

Review

An Overview of International Guidelines Focusing on the Long-Term Management of Coeliac Disease

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Abstract: Coeliac disease (CD) is an autoimmune disorder characterised by, but not isolated to, intestinal enteropathy in response to exposure to gluten in predisposed individuals. The mainstay of the management of CD is a strict, lifelong gluten free diet (GFD). Although numerous publications have focused on pathways to guide the diagnosis of CD, recommendations for the care of patients after diagnosis are less well established. This manuscript aimed to review the available published guidelines focusing on the ongoing management and follow-up of patients after diagnosis with CD and commencement of a GFD. All available guidelines recommend strict adherence to a GFD with most recommending an annual review by a specialist clinician, focusing on symptoms, adherence and growth. In addition to monitoring micronutrient status, some guidelines suggest monitoring bone mineral density in at-risk groups and screening for other autoimmune disorders. The benefit of multi-disciplinary input was outlined in many guidelines, in particular, the involvement of a specialist dietitian to provide nutritional counselling and support. While the available guidelines provide key messages, they highlight a lack of strong evidence and some inconsistencies. Further evidence is required to support high quality, best-practice management strategies that will optimise the outcomes of patients with CD.

Keywords: coeliac disease; gluten-free diet; monitoring; outcomes; guidelines

1. Background

Coeliac disease (CD) is an autoimmune disorder characterised by intestinal enteropathy in response to intestinal exposure to gluten in predisposed individuals. Just a few decades ago, it was thought to be an uncommon disease of childhood affecting predominantly European populations. It has since been shown to be present universally and can develop at any age while individuals are consuming gluten-containing foods [1–3]. Furthermore, it is also now clear that CD may have variable presentation patterns ranging from no symptoms to a wide range of gastrointestinal or extra-gastrointestinal symptoms.

The global prevalence of CD is thought to be around 1% [2–7], with recent increases in prevalence noted [2,4]. In 2018, Singh et al. [2] described the international pooled prevalence of coeliac disease to be 1.4% based on serology and 0.7% when based on biopsy results. The prevalence rates were shown to be highest in Europe and Oceania (0.8%) and lowest in South America (0.4%). Significant variation in prevalence has also been shown within continents with definitive explanations for these differences remaining unclear. In 2010, Mustalahti et al. [6] observed an eight-fold difference in prevalence between Germany (0.3%) and nearby Finland (2.4%) in 30–64 year olds. The authors postulated that both environmental and genetic factors may be contributing to these variances [6]. The prevalence also appears to be higher in certain groups within populations, namely relatives of those with coeliac

disease [8], females [1,2], those with other autoimmune disorders [1] (such as type 1 diabetes [9] and autoimmune thyroid), Down syndrome and Turner syndrome [10,11].

There are numerous evidence-based international guidelines focusing on the diagnosis of CD [10–18]. However, the ongoing management of individuals following their diagnosis is equally important in order to ensure optimal outcomes. This manuscript aimed to review the current guidelines focusing on the care of patients after diagnosis with CD.

2. Management of Coeliac Disease

Currently, the only treatment for CD is the lifelong exclusion of gluten from the diet. This involves the avoidance of certain cereals, such as wheat, barley, rye and in most cases, oats from the diet, thereby comprising a gluten-free diet (GFD).

With these cereals being staples in many diets internationally, careful dietary modification must be undertaken to ensure that appropriate substitutions are incorporated into the diet, to ensure ongoing nutritional adequacy, especially in growing children. GFDs lacking these substitutions have been shown to be low in nutrients such as fibre, vitamin D, vitamin B12, folate, calcium and iron, potentially leading to deficiencies [17,19,20]. These dietary inadequacies have been shown in individuals who have just started a GFD and in those well-established on the diet [21].

Conversely, without careful consideration of these substitutions, increased concentrations of heavy metals have been seen in people following a GFD [22]. In particular, increased reliance of monograins in the diet could increase the risk of excessive intakes of certain metals. For example, high arsenic levels have been noted in individuals consuming predominantly rice based products in their diet [23,24].

Gluten free products can be more energy dense than their gluten-containing contemporaries, posing an added challenge to weight management [19,25]. Finally, the cost of gluten free products tends to be higher than gluten-containing alternatives. This is particularly relevant if appropriate, naturally gluten-free products are not well utilised as part of the diet [25,26].

Even small amounts of gluten can be harmful for those with CD meaning that exclusions of all gluten containing products must be strict [16]. Hidden sources or potential sources of contamination in food products with gluten resulting in inadvertent exposure must also be considered. This can add significant stress to people living with CD when it comes to travel and eating out where access to suitable options could be limited and contamination risks are higher [13]. The social implications of following a restricted diet must also be considered, particularly during the adolescent years when independence and social conformity are priorities and during childhood when lack of understanding could challenge adherence [27,28].

Due to the multiple challenges of maintaining a GFD, patients often report a high treatment burden [29]. This highlights the importance of appropriate support and guidance from skilled professionals to develop the skills required to successfully adopt and maintain the diet. It is thought that adherence to a strict GFD ranges from 42–95% and is not necessarily affected by the degree of symptoms at diagnosis [16,30–33]. Once the GFD is adopted in those diagnosed with CD, symptom resolution can be achieved in the first few weeks with subsequent resolution of the mucosal changes. However, mucosal healing may take many months, with more rapid improvements typically seen in children [10,34,35].

3. Adverse Outcomes Associated with Coeliac Disease

The benefits of well-controlled CD are not just limited to symptom resolution in those who are symptomatic. Untreated coeliac disease predisposes the patient to a number of additional risk factors affecting health outcomes.

Villous atrophy as a result of exposure to dietary gluten leads to suboptimal absorption of nutrients and consequent micronutrient deficiencies such as iron and folate. Additionally, the small intestinal changes can also result in secondary lactose intolerance and associated symptoms until mucosal healing and lactase regeneration can occur [36]. Due to the suboptimal absorption of nutrients,

bone mineralisation and dental enamel can also be affected, increasing the risk of osteoporosis, fractures and dental caries [37,38]. Untreated CD can also be associated with elevated hepatic transaminases, which tend to resolve within a year or so of a GFD [39].

In children, untreated CD can result in poor growth with improved anthropometry seen on commencement of a GFD [40,41]. Reproductive health can also be affected with delayed puberty, reduced fertility and increased risk of obstetric complications reported [12,42].

Finally, more generalised symptoms such as increased fatigue are also reported [43]. All of these factors likely contribute to the reduced quality of life seen in those with untreated CD [44].

The overall mortality risk of CD is not fully clear but appears to be slightly elevated [45,46]. Removal of gluten from the diet and strict adherence to a GFD is generally thought to reduce these risks [47]. Further concerns relate to the increased risk of developing Non-Hodgkin's lymphoma [45,46,48]. Conversely, Scandinavian investigators noted a reduced risk of breast cancer, and breast and lung cancers respectively in their cohorts [48,49].

Once non-adherence is ruled out, persistent symptoms or abnormal serology despite a strict GFD is considered non-responsive coeliac disease (NRCD): this is thought to occur in 10–19% people with CD [50]. One study found that the most common cause of NRCD was in fact accidental exposure to gluten (35%) with only 10% of cases being refractory CD, highlighting the importance of robust education on following the GFD [50].

4. International Guidelines Focusing on the Ongoing Management of Patients with Coeliac Disease

Due to the challenges associated with adherence to the GFD and the undesirable effects of untreated, active CD, effective management strategies must be adopted. However, to date, there is limited evidence as to how this should be best applied to the ongoing clinical management of these patients in order to optimise adherence. This includes factors such as the required frequency of review, specific investigations and monitoring indicated at these reviews, assessment of adherence to the GFD and which health professionals should be involved for optimal outcomes.

A number of international peak bodies have proposed strategies for the ongoing follow-up of patients diagnosed with CD (Table 1). The available guidelines and recommendations were identified through database searches using Medline and Embase with search limits focused upon guidelines and expert opinion, written in English, from peak bodies internationally between January 2005 and April 2020. Evidence contained within these guidelines was a combination of evidence-based practice, where available, and expert consensus process.

Table 1. Comparison of suggested strategies for the management of confirmed coeliac disease by major international expert groups within the last 15 years.

GUIDELINE	WGO [10]	BSPGHAN [12]	BSG [13]	NICE [14]	Expert Panel [51]	NASPGHAN [16,17]	ACG [18]	AGA [52]	ESsCD [53]
Advise strict GFD	Y	Y	Y	Y	Y	Y	Y	Y	Y
Frequency of review	Annual, 3–6 monthly first year	Annual, 3–6 monthly first year	Annual once stable	Annual	-	Annual once symptom-free	Annual, 3–6 monthly first year	Annual	3–6 monthly first year, then 1–2 yearly
Adherence	Y	Y	Y	Y	-	Y	Y	Y	Y
Symptom review	Y	Y	Y	Y	-	Y	Y	Y	Y
Anthropometry	-	Y	-	Y	Y	Y	Y	Y	-
Micronutrients	Correct deficiencies (e.g., folate, Ca, Fe)	Assess intake	Y FBC, ferritin, folate, B12, Ca, ALP, AST	If concerns	FBC or if previously abnormal	FBC, vitamin D, others as indicated	If concerns previously	N	On diagnosis, then repeat if concerns
Serology (DGP IgA/TG IgA)	Periodical	Y	Y	Not used in isolation	Y	Y	Y	Y	Y
Autoimmune screening	-	-	Y TSH, glucose	-	Y for thyroid, Education for identifying diabetes	Y Thyroid	-	-	Y
Bone density	-	-	1 year on GFD in those >55 years of age or risk factors	As per NICE osteoporosis guide	N Unless poor adherence or abnormalities detected	-	-	-	Adults, on diagnosis. Repeat five yearly or more often if abnormal
Dietary review	By dietitian recommended, including vitamins, Ca and fibre	Fe, Ca intake GF oats once at baseline	Y Ca intake ≥1000 mg/d	Consider need for specialist advice	Education on vitamin D and Ca intake	Yes, if TTG remains elevated	Y	Y	Y
Repeat Biopsy	N	-	If unresponsive on GFD	If persistent symptoms or serology on GFD	-	If poor response to GFD	If unresponsive or relapse in symptoms	Y	If unresponsive or relapse in symptoms
Clinicians involved	MDT approach - Dietitian - Psychology as required	Regular monitoring by dietitian, paediatrician or gastroenterologist	Clinician(s) with gastrointestinal and dietetic expertise	GP or dietitian	Access to a dietitian	Physician and dietitian. Psychology as required	Health-care practitioner and dietitian	Team approach, including dietitian	Gastroenterologist and dietitian
Local coeliac society		Y	Y	Y	-	Y	-	-	Y

Y = yes, N = no, - = not commented on, FBC = Full blood count, Fe = iron, Ca = calcium, B12 = vitamin B12, ALP = alkaline phosphatase, AST = aspartate aminotransferase, TSH = Thyroid stimulating Hormone, DGP = deamidated gliadin peptide, TTG = tissue transglutaminase antibodies, GP = General Practitioner, MDT = multidisciplinary team, ACG = American College of Gastroenterology, AGA = American Gastroenterological Association, BSG = British Society of Gastroenterology, BSPGHAN = British Society of Paediatric Gastroenterology, Hepatology and Nutrition, ESsCD = European Society for the Study of Coeliac Disease, NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, NICE = National Institute for Health and Care Excellence, WGO = World Gastroenterology Organisation.

4.1. World Gastroenterology Organisation Guidelines

The World Gastroenterology Organisation (WGO) provided initial guidelines in 2013 [10], which were subsequently updated in 2017 [54]. These were aimed to provide global guidelines to firstly the diagnosis of CD and secondly the management of CD after diagnosis.

The first guideline firmly established the need for a strict GFD for life, with the statement that remission (clinical, serological and histological) would be expected to occur in most patients following this regimen [10]. Recommendations were made for clinical review with multidisciplinary inputs every three to six months for the first year, followed by annual review thereafter. The clinical review was expected to focus on symptom improvement and laboratory tests. The role of serological tests (de-amidated gliadin peptides (DGP) or tissue transglutaminase (TTG)) coinciding with clinical review and then periodically was detailed, with emphasis that these tests are not sensitive to trace exposure but was the preferred method for assessing compliance to GFD. Repeat small bowel biopsy (SBB) was not recommended. Dietetic involvement from diagnosis and at each clinical review was strongly emphasised, with provision of initial education and ongoing dietary support and review.

The updated guideline in 2017 reiterated many of these recommendations, but did provide expanded discussion about some aspects [54]. A strict life-long GFD was strongly recommended, with further discussion about the requirements of a GFD, and permitted levels of gluten exposure. In terms of clinical review, particular recommendation was made that children should be seen annually by a paediatrician or paediatric gastroenterologist until their final adult height was acquired. Requirements for bone mineral density scanning and vaccinations for pneumococcus, meningococcus and *Haemophilus pneumoniae* were outlined. Serological testing with DGP or TTG was recommended every three to six months until test results have normalised and then every one to two years to monitor for adherence to GFD. The potential role of faecal testing for gluten immunogenic peptides (GIP) was referenced. The role of repeat SBB was mentioned in the context of controversy with variable practice acknowledged. However, repeat SBB testing was strongly advised in individuals with persistent symptoms.

The input of nutritionists was once again strongly recommended with similar roles to those described in the first guideline. In addition, a dietetic review was recommended every three to six months until clinical remission, and then every one to two years thereafter. This guideline also clearly emphasised the role of CD support groups and psychological input in those who were struggling with the diagnosis and the management.

4.2. BSPGHAN and Coeliac UK

These guidelines focusing on aspects of CD in children were jointly developed by the two organisations and published in 2013 [12]. The first follow-up recommendation was for clinical review by a specialist paediatric dietitian and a paediatric gastroenterologist or a paediatrician with a special interest 6–12 months after diagnosis to review adherence, document symptomatic improvement and to repeat serology. Follow-up was then recommended to be every one to two years with repeat serology on each occasion, with an eventual goal to transition to adult services. Additional comments emphasised the need for access to a paediatric dietitian within one to two weeks of diagnosis, and then as required and encouragement was made to join Coeliac UK for support. None of the recommendations or statements were supported by reference to published research.

4.3. British Society of Gastroenterology

This guideline focused on the management of adults diagnosed with CD and was based on the opinions of a panel of 21 individuals [13]. A regular review for the first 12 months after commencement of a strict GFD with a dietitian and a gastroenterologist was recommended, with subsequent annual review thereafter. Encouragement was given to join a coeliac support organisation. The regular assessment of micronutrient status, clinical state and serology was detailed along with regular assessment of

adherence. Follow-up SBB should be considered but was recommended in those who appeared non-responsive to a GFD. Additional comments included ensuring adequate calcium, screening for osteoporosis and the consideration of inclusion of oats. Recommendations were supported by Grade C and D levels of evidence.

4.4. NICE

This guideline provided short recommendations for the management of individuals after diagnosis of CD [14]. The evidence was considered, with each of the management/follow-up guidelines supported by low to moderate observational or qualitative data, along with expert input from the panel. The commencement of a GFD was recommended to occur in conjunction with detailed education from a knowledgeable health care provider. A subsequent annual review was suggested to review anthropometry, symptoms, and consideration of the need for further specialist dietetic input. In addition, if concerns were raised during annual review, then individuals should be considered for assessment of bone health, measurement of micronutrients, and serological tests. Caution was made to avoid reliance upon serology testing as the sole marker of adherence. In addition, the importance of encouragement to join a support organisation, awareness of associated mental health concerns and the potential role of follow-up small bowel biopsy were all mentioned.

4.5. Expert Panel

Snyder et al. [51] reported the outcomes of an expert panel focused on aspects of the diagnosis and management of CD in children as informed by available evidence. The authors acknowledged that there was inadequate data to support most of the areas considered. They focused on a number of key aspects, predominantly pertinent to the initial assessment and diagnosis of children with CD. The report was accompanied by an online supplement that provided background information and summaries of the data supporting aspects such as bone health.

The panel strongly supported the introduction of a strict GFD for life after diagnosis, with education and support from an experienced paediatric dietitian. The assessment of growth and routine serologic testing at regular intervals was recommended, but specific details such as frequency of assessment were not considered. A routine periodic assessment of thyroid function and full blood count was also recommended. Other tests such as hepatic transaminases, vitamin D and bone densitometry were suggested to be completed where indicated only. Routine vitamin supplementation was not recommended, however, individualised discussion about calcium and vitamin D optimisation was suggested.

4.6. NASPGHAN

The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published a clinical guideline in 2005 and more recently (in 2016) a clinical report on the diagnosis and treatment of CD in children [16,17]. Although the clinical report focused on various gluten-related disorders, it included a section on the management of CD after diagnosis. Commencement of and adherence to a strict GFD after initial education from an experienced paediatric dietitian was emphasised. A regular review was recommended initially, with follow-up by a paediatric gastroenterologist or paediatrician with wide knowledge about CD and a dietitian. The referral to a support group was considered beneficial and psychological support noted for some children.

A recommendation was made for regular repeated assessment of serology after diagnosis to document adherence and to provide a guide of mucosal healing. Upon resolution of symptoms and documentation of normalised serological tests, ongoing follow-up should then be annual with paediatric and dietetic personnel. A baseline assessment of other tests (e.g., thyroid function, full blood count, vitamin D, iron status and others as indicated) and an annual review of thyroid function, full blood count and vitamin D suggested.

4.7. ACG

The American College of Gastroenterology (ACG) published a clinical guideline focused on the diagnosis and management of CD with relevance to adults and children [18]. The commencement of a life-long strict GFD was strongly recommended, as was the provision of education and support from a dietitian well-versed in CD and the use of the GFD. Regular review by an individual with specific knowledge about CD to detect symptoms, assess adherence and document growth was recommended strongly, with moderate evidence support. There was discussion about the best person to facilitate ongoing review after diagnosis, with comments from published literature. An annual follow-up was suggested, although limited evidence for this recommendation was acknowledged.

Furthermore, a regular assessment of serologic tests was suggested to monitor for adherence along with symptom review. The performance of other investigations (such as measurement of vitamin D levels) was suggested to occur only to document any indicator that was abnormal at diagnosis.

4.8. AGA

The American Gastroenterological Association (AGA) recently provided a clinical practice update to the diagnosis and management of CD in adults and children, with particular focus on serologic testing [52]. The document strongly supported the use of GFD with management within a team setting including an experienced dietitian. An annual follow-up was suggested, with note made of the importance of anthropometric assessment in children. It was recommended that serology be performed 6 and 12 months after diagnosis, and then annually thereafter.

4.9. European Society for the Study of Coeliac Disease

The European Society for the Study of Coeliac Disease also recently published a comprehensive guideline to many aspects of diagnosis and management of CD in adults and children [53]. This document recommended regular follow-up in the first year after commencement of a GFD, with follow-up ideally including a gastroenterologist and a specialist dietitian. A schema for follow-up was provided, outlining frequency and steps to be considered at each review. This included annual serology and thyroid function, with possibility of other tests when indicated. The guideline emphasised four aspects to ascertaining adherence to GFD: clinical review, dietetic review, serology and the possibility of repeat small bowel biopsy. Encouragement was also given to suggest patients join local support groups. Similar comments in a separate section were specifically made about children and adolescents.

5. Summary and Discussion of International Guidelines Focusing on the Ongoing Management of Coeliac Disease

Each of the guidelines published over the last 15 years on the ongoing management of both adults and children diagnosed with CD recommended annual review with a specialist clinician with most recommending more frequent review in the first year following diagnosis [10,12–14,16–18,52,53]. Expert recommendations by Snyder et al. [51] did not outline suggested review timeframes.

All guidelines advise strict lifelong adherence to a GFD. Some guidelines suggest the inclusion of pure oats in the diet at diagnosis with subsequent monitoring of tolerance [13,18], whereas others suggest delaying the introduction of oats until a stable baseline is achieved following diagnosis [12].

Most guidelines suggest review of symptoms, adherence and growth (in children) at clinical review [10,12–14,16,18,51–53]. Repeat serology tests (e.g., TTG) were recommended in all documents with the caveat that this should not be used in isolation to assess adherence and villous recovery.

Monitoring for other autoimmune conditions associated with CD was suggested in four guidelines [13,16,51,53]. All suggested checking thyroid function, with one also advising to measure blood glucose levels. Another recommended to educate the patient and family about the early signs and symptoms of diabetes as an alternative to screening.

Bone mineral density during follow-up was only discussed in four guidelines [13,14,51,53]. The UK guidelines for adults with CD suggested measuring bone density after one year on a GFD if patients are over 55 years old or have other risk factors for osteoporosis [13,14]. Snyder et al. [51] suggest to measure bone density in those children with poor adherence to a GFD.

There was some variation in recommendations for micronutrient monitoring. Micronutrients and tests of interest in the various documents included full blood count, iron, folate, vitamin B12, vitamin D, calcium and liver chemistry. Some guidelines suggest more extensive micronutrient testing on diagnosis with ongoing monitoring if there were initial concerns [18,51,53], while others suggested checking only if there were concerns. The 2013 WGO guidelines took a different stance, advising detection of potential deficiencies through dietary assessment rather than biochemical testing [10]. In addition to this, Snyder et al. [51] suggest routine multivitamin supplementation on diagnosis for all children.

With regards to who should manage patients with coeliac disease, the WGO guidelines highlighted the importance of a multidisciplinary approach to care; this included psychological counselling where dietary adherence was an issue [10]. Other guidelines also recommend local coeliac societies for ongoing support between reviews, on the basis that this may improve adherence to the GFD [10,12–14,33,53]. Psychological support was also mentioned in several guidelines.

In addition to a clinician, all guidelines outlined the benefit of access to a dietitian with expertise in CD to assess adherence, assess nutritional adequacy and support adherence to the GFD. Nutritional assessment as part of annual review was recommended in all guidelines to differing extents.

Several guidelines discussed which healthcare professionals should ideally be involved in providing ongoing review of patients following diagnosis. While joint gastroenterology and dietetic clinics were considered most favourable by a number of guidelines, there was a prevailing narrative of the value of close dietetic review and support. One report has indicated that patient preference is for dietetic involvement [55]. A past study from Finland has suggested ongoing review by general practitioners (GP) was effective [56]. More recently, a study from the UK evaluated the effectiveness of GP follow-up with comparison to a telephone review protocol [57]. Many of those who were discharged to GP review were lost to follow-up, with less than one third having an annual review. Conversely, more of those followed by telephone had assessment of weight, review of symptoms and check of adherence. However, those who did attend GP review were more likely to receive calcium and/or vitamin D supplements.

6. Conclusions

Due to the importance of the adherence to a strict GFD in optimising the outcome of those with CD, it is imperative that quality, evidence-based management strategies are implemented to provide patients with CD with the knowledge, skills and support to effectively manage their condition. A number of different models have been trialled internationally, such as dietitian- or nurse-specialist-led clinics and endorsed membership to local coeliac societies to better utilise clinician time and resources and achieve good clinical outcomes [58,59]. Further studies are needed to compare the effectiveness of different management strategies to establish best-practice guidance for the long-term management of patients with CD.

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