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Bacterial overgrowth: nutrition as part of the therapeutic concept

Small Intestinal Bacterial Overgrowth (SIBO)

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SIBO diagnostics

A particular challenge in diagnosing SIBO is the wide variety of causative diseases, which may overlap with the symptoms of the bacterial overgrowth itself. In addition, the clinical picture differs depending on the bacterial species, the location of the bacterial overgrowth and the density of the bacteria [18]. Therefore a SIBO diagnosis should be considered in all patients with the aforementioned non-specific gas-related complaints, including micronutrient deficiencies and steatorrhea. An anamnestically important information is the above mentioned fact that SIBO is not a primary condition, but rather a secondary caused by the pathological changes in the intestines, as described above [30].

Breath tests

Breath gas tests measure the release of gases through exhaled air during the intraluminal, bacterial metabolism of an administered test substance. This preferential test method is non-invasive, requires little effort and is most cost-effective [13]. The normalization of a positive test result following specific therapy confirms efficacy of that therapy and is associated with an improvement of the symptoms [31].

The most commonly used breath tests today are hydrogen breath tests with lactulose as test substance. Lactulose cannot be broken down by enzymes in the human body and consecutively reaches the colon, where its fermentation increases hydrogen (H_2) concentration. Hence, an observable increased H_2 concentration indicates the fermentation of lactulose in the small intestine and/or in the colon (◆ Figure 1). However, breath gas curves cannot always be interpreted correctly. A relatively distal colonization, altered transit times or short bowel syndrome may lead to false-positive or false-negative interpretations of the breath gas curve, for example if only one increase is detectable [32] (◆ Figure 2 and Figure 3).

Due to the interpretation difficulties in SIBO diagnostics by testing with lactulose, some professionals prefer breath gas measurement with glucose. In healthy people glucose is absorbed completely in the upper sections of the small intestine. Consequently no increase in H_2 occurs. However, in case of bacterial overgrowth the glucose is fermented by the bacteria located in the small intestine, producing H_2. This increased gas production is detectable in the breath gas analysis (◆ Figure 4). An increase in H_2 concentration of 12 ppm above the baseline value is generally considered as a pathological deviation [13]. However, the test parameters (test time, amount of test substance, critical gas quantities, etc.) are not standardized, which makes it all the more difficult to compare studies. If bacterial overgrowth is present distally, or if glucose absorption is very fast, the glucose is already completely absorbed in the duodenum and upper jejunum and a false-negative result may occur [32] (◆ Figure 5).

If the patient has gastroparesis, both tests may indicate false-negative results because the test substance may not reach the dislocated colonies during the testing period. Patients with lung diseases, smokers and athletes may also show false breath gas values. Overall, the test using glucose appears to have a higher sensitivity and specificity than the lactulose test. However, with both methods, there is a tendency towards overdiagnosis [2]. The Rome consensus conference concluded that at the moment, the glucose breath test is the most accurate non-invasive test for diagnosing SIBO. The

test quantity	50 g
liquid quantity	250 mL
test duration	180 min
sampling	every 15 min
threshold value	12 ppm
sensitivity	62.5 %
specificity	81.8 %

Tab. 2: **Test parameters for the glucose breath test** [24]

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suggested parameters are: a test quantity of 50 g of glucose in 250 mL of liquid and a test duration of 120 min with sampling at 15 min intervals, and a threshold of 12 ppm above the baseline [24] (◆ Table 2).

An additional challenge is that the microbiota of "non-producers" (about 20% of the human population) metabolizes H2 and quickly converts it to methane (CH_4) and water (H_2O). This causes a false-negative H_2 breath test, as well. A cross-checked lactulose test with no H_2 increase may prove a "non-producer". In this case, an additional methane breath test should be considered [12].

Genomic and metabolomic techniques promise greater insights into the microbiome and consequently, may improve the diagnostic options in the future [4].

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Treatment of SIBO

Like the diagnostics, the therapy is also rather based on empirical experimentation with different therapeutic procedures than on an evidence-based standardized recommendation. A particular challenge is that treatment decisions have to be made while taking into consideration the causes, symptoms and complications all at the same time, and treatment must also be individually tailored to the patient. The following three approaches are traditionally cited as treatments for SIBO:

- treatment of underlying causes,
- direct treatment of the bacterial overgrowth and
- removal of any nutritional deficiencies [2].

Approaches that use special diets to treat SIBO (or at least achieve significant symptom relief) are currently being investigated.

Treatment of the underlying cause

The cornerstone of SIBO therapy is the elimination of the underlying

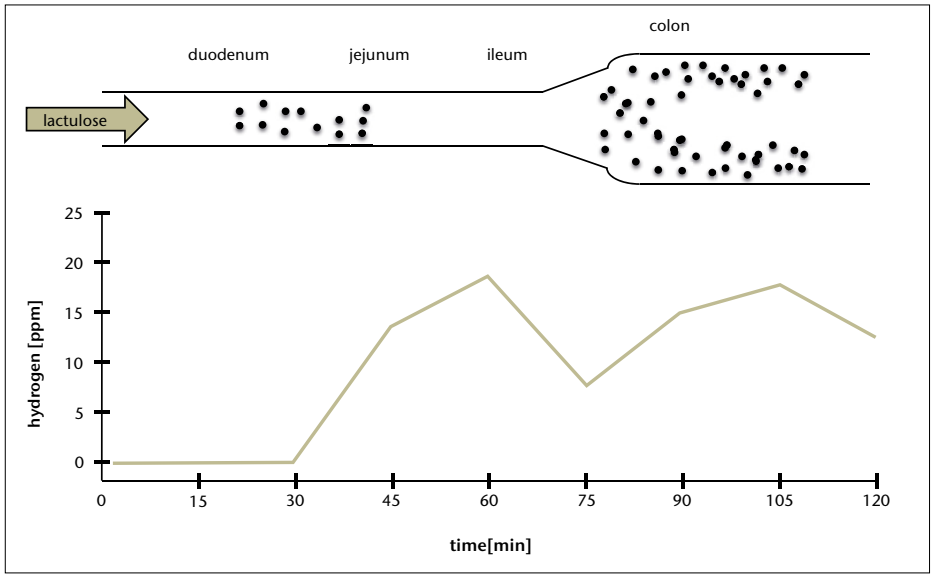

Fig. 1: **Lactulose breath test in the case of proximal bacterial overgrowth** [own illustration according to (32)]

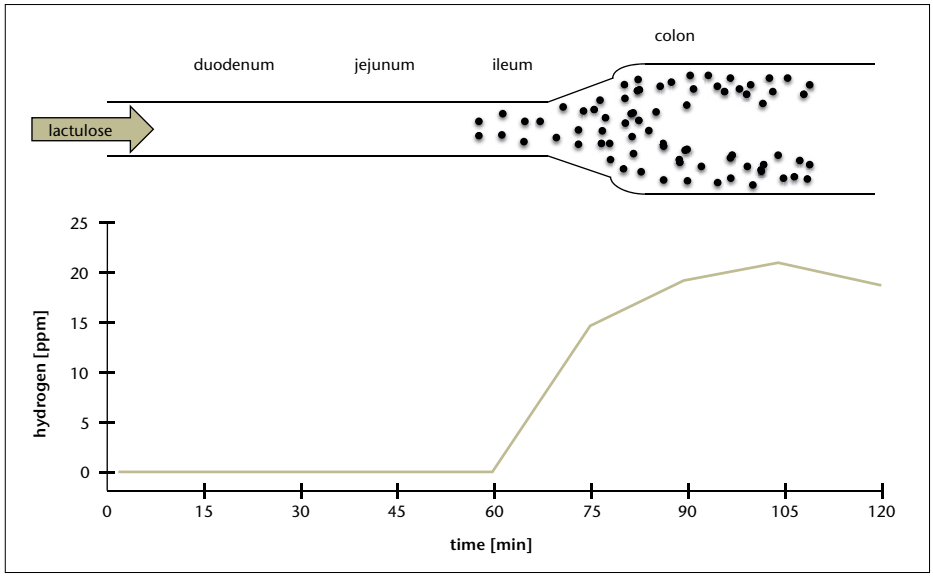

Fig. 2: **Lactulose breath test in the case of distal bacterial overgrowth** [own illustration according to (32)]

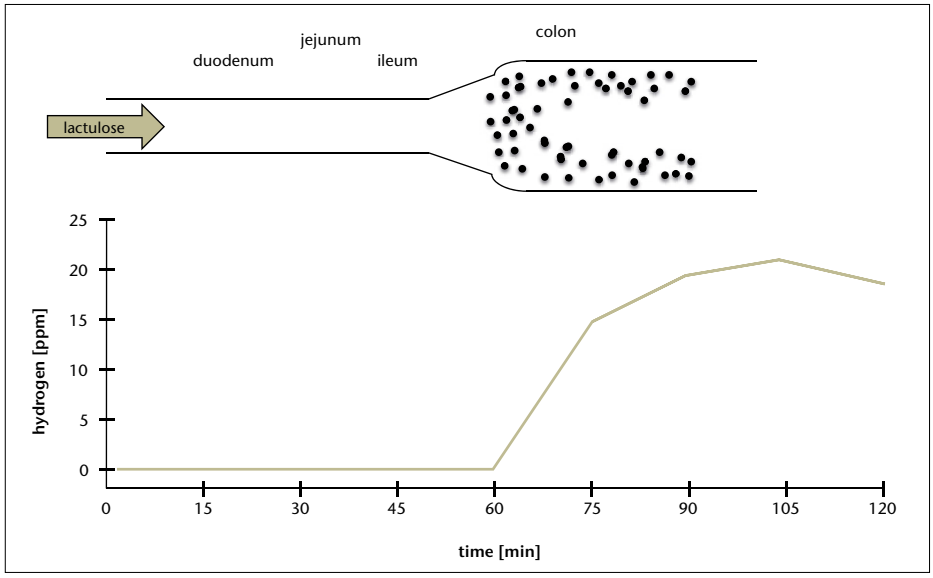

Fig. 3: **Lactulose breath test in the case of accelerated transit through the small intestine** [own illustration according to (32)]

disease or structural defect in order to allow treatment of the bacterial overgrowth itself and to prevent relapse. This may include the surgical correction of an anatomical abnormality. If the patient is taking medication that inhibits motility or gastric acid secretion, it should be replaced, discontinued or at the very least restricted [25]. In case of motility disorders, prokinetic drugs can stimulate peristalsis and reduce the risk of recurrence [33].

Direct treatment of the bacterial overgrowth

Antibiotics: Due to the co-existence of numerous different bacteria (with their various levels of sensitivity to antibiotics being equally numerous), today, broad-spectrum antibiotics are generally used for treatment. Norfloxacin, amoxicillin/clavulanic acid, ciprofloxacin and others have been found to produce an improvement in symptoms in various studies. Combination therapies were developed in order to treat both aerobic and anaerobic bacteria at the same time, thus increasing the probability of successful treatment. A 7–10 day course of antibiotic treatment can improve symptoms for a few months. However, to date there is no consensus regarding the most effective dose or the optimum duration of treatment [29].
The numerous side effects (as diarrhea, constipation, dizziness, weakness, skin rash, dyspepsia) are problematic; they occur due to the systemic effects of the medication. Recently there has been a growing interest in non-absorbable, locally acting antibiotics such as rifaximin and neomycin. The focus is now on rifaximin due to the low success rate of neomycin (20%) [34]. A meta-analysis showed that there was an average breath gas normalization rate of 49.5% for rifaximin monotherapy [31] with a simultaneous improvement in symptoms [29]. The fact that this drug has only minor side effects and the lack of much evidence of resistance also work in this drug's favor [25]. The major problem with this drug is that it is not approved for the treatment of SIBO, and therefore has to be used as an "off-label" drug. On this account patients sometimes have to bear the comparatively high cost of the drug themselves [35].
Relapses following antibiotic therapy are a major problem. In 13% of the subjects the glucose test was once again positive after 3 months, in 28% after 6 months and in 44% after 9 months. The burden in terms of symptoms was also increased and reflected the breath test results [36].

Probiotics and prebiotics: Due to the possible side effects of antibiotic therapy, as well as the hazard of resistance and the presumably negative effect on the microbiome and the protective biofilm of the intestinal epithelium, alternative treatment options have been proposed [35]. One approach to altering the bacterial composition may be probiotics and prebiotics, whose efficacy has been demonstrated in various GIT disorders with dysbiosis (e.g. IBS) [35, 37–39].
Hydrolyzed guar gum has had some initial success in combination with rifaximin. The authors suspect that the crucial mechanisms are improved intestinal clearance and positive effects on the composition of the microbiota [40]. Overall, the findings for probiotics and prebiotics in the context of SIBO are based on pilot studies with contradictory results. Randomized, blinded studies are required in order to present evidence-based recommendations.

Antimicrobial plants: Antimicrobial plants have also been tested as possible treatments for SIBO. In a study, 46% of the patients exhibited a normalized lactulose breath test (34% in the rifaximin control group, without statistical difference) after treatment with a combined herbal preparation (including oregano and thyme oil, berberine and wormwood extract, threeleaf goldthread, and barberry root [preparations: Dysbiocide/FC Cidal]). Patients who did not respond to rifaximin as an initial treatment also achieved treatment success using the plant preparations [35]. One case report also reported positive effects for peppermint oil [41].
Treatment with plant extracts could be a cost-effective and gentle alternative to antibiotics, especially for relapsed patients.

Removing deficiencies

The treatment of deficiencies is primarily indicated in the case of serious forms of SIBO. For example, the status of the fat-soluble vitamins A, D, and E should be checked in the case of steatorrhea. Other deficiencies caused by the clinical manifestation described above must be individually recorded and treated [2]. In the case of severe weight loss, a strategy for achieving or maintaining a healthy body weight should be developed, for example through supplementation of MCT fats (medium-chain triglycerides) or digestive enzymes.

Nutrition therapy approaches

In a study, IBS patients with a positive lactulose test received a hydrolyzed formula diet with maltodextrin as the main component, which should be completely absorbed in

Overview 2: **Possible mechanisms of action of a formula diet for treatment of bacterial overgrowth** [42]

- elimination of bacteria or reduction of bacterial growth through reduced substrate availability
- transporting bacteria away from the susceptible area by stimulating motility
- modulation of microbiota composition

the upper section of the small intestine. 80% of the participants had a negative lactulose test result after 14 days (85% after 21 days) and a clear improvement of their symptoms. In 6 out of the 11 patients who were not successfully treated, it was established that there were other reasons for non-response. 83% of those who did a new breath test after one month still had a negative result.

One possible explanation for this is that the bacteria simply "starved", since no substrates were available to them. The authors also postulate that increased cholecystokinin release due to the formula diet and the resulting increased secretion of bile acids resulted in increased stimulation of motility. Hereby the colonies are transported to the lower intestinal segments. Furthermore, it is postulated that a formula diet increases the secretion of immunoglobulins, which could lead to the elimination of microorganisms from the small intestine. A third possible effect is the direct effect of formula diets on the microbiota. It has been observed in stool analyses that it is not only the composition that changes; the total number of bacteria is also reduced. These effects have also been observed in the case of bacterial overgrowth in the upper sections of the small intestine, where the bacteria might still be able to use the nutrients.

The actual mechanism of action of the formula diet has not yet been clarified, but it appears to be multifactorial [42] (◆ Overview 2). These findings suggest that nutrition therapy could also be used to influence the microbiota in the future.

The first approaches to symptom relief in the case of SIBO were the introduction of a lactose-free diet to compensate for the reduced availability of lactase [4]. The avoidance of non-absorbable sugar alternatives or sweeteners such as sorbitol, aspartame and saccharin, plus other modifications of lifestyle and diet, such as the elimination of carbonated beverages and avoiding chewing gum or drinking through a straw, can also reduce flatulence [3].

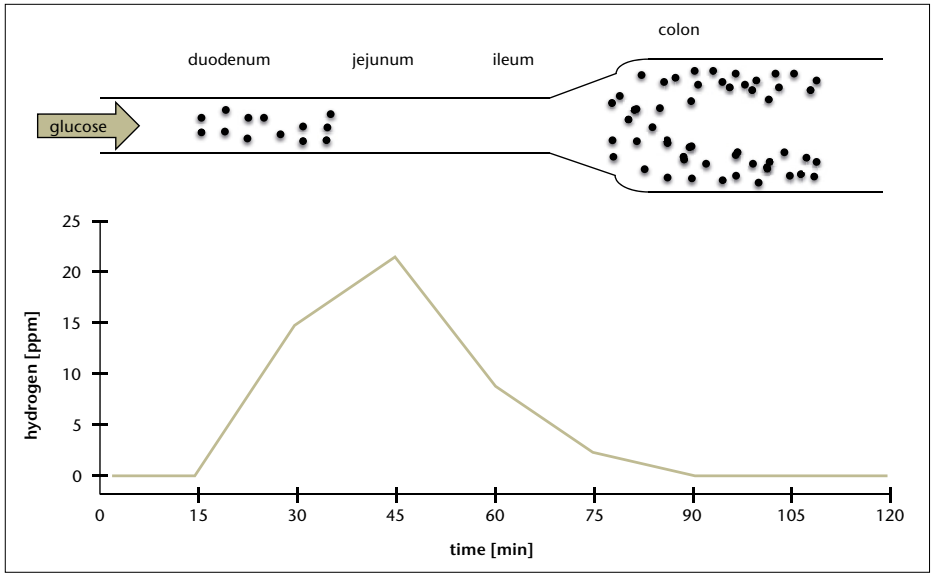

Fig. 4: **: Glucose breath test in the case of proximal bacterial overgrowth** [own illustration according to (32)]

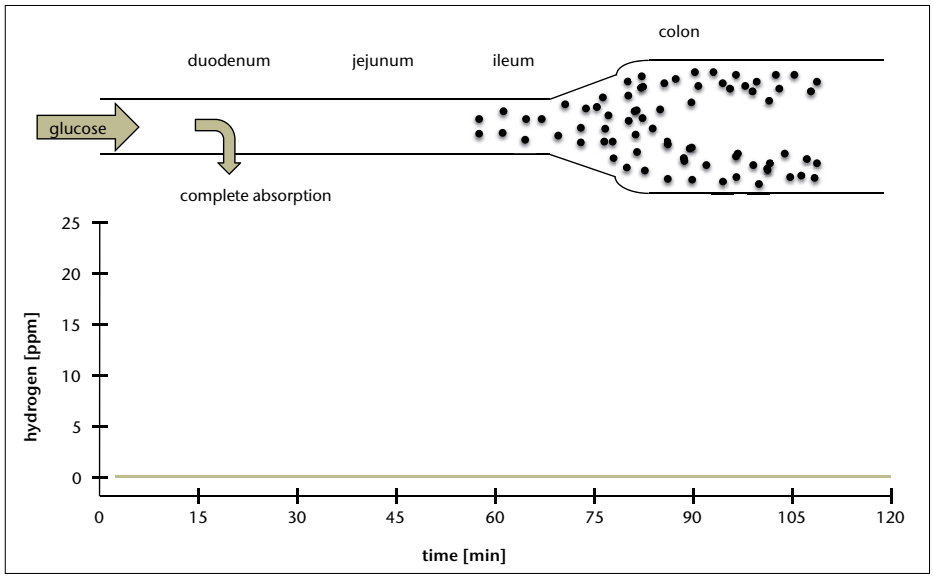

Fig. 5: **Glucose breath test in the case of distal bacterial overgrowth** [own illustration according to (32)]

In the case of steatorrhea, partial substitution of long-chain fatty acids using MCT can provide relief [43]. Previously, in the case of steatorrhea, a high-carbohydrate, low-fat diet was recommended for alleviation of symptoms. However, since carbohydrates are a easy fermentable substrate for undesirable bacteria, a reduction in the carbohydrate content of the diet can relieve symptoms and improve energy and vitamin uptake [44].

Conclusion and importance for practice

In future, nutrition therapy for SIBO should go beyond compensating deficiencies. The aim should be the relief of symptoms specifically by avoiding individual foods. Therapeutic approaches and dietary concepts that will have a long-term influence on the microbiota are desirable. In cases of moderate bacterial overgrowth, nutrition therapy

alone might be sufficient. In more severe cases, it could be used to support antibiotic therapy, especially in order to promote a beneficial microbiota following treatment and thus prevent relapse. In cases where it is not possible to remedy the underlying cause, dietary therapy may also prevent or reduce a cyclic pattern of antibiotic use at regular intervals or at least reduce how often this is needed.

To date the main limiting factor is that the link between diet, small intestine microbiota, their metabolic activity and disease symptoms have not yet been fully investigated. However, some studies have given an indication of which mechanisms could constitute an approach:

- Very rapidly absorbed nutrients could reduce the overall substrate availability for the bacteria [18, 42].
- Customizing the nutrient composition of the diet could inhibit the growth of undesirable species and promote the growth of desirable species. For example, the bacterial species that are responsible for gas-related complaints can ferment short-chain carbohydrates particularly well [7]. On the other hand, the consumption of certain food ingredients such as probiotics and prebiotics or antimicrobial plants may have a positive effect on the microbiota [28].
- Bile acids have an antibacterial effect and they stimulate peristalsis; increased bile acid secretion can thus reduce the number of bacteria in the upper small intestine [15, 42]. In a fat-rich diet, it was observed that bile acid secretion is increased and that this restricts the growth of certain bacterial species [1].
- Increasing the jejunal secretion of immunoglobulins through a special diet could help to support the "self-cleaning" mechanism of the intestines [42].

You can read the first part of this article in ERNÄHRUNGS UMSCHAU issue 4/2017.

The literature references for this article can be found in ERNÄHRUNGS UMSCHAU issue 4/2017.

Conflict of Interest
The authors declare no conflict of interest.

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