Abstract. – BACKGROUND: Gut microbiota plays several beneficial effects on the human host. Its qualitative and/or quantitative unbalance may facilitate the occurrence of small intestinal bacterial overgrowth (SIBO).

AIM: To review the available data in order to propose a practical approach to SIBO diagnosis in the clinical setting.

MATERIALS AND METHODS: Full papers from 1990 to present available on the PubMed database concerning the topic of SIBO diagnosis were critically reviewed.

RESULTS: SIBO is common in the presence of one or more predisposing conditions. The clinical picture of SIBO patients is extremely variable, depending on underlying disorders, and both patients and microbiota characteristics. SIBO could be asymptomatic, or leading to specific gastrointestinal IBS-like symptoms. In worst cases it may configure a real malabsorption syndrome. Culture of intestinal aspirates remains at present the gold standard for SIBO diagnosis. However a lot of limitations including high costs and invasivity prevent from using this test in the clinical practice. Hydrogen lactulose and especially glucose breath tests are at present the most utilized to reach SIBO diagnosis in the clinical setting, due to their low costs, non invasivity, sufficient accuracy and reproducibility.

CONCLUSIONS: SIBO should be suspected in the presence of IBS-like symptoms and/or malabsorption syndrome occurring in the presence of disorders predisposing to SIBO development. The most common diagnostic tool is represented at present by hydrogen breath tests.

Key words: Small intestinal bacterial overgrowth, Gut microbiota, Diagnosis, Hydrogen breath test, Glucose, Lactulose.

Introduction

Adult humans live in symbiosis with several bacteria species exceeding the number of host somatic cells by at least one order of magnitude. Human intestinal microbiota create a complex polymicrobial ecology composed of viruses, parasites, yeast and, above all, bacteria. Specifically the duodenum and proximal jejunum normally contain small numbers of bacteria (lactobacilli and enterococci, gram-positive aerobes or facultative anaerobes, coliforms may be transiently present). The bacterial concentration varies along the gastrointestinal tract increasing from $10^3$ colony-forming units (CFU)/ml in the upper intestinal tract to $10^{14}$ CFU/ml in the colon.

The intestinal microbiota was found to play different beneficial effects on the host: protection against pathogenic microorganisms, stimulation of the human immune system, a trophic function on the intestinal mucosa thus participating to the integrity of the gut barrier, production of various nutrients and vitamins. In addition, a favourable effect of gut microbiota on the intestinal motor function has been suggested by recent studies.

Any unbalance (qualitative and/or quantitative) of this important complex microbiological could have different consequences both locally and systemically, including the occurrence of small intestinal bacterial overgrowth.

There are several mechanisms that may limit overgrowth of intestinal bacterial populations. Among these: anatomic and functional factors (gastric acidity, the continence of ileo-cecal, the bile and pancreatic secretions antibacterial bile secretion and pancreatic), mechanical factors (intestinal peristaltic activity) and factors that inhibit the adhesion of bacteria to the epithelium (production of secretory IgA, the integrity of the mucus layer, epithelial desquamation). It is clear that all the anatomical and/or functional mechanisms able to impair these delicate and complex protection system can determine an abnormal growth of bacteria in the intestinal segments proximal.

Small intestinal bacterial overgrowth (SIBO) is a condition characterized by abnormally high
bacterial population level in the small intestine, exceeding $10^6$ organisms/ml\(^6,7\).

The aim of the present review is to analyze the available literature data in order to propose a practical approach to SIBO diagnosis in the clinical setting.

**Predisposing conditions**

The prevalence of SIBO is unknown at present. In fact it is generally under-diagnosed, because its unspecific symptoms are often attributed to underlying disease predisposing to SIBO\(^6\). In fact SIBO is extremely common in the presence of one or more of the predisposing conditions. In addition its recurrence after successful antibiotic treatment is high if the underlying disease is not removed/removable\(^6\).

The prevalence of SIBO rises with age (about 50% in persons > 75 years old)\(^9\). In fact ancient age is associated to a progressive disruption of more than one of defense mechanisms: decrease of both gastric acid production and intestinal motility are common findings in older people. Diseases associated to achlorhydria such as gastric atrophy or chronic administration of proton pump inhibitors may cause bacterial overgrowth in the stomach and duodenum\(^10\).

SIBO complicates 30%-40% of patients with chronic pancreatitis\(^11\). Multiple factors can be involved, as the absence of the antibacterial effects of proteolytic enzymes due to the exocrine pancreatic insufficiency, the motility disorders and drug or alcohol consumption. An increased prevalence of SIBO (56%) has been found in patients with cystic fibrosis also\(^12\).

Syndromes associated to an immune system dysfunction (such as AIDS, IgA deficiency, common variable immunodeficiency) bring to an increased susceptibility to any infection, including SIBO\(^13,14\).

Functional dyspepsia and SIBO share the motility disorder as one of the main etiologic factors: studies showed a high prevalence of SIBO in patients with functional dyspepsia, in particular in patients in treatment with proton pump inhibitors\(^15\). SIBO has been also detected in up to 60% of patients with gastroparesis\(^16\).

Thyroid activity may influence gut motility through neurological and muscular mechanisms\(^17\). Several studies showed hypothyroidism to be associated with a slower oro-cecal transit time both in animal and human subjects\(^18,19\). SIBO is associated with all the anatomical disorders characterized by intestinal obstruction and/or stagnation, as adhesion, strictures, tumors.

Tursi et al\(^20\) found SIBO in 59% of patients with diverticulitis. This association could be based on a slow oro-cecal transit with the resulting stasis of feces in the colon probably due to slower large bowel transit with stasis of feces in the colon.

Celiac disease is variably complicated by SIBO (9%-55%)\(^21-23\). The prevalence increases in patients which do not respond to the gluten-free diet or with a concomitant lactose intolerance\(^24\).

SIBO was found in about 25% of patients affected by Crohn’s disease, especially in patients undergoing surgery\(^25\).

Besides a lower absorption capacity, the short bowel syndrome brings to an accelerate transit of chimes, and consequently to a failure of food digestion. In particular the loss of the oro-cecal valve allow the passage of bacterial flora from the colon to the small bowel.

SIBO in also associated with liver disease. The gut alteration and the slow transit\(^26\) due to portal hypertension in liver cirrhosis predispose to development of SIBO\(^27\), which is itself a risk factor for the onset of spontaneous bacterial peritonitis\(^28\), the pathogenesis being still not fully clarified.

**Clinical patterns**

Small intestinal bacterial overgrowth is generally considered a malabsorption syndrome, although the clinical manifestations largely vary in different subjects. Many factors such as the entity of contamination, the intestinal tract affected, the underlying predisposing conditions and the bacterial species involved may help to explain this strong variability\(^2\). In particular, disorders associated to failure of intestinal clearance (due to failure of small bowel motility or intestinal anatomical abnormalities) generally lead to a more symptomatic and severe SIBO. In fact, in the presence of failure of intestinal clearance, SIBO is often distal, colonizing ileum and jejunum, only occasionally arriving to duodenum and stomach. Prevalent bacteria are enterobacteriaceae (in severe forms strict anaerobic species of colonic type could be observed). In the presence of failure of the gastric acid barrier, SIBO is often proximal (stomach, duodenum, proximal jejunum) and prevalent bacteria are Gram positive bacteria coming from upper respiratory tract\(^29\).
SIBO may be asymptomatic or have symptoms such as fullness, abdominal pain, flatulence, diarrhea, dyspepsia, malabsorption of nutrients, weight loss or no weight gain and/or signs of malabsorption, similar to those observed in IBS patients. The presence of a high bacterial load in the small intestine causes a precocious and abnormal deconjugation of bile acids with increased resorption at jejunal and secondary malabsorption of lipids.

In severe cases there are signs of malabsorption (weight loss, steatorrhoea, malnutrition), liver lesion, a skin manifestation (rosacea), arthralgias and deficiency syndromes (anaemia, tetany in hypoglycaemia induced by vitamin D deficiency, metabolic bone disease, polyneuropathy due to vitamin B12 deficiency, etc.)

In the latter spectrum of pathophysiological events the most important aspect is the malabsorption carbohydrates; the presence of bacteria in fact determines a marked luminal fermentation of these molecules, with overproduction of water, short chain fatty acids and gases (including carbon dioxide, hydrogen and methane). In patients with SIBO the fermentation of substrates was achieved already at the level of the small intestine, resulting in the onset of intestinal symptoms quite comparable to that of patients with IBS.

SIBO diagnosis

The gold standard for diagnosis of SIBO is still aspiration and direct culture of the jejunal aspirate. The principal limitation of this test are: high costs, invasivity, scarce reproducibility, bacteria cultivation-resistance, possible contaminations by oropharyngeal flora. In addition, the irregular distribution of bacteria may lead to false negatives.

For these reasons hydrogen breath tests (HBT) are the most common diagnostic tool for SIBO, diagnosis since they are noninvasive, cheap, simple and safe. These tests are based on the measurement of hydrogen (and methane) in breath samples: these gases are produced by bacteria as a consequence of carbohydrate fermentation after oral ingestion of glucose and lactulose, pass through the blood circulation and reach the lung, where are expelled. So the diagnosis of SIBO is established on the increase of hydrogen value respect the baseline sample.

Unfortunately, breath tests have not yet been standardized, in term of substrate concentration, duration of tests, time intervals of breath sampling and cut-off values. The Consensus Rome Conference established that after the baseline breath sample there should be administrated 50 g of glucose and 10 g of lactulose: measurement then occurs every 15 minutes for 2 or 4 hours, respectively for the glucose and lactulose breath test.

Glucose is rapidly absorbed in the proximal small bowel and usually does not reach the colon, so it is a suitable substrate to detect proximal small bowel overgrowth. A rise in H₂, after the assumption of the substrate, means that glucose meets bacteria in the small bowel, before its absorption. Because of its early absorption, GBT may not able to diagnose SIBO of the distal small intestine (ileum). According to most authors, the diagnosis of SIBO is established when the hydrogen level measured in breath sample increases ≥12 parts per million at 120 min respect the baseline value for glucose breath test (GBT). Sensitivity and specificity are 62.5% and 77.8 %, respectively compared to the gold standard (jejunal culture).
A variety of criteria have been used for defining a positivity for the lactulose breath test: pick of hydrogen > 20 ppm above baseline in 90 or 180 min, methane increase > 5 or > 10 ppm above baseline, dual hydrogen peaks 10 ppm above baseline with a decrease of 5 ppm from before the second peak, and two consecutive hydrogen peaks of 10 ppm above baseline that is different from the colonic peak defined as being 20 ppm above baseline. At present, the most used criterion is the presence of two peaks, the first due to bacterial activity in the small intestine (SIBO) and the second when lactulose reaches the colon. However, it is difficult to differ between an early H² peak caused by SIBO and a fast transit; thus, the non-standardized criteria, and lower diagnostic accuracy (55% versus 71% of Glucose) makes lactulose breath test not indicated to diagnostic for SIBO.

Some authors suggested that methane measurement on breath samples may increases diagnostic accuracy of sugars breath test by the identification of the so called “methane-producers” subgroup of SIBO patients. However, available data led Rome Consensus Conference to not recommend at present to assess methane in glucose breath testing to improve its sensitivity.

An alternative breath test for the diagnosis of SIBO is represented by the cholyl1-13C-glycine hydrolase breath test. It is based on the deconjugation of cholyl1-13C-glycine fact that will be more rapid in bacterial overgrowth. The reported sensitivity for this test is 70%; the false negative can be attributed to the possible lack of cholyl-glycine hydrolase in colonization bacteria, while on the other hand, bile acids could bring to a rapid deconjugation of chomiglycine in the proximal colon and, consequently, to a false positive result. Lactose 13C-ureide breath test has been proposed as a diagnostic tool for SIBO diagnosis: its specificity is 100%, with a lower reported sensitivity (66%) when compared to the gold standard culture on intestinal aspirate. At present, these two tests utilizing 13C are not clearly superior in terms of accuracy with respect to hydrogen glucose breath test, in the face of higher costs and the necessity of a mass spectrometer for the measurements.

SIBO recurrence is a common event in the case of persistence of predisposing conditions, being often chronic and difficult or impossible to definitively removed. Recurrence was observed in about 40% of successfully treated SIBO subjects that had IBS as predisposing condition at 9 months-follow up. Interestingly, a good correlation was observed among SIBO recurrence, gastrointestinal symptoms relapse and GBT abnormal results, thus, suggesting that GBT is an useful diagnostic tool to monitor SIBO patients after antibiotic decontamination. Similar percentage of recurrence were recently observed in patients with Parkinson’s disease and SIBO positivity at 6 months since eradication.

### Conclusions

SIBO is often underdiagnosed in the clinical practice. It should be suspected in the presence of predisposing disorders, that are clinical conditions associated to an impairment of one or more of the physiologic mechanisms of the human host to prevent abnormal growth of gut flora.

According to literature data, Rome Consensus Conference suggests to use the hydrogen breath test (especially glucose breath test) to achieve SIBO diagnosis.

SIBO is often a recurrent disorder also after successful antibiotic decontamination, when the associated predisposing condition/s is/are not removable. For this reason it is important to clinically monitor the patients in the time, and, in the presence of symptoms relapse, the physician should consider SIBO recurrence, then administering to the patient hydrogen breath test to confirm SIBO diagnosis.

#### Conflict of interest

The Authors declare that they have no conflict of interests.

#### References


Diagnosis of small intestinal bacterial overgrowth in the clinical practice


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