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TOPIC HIGHLIGHT

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Small intestinal bacterial overgrowth syndrome

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Abstract

Human intestinal microbiota create a complex polymicrobial ecology. This is characterised by its high population density, wide diversity and complexity of interaction. Any dysbalance of this complex intestinal microbiome, both qualitative and quantitative, might have serious health consequence for a macro-organism, including small intestinal bacterial overgrowth syndrome (SIBO). SIBO is defined as an increase in the number and/or alteration in the type of bacteria in the upper gastrointestinal tract. There are several endogenous defence mechanisms for preventing bacterial overgrowth: gastric acid secretion, intestinal motility, intact ileo-caecal valve, immunoglobulins within intestinal secretion and bacteriostatic properties of pancreatic and biliary secretion. Aetiology of SIBO is usually complex, associated with disorders of protective antibacterial mechanisms (e.g. achlorhydria, pancreatic exocrine insufficiency, immunodeficiency syndromes), anatomical abnormalities (e.g. small intestinal obstruction, diverticula, fistulae, surgical blind loop, previous ileo-caecal resections) and/or motility disorders (e.g. scleroderma, autonomic neuropathy in diabetes mellitus, post-radiation enteropathy, small intestinal pseudo-obstruction). In some patients more than one factor may be involved. Symptoms related to SIBO are bloating, diarrhoea, malabsorption, weight loss and malnutrition. The gold standard for diagnosing SIBO is still microbial investigation of jejunal aspirates. Non-invasive hydrogen and methane breath tests are most commonly used for the diagnosis of SIBO using glucose or lactulose. Therapy for SIBO must be complex, addressing all causes, symptoms and complications, and fully individualised. It should include treatment of the underlying disease, nutritional support and cyclical gastro-intestinal selective antibiotics. Prognosis is usually serious, determined mostly by the underlying disease that led to SIBO.

Key words: Bacterial overgrowth; Breath test; Hydrogen; Methane; Small intestine

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INTRODUCTION

Human intestinal microbiota create a complex polymicrobial ecology. This is characterised by its high population density, wide diversity and complexity of interaction. The duodenum and proximal jejunum normally contain small numbers of bacteria, usually lactobacilli and enterococci, gram-positive aerobes or facultative anaerobes ($< 10^4$ organisms per mL). Coliforms may be transiently present ($< 10^3$ bacteria per mL) and anaerobic *Bacteroides* are not found in the jejunum in healthy people. Up to one third of jejunal aspirates might be sterile in healthy volunteers. The distal ileum is a transition zone between sparse populations of aerobic bacteria of the proximal small intestine and very dense populations of anaerobic micro-organisms in the large bowel[1-3]. The epithelial surface of the small intestine in a healthy human is not colonised. Occasional groups of bacteria can be found in low concentrations within the lumen. Bacteria do not form clusters and spatial structures, and the luminal contents are separated from the mucosa by a mucus layer[4].

Any dysbalance of this complex intestinal microbiome, both qualitative and quantitative, might have serious health consequences for a macro-organism, including small intestinal bacterial overgrowth syndrome (SIBO).

DEFINITION

SIBO is a very heterogeneous syndrome characterised by an increased number and/or abnormal type of bacteria in the small bowel. Most authors consider diagnostic of SIBO to be the finding of $\geqslant 10^5$ bacteria [i.e. colony-forming units (CFU)] per mL of proximal jejunal aspiration. The normal value is $\leqslant 10^4$ CFU/mL[3, 5-7].

PREVALENCE

The overall prevalence of SIBO in the general public is unknown. In general, SIBO is substantially underdiagnosed. There are several reasons for this fact. Some patients may not seek healthcare or SIBO may not be properly diagnosed by medical investigations. SIBO might be asymptomatic or with non-specific symptoms only, and last but not least, all symptoms might be incorrectly ascribed to the underlying disease (leading to SIBO). Of course, diagnostic yield also depends on the methods used for investigation. According to different studies with the investigation of small sets of clinically healthy people as a control, findings consistent with SIBO were found in 2.5% to 22%[8-17].

In particular diseases and disorders, literature data on prevalence differ substantially. For instance, the prevalence of SIBO in patients fulfilling diagnostic criteria for irritable bowel syndrome was 30%-85%[9-11,16,18,19]. The prevalence of SIBO in coeliac disease non-responding to a gluten-free diet was up to 50%[20]. In liver cirrhosis, SIBO was diagnosed in more than 50% of cases[21,22]. In a small group of elderly people (70 to 94 years old) with lactose malabsorption, SIBO was documented in 90%[23]. An interesting study was performed on asymptomatic morbidly obese subjects and SIBO was found in 17% (compared to 2.5% in non-obese persons)[15].

AETIOLOGY

There are several endogenous defence mechanisms for preventing bacterial overgrowth: gastric acid secretion, intestinal motility, intact ileo-caecal valve, immunoglobulins within intestinal secretion and bacteriostatic properties of pancreatic and biliary secretion[24].

The aetiology of SIBO is usually complex, associated with disorders of protective antibacterial mechanisms (e.g. achlorhydria, pancreatic exocrine insufficiency, immunodeficiency syndromes), anatomical abnormalities (e.g. small intestinal obstruction, diverticula, fistulae, surgical blind loop, previous ileo-caecal resections) and/or motility disorders (e.g. scleroderma, autonomic neuropathy in diabetes mellitus, post-radiation enteropathy, small intestinal pseudo-obstruction). In some patients more than one factor may be involved. "Aetiological" and "predisposing" factors cannot be separated in some patients. SIBO may occur in elderly people without any evident underlying small intestinal pathology.

In some cases, a vicious circle arises: an underlying disease is complicated by SIBO and then SIBO directly (as a morphological impact) or vicariously (by malabsorption or nutrient deficiency) causes further deterioration of the underlying disease.

Out of all diseases and disorders associated with SIBO (listed below in detail), 90% of cases comprise small intestinal motility disorders (of various aetiology) and chronic pancreatitis[2].

Achlorhydria

Achlorhydria (due to chronic atrophic gastritis) and long-term administration of proton pump inhibitors may cause bacterial overgrowth in the stomach and duodenum. Proton pump inhibitors not only increase duodenal bacterial colonisation but also accelerate intestinal transit[24].

Exocrine pancreatic insufficiency

Chronic pancreatitis is complicated by SIBO in 30%-40% of cases[7,25]. Multiple factors can be involved: exocrine pancreatic insufficiency (with absence of anti-bacterial effect of proteolytic enzymes), abnormal chyme in the small intestinal lumen, motility disorders, administration of painkillers and ongoing alcohol consumption in some of patients. Cystic fibrosis is also associated with increased risk of SIBO. Fridge *et al*[26] diagnosed SIBO in 14/25 (56%) patients with cystic fibrosis. SIBO may be a causative fac-

tor of diarrhoea in advanced pancreatic cancer[27] apart from pancreatic exocrine insufficiency, chemotherapy or previous surgery.

Immunodeficiency syndromes

Various immunodeficiency syndromes, such as IgA deficiency, common variable immunodeficiency, AIDS and others, are complicated by miscellaneous infection complications, including SIBO[28,29].

Small intestinal obstruction and stagnation

All anatomical pathology associated with small intestinal obstruction and stagnation could be associated with SIBO, e.g. strictures, adhesions, tumours of the small bowel. Large and/or multiple duodenal and jejunal diverticula are often complicated by SIBO. Sequelae of previous abdominal surgery (afferent loop syndrome after Billroth-Ⅱ gastric resection, Roux-en-Y stasis syndrome, bariatric bypass surgery) may also lead to SIBO (with metabolic and nutritional disarrangement)[7,30-32]. Small intestinal pseudo-obstruction and some neurological diseases (e.g. myotonic dystrophy, Parkinson disease, Chagasic enteropathy) can be complicated by SIBO that is responsible for malabsorption and weight loss[33-36]. Spinucci *et al*[37] described an interesting case of endogenous ethanol production in a patient with chronic intestinal pseudo-obstruction and SIBO.

Tursi *et al*[38] investigated bacterial overgrowth in the small bowel in patients with acute diverticulitis of the colon. Small intestinal overgrowth was found in 53/90 (59%) subjects. The authors assumed that the primary mechanism is a slow large bowel transit with stasis of faeces in the colon. This results in dysmicrobia in the large bowel with metabolic changes and induction of inflammation. Subsequent reverse peristalsis facilitates colonisation of the small intestine by bacteria coming from the large bowel. SIBO deteriorates symptoms of acute colonic diverticulitis, protracts the course of the disease and thus could be an independent risk factor for future relapses of acute diverticulitis of the large bowel. Rifaximin was effective in the treatment of both acute colonic diverticulitis and SIBO in these patients[38].

Irritable bowel syndrome

The aetio-pathogenesis of irritable bowel syndrome has not yet been satisfactorily clarified. Symptoms of SIBO and irritable bowel syndrome overlap to a large degree. As mentioned earlier, SIBO is frequently found in persons fulfilling criteria of irritable bowel syndrome (30%-85%)[9-11,16,18,19]. According to authors of the bacterial hypothesis, SIBO is the primary event and irritable bowel is secondary to SIBO. In some patients, the onset of irritable bowel is preceded by infective gastroenteritis (so-called post-dysenteric bowel disturbance)[39]. Analysis of the microbial genome found different faecal microbiota in healthy people and patients with irritable bowel (e.g. phylotypes *Coprococcus*, *Collinsella*, *Coprobacillus*)[40-42]. Believers in an opposite hypothesis stated that irritable bowel is a primary factor (with motor disturbance, visceral afferent hypersensitivity, psycho-social dysfunction) in which motility disorders enable "secondary" bacterial overgrowth[40,43]. A third group of authors recommend strict distinction between irritable bowel syndrome (the hydrogen breath test with lactulose must be negative) and SIBO (in such a case, it is not irritable bowel despite the diagnostic criteria having been met) in patients with identical symptoms[44]. The last authors stated an opinion that SIBO does not play any significant role in the pathogenesis of irritable bowel[45].

Pimentel *et al*[12] found abnormal lactulose breath test results in 93/111 (84%) patients with irritable bowel syndrome. Successful treatment of SIBO using neomycin (in 35% of patients) was associated with relief of subjective symptoms. There was another interesting finding in this study: a subgroup of persons with a methanogenic phenotype was associated with constipation in 100% (constipation-predominant irritable bowel syndrome)[12]. Another study found that methanogenic status was never associated in irritable bowel syndrome with diarrhoea and Crohn's disease or ulcerative colitis with diarrhoea[13]. The association of methanogenic phenotype and constipation was also revealed by other authors[8].

Coeliac disease

A wide range of 9% to 55% of patients have been diagnosed with SIBO as a complication of coeliac disease[20,46-48]. The prevalence of SIBO is high, especially in patients who do not respond to a gluten-free diet and/or have lactose intolerance[20,46,47].

Crohn's disease

SIBO is frequently found in Crohn's disease (in about 25%). Loss of the ileo-caecal valve (due to previous ileocaecal resection) and/or large entero-enteric and enterocolic fistulae are important predisposing factors[49-55]. Castiglione *et al*[56] found bacterial overgrowth more frequently in those who underwent surgery (30%) compared to non-operated patients (18%). Furthermore, SIBO may mimic an acute flare of Crohn's disease (including increased bowel movements and lower body weight)[57]. Smokers may exhibit increased H_2 production which could lead to false positive test results. However, in the study by Klaus *et al*[57] there was no difference in the proportion of smokers and their respective daily consumption of cigarettes between patients with Crohn's disease with and without SIBO.

Short bowel syndrome

The problem of short bowel syndrome is not limited only to the reduced absorptive surface area. The loss of the ileocaecal valve and the loss of the ileal break from resection of the distal small bowel would accelerate the transit of chyme throughout the entire gastrointestinal tract. Undigested food becomes a substrate for bacterial fermentation. Large intestinal bacterial flora colonise proximally into the small intestine to result in SIBO. Because digestion and absorption cannot be completed without adequate time, these patients face chronic postprandial diarrhoea.

These problems may be exacerbated by SIBO that further accelerates transit and worsens digestion, absorption and malnutrition[58].

SIBO is an independent negative factor deteriorating adaptation of the small intestine in children after excessive bowel resections. SIBO lengthens the dependence of these patients on total parenteral nutrition and deteriorates malabsorption and hepatopathy associated with short bowel syndrome[59,60]. SIBO may lead to intestinal failure in these patients[61].

Non-alcoholic steatohepatitis

Wigg *et al*[17] found a higher prevalence of SIBO (11/22, 50%) in non-alcoholic steatohepatitis (NASH) compared to healthy control subjects (5/23, 22%). Higher values for the xylose-lactulose test in patients with NASH correlated with higher serum levels of tumor necrosis factor-α (TNF-α). However, they were not associated with increased intestinal permeability or increased serum endotoxin[17]. In another study of NASH[62], SIBO was diagnosed in half of the patients (6/12) but only in one subject (1/11, 9%) in the healthy control group. Treatment with ciprofloxacin suppressed bacterial overgrowth, increased serum insulin and decreased endogenous ethanol production but did not influence serum acetylated ghrelin (half values compared to controls). Changes in fasting insulin and ethanol following ciprofloxacin suggest that these parameters may be influenced by small intestinal bacterial activity[62]. In an experimental model of NASH in rats, there was a slower transit time and higher quantity of coliform bacteria (*Escherichia coli*). Treatment with gentamicin (cidomycin) accelerated the transit time, decreased TNF-α levels and alleviated severity of liver involvement in experimental animals. Thus SIBO might play an important role in the pathogenesis of NASH[63].

Liver cirrhosis

Portal hypertension in liver cirrhosis substantially changes the intraluminal milieu of the gut. Liver cirrhosis is an independent risk factor for SIBO. Small intestinal motility disorder, especially slow transit in advanced liver disease (Child-Pugh C) may partake in SIBO[64,65]. SIBO was diagnosed in 50%-60% of patients with liver cirrhosis[66,67]. SIBO is a risk factor for the development of spontaneous bacterial peritonitis[22,68], however, its role in the pathogenesis has not yet been fully clarified[22]. Prevalence of SIBO was higher in those patients with liver cirrhosis who had spontaneous bacterial peritonitis (14/20, 70%) compared to those without it (4/20, 20%)[64]. However, this finding was not confirmed in other studies[66]. SIBO might correlate with systemic endotoxaemia[69]. It is necessary to remind ourselves that glucose hydrogen breath test in liver cirrhosis correlates only to a small degree with microbiological analysis of jejunal aspirates (sensitivity 27%-52%, specificity 36%-80%)[70].

Scleroderma

Scleroderma (systemic sclerosis) is a chronic connective tissue disease that affects the gastrointestinal tract in more than 80% of patients[71]. Severe small bowel involvement by scleroderma can present as chronic intestinal pseudo-obstruction and SIBO. The reported prevalence of SIBO in scleroderma was 43% to 56%[72,73]. In our series, SIBO was proved in 4/15 (27%) patients with systemic sclerosis by means of glucose hydrogen and methane breath tests. Half the cases of SIBO had neither diarrhoea nor other signs of malassimilation at the time of examination. There was a tendency towards a higher dose of systemic glucocorticosteroids in persons with positive hydrogen and methane breath tests[74].

Autonomic neuropathy in diabetes mellitus

Gastrointestinal symptoms are present in 50%-70% of patients with diabetes mellitus. Delayed gastric emptying (or even diabetic gastroparesis) and intestinal motility disorders are the most important findings (with an unfavourable impact on glycaemic control). Impaired intestinal motility is often followed by SIBO[75-77]. In diabetes mellitus, first and foremost all results must be interpreted according to the diagnostic method that was used. Cuoco *et al*[78] performed the lactulose hydrogen breath test and found that 21/74 (28%) of subjects were affected by SIBO and delayed oro-caecal transit time. After treatment with rifaximin, three patients still showed SIBO, five persistent delayed transit time without SIBO and 13 persons (62%) experienced a significant improvement in their oro-caecal time (without SIBO)[78]. Reddymasu *et al*[79] used hydrogen and methane breath tests after glucose challenge. Thirty out of fifty (60%) patients had a positive breath test result for SIBO on the basis of hydrogen (63%), methane (27%) or both criteria (10%). SIBO was more likely in diabetic patients with gastroparetic symptoms of longer duration[79].

In about one third of patients with diabetes, SIBO was associated with cardiovascular autonomic neuropathy[77]. SIBO in diabetes may rarely manifest itself as protein-losing enteropathy[80].

Radiation enteropathy

SIBO and lactose intolerance may occur during and/or after pelvic (or abdominal) radiotherapy[81-83].

Fibromyalgia

Pimentel *et al*[14] found that 42/42 (100%) patients with fibromyalgia had an abnormal lactulose hydrogen breath test. This was a significantly higher rate compared to patients with irritable bowel syndrome (93/111, 84%) and clinically healthy persons used as a control (3/15, 20%). Patients with fibromyalgia also had a higher hydrogenic profile that correlated with somatic pain[14].

Other disorders and diseases associated with SIBO

Various diseases and disorders have been described to be associated with or complicated by SIBO, such as lymphoproliferative diseases (lymphoma, chronic lymphocytic leukaemia), benign lymphoid hyperplasia of the ileum, metabolic bone disease, acromegaly, hypothyreosis, alcoholism and rosacea[7,84-87]. The prevalence of SIBO rises with age (about 50% in persons > 75 years old)[88].

MICROBIOLOGY, PATHOGENESIS, PATHOPHYSIOLOGY AND PATHOLOGY

The total bacterial count in the proximal jejunum is < 10^4 bacteria per mL of jejunal content in healthy people. In the ileum, enteric bacterial populations increase in amount (including coliforms) up to 10^9 CFU/mL in the terminal ileum. There are several beneficial effects of normal small intestinal bacteria to the host. They can be extrapolated from experimental studies in germ-free animals. The small intestinal villi of these animals are thin and unusually regular, with relatively shortened crypts. The enterocytes are cuboidal rather than columnar. In addition, the number and size of Peyer's patches, the degree of leukocyte infiltration in the lamina propria, and the rate of mucosal regeneration are reduced. The introduction of micro-organisms rapidly restores the normal morphologic appearance and physiologic function of the small bowel mucosa[7].

Normal autochthonous bacterial flora of the gastrointestinal tract is an important factor for preservation of its integrity and normal functioning in humans. They participate in the protection of macro-organisms against pathogenic micro-organisms, stimulate the human immune system and influence the metabolic and trophic function of the intestinal mucosa. Enteric bacteria produce some nutrients (e.g. short-chain fatty acids) and vitamins such as folates and vitamin K. Last but not least, they impact the sensor and motor function of the gut. On the other hand, intestinal bacteria are influenced by many factors, first of all by the amount and composition of food, but also by environmental (and geographic) effects, drugs, alcohol and probably by several other factors (lifestyle, psychosomatic stress, *etc.*)[5,89]. The prevalence of bacteria in different parts of the GI tract appears to be dependent on several factors, such as pH, peristalsis, redox potential, bacterial adhesion, bacterial co-operation and antagonism, mucin secretion, diet and nutrient availability[90].

There are several host defence mechanisms to prevent excessive colonisation of the small bowel by bacteria: antegrade peristalsis prevents attachment of ingested micro-organisms; gastric acid and bile destroy many micro-organisms before they leave the stomach; digestion by proteolytic enzymes helps destroy bacteria in the small intestine; the intestinal mucus layer traps bacteria; an intact ileo-caecal valve inhibits retrograde translocation of bacteria from the colon to the small bowel; the immune system plays a role as evidenced by the high prevalence of bacterial overgrowth in patients who have immunodeficiency; the largest fraction of immunoglobulins secreted in the human body is the secretory IgA originating in the gastrointestinal tract, which aids in preventing bacterial proliferation[7,91]. SIBO may develop if some of the natural defensive mechanisms of a macro-organism (listed above) are disrupted.

In most patients, SIBO is not caused by a single bacterial strain. In general, there is an extension of colonic bacteria into the small bowel. Less frequently, the "normal" amount of small intestinal bacteria increases. Bouhnik *et al*[92] investigated samples of jejunal juice in 63 patients with diarrhoea and/or malabsorption. The diagnostic criteria of SIBO were fulfilled in 55 persons (87%). The authors identified 141 micro-aerophilic strains (*Streptococcus* 60%, *Escherichia coli* 36%, *Staphylococcus* 13%, *Klebsiella* 11% and others) and 117 anaerobes (*Bacteroides* 39%, *Lactobacillus* 25%, *Clostridium* 20% and others)[92].

SIBO may be accompanied by both maldigestion and malabsorption. Bacteria in SIBO might significantly interfere with enzymatic, absorptive and metabolic actions of a macro-organism. Due to injury of the brush-border of enterocytes, the activity of disaccharideses may be decreased. If bacteria simultaneously metabolise fructose, lactose and sorbitol, malabsorption of saccharides may occur. Injured small intestinal mucosa can have undesirable consequences in increased intestinal permeability and/or protein-losing enteropathy. Deficiency of vitamin B_{12} results from the consumption of this vitamin by anaerobic micro-organisms. Bacteria may also utilise intraluminal protein in the small bowel, this may lead to protein deficiency for the macro-organism and excessive production of ammonia by bacteria. Deconjugation of bile acids by bacteria results in malabsorption of fat and liposoluble vitamins. Extensively formed lithocholic acid is poorly absorbable and acts enterotoxically[5,7,93-95].

Bacteria produce various toxic agents that may have surprising systemic effects. These agents are ammonia, D-lactate, endogenous bacterial peptidoglycans and others. SIBO is regularly associated with increased serum endotoxin and bacterial compounds stimulating production of (pro)inflammatory cytokines[7,96]. SIBO might be associated with endogenous production of ethanol (probably synthesised by *Candida albicans* and *Saccharomyces cerevisiae*). Serum ethanol disappears after successful treatment of SIBO[37].

Small intestinal bacterial overgrowth has a negative impact not only on the function but also on the morphological structure of the small bowel. Microscopic inflammatory changes (especially in the lamina propria) and villous atrophy are found regularly. In such a case, the villous atrophy in SIBO must be distinguished from that of coeliac disease. Macroscopic changes may also be visible in some patients. Hoog *et al*[97] found small intestinal mucosal breaks (erosions or ulcers) in 16/18 patients with chronic myopathic or neuropathic motility disorders of the small bowel by means of wireless capsule endoscopy.

In some patients with short bowel syndrome, bacterial overgrowth can, to some extent, paradoxically exert a favourable effect on the macro-organism. Bacteria may partly metabolise saccharides and thus form some further energy substrates more easily utilisable by a diseased human.

CLINICAL FEATURES

Clinical symptoms are expressed more or less according to the severity of involvement and they are modified by a primary underlying disease. SIBO may be clinically asymptomatic or can resemble irritable bowel syndrome with

non-specific symptoms (bloating, flatulence, abdominal discomfort, diarrhoea, abdominal pain). In more severe cases, there are signs of malabsorption (weight loss, steatorrhoea, malnutrition), liver lesion, skin manifestation (rosacea), arthralgias and deficiency syndromes (anaemia, tetany in hypocalcaemia induced by vitamin D deficiency, metabolic bone disease, polyneuropathy due to vitamin B_{12} deficiency, impaired barrier function of the gut, *etc.*). Anaemia is usually macrocytic (megaloblastic) due to vitamin B_{12} deficiency. It could also be microcytic iron deficiency (due to occult gastrointestinal blood loss) or normocytic (as anaemia of chronic disease)[3,5-7]. Serum folate and vitamin K levels are usually normal. Serum vitamin K can even be increased owing to its bacterial overproduction. Moreover, there are some concerns as to whether endogenous intestinal production of vitamin K by bacteria might interfere with warfarin treatment in SIBO[98-100]. In the case of oedema of lower extremities, the aetiology is usually more complex (anaemia, malnutrition, hypoproteinaemia, vitamin B_{12} deficiency).

D-lactic acidosis is a severe complication of patients with short bowel syndrome (with intact large bowel). It is caused by an excessive overgrowth of lactobacilli. Non-absorbed saccharides pass from the small intestine to the large bowel and they are fermented down to the D-isomer of lactic acid. There is no human pathway to metabolise D-lactic acid. D-lactic acid is absorbed from the large bowel; its serum concentration is regularly increased in these patients. Nevertheless, most patients remain asymptomatic. In clinically expressed cases, leading symptoms comprise characteristic neurologic abnormalities including confusion, cerebellar ataxia, slurred speech, and loss of memory. Patients exhibit some degree of altered mental status. They may complain of or appear to be drunk in the absence of ethanol intake. In the treatment, it is necessary to compensate metabolic acidosis and administer peroral antibiotics (metronidazole, rifaximin). To prevent this serious complication, it is important to reduce peroral intake of simple sugars, polysaccharides given in smaller amounts together with a higher intake of fat[101].

DIAGNOSTICS

It is mandatory to consider SIBO in all cases of complex non-specific dyspeptic complaints (bloating, abdominal discomfort, diarrhoea, abdominal pain), in motility disorders, anatomical abnormalities of the small bowel and in all malassimilation syndromes (malabsorption, maldigestion)[3,5-7].

Physical investigation usually provides non-specific findings and could be modified by a primary underlying disease. The abdomen may be distended and a small intestinal succussion splash might be identified. Physical investigation can further reveal latent tetany, polyneuropathy and skin manifestation (rosacea).

Laboratory tests usually find anaemia, low serum vitamin B_{12} levels and laboratory signs of malnutrition (lymphopenia, low serum prealbumin and transferrin).

The gold standard for diagnosing SIBO is still microbial investigation of jejunal aspirates. Such a sample can be obtained by a special sonde or by means of enteroscopy. Nowadays, there are commercially available special aspiration catheters (with a spiral pattern of holes at the distal tip) for contaminate-free collection of fluids. Microbial investigation places high demands on the quality of laboratory work (determination of quantitative proportion of anaerobes) and has several difficulties (low reproducibility and identifying cultivation-resistant bacteria). Distribution of bacterial overgrowth might be irregular and that is why a single investigation might not detect it. Bacterial overgrowth may be restricted to a particular, difficult-to-access area for aspiration (e.g. a blind loop)[7].

Hydrogen and methane breath tests are currently the most important diagnostic methods. The principles and methods of hydrogen and methane breath tests were described in detail elsewhere[102-105]. In humans, hydrogen and methane are exclusively produced by intestinal bacteria, namely in the large bowel in healthy people and also in the small intestine in the case of SIBO. About 80% of hydrogen and methane is expelled by flatus, 20% is exhaled by lungs and can be measured in breath[106]. Hydrogen and methane breath tests to diagnose SIBO are performed after peroral glucose or lactulose challenge. Most authors (including our Department) use gas chromatography for breath analysis. A parallel measurement of CO_2 and correction of hydrogen values to CO_2 concentration make the measurement more precise[7,74,103,104]. Low humidity (< 25%) must be maintained in the laboratory atmosphere to obtain consistent measurements. There is an early increase in breath hydrogen and/or methane (single early peak) after glucose administration due to bacterial glucose fermentation in the small bowel. There are two peaks in the lactulose breath test, the first one owing to bacterial activity in the small intestine, the second one after lactulose reaches the colon. Unfortunately, hydrogen and methane breath tests have not yet been standardised, particular protocols differ in dose (and concentration) of the test substrate, duration of tests, time intervals of breath sampling and basic and peak cut-off values. According to most authors, basal cut-off values of hydrogen and/or methane in positive breath tests are $\geqslant$ 20 parts per million (ppm), 10-20 ppm is a grey zone. After a glucose challenge, an increase $\geqslant$ 12 ppm at 120 min is a positive result for bacterial overgrowth. A lactulose breath test is assessed as positive if there is a biphasic course or an early plateau pattern with a hydrogen increase of $\geqslant$ 12 ppm is found (possibly with an increase in methane at the second peak)[104,107-110].

The hydrogen breath test is considered to be more accurate for the diagnosis of SIBO compared to the methane breath test according to most authors[111-114]. There is a sensitivity of 62.5% and specificity of 82% (diagnostic accuracy of 72%) after glucose and 52% and 86% (diagnostic accuracy of 55%) after lactulose administration[109]. Hydrogen alone, methane alone or both gases simultaneously might be found in breath samples. That is why it is important to always determine both gases in the breath samples. There are several advantages of hydrogen and methane breath tests. They are non-invasive, non-toxic,

relatively easily available and performed at a low cost.

However, hydrogen and methane breath tests have some drawbacks with possible false results and difficulties in their interpretation. Very rapid absorption of glucose in the proximal jejunum can be responsible for a false negative result. In the case of bacterial overgrowth in the terminal ileum, it might be difficult to distinguish a pathological ileal peak from a "normal peak" after the caecum is reached. In short bowel syndrome (with intact large bowel), the test substrate may reach the colon very quickly and cause a false positive result. In the case of a low density of anaerobes, breath can be false negative[109,113,115-117]. If there is only one peak of hydrogen recorded in the lactulose breath test and the second peak is absent for hydrogen and methane, this could be assessed as a combination of SIBO and fermentative colopathy[108]. Results of hydrogen and methane breath tests are usually difficult to interpret in the case of advanced lung disease. In the case of a high concentration of hydrogen and low concentration of methane, analytical precision for methane determination is less accurate[104].

All hydrogen and methane are produced by so called "hydrogenic and methanogenic" bacteria in humans[103,104,106,118]. However, most authors usually do not specify which particular bacteria constitute these producers. Nitrogen, oxygen, carbon dioxide, hydrogen and methane account for more that 99% of expelled intestinal gas. Hydrogen is produced by bacterial fermentation of saccharides in the intestinal lumen. Concurrently, hydrogen is consumed by other intestinal bacteria to synthesise methane, acetate and hydrogen sulphide. Methane is synthesised solely by bacteria in the intestine (four mmols of hydrogen and one mmol of carbon dioxide create one mmol of methane and water). This reaction reduces the volume of gas that would otherwise be present in the colon[119-124]. The question of intestinal methane producers has not been definitely solved yet. *Methanobrevibacter smithii*, *Methanosphaera stadtmanae* and other *Methanobacteriales* are able to synthesise methane and some authors consider *Methanobrevibacter* to be the major producer of methane in the gut of humans[125,126]. It was assumed (based on 16S ribosomal DNA studies) that *Methanobrevibacter smithii* could make up about one in ten of all the prokaryotes in the human gut[127]. However, there is no final proof available that *Archea* (*Methanobrevibacter* and others) would be the prevailing microorganisms in the methanogenic phenotype of the human gut. We hypothesised that common coliform bacteria could also synthesise methane[128], however, this assumption was not proved by our further studies[129,130]. McKay *et al*[131] found that several anaerobes (*Bacteroides*, *Clostridium* and others) produced hydrogen but rarely methane. Hydrogen is also produced by *Enterobacteriaceae*[128,132].

In adult Caucasians, only 30%-50% of persons produce methane while hydrogen is produced by 90%-98% of people[104]. Most subjects with lactose intolerance who do not produce hydrogen would form methane after lactulose administration instead of hydrogen[133]. Bile in the intestinal lumen is an important suppressor of methanogenesis in humans[134]. According to some authors, a methanogenic phenotype is associated with constipation[8,12]. Methane production has been related to more severe colonic impaction in children with encopresis[135]. Higher production of methane has been detected in colorectal adenomas and cancer[136]. However, there is a general agreement that constipation itself is not a risk factor for the development of colorectal cancer.

Hydrogen and methane breath tests can be combined with a simultaneous D-xylose breath test[107,110]. This combination increases the sensitivity of non-invasive diagnostics of SIBO[107,114]. The cholyl-1-^{13}C-glycine hydrolase breath test is another possible alternative for the diagnosis of SIBO. The principle of this test is based on the fact that bacterial overgrowth will cause more rapid deconjugation of cholyl-1-^{13}C-glycine[137]. The reported sensitivity for this test was 70%[138]. The lack of sensitivity was attributed to bacterial overgrowth with species lacking cholylglycine hydrolase[137]. On the other hand, patients with bile acids malabsorption in the ileum might have a false positive result in this breath test after rapid deconjugation of cholylglycine in the proximal colon[139]. Berthold *et al*[140] recently proposed a lactose-^{13}C-ureide breath test for the diagnosis of small bowel bacterial overgrowth. This test should have 100% specificity (and thus predict positive culture in SIBO) but lower sensitivity (66%)[140].

There are several other tests to diagnose SIBO, for instance evaluation of short-chain fatty acids in jejunal aspiration[141], serum non-conjugated bile acids, urinary output of p-aminobenzoic acid (after peroral administration of colil-PABA) or urinary indican[6]. However, none of these tests has yet acquitted itself well in routine clinical practice.

If it is impossible to perform any diagnostic test for SIBO (if no test is available for a particular department) on a patient with legitimate suspicion of SIBO, it is possible to consider the exceptional use of an empiric therapeutic test with rifaximin (for 7-10 d). Quick disappearance of symptoms supports a possible diagnosis of SIBO, however, this is not definite outright proof of SIBO. On the other hand, demonstration of SIBO is not 100% proof of causal association between bacterial overgrowth and clinical symptoms (or laboratory abnormal results).

In some patients with SIBO, secondary inflammatory changes might be found not only in the small bowel but also in the colon as a response to absorbed bacterial antigens. This inflammatory involvement can cause separate symptoms[7]. Successful treatment with 5-aminosalicylates and glucocorticosteroids supports this theory[142].

DIFFERENTIAL DIAGNOSIS

Diagnosis and differential diagnosis of SIBO is difficult if this possibility is not considered. It is necessary to distinguish functional disorders (of no organic cause) and chronic gastrointestinal infections (e.g. giardiasis).

The relationship between SIBO and irritable bowel syndrome was discussed above. Esposito *et al*[44] proposed use of the lactulose breath test to distinguish SIBO and

irritable bowel syndrome. Parodi *et al*[143] recommend differentiating patients fulfilling the diagnostic criteria of irritable bowel syndrome (IBS-like symptoms) from functional bloating. If SIBO is proved, the first group will profit from antibiotic treatment while the second group will not[143].

It is always necessary to consider SIBO in the case of unexplained deterioration of the clinical status of patients with Crohn's disease, chronic pancreatitis or scleroderma. SIBO must be taken into account in coeliac disease non-responding to adequate gluten-free diet. SIBO is a crucial point in the differential diagnosis of short bowel syndrome and all other malassimilation syndromes (both with maldigestion and malabsorption).

On the other hand, some other intestinal disorders might mimic SIBO and must be considered in the differential diagnosis. Flatulence, abdominal bloating and distension, and malabsorption of mono- or disaccharides (like fructose or lactose) must be taken into account. Pneumatosis cystoides intestinalis is usually asymptomatic but it may be associated with abdominal pain, bloating and/or diarrhoea[106].

PRINCIPLES OF TREATMENT

Therapy for SIBO must be complex (addressing all causes, symptoms and complications) and fully individualised. It should include treatment of the underlying disease, nutritional support and cyclical gastro-intestinal selective antibiotics.

The most important thing is always treatment of the basic underlying disease if possible. Nutritional support is mandatory in SIBO associated with malnutrition, weight loss and nutrient deficiency. We usually use individualised diet, enteral nutrition by fine-bore naso-jejunal tube or nutritional support by sipping of polymeric formulas. In several patients, it is necessary to exclude lactose from the diet, to reduce other simple sugars, to increase coverage of energy needs by fat and to administer MCT oils (medium-chain triacylglyceroles).

Antibiotic treatment should selectively target those bacterial strains that cause SIBO. The choice of antibiotics should be based on sensitivity testing to particular antibiotics. However, this requirement is difficult to achieve in clinical practice as various bacteria are usually found simultaneously, each with different sensitivity to antibiotics. There is no common agreement concerning choice, dosing and duration of antibiotic therapy. In general, long-term treatment with broad-spectrum antibiotics is not the optimal solution as such a therapy is associated with several problems (intolerance by the patient, dysmicrobia, diarrhoea, *Clostridium difficile* expansion, possible increased resistance to antibiotics, financial cost, *etc.*).

Tetracycline was considered the treatment of choice for a long time. Di Stefano *et al*[144] administered tetracycline to patients with SIBO for 7 d (1000 mg/d) and achieved normalisation of the hydrogen breath test together with relief of symptoms in only 3/11 (27%) subjects[144]. Various antibiotics were tried in other small clinical studies. Attar *et al*[145] administered a placebo, norfloxacin (800 mg/d), amoxicillin clavulanate (1500 mg/d) and *Saccharomyces boulardii* (1500 mg/d) successively in 7-d intervals in 10 patients. Norfloxacin and amoxicillin clavulanate significantly decreased the frequency of diarrhoea compared to the placebo (in 9/10 and 6/10 patients, respectively), but the hydrogen breath test was normalised in only 3 and 5 subjects[145]. In Crohn's disease, Castiglione *et al*[56] achieved normalisation of the hydrogen breath test in 13/15 (87%) persons treated with metronidazole (750 mg/d) and in 14/14 (100%) treated with ciprofloxacin (1000 mg/d)[56]. Di Stefano *et al*[146] divided 21 patients with a blind loop syndrome into three different treatment groups: (1) rifaximin followed by metronidazole, or (2) two courses of metronidazole, or (3) two courses of rifaximin. Both antibiotics were effective; metronidazole markedly reduced both hydrogen breath tests and patients' symptoms[146]. However, rifaximin was more effective than metronidazole in another study (63% *vs* 44%)[147]. A drawback in all of these studies was not only the small set of patients but also the absence of long-term follow-up. Pimentel *et al*[12] administered neomycin or a placebo to 111 patients with irritable bowel syndrome (84% abnormal lactulose breath test). Neomycin improved both symptoms and the breath test in 35% of persons compared with 11% in the placebo group[12]. Some other peroral antibiotics, such as cephalexin, trimethoprim-sulfamethoxazole, levofloxacin and gentamicin were used for the therapy of SIBO[7].

The greatest experience for treatment of SIBO was acquired with rifaximin[43,148-154]. Rifaximin is a semi-synthetic rifamycin-based non-systemic antibiotic, with a low gastrointestinal absorption and good bactericidal activity. The antibacterial action covers Gram-positive and Gram-negative organisms, both aerobes and anaerobes[155]. According to different studies, rifaximin improves symptoms in 33%-92% and eradicates small intestinal bacterial overgrowth in up to 80% of patients[151,152]. Most authors recommend administering rifaximin for 7-10 d as one treatment course or as a cyclic therapy. Higher doses (1200 or 1600 mg/d) are more effective than standard doses (600 or 800 mg/d)[148,154]. Rifaximin is probably the only antibiotic that is capable of achieving a long-term favourable clinical effect in patients with irritable bowel and SIBO[43].

Prebiotics and probiotics exert various beneficial effects in the macro-organism, they strengthen the barrier function of the gut, inhibit several pathogens, modify the inflammatory response of the bowel, and they also reduce visceral hypersensitivity[156-159]. They seem to be more effective in influencing the clinical symptoms of irritable bowel syndrome compared to a placebo[159,160]. Studies dealing with the therapeutic use of prebiotics or probiotics in SIBO (except irritable bowel syndrome) are limited[161-163], and it is not therefore possible to recommend them for general clinical use[157,158]. *Lactobacilli*-based probiotics are contraindicated in patients with a risk of D-lactic acidosis. Very little data are available from experimental studies. Short-term administration of the hydrogenic probiotic *Escherichia coli 1917 Nissle* (3.5×10^{10} bacteria per

day for 14 d) did not influence methanogenic phenotype of experimental non steroidal anti-inflammatory drug-enteropathy in pigs[129].

Prokinetics seem to be a logical therapeutic step in SIBO due to motility disorders. Several studies tried metoclopramide, cisapride (which was later withdrawn from the market), domperidone, erythromycin, itopride, tegaserod and octreotide. However, there are only limited data suggesting that this treatment would be effective over the long term[7,71]. Cyclic lavages of the small bowel (e.g. by polyethylene glycol) can be considered as supportive therapy in cases of relapsing SIBO[7].

Surgical treatment must always be considered where possible to correct gastrointestinal pathology (entero-colic fistulae, blind loops, bowel obstruction, multiple small intestinal diverticula, *etc.*). Specialised non-transplant surgery can provide interventions in short bowel syndrome improving intestinal motility (STEP - serial transverse enteroplasty), slowing intestinal transit (valves, reversed segments, colon interposition) or increasing mucosal surface area of the gut (creation of "neo-mucosa", sequential intestinal lengthening)[164].

PROGNOSIS

The prognosis of SIBO is determined mostly by the underlying disease leading to bacterial overgrowth. Ultimately SIBO might result in intestinal failure[61]. In scleroderma with gastrointestinal involvement (SIBO, intestinal pseudo-obstruction, malnutrition), the overall 5-year mortality is more than 50%[71].

The relapse rate of SIBO after successful treatment is high. Lauritano *et al*[165] found recurrence of SIBO in 44% (35/80) of patients nine months after successful treatment with rifaximin. Apart from the basic underlying disease, further risk factors for recurrence of SIBO have been identified including older age (OR 1.1), appendectomy in the patient's history (OR 5.9) and long-term treatment with proton pump inhibitors (OR 3.5)[165].

CONCLUSION

SIBO is defined as an increase in the number and/or alteration in the type of bacteria in the upper gastrointestinal tract. The aetiology of SIBO is usually complex, associated with disorders of protective antibacterial mechanisms (e.g. achlorhydria, pancreatic exocrine insufficiency, immunodeficiency syndromes), anatomical abnormalities (e.g. small intestinal obstruction, diverticula, fistulae, surgical blind loop, previous ileo-caecal resections) and/or motility disorders.

SIBO is often misdiagnosed and generally underdiagnosed. Clinical symptoms might be non-specific (dyspepsia, bloating, abdominal discomfort). Nevertheless, SIBO can cause severe malabsorption, serious malnutrition and deficiency syndromes. Non-invasive hydrogen and methane breath tests after glucose or lactulose challenge are most commonly used for the diagnosis of SIBO. Therapy of SIBO must be complex and should include treatment of the underlying disease, nutritional support and cyclical gastrointestinal selective antibiotics. Prognosis is usually serious, determined mostly by the underlying disease that led to SIBO.

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