EDITORIAL

Small intestinal bacterial overgrowth. A position paper of ASENEM-SEPD

Small intestinal bacterial overgrowth (SIBO) is a condition that was described decades ago and has recently aroused special interest among both medical professionals and the general population, likely because of increased availability of diagnostic testing and extensive coverage by the media and social networks. In view of the large amount of—often conflicting—information available, the need has arisen to develop a joint position paper of the Sociedad Española de Patología Digestiva (SEPD) and Asociación Española de Neurogastroenterología y Motilidad (ASENEM) to discuss up-to-date scientific information.

SIBO is defined as the presence of excessive bacteria in the small intestine (SI), which causes a number of nonspecific gastrointestinal symptoms including distension, abdominal pain, tympanites, rumbling, diarrhea or constipation, and flatulence, usually the result of bacterial nutrient fermentation. It may rarely manifest with malnutrition and vitamin and mineral deficiencies (B12, D, A, E, calcium, iron) (1,2). The microbiota of patients with SIBO has not been hitherto characterized due to wide variability between individuals as well as populations; however, several studies agree on an increased prevalence of *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter* spp, and *Enterococcus* spp in jejunal aspirates from individuals with SIBO. A predominance of methane-producing microbiota (intestinal methanogen overgrowth, IMO), made up of strict anaerobic prokaryotes belonging to the Archaea kingdom, particularly *Methanosphera stadmania*e and *Methanobrevibacter smithii* (3).

Multiple *factors potentially predisposing* to microorganism proliferation in the SI and/or antegrade migration of colonic bacteria to the SI have been described. Particularly relevant are the loss of barriers physically separating the SI from the colon, as in surgical ileocecal valve resections or reconstructions involving blind loops (Roux-en-Y), and conditions involving intestinal motility such as gastroparesis, vagotomy, chronic intestinal pseudo-obstruction, scleroderma, or neurodegenerative diseases (1).

Other systemic conditions such as hypochlorhydria, diabetes mellitus, liver cirrhosis, chronic kidney disease, chronic pancreatitis, Parkinson's disease, and opioid use have also been associated with SIBO; however, a *potential pathogenic role could not be established,* hence their systematic screening cannot be currently recommended (1,4).

As regards digestive functional disorders, some studies have shown that in patients with irritable bowel syndrome (IBS) the prevalence of SIBO is higher (odds ratio = 3.7) for the diarrhea subtype (35.5 %) than the constipation subtype (22.5 %) (5); however, *controversy* exists regarding the role of SIBO in the pathogenesis of these conditions. Importantly, up to 20 % of healthy subjects with no gastrointestinal complaints may have a positive SIBO test, hence we recommend not to investigate it in such cases (4-6).

The gold-standard diagnostic test for SIBO is jejunal aspirate culture, which is conclusive when more than 10^3 or 10^5 colony forming units per milliliter (CFU/mL) are found (1,7). However, this test is both invasive and costly as it requires gastroscopy or jejunal intubation; fails to reach the ileum, thus underdiagnosing distal SIBO (4); and has not been standardized (3,7).

As an alternative to jejunal aspirate culture a breath test (BT) may be used for diagnosing SIBO. This is a low-risk, low-cost indirect test that assesses intestinal bacterial fermentation after administration of a substrate *by measuring hydrogen (H_2) and methane (CH_4)* in expired alveolar air (2). The test is based on the premise that human cells are unable to produce H_2 y CH_4, hence the detection of said gases in the breath is a surrogate indicator of bacterial fermentation.

A breath test requires prior preparation of the patient with avoidance of antibiotics for 2-4 weeks, fasting, use of an antiseptic solution to cleanse the oral cavity immediately before testing, a low-fiber, low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet for 24 hours before testing, abstinence from smoking, minimal physical efforts prior to and during the test, and withdrawal of intestinal motility altering drugs such as opioids, antispasmodics, prokinetics, antidepressants, and nonabsorbable sugar laxatives for at least 1 week before testing (7,8).

Two distinct substrates may be used: glucose (50 g according to European guidelines or 75 g according to the North American Consensus), which is rapidly absorbed in the duodenum and jejunum, practically failing to reach the colon; or lactulose (10 g), a non-absorbable sugar that is usually fermented by the colonic microbiota; an early elevation (< 90 minutes) of H_2 and/or CH_4 may indicate SIBO (1,7,8). The sensitivity and specificity of lactulose BT are 42 % and 70.6 %, respectively, and those of glucose BT are moderately higher at 54.5 % for sensitivity and 83.2 % for specificity, hence glucose is recommended over lactulose (6).

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With respect to BT interpretation, current SIBO positivity criteria are a hydrogen increase > 20 ppm from baseline within 90 minutes after substrate ingestion, or a methane increase above 10 ppm at any time point during the test. These criteria are hardly restrictive, which accounts for low sensitivity and specificity (6). The reported prevalence of SIBO varies according to the population studied and the diagnostic method/criteria used for diagnosing SIBO, it being overestimated in studies relying on breath tests (40 %) as compared to aspirate culture (19 %) (4). The *primary limitation* of BT is the high intra- and inter-individual variability of oro-cecal transit time (OCTT). In patients with accelerated OCTT (< 90 minutes) BT may yield a false positive result because of early substrate arrival in the colon (9-12).

SIBO treatment should be based on the identification and correction (when possible) of underlying causes in order to prevent relapsing symptoms and to redress nutritional deficiencies. Antibiotic use in patients with nonspecific symptoms who were diagnosed with SIBO using BT is questionable. While current clinical practice guidelines suggest using non-absorbable antibiotics such as rifaximin, the level of evidence is low, with highly variable success rates (59 to 63 %) depending on dosage (600 to 1600 mg per day) and treatment length (7 to 28 days) (13,14), an H_2 breath test normalization rate of 50 % (3), and symptom improvement in up to 81 % of patients (5). In contrast, broader spectrum antibiotics, even in cyclic administration, may be required for patients with severe, persistent SIBO, usually in the setting of severe intestinal dysmotility.

Low-FODMAP diets may temporarily improve meteorism and distension as they diminish fermentation of dietary substrates; however, these are highly restrictive diets that may in the long run have undesirable consequences on nutritional status and microbiota, hence their use is not recommended in the management of SIBO.

To conclude, SIBO diagnosis requires a thorough assessment of patient symptoms, appropriate test sample collection with the appropriate substrate, and correct interpretation of the results in order to perform a differential diagnosis with functional disorders such as IBS or other conditions with accelerated OCTT. Treatment should be aimed at improving the clinical syndrome by redressing or correcting the underlying disorder (when possible) as well as nutritional deficiencies, rather than just breath test normalization.

SUMMARY OF RECOMMENDATIONS
1. The presently available clinical evidence suggests that **most patients with nonspecific symptoms** such as abdominal distension, meteorism, flatulence, intermittent diarrhea, and other abdominal complaints **do not have SIBO. Therefore, we do not recommend that SIBO be ruled out using BT in patients with nonspecific digestive complaints lacking SIBO-predisposing factors**
2. **We recommend that SIBO be ruled out in patients with risk factors such as intestinal surgery or motility-impairing conditions, with impaired quality of life, nutritional deficiencies or severe symptoms, carefully selecting the diagnostic method and substrate to be used**
3. We recommend that glucose rather than lactulose be used as BT substrate given its higher sensitivity and specificity
4. **We recommend that BTs for SIBO diagnosis be interpreted by specialized medical staff**
5. **Systematic antibiotic use should be avoided in patients with highly prevalent functional conditions such as irritable bowel syndrome**

Conflict of interests: the authors declare no conflicto of interest.

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