British Society of Gastroenterology

The Management of Adults with Coeliac Disease

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Summary

There is clear evidence that coeliac disease is a common gastrointestinal disease affecting up to 1% of the adult population. Individuals may go undetected for many years. This is despite multiple presentations to both primary and secondary care. This may reflect that fact that affected individuals have subtle gastrointestinal symptoms or no gastrointestinal symptoms.
An active case finding strategy will increase the number of patients detected with coeliac disease. Testing for coeliac disease should incorporate an IgA level, Tissue Transglutaminase antibody and/or Endomysial antibody (depending on what is locally available). In patients with a positive antibody a duodenal biopsy should be undertaken to confirm the presence of villous atrophy. In patients who are antibody negative but the clinician is suspicious then a duodenal biopsy should still be undertaken having ensured that the patient is not on a self-imposed gluten-free diet (GFD).
The cornerstone of treatment is a GFD. Patients require regular dietetic support with the opportunity or access to a gastroenterologist should further problems arise. Follow-up may be in primary or secondary care as long as the support is adequate (as noted previously).
In patients with persisting symptoms they should be investigated carefully with particular reference to ensuring that refractory coeliac disease is excluded.

Advice for commissioners

The diagnosis of coeliac disease could be optimised by offering remuneration for the number of cases of coeliac disease diagnosed in primary care in a similar fashion to the quality and outcomes framework initiative.
There is a significant shortfall in dietetic services throughout the UK. Coeliac UK (National Patient Charity) have estimated that there is only 1 hour of a dieticians' time per month of 100,000 population in 25% of units currently available to provide this service. There is an urgent need to provide increased funding to dietetic services nationwide in order to ensure that patients with coeliac disease are optimally managed. This approach could also potentially be cost-effective if the dietetic service were to replace current consultant capacity for the provision of this service.

1.0 Preface

1.1   Purpose of Guidelines

These guidelines are intended to assist in the diagnosis and clinical management of adults with coeliac disease within the United Kingdom. These guidelines are primarily intended for adult patients. Coeliac disease in children presents a different clinical context with specific management challenges. Separate guidelines exist but the issue of childhood coeliac presentation is discussed here briefly.

1.2   Formulation of guidelines

The guidelines were compiled following a comprehensive literature search. The principle authors circulated an initial draft to other authors whose suggested inclusions and changes were then incorporated.

A considerable bulk of literature exists regarding the serological, histological and clinical features of coeliac disease. These guidelines aim to provide a current consensus on which to base the diagnosis and management of coeliac disease but clearly future research is likely to clarify some unresolved questions. Many aspects of coeliac disease have not been fully defined or evaluated prospectively. In part, this is due to the difficulty in designing appropriate and ethical studies in these areas. Where there is insufficient evidence, the authors have relied on a reasonable and safe consensus of opinion in formulating appropriate guidelines based on current evidence.

1.3   Grading of recommendations
Recommendations are graded in accordance with the available category of evidence, as outlined by the North of England evidence-based guidelines development project (1). These are summarized below.

Ia – Evidence obtained from meta-analysis of randomised controlled trials.
Ib – Evidence obtained from at least one randomised controlled trial.
IIa – Evidence obtained from at least one well designed controlled study without randomisation.
IIb – Evidence obtained from at least one other type of well designed quasi experimental study.
III – Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case studies.
IV – Evidence obtained from expert committee reports or opinions, or clinical experiences of respected authorities.

Grade A – requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency, addressing the specific recommendation (evidence categories Ia, Ib).
Grade B – requires the availability of clinical studies without randomisation on the topic of recommendation (evidence categories IIa, IIb, III).
Grade C – requires evidence from expert committee reports or opinions, or clinical experience or respected authorities, in the absence of directly applicable clinical studies of good quality (evidence category IV).

1.4   Authorship and scheduled review of guidelines

The authors comprise practising Gastroenterologists with a special interest in coeliac disease. Input and feedback was sought from both paediatric gastroenterology, and gastroenterologists without a specialist interest in coeliac disease. The guidelines were then reviewed by the BSG small bowel and nutrition committee. This document replaces the previously published guidelines and the content will be reviewed in the light of future developments and available evidence.

2.0 Introduction

2.1 Overview and terms

Coeliac disease is an inflammatory condition of the small intestinal mucosa that is induced by the ingestion of gluten and which improves clinically and histologically when gluten is excluded from the diet. The disorder is alternatively termed 'coeliac sprue' or 'gluten-sensitive enteropathy'. The term 'gluten' is often used, as it is here, as a generic term to collectively describe all the cereal proteins that are toxic to individuals with coeliac disease. Wheat, barley and rye have all been shown to cause intestinal inflammation in coeliac patients, but the possible toxicity of oats continues to be debated.

Coeliac disease is a common condition, affecting up to 1 in 100 individuals in the UK. The previous belief that coeliac disease was restricted to populations in Northern Europe has been dispelled by recent epidemiological studies, confirming similar prevalence in Caucasian populations worldwide. In clinical practice, the number of people diagnosed with coeliac disease falls far short of the expected prevalence, suggesting that there is a large excess of undiagnosed cases in the population, possibly by a five or ten-fold multiple of existing patients. This situation has been described as the 'coeliac iceberg'. Many of these individuals may have no gastrointestinal symptoms and could be described as 'atypical' coeliac disease. It is now accepted that 'typical' coeliac disease encompasses patients presenting with gastrointestinal symptoms (even if they are subtle) and/or anaemia.

Coeliac disease is diagnosed by small intestinal biopsy with characteristic morphological changes, typified by villous atrophy and intra-epithelial lymphocytosis. These abnormalities improve when gluten is excluded from the diet, and can be shown to recur with a gluten challenge.

The availability of serological tests for coeliac specific antibodies has made it easier to investigate cases of possible coeliac disease. Improved detection and awareness has resulted in an increase in the diagnosis, particularly in those without the 'typical' gastrointestinal symptoms and/or anaemia. These patients are often described as having 'atypical' coeliac disease although they may now account for a considerable proportion of newly diagnosed patients. Coeliac disease can present at any age and has a wide range of clinical manifestations. The average age of diagnosis has risen and in the UK it is now between the 4th to 6th decade (Coeliac UK 2005).

Coeliac disease has been shown to be associated with substantial morbidity and an increase in mortality above age-matched controls. The risks appear to be reduced by treatment with a gluten-free diet, which requires specific modification of food intake under the guidance of an experienced dietician.

2.2 Epidemiology

Epidemiological studies in the UK have indicated the prevalence of coeliac disease to be between 0.5-1.0%. There are figures of the same order of magnitude in Caucasian populations worldwide including the USA, South America (2) and Australia (3). We had thought that coeliac disease almost exclusively affected people of European origin. However, serological screening has revealed that coeliac disease is common not only in Europe and in people of European ancestry but also in other racial groups, for example, in developing countries where the major staple diet is wheat (Southern Asia, the Middle East, North West and East Africa, South America) (3). There may be geographical sparing in regions that have a rice-based diet. Nevertheless the strongest determinant may still be the prevalence of genes predisposing to coeliac disease (HLADQ2 and DQ8).

There is a clear gap between the estimated prevalence of coeliac disease in the general population and the number of people who have actually been diagnosed. This suggests that there is a large excess of undiagnosed individuals, possibly as many as 5-10 cases for each existing patient (4). In the US, with an expected prevalence of about 1%, the number of registered cases amounts to only about 1 in 1000 of the population (5).

2.3 Genetics of coeliac disease

Coeliac disease occurs in genetically susceptible individuals, related to possession of particular HLA class II molecules(6). Approximately 95% of patients express HLA-DQ2 and the remainder express DQ8. Twenty to thirty percent of the general population are HLA-DQ2 positive, so clearly there are other, as yet, unidentified factors determining the onset of coeliac disease in a fraction of this group. It is estimated by linkage studies that HLA genes account for only 40% of the heritability of coeliac disease. HLA typing indicating lack of DQ2 or DQ8 has a high negative predictive value for coeliac disease and may occasionally be helpful in excluding the diagnosis in ambiguous cases. Recent genetic studies have also indicated that HLA may not be the only contributing genetic factor (7).

2.4 Cereal toxicity and disease pathogenesis

Coeliac disease is induced by an immunological response to a normal constituent of our diet. Inflammation in the small intestine is precipitated by storage proteins derived from the closely related cereals, wheat, rye and barley. These grains have been selected for high protein content, specifically for their dough-forming properties and optimal baking characteristics.

Wheat, rye and barley have been demonstrated to be toxic in coeliac patients. In wheat these proteins can be obtained by washing out the starch, leaving a cohesive mass known as gluten. Gluten can be further separated into gliadins (prolamin fraction) and glutenins,

based on their solubility in ethanol. In rye and barley, the prolamin fractions are called secalins and hordeins respectively. The term 'gluten' is often used to refer to all these proteins for simplicity. The structural basis of these fractions has been studied extensively with much of the work focusing on wheat and gliadin. As there are no animal models of coeliac disease, studies of disease pathogenesis have relied on intestinal organ culture *in vitro* (8), T cell studies (9) and *in vivo* challenges (10). In patients with coeliac disease, whether treated or untreated, CD4+ T cells can be cultured from the intestinal mucosa, that are specific to gluten. These gluten sensitive T cells can be shown to react to particular peptide fragments, which has led to the theory that coeliac disease is a T cell mediated disease against toxic epitopes within gluten. An immunodominant peptide, to which the majority of coeliacs react, has been described in one region of gliadin (9). The antigenicity of this peptide is greatly enhanced by deamidation, which is mediated by the enzyme tissue transglutaminase. Antibodies to tissue transglutaminase can be found in the circulating blood of coeliac patients who are consuming gluten and levels falls on a gluten free diet (11).

3.0 **Clinical Presentation**

3.1 The changing pattern of incidence

Coeliac disease can present at any age and has a wide spectrum of clinical manifestations. In the developed world, there has been a shift in the observed pattern of incidence. The classical presentation of the malnourished, lethargic child is uncommon. In contrast, many more cases of coeliac disease are being diagnosed in adults. In the UK, the average age of diagnosis is now over the age of 40 (Coeliac UK 2001). In two studies, 20% of newly diagnosed cases were in those aged over 60 years(5,12). In those over 60 years the delay in diagnosis may be particularly substantial (11). The clinical diagnosis of coeliac disease remains twice as common in women (3), which may be due to greater symptom reporting in females.

More cases of coeliac disease are now diagnosed as a result of testing patients without gastrointestinal symptoms (atypical presentation). Clinicians are more aware of the atypical manifestations of coeliac disease. Diagnosis is often now made outside the gastroenterology clinic, in primary care or in other specialty clinics. However, many of the associations reported may be limited by only reporting case series and not using case control methodology (13).

3.2 Natural history of coeliac disease

Gluten is generally introduced to the diet after one year and yet many individuals will not develop manifestations until later in life. A proportion of adults with positive coeliac serology have normal small bowel histology or marginal abnormalities without villous atrophy. These observations have led to the proposition of the condition of 'latent' or 'potential' coeliac disease(14,15). The risks of 'latent' coeliac disease are not clear, but these individuals may have the potential to develop coeliac disease with villous atrophy (16). It is acknowledged that patients often suffer symptoms for an extended period prior to the eventual diagnosis

of coeliac disease(17). Sometimes patients describe a trigger event such as gastroenteritis, overseas travel, stress or surgery. Coeliac disease does not appear to remit and is therefore a lifelong condition. Despite this, patients are seen who were diagnosed as having coeliac disease in childhood who do not now adhere to a gluten-free diet with no apparent detriment. In some cases, these individuals were advised to return to gluten consumption in adulthood but others were lost to follow up and voluntarily returned to a normal diet. One possible reason for this is that an incorrect diagnosis of coeliac disease was made in childhood.

More recently, for the first time a Finnish group have reported falling levels of antibodies over time in individuals who were suspected of having coeliac disease. These individuals were not on a gluten-free diet but they initially had positive antibody profiles. This may suggest that some individuals eating a normal diet (ie gluten containing) can avoid developing coeliac disease if they alternatively develop an immune tolerance of gluten (18).

3.3 Presentation in childhood

In the past coeliac disease was inextricably associated with childhood, but the changing incidence finds that only 9% of all coeliac patients are diagnosed under the age of 16 years (Coeliac UK 2005). This is partly due to the exclusion of gluten in infant formula and the increase in diagnosis rate in the adult population. However, studies have found equivalent rates of positive coeliac serology in children as in the adult population(19-22), suggesting that the disease predisposition is evident from early in life. Symptoms in children depend on the age at presentation. Under the age of two years the clinical picture is characterized by a lethargic or irritable child, with loose pale stools and a bloated abdomen. In infants vomiting, anorexia and constipation may be seen. Between the ages of 2 and 16 years coeliac disease presents with gastrointestinal symptoms, nutritional deficiencies and impaired growth. Short stature or growth delay may be picked up during weight and height assessment with sufferers falling below their expected centile. Anaemia or delayed bone age may be identified during unrelated testing. First degree relatives of individuals with coeliac disease have a 1 in 10 chance of also being affected (23-25). Children with Down's Syndrome have a 3.2-10.3% chance of having coeliac disease (26,27). As in adults, diarrhoea, abdominal pain and lethargy may occur.

3.4 Gastrointestinal symptoms in adults

Spectrum of severity

There is a spectrum of gastrointestinal presentation ranging from generalized malabsorption to those with mild abdominal symptoms. Coeliac disease affects the proximal small bowel with variable sparing of the ileum distally. The small intestine has considerable functional reserve and there appears to be a variable sensitivity to gluten between patients. Progressive involvement of the distal small bowel leads to the onset of typical gastrointestinal manifestations such as diarrhoea or nutrient malabsorption (28). Severe cases of malabsorption are uncommon but are still often described as the classical presentation. These patients may present dramatically with protein-energy malnutrition, weight loss, steatorrhoea, abdominal distension, low serum albumin and electrolyte disturbances. (29)

Symptoms

The majority of symptomatic individuals present with the gradual onset of gastrointestinal symptoms with diarrhoea, abdominal pain, bloating and often the observation that these problems are exacerbated by consuming certain foods. Other persistent or unexplained gastrointestinal symptoms may also occur such as nausea and vomiting. Overall, diarrhoea occurs in less than 50% of patients at presentation compared with nearly 100% of patients who presented in the 1960s (17,30). Abdominal pain, bloating and altered bowel habit may occur in the absence of malabsorption and this picture may be indistinguishable from irritable bowel syndrome. Patients satisfying the Rome II criteria have a 5% risk of having undiagnosed coeliac disease as the cause of their symptoms and therefore this group should be screened with serological testing (31). Weight loss is an uncommon feature and tends to signify a dramatic presentation with more extensive disease. In contrast, at least 30% of patients are overweight at time of diagnosis(17,32). Constitutional symptoms such as lethargy, low mood and poor appetite are frequently reported in association or on their own.

Signs

Abnormal clinical signs are uncommon in uncomplicated coeliac disease. Weight and height should be recorded, particularly as short stature may be a presenting feature. Patients should be examined for oral apthous ulceration, angular stomatitis, skin rashes and clinical evidence of anaemia, all of which are associated with coeliac disease. Abdominal examination may reveal mild tenderness and increased bowel sounds. In severe cases there may be evidence of abdominal distension, peripheral oedema, leuconychia and excessive bruising.

Malabsorption

Intestinal inflammation and increased intestinal transit can be significant enough to result in impaired macronutrient absorption and a negative calorie and protein balance, which can be exacerbated by anorexia. Under these circumstances patients become catabolic and lose weight. Less extensive involvement results in specific nutrient deficiencies. Deficiencies of iron, folate, calcium, B_{12} and fat-soluble vitamins D, E and K are found in coeliac disease. Correspondingly patients can develop anaemia, osetomalacia and, rarely, clotting disorders.

3.5 <u>Anaemia, haematological and biochemical features</u>

Anaemia

Anaemia is now a common presentation of coeliac disease and the diagnosis should be considered in patients undergoing evaluation for anaemia. The prevalence of coeliac disease in patients with uncomplicated iron deficiency anaemia varies from 3-12% (33). In all anaemic patients undergoing a gastroscopy as part of their evaluation, distal duodenal biopsy should be performed. At least 50% of coeliacs have evidence of anaemia at presentation (34), although this figure may be biased towards symptomatic individuals. Iron deficiency is the commonest picture followed by low folate, which when combined may

result in a mixed picture. The blood film may show either a hypochromic, microcytic or a dimorphic appearance. B_{12} deficiency may not be expected as absorption is co-factor dependent and occurs in the, often unaffected, terminal ileum. However, B_{12} levels are statistically lower in coeliacs compared with controls and 12% of patients have actual deficiency. This does not appear to be due to an association with autoimmune gastritis[35]. Some individuals may be identified who have demonstrably low stores of iron or folate in the absence of anaemia. The haemoglobin returns to normal with a gluten free diet although deficiencies may need to be corrected to expedite recovery [36].

Other haematological and biochemical abnormalities

Abnormal liver function may be noted in newly diagnosed patients with coeliac disease. The aetiology is thought to be a non-specific hepatitis. It is anticipated that the liver function abnormalities (predominantly an elevation of the transaminases) are reversible and will normalise within 6-12 months on a GFD. Some coeliac patients may have liver function abnormalities due to associated unrecognised autoimmune diseases (primary biliary cirrhosis, autoimmune hepatitis or primary sclerosing cholangitis). Finally it is possible to have undiagnosed coeliac disease as the underlying cause for patients who may be referred primarily with abnormal liver function [37,38].

In older patients there may be features of hyposplenism on the blood film [39] (Howell-Jolly bodies, target cells and elevated platelet count). In marked malabsorption, hypoalbuminaemia is seen and prothrombin time may be prolonged due to vitamin K deficiency.

3.6 <u>Non-gastrointestinal manifestations and disease associations</u>

Autoimmune diseases

Coeliac disease has been shown to be associated with other autoimmune conditions. Individuals with type I diabetes have been shown to have a 4-7% chance of having concomitant coeliac disease [40-43]. There is limited data to suggest that that glycaemic control and insulin requirements may be improved by a gluten-free diet. A similar increased prevalence of coeliac disease is found in autoimmune thyroid disease [44,45] and some rarer conditions such as Addison's disease, autoimmune hepatitis and alopecia areata. Certain connective tissue diseases have been reported in case series as possibly associated with coeliac disease (Sjogren's disease, Systemic Lupus Erythomatosis) [13,46]. These patients are often routinely sampled for auto-antibody titres and coeliac serology [46] may be found to be positive, requiring further investigation. Refractory or disproportionate anaemia in such groups may be explained by co-existence of coeliac disease. The risk of autoimmune diseases may be reduced by following a gluten free diet however the data assessing this relationship is conflicting [47-49].

Dermatitis herpetiformis

Dermatitis herpetiformis is a cutaneous manifestation of coeliac disease..The rash can precede any evidence of enteropathy and only 20% have gastrointestinal symptoms. It

manifests as an intensely itchy, blistering rash on the trunk and extensor surfaces of the limbs. Diagnosis is confirmed by skin biopsy of an adjacent non-blistered area. In 98% there is granular deposition of IgA at the papillary dermo-epidermal junction (50). Nearly 100% have an abnormal duodenal biopsy if serial samples are taken but inflammation may be minor, patchy, or distal and be missed initially. A gluten-free diet is advised but improvement will often take 6-12 months to be seen. Dapsone at a dose of 50-100 mg daily is usually prescribed for this initial period and continued thereafter at the minimum dose required to control the rash. Dapsone has no effect on any of the other manifestations of coeliac disease.

Neurological and Psychological illness

Patients with coeliac disease can exhibit a varied range of unexplained neurological disorders (51), such as peripheral neuropathy, cerebellar ataxia (52), myopathy (53), epilepsy with cerebral calcifications (54,55), myelopathy, encephalopathy , cranial nerve palsy, migraine, haedache or combinations of these (51-55). The role of associated circulating anti-neuronal antibodies is unclear (56). Some patients develop psychological disturbances and may exhibit frank psychosis. Depression and low mood are seen more commonly in coeliac patients, although this may result from physical morbidity. These symptoms often respond at least partially to a gluten-free diet but not in all cases (57). Vitamin and trace element supplementation has been tried as some cases have been reported to respond to vitamins A, B and E.

Fertility and pregnancy

Coeliac disease is associated with amenorrhoea and subfertility (58). Women are more likely to suffer recurrent miscarriage, low birth weight children and increased infant mortality(59,60). Women presenting to infertility clinics may be investigated for occult coeliac disease. Males can be similarly affected with subfertility and indirectly with low birth weight children (61,62).

Other rare presentations

As coeliac disease was initially assumed to be uncommon, a large number of associations have been reported in the literature (13,63). Some of these apparent associations are likely to be due to chance and unlinked cases of rare conditions are not reported. The place of malignancy is discussed in 6.3.

4.0 **Investigation and diagnosis of coeliac disease**

4.1 Coeliac Serology

It was recognized over thirty years ago that certain circulating antibodies were specific to patients with coeliac disease. Titres of these antibodies fall when a gluten-free diet is

instigated. Anti-gliadin antibodies were first identified in 1971 and found to be sensitive in predicting coeliac disease. Early tests detected anti-gliadin antibodies but the sensitivity and specificity ranges from 60-80% in clinical practice. A recent assessment of their use demonstrated at best a specificity of 82%, with IgA class being better than IgG, but with poor reproducibility of 62% (64). Most centres no longer use gliadin antibodies in the diagnostic work-up for coeliac disease but there has been recent interest in the role of deamidated gliadin antibodies. However, further work is required to validate these preliminary observations (65).

IgA endomysial antibodies (EMA) were shown to be highly specific for coeliac disease with values in excess of 99% reproduced in several studies. However this test is labour intensive and uses indirect immunofluorescence on human umbilical cord or monkey oesophagus, giving a specific subjectively assessed staining pattern. Initial reports quoted sensitivity values of 100% or near but in clinical practice reports suggest a lower figure in the range 80-95%(66,67). The major auto-antigen for EMA was found to be tissue transglutaminase, a ubiquitous intracellular enzyme which is involved in disease pathogenesis.

With increasing numbers of individuals being tested for coeliac disease, it is important to use a satisfactory method for testing serum samples. As IgA EMA is the most specific test it might be attractive to use this in isolation. However this is likely to underestimate the prevalence and case finding by 20%. Added to this is the labour-intensive method for EMA tests. It is common practice to test for either TTG antibody and/or EMA. Most centres will concurrently ensure that IgA deficiency is not present by checking an IgA immunoglobulin level. Some centres are using IgG based tests as an alternative if IgA deficiency is present. All of these tests can become negative on a gluten-free diet, usually by one year but often titres fall sooner. Before testing, gluten intake should be confirmed and noted to avoid a false negative. It should be remembered that these serological tests are prone to cross-reactivity and error. Their use cannot replace the gold-standard of duodenal biopsy in diagnosing coeliac disease. In ambiguous cases where the individual may have already commenced a gluten-free diet – HLA typing may be beneficial to either refute or support the diagnosis.

IgA tissue transglutaminase antibodies (TTG) have been shown to have both high sensitivity and high specificity at 98% and 95% respectively, with a high correlation with EMA results. TTG tests have the advantage that they rely on an enzyme-linked immunosorbent assay (ELISA). This is simpler, cheaper and can be performed in batches. Use of guinea pig TTG has been largely replaced by use of human recombinant TTG, which allows better standardization. False positives are more likely to occur with an ELISA system as cross-reactivity of antibodies in the serum can occur, particularly in patients with autoimmune diseases.

It has become practice in many laboratories therefore to use a combination of TTG and EMA testing. One method is two step testing - samples are initially tested for IgA TTG antibodies and positive results are then tested using an EMA test; positive EMA individuals should be referred for duodenal biopsy. Those with only TTG positive results need to be considered for further evaluation but the majority of these have antibody titres at the lower range compared with those who are also EMA positive.

There are several pitfalls in evaluating coeliac serology. IgA tests have excellent specificity but IgA deficiency is over-represented in coeliac disease with 2.5% of cases being affected,

compared with 0.25% overall prevalence. These individuals may have no detectable IgA isotype antibodies but may produce positive results for IgG TTG or EMA.

Although EMA is very specific recent work has demonstrated that the sensitivity is much lower in those with less severe lesions (68,69).

Additionally, it is important to note that the sensitivity of these tests vary between laboratories and that some authorities have reported low sensitivity in the region of 50-60% for these tests. Knowledge of the local availability of these tests will help the clinician understand the limitation of a negative result. If the clinical suspicion is high (anaemia, family history of coeliac disease, symptoms etc.) then gastroscopy and duodenal biopsy should be performed (29).

4.2 <u>Small bowel histology</u>

Diagnosis of coeliac disease requires a small intestinal biopsy, which can be easily obtained during routine upper gastrointestinal endoscopy. A duodenal biopsy is the 'gold standard' for the diagnosis of coeliac disease. Duodenal biopsy should be performed in all patients suspected of having coeliac disease and all those who merit exclusion of coeliac disease. The diagnostic value of duodenal biopsy is extremely good with high positive and negative predictive values and the additional risk of performing a biopsy is very small. Duodenal biopsies should be taken in those with positive coeliac antibodies, iron deficiency anaemia, folate deficiency, osteomalacia, malabsorption, abnormal duodenal appearances and significant unexplained weight loss. Negative coeliac serology should not preclude duodenal biopsy in those who have other indications (70).

Duodenal appearances at endoscopy

Visible abnormalities have been described at endoscopy such as mucosal pallor, visible vessels, mosaic pattern, micro nodular appearance, scalloping and reduction in duodenal folds. These changes have been shown to correlate with degrees of villous atrophy (71) but appearances are often normal and this cannot be relied upon for diagnosis (72). The use of magnifying endoscopes can readily identify marked villous atrophy but offers no advantage with a reduced sensitivity, compared with the gold standard of a biopsy.

Pathological analysis and potential pitfalls in diagnosing coeliac disease

It is important to note whether patients are currently consuming gluten and whether samples are taken for diagnosis, to check for mucosal recovery or as part of a gluten challenge. The histological abnormalities in the small bowel mucosa are usually more pronounced proximally and therefore samples taken from the second part of the duodenum or beyond should be representative. Certain patients in specialist centres occasionally require a more distal biopsy and this can be carried out by suction capsule (in children) or push enteroscopy. At least four samples should be taken with large forceps to ensure that decent sized specimens are obtained for analysis and that patchy changes are less likely to be missed. Despite this practice, false negatives can occur (73,74) . If the clinical suspicion is high, repeat duodenal biopsy or sampling of more distal small bowel should be considered. Immunosuppression can also be an important cause of falsely normal or equivocal histology.

Specimens should be correctly orientated prior to mounting, preferably with low powered magnification, and then cut to 3 or 4 μm thickness. In assessing villous height and crypt depth, it is necessary to identify at least 3 or 4 intact adjacent villi that are cut perpendicularly. Tangentially cut sections can lead to an artificial appearance of villous atrophy and a potential over-diagnosis of coeliac disease(75). Additionally, villi adjacent to lymphoid follicles are often blunted in normal individuals so analysis of these areas should be avoided. If specimens show evidence of Brunner's glands, gastric metaplasia, and duodenitis then the sample should be disregarded and repeated more distally. Conversely, there has been recent interest and support for also taking a duodenal bulb biopsy (76).

The characteristic histological findings are blunted or flat villi, hyperplastic crypts, loss of surface enterocyte cell height and a lymphocytic infiltration of the lamina propria. These changes occur in response enterocyte injury, mucosal inflammation and increased epithelial proliferation. There is a specific increase in the number of intra-epithelial lymphocytes (IELs) above normal, particularly at the villous tips (77). This is the earliest discernable abnormality using light microscopy.

Classification of coeliac lesions (78,79)

The Marsh classification has been adopted to describe the progression of the abnormalities in the coeliac mucosa. The initial categorization has been modified slightly to improve its application in clinical practice, although its use is not universal. A Marsh type I lesion (termed 'infiltrative') comprises normal mucosal architecture with a lymphocytic infiltration of the villous epithelial layer. The arbitrary threshold for a normal IEL count is debated but generally in excess of 40 per 100 surface enterocytes is taken to denote a significant elevation. Staining for CD3 can be used to facilitate identification and counting of IELs. A Marsh II lesion ('hyperplastic') exists if, in addition to a lymphocytosis, there is crypt hyperplasia demonstrated by crypt branching and elongation, and increased mitotic activity. The villus height/crypt depth ratio (VH/CD) will often become reduced below a normal value of 3-5. The hallmark of Marsh III lesions ('destructive') is villous atrophy. Marsh IIIA denotes partial villous atrophy, which is denoted as a VH/CD ratio below 1. Marsh IIIB describes subtotal villous atrophy where separate villi are still recognizable. Marsh IIIC is characterized by total villous atrophy with no discernable digitations, resembling colonic mucosa. A Marsh IV lesion ('hypoplastic') describes a rare histological finding of a flat, atrophic mucosa thought to signify irreversible injury due to chronic inflammation. It appears that these abnormalities are related to refractory coeliac disease and the development of enteropathy associated T cell lymphoma. In these conditions, an abnormal monoclonal T lymphocyte population with an aberrant phenotype has been demonstrated. These cells are highly specific, such that their presence may represent a cryptic intestinal lymphoma (80).

Minimal change lesions

As with the clinical presentation of coeliac disease, it is recognized that the pathological lesion is part of a spectrum of severity, with more subtle abnormalities constituting a significant number of the cases. Traditionally a diagnosis of coeliac disease was made on finding mucosal abnormalities equivalent to a Marsh III lesion. It is now clear that many

individuals have gluten-sensitive inflammation without villous atrophy. These borderline histological abnormalities have been shown to improve on a gluten-free diet (81). Marsh I lesions pose a particular problem as their interpretation is often controversial with poor inter-observer correlation. Added to this the natural history has not been elucidated. It is not yet known whether these individuals have the same adverse health risks as the traditional coeliac with villous atrophy. The morbidity data that is currently available is largely obtained from those who were symptomatic and were diagnosed with villous atrophy. This data cannot logically be extrapolated to apply to those with Marsh I-II lesions. Clearly if an individual has symptoms or clinical manifestations attributable to coeliac disease, a gluten-free diet should be advised. The decision is more difficult in the case of an apparently healthy person with positive coeliac serology and a Marsh I lesion. It may be difficult to convince such a person to follow a gluten-free diet, although it should be noted that some asymptomatic individuals report unexpectedly feeling better on a gluten-free diet (81). Further work is required to characterize the natural history and relative health risks of borderline lesions (82). However it may at least be prudent to follow these patients in clinical practice, to look for the development of potential complications such as anaemia and osteoporosis. It should be remembered that an intra-epithelial lymphocytosis is a non-specific response to any adverse stimulus in the intestine and can also be found transiently in healthy individuals who do not have coeliac disease. In one study, approximately 10% of individuals with an unexplained elevated IEL count went on to be diagnosed with coeliac disease, although suspected coeliacs had already been excluded (83). An elevated IEL count in itself is insufficient to diagnose coeliac disease and requires correlation with clinical symptoms, serological parameters and HLA typing. However, not all individuals with these minor abnormalities will be identified using coeliac antibody testing. Many early studies reporting on the sensitivity of coeliac antibody tests focused on Marsh III lesions and did not include many cases with lesser changes. The literature suggests that the sensitivity of TTG antibody and EMA may be much lower in Marsh I and II lesions (84), which further adds to the diagnostic dilemma.

Repeat small bowel biopsy

Central to the pathology of coeliac disease is the demonstration that these abnormalities improve with a gluten-free diet and then recur with a further gluten challenge. Clearly this series would require three separate endoscopic procedures and the re-introduction of gluten with the potential to cause further illness. For this reason, many clinicians base the diagnosis on as single characteristic biopsy supported by positive serology. There is no consensus between the guidelines produced by several advisory bodies (85,86)(UEGW working group 2001).

Repeat biopsy to check mucosal recovery on a gluten-free diet has some benefits. Demonstration of histological improvement makes the diagnosis more secure and allows the physician to check adequate adherence with the gluten-free diet. This information is also reported as being re-assuring to the patient. A recovery biopsy also provides a comparison if patients should develop future problems, as a further examination of small bowel histology is often required as part of their assessment.

The argument against performing a second endoscopy is that it is an unnecessary expense and a further invasive procedure. The information obtained will not necessarily influence management and is viewed as being superfluous by some physicians. Coeliac serology can

be used as an approximate marker of dietary adherence, although a fall in titre does not necessarily correlate with histopathological improvement. Mucosal recovery has been shown to be protracted in some individuals and may take over 18 months (87). At one year, a percentage of biopsies will be abnormal due to non-adherence or despite a strict gluten free diet. The treatment advice - to adhere to a gluten-free diet - is the same irrespective of the biopsy results. However, re-education by a dietitian specialised in coeliac disease may be beneficial to the patient. In straightforward cases, where patients report symptomatic improvement and a fall in coeliac antibody titres on a gluten-free diet, there is no clear need for a repeat biopsy. In those whose antibodies do not fall within 12 months, dietary adherence should be checked and repeat biopsy performed as necessary by mutual consent. In cases where there is diagnostic ambiguity a recovery biopsy is likely to be helpful. Particular examples are patients with initial negative serology, patients with continued symptoms, and those with minimal or ambiguous histological changes.

Gluten challenge is now rarely performed unless there is diagnostic difficulty. The most likely scenario for needing to gluten challenge is in a patient who is already on a gluten free diet despite not having been diagnosed with coeliac disease. With increasing public awareness of coeliac disease, individuals may modify their diet prior to attending their physician. For example, patients with irritable bowel syndrome (who do not have coeliac disease) may report symptomatic improvement with the restriction or total exclusion of wheat from the diet. The improvement is usually not sustained, particularly as a wheat-free diet tends to be low in fibre. A diet low in gluten may normalize small bowel histology (and coeliac serology) and thus gluten intake should be resumed prior to testing. There is little published evidence that delineates the role of gluten challenge in clinical practice. One group of investigators were able to induce a deterioration in histology for those with initial borderline changes. However, this study required patients to consume large quantities (30 grams) of gluten per day (88,89). Some experts recommend that formal gluten challenge should comprise a daily intake of approximately 10 g gluten and this can be achieved by consuming four slices of bread each day for a minimum of 4 to 6 weeks. If patients should be particularly symptomatic it may be helpful to shorten this period, as 2 weeks may be satisfactory. The development of symptoms on gluten challenge is not sufficient to make the diagnosis. This whole process is a pragmatic approach and is an area which requires further evaluation and research (13,90,91).

Differential diagnosis

Coeliac disease is the commonest cause of enteropathy by some margin. However, it should be appreciated that villous atrophy and an intra-epithelial lymphocytosis are not exclusive to coeliac disease. Other causes of enteropathy can be responsible such as infective gastroenteritis, bacterial overgrowth, lactose intolerance, giardiasis, anorexia nervosa, ischaemic enteritis, tuberculosis, Crohn's disease, hypogammaglobulinaemia, tropical sprue, Whipple's disease, collagenous sprue, autoimmune enteropathy, soya protein intolerance, Zollinger-Ellison syndrome, intestinal lymphoma, HIV enteropathy and other immunodeficiency states. With respect to self-limiting gastrointestinal infections, these changes will resolve spontaneously. The other more rare causes listed here should at least be remembered in cases that do not appear typical of coeliac disease or do not respond as expected to a gluten-free diet (91).

5.0 Treatment of coeliac disease

The gluten-free diet

The treatment of coeliac disease is a lifelong gluten-free diet. 'Gluten' is used here as a generic term to encompass all the proteins derived from wheat, rye and barley. Wheat flour is a particularly ubiquitous constituent of a modern diet being contained in bread, breakfast cereals, pasta, pizza, pastry, biscuits, cakes and sauces. A typical daily diet contains an estimated 10-20 g of gluten, derived from multiple sources and a gluten-free diet therefore necessitates a calculated avoidance of many foods. The Codex standard (used in the UK and Europe) now suggests that food containing less than 20 ppm (parts per million) of gluten can be labelled as 'gluten free' and that foods containing between 21-100 ppm of gluten can be labelled as 'very low gluten'.

Trace amounts of gluten

It may be difficult to completely avoid gluten intake without being particularly fastidious. There is limited data available on the safe threshold for daily consumption of gluten in coeliac disease. Individuals have variable sensitivity to gluten, but the safe daily limit is likely to be in the region of 10 mg each day. A microchallenge study suggested that some patients with coeliac disease can safely consume up to 50 mg of gliadin daily, with some histological abnormalities seen at a dose of 100 mg. However it is clear from anecdotal reports that some patients appear to be exquisitely sensitive to small amounts of gluten intake, given that all patients will be exposed to small amounts of gluten contamination within their diet anything other than a strict gluten free diet cannot be recommended (92-94). A minority of patients consuming wheat starch may continue to have problems. It has been reported that these individuals may derive clinical benefit from a wheat-free gluten-free diet.

The role of the dietician and other sources of information

Following a gluten-free diet requires specific education, which should be provided by a dietician with experience in coeliac disease. This should involve a simple explanation of the principles of a gluten-free diet and provision of written information on which foods contain gluten, how to obtain gluten-free products and how to access and use relevant sources of information. Most centres ensure that there are at least two separate appointments with a dietician as it is likely that questions will arise in the first few months of a gluten-free diet. Emphasis should be given to encouraging adherence with a gluten-free diet and the use of alternative products. Following this, patients should ideally have access to a dietician, independently where possible or via their primary or secondary care physician. Individuals should be encouraged to join Coeliac UK, or an equivalent association in their country. These associations provide information and support to newly diagnosed coeliac patients. Coeliac UK publishes a book (directory), updated each year, listing gluten-free products and manufacturers. Coeliac UK also provide a nationwide support group network and a wide range of information leaflets.

Oats in coeliac disease

Wheat, rye and barley have been shown definitively to be toxic in coeliac individuals. The role of oats in coeliac disease remains controversial. It was initially assumed that oats were toxic due to the observation that patients had continued symptoms whilst ingesting oats. However it became clear that many sources of oats are significantly contaminated with wheat flour during processing. Oats are taxonomically derived from a different subtribe from wheat, rye and barley and do not share the same homologous sequences as these cereals. Several studies have reported the safety of consuming large amounts of pure oats in newly diagnosed coeliacs using clinical, serological and histological parameters (95,96). Some further confusion has arisen recently as a published case series of 19 patients, consuming 50 g pure oats daily, demonstrated that one patient developed partial villous atrophy and a rash during the 12- week challenge (95). Several patients developed gastrointestinal symptoms and 5 were shown to have an increase in intestinal IFN-γ, although histology did not deteriorate. Given this, and the fact that oats from unselected manufacturers may be heavily contaminated, the exclusion of oats in a gluten-free diet is still advised by some. Although, it is possible that a small minority of coeliac individuals will not tolerate oats, the weight of evidence supports the safety of oats obtained from gluten-free manufacturers. We recommend that labelled gluten-free oats can be consumed safely by coeliac patients. As the literature suggests that a small minority of patients may become unwell with oats, it may be helpful to exclude oats in the first six to twelve months of a gluten-free diet before re-introduction. This pragmatic approach allows time for patients to settle on their GFD and allows clinicians an opportunity to ensure adherence to the GFD without the potential difficulties of side effects/symptoms due to oats. In cases where the reintroduction of oats into the diet results in symptoms – it may be worth considering a repeat duodenal biopsy to ensure histological remission (96).

Alternative products

It is important that coeliac patients are advised on alternative foods to include in their diet to maintain a healthy and varied intake and to increase the likelihood of adherence. Many ingredients are naturally safe such as fruits, eggs, cheese, vegetables, meat and fish. Bread, breakfast cereals and pasta are staple ingredients of a modern diet. In order to replace these foods and to maintain variety and palatability, manufacturers produce a range of gluten-free substitute products such as bread, pizza and pastry. These are based on gluten-free wheat or other cereals which are safe such as maize, sorghum, rice and oats. Gluten-free wheat is simply wheat starch, separated from wheat flour and this can be used in cooking or baking as an alternative. Unfortunately the baking and taste properties of wheat starch are inferior and additionally, small amounts of gluten can remain sufficient to cause intestinal injury in sensitive patients. Certain individuals are sufficiently sensitive to require a wheat-free diet which entails avoiding any products that are manufactured with wheat.

Pitfalls in following a gluten-free diet

There are a number of potential pitfalls that can lead to ingestion of gluten. Food may not be labelled and both food labels and lists cannot be guaranteed to be correct. The ingredients of processed food, sauces and pre-prepared meals should be carefully checked

as these often contain unexpected sources of gluten. Eating away from home is clearly a specific problem as there is no clear way of ensuring that meals are free from gluten. Restaurants and chefs tend to have poor awareness of the requirements of coeliac patients but this is likely to improve in the future. As discussed above, oats may be contaminated during harvesting and milling with wheat, which might explain why they can cause symptoms in some patients. Additionally purified wheat starch sometimes still contains traces of gluten proteins and can cause problems for certain patients. Other potential sources of hidden gluten are malted cereals, beer or lager, flavourings and cooking sauces which are often thickened with flour.

Adherence

Patient adherence to a gluten-free diet has repeatedly been shown to be poor with 20-80% admitting to either occasional or prolonged lapses. One of the reasons for this is probably due to a perception that the diet is inconvenient, restrictive and unpalatable. It is important that nutritional advice should focus on alternatives and replacement products, rather than dwell on banned foods. Other factors which may reduce adherence are lack of available information on food content, social stigma (psychosocial issues) and the cost of gluten-free products. The inability to read food labels (in English or any language) may also play a role in individuals who have illiteracy or visual impairment. Concurrent psychiatric disease, an inability to cook or the involvement of others in the preparation of food consumed (such as in institutional care) may all affect adherence. Finally, individuals who do not have many symptoms may believe that adherence is unnecessary. In particular, if lapses do not induce any adverse effects then further indiscretions may be more likely to occur. Those who experience symptoms readily on eating gluten are more likely to comply with the diet. It should be noted that in patients who continue to experience symptoms non-adherence is the main contributory factor. The vast majority of patients, who remain symptomatic, improve when a strict GFD is applied (97,98).

Nutritional supplements

Patients may require additional nutritional supplementation. In early treatment calorific intake may be inadequate and may require augmentation. Calcium supplements may be used to ensure at least 1500 mg daily intake. Fibre intake is often inadequate and can be increased by rice bran or Ispaghula husks (99,100).

Prescription of gluten-free products

Gluten-free products are more expensive than conventional ingredients and this may adversely affect adherence. Gluten-free products are available on prescription by GPs, using a standard FP-10 form. In the UK, prescriptions must be labelled 'ACBS' (Advisory Committee on Borderline Substances). There is a published document, 'Gluten-free foods: a prescribing guide' available free of charge for healthcare professionals. This recommends the minimum monthly prescription of gluten-free foods on the basis that approximately 15% of energy intake is derived from these products.

5.1 <u>Follow up of coeliac patients</u>

Individuals with coeliac disease are at risk of complications. The follow-up care of patients with coeliac disease (after the diagnosis) varies hugely within the UK. This ranges from patients with coeliac disease being seen in specialist clinics to the other extreme of being discharged back to the community without any provision of a specialist service (either in primary or secondary care). In addition, the individuals providing the follow-up care could be family practitioners, gastroenterology consultants, nurse specialists or dietitians, A recent patient survey suggested that the 'model' which patients may prefer is for follow-up to be with a dietitian but to have access to a gastroenterologist concurrently if required. Nationwide there is a significant under resource issue which needs to be resolved particularly as the number of new cases being diagnosed continue to rise (101,102). There is a paucity of literature evaluating the value of follow-up clinics. However, with what little evidence there is – this may suggest that routine follow up increases adherence. (103,104). In keeping with other guidelines we suggest that patients have a full blood count and check of calcium, ferritin, folate and B_{12} every year. Bone densitometry should be monitored. Coeliac UK is an important source of information and membership should be encouraged. Clinicians should be aware of the possibility of developing associated autoimmune disease and lymphoma and investigate and refer patients with further symptoms accordingly.

6.0 Complications of coeliac disease

6.1 <u>Osteoporosis</u>

Coeliac disease is associated with reduced bone mineral density, which increases the risk of osteoporotic fracture. In one study, about half of treated coeliac individuals have evidence of osteoporosis, defined as a reduction in bone densitometry score of greater than two standard deviations below peak bone mass (T score). In untreated coeliacs, up to 70% have evidence of reduced bone density and the prevalence increases in relation to age and the presence of symptoms. There are separate guidelines that discuss the issue of osteoporosis in coeliac disease but the main messages are summarized in this section (105). Several studies have confirmed that bone density scores improve in adults on a gluten-free diet with benefit detectable at one year. In those diagnosed in childhood and following a gluten-free diet, bone densitometry has been shown to be normal in adulthood. Therefore there is clear evidence that a gluten-free diet should be recommended as the core management strategy for prevention of osteoporosis. Conservative measures are important to minimize other risk factors. Therefore smoking cessation, avoidance of excessive alcohol intake and exercise are recommended. Calcium intake affects bone density in coeliacs with a daily intake of 1500 mg providing maximal benefit. If dietary intake is likely to be insufficient then supplementation is recommended. Coeliacs may avoid milk intake due to secondary lactose intolerance so alternative sources should be advised. Measurements of serum calcium and alkaline phosphatase are not a reliable indicator of calcium malabsorption or vitamin D deficiency, which may co-exist leading to osteomalacia. A parathyroid or vitamin D level should be checked if patients have demonstrated osteopaenia or are high risk – those on steroids, with low body mass, and abnormal small bowel histology for example (105).

Dual energy x-ray absorptiometry (DXA) is the most widely used test to assess bone mineral density. Bone densitometry should be checked at diagnosis with a DXA scan. The rationale for this is three fold. Firstly many patients will have had coeliac disease for several years prior to diagnosis, so there is often a significant latent period of calcium malabsorption. It is not possible to reliably predict which patients will have a reduced BMD at the time of diagnosis. Children with untreated disease have evidence of bone loss in early adulthood. A gluten-free diet in children results in normal bone density in adulthood. Finally, osteoporosis has a reversible and an irreversible component and early recognition of osteopaenia is vital to minimize further bone loss. The mainstay of managing osteoporosis is to identify those who are at risk and early intervention to reduce fracture risk. These strategies depend on early recognition by a single assessment or demonstration of progressive bone loss on follow up scans. Coeliac disease is a risk factor for osteoporosis even if a gluten-free diet is followed. Therefore women with treated coeliac disease are at an additional risk even when pre-menopausal state. Males can also be at risk as testosterone levels can be reduced with an adverse effect on bone mass. Finally it is sensible to have a baseline investigation for future comparison as consideration for treatment may depend on demonstrating an excessive rate of bone loss. If a DEXA scan is abnormal but insufficient to commence therapy then it should be repeated after 3 years. If DXA is normal then it should be repeated at age 55 years in males or at the menopause in women. Other risk factors such as steroid use, episodes of non-adherence or non-responsive coeliac disease should warrant periodic re-assessment If osteopaenia is identified, treatment should be offered as recommended by the guidelines (bisphosphonates, calcitonin, HRT) and patients should be reviewed in the appropriate metabolic bone clinic (105,106).

6.2 Autoimmune diseases

Coeliac disease is associated with other autoimmune diseases, which may occur before, after or concomitantly with the diagnosis of coeliac disease. In certain groups the diagnosis of coeliac disease may be directly beneficial to their management. There is limited data to suggest that a gluten-free diet may improve glycaemic control or reduce the requirement of thyroxine in those with co-existing diabetes or hypothyroidism respectively.

There is some evidence to suggest that following a gluten free diet will reduce the likelihood of autoimmune diseases developing. However, as noted before this assertion is not unanimous with conflicting data having been published. One study showed that the prevalence of autoimmune disease was related to the duration of gluten exposure suggesting a protective effect of a gluten-free diet. Furthermore organ-specific auto-antibody levels fall on a gluten-free diet, which may suggest a role in reducing autoimmunity (47,48,49).

6.3 Malignancy

Much work has focused on the early observation of increased cancer incidence in coeliac patients. Recent work has indicated that the risk is not as significant as was initially estimated. The most common association is an increased incidence of intestinal lymphoma, although again early studies overestimated the risk with a quoted odds ratio (OR) of 100.

The risk was estimated in a Northern Ireland population using pathology reports of small bowel lymphoma (107). An overall OR of 27.98 (11.88-65.81) is given for risk of lymphoma compared with age-matched controls. This was broken down into previously undiagnosed CD (12 cases) and diagnosed CD (one case). Overall incidence was 1 in 1000 cases with a differentiation between undiagnosed (1/952) and diagnosed CD (1/1756) but the small numbers limit the value of the figures obtained. A population based study in Derby used a database of diagnosed coeliac patients to determine an OR of 5.74 (1.56-14.69) using the UK cancer registry to provide a background value for lymphoma incidence although an excess risk of small bowel lymphoma was not proven (108).

An Italian study looked for coeliac disease in cases of non-Hodgkin's lymphoma and found 6 cases out of 653 and compared this with the prevalence of coeliac disease in controls. The OR was 3.1 (1.3-7.6) for NHL but 16.9 for intestinal lymphoma (7.4-38.7)(109).

A European multicentre study studied the prevalence of coeliac disease in 1446 patients with lymphoma at any site and compared this with the incidence of coeliac disease in a control group. They found 17 cases of NHL and CD, of which only 8 were Enteropathy associated T-cell Lymphoma (EATL), giving an OR of 2.6(1.4-4.9) for the risk of developing lymphoma in coeliac patients. All but 2 had followed a gluten-free diet. 13/17 coeliac patients were already diagnosed and 11/13 had been adherent to a gluten-free diet for a mean of 9.6 years (110).

Given that silent coeliac disease is common and that the incidence of intestinal lymphoma is small (0.5-1.2% amongst all cases of non-Hodgkin's lymphoma), the risk is probably very low (110).

The risk of other gastrointestinal malignancies has been reported to be elevated. Early work indicated an increase in risk of all malignancies but in particular oesophageal adenocarcinoma.

Evidence exists that a strict gluten-free diet may be protective and reduce the risk of malignancy to that of the general population (after at least 5 years of a gluten-free diet (111,112).

6.4 Mortality in coeliac disease

Early studies, prior to the widespread application of treatment with a gluten-free diet, reported a high mortality, with 20% of coeliac patients dying mainly from malnutrition. In this era, only the more severe cases were diagnosed and it is now recognized that coeliac disease usually has a far more benign course. Several cohort studies (113-115) have shown a 2-3 fold increase in standardized mortality ratio (SMR). One such study in Italy showed that 1072 individuals with coeliac disease had an overall standardized mortality ratio (SMR) of 2 (95% CI, 1.5-2.7), as compared with their age-matched relatives with an excess of 27 deaths (116). The adjusted SMR, when accounting for treatment, was 0.5 (0.2-1.1) for those adhering to a gluten free diet and 6 (4.0-8.9) in those who did not appear to comply. A delay in diagnosis appeared to increase mortality as did the presence of more severe symptoms and the first three years after diagnosis. The majority of excess deaths were attributed to non-Hodgkin's lymphoma with 16 deaths compared with the expected figure of 0.2 in the control group.

More recent population based studies have estimated only a modest or not significant increase in mortality in coeliac patients(117,118). In the UK, a recent population based cohort study of 4732 coeliac patients reported a significant hazard ratio for mortality of 1.31(1.13-1.51), largely attributable to events in the first year after diagnosis. If this first year was excluded, to reduce ascertainment bias from incident cases, then the ratio for mortality was not significant 1.17 (0.98-1.38). Similarly modest hazard ratios were reported for malignancy (1.29 (1.06-1.55)), again becoming non-significant when the first year after diagnosis was excluded (1.10 (0.87-1.39). The risk of lymphoproliferative disease was 4.27 (2.36-7.74) which remained significant despite excluding the first year. Interestingly a reduced risk of breast and lung cancer was also observed (90). A trend towards reduced risks of vascular disease have previously been reported by the same author (119). These observations may be due to reduced exposure to the adverse effects of obesity and excess fats in the diet.

There is little available information regarding the relative risks of 'silent' coeliac disease. Studies to date have involved patients who were diagnosed with symptoms and have not included many individuals who had asymptomatic disease. As there are likely to be many people with undetected coeliac disease, it would be informative to establish the importance of diagnosing these cases. Patients who do not report symptoms are less likely to adhere to a gluten free diet.

6.5 Risk of pneumococcal sepsis

Although there are no controlled trials, several case reports illustrate the potential for overwhelming pneumococcal sepsis due to hyposplenism (120-123). The department of health guidelines recommend that all patients with coeliac disease receive vaccination against pneumococcus and we would recommend this.

7.0 Non-responsive coeliac and refractory coeliac disease

7.1 Definition

The majority of individuals with coeliac disease report a rapid clinical improvement after starting a gluten-free diet. Symptoms usually resolve within a few weeks, preceding histological recovery, which can take 12-24 months or remain incomplete. 5-30% patients do not report an early symptomatic improvement after commencing treatment and some of these will still have persisting symptoms after 6-12 months. These individuals have been described as having non-responsive coeliac disease. This definition should also include those with continued clinical manifestations such as anaemia and encompass those with abnormal duodenal histology. A smaller number of patients will develop further secondary symptoms after an initial response to a gluten-free diet. Non-responsive coeliac disease is not intended to be a diagnostic term but rather a clinical description to allow a pragmatic and systematic approach to evaluate and investigate these patients.

Refractory coeliac disease is defined by continued and severe clinical manifestations in patients who have demonstrated persistence of villous atrophy and small bowel inflammation despite a strict gluten-free diet for one year. The period of one year was

suggested to allow for a permissible delay in mucosal recovery often seen in gluten-sensitivity. However, patients with refractory coeliac disease will often present within this time frame due to their degree of ill health.

Approximately 10% of individuals with non-responsive coeliac disease will have true refractory coeliac disease, which tends to be over-diagnosed. Refractory coeliac disease represents a distinct entity that is discussed further in the next section.

7.2 <u>Non-responsive coeliac disease</u>

Review of diagnosis and gluten-free diet

In individuals who do not report symptom improvement after starting a gluten-free diet, an identifiable cause can be established in 90%. In some cases patients were discovered not to have coeliac disease, and this was the explanation for their failure to improve (124,125). The validity of the diagnosis coeliac disease should be checked, which in the majority of cases will involve reviewing the clinical history and the original antibody and biopsy results. It is important to assess the original biopsy, as failure to orientate the mucosa can result in a false diagnosis of villous atrophy. In addition, HLA typing may also be useful – if an individual does not have the HLA DQ2 or DQ8 pattern then it is highly unlikely that they have coeliac disease.
In the remaining group with coeliac disease, the commonest cause of persisting symptoms is either deliberate or inadvertent failure to adheren to the GFD. These issues should be explored openly with either a dietician or a physician who is experienced in coeliac disease. In these cases, small bowel histology will continue to be abnormal although may show some improvement if an overall reduction in gluten intake has occurred. Repeat duodenal biopsy can be avoided if patients admit to or are identified as having transgressed and then subsequently report clinical improvement. Coeliac serology may be unreliable as recovery and titres may fall with partial gluten withdrawal (126). Small bowel permeability tests may also provide a clue as to whether significant small intestinal inflammation persists. Biopsy remains the gold standard in ambiguous cases where gluten intake is suspected. A few patients appear to be exquisitely sensitive to trace amounts of gluten in their diet. Products based on wheat starch generally do not cause problems in the majority of coeliac patients but anecdotally symptoms and histology improve after these products are withdrawn from the diet (94)

Lactose intolerance

Secondary lactose intolerance is common in coeliac disease (127). The inflammatory and architectural changes in the small intestinal mucosa result in loss of disaccharidase enzymes from the brush border. Therefore coeliac patients often report intolerance to milk and other dairy products. This should resolve when adequate histological recovery occurs and villous architecture is restored. It is advised that intake of dairy produce is limited in the first 3-6 months of a gluten-free diet, particularly if diarrhoea or abdominal pain persists after a few weeks. Some individuals will remain lactase deficient, possibly due to primary intolerance, and this should be considered as a cause for continued symptoms.

Colonoscopy and lymphocytic colitis

After initial assessment, further investigations are warranted to look for a co-existing diagnosis or evidence of refractory coeliac disease. In patients with diarrhoea, colonoscopy and random colonic biopsy should be performed. The typical feature of lymphocytic colitis is a chronic inflammatory cell infiltrate in the lamina propria, rather than an intra-epithelial lymphocytosis, which is often seen in active coeliac disease. Collagenous colitis has also been reported. There is debate about the relevance of the colonic lymphocytosis as this finding can be found in asymptomatic, untreated and refractory coeliac patients. This lymphocytosis may regress with a gluten-free diet and it is suggested that this finding may be simply represent continued gluten intake, be an incidental finding, or as a part of refractory coeliac disease. However, in those diarrhoea and clear histological abnormalities and diarrhoea, treatment is recommended. Treatment is sub-optimal but overall the natural history is benign which is in keeping with other forms of microscopic colitis (128,129).
Patients with coeliac disease may be more likely to have inflammatory bowel disease. However, in these reports microscopic colitis is most frequently described (128,129).

Pancreatic insufficiency

Pancreatic insufficiency has been reported to occur in association with coeliac disease. There may be a role for faecal elastase or a trial of treatment with pancreatic supplements may be advisable in those in whom pancreatic insufficiency is suspected (130,131)

Bacterial overgrowth

A further diagnosis to consider is small bowel bacterial overgrowth. This condition is under-diagnosed in the general population and does also occur in coeliac patients. The mucosal abnormalities may theoretically predispose to bacterial colonization. Diagnosis is difficult either by duodenal aspiration or breath test. These tests have low sensitivity and specificity. The duodenal histology may be normal, abnormal or show patchy changes which are difficult to detect. In one study 10 out of 15 coeliac patients with diarrhoea had a positive breath test and benefited from treatment with antibiotics (132). Treatment may be advised empirically if this diagnosis is suspected. Patients may require treatment with alternating antibiotics for several weeks. Given the poor quality of tests available for bacterial overgrowth and the uncertainty regarding this diagnosis, it is probably reasonable to rely on symptomatic improvement as a guide to treatment.

Functional disorders

Continued symptoms in coeliac patients may be functional (133). In 10% of non-responsive patients repeat duodenal histology and further investigations are normal and the symptoms pattern is consistent with criteria for irritable bowel syndrome. This raises the possibility that the original symptoms at presentation were functional and that the coeliac disease was

an incidental diagnosis, which would explain the lack of expected improvement. A gluten-free diet is often inadequate in providing fibre intake and this may exacerbate constipation. Fibre supplementation may help patients or may exacerbate the problem. Other strategies for irritable bowel syndrome can be implemented as required but clearly the gluten-free diet should be continued if the diagnosis of coeliac disease is valid.

Coeliac patients may suffer from a range of conditions that afflict the general population and they should be investigated accordingly. It is not satisfactory to attach all subsequent gastrointestinal symptoms to a previous diagnosis of coeliac disease particularly in cases where symptoms were initially well controlled with a gluten-free diet.

7.3 <u>Refractory coeliac disease</u>

Clinical diagnosis

Refractory coeliac disease has been defined in those who, despite a strict gluten-free diet, have continued clinical manifestations that are associated with marked histological abnormalities (Marsh III) after one year. One year is an arbitrary period to reflect the slow histological recovery seen in many patients, although clearly the clinical picture needs to be considered. Weight loss, low albumin, severe diarrhoea and disproportionate anaemia warrant expeditious investigation. In the past this condition was over-diagnosed, mainly in individuals who continue to ingest gluten. True refractory coeliac disease is uncommon but again epidemiological data is limited. There are a number of rare disorders, which can mimic refractory coeliac disease and these are discussed below. Previously responsive coeliac patients who develop this condition despite continuing a gluten-free diet can be termed as having secondary refractory coeliac disease.

Histological diagnosis

Individuals with refractory coeliac disease often have an abnormal population of intra-epithelial lymphocytes detectable in their small bowel mucosa and sometimes elsewhere in their gastrointestinal tract. In active coeliac disease, intra-epithelial lymphocytes are predominantly CD8+ and express surface CD3, a universal lymphocyte marker, together with polyclonal T cell receptors. In a study of refractory patients 84% were found to have an abnormal population of intra-epithelial lymphocytes, which are CD103+, CD8- and CD4- and without surface CD3-TCR complexes, although CD3 is found intracellularly (133). In addition the majority of these can be shown to have a clonal TCR-γ gene rearrangement, detectable by PCR analysis of biopsy specimens. The presence of this aberrant T cell phenotype has been termed Type II refractory coeliac disease with the minority without these cells denoted Type I. Type II disease is associated with a greater mortality at two years (41%) than type I disease (14%). The major cause of death is the development of enteropathy associated T cell lymphoma (EATL). The risks appear to be greater in those with an abnormal IEL population, both in terms of lymphoma risk (53% v 43%) and mortality (70% v 30%). EATL is characterized by malignant lymphoid tissue with the same immunophenotype seen in refractory coeliac disease – CD4-, CD8-, CD3+, CD103- and clonal TCR-γ gene rearrangements. The presence of this T cell phenotype is thought to represent a cryptic T cell lymphoma. In a study of a cohort of 41 patients with coeliac disease (21 with refractory

coeliac disease), 3 (14%) in the refractory coeliac disease group developed T cell lymphoma during a mean of 9.5 years follow-up (80).

If an individual is suspected as having refractory coeliac disease, it is recommended that additional immunohistochemistry analysis is performed to look for abnormal IEL population and TCR gene rearrangements as this will predict the increased risk of lymphoma. This IEL population can be found diffusely in the gastrointestinal tract and standard biopsy from the duodenum is likely to be sufficient. A formalin fixed, paraffin-embedded sample is satisfactory for staining and PCR analysis.

Enteropathy-associated T cell lymphoma (EATL)

Early diagnosis of EATL is difficult. The majority are advanced and incurable at discovery and may require surgical treatment for perforation, haemorrhage or obstruction. The majority of tumours occur in the proximal small intestine but primary extra-intestinal sites can be affected. Many modalities have been employed to diagnose intestinal lymphoma, such as CT, barium meal, MR imaging, laparoscopy, enteroscopy and wireless capsule. CT scanning has the best sensitivity for visualizing bowel thickening and mass effect. Contrast studies may pick up obstruction and subtle mucosal changes and ulcerative jejunitis. The incidence of ulcerative jejunitis correlates strongly with Type II refractory coeliac disease and the development of EATL. Unfortunately the imaging findings in intestinal lymphoma are non-specific and diagnosis requires biopsy material. Endoscopic biopsy is ideal for proximal lesions but laparoscopy may be required to perform full thickness biopsy of suspected lesions that are distal to the reach of an endoscope. EATL carries a worse prognosis than other cases of non-Hodgkin's lymphoma.

This malignancy accounts for 1.2% of all non-Hodgkin's lymphomas and typically affects the small intestine, although it can occur in extra-intestinal sites. Only about one third of small bowel lymphoma occurs in association with coeliac disease. The term enteropathy-type intestinal T cell lymphoma (EITCL) is used to distinguish primary lymphomas affecting the bowel in coeliac patients.

Differential diagnosis

Several rare conditions may mimic the presentation of primary refractory coeliac disease. These conditions may be indistinguishable from refractory coeliac enteropathy as none of them exhibit gluten-sensitivity. Autoimmune enteropathy is characterized by the presence of circulating anti-enterocyte antibodies and villous atrophy without a significant increase in intra-epithelial lymphocyte count. This rare disorder was first described in children who were not gluten sensitive and did not have HLA DQ2 or DQ8 (134).

Primary intestinal lymphoma that is not associated with coeliac disease can present with weight loss, diarrhoea and abnormal small bowel histology which fails to improve on a gluten-free diet. Non-enteropathy associated lymphomas account for two thirds of all intestinal lymphomas. These individuals have a better prognosis than those with EATL and aggressive treatment is advocated.

A final group of conditions which may be confused with refractory coeliac disease are immunodeficiency states. These include combined variable immunodeficiency, hypogammaglobulinaemia and human immunodeficiency virus infection. Absence of IgG or IgM and low CD4 counts predispose the small bowel to recurrent infections, which present with weight loss, diarrhoea and villous atrophy.

7.4 Treatment of refractory coeliac disease

In 90% of coeliac patients with continued symptoms, an identifiable cause can be established and managed accordingly. It is important to identify those with refractory coeliac disease as they have a significant risk of lymphoma and death. A strict gluten-free diet must be ensured including exclusion of all potential sources of trace amounts of gluten. Thereafter if clinical manifestations persist with confirmed villous atrophy, a diagnosis of refractory coeliac disease should be made. Where possible, biopsy material should be sent for analysis for an abnormal clonal IEL population, which is likely to further stratify the risk of future serious complications. Following this, patients should be screened accordingly for evidence of lymphoma and kept under regular review for this consideration. EATL is difficult to diagnose but early stage tumours are likely to respond better to treatment.

Patients with refractory coeliac disease are usually ill and require treatment for their symptoms. The main threat is malabsorption and failure to maintain sufficient calorific intake. There is very little evidence-base for managing these patients but the literature describes successful treatment in many case reports and case series.

The treatment of refractory coeliac disease is poor. The cohort described by Cellier et al (80) had a high mortality irrespective of treatment, although this group was managed by many different physicians. The literature consists of case reports and case series. The studies published with positive results often report high rates of unequivocal remission of refractory coeliac disease that are at odds with the poor outcome seen in longitudinal cohorts. This may be due to the short follow up periods in these studies or the patients selection. There has been a tendency to diagnose refractory coeliac disease too readily. For example in one study of 55 patients labelled to have refractory coeliac disease in all but 9 patients an identifiable alternative cause for continued symptoms diagnosis was found – in most cases inadvertent gluten intake.

It is therefore clear that the foundation of treatment should be to ensure and continue a gluten-free diet. Remission is unlikely to occur spontaneously if gluten continues to be consumed. Patients with weight loss and impaired absorption have been given parenteral nutrition and this can reverse the catabolic state of refractory patients. Anecdotally, the use of steroids has been reported to induce clinical remission. Many of the early studies occurred prior to the modern definition of refractory coeliac disease and it is likely that these trials comprised a heterogeneous group of patients. There are several case series reporting histological and symptomatic recovery with oral prednisolone and this is often tried in the first instance. No controlled trials exist and no universal dose regimen has been adopted. As treatment is likely to be prolonged, a low-moderate dose is suggested by some 10mg/daily (135). Mucosal recovery and symptomatic progress should be monitored because if treatment is not successful steroids should be withdrawn. Azathioprine has been used in conjunction with prednisolone to provide long-term immunosuppression as a logical steroid sparing agent. One case series using prednisolone, followed by 2mg/kg azathioprine for one year, reported improvement in 8 out of 10 Type I refractory coeliac patients but no improvement in 8 patients with type II disease, seven of whom died (136). A further study

reported 5 out of 7 improving over a mean of 11 months using combined azathioprine and prednisolone at high dose (1mg/kg/day), in conjunction with nutritional support (137). Five patients in this study had proven TCR clonality and the 2 that did not respond died. Several other case reports have described histological recovery with prednisolone, sustained with azathioprine (136). Cyclosporin has also been used and one pilot study treated 13 patients with standard immunosuppressive doses (serum range 100-200 mg/ml) for 12 months ((138). Eight out of 13 improved histologically and 2 further showed a clinical improvement with no serious adverse effects. In 5/13 villous architecture returned to normal. In all these studies there is no long-term follow up and late relapse has been reported when therapy is withdrawn. There is no evidence that immunosuppression alters the risk of developing lymphoma. None of these treatments should be used as an alternative to a gluten free diet. Most recently the monoclonal antibody, Infliximab, has been reported as inducing remission in individual cases (139),. An elemental diet has been proposed to induce recovery in a few individuals(140),(141).

Due to the complex nature in such cases, it is recommended that patients thought to have refractory coeliac disease should be referred to a specialist centre for further investigation and treatment.

8.0 **Recommendations**

8.1 Screening for coeliac disease

There is currently not enough evidence to support population screening for coeliac disease.

8.2 Testing for coeliac disease

Offer serological testing for coeliac disease in the presence of these signs, symptoms and conditions (as per NICE Guidelines) (13):

Chronic or intermittent diarrhoea
Failure to thrive or faltering growth (children)
Persistent or unexplained gastrointestinal symptoms including nausea and vomiting
Prolonged fatigue ('tired all the time')
Recurrent abdominal pain, cramping or distension
Sudden or unexpected weight loss
Unexplained iron-deficiency anaemia, or other unspecified anaemia
 (Recommendation grade B)

Conditions
Autoimmune thyroid disease
Dermatitis Herpetiformis
Irritable bowel syndrome
Individuals who have a first degree relative with coeliac disease
Type I diabetics, particularly if there are unexplained symptoms or poor glycaemic control
Patients with a history of other autoimmune diseases with other unexplained symptoms
(Recommendation grade B)

There is a comprehensive list of conditions for which it is suggested that seroligcal testing should be 'considered' rather than offered. Examples of these conditions include subfertility, Addison's disease, Down's Syndrome, or dental enamel defects. (cite NICE)

8.3 Exclusion of coeliac disease

Testing for coeliac auto-antibodies is satisfactory to exclude coeliac disease in the majority of cases as the best serological tests have 95% negative predictive value.
(Recommendation grade B)

Laboratories expertise will vary but, in clinical practice and a combination of tissue transglutaminase antibody and EMA is the most robust and reliable approach.
(Recommendation grade B)

In all cases, an IgA immunoglobulin level should be checked and if there is evidence of IgA deficiency then an IgG isotype of auto-antibodies should be measured (either IgG TTG antibody or EMA).
(Recommendation grade B)

As serological tests are not infallible, if there is a high suspicion of coeliac disease formal duodenal biopsy is advised even if serology is repeatedly negative.
(Recommendation grade C)

8.4 Duodenal biopsy

If EMA and/or TTG serology is positive, patients should undergo duodenal biopsy, preferably whilst still consuming a normal diet.
(Recommendation grade C)

In highly symptomatic or unwell patients, who may be compelled to stop gluten immediately, duodenal biopsy should be carried out at the earliest opportunity.
(Recommendation grade C)

For patients who have already discontinued gluten, duodenal biopsy should be performed after a suitable gluten challenge (four slices of bread each day for two-six weeks)
(Recommendation grade C)

If gastroscopy is undertaken in patients with unexplained anaemia or weight loss, it is sensible to perform duodenal biopsy during the procedure.
(Recommendation grade B)

At least four decent-sized biopsy samples should be taken from the second part of the duodenum or beyond.
(Recommendation grade C)

Specimens should be carefully orientated prior to mounting and cutting of slides.
(Recommendation grade C)

8.5 <u>Histological analysis</u>

Reference should be made of intraepithelial cell count, any cellular infiltrate, villous atrophy and crypt hyperplasia, where abnormal.

Comment should be made regarding incorrectly orientated specimens and where insufficient material is available so the clinician can consider repeat biopsy.

In the diagnosis of coeliac disease, there should be a confident description of the typical changes of enteropathy with villous atrophy and crypt hyperplasia.

If there is histological ambiguity, then repeat biopsy should be considered in context of clinical symptoms. If diagnostic doubt persists then biopsy after a gluten-free diet and possibly gluten challenge can be performed.

Where possible histology should be reviewed in the clinical context of the patient - coeliac serology, current diet, symptoms should be noted and comparison made to any previous specimens.
(Recommendation grade C)

8.6 <u>Diagnosis of coeliac disease</u>

Diagnosis of coeliac disease should not be made by symptomatic response to gluten withdrawal or challenge.
(Recommendation grade B)

Formal duodenal biopsy is mandatory for the diagnosis.
(Recommendation grade C)

The typical features of villous atrophy should be identified by an appropriately experienced histopathologist.
(Recommendation grade C)

An isolated increase in intraepithelial lymphocyte in the absence of villous atrophy should be interpreted in the context of coeliac serology, symptoms and HLA typing. Symptomatic patients with positive serology (EMA or TTG antibody) may be treated with a gluten-free diet. If there remains diagnostic doubt, then a repeat biopsy after a gluten-free diet should be performed to look for improvement.
(Recommendation grade C)

Repeat biopsy is not mandatory if symptoms and clinical parameters improve. If problems persist beyond six months then repeat biopsy is indicated and the diagnosis of coeliac disease should be reviewed to ensure it is correct.
(Recommendation grade C)

8.7 <u>Treatment of coeliac disease</u>

Patients with coeliac disease should be treated with a lifelong gluten-free diet with advice to avoid wheat, rye and barley proteins.
(Recommendation grade B)

All patients should see a dietician with experience in coeliac disease. They should provide formal education for a gluten-free diet and attention drawn to food labeling and potential pitfalls. Ideally a second appointment should be offered after 3-6 months to check and answer any questions which have arisen and assess adherence.
(Recommendation grade C)

Written information should be provided and all patients should be advised to join Coeliac UK.
(Recommendation grade C)

Oats are usually safe in coeliac disease, provided they are obtained from a listed supplier with the guarantee that they are free from contamination with wheat.
(Recommendation grade A)

Symptomatic patients should be advised to avoid excessive milk ingestion in the first six months of a gluten-free diet.
(Recommendation grade C)

Patients should be offered pneumococcal vaccination.
(Recommendation grade C)

8.8 <u>Continued symptoms in coeliac patients</u>

If symptoms persist after 6 months on a gluten-free diet, dietary adherence should be first be carefully checked by a dietician. In these cases, it may be helpful to request a wheat-free diet with exclusion of all sources of wheat flour.

Following this, a repeat duodenal biopsy should be performed and compared with the initial biopsy, to look for any improvement or persistence of the small bowel abnormalities.

If symptoms persist and duodenal histology is not improved despite a strict gluten free diet for over one year, patients should be referred to a gastroenterologist with experience in the investigation of refractory coeliac disease.

The investigation of refractory coeliac disease is likely to involve repeat duodenal biopsy with samples sent for T cell receptor monoclonality and stringent exclusion of enteropathy-associated small bowel lymphoma.

(Recommendation grade C)

8.9 Follow up of coeliac patients

Asymptomatic coeliac patients should have blood taken yearly for FBC, ferritin, folate, B12 and bone profile. Coeliac serology may be of interest to assess adherence.

New or changed symptoms should be investigated accordingly and treated. It will usually be of value to repeat duodenal biopsy. It may be helpful to review dietary adherence. Small bowel bacterial overgrowth and microscopic colitis should be excluded.

If symptoms remain unexplained by conventional investigation, then specialist investigations should be undertaken to exclude secondary refractory coeliac disease and the possibility of enteropathy-associated T cell lymphoma.

(Recommendation grade C)

8.10 Osteoporosis

See separate guidelines for management of osteoporosis.

All patients should have bone density measured at presentation (by DEXA scan).
Females with normal bone density at presentation should be re-assessed after the menopause (and males at age 55).

Those with abnormal bone density should be re-assessed every three years.

Osteoporosis should be actively treated according to published guidelines.

All individuals with coeliac disease should be advised to consume 1500 mg calcium per day and adopt other conservative measures to reduce risk of osteoporosis.

(Recommendation grade C)

9.0 **Sources of information**

Coeliac UK
Suites A-D
Octagon Court
High Wycombe
Bucks, HP11 2HS
T: 01494 437 278
F: 01474 349
Website: www.coeliac.org.uk

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