Investigation of diarrhoea in adults

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Definition

Patients complaining of diarrhoea may actually have other conditions (including tenesmus and faecal incontinence). The first task is to clarify this. The passage of more than three liquid stools per day or a stool weight of greater than 200 g in 24 hours is a reasonable definition for European populations.

Background

The annual incidence of diarrhoea of more than four weeks' duration is about 5%[1]. Many cases are self-limiting and require no special attention. Acute diarrhoea lasting 12–72 hours is highly prevalent and rarely leads to hospital referral, but the more severe cases that present can be assessed along the same lines as simple cases. The differential diagnosis is wide and a thorough systematic approach is warranted.

History

The history provides the key. Organic disease is more likely if the diarrhoea is of less than three months' duration, predominantly nocturnal and if there is weight loss. Other relevant factors include recent travel, contact with others with diarrhoea, exposure to antibiotics and drug usage (prescribed, over-the-counter and recreational). Because of disease associations and the gastrointestinal (GI) manifestations of other conditions, it is helpful to document comorbidity, a family history of inflammatory bowel disease, coeliac disease or GI malignancy. Endocrine disease and alcohol abuse may predispose to diarrhoea, and it is easy to overlook diarrhoeal effects of drugs such as beta-blockers and non-steroidal anti-inflammatory agents. Many diet foods are sweetened with the laxative sorbitol, as is chewing gum. Previous surgery may contribute to diarrhoea through loss of absorptive area, bile salt malabsorption, or bacterial overgrowth. Over 10% of patients develop diarrhoea after cholecystectomy for reasons that are unclear.

Examination

Examination of the patient with diarrhoea is rarely informative unless there are features of an associated condition. The perianal disease of Crohn's disease, and signs of thyrotoxicosis, pyoderma or scleroderma can be helpful. The opportunity should be taken to document the patient's current and usual weight. Only occasionally in Western practice will there be features of a specific nutritional deficiency.

Digital rectal examination should be considered mandatory. It helps to distinguish the patient with disordered perception from one with true diarrhoea. The presence of local perianal/anal disease or blood on the examining finger is also of obvious importance.

Initial investigations

Full blood count, standard biochemistry and an inflammatory marker (erythrocyte sedimentation rate or C-reactive protein) aid the distinction of organic from functional disorder. It is rare for all these to be normal in the organic conditions, but they are normal in the functional disorders. A patient with malabsorption of both iron and vitamin B12 or folate may present a normal mean corpuscular volume but the red cell distribution width will be above the normal upper limit of around 14. If doubt remains, red cell folate, serum vitamin B12 and ferritin concentrations should be obtained. Many authorities would argue that all patients with chronic diarrhoea should have coeliac antibodies sought even when the haematinics are normal[2,3].

Coeliac antibodies

Coeliac disease is common (>0.2% seroprevalence in Western populations, higher in those with other autoimmune

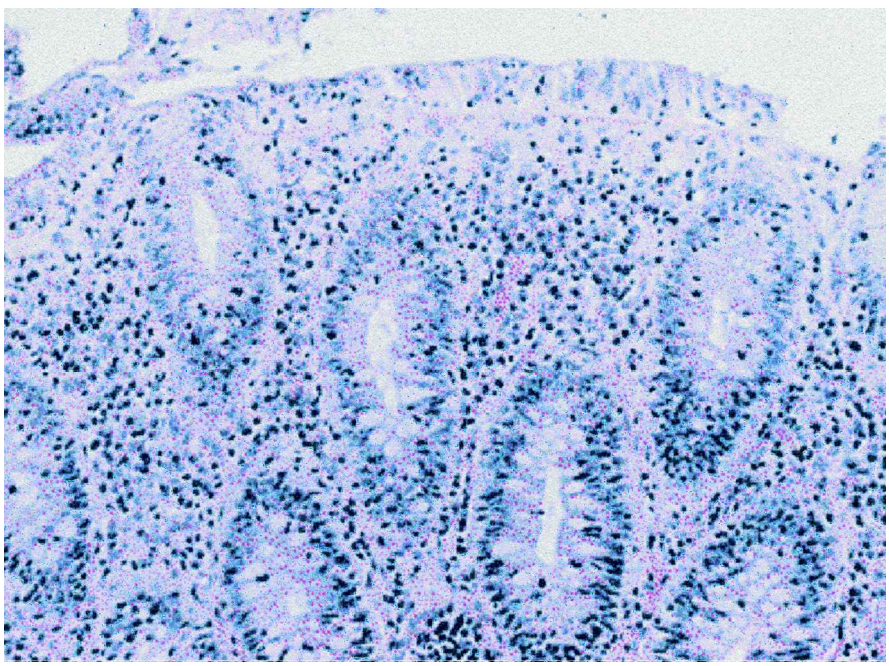

Fig 1. Microscopic colitis in a 56 year old woman with severe diarrhoea. Colonoscopy was apparently normal.

conditions), but it is often subtle in its adult presentation – mild diarrhoea with anaemia is most frequent. Immunoglobulin (Ig) A anti-endomysial antibody (to tissue transglutaminase) is the single most reliable test (>95% accuracy). However, there are false negatives, and the investigation is unhelpful if the patient has IgA deficiency, which is more common in coeliacs than in the general population (2.5% vs 0.2%). A few additional cases of coeliac disease are identified from antibodies to gluten or reticulin and by tests for IgG antibodies[4].

Stool examination

It is rare to identify an infective cause when symptoms have lasted more than four weeks. Nonetheless some pathogens may present insidiously. The possibility of superadded infection in a patient with another cause of diarrhoea should also be considered, for example *Clostridium difficile* or cytomegalovirus complicating ulcerative colitis. Conventional examination of three stool samples for ova, cysts and parasites has a sensitivity of greater than 70%, and stool ELISA for giardiasis has reduced the need for intestinal biopsies[5]. Measurement of stool osmolality and osmotic gap after a 48-hour fast can be helpful in the difficult case[6]. There is no value from occult blood testing in the evaluation of diarrhoea, but GI inflammation is usefully confirmed by elevated stool calprotectin; this may soon find a place in routine clinical practice[7].

Endoscopic and histological assessment

Immediate examination of the lower bowel by rigid or flexible sigmoidoscopy is invaluable. It permits a confident diagnosis of ulcerative colitis and of a number of infective colitides including pseudomembranous colitis (clostridial infection). When normal, it helps to increase confidence in a functional diagnosis. It provides some indirect information about more proximal disease. Rectal histology may yield Crohn's disease, despite a normal endoscopy.

There should be a low threshold for colonoscopy to seek proximal colonic neoplasia, Crohn's disease and microscopic colitis (Fig 1). Abnormality at colonoscopic ileoscopy is present in more than 15% of patients with diarrhoea and ileal visualisation should always be the aim[8].

Upper GI endoscopy is advised in patients with inconclusive investigations in order to perform a duodenal biopsy (Fig 2(a) and (b)) and for a histological baseline in patients with serologically diagnosed coeliac disease.

Peroral ileoscopy and endoscopic ultrasound examination are rarely indicated in the investigation of diarrhoea.

Radiology

The small bowel barium follow-through and/or intubation meal remain the standard means of imaging the small bowel (the choice depends on the radiologist's preference). Crohn's disease, intestinal tuberculosis, amoebiasis and small bowel neoplasia can be readily

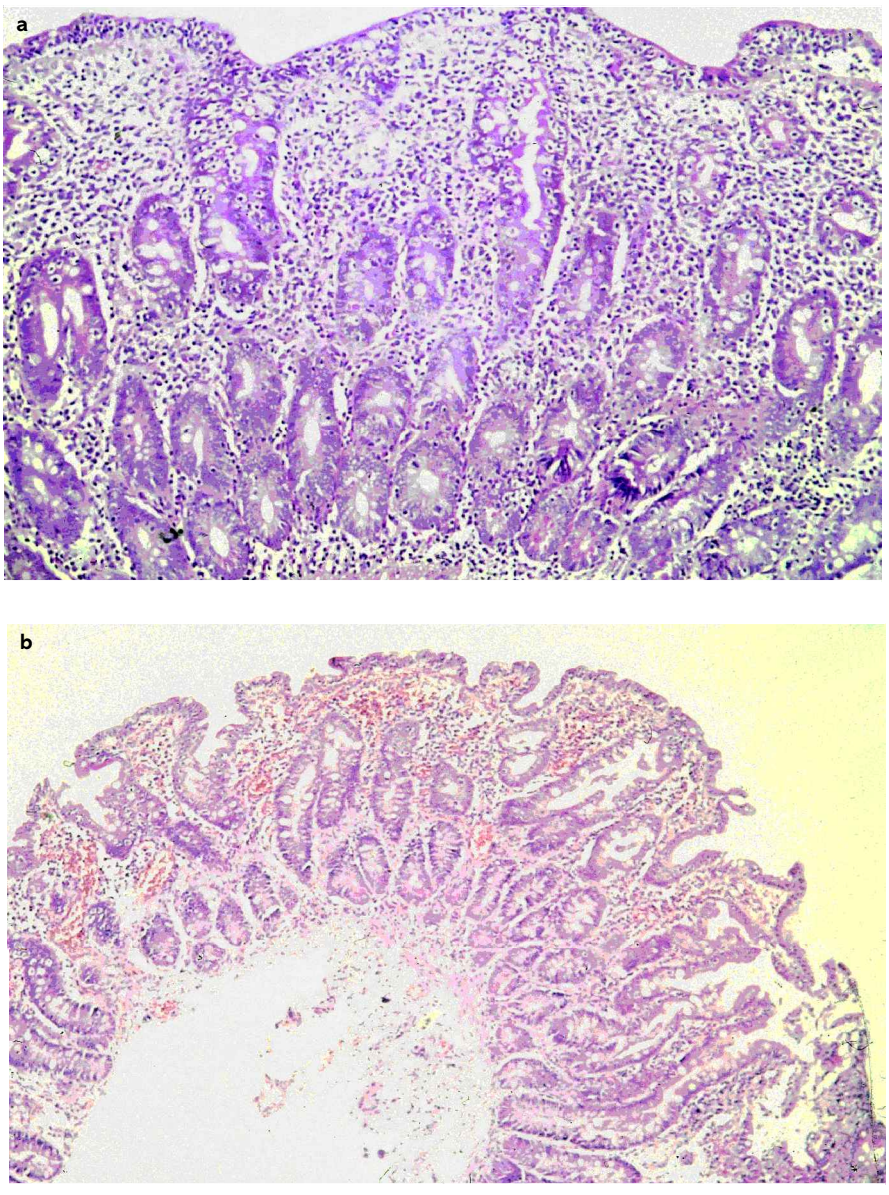

Fig 2. Biopsies from upper gastrointestinal endoscopy in a patient with coeliac disease and inconclusive investigations: (a) at baseline there is total villous atrophy; **(b)** three months later after a gluten-free diet there is considerable improvement.

identified (sensitivities and specificities are both >90%).

The radiolabelled white cell scan is a reasonable screening tool in the patient suspected of harbouring inflammatory bowel disease and in whom a non-invasive test is preferred. The sensitivity is similar to that of barium imaging.

The thickness of the intestinal wall at ultrasound scanning is informative (>4 mm indicates important intestinal pathology). The ultimate place of computed tomography (CT) and magnetic resonance imaging (MRI) is yet to be established, but both are good at identifying focal disease, the site of obstructing lesions and associated extra-intestinal disease.

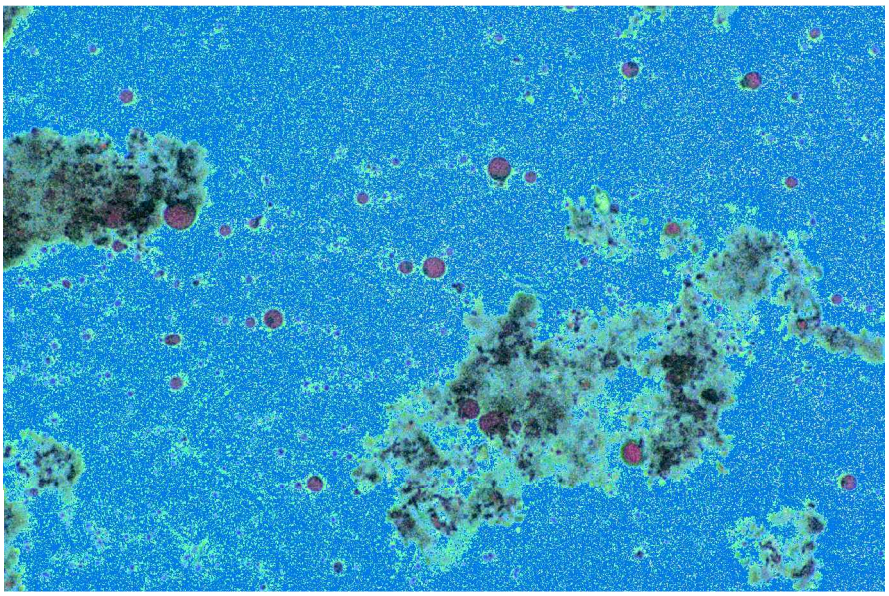

Fig 3. Sudan stain for fat on a stool smear.

Intestinal function tests

Tests for malabsorption are mostly non-diagnostic. Only stool fat, stool elastase, bile salt scanning and hydrogen breath testing are worth consideration by the non-specialist.

The three-day faecal fat test allows confirmation of pancreatic steatorrhoea (>13 g/day). Severe disease of the small bowel can also lead to steatorrhoea. However, stool fat collection is unpleasant and often incomplete or insufficiently correlated with dietary fat intake. Many laboratories no longer offer the test but can do Sudan stain for fat on a stool smear (Fig 3). Breath tests for fat malabsorption are insufficiently reliable.

The xylose absorption test is easy to perform, but is of limited diagnostic value because it is abnormal in most forms of intestinal mucosal disease. It is no longer recommended. Intestinal permeability is also abnormal in a wide range of GI conditions, but its diagnostic value is limited and there is little justification for its routine estimation[9].

Bile salt malabsorption

Malabsorption of bile salts/acids may provoke diarrhoea. This happens in Crohn's disease, but it can also occur idiopathically and after cholecystectomy[10]. It may be assessed by a therapeutic trial of a bile salt binding agent such as cholestyramine, or more reliably by measurement of the turnover of radiolabelled bile acid. The method most used is the ^{75}Se homotaurocholate (^{75}SeHCAT) scan[10] which involves the ingestion of this synthetic bile acid. The retained fraction is assessed by whole body counting at seven days, less than 15% retention indicating malabsorption.

Lactose malabsorption

Lactase deficiency (the normal state of the non-Caucasian adult) is a cause of mild diarrhoea. It may be identified by measurement of lactase in mucosal biopsies, or more usually by assessing the rise in breath hydrogen due to malabsorbed lactose reaching the colon (Fig 4). The clinical response to a 25–50 g oral lactose challenge identifies the problem less precisely but almost as effectively. The clinical significance of lactose malabsorption is slight if less than 240 ml milk is consumed per day.

Pancreatic abnormality

The diagnosis of chronic pancreatitis will usually be made from imaging (calcification or characteristic features on ultra-

Table 1. Some rarer causes of diarrhoea and potential routes to their diagnosis.

Cause of diarrhoea	Potential route to diagnosis
Hormone secreting tumours arising from pancreatic tissue	Serum gut hormone profile VIP, glucagon, gastrin, etc
Carcinoid syndrome	24-hour urinary (5HIAA) Hepatic imaging (secondaries usual)
Mesenteric ischaemia/ischaemic colitis	Doppler ultrasound Colonoscopy (with angiography for more subtle abnormalities)
Amyloid	Histology from rectum Amyloid protein scanning
Heavy metal poisoning	Heavy metal screen of blood and urine
Systemic mastocytosis	Jejunal biopsy Blood histamine level
Whipple's disease	Jejunal biopsy

5HIAA = 5-hydroxyindoleacetic acid; VIP = vasoactive intestinal peptide.

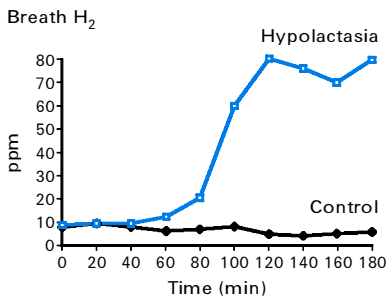

Fig 4. Identification of lactase deficiency by assessing the rise in breath hydrogen due to malabsorbed lactose reaching the colon.

Key Points

- Careful history should be taken of onset of diarrhoea, associated illnesses and drugs
- Examination is more relevant to the search for associated conditions than for the cause of diarrhoea itself
- Estimation of coeliac antibodies should be routine
- Stool microbiology is rarely helpful with a history of more than four weeks' duration
- Lower gastrointestinal endoscopy should include ileoscopy whenever possible
- Barium studies of small bowel still predominate but isotope white cell scans are gaining ground
- Tests of intestinal and pancreatic function are of only modest value

KEY WORDS: bacterial overgrowth, bile salt, coeliac, Crohn, diarrhoea, lactose intolerance, laxative, malabsorption, pancreatitis, steatorrhoea

sound, CT, MRI or endoscopic retrograde cholangiopancreatography – see Fig 5). Frank steatorrhoea will also prompt diagnosis, but about 90% of the acinar tissue must first be destroyed.

The 'direct' intubation tests are difficult to standardise and are invasive for the patient. They are better than the indirect tests but have limited sensitivity and specificity. They are rarely available in the UK.

Serum enzymes are abnormal in about 45% of patients with established pancreatic insufficiency. There is little to choose between lipase, trypsin/trypsinogen and amylase. Faecal enzymes may be more informative, but evidence for the reliability of elastase (probably the best single option) is only modest[11].

Maldigestion can be diagnosed from the indirect tests when it is moderate to severe, which is when structural changes are most likely to be present on imaging. Dynamic tests of pancreatic function depend on the action of pancreatic enzymes on orally administered substrate. The p-aminobenzoic acid (PABA) test relies on hydrolysis to release PABA, which is then absorbed and excreted in the urine where it can be measured. The pancreolauryl test uses a fluoroscein label released by pancreatic esterase. Both these tests are technically straightforward but unreliable (<50%) in other than advanced disease[12].

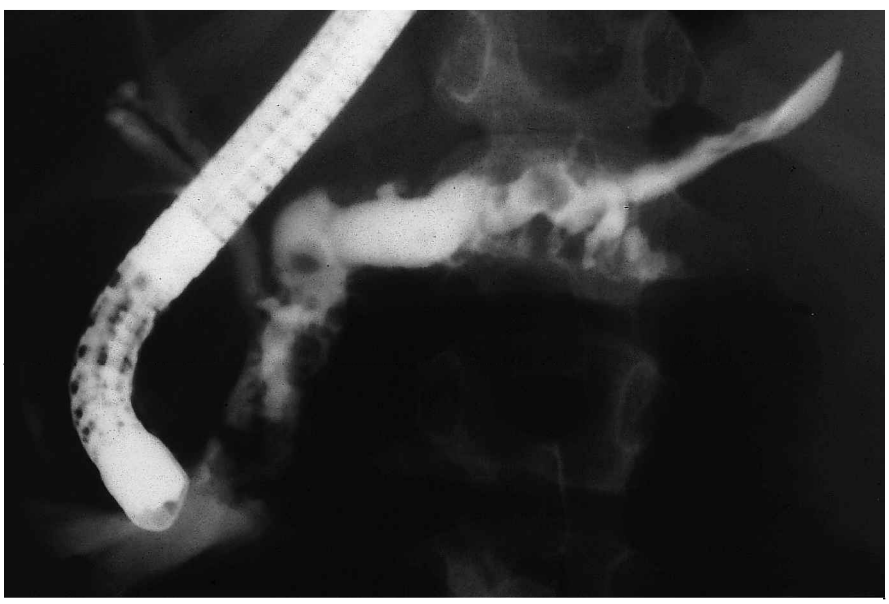

Fig 5. Endoscopic retrograde cholangiopancreatography (ECRP) showing severe dilatation and disruption of the pancreatic duct in chronic pancreatitis.

Small bowel bacterial overgrowth

The small bowel content is normally almost sterile (ca 10^4 colony forming units/ml) but overgrowth may develop and be responsible for diarrhoea when structural abnormalities exist (eg diverticula, a postoperative blind loop) or functional intestinal disorders occur (eg diabetic neuropathy, scleroderma). Positive culture (>10^6 organisms/ml) of a small bowel aspirate is almost diagnostic but does also occur in healthy individuals[13]. A functional test is therefore arguably more informative. Simple hydrogen breath tests fill this need. Bacteria, but not mammalian cells, ferment carbohydrates to hydrogen. A glucose drink probably provides the most informative substrate, but sensitivity and specificity are only of the order of 75%.

Factitious diarrhoea

Factitious diarrhoea caused by laxative abuse or the addition of water or urine to

stool specimens is a common cause of reported chronic diarrhoea in those presenting to hospitals[14]. About 4% of patients in district general hospitals have factitious diarrhoea, rising to 20% in tertiary centres. The most important diagnostic tool is a high index of suspicion. Low stool osmolality (from dilution) or the presence of magnesium (laxatives) or creatinine (dilution with urine) can be combined with a laxative screen if the diagnosis is suspected. 'Locker searches' are probably no longer ethically acceptable.

Acknowledgements

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