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section 15 Gastroenterological disorders 2916 intestine) and result from multiple factors, particularly stasis in the biliary tract due to low levels of gut hormones such as cholecysto kinin. d-lactic acidosis occasionally occurs in patients with a short small intestine in continuity with colon. This is generated by colonic bacterial fermentation of malabsorbed carbohydrates, particularly mono- and oligosaccharides (Table 15.10.7.3). Patients requiring long-term parenteral nutrition with a very short remaining intestinal remnant (<50 cm) are particularly likely to de velop intestinal failure-associated liver disease. This usually presents as cholestatic liver disease, but it may be insidious and present late as cirrhosis. Recurrent sepsis promotes the condition, with the intra venous feeding line a common site. Osteoporosis is common in pa tients on parenteral nutrition and made more likely in the presence of liver disease and recurrent sepsis. FURTHER READING Carlson G (2001). Acute intestinal failure: surgical causes and manage ment. In: Nightingale J (ed) Intestinal failure, pp. 39–49. Greenwich Medical Media Ltd, London. Jeejeebhoy KN (2008). The use of enteral nutrition in the adult with intestinal failure. In Langnas AN, et al. (eds) Intestinal failure: di- agnosis, management and transplantation, pp. 160–66. Blackwell Publishing, Oxford. Middleton SJ, et al. (2011). Intestinal transplantation. In: Klein AK, Lewis CJ, Madsen LC (eds) Organ transplantation: a clinical guide, pp. 303–11. Cambridge University Press, Cambridge. Nightingale J, et al. (2006). Guidelines for management of patients with a short bowel. Gut, 55 Suppl 4, iv1–iv12. 15.10.8 Malabsorption syndromes in the tropics Vineet Ahuja and Govind K. Makharia ESSENTIALS Causes of secondary malabsorption that are most common in the tropics include (1) progressive wasting in people infected with HIV, which is known as ‘slim disease’; (2) various infections—protozoal (e.g. Giardia lamblia, Cryptosporidium parvum), helminthic (e.g. Capillaria philippinensis, Strongyloides stercoralis), and bacterial (Mycobacterium tuberculosis); (3) immunoproliferative small intestinal disease; and (4) hypolactasia. Coeliac disease and Crohn’s disease also occur. When patients with conditions that can cause secondary malabsorption are

excluded, a group remains who have chronic diar- rhoea, malabsorption, and its nutritional sequelae. This primary or idiopathic malabsorption syndrome is called ‘tropical sprue’, which occurs against the background of tropical enteropathy (describing the fact that the morphology of the mucosa of normal gut is different in tropical preindustrialized countries from that in temperate-zone industrialized countries). The aetiology of tropical sprue is not known: epidemiological data suggests an infective cause, but no causal agent has been identified. Presentation is typically with loose or watery stools lasting for several weeks or months, and with symptoms and signs of nutritional de- ficiency. Management involves symptomatic relief from diarrhoea, and correction of fluid and electrolyte abnormalities and nutritional deficiencies. Attempts at specific curative measures—folic acid and tetracyclines—are usually given for up to 6 months. Introduction Malabsorption in the tropics is considered an independent entity because of the distinctiveness of its causes as well as its public health significance in comparison to temperate areas. It comprises the primary malabsorption syndrome of tropical sprue, and various secondary causes, predominant of which are the protozoal, hel minthic, and mycobacterial infections that are much more prevalent in the tropics. The last two decades, however, have seen a decline in the incidence of tropical sprue and a perceptible shift towards cosmopolitization of the causes of chronic diarrhoea in the tropics. Generic descriptions of malabsorption syndrome in the tropics can be traced back to as early as 6 to 12 bc when in an Ayurvedic (Indian) medical treatise, ‘Charaka Samhita’, a condition charac terized by chronic diarrhoea was described as ‘Grahani Vyadhi’. In 1759, William Hillary published the first book in English on tropical diarrhoeal diseases and observed that these were more common in indigenous residents of Barbados than English settlers. William Twining gave the first accurate description of tropical sprue in 1818 from General Hospital, Kolkata, India. Manson in 1880 introduced the term ‘sprue’ for the wasting diarrhoeal illness common in the tropics. From 1962 onwards, investigators in Thailand, South India, Puerto Rico, Haiti, and Bangladesh noted a high incidence of malabsorption and histological evidence of chronic enteritis in asymptomatic - apparently normal members of the native-born population and coined the term tropical enteropathy. The mysticism associated with tropical enteropathy continues, and it has been renamed as ‘envir onmental enteropathy’ or ‘environmental enteric dysfunction’ in the last few years, suggesting that environmental factors are of more im portance than latitude or climate. Table 15.10.8.1 lists the various causes of malabsorption prevalent in the tropics. Noninfectious causes of tropical malabsorption Environmental (tropical) enteropathy Environmental enteropathy, previously known as ‘tropical enterop athy’, owes its origin to the finding of abnormal small intestinal mu cosal changes such as a decrease in the villous height, an increase in the crypt depth, and an increase in intraepithelial lymphocytes and lymphocytic infiltration of the lamina propria in adults from low- and middle-income countries. Some of these individuals dem onstrate abnormal d-xylose absorption, impaired fat and vitamin B12 absorption, and an increase in intestinal permeability. Despite these findings, many remain largely asymptomatic, revealing the

 subclinical nature of this enteropathy, the presence of which has been confirmed in infants as well as adults. Pathophysiology Environmental enteropathy is possibly an effect of repetitive ex posure to faeco–oral contamination causing chronic mucosal im mune stimulation and resulting in morphological changes in the intestinal mucosa. The condition can be acquired and reversed: a 1971 study of United States of America Peace Corps volunteers posted in Pakistan showed that jejunal biopsies of some had villous blunting with chronic inflammation, along with abnormalities of carbohydrate malabsorption. Two to three years following migra tion back to the United States of America, there was a reversal of

carbohydrate malabsorption and normalization of jejunal mucosal abnormalities in five of the volunteers who underwent jejunal bi opsy. Similarly, studies on asymptomatic Indian and Pakistani im migrants residing in New York showed mucosal abnormalities within 2 years of migration and reversal of these abnormalities with an increased period of stay in the United States of America. Further evidence that these changes are environment dependent and not genetic was provided by a study from South India which showed that stillborn fetuses had normally elongated crypts, but enteropathic changes were demonstrated as early as 8 weeks after birth. A Zambian study noted jejunal mucosal abnormalities in 200 asymptomatic adults, with intestinal permeability changes that were more severe in lower than higher socioeconomic groups. Environmental enteropathy is absent in tropical locations such as Singapore and Qatar, which have a higher-income population. Geographical variations have been shown in a large study involving asymptomatic adults from 14 countries across the world. Intestinal absorption and permeability aberrations were found in tropical ra ther than temperate countries, and there was a close correlation of the intestinal absorptive capacity of people in each country with national gross domestic product per capita, independent of cli mate, suggesting that socioeconomic factors may play a more significant role. Modifiable causes Environmental enteropathy has been linked to zinc deficiency; lack of proper water, sanitation, and hygiene (WASH) interven tions; and possibly altered gut microbiome. Zinc deficiency may be a consequence of impaired absorption and may be a poten tial driver of enteropathy through its effects on gut immunity and epithelial cell function. Faecal transplantation from malnourished Malawian children into germ-free (gnotobiotic) mice resulted in the mice becoming malnourished, suggesting the importance of the microbiome. The presence of environmental enteropathy in developing countries has triggered public health problems of child hood stunting and anaemia, and is possibly the reason for the poor response to oral vaccines for polio and rotavirus. Tropical sprue Tropical sprue is an acquired intestinal malabsorption syndrome of unknown aetiology that affects residents and tourists of trop ical regions. It has been suggested that persistent infection may be responsible, hence it is also referred to as ‘postinfective tropical malabsorption’. European and American expatriate residents in the tropics were considered to be the primarily affected population until Baker and Mathan in South India suggested that the indigenous population was equally affected. Definition In 1970, Klipstein from Puerto Rico and Baker from Vellore, India, suggested that tropical sprue should be regarded as a syndrome which occurs among the indigenous population and visitors to cer tain tropical regions, and included in this syndrome would be all per sons who have malabsorption of two or more unrelated substances for which no aetiology can be ascertained. No single clinical mani festation or laboratory abnormality is diagnostic of tropical sprue. A present-day working definition of tropical sprue includes (a) compatible clinical presentation; (b) demonstration of malabsorption of two or more unrelated substances; (c) abnormal small intestinal mucosal histology, which may be patchy; (d) exclu sion of other specific causes for malabsorption syndrome (except small intestinal bacterial overgrowth); and (e) response to treatment with folic acid and antibiotics such as tetracycline. Other terms used in this context have been ‘acute tropical sprue’ and ‘chronic tropical sprue’. Acute tropical sprue manifests as a rapid onset of diarrhoea and malabsorption and is observed either in expatriates visiting endemic areas or during epidemics in indi genous population. Chronic tropical sprue is an insidious onset of malabsorption symptoms seen in natives of sprue-prone areas. Epidemiology Tropical sprue occurs in the warm and hot geographical regions located between the tropic of Cancer and the tropic of Capricorn Table 15.10.8.1 Causes of malabsorption in the tropics Noninfectious causes Infectious causes Tropical sprue Protozoal: Giardia intestinalis, Cryptosporidium parvum, cystoisosporiasis (Cystoisospora), Cyclospora cayetanensis, microsporidia

(Enterocytozoon bieneusi and Encephalitozoon intestinalis) Coeliac disease Nematohelminthes: Strongyloides stercoralis, Capillaria philippinensis Small intestinal bacterial overgrowth Bacterial: Mycobacterium tuberculosis Crohn's disease Viral: HIV enteropathy Immunoproliferative small intestinal disease (IPSID) Combined variable immunodeficiency disease (CVID) Idiopathic tropical pancreatitis Environmental enteropathy (also called tropical enteropathy)

section 15 Gastroenterological disorders 2918 on either side of the equator, but it has not been reported from all tropical countries. It is endemic in India, Puerto Rico, and Cuba; oc curs commonly in South and South-East Asian countries including Myanmar, Sri Lanka, Vietnam, Indonesia, and the Philippines, and Middle-East Asian countries; has been reported from Central American and South American countries such as Mexico, Venezuela, Colombia, Haiti, and the Dominican Republic; but it has not been reported from the tropical islands of Jamaica and Bahamas, or in most African countries. Tropical sprue occurs sporadically, although frequent epidemics have been reported. Household epidemics were recognized by Mathan from South India and Bahr in 1915, who described 'sprue houses' where successive tenants were attacked with sprue. Crombie described an epidemic of 'Hill Diarrhea' in Shimla in 1880, which possibly fitted the description of tropical sprue. Epidemic tropical sprue was reported following acute diarrhoea in prisoner of war camps, affecting both British and Indian soldiers in the Second World War, as well as from villages in South India. A documented study of an epidemic involving an estimated 100 000 people in 1961 in the North Arcot district in South India was done by Baker and Mathan. The highest incidence was ob served in the adults in the thirties to forties age group, with children showing a lower attack rate. An alarmingly high mortality rate of 40% was reported. Some cases remained symptomatic up to a year after disease onset. The public health importance of tropical sprue has decreased in recent years as epidemics of tropical sprue have not been reported since 1978. Improvements in WASH may be responsible for the de cline of sporadic cases. This has been documented in Puerto Rico, where studies by the United States of America army sprue team showed a decline in incidence from 7.4 to 0.3/100 000 in the period 1953 to 1961. Similarly, a decline in the incidence from 2% in 1927 to 0.5% in 1957 has been reported from Cuba. Aetiology No single agent has been incriminated as causing tropical sprue. Most of the evidence suggests that it is caused either by enteric in fection or by poor nutrition, or a combination of both. Features favouring an infective aetiology include epidemic spread of the dis ease, intrafamilial spread, clustering in certain areas, acute onset of diarrhoeal illness, people affected in the first wave of an epidemic are not affected in the second wave, appearance of symptoms in vis itors to tropical areas within a few weeks to months, and response to antibiotics. Coliform toxin-producing bacteria (Klebsiella pneumoniae, Escherichia coli, and Enterobacter cloacae) have been isolated from the jejunum of patients with tropical sprue. Protozoa (Cryptosporidium parvum, Cystoisospora belli, Blastocystis homi- nis, and Cyclospora cayetanensis) have been identified in faecal samples and jejunal biopsies of patients with protracted diarrhoea in the tropics. Viral particles resembling orthomyxovirus and cor onaviruses (so-called Grahani agents) have been demonstrated in the faeces of 90% of tropical sprue patients from South India, al though these viruses were also isolated from control subjects and children without diarrhoea. Tropical sprue in visitors to tropical countries may be due to persistent enteric infection with patho gens such as enteropathogenic E. coli, Giardia intestinalis, or Cyclospora cayetanensis. Causative nutritional factors include protein malnutrition, folic acid deficiency, and high unsaturated fatty acid consumption. Folate deficiency has been suggested as it predisposes to bacterial over growth as well as impaired jejunal mucosal function. An experi mental study in a primate model of tropical sprue demonstrated development of symptoms within

2 months with a protein intake of 2%, as compared to 5 months in primates given a protein intake of 5%. Excessive dietary unsaturated fat may result in persistence of enteric bacterial contamination and has been suggested as a coaetiological agent in Puerto Rico and Haiti. Pathogenesis The hypothesized cascade of events leading to tropical sprue includes bacterial colonization, impaired small intestinal perme ability, alteration of gut immune responses, increased orocaecal transit time, unabsorbed fat triggering the ‘ileal brake’, bac terial overgrowth, and consequent mucosal inflammation and malabsorption in a self-perpetuating cycle. Bacterial colonization causes altered enterocyte brush border integrity, disturbed mo tility, deconjugation of fatty acids, fatty acid malabsorption, and steatorrhoea. Ghoshal from Lucknow, India, has shown that in patients with tropical sprue, compared to controls, infusion of fat into the proximal small intestine inhibits antroduodenal motility, delays duodenocaecal transit time, and increases plasma levels of peptide tyrosine-tyrosine and neurotensin. This leads to small-bowel stasis, impaired small intestinal permeability and consequent bacterial overgrowth, resulting in passage of larger amounts of fluid into the colon, which should be compensated for by increased absorption. However, Ramakrishna from Vellore, India, has shown that colonic abnormality in tropical sprue prevents this compensatory mech anism, predisposing to occurrence of diarrhoea. The characteristic structural alteration of the intestine in tropical sprue includes involvement of both jejunum and ileum, as compared to sparing of the ileum in coeliac disease, and the predominance of involvement of the crypts is suggestive of an intestinal stem cell defect, rather than involvement of villi as seen in coeliac disease. Environmental enteropathy is not considered as a part of tropical sprue and the differences are shown in Table 15.10.8.2. Clinical features The temporal profile of symptoms in tropical sprue is an initial phase of acute or insidious onset of diarrhoea, with abdominal bloating, anorexia, and fatigue, which lingers on to the second phase of nu tritional deficiencies, and finally the third phase of severe anaemia. Adults are mostly affected, and a constellation of classic symptoms includes mild to severe chronic diarrhoea, pale, bulky, offensive odour stools suggestive of steatorrhoea, crampy abdominal pain, bloating, anorexia, and weakness. In some cases, malnutrition can occur even in the absence of diarrhoea. In visitors to tropical coun tries, acute diarrhoea associated with fever and malaise in the first week is the predominant symptom. Physical examination shows signs of nutritional deficiencies such as angular stomatitis, cheilitis, and glossitis due to vitamin B defi ciency; pallor due to folate and vitamin B12 deficiency causing meg aloblastic anaemia; peripheral oedema and hair changes secondary to hypoproteinaemia; hyperpigmentation of knuckles and buccal mucosa due to vitamin B12 deficiency causing increased melanin synthesis; and

15.10.8 Malabsorption syndromes in the tropics 2919 Table 15.10.8.2 Differences between tropical sprue and environmental (tropical) enteropathy Characteristics Tropical sprue Environmental (tropical) enteropathy Age group affected Mostly adults Adults as well as children Disease course Progressive course with occasional spontaneous remission Remission and relapses observed, depending on place of residence Symptoms and signs of malabsorption Present Absent or subclinical Tests of malabsorption Abnormal Abnormal in 50% of cases Small-bowel histology Morphological alterations in the form of partial villous atrophy and chronic lymphocytic inflammation Morphological alterations in the form of partial villous atrophy and chronic lymphocytic inflammation Response to therapy Mostly a quick response, with normalization of intestinal function and morphological changes Response as seen in tropical sprue is not observed peripheral neuropathy. Folate deficiency is seen more often in India, while vitamin B12 deficiency predominates in some other places. A chronic malabsorption state may lead to deficiency of fat-

soluble vitamins (A, D, E, and K). Night blindness and corneal xerosis due to vitamin A deficiency may rarely occur. Uncommon manifestations include stupor and listlessness secondary to hypomagnesaemia and hypophosphataemia, and periodic paralysis due to hypokalaemia. The clinical course of tropical sprue is very variable: it can remit spontaneously or result in chronic malnutrition. Diagnosis and investigation The diagnostic steps involve demonstrating the presence of malabsorption and alterations in small-bowel mucosal histology, and excluding secondary causes of malabsorption. Carbohydrate malabsorption (d-xylose test—although note the caveats expressed in Chapter 15.10.1), steatorrhoea (faecal fat test), and vitamin B12 and folate deficiency (decreased serum vitamin B12 and folate levels, and increased serum methylmalonic acid) should be checked for in every suspected case of tropical sprue. Two abnormal tests in an appropriate clinical context are consistent with a diagnosis of tropical sprue in the absence of other causes of malabsorption. In addition, investigations evaluating nutritional deficiencies should be performed to plan management. A confirmation of diagnosis is achieved by folate supplementation, which shows prompt resolution of clinical and laboratory abnormalities. An estimate of 5-h urinary d-xylose is made after administration of 5 g of d-xylose and normal d-xylose excretion is greater than 1.2 g at 5 h. Steatorrhoea is assessed by either the 24-h faecal fat estima tion method of van de Kramer, or the more easily available test of the Sudan stain for fat globules in stool samples. Stool examinations for parasites should be performed. Other causes of malabsorption should be ruled out as outlined in Table 15.10.8.3. A contrast-enhanced CT (enterography) scan of the abdomen will exclude abdominal lymphadenopathy and intestinal ulceroconstric tive lesions and is the preferred modality over small-bowel barium series. Upper gastrointestinal endoscopy may show normal duodenal folds or scalloping of duodenal folds due to villous atrophy, and biopsy of distal duodenum should be taken. Partial villous atrophy is seen on mucosal biopsies. Normal duodenal crypt to villous ratio of 3:1 or 4:1 is reduced to 2: 1 or 1:1 (Figs. 15.10.8.1a and 15.10.8.1d–15.10.8.1f). Villous fusion and an increase in lamina propria lymphocytes may also be seen. Management Treatment requires fluid and electrolyte supplementation, depending on the severity of diarrhoea, redressing nutritional de ficiencies, and a therapeutic trial with folate or a combination of antibiotics and folate. A high-calorie, high-protein, and low-fat diet, with restriction of long-chain fatty acids, is advisable. Folic acid (10 mg daily) is given for a period of 6 months, and normalcy of appetite and weight gain has been observed within 2 weeks of its initiation. The addition of an antibiotic results in rapid re versal of intestinal histology and function. The standard antibac terial therapy consists of 1 g oral tetracycline given daily in divided doses, or 100 mg of oral doxycycline given twice daily, for a period of 4 to 8 weeks. In nonresponsive cases, antibiotics can be con tinued for a period of 6 months. Vitamin B12 supplementation, ini tially parenteral and thereafter oral, should be given if deficiency of vitamin B12 is documented. Coeliac disease Coeliac disease has been considered as a disease of temperate countries, but in the last decade it has been increasingly been rec ognized in tropical countries. Makharia from New Delhi, India, has shown a community prevalence of 1% in North India, which is akin to that in temperate countries. There is a remarkable overlap between clinical, haematological, and histological features in coeliac disease and tropical sprue. Complete villous atrophy occurs in coeliac disease and is not seen in tropical sprue (Figs. 15.10.8.1b and 15.10.8.1c). Tropical sprue is associated with a more prom inent eosinophilic infiltrate in the duodenum compared to coeliac disease. Crohn’s disease Malabsorption in Crohn’s disease is consequent to involvement of small intestine, small intestinal bacterial overgrowth secondary to stricturing disease, bile salt malabsorption due to terminal ileal involvement, short-bowel syndrome due to repeated intestinal re section, and opportunistic enteric infections due to immunosup pressive medications. Traditionally, tropical regions have been

considered as low-prevalence areas for Crohn’s disease, but it is in creasingly being diagnosed. Phenotypically, there is an amazing re semblance between Crohn’s disease and intestinal tuberculosis, and differentiating one from the other is a perplexing challenge faced by physicians in these regions.

section 15 Gastroenterological disorders 2920 Primary immunodeficiency syndromes Common variable immunodeficiency is a genetic immune defect characterized by significantly decreased levels of IgG, IgA, and/or IgM with poor or absent antibody production, with exclusion of other causes of hypogammaglobulinaemia. The main gastrointes tinal manifestation of common variable immunodeficiency is tran sient or persistent diarrhoea. Giardia lamblia is the most common offender; other infections include cytomegalovirus, Salmonella spp., Clostridium difficile, and Campylobacter jejuni. Endoscopic mucosal biopsies show nodular lymphoid hyperplasia and a characteristic ab sence of plasma cells, apart from villous blunting (Fig. 15.10.8.2d). Immunoproliferative small intestinal disease Immunoproliferative small intestinal disease (IPSID), while more commonly seen in the Mediterranean region, has also been reported from tropical countries. It is characterized by clonal proliferation of plasma cells in the small intestine that produce abnormal α heavy chain immunoglobulins, which is thought to be in response to chronic or recurrent enteric infections in childhood. Recently, IPSID was shown to be associated with Campylobacter jejuni infection. The disease is more common in the second and third decade of life. Diffuse involvement of intestinal mucosa leads to malabsorption, chronic diarrhoea, and abdominal pain. Clubbing of the fingers is often seen, and abdominal masses may be palpable. The diagnosis of IPSID should be suspected in patients with malabsorption who have abdominal pain and clubbing. Intestinal mucosal biopsies, which characteristically show dense cellular lymphoplasmacytic infiltrate in the lamina propria leading to ef facement of the crypts, confirm the diagnosis (Figs. 15.10.8.2a and 15.10.8.2b). High levels of α heavy chain in the jejunal fluid are seen. IPSID is a premalignant condition and progresses over a vari able time period to lymphoplasmacytic and immunoblastic lymphoma. All patients with IPSID should therefore undergo Table 15.10.8.3 Differentiating features of various causes of malabsorption in the tropics Differential diagnosis Differentiating features Coeliac disease • Coeliac serology will be positive in most cases • Duodenal histology—complete villous atrophy may be seen in in coeliac disease, but not in tropical sprue • Gluten-free diet—response in coeliac disease Crohn’s disease • May have symptoms of bloody diarrhoea or recurrent partial bowel obstruction • CT abdomen may reveal evidence of stricturing or fistulizing disease • Colonoscopy may show colonic involvement Small intestinal bacterial overgrowth • Predisposing factors—previous surgery, diabetes, scleroderma • No villous atrophy on duodenal biopsy Immunoproliferative small intestinal disease • Serum electrophoresis for α chain disease Tropical pancreatitis • Marked steatorrhoea and abdominal pain • Abdominal X-ray—pancreatic calcification • Ultrasonography—ductal dilatation/pancreatic atrophy Combined variable immunodeficiency • Past history of recurrent sinopulmonary infection • Serum immunoglobulin profile HIV enteropathy • HIV positive • Duodenal biopsy may show similar changes to those in tropical sprue Intestinal tuberculosis • Symptoms of partial bowel recurrent obstruction may be present • Tissue biopsy positive for acid-fast bacilli stain and/or culture • Caseating granulomas on tissue biopsy • Colon may be involved • Concomitant pulmonary tuberculosis may be present Giardiasis • Three stool specimens on 3 separate days for cysts and trophozoites • Faecal immunoassays Cryptosporidiosis • Multiple stool specimens for modified acid-fast staining, direct fluorescent antibody (DFA) • Faecal enzyme immunoassays for detection of Cryptosporidium spp. antigens Cystoisosporiasis • Multiple stool specimens for modified acid-fast

staining Cyclospora • Multiple stool specimens for modified acid-fast staining • Autofluorescent oocysts—stool containing the parasite is viewed under an ultraviolet fluorescence microscope and the parasite appears blue or green against a black background Enterocytozoon bieneusi and Encephalitozoon intestinalis • Faecal smears stained with 'quick-hot gram chromotrope' technique and viewed under light microscopy for spores • Immunofluorescent (IFA) assays Leishmaniasis • Serological tests • Bone marrow aspiration • Demonstration of amastigotes on duodenal biopsy Strongyloidiasis • Microscopic identification of larvae (rhabditiform and occasionally filariform) in the stool or duodenal fluid Capillariasis • Demonstration of eggs, larvae, and/or adult worms in the stool or in intestinal biopsies.

15.10.8 Malabsorption syndromes in the tropics 2921 (a) (b) (c) (d) (e) (f) Fig. 15.10.8.1 Photomicrographs showing (a) normally oriented duodenal biopsy with a crypt-to-villous ratio of 1:3 (×100); (b) mild villous flattening (×100) and (c) marked villous flattening (×100) with hyperplastic crypts (arrows) are noted in coeliac disease; (d) duodenal biopsy in tropical sprue showing altered crypt-to-villous ratio and hyperplastic crypts (×100); (e) increased intraepithelial lymphocytes (arrows) (×200) and (f) macrocytosis of the epithelial cell nuclei (arrow) are also seen (×200). (a) (b) (c) (d) Fig. 15.10.8.2 (a, b) Duodenal biopsy in IPSID shows shorted and broadened villi with dense infiltrate of IgA-positive plasma cells (arrow) in the lamina propria ((a) ×100; (b) ×100)); (c) giardia trophozoites (arrow) noted in a duodenal biopsy (×200); and (d) duodenal biopsy with shortened villi and large reactive lymphoid follicles (arrows) in the lamina propria in a case of combined variable immune deficiency (×40).

section 15 Gastroenterological disorders 2922 staging of the disease using laparoscopy or laparotomy prior to therapy. Patients with early disease can be treated with anti biotics such as tetracycline for a prolonged period (at least 1 year). Chemotherapy is recommended, together with antibiotics, for patients with advanced disease. Idiopathic tropical chronic pancreatitis A distinct nonalcoholic type of chronic pancreatitis of uncertain aetiology has been described exclusively from tropical areas, and this has been termed tropical chronic pancreatitis. Its prevalence is decreasing, and the idiopathic chronic pancreatitis as seen in Western countries is being recognized increasingly in tropical re gions. Classical features of tropical chronic pancreatitis are younger age at onset, large intraductal pancreatic calculi, accelerated dis ease course with steatorrhoea and insulin requiring diabetes, and a high susceptibility to pancreatic cancer. The recognized triad of tropical pancreatitis is presence of abdominal pain, steatorrhoea, and diabetes. Overt steatorrhoea is seen in approximately 20% of the patients and treated with low-fat diet and pancreatic enzyme re placement therapy. Infectious causes of tropical malabsorption Protozoa Giardia intestinalis, Cryptosporidium parvum, cystoisosporiasis (Cystoisospora belli), Cyclospora cayetanensis, and the microsporidia (Enterocytozoon bieneusi and Encephalitozoon intestinalis) are common causes of prolonged diarrhoea and malabsorption. Giardia is a major cause of diarrhoea in children and in travellers. Malabsorption in giardiasis is due to diffuse shortening of microvilli, disruption of epithelial tight junctions, increased intestinal permeability, and deconjugation of bile salts. Severe, persistent, or recurrent giardiasis should lead to suspicion of asso ciated IgA deficiency. Giardia cysts can be observed in fresh smears (Fig. 15.10.8.3a), on formalin-ethyl acetate, or permanent stained smear (Fig. 15.10.8.2c). Detection rates can be increased by testing for giardia antigen in stool. Modified acid-fast stain of stool is used to demonstrate oocysts of cryptosporidia, cytoisospora, and cyclospora (Figs. 15.10.8.3b– 15.10.8.3d). In addition, the use of an enzyme immunoassay on stool specimens increases sensitivity and specificity of detection of

cryptosporidia. Microscopic demonstration of large, typic ally shaped oocysts is the basis for diagnosis of cystoisosporiasis. Cyclospora oocysts stained by trichrome or modified acid-fast stain are seen as refractile spheres with a central morula, resembling wrinkled cellophane. Microsporidial spores in stool are diagnosed by immunofluorescent assays or a recently developed ‘quick-hot gram chromotrope’ staining technique (Fig. 15.10.8.3e). Table 15.10.8.4 shows the agents used to treat infectious causes of malabsorption. Nemathelminthes Strongyloides stercoralis can cause anaemia, chronic diarrhoea, and protein-losing enteropathy. Hyperinfection occurs in the malnourished, patients on corticosteroids, and in those with coinfection with human T-cell lymphotropic virus type 1. Multiple stool samples should be tested as the sensitivity of widely used diagnostic procedures, such as direct faecal smear, Baermann technique, and Koga agar plate culture is not satisfactory when (e) (f) (a) (b) (c) (d) Fig. 15.10.8.3 (a) Wet mount showing trophozoite of Giardia intestinalis; (b) modified acid-fast (MAF) staining showing oocysts of Cryptosporidium parvum (size: 4–6 µm); (c) MAF staining showing oocysts of Cyclospora cayetanensis (size: 8–10 µm); (d) MAF staining showing oocysts of Cystoisospora belli (size: 20–30 × 10 to 15 µm); (e) modified trichrome staining showing spores of microsporidia (size: 1–2 µm); and (f) wet mount showing larva of Strongyloides stercoralis.

 used on a single stool specimen (Fig. 15.10.8.3f). Serology is a useful tool but has a low specificity. Intestinal capillariasis caused by Capillaria philippinensis is a common cause of malabsorption in South East Asia, chiefly Thailand and the Philippines. Patients present with chronic watery diarrhoea, steatorrhoea, chronic abdominal pain, and protein- losing enteropathy. It typically involves long segments of jejunum or ileum. Diagnosis is made either on stool examination, or from tissue obtained from jejunum or ileum by enteroscopy. Bacteria Intestinal tuberculosis caused by Mycobacterium tuberculosis can in volve any part of the gut and most commonly involves the ileocaecal area as an ulcerative or ulcerohypertrophic form. It can present as chronic diarrhoea, partial recurrent intestinal obstruction, or pro tein-losing enteropathy. Loss of absorptive surface due to diffuse ulceration, bacterial overgrowth secondary to stricture formation, bile salt deconjugation, bile salt diarrhoea due to terminal ileal dis ease, and lymphatic obstruction are causes of malabsorption. In one study, biochemical evidence of malabsorption was found in 75% of patients with intestinal tuberculosis with intestinal obstruction, but in only 40% of patients without obstruction. The diagnosis is established by cross-sectional imaging, small-bowel or large-bowel endoscopy, tissue biopsy, and acid-fast bacilli stain and culture. Antitubercular therapy for 6 months is usually sufficient for treating the infection. Viruses HIV enteropathy can cause chronic diarrhoea and malabsorption in patients with AIDS, even in the absence of demonstrable opportunistic pathogen infection. Intestinal CD4 cells are preferen tially destroyed in HIV infection. Changing scenario of malabsorption syndrome in the tropics Until 10 years ago, tropical sprue was a leading cause of malabsorption in tropical countries. Socioeconomic improvement, better sanita tion, hygiene, and a decrease in water-borne diseases in recent years have led to a decline in its incidence. Coeliac disease was initially thought to be a rare or uncommon disease in tropical countries, but it is now increasingly recognized in many tropical countries, including India. This may be because of the widespread diffusion of Western dietary habits, thus increasing consumption of gluten- containing cereals. Approach to a patient with malabsorption syndrome After routine clinical, haematological, and biochemical evaluation, tests for confirmation of malabsorption (d-xylose, faecal fat esti mation, vitamin B12, folate, and serum methylmalonate) should be performed. The first line of investigation includes stool microscopy for parasites and ova, serological tests for HIV and coeliac

disease, endoscopic examination, and duodenal biopsies. The next step is to check serum immunoglobulin levels, thyroid profile, glucose hydrogen breath test for bacterial overgrowth, and CT enterography (Fig. 15.10.8.4). Table 15.10.8.4 Therapeutic choices for infective causes of malabsorption Infective cause of malabsorption Therapy Giardia intestinalis Metronidazole 250–400 mg three times daily orally for 5 days Or tinidazole 2 g single dose orally Or nitazoxanide 500 mg twice daily orally for 3 days Or albendazole 400 mg once daily orally for 5 days Cryptosporidium parvum Nitazoxanide 500 mg twice daily orally for 3 days Cystoisosporiasis (Cystoisospora) Trimethoprim/sulfamethoxazole 160 mg/800 mg two times daily orally for 10 days Immunocompromised patients: Trimethoprim/sulfamethoxazole 160 mg/800 mg four times daily orally for 10 days, followed by maintenance therapy 160 mg/800 mg twice daily for 3 weeks Cyclospora cayetanensis Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily orally for 7 days Or ciprofloxacin 500 mg twice a day orally for 7 days Followed by maintenance therapy in patients with HIV: trimethoprim/sulfamethoxazole 160/ 800 mg three times a week for 10 weeks Or ciprofloxacin 500 mg three times a week for 10 weeks Enterocytozoon bieneusi Fumagillin 20 mg three times daily for 2 weeks Encephalitozoon intestinalis Albendazole 400 mg twice daily for 3 weeks Strongyloides stercoralis Ivermectin 200 µg/kg single dose orally for 2 days May be extended to 5–7 days in disseminated infection Capillaria philippinensis Albendazole 200 mg twice daily orally for 10 days Or mebendazole 200 mg twice daily orally for 20 days Mycobacterium tuberculosis Isoniazid, rifampicin, pyrazinamide, ethambutol for 2 months Followed by: Isoniazid and rifampicin for 4 months HIV enteropathy Antiretroviral therapy

section 15 Gastroenterological disorders 2924 FURTHER READING Baker SJ, Mathan VI (1971). Tropical sprue in Southern India. In: Wellcome Trust (ed) Tropical sprue and megaloblastic anemia, pp. 189–260. Churchill Livingstone, Edinburgh. Brown IS, et al. (2014). Tropical sprue: revisiting an underrecognized disease. Am J Surg Pathol, 38, 666–72. Cook GC (1984). Aetiology and pathogenesis of postinfective tropical malabsorption (tropical sprue). Lancet, 31, 721–3. Ghoshal UC, et al. (2003). Tropical sprue is associated with con tamination of small bowel with aerobic bacteria and reversible prolongation of orocecal transit time. J Gastroenterol Hepatol, 18, 540–7. Ghoshal UC, et al. (2014). Tropical sprue in 2014: the new face of an old disease. Curr Gastroenterol Rep, 16, 391. Ghoshal UC, Gwee KA (2017). Post-infectious IBS, tropical sprue and small intestinal bacterial overgrowth: the missing link. Nat Rev Gastroenterol Hepatol, 14, 435–41. Gorbach SL, et al. (1969). Bacterial contamination of the upper small bowel in tropical sprue. Lancet, 1, 74–7. Klipstein FA, Baker SJ (1970). Regarding the definition of tropical sprue. Gastroenterology, 58, 717–21. Klipstein FA, Samloff IM, Schenk EA (1966). Tropical sprue in Haiti. Ann Intern Med, 64, 575–94. Korpe PS, Petri WA Jr (2012). Environmental enteropathy: critical implications of a poorly understood condition. Trends Mol Med, 18, 328–36. Makharia GK, et al. (2014). Issues associated with the emergence of coeliac disease in the Asia–Pacific region: a working party report of the World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology. J Gastroenterol Hepatol, 29, 666–77. Mathan VI, Baker SJ (1968). Epidemic tropical sprue and other epi demics of diarrhea in South Indian villages. Am J Clin Nutr, 21, 1077–87. Ramakrishna BS, Mathan VI (1982). Water and electrolyte absorption by the colon in tropical sprue. Gut, 23, 843–6. Sharma P, et al. (2019). Clinical, endoscopic, and histological differ entiation between celiac disease and tropical sprue: a systematic review. J Gastroenterol Hepatol, 34, 74–83. Fig. 15.10.8.4 An algorithmic approach to investigation of malabsorption in the tropics.

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