

# Bacterial overgrowth: nutrition as part of the therapeutic concept

## Small Intestinal Bacterial Overgrowth (SIBO)

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### Abstract

Small Intestinal Bacterial Overgrowth (SIBO) is a heterogeneous disorder that is characterized by a quantitative and/or qualitative change in the microorganisms present in the small intestine, which usually has few microorganisms. This bacterial overgrowth is not to be confused with dysbiosis, which is the term for an altered microbiota in the large intestine when there is a disease or when there are clinical symptoms. Originally, it was linked to a postoperative anatomical context. However, today, it is also increasingly associated with functional diseases of the gastrointestinal tract, such as irritable bowel syndrome and other diseases. In this context, it is assumed that it is rather the composition of the bacterial species that is more crucial than the number of bacteria. Thus, factors affecting the microbiota are now coming into focus as possible risk sources as well as potential treatment approaches. Alongside traditional therapy, special nutrition could be effectively applied to re-establish a healthy microbiota, reduce bacterial gas formation, and prevent relapse. Avoiding rapidly fermentable carbohydrates, stimulating bile acid secretion and immunoglobulin release, along with selectively growing favourable microbiota are the first-line approaches to dietary intervention.

**Keywords:** bacterial overgrowth, SIBO, nutrition therapy, microbiota, small intestine

### Introduction

Humans live in a state of constant symbiosis with their intestinal microbiota, which is largely made up of bacteria. Its main characteristics are a high density, a high level of diversity and complex mechanisms of interaction. The majority of bacteria is found in the large intestine, where they play a critical role in digestion, synthesis, and absorption of nutrients. Studies have shown that nutrition is a major impacting factor on the composition of the microbiota, and therefore also greatly influences its characteristics (current overview in [1]). Bacterial overgrowth is characterized by a change in the microbial coloni-

zation of the small intestine, which usually has few microorganisms (Small Intestinal Bacterial Overgrowth [SIBO]). It is not to be confused with dysbiosis, which is the term for an altered composition of the microbiota in the large intestine when there is a disease or clinical symptoms at the same time. Bacterial overgrowth was initially linked to abnormal anatomy or impaired motility of the gastrointestinal tract (GIT), and was defined in a quantitative manner, using an assessment of the number of bacteria. However, SIBO is now also being linked to various other factors, and particularly to functional diseases of the GIT, such as irritable bowel syndrome (IBS). This raises the question whether the composition or characteristics of the small intestinal microbiota are the determining factors for disease and whether the quantitative definition might be too simplistic.

Whilst there are already several nutrition therapy approaches for treating dysbiosis in the large intestine (such as administering synbiotics and probiotics), the dietary interventions that can be applied to SIBO are currently limited to balancing out any nutritional deficiencies.

For this review, a systematic literature research was conducted in the literature database PubMed. For a first overview, currently available data (meta-analyses, systematic reviews and reviews, all from the last ten years) were searched for using the search terms "Small Intestinal Bacterial Overgrowth" and "SIBO" and were evaluated. In the second step current studies were additionally searched regardless of article type (all from the last ten

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years; search term “SIBO”). With regard to the connection between SIBO and nutrition, the search term “SIBO” was combined with the terms “treatment” and “diet” without using any filters. Further papers were found in the literature references of relevant papers. Furthermore published literature on the topic from the Central Medical Library was screened and reviewed.

## Microbial colonization of the GIT

In a healthy person whose acid barrier is intact, there are very few microbes in the stomach and the upper small intestine. There is a transient microbiota with  $< 10^4$  CFU/mL (colony forming units per milliliter) chyme, mainly composed of aerobic and gram-positive bacteria [2, 3]. A quantitative more pronounced microbiota in these upper intestinal sections would cause competition in the processing and uptake of nutrients and produce excessive amounts of gases [4]. Distally, the microbiota changes in terms of numbers and composition. The ileum serves as a transitional zone. The number of microorganisms is already around  $10^6$  CFU/mL at the ileocecal valve [5]. This sphincter is permanently contracted and serves as an anatomical barrier against the colon, in order to prevent backwash of the anaerobic microbiota which is much more dense there. In the colon, the number of microorganisms reaches  $10^{11}$ – $10^{12}$  CFU/mL, and coliform bacteria are present [5]. Any disturbance in the regional balances, or any shift in the distribution of the gastrointestinal microbiota can potentially lead to bacterial overgrowth or at least contribute to its occurrence [3].

## The influence of nutrition on the microbiome


The intestines are first colonized with microorganisms in the womb, but this process intensifies during birth. Bacteria need substrates from

## Glossary

- achlorhydria:** absence of gastric acid in the gastric secretions
- aerobic:** organisms whose metabolism requires atmospheric oxygen
- anaerobic:** organisms whose metabolism works without atmospheric oxygen
- aspirate:** material that has been harvested through suction; in this case: from the intestines
- cholecystokinin:** a peptide hormone that stimulates the secretion of enzymes from the pancreas and stimulates the secretion of bile acid
- distal:** in anatomy, this means far from the middle of the body
- distension:** expansion or excessive expansion of an anatomical structure
- endogenous:** something that is created from within
- flatulence:** increased formation of intestinal gases, which subsequently escape rectally; also colloquially referred to as bloating
- intraluminal:** within the lumen, in this case: in the intestine
- meteorism:** when excess gases accumulate in the gastrointestinal tract without subsequently being released; results in what is colloquially referred to as a bloated stomach and causes abdominal pain
- motility:** the ability to move actively
- oropharyngeal:** originating in the mouth/pharynx
- peristalsis:** a wave pattern of contraction and relaxation of the smooth muscle of hollow organs that transports the contents of the organs; controlled by the enteric nervous system
- permeability:** here: the ability of a material (e.g. intestinal epithelium, cell wall) to allow other substances (e.g. gases, liquids) to pass through
- proximal:** in anatomy, this means near the middle of the body
- sphincter:** closing muscle
- stasis:** congestion/stagnation
- steatorrhea:** the pathological presence of excess fat in feces due to malassimilation; also known as: fatty stool
- strictures:** a severe narrowing (also known as stenosis) of the lumen of a hollow organ, in this case: the intestines
- transient:** temporary, not permanent

which they can extract energy and the components they need to build cellular constituents [1], therefore nutrition has a high impact on the microbiota<sup>1</sup>. Short-term changes in nutrition have an effect on proportional composition, but the long-term nutrition habits determine which species are generally available [6]. Potentially, all dietary ingredients that are not absorbed in the small intestine can be a substrate for the bacteria found in the colon. In terms of quantity, indigestible polysaccharides (such as resistant starch, cellulose, pectin and inulin) are the most important substrates. Unlike the pancreas and the small intestine, the colon bacteria have enzyme

systems that can break down these chain structures [1]. The metabolic activity of the colon microbiota therefore depends on how many substrates reach the large intestine [6]. Since there is almost no oxygen in the colon, metabolism takes place through fermentation: Substrates are not completely converted into CO<sub>2</sub> and water, but rather into short-chain fatty acids (acetate, propionate, and butyrate) and intestinal gases (hydrogen [H<sub>2</sub>], carbon dioxide [CO<sub>2</sub>], and methane [CH<sub>4</sub>]).

<sup>1</sup>  “Nutrition-mediated effects of the intestinal microbiota” by BLAUT in ERNÄHRUNGS UMSCHAU 12/2015 [1]

Ultimately, personal diet not only determines which substrates are available to the bacteria; it also determines the intestinal environment. The decisive factors are the spectrum and concentration of bile acids and fermentation products, the pH value and the redox potential. The interaction between host and intestinal bacteria affects the entire metabolism as well as the immune system. However, it has not yet been clarified whether changes to the microbiome that have been observed in certain diseases were the cause of the disease or its result [1].

Currently available publications mainly focus on the microbiota in the colon, while composition and function of the microbiota in the small intestine remain largely un-researched. One of the major obstacles here is the difficulty of taking a local sample. However, ZOETENDAL et al. [7] have managed to create an ecological model of the small intestine microbiota by taking several samples per subject, using phylogenetic microarray technique, and methods that do not rely on cultures. They found that the diversity of species is lower in the small intestines than in the colon, but even in healthy people fermenting bacteria are present. Interestingly, the bacteria react very quickly to available short chain carbohydrates, which becomes obvious through changes in the pH value and the formation of metabolites. With a constant supply of nutrients from food, the bacteria can multiply locally and establish themselves permanently. Here, they compete with the host organism for nutrients. The microbiota of the small intestine can adapt to nutrient availability very quickly, which means that the proportions of the various bacterial species are always subject to change over time [7]. However, analyses of the microbiota following dietary interventions (such as the low-FODMAP diet in the case of functional GIT disorders) are almost exclusively limited to samples from the colon/feces [8–10].

## SIBO

SIBO is a heterogeneous condition that is characterized by a quantitative and/or qualitative change in the microorganisms present in the small intestine, which generally has few microorganisms [2]. Based on the location, this bacterial overgrowth must be clearly differentiated from dysbiosis, which is the term for an altered composition of the microbiota of the large intestine compared to that of a healthy person. Dysbiosis is often linked to diseases such as diabetes mellitus, asthma, and inflammatory bowel disease (IBD). Recent studies have also shown a possible link with obesity. It is postulated that changes in the colon's microbiota may contribute to the occurrence or persistence of obesity [11].

To date, SIBO has generally been defined quantitatively, based on the number of colony-forming units per milliliter of small intestinal aspirate. The most used figure is  $\geq 10^5$  CFU/mL in the proximal small intestine [12]. Historically, this threshold value came about at the time when SIBO was almost exclusively diagnosed following blind loop syndrome or short bowel syndrome. More recent publications also cite lower values. KELLER et al. [13] define a bacterial count  $\geq 10^4$  CFU/mL of jejunal aspirate as pathological; KOSHINI et al. [12] set review an upper limit of  $10^3$  CFU/mL for healthy patients in their systematic. The length and location of the affected intestinal segment have

not yet been examined in more detail and definition is currently not based on bacterial species [14].

## Etiology

The etiology of SIBO is complex, and it initially results from disorders of the endogenous defense mechanisms against bacterial overgrowth (♦ Overview 1). Although various factors may be involved, it is often impossible to differentiate between predisposing and etiological causes [2]. Ultimately, risk factors for the occurrence of bacterial overgrowth (♦ Table 1) are based on disorders of at least one protective factor.

In healthy people, excessive bacterial colonization of the small intestine is prevented by the chyme being transported onwards. If motility is impaired or if there is an anatomical obstacle, stasis of the chyme occurs, which provides the basis for bacterial colonization and growth [15]. Connections between the proximal small intestine and the colon such as fistulas can be the cause of colonization of the small intestine, particularly with bacteria from the colon [15, 16].

In the stomach normal acid secretion kills 99% of all bacteria and the majority of living organisms within 5 minutes. If this mechanism is impaired or suppressed, the number of gram-positive bacteria in the stomach and the upper small intestine increases. However, it is assumed that the colonization is temporary with well-functioning peristalsis [17].

### OVERVIEW 1: FACTORS PROTECTING AGAINST BACTERIAL OVERGROWTH IN THE SMALL INTESTINE [2, 4]

- intact intestinal motility and peristalsis
- intact ileocecal valve
- intact gastric acid secretion
- intact intestinal mucosa with protective mucosal layer and intrinsic antibacterial mechanisms (such as defensins and immunoglobulins)
- enzymatic and bacteriostatic effectiveness of the pancreatic and biliary secretions
- the protective effects of the commensal microbiota

## Etiology: Elements discussed

The effect of gastric acid-inhibiting medications in the pathogenesis of SIBO has been a topic of discussion for some years. H<sub>2</sub> receptor blockers do inhibit maximum acid secretion, but not baseline acid secretion, meaning that the overall pH value is sufficiently acidic [18] and has no connection with SIBO [14]. Conversely, proton pump inhibitors allow the pH value to increase comparatively strongly, which increases bacterial density by 50 to 100 times [17]. The studies conducted to date have yielded conflicting results. This can be attributed to the use of different test methods, limit values, patient populations and medications. These studies suggest that proton pump inhibitors do not represent a risk factor for SIBO according to the classical definition (> 10<sup>5</sup> CFU/mL) but that they do represent a risk factor for an increased bacterial density compared to controls [14, 19, 20].

It has been suspected for some time now that there may be a link between bacterial overgrowth and irritable bowel syndrome. The fact that the symptoms are similar to the symptoms of gas-related complaints (distension, flatulence, meteorism) further suggests that there may be a connection. However, the study results are conflicting. The measured prevalence of SIBO in IBS patients fluctuates (4–84%) and it appears to be dependent on the selected testing and evaluation method. However, since the SIBO rates are consistently above the rates for the controls (1–40%), a link seems likely [21, 22]. In addition, the antibiotic therapy of SIBO significantly relieves symptoms in many patients with IBS, although it is suspected that this is due to the effect of the locally acting antibiotic on the microbiota [21, 23]. However, without a uniform method of diagnosis, there can be no satisfactory result, especially since the Rome consensus conference deemed breath gas tests unsuitable for the diagnosis of SIBO in patients with irritable bowel syndrome [24].

Reduction of acid secretion caused by surgery cannot itself produce a clinically significant bacterial overgrowth, but it can promote its development in people with functional disorders associated with stasis [15].

Other risk factors have multifactorial effects and involve the impairment of several protective factors (♦ Table 1). It is postulated that there is a link with other factors due to the increased prevalence of SIBO within the affected groups. The mechanisms of action are also multifactorial, but they have not yet been clarified.

## Prevalence

Inconsistent diagnostics, only partially clarified connections with various diseases and varying study designs have led to controversial prevalence data. The SIBO preva-

lence in controls fluctuates between 0 and 35% [12]. Generally, it is assumed that the disease is significantly underdiagnosed. Not all patients consult a physician, and in addition, many are incorrectly diagnosed. Reasons why SIBO may remain undetected and untreated include an asymptomatic course and attribution of the symptoms to the underlying disease [25].

## Pathogenesis

In case of bacterial overgrowth increased numbers of *Enterobacteriaceae* may occur in the small intestine in particular. Those are usually derived from the colon microbiota [3]. In case of achlorhydria, it may solely be the number of oropharyngeal bacteria that is elevated, but this is less common [13]. Typically various species of bacteria are involved,

which consecutively leads to corresponding symptoms [2]. Gram-negative aerobic and anaerobic species that metabolize carbohydrates, and consequentially produce gas, tend to cause gas-related complaints. On the other hand, coliform bacteria such as *Klebsiella* produce toxins that have damaging effects on the mucosa and on the absorption of nutrients [26].

These processes also occur in the small intestine. In addition to intestinal gases, toxins and other metabolites are formed, which can have a strong influence on the mucosa. This can lead to the loss of brush border enzymes (especially disaccharidases such as lactase), which results in carbohydrate malassimilation. This in turn provides more carbohydrates for bacterial metabolism, which exacerbates the problem, causing a vicious cycle. In severe cases, increased permeability of the mucosa can lead to protein-losing enteropathy or systemic inflammatory reactions and liver damage. In addition to proteins and carbohydrates, some species of bacteria also metabolize vitamin B<sub>12</sub>, plus B<sub>1</sub> and B<sub>3</sub>. Others can synthesize vitamin K and folate, as well as D-lactate, alcohol and acetaldehyde. The latter set of substances can cause systemic complications in case of a very severe bacterial overgrowth. Finally, the bacterial deconjugation of bile acids can further impair the absorption of fats in the ileum [4].

## Symptoms and clinical manifestation

In case of very mild bacterial overgrowth, usually only non-specific symptoms such as meteorism and distension, abdominal pain and cramps, flatulence and diarrhea occur. These primarily result from the formation of gas, short-chain fatty acids and other fermentation products [4]. SIBO patients may also have a slow rate of transit in the small intestine, which promotes bacterial growth as well [27].

small intestine stasis	
<b>motility disorders</b>	<b>anatomical abnormalities</b>
<ul style="list-style-type: none"> <li>• neuropathies or myopathies, including as a result of: <ul style="list-style-type: none"> <li>• connective tissue disorders</li> <li>• chronic drug intake (e.g. analgesics, motility inhibitors, opiates)</li> </ul> </li> <li>• enteritis</li> <li>• gastroparesis</li> <li>• infectious diseases</li> <li>• metabolic and endocrine disorders</li> <li>• chronic intestinal pseudo-obstruction</li> </ul>	<ul style="list-style-type: none"> <li>• small intestine diverticulosis</li> <li>• postoperative state (such as blind loop syndrome or short bowel syndrome)</li> <li>• strictures (e.g. due to Crohn's disease, lymphoma or radiotherapy)</li> <li>• tumors</li> </ul>
<b>connection between proximal and distal</b>	
<ul style="list-style-type: none"> <li>• gastrocolic/jejunocolic fistulae</li> <li>• functional disorder or resection of the ileocecal valve</li> </ul>	
<b>impaired defense mechanisms</b>	
<b>achlorhydria</b>	<b>immunodeficiency/immunosuppression</b>
<ul style="list-style-type: none"> <li>• chronic gastritis (e.g. due to <i>Helicobacter pylori</i>)</li> <li>• postoperative state (e.g. following a gastrectomy or vagotomy)</li> </ul>	<ul style="list-style-type: none"> <li>• congenital (e.g. IgA deficiency, variable immunodeficiency syndrome)</li> <li>• acquired (e.g. HIV/AIDS, severe malnutrition, steroid therapy, immunosuppressive therapy)</li> </ul>
<b>multifactorial factors</b>	<b>unexplained factors</b>
<ul style="list-style-type: none"> <li>• alcoholism</li> <li>• inflammatory bowel disease</li> <li>• diabetes mellitus</li> <li>• advanced age</li> <li>• intestinal failure</li> <li>• liver cirrhosis</li> <li>• cystic fibrosis</li> <li>• terminal kidney failure</li> <li>• celiac disease</li> </ul>	<ul style="list-style-type: none"> <li>• fibromyalgia</li> <li>• reflux esophagitis</li> <li>• irritable bowel syndrome</li> <li>• restless legs syndrome</li> <li>• rheumatoid arthritis</li> <li>• socio-economic status</li> <li>• being overweight</li> <li>• proton pump inhibitors</li> </ul>

Tab. 1: **Etiological factors associated with SIBO** [4, 13, 15, 17, 18, 26, 28, 45, 46]  
SIBO = Small Intestinal Bacterial Overgrowth

Lactose intolerance may occur as a secondary effect through lactase deficiency [13]. In patients showing the symptoms mentioned above, it is very difficult to distinguish between bacterial overgrowth and other functional, gastroenterological diseases such as intolerances or irritable bowel syndrome [4]. Thus, many SIBO patients are initially diagnosed with IBS, lactose intolerance or fructose malabsorption [3]. In elderly patients in particular, the course of SIBO can be asymptomatic [28], in which case it does not require any treatment and is more of a random diagnosis. If there is a massive pathological increase in numbers of microorganisms, this primarily leads to diarrhea and steatorrhea, as well as to weakness and weight loss, which may be attributed to the malassimilation of carbohydrates, proteins and fats [4]. Caused by protein-losing enteropa-

thy hyperalbuminemia and edema may also occur. In addition, some of the people who are affected reduce their food intake in order to ease the symptoms, which leads to weight loss and a worsening of their general state of health [15]. Macrocytic anemia and neurological changes could be a result from a potential vitamin B<sub>12</sub> deficiency. Malabsorption of fat may cause an inadequate intake of fat-soluble vitamins (A, D, E), which may lead to symptoms (such as peripheral neuropathy, hypocalcemia, osteoporosis or night blindness). High serum levels of vitamin K from bacterial self-synthesis may render coagulation inhibitors ineffective [29]. Iron deficiency anemia has also been observed in the context of SIBO, although it is postulated that insufficient absorption (due to the effects of bacterial toxins, short-chain fatty acids and deconjugated bile acids) is the cause [29].

#### Conflict of Interest

The authors declare no conflict of interest.

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