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ORIGINAL ARTICLE

Australasian Pediatric Gastroenterologists' Perspectives and Practices of Celiac Disease Diagnosis and Management

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Abstract

Background The application of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) celiac disease (CeD) guidelines by pediatric gastroenterologists in Australia and New Zealand (Australasia) is unknown. Similarly, long-term management practices for patients with CeD are also unknown in this region.

Aims This study aimed to explore the perceptions and practices of Australasian pediatric gastroenterologists in diagnosing and managing patients with CeD.

Methods Australasian pediatric gastroenterologists and trainees were invited to complete an anonymous online survey over a 3-week period.

Results The survey was completed by 28 respondents, 24 from Australia and four from New Zealand. Tissue transglutaminase antibody IgA was the most frequently ordered initial serologic test. Fifteen (54%) respondents relied on duodenal biopsies for the confirmation of CeD, six (21%) followed the ESPGHAN guidelines and the remaining seven offered either biopsy confirmation or no-biopsy diagnosis according to the parents' wishes. Following diagnosis, five (18%) respondents discharged patients from care, three (11%) discharged patients after one follow-up visit, one (4%) reviewed patients for 12 months, six (21%) reviewed patients until celiac antibodies normalized and children were clinically asymptomatic, and 13 (46%) reviewed patients until transition to adult care.

Conclusion Tissue transglutaminase antibody IgA was the most common initial serologic test ordered by this group of Australasian pediatric gastroenterologists. Half of these physicians rely solely on duodenal biopsy for the confirmation of CeD diagnosis: a minority routinely use the ESPGHAN guidelines. Physicians reported a wide range of CeD follow-up practices.

Keywords Celiac disease · Pediatrics · Diagnosis · Gastroenterologist · Follow-up · ESPGHAN

Introduction

Celiac disease (CeD), an immune-mediated enteropathy triggered by recurrent exposure to gluten in genetically susceptible individuals, is recognized worldwide [1, 2]. The prevalence of CeD in Australasian (Australia and New Zealand (NZ)) adults is approximately 1.2% [3, 4]. A rising rate, however, has been noted in NZ children [5].

CeD presentations in children can range from typical gastrointestinal malabsorptive symptoms to asymptomatic, and children suspected of having CeD are required to undertake at least an initial celiac serologic test. Conventionally, any children with positive celiac antibodies also require an intestinal biopsy for CeD confirmation. In 2012, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) revised their CeD diagnostic guidelines (ESPGHAN guidelines) to incorporate a

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no-biopsy pathway for a subgroup of children who fulfilled their criteria [6]. More recently (available from late 2019 as early online access), the ESPGHAN guidelines were further updated, expanding the no-biopsy criteria (tissue transglutaminase antibody IgA (TGA IgA) ≥ 10-fold the upper limit of normal and positive endomysial antibodies IgA (EMA IgA)) to include all children regardless of symptoms at presentation or at-risk groups, while the requirement of celiac HLA typing as a part of the no-biopsy pathway was also omitted [7]. The utilization of the no-biopsy pathway being part of the ESPGHAN guidelines has increasingly been recommended in worldwide clinical practices, including during the COVID-19 pandemic [8–10]. However, the influence of such guidelines among the practices of Australasian pediatric gastroenterologists is unknown.

The only current treatment for individuals diagnosed with CeD is a strict life-long gluten-free diet (GFD). Currently, there is limited literature on the best-practice guidance for the long-term management of patients with CeD. A number of international organizations and experts have provided their recommendations with some similarities and variations as summarized by Hall and Day [11]. There is no previous published literature on the follow-up practices of children diagnosed with CeD by Australasian pediatric gastroenterologists.

In view of the increased acceptance of ESPGHAN guidelines in practice and the interest of long-term management of children with CeD, a cross-sectional survey was conducted involving Australian and NZ pediatric gastroenterologists. The study aimed to explore the practices and perspectives of the gastroenterologists with regard to screening for and diagnosing CeD and also how they subsequently manage their patients with CeD.

Methods

Participants

Australian and NZ pediatric gastroenterologists including trainees were invited via an email listserv of the Australasian Society of Paediatric Gastroenterology, Hepatology and Nutrition (AuSPGHAN) bulletin board. This email listserv bulletin board is a closed group and consisted of 78 currently practicing or previous pediatric gastroenterologists and trainees who worked/trained in Australia or New Zealand. It was not possible to determine the members' practicing geographical location through the email listserv.

Anonymous Online Survey

The anonymous online survey was conducted using an online platform, Qualtrics© Version 2019 (Utah, USA) and ran over a 3-week period (15 November 2019 till 5 December 2019). Reminder emails were sent at weekly intervals via the AuSPGHAN bulletin board. Participants accessed the survey using Qualtrics© weblink provided in the invitation email. The weblink opened an external web browser providing participants with survey participation information before they proceed to undertake the survey. The questionnaire consisted of three themes: celiac screening practices, diagnostic methods (intestinal biopsy and/or ESPGHAN guidelines) used to confirm CeD and follow-up practices for those children confirmed to have CeD (Supplementary Questionnaire). Reasons for and against why respondents chose to or not to routinely use the ESPGHAN guidelines were sought. At the end of the survey, respondents had the option of providing their demographic details.

This study was approved by the subcommittee of the University of Otago Human Ethics Committee (Health).

Statistical Analysis

Data were exported from Qualtrics© into IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for descriptive statistical analysis. Results were expressed as median ± interquartile range (IQR). Fisher's exact test was used to analyze contingency tables. A p value of less than 0.05 was considered statistically significant.

Results

Background of Respondents

Twenty-eight practicing Australasian pediatric gastroenterologists and trainees completed the survey. Of the 28 respondents, 24 (82%) were from Australia and 4 (18%) were from New Zealand. All respondents provided their background details (Table 1).

Celiac Screening Practices

Twenty-six respondents (93%) chose TGA IgA as their most frequently ordered initial celiac serology test for children of any age (Fig. 1). Deamidated anti-gliadin peptide IgG (DGP IgG) was ordered significantly more frequently in children under two years of age than in children over two years old, (20 of 28, 71% versus 13 of 28, 46% ($p = 0.04$), respectively). Up to a third of the physicians reported that other celiac serologic tests including tissue transglutaminase antibody IgG (TGA IgG), EMA IgA and deamidated anti-gliadin peptide IgA (DGP IgA) were also ordered for children suspected of having CeD.

There was no difference in the frequency of the initial celiac serology tests ordered between the respondents of the

Table 1 Background characteristics of the 28 respondents who completed the survey

	N (%)
Male	24 (86)
Age (years)	
< 30	0
30–40	6 (21)
41–50	11 (39)
51–60	6 (21)
> 60	5 (18)
Australia	24 (86)
New South Wales	7
Queensland	2
South Australia	5
Victoria	9
Western Australia	1
New Zealand	4 (14)
Auckland	4
Practice	
Public hospital/academic	24 (86)
Private	18 (64)
Position	
Consultant	26 (93)
Advanced trainee (fellow)	2 (7)

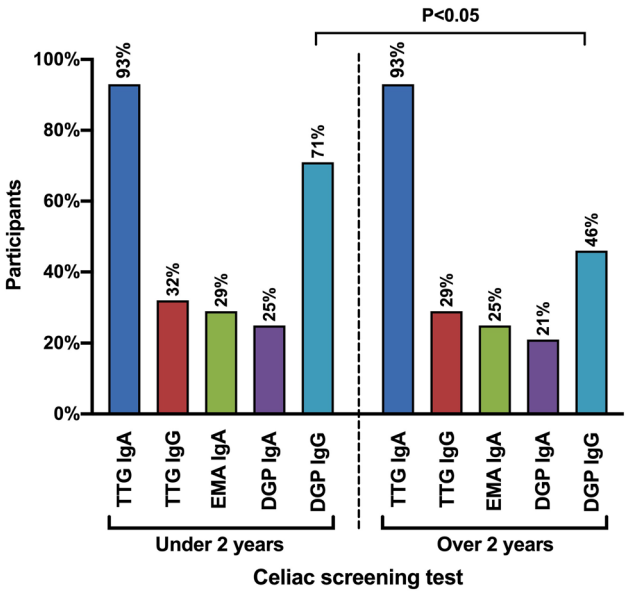

Fig. 1 Views of 28 Australian and New Zealand pediatric gastroenterologists on their practices of ordering celiac screening tests including anti-tissue transglutaminase IgA (TTG IgA), anti-tissue transglutaminase IgG (TTG IgG), endomysial antibodies IgA (EMA IgA), deamidated anti-gliadin peptide IgA (DGP IgA) and deamidated anti-gliadin peptide IgG (DGP IgG) in children suspected of having celiac disease. DGP IgG test was preferred in children under 2 years of age (Fisher's exact, $p < 0.05$)

two countries (data not shown). Moreover, all but two of the respondents reported routinely requesting total IgA levels. Of these two, one respondent reported this was because the laboratory routinely performs the test. The other respondent did not provide a reason.

In addition to celiac antibody tests, gastroenterologists also frequently ordered iron studies (96%) and a full blood count (93%) as part of the screening investigations (Supplementary Figure 1). Only one respondent reported not routinely ordering any additional tests.

Celiac Diagnostic Practices

Among all respondents, 15 (54%) relied on duodenal biopsies for confirmation of CeD diagnosis and six (21%) followed the ESPGHAN guidelines (three followed 2012 ESPGHAN guidelines [6] and three followed 2020 ESPGHAN guidelines [7]). The remaining seven respondents offered both options (either intestinal biopsy confirmation or no-biopsy 2012 ESPGHAN guidelines (if criteria fulfilled)), according to the parents' wishes (Fig. 2a).

The celiac diagnostic practices were different between the two countries. Almost two-thirds of the Australian respondents ($N = 15$, 63%) relied solely on intestinal biopsies (Fig. 2b). In contrast, three-quarters of the NZ respondents ($N = 3$) used the ESPGHAN guidelines only and one respondent offered both options (biopsy confirmation or no-biopsy ESPGHAN guidelines). A quarter ($N = 6$) of the Australian gastroenterologists offered both options and the remaining 22% followed the ESPGHAN guidelines only.

When intestinal biopsies were required, all endoscopists reported that at least one mucosal biopsy was obtained from the first part of duodenum and at least two biopsies from either second or third parts of the duodenum. In addition, one respondent took biopsies from the fourth part of duodenum and two others took biopsies from the jejunum (Supplementary Table 1).

Respondents' Perspectives on the Application of ESPGHAN Guidelines in Clinical Practice

Of the six respondents who claimed to use an ESPGHAN guideline in their practice, all felt that there was good evidence to support practice and that this helped to reduce the need for endoscopy (Fig. 3). Four gastroenterologists also felt the guidelines help to reduce endoscopy waiting time. Additional reported benefits included support from peers ($N = 2$), hospital ($N = 2$) and laboratory services ($N = 3$).

Of the 15 respondents who claimed not to use the ESPGHAN guidelines in their practice, the most frequent reason for not using the guidelines was due to physicians' personal experience with false positive celiac serology results ($N = 10$). Six clinicians felt there was insufficient

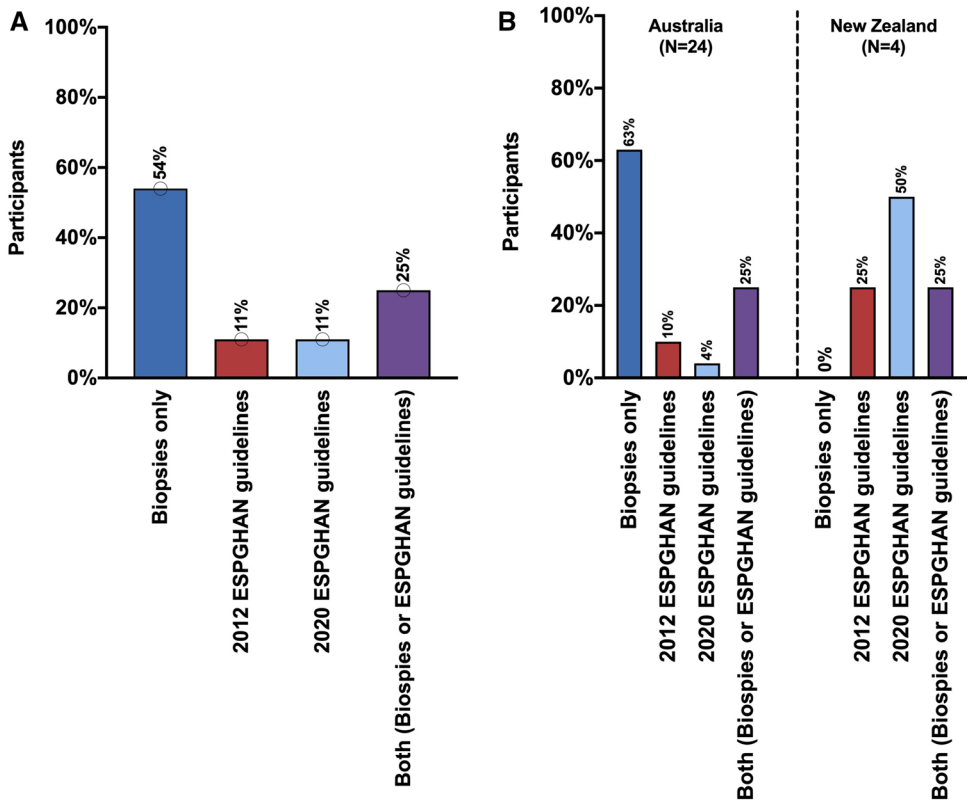

Fig. 2 Celiac diagnostic practices. **a** Methods used by all respondents to confirm celiac disease in children. **b** Comparing diagnostic practices between Australia and New Zealand respondents

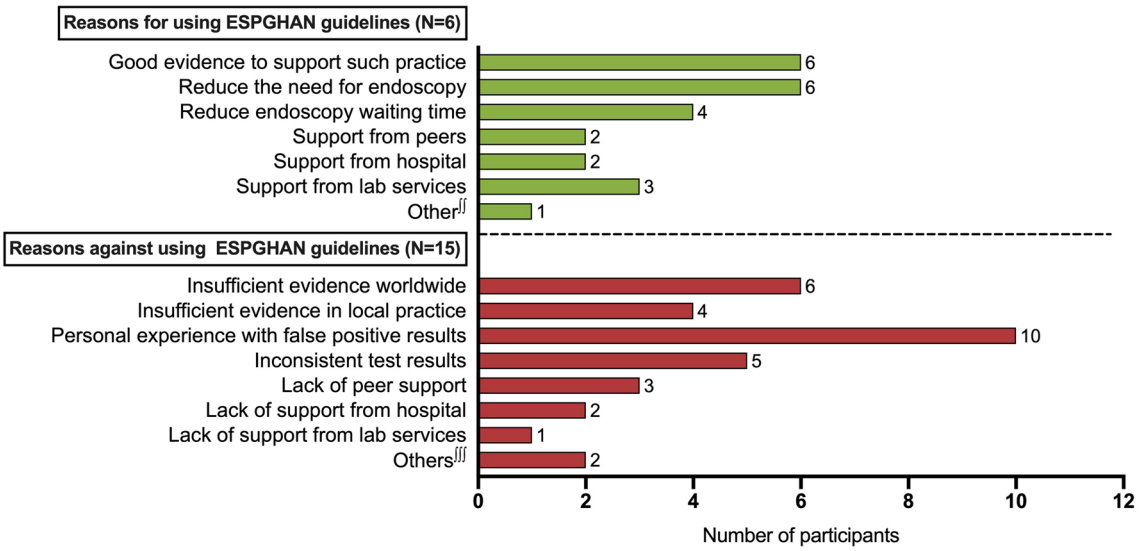

Fig. 3 Respondents' perspectives of applying the ESPGHAN celiac disease diagnostic guidelines in their practice. ‖ Other, prospective trial to validate local population ($N=1$); ‖‖ Others, life-long disease, confirm with biopsies ($N=1$) and hospital practice ($N=1$)

evidence worldwide, and four others felt that there was inadequate local evidence. Inconsistent test results were mentioned by five respondents. Other reasons provided included lack of support from peers ($N=3$), hospital ($N=2$), or laboratory services ($N=1$).

Follow-Up Following Diagnosis of Celiac Disease

Following receipt of the celiac diagnostic investigation results, 71% of respondents would offer face-to-face consultation and 54% would call parents or patients to discuss

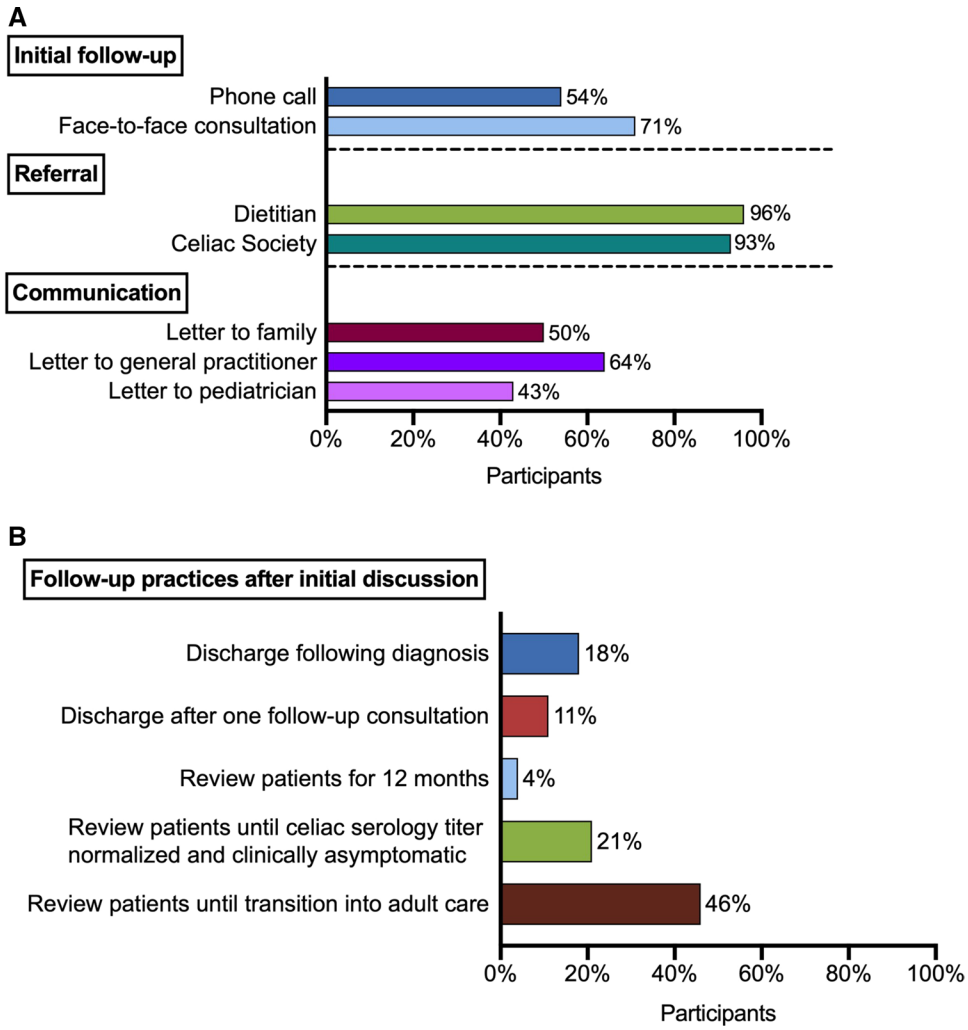

Fig. 4 Follow-up practices reported by 28 respondents following celiac diagnostic investigations. **a** Initial follow-up practices including referrals and communications. **b** Long-term follow-up practices following initial follow-up

their results, with some offering both options (Fig. 4a). Furthermore, 96% of physicians would refer their patients to see a dietitian and 93% to their local Celiac Society. A written letter was also completed by 50% of respondents to the family, 64% to the patient's general practitioner, and 43% to the patient's pediatrician (if any).

Almost half of the respondents (46%) continued to review their patients diagnosed with CeD until transition into adult care (Fig. 4b). A smaller number (21%) of clinicians follow patients until their celiac serology titer has normalized and the children were clinically well. Eighteen percent of gastroenterologists discharged patients from their care following diagnosis, 11% offered one follow-up consultation before discharging from care, while 4% reviewed their patients for 12 months.

The twenty respondents who continued to review their patients regularly after CeD diagnosis were asked about the assessments and discussions that occurred during follow-up visits. The majority of respondents (95%) assessed their patient's adherence to a GFD and growth (Supplementary Figure 2). Others screened for micronutrient deficiencies (80%) and autoimmune comorbidities (75%), discussed potential future treatment (75%), discussed healthy diet (50%), and lastly, some included a discussion about maximizing the patient's quality of life (40%). Unfortunately, one respondent did not provide any response.

Moreover, 18 of 20 respondents within this group would request blood tests prior to a follow-up visit (Supplementary Figure 3). TGA IgA (89%) was among the most commonly requested celiac serology test during routine follow-up. All respondents screened for iron deficiency. Thyroid function testing (78% of respondents) was among the most ordered test for screening autoimmune comorbidities.

When patients were discharged from gastroenterology care, all respondents referred patients back to their general practitioner, except for those who were reviewed until transition into adult care. Of the 13 pediatric gastroenterologists who continued to review patients until adulthood, 62% referred patients back to the general practitioner, 23% to an

adult gastroenterologist, and 15% to both general practitioner and an adult gastroenterologist.

Discussion

The current study identified wide variations in the practices of Australasian pediatric gastroenterologists with regard to screening children for CeD, diagnosis of CeD, and subsequent review of children with CeD. TGA IgA was the most frequently ordered initial serology test in any child suspected of CeD. Overall, half the respondents relied solely on duodenal biopsies for the diagnosis of CeD. However, NZ respondents reported they only relied on either the ESPGHAN guidelines or offered both options (intestinal biopsy confirmation or no-biopsy ESPGHAN CeD diagnosis) according to the parents' wishes. Follow-up practices were also widely reported, with almost half the physicians reviewing their patients until adulthood, whereas others discharged patients from their care at various times after diagnosis. For those who routinely reviewed children with CeD, the management involving assessments and discussions varied during visit.

TGA IgA was the most frequently ordered initial serology test by this group of pediatric gastroenterologists to screen CeD in children of all ages. This finding is aligned with international guidelines recommending TGA IgA as the first line of testing [7, 8, 12–18], with the majority also recommending simultaneous measurement of total IgA levels [7, 8, 12, 14, 16–18]. In contrast, the World Gastroenterology Organisation (WGO) guideline recommends that either TGA IgA or EMA IgA or both can be used for initial testing (without specifying an age grouping) [13].

In addition to ordering TGA IgA, this study found that the DGP IgG test was more frequently ordered for children under two years of age compared to those over two years of age. IgA-based serology tests are noted to be less sensitive in young children consequent to immature IgA responses [19, 20]. The most recent revised 2020 ESPGHAN guideline recommends testing for total IgA and TGA IgA in children of any age and suggests that IgG-based serology tests (DGP, EMA or TGA) are considered only in those with low IgA levels [7]. The authors of these guidelines felt that the combination of various IgA- and IgG-based serology tests did not improve test sensitivity once patients with low IgA levels were excluded [7]. The recommendation of using TGA IgA as the initial serology test in all children is further supported by a recent North American multicenter retrospective study [21].

Despite the inclusion of the no-biopsy pathway in the ESPGHAN guidelines, half of the Australasian gastroenterologists included in this study reported that, they still rely solely on biopsy as a confirmatory test for CeD diagnosis. Although six (21%) respondents reported they routinely follow the ESPGHAN guidelines, half of them followed the latest ESGPHAN CeD guidelines. In the latest 2020 ESGPHAN CeD guidelines, it is mentioned that the physician should discuss the two options (biopsy or no-biopsy) of diagnosing CeD with the patient/parents if the patient fulfils the no-biopsy criteria [7]. For this reason, those respondents who chose to follow the 2020 ESPGHAN guidelines can be thought to fall in the same category as those respondents who offered both biopsy and no-biopsy options (when 2012 ESPGHAN criteria fulfilled) according to parental wishes. These results were intentionally not merged together to avoid confusion.

When the practices of diagnosing CeD were stratified by country, none of the NZ respondents relied solely on biopsy for CeD confirmation compared to almost two-thirds of the Australian physicians who continued to rely solely on biopsy for disease confirmation. It is important to note that there were a low number of participants from NZ and all were located in Auckland, where this region had prospectively studied the efficacy of utilizing the 2012 ESPGHAN guidelines in their local population [22]. It is interesting to note, however, that since the current survey was conducted, a Western Australian study has been published that reports prospectively applying the 2020 ESPGHAN guidelines to their local population [23], suggesting that local practice may be changing in this state.

Although not all respondents provided their views about the ESPGHAN guidelines, all six respondents who used the ESPGHAN guidelines in their practice believed there is sufficient evidence to apply such practice locally. Meanwhile, two-thirds of the clinicians who did not use the guidelines had experience of false positive celiac serology results, six responders felt there was insufficient evidence worldwide, and four others felt inadequate evident in their local practice. Only one respondent reported that a prospective study was carried out locally to support the implementation of the ESPGHAN guidelines. The present survey did not investigate the specific aspects of insufficient evidence and should be explored in future studies, including whether the false positive results were due to antibody titers less or $\geq$ 10-fold the upper limit of normal. However, variable standardization in laboratory assay and references may play a role in the implementation of such guidelines [24]. Hence, it is crucial that findings from one region cannot be generalized to other regions of the same country or to another country. On the other hand, the current survey also found regular users of the ESPGHAN guidelines believed the integration of the no-biopsy pathway helps to reduce the need for endoscopy. This is supported by a number of studies demonstrating the potential extent of endoscopy reduction up to 60% [9, 22, 23, 25–27].

Predictably, the present group of physicians reported an extensive range of follow-up practices. This variability is

likely consequent to the paucity of evidence-based follow-up protocols for children with CeD. While the current study only explored the follow-up practices of the individual respondents, the rationales supporting such practices should be considered in future studies. International guidelines and experts do recommend children with CeD should be followed up following their diagnosis [8, 12–18, 28]. One study reported that children with CeD who are lost to follow-up have reduced adherence to GFD (regression analysis = 0.27, $p = 0.001$) and a higher prevalence of positive celiac serology tests (50% compared to 25% of regular follow-up patients, $p = 0.01$) [29]. This highlights the importance of follow-up following CeD diagnosis. However, as to which healthcare professional (dietitian, general practitioner, adult gastroenterologist or general physician with CeD interest) is best suited to continue care once adulthood is achieved remains unclear. In a 28-year follow-up study of 50 adults who were diagnosed with CeD during childhood, the authors found that a third were not adherent to their GFD and only 22% were enrolled in an adult gastroenterology clinic [30]. These patients did not receive any medical or dietary supervision after transition to adulthood. Recently, two adult transfer of care models were introduced, but neither has been prospectively validated [31, 32].

In a different approach, Sbravati et al. [33] prospectively assessed the GFD adherence of 200 children over two intervals (at least 24 months) following transition from a single referral center to a general pediatrician once remission was achieved. Adherence was assessed using the TGA IgA and Biagi Score [34]. The study found such practice is a reasonable approach to ongoing management of CeD [33]. However, in this study, age over 13 years and non-Italian ethnicity were both found to be associated with GFD non-adherence. Hence, the authors advocated that specific attention is required for adolescents and foreign nationalities when counseling on GFD is required.

For those clinicians who regularly reviewed children with CeD, the top five assessments and discussions conducted were: assessing patient's adherence to a GFD, growth, screening for micronutrient deficiencies and autoimmune comorbidities, and discussion about potential future treatments. All of the organization guidelines and expert reports emphasize the importance of assessing adherence to a GFD during follow-up [8, 12–18]. However, not all guidelines provide recommendations on assessing growth, screening for micronutrient deficiencies, or autoimmune comorbidities [11]. Specifics on how GFD adherence was assessed by clinicians were not explored in this survey. Resolution of symptoms was not specifically asked in the present study as the study focused on routine assessments and discussions occurring in a follow-up visit when the patient is asymptomatic.

Most international guidelines do not recommend repeat duodenal biopsies in children with CeD during follow-up unless the celiac serology remains persistently high or minimal changes and/or non-resolution of symptoms [12, 14–17]. Instead, celiac serology is used in conjunction with adherence assessment by the clinician with/without dietitian input. All guidelines suggest at least testing TGA antibodies during follow-up with some variations among their recommendations [8, 12–18]. The current study findings of TGA IgA being the most frequently ordered initial test during follow-up are aligned with the guidelines.

This is the first report on the perspectives and practices of CeD by Australasian pediatric gastroenterologists. Nevertheless, the study has some limitations. Firstly, the survey was conducted prior to the COVID-19 pandemic, during which many healthcare systems have changed to adapt to the new challenges. The practices of the physicians in the region may have changed in the face of these events. Secondly, this survey was performed about a month after the 2020 ESPGHAN CeD diagnosis guideline preprint was released, but prior to the in-print publication date. This survey was not designed to assess the respondent's knowledge or awareness of the two guidelines, nor was it designed to assess when practitioners may have changed their practice. Thirdly, the design of the study did not enable clarification of several aspects and did not capture the attitudes of other disciplines, such as dietitian involvement in the follow-up practices. More comprehensive understanding could be obtained if data such as patient volume and serology tests ordered could be matched with a physician's response, compared to a self-reported survey. A limited array of options for answers in the survey may have been misinterpreted by participants, especially trainee or clinicians with low patient load. In addition, the use of an online survey following an email invitation may have led to a selection bias. The total number of pediatric gastroenterologists and trainees in Australia is substantially larger than in NZ, meaning that the findings of the study may be biased more toward Australian practices. However, the geographical spread of the respondents suggests that the findings are likely representative of the relevant regions, especially as all the NZ respondents were from the Auckland region. The nature of the bulletin board system means that was not possible to ascertain the current employment status of the respondents or to confirm their geographical location.

In conclusion, this study highlights key similarities and some variations in CeD practice by this group of pediatric gastroenterologists across Australasia. Overall, the ESPGHAN guidelines were not widely used in Australasia. In addition, physicians reported a wide range of CeD follow-up practices. Further studies are needed to compare the effectiveness of different diagnostic and management strategies to establish best practice guidance for children with CeD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-021-06988-2.

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Declarations

Conflict of interest SSCH received his scholarship from Freemasons New Zealand. No further disclosures.

Research involving human participation and/or animals This study was approved by the subcommittee of the University of Otago Human Ethics Committee (Health). This study did not involve any direct patient contact.

Informed consent Informed consent was not obtained from participants in this study as the survey was conducted anonymously. Participants were given the option of providing their demographic details at the end of the survey.

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