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The 2026 British Society of Gastroenterology guidelines on the diagnosis and management of adult coeliac disease

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ABSTRACT

This document outlines an updated guideline from the British Society of Gastroenterology, detailing the standards for diagnosing and managing adult coeliac disease (CD). A multidisciplinary panel from across the UK, Sweden, Italy and Australia contributed to the development of these guidelines. This update is prompted by recent advancements in the diagnosis and treatment of adult CD. The primary goal is to emphasise evidence-based practices to enhance the management of adult CD, with the aim of improving patient care.

EXECUTIVE SUMMARY

Recommendations (REC): Evidence-based statements subjected to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

Good practice statements (GPS): Actionable statements informed by indirect and/or limited evidence which were not subject to GRADE assessment.

Expert opinions (EO): Statements that did not meet the criteria for either of the above but were considered important to the guideline audience.

Diagnosis

- REC 1: We recommend that patients consume a gluten-containing diet prior to testing for coeliac disease (CD). *GRADE: high certainty of evidence; strong recommendation; agreement 100% (abstain 0/33)*.
- GPS 1: Patients with test results suggestive of CD (eg, newly positive coeliac serology and/or positive duodenal histology) should be referred to secondary care for further assessment. *Agreement 100% (abstain 0/33)*.
- REC 2: We recommend testing for IgA-tissue transglutaminase (tTG) antibodies as the first-line investigation for CD. *GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 0/33)*.
- GPS 2: We advise screening for selective IgA deficiency (sIgAD) in patients with suspected CD alongside measuring IgA-tTG levels. *Agreement 100% (abstain 0/33)*.
- REC 3: We suggest measuring IgG-based coeliac serology and upper gastrointestinal (GI) endoscopy with duodenal biopsies in individuals with sIgAD and clinical suspicion for CD. *GRADE: low certainty of evidence; conditional recommendation; 100% agreement (abstain 1/33)*.
- REC 4: We recommend that at least four biopsies from the second part of the duodenum (D2) and two biopsies from the duodenal bulb (D1) are sampled when biopsies are required for the investigation of suspected CD. *GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 6/33)*.
- GPS 3: Where possible, a single-bite biopsy technique should be employed to acquire duodenal tissue samples. *Agreement 100% (abstain 7/33)*.
- EO 1: We advise the use of a histological grading system to help with consistency and standardisation of histology reporting. *Agreement 96% (abstain 6/33)*.
- GPS 4: Human leucocyte antigen (HLA) genotyping should be performed in specific circumstances to exclude CD. A negative DQ2 or DQ8 genotype indicates that patients are highly unlikely to have CD and an alternative diagnosis should be considered. *Agreement 97% (abstain 2/33)*.
- REC 5: We recommend that a diagnosis of CD can be made in patients with positive coeliac serology and duodenal biopsies demonstrating increased intraepithelial lymphocytes (IELs) (>25/100 epithelial cells) plus crypt hyperplasia with/without villous atrophy: this equates to a Marsh 2 or 3 histology grading stage. *GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 4/33)*.
- GPS 5: A diagnosis of potential CD can be made in patients with persistently positive coeliac

serology, duodenal biopsies demonstrating no changes or an isolated increase in IELs (>25/100 epithelial cells) (ie, Marsh 0–1 histology) and a positive HLA-DQ2 and/or HLA-DQ8 genotype. *Agreement 93% (abstain 3/33)*.

- GPS 6: A diagnosis of seronegative CD can be made in patients without elevated coeliac serology (including IgG-based tests), but with duodenal biopsies demonstrating villous atrophy (ie, Marsh 3 histology), a positive HLA-DQ2 or HLA-DQ8 genotype and improvement on a gluten-free diet (GFD). *Agreement 96% (abstain 6/33)*.
- GPS 7: A diagnosis of CD should not be made in the case of negative coeliac serology and duodenal biopsies demonstrating an isolated increase in IELs (>25/100 epithelial cells) (ie, duodenal lymphocytosis) and other causes should be explored. *Agreement 97% (abstain 3/33)*.
- REC 6: We suggest that in symptomatic adults being assessed in secondary-care settings, a diagnosis of CD can be made without duodenal biopsies when IgA-tTG titre ≥10 × upper limit of normal. This 'no-biopsy' pathway is optional and should be adopted only after shared decision-making with the patient. *GRADE: moderate certainty of evidence; conditional recommendation; agreement 94% (abstain 1/33)*.
- GPS 8: We advise testing patients with clinical suspicion for CD (*case finding*). *Agreement 100% (abstain 0/33)*.
- GPS 9: Duodenal biopsies should be performed in patients with iron deficiency anaemia undergoing upper GI endoscopy, (1) in those with positive coeliac serology that does not meet the serology-only criteria; (2) if serology has not been performed prior to upper GI endoscopy; (3) recurrent or persistent anaemia even if coeliac serology is negative. *Agreement 100% (abstain 3/33)*.
- GPS 10: We advise screening for CD in high-risk groups (*screening*). *Agreement 100% (abstain 0/33)*.
- REC 7: For the gluten challenge, we recommend a dose of 3–6 g of gluten daily for at least 6 weeks. *GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 1/33)*.
- REC 8: We suggest a trial of a GFD for symptomatic patients with potential CD under the guidance of a specialist dietitian. *GRADE: low certainty of evidence; conditional recommendation; agreement 93% (abstain 3/33)*.
- EO 2: Symptomatic or asymptomatic patients with potential CD who continue a gluten-containing diet should be counselled about the risk of progression to overt CD. *Agreement 100% (abstain 2/33)*.
- GPS 11: For patients with potential CD who continue a gluten-containing diet, we advise repeating serology and biopsies if new symptoms develop, or after 1–2 years if stable, in discussion with the patient. *Agreement 100% (abstain 2/33)*.

The gluten-free diet

- REC 9: We recommend that patients diagnosed with CD maintain a life-long GFD to help improve symptoms, quality of life and reduce the risk of complications associated with the condition. *GRADE: low certainty of evidence; strong recommendation; agreement 94% (abstain 0/33)*.
- GPS 12: At the point of diagnosis, we advise that patients are signposted to an established disease advocacy group (eg, Coeliac UK) for reliable information about CD and the GFD. *Agreement 97% (abstain 2/33)*.
- REC 10: We suggest that gluten-free oats ingestion should be discussed with patients with CD and advised as soon as the GFD is commenced in the setting of appropriate clinical follow-up. *GRADE: moderate certainty of evidence; conditional recommendation; agreement 100% (abstain 2/33)*.
- REC 11: We suggest a combined approach for assessing GFD adherence, as no one test provides adequate information in isolation. *GRADE: moderate certainty of evidence; conditional recommendation; agreement 97% (abstain 1/33)*.
- EO 3: Resolution of symptoms and/or mucosal healing should be the key treatment goals in CD. However, treatment targets should be considered in the context of the general well-being of the individual and personalised as appropriate. *Agreement 97% (abstain 1/33)*.

Follow-up

- GPS 13: All patients diagnosed with CD should undergo regular follow-up for up to 2 years after diagnosis. Following this:
  - Repeat duodenal biopsies should be considered in discussion with patients before decisions about longer-term follow-up are made.
  - Patients who have responded well to a GFD may be considered for patient-initiated follow-up (PIFU).
  - Longer-term systematic follow-up is advised for patients who: (1) are poorly adherent to the GFD (or are at risk of poor adherence); (2) have not responded adequately to a GFD; and/or (3) have developed complications associated with CD. *Agreement 90% (abstain 2/33)*.
- REC 12: We recommend that duodenal histology is the only way to assess for mucosal inflammation in established CD on a GFD. *GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 3/33)*.
- GPS 14: Patients should be assessed and monitored for deficiencies in iron, folate, vitamin B12, vitamin D and calcium at diagnosis and during follow-up. Supplementation should be provided in line with general guidance where required. *Agreement 100% (abstain 1/33)*.
- EO 4: We do not advise supplementation to prevent nutritional deficiencies over and above national recommendations for the general population. *Agreement 100% (abstain 2/33)*.
- GPS 15: All newly diagnosed adult patients should have a dual-energy X-ray absorptiometry (DXA) scan 1 year after starting a GFD. *Agreement 94% (abstain 2/33)*.
- GPS 16: A repeat DXA scan should be performed in individuals with persisting villous atrophy and/or refractory coeliac disease (RCD) after an appropriate timeframe (ie, 2–3 years). *Agreement 86% (abstain 3/33)*.
- GPS 17: We advise that all adult patients diagnosed with CD receive the pneumococcal vaccination; those with RCD and/or on long-term immunosuppressive medication should receive a booster after 5 years. *Agreement 93% (abstain 3/33)*.
- GPS 18: We advise that patients with established CD transitioning from paediatric to adult care are offered follow-up in the adult service, in accordance with adult guidance. *Agreement 94% (abstain 2/33)*.

Non-responsive and refractory coeliac disease

- EO 5: Patients with suspected RCD should be referred to a specialist centre for support with diagnosis and management by an experienced multidisciplinary team including dietitians, gastroenterologists, pathologists and haematologists. *Agreement 97% (abstain 0/33)*.

- REC 13: We recommend the use of flow cytometry to immunophenotype small intestinal IELs as the reference standard to diagnose RCD2. *GRADE: low certainty of evidence; strong recommendation; agreement 96% (abstain 9/33).*
- REC 14: We recommend that patients with suspected RCD undergo small bowel imaging. Device-assisted enteroscopy should be planned for tissue sampling where required. *GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 10/33).*
- REC 15: We suggest open-capsule budesonide as a first-line treatment of RCD1 alongside maintaining a strict GFD. *GRADE: low certainty of evidence; conditional recommendation; agreement 100% (abstain 10/33).*
- GPS 19: We advise that thiopurines such as azathioprine are considered as steroid-sparing agents in RCD1 if treatment is required over the longer-term. *Agreement 100% (abstain 11/33).*
- EO 6: Treatment of RCD2 should be individualised and considered in a specialist MDT setting. *Agreement 96% (abstain 5/33).*

BACKGROUND

Coeliac disease (CD) is a chronic, autoimmune disorder that occurs in genetically predisposed individuals, with a reported prevalence of approximately 1%.[1] The disease is primarily characterised by small intestinal enteropathy. However, its manifestations are diverse and can affect both the gastrointestinal (GI) tract and extraintestinal sites across the body. Inflammation and tissue damage in the small intestine result from an abnormal immune response to ingested gluten. A lifelong gluten-free diet (GFD) is currently the only accepted treatment in CD.

The British Society of Gastroenterology (BSG) first published guidelines for the management of adult CD in 1996, with a subsequent update in 2014.[2] Since then, over 4000 PubMed publications on adult CD have introduced new developments in the diagnosis and management of the condition. As a result, the BSG's Clinical Services and Standards Committee (CSSC) commissioned these updated guidelines, which are based on a comprehensive review of recent literature.

OBJECTIVE AND SCOPE

The objective of this guideline is to update the BSG recommendations for the diagnosis and management of adult CD in line with the latest evidence, to inform clinical decisions and standards of care, with the goal of improving patient care. As a result, previous recommendations have been reconsidered, and new recommendations have been introduced. These guidelines are intended for a wide-ranging target audience comprising healthcare providers, including dietitians and physicians within primary and secondary care settings, as well as policymakers working within the field of CD. This guideline does not include a health economic analysis. A patient-friendly summary can be found in online supplemental file 1a.

These BSG guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations, but we advise that reasons for this are documented in the medical record. BSG guidelines are intended to be an educational device to provide information that may assist in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring or discouraging any particular treatment.

METHODOLOGY

This guideline was developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology,[3] following the principles of the Appraisal of Guidelines for Research & Evaluation (AGREE II) tool,[4] and in accordance with the BSG Guidelines Advice Document.[5] This guideline was designed and written by members of the Guideline Development Group (GDG), comprising a multidisciplinary panel of experts from across the UK, Italy, Sweden and Australia, including 20 physicians, 3 dietitians and 3 patient representatives.

The GDG initially identified areas relating to the diagnosis and management of adult CD that were deemed important (online supplemental file 1b). Where possible, research questions were developed relating to these themes using Population, Intervention, Comparator, Outcome or Population, Exposure, Outcome frameworks and comprehensive literature searches were performed using PubMed Medline (online supplemental file 1c). Searches were limited to articles published in English and typically dated since 2012, to account for new evidence since the previous guideline literature search.[2] In certain instances, where specified, the date ranges were modified to help support the assimilation of evidence. The bibliographies of identified studies were reviewed, alongside input from the GDG, to help find additional relevant material. For diagnostic accuracy studies, we performed meta-analysis of adult data using a random-effects bivariate model to estimate pooled sensitivity and specificity of the available serological assays (online supplemental file 1d). For the remaining questions, systematic analysis was not possible because of insufficient data or not conducted because of established knowledge and understanding. Research questions and themes were revised through discussion (two virtual and one face-to-face meeting in May, June and September 2024, respectively). Evidence-based statements relating to these themes were developed as 'recommendations' using the GRADE framework with the help of the GRADEPro.org platform. The certainty of evidence for recommendations was assessed by two members of the GDG (HAP, MGS, SAR or NN), blinded to one another's assessment (online supplemental file 1d). Assessments were reviewed and where necessary, moderated by DSS to determine agreement. Actionable statements informed by indirect and/or limited evidence were developed as 'good practice statements' which were not subject to GRADE assessment. Statements that did not meet the criteria for either, but were considered of importance to the guideline audience, were developed as 'expert opinion', as in recent guidelines.[6]

Recommendations, good practice statements and expert opinions (further referred to collectively as statements) were voted on by all members of the GDG. We also engaged the views of other relevant parties by inviting a broader group of healthcare professionals to vote on drafted statements, creating a final Guideline Consensus Group for voting comprising 33 individuals. Electronic voting was performed anonymously via an online platform. Participants were able to abstain from voting on specific statements where they either did not have sufficient knowledge or identified themselves as having a conflict which precluded voting. Agreement was predefined as ≥80% of the sum of the votes of strongly agree, plus agree with minor reservation. Any statements that did not reach the desired level of

agreement after round 1, and/ or were modified through discussion at virtual meetings (May 2025), underwent further voting. All statements achieved the desired agreement after two rounds of voting. The result of this process was a set of recommendations with a corresponding level of certainty of evidence and recommendation, as well as a set of good practice statements and expert opinions with a level of agreement. Relevant aspects supporting the *justification* and *implementation* of recommendations were highlighted in the text to provide context and practical guidance for their use.

In addition, during the guideline development process, a number of key performance indicators (KPIs) - which represent indicators of high-quality care for patients with CD - were drafted by the GDG (see Key performance indicators). The final document underwent review by the BSG CSSC before being submitted for publication via peer review. Where relevant, the literature was screened for updates during the guideline review process. The GDG foresees no major barriers to implementation of the current clinical recommendations.

EVIDENCE AND RECOMMENDATIONS

DIAGNOSIS

Recommendation 1

We recommend that patients consume a gluten-containing diet prior to testing for CD.

GRADE: High certainty of evidence; strong recommendation; agreement 100% (abstain 0/33).

Justification: Diagnostic tests presently used in routine clinical practice (ie, serology and small bowel histology) detect changes associated with an immunological response to dietary gluten. Therefore, individuals with suspected CD must consume adequate amounts of gluten prior to diagnostic testing.

Implementation: For those who have already started a GFD prior to diagnostic testing, an intake of 3–6 g gluten daily for at least 6 weeks is considered sufficient. If dietary gluten intake has not been purposefully restricted and is usually consumed within at least one meal a day, then it is reasonable to advise continuing this usual diet prior to testing.

Good practice statement 1

Patients with test results suggestive of CD (eg, newly positive coeliac serology and/or positive duodenal histology) should be referred to secondary care for further assessment. *Agreement 100% (abstain 0/33*).

CD can be diagnosed by detecting coeliac-specific antibodies in serum and demonstrating characteristic mucosal inflammation on duodenal biopsies obtained during upper GI endoscopy.[2 7 8] In some cases, a diagnosis can be made based solely on high antibody titres,[7 9] while in others, it relies on histopathological changes on duodenal biopsies despite negative serology.[10] In either scenario, the diagnostic tests available in routine clinical practice detect the effects of an immunological response to dietary gluten[11 12], which typically resolve on a GFD. Therefore, patients must continue to consume adequate amounts of gluten (ie, a gluten-containing diet) for accurate testing.

While serological tests and/or duodenal histology are highly sensitive for a diagnosis of CD, positive results may not exclusively indicate the condition, and borderline or discordant test results can occur which can make the diagnosis of CD challenging. However, reaching a diagnosis is essential to enable patients to get the correct advice and support to manage the condition. Therefore, we recommend that individuals with test results indicative of CD (ie, newly positive coeliac serology and/ or positive duodenal histology) are referred to secondary care to confirm or exclude the diagnosis before a GFD is started, which aligns with recently devised GI diagnostic pathways in the UK.[13]

Coeliac serology

Serological tests used in clinical practice

Several different assays measuring a wide variety of disease-associated antibodies exist in CD. The most commonly used tests in current clinical practice detect the presence of immunoglobulin (Ig)A antibodies directed towards tissue transglutaminase (tTG)-2, the endomysium (EMA) or deamidated gliadin peptides (DGP) (referred to collectively as 'coeliac serology'). TTG and DGP-based tests are based on immunoassay methods (ie, enzyme-linked immunosorbent assay, fluorescence enzyme immunoassay, or chemiluminescence immunoassay), which provide a quantitative measure of antibody in blood, derived from comparison with a calibration curve. The EMA test is based on indirect immunofluorescence, which provides a qualitative measure of the antibody in blood and is typically reported as a binary outcome (ie, positive or negative result), although semi-quantitative titres may also be reported.

Diagnostic accuracy of serological tests

Recommendation 2

We recommend testing for IgA-tTG antibodies as the first-line investigation for CD.

GRADE: Moderate certainty of evidence; strong recommendation; agreement 100% (abstain 0/33).

Justification: A positive IgA-tTG has demonstrated a high sensitivity and specificity for a diagnosis of CD. IgA-tTG is widely available. It is also commonly included in proficiency testing schemes within the UK through the National External Quality Assessment Service (UK-NEQAS).

Implementation: IgA-tTG titres should be checked in individuals with suspected CD or used for screening in high-risk conditions. A positive result should be followed with referral into secondary care for further definitive management which may include duodenal biopsy.

A positive IgA-tTG test (ie, >1 × upper limit of normal (ULN)) has a high sensitivity for CD diagnosis (pooled sensitivity 90% (95% CI 86% to 93%) using commonly used assays; see online supplemental file 1d. A positive test in this setting indicates individuals who warrant a duodenal biopsy to confirm the diagnosis of CD. The high sensitivity of this test is thus important as it is likely to select most cases of possible CD to progress to confirmatory biopsy. In comparison with IgA-tTG tests, the EMA test is more costly, labour-intensive and may be subject to interobserver variability owing to its intrinsic methodology.[14] IgA-DGP tests demonstrate a high sensitivity and specificity in CD.[15] However, some evidence suggests that antibodies to DGPs alone, or in the absence of positive IgA-tTG antibodies, have a low predictive value for CD.[16 17] Additionally, DGP tests are less widely available in clinical practice in the UK, together supporting IgA-tTG as the most appropriate first-line test for CD diagnosis.

Selective IgA deficiency

Good practice statement 2

We advise screening for selective IgA deficiency (sIgAD) in patients with suspected CD alongside measuring IgA-tTG levels. *Agreement 100% (abstain 0/33).*

Recommendation 3

We suggest measuring IgG-based coeliac serology and upper GI endoscopy with duodenal biopsies in individuals with sIgAD and clinical suspicion for CD.

GRADE: Low certainty of evidence; conditional recommendation; 100% agreement (abstain 1/33).

Justification: Patients with CD and sIgAD will not mount IgA-tTG responses. IgG-based coeliac serology should therefore be measured in place of IgA-tTG in those with sIgAD and clinical suspicion for CD. IgG-based coeliac serology has variable sensitivity in diagnostic accuracy studies; therefore, duodenal histology is also required to confirm/exclude CD in this setting.

Implementation: IgG-coeliac serology (ie, IgG-tTG or IgG-DGP where available) should be checked in those with sIgAD (ie, isolated total serum IgA level<0.07 g/L). IgA-tTG responses are detectable in individuals with marginally low total serum IgA levels not meeting the criteria for sIgAD (ie, serum IgA>0.2 g/L; typical normal range 0.8–4 g/L), meaning IgG-coeliac serology testing is not warranted in this setting; immunology laboratories should be consulted to clarify local policies as assay thresholds may vary.

SIgAD is a common primary immunodeficiency that affects around 1 in 500–700 individuals depending on the population analysed.[18] SIgAD characteristically demonstrates an isolated decrease in total serum IgA levels (<0.07 g/L), with normal levels of other immunoglobulin isotypes (IgG, IgM, IgE, IgD), meaning individuals are at risk of false negative IgA-based antibody tests. For reasons that likely relate to shared genetic susceptibility, ~6% of patients with sIgAD have CD[19] and ~2% of patients with CD have sIgAD[20] which is more common than in the general population. SIgAD should therefore be screened for in those with suspected CD; this can be achieved by a one-off measurement of total IgA in blood. Alternatively, it is possible to identify patients that require further investigation for IgA deficiency by identifying low background signal on the IgA-tTG assay.[21] This removes the need to separately check total serum IgA in every case which has cost-saving implications.[22] However, it is not clear whether this technique can be applied across all commercial tTG assays in current routine clinical use.

If sIgAD is present, IgG-based coeliac serology tests should be checked in those with suspicion for CD. IgG-tTG has variable sensitivity across studies (31–97%)[15]; IgG-DGP assays demonstrate a higher diagnostic accuracy but are less widely available in the UK. Therefore, upper GI endoscopy and duodenal biopsies should be performed alongside IgG-based coeliac serology in those with sIgAD and clinical suspicion for CD. IgG-coeliac serology is important in this setting to differentiate IgG-positive CD (ie, seropositive CD) from seronegative CD or other causes of seronegative villous atrophy.

Duodenal biopsies

Biopsy number and location

Recommendation 4

We recommend that at least four biopsies from the second part of the duodenum (D2) and two biopsies from the duodenal bulb (D1) are sampled when biopsies are required for the investigation of suspected CD.

GRADE: Moderate certainty of evidence; strong recommendation; agreement 100% (abstain 6/33).

Justification: Sampling multiple biopsies from the first and second parts of the duodenum confers an increased diagnostic yield of CD compared with situations where either D1 biopsies were omitted or fewer D2 biopsies were sampled. This finding may be explained by the patchy nature of the disease.

Implementation: During endoscopy, multiple biopsies from the first and second part of the duodenum should be sampled. We suggest that D1 and D2 biopsies be placed into separate pathology pots to aid with histological interpretation.

A large study from the USA involving 132,352 patients without known CD who underwent duodenal biopsy between 2006 and 2009 showed that taking ≥4 duodenal biopsy samples resulted in a doubling of the diagnostic rate of CD compared with when<4 biopsies were taken (1.8% vs 0.7%, respectively; p<0.0001).[23] Similar results were found in a more recent UK study of 1423 patients who underwent duodenal biopsy sampling for suspected CD between 2012 and 2013 (CD diagnosis if ≥4 biopsies taken: 10.1% vs <4 biopsies taken: 4.6%; p<0.0001).[24] Notably, in both studies adherence to this standard only occurred in 35–40% of cases.[23 24] Raising awareness among endoscopists through discussion at departmental meetings and displaying informative posters around the endoscopy unit increases adherence to biopsy recommendations and CD diagnosis,[25] suggesting that simple educational measures may impact CD diagnosis and should be promoted locally.

Duodenal changes typical of CD can be isolated to D1 (see Ultrashort coeliac disease). A recent meta-analysis (n=7 studies) reported that D1 biopsies demonstrated an 8% (95% CI 6% to 10%) increase in the diagnostic yield of CD.[26] Within D1, the lower villous: crypt height ratio, abundant Brunner's glands, presence of intraepithelial neutrophils and/or gastric metaplasia or peptic duodenitis may impact the histological interpretation of CD-related changes.[27] Therefore, while sampling D1 and D2 biopsies into the same pot may reduce the processing costs of pathology reporting (in the NHS, the cost is typically based on the number of sample pots), the potential compromise of histological analysis may lead to patient-related quality of life (QoL) and/or associated health-related costs. To mitigate this risk, we suggest that D1 and D2 samples be placed into separate pathology pots.

Biopsy handling

Good practice statement 3

Where possible, a single-bite biopsy technique should be employed to acquire duodenal tissue samples. *Agreement 100% (abstain 7/33).*

Histological assessment in CD depends on obtaining the right number of biopsies and ensuring that high-quality samples are provided to the pathology department. High-quality samples are considered as those with at least 3–5 consecutive, parallel,

expanded villi from the base to the tip.[28] Some experts advocate orienting biopsy samples directly in the endoscopy unit, as this may help ensure sufficient material is available for histological assessment.[29] However, it is common practice that biopsies are placed directly into pathology pots and thus are typically free-floating in formalin. The biopsy technique may influence the histological quality of samples, with one study in patients with suspected CD showing that taking one tissue sample per pass of the forceps (single-bite technique) improves the yield of well-orientated biopsy specimens and reduces the risk of specimen loss, compared with taking two bites per pass of the forceps (double-bite technique).[30] However, other data suggest comparable histological quality of samples obtained between techniques,[31] although concerns remain regarding artefactual damage associated with double-bite sampling. Therefore, we recommend that a single-bite biopsy technique should be used in suspected CD.

Histology grading schemes and reporting

Expert opinion 1

We advise the use of a histological grading system to help with consistency and standardisation of histology reporting. *Agreement 96% (abstain 6/33).*

The Marsh criteria identify evolving histopathological phases in CD (Marsh stage 0–3; a Marsh stage 4 was originally reported, but is infrequently used in modern reporting)[11]. The Marsh 3 stage (presence of villous atrophy) can be divided into three subcategories (3a–c),[32] but the relevance of these grades in routine clinical practice is uncertain. In addition to the Marsh system, the Corazza and Villanacci scheme also grades the histological changes within the small intestine in CD and is widely used in clinical practice.[33] Several studies have evaluated the agreement between these histological grading systems for CD diagnosis.[34–36] However, there is a general lack of standardisation in study design. Beyond this, other histological grading schemes exist for CD, including quantitative measurements of the mucosal injury in CD.[37 38] However, these techniques are not widely used in routine clinical practice presently.

In clinical practice, histology reports may be descriptive and use non-quantifiable terms (eg, blunting or marked atrophy). Moreover, in our experience, details regarding biopsy sampling (ie, number/site/adequacy) are not commonly included on pathology reports. This may impact clinical interpretation of pathology findings by gastroenterologists, although there is no data supporting these assumptions. To mitigate against this possible risk and help with the consistency and standardisation of reporting, we suggest the use of a histological grading system along with specific details that should be included on the pathology report (box 1).

Box 1 Suggested minimum information to be included on histology pathology reports in suspected coeliac disease (CD)

1. The number of biopsy fragments present
2. A comment on the overall adequacy of interpretation based on the samples received
3. A descriptive account of any pathological changes
4. A comment on whether the changes are associated with CD
5. A grading system for CD-associated changes if present

HLA typing

Good practice statement 4

Human leucocyte antigen (HLA) genotyping should be performed in specific circumstances to exclude CD. A negative DQ2 or DQ8 genotype indicates that patients are highly unlikely to have CD and an alternative diagnosis should be considered. *Agreement 97% (abstain 2/33).*

CD has a strong genetic component. Over 99% of patients with CD possess specific HLA-DQA1 and DQB1 genes that encode the CD-associated heterodimer proteins DQ2 and/or DQ8.[39 40] Approximately 90% of patients with CD express the HLA-DQ2.5 heterodimer, formed by the HLA-DQA1*05 and DQB1*02 alleles.[40 41] The remaining patients (5–10%) typically express HLA-DQ8, commonly encoded by the combination of the HLA-DQB1*03:02 and HLA-DQA1*03 alleles, or less frequently, HLA-DQ2.2, which is encoded by the HLA-DQA1*02 and DQB1*02 alleles.[40 41]

Testing negative for HLA-DQ2 or DQ8 makes CD very unlikely.[41] However, the diagnostic utility of HLA testing for CD diagnosis is limited due to the high prevalence of these heterodimers in the general population (around 30–40% in the Western population).[39 40] Therefore, it is widely recommended that HLA-typing should not be used as an initial diagnostic test for CD,[2 7] but it may be useful in certain clinical scenarios to exclude CD; this includes (1) patients who have started a GFD before formal CD testing, (2) in those with coeliac-like changes on duodenal biopsies but negative coeliac serology and (3) individuals suspected of having CD who do not respond to a GFD. In addition, HLA typing may be used to support a diagnosis of potential CD where appropriate (see Potential coeliac disease).

Recent studies have noted that in rare cases, the presence of HLA-DQA1*05 alone without the corresponding DQB1*02 allele (which often occurs in HLA-DQ7.5 (as HLA-DQA1*0505 and DQB1*0301)) may still predispose individuals to CD.[42] However, the prevalence of HLA-DQ7.5 is variable across different populations, and its representation in studies assessing HLA genotypes in CD may be impacted by the methods employed.[43 44] Therefore, CD should not be ruled out based on the presence of the HLA-DQ7.5 genotype alone, and expert advice should be considered, as its significance as a genetic risk factor for CD is less well understood than for HLA-DQ2 and DQ8.

Interpreting HLA results can be challenging, in part as they can be presented in different formats, including molecular nomenclature (eg, HLA-DQA1*05), serological nomenclature (eg, HLA-DQ2) or the nomenclature commonly used in CD (eg, HLA-DQ2.5).[41] This may compromise the interpretation of results.[45] Recent UK-NEQAS guidelines outline recommendations for standardising reports to prevent ambiguity and aid clinical interpretation.[41]

Making a diagnosis of coeliac disease

Serology-biopsy pathway

Recommendation 5

We recommend that a diagnosis of CD can be made in patients with positive coeliac serology and duodenal biopsies demonstrating increased intraepithelial lymphocytes (IELs) (>25/100 epithelial cells) plus crypt hyperplasia with/without villous atrophy: this equates to a Marsh 2 or 3 histology grading stage.

GRADE: Moderate certainty of evidence; strong recommendation; agreement 100% (abstain 4/33).

Table 1 Possible reasons for discordance between serology and duodenal histology

	Serology	Histology
False positive	Chronic liver disease, autoimmune diseases including type 1 diabetes and enteric infections; assay variability	Interobserver variability; artefactual changes during sampling or specimen preparation
False negative	Immunosuppressive medication; immunodeficiency disorders; gluten withdrawal	Interobserver variability; gluten withdrawal; insufficient number of samples; artefactual changes during sampling or specimen preparation

Justification: The presence of positive coeliac serology and characteristic small bowel inflammation is highly accurate for a diagnosis of CD. Histological manifestations of gluten-induced mucosal inflammation may appear as subtle changes in villous height to crypt ratio and/or overt villous atrophy. Duodenal lymphocytosis in isolation is not specific to CD.

Implementation: Diagnostic tests should be performed on a gluten-containing diet. Accurate interpretation of duodenal histology requires obtaining a sufficient number of biopsies from the correct location. Discordance between serology and histology may occur. In cases of diagnostic uncertainty, GI pathologist review and an alternative explanation for test results should be considered (table 1).

Good practice statement 5

A diagnosis of potential CD can be made in patients with persistently positive coeliac serology, duodenal biopsies demonstrating no changes or an isolated increase in IELs (>25/100 epithelial cells) (ie, Marsh 0–1 histology) and a positive HLA-DQ2 and/or HLA-DQ8 genotype. *Agreement 93% (abstain 3/33)*.

Good practice statement 6

A diagnosis of seronegative CD can be made in patients without elevated coeliac serology (including IgG-based tests), but with duodenal biopsies demonstrating villous atrophy (ie, Marsh 3 histology), a positive HLA-DQ2 or HLA-DQ8 genotype and improvement on a GFD. *Agreement 96% (abstain 6/33)*.

Good practice statement 7

A diagnosis of CD should not be made in the case of negative coeliac serology and duodenal biopsies demonstrating an isolated increase in IELs (>25/100 epithelial cells) (ie, duodenal lymphocytosis) and other causes should be explored. *Agreement 97% (abstain 3/33)*.

The presence of positive coeliac serology (ie, tTG/DGP>1× ULN and/or positive EMA) and duodenal villous atrophy (ie, Marsh 3 lesion) is well established to be conclusive for a diagnosis of CD (figure 1A).[2 8 46] The presence of raised IELs plus crypt hyperplasia (ie, Marsh 2 lesion) is also considered sufficient for a diagnosis of CD, based on the findings that reciprocal villous changes occur in the setting of crypt elongation which are indicative of gluten-induced inflammation.[47–50] However, true Marsh 2 lesions are rare in practice.

The presence of persistently positive coeliac serology (ie, ≥2 independent tests on a gluten-containing diet) with HLA-DQ2/HLA-DQ8 positivity and normal duodenal biopsies (ie, Marsh 0) or an isolated increase in IELs (>25/100 epithelial cells; ie, Marsh 1 histology), is consistent with a diagnosis of potential CD[51] (figure 1C; see Potential coeliac disease). Negative coeliac serology with HLA-DQ2/HLA-DQ8 positivity and duodenal villous atrophy (ie, Marsh 3 histology) is consistent with a diagnosis of seronegative CD[10] (figure 1B; see Seronegative coeliac disease). Importantly, factors relating to false negative/positive test results (table 1) may lead to discordance between serology and histology results and thus need careful consideration before a diagnosis of potential CD or seronegative CD is made. Furthermore, other causes of seronegative villous atrophy (table 2) should be excluded prior to a diagnosis of seronegative CD.[52] Isolated duodenal lymphocytosis in an otherwise normal small bowel biopsy sample is not specific for CD and may be related to other factors (table 2).

Interobserver variability in histological analysis of duodenal biopsies may impact diagnostic outcomes. In a recent study of 13 GI pathologists who independently classified 100 digitised whole-slide images of duodenal biopsies, the general concordance for histological diagnosis of CD was 0.73 (±0.08) with a corresponding κ=0.59 (±0.11) indicating only moderate agreement[53] and others have shown a 20% increase in CD diagnosis after biopsy review by a GI pathologist.[54] Including additional data (such as tTG titres and haemoglobin levels) improved the agreement of histology reporting,[53] highlighting the importance of evaluating histology in the appropriate clinical context with specialist pathologists. Quantitative measurements of mucosal injury in CD and automated analysis may provide reduced variability and increased reliability for histological diagnosis.[55] However, these techniques are not widely available nor used in routine clinical practice presently.

No-biopsy pathway

Recommendation 6

We suggest that in symptomatic adults being assessed in secondary-care settings, a diagnosis of CD can be made without duodenal biopsies when IgA-tTG titre ≥10× ULN. This 'no-biopsy' pathway is optional and should be adopted only after shared decision-making with the patient.

GRADE: Moderate certainty of evidence; conditional recommendation; agreement 94% (abstain 1/33).

Justification: Recent studies, including a meta-analysis, demonstrate that IgA-tTG ≥10× ULN has an excellent specificity and positive predictive value (PPV) for CD in moderate-to-high pretest probability settings. Although several studies had a high risk of bias, the findings were consistent across diverse populations. While some patients may prefer a serology-based diagnosis, others may still value histological confirmation before committing to a lifelong GFD, hence the need for individualised discussion.

Implementation: Laboratories must apply the 10 × ULN threshold to their specific assays and participate in quality assurance. This pathway should be confined to settings where the clinical suspicion of CD is high (i.e. symptomatic patients in secondary care); its accuracy may diminish in low-prevalence or primary-care contexts. Repeating serology (ie, IgA-tTG in a second blood sample) may be considered, but current evidence is insufficient to suggest this approach. Endoscopy remains an important consideration in patients with red-flag symptoms or

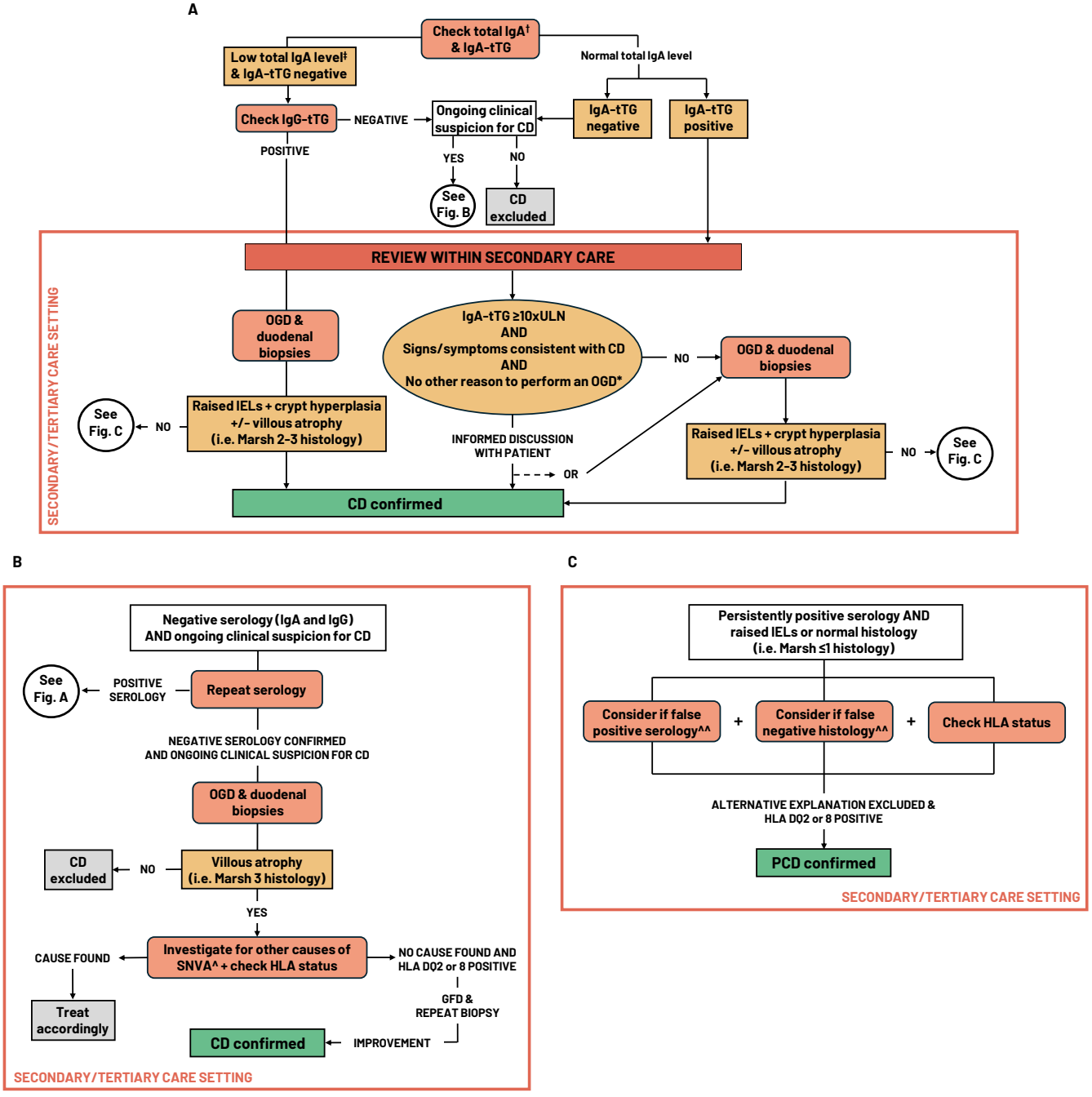


Figure 1 Diagnostic pathways for coeliac disease (A), seronegative coeliac disease (B) and potential coeliac disease (C). †Some Immunology laboratories may be able to detect low total serum IgA levels based on low background signal on the IgA-tTG assay, which removes the need for total serum IgA testing. ‡IgA-tTG responses may be detectable in individuals with marginally low total serum IgA levels (i.e. total serum IgA level >0.2g/L) not meeting the criteria for selective IgA deficiency; Immunology laboratories should be consulted to clarify local policies in this instance. *Such as red-flag signs/symptoms or recent diagnosis of another autoimmune condition. ^^Reasons for discordance between serology and histology can be found in Table 1. ^Causes of SNVA are listed in Table 2. Factors to consider before making a diagnosis of CD via the no-biopsy pathway are outlined in Table 3. CD, coeliac disease; GFD, gluten-free diet; HLA, human leucocyte antigen; IELs, intra-epithelial lymphocytes; OGD, oesophago-gastro-duodenoscopy; PCD, potential coeliac disease; SNVA, sero-negative villous atrophy; tTG, tissue transglutaminase; ULN, upper limit of normal.

when alternative diagnoses are suspected. Other autoimmune conditions, particularly type 1 diabetes (T1D), can lead to transient increases in tTG antibody levels around the time of diagnosis. Clinicians should therefore use caution and perform duodenal biopsies before diagnosing CD in this setting. Comprehensive follow-up as outlined in this guideline is critical, irrespective of the diagnostic pathway chosen by patients.

Due to the disruption of endoscopic services amidst the COVID-19 pandemic, the BSG adopted an interim no-biopsy guideline in adult CD that removed the requirement for confirmatory duodenal biopsies in select cases.[56] Several studies have confirmed that an IgA-tTG titre ≥10 × ULN is highly specific and predictive for adult CD,[57 58] including a recent international multicentre study[59] and meta-analysis.[9] Furthermore, data indicate a very low incidence of significant concurrent pathology that would have been missed if upper GI endoscopy was avoided in serology-positive patients.[60] However, the accuracy of this approach may be less reliable in low CD suspicion/prevalence settings. In line with this, a recent meta-analysis (n=18 studies) estimated that the PPV of an IgA-tTG titre ≥10 xULN for histology compatible with CD was <95% when the prevalence of CD was <10%,[9] which aligns with common scenarios where coeliac serology is checked (eg, within a primary care setting).

Only around 20–30% of adults with raised tTGs will reach this 10 × ULN threshold,[9 56 57] meaning this approach only applies to a minority of patients. However, for these individuals, the no-biopsy approach provides an alternative diagnostic pathway to consider, which may be preferable for some[61] and improve the process for others.[62] It is also noteworthy that there is an established concern about how underdiagnosed the condition is based on current diagnostic approaches, in-part owing to factors such as delays to diagnostic endoscopy,[24 63 64] incorrect biopsy sampling[24 25] and variability in the analysis of duodenal histology.[53 54] Moreover, evidence predating adult serology-only pathways suggests that a proportion of patients with positive serology are lost to follow-up in primary care,[65] which may impact patient outcomes. In light of this, the GDG discussed the practical and pragmatic implementation of the no-biopsy approach into routine clinical practice, to support the pathway to CD diagnosis while mitigating the risk of false-positive results using this strategy. Several factors were considered in this manner:

1. All the data on the accuracy of tTG titres ≥10 × ULN comes from secondary care; this introduces a natural selection bias within the examined cohorts that augments the pretest probability of disease/test accuracy. Therefore, the diagnosis must be made in secondary care. Furthermore, confirmation of the diagnosis within secondary care may help facilitate patient guidance and support, which risks being diminished if the diagnosis is decentralised to primary care without appropriate pathways in place.[62]
2. The majority of data derives from cohorts with clinical suspicion for disease. While it is accepted that the manifestations of CD are widespread and difficult to define, certain clinical features are considered as suggestive of CD (box 2). Of particular importance, the data indicate that this approach is not accurate nor applicable in asymptomatic/screening settings.[66]
3. While repeat testing may be considered, there is no evidence in adults that a same-sample or second-sample EMA or tTG test adds to the diagnostic accuracy of this approach, and there are no data regarding the appropriate timing of repeat sampling. Furthermore, IgA-tTG titres may change in-between tests if, for example, patients reduce their gluten intake,[67 68] which could lead to diagnostic uncertainty.
4. Data specific to patients with CD indicate a very low incidence of significant concurrent pathology that would have been missed if endoscopy was avoided in serology-positive patients.[57 59 60 69 70] However, it remains crucial to carefully evaluate patients individually for red-flag symptoms or other risk factors that warrant endoscopy irrespective of coeliac serology levels, particularly in older individuals, in line with other guidelines.[71 72]
5. Several different IgA-tTG assays are in current clinical use[73] and different kits may have different diagnostic performance for CD.[74 75] Therefore, we advocate that centres using this strategy either participate in external tTG assay quality assurance (ie, UK-NEQAS) or local audit is undertaken to confirm the accuracy and applicability of this pathway where this is not possible. The latter may enable adaptation of the no-biopsy pathway around local resources, but we caution against the use of a lower tTG titre threshold for diagnosis (ie, <10 × ULN), as this may increase the false-positive rate of this approach.
6. Individuals with a recent diagnosis of another autoimmune disease may demonstrate falsely elevated tTG titres, including children with T1D.[76] Whether tTG titres are falsely elevated ≥10 × ULN in adults with T1D or a recent alternative autoimmune diagnosis is unclear, but caution should be taken when considering a no-biopsy diagnosis in this patient group and duodenal biopsies should be performed to confirm the diagnosis in this setting.

It is noteworthy that consideration of these parameters within the no-biopsy framework does not entirely reduce the risk of a false positive CD diagnosis using this strategy, and a small proportion of individuals may be misclassified as CD rather than potential CD (positive coeliac serology and normal or minimal changes on duodenal histology (see Potential CD)) using this pathway. These factors need to be discussed with patients and balanced against the pros and cons of a serology-biopsy pathway for diagnosis (table 3).

Table 2 Causes of increased intraepithelial lymphocytes (IELs) ± villous atrophy on duodenal biopsies. Adapted from [251]

	Increased IELs without villous atrophy	Increased IELs and villous atrophy
Infections	*Helicobacter pylori*, viral gastroenteritis, giardiasis, cryptosporidium	Giardia, Whipple disease, tuberculosis, AIDS enteropathy
Drugs	NSAIDs, proton-pump inhibitors	NSAIDs, mycophenolate mofetil, colchicine, angiotensin II receptor blockers, methotrexate, immune checkpoint inhibitors, chemoradiation
Other	Crohn's disease, microscopic colitis, common-variable immunodeficiency, graft-versus-host disease, autoimmune enteropathy, small bowel bacterial overgrowth, peptic duodenitis, food allergies, autoimmune disease (eg, connective tissue diseases, multiple sclerosis, thyroiditis)	Crohn's disease, microscopic colitis, common-variable immunodeficiency, graft-versus-host disease, autoimmune enteropathy, tropical sprue, small bowel bacterial overgrowth, collagenous sprue, eosinophilic enteritis, amyloidosis

NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3 Factors to consider regarding a serology-biopsy and no-biopsy pathway for adult CD

	Serology-biopsy diagnosis	Serology-only diagnosis
Arguments for	► Facilitates histological monitoring of enteropathy ► Histological confirmation may be required for a GFD to be prescribed ► Enables detection of potential and seronegative CD ► May provide reassurance for some ► Future pharmacological therapies may mandate that histological evidence is required to qualify for treatment	► Widely available and inexpensive ► May reduce time to diagnosis ► Avoids the risks associated with endoscopy ► Reduces healthcare costs and utilisation ► Low environmental impact
Arguments against	► Long waiting times leading to delays in diagnosis ► Requires ongoing gluten exposure ► Gastroscopy is often poorly tolerated ► Adherence to biopsy guidelines is low ► Histological interpretation is variable ► High carbon footprint	► TTG antibody assays are not standardised which may impact accuracy ► Inappropriate initiation of a GFD without proper assessment ► Fails to identify potential or seronegative CD

Adapted from Shiha *et al*.[252]
CD, coeliac disease; GFD, gluten-free diet; TTG, tissue transglutaminase.

Who to test for coeliac disease

Case finding

Good practice statement 8

We advise testing patients with clinical suspicion for CD (*case finding*). *Agreement 100% (abstain 0/33*).

CD may present with a diverse spectrum of GI and/or extraintestinal signs or symptoms; aside from dermatitis herpetiformis, there is no one feature that is strongly predictive of the condition.[77] Previous National Institute for Health and Care Excellence (NICE) Guidelines have outlined instances in which the presence of certain manifestations should trigger serological testing for CD (Boxes 2 and 3).[8] Case finding in CD using serology may miss those who have not mounted detectable systemic antibody responses. Therefore, where clinical suspicion remains high despite negative coeliac serology, an upper GI endoscopy with duodenal biopsies should be performed.

Iron deficiency anaemia

Good practice statement 9

Duodenal biopsies should be performed for patients with iron deficiency anaemia (IDA) undergoing upper GI endoscopy, (1) in those with positive coeliac serology that does not meet the no-biopsy criteria; (2) if serology has not been performed prior to upper GI endoscopy; (3) recurrent or persistent anaemia even if coeliac serology is negative. *Agreement 100% (abstain 3/33*).

Iron deficiency anaemia (IDA) is a common manifestation of CD and CD is present in 3–5% of patients with IDA.[78] While coeliac serology should be performed in all patients with IDA, there is no consensus on the duodenal biopsy strategy in these individuals. This is important as IDA is a major referral criterion for straight-to-test endoscopy, IgA-tTG is highly sensitive for the condition, and seronegative CD only accounts for a minority of CD (around 2–3% of all cases).[27] Previous CD BSG Guidelines advocated duodenal biopsies for all patients undergoing upper GI endoscopy due to anaemia.[2] However, no comparative studies have evaluated the benefit or cost-effectiveness of this approach. Recent BSG IDA Guidelines suggest serological screening or duodenal biopsy during gastroscopy in IDA.[79] Accordingly, we recommend that duodenal biopsies for IDA patients undergoing upper GI endoscopy are limited to certain scenarios as outlined in the above statement.

Screening

Good practice statement 10

We advise screening for CD in high-risk groups (*screening*). *Agreement 100% (abstain 0/33*).

Symptoms in CD vary, with some patients reporting no symptoms (asymptomatic CD). Despite an increasing awareness of CD, both among the public and in healthcare, the disease may be missed and high-risk groups should therefore be screened for CD. However, at present CD does not fulfil the WHO criteria for general population screening.[80] Instead, coeliac screening should be performed in diseases and conditions where the prevalence of undiagnosed CD is substantially higher than in the general population.[81]

Situations that require screening for CD can be divided into four groups: (1) conditions mimicking CD (eg, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and microscopic colitis (MC)); (2) certain autoimmune conditions; (3) first-degree relatives; and (4) other conditions where evidence suggests

Box 2 Test for coeliac disease in people with any of the following. (relevant to the no-biopsy pathway). Adapted from.[8]

⇒ Persistent unexplained abdominal or gastrointestinal symptoms
⇒ Prolonged fatigue
⇒ Unexpected weight loss
⇒ Severe or persistent mouth ulcers
⇒ Unexplained iron, vitamin B12 or folate deficiency

Box 3 Consider testing for coeliac disease in people with any of the following. Adapted from [8].

⇒ Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
⇒ Dental enamel defects
⇒ Persistently raised liver enzymes with unknown cause
⇒ Unexplained subfertility or recurrent miscarriage
⇒ Metabolic bone disorder (reduced bone mineral density or osteomalacia)

a high prevalence of CD. Box 4 contains an overview organised per organ system of conditions that should be screened for CD.

A single IgA-tTG should be measured in these conditions to screen for CD. This should be repeated if the patient develops clinical suspicion for CD. The exception is patients with sIgAD in whom IgG-based coeliac serology should be tested. Screening should ideally be performed before a patient with another disease starts immunosuppressive therapy, as this could potentially impact on serology and histology. Positive screening serology should be confirmed by histology before a CD diagnosis is made, as screening is based on associations with CD, not strictly clinical suspicion, which may impact on the diagnostic accuracy of the tTG titre for diagnosis.[9]

How to approach a gluten challenge

Recommendation 7

For the gluten challenge, we recommend a dose of 3–6 g of gluten daily for at least 6 weeks.

GRADE: moderate certainty of evidence; strong recommendation; agreement 100% (abstain 1/33).

Justification: A gluten challenge for a duration of 6 weeks consuming at least 3 g, but preferably 6 g, of gluten daily is likely to lead to histoconversion in most patients with adult CD, while minimising the symptom burden associated with higher daily gluten doses.

Implementation: If available, HLA genotyping should be considered as an initial test before undertaking a gluten challenge, as this may avoid the need for a gluten challenge and further diagnostic testing. Gluten sources and 3 g gluten food equivalents are outlined in table 4. Higher doses of gluten will improve diagnostic accuracy. However, higher doses (ie, >6 g/day) are associated with increased symptom burden. If the gluten challenge is poorly tolerated despite attempting measures to improve it, we recommend patients try halving the daily gluten dose and proceeding for an additional 6 weeks. Wheat is best used as a source of gluten for a gluten challenge. Upper GI endoscopy with duodenal histology is the preferred diagnostic readout over coeliac serology, because seroconversion after 6 weeks of gluten ingestion can be low.

Box 4 Conditions where coeliac screening is recommended.

- ⇒ **Gastrointestinal diseases**: Irritable bowel syndrome, inflammatory bowel disease, microscopic colitis, autoimmune atrophic gastritis
- ⇒ **Endocrinological disorders:** Type 1 diabetes mellitus, autoimmune thyroid disease (Hashimoto's and Graves' disease), Addison's disease.
- ⇒ **Liver/spleen/pancreatic disorders**: Autoimmune hepatitis, hyposplenism with severe bacterial infections, idiopathic pancreatitis
- ⇒ **Skin disorders and connective tissue disorders**: Dermatitis herpetiformis (biopsy needed to confirm coeliac disease), Sjögren syndrome
- ⇒ **Gynaecological disorders**: Delayed menarche, premature menopause
- ⇒ **Genetic conditions**: Down syndrome, Turner syndrome, Williams (Beuren) syndrome
- ⇒ **Other disorders**: Selective IgA deficiency, chronic fatigue syndrome, IgA nephropathy
- ⇒ **First-degree relatives**

Table 4 Food portions that contain approximately 3 g of gluten that can be used for a gluten challenge

Gluten-containing food	3 g gluten exchange
Sourdough spelt bread#	60 g (1.5–2 slices bread/medium bread roll)
Wheat-based breakfast cereal (eg, Shredded wheat/Weetabix)	25 g wheat-based cereal (two Weetabix or two fist-sized portions of cereal)
Wheat-based bread	60 g (1.5–2 slices bread/medium bread roll)
Wheat-based cooked pasta	90 g cooked pasta (a fist-sized portion)
Wheat-based biscuits	50 g (3–5 biscuits)
Wheat gluten flour or vital wheat gluten (eg, Bob's Red Mill, Buy Whole Foods Online, NKD, or Lotus brand gluten found in health food shop/online)*	7.5 g (1.5–2 teaspoons)

#Sourdough spelt bread is lower in fermentable oligosaccharides, disaccharides, monosaccharides and polyol content so may be better tolerated compared to wheat-based foods.
Based on Schalk *et al*.[253]
*Gluten flour/vital wheat gluten is raw and like any raw flour it is recommended to be cooked or baked prior to consumption.

A gluten challenge may be indicated, (1) in the diagnostic work-up in an individual who has clinical indication to assess for CD but has been following a GFD for 1 month or more, or (2) if there is uncertainty regarding the diagnosis of CD, this will include equivocal results, especially if they occurred while the patient was on a low/no gluten diet. If there is a suspicion of wheat allergy, this should be formally investigated before attempting a gluten challenge.

The goal of a gluten challenge is to improve the accuracy of CD diagnosis. However, the optimal amount and length of gluten intake to consistently trigger diagnostic changes in coeliac serology or duodenal histology is likely to vary considerably between patients. Reliable diagnostic changes occur with longer duration of gluten exposure and/or higher gluten dose.[12 82] Counselling patients on how to undertake a gluten challenge, how to improve its tolerability and what to expect may help improve adherence and diagnostic outcomes; suggestions on how to support patients with a gluten challenge are outlined in box 5. Support from a specialist dietitian and/or medical team with expertise in CD can help personalise this approach.

A gluten challenge with a duration of 6 weeks consuming 3–6 g daily of gluten protein is likely to lead to histoconversion in most patients with adult CD.[83 84] For shorter periods of time (2 weeks) higher doses of gluten (10 g) are required to consistently lead to histoconversion.[12] However, higher dose challenges (ie, >6 g gluten/day) may be less well tolerated by patients than lower doses for longer periods.[85] Gluten sources and 3 g gluten food equivalents are outlined in table 4.

Potential coeliac disease

Recommendation 8

We suggest a trial of a GFD for symptomatic patients with potential CD under the guidance of a specialist dietitian.

GRADE: Low certainty of evidence; conditional recommendation; agreement 93% (abstain 3/33).

Justification: Studies have shown that patients with potential CD demonstrate improvement in GI and/or malabsorptive symptoms on a GFD.

Box 5 Tips to help improve tolerability of the gluten challenge

The type of gluten and how it is consumed may affect tolerability. To improve the tolerability of the gluten challenge, it may be helpful to:

1. Reassure patients that short-term gluten challenge is safe. Early acute symptoms such as nausea, vomiting, abdominal pain, diarrhoea, headache and lethargy are common but typically reduce in severity within a few days of the challenge. Further, symptoms are not always caused by gluten and may be related to dietary fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) triggering irritable bowel symptoms or a nocebo effect. Avoiding hypervigilance to symptoms may help.
2. Encourage patients to select gluten-containing foods that are lower in FODMAP content where possible. FODMAPs can trigger irritable bowel syndrome symptoms that may be common in people following a gluten-free diet.
3. Commence a graded gluten challenge. For example, start with a half dose of gluten for the first two days before increasing to the full daily dose.

Implementation: Patients with potential CD and GI/malabsorptive symptoms should be referred to a specialist dietitian for consideration of a trial GFD. This approach should be reconsidered if there is no clinical improvement after around 3–6 months and an alternative cause for symptoms should be explored. We advise follow-up for individuals with potential CD established on a GFD in the same manner as for those with CD.

Expert opinion 2

Symptomatic or asymptomatic patients with potential CD who continue a gluten-containing diet should be counselled about the risk of progression to overt CD. *Agreement 100% (abstain 2/33)*.

Good practice statement 11

For patients with potential CD who continue a gluten-containing diet, we advise repeating serology and biopsies if new symptoms develop, or after 1–2 years if stable, in discussion with the patient. *Agreement 100% (abstain 2/33)*.

Potential CD is used to describe persistently seropositive individuals, with coeliac-compatible HLA genetics, and normal or minimal changes on duodenal biopsies (ie, Marsh 0–1) (figure 1C). Potential CD accounts for around 10–18% of CD cases and is generally considered as an early manifestation within the broad spectrum of CD.[86] However, before a diagnosis of potential CD is reached, it is important to explore possible reasons for discordance between serology and histology (table 1) and consider repeating the tests on an appropriate gluten-containing diet to minimise doubt.

Patients with potential CD typically present with symptoms similar to conventional CD but have fewer nutritional deficiencies[87] and a lower risk of lymphoproliferative malignancy.[88] A recent meta-analysis on the clinical outcome of patients with potential CD found that approximately a third of adults who continue to consume gluten developed villous atrophy during follow-up (39%; 95% CI 13% to 65%), while another third achieved normalisation of serology.[51] However, not all patients underwent D1 sampling across the included studies.

Ten studies including adult and paediatric cohorts have reported the clinical outcomes of patients with potential CD who followed a GFD.[51] Across these studies, 50% (95% CI 34% to 65%) of patients with potential CD started a GFD.[51] The pooled proportion of symptom improvement after adhering to a GFD was 88% (95% CI 79% to 97%); heterogeneity was very high between studies (I^2=93.25%).[51] Symptoms were typically GI and/or malabsorptive. However, symptoms are not specific in CD. A retrospective study of adult potential CD demonstrated that 29% (12/41) of patients who were symptomatic at diagnosis and started a GFD had ongoing symptoms, of which 50% (6/12) had an alternative cause (ie, not CD) for their symptoms on further investigation.[89] Therefore, a trial GFD may be considered in symptomatic potential CD under the guidance of a specialist dietitian, but should be reconsidered if there is no improvement and an alternative cause for symptoms should be explored. The role of a GFD in asymptomatic patients is unclear.

There is no clear evidence or consensus on the follow-up of patients with potential CD. It seems reasonable to follow-up those with potential CD established on a GFD in the same manner as CD (see Follow-up). We also suggest repeating serology and biopsies in patients with potential CD who continue a gluten-containing diet if new symptoms develop, or after a time-period of around 1–2 years if they remain stable in discussion with the patient, to evaluate for progression to overt CD, or normalisation of results; although data are lacking in this area.

Seronegative coeliac disease

Seronegative CD is diagnosed when villous atrophy is present with coeliac-compatible HLA genetics, without elevated IgA-based and IgG-based coeliac antibodies and improvement in enteropathy is demonstrated on a GFD.[10] Seronegative CD accounts for around 2–3% of CD and around a third of patients with seronegative villous atrophy.[27] Therefore, other causes of seronegative villous atrophy should be excluded before a diagnosis of seronegative CD is made (table 2),[52] as well as exploring reasons for possible discordance between serology and histology (table 1). SIgAD should specifically be considered and IgG-based coeliac tests checked if present; sIgAD with positive IgG-coeliac serology is not considered as seronegative CD, but rather within the scope of seropositive CD.

Patients with seronegative CD should be commenced on a GFD as with conventional CD. A follow-up biopsy is suggested to check for improving enteropathy with a GFD as this forms an important step for diagnosis.[27] Repeat biopsies may be considered after 1–2 years of a GFD to allow time for mucosal healing to occur in-line with CD. In instances of diagnostic uncertainty, a gluten challenge and re-biopsy may help to differentiate from other non-coeliac enteropathies.

Seronegative CD appears to affect older individuals and has a more aggressive disease phenotype than seropositive CD. A recent multicentre study, with the largest series of patients with seronegative CD, reported a statistically significant worse outcome with frequent findings of complications in seronegative CD compared with conventional CD (20.2% vs 1.8%; p<0.001).[90] Therefore, consideration should be given to referring patients with seronegative CD and ongoing enteropathy despite adequate adherence to a GFD to a national referral centre/specialist centre for support with management (see Non-responsive coeliac disease).

Ultra-short coeliac disease

Ultra-short CD (USCD) refers to coeliac-like enteropathy with villous atrophy present only within D1 alongside positive coeliac serology. Adult studies suggest that USCD accounts for around 8% of adult CD.[26] However, the lower villous:crypt ratio, intraepithelial neutrophils, presence of gastric metaplasia or peptic duodenitis may complicate the interpretation of CD-related changes in D1.[27 91] Therefore, if coeliac serology is negative in a patient with CD-like histological changes isolated to D1, USCD is excluded and an alternative diagnosis should be considered.[27] Bone densitometry results and clinical response to a GFD are similar in both USCD and conventional CD,[92 93] supporting the management of USCD in the same way as conventional CD.

THE GLUTEN-FREE DIET: THE ONLY CLINICALLY PRESCRIBED TREATMENT FOR COELIAC DISEASE

The term gluten not only refers to wheat-based proteins (gliadins) but also those found in barley (hordeins), rye (secalins) and cereal hybrids such as triticale.[2] In the UK and across Europe, a gluten-free claim is voluntary but when foods are labelled as 'gluten-free' they must contain 20 parts per million (ppm) of gluten or less.[94] Assimilated Regulation (EU) No. 828/2014 defines and regulates the threshold for labelling food as gluten free.[95] This threshold is based on estimates that consuming a diet with foods with levels exceeding 20 ppm of gluten are sufficient to initiate the immunological response in individuals with CD. Products that include gluten-free wheat starch, in which gluten has been removed to below 20 ppm, are permitted and may form part of the GFD. By contrast, in countries such as Australia and New Zealand, foods labelled as 'gluten free' must not contain any detectable gluten and must not be made from any ingredients derived from gluten-containing cereals. As a result, the definition of the GFD and its implementation can vary internationally, depending on regulatory frameworks and labelling laws.

Assimilated Regulation (EU) No.1169/2011 of the Food Information to Consumers Regulation sets the mandatory legal requirements to communicate the presence of allergens in food including cereals such as wheat, rye, barley and oats.[96] This provides patients with information on whether a food contains any gluten-containing cereals so they can be avoided. Given that even small amounts of gluten can activate the immune response in CD, strict avoidance is required at both the ingredient and cross-contact level.[97] Cross-contact refers to the unintended presence of gluten-containing cereals with foods that do not naturally contain gluten during preparation, cooking or manufacturing. The risk of cross-contact is communicated via voluntary precautionary allergen labelling, such as 'may contain wheat and/or other gluten-containing cereals or made in a factory that handles wheat and/or other gluten-containing cereals'.

Health impact of the gluten-free diet

Recommendation 9

We recommend that patients diagnosed with CD maintain a lifelong GFD to help improve symptoms, QoL and reduce the risk of complications associated with the condition.

GRADE: low certainty of evidence; strong recommendation; agreement 94% (abstain 0/33).

Justification: The GFD is the only treatment currently available for CD. Observational studies have demonstrated that a GFD improves symptoms and QoL. A GFD also improves small bowel inflammation which may indirectly impact complications associated with CD such as low bone mineral density (BMD) and the risk of lymphoproliferative malignancy, although the absolute risk of the latter in CD is low.

Implementation: We recommend that all patients with newly diagnosed CD are referred to a specialist dietitian for guidance on how to follow a nutritionally balanced GFD, understanding the potential negative effects of the diet on QoL, and general lifestyle measures to maintain health and well-being.

Good practice statement 12

At the point of diagnosis, we advise that patients are signposted to an established disease advocacy group (eg, Coeliac UK) for reliable information about CD and the GFD. *Agreement 97% (abstain 2/33).*

A life-long GFD is the only current recommended treatment in CD. There are no randomised placebo-controlled trials evaluating the long-term health impact of the GFD in CD and observational data is unable to control for absolute GFD-adherence, nor the psychosocial challenges of instituting a GFD, among other factors, which may impact the interpretation of studies within the literature. Specialist dietitians with expertise in CD and the GFD are optimally placed to support patients through the transition to, and maintenance of, a GFD (box 6). For practical guidance and patient resources, the Coeliac UK website provides regularly updated information on gluten-free living: www.coeliac.org.uk/.

Symptoms and small bowel inflammation

A GFD leads to an improvement in GI and extraintestinal symptoms reported prior to diagnosis within weeks in most.[98] Up to one-third will continue to have persisting symptoms despite reporting adherence to a GFD, which is often due to ongoing gluten exposure.[99] However, symptoms in CD may be multifactorial, including being related to non-coeliac pathologies such as IBS, which commonly coexist.[100]

Small bowel enteropathy improves with adherence to a GFD, although the timespan of mucosal healing is variable among individuals and typically takes 1-2 years or longer.[101 102] Poor GFD adherence is a significant predictor of persisting villous atrophy on follow-up biopsy.[103] In turn, the GFD may reduce the risk of complications such as low BMD and lymphoproliferative malignancy which are associated with persisting villous atrophy by promoting mucosal healing[88 104 105]; although notably, the absolute risk of lymphoproliferative malignancy in CD is low.[88]

Nutritional considerations and metabolic outcomes

People with CD commonly present with haematinic and/or vitamin deficiencies at diagnosis, which may resolve with mucosal healing and appropriate supplementation.[106] Many gluten-free products differ nutritionally from gluten-containing equivalents and are not subject to the UK's mandatory fortification of white wheat flour with calcium, iron, thiamine, niacin and folic acid. If fortified gluten-free substitute products are not selected, and a variety of foods that by nature do not contain gluten are not consumed in sufficient quantity, micronutrient deficiencies may persist or develop after diagnosis.[107] There is limited evidence to support specific recommendations on routine haematinic

Box 6 The role of the specialist dietitian in coeliac disease (CD)

In this context, a specialist dietitian refers to a registered dietitian with enhanced knowledge and clinical experience in the management of CD. Such professionals play a central role in supporting adherence to a nutritionally adequate gluten-free diet (GFD) to reduce the risk of long-term complications, with the aim of improving quality of life and well-being. At diagnosis, referral to a specialist dietitian is essential to assess nutritional status, identify psychological and behavioural factors influencing dietary habits and guide the transition to a strict, lifelong GFD. Dietary advice is personalised by considering social, cultural, financial, environmental and biological factors that influence food choice.[254] This includes educating patients on selecting appropriate gluten-free products, achieving adequate intake of key nutrients such as fibre, calcium, folate and iron and reducing the risk of nutritional deficiencies. Patients may also be supported in identifying fortified products or those with favourable nutrient profiles and in avoiding excessive dietary restriction. These consultations also provide an opportunity to reinforce long-term dietary confidence on the GFD and offer broader advice on healthy lifestyle practices.

Ongoing dietetic support is important to adapt dietary guidance over time. Provision of specialist dietetic care for CD is widely under-resourced, with limited access to dedicated clinics and insufficient time allocated for dietary assessment, education and follow-up.[255] In many healthcare systems, referrals to specialist dietitians remain inconsistent and existing roles are not fully embedded within CD services, despite evidence that patients consistently prefer dietitian-led follow-up with medical support available as required.[256] These gaps in service delivery contribute to inconsistencies in the quality and continuity of dietary care. Strategic investment, alongside clearer guidance on service configuration and whole-time equivalent provision for specialist dietitians, is needed to improve access and ensure equitable, high-quality dietetic support for people with CD.[257]

Some centres in the UK have developed dietitian-led initiatives to support the care of patients with CD in a more extended role which can include requesting blood tests and/or DXA bone scans, through an agreed formalised pathway with support from gastroenterology and primary care services. This has the benefit of both ensuring patients get adequate ongoing dietetic support as well as monitoring for associated complications. The limited observational data that exists for these types of services has shown a positive impact on patient satisfaction, GFD adherence and hospital cost-savings.[258] However, multisite service evaluation is required to understand the wider impact of these services.

or micronutrient supplementation. Current best practice includes supporting individuals to follow a nutritionally adequate diet based on healthy eating principles, monitoring for deficiencies and supplementing as clinically indicated, in line with national and international guidelines (see Blood tests and nutrient supplementation).

Metabolic alterations have also been reported following the commencement of a GFD. In some individuals, weight normalisation has been observed - characterised by weight gain in those underweight at diagnosis and modest weight loss in overweight individuals[108]; this may be the result of dampened inflammation and/or changes in energy balance through diet or physical activity. Some evidence suggests increased rates of metabolic syndrome and metabolic dysfunction-associated steatotic liver disease in people with established CD on a long term GFD.[109–111] By contrast, others have reported no increased risk of obesity or type 2 diabetes in individuals with CD following a GFD,[112 113] although further research is needed to clarify the longer-term metabolic outcomes in this population.

Alongside promoting a nutritionally adequate diet, specialist dietitians are also well positoned to provide guidance on regular physical activity and maintaining a healthy weight in line with general population recommendations. Under these circumstances, there is no evidence to suggest that following a GFD results in adverse nutritional or metabolic outcomes beyond those observed in the general population.

Quality of life

Numerous studies have found a positive association between GFD adherence and QoL in adults with CD using generic and disease-specific QoL measures.[114] However, several factors may impact QoL in CD, including persistence of symptoms, clinical presentation, age at diagnosis, gender and psychosocial elements (such as perceived challenges of a GFD, psychological distress and coping strategies).[114 115] Patients may also be at increased risk for food insecurity, as the GFD is substantially more expensive and difficult to access.[116] Moreover, hypervigilance towards maintaining a strict GFD and disordered eating behaviours on a GFD may negatively impact psychological health and QoL in patients with CD[117 118] and patients should be counselled about these risks and supported accordingly.

Oats

Recommendation 10

We suggest that gluten-free oats ingestion should be discussed with patients with CD and advised as soon as the GFD is commenced in the setting of appropriate clinical follow-up.

GRADE: moderate certainty of evidence; conditional recommendation; agreement 100% (abstain 2/33).

Justification: Oat ingestion may help counter some of the limitations of the highly restrictive GFD. Clinical studies in patients with CD using gluten-free oats have generally showed they are safely consumed by most patients.

Implementation: The potential benefits of oats ingestion should be discussed with the patient.

Standard commercial brand oats are frequently contaminated with gluten and should be avoided by people with CD. Only oats that are confirmed to be gluten-free should be recommended and can be included as soon as the GFD is commenced. Informed decision-making about whether to include or exclude uncontaminated gluten-free oats from the diet needs to be supported by clear food labelling. If patients experience adverse symptoms while including gluten-free oats in their diet, medical follow-up is recommended.

Oats are a highly nutritious cereal that have been associated with a range of positive health outcomes in general population studies. Oats contain quality protein and are a good source of resistant starch and soluble (eg, beta-glucan) and insoluble fibre, as well as polyunsaturated fatty acids and phytochemicals (eg, avenanthramide) that may confer beneficial health properties.[119] Reported health benefits include improved cardiovascular disease risk markers including reduced total cholesterol

and low-density lipoprotein, improved body mass index, bodyweight and waist circumference, reduced postprandial blood glucose and insulin response and improved fasting glucose and HbA1c.[120–122] Oat ingestion may therefore offer several advantages including improving metabolic profiles, enhancing fibre intake and expanding the range of food choices of the highly restrictive GFD, although more studies are needed to assess these outcomes.

Multiple studies have confirmed that commercial oats are commonly and often extensively contaminated with gluten-containing cereals such as wheat, rye and barley.[123 124] This can occur during oat cultivation, harvesting, storage, transport and processing. The production of oats free from contamination ('uncontaminated oats') requires the strict application of rigorous protocols not applied during standard commercial production, and only with this in place can oats reliably contain 20 ppm or less of gluten.

Clinical studies in patients with CD using uncontaminated oats (gluten-free oats) have generally shown that they are safely consumed by most patients, that is, adverse symptoms and/or small intestinal damage are uncommon.[125] Long-term oats ingestion in CD has also been associated with improved QoL.[126] However, some studies have shown a minority of patients with CD (less than 10%) may experience adverse symptoms, immune activation or histologic inflammation or damage in response to oats or oat protein (avenin) similar to that seen after gluten-containing cereals such as wheat.[127–129]

Oat sensitivity may present as adverse symptoms or worsening of small intestinal inflammation,[128 129] and therefore, clinical follow-up is recommended. Symptom monitoring may be the most practical approach, as repeat biopsies are not feasible in many centres and serology may not be a sensitive enough marker to determine oat sensitivity. If patients consistently report symptoms or have persistent disease activity after consuming gluten-free oats, it is advisable to consider a period of complete oat removal from their diet. If both the clinician and patient feel confident the patient is sensitive to gluten-free oats, it would be advisable to avoid all forms of oats long-term.

Assessing gluten-free diet adherence

Recommendation 11

We suggest a combined approach for assessing GFD adherence, as no single test provides adequate information in isolation.

GRADE: moderate certainty of evidence; conditional recommendation; agreement 97% (abstain 1/33).

Justification: Observational studies have demonstrated that dietitian assessment, dietary questionnaires or symptom reporting alone do not accurately reflect ongoing gluten exposure. In addition, coeliac serology including tTG titres in isolation are not reliable as an accurate marker of strict GFD adherence.

Implementation: Assessment of GFD adherence should be centred on specialist dietitian review and symptom assessment. Dietary questionnaires may be useful where access to specialist dietitians is limited. It should also be considered that symptoms in CD may be multifactorial and reflect associated conditions such as disorders of gut–brain interaction (DGBI) rather than gluten ingestion.

Owing to the ubiquitous nature of gluten, maintaining a GFD is complex and typically requires a significant shift in dietary and lifestyle routines to accommodate its exclusion from all sources—including packaged foods, food prepared at home and meals consumed outside the household. Indeed, multiple studies have reported the rate of strict adherence to a GFD in adult CD lies between 40% and 90%.[130] Barriers to adherence to the GFD are multifactorial and can include cost, limited availability and/or knowledge of gluten-free foods and the impact on social participation and QoL, among others.[130 131]

Assessing adherence to the GFD can be challenging, owing to a lack of an objective marker of gluten exposure. Furthermore, the lack of an appropriate reference standard for adherence has been a major limitation to the quality of evidence within the literature. The more recent development of gluten immunogenic peptide (GIP) assays, which detect a major wheat gliadin peptide in urine or stool, may provide an objective measure of short-term gluten exposure.[132] However, these tests are not available in routine clinical practice within the UK or in many other countries outside of specialist referral centres and therefore, they are beyond the scope of this guideline; other expert guidelines have recently outlined their use and limitations in clinical practice.[133]

Evaluating dietary habits

Specialist dietitians play an essential role in monitoring symptoms and nutritional status CD (box 6). Dietetic assessment is also considered the closest to a gold standard for GFD adherence assessment. However, studies evaluating the effectiveness of dietitian assessments in monitoring GFD adherence in adults with CD are limited. Available research suggests that dietitian assessment may miss dietary transgressions when compared with GIP testing or duodenal histology as reference standards.[134 135] Methods used in this context - including self-reported tools such as 24-hour dietary recalls, multiday food diaries, and food frequency questionnaires - are limited by their subjective nature and reliance on patients' recall and behaviour. Notably, there is significant variability in how dietetic assessments are conducted and establishing standardised frameworks may enhance consistency and effectiveness of dietetic consultations.[136]

Structured questionnaires which measure patients' attitudes and strategies towards gluten avoidance have been developed to address the limitations of self-reported GFD adherence (ie, inadvertent gluten exposure). The Biagi Test and Coeliac Disease Adherence Test are two commonly used patient-reported questionnaires used in clinical practice.[137 138] The accuracy of these test scores reported in studies varies, depending on which reference standard is used, and there is generally adequate correlation with dietary assessment,[137] but low correlation with GIP measurements or presence of villous atrophy on duodenal biopsies.[136 139] However, these questionnaires are quick to administer and do not require prior experience in CD, so may be useful where access to dietitians is limited.

Evaluating for gluten-related symptoms

In double-blind, sham-controlled gluten challenge studies, symptoms such as nausea and vomiting are associated with acute gluten exposure[140] and can be managed with simple measures (box 7). By contrast, diarrhoea, fatigue and abdominal pain are poor predictors of acute gluten intake but commonly reported in observational and unmasked gluten-challenge studies.[141] These differences may reflect the distinct symptoms of chronic versus acute gluten exposure or the influence of anticipation of gluten intake.[141 142] DGBIs are common in established CD and may complicate symptom assessment.[143] Furthermore, about 20% of patients are asymptomatic at diagnosis,[144] suggesting that gluten exposure does not consistently drive noticeable symptoms for all

Box 7 Management approach for acute gluten exposure

⇒ Reassurance that symptoms will settle and are highly unlikely to cause long-term damage
⇒ Help identify possible sources of gluten exposure
⇒ Ensure adequate hydration
⇒ Analgesia where required
⇒ Ondansetron for vomiting if protracted

patients, and other evidence suggests that gluten-induced symptoms may change depending on the frequency of gluten exposure.[142] Therefore, while assessing symptoms in patients with established CD is important, symptom reporting alone does not reliably inform on GFD adherence nor ongoing mucosal inflammation.[145 146]

Coeliac serology

Coeliac antibody titres decrease within weeks to months after starting a GFD in most patients and persistently elevated coeliac antibody levels were found to be associated with poor adherence to the GFD in small cohort studies.[147 148] However, the temporal relationship between gluten ingestion and antibody titres is unclear. Gluten challenge studies suggest that daily gluten ingestion for >4 weeks is required to generate antibody responses in CD.[82 149] This suggests that serology lacks the sensitivity to identify intermittent gluten exposure in established CD and a negative tTG level should thus not be considered as a marker of strict dietary gluten exclusion. Taken together, coeliac serology considered in isolation is a poor marker of adherence to the GFD. However, the trend of tTG titres may provide some information on ongoing gluten exposure in established CD - for instance, persistently, or newly, positive tTG titres may indicate dietary transgressions in the appropriate clinical context, although robust data in this area is lacking. Moreover, while coeliac serology is highly predictive of villous atrophy at diagnosis, antibody levels provide no information on mucosal inflammation following diagnosis once a GFD has been started.[150]

Treatment targets

Expert opinion 3

Resolution of symptoms and/or mucosal healing should be the treatment goals in CD. However, treatment targets should be considered in the context of the general well-being of the individual and personalised as appropriate. *Agreement 97% (abstain 1/33*).

Resolution of symptoms or mucosal healing may be considered as appropriate treatment targets in CD. However, the evidence base supporting either endpoint is limited, notwithstanding the lack of appropriately controlled comparative studies.

High symptom burden is associated with lower QoL in CD.[114] Negative thoughts about illness, coping difficulties, pain catastrophising and psychological distress associated with GI symptoms impact QoL in patients.[115] QoL may improve with symptom improvement[151] which makes this an attractive treatment target. However, in CD, some individuals may not experience troublesome symptoms,[144] symptoms may be multifactorial including being related to non-coeliac causes such as DGBIs[100 143] and symptoms do not correlate with active inflammation,[145 146] meaning this should not be regarded as the only focus of treatment.

Large population studies have shown that persistent villous atrophy is associated with adverse health outcomes such as low BMD and lymphoproliferative malignancy.[104 105] Conflicting results have been found with regards to associations between persisting villous atrophy and fracture and mortality outcomes in other studies[103 152–155]; reviewed in[156]. Importantly, these population studies are subject to selection bias as they only included patients who underwent a follow-up biopsy, they do not control for length of follow-up, nor degree of adherence to the GFD. Despite these limitations, patients with positive serology and normal small bowel biopsies show no statistically significant risk of lymphoproliferative malignancy (HR 0.97; 95% CI 0.44 to 2.14)[88] which emphasises the importance of considering mucosal healing as a treatment target in CD.[46]

Mucosal healing across these studies refers to a resolution of duodenal villous atrophy. The long-term implications of intraepithelial lymphocytosis remain unclear.[157] The only way to determine mucosal healing is up-to-date duodenal biopsies (see Follow-up biopsy).[145 150 158] Notably, the only current way to achieve symptom improvement and mucosal healing in CD is a strict GFD, and the restrictive nature of this approach may itself be detrimental to the QoL and/or mental health of some individuals.[117 159] Fundamentally, therefore, achieving an acceptable balance between disease control and overall well-being should be prioritised, with treatment targets tailored to the individual where necessary. Moreover, treatment targets should be re-evaluated if drug therapy achieves licensing in CD.

FOLLOW-UP

Follow-up strategy

Good practice statement 13

All patients diagnosed with CD should undergo regular follow-up for up to 2 years after diagnosis. Following this:

1. Repeat duodenal biopsies should be considered in discussion with patients before decisions about longer-term follow-up are made.
2. Patients who have responded well to a GFD may be considered for patient-initiated follow-up (PIFU).
3. Longer-term systematic follow-up is advised for patients who: (a) are poorly adherent to the GFD (or are at risk of poor adherence); (b) have not responded adequately to a GFD; or (c) have developed complications associated with CD. *Agreement 90% (abstain 2/33*).

The recommended framework for follow-up has typically comprised regular consultations for all patients by dietitians and/or physicians over the long-term.[2] However, real-world data suggests that follow-up is highly inconsistent, with only a minority of patients undergoing the follow-up in-line with recommendations.[160–162] A major limitation in this setting is access to resources to provide follow-up for everyone. Evidence suggests that follow-up may help with GFD adherence,[163] which itself is an important determinant of health in CD. However, it is unclear what role follow-up provides in the longer term to patients who are adherent to the GFD and managing well with their condition. On the other hand, certain patient groups are at risk of poor GFD adherence[161–166] and morbidity in CD[102 156]; these individuals may benefit from a structured long-term follow-up programme aimed at improving and supporting health outcomes, although data is lacking in this area.

To this end, we advocate regular follow-up for up to 2 years after diagnosis for all patients, to monitor and support individuals

Table 5 Patients who should be considered for longer-term structured follow-up

Patient group	Examples
Patients with poor adherence to GFD	Self-reported GFD transgressions Dietary non-adherence identified through clinical review
Patients with a lack of response to the GFD	Ongoing symptoms Abnormal laboratory indices Persisting enteropathy
Patients who have developed complications or related problems	Low BMD Malnutrition Refractory CD Hypervigilance or disordered eating patterns Significant weight gain or weight loss
Patients at risk of poor GFD adherence	Teenagers/young adults[164 166]; particularly those undergoing lifestyle transitions (eg, moving home or going to university) Ethnic minorities[163 165] Patients with a history of mental health conditions or psychological distress[161] Those without symptoms after gluten ingestion[161] Lack of food knowledge or understanding of the GFD,[131 165] or significant concern over cost of the GFD[131 162] Individuals who have restricted access to gluten-free products[163 165]

BMD, bone mineral density; CD, coeliac disease; GFD, gluten-free diet.

transitioning onto a GFD. Follow-up should be provided by specialist dietitians with expertise in CD and/or physicians with experience in CD where possible.

Following this initial period, we suggest that patients who have adjusted to the GFD and who have demonstrated a good clinical response may be considered for PIFU, whereby patients request follow-up appointments based on individual need, rather than attending routinely scheduled clinics. To help facilitate this, patients should receive instructions on how to request an appointment if needed. By contrast, we recommend longer-term systematic follow-up for certain patient groups including those who are poorly adherent to the GFD (or are at risk of poor adherence), have not responded adequately to a GFD, or have developed complications associated with CD (table 5).

We suggest that the time interval between follow-up is dependent on patient acuity. Individuals undergoing longer-term regular follow-up may be considered for transition to PIFU once their disease is stable. Conversely, individuals should re-enter a structured follow-up programme if they experience ongoing issues in the community. A schematic providing a framework for initial and follow-up consultations is illustrated in figure 2. Decisions about which patients require follow-up can be adapted based-on local healthcare resources.

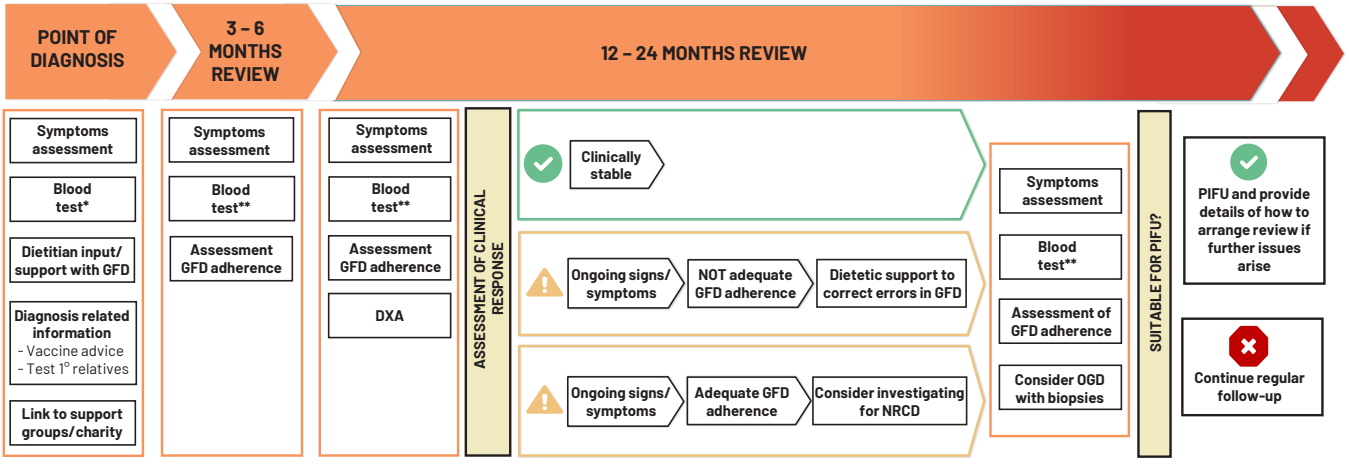
Recommendation 12

We recommend that duodenal histology is the only way to assess for mucosal inflammation in established CD on a GFD.

GRADE: Moderate certainty of evidence; strong recommendation; agreement 100% (abstain 3/33).

Justification: Observational studies have demonstrated that dietary assessment, symptom reporting and tTG titres do not correlate with mucosal inflammation nor healing in established CD on a GFD.

Implementation: Up-to-date duodenal biopsies should be performed when assessment of persisting mucosal inflammation or mucosal healing is required. The length of time to gain mucosal healing is highly variable and should not be considered before at least 1–2 years after starting a GFD. As with diagnosis, we advocate taking multiple biopsies from D1 and D2 when performing duodenal biopsies in established CD on a GFD. Differentiating slow healing, from persisting inflammation due to ongoing dietary gluten exposure, or immune refractoriness to the GFD may be challenging and requires consideration of the clinical context. Specialist GI pathologist review may be helpful in this setting.



***At diagnosis:** Full blood count, liver function test, folate, ferritin, vitamin B12, vitamin D, calcium, thyroid function test
****At follow-up:** repeat testing at clinician discretion, but should include at least a full blood count, liver function test, haematinics and vitamin D a year after starting a GFD

Figure 2 Schematic outlining the main elements of follow-up. DXA, dual-energy xray absorptiometry; GFD, gluten-free diet; OGD, oesophago-gastro-duodenoscopy; NRCD, non-responsive coeliac disease; PIFU, patient-initiated follow-up.

Box 8 Weighted 5-point score to stratify patients by risk of persistent villous atrophy[103]

Factors to consider:
⇒ Age at diagnosis ≥45 years: 1 point
⇒ Classical presentation of CD at diagnosis*: 1 point
⇒ No clinical response to a GFD: 1 point
⇒ Poor GFD adherence: 2 points
Risk of persisting villous atrophy:
⇒ Score 0–1: 5%; low risk. Score 2: 16%; intermediate risk. Score ≥3: 73%; high risk

*weight loss, diarrhoea and/or steatorrhoea. CD, coeliac disease; GFD, gluten-free diet.

Follow-up biopsy

There is no data supporting the necessity of routine follow-up biopsies in adult CD, in the absence of new or persisting signs or symptoms, or patient preference. However, mucosal healing is regarded as an important treatment goal for CD. Therefore, we recommend considering histological assessment and discussing this with patients before establishing longer-term follow-up arrangements. A recently developed and externally validated 5-point score can help inform on the risk of persistent villous atrophy, which may help with decision making regarding the need for histological assessment (box 8).[103] A score of ≥3 identifies patients at high risk of persistent villous atrophy in CD; a score of 0–1 suggests a low risk of persistent villous atrophy.[103]

The length of time to gain mucosal healing is highly variable[167–169] and it is not possible to specify a precise timeframe for histological assessment of healing, but it is suggested that biopsies in this context should not be considered before at least 1–2 years after starting a GFD.[133] As with diagnosis, we advocate taking four biopsies from D2 and two from D1 when performing duodenal biopsies in established CD. Where diagnostic biopsies were taken, follow-up histology slides may be compared with histology taken at index diagnosis, to ascertain whether improvement has occurred. Patients diagnosed via a no-biopsy pathway are considered to have an enteropathy with villous atrophy and follow-up biopsies should be evaluated with reference to this. As with diagnosis, limitations in histological interpretation may also occur in established CD and should be considered; review by a specialist GI pathologist may be helpful in cases of uncertainty.

Blood tests and nutrient supplementation

Good practice statement 14

Patients should be assessed and monitored for deficiencies in iron, folate, vitamin B12, vitamin D and calcium at diagnosis and during follow-up. Supplementation should be provided in line with general guidance where required. *Agreement 100% (abstain 1/33).*

Expert opinion 4

We do not advise supplementation to prevent nutritional deficiencies over and above national recommendations for the general population. *Agreement 100% (abstain 2/33).*

Anaemia is common at diagnosis of CD (12–85% of cases).[170–172] Deficiencies in iron, folate, calcium, vitamin B12 and vitamin D are also commonly observed at diagnosis.[171 172] Therefore, a full blood count, haematinics and vitamin D should be checked at diagnosis (figure 2). Calcium should also be checked, but dietary history is an important component of assessing adequate dietary calcium intake, as serum calcium is tightly regulated and does not correlate with dietary intake.[173] Low levels of vitamin B6, magnesium and zinc are also reported and should be monitored for in cases of severe malabsorption.[171 172]

Haemoglobin levels typically improve on a GFD in most patients alongside improvements in mucosal inflammation.[106] However, anaemia and haematinic deficiencies may persist in some,[174 175] and nutrient shortages may worsen symptoms. Therefore, we recommend repeating blood tests at least a year after a GFD (figure 2). Nutrient deficiencies should be addressed through supplementation with oral, intravenous or intramuscular replacement, depending on how early in the disease course the deficiency occurs, as active enteropathy may impact absorption and the bioavailability of oral supplements.

Elevated liver enzymes are a common finding in active CD (13–60% of cases).[176] CD is associated with an increased risk of liver disease, although the absolute risk is low (adjusted HR 2.01, 95% CI 1.82 to 2.22).[177] Liver function tests should be checked at diagnosis and follow-up. Moreover, several lines of evidence (meta-analysis of 13 studies; 15 629 CD cases and 79 342 controls) have demonstrated that the prevalence of thyroid disease is higher in patients with CD than controls (OR 3.08, 95% CI 2.67 to 3.56).[178] Therefore, it seems reasonable to check thyroid function at CD diagnosis, and thereafter in the setting of clinical suspicion. It is not clear whether there is any merit in testing for other autoimmune conditions in adult CD in the absence of clinical suspicion.

Bone health

Good practice statement 15

All newly diagnosed adult patients should have a DXA scan 1 year after starting a GFD. *Agreement 94% (abstain 2/33).*

Good practice statement 16

A repeat DXA scan should be performed in individuals with persisting villous atrophy and/or refractory coeliac disease (RCD) after an appropriate timeframe (ie, 2–3 years). *Agreement 86% (abstain 3/33).*

Metabolic bone disease is a common manifestation of CD. The prevalence of osteopenia or osteoporosis is reported to range from 38% to 72% at diagnosis.[179] Low BMD is generally considered a key factor contributing to the increased fracture risk observed in patients with CD. A meta-analysis reported an approximately 30% increased risk of any fracture among individuals with CD,[180] which is comparable to the findings of a recent nationwide registry-based Danish cohort study.[181]

In light of this, assessment of bone health around the time of CD diagnosis is important. The optimal timing for screening for bone disease in CD varies across international guidelines. Previous BSG guidelines recommended a dual-energy xray absorptiometry (DXA) scan only in patients with additional risk factors of osteoporosis or those older than 55 years.[2] However, while low BMD at the time of CD diagnosis is associated with risk factors typical of osteoporosis such as female sex, older age and low BMI,[179 182–185] reduced BMD is also observed in individuals with CD who do not present with these risk factors, such as men and patients with a normal BMI.[182 184] Furthermore, low BMD for age is not uncommon in newly diagnosed patients with CD younger than 55 years old.[182 184] Indeed,

osteoporosis has been identified in 8% of patients with CD aged 35–44 years (n=198) and in 27% of coeliac patients aged 45–54 years (n=118) around the time of diagnosis.[184] This suggests that adopting a more universal approach for bone health assessment in CD may help identify clinically significant disease. Accordingly, we suggest that all adults with CD undergo DXA assessment.

Notably, most people reach their peak bone mass between 20 and 30 years of age.[185] Therefore, a DXA scan may be deferred for younger adults with CD who have no additional risk factors for osteoporosis, to enable evaluation of BMD after peak bone mineralisation has occurred. However, this decision should be balanced against longer-term follow-up arrangements to ensure that bone health is not overlooked. Moreover, clinical judgement should guide decisions on whether repeat DXA testing is warranted in patients who have recently undergone assessment prior to CD diagnosis.

Adherence to a GFD leads to meaningful changes in BMD,[179] with most changes occurring in the first year after diagnosis.[186 187] Therefore, the baseline DXA scan should be performed around a year after diagnosis, to document BMD following implementation of a GFD, in-line with previous guidance.[2] This baseline DXA scan can enable assessment of BMD and the need for initiation of pharmacological interventions to improve bone health, where appropriate, with further decision support provided by a fracture risk assessment using tools such as fracture risk assessment tool (FRAX).[188] Studies have reported that fracture risk assessment tools can aid in stratifying patients for BMD assessment and accurately predict fracture risk without prior DXA measurements, when CD is included in the FRAX calculation as a secondary risk factor for major osteoporotic fractures.[183 189] However, these tools are not widely validated in younger adults and there are limited data in men with CD. Nevertheless, future studies may help to further validate their use in patients with CD and support their integration into management guidelines.

Malabsorption of calcium and vitamin D, secondary hyperparathyroidism and chronic inflammation have been associated with bone disease in CD.[190 191] Therefore, it seems reasonable to repeat a DXA scan in individuals with persisting villous atrophy or refractory coeliac disease (RCD) after an appropriate timeframe (ie, 2–3 years). However, the benefit or cost-effectiveness of this strategy has not been evaluated.

Dietary intake is a modifiable factor that should be optimised for bone health. The UK Reference Nutrient Intake per day is 700 mg for calcium and 400 IU for vitamin D[192]; in the context of osteoporosis, higher levels (ie, 800–2000 IU/day) may be appropriate,[193] although there is limited data specific to CD in this setting. Coeliac UK has developed a useful fact sheet about dietary calcium (available at https://www.coeliac.org.uk/calcium-guide/). If there is adequate calcium and vitamin D intake, then no supplementation is required. Other modifiable risk factors for osteoporosis (eg, smoking, alcohol, etc) should be addressed and patients should be encouraged to engage in weight-bearing exercise. Pharmacological interventions and monitoring of those with low BMD should be offered in line with recommended osteoporosis guidelines.[193]

Vaccinations

Good practice statement 17

We advise that all adult patients diagnosed with CD receive the pneumococcal vaccination; those with RCD and/or on long-term immunosuppressive medication should receive a booster after 5 years. *Agreement 93% (abstain 3/33).*

CD is associated with an increased risk of pneumococcal infection,[194] which may in-part be linked to hyposplenism impairing humoral responses to encapsulated bacteria like *Streptococcus pneumoniae*.[195] Screening for hyposplenism in clinical practice may not be sufficiently sensitive to identify at-risk patients.[196] Therefore, we advise that all adult patients with CD are vaccinated against pneumococcal infection at diagnosis.

Different types of pneumococcal vaccines are available: pneumococcal conjugate vaccines (eg, PCV13, PCV15 and PCV20) and the polysaccharide 23-valent vaccine (PPV23). In the UK, PCV13 or PCV15 is administered to under 1 year olds as part of the Childhood Immunisation Programme.[197] The PPV23 is administered to risk groups aged ≥2 years and to all adults over 65 years as part of the UK Pneumococcal Immunisation Programme. PCV20 is being introduced to replace PPV23 for this purpose.[198] While recent evidence suggests that the conjugated vaccine may provide superior protection in CD,[196] further studies are required before formal recommendations can be made on specific vaccine types.

Public Health England recommends a booster pneumococcal vaccine after 5 years in patients who are asplenic or who have reduced spleen function.[197] It seems reasonable and pragmatic to give boosters to patients who have defined ongoing active disease - such as RCD - and/or those who are on long-term immunosuppression (ie, steroids or azathioprine), although there is little evidence to guide decision-making in these groups.

It is unclear whether there is any benefit in additional vaccination against other encapsulated bacteria, such as *Haemophilus* and *Meningococcus*, or *Influenza*, for individuals with CD outside of current Public Health England recommendations.[197] In addition, some evidence suggests that coeliac patients generate a lower protective humoral response following hepatitis B virus (HBV) vaccination compared with non-affected controls.[199] Therefore, it is important to assess the serologic response to HBV in newly diagnosed patients with CD who have previously been vaccinated and consider the need for booster doses where necessary.

Supporting psychological well-being

A diagnosis of CD and the subsequent impact of shifting towards a GFD can have a major impact on an individual's life. While health-related QoL improves with a GFD, it may be lower in CD than healthy controls[114] and conditions such as anxiety and depression are more likely in CD than in otherwise healthy individuals.[200 201] All patients with a diagnosis of CD should be directed towards a disease advocacy group (eg, Coeliac UK) where they may be able to join online communities, local groups and receive peer support which may positively impact GFD adherence and psychological well-being.[202 203] In addition, patients should be signposted towards support for mental health where appropriate (eg, NHS Talking Therapies[204]).

Transfer from childhood to adult services

Good practice statement 18

We advise that patients with established CD transitioning from paediatric to adult care are offered follow-up in the adult service, in accordance with adult guidance. *Agreement 94% (abstain 2/33).*

Recommendations for how to facilitate the transition to adult healthcare for patients with CD have been developed and should be consulted to inform on best practices.[205] Fundamentally, adolescents transitioning into adult services should be offered access to follow-up as outlined presently, which should include regular follow-up for up to 2 years in adult services, after which time longer-term follow-up plans should be considered. Further regular follow-up into young adulthood may be beneficial to support important milestones through

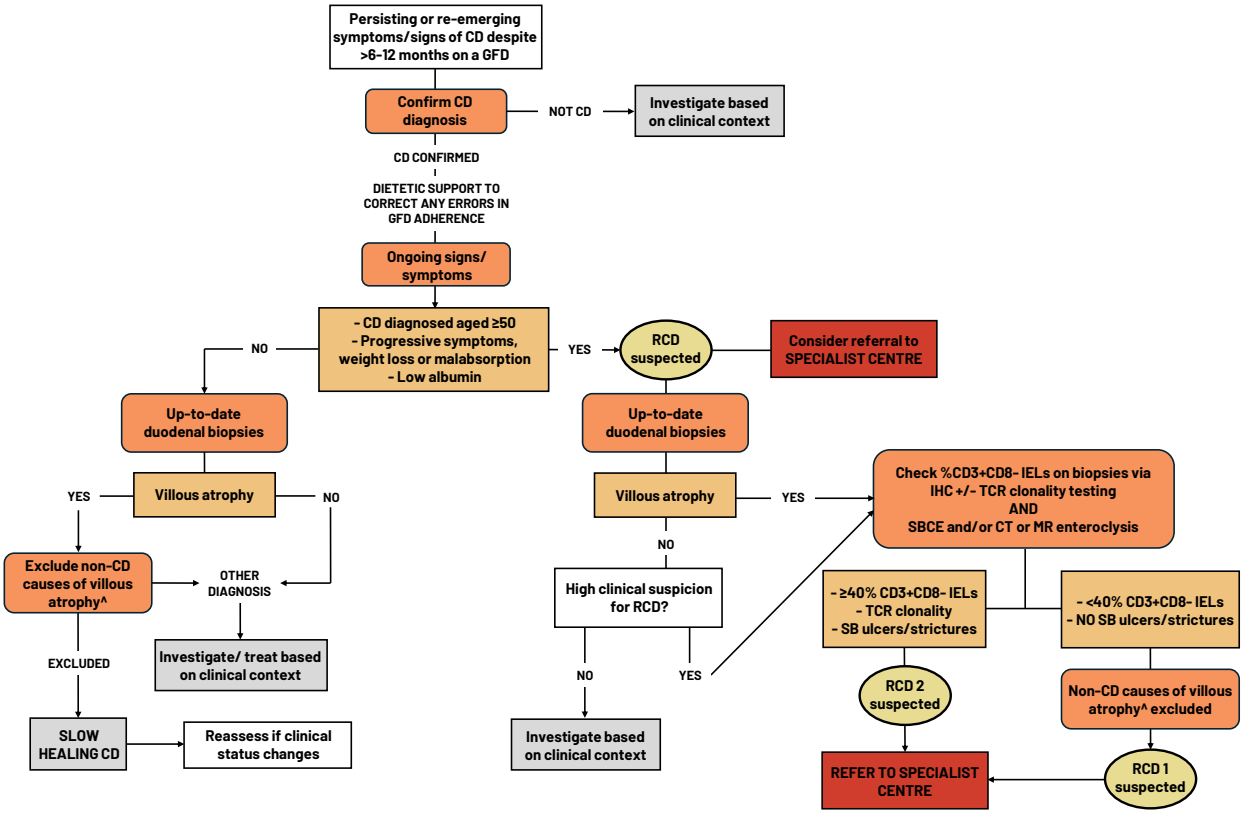


Figure 3 Approach to a patient with established CD and persisting signs/ symptoms. Key steps in this pathway include: (1) Confirm the index diagnosis: Particular care should be taken when evaluating patients with a historical diagnosis of CD and/or seronegative CD. Where there is uncertainty about the original CD diagnosis, gluten challenge and repeat testing should be considered. (2) Assess adherence to the GFD: Ongoing gluten exposure is a common cause of NRCD so a detailed assessment of GFD adherence should be performed in all patients. (3) Evaluate for persisting enteropathy: Up-to-date duodenal biopsies are the only accurate test to assess for persisting mucosal inflammation in patients with CD on a GFD. Mucosal healing can normally take 1–2 years and there is no marker to differentiate slow healing, ongoing gluten ingestion and RCD, but patients with slow healing may appear systemically well and display non-progressive signs or symptoms of malabsorption. By contrast, patients with persisting enteropathy within the scope of RCD typically are older individuals (i.e. >50 years old) and/ or present systemically unwell with malabsorption. (4) Consider non-coeliac causes for symptoms: In the absence of enteropathy, alternative diagnoses should be considered; the clinical context should dictate further investigation, but inflammatory bowel disease, microscopic colitis and disorders of gut-brain interactions should be given particular consideration given their high prevalence in CD. ^Non-CD causes of villous atrophy are listed in Table 2. CD, coeliac disease; GFD, gluten-free diet; IELs, intraepithelial lymphocytes; IHC, immunohistochemistry; RCD, refractory coeliac disease; SBCE, small bowel capsule endoscopy; TCR, T-cell receptor.

school and other life events (eg, moving away from family support), which may impact GFD adherence and thus disease control.[206]

NON-RESPONSIVE AND REFRACTORY COELIAC DISEASE

Non-responsive coeliac disease

Most patients will see an improvement in their symptoms shortly after starting a GFD. Despite this, up to a third of adult coeliac patients on a GFD continue to suffer with persistent or chronic symptoms.[207] Non-responsive CD (NRCD) is defined as the persistence or re-emergence of symptoms, signs or laboratory abnormalities typical of CD after 12 months on a GFD. However, it is a vague term that encompasses a broad range of disorders that are both related and/or unrelated to CD itself. Therefore, a comprehensive work-up is often required for patients seen in clinic (figure 3).

Adult cohort studies have shown that ongoing gluten exposure is the most common cause of persistent or chronic symptoms in CD occurring in 22–45% of cases.[99 208 209] Other causes of symptoms in adult NRCD include IBS/functional causes (19–30% of patients), MC (3–11%), slow healing (11%) and IBD (2–7%).[99 208 209] An association between CD and IBD, MC, and DGBIs such as IBS has been confirmed in other studies at the time of coeliac diagnosis,[100 143 210 211] suggesting that coexisting conditions may contribute to symptom burden in some patients. Pancreatic exocrine insufficiency, lactose/fructose malabsorption, and small bowel bacterial overgrowth are frequently reported in both active CD and NRCD.[212–214] However, mucosal inflammation in CD may impact orocaecal transit, enterocyte loss and microbial colonisation within the small bowel, which may influence both the accuracy and interpretation of tests for these conditions. Therefore, their true prevalence in patients with CD remains uncertain.

Refractory coeliac disease

Overview

Expert opinion 5

Patients with suspected RCD should be referred to a specialist centre for support with diagnosis and management by an experienced multidisciplinary team including dietitians, gastroenterologists, pathologists and haematologists. *Agreement 97% (abstain 0/33).*

RCD is characterised by the persistence, or re-emergence, of symptoms or signs of malabsorption and/or intestinal failure with the presence of ongoing villous atrophy despite strict adherence to a GFD for at least 12 months, in the absence of other identifiable causes.[215] RCD typically occurs in patients diagnosed with CD aged 50 years or older.[216–219] Common symptoms include abdominal pain, diarrhoea and weight loss; anaemia, hypoalbuminaemia and haematinic deficiencies are also typically present.[217–219] The prevalence and epidemiology of RCD remain unclear, largely owing to challenges in diagnosis, but it is estimated to affect less than 1% of the CD population.[220] RCD can be further classified into two subtypes based on specific immunological and diagnostic features:

RCD Type 1 (RCD1) This is a diagnosis of exclusion, made only after thorough investigation for gluten exposure, RCD2 and non-coeliac-related causes of villous atrophy. In this subtype, there is histologically detectable villous atrophy and duodenal IEL display immunophenotypic changes similar to active CD. RCD1 typically follows a benign course that can be managed with oral immunosuppressive therapy; the 5-year survival rate is generally around 80–95%.[209 216–219]

RCD2 This is a low grade intraepithelial cell lymphoma that typically runs an aggressive course.[220] RCD2 is characterised by an increased number of abnormal ('aberrant') IELs; these cells do not express the T-cell marker CD3 on the cell surface but do express intracellular CD3 and they lack surface CD8.[220] Patients with RCD2 often show systemic symptoms like weight loss, low albumin and nutrient deficiencies due to severe mucosal inflammation.[217 218] Symptoms such as GI bleeding, fever, night sweats and bowel obstruction may indicate complications related to RCD2 such as ulcerative jejunitis or enteropathy-associated T-cell lymphoma (EATL). Treatment options for RCD2 are limited; the 5-year survival rate for RCD2 is approximately 50%.[209 216–219] Once EATL develops, the 5-year survival rate drops to around 10%.[216–219]

Due to the complexity and rarity of RCD, we recommend that patients are diagnosed and managed in specialised tertiary or national referral centres with extensive experience in this condition. In the UK, specialist teams at Sheffield and Cambridge Teaching Hospitals NHS Trusts have been approved as Rare Diseases Collaborative Network Centres for Non-Responsive and Refractory Coeliac Disease. These centres provide facilities for a national registry for patients and support with the diagnosis and management of RCD and complicated NRCD. Advice from such specialist centres may also be sought in cases of persistent or unexplained symptoms suggestive of CD, even when classical diagnostic pathways are inconclusive.

Diagnosis

Recommendation 13

We recommend the use of flow cytometry to immunophenotype small intestinal IELs as the reference standard to diagnose RCD2.

GRADE: Low certainty of evidence; strong recommendation; agreement 96% (abstain 9/33).

Justification: Flow cytometry has demonstrated superior accuracy for a diagnosis of RCD2 compared with immunohistochemistry (IHC) and TCR clonality studies.

Implementation: Samples should be processed for flow cytometry according to local protocols ideally on the same day as sampling, or within 24 hours. The flow cytometry panel should include at least the following antibody markers: CD45, CD7, CD103, surface CD3, intracytoplasmic CD3. The presence of ≥20% sCD3−cCD3+ cells (of the total lymphocyte population) within the appropriate clinical context is consistent with a diagnosis of RCD2.

Recommendation 14

We recommend that patients with suspected RCD undergo small bowel imaging. Device-assisted enteroscopy should be planned for tissue sampling where required.

GRADE: Moderate certainty of evidence; strong recommendation; agreement 100% (abstain 10/33).

Justification: Observational studies have demonstrated that significant small bowel lesions may be located in the jejunum and ileum, blind to standard gastroscopy in patients with RCD.

Implementation: Patients with suspected RCD should undergo small bowel imaging with small bowel capsule endoscopy (SBCE) or CT/MR enteroclysis depending on local availability. Cross-sectional imaging is important before SBCE in those with suspected GI obstruction, due to risks of capsule retention.

An important consideration for the diagnosis of RCD2 is the detection of aberrant IELs in small intestinal biopsies. The most accurate method to achieve this is by flow cytometry; the presence of ≥20% sCD3−cCD3+ cells (of the total lymphocyte population) within the appropriate clinical context is considered adequate for a diagnosis of RCD2.[221 222] Enumerating CD3+CD8 IELs in sectioned small bowel biopsies by IHC has been suggested as an alternative way of identifying RCD2; ≥40–50% CD3+CD8- IELs is considered appropriate for diagnosis.[222] However, IHC lacks the sensitivity and specificity of flow cytometry.[221 223] TCR clonality assessment by PCR analysis of DNA from small intestinal biopsies has also been suggested as a modality for RCD2 diagnosis. However, studies have demonstrated that clonal rearrangement of the TCR is not unique to RCD2 and can occur in uncomplicated CD.[224 225] It is notable that these studies were not designed prospectively, diagnostic accuracy was not a primary endpoint and they lacked a reference standard for defining RCD subtypes, which hampers comparability. Furthermore, they are mostly monocentric and conducted based on local protocols. Despite this, flow cytometry has demonstrated superior accuracy for RCD2 across different settings and is available within specialist centres, including national referral centres in the UK.

Up to 40% of lesions in patients with (RCD) can be in the jejunum and ileum, blind to standard gastroscopy.[226 227] Therefore, patients with suspected RCD should undergo SBCE or CT/MR enteroclysis, depending on local availability.[228–230] Cross-sectional imaging is important before SBCE in those with suspected GI obstruction, due to risks of capsule retention. Once a small bowel lesion is identified beyond the reach of a standard gastroscope, device-assisted enteroscopy (DAE) should be planned to obtain targeted biopsies.[226–228] Fluorodeoxyglucose positron emission tomography (FDG-PET) may identify additional sites of disease to that detected by conventional CT-based staging,[231] but it is unclear whether this impacts management in RCD2/EATL.

Treatment

Recommendation 15

We suggest open-capsule budesonide (OCB) as a first-line treatment of RCD1 alongside maintaining a strict GFD.

GRADE: Low certainty of evidence; conditional recommendation; agreement 100% (abstain 10/33).

Justification: Observational studies have demonstrated that OCB induces favourable clinical and histological outcomes in patients with RCD1.

Implementation: The open-capsule regimen described comprises 3 mg capsules taken three times a day with the morning dose contents opened and ground between the teeth, lunchtime dose capsule opened and swallowed without grinding, and evening dose capsule taken whole.

Good practice statement 19

We advise that thiopurines such as Azathioprine are considered as steroid-sparing agents in RCD1 if treatment is required over the longer-term. *Agreement 100% (abstain 11/33).*

Expert opinion 6

Treatment of RCD2 should be individualised and considered in a specialist MDT setting. *Agreement 96% (abstain 5/33).*

Nutritional support via the least invasive route is a central focus of treatment for RCD, as involuntary weight loss is frequently observed alongside macronutrient and micronutrient deficiencies, typically resulting from malabsorption and significant energy losses.[232] Beyond this, current pharmacological treatment options in RCD1 include steroids and thiopurines; studies are limited to small, open-label, often retrospective studies and there have been no randomised controlled studies in this setting.

OCB is well tolerated and leads to clinical and histological improvement in RCD1 patients (clinical: 92–94%, histological: 79–89%)[233 234] and was shown to be superior to closed-capsule budesonide (CCB) (complete duodenal healing in 19/35 (54%) with OCB compared with 1/16 (6%) with CCB; $p<0.001$).[234] The rationale of the open-capsule regimen is to enable the budesonide to be distributed more proximally in the gut than its packaged formulation. However, there is no data specifically evaluating drug distribution within the small bowel using this approach. There is also limited data on the optimal length of treatment; treatment duration of 9 mg budesonide in studies commonly falls around 3–4 months. Tapering regimens have not been formally assessed, but a weaning regimen comprising 3 mg budesonide dose reduction every 3 months with a final alternate day 3 mg regimen has been described with some success,[233] although recurrence in symptoms on stopping steroids is common (25–86%).[233 235]

Azathioprine (2–2.5 mg/kg/day), mercaptopurine (1 mg/kg/day), and the nonconventional thiopurine derivative tioguanine have been used in RCD1 both in combination with, or as alternatives to, steroids,[209 216–219 236 237] with some benefit demonstrated.[236] However, the risks of exposing patients to the toxicities associated with treatment need to be balanced against the challenges in differentiating RCD1 from slow healing and ongoing gluten ingestion. Therefore, we suggest that treatment is reconsidered after 2–3 years to help establish the diagnosis of RCD1 rather than a slow response to gluten withdrawal. Furthermore, as the risks associated with long-term thiopurine therapy, including lymphoma, increase with age in other chronic inflammatory GI conditions,[238] we advise caution regarding their prolonged use in older adults with CD.

Treatment options in RCD2 include cladribine, an adenosine nucleoside analogue, which has been used as a first-line treatment, or in those who have failed a steroid trial.[239] Autologous haematopoietic stem cell transplantation has been used for RCD2 patients refractory to cladribine treatment and shown some clinical, histological, and immunological improvements, as well as potential survival benefits in open-label observational studies.[239 240] However, there is limited evidence that any treatment in RCD2 reduces progression to EATL. Other therapies, including those targeting the Janus Kinase/Signal Transducers and Activators of Transcription (JAK-STAT) signalling pathway, have recently shown promise of potential benefit in early studies.[241]

Follow-up

Patients with RCD require monitoring and regular screening with small bowel histology and SBCE to accurately assess disease status. The therapeutic primary endpoint (eg, reduction in % of aberrant IEL, clinical, histological or endoscopic remission, or development of EATL) remains unclear and it is difficult to define prognostic factors in RCD.[218] As a result, the optimal interval for surveillance remains uncertain and requires further research to establish a standardised approach. Despite these knowledge gaps, a follow-up schedule in stable disease of at least 12-monthly for RCD1 and 6-monthly for RCD2 is advised.

KEY PERFORMANCE INDICATORS

In 2016 NICE published quality standards for CD to describe indicators of high-quality care for coeliac patients.[242] Quality standards align with KPI by defining quality metrics that signify high-quality care, facilitate benchmarking for service comparability and highlight areas for improvement.[243] As part of the guideline process, we examined whether these indicators were still applicable and updated them in line with current recommendations.

A GDG meeting was held at the 2024 International Celiac Disease Symposium in Sheffield, UK. Nineteen of the 26 GDG members were present. Quality standards were reviewed in line with current guideline recommendations and new indicators drafted. These were modified through further discussion. This process resulted in the development of seven KPIs (table 6). The purpose of these KPIs is to help standardise key aspects of patient care and service delivery in adult CD.

IMPACT ON CLIMATE CHANGE AND SUSTAINABILITY STRATEGIES

The healthcare sector is responsible for around 4% of total greenhouse gas emissions worldwide and GI endoscopy is

Table 6 Key performance indicators (KPIs) for recognising, assessing and managing adult coeliac disease

KPI	Statement	KPI setting	Target
1	Percentage of people at increased risk or with symptoms suggestive of coeliac disease who are offered serological testing while on a gluten-containing diet.	Primary/specialist care	90%
2	Percentage of people with positive serology who are referred to a specialist and advised to continue with a gluten-containing diet until the diagnosis is confirmed.	Primary care	95%
3	Percentage of people investigated for coeliac disease who had an endoscopic intestinal biopsy within 6 weeks of their referral to specialist services.	Specialist care	90%
4	Percentage of endoscopies undertaken to investigate for suspected coeliac disease, where at least four D2 and two D1 biopsies are taken.	Specialist care	95%
5	Where appropriate, percentage of patients diagnosed with coeliac disease via the no-biopsy pathway who met all required criteria (ie, symptomatic patients with an IgA-tTG titre≥10× upper limit of normal in secondary care, in the absence of another reason to perform an upper GI endoscopy).	Specialist care	95%
6	Percentage of patients with a new diagnosis of coeliac disease who receive a formal consultation with a specialist dietitian within 3 months of diagnosis.	Specialist care	90%
7	Percentage of patients with coeliac disease who are formally assessed for the need for ongoing follow-up within 24 months of their initial diagnosis.	Primary/specialist care	95%

GI, gastrointestinal; tTG, tissue transglutaminase.

estimated to be one of the highest hazardous waste generators in hospitals.[244] International and national gastroenterology societies have recognised the urgent need to take action to achieve sustainable healthcare. The NHS has committed to achieve a net-zero healthcare by 2040, promoting initiatives to raise awareness, strategies and policies to decrease waste and move towards a carbon neutral status.

Specific data addressing the environmental impact of CD diagnosis and management are scarce. Most of the recent research focuses on the environmental impact of GI endoscopy and possible strategies to mitigate its impact, which can be extrapolated and applied to CD. A recent Italian study has shown that the carbon emissions due to inappropriate endoscopy range from 3527 to 4749 metric tonnes of CO_2 per year,[245] underscoring the importance of case selection for endoscopy. Additionally, Shiha *et al* showed that by implementing the serology-only approach for the diagnosis of CD in the UK, approximately 3000 endoscopies per year could be avoided, resulting in over £2.5 million saved in direct and indirect costs and a reduction in the carbon footprint by 87 tonnes of CO_2 per year.[246] Beyond this, we advocate adopting the European Society of Gastrointestinal EndoscopyESGE's '5 Rs' strategy[247] (Reduce, Reuse, Recycle, Research, Rethink) to help impact carbon emissions in clinical practice relating to CD.

AREAS FOR FURTHER RESEARCH AND EMERGING TECHNOLOGIES

Areas of future research based around recommendations within this guideline include: refining diagnostic pathways in CD, including the standardisation of serology and automation of duodenal histology assessments; developing interventional approaches to support QoL of patients on a GFD; optimising case selection for longer-term follow-up, including assessing the need for bone health monitoring and vaccinations for all patients; identifying a marker of mucosal healing; and evaluating the role of novel therapies in RCD2 (eg, anti-IL15 therapies and drugs targeting the JAK-STAT pathway).

Advancements in the understanding of CD pathophysiology have led to the recent development of novel technologies for diagnosis including whole blood interleukin 2 assays and HLA-DQ-gluten tetramer-based workflows.[248 249] While these tests may further reduce the need for upper GI endoscopy (and gluten ingestion) for CD diagnosis, it is important to explore how their use can be expanded beyond academic environments and specialist centres. Additionally, a major focus of research in CD has been how to effectively reduce the burden of the GFD from affected individuals. To this end, the recent past has seen an increasing development of non-dietary therapies in CD.[250] Whether drugs can provide an effective alternative to the GFD remains to be determined, but it is likely that therapies which provide relief for occasional and/or inadvertent gluten exposure will be introduced to the management of CD in the near future.

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