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Treatment of small intestine bacterial overgrowth

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Abstract. – Removal of the predisposing condition, appropriate nutritional support to reintegrate both caloric and vitamin requirements and suppression of the contaminating bacterial flora represent the main of goals of the treatment of small intestine bacterial overgrowth. Generally, the polymicrobic nature of contaminating flora requires the administration of wide-spectrum antibiotics, but as yet we don't know which is the best pharmacological approach, in terms of drug, dosage and duration of therapy.

There is no conclusive information regarding the most effective therapy that should be used. This paper reviews the efficacy of the different therapeutic approaches used.

Key Words:

Small intestine bacterial overgrowth, Therapy, Hydrogen breath test, Rifaximin, Non absorbable antibiotics, Diarrhoea, Intestinal gas production.

Introduction

The treatment of small intestine bacterial overgrowth (SIBO) is a clinical challenge for physicians, as data contained in the peer review literature don't offer conclusive information on the most effective therapeutic approach. In this paper, the available data are reviewed in order to suggest some possible approaches.

Clinical and Pathophysiological Aspects

SIBO is due to the presence of more than 10^6 colony forming units per ml of intestinal aspirate and/or colonic type species[1]. This condition is generally accompanied by malabsorption and the consequent clinical syndrome is characterised by major symptoms, such as diarrhoea, steatorrhea and weight loss, abdominal pain, together with bloating and flatulence, although asymptomatic cases, mostly among the elderly[2], have been described. An impairment in nutritional status is therefore frequently present and several nutritional deficits have been described[3-9].

Malabsorption in SIBO is considered the consequence of abnormalities occurring mainly in the intraluminal environment. In fact, the excessive number of intraluminal bacteria interfere with the absorption process. However, in some cases, the presence of bacterial species capable of more aggressive adhesion to small bowel epithelium is probably the cause of direct damage to the absorptive surface, in particular in blind loop syndrome[10,11].

Generally speaking, it is not easy to discriminate between the relative role of the predisposing condition and that of bacterial overgrowth in the pathogenesis of malabsorption. In fact, gastrectomy, ileo-colonic fistula and short bowel may be causes of malabsorption regardless of the concomitant presence of bacterial overgrowth. The pathophysiological role of bacteria is carried out by their ability to metabolize nutritional substances, such as carbohydrates, lipids and proteins, normally absorbed in the small bowel. This involves two types of problems: first, the nutritional defect, due to the lack of caloric substrates available for absorption; second, a series of effects carried out by the products of bacterial metabolism, such as increased carbohydrate fermentation[12], responsible for the presence of symptoms like flatulence, bloating, abdominal colicky pain and abdominal distention; increased levels of Short Chain Fatty Acid (SCFA), responsible for an irritation of the colonic wall, acidification of both bowel lumen and feces and, finally, diarrhoea accompanied by abdominal pain; reduced mucosal disaccharidase activity due to its inactivation by proteases secreted by anaerobic bacteria[13].

Aims of the Therapy

The aims of the therapy of SIBO are listed in Table I. First, physicians should take into consideration the appropriateness of removing the predisposing condition. The importance of the role of these conditions (Table II) was shown by the demonstration of SIBO presence in around three-quarters of patients with malabsorption symptoms associated with a predisposing condition[14]. Their removal, however, is not always possible. In patients who have undergone surgical reconstruction with loss of gastric acid filter or ileocecal valve, a complete recovery of this syndrome is never possible and bacterial overgrowth will always represent a clinical problem to be taken into consideration. On the other hand, in patients with stenosizing or fistulizing Crohn's disease, the timing of surgery is subject to complex evaluation and, therefore, relapsing symptoms of SIBO syndrome often have to be dealt with.

Appropriate nutritional support is also mandatory. The aim of this therapeutic measure should be the reintegration of both caloric and vitamin requirements, often defective in these patients. The need for nutritional support is caused both by the predisposing condition and by the malabsorption syndrome. Moreover, the suppression of the contaminating bacterial flora represents the main aim.

Table I. Aims of the therapy of small intestine bacterial overgrowth.

Nutritional Support
Minerals
Vitamins
Caloric requirements
Removal of predisposing conditions
Surgery
Prokinetics (?)
Suppression of contaminating flora
Antibiotics
Probiotics (?)

Table II. Conditions predisposing to small intestine bacterial overgrowth.

Anatomical defects
Blind loops
Strictures
Fistula
Diverticula
Gastric resections
Ileo-colonic resections
Functional defects
Impaired motility causing intestinal stasis
Ageing
Reduced gastric acid secretion
Reduced activity of intestinal immune system

Therapeutic Approaches

Prokinetics

In some patients with SIBO due to intestinal stasis secondary to motility defects, the restoration of normal intestinal motility may represent an effective approach. Prokinetic agents have been shown to improve intestinal motility[15,16] and the use of this therapeutic approach has been shown to be effective: in patients with scleroderma, low-dose octreotide proved to be useful in the reduction of bacterial overgrowth[17]. Unfortunately, cisapride was recently removed from the market due to cardiotoxicity, and, apart from an erythromycine analog without antibiotic effects which showed no effects in rats[18], no alternative drugs are available and, consequently, the role of these agents in the therapy of SIBO still needs to be explored. Preliminary data suggest that $5HT_{1A}$ agonist buspirone[19] and $5HT_4$ partial agonist tegaserod[20] induce increased intestinal motility in healthy volunteers. These new therapeutic approaches may represent an effective alternative, but no data are available as yet.

Antibiotics

The polymicrobic nature of contaminating flora requires the use of wide-spectrum antibiotics[21,22]. The choice of the drug is frequently empirical because small bowel aspiration and culture are impractical and if performed will show with certainty multiple organisms with different levels of antibiotic sensitivity. However, the most important reason for the use of wide-spectrum antibiotics is due to the lack of information: we do not know which of them should be eliminated to achieve an improvement of symptoms[21]. Several antibiotics have been shown to be effective (Table III). However, as very obvious from this Table, available data are very fre-

Table III. Antibiotic regimens used in small intestine bacterial overgrowth.

Drug	Dose	N.	Predisposing conditions	Responders
Tetracycline				
Kahn et al, 1966	250 mg q.i.d.	4	Sclerodermia	75%
Goldstein et al, 1961	250 mg q.i.d.	1	Billroth II	+
Gorbach et al, 1969	250 mg q.i.d.	1	Ileocolonic anastomosis in Crohn's disease	–
Bjorneklett et al, 1983	NA	3	Small bowel diverticulosis	100%
Di Stefano et al, 2000	333 mg t.i.d.	11	GI surgery, intestinal stasis	27%
Chloramphenicol				
Goldstein et al, 1961	500 mg q.i.d.	1	Billroth II	+
Lincomycin				
Bjorneklett et al, 1983	NA	1	Radiation fibrosis	-
Gorbach et al, 1969	500 mg t.i.d.	2	Small bowel diverticulosis	50%
Ampicillin				
Goldstein et al, 1970	250 mg q.i.d.	1	Diabetic autonomic neuropathy	+
Metronydazole				
Bjorneklett et al, 1983	NA	6	Radiation fibrosis, small bowel diverticulosis	83%
Cotrimoxazole				
Elsborg et al, 1977	400 mg b.i.d	1	Small bowel dicerticulosis	+
Norfloxacin				
Attar et a,l 1999	400 mg b.i.d.	10	GI surgery or intestinal stasis	30%
Amoxicillin-clavulanic acid				
Attar et al 1999	500 mg t.i.d.	10	GI surgery or intestinal stasis	50%
Rifaximin				
Trespi et al, 1999	400 mg t.i.d.	8	Chronic pancreatitis and Billroth II	100%
Di Stefano et al, 2000	400 mg t.i.d.	10	GI surgery or intestinal stasis	70%

quently based on the description of single cases among reports of more numerous series. Although anaerobes are responsible for the main metabolic alterations, tetracyclines[23,24,25] have been used for a long time and with satisfactory results, in spite of their poor activity against these bacteria[3,22,26]. A rapid improvement of symptoms was evident in most cases after a single therapeutic course of 10-14 days at a 250 mg qid dose[3]. Aerobe suppression induced by tetracyclines probably did not render the intraluminal microclimate favourable to anaerobes, due to the increased bioavailability of oxygen[21]. However, it was recently reported that about 60% of patients do not respond to this treatment[27]. Metronydazole[3,25], ampicillin[28] and erythromycin[29] have been used as an alternative to tetracycline, while other active drugs against anaerobes, such as lincomycin[30,25,31] and chloramphenicol[3,24], due to the high risk of severe side effects, are no longer used. Neomycin was shown to be of little efficacy when used alone in this condition[31]. Little information is available on cotrimoxazole, which proved to be effective at low dosage in one case report[32].

If contaminating flora is sensitive to the antibiotic administered, in most patients a single course of 7 to 10 days of therapy is able to induce an improvement of symptoms[33]; on the contrary, in others a quick relapse of symptoms is evident, but can be treated with the same antibiotic treatment[3,29]; in these cases, good results can be achieved with intermittent antibiotic treatment[3].

A recent study determined the bacterial populations contaminating the upper gut in SIBO patients and their antibiotic susceptibility. Amoxicillin-clavulanic acid and cefoxitin were efficient on > 90% of anaerobic strains, while aminopenicillins, cephalosporins and cotrimoxazole were efficient on microaerophilic populations. Erythromycin, clindamycin and rifampicin were not efficient. Data on metronidazole and fluoroquinolones are not available[34].

Rifaximin, a non-absorbable derivative of rifamycin, showed a promising bactericidal action against both aerobes and anaerobes,

such as bacterioides, lactobacilli and clostrides[35,36]. The development of resistance against this antibiotic is a frequent event. However, the withdrawal of therapy permits rapid disappearance of the phenomenon, probably due to the incapacity of resistant strains to permanently colonize the human intestine[37]. Bacterial resistance does not therefore represent an obstacle to subsequent courses of rifaximin. Controlled clinical trials demonstrated rifaximin's efficacy in adult and pediatric patients with infectious diarrhea[38,39], hepatic encephalopathy[40], post-surgical complications[41] and colonic diverticulosis[42]. On the contrary, there are very few reports on the efficacy of rifaximin in the treatment of SIBO[43-45].

The most important evidence is probably offered by a recent double-blind, randomized trial which showed a higher therapeutic effect of rifaximin in comparison to tetracycline in a cohort of SIBO syndrome patients[44]: in particular, rifaximin administration produced a significant reduction of breath hydrogen levels at fasting, a peak of hydrogen excretion and cumulative breath hydrogen excretion after an oral dose of 50 g of glucose. A normalization of the test results was evident in 70% of the sample studied.

A significant improvement of symptom severity without side effects was also evident after rifaximin administration but not after tetracycline, thus reinforcing the validity of the therapeutic approach adopted. Rifaximin has proved to be effective in the treatment of gas-related symptoms: in fact, in a recent paper, a 7-day course of therapy significantly improved the severity of symptoms in a cohort of patients suffering from functional abdominal complaints[46]. This effect should also be important in patients with SIBO syndrome: it could probably become more evident if courses of therapy longer than one week are prescribed, in view of the interference on the therapeutic efficacy due to the presence of the predisposing conditions.

Another recent controlled trial showed a good therapeutic effect of both amoxicillin-clavulanic acid and norfloxacin in SIBO patients[47]. However, a rapid relapse of diarrhoea just a few days after the withdrawal of antibiotics was evident. In this paper, the efficacy of probiotics in SIBO patients was also evaluated, but no significant effect was described. While on one hand these results confirm the frequent need for several courses of antibiotic therapy in SIBO patients, on the other they support the hypothesis that rifaximin may represent a good choice on the basis of its excellent tolerability.

In a cohort of 145 patients with Crohn's disease the presence of SIBO was confirmed by hydrogen breath test after glucose administration in 20% of patients[48]. Both metronidazole and ciprofloxacin proved to be effective in the management of bacterial overgrowth and breath hydrogen excretion normalized in 86% and 100% of patients, respectively. In the metronidazole group, one patient out of 15 withdrew after two days because of nausea and, together with the other two patients resistant to metronidazole, was successfully treated with ciprofloxacin. After a 1-year period of follow-up, only one patient presented a recurrence of bacterial overgrowth. This study suggests, therefore, that ciprofloxacin is more effective than norfloxacin in the treatment of SIBO and confirms that side effects represent a major problem for the therapy with metronidazole. Moreover, in 50 consecutive patients with various malabsorption syndromes, 42% of jejunal aspirates showed a bacterial count greater than 10^5 CFU/ml. *Streptococcus* species and *Escherichia coli* were the commonest gram positive and negative isolated bacteria, respectively, and proved to be more sensitive to quinolones than to tetracycline, ampicillin, erythromycin and cotrimoxazole [49]. Unfortunately, no data are available on rifaximin.

Probiotics

Apart from the already mentioned negative study dealing with probiotics and SIBO therapy[47], another paper evaluated the effect of two different *Lactobacillus* strains, namely *L. casei* and *L. acidophilus* strains cereal. The effect of these two strains was compared vs. placebo. A short-term improvement of the number of bowel movements and breath hydrogen excretion was achieved by probiotic treatment, suggesting that probiotics may represent an important tool in the treatment of SIBO only if prolonged courses are adopted[50].

In conclusion, the pivotal topic in the therapy of SIBO syndrome is probably represented by the careful evaluation of clinical poly-

morphism of these patients: the presence of several predisposing conditions, very different on pathophysiological and clinical grounds, may condition the clinical response of individual patients, thus modifying the overall efficacy of the individual therapeutic programmes. Preliminary results, in fact, have shown that patients with SIBO and blind loop syndrome show a better clinical response after metronidazole therapy than after rifaximin, suggesting that a lower drug availability at blind loop level may be responsible for this lower efficacy[51]. It is, therefore, possible that the study of subgroups of patients will give us useful informations and will clarify several still non-standardised issues such as the optimal dosage and the duration of the therapy. The availability of nonabsorbable antibiotics in clinical practice will surely add important information.

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