# 15.10.1 Differential diagnosis and investigation o

# 15.10.1 Differential diagnosis and investigation of malabsorption 2875

15.10 Malabsorption CONTENTS 15.10.1 Differential diagnosis and investigation of malabsorption 2875 Alastair Forbes and Victoria Mulcahy 15.10.2 Bacterial overgrowth of the small intestine 2879 Stephen J. Middleton and Raymond J. Playford 15.10.3 Coeliac disease 2884 Peter D. Mooney and David S. Sanders 15.10.4 Gastrointestinal lymphomas 2892 Kikkeri N. Naresh 15.10.5 Disaccharidase deficiency 2902 Timothy M. Cox 15.10.6 Whipple's disease 2909 Florence Fenollar and Didier Raoult 15.10.7 Effects of massive bowel resection 2911 Stephen J. Middleton, Simon M. Gabe, and Raymond J. Playford 15.10.8 Malabsorption syndromes in the tropics 2916 Vineet Ahuja and Govind K. Makharia 15.10.1 Differential diagnosis and investigation of malabsorption Alastair Forbes and Victoria Mulcahy ESSENTIALS Malabsorption is defined as defective mucosal absorption in the intestine, with clinical presentation ranging from diarrhoea or steatorrhoea with massive weight loss, through to abdominal bloating, fatigue, changes in bowel habit, or anaemia. There are many causes, but the commonest in adult life are coeliac disease, Crohn's disease, and bile salt malabsorption. Simple blood tests may prompt suspicion of malabsorption, will sometimes go a long way to providing a diagnosis, and will guide fur- ther investigation with specific tests, for example, serum antibody to tissue transglutaminase (coeliac disease), endoscopic examinations, imaging studies, breath tests, and tests of bile salt absorption. Treatment for malabsorption is directed (where possible) to the underlying cause as specific agents to address the malabsorption it- self are lacking. General nutritional support and replacement of indi- vidual deficiencies are crucial. Introduction Malabsorption leads to a wide spectrum of clinical presentations, ranging from dramatic diarrhoea or steatorrhoea with massive weight loss, through to more subtle features such as abdominal bloating, fatigue, changes in bowel habit, or anaemia. Malabsorption is defined as defective mucosal absorption and should be distin guished from maldigestion—the defective hydrolysis of nutrients— with which it commonly coexists. The emphasis in this chapter will be on intestinal malabsorption: pancreatic insufficiency is addressed in Chapter 15.26.2. Normal

absorption The processes of absorption are complex and involve several stages, commencing with the cerebral phase of digestion triggered by the sight, smell, and thought of food, which trigger the digestive pro cess, with salivary and gastric secretion mediated by the autonomic nervous system. The presence of nutrients in the mouth and upper gastrointestinal tract adds to these secretions via humoral and local neural mechanisms, but most of the digestive process is ini tiated in the duodenum. The delivery of chyme from the stomach is adjusted to allow efficient mixing with the pancreaticobiliary se cretions; this combination with bile salts and bicarbonate (as well as the pancreatic enzymes) provides optimal conditions for nu trient digestion. Digestion and fluid secretion dominate in the duodenum and proximal jejunum, while the bulk of nutrient absorption takes place in the distal jejunum and ileum. Enzymatic digestion occurs not only in the lumen but also in the intestinal brush border, absorption of small oligopeptides generally being superior to that of monomeric amino acids. The terminal ileum has special and almost unique cap acity for absorption of vitamin B12 and bile salts. In health, by the time the intestinal chyme leaves the ileum and enters the colon, most

section 15 Gastroenterological disorders 2876 nutrients have been digested and absorbed, the colon serving mainly to dehydrate the luminal contents through absorption of salt and water and temporarily to store the residuum. Absorption occurs through several pathways. Transcellular ab sorption occurs via entry to the cell at the brush border membrane, with passage through the cytoplasm, and exit from the cell at the basolateral membrane. This depends on passive and active trans port, and also on endocytosis. Passive transport by diffusion oc curs mainly when the molecules are small and can simply diffuse through the membrane via a paracellular route, and the term has come to include facilitated diffusion where transportation is aug mented by a transport protein and a concentration gradient. This allows small molecules to be transported across electrical and chemical gradients. Active transport generally uses a transport pro tein, but also requires energy to move nutrients against a concentra tion gradient. Endocytosis may occur when molecules are too big otherwise to cross the cell membrane, but in most cases digestion renders nutrients sufficiently small that absorption can proceed without this. In endocytosis, a portion of the cell membrane sur rounds and engulfs the target molecule(s). The membrane is then disassembled and the contents are released, a process sometimes accomplished by exocytosis. Causes of malabsorption There are many causes of malabsorption, including frank mucosal damage, congenital or acquired reduction in absorptive surface, defects in intracellular hydrolysis, and defects of ion transport, as well as malabsorption linked with maldigestion as in the case of pancreatic insufficiency, cholestasis, or impaired enterohepatic circulation. A list of potential causes can appear encyclopaedic (Table 15.10.1.1) and is yet not exhaustive, but most of these are either rare, or conditions (as in the case of diabetes) where the malabsorption contributes only a small part of the overall morbidity. The commonest causes of de novo presentation with malabsorp tion in adult life are coeliac disease, Crohn’s disease, and bile salt malabsorption. The patient’s age and medical background will guide the creation of an appropriate differential diagnosis. In many Table 15.10.1.1 Some causes of malabsorption and distinguishing associated features; all can be responsible for diarrhoea and weight loss, all may result in anaemia, and most will at times cause some abdominal discomfort Condition Associated features Adrenal insufficiency Hyponatraemia, hyperkalaemia Amyloidosis Nephrotic syndrome, cardiomyopathy, macroglossia Bacterial overgrowth Previous abdominal surgery, motility disorders, small-bowel diverticula, strictures Bile salt malabsorption Often mild nonspecific symptoms Carcinoid syndrome Flushing, hypokalaemia, right heart failure symptoms Cholestatic liver disease Jaundice, features of chronic

liver disease Coeliac disease Growth retardation, delayed menarche Crohn’s disease Abdominal pain, aphthous ulcers, extraintestinal features (arthritis, uveitis, erythema nodosum, pyoderma gangrenosum) Cystic fibrosis Respiratory features, growth retardation, history of meconium ileus/distal intestinal obstruction syndrome, steatorrhoea Cystinuria Renal stones Chronic infections Tropical sprue, giardiasis, tuberculosis, HIV/AIDS Diabetes mellitus Long-term poor control and complications, gastroparesis Disaccharide deficiency Dietary links to symptoms Drugs Often unpredictable, but also orlistat, laxatives Diverticula (jejunal) Often mild nonspecific symptoms Eosinophilic enteritis Dysphagia Gastrectomy Vitamin B12 deficiency Hypogammaglobulinaemia Recurrent infections Intestinal ischaemia Ischaemia in other organs systems Intestinal lymphangiectasia Protein-losing enteropathy Lymphoma Lymphadenopathy (clinical or on imaging) Pancreatic insufficiency Abdominal pain, steatorrhoea Radiation enteropathy History of radiotherapy Scleroderma Raynaud’s syndrome, dysphagia, skin changes, calcinosis Short bowel syndrome Major intestinal resection for any cause Specific transporter defects Usually childhood presentation Whipple’s disease Lymphadenopathy, fever, arthritis, endocarditis

15.10.1 Differential diagnosis and investigation of malabsorption 2877 cases, associated features will helpfully steer the clinician towards the correct explanation. Clinical features History: suspicion of malabsorption Malabsorption will be readily suspected in the patient with diar rhoea and weight loss in whom gastrointestinal pathology is already known, especially if there are few other symptoms. The primary diagnosis of malabsorption is, however, often delayed or overlooked entirely, as in its milder forms it may be difficult to recognize and assess. A suspicion of its presence will come from key factors in the patient’s history such as a family history of coeliac disease or previ ously unexplained anaemia. Questioning the patient should cover areas such as change in bowel habit, change in stool consistency or colour, bloating, and weight loss, but also symptoms referable to other systems such as (for example) musculoskeletal pain from malabsorption-related vitamin D deficiency. Enquiry should include a detailed past medical history encompassing surgical history, previous medical treatments such as radiotherapy, and documentation of pancreatic disease or its risk factors, as well as family history. Attention to associated symptoms can also be productive (Table 15.10.1.1). Examination Examination of the patient with isolated malabsorption is of limited value, as apart from evidence of weight loss or growth re tardation there may be no signs. Nonetheless, conventional nu tritional screening including documentation of weight loss and current body mass index will often be informative.
A more detailed assessment may include anthropometric measurements such as skin-fold thickness and analysis of the body composition, but the diagnostic process will be most helped by the discovery of signs of anaemia (pallor, glossitis, cheilosis, stomatitis, koilonychia), of vitamin deficiencies (bruising, tetany, oedema, hyperpigmented dermatitis), or features of underlying conditions or past surgery (Table 15.10.1.1). Investigations General laboratory investigations Simple blood tests may prompt suspicion of malabsorption, will guide further investigation, and will sometimes go a long way to providing a diagnosis. Even in the absence of anaemia the mean cor puscular volume can indicate evidence of iron, vitamin B12, or folate deficiency. The dimorphic picture from combined iron and folate deficiency, with a consequently raised red cell distribution width, may be the first pointer to a diagnosis of coeliac disease. The lipid profile may also be suggestive, with triglycerides de creased in severe fat malabsorption, and cholesterol low in bile salt or fat malabsorption. A low albumin is more often a nonspecific marker of illness and inflammation, but may be dramatically low in lymphangiectasia and protein-losing enteropathy. Alkaline phosphatase is increased in calcium and vitamin D malabsorption, and decreased with zinc

malabsorption. Low levels of calcium, phosphorus, iron, ferritin, magnesium, and zinc may all point to malabsorption, as may a low folate or vitamin B12 when these have been measured to elucidate a finding of anaemia or ab normal mean corpuscular volume. Paradoxically, raised folate levels may be seen in malabsorption associated with small-bowel bacteria overgrowth. Coagulation screening may lead to the discovery of vitamin K malabsorption. Specific laboratory investigations Exclusion of coeliac disease The most important serological testing in respect of malabsorption is that for coeliac disease, given the high prevalence of the condi tion and the remarkable (>95%) accuracy of serological prediction. Historic reliance on tests for antibodies to gluten and endomysium has been succeeded by use of the more sensitive antibody to tissue transglutaminase. Screening for antibodies to deamidated gliadin peptide is also valuable. Concurrent IgA deficiency accounts for most of the few false-negative results, hence it is important to measure the immunoglobulins for this reason, as well as to detect other considerably rarer immunodeficiency states associated with malabsorption. Coeliac disease can also be excluded immunologically, since it does not develop unless the individual has alleles encoding HLA DQ2 or DQ8. This observation can be important in helping to confirm a diagnosis of noncoeliac gluten sensitivity in patients with dietary intolerance of wheat, but in whom other tests are normal. Other investigations Vitamin B12 deficiency may be associated with chronic disease or prior resection of the distal ileum, but also in pernicious an aemia where the defect is an autoimmune loss of the intrinsic factor which is required for its absorption. Antibodies to the gas tric parietal cells and/or to intrinsic factor itself provide a specific diagnosis. Comparable risk occurs after total or subtotal gastrec tomy, and vitamin B12 deficiency may be seen in the context of severe chronic gastritis. The Schilling test, which depends on the intestine’s handling of radioisotopic vitamin B12, is now largely defunct. Biochemical assessment of pancreatic disease has a long and largely unhappy history, but the detection of a low faecal elastase can lend support to a diagnosis of exocrine pancreatic insufficiency. When standard liver biochemistry is abnormal it will be appro priate to seek serological evidence of autoimmune liver disease (especially primary biliary cholangitis) and to exclude metabolic causes which may occasionally be associated with malabsorption. Measurement of the gut hormones, such as gastrin, pep tide YY, vasoactive intestinal peptide, chromogranin A, and 5- hydroxyindoleacetic acid, will form part of the diagnostic pathway in patients with prominent diarrhoea in whom a neuroendocrine tumour is suspected. Measurement of faecal bile acids is not generally performed outside a research context. Raised faecal calprotectin is not a consequence of malabsorption, but may be found in those with Crohn’s disease-related inflammation who also have an element of malabsorption. Stool and urine tests can be used to rule out laxative misuse if this is suspected.

section 15 Gastroenterological disorders 2878 Endoscopic tests The usual role of endoscopic assessment in patients suspected of having malabsorption is to provide duodenal histology to support or refute a diagnosis of coeliac disease. This will also permit diag nosis of chronic infection with giardia and of Whipple’s disease. Endoscopic appearances may be suggestive: mosaic-like scalloping of the duodenal folds is suggestive of villous atrophy in coeliac dis ease; aphthous ulcers are typical of Crohn’s disease; and white punc tate lesions can be seen in primary or secondary lymphangiectasia. Ileocolonoscopy with terminal ileal views can show inflamma tion or ulceration indicative of Crohn’s disease, and colonic biop sies may yield a diagnosis of microscopic colitis which, by virtue of chronic diarrhoea, may generate a suspicion of malabsorption given its association with coeliac disease. Further small-bowel views can be obtained with push enteroscopy, double-balloon enteroscopy, or wireless capsule endoscopy, but the last cannot provide ma terial for the histological assessment which may be diagnostic ally critical in patients with small intestinal

lymphoma, intestinal lymphangiectasia, or eosinophilic enteritis. Only very rarely is lapar otomy or laparoscopy required for full-thickness biopsies from the jejunum or ileum. There are several congenital defects that can lead to malabsorption, including specific amino acid transport defects and monosaccharide transport defects. Paediatric centres are alert to these, but they are rarely encountered in adult practice. Metabolic assessment of small intestinal biopsies will be required in many cases. Autoimmune polyglandular syndrome type 1—from a recessive defect in the auto immune regulator gene AIRE—generally presents with low-grade chronic or recurrent infection (typically candidal) and a set of endo crine deficiencies. There is usually an element of malabsorption and intestinal histology demonstrates mucosal atrophy. Imaging studies A simple abdominal X-ray can detect pancreatic calcification in chronic pancreatitis. Small-bowel barium enteroclysis or MRI may indicate a small-bowel origin for disease via focal or diffuse abnor malities such as stagnant loops of bowel, diverticula, hypomobility, dilatation, or small-bowel tumours. Signs of Crohn’s disease include ulceration, distorted, thickened folds, and fistulae. Postsurgical anatomy may usefully be ascertained and the length of remaining intestine in short-bowel syndrome can be identified. CT imaging with contrast can also be used to assess inflammatory bowel disease, intestinal lymphoma, and pancreatic disease, with additional CT angiography if the clinical context suggests mesenteric ischaemia. Magnetic resonance cholangiopancreatography (and rarely, endo scopic retrograde cholangiopancreatography) can provide diag nostically discriminant information about the pancreas and biliary tree, particularly with respect to primary sclerosing cholangitis or chronic pancreatitis and tumours at these sites, each of which rarely presents with malabsorption. Specific radiology for neuroendocrine tumours can include octreotide scintigraphic scans or positron emission tomography imaging. Other diagnostic investigations Breath tests Hydrogen breath testing depends on the inability of human metabolism to produce hydrogen from carbohydrates and the efficient exhalation of any absorbed hydrogen produced by gut bacteria; it can therefore be used to identify small-bowel bacterial overgrowth. Breath testing is also a more direct test of maldigestion/ malabsorption in the case of lactose intolerance. Lactose is nor mally hydrolysed to glucose and galactose in the proximal small intestine, where these are then fully absorbed. In lactase deficiency, intact disaccharide reaches the colon and provides a substrate for colonic bacteria and the potential for hydrogen generation. Intestinal biopsy and assay of brush border enzymes is thus rarely required. Comparable breath tests in which the substrate is a lipid can be used to estimate maldigestion from pancreatic insufficiency. Tests of bile salt absorption Bile salt malabsorption in ileal disease or primary bile acid diar rhoea can be investigated with a synthetic bile salt retention scan. The patient swallows a capsule containing 75SeHCAT and is scanned at 1 to 3 h and then again at 7 days. The percentage retention is meas ured, and when less than 15% of the initial value indicates bile salt malabsorption from loss of its normal enterohepatic circulation. This may be found in any patient in whom there has been distal ileal resection, as well as in those with a primary defect. Radiolabelled bile salt breath tests are no longer performed. Tests of intestinal permeability and absorptive function The xylose absorption test relies on active uptake of this non metabolized pentose after oral administration and its subsequent detection in blood or urine, the notion being that this process de pends only on an intact mucosa and conditions that affect the mucosa would reduce absorption. Unfortunately the test is not robust—neither its sensitivity nor specificity is sufficient to earn it clinical value—and it has become obsolete. The permeability of the intestine is often disturbed in malabsorptive states, but the relationship is a complex one, also encompassing the effects of inflammation. Tests of permeability have accordingly not found a place in clinical practice, although in the research context assessment may utilize radiolabelled Cr-EDTA, a sugar mixture such as rhamnose with lactulose, or a macromolecule such as poly ethylene glycol. Intestinal absorptive function thus

remains poorly quantified, and there is no method that provides a numerical equivalent to (for example) the serum creatinine as a marker of renal impair ment. The most promising parameter in this respect is the plasma citrulline. This is a nonprotein amino acid which is almost exclu sively produced—from glutamine—in the small intestine. The levels are predictably low in patients with extreme short-bowel syndrome and have prognostic significance. Modestly disturbed levels are more difficult to interpret in the individual patient, and at present assays are performed routinely only in patients with small-bowel transplants in whom falling levels correlate well with insipient organ rejection. Management The treatment of malabsorption is always directed at its underlying cause, and the success or otherwise of this approach is dependent

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