# 15.10.2 Bacterial overgrowth of the small intestin

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15.10.2 Bacterial overgrowth of the small intestine 2879 on the diagnosis and its response to treatment. There has until re cently been no overarching treatment for intestinal malabsorption itself. The endogenous hormone glucagon-like peptide 2 is one of the glucagon family and is secreted from the L-cells of the intestine in response to luminal nutrients, whence it acts as a small-bowel growth factor. Its exogenous administration in patients with short- bowel syndrome confirms that the effect can be utilized thera peutically, and longer-acting analogues are becoming available for clinical use. FURTHER READING Barkun AN, et al. (2013). Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. Can J Gastroenterol, 27, 653–9. Battat R, et al. (2014). Vitamin B12 deficiency in inflammatory bowel disease: prevalence, risk factors, evaluation, and management. Inflamm Bowel Dis, 20, 1120–8. Cynober L, Moinard C, De Bandt JP (2010). Citrulline: a new major signaling molecule or just another player in the pharmaconutrition game? Clin Nutr, 29, 545–51. Fasano A, et al. (2015). Nonceliac gluten sensitivity. Gastroenterology, 148, 1195–204. Forbes A (2014). Crohn's disease: rehabilitation after resection. Dig Dis, 32, 395–8. Jeppesen PB, et al. (2012). Teduglutide reduces need for parenteral nu trition among patients with short bowel syndrome with intestinal failure. Gastroenterology, 143, 1473–81. Juckett G, Trivedi R (2011). Evaluation of chronic diarrhea. Am Fam Physician, 84, 1119–26. Kelly CP, et al. (2015). Advances in diagnosis and management of ce liac disease. Gastroenterology, 148, 1175–86. Mooney PD, Hadjivassiliou M, Sanders DS (2014). Coeliac disease. BMJ, 348, g1561. Nadhem ON, et al. (2015). Review and practice guidelines for celiac disease in 2014. Postgrad Med, 127, 259–65. Papadia C, et al. (2014). Diagnosing small bowel malabsorption: a re view. Intern Emerg Med, 9, 3–8. 15.10.2 Bacterial overgrowth of
the small intestine Stephen J. Middleton and Raymond J. Playford ESSENTIALS Small intestinal bacterial overgrowth can be defined as the presence of excessive bacteria in the small intestine which can interfere with digestion and absorption. Predisposing causes include sustained hypochlorhydria induced by proton pump inhibitors, small intes- tinal dysmotility and stasis due to anatomical or motor abnormal- ities, and reduced antibacterial activity as seen in immunological deficiency and chronic pancreatitis. Presentation is predominantly from consequences of malabsorp tion, including gastrointestinal symptoms (e.g. diarrhoea or steatorrhoea) and features

of specific nutrient malabsorption
(e.g. osteoporosis, anaemia, neuropathy, and night blindness). Definitive diagnosis is difficult, requiring a properly collected and appropriately cultured aspirate from the proximal small intestine re- vealing a total concentration of a mixed growth of bacteria generally greater than 105 organisms/ml. Alternative investigations frequently used include glucose/lactulose breath tests or either the 13C- or 14C-xylose breath test, with elevated levels of 13CO2 or 14CO2 found in the breath. There may be low levels of cobalamin (metabolized by Gram-negative anaerobes), increased serum folate (synthesized by overgrowth flora), and increased urinary indicans (intraluminal product of bacterial tryptophan metabolism). Aside from treatment of any nutritional deficiencies, spe- cific treatment is with an antimicrobial that is effective against both aerobic and anaerobic enteric bacteria (e.g. doxycycline, amoxicillin–clavulanic acid, rifaximin, or ciprofloxacin), which can be administered in rotation to reduce antibiotic resistance. Where possible and appropriate, correction of any underlying cause should also be performed. Introduction Small intestinal bacterial overgrowth (SIBO) can be defined as the presence of excessive bacteria in the small intestine. It causes a var iety of symptoms and clinical manifestations which depend upon the type, density, and metabolic characteristics of colonizing bac teria and the response of the host. SIBO can result in diarrhoea, malabsorption syndromes re sulting in weight loss, specific nutritional deficiencies, and more generalized complications such as osteoporosis. Bloating, flatu lence, and abdominal discomfort are common and can result in clinical features similar to those of irritable bowel syndrome (IBS). There is increasing recognition that SIBO is commoner than previ ously thought and occurs in patients with normal gastrointestinal anatomy. It has been found to be a frequent cause of diarrhoea and malabsorption in elderly patients who have developed age-related small-bowel dysmotility. Prevalence The incidence of SIBO is increased in some disease states, but is also present in a few apparently healthy control subjects (Table 15.10.2.1). Gastrointestinal surgery, in particular the formation of a ‘blind loop’ such as that found in a Roux-en-Y reconstruction, has been widely appreciated as a cause of SIBO for many years. However, it is now evident that many conditions, particularly those that result in dysmotility, are also associated with SIBO in the absence of surgery and with normal anatomy. Of particular interest is the recent obser vation that many patients with clinical features of IBS also have SIBO, but it remains unclear if these patients have SIBO alone or both conditions exist in association.

section 15 Gastroenterological disorders 2880 Pathology SIBO is characterized by an increase in the density of bacteria com monly found as normal gut commensals and it is generally con sidered to result from a deficiency of the normal process which maintains homeostasis of resident enteric bacteria. Researchers have identified disturbances in gut motility, immune function, anatomy, and mucosal function as likely causes of SIBO. SIBO can be defined as a bacterial count in the small bowel of greater than 105 colony forming units (CFUs)/ml, as compared to 103 CFUs/ml which is considered to be the upper limit of normal. This is often associated with inflammatory changes in the small- bowel mucosa, including blunting of the villi, atrophy of mucosa and crypts, and elevation of the intraepithelial lymphocytes. These changes resolve with antibiotic therapy. Under normal circumstances, most resident bacteria in the small intestine are Gram positive. However, in SIBO, Gram-negative or ganisms, enterococci and anaerobes, which are more typical of co lonic flora, become predominant and the pathological effects on intestinal function are considered to arise from their metabolic and immunogenic properties as well as their numbers. Bacteria that deconjugate bile salts tend to cause fat malabsorption, whereas those that ferment carbohydrate produce flatulence and bloating. Certain bacteria, particularly the Gram-negative popu lation such

as klebsiella, produce substances toxic to the intestinal mucosa leading to diarrhoea and malabsorption. Aetiological factors Abnormal luminal environment Hypochlorhydria Reduced gastric acid production is often associated with conditions such as gastric atrophy, Helicobacter pylori infection, and following vagotomy. Studies have found SIBO to be present in about 50% of pa tients taking standard doses of proton pump inhibitors and around 15% of those on H2 antagonists. Pancreatic exocrine deficiency Chronic pancreatitis is associated with a 30% incidence of SIBO, probably due to pancreatic exocrine insufficiency which leads to re duced levels of antibacterial proteolytic enzymes and maldigestion of food and luminal substances, facilitating the overgrowth of bac teria. Furthermore, associated motility disturbances due to the use of powerful analgesics cause stasis and reduced bacterial clearance. This may in part explain the high incidence of SIBO in cystic fi brosis (approximately 50%) and pancreatic cancer. Gastrointestinal dysmotility Under normal circumstances, regular sweeping peristaltic con tractions generated by the intermittent aboral migratory motor complex limit the amount of food remaining in the small intes tine between meals. Disturbances of motility which reduce the ef fectiveness of this process may result in the presence of excessive quantities of food debris in the lumen, which can promote bac terial proliferation and overgrowth. Neuropathic and myopathic processes often underlie motility disturbances, although these are not commonly histologically characterized as this requires a full-thickness intestinal biopsy. Systemic diseases such as diabetes, scleroderma (Fig. 15.10.2.1), and polymyositis may cause intes tinal muscle damage. Cirrhosis and renal failure have been associ ated with disorders of peristalsis leading to stasis and SIBO. Isolated gastroparesis may result in considerable gastric residue and bacterial overgrowth, which may then provide the small intestine with excessive quantities of bacteria. This is often associated with diabetes but can also be caused by viral infections and certain medications. Patients diagnosed with IBS have recently been reported to have evidence of SIBO in 30 to 80% of cases. As SIBO produces symptoms which are similar to those of IBS, many believe that these patients have SIBO rather than IBS; others feel that SIBO has arisen because of dysmotility caused by IBS. Structural abnormalities Surgical procedures that result in regions of relative stasis are com monly associated with SIBO, with the blind loop fashioned in the Billroth II and Roux-en-Y anastomoses following antral gastrec tomy being good examples. Nonsurgical anatomical disorders asso ciated with stasis include diverticula, which can be large and sparse or small and numerous (Fig. 15.10.2.2). Stasis also occurs proximal to strictures where the intestine may be dilated in conditions such as Crohn’s disease, scleroderma, and following radiotherapy. Table 15.10.2.1 Conditions predisposing to SIBO Healthy subjectsa Structural abnormalities Small intestinal diverticulosis Small intestinal strictures Blind loops (Roux loops) Resection of ileocaecal valve Gastrectomy Coloenteric fistulation Disorders of motility Intestinal myopathy Intestinal neuropathy Gastroparesis Pseudo-obstruction Drug induced intestinal stasis Age related dysmotility Parkinson’s disease Muscular dystrophy Mucosal damage/dysfunction Crohn’s disease Coeliac disease Immunodeficiency Organ dysfunction Cirrhosis Renal failure Hypochlorhydria Pancreatitis Metabolic Diabetes Drugs Acid suppression Intestinal stasis (i.e. opiates) a Incidence reported as 0 to 20% in studies, uncertain aetiology.

 Mucosal-associated immune dysfunction Bacterial populations in the intestine are also regulated by the mu cosal immune system and its dysfunction can result in SIBO. Studies have demonstrated SIBO in patients with isolated subgroup as well as more generalized immunoglobulin deficiency and T-cell dysfunction. This is also seen in patients following intestinal trans plantation who receive powerful immunosuppression and also have a degree of dysmotility. A high incidence of SIBO has also been re corded in chronic

lymphocytic leukaemia (approximately 50%) and lymphoma. Disorders of the intestinal mucosa Conditions that cause damage and dysfunction of the mucosa such as coeliac disease, radiation enteritis, and Crohn's disease are associated with SIBO, a common cause of ongoing diarrhoea in coeliac patients after treatment with a gluten-free diet (approxi mately 60%). It is likely that in addition to associated motility dis turbances a dysfunctional mucosa allows excessive proliferation of bacteria through impairment of innate and acquired immunity. Age-associated SIBO Studies in elderly populations have demonstrated an incidence of SIBO of between 15 and 30%. Immobility and comorbidity tend to be the main risk factors, and although age-related dysmotility has been widely suggested as the underlying cause, this remains controversial. Miscellaneous conditions Several studies have detected an association between non alcoholic steatohepatitis (NASH) and SIBO. A role for SIBO in the pathogenesis of NASH has been postulated, and slow intes tinal transit times have been found in some experimental models of NASH. Patients with chronic alcoholism in the absence of cirrhosis have elevated levels of intestinal bacteria, believed to be a result of mucosal damage, and patients with Parkinson's disease are more likely to have SIBO, which may be due to a neurological mani festation of the disorder or a consequence of drug therapy for the condition. Fig. 15.10.2.1 Small bowel filled by reflux during a barium enema performed in a patient with recurrent bloating and air-filled small bowel loops on abdominal radiographs. This spot image shows the hide-bound appearance with flattened edges of crowded thin folds (arrow). On the opposite wall, wide-mouthed sacculations are present, permitting the diagnosis of scleroderma. From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press. (a) (b) Fig. 15.10.2.2 Malabsorption from small-bowel diverticulosis. CT scan (a) shows dilated loops of small bowel and dilution of enteric contrast material. With small-bowel malabsorption, fluid-filled large diverticula may have the same diameter as dilated loops and be completely obscured. It may be the tiny diverticula (arrows) that are most clearly seen. (b) A spot radiograph from a small-bowel series confirms small-bowel diverticulosis with many large diverticula (arrow). From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press.

 Clinical features Clinical manifestations vary according to the metabolic and im munogenic properties of the bacteria and the response of the host. Abdominal bloating, discomfort or pain, and flatulence, with or without diarrhoea, commonly occur and often closely overlap with the symptoms of IBS making differential diagnosis difficult. When significant malabsorption is present, weight loss and steatorrhoea may occur, and specific nutrient deficiencies can cause metabolic bone disease and hypocalcaemia (vitamin D), polyneur opathy and megaloblastic anaemia (vitamin B12), iron deficiency anaemia, and (occasionally) protein-losing enteropathy. Night blindness from vitamin A deficiency and vitamin E deficiency causing neuropathy and T-cell abnormalities has been reported. The main nutritional consequences are summarized in Box 15.10.2.1. In some cases, bacterial fermentation of sugars and easily fer mentable polysaccharides produces d-lactate, for which there is no human metabolic pathway. Elevated serum levels of lactic acid may result in clinically significant d-lactic acidosis. Diagnosis Bacterial culture Direct estimation of the quantity and nature of bacteria within the lumen of the small intestine is generally considered to be the gold standard for diagnosis. However, the difficulties associated with collection and culture of bacteria have made this unpopular as a clinical tool. Molecular techniques to quantify intestinal bacteria have not yet been validated but offer a potential solution to the diffi culties of culturing fastidious organisms. Breath tests The less invasive indirect diagnostic techniques are most commonly used in clinical practice. The hydrogen breath

test is the simplest example and is based on the premise that hydrogen is not produced by mammalian cells and therefore a significant rise in detectable hydrogen in the breath, following consumption of a fermentable substrate, can be assumed to be arising from bacterial fermentation of that substrate (Table 15.10.2.2). The substrates used in this test include glucose, lactulose, and xylose. Glucose is usually completely absorbed by the intestine and there fore will rarely give rise to hydrogen from fermentation by colonic bacteria. For this reason, it is often preferred to lactulose, which is poorly absorbed and produces a hydrogen peak from colonic bac teria that must be distinguished from an earlier peak if small-bowel bacterial fermentation is present. This distinction can sometimes be difficult to determine, and may lead to less diagnostic accuracy, particularly if intestinal transit is rapid (such as in short-bowel syn drome), resulting in lower sensitivity and specificity. However, the proximal absorption of glucose may result in failure to detect over growth of the distal small intestine. Xylose is less easily absorbed and more reaches the distal small intestine, giving the potential ad vantage of providing a better assessment of the entire small bowel. Unfortunately, incomplete absorption is more likely and the risk of confusion with colonic fermentation is increased. Breath methane is also an indicator of bacterial fermentation, and a combination of measurements of methane and hydrogen is becoming more commonly used. This allows detection of those bac teria which produce either only hydrogen (approximately 50%) or methane (approximately 10–15%). There is lack of consensus about the breath hydrogen levels used to define bacterial overgrowth. A rise in hydrogen concentration of at least 20 parts per million (ppm) after a glucose challenge and at least 12 ppm after lactulose are usually taken to indicate bacterial overgrowth. Their diagnostic accuracy is reported to be approxi mately 70% and 50% respectively. A further method of breath sample analysis using radioisotope-labelled substrates has been developed but is generally considered to be no more accurate than hydrogen and methane analysis. This Box 15.10.2.1 Main nutritional consequences of SIBO • Weight loss • Fat malabsorption (steatorrhoea) • Vitamin and mineral deficiency: — Fat-soluble vitamins (A, D, E, K) — Vitamin B12 — Iron — Magnesium — Calcium • Increased serum levels of: — Folate — d-lactate • Hypoproteinaemia/hypoalbuminaemia Table 15.10.2.2 Indirect tests for detecting bacterial overgrowth of the small intestine Test Measurement End point Comment Glucose 50 g oral Breath hydrogen/methane Rise in [breath] of ≥20/≥12 ppm respectively Measurement of both gases improves accuracy Lactulose 10 g oral 13C/14C-d-xylose oral Breath 13CO2/14CO2 Individual laboratory normal ranges Limited by expense and radioactivity 13C/14C-glycocholate oral Breath 13CO2/14CO2 Individual laboratory normal ranges Sensitivity lower as only detects deconjugating bacteria Bacterial metabolites in urine Urine 4-hydroxyphenylacetic acid Individual laboratory normal ranges Useful in paediatric practice Urinary indicans Individual laboratory normal ranges Sensitivity and specificity is lower than breath tests Therapeutic trial of antibiotics Clinical effect Improvement of symptoms May cause diagnostic confusion as other conditions can respond to antibiotics

15.10.2 Bacterial overgrowth of the small intestine 2883 employs 13C- and 14C-labelled xylose or glycocholic acid, which when fermented produces isotope-labelled CO2 that is excreted and measured in breath samples. The use of isotopes is expensive, and they cannot be used in children and pregnancy. The glycocholic breath test only detects bacteria which are able to deconjugate, and these may be absent in up to 30% of cases of SIBO. Management The aims of treatment can be divided into three areas: eradicating the overgrowth of bacteria, restoring any nutritional deficiencies, and resolving the underlying cause where possible (Box 15.10.2.2). In many cases, the consequences of SIBO are minor and the risks and inconvenience of treatments such as long-term antibiotics or reconstructive surgery may be greater than the potential bene fit. Patients may

prefer symptomatic control with antidiarrhoeal agents. Eradicating bacterial overgrowth Antibiotics A mixed population of bacteria is present in bacterial overgrowth, making selection of antibiotics difficult, a matter further com pounded by the inability to culture more than about 20% of species present in the resident intestinal flora. Attempts to identify bacteria have found a mixture of aerobes (such as streptococci, Escherichia coli, staphylococci, and klebsiella) and anaerobes (such as bacteroides, lactobacillus, and clostridium). Broad-spectrum anti biotics have therefore been used, often in rotation, to reduce the risk of developing colonization with resistant organisms. Tetracycline has been extensively employed in the past, but newer regimens including ciprofloxacin, amoxicillin/clavulanate, and doxycyc line have been reported to have superior efficacy (Box 15.10.2.3). Recent studies of the efficacy of metronidazole and rifaximin have reported encouraging results with examples of long-term remis sion, although most advocate repeated courses of 7 to 10 days or inclusion in a cyclical regimen with other antibiotics. Long-term studies suggest that, after a single course, there is a relapse rate of at least 50% at 9 months. Resistant cases may respond to the oral administration of anti biotics with poor oral bioavailability such as gentamicin, but only anecdotal evidence of efficacy is available. Probiotics There have been few randomized controlled trails of probiotics as treatment for SIBO. A trial in paediatric patients with proton pump inhibitor-induced SIBO failed to reveal any benefit from the combination of Lactobacillus rhamnosus and L.  acidoph- ilus. However, a randomized double-blind trial of L. casei and L.  acidophillus significantly reduced diarrhoea, whereas another randomized study did not find any benefit from L.  fermentum. Overall, it appears that there is inadequate evidence to support the use of probiotics as treatment for SIBO at present. Nutritional support The primary aim should be to replace any nutritional deficiencies and encourage normalization of body weight. Particular atten tion should be given to replacement of likely deficiencies detailed in Box 15.10.2.1. Enhanced absorption of energy-providing foods may be possible by dietary manipulation to encourage consumption of those foods which appear to be absorbed. Patients with marked steatorrhea may benefit from a diet richer in carbohydrates than fat, and the opposite should be considered where bloating and flatulence are the main symptoms. Treating the cause of bacterial overgrowth Structural abnormalities such as strictures and blind loops may be amenable to reconstructive surgery and large, single small-bowel diverticulum can sometimes be resected. Disorders of motility are difficult to treat: most neuropathies and myopathies do not respond adequately to medical treatment. Gastroparesis occasionally re sponds to prokinetic agents, and when associated with diabetes may improve with optimization of blood glucose control. The response to gastric pacemakers has generally been disappointing. When the result of a metabolic abnormality such as hypothyroidism or an elec trolyte disturbance, pseudo-obstruction can often be treated, but unfortunately in many cases a reversible cause cannot be found. A careful review of all medications is important. Opiates are of particular concern, but antidepressants with anticholinergic prop erties can also sometimes be implicated. Control of inflammatory conditions of the mucosa such as coeliac disease and Crohn’s dis ease should be confirmed and optimized, and in cases of immuno deficiency, therapy such as immunoglobulin replacement must be adequate. FURTHER READING Dukowicz AC, Lacy BE, Levine GM (2007). Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol (N Y), 3, 112–22. Grace E, et  al. (2013). Review article:  small intestinal bacterial overgrowth—prevalence, clinical features, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther, 38, 674–88. Sachdev AH, Pimentel M (2013). Gastrointestinal bacterial over growth:  pathogenesis and clinical significance. Ther Adv Chronic Dis, 4, 223–31. Box 15.10.2.2 Targets for treatment of SIBO • Treat overgrowth of bacteria • Resolve nutritional deficiencies • Treat the underlying cause of SIBO Box 15.10.2.3 Antibiotics with supporting evidence of efficacy in SIBO • Rifaximin • Ciprofloxacin • Norfloxacin •

Amoxicillin/clavulanate • Metronidazole + trimethoprim/sulfamethoxazole • Metronidazole + cephalexin

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