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Review Article

Bacterial Super growth Treatment of Small Intestine: Systematic Review

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Abstract

Introduction: Bacterial overgrowth in the small intestine (SBID) is a disease characterized by a greater number of intestinal bacteria and a change in the gastrointestinal bacterial composition. Treatment is a challenge in clinical practice and is not systematic.

Objectives: systematic review to verify the treatment of small intestinal bacterial overgrowth. comparing drug efficacy and adverse effects.

Methods: The most relevant studies were analyzed in the MedLine databases, including only controlled and randomized clinical trials (ECCR) and meta-analyzes. The search strategy used the following keyword combinations: "Bacterial overgrowth" [ti] AND "treatment" [ti]. To identify the study designs, the following terms were used: Clinical Trials.

Results: 16 articles were included in the scope of this review, which showed comparisons between different antibiotics and dosages, still without consensus in the literature. It is observed that the treatment must be based on broad-spectrum antibiotic therapy.

Conclusion: The treatment of bacterial overgrowth is based on broad-spectrum antibiotic therapy. Rifaximin seems to be the the best choice, but without a defined dose. More studies are needed for this.

Keywords: Inflammatory bowel diseases; Small intestine; Microbiology; Bacterial infections

Introduction

Intestinal bacterial overgrowth is defined by excessive growth of bacteria in the small intestine, causing gastrointestinal symptoms. These include nausea, bloating, constipation or diarrhea, and flatulence. Aerobic and anaerobic gram-negative bacteria act on carbohydrates by increasing gas formation, disrupting nutrient absorption, altering intestinal rhythm and even causing inflammation of the intestinal epithelium. In severe cases, it presents with anemia, hypovitaminosis and weight loss [1,2]. Some diseases may favor the occurrence of this entity, such as Crohn's disease, IgA deficiency, HIV, use of antisecretory agents and opioids, pancreatic insufficiency, advanced age, liver cirrhosis, among others [1,2].

The big challenge is still the diagnosis, as the symptoms are common to other diseases and even to functional syndromes. In addition, little available diagnostic tests are needed, such as breath tests, in which we can measure the level of exhaled hydrogen or methane. Carbohydrates such as lactulose and glucose are the most commonly used substrates in hydrogen testing, with glucose providing the most accurate test. Measurement of methane, in addition to hydrogen, can increase the sensitivity of the breath test for bacterial overgrowth [3,4].

Treatment consists of controlling the bacterial population by means of antibiotics. Still much discussed in the literature about dosage and class, the most common are: metronidazole,

ciprofloxacin, tetracyclines, rifaximin, amoxicillin-clavulanate, the controversial use of probiotics and prebiotics, in addition to empirical treatment with broad-spectrum antibiotics, which is evidently necessary. However, little systematic and reproducible [4-6]. Therefore, the objective of the present study was to verify, through a systematic review, the treatment of bacterial overgrowth of the small intestine, comparing the different drugs used, and their effectiveness.

Methods

The most relevant studies originally published in English in the last five years were analyzed, using the MedLine (National Library of Medicine and National Institutes of Health) and SciELO databases as a reference, with the objective of selecting the studies with the greatest scientific evidence, contemplating only clinical trials and descriptive studies. The search strategy used the following keywords: "Bacterial overgrowth"[ti] AND "treatment"[ti]. To identify the study designs, the following term was used: clinical trials. The inclusion and exclusion criteria were applied based on the types of studies, language, type of therapy and date of publication from the points raised in each exposed item (Chart 1). For the selection of studies, the inclusion and exclusion criteria presented in Table 1 were applied.

Table 1: Inclusion and exclusion criteria applied in the selection of studies.

Inclusion criteria	
Outline	· clinical trials
Patients	· people with bacterial overgrowth
Intervention	. treatment of bacterial overgrowth
Language	· English and Portuguese
Exclusion Criteria	
Outline	· Case reports and case series
Intervention	· Unclear, poorly described or inappropriate interventions
Publication form	. only in summary
Main Clinical Outcomes	
· Therapeutic options.	

Results

Initially, 65 studies involving bacterial overgrowth were identified. However, after applying the "clinical trials" filter, 17 studies were found. After reading the articles found and exclusion by abstracts, 13 articles were selected, two of which were excluded since they did not address the treatment of bacterial overgrowth, but the factors associated with its occurrence, the other excluded, as it addressed overgrowth in dogs and another did not have the full abstract article. In Figure 1 we will present a summary of the works selected and reviewed in the present study Table 2.

Table 2: PPI (proton pump inhibitor); IBS (irritable bowel syndrome); SIBO (Small Intestinal Bacterial Overgrowth).

Author / Year	Sample	Method / Intervention	Results
Stozer, et al. [7]	30 patients, with only 14 patients completing the study	Double blind study. 1st phase: placebo for 2 weeks. 2nd phase: one group received placebo and another Lactobacillus fermentum. 3rd phase: 4 weeks without intervention. 4th phase: group that previously received placebo now received Lactobacillus fermentum.	Lactobacillus fermentum in this study did not significantly alter the investigated parameters.
Di Stefano, et al. [8]	21 patients with SIBO	Double-blind, randomized, controlled trial comparing the effects of 7-day use of rifaximin (1200 mg/day) with 7-day chlortetracycline 1 g/day. A hydrogen (H2) breath test and laboratory tests were performed. All these tests were repeated 3 days after the end of treatment.	Fasting, peak and total H2 excretion decreased in the group of patients treated with rifaximin, while chlortetracycline did not modify these parameters. The H2 breath test normalized in 70% of patients after rifaximin and in 27% of patients after chlortetracycline. Symptom improvement was greater in patients treated with rifaximin.
Madrid, et al. [9]	34 patient with liver cirrhosis	They randomly used cisapride (12), an alternating regimen of norfloxacin and neomycin (12), or placebo (10) for 6 months. At 3 and 6 months, small bowel manometry was performed, and orocecal transit time and small bowel bacterial growth were also investigated using the H2 breath test.	After 6 months, cisapride and antibiotics improved fasting cyclic activity, reduced the duration of orocecal transit, and decreased bacterial growth in the small intestine. Cisapride administration was also followed by an increase in the amplitude of contractions, which did not occur with placebo. There was liver improvement at 3 and 6 months with cisapride and antibiotics.

Castiglione, et al. [10]	145 patients with Crohn's disease. 29 patients with confirmed SIBO.	Randomized in: Group A: metronidazole 250 mg/10 days/ orally. Group B: ciprofloxacin 500 mg 12/12h/ 10 days/ orally. The breath test was repeated at the end of treatment.	29 patients (20%) with SIBO. Normal test in 13 patients who used metronidazole. Also in 14 patients treated with ciprofloxacin (P = ns). In both, there was improvement in: abdominal distension (Group A 85% and Group B 83%), stool softness (44% and 50%) and abdominal pain (50% and 43%).
Lauritano, et al. [11]	90 patients with bacterial overgrowth in the small intestine.	Rifaximin 600 mg / day (group 1); rifaximin 800 mg/day (group 2) and rifaximin 1200 mg/day (group 3). Glucose breath test, adherence, and incidence were reassessed 1 month after the end of therapy.	The glucose breath test normalization rate was higher in group 3 (60%) compared to group 1 (17%; P < 0.001) and group 2 (27%, P < 0.01). No significant differences were found in patient compliance and incidence of side effects. Higher doses improve efficacy without increasing side effects.
Majewski, et al. [12]	20 symptomatic between 19 and 85 years old.	20 symptomatic patients aged 19 to 85 years with the presence of overgrowth were prospectively studied openly.	Absence of adverse effects. Rifaximin was a safe and effective treatment in reducing symptoms, especially when diarrhea was the dominant symptom; and normalized the SIBO in approximately 50% of the patients.
Scarpellini, et al. [13]	80 patients	Group 1 Rifaximin 1600 mg / day Group 2: Rifaximin 1200 mg / day Compared bacterial growth by breath test before and after treatment.	Rifaximin 1600 mg/day showed greater efficacy for the treatment of SIBO in the small intestine compared to group 2.
Soifer, et al. [14]	50 patients with chronic abdominal distention (Rome III criteria) and the diagnosis of SIBO is made by a lactulose H2 breath test.	Randomized to receive metronidazole or a probiotic. 25 subjects treated with metronidazole 500 mg/5 days. 25 patients used probiotics.	13 (52%) individuals receiving metronidazole and 20 (82%) receiving the probiotic reported clinical improvement after treatment, with greater favorability with the use of the probiotic (P = 0.036).
Collins, et al. [15]	75 children (8 -18 years old) with chronic abdominal pain	The sample was randomized in a double-blind manner into two groups: Group 1 – received rifaximin 550mg for 10 days Group 2 – received placebo 3x a day Repeated questionnaire and breath test 2 weeks after treatment	49 children received rifaximin and 26 received placebo. 94% of children who received rifaximin and 92% of those who received placebo had an abnormal baseline lactulose breath test. 20% of rifaximin-treated children achieved a standardized repeat breath test.
Scarpellini, et al. [16]	50 children with IBS	All were submitted to the breath test before and one month after treatment with rifaximin 600 mg/day/1 week. All IBS patients completed a Visual Analogue Scale (VAS) to score gastrointestinal symptoms at baseline and one month after treatment.	Prevalence of overgrowth in IBS - 66%. Normalization rate after treatment - 64%. Adherence was excellent and no relevant side effects were observed. The score was higher in IBS patients with SIBO than in patients without this alteration.
Tahan, et al. [17]	20 patients between 6 e 10 years old with SBID that have no diarrhea more than 30 days.	The 20 patients used trimethoprim-sulfamethoxazole (30mg/kg) and metronidazole (20mg/kg) 2 doses/day for 14 days. One month later, they performed the second breath test.	After treatment, 19 (95.0%) of the 20 children showed no evidence of SIBO. Trimethoprim-sulfamethoxazole and metronidazole were effective.
Khalighi, et al, [18]	30 patients - chronic abdominal pain or diarrhea and a positive hydrogen test.	Randomized and double-blinded in 2 groups: user of probiotic drugs and control group. Control group - minocycline (200mg/day/15 days). Users of probiotics-minocycline 200mg/day/15 days, and probiotic lactol 2 times/day/15 days postprandial.	Negative test in 93.3% of those receiving lactol, and 66.7% of controls. In those who received lactol, abdominal pain ceased (p = 0.002). Flatulence, eructations and diarrhea improved. (p<0.05).
Del Piano, et al. [19]	65 individuals, 25 men and 40 women.	Group A- 29 patients treated with PPI for 3 months Group B: 36 patients were included as a control population Assessment of gastric juice was performed. Group A - patients with bacteria 105 cells/ mL were selected for an intervention study with the 4 lactobacilli.	The significant decrease in intragastric acidity induces relevant bacterial overgrowth, contributing to an increased risk of infections and intestinal diseases. The 2-week use of the 4 lactobacilli tested proved to be effective in reducing total bacteria and coliforms in the gastric environment in subjects chronically treated with PPIs.

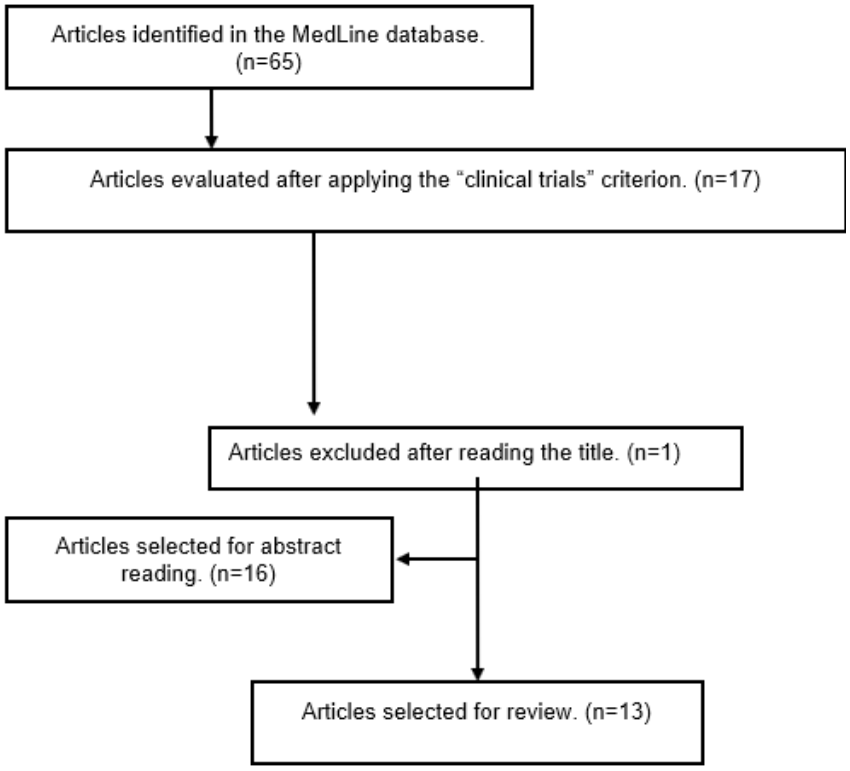

Figure 1: Summary of studies and their main results involving bacterial overgrowth.

Discussion

The treatment of intestinal bacterial overgrowth is based on the use of broad-spectrum antimicrobials, but there is still no consensus on class and dosage. Even as the biggest challenge for choosing the best treatment is the comparison of antibiotics. Studies such as Castiglione et al. [10] who compared treatment with metronidazole and ciprofloxacin for 10 days, do not show significant differences between the two treatments. In his analysis, both methods were considered effective, with metronidazole being better in symptomatic control. Furthermore, it was found that in the study by Tahan, et al. [17] comparison between treatment with metronidazole and trimethoprim-sulfamethoxazole for 14 days, showing similar efficacy between the two treatments.

In the articles by Scarpellini, et al. [16], Majewski, et al. [12], Collins, et al. [15], Scarpellini, et al. [13], Lauritano, et al. [11] and Di Stefano, et al. [8] success has been observed with rifaximin therapy. However, there is still much debate about dosage. In the study by Scarpellini, et al. [16], patients who were treated with rifaximin 600mg/day for 1 week showed good tolerance and improvement of symptoms, in addition to negative results in post-treatment breath tests. According to Majewski, et al. [12], patients were treated with rifaximin at a dose of 800mg per day for 4 weeks. No adverse effects were observed, being a safe and effective treatment in reducing symptoms, especially when diarrhea was the dominant symptom; normalized bacterial overgrowth in approximately 50% of patients.

[11,13] studied different dosages of rifaximin. In the study by Scarpellini, et al. [13] it was observed that Rifaximine 1600 mg / day showed significantly greater efficacy for the treatment of bacterial overgrowth in the small intestine compared to 1200 mg with similar compliance and side effect profile. Similar to what was observed in the study by Lauritano, et al. [11] who compared dosages of 600/800 and 1200mg for 7 days, showing better efficacy with the use of higher doses without changing adherence and side effects. Questioning the need for high doses for symptomatic benefits, we have the study by Collins, et al. [15], randomized, double-blind, in which one group received rifaximin 550mg for 10 days and the other group received placebo 3 times a day. They were submitted to a questionnaire and breath test 2 weeks later, where there was no significant difference in the improvement of symptoms, but rifaximin proved to be effective in normalizing the breath test.

In addition, Di Stefano, et al. [8], showed the comparison of treatment with chlortetracycline 1 g/day with rifaximin 1200mg/day for 7 days, with better efficacy in the group treated with rifaximin. The H2 breath test normalized in 70% of patients after rifaximin and in 27% of patients after chlortetracycline. Symptom improvement was significantly greater in rifaximin-treated patients.

In the study by Madrid, et al. [9], performed in cirrhotic patients, who randomly used cisapride, an alternating regimen of norfloxacin, neomycin or placebo during a period of 6 months. It was observed that these medications have value for the treatment

of bacterial overgrowth, showing a significant decrease. Still much discussed and controversial the effectiveness of probiotics in the treatment, it was verified in the study by Soifer, et al. [14] on therapeutic success in the group that used the medication, mainly in symptom control. Similar to that evaluated by Khalighi, et al. [18] who demonstrated the effectiveness of the use of probiotics in the maintenance treatment after the use of broad-spectrum antibiotics, showing a decrease in symptoms. However, in the study by Stozer, et al. [7], the use of probiotics was not relevant.

Therefore, it is suggested that several antibiotics present good results. According to the studies by [8, 11,13,16] the advent of rifaximin, although questionable about dosage, presents well tolerated by the patients studied, with few side effects observed, in addition to therapeutic success with negative respiratory tests. In addition, suggested by the scope safety in the use of high dosages of medication. However, better longitudinal studies are needed for adequate dosage action and therapeutic success.

Conclusion

Finally, more longitudinal and prospective studies are needed to evaluate the best treatment and define dosages. Rifaximin seems to be a promising drug in the treatment, although the dosage has not yet been defined. For the time being, there is a tendency to individualize treatment with broad-spectrum antibiotic therapy. We observed good results with different antimicrobial classes.

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Conflict of Interest

No conflict of interest.

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