). Ideally, in order to assess whether the risk of overlooking
other conditions justifies routine endoscopy, the prevalence of these
conditions should be known in individuals without suspicion of CD. It
may in general be said that CD patients should be monitored while on
a GFD to ensure that no additional GI issues might have been missed.

Of the 6 relevant studies (Table S10, Supplemental Digital
Content, http://links.lww.com/MPG/B719), 5 were retrospective. In
the retrospective studies, biopsies from the oesophagus and gastric
mucosa were not taken routinely, making the findings difficult to
interpret and prone to selection bias. No serology results were
reported in the retrospective studies and a no-bioy approach could
not be determined (Table S20, Supplemental Digital Content, http://
links.lww.com/MPG/B719).

Macroscopic Peptic Mucosal Lesions and
Helicobacter pylori Infections

In a mixed paediatric and adult cohort of 240 patients with
biopsy-proven CD, peptic lesions in the stomach or duodenum were
found in 12%. No control group was reported. In another retrospec-
tive study, abnormal findings were reported in 11 of 115 paediatric
patients (86). One prospective study systematically assessed macro-
scopic findings and H pylori status during upper endoscopy at the
time of CD diagnosis in children (n = 653) (4). H pylori infection was
searched for in 442 patients with only 21 (4.5%) found positive. This
figure is very low considering that children were recruited also from
high H pylori-prevalent countries like Iran, Russia, Israel, and from
Eastern Europe and suggest a negative association between CD and H
pylori infection. In the total cohort (n = 653), erosions were found in
the oesophagus in 24 (4%), in the stomach in 21 (3%), and in the
duodenum in 43 (6%) children including 2 with shallow ulcers. Only
3 (4.7%) of 64 children with gastroduodenal lesions were H pylori-
positive, an infection rate equal to the total cohort. Duodenitis
including shallow ulcerations in the absence of H pylori in CD
children has been reported (88) and may indicate a higher vulnera-
bility to gastric secretion of the inflamed mucosa in CD. Whether the
rate of reflux esophagitis of 4% in CD is higher than a paediatric
background population is unclear. Dysmotility with delayed gastric
emptying in untreated CD may promote reflux disease. No long-term
data are available in affected children during a GFD.

Eosinophilic Oesophagitis

Four studies described eosinophilic oesophagitis (EoE) in
CD and non-CD cases (4,89–91). The first case-control study, with
controls undergoing endoscopy for other reasons except CD, found
a similar frequency in children with CD and in a highly selected
case-control group without CD (89). In a cross-sectional study from a
large pathology database, including patients with available oeso-
phageal and duodenal biopsies, a weak association between EoE and
CD was found, which was not significant for children (90). The
third study found signs of oesophageal eosinophilia in 4% of
children with CD but had no comparator group (91). Lastly, in
the only population-based study, not a single case of EoE was
identified from 653 children with CD (92). A systematic review did
not find an association between EoE and CD (93).

Statement

There is no evidence to support that relevant diagnoses are
missed if upper endoscopy with biopsies are omitted to
diagnose CD.

Recommendation

We recommend that the decision to omit upper endoscopy
with biopsies can be taken without the consideration of missing
other pathologies or diagnoses [11].

Voting

Statement and Recommendation: Agree: 18 Disagree: 0 Abstain: 0
Algorithm

On the basis of the evidence, the algorithms from the 2012 ESPGHAN guidelines have been modified into a common algorithm (Fig. 4) in subjects with normal IgA (Fig. 4A), with low or absent IgA (Fig. 4B) and with instructions for duodenal biopsies (Fig. 4C).

CONCLUSIONS AND FUTURE DIRECTIONS

These guidelines take into consideration new evidence (Table 3), mostly arising from studies inspired by the publication of the previous guidelines (1). Not all of the statements in the 2012 guidelines were supported by a similar degree of evidence. The most informative studies conducted in recent years have confirmed the substantial correctness of the 2012 guidelines (see supplementary material S23, Supplemental Digital Content, http://links.lww.com/MPG/B719), but at the same time indicate that we should consider the process far from being concluded.

Serology

The specificity of TGA-IgA at low titres, particularly in the absence of EMA-IgA, and the consequent clinical decision needs further investigation. The importance of EMA-IgA and TGA-IgA in the recommended repeat blood sample in the serological diagnosis has not been fully clarified by the existing literature. As EMA-IgA allows to selectively detect antibodies against certain TG2 epitopes, new submolecular TGA assays with coeliac epitope-specific target
The preparation of these guidelines has been supported by ESPGHAN. We thank Dr Klaus Giessiepen for important help in the early phases of this work and Drs Tove Frandsen and Julie Bolvig Hansen for their great help with the literature search.

**REFERENCES**

Intestinal biopsy is not always

Strongly positive tissue

Antibodies against deamidated


