# ESPGHAN Position Paper on Management and Follow-up of Children and Adolescents With Celiac Disease

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**ABSTRACT**

There is a need for consensus on the recommendations for follow-up of children and adolescents with celiac disease.

**Objectives:** To gather the current evidence and to offer recommendations for follow-up and management.

**Methods:** The Special Interest Group on Celiac Diseases of the European Society of Paediatric Gastroenterology Hepatology and Nutrition formulated ten questions considered to be essential for follow-up care. A literature search (January 2010–March 2020) was performed in PubMed or Medline. Relevant publications were identified and potentially eligible studies were assessed. Statements and recommendations were developed and discussed by all coauthors. Recommendations were voted upon: joint agreement was set as at least 85%.

**Results:** Publications (n = 2775) were identified and 164 were included. Using evidence or expert opinion, 37 recommendations were formulated on: The need to perform follow-up, its frequency and what should be assessed, how to assess adherence to the gluten-free diet, when to expect catch-up growth, how to treat anemia, how to approach persistent high serum levels of antibodies against tissue-transglutaminase, the indication to perform biopsies, assessment of quality of life, management of children with unclear diagnosis for which a gluten-challenge is indicated, children with associated type 1 diabetes or IgA deficiency, cases of potential celiac disease, which professionals should perform follow-up, how to improve the communication to patients and their parents/caregivers and transition from pediatric to adult health care.

**Conclusions:** We offer recommendations to improve follow-up of children and adolescents with celiac disease and highlight gaps that should be investigated to further improve management.

**What Is Known**

- There is a need for consensus on the methods regarding follow-up children and adolescents with celiac disease.

**What Is New**

- The Special Interest Group on Coeliac Diseases of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) formulated 10 questions considered to be essential for the follow-up care.
- Based on the available evidence from the literature or on expert opinion, 37 recommendations to improve follow-up were formulated.
- Gaps in knowledge were identified that should be investigated to further improve follow-up.

**Key Words:** celiac disease, children and adolescents, follow-up, position paper European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)

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It is generally accepted that clinical follow-up of children and adolescents with celiac disease (CD) is necessary to assess growth and development, resolution of their symptoms and possible complications and monitor compliance to the treatment with a gluten-free diet (GFD). However, the current follow-up approach is largely based on local practice and opinion with lack of evidence-based approaches. The responses to an enquiry of the Special Interest Group (SIG) on CD of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) among pediatricians and pediatric gastroenterologists across Europe showed significant variation in the methods of following-up their patients and offered scope for improvement (1).

The aim of this position paper was to therefore gather and evaluate the current evidence for the management and follow-up of CD in children and adolescents and offer recommendations on this topic.

## METHODS

In 2019, ESPGHAN established a working group within the SIG on CD to develop a position paper on the management and follow-up of children and adolescents with CD. The working group consisted of pediatric gastroenterologists, a methodologist (PW), two adult gastroenterologists (CCi, AAT), a biologist (MR), and a representative of the Association of European Celiac Societies (AOECS) (TK). During several group meetings, 10 focused clinical questions considered to be essential for follow-up care were formulated (Table 1). Smaller working groups, consisting of 3 to 5 coauthors, focused on each clinical question. All questions were then discussed jointly at two face-to-face meetings and at eight videoconferences.

## Search for and Inclusion of Studies

### Eligibility Criteria

We searched in PubMed or in Medline for articles published in English from January 2010 to March 2020, relevant to children and adolescents (<18 years) diagnosed with CD according to the ESPGHAN criteria (2,3). However, if a paper published before or after these dates was considered particularly important for an individual question, it was also included and this information was specified in the corresponding search results for the question, both in the Summary Table of the Literature (Appendix, Supplemental Digital Content, *http://links.lww.com/MPG/C861*) and in the individual section

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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 is at the discretion of physicians.

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TABLE 1. Questions and recommendations on the follow-up of children and adolescents with celiac disease

| Questions and recommendations |
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| **1. Is follow-up and management of celiac disease needed?** |
| *We recommend follow-up for children and adolescents after the diagnosis of CD has been established.* |
| **2. Who should do the follow-up of which patients and which is the role of the dietitian? What is the role of self-care and E-health?** |
| *The regular follow-up visits of children with CD are preferably carried out by a physician or a dietitian experienced in managing the disease. Local conditions and practices may determine how to apply these recommendations, but self-care treatment without access to adequate health care and dietitians is not recommended.* |
| **3. What should be the frequency of follow-up and what should be assessed?** |
| 3.1. *The first follow-up visit should be scheduled 3–6 months after CD diagnosis, but with easy access to the celiac service if earlier advice is needed, and sooner review if there are concerns regarding how the family is coping with the diet, if there are ongoing issues with growth or persistent symptoms or a need to repeat bloodwork earlier. Subsequent visits should be every 6 months until normalization of TGA levels, and every 12–24 months thereafter.* |
| 3.2. During follow-up patients should be evaluated for:<br>*3.2.I. Gastrointestinal and extraintestinal signs and symptoms.*<br>*3.2.II. Anthropometric measurements and growth parameters.*<br>*3.2.III. IgA-TGA using the same assay as at diagnosis as a surrogate marker for improvement/healing of the small-bowel mucosa. IgG based tests and RIA based IgA-TGA measurements are not suitable for follow-up in IgA sufficient patients. IgA insufficient patients with CD should be followed with IgG based tests.*<br>*3.2.IV. A complete blood cell count, micronutritional status (*eg, *hemoglobin, iron, vitamin B12, and vitamin D levels) and ALT measurements, should be performed after clinical evaluation at time of diagnosis. Any abnormality should be followed and deficiencies corrected until normalization. If abnormalities persist, additional diagnoses should be considered and appropriately investigated.*<br>*3.2.V. Screening for thyroid disease with TSH and thyroxine (and autoantibodies if indicated) may be considered during follow-up after clinical evaluation at the discretion of the clinician.*<br>*3.2.VI. Routine bone-density screening is not recommended.*<br>*3.2.VII. HBV antibody levels may be measured in previously immunized patients if this is considered important in the population. A booster dose should be given if inadequate levels are present.* |
| **4. Adherence to the gluten-free diet** |
| **4.1. Should the adherence to the diet be assessed during follow-up and if so, how?** |
| *Since a gold standard method is still missing, adherence to the GFD should be assessed multidimensionally through a careful evaluation of symptoms, dietary interview, or dietary questionnaires and laboratory tests.* |
| **4.2. What is the role of detection of gluten immunogenic peptides (GIPs) in the assessment of the compliance to the gluten-free diet?** |
| *Further data are needed before a recommendation on stool/urinary GIPs determination to assess compliance to the GFD in clinical practice can be formulated.* |
| **5. Common issues during follow-up and management of CD** |
| **5.1. When to expect catch-up growth?** |
| *In the prepubertal/pubertal child, if significant catch-up growth in height is not reached within 1 year after initiating the GFD, despite strict dietary adherence, additional investigations, and consultation with a pediatric endocrinologist are recommended to rule out other causes of short stature.* |
| **5.2. Is a lactose-free diet necessary?** |
| *We recommend a trial with lactose-reduced diet only in CD patients with symptoms suggestive of lactose intolerance (such as ongoing diarrhea, abdominal pain, or gassiness) despite adhering to the GFD.* |
| **5.3. Chronic tiredness in well-controlled celiac disease?** |
| *There are no specific recommendations for chronic fatigue in CD except to follow a GFD.* |
| **5.4. Irritable bowel syndrome (IBS) in celiac disease?** |
| *IBS in children with CD on a GFD should be treated similarly as in children without CD.* |
| **5.5. How to treat anemia and/or sideropenia?** |
| *Young children with anemia due to iron, folate, or vitamin B12 deficiency should receive supplementation in addition to the GFD, since improvement over time may take too long in these children in a critical period of brain development and rapid catch-up growth. A low threshold for supplementation may also be considered for older children. The disappearance of anemia should be confirmed in all cases. Adherence to the GFD should be checked, and other causes for anemia should be excluded in children who do not recover despite a strict GFD. Concerning sideropenia without anemia, an expectant attitude may be appropriate on GFD as long as there is improvement in iron stores without supplementation.* |
| **6. Specific issues during follow-up and management** |
| **6.1. How to approach persistent high serum levels of antibodies against tissue-transglutaminase (TGA)?** |
| *Lack of decreasing IgA-TGA levels after 6–12 months on a GFD or persisting positive IgA-TGA levels should be assessed by carefully reviewing dietary compliance and testing IgA-TGA using the same test from the same manufacturer.* |
| **6.2. When is it necessary to (re)biopsy?** |
| *Routine assessment of mucosal healing by small-bowel biopsies is not recommended in children with CD following a GFD. We recommend considering (re) biopsy only in selected CD cases; based on specific clinical grounds, for example, when doubts about the original diagnosis or suspicion of occurrence of an additionalcondition.* |
| **6.3. Refractory celiac disease in children: does it exist?** |
| *We recommend properly investigating other causes of an apparent "refractory CD" in children, including ongoing inadvertent ingestion of gluten and other possible concomitant enteropathies, such as Crohn'sdisease, autoimmune enteropathy, small-bowel bacterial overgrowth, cow's milk protein allergy and pancreatic insufficiency.* |
| **7. Should the quality of life (QOL) be assessed during the follow-up and if so, how?** |
| *We recommend assessing the HRQOL of children and adolescents with CD during follow-up by means of validated, CD-specific HRQOL questionnaires. These questionnaires may be administrated during or before the follow-up consultations, either on paper or by e-consultation. The results should be interpreted by the physician together with the parents/care givers, and if age adequate, also with the child.* |
| **8. Should follow-up of children with special situations be different from the one in the average CD patient?** |

TABLE 1. *Continued*

| Questions and recommendations |
|---|
| **8.1. In cases of unclear diagnosis** |
| *In cases of uncertain CD diagnosis, HLA typing should be performed before gluten-challenge to detect children in whom the occurrence of CD is unlikely.* |
| **8.1.1. How to perform a gluten-challenge?** |
| *8.1.1.II. To avoid unnecessary exposure to gluten in CD children with an early response to the challenge serum IgA-TGA determination may be considered 1 month after starting and this should be measured every 3 months during daily ingestion of 10–15 g of gluten for 12 months. Earlier evaluation is recommended in case of suggestive symptoms.* |
| *8.1.1.IV. In the absence of symptoms or specific CD-antibodies after 1 year of formal gluten-challenge, the child should be allowed to have a normal gluten-containing diet and follow-up visits with measurement of specific celiac-antibodies should be offered annually or every other year. Earlier evaluation is recommended in case of suggestive symptoms.* |
| **8.2. In children with associated type 1 diabetes (T1D)?** |
| *8.2.I. We recommend the same frequency and follow-up tests in children with CD and T1D as inchildren with isolated CD, with (additional) special attention to test for thyroid involvement and diabetic retinopathy.* |
| *8.2.II. We recommend developing the follow-up plan in conjunction with an endocrinologist/diabetologist and a dietitian, also considering the need for psychological and social support.* |
| **8.3. In children with associated IgA deficiency?** |
| *8.3.I. We recommend the same follow-up practice in IgA deficient children with CD than in IgA sufficient children with CD.* |
| *8.3.II. At follow-up visits CD-specific IgG antibodies(TGA, EMA or DGP)should be assessed.* |
| **8.4. In cases of potential CD?** |
| *8.4.I. In the presence of symptoms attributable to gluten, a trial of a GFD should be discussed with the family.* |
| *8.4.II. If left on a regular diet, we recommend annual follow-up visits, with attention towards growth and nutritional status, including bone health.* |
| *8.4.III. Duodenal biopsies should be performed in case of appearance of symptoms and/or of increased elevation of the CD antibody levels. In other cases with persistent serological positivity, on individual basis and in dialogue with the patient/caregivers, duodenal biopsies may be considered during follow-up.* |
| **9. How to improve communication: To parents? To patients?** |
| **9.1. Communication of diagnostic certainty to parents and children** |
| *The pediatric gastroenterologist/pediatrician should communicate to the patient and the parents/caregivers that the CD diagnosis is made with certainty and according to current evidence-based guidelines. All results (serology, histopathology, HLA if done) with dates of performance should be provided in writing for later proof of CD diagnosis.* |
| **9.2. Patient empowerment** |
| *9.2.I. The pediatric gastroenterologist/pediatrician and dietitian should communicate the need for a lifelong GFD and regular monitoring and facilitate access to professional dietary counseling knowledgeable on GFD.* |
| *9.2.II. We recommend providing education using oral and written information (leaflets, E-learnings etc.)about the disease and benefits of adhering to the diet. Later health risks should be brought into perspective without inducing fear or anxiety considering the patient's age and complications at the time of diagnosis and compliance with dietary recommendations.* |
| **9.3. Emotional and social support** |
| *9.3.I. Emotional and practical support from personal contact with other individuals with CD (Celiac/parent support groups, patient organizations, etc.) should be provided to reduce eventual feelings of social isolation.* |
| *9.3.II. Patients, especially adolescents, perceiving lifestyle changes related to CD diagnosis, including the GFD and emotional coping, as difficult warrant particular attention and support.* |
| **10. How to organize the transition from pediatric care to adult health care?** |
| *Even though current data is insufficient, we recommend a formal transfer of medical care of an adolescent with CD to facilitate the transition to adult care. The transfer should be structured and, at minimum, include a transition letter or "celiac passport" providing data on the basis of diagnosis, follow-up, anthropometric data, possible comorbidities and dietary adherence level.* |

CD = celiac disease; GFD = gluten-free diet; GIPs = gluten immunogenic peptides; HLA = human leukocyte antigen; HRQOL = health-related quality of life; IBS = irritable bowel syndrome; RIA = radio immune assay; TGA = antibodies against tissue-transglutaminase; T1D = type 1 diabetes.



of the question. The basic search strategy with emphasis on CD in children was shared by all groups and broadening of the inclusion of publications was allowed according to the specific question. Full search strategies for each question are presented in the Summary Table of the Revised Literature (Supplemental Digital Content, *http://links.lww.com/MPG/C861*). We excluded single case reports, commentaries, abstracts, nonsystematic reviews of the literature such as narrative reviews and expert opinions and studies performed exclusively in adults. In particular, if a narrative review was considered especially important or if no pediatric studies were available, this information was also included and specified for the corresponding single question as well as in the Summary Table of the Revised Literature (Supplemental Digital Content, *http://links.lww.com/MPG/C861*). Relevant papers were identified by review of their title and abstract contents. In case of potentially eligible studies, full texts were assessed. The final choice of studies was agreed upon by discussion and consensus. For each question, a short summary of the selected papers was provided, including study design (prospective or retrospective, cross-sectional, or case-control), age of the study population, sample size, study objectives, and main findings (Summary Table of the Revised Literature, Supplemental Digital Content, *http://links.lww.com/MPG/C861*).

## Strength of Recommendations

A recommendation was given for each (sub)question after an open discussion involving all coauthors, followed by a close individual voting. Agreement was set at 85% for each recommendation. When no agreement was reached, another round of discussions was performed to formulate a new recommendation upon which a final vote was taken. The recommendations are presented in Table 1.

## Ethics and Regulations

All guideline members' conflicts of interest have been noted and registered on the ESPGHAN website. The development of the

position paper was funded by ESPGHAN and was performed in collaboration with AOECS.

## RESULTS

Overall, 2775 publications were identified of which 164 informed these recommendations (Summary Table of the Literature, Supplemental Digital Content, *http://links.lww.com/MPG/C861*).

## Question 1: Is Follow-up and Management of CD Needed?

A search was conducted in Medline using the search terms celiac, celiac, children, adherence, and follow-up. The search identified a total of 356 records, of which 12 were included for this question: 8 primary observational studies (7509 children) and 4 systematic reviews (640 studies). We included 1 study in both adults and children (6), 1 systematic review until the age of 20 years (12), and another one without an age specification (13).

One goal of short-and medium-term follow-up is the monitoring of the improvement of symptoms after starting the GFD. In patients with inadequate improvement (symptoms, catch-up growth, serology) after short-medium-term adherence to the diet, it is necessary to investigate hidden sources of gluten in the diet and to consider the presence of other pathologies. Complications should be checked for. Another general goal is to ensure education on the condition and social support and to motivate the child with CD and their family (4,5), reinforcing at each visit the importance of dietary compliance which may vary between 4% and 90% (6–9). Strict adherence to GFD has a positive impact on the improvement of symptoms (10) and it may also allow prevention of CD-associated complications. Whether the risk for associated autoimmune diseases can be reduced by early diagnosis and treatment of CD remains controversial (11). During one of the first visits after the diagnosis, information on the increased risk of CD among first degree relatives and their indication of CD screening according to the ESPGHAN diagnostic guidelines (3), should be part of the family education. Information on new treatment avenues should also be given during follow-up.

Current recommendations on follow-up are largely based on expert opinion (12,13). Reports have emerged that may help shape the follow-up content of the follow-up visits (14). The chronic and systemic nature of CD makes a multidisciplinary team advantageous for follow-up, including a pediatric gastroenterologist, dietitian-nutritionist, and in some cases, an immunologist, pathologist, and psychologist. Consultation with a pediatric gastroenterologist or a pediatrician with expertise in CD is recommended for diagnosing the disease. They should likewise be involved in the monitoring and adequate interpretation of the laboratory test results requested during follow-up, as well as in the identification and management of possible associated complications. During adolescence, the transfer to adult health care is initiated and organized, depending on the patient's understanding of the condition, readiness and required maturity to transition into adult services (15).

### Statement and Recommendation

We recommend follow-up for children and adolescents after the diagnosis of CD has been established. *100% Agreement.*

## Question 2: Who Should Do the Follow-up of Which Patients and Which Is the Role of the Dietitian? What is the Role of Self-care and E-Health?

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up, gluten-free diet, pediatrician, pediatric expert in the field of celiac, general doctor, dietitian, and e-health. The search identified a total of 111 records, of which 4 were included: 2 primary observational studies (381 children) and 2 randomized clinical trials (RTC) in both children and adults (17, 18) (365 patients <25 years).

Children with CD have traditionally been followed by pediatric gastroenterologists or pediatricians and sometimes after a period of a GFD by a dietitian (3). The indicated person to conduct the follow-up of children with CD differs substantially between countries and even regionally within countries applying the same health care system. The general recommendation by most studies indicates that access to a dietitian or a physician with an interest in CD is important for adequate treatment and evaluation of adherence to the GFD (see question 1). There is, however, a paucity of studies that compare long-term effects of dietary compliance depending on who conducts the follow-up. The only study investigating compliance to the diet in children followed by a dietitian or a by a physician showed no differences in outcome, albeit dietitian-led visits being less expensive (16).

A cornerstone of successful treatment of children with CD is how they adapt to the GFD. Educating children, adolescents, parents, and guardians (and extended family) about the GFD constitutes an important component of the follow-up visits (see question 9). Whether education in self-care of children with CD should be separated from physical follow-up visits may depend on local conditions and practices. Communication over the internet offers new opportunities to connect to the patient and families and are under development. E-learning is defined as all forms of electronically mediated teaching. Electronic health technologies (E-health) is the use of information and communication technologies, such as smartphone applications, in support of health and disease management. Utilizing E-learning and E-health as a replacement for physical follow-up visits of children with CD has recently been evaluated. Three studies of which two were RCTs (17,18) have investigated E-health in the follow-up of patients with CD. Haas et al studied the influence of Text Message intervention in newly diagnosed children and young adults. Vriezinga et al compared online consultation versus in-office outpatient visits. Both interventions positively affected self-management, QoL, patient satisfaction, and in one study reduced health care costs compared with conventional in-office standard of care. Another RCT by Connan et al prospectively studied a small number of participants (n = 33) and found an improvement in knowledge about CD by introducing interactive E-learning methods (19).

### Statement

There is evidence that the follow-up of children with CD should be performed by a physician and a dietitian with experience in managing and evaluating patients on a GFD. While a dietician-led follow-up of CD has shown promising results and may come at a lower cost, more research is needed before stating whether a dietitian, a physician, or both should conduct the long-term follow-up. E-health interventions seem promising tools in CD-care, which utilization and effectiveness in CD-care should be further explored.

### Recommendations

The regular follow-up visits of children with CD are preferably carried out by a physician or a dietitian experienced in managing the disease. Local conditions and practices may determine how to apply these recommendations, but self-care treatment without access to adequate health care and dietitians is not recommended. *93% Agreement.*

## Question 3: What Should Be the Frequency of Follow-up and What Should Be Assessed?

A search was conducted in Pubmed using the search terms celiac, celiac, children, and follow-up. The search identified a total

of 382 records, of which 30 were included for this question: 17 primary observational studies (1,599,387 children) and 13 reviews (772 studies). We included 1 guideline in adults (30), one publication in adults and children (23) and one systematic review (35) in adults. We also included 5 studies published before 2010 (38,39,45,46) and 1 after March 2020 (36).

Current literature does not provide solid evidence on the optimal frequency of follow-up. Despite a lack of high-quality studies, a first follow-up visit scheduled 3–6 months after CD diagnosis is recommended, but with easy access to the celiac service if earlier advice is needed and with earlier clinic review depending on family knowledge, concerns and difficulties with the diet, and importantly, if symptoms persist or worsen despite strict adherence to GFD, or if clinical presentation (eg, malnutrition) or laboratory abnormalities at diagnosis require earlier follow-up. Intervals for further follow-up visits should also take the "above mentioned" issues under consideration, and be scheduled at a 6–12 months interval and every 12–24 months afterwards.

Pediatric patients on a strict GFD usually show rapid resolution of CD-related gastrointestinal symptoms, such as bloating, diarrhea, abdominal pain, weight loss, as well as of extraintestinal manifestations such as anemia, delayed puberty, and stomatitis (20). Inconsistent or no follow-up is associated with poor dietary adherence (10).

Normalization of serology is widely used during follow-up as a proxy for mucosal healing in children with high positive and negative predictive values (21–23). A significant reduction in levels of IgA against tissue-transglutaminase (TGA) is already seen after 3 months of GFD if measured with the same assay. However, TGA levels remained above 1× the upper level of normal (ULN) in 83.8% and above 10× ULN in 26.6% of studied children after 3 months on GFD (24). Full normalization of both TGA levels and histopathology may take over 2 years, particularly in those with severe small-bowel lesions and high TGA levels at diagnosis (25–27). IgG based tests and radio immune assay (RIA) based TGA measurements are not suitable for monitoring response to a GFD in IgA sufficient patients with CD.

Bone health may be compromised in CD patients (28) and in children bone disease is mostly asymptomatic and associated with decreased growth and bone quality (29). In contrast to that observed in adults (30), CD in children does not seem to be associated with an increased fracture risk (31). A reduced bone mineral density (BMD) may be present at CD diagnosis in children and adolescents (29,32). Although a longer follow-up might be needed in some cases to ensure a proper BMD recovery (33), in most cases, 1 year on a strict GFD is sufficient to restore bone mass (12,14,28). Therefore, routine BMD testing is neither required nor cost-effective. When bone loss has been identified for clinical reasons serial bone-density tests should be conducted every 1 to 2 years until normalization (12).

Vitamin D levels have been investigated in CD children in several studies that are heterogeneous in their design and outcomes. Some of these demonstrate low vitamin D levels at diagnosis (12,14,34–36), but the impact of the GFD on vitamin levels remains uncertain. Although the evidence is not strong, assessment of vitamin D status, in case of abnormal levels at CD diagnosis, and correction of any ongoing deficiency should be considered good patient care to optimize bone health.

The liver is a common site of extraintestinal manifestations of CD, usually presenting with raised aminotransferases. Liver function should be monitored during follow-up if abnormal at diagnosis (12).

As CD children may present with micronutrient deficiencies, investigations for iron (commonest), folate, and vitamin B12 deficiencies are relevant at diagnosis and, if abnormal, these should be monitored until normalization, either via the GFD or supplementation in case of anemia or depleted iron stores.

The risk of autoimmune thyroid disease is increased in CD patients as reported by a large population study (37) and several case-control studies (38–40). However, other studies show no added benefit of thyroid disease testing in CD children in the absence of symptoms (14). Based on the current literature, there is no evidence to advise whether assessment of thyroxin or thyroid stimulating hormone (TSH) blood levels should be monitored during follow-up, and in which frequency.

Concerning immunization, HBV vaccine has been shown to potentially have a reduced response, with 50% of patients with CD having a poor antibody response versus 11% of controls in case of vaccination within the first 6 months of life (41–43). In addition, one study reported reduced protection after HAV vaccination (42). Whether this is related to genetic host susceptibility or to other factors has not been clarified. Based on the above, screening for HBV immunization status has been suggested in newly diagnosed CD children (12). There is no current evidence indicating that response to HBV vaccine should be evaluated during follow-up. However, if a poor antibody response is detected, revaccination should be performed (43). A second dose effectively induces protective levels in those CD children (41–44). Several studies detected no differences between CD children and controls in the immune response to poliomyelitis, diphtheria, mumps, and pertussis (45), rubella, tetanus (45,46), haemophilus influenzae type b (46) and measles (45,47). There is therefore currently no evidence to support routine checking of vaccine response during follow-up.

The question about who should follow-up the patient is the subject of question 2 in this paper. In general, and based on the resources available in each national system, a pediatric gastroenterologist or a pediatrician with special interest/experience in pediatric gastroenterology or an experienced dietitian could follow the patient with CD.

## Statements

1. The current literature does not provide evidence on the optimal frequency of follow-up or what should be assessed during visits.
2. Normalization of IgA-TGA levels is widely used as a proxy for mucosal healing in children.
3. Nutritional deficiencies may be present at the time of CD diagnosis.
4. Children with CD have an elevated risk of autoimmune thyroid diseases.
5. A reduced BMD may be present at CD diagnosis.
6. Vaccine responses in children with CD are identical to those of the general population, except for a moderate level of evidence of poor seroconversion in response to HBV vaccination.

## Recommendations

1. The first follow-up visit should be scheduled 3–6 months after CD diagnosis, but with easy access to the celiac service if earlier advice is needed, and sooner review if there are concerns regarding how the family is coping with the diet, if there are ongoing issues with growth or persistent symptoms or a need to repeat bloodwork earlier. Subsequent visits should be every 6 months until normalization of the TGA levels, and every 12–24 months thereafter. *93% Agreement.*
2. During follow-up patients should be evaluated for:
   I. Gastrointestinal and extraintestinal signs and symptoms. *100% Agreement.*
   II. Anthropometric measurements and growth parameters. *100% Agreement.*

III. IgA-TGA using the same assay (ELISA or EIA) as at diagnosis, as a surrogate marker for improvement/healing of the small-bowel mucosa. IgG based tests and RIA based IgA-TGA measurements are not suitable for follow-up in IgA sufficient patients. IgA insufficient patients with CD should be followed with IgG based tests. *100% Agreement.*
IV. A complete blood cell count, micronutritional status (eg, hemoglobin, iron, vitamin B12, and vitamin D levels) and ALT measurements, should be performed after clinical evaluation at time of diagnosis. Any abnormality should be followed and deficiencies corrected until normalization. If abnormalities persist additional diagnoses should be considered and appropriately investigated. *91% Agreement.*
V. Screening for thyroid disease with TSH and thyroxine (and autoantibodies if indicated) may be considered during follow-up after clinical evaluation at the discretion of the clinician. *91% Agreement.*
VI. Routine bone-density screening is not recommended. *93% Agreement.*
VII. HBV antibody levels may be measured in previously immunized patients if this is considered important in the population. A booster dose should be given if inadequate levels are present. *91% Agreement.*

## Question 4: Adherence to the Gluten-free Diet.

### Question 4.1: Should the Adherence to the Diet Be Assessed During Follow-up and If So, How?

A search was conducted in Medline using the search terms celiac, celiac, children, adherence, follow-up, gluten-free diet, dietitian, teenagers, questionnaires, score, E-Health/App. The search identified a total of 54 records, of which 9 were included for this question: 6 primary observational studies (306 children) and 3 systematic reviews (15,470 studies). We included 2 studies in adults and children (53, 54) and 2 in adults (50, 55). We included Harder et al published after March 2020.

There is general consensus about the need to assess adherence to the GFD during the follow-up of CD patients (48–50). Despite the absence of a gold standard to assess dietary compliance, a dietary evaluation by a trained dietitian is considered the best method, as it is the cornerstone of dietitians to asses and manage diets, but this is time-consuming and requires expert personnel. Short dietary questionnaires and TGA determinations in serum fail to detect dietary transgressions in children and adolescents with CD, showing poor sensitivity to identify all patients who consume gluten (51–53). There is a limited range of questionnaires specific for children. Long questionnaires specific for children may be useful to assess diet compliance, especially in settings with no dietitian consultation available (51).

In spite of the wide use of determination of specific CD-antibodies, especially TGA in serum as a surrogate marker of GFD adherence, negative TGA results do not correlate well with dietary compliance (21,54).

Further development of E-Health resources for assessment of adherence to the GFD are needed, as most available CD smartphone apps lack clinical validation (55).

*Statement*

The assessment of adherence to the GFD is one of the primary goals of CD follow-up.

*Recommendation*

Since a gold standard method is still missing, adherence to the GFD should be assessed multidimensionally through a careful evaluation of symptoms, dietary interview and/or dietary questionnaires and laboratory tests. *100% Agreement.*

### Question 4.2: What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of compliance to the gluten-free diet?

A search was conducted in Medline using the search terms celiac, celiac, children, adherence, follow-up, gluten immunogenic peptides, gluten-free diet, compliance, adherence, diet, monitor, aftercare, secondary care and health care. The search identified a total of 28 records, of which 7 were included: 5 primary observational studies (1 in children, 2 in both adults and children, and 2 in adults) (129 children) and 2 systematic reviews (990 publications). We included studies in adults (57, 58) and in both adults and children (53, 54, 56). We included Silvester (58) and Stefanolo (57) published after March 2020.

A small fraction of ingested gluten peptides is excreted in urine and in stools, thereby revealing recent gluten exposure. Measurement of GIPs in stool or urine has been introduced as a tool to detect gluten ingestion in patients adhering to a GFD (53,54,56–58). GIPs may be detected using specific monoclonal antibodies, A1 or G12, recognizing gluten epitopes by lateral flow immunochromatography (LFIA) (stool or urine) or ELISA (stool). Compared with other methods to evaluate adherence, GIP testing disclosed the lowest adherence rate to the GFD (75%), suggesting that this assay is more sensitive than others to detect cases occasionally exposed to inadvertent gluten ingestion (9). Repeated GIP positivity over a span of multiple days has been reported to correlate with intestinal mucosa damage (49,54). Now that GIPs are available for use in clinical settings and for disease self-managing by the patient, some questions remain to be answered, as the indication for urine or stool testing, the latency between gluten exposure and appearance in stool/urine, the relationship between the quantity of ingested versus eliminated gluten in stool/urine and the role of these tests in the assessment of long-term adherence to GFD.

*Statement and Recommendation*

Further data are needed before a recommendation on stool/urinary GIPs determination to assess compliance to the GFD in clinical practice can be formulated. *93% Agreement.*

## Question 5: Common Issues During Follow-up and Management of CD

A search was conducted in Medline using the search terms celiac, celiac, children, follow-up, catch-up, growth and development, lactose intolerance, chronic tiredness, fatigue, irritable bowel syndrome, anemia and iron deficiency. The search identified a total of 58 records, of which 18 were included: all primary observational studies (1,590,861 children). Two papers on adults and children were included (64, 67).

### Question 5.1: When to Expect Catch-up Growth?

Four original studies were included (29, 59–61). All studies but one were retrospective and with a limited sample size. Only one study assessed the correlation between recovery of growth velocity and decrease in CD antibody levels (61). Maximum catch-up growth in weight and (in the prepubertal child) also in height, is expected within the first six months on a GFD (61) and it can continue for 2–3 years, at which time the child is predicted to reach the expected height. Age at diagnosis may influence final/target height (59), but it is controversial whether it is possible to prevent permanent height reduction by early dietary treatment. Negative TGA is associated with a rapid weight recovery but does not seem to have the same long-term effect on catch-up of height (29,59,60).

*Statement*

In a child with impaired growth at the time of CD diagnosis, catch-up growth in weight and height is usually expected within

six months after starting the GFD, after which, depending on the patient's age and continuance of the diet for 1–2 years, expected height is reached.

*Recommendation*

In the prepubertal/pubertal child, if significant catch-up growth in height is not reached within 1 year after initiating GFD, despite strict dietary adherence, additional investigations and consultation with a pediatric endocrinologist are recommended to rule out other causes of short stature. *93% Agreement.*

### Question 5.2: Is a Lactose-free Diet Necessary?

Untreated CD may cause secondary lactose intolerance due to villous damage, but this is not a consistent finding. The prevalence of genotypes predisposing to adult-onset primary hypolactasia in CD patients is comparable to the rate within the general population (62,63).

*Statement*

CD patients may develop primary lactose intolerance over time, similar to the general population. Patients can also have secondary lactase deficiency due to villous damage, but are usually lactose-tolerant and there is no evidence of the benefits of temporary lactose-free diet on top of the GFD, unless clinical symptoms are highly suggestive of concomitant lactose intolerance (such as ongoing diarrhea, abdominal pain, or gassiness after starting GFD).

*Recommendation*

We recommend a trial with lactose-reduced diet only in CD patients with symptoms suggestive of lactose intolerance (such as ongoing diarrhea, abdominal pain and/or gassiness) despite adhering to the GFD. *93% Agreement.*

### Question 5.3: Chronic Tiredness in Well-controlled Celiac Disease?

Only two papers (64,65) were found, both reporting that children had greater and more significant improvements of chronic tiredness on a GFD compared to adults with CD. Fatigue improved significantly in 81% of children on a strict GFD and only 3 of the 40 children had persistent chronic fatigue after one year on the diet.

*Statement*

CD children on GFD have a significant improvement in chronic fatigue.

*Recommendation*

There are no specific recommendations for chronic fatigue in CD except to follow a GFD. *97% Agreement.*

### Question 5.4: Irritable Bowel Syndrome (IBS) in Celiac Disease?

Similar prevalence of abdominal pain and functional gastrointestinal disorders have been demonstrated in CD on a GFD for at least six months vs. controls on a regular diet (66). In both CD patients and in controls, the most common functional gastrointestinal disorder was IBS.

*Statement*

No increased frequency of IBS has been demonstrated in children with CD on a GFD.

*Recommendation*

IBS in children with CD on a GFD should be treated similarly as in children without CD. *93% Agreement.*

### Question 5.5: Anemia or sideropenia

Seventeen studies were evaluated and ten pediatric studies were included (14,37,64,67–73). Only one study was prospective (71). Anemia is a frequent finding (12–24%) in children with untreated CD (64,67–70). It is usually caused by iron deficiency, but also vitamin B12 and folate deficiencies and anemia of chronic disease may contribute. In one large nationwide study, anemia, regardless of the underlying etiology, was significantly more common in adolescents with CD compared to controls (37). However, prevalence of subclinical iron deficiency is rarely reported during follow-up. In most cases (84%-96%) anemia improves or recovers on a GFD (14,64,67,70,72). Poor compliance to GFD may hamper recovery (70,73). Evidence is lacking regarding the incremental benefit of routinely adding iron supplementation.

*Statement*

CD is a common cause of anemia and associated nutritional deficiencies in children. Abnormal values should be monitored until normalization on a GFD. An adequate response can be expected within one year from initiating GFD, although more prospective evidence is needed. Poor dietary compliance and/or reduced nutritional iron-content predispose to non-recovery of anemia.

*Recommendation*

Young children with anemia due to iron, folate or vitamin B12 deficiency should receive supplementation in addition to the GFD, since improvement over time may take too long in these in children in a critical period of brain development and rapid catch-up growth. A low threshold for supplementation may also be considered for older children. The disappearance of anemia should be confirmed in all cases, adherence to the GFD should be checked, and other causes for anemia should be excluded in children who do not recover despite a strict GFD. Concerning sideropenia without anemia, an expectant attitude may be appropriate on the GFD as long as there is improvement in iron stores without supplementation. *95% Agreement.*

## Question 6: Specific Issues During Follow-up and Management.

### Question 6.1: How to Approach Persistent High TGA Levels During Follow-up?

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up, persistent or elevated transglutaminase, antibody, and gluten-free diet. The search identified a total of 167 records, of which 17 were included: all primary observational studies (2128 children). We included one article published after March 2020 (26).

Although CD serology markers (IgA-TGA and endomysial autoantibodies (EmA)) work very well for diagnosis, these are less accurate for dietary monitoring (74,75). Dynamics of CD-antibodies after diagnosis may vary according to the adherence to the GFD, the timeframe of testing, type of antibodies, age at diagnosis, coexisting diseases (IgA deficiency, type 1 diabetes), antibody levels at diagnosis, and by assays used (25,26,76–83).

During follow-up, continuous decreasing levels of IgA-TGA, until values below cutoff of normality are reached, and a negative EmA cautiously reflects sufficient dietary compliance (84,85). On a GFD, IgA-TGA levels decrease over time and are expected to normalize by 18–24 months after starting the diet (84) depending on the serology kit used. No data are available on how slightly elevated IgA-TGA at follow-up should be addressed. However, it is reasonable to suspect that persistently slightly elevated IgA-TGA levels imply inadequate dietetic compliance in most patients with CD.

Different methods are available to detect CD-antibodies in serum: enzyme-linked immunosorbent assay (ELISA); chemiluminescence; radioimmunoassay (RIA). For decades, the most widely used CD serology assessment method has been ELISA and the majority of clinical evidence available has been addressed by this technique. Persistent positivity of chemiluminescence IgA-TGA should be interpreted with caution since it has a slower decrease over time (26) and should be better integrated with ELISA assay since more follow-up data are available on this latter technique with regards to dietary monitoring. Nevertheless, it should be clear that CD-specific antibody measurement does not suffice to evaluate compliance to a GFD and to establish complete recovery of mucosal healing. Gastrointestinal symptoms, with or without slightly elevated CD-antibodies, may persist in a small percentage of children claiming optimal dietary adherence (86,87) (see also question 6.2).

*Statements*

IgA-TGA levels are expected to normalize by 18–24 months following the start of a strict GFD.

*Recommendation*

Lack of decreasing IgA-TGA levels after 6–12 months on a GFD or persistently positive IgA-TGA levels should be assessed by carefully reviewing dietary compliance and testing IgA-TGA using the same test from the same manufacturer. *93% Agreement.*

### Question 6.2: When Is it Necessary to (Re)biopsy?

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up, repeated, biopsy and follow-up biopsy. The search identified a total of 225 records, of which 8 were included: 6 primary observational studies (592 children) and 2 systematic reviews (87 studies). We included 3 studies in both adults and children (21, 89, 90).

After CD diagnosis, duodenal biopsies to assess mucosal healing may be considered as an ultimate option to discuss thoroughly with the family and to dismiss any further doubt about compliance and responsiveness to the GFD. This may be of clinical value even in those asymptomatic children whose parents claim strict dietary adherence but with still, mostly slightly, elevated IgA-TGA after 24 months on a GFD. Following this path, in the case of normal duodenal mucosa (Marsh 0 and Marsh 1) the family can be reassured (75). In case of persisting major mucosal abnormalities (ie, Marsh 2 (crypt hyperplasia) and/or Marsh 3 (villous atrophy)), better dietary compliance should be encouraged.

In the scarce literature regarding persisting villous atrophy in CD children on a GFD, we found a prevalence of 2%-19% at 1–3 years after CD diagnosis (75,85–89). The discrepancy in frequencies is possibly due to the heterogeneity in study design of the different studies, including the inclusion criteria, duration of the GFD and methods of assessment of dietary compliance. A meta-analysis demonstrated that children had higher frequency of complete histological recovery (65%) and regression of abnormal villous/crypt depth ratio (74%) than adults (24% and 58%, respectively) (90). Moreover, younger age at diagnosis was related to less severe initial histologic damage; and male gender predisposed for achieving mucosal recovery. Vécsei et al concluded that antibody tests are of limited value in predicting the mucosal status in the early post-diagnosis years but that they perform better after a longer period of time on GFD. The study also found that negative EmA most reliably predicts mucosal healing (85). These results are in accordance with a prospective longitudinal study performed in Australia in which no persistent villous atrophy was found in 97 negative IgA-TGA CD children with a median time to re-biopsy of 1.4 years on a GFD (range 1.0–12.4 years) (75). However, in the retrospective study performed by Leonard et al, serology as predictor of Marsh 3 histology at repeat biopsy was poor (86). A recent meta-analysis concluded that IgA-TGA has low sensitivity in detection of persistent villous atrophy, but the authors did not specify the levels of antibodies (only positive or negative) (21).

*Statements*

1. There are few and heterogeneous studies addressing the question "if and when" to perform (re)biopsy.
2. Slightly elevated IgA-TGA levels in CD children on a GFD are unlikely to be correlated with mucosal injury.

*Recommendation*

Routine assessment of mucosal healing by small-bowel biopsies is not recommended in children with CD following a GFD. We recommend considering (re)biopsy only in selected CD cases; based on specific clinical grounds, for example, when doubts about the original diagnosis or suspicion of occurrence of an additional condition. *100% Agreement.*

### Question 6.3: Refractory Celiac Disease in Children: Does It Exist?

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up, unresponsive, refractory, nonresponsive, and nonresponsive. The search identified a total of 69 records, of which 7 were included: 6 observational studies (252 children) and 1 systematic review (5 studies in children). We included studies in both adults and children ( 21,64,92,93).

Refractory celiac disease is defined by persistent or recurrent villous atrophy and malabsorptive symptoms in CD patients despite adherence to a strict GFD. Although well described and characterized in adults, the occurrence of refractory CD in children is very rare. Our search did not find any report on refractory CD in children in 6 of the 7 papers (21,56,64,91–93). Only one paper (94) described 3 cases of celiac children "not responding to the GFD." However, 2 of the patients were negative at immunohistochemistry for CD3 changes consistent with refractory CD and in addition they eventually responded to a strict GFD. In the third patient, who was apparently permanently nonresponsive, specific immunochemical testing for refractory CD was not performed. The paucity of these challenging cases underline the importance of referring suspected child/adolescent cases to tertiary care centers (with available expert pathologists) and the duty of reporting cases of pediatric refractory CD in the medical literature.

*Statement*

There is very poor evidence for the existence of refractory CD in children.

*Recommendation*

We recommend properly investigating other causes of an apparent "refractory CD" in children, including ongoing inadvertent ingestion of gluten and other possible concomitant enteropathies, such as Crohn's disease, autoimmune enteropathy, small-bowel bacterial overgrowth, cow's milk protein allergy, and pancreatic insufficiency. *100% Agreement.*

## Question 7: Should the Quality of Life (QOL) Be Assessed During Follow-up and If So, How?

A search was conducted in Medline using the search terms celiac, celiac, children, follow-up, and quality of life/QoL. The search identified a total of 89 records, of which 18 were included: 16 primary observational studies (16,043 children) and 2 systematic reviews (39 studies). The study from (110), published after March 2020, was also included.

Most of the included studies assessed the health-related quality of life (HRQOL) in CD during follow-up after starting treatment with a GFD (4,82,95–109). Ten studies used generic HRQOL questionnaires: SF-12; KIDSSCREEN-52, Nowicki-Strickland Locus of Control Scale, KINDL, Pediatric QoL Inventory Test, PedsQL, Kidscreen, EQ-5D test, General Purpose HRQOLScale for Children, Inventory of Life Quality in Children and Adolescents; Berner Subjective Well-being Inventory. Nine of these studies found similar HRQOL in children with CD as in control children (4,82,95,96,99,100,102,103,106). However, five of the six studies using CD-specific HRQOL questionnaires (CDDUX, CDQL, CDQOL Scale-KINDL, CDPQOL) found that the HRQOL of children and adolescents with CD was poor or neutral (82,96,100,105,109). A model of a questionnaire for assessment of CD-specific HRQOL is provided in Annex 1 (Supplemental Digital Content, *http://links.lww.com/MPG/C861*). Parents gave lower HRQOL scores as compared to their children (96,97). These findings are in agreement with those from studies reported in a recent systematic review and meta-analysis of the literature (110). Food situations at school, meals at home and meals outside home are factors repeatedly found to have a negative impact on emotions, social relationships, and management of the daily life of CD children and adolescents. These factors include feeling different at times, feeling unhappy when eating, feeling angry about having to follow a GFD and in general difficulties in accepting the diet. In the only study on the subject, physicians were found to overestimate the HRQOL of children and young adults with CD during follow-up (109). While a little-studied area of CD-care, when indicated, one can consider it as good clinical practice to refer to a psychologist, preferably with knowledge of CD and coping strategies.

### Statement

When assessed by CD-specific questionnaires, the HRQOL of children and adolescents with CD on a GFD is reported to be neutral or poor.

### Recommendation

We recommend assessing the HRQOL of children and adolescents with CD during follow-up by means of validated, CD-specific HRQOL questionnaires. *87% Agreement.* These questionnaires may be administrated during or before the follow-up consultations, either on paper or by e-consultation. The results should be interpreted by the physician together with the parents/care givers, and if age adequate, also with the child.

## Question 8: Should Follow-up of Children With Special Situations Be Different From the One in the Average CD Patient?

### Question 8.1: In Cases of Uncertain Diagnosis: When and How to Perform Gluten-challenge?

A search was conducted in Pubmed using the search terms celiac, celiac, children, follow-up, and gluten-challenge. The search identified a total of 850 records, of which 20 were included: 9 RCT (1 in children: 23 children) and 8 primary observational studies (2 in children: 194 children). We included 14 studies in adults (116–122, 159–165) and 2 studies in both adults and children (3, 111). We included 4 studies published before 2010 (111–114) and 1 after March 2020 (161).

In situations where a GFD was started before the diagnosis was completed, the reintroduction of gluten into the diet, or the so-called gluten-challenge is currently the only method to secure the diagnosis.

Due to its high negative predictive value, HLA-DQ2 and DQ8 typing is the most reliable test to select those children in which the CD diagnosis is extremely unlikely (3). However, in HLA-DQ2 and/or DQ8 positive children, the uncertain diagnosis may be assessed by gluten reintroduction, followed by monitoring of symptoms, measurements of CD-specific antibodies and small-bowel mucosal biopsy in selected cases. ESPGHAN 2012 CD diagnosis guidelines provided indications on how to perform a gluten-challenge (2). However, the amount of gluten to be used and the appropriate duration of the challenge remains a matter of debate. In general, the amount of gluten in one slice of bread is about 3–5 g and the regular daily gluten intake has been estimated to be 10–20 g/day in adults and about 5–15 g/day in children, depending on the age (2,111,112). In practice, 10–15 g/day of gluten followed by first clinical and serological assessment after 3 months of challenge is usually used for CD diagnosis. As a rule, CD may be considered less probable in children without specific CD-antibodies in serum and normal small-bowel mucosa after up to 2 years of gluten-challenge. However, cases of children relapsing after gluten-challenge as long as 19 years after the challenge have been reported (113). Gluten-challenge studies in children using a gluten amount of 5–10 g/day resulted in serological relapse in 66% of 134 CD children after 3 months and in 89.9% after 6 months. The challenge duration for histological relapse was about 6 months (114). One study reported 71% of 41 CD children developing gastrointestinal symptoms after a gluten-challenge with 1–3 slices of wheat bread per day during 3 consecutive days (115). A previous study demonstrated duodenal mucosal deterioration and positive celiac autoimmunity in 10 long-term treated CD children after a challenge with 14 g gluten/day for 3–12 months (112).

As CD causes malabsorption and attenuated growth, gluten-challenge is usually avoided in toddlers and adolescents. In adults, randomized blinded gluten-challenges were performed as part of several CD pharmaceutical trials. Different amounts of gluten were given, concluding that 2 g of daily gluten ingested for 6 weeks induced small-bowel injuries and symptoms in most of the patients, and that 2–4 g of daily gluten for 10 weeks induces symptoms as well as serological and histological relapse in the majority of CD patients (116–119). Even shorter challenges of 2–10 weeks with 2–4 g or 3 g of gluten/day have been proposed (120,121). However, it has been argued that short gluten-challenges of 2 weeks are prone to false negative conclusions when only conventional histology is used for the mucosal assessment (122).

#### *Statements*

I. Gluten-challenge is indicated in children suspected of CD but in whom a GFD was initiated before the CD diagnosis was certain. Challenge should be avoided during periods of accelerated growth. The gluten-challenge should be performed under the supervision of a pediatric gastroenterologist.
II. Gluten ingestion of 10–15 g/day for 3–6 months is expected to induce small-bowel abnormalities in the majority of CD children.
III. The optimal amount of daily gluten intake and the shortest time for an effective gluten-challenge are still unknown.

#### *Recommendations*

In cases of uncertain CD diagnosis, HLA typing should be performed before gluten-challenge in order to detect children in whom the occurrence of CD is unlikely. *100% Agreement.*

*Question 8.1.1: How to Perform a Gluten-Challenge?*

I. In children with HLADQ2 and/or DQ8 positivity with an indication for gluten-challenge, intestinal biopsies before starting the challenge may be considered at the discretion of the clinician and in dialogue with the patient/caregivers. 77% *Agreement.* As this recommendation did not reach threshold for agreement (85%) it is not included in the recommendations in this paper (Table 1).
II. To avoid unnecessary exposure to gluten in CD children with an early response to the challenge serum IgA-TGA determination may be considered 1 month after starting, and this should be measured every 3 months during daily ingestion of 10–15 g of gluten for 12 months. Earlier evaluation is recommended in case of suggestive symptoms. *100% Agreement.*
III. In case of symptoms suggestive of CD and/or specific CD-antibodies, small-bowel biopsies should be performed. 82% *Agreement*. As this recommendation did not reach threshold for agreement (85%) it is not included in the recommendations in this paper (Table 1).
IV. In the absence of symptoms and/or specific CD-antibodies after 1 year of formal gluten-challenge, the child should be allowed to have a normal gluten-containing diet and follow-up visits with measurement of specific CD-antibodies should be offered annually or every other year. Earlier evaluation is recommended in case of suggestive symptoms. *93% Agreement.*

## Question 8.2: Follow-up of Patients With CD and T1D

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up and diabetes. The search identified a total of 151 records, of which 10 were included: 7 studies in children (3295 children) and 3 studies in both adults and children (123–125).

There are few studies focusing on the follow-up of children with CD and T1D, and they are mostly retrospective in nature. Most of the authors compared outcomes in patients with T1D and CD to patients with T1D only (123–127). Few compared patients with both diseases to patients with CD only (79,128,129). Some studies are nationwide, multicentric, registry-based focusing on a single country (123–126); others are single-center studies (130). The number of patients in most of the studies is low. Most patients with CD and T1D are detected through screening and are usually asymptomatic, with some having potential CD. Data on long-term follow-up of patients with both diseases show that they have an increased risk of thyroid pathology compared with isolated T1D (124) or to isolated CD (128) and of diabetic retinopathy compared with isolated T1D (123). It has also been shown that growth can be affected for a prolonged time despite strict GFD (126). On the other hand, the risk of fractures and nephropathy was not found to be higher in patients with both CD and T1D compared to isolated T1D (125,128,131). The long-term outcome of CD in T1D patients is similar to the one in CD without T1D in terms of compliance with the GFD and achieving remission of CD (129,130). However, some patients who perceived themselves to be asymptomatic had more problems with compliance with a GFD, warranting a stricter follow-up in selected cases (79).

*Recommendations*

I. We recommend the same frequency and follow-up tests in children with CD and T1D as in children with isolated CD, with (additional) special attention to test for thyroid involvement and diabetic retinopathy. *93% Agreement.*
II. We recommend developing the follow-up plan in conjunction with an endocrinologist/diabetologist and a dietitian, also considering the need for psychological and social support. *100% Agreement.*

## Question 8.3: Follow-up of Patients With CD and IgA Deficiency

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up and IgA deficiency. The search identified a total of 24 records, of which 2 were included: 2 primary observational studies (191 children), one of them prospective. We included 1 article published after March 2020 (132).

Selective IgA deficiency is the most prevalent primary immunodeficiency in the general population (1:300–700). Children with selective IgA deficiency are at a 10- to 15-fold higher risk of developing CD. Limited data on the follow-up of children with CD and selective IgA deficiency is available, with low number of affected children (88). Studies show prolonged recovery time of serological and mucosal changes after the introduction of GFD during follow-up, with half of IgA deficient CD patients having elevated serum IgG specific CD-antibodies after 2 years on a GFD (132). No other findings were found to be specific during follow-up of selective IgA deficient CD patients.

*Statement*

Data from the literature on patients with selective IgA deficiency indicate a longer recovery time for serum IgG CD-antibodies after starting a GFD.

*Recommendation*

I. We recommend the same follow-up practice in IgA deficient children with CD than in IgA sufficient children with CD. *93% Agreement.*
II. At follow-up visits CD-specific IgG antibodies (TGA, EMA or DGP) should be assessed. *100% Agreement.*

## Question 8.4: Potential Celiac Disease

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up and potential celiac disease. The search identified a total of 80 records, of which 9 were included: 8 performed in children (835 children) and 1 in both adults and children (137).

Potential CD is defined as the presence of CD-specific antibodies and compatible HLA, but normal duodenal architecture. It can either be asymptomatic or symptomatic. The patient may or may not develop villous atrophy later. Once diagnosed, the most important decision to be taken is whether to treat it with a GFD or not. That decision depends on the predictable evolution, the alleviation of possible symptoms by GFD and the possible risk inherent to a long-term regular diet, including bone health, because the presence of alterations may represent a valid reason to start a GFD, otherwise not prescribed if the subject is asymptomatic. Bone health should be monitored by assessment of serum levels of calcium, phosphate, alkaline phosphatase, vitamin D, and eventually mineralometry performed at the discretion of the physician. The first two issues find some evidence in the literature (133–140). All studies but one (133) indicate that the evolution to villous atrophy occurs in a minority (5–20%) of the cases with a cumulative incidence of approximately 50%. The majority remain as "potential CD," with a significant percentage of those normalizing their CD-antibodies, which is frequently observed in younger children. Factors predicting evolution to villous atrophy are genetic profile, intraepithelial

lymphocytic infiltration, and intestinal CD-antibodies deposits (138). A GFD does not always improve symptoms (141). No information is available on the long-term risks if left on a regular gluten-containing diet.

*Statement*

In the literature there is insufficient data for evidence-based management of patients with potential CD.

*Recommendation*

I. In the presence of symptoms attributable to gluten, a trial of a GFD should be discussed with the family. *90% Agreement.*
II. If left on a regular diet, we recommend annual follow-up visits, with attention towards growth and nutritional status, including bone health. *97% Agreement.*
III. Duodenal biopsies should be performed in case of appearance of symptoms and/or of increased elevation of the CD antibody levels. In other cases with persistent serological positivity, on an individual basis and in dialogue with the patient/caregivers, duodenal biopsies may be considered during follow-up. *95% Agreement.*

## Question 9: How to Improve Communication: To Parents? To Patients?

A search was conducted in Medline using the search terms celiac, celiac, children, follow-up, gluten-free diet, communication, patient satisfaction, caregivers/education, education, consultants/education, consultants/organization, and administration. The search identified a total of 46 records and 14 publications were included: 12 primary observational studies (638 children) and 2 literature reviews (34 studies). We included 4 studies in adults (143,145,149,150), 1 in both adults and children (148) and 2 published before 2010 (142,147).

Communication between the caring physician and other health care professionals with the parents and patients includes much more than providing information on the disease. Communication shapes the patient's/parent's relationship with the caring medical team and the trust in evidence-based medicine. Communication in pediatrics is generally triadic and should be addressed towards both the parents and the child with language appropriate to the age of the child (142). How the physician communicates the initial diagnosis to the patient/parents affects the degree of acceptance of the diagnosis and may influence the impact of the disease on the intrafamily relationship. In adults with CD, it has been shown that negative perceptions of having CD were associated with dissatisfaction with the quality of doctor-patient communication (143).

### Question 9.1: Communication of Diagnostic Certainty to Parents and Children

The information at all times, but most importantly at the time of the diagnosis, should be given to the patient/family in lay terms in a relaxed atmosphere. It should include explanations of the results of the diagnostic work-up and the implications of the lifelong disease for the patient's life and the family. The documentation of confirmed diagnosis is important, particularly if the child was diagnosed early in life, to avoid later doubt by the patient and future caring physicians. Ideally, a celiac passport should be used for documentation (in Germany free available from the German Celiac Society DZG: https://www.dzg-online.de/der-zoeliakiepass.1074.0.html). If the diagnostic criteria were not fulfilled, and there is doubt about the diagnosis, the physician should not name it as "CD," but as "suspected CD," and action should be taken to confirm or reject the diagnosis.

*Statement*

Communication and documentation of the CD diagnosis based on evidence-based guidelines are crucial to avoid later doubts about the diagnosis, both by the patient or other caring physicians.

*Recommendations*

The pediatric gastroenterologist/pediatrician should communicate to the patient and the parents/caregivers that the CD diagnosis is made with certainty and according to current evidence-based guidelines. All results (serology, histopathology, HLA if done) with dates of performance should be provided in writing for later proof of CD diagnosis. 97% Agreement.

### Question 9.2: Patient Empowerment at Diagnosis and During Follow-up

The diagnosing physician should communicate the benefits of an early diagnosis in childhood as compared to undiagnosed and untreated disease until adulthood in a structured way. To patients with symptoms affecting their QoL, this is obvious (immediate benefit). For screening-detected persons with minor or no symptoms (144,145) or those who do not remember their symptoms due to young age at diagnosis, the motivation to adhere to a GFD is based on internalizing the risks/possible consequences to later health (146) and enduring beliefs of being spared negative consequences (146).

Knowledge about the disease may be provided using different tools, including information leaflets, web-based documentation, or E-learnings (19,147). A modular E-learning tool for patients and their household members has been developed within an EU-funded project and is freely available in 6 languages: https://celiacfacts-onlinecourses.eu/?lang=en. Although children diagnosed early in life usually accept the GFD as normal, they need to be informed, reassured and empowered for autonomy and taking responsibility for their CD, particularly during adolescence (148). A well-informed patient is more likely to adhere to the GFD and to reconstruct normality (149,150). Better knowledge of the risks and benefits of the disease may also reduce anxiety. Informed patients with trust in evidence-based medicine are less likely to follow unproven, sometimes risky treatments and intervention or spend money on these treatments or diagnostics of unproven value.

*Statements and recommendations*

I. The pediatric gastroenterologist/pediatrician and dietitian should communicate the need for a lifelong GFD and regular monitoring and facilitate access to professional dietary counseling knowledgeable on GFD. *100% Agreement.*
II. We recommend providing education using oral and written information (leaflets, E-learnings etc.) about the disease and benefits of adhering to the diet. Later health risks should be brought into perspective without inducing fear or anxiety considering the patient's age and complications at the time of diagnosis and compliance with dietary recommendations. *97% Agreement.*

### Question 9.3: Emotional and Social Support

Patients and parents should be informed about the value of the national or local celiac patients' associations where they can meet families, participate in different programs and collect valuable and updated information about the disease, gluten-free products or even practical hints on reorganizing the household. Members of CD patients' associations may benefit by receiving psychosocial

support by peer groups, which in turn may ensure better adherence to the diet and outcome (10). The CD patients' organizations in Europe usually are members of the AOECS: http://aoecs.org/members and encourage to name the condition in the social environment as something, which is "quite common," and "most people are aware of CD" (151). In their daily life, many individuals suffering from a chronic disease may not like to be considered a "patient," but as a person affected with a certain disease or condition. This is particularly true for CD, as the GFD reverts the enteropathy and alleviates most, if not all, signs and symptoms that may be present at the time of diagnosis. Children in particular may be sensitive to the word "patient" which implies feeling "sick." Therefore, the wording used should be carefully chosen and may be mutually decided upon with the affected child, including the wording she/he will use describing CD to their friends, peers and other social contacts in their daily life. Particularly, some screening identified adolescents perceive the change of their lifestyle (GFD) more as a burden than as potential benefit (152). This feeling of stigmatization and social isolation needs to be addressed in the patient-physician communication and requires particular attention and support (107).

*Statements and recommendations*

I. Emotional and practical support from personal contact with other individuals with CD (Celiac/parent support groups, patient organizations, etc.) should be provided to reduce eventual feelings of social isolation. *97% Agreement.*
II. Patients, especially adolescents, perceiving lifestyle changes related to CD diagnosis, including the GFD and emotionally coping, as difficult warrant particular attention and support. *100% Agreement.*

## Question 10: How to Organize the Transition From Pediatric Care to Adult Health Care?

A search was conducted in PubMed using the search terms celiac, celiac, children, follow-up, childhood celiac, and transition of care. The search identified a total of 85 records, of which 7 were included: 4 primary observational studies (17,172 children) and 3 reviews/guidelines (156 (10 studies), 15,157). Two studies on adults were included (154,155).

The transition between pediatric and adult care for young people with chronic illness, including CD, is often poorly organized, with potential negative consequences on the QoL. There is a general agreement that adolescent services need to be improved. Still, there is little empirical data on which policies can be used (153). The organization of transition from the pediatric to adult care for individuals with CD is necessary to prevent gaps in management (15).

Studies on the transition process in CD are scarce. We identified nine relevant original papers, several of which were performed in young adults after transition. These provided only retrospective, descriptive data without any long-term follow-up. Importantly, there are gaps in follow-up care after transition. Dietary compliance tends to be low in young adults and surprisingly, there are suggestions that follow-up care is not associated with a higher compliance and good quality of health (154). Moreover, the transition of care in CD appears often to be inconsistent, particularly among asymptomatic patients (155).

A systematic review of the literature on the transfer of care among different chronic diseases suggested that the most commonly used strategies in successful programs were patient education and specific transition clinics jointly staffed by pediatric and adult physicians or dedicated young adult clinics within adult services (156). The pediatrician should write a transition letter to facilitate care transition (15,35,157),. The transition letter should contain details on the basis of CD diagnosis and a summary of important follow-up information such as serology, growth data, comorbidities, and dietary adherence.

Young adults should have the chance to trust and improve their own abilities to cope with their disease burden and the necessary dietary restrictions (153). Furthermore, although there is little evidence, as for other diseases, building a good relationship between the young adult and the treating medical team may be relevant to ensure good management of the disease (153).

There is no evidence in the literature about the exact age to start the transition process in pediatric celiac patients. Physician organizations from the United States had suggested that the transition be commenced at age 12–13 years, developing a transition plan at age 14–15 years, with the actual transfer taking place at ≥18 years of age (158). This proposed timeline is based on expert opinion, as the quality indicators and metrics used to evaluate transition outcomes are still being developed. The transition should start according to the general health care organization in a given country, taking into consideration the adolescent's physical, mental, psychosocial development, and other factors, such as the level of disease activity, dietary adherence, and the patient's autonomy in disease management.

*Statements*

1. There are no prospective studies on the transfer of care from pediatric to adult medical care in CD.
2. Retrospective data show that the transition to adult care is inconsistent, particularly among asymptomatic patients.
3. There is no evidence in the literature about the age to start the transition process in pediatric celiac patients.

*Recommendation*

Even though current data are insufficient, we recommend a formal transfer of medical care of an adolescent with CD to facilitate the transition to adult care. The transfer should be structured and, as a minimum, include a transition letter or "celiac passport" providing data on the basis of diagnosis, follow-up, anthropometric data, possible comorbidities, and dietary adherence level. *93% Agreement.*

## DISCUSSION

In this paper, we present a summary of the literature on the follow-up of children and adolescents with CD and we provide recommendations on how to approach it. Although the searched and identified literature encompass an impressive representation of the pediatric population with CD, most of the included studies are observational and retrospective, as shown in the Summary Table of the Revised Literature (Supplemental Digital Content, *http://links.lww.com/MPG/C861*). In addition, the exclusion of case reports by the methods may have had an impact on the underestimation of refractory CD, which is such a rare event in pediatrics. For this reason, we stress the importance of referring suspected cases to specialized centers and of reporting cases in the medical literature.

Although some of the provided recommendations have been based on available evidence (Table 1: 1; 3.2.II–VI; 4.1, 4.2; 5.1–5.4; 6.1–6.3; 7; 8.1, 8.2.1, 8.2.II, 8.3.I, 8.3.II; 9.2.I, 9.3.1), others have been based on expert opinion (Table 1: 2; 3.1, 3.2.IV, V, VII; 5.5; 8.1.1.II, 8.1.1.IV, 8.4.I–8.4.III; 9.1, 9.2.II, 9.3.I; 10). Nevertheless, upon voting, agreement was present for 95% of the 39 statements and 37 recommendations were formulated.

Gaps in knowledge were identified indicating fields for future prospective research.

These include the frequency of follow-up visits and the laboratory tests that should be performed, including vitamin D

determinations and control of thyroid disease. Also, how to treat sideropenia and how to address persistent slightly elevated levels of serum IgA-TGA in children adhering to the GFD are knowledge gaps that were addressed based on expert opinion and available evidence. The need for a reliable method to assess adherence to the GFD was identified, as well as the importance of studying the performance of GIPs determinations in clinical practice.

Although some evidence supports the assessment of QOL during follow-up, it remains unknown what the frequency of assessments should be, taking into account the time-consuming and economic aspects of follow-up.

Although three recommendations are provided on how to perform a gluten-challenge in children with uncertain diagnosis of CD adhering to a gluten-free diet (Table 1: 8.1, 8.1.1.II and 8.1.1.IV), these are mainly based on expert opinion, since there is little evidence on this topic. This was also the reason to avoid formulating a recommendation on the quantity of gluten that should be ingested during a gluten-challenge, even if, as stated, gluten ingestion of 10–15 g/day for 3–6 months is expected to induce small-bowel abnormalities in the majority of CD children. In addition, no consensus was reached on whether intestinal biopsies should be performed before starting or after the gluten-challenge (8.1.1.I and 8.1.1.III), since a substantial number of the coauthors found that serum IgA-TGA levels ≥ 10× ULN should be enough to confirm a relapse of CD after gluten-challenge. All these reasons make future prospective research on gluten-challenge in children necessary. Surrogate biomarkers of CD-specific small-bowel damage, such as cytokines and gliadin-specific T cells recruited in peripheral blood after short-time gluten exposure, are promising tools to develop less invasive forms of gluten-challenge. This may involve new immunohistochemical markers of morphological changes of the mucosa such as APOA4:Ki67 ratios (159,160), detection of the HLA-DQ-gluten tetramer and increase in IL2 in peripheral blood (122) or changes in gut-homing CD8T-cells, HLA-DQ restricted gluten-specific CD4 T cells, all proposed as markers of T-cell response in CD patients after short-term gluten intake (161–165).

Similarly, there is little information available on how to follow children with potential CD and long-term studies on this topic are needed. In addition, there is a paucity of studies that compare long-term effects on dietary compliance depending on who does the follow-up and more studies are warranted to evaluate if physical follow-up visits can be replaced by E-health services.

Finally, there are few studies on the effect of communication between the physician and the patient/parents/caregivers on the long-term health status of CD children and no prospective studies on the transfer of care from pediatric to adult medical care in CD. In conclusion, we present here an update of the present knowledge on the follow-up of children and adolescents with CD and provide recommendations accordingly. Furthermore, we have identified and highlighted gaps in knowledge that warrant more research to improve further follow-up of CD children and adolescents.

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