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CLINICAL REVIEW

Coeliac disease

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Coeliac disease is a common autoimmune condition characterised by a heightened immunological response to ingested gluten, with estimated prevalence rates in adults of 0.2-1% in the United States and Europe. Contemporary studies suggest that the prevalence of this disease is increasing.[3-5] Meta-analyses have shown that for every patient identified as having coeliac disease seven to eight remain undiagnosed. Here, we will summarise recent evidence on how the investigation and diagnosis of coeliac disease can be improved and also provide an evidence based approach to managing patients with newly diagnosed coeliac disease and those who do not respond to a gluten-free diet as expected. Evidence is taken from meta-analyses, systematic reviews, and randomised controlled trials where possible.

Who gets coeliac disease?

In the past coeliac disease was considered to be a disease that affects white populations only, but it is now clear that coeliac disease is a global problem. Clinicians in China and the Indian subcontinent are now recognising patients with this disease. Possible reasons for this increased prevalence are the introduction of wheat into these ethnic groups as their diet becomes more westernised and an increasing trend in all autoimmune diseases. Patients at increased risk include those with another autoimmune condition or a family history of coeliac disease. Patients with a first degree relative with coeliac disease have a 5-11% chance of being affected.[10-12] Second degree relatives also seem to be at increased risk (~2.5%), although the exact prevalence in this population is uncertain. There is a strong genetic component to coeliac disease—90% of patients carry genes encoding HLA DQ2. Most of the remainder carry the HLA DQ8 haplotype. In common with other autoimmune conditions it is more common in females than males (1.5-2:1).[14-17]

How does coeliac disease present?

Until the 1980s, coeliac disease was considered a rare condition that usually presented in childhood with symptoms of malabsorption—weight loss, chronic diarrhoea, or failure to thrive. This is best described as "classical" coeliac disease and remains relatively rare. Coeliac disease is now known to be common, presenting in adulthood usually in the fourth or fifth decade of life with "non-classical" symptoms. Non-classical presentations include irritable bowel syndrome-type symptoms, abdominal pain, altered bowel habit, and anaemia (most commonly iron deficiency). Clinicians need to be aware of the variable manifestations of coeliac disease, which may not include abdominal symptoms or signs of malabsorption.

Who should we test for coeliac disease?

Current national and international guidelines recommend case finding in at risk groups as the best method of case detection.[21-23] The aim of case finding is to identify patients at an early stage and potentially reduce the risks of developing complications of coeliac disease such as lymphoma, osteoporosis, and anaemia.

Recent US guidelines recommend testing for coeliac disease in patient populations with a prevalence of coeliac disease more than twice that of the general population. This approach has been shown to be useful in prospective case finding studies in patients with classical symptoms or sequelae of malabsorption, such as anaemia or osteoporosis.[14-17] These same studies also show that the prevalence of coeliac disease is higher in patients with more non-specific symptoms, although there was heterogeneity in the patient populations studied. The best evidence for testing for abdominal symptoms comes from two meta-analyses in patients fulfilling the Rome III diagnostic criteria for irritable bowel syndrome. Symptoms of this syndrome are seen in 38% of patients with coeliac disease, and the prevalence of coeliac disease is 4.1% in patients with irritable bowel syndrome. Evidence for testing in patients with other abdominal symptoms is less compelling, although a recent systematic review of diagnostic testing for coeliac disease in secondary care showed a prevalence of 2-13% in patients presenting with all abdominal symptoms. The web table (on bmj.com) summarises the patient groups where testing is recommended.[26-29]

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Extra table supplied by the author (see http://www.bmj.com/content/348/bmj.g1561?tab=related#webextra)

Summary points

- Adult coeliac disease is a common autoimmune condition with an estimated prevalence of 1%
- Test for coeliac disease in patients with unexplained anaemia, weight loss, diarrhoea, or gastrointestinal symptoms, particularly irritable bowel syndrome, and in first degree relatives of index cases
- Confirm the diagnosis with duodenal biopsy in all adult patients
- Treatment with a lifelong strict gluten-free diet is currently the only treatment of known effectiveness
- Patients should have access to an expert dietitian for advice on a gluten-free diet and for assessment of adherence if symptoms persist on institution of the diet
- Regular follow-up is necessary to assess adherence and micronutrient deficiency

Sources and selection criteria

We searched Medline and the *Cochrane Database of Systematic Reviews* with the search terms "coeliac disease" or "celiac disease". Studies included those in adult and paediatric populations but preference was given to adult studies in the past five years. We focused on meta-analyses and systematic reviews where possible.

What tests should we use?

The three most widely available serological tests—endomysial antibody (EMA), tissue transglutaminase (tTG) antibody, and deamidated gliadin peptide (DGP) antibody—have excellent sensitivity and specificity in appropriate patient groups. EMA testing is highly accurate, with a sensitivity and specificity of 95% or more in patients with overt villous atrophy. However, it is subjective, labour intensive, and the substrates of monkey oesophagus or human umbilicus have limited availability. tTG assays are generally cheaper than EMA testing and may be more reliable. One weakness of tTG assays, however, is that their accuracy varies between manufacturers. The best assays have a higher sensitivity than EMA testing and a comparable specificity, both around 98%. More recently DGP assays have become available. However, a recent meta-analysis has shown that they are inferior to tTG assays, and they are not currently recommended by the National Institute for Health and Care Excellence. tTG is currently the preferred first line test owing to its high sensitivity and negative predictive value. Point of care tests are now commercially available in high street pharmacies and on the internet for patients to purchase. Further research is needed to ascertain their utility. Clinicians should treat the results of such tests with caution and confirm them with standard serology; gastroenterology referral should also be considered. Counsel patients not to start a gluten-free diet until investigations are completed.

Is a duodenal biopsy still needed for diagnosis?

Currently, most patients are diagnosed on the basis of positive coeliac serology followed by a confirmatory duodenal biopsy showing the presence of villous atrophy and increased intraepithelial lymphocytes (Marsh 3a-c; table 1⇓). However, recent European paediatric guidelines suggest an algorithm for avoiding biopsy in children with clinical symptoms, very high antibody titres (tTG >10× normal and positive EMA), and an appropriate genotype. This is understandable because endoscopic evaluation often requires a general anaesthetic in children. Duodenal biopsy to confirm diagnosis is still needed in adults for several reasons. Firstly, although serology seems to be an excellent marker, studies into these tests are performed in high prevalence populations. This ascertainment bias overestimates the performance of a diagnostic test. As the threshold for serological testing is lowered, the disease prevalence within the tested population will fall. As a result the positive predictive value of the test will also fall. For example, in a recent cohort of 2000 patients with a 3.9% prevalence of coeliac disease, the positive predictive value of tTG was only 28.6%, despite sensitivity and specificity of greater than 90%. Secondly, the clinical response to a gluten-free diet is not diagnostic of coeliac disease, particularly in patients with irritable bowel syndrome, whose symptoms may be gluten sensitive in the absence of coeliac disease. Finally, if patients do not respond to a gluten-free diet as expected, any uncertainty in the initial diagnosis can make subsequent evaluation problematic. Patients should remain on a gluten containing diet until endoscopy because histological features may normalise on a gluten-free diet.

What if serological tests are positive but duodenal biopsy is non-diagnostic?

As previously discussed, a diagnosis of adult coeliac disease requires a duodenal biopsy that shows villous atrophy. However, in some cases a biopsy may be normal or show evidence of increased intraepithelial lymphocytes without villous atrophy (Marsh 1; table 1). These changes are non-specific and are seen in many other conditions, including *Helicobacter pylori* infection or as a result of non-steroidal anti-inflammatory use. Coeliac disease is subsequently confirmed on repeat gastroscopy and biopsy in 16-43.3% of patients. As a result, a diagnosis of coeliac disease cannot be made on the basis of an increased number of intraepithelial lymphocytes and positive serological testing alone. In these patients a repeat gastroscopy and duodenal biopsy should be considered after a six week gluten challenge of 10 g of gluten (equivalent to four slices of bread) a day.[21-23] Some patients may not tolerate this amount of gluten and evidence is emerging that shorter challenges with less gluten might be sufficient, although clinical data are lacking.

Duodenal biopsies are usually taken from the distal duodenum. However, recent evidence suggests that an additional biopsy from the first part of the duodenum may increase the diagnostic yield because this is the only site of villous atrophy in 1.8-12.5% of newly diagnosed patients. HLA genotyping may also be useful in this situation because the absence of the HLA DQ2 and DQ8 haplotypes has a near 100% negative predictive value. However, 25-40% of the healthy population also carry these alleles, so genotyping should not be used for routine diagnosis. This same strategy can be used for patients with positive serological but normal histological results and a high index of suspicion of coeliac disease. Coeliac serology testing is not 100% specific and false positives do occur, particularly in patients with other autoimmune conditions or conditions that lead to a raised total IgA level.

What if serological testing is negative but the clinical suspicion of coeliac disease is high?

Although modern serological testing is highly sensitive, cases of antibody negative coeliac disease do exist, particularly when a single test is used in the diagnostic algorithm. Selective IgA deficiency, present in 2% of patients with coeliac disease, is a common cause of false negative coeliac serological results because standard tests are based on the IgA subclass of antibody. Immunoglobulin levels should be checked alongside standard serological tests, and duodenal biopsy is recommended in IgA deficient patients.[21-23] Patients must be on a gluten containing diet at the time of serological testing because results may normalise on a gluten-free diet.

IgA deficiency is not the only cause of antibody negative coeliac disease. In the 11 studies reported in a recent meta-analysis of IgA tTG the mean rate of tTG negative coeliac disease was 7%. A prospective study of a clinical decision tool for diagnosing coeliac disease found that patients without high risk symptoms of anaemia, weight loss, or diarrhoea could safely have coeliac disease excluded on the basis of negative serological testing. However, this algorithm has yet to be validated by other groups. The diagnosis of antibody negative coeliac disease can also be problematic because other causes of villous atrophy need to be considered. Again, HLA genotyping can be useful in this situation if it proves negative. Patients on immunosuppressants or steroids may also have negative serological results in the presence of villous atrophy. Finally, wheat or gluten can induce symptoms in patients without coeliac disease and self reported sensitivity is not always caused by coeliac disease. Refer all patients in whom coeliac disease is suspected but the histological or serological (or both) results are not diagnostic to a gastroenterologist with an interest in coeliac disease.

How is coeliac disease managed?

Currently, the only effective treatment for coeliac disease is a gluten-free diet. However, many patients find available gluten-free foods unpalatable and report social difficulties related to eating out. It can be difficult to assess adherence but this is important, particularly in patients who continue to have symptoms. Adherence is assessed in five ways: patient reported adherence, dietetic assessment, a validated adherence questionnaire, coeliac serological testing, or a repeat duodenal biopsy. A recent systematic review that used qualitative methods estimated that adherence to a strict gluten-free diet ranged from 42% to 91%, although complete non-adherence was rare. Factors that were most associated with good adherence were follow-up with an expert dietitian and membership of a coeliac disease advocacy group, both of which should be strongly encouraged.

Many clinicians think that a repeat duodenal biopsy is the most objective measure of adherence. A recent UK cohort study has shown that follow-up biopsy before discharge to primary care services is a useful way to risk stratify patients who are likely to have more severe disease and complications. However, mucosal healing can take several years, and the ideal timing of a follow-up biopsy is not known. Repeat duodenal biopsy is invasive, so quantitative serological measurements are often used as a surrogate marker of intestinal healing. However, serological and histological findings do not seem to correlate in a linear manner.

Adherence is complicated to assess and is probably best measured using a combination of factors. Patients should have access to a dietitian to assess adherence in conjunction with repeat serological testing and gastroenterology input to assess for resolution of symptoms. Repeat duodenal biopsy is probably best reserved for patients with raised serological markers, persistent symptoms, or nutrient deficiencies. Patients who are stable and seem to be adhering to a gluten-free diet should be seen in primary or secondary care on an annual basis to assess symptoms and discuss adherence.

What should we do if the patient doesn't respond to a gluten-free diet?

Although most patients with coeliac disease will respond to a gluten-free diet, 7-30% of patients have persistent symptoms. Some patients may have been initially misdiagnosed with coeliac disease and the diagnosis must be confirmed by reviewing the histological and serological results and history. The most common reason for persistent symptoms in patients with confirmed coeliac disease is persistent exposure to gluten. Several well documented associations with other gastrointestinal conditions, such as bacterial overgrowth of the small bowel, pancreatic insufficiency, and microscopic colitis, may also contribute to ongoing gastrointestinal symptoms.

Patients who do not respond to a gluten-free diet are described as non-responsive, and in a small number of these persistent symptoms will be the result of refractory coeliac disease. This is a rare condition, which is defined as a persistence of villous atrophy despite strict adherence for 12 months to a gluten-free diet. It can be a precursor to enteropathy associated T cell lymphoma (EATL). Patients with refractory coeliac disease will have persistent symptoms including persistent nutritional deficiencies, weight loss, and malabsorption. These patients require urgent evaluation by a gastroenterologist. The box provides a comprehensive list of the causes of non-responsive coeliac disease. Table 2⇓ summarises several new treatments that are under development for coeliac disease.

What long term risks are associated with coeliac disease and how are they managed?

The potentially serious sequelae of coeliac disease can be prevented by adherence to a strict lifelong gluten-free diet. These associated risks include the development of lymphoma and osteoporosis as well as hyposplenism, anaemia, and other micronutrient deficiencies.

Lymphoma

Older estimates suggested that the relative risk of lymphoma was 40-100 times that seen in the general population.[50-55] However, as the detection of coeliac disease has improved, newer studies have shown only a modest risk.[56-58] A recent meta-analysis found a fourfold increased risk of non-Hodgkin's lymphoma (including EATL) compared with the general population, with an estimated one in 2000 patients with coeliac disease developing lymphoma each year. Evidence for the protective effect of a gluten-free diet against the development of lymphoma is circumstantial. EATL is often diagnosed at the same time or soon after the diagnosis of coeliac disease, before the patient can start an effective gluten-free diet. A recent large population based study showed that persistent villous atrophy, which is more common in patients with poor adherence to a gluten-free diet, was associated with increased risk of lymphoma, with a hazard ratio of 2.26 compared with those with mucosal healing on follow-up biopsy. However, direct

Causes of persistent symptoms in coeliac disease

- Continued exposure to gluten
- Bacterial overgrowth of the small bowel
- Exocrine pancreatic insufficiency
- Microscopic colitis
- Irritable bowel syndrome
- Lactose intolerance
- Refractory coeliac disease
- Cancer—small bowel lymphoma or adenocarcinoma

evidence of benefit is sparse. EATL is rare, so studies are small and data are conflicting.

Osteoporosis

Osteoporosis is prevalent in patients with coeliac disease, with 32-80% having abnormal bone mineral density, and a strict gluten-free diet has been shown to improve bone mineral density. In a recent study of 95 patients with newly diagnosed coeliac disease, adherence to a strict gluten-free diet significantly improved mean bone mineral density, independent of other risk factors and the effect of exercise. This validates results from a previous systematic review. However, patients with silent or subclinical disease may not have metabolic bone disease to the same extent as those with classical coeliac disease. Current national guidelines recommend that patients are given lifestyle advice and that a baseline DEXA (dual energy X ray absorptiometry) scan should be requested to assess bone mineral density at diagnosis. The scan should be repeated at menopause or 55 years of age for men, or if there is a suspected fragility fracture. Loss of bone density at a greater than expected rate should prompt measurement of vitamin D levels, dietary review of adherence, consideration of repeat intestinal mucosal biopsy, and review of additional risk factors.

Other management points

Patients with coeliac disease can have hyposplenism, which results in a higher risk of infection from encapsulated bacteria. National guidelines recommend vaccinations against *Streptococcus pneumoniae*, meningitis C, and *Haemophilus influenzae* B, as well as an annual influenza vaccination, in this population.

Anaemia and other micronutrient deficiencies are common in newly diagnosed coeliac disease. Clinicians should measure iron, vitamin B_{12}, folic acid, vitamin D, and calcium levels at diagnosis. Appropriate replacement is required on diagnosis, with annual monitoring of haemoglobin, vitamin B_{12}, folate, serology, and immunoglobulins. Adherence to a gluten-free diet may prevent recurrence of nutrient deficiencies if oral intake is sufficient.

Finally, quality of life studies of patients with coeliac disease on a gluten-free diet show that they have a lower quality of life in both the short and long term compared with the general population and patients with other chronic gastrointestinal conditions, such as ulcerative colitis. Appropriate investigation and management of symptoms as well as support with a gluten-free diet may improve quality of life.[70-72]

What should you tell the patient diagnosed with coeliac disease?

- The prognosis for coeliac disease is good, with a normal life expectancy
- A gluten-free diet is currently the only known treatment for coeliac disease. Adherence to the diet should lead to healing of the small bowel
- The risk of lymphoma is greater than in the general population but remains small, and a gluten-free diet may reduce this risk
- On average, patients with coeliac disease have reduced bone mineral density. Patients should maintain adequate calcium and vitamin D intake. A gluten-free diet should prevent further bone loss and may improve bone density
- If patients do not respond to a gluten-free diet as expected they should seek medical advice because this may indicate gluten exposure or another condition that needs investigating
- Close family members have a one in 10 chance of having coeliac disease and current guidelines recommend offering serological testing for first degree relatives

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1 Ludvigsson JF, Rubio-Tapia A, van Dyke CT, Melton LJ 3rd, Zinsmeister AR, Lahr BD, et al. Increasing incidence of celiac disease in a North American population. *Am J Gastroenterol* 2013;108:818-24.
2 Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010;42:587-95.
3 Catassi C, Kryszak D, Bhatti B, Sturgeon C, Helzlsouer K, Clipp SL, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. *Ann Med* 2010;42:530-8.
4 Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, et al. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther* 2007;26:1217-25.
5 Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology* 2009;137:88-93.
6 Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120:636-51
7 van Heel DA, West J. Recent advances in coeliac disease. *Gut* 2006;55:1037-46.
8 Kochhar R, Sachdev S, Kochhar R, Aggarwal A, Sharma V, Prasad KK, et al. Prevalence of coeliac disease in healthy blood donors: a study from north India. *Dig Liver Dis* 2012;44:530-2.
9 Wang XQ, Liu W, Xu CD, Mei H, Gao Y, Peng HM, et al. Celiac disease in children with diarrhea in 4 cities in China. *J Pediatr Gastroenterol Nutr* 2011;53:368-70.
10 Esteve M, Rosinach M, Fernandez-Banares F, Farre C, Salas A, Alsina M, et al. Spectrum of gluten-sensitive enteropathy in first-degree relatives of patients with coeliac disease: clinical relevance of lymphocytic enteritis. *Gut* 2006;55:1739-45.
11 Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163:286-92.

Questions for future research

What is an effective follow-up strategy for patients with coeliac disease?

Is there a role for point of care tests in diagnosis or monitoring of adherence?

Will new treatments become a useful adjunct to a gluten-free diet?

Will genetically modified "non-toxic" wheat allow consumption of a normal diet in the future?

Tips for non-specialists

A duodenal biopsy is still needed to diagnose coeliac disease. Patients should remain on a gluten containing diet until biopsy is performed

Be aware of the complications of coeliac disease—including anaemia and micronutrient deficiency (vitamin D, calcium, vitamin B_{12}, folate, and iron), osteoporosis, and lymphoma—and monitor stable patients annually to make sure they remain well

Refer patients with persistent symptoms to an expert gastroenterologist, especially if they are losing weight, have severe micronutrient deficiency, or have other symptoms suggestive of malabsorption despite a gluten-free diet

A gluten-free diet is the only treatment that can prevent complications from coeliac disease. Although coeliac serological testing can be helpful in assessing the response to a gluten-free diet, an interview with an expert dietitian is the best method of assessing dietary adherence

Additional educational resources

Resources for healthcare professionals

National Institute for Health and Clinical Excellence. Coeliac disease: recognition and assessment of coeliac disease. 2009. www.nice.org.uk/nicemedia/pdf/CG86FullGuideline.pdf. Useful guideline that explains the diagnosis of coeliac disease and which patient groups should be tested

Ciclitira P, Dewar DH, McLaughlin SD, Sanders DS. The management of adults with coeliac disease. British Society of Gastroenterology, 2010. www.bsg.org.uk/images/stories/clinical/bsg_coeliac_10.pdf. Useful for the long term management of coeliac disease as well as initial diagnosis

Resources for patients

Coeliac UK (www.coeliac.co.uk)—National charity and advocacy group for people with coeliac disease and dermatitis herpetiformis

Celiac Disease Foundation. (www.celiac.org)—Provides support and information to people affected by coeliac disease

12 Rubio-Tapia A, Van Dyke CT, Lahr BD, Zinsmeister AR, El-Youssef M, Moore SB, et al. Predictors of family risk for celiac disease: a population-based study. *Clin Gastroenterol Hepatol* 2008;6:983-7.
13 Hadithi M, von Blomberg BM, Crusius JB, Bloemena E, Kostense PJ, Meijer JW, et al. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. *Ann Intern Med* 2007;147:294-302.
14 Berti I, Della Vedova R, Paduano R, Devetta M, Caradonna M, Villanacci V, et al. Coeliac disease in primary care: evaluation of a case-finding strategy. *Dig Liver Dis* 2006;38:461-7.
15 Hin H, Bird G, Fisher P, Mahy N, Jewell D. Coeliac disease in primary care: case finding study. *BMJ* 1999;318:164-7.
16 Mooney PD, Leeds JS, Libzo N, Sidhu R, Evans KE, Hall EJ, et al. Case-finding for coeliac disease in secondary care: A prospective multicentre UK study. *Dig Liver Dis* 2014;46:32-5.
17 van der Windt DA, Jellema P, Mulder CJ, Kneepkens CM, van der Horst HE. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. *JAMA* 2010;303:1738-46.
18 Davidson LS, Fountain JR. Incidence of the sprue syndrome; with some observations on the natural history. *BMJ* 1950;1:1157-61.
19 Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2013;62:43-52.
20 McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in north america: impact of serological testing. *Pediatrics* 2009;124:1572-8.
21 National Institute for Health and Clinical Excellence. Coeliac disease: recognition and assessment of coeliac disease. 2009. www.nice.org.uk/nicemedia/pdf/CG86FullGuideline.pdf.
22 Ciclitira P, Dewar DH, McLaughlin SD, Sanders DS. The management of adults with coeliac disease. British Society of Gastroenterology, 2010. www.bsg.org.uk/images/stories/clinical/bsg_coeliac_10.pdf.
23 Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656-76; quiz 77.
24 Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2013;11:359-65e1.
25 Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BM, Moayyedi P. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med* 2009;169:651-8.
26 Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136-60.
27 Sanders DS, Hurlstone DP, Stokes RO, Rashid F, Milford-Ward A, Hadjivassiliou M, et al. Changing face of adult coeliac disease: experience of a single university hospital in South Yorkshire. *Postgrad Med J* 2002;78:31-3.
28 Hadjivassiliou M, Sanders DS, Grunewald RA, Woodroofe N, Boscolo S, Aeschlimann D. Gluten sensitivity: from gut to brain. *Lancet Neurol* 2010;9:318-30.
29 Sainsbury A, Sanders DS, Ford AC. Meta-analysis: coeliac disease and hypertransaminasaemia. *Aliment Pharmacol Ther* 2011;34:33-40.
30 Leffler DA, Schuppan D. Update on serologic testing in celiac disease. *Am J Gastroenterol* 2010;105:2520-4.
31 Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). *Aliment Pharmacol Ther* 2006;24:47-54.
32 Naiyer AJ, Hernandez L, Ciaccio EJ, Papadakis K, Manavalan JS, Bhagat G, et al. Comparison of commercially available serologic kits for the detection of celiac disease. *J Clin Gastroenterol* 2009;43:225-32.
33 Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. *Aliment Pharmacol Ther* 2010;31:73-81.
34 Korponay-Szabo IR, Szabados K, Pusztai J, Uhrin K, Ludmany E, Nemes E, et al. Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. *BMJ* 2007;335:1244-7.
35 Mooney PD, Kurien M, Sanders DS. Simtomax, a novel point of care test for coeliac disease. *Expert Opin Med Diagn* 2013;7:645-5.
36 Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999;11:1185-94.
37 Hopper AD, Hadjivassiliou M, Hurlstone DP, Lobo AJ, McAlindon ME, Egner W, et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. *Clin Gastroenterol Hepatol* 2008;6:314-20.
38 Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011;106:508-14; quiz 15.
39 Carroccio A, Mansueto P, Iacono G, Soresi M, D'Alcamo A, Cavataio F, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol* 2012;107:1898-906; quiz 907.
40 Aziz I, Evans KE, Hopper AD, Smillie DM, Sanders DS. A prospective study into the aetiology of lymphocytic duodenosis. *Aliment Pharmacol Ther* 2010;32:1392-7.
41 Rosinach M, Esteve M, Gonzalez C, Temino R, Marine M, Monzon H, et al. Lymphocytic duodenosis: aetiology and long-term response to specific treatment. *Dig Liver Dis* 2012;44:643-8.
42 Leffler D, Schuppan D, Pallav K, Najarian R, Goldsmith JD, Hansen J, et al. Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. *Gut* 2013;62:996-1004.
43 Evans KE, Aziz I, Cross SS, Sahota GR, Hopper AD, Hadjivassiliou M, et al. A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. *Am J Gastroenterol* 2011;106:1837-742.
44 Hopper AD, Cross SS, Hurlstone DP, McAlindon ME, Lobo AJ, Hadjivassiliou M, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. *BMJ* 2007;334:729.
45 Biagi F, Andrealli A, Bianchi PI, Marchese A, Klersy C, Corazza GR. A gluten-free diet score to evaluate dietary compliance in patients with coeliac disease. *Br J Nutr* 2009;102:882-7.
46 Hall NJ, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. *Aliment Pharmacol Ther* 2009;30:315-30.
47 Sharkey LM, Corbett G, Currie E, Lee J, Sweeney N, Woodward JM. Optimising delivery of care in coeliac disease - comparison of the benefits of repeat biopsy and serological follow-up. *Aliment Pharmacol Ther* 2013;38:1278-91.

48 Kaukinen K, Sulkanen S, Maki M, Collin P. IgA-class transglutaminase antibodies in evaluating the efficacy of gluten-free diet in coeliac disease. *Eur J Gastroenterol Hepatol* 2002;14:311-5.
49 Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. *Gut* 2010;59:547-57.
50 Logan RF. Malignancy in unrecognised coeliac disease: a nail in the coffin for mass screening? *Gut* 2009;58:618-9.
51 Cooper BT, Holmes GK, Cooke WT. Lymphoma risk in coeliac disease of later life. *Digestion* 1982;23:89-92.
52 Gough KR, Read AE, Naish JM. Intestinal reticulosis as a complication of idiopathic steatorrhoea. *Gut* 1962;3:232-9.
53 Harris OD, Cooke WT, Thompson H, Waterhouse JA. Malignancy in adult coeliac disease and idiopathic steatorrhoea. *Am J Med* 1967;42:899-912.
54 Holmes GK, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease--effect of a gluten free diet. *Gut* 1989;30:333-8.
55 Holmes GK, Stokes PL, Sorahan TM, Prior P, Waterhouse JA, Cooke WT. Coeliac disease, gluten-free diet, and malignancy. *Gut* 1976;17:612-9.
56 Card TR, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. *Aliment Pharmacol Ther* 2004;20:769-75.
57 Olen O, Askling J, Ludvigsson JF, Hildebrand H, Ekbom A, Smedby KE. Coeliac disease characteristics, compliance to a gluten free diet and risk of lymphoma by subtype. *Dig Liver Dis* 2011;43:862-8.
58 West J, Logan RF, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. *BMJ* 2004;329:716-9.
59 Kane EV, Newton R, Roman E. Non-Hodgkin lymphoma and gluten-sensitive enteropathy: estimate of risk using meta-analyses. *Cancer Causes Control* 2011;22:1435-44.
60 Gale J, Simmonds PD, Mead GM, Sweetenham JW, Wright DH. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. *J Clin Oncol* 2000;18:795-803.
61 Novakovic BJ, Novakovic S, Frkovic-Grazio S. A single-center report on clinical features and treatment response in patients with intestinal T cell non-Hodgkin's lymphomas. *Oncol Rep* 2006;16:191-5.
62 Lebwohl B, Granath F, Ekbom A, Smedby KE, Murray JA, Neugut AI, et al. Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: a population-based cohort study. *Ann Intern Med* 2013;159:169-75.
63 Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med* 2003;115:191-5.
64 Silano M, Volta U, Vincenzi AD, Dessi M, Vincenzi MD, Collaborating Centers of the Italian Registry of the Complications of Coeliac D. Effect of a gluten-free diet on the risk of enteropathy-associated T-cell lymphoma in celiac disease. *Dig Dis Sci* 2008;53:972-6.
65 Meyer D, Stavropolous S, Diamond B, Shane E, Green PH. Osteoporosis in a North American adult population with celiac disease. *Am J Gastroenterol* 2001;96:112-9.
66 Passananti V, Santonicola A, Bucci C, Andreozzi P, Ranaudo A, Di Giacomo DV, et al. Bone mass in women with celiac disease: role of exercise and gluten-free diet. *Dig Liver Dis* 2012;44:379-83.
67 Bianchi ML, Bardella MT. Bone in celiac disease. *Osteoporos Int* 2008;19:1705-16.
68 Corazza GR, Di Sario A, Cecchetti L, Jorizzo RA, Di Stefano M, Minguzzi L, et al. Influence of pattern of clinical presentation and of gluten-free diet on bone mass and metabolism in adult coeliac disease. *Bone* 1996;18:525-30.
69 Ludvigsson JF, Olen O, Bell M, Ekbom A, Montgomery SM. Coeliac disease and risk of sepsis. *Gut* 2008;57:1074-80.
70 Barratt SM, Leeds JS, Sanders DS. Quality of life in coeliac disease is determined by perceived degree of difficulty adhering to a gluten-free diet, not the level of dietary adherence ultimately achieved. *J Gastrointestin Liver Dis* 2011;20:241-5.
71 Hallert C, Lohiniemi S. Quality of life of celiac patients living on a gluten-free diet. *Nutrition* 1999;15:795-7.
72 Barratt SM, Leeds JS, Robinson K, Shah PJ, Lobo AJ, McAlindon ME, et al. Reflux and irritable bowel syndrome are negative predictors of quality of life in coeliac disease and inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2011;23:159-65.

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Tables

Table 1| Modified Marsh criteria for the histological diagnosis of coeliac disease

Marsh-Oberhuber stage	Description
Stage 0	Normal duodenal mucosa
Stage 1	Increased intraepithelial lymphocytes (IELs) >25 IELs/100 enterocytes (non-specific finding)
Stage 2	Stage 1 plus crypt hyperplasia (non-specific finding)
Stage 3a	Increased IELs, crypt hyperplasia, and partial villous atrophy
Stage 3b	Increased IELs, crypt hyperplasia, and subtotal villous atrophy
Stage 3c	Increased IELs, crypt hyperplasia, and total villous atrophy

Table 2| **Treatments under development**

New treatment	Mechanism
Genetically modified wheat	Strains of wheat in which gluten is absent or doesn't trigger an immune response
Therapeutic vaccine	Desensitisation to gluten
Zonulin inhibitors	Reduce intestinal permeability
Transglutaminase inhibitors	Block transamidation of gluten
Probiotics	Reduce intestinal inflammation and accelerate mucosal healing on a gluten-free diet
Peptidases	Enzymatically degrade gluten in the gut