Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition

Ramesh P Arasaradnam,1,2,3 Steven Brown,4 Alastair Forbes,5 Mark R Fox,6,7 Pali Hungin,8 Lawrence Kelman,9 Giles Major,10 Michelle O’Connor,9 Dave S Sanders,4 Rakesh Sinha,11 Stephen Charles Smith,12 Paul Thomas,13 Julian R F Walters14

ABSTRACT
Chronic diarrhoea is a common problem, hence clear guidance on investigations is required. This is an updated guideline from 2003 for the investigations of chronic diarrhoea commissioned by the Clinical Services and Standards Committee of the British Society of Gastroenterology (BSG). This document has undergone significant revision in content through input by 13 members of the Guideline Development Group (GDG) representing various institutions. The GRADE system was used to appraise the quality of evidence and grading of recommendations.

These guidelines deal with clinical assessment in primary and secondary care of a patient with diarrhoea, the exclusion of cancer or inflammation, and detecting common disorders such as bile acid diarrhoea, microscopic colitis, lactose malabsorption or post radiation diarrhoea, together with rarer causes of malabsorption and surgical disorders as outlined in figure 1. Options for therapy are not dealt with as it is beyond the remit of this guideline, nor has the cost effectiveness of investigations been addressed due to paucity of available evidence.

1 PREFACE
1.1 Purpose of guidelines
The guidelines are directed at consultant gastroenterologists, gastrointestinal surgeons, specialist registrars in training and general practitioners, and refer specifically to adult not paediatric gastroenterology. Their purpose is to provide guidance on the best available methods of investigating symptoms of chronic diarrhoea. Given this broad symptom-based focus, the guidelines cover a wide range of gastroenterological conditions and are not intended as a comprehensive review of all aspects of the clinical conditions mentioned herein, but rather an attempt to rationalise the approach to investigation in the context of this common clinical scenario.

1.2 Development of guidelines and rigour
The guidelines were prepared following a comprehensive literature search by the guideline development group (GDG). The GDG membership comprises elected members of the BSG, Association of Coloproctology of Great Britain and Ireland, Association of Biochemistry UK, British Institute of Radiology, Primary Care Society for Gastroenterology, and nurse and patient representatives. Each main section was authored by a designated member of the GDG following a comprehensive review of the literature including NICE, American and European guidelines. This involved a review of electronic databases (Medline and PubMed) using keywords (in both British and American spelling) such as ‘((diarrhoea-predominant irritable bowel syndrome’ OR ‘chronic diarrhoea’ OR ‘functional diarrhoea’ OR ‘loose stools’ OR ‘faecal urgency’ OR ‘faecal incontinence’ OR ‘stool frequency’) AND (((diarrhoea TITLE/Abstract)) AND (investigation OR diagnostic OR diagnosis) AND (‘faecal incontinence’ OR ‘stool frequency’)) AND ‘stool frequency’). Additional terms related to the specific conditions mentioned in the text (eg, coeliac disease, bile acid diarrhoea or malabsorption and small bowel bacterial overgrowth). The time frame for literature review was from 2002 to April 2017. A total of 1292 key papers and relevant abstracts in English in peer-reviewed journals were identified and read, and relevant work has been cited and referenced. An initial draft document was produced and subsequently reviewed and modified in accordance with the AGREE tool.1 Two face-to-face meetings as well as a further two telephone meetings were held in preparing this guideline. We used a modified Delphi system to a maximum of three rounds for any contentious issues. A final decision was made once agreement was reached by 70% of the group. The lead author acted as facilitator. The review was undertaken through submission to members of the BSG Clinical Standards Service Committee as well as to BSG Council and finally international peer review.

1.3 Grading of recommendations
In accordance with the BSG advice on production of guidelines, the GDG applied the GRADE system.2 Strength of recommendation was strong, moderate or weak. Where the recommendation was unanimous a ‘strong’ recommendation was used, and where the decision was by majority and the recommendation was moderate or weak, ‘we suggest’ was used. We graded the evidence based on levels 1–5 as per the Oxford Centre for Evidence Based Medicine.3 In brief, Level 1a–c ranges from systematic reviews with homogeneity, individual

Correspondence to
Professor Ramesh P Arasaradnam, Department of Gastroenterology, University Hospitals Coventry & Warwickshire, Coventry, CV2 2DX, UK; r.arasaradnam@warwick.ac.uk

Received 21 December 2017
Revised 28 February 2018
Accepted 11 March 2018
Published Online First
13 April 2018

For numbered affiliations see gutjnl-315909 (http://dx.doi.org/10.1136/gutjnl-2017-315909).

For additional material see gutjnl-315909 (http://dx.doi.org/10.1136/gutjnl-2017-315909).


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randomised controlled trials (RCTs); Level 2a–c ranges from systematic reviews of cohort studies, low quality RCTs and outcomes research; Level 3a–b ranges from systematic reviews with heterogeneity and individual case control studies; Level 4 are poor quality cohort or case series; and Level 5 is expert opinion without critical appraisal.

Specific RCTs addressing the investigation of ‘chronic diarrhoea’ are absent. Thus our grading of evidence was based on

Figure 1  Algorithm for the investigation of chronic diarrhoea based on clinical differential diagnosis.
Guidelines

Summary of all recommendations

We recommend the following investigation algorithm based on the clinical differential diagnosis outlined in figure 1.

Clinical assessment
► We recommend a careful detailed history to plan investigations (Grade of evidence level 1, Strength of recommendation strong).
► We recommend screening blood tests for the exclusion of anaemia, coeliac disease, etc as well as stool tests for inflammation (Grade of evidence level 1, Strength of recommendation strong).
► We recommend making a positive diagnosis of irritable bowel syndrome (IBS) following basic blood and stool screening tests (Grade of evidence level 2, Strength of recommendation strong).

Cancer or inflammation
► We recommend excluding colorectal cancer in those with altered bowel habit±rectal bleeding by colonoscopy (Grade of evidence level 1, Strength of recommendation strong).
► We suggest use of testing for faecal blood loss by faecal immunochemical testing in primary or secondary care, either as an exclusion test or to guide priority of investigations in those with lower gastrointestinal symptoms (chronic diarrhoea) but without rectal bleeding (Grade of evidence level 2, Strength of recommendation weak).
► Faecal calprotectin is recommended to exclude colonic inflammation in those suspected with IBS and under the age of 40 (Grade of evidence level 1, Strength of recommendation strong).

Secondary clinical assessment
► If symptoms persist despite normal first-line investigations and treatment, then referral for further investigations is recommended (Grade of evidence level 5, Strength of recommendation strong).
► We recommend blood and stool tests to exclude malabsorption and common infections (especially in the immunocompromised or elderly) (Grade of evidence level 2, Strength of recommendation strong).

Common disorders
► In those with functional bowel or IBS-diarrhoea, a positive diagnosis of bile acid diarrhoea should be made either by $^{75}$SeHCA T testing or serum bile acid precursor $7\alpha$-hydroxy-4-cholesten-3-one (depending on local availability) (Grade of evidence level 1, Strength of recommendation strong).
► There is insufficient evidence to recommend use of an empirical trial of treatment for bile acid diarrhoea rather than making a positive diagnosis (Grade of evidence level 5, Strength of recommendation strong).
► We recommend colonoscopy with biopsies of right and left colon (not rectal) to exclude microscopic colitis (Grade of evidence level 1, Strength of recommendation strong).

Malabsorption
► If lactose maldigestion is suspected, we suggest hydrogen breath testing (if available) or withdrawal of dietary lactose/carbohydrates from the diet (Grade of evidence level 3, Strength of recommendation weak).
► MR enterography is recommended for evaluation of small bowel abnormalities depending on availability (Grade of evidence level 1, Strength of recommendation strong).
► Video capsule endoscopy (VCE) is recommended for assessing small bowel abnormalities depending on local availability (Grade of evidence level 1, Strength of recommendation strong).
► We do not recommend small bowel barium follow through or barium enteroclysis for the evaluation of small bowel abnormalities due to its poor sensitivity and specificity (Grade of evidence level 5, Strength of recommendation strong).
► We recommend enteroscopy only for targeted lesions identified by MR enterography or VCE and not for diagnosis of chronic diarrhoea (Grade of evidence level 4, Strength of recommendation strong).
► We recommend faecal elastase testing when fat malabsorption is suspected. We do not recommend PABA testing (Grade of evidence level 1, Strength of recommendation strong).
► MRI (rather than CT) is recommended for assessing structural anomalies of the pancreas in suspected chronic pancreatitis (Grade of evidence level 2, Strength of recommendation strong).
► If small bowel bacterial overgrowth is suspected, we recommend an empirical trial of antibiotics as there is insufficient evidence to recommend routine hydrogen or methane breath testing (Grade of evidence level 3, Strength of recommendation strong).

Surgical and structural disorders
► We recommend use of anorectal manometry and endoanal ultrasound only when other local pathology has been excluded and conservative measures exhausted (Grade of evidence level 3, Strength of recommendation strong).
► We recommend radiological modalities for the investigation of fistulae—MRI or CT with contrast follow through (Grade of evidence level 3, Strength of recommendation strong).

Rare causes
► Diarrhoea due to hormone secreting tumours is rare, hence we recommend testing only when other causes of diarrhoea have been excluded (Grade of evidence level 4, Strength of recommendation strong).
the level of evidence (1–5) and the strength of our recommenda-
tion (strong, moderate or weak).

1.4 Scheduled review of guidelines
These guidelines will be subject to future revisions within 5 years
to take into account new developments and alternative investi-
gative methods.

1.5 Possible audit goals
The aim of these guidelines was to establish an optimal inves-
tigative scheme for patients presenting with chronic diarrhoea
that would maximise a positive diagnosis while minimising the
number and invasiveness of investigations. These two poten-
tially opposing directives are influenced by the potential seri-
ousness of the diagnostic outcome. Thus a low threshold for the
use of colonoscopy is acceptable in the context of the frequency
and clinical significance of colonic neoplasia in older subjects.
However, there is less need for extensive investigation where the
probability of benign disease is high (eg, in young patients with
functional symptoms). Suggested goals for future audit include:

1. All patients undergoing colonoscopy for chronic diarrhoea
should undergo biopsies of the right and left colon for histo-
logical examination.
2. Reduction of missed diagnoses of colorectal cancer to <1%
through utility of faecal immunochemical testing (FIT) and
endoscopic examination.
3. Minimising inappropriate first-line investigations (eg, colo-
noscopy) in patients less than 40 years of age without rectal
bleeding and normal faecal calprotectin.
4. Initial non-invasive investigations, including coeliac serology,
faecal calprotectin and possibly FIT, should be completed in
primary care prior to specialist referral.
5. All patients with persistent undiagnosed chronic diarrhoea
should be investigated for bile acid diarrhoea with SeHCAT
or serum 7-alpha-hydroxy-4-cholesten-3-one or faecal bile
cacid measurement where available.

2 INTRODUCTION

2.1 Definition
Diarrhoea may be defined in terms of stool frequency, consis-
tency, volume or weight. Patients’ concept of diarrhoea often
focuses around stool consistence. Indeed, faecal consistence is
determined by the water-holding capacity of the stool (ie, the
amount of non-bound ‘free’ water), and this perhaps best defines
the concept of diarrhoea. However, quantification of this in clin-
ical terms can be difficult to separate these on clinical grounds alone. The
decision on whether to focus investigations on any one of these
criteria incorporates access to small bowel and
digestive pathways that should be adopted. Diarrhoea may result
from: (a) colonic neoplasia; (b) inflammation; (c) small bowel
inflammation; (d) small bowel malabsorption; (e) maldigestion
due to pancreatic insufficiency; or (f) motility disorders, and it
can be difficult to separate these on clinical grounds alone. The
decision on whether to focus investigations on any one of these
areas remains largely a matter of clinical judgement although,
as will be discussed, the prevalence and potential seriousness of
certain conditions (eg, colonic neoplasia) necessitates their
exclusion early in the investigative scheme.

A further problem in the development of these guidelines has been the large number of investigative methods reported,
particularly with regard to malabsorption. This reflects the failure of any single test to become established as the standard
and, indeed, many of the available methods have not found a
wide acceptance because of inadequate sensitivity, specificity
or ease of use. Moreover, there is considerable variation in
protocols and analytical methods between laboratories that
leads to poor reproducibility of results. It is also unclear
what place some of these tests (some of which were devised
prior to the advent of endoscopy) hold in the current inves-
tigative scheme that incorporates access to small bowel and
colic histology. To circumvent this somewhat, we propose

2.2 Prevalence
Chronic diarrhoea is one of the most common reasons for
referral to a gastroenterology clinic. Prevalence rates in Western
populations are difficult to estimate, partly through popula-
tion differences but also through difficulties in definition. In
two population surveys, Talley et al reported a prevalence of
‘chronic diarrhoea’ of between 7% and 14% in an elderly popu-
lation, a proportion of which is likely to include patients with
motility disorders (ie, ‘functional bowel disease’). Using a defini-
tion based on excessive stool frequency without the presence of
abdominal pain, estimates of the prevalence of chronic diarrhoea
in a Western population are 4–5%. The

2.3 Difficulties in establishing guidelines for the investigation
of chronic diarrhoea
Reported change in stool frequency or form is characteristic of
irritable bowel syndrome (IBS) and indeed forms part of the defi-
nition of the condition, which relies on symptom-based criteria
and negative physical examination. Although stool weight
does not usually increase in IBS, as symptom reporting forms the
basis for the diagnosis and stool weight is rarely performed early
in the course of investigation, considerable overlap between
functional bowel disease and true ‘diarrhoea’ occurs. As IBS
may affect 10–13% of the population, there is clearly the
potential for inappropriate investigation of patients reporting
diarrhoeal symptoms. Conversely, new onset of diarrhoea may
reflect serious organic disease such as colonic neoplasia. It is this
wide diagnostic potential given similar reported symptoms that
makes the introduction of specific guidelines difficult.

The broad range of conditions which lead to diarrhoea also
make it difficult to be too prescriptive with regard to the inves-
tigative pathways that should be adopted. Diarrhoea may result
from: (a) colonic neoplasia; (b) inflammation; (c) small bowel
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Guidelines

in figure 1 an outline algorithm for the investigation of chronic diarrhoea based on clinical differential diagnosis. This will be used to guide the text in this document.

3 PRIMARY CLINICAL ASSESSMENT

The initial assessment of patients with chronic diarrhoea can be mostly carried out in the primary care setting. The importance of careful history taking and examination cannot be overemphasised.

3.1 Initial presentation in primary care

In most countries where there is a split primary/secondary care system, the first consultation is with the primary care physician. Around 10% of all consultations in primary care are for gastroenterological problems, of which half are for lower gastrointestinal (GI) problems.16 Most of these are for self-limiting symptoms or for functional GI disorders and only a very small proportion comprise chronic or persistent diarrhoea. Based on the accepted definition of chronic diarrhoea being abnormal passage of ≥3 loose stools per day for more than 4 weeks and a rate of 3–5% per year,17 a primary care physician with an average list size of 1700 patients may have 50–85 such patients each year. Only a proportion of these will consult, with many managing with self- or pharmacy-based treatments, while others will be managed within primary care, often with antidiarrhoeals.

No data are available on the proportion referred to secondary care, but these are likely to be a small minority of the total number of people with chronic diarrhoea in the community. First-line investigations are normally performed within primary care and patients may be referred if their condition causes interference with normal activities or a compromise of quality of life sufficient to warrant further action. As with other conditions, many patients merely adapt their lives to their symptoms. No formal primary care referral guidelines or recommendations exist for patients with chronic diarrhoea, but the presence of normal first-line investigations with symptoms severe enough to impair quality of life and not responding to treatment constitutes a rationale for referral.

The impact of the symptoms of chronic diarrhoea and the differential diagnoses that need to be considered are clearly different in individual patients. A patient with recent change in bowel habit to include diarrhoea over 6 weeks is likely to need a different approach compared with another patient who has suffered from intermittent watery diarrhoea which has been present for over 5 years. Blood, stool (if an infectious aetiology or if an inflammatory component is suspected) and serological tests (for coeliac disease, hyperthyroidism and anaemia) should be performed in primary care as an initial assessment. Equally, if alarm features (such as unexplained change in bowel habit, persistent blood in the stool and unintentional weight loss) are detected, then referral for further investigations should be initiated.

3.2 History and examination: secondary care assessment

A detailed history is essential in the assessment of patients with chronic diarrhoea. This should attempt (a) to establish the likelihood that the symptoms are organic (as opposed to functional) based on presence of ‘alarm features’ as outlined above; (b) to distinguish malabsorptive from colonic/inflammatory forms of diarrhoea; and (c) to assess for specific causes of diarrhoea.

Symptoms suggestive of an organic disease include a history of diarrhoea of <3 months’ duration, predominantly nocturnal or continuous (as opposed to intermittent) diarrhoea and significant weight loss. The absence of these, in conjunction with positive symptoms such as those defined in the Rome IV criteria (improved clinical validation)18 and a normal physical examination, are suggestive of a functional bowel disturbance, but only with a specificity of approximately 52–74%.19 Unfortunately, these criteria do not reliably exclude inflammatory bowel disease (IBD), microscopic colitis or bile acid diarrhoea, all of which are relatively common and treatable with specific approaches.20

Malabsorption is often accompanied by steatorrhoea and the passage of bulky malodorous pale stools. However, milder forms of malabsorption may not result in any reported stool abnormality. Colonic, inflammatory or secretory forms of diarrhoea typically present with liquid loose stools with blood or mucous discharge.

Specific risk factors which increase the likelihood of organic diarrhoea or point to potential lines of investigation should be sought (see box 1). These include:

1. Family history: particularly of neoplastic, inflammatory bowel or coeliac disease.
2. Previous surgery: extensive resections of the ileum and right colon lead to diarrhoea due to lack of absorptive surface and hence fat and carbohydrate malabsorption, decreased transit time or changes in the bile acid pool including malabsorption.21 Bacterial overgrowth can often be a problem in this situation, particularly in bypass operations such as in gastric surgery and jejunoileal bypass procedures for morbid obesity. Shorter resections of the terminal ileum can lead to bile acid diarrhoea, which typically occurs after meals and usually responds to fasting and bile acid sequestrants (see sections 5 and 6).
3. Previous pancreatic disease.
4. Systemic disease: thyrotoxicosis and hypoparathyroid disease, diabetes mellitus,23 adrenal disease or systemic sclerosis may predispose to diarrhoea through various mechanisms including endocrine effects, autonomic dysfunction, small bowel bacterial overgrowth or the use of concomitant drug therapy.
5. Alcohol: diarrhoea is common in alcohol abuse. Mechanisms include direct toxic effect on intestinal epithelium, rapid gut transit, decreased activity of intestinal disaccharidases and decreased pancreatic function.24
6. Diet: excessive intake of caffeine (eg, coffee, energy drinks), milk in patients with lactase deficiency, food additives (eg, sorbitol), fructose and other FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) should be sought (see section 5.3).
7. Drugs: up to 4% of cases of chronic diarrhoea may be due to medications (particularly magnesium supplements, anti-hypertensives (eg, ACE inhibitors) and non-steroidal anti-inflammatory drugs, newer gliptins (dipeptidyl peptidase-4 inhibitor), theophyllines, antibiotics, antiarrhythmics and antineoplastic agents).25
8. Recent overseas travel or other potential sources of infectious gastrointestinal pathogens.
9. Recent antibiotic therapy and Clostridium difficile infection: many different tests are now available for the detection of C. difficile, but most clinical laboratories use a commercial enzyme immunoassay for C. difficile toxin (details in section 3.3.3).
3.3 Initial investigations

3.3.1 Blood tests

Abnormal initial screening investigations such as a high erythrocyte sedimentation rate, anaemia or low albumin have a high specificity for the presence of organic disease.26 The presence of iron deficiency is a sensitive indicator of small bowel enteropathy, particularly coeliac disease,27 but is obviously not a specific test. Guidelines regarding the approach to a patient with iron deficient anaemia have previously been published.28 A basic screen for evidence of malabsorption should include full blood count, urea and electrolytes, liver function tests, vitamin B12, folate, calcium, ferritin, erythrocyte sedimentation rate and C reactive protein. Thyroid function tests should also be performed at this stage with a suppressed thyroid-stimulating hormone being the best predictor for hyperthyroidism.

3.3.2 Serological tests for coeliac disease

Coeliac disease is defined as a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals.29 Epidemiological studies screening cohorts of healthy adult volunteers in the USA, UK and other European countries consistently report a prevalence of 0.5–1%.30–32 There is some evidence that the prevalence is increasing,33–35 and despite being a common global phenomenon, diagnosis is often delayed.36–37

The development of highly accurate serological tests and large epidemiological studies have contributed to our current understanding of coeliac disease. It is now recognised that the majority of patients may have more subtle presenting symptoms, adult presentations are more frequent than paediatric, and there is a ‘pre-coeliac’ state.32 38 39

Recognition of the coeliac iceberg has improved understanding and detection of coeliac disease.40 The visible iceberg above the waterline depicts patients with typical GI symptoms such as diarrhoea and weight loss. The subsequent stratum just below the waterline represents patients considered to have atypical presentations. They may have vague, non-specific GI symptoms such as bloating, or conditions associated with coeliac disease such as iron deficiency anaemia, osteoporosis and persistently abnormal liver function tests.40–42 Among certain groups the prevalence of coeliac disease will be higher (e.g. type 1 diabetes, autoimmune thyroid disease or a first-degree relative with coeliac disease).43

Diarrhoea may be present in 43–85% of patients with newly diagnosed coeliac disease.40–42 44 45 Conversely, the prevalence of coeliac disease in patients referred to secondary care with chronic diarrhoea has been reported to range from 3% to 10%.46–47 Given the delays in diagnosis for patients with undetected coeliac disease and the fact that the tests are inexpensive43 suggests that serological testing for coeliac disease in patients presenting with chronic diarrhoea is mandatory.

Endomysial antibody (EMA) and tissue transglutaminase antibody (TTG IgA) have a combined sensitivity and specificity of over 90% when used in combination in selected populations with a high prevalence of coeliac disease.48 49 However, when the prevalence of coeliac disease falls to 1%, as found in screening populations, the positive predictive value of these tests falls to around 80% or less.48 49 The sensitivity of the serological tests also falls well below 90% when histological grades less than Marsh 3 (villous atrophy) are considered.38–52 An IgA immunoglobulin level is also necessary as both EMA and TTG are IgA-based. In the presence of IgA deficiency, IgG EMA or IgG TTG should be performed.53 Finally, if the clinician is still suspicious, then a duodenal biopsy should be performed even in the presence of negative antibodies. Antibody-negative coeliac disease accounts for 6.4–7% of cases of patients presenting with coeliac disease.48 53

3.3.3 Immunodeficiency and infections

Immunodeficiency states complicate diagnosing the cause of diarrhoea. The first step is to identify the immunodeficiency. Beyond the common primary and haematological causes, clinicians should be aware that chronic diarrhoea is a common symptom in patients newly diagnosed with human immunodeficiency virus

Box 1 Causes of chronic diarrhoea

Common

► IBS-diarrhoea
► Bile acid diarrhoea
► Diet
  – FODMAP malabsorption
  – Lactase deficiency is highly prevalent in non-Caucasian ethnic groups
  – Artificial sweeteners (e.g. sorbitol, xylitol in chewing gum, soft drinks)
  – Caffeine (e.g. coffee, coke, energy drinks)
  – Excess alcohol
  – Excess liquorice
► Colonic neoplasia
► Inflammatory bowel disease
  – Ulcerative colitis
  – Crohn’s disease
  – Microscopic colitis
► Coeliac disease
► Drugs
  – Antibiotics, in particular macrolides (e.g. erythromycin)
  – Non-steroidal anti-inflammatory drugs
  – Magnesium-containing products
  – Hypoglycaemic agents (e.g. metformin, gliptins)
  – Antineoplastic agents
  – Others (e.g. furosemide, Olestra)
► Overflow diarrhoea

Infrequent

► Small bowel bacterial overgrowth
► Mesenteric ischaemia
► Lymphoma
► Surgical causes (e.g. small bowel resections, faecal incontinence, internal fistulae)
► Chronic pancreatitis
► Radiation enteropathy
► Pancreatic carcinoma
► Hyperthyroidism
► Diabetes
► Giardiasis (and other chronic infection)
► Cystic fibrosis

Rare

► Other small bowel enteropathies (e.g. Whipple’s disease, tropical sprue, amyloid, intestinal lymphangiectasia)
► Hypoparathyroidism
► Addison’s disease
► Hormone secreting tumours (VIPoma, gastrinoma, carcinoid)
► Autonomic neuropathy
► Factitious diarrhoea
► Brainerd diarrhoea (possible infectious cause not identified)
Guidelines

We recommend an initial screening blood test (full blood count, ferritin, tissue transglutaminase/EMA and thyroid function test) as well as stool tests for inflammation (faecal calprotectin) should be undertaken in primary care (Grade of evidence level 3, Strength of recommendation strong).

We recommend screening for coeliac disease using serological tests (tissue transglutaminase or EMA), which have a high sensitivity and specificity for the disease (Grade of evidence level 1, Strength of recommendation strong).

If IgA deficient, we recommend either IgG EMA or IgG TTG should be performed (Grade of evidence level 2, Strength of recommendation strong).

HIV infection should be excluded in those who are immunocompromised and present with chronic diarrhoea (Grade of evidence level 2, Strength of recommendation strong).

We recommend combination testing for *Clostridium difficile* infection; confirmation of the presence of the organism by glutamate dehydrogenase enzyme immunoassay or PCR and determining if these are toxin-producing (toxin EIA) (Grade of evidence level 2, Strength of recommendation strong).

4.1 Stool tests

The Bristol stool chart (see online supplementary material), which is validated, is a good tool to determine stool consistency and guide subsequent investigations. Stool weights are no longer used or recommended due their limited clinical value.

4.1.1 Faecal calprotectin

The inflammatory marker faecal calprotectin has recently been shown to be of value and the subject of a NICE Diagnostic Guideline (DG11). Calprotectin is released when inflammatory processes occur due to the degranulation of neutrophil granulocytes. When the inflammation is within the intestinal tract, calprotectin is released into the intestinal lumen and is stable enough to be measured in faeces. NICE recommends the use of faecal calprotectin as an option in the differential diagnosis of IBS and IBD in adults with recent onset lower GI symptoms in whom cancer is not suspected. Thus patients with low calprotectin levels are unlikely to have any active inflammatory processes at the time of sample collection, making a diagnosis of IBD less likely. NICE uses the commonly quoted 50 μg/g faeces as the decision level above which IBD is more likely, although other causes of raised calprotectin include colorectal cancer, infectious gastroenteritis and non-steroidal anti-inflammatory drugs. This strategy should lead to a reduced level of secondary care referrals with associated lower cost and morbidity. There is some evidence that calprotectin levels >250 μg/g faeces suggest active inflammation correlating quite well with endoscopic inflammation. The issue of indeterminate levels still remains elusive, although one study that looked at the 12-month outcome of indeterminate faecal calprotectin levels (50–249 μg/g faeces) noted an 8% chance of developing IBD compared with 1% in those with levels <50 μg/g faeces. For further details see online supplementary material.

4.1.2 Faecal occult blood test (FOBT)/faecal immunochemical technique (FIT)

The detection of excess blood in faeces has been used for many years in the diagnosis of colorectal cancer. There are two types of faecal occult blood test: the older gFOBT based on the oxidation of guaiac gum and the newer FIT for the detection of faecal haemoglobin, which uses an immunochemical technique to detect blood. Current European guidelines for colorectal cancer screening recommend the use of faecal haemoglobin and, although the UK still uses the older test, plans are well advanced to change to faecal haemoglobin in both Scotland and England in 2018 for screening. Emerging studies indicate that, in those with lower GI symptoms suggestive of colorectal cancer, FIT testing has a high negative predictive value (0.99) with the optimal cut-off between 7 and 10 μg/g faeces. With the appropriate quality assurance processes in place and good clinical judgement, there is good evidence that using faecal haemoglobin in symptomatic patients may be of benefit in reducing the burden of unnecessary colonoscopic examinations. For further details see online supplementary material.

4.2 Endoscopic and histological assessment

In most patients with chronic diarrhoea, some form of endoscopic investigation will be necessary. In young patients (less than 40 years) reporting ‘diarrhoea’ but who have other typical symptoms of a functional bowel disorder and negative initial investigations, a diagnosis of IBS may be made in the primary care setting without recourse to further investigations.

(HIV), Clinicians should be aware of HIV prevalence estimates in their region and test accordingly. Once an immunodeficiency has been identified, potential chronic infection with pathogens such as cryptosporidia or norovirus should be investigated.

Chronic diarrhoea due to infectious agents is unusual in the immunocompetent patient. Protozoan infections, such as giardiasis and amoebiasis, are most likely to result in chronic infections. Examination of three fresh stools for ova, cysts and parasites remains the mainstay of diagnosis and has a sensitivity of approximately 60–90% for detection of these organisms. If there is doubt about persisting *Giardia* infection, then the use of a stool ELISA (92% sensitivity and 98% specificity) has largely replaced the need for intestinal biopsies and wet (saline and iodine mount) preparations. Short course treatment with metronidazole or tinidazole is effective. Serological testing (indirect haemagglutination test or ELISA) can be a useful adjunct in cases of amoebic liver abscess—more so in endemic areas. Clinicians should liaise with their local microbiology services to establish the diagnostic methods used, which may include transition to newer ELISA-based assays with greater sensitivity and specificity.

A notable exception is *Clostridium difficile* infection where diarrhoea can persist through failure of initial treatment or rapid relapse, which has consistently occurred in one in four patients in the placebo arms of recent clinical trials. Identification of a wide variation in testing approaches across Europe has led to recommendations for a standardised two-stage approach. The first step identifies the presence of the organism with glutamate dehydrogenase enzyme immunoassay (EIA), nucleic acid amplification testing or PCR. The second stage looks to demonstrate active *C. difficile* toxin production through toxin EIA. Such a combination of a sensitive and then a specific test gives high negative and positive predictive values where tests agree. Where they do not, clinical judgement on the likelihood of infection will determine the need for treatment. The phenomenon of post-infectious IBS after *C. difficile* infection is recognised, hence clinicians should be wary of excessive antimicrobial therapy on the basis of PCR alone, especially in the absence of clear evidence of toxin production.

<table>
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<tr>
<th>Recommendations</th>
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<td>If IgA deficient, we recommend either IgG EMA or IgG TTG should be performed (Grade of evidence level 2, Strength of recommendation strong).</td>
</tr>
<tr>
<td>HIV infection should be excluded in those who are immunocompromised and present with chronic diarrhoea (Grade of evidence level 2, Strength of recommendation strong).</td>
</tr>
<tr>
<td>We recommend combination testing for <em>Clostridium difficile</em> infection; confirmation of the presence of the organism by glutamate dehydrogenase enzyme immunoassay or PCR and determining if these are toxin-producing (toxin EIA) (Grade of evidence level 2, Strength of recommendation strong).</td>
</tr>
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is some evidence that using anti-vinculin and anti-cytotoxophilic
distressing toxin B antibodies may help with making a positive
diagnosis of IBS. However, patients under 40 years without
typical symptoms of functional bowel disorder and/or severe
symptoms and documented diarrhoea (as previously defined)
should have further evaluation (see section 3.2.3).

4.2.1 Colonoscopy
Screening colonoscopy in asymptomatic individuals detects
colonic adenomas in 14.4–37.5% of cases, but few studies have
addressed the frequency of neoplasia in symptomatic patients,
and none has specifically addressed the prevalence of adenomas
in patients undergoing colonoscopy for diarrhoea. Neugut and
colleagues8 showed that, of 861 patients (with rectal bleeding),
only 154 had a change in bowel habit of which 7% of these
had colonic neoplasms. This would suggest that change in
bowel habit is a poor guide to the prevalence of neoplasia unless
advanced to the point of malignancy. Almost half had neoplasia
proximal to the splenic flexure, indicating the need for full colon-
oscopy rather than flexible sigmoidoscopy in these patients.78 79

In addition to neoplasia, colonoscopy also has a diagnostic
yield for other conditions ranging from 7% to 31%, with IBD and
microscopic colitis being most commonly found. Hence both right-
and left-sided colonic biopsies are necessary (see further
details in section 5.2).80–83 Routine ileoscopy further adds to the
value of colonoscopy. This led to a positive diagnosis in 18% of
non-HIV patients who complained of diarrhoea.84 In patients
in whom IBD is suspected, the value of ileoscopy and biopsy is
further enhanced: 36% of patients with a normal colonoscopy
and diarrhoea had terminal ileal disease.85 Although these results
clearly reflect considerable referral bias, when taken together
they suggest that, in chronic diarrhoea of uncertain origin, colo-
oscopy and ileoscopy with biopsy will lead to a diagnosis in
approximately 15–20% of cases.

Colonoscopy is more sensitive than barium enema and, given
this and the need to obtain histology to exclude colitis, barium
studies of the colon are no longer indicated in chronic diar-
rahoea.86 87

4.2.2 Flexible sigmoidoscopy
Unprepared rigid sigmoidoscopy has long been used in the
outpatient setting to quickly assess the rectum and stool. This
remains an appropriate examination in those younger patients
who on clinical grounds are believed to have a functional bowel
disorder. Some authors conclude that, in this age group, most
pathology occurs in the distal colon and is thus accessible with a
flexible sigmoidoscope.8 In one study that examined the
prevalence and anatomical distribution of colonic pathology
in patients presenting with non-HIV-related chronic diarrhoea,
15% of patients had colonic pathology.88 Some 99% of these
diagnoses could have been made from biopsies of the distal
colon using a flexible sigmoidoscope, the primary diagnoses
being microscopic colitis, Crohn’s disease and ulcerative colitis.
Other sources point more strongly to the need for full colonos-
scopy in chronic diarrhoea of uncertain aetiology.57 62

4.2.3 Upper gastrointestinal endoscopy
There is little information on the diagnostic yield of upper GI
endoscopy in patients whose diarrhoea is suspected to be due to
malabsorption. This will clearly vary depending on the cohort of
patients being investigated, referral criteria and degree of suspi-
cion for any given underlying diagnosis. Coeliac disease should
be considered and investigated as per section 3.3.2.

4.3 Small bowel imaging and visualisation for inflammation
4.3.1 Small bowel imaging for abnormality (eg, inflammatory bowel
disease)
Traditionally the small bowel barium follow through (SBBFT)
or barium enteroclysis was the standard means of assessing small
towel mucosa. However, barium examinations have both a
low sensitivity and specificity in the detection of small bowel
abnormalities.89 Ultrasonography (USS) may be used to assess
the bowel, and the advantages include its non-invasiveness and
availability. USS has been shown to have high sensitivity in the
detection of terminal ileal pathology but its accuracy for
disease proximal to the terminal ileum is lower compared with
CT and MRI.90–92 The significant disadvantages of USS include
the difficulty of viewing the GI tract in its entirety and high oper-
ator dependence.

Cross-sectional modalities such as CT and MRI have emerged
as the preferred imaging tests for evaluation of the small bowel.
Specialised small bowel imaging procedures such as CT and
MR enterography and enteroclysis have become preferred, as
comparative studies have shown their superiority compared with
SBBFT.93 95

The enterographic technique (CT or MR) is based on imaging
after ingestion of a large amount of oral contrast over a set time
period whereas the enteroclysis procedure requires nasojugal
intubation. The main disadvantage of an enteroclysis examina-
tion is the nasojugal intubation, which is uncomfortable for
patients leading to greater patient preference for enterography
examinations.96 97

Recent validated studies have reported high accuracy of
MR enterography examination for small bowel abnormalities
compared with surgical findings.94 98–101 Further advances in
MR technology with diffusion-weighted imaging (MR- DWI)
are proving important for the diagnosis and assessment of
bowel abnormalities.102 103 Although CT is also widely used
in abdominal imaging, its main disadvantage is the associated
radiotherapy burden. A recent meta-analysis has concluded
that it is preferable to use a non-ionising modality such as USS
or MRI in order to reduce radiation exposure.98 104 Several
comparative studies also report that MRI has higher sensi-
tivity than CT in the detection of small bowel diseases and
neoplasms.94 96 98–100 103 105

Current evidence-based analysis indicates that either CT or
MR enterography (depending on availability) should be the
preferred initial test for the diagnosis of small intestinal abnor-
malities in patients with chronic diarrhoea. MRI is the preferred
option as it does not entail high-dose radiation compared with
CT imaging.101 103

4.3.2 Video capsule endoscopy
Capsule endoscopy has a role either as a means to distinguish
small bowel abnormalities or to assess further the small bowel
after a negative radiological (MR or CT) investigation. However,
in some centres this may be viewed as a first-line investigation of
the small bowel due to its non-invasive nature (patient tolera-
bility and acceptance) as well as increased diagnostic yield when
compared by meta-analysis and systematic review against other
small bowel investigations.106

When specifically considering coeliac disease, capsule endos-
copy is not recommended and patients should be encouraged to
have a duodenal biopsy in order to obtain a histological diag-
nosis. For patients who are unable or unwilling to undergo a
gastroscopy, a small bowel capsule may help to demonstrate
villous atrophy in the presence of positive coeliac serology.
4.3.3 Enteroscopy
Small bowel enteroscopy has been evaluated as a complementary investigation to SSBF and capsule endoscopy, either as a means to distinguish small bowel abnormalities or to assess further the small bowel after a negative radiological investigation. A key feature of enteroscopy studies in assessing inflammation or obscure bleeding is the consistently high false negative rate of prior upper and lower endoscopy, emphasising the need to ensure that adequate visualisation and biopsy of the duodenum and ileum have been achieved. Push enteroscopy may have some value to obtain jejunal biopsies in determining rare causes of diarrhoea—for example, cyclospora infections, sprue-related strongyloidosis or those with malabsorption/raised IgA TTG and non-diagnostic duodenal biopsies. Device-assisted enteroscopy (double balloon, single balloon or spiral) is complementary to capsule endoscopy and should be reserved for targeting lesions (and obtaining histology) or therapeutic intervention when abnormalities are identified by small bowel imaging or capsule endoscopy.

5 COMMON DISORDERS
5.1 Bile acid diarrhoea
Given that a third of patients labelled with diarrhoea-predominant IBS actually suffer from bile acid diarrhoea, this condition is more common than initially perceived with a significant impact on patients. Bile acids are required for the digestion of fat and are synthesised from cholesterol in the liver and excreted in the bile mainly in the form of glycine or taurine conjugates. This process is regulated through a negative feedback manner by nuclear farnesoid receptor as well as by fibroblast growth factor 19 (FGF-19), a protein released from ileal enterocytes. Up to 95% of bile acids are reabsorbed through the enterohepatic circulation.

SeHCAT testing (the standard radio-labelled test used to identify bile acid diarrhoea: tauroselcholic (Se) acid) was first described in 1982. A retention of 10–15% at 7 days is usually defined as mild bile acid loss, 5–10% as moderate and 0–5% as severely abnormal. These values also predict response to therapy with bile acid sequestrants.

The serum bile acid precursor 7α-hydroxy-4-cholene-3-one is an intermediary product in the synthesis of bile acids from cholesterol by the liver enzyme CYP7A1 and so provides a measure of bile acid synthesis. It has a negative predictive value of 95% and positive predictive value of 74% compared with SeHCAT, hence making it attractive as a screening test for excessive bile acid turnover. Levels above 47.1 ng/mL are indicative of bile acid diarrhoea. C4 requires a fasting sample, like FGF-19; both undergo diurnal and postprandial variation, with false positives also occurring in those with liver disease.

Faecal bile acid measurement is another option with values >2300 µmol/48 hours indicative of bile acid diarrhoea. However, as dietary fat intake and consequently bile acid levels are variable, it requires a 48-hour sample. Moreover, is cumbersome and not yet commercially available in the UK. Additionally, other less invasive and economical tests such as urine testing for 2-propanol and acetone are currently being evaluated. A summary table of tests in bile acid diarrhoea are presented in these studies.

Up to 30% of patients with diarrhoea-predominant IBS have evidence of bile acid diarrhoea as determined by SeHCAT testing. Compared with controls, IBS patients had lower SeHCAT values and higher C4 levels but similar FGF-19 levels. More than 50% responded to bile acid sequestrants (colestipol). In addition to patients with ileal disease (eg, Crohn’s disease), bile acid diarrhoea has also been reported in patients following cholecystectomy and post-infectious diarrhoea. For those not responding to treatment, other additional causes should be sought (eg, bacterial overgrowth, pancreatic insufficient or microscopic colitis), even if SeHCAT testing has been abnormal. Another under-recognised group are those with cancer who have received pelvic chemoradiotherapy as >50% have bile acid diarrhoea.

The NICE DG7 diagnostic guidance report on SeHCAT in 2013 and subsequent update in 2016 recognised the potential for patient and system benefits associated with SeHCAT investigations. One study suggests that the economic evaluation needs to be reconsidered as the impact of not making a positive

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**Recommendations**

- **We recommend use of faecal calprotectin in younger patients (under 40 years) with chronic diarrhoea in whom inflammation is suspected and not cancer (Grade of evidence level 1, Strength of recommendation strong).**
- **Cut-off of 50 µg/g faeces (assay-dependent) is recommended to distinguish functional bowel disorder from organic inflammatory bowel disease (Grade of evidence level 1, Strength of recommendation strong).**
- **In patients with typical symptoms of functional bowel disease, normal physical examination and normal screening blood and faecal tests (calprotectin), a positive diagnosis of IBS can be made (Grade of evidence level 2, Strength of recommendation strong).**
- **For those with lower gastrointestinal symptoms suspicious of colon cancer (without rectal bleeding), we suggest faecal immunological testing as a rule out test to guide need for referral or urgency of investigations either in primary or secondary care; (Grade of evidence level 2, Strength of recommendation weak).**
- **In patients with chronic diarrhoea, we recommend colonoscopy (with ileoscopy) and biopsy as the preferred investigation of the lower bowel (Grade of evidence level 1, Strength of recommendation strong).**
- **In younger patients (under 40 years) with a normal faecal calprotectin and in whom functional bowel disease is suspected, we recommend a flexible sigmoidoscopy with biopsy (Grade of evidence level 3, Strength of recommendation strong).**
- **We recommend either MR enterography or video capsule endoscopy (VCE) (depending on local availability) rather than CT as first-line investigation for diagnosing inflammation within the small bowel (Grade of evidence level 1, Strength of recommendation strong).**
- **We do not recommend VCE for the diagnosis of coeliac disease due to insufficient evidence (Grade of evidence level 5, Strength of recommendation strong).**
- **Ultrasonography of the small bowel, while attractive due to its non-invasive nature and absence of radiation exposure, has a limited diagnostic role hence cannot be recommended routinely (unless other modalities are unavailable) (Grade of evidence level 4, Strength of recommendation strong).**
- **Enteroscopy (device assisted) has limited diagnostic value for chronic diarrhoea and we recommend its role mainly for targeting predefined lesions (Grade of evidence level 4, Strength of recommendation strong).**
diagnosis leads to repeat (unnecessary) testing with additional cost to the NHS. More recently it has been shown that making a positive diagnosis of bile acid diarrhoea (in this study using SeHCAT) was economically beneficial as those who had negative SeHCAT tests underwent significantly more investigations (1.8x more), especially cross-sectional imaging (13x more likely), although those with a positive SeHCAT had more clinical appointments.

A systematic review and meta-analysis comprising 36 studies and 5028 patients on bile acid diarrhoea biomarkers concluded that SeHCAT had the highest diagnostic yield to date (limited by study heterogeneity), with 25% previously diagnosed as having functional diarrhoea actually having primary bile acid diarrhoea.

In a series of 264 patients where 53% had bile acid diarrhoea, 44% failed to respond to cholestyramine alone. Half of these non-responders derived benefit from colesvelam (unlicensed but used with extended indication). Thus, lack of response to cholestyramine does not constitute exclusion of bile acid diarrhoea, hence therapeutic trials of bile acid sequestrants (cholestyramine or colesvelam) are not recommended. Pooled data from 15 studies show a dose-response relationship between the severity of malabsorption and the effect of treatment with a bile acid sequestrant: clinical response to cholestyramine occurred in 96% of patients with having functional diarrhoea actually having primary bile acid diarrhoea.

There are also logistic considerations for high throughput nuclear medicine departments as other concurrent studies may result in background radiation which could affect the nuclear medicine departments as other concurrent studies

5.2 Microscopic colitis
Collagenous colitis and lymphocytic colitis are two forms of microscopic colitis, both commonly presenting with chronic, non-bloody watery diarrhoea and with few or no endoscopic abnormalities. They were first described around 1980. Histological features are distinct from ulcerative colitis or Crohn’s disease and are not reliably detected on macroscopic examination at colonoscopy. Microscopic examination shows an increased number of intraepithelial and lamina propria lymphocytes (>20/100 µm) in both forms of microscopic colitis, together with a thickened subepithelial collagen band (>10 µm) in collagenous colitis.

These conditions have been the subject of several recent systematic reviews and meta-analyses and data from these have been used to inform the current guidance. The clinical presentation, risk factors, pathology, disease course and response to treatment have been reviewed and compared for lymphocytic and collagenous colitis. The epidemiology and trends have been reviewed and compared for lymphocytic and collagenous colitis. A systematic review and meta-analysis comprising 36 studies and 5028 patients on bile acid diarrhoea biomarkers concluded that SeHCAT had the highest diagnostic yield to date (limited by study heterogeneity), with 25% previously diagnosed as having functional diarrhoea actually having primary bile acid diarrhoea.

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There are also logistic considerations for high throughput nuclear medicine departments as other concurrent studies may result in background radiation which could affect the nuclear medicine departments as other concurrent studies...
Fructose is a hexose monosaccharide that is found in food on its own, as a disaccharide with glucose-forming sucrose and as longer chain polymers called fructans. Fructose is usually absorbed at the epithelium via the facilitative transporter GLUT5 and the GLUT2 glucose-fructose co-transporter. The modern diet may contain high levels of isolated fructose or fructose in excess of glucose that exceed the absorption capacity of the small bowel (eg, soft drinks sweetened with corn syrup). Undigested fructose then passes into the colon and is fermented in the same manner as lactose in patients who are deficient in small intestinal lactase due to non-persistence of this enzyme expression into adult life.

Fructans are present in large concentrations in wheat, a staple of the diet for many populations (eg, bread, noodles). Fermentation of fructans by colonic bacteria is the cause of ‘wheat intolerance’ in many patients without coeliac disease. Similarly, sorbitol and other non-absorbed sugar alcohols (‘polyols’) used as artificial sweeteners pass unchanged into the colon and can induce diarrhea if taken in large quantities (eg, diet drinks, chewing gum).

Interpretation of carbohydrate breath tests is particularly contingent on the challenge dose used. Double-blind randomised controlled dietary challenge studies show a dose-response relationship between the intake of lactose, fructose and fructans with the likelihood of malabsorption (as assessed by an increase in breath hydrogen) and the development of abdominal symptoms, including diarrhea. The prevalence of primary lactase deficiency based on the presence of the 13910 C/C genotype in the promoter region of the lactase enzyme gene is 2–15%, predominantly in Caucasian populations in Northern Europe. A recent meta-analysis of epidemiological data reported that 68% (95% CI 64% to 72%) of the world’s population are lactase-deficient, and this approaches 100% in the Han Chinese population. There is a high level of concordance between the presence of this genotype and lactose malabsorption. In contrast, there is no unique genotype linked with fructose or fructan malabsorption and a review of nine studies found that 25 g fructose may induce an increase in breath hydrogen in 40% of healthy subjects, but rarely induces symptoms. Prospective studies have shown that self-reported dietary intolerance is a poor predictor of objective test results or even response to dietary restriction. Thus, breath testing after carbohydrate challenge could be useful if it identifies the cause of symptoms and predicts response to therapy. A positive lactose breath test fulfils these criteria, although avoidance of dairy products alone is rarely sufficient treatment in patients with IBS. No trials have directly addressed patients with isolated diarrhea but, in diarrhoea-predominant IBS, two randomised controlled trials and one prospective study have found no relationship between the result of breath testing and response to dietary fructose reduction. At present, fructose breath testing cannot be said to inform diagnosis and treatment of fructose intolerance.

5.4 Post radiation diarrhea

This is increasingly more common given that there is a three-fold rise in cancer survivors in the last three decades. Many of the causes of chronic diarrhea discussed in other sections of these guidelines are common in people who have been treated for GI and other cancers (eg, bile acid diarrhea, pancreatic insufficiency). Specific guidance is now available as to how to investigate such patients, especially for the late effects of radiation therapy.

5.5 Rapid intestinal transit

Many conditions associated with diarrhoea have been ascribed to abnormalities of gut motility and increased intestinal transit time. These include post-surgical states (eg, vagotomy), endocrine conditions (eg, hyperthyroidism), bile acid diarrhea, autonomic neuropathy (eg, diabetes) and, most often, primary functional diarrhoea. Assessment of the contribution of disordered motility and transit to diarrhoeal disease is hampered by the fact that (a) many of these conditions have multifactorial aetiologies; (b) available tests have limited ability to identify the cause of symptoms; and (c) wide individual variation in normal values precludes a definitive diagnosis in all except the most severe cases.

Detailed measurements of motility can be acquired by small intestinal or colonic manometry, ideally with high-resolution technology that clearly visualises propulsive and retrograde contractions that promote and inhibit transit. Pressure measurements are abnormal in the presence of obstruction and gross neuromuscular dysfunction, but findings in patients with severe symptoms do not correlate well with pathology on small bowel biopsy. In patients with chronic diarrhea and IBS, the results are almost always normal and such invasive techniques are not well tolerated.

Recommendations

- If functional bowel disease or IBS-diarrhoea is suspected, we recommend that bile acid diarrhea should be excluded with either 75SeHCAT testing or fasting serum C4 (7α-hydroxy-4-cholesten-3-one) levels. A test and treat approach is recommended as opposed to blind empirical therapy unless no diagnostic test is available (Grade of evidence level 1, Strength of recommendation strong).
- Patients with very low 75SeHCAT values are most likely to have a response to treatment with bile acid sequestrants. We recommend this is tried if the 75SeHCAT value is <15% or the fasting serum C4 is raised above defined laboratory values (Grade of evidence level 2, Strength of recommendation strong).
- We recommend colonic biopsies to exclude microscopic colitis. These should be at least from the left side (not rectal) and, as microscopic colitis can be patchy, right-side biopsies may improve diagnostic yield (Grade of evidence level 1, Strength of recommendation strong).
- Both glucose and lactulose hydrogen breath tests have poor sensitivity and specificity and are not recommended for the diagnosis of small bowel bacterial overgrowth (Grade of evidence level 2, Strength of recommendation strong).
- The utility of concurrent hydrogen and methane breath testing with measurements of oroaeal transit time could reduce a false positive diagnosis due to variability in intestinal transit, but has not been subject to definitive clinical study hence cannot be recommended (Grade of evidence level 4, Strength of recommendation strong).
- We recommend investigating for intestinal transit with manometry only if there is clinical suspicion and failure to respond to therapy (Grade of evidence level 4, Strength of recommendation strong).
Only patients who remain undiagnosed after extensive traditional investigation and failed medical therapy should be considered for manometry studies. In the future non-invasive MRI may find a role in the diagnosis of diarrhoeal conditions. Recent studies have shown that this technique can provide comprehensive measurements of both motility and transit and can identify specific abnormalities in patients with diarrhoea-predominant IBS.

6 TESTS FOR MALABSORPTION

Malabsorption may occur as a result of a defective luminal environment such as inadequate bile acid or enzyme function, failure of epithelial transport due to mucosal disease or structural disorders (eg, fistula, surgical resection). Although there are generally coexisting deficiencies of fat, carbohydrate, protein, vitamins and minerals, the effects of one of these may predominate. Thus, pancreatic exocrine insufficiency is the most frequent cause of severe predominant steatorrhoea where faecal fat excretion exceeds 13 g/day (47 mmol/day). This is rare in mucosal or structural disease, although milder forms of steatorrhoea are common. In comparison, carbohydrate malabsorption is predominantly associated with mucosal disease or dysfunction. Approaches to investigation involve either detection of the relevant compound in faeces or detection of an absorbed substance in the blood, urine or other tissues. A variation of the latter is the use of breath testing, which relies on the breakdown and bacterial fermentation of the test substance. These investigations (stool fat, isotope breath or faecal tests, sugar and other permeability tests) were detailed by a previous version of these guidelines and will not be covered further here because, with the exception of hydrogen breath tests (see section 6.5.2), none have received significant support in publications since 2003 and they have not established themselves in clinical practice outside specialist centres.

6.1 Fat malabsorption

Pancreatic exocrine insufficiency can lead to malabsorption (or more correctly maldigestion) and diarrhoea due to impairment of pancreatic enzyme and bicarbonate secretion. In adults, this is usually the result of chronic pancreatitis, pancreatic carcinoma or pancreatic surgery. Maldigestion of fat can result in steatorrhoea and weight loss but may not be clinically apparent. Steatorrhoea can be caused by small bowel malabsorption and clinical assessment of steatorrhoea (eg, by stool inspection) is unreliable. Symptoms of pancreatic exocrine insufficiency usually develop 10–15 years after first symptoms of chronic pancreatitis and when secretion of lipase and other pancreatic enzymes is reduced to <10% of normal values. The diagnosis of advanced chronic pancreatitis in patients presenting with diarrhoea is often suggested by the clinical history and confirmed with imaging. A number of recent guidelines outline the current strategies for diagnosing chronic pancreatitis. There are international variations in practice depending on the availability of various modalities such as endoscopic ultrasound (EUS) and direct pancreatic function tests. However, there is a broad agreement that invasive direct pancreatic function testing has become largely redundant in routine clinical practice, replaced by indirect pancreatic function testing and imaging. It is also recognised that there is currently no ideal test to diagnose chronic pancreatitis in early/mild disease.

6.1.1 Faecal elastase

Three-day faecal fat estimation is laborious, unpleasant and is no longer performed in UK laboratories. Stool chymotrypsin assays have been replaced by faecal elastase because of its greater stability and the improved sensitivity of the test.

Human elastase-1 is an anionic protease belonging to the family of serine proteases along with other digestive enzymes such as chymotrypsin and trypsin. Its ability to degrade elastin is unique, but it is also stable in stool for up to a week at room temperature reaching concentrations 5–6 times higher than duodenal juice. This stool test has emerged as a preferred test of pancreatic function and has largely replaced invasive and indirect pancreatic function tests in many centres. Normal values are 200–500 μg/g, with 100–200 μg/g in mild to moderate insufficiency and <100 μg/g in severe insufficiency. The test is unaffected by simultaneous enzyme therapy or diet and requires only a single 100 mg stool sample. Faecal elastase-1 has been well characterised as a sensitive biomarker for moderate to severe pancreatic insufficiency with sensitivities of 73–100% and specificities of 80–100%. However, faecal elastase is not useful in cases of mild pancreatic insufficiency with sensitivities of <60% and is not able to reliably distinguish pancreatic from non-pancreatic malabsorption. A comparison of faecal elastase with other non-invasive tests suggests superior sensitivity to the para-amino benzoic acid test and the pancreolauryl test. The test should be used with care in patients with liquid stool and this can lead to false positive results (ie, low levels of faecal elastase due to dilution).

6.2 Pancreatic imaging

The progressive inflammatory change that occurs in chronic pancreatitis leads to significant changes in pancreatic structure. Focal segmental or diffuse destruction of the parenchyma occurs in the early stages while structuring, dilation of the duct and calcification tend to occur late in the disease. There has been debate around the significance of the sometimes subtle changes found at EUS or endoscopic retrograde pancreatography (ERP) in the diagnosis of early chronic pancreatitis, particularly in patients presenting with abdominal pain. For more advanced pancreatic disease with significant morphological change, CT scanning has become the initial imaging of choice given the poor sensitivity of USS in this situation (approximately 60%) and in assessing for pancreatic malignancy. Its sensitivity in detecting early pancreatic changes is unknown, but it is significantly less than EUS or magnetic resonance cholangiopancreatography (MRCP)/ERP. Newer non-invasive methods for diagnosing pancreatic cancer are beginning to emerge.

MRCP with secretin (MRCP-S) appears to significantly increase the diagnostic yield in patients with asymptomatic hyperamylasaemia and showed equivalent sensitivity to endoscopic retrograde cholangio-pancreatography (ERCP) in determining ductal changes in patients with idiopathic recurrent pancreatitis. The technique has been proposed as an alternative to direct pancreatic function tests, but issues of standardisation and interpretation remain to be resolved. Quantitative MRCP after secretin has also been correlated with faecal elastase and pancreolauryl testing and has been shown to correlate with histology. However, it is a specialised procedure and not recommended for initial diagnostic investigation for chronic pancreatitis.

EUS is able to detect mild parenchymal and ductal abnormalities not seen on CT. Comparison with ERCP in seven studies revealed sensitivity of 68–100% with specificity of 78–97% based on standard scoring of nine criteria. A study of 83 patients showed EUS to have an equivalent diagnostic accuracy for early and late stage chronic pancreatitis when compared with secretin direct


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pancreatic function tests. Two studies comparing MRCP-S and EUS with ERCP have suggested a slightly higher sensitivity of EUS for changes suggestive of chronic pancreatitis, but it remains questionable whether some of the subtle findings at EUS have clinical relevance. Based on these and other studies, both EUS and MRCP-S would seem effective diagnostic tests for chronic pancreatitis, which are best used in a complementary fashion.

Local availability will inevitably dictate the choice of test, and both modalities would seem to be useful in assessing patients with early/mild forms of chronic pancreatitis, particularly if other approaches such as CT or pancreatic function tests are negative or equivocal. MRI with MRCP protocol is more sensitive and accurate in the detection of chronic pancreatitis, as also recommended by the American Pancreatic Association.

6.3 Invasive pancreatic function testing

Invasive tests of pancreatic function involving direct measurement of pancreatic secretions (catheter aspiration of secretions after secretin, cholecystokinin stimulation or a standard test meal—the ‘Lundh test’) have historically been regarded as the gold standard for determining exocrine pancreatic function. These tests are reported to correlate findings at ERCP, but reasons for abnormal orocaecal transit have been reported to malabsorption. However, patients with anatomical or functional overgrowth (SBBO) in patients presenting with diarrhoea and/or and EUS with ERCP have suggested a slightly higher sensitivity for chronic pancreatitis, which are best used in a complementary fashion.

6.4 Non-invasive pancreatic function testing

These tests assess pancreatic enzymes or the consequences of maldigestion by measurement of stool, serum, urine or breath. The tests include fat, elastase and chymotrypsin measurement in stool, urine tests requiring detection of markers in urine or breath released from the gut and absorbed following digestion of synthetic substrate by pancreatic enzymes. All of these tests require significant loss of pancreatic function before becoming positive, with poor sensitivity and specificity in mild/early pancreatic disease.

6.4.1 Urine and breath tests

The two tests (NBTP and pancreolauryl) previously in use are now of largely historical interest as neither, to our knowledge, is in use in the UK due to their poor sensitivity and specificity.

Equally, while European guidelines have recommended the use of the C13 mixed triglyceride breath test as an alternative to faecal elastase testing, it is not widely available with poor sensitivity in mild/moderate disease and therefore not recommended.

6.5 Small bowel bacterial overgrowth (SBBO)

6.5.1 Introduction

The small bowel normally has little bacterial colonisation with concentrations in the proximal jejunum of less than 10^6 colony forming units (cfu)/mL in the normal healthy state compared with 10^9–10^13 in the colon.

Few data exist on the prevalence of small bowel bacterial overgrowth (SBBO) in patients presenting with diarrhoea and/or malabsorption. However, patients with anatomical or functional reasons for abnormal orocaecal transit have been reported to be at increased risk. Such predisposing factors include diabetes, scleroderma, intestinal pseudo-obstruction, prior surgery (eg, terminal ileal resection), diverticulosis or strictures of the small bowel, Gastric surgery, in particular that involving a blind loop, is associated with a high prevalence of SBBO: up to 50% of patients with gastrojejunostomy and vagotomy compared with 5% of those with vagotomy and pyloroplasty, although the clinical significance of this finding is unclear. Authors have also reported a high prevalence of SBBO in situations associated with achlorhydria such as old age or medical therapy with proton pump inhibitors. However, the clinical relevance of SBBO in this context has not been demonstrated.

Part of the difficulty in establishing a confident diagnosis of SBBO is the lack of a standardised investigative tool. Culture of a small bowel aspirate is the most direct method of investigation of bacterial overgrowth and has been considered to be the gold standard for diagnosis of this condition by some authors.

The presence of >10^4 cfu/mL in either aerobic or anaerobic conditions is conventionally regarded as the criterion for a positive culture, although lower thresholds have been proposed. However, bacterial overgrowth, particularly due to coliforms and enterococci, may occur in apparently healthy individuals with no evidence of malabsorption, so the clinical relevance of such a positive result may be difficult to determine. Although malabsorptive syndromes have primarily been associated with anaerobic organisms, isolation and categorisation of bacterial anaerobes are not routinely performed in many laboratories. Furthermore, the lack of standardisation of bacterial counts, the possibility of sampling errors and the need for intubation make a simpler, less invasive investigation desirable.

6.5.2 Breath tests

Breath tests have been an attractive alternative to culture of small bowel aspirates for many years. However, the sensitivity and specificity of these tests are in general poor.

Hydrogen breath testing is based on the ability of some bacteria to ferment carbohydrates with an end product of hydrogen, which is not produced by mammalian cells. It was originally proposed that breath testing after a carbohydrate load resulted in a double peak due to metabolism by small bowel bacteria, followed by a more prolonged peak due to metabolism by colonic bacteria. The reproducibility of this double peak pattern has been challenged as the appearance of the initial peak is more likely to be due to fermentation by oropharyngeal flora or variation in oroaeal transit times and fermentation of carbohydrate in the caecum. In addition, a false negative result may occur in the 3–25% of individuals whose bacterial flora are not hydrogen producers. This may in part be due to variations in the particular species of bacteria involved in small bowel colonisation as, for example, none of Staphylococcus aureus, Enterococci spp, Serratia or Pseudomonas spp produce hydrogen.

Because of these problems, it is unsurprising that several studies have now shown the sensitivity and specificity of hydrogen breath tests to be low. Recently, Erdogan et al found that glucose breath testing had a sensitivity less than 50% compared with duodenal aspirate, regardless of whether or not methane measurement was added to hydrogen. Both the positive and negative predictive values for breath testing were less than 70%. Corazza and colleagues found sensitivities of 62% and 68% for glucose and lactulose-hydrogen breath tests, respectively. These studies support the poor results with the 10 g lactulose test reported by Riordan and colleagues, with a sensitivity of only 17% and a specificity of 70%. The authors used scintigraphy to
7 SURGICAL/STRUCTURAL CAUSES OF DIARRHOEA

There is significant overlap of the type of patient referred to a surgeon rather than a gastroenterologist and many of the assessment and investigation recommendations are relevant. Often patients are directed towards surgeons through the urgent pathway where there is a need to exclude organic disease. In respect of these patients, investigations should follow the same assessment and investigation pathway as detailed above and in the NICE guidance CG131 (https://www.nice.org.uk/guidance/cg131). There is a tendency—once organic disease, particularly neoplasia and IBD, have been excluded—for the surgeon to either reassure the patient and discharge or refer on to a gastroenterologist. This may be appropriate but it is prudent for the surgeon to bear in mind other potential organic aetiologies. For instance, unrecognised cases of coeliac disease are sometimes seen in colorectal clinics. Patients present with vague GI symptoms, iron deficiency anaemia or chronic diarrhoea and are often falsely diagnosed as diarrhoea-predominant IBS.211

7.1 Faecal incontinence

Some groups of patients are directed towards surgeons because diarrhoea is not the primary patient-perceived symptom. A typical example is faecal incontinence. Such patients may well have a compromised sphincter complex but fail to maintain continence because of the underlying diarrhoea. Although an important risk factor for incontinence along with age, obstetric trauma, pelvic surgery, obesity and other medical conditions such as diabetes and stroke, it may not be recognised and investigated appropriately. Again, NICE gives guidance as to appropriate management with baseline assessment aimed at addressing underlying conditions such as potentially treatable causes of diarrhoea (https://www.nice.org.uk/guidance/cg49). An associated group who may complain of both faecal incontinence and diarrhoea are those with severe faecal loading where the diarrhoea is essentially overflow. Typical patients tend to be those with cognitive or behavioural issues, have learning difficulties, or those with neurological or spinal disease. A focused baseline assessment should therefore include an anorectal examination which will identify impaction and, for instance, rectal prolapse. Plain radiography or radio-opaque marker studies have been used but there is poor correlation between the two.224 Specialist investigations include anorectal manometry and endoanal ultrasound, but there are no accepted standards for performing these specialist tests. The evidence behind their use is limited to the fact that they are better than simple clinical assessment in deciding surgical management. Therefore, they should only be instigated once conservative measures for faecal incontinence have been exhausted and surgical intervention is contemplated.

7.2 Post-surgical diarrhoea

There is a third group of ‘surgical’ patients with diarrhoea. These are the patients who have developed diarrhoea as a result of surgical intervention. The underlying aetiology of the diarrhoea may be attributed to pyloric dysfunction, bile salt malabsorption, bacterial overgrowth or gut bypass reducing absorptive capacity. Upper GI surgery may result in damage or division of the vagus nerve accompanied in part by reduction in capacity of the stomach in the case of gastric resection. Rapid gastric emptying may result in osmotic diarrhoea and associated symptoms of ‘dumping’ syndrome. Surgery can also provide an ideal environment for bacterial colonisation and overgrowth leading to chronic diarrhoea. GI tract surgeries that create a blind loop (eg, a Billroth II procedure or a Roux-en-Y anastomosis) may predispose to stasis and overgrowth due to abnormal motility and ineffective clearance of retained food and secretions.225 In addition, those who have undergone jejunoileal bypass, an end-to-side enterointeretic anastomosis or the creation of a Koch distal ileal pouch are at risk. In the same way, small bowel strictures may lead to bacterial stasis and overgrowth. These may occur
after surgery but can also be seen after radiotherapy, in Crohn’s disease and secondary to some medications.226

Small and large bowel resection clearly reduces absorptive capacity. At the extreme, this results in short bowel syndrome characterised clinically by chronic diarrhoea, dehydration, electrolyte abnormalities and malnutrition. The severity and management depend on the site and extent of the intestinal resection, whether there is disease in the residual bowel and the degree of adaptation of the remaining bowel. However, even a simple limited right hemicolectomy may result in diarrhoea as a result of loss of the ileocaecal valve and resorptive capacity of the right colon. This increases the risk of developing bacterial overgrowth because of retrograde movement of bacteria from the colon into the small intestine. This has been clearly demonstrated in one trial of patients with Crohn’s disease which showed that resection of the ileocaecal valve almost doubled the prevalence of bacterial overgrowth.227

7.3 Fistulae
The common theme in many of these surgical conditions is structural change. However, structural change may not necessarily be surgically induced. Disease processes can also predispose to gut bypass, bile acid diarrhoea and bacterial overgrowth. Fistula formation, such as commonly seen in Crohn’s disease, is one example of gut bypass. Cholecystoenteric fistulae are a potential cause of bile acid diarrhoea, particularly if the fistula is to the colon.228 Small bowel diverticula which occur in approximately 1–6% of the population may harbour bacteria and result in bacterial overgrowth.229

7.4 Investigations
In terms of investigation, clearly surgically-induced structural change may be obvious from the history. A digital rectal examination is essential. It allows clinical assessment of the sphincter complex and will exclude faecal impaction as well as low anorectal lesions. Further investigations, if required, to examine for structural change are mainly radiological; CT scanning and contrast studies will identify the structural changes.

8 RARE CAUSES
8.1 Neuroendocrine tumours
Hormone secreting tumours arising from gastroenteropancreatic tissue are rare causes of diarrhoea. The prevalence of functional pancreatic endocrine tumours is approximately 10 per million population, the incidence ranging from 1/10⁶ cases per year in the case of gastrinomas to fewer than 1/10⁷ cases per year for vasoactive intestinal peptide (VIP)omas and glucagonomas.230 Even this incidence value is likely to be an overestimate. Diarrhoea occurs as part of a symptom complex varying according to the tumour type (eg, 100% cases in VIPoma, approximately 65% in gastrinoma). Although diarrhoea has been reported at a prevalence of 15% in glucagonoma, this again is probably an overestimate. A wide variety of other symptoms may accompany hypersecretion of these hormones and detailed discussion is available elsewhere.231

Confirmation of the diagnosis in each case requires demonstration of an elevated serum hormone concentration. A VIP secreting tumour may be suspected in the context of large volumes of secretory diarrhoea (>1 litre/day), dehydration and hypokalaemia. Normal values for circulating VIP are less than 170 pg/mL, while mean VIP serum concentrations in patients with functioning tumours range from 675 to 965 pg/mL.232 As serum levels fluctuate, the assay should be performed during an episode of diarrhoea. Similarly, serum gastrin levels in patients with gastrinomas are considerably higher than the normal range of 150 pg/mL, with average values of approximately 1000 pg/mL. However, comparable values can be found in patients with pernicious anaemia, other types of atrophic gastritis or potent acid suppressant therapy.233 Raised levels, although not to the same degree, also occur in other conditions such as diabetes mellitus, renal insufficiency and rheumatoid arthritis.

Diarrhoea is often a prominent feature (occurring in up to 50% of cases234 in carcinoid syndrome, which accounts for 20% of midgut neuroendocrine tumours.235 This almost always occurs in the context of hepatic metastases, even if the primary site remains undefined. The clinical diagnosis of ‘malignant disease’ is usually evident. A raised 24-hour urinary 5-hydroxyindoleacetic acid (above the local reference laboratory value) has a high sensitivity and specificity (88%).236 For the condition and correlates with tumour bulk, bioactive product secretion and, frequently, with the severity of symptoms.237 However, this is subject to patients adhering to dietary restrictions and often a 3-day dietary intake should accompany the sample so the laboratory can assess for any dietary interference (eg, serotonin-rich food such as bananas).238

8.2 Factitious diarrhoea
Factitious diarrhoea caused by laxative abuse or the spurious adding of water or urine to stool specimens has been recognised as a relatively common cause of reported chronic diarrhoeal symptoms in Western populations. The likelihood of this diagnosis increases as more numerous and repeated investigations reveal negative results. Thus, although only 4% of patients visiting district gastroenterology clinics had factitious diarrhoea, this value increased to 20% of those evaluated at tertiary referral centres, which made it the most common cause of diarrhoea of previously undetermined origin.15 Similarly, a survey of patients who had undergone extensive evaluation revealed 33% who were found to be taking laxatives or diuretics; 22% had undiagnosed colitis (ulcerative or microscopic colitis), 7% had faecal incontinence and 7% had other organic disorders.26

Repeated analysis of stool and urine is wise, as patients may ingest laxatives intermittently. Alkalisation assays, although simple to use (phenolphthalein, some anafruquinones and rhubarb turn the stool red, bisacodyl turns it purple-blue), are not of sufficient sensitivity and should be abandoned. A screen for ‘laxative abuse’ should include the detection of anafruquinones, bisacodyl and phenolphthalein in urine and magnesium and phosphate in stool, and should be carried out in a specialist
laboratory. Laboratories in the UK performing these tests should participate in the UK External Quality Assessment scheme for the detection of laxatives.

9 SUMMARY AND CONCLUSIONS

Establishing a clear definition of diarrhoea based on history alone can prove difficult, and this tends to lead to overinvestigation of functional diarrhoea including IBS. Serological testing for coeliac disease, the most common small bowel enteropathy in Caucasian populations, should be performed early in the course of investigations. The initial assessment should direct the clinician to determine whether further investigation is necessary and, if so, whether the focus should be on colonic, small bowel or pancreatic disease. This analysis could reasonably be performed in the primary care setting.

Most chronic diarrhoea is due to colonic abnormalities. Colonic investigations should be age stratified, in keeping with the risk of neoplasia and inflammation, and the high prevalence of bile acid diarrhoea estimated to be similar to coeliac disease. This analysis could reasonably be performed if so, whether the focus should be on colonic, small bowel or pancreatic disease. This analysis could reasonably be performed in the primary care setting.

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REFERENCES


