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# Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole

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**Abstract. – *Background and Objectives:*** **Few controlled trials on antibiotic therapy for small intestinal bacterial overgrowth are available at present. Aim of the study was to assess efficacy, safety and tolerability of rifaximin with respect to metronidazole for the treatment of small intestinal bacterial overgrowth.**

***Material and Methods:*** **We enrolled 142 consecutive patients with diagnosis of small intestinal bacterial overgrowth. Diagnosis of small intestinal bacterial overgrowth based on the clinical history and the positivity of glucose breath test. Patients were randomised to two 7-day treatment groups: rifaximin 1200 mg/day and metronidazole 750 mg/day. Glucose breath test was reassessed 1 month after. Compliance and side-effect incidence were also evaluated.**

***Results:*** **One drop-out was observed in rifaximin group. Five drops-out occurred in metronidazole group. The glucose breath test normalization rate was significantly higher in the rifaximin with respect to the metronidazole group (63.4% versus 43.7%; $p<0.05$; OR 1.50, 95% CI 1.14-4.38). The overall prevalence of adverse events was significantly lower in rifaximin with respect to metronidazole group.**

***Discussion:*** **Rifaximin showed an higher SIBO decontamination rate than metronidazole at the tested doses, both with a significant gain in terms of tolerability. Either the present study or recent evidencies suggest that rifaximin represents a good choice for the management of patients affected by SIBO.**

*Key Words:*

Bacterial overgrowth, Glucose breath test, Rifaximin, Metronidazole.

## Abbreviatons

SIBO: small intestinal bacterial overgrowth
CFU: colony-forming unit
GBT: glucose breath test
$H_2$: hydrogen
IBS: irritable bowel syndrome

## Introduction

Small intestinal bacterial overgrowth (SIBO) is a common clinical syndrome due to an increased level of bacteria exceeding the presence of more than $10^5$ CFU/mL of intestinal aspirate or of colonic-type species within the small bowel[1,2].

SIBO symptoms could be many and variably associated; abdominal pain or discomfort, bloating, diarrhoea and/or signs of malabsorption are the most common[1,2]. Recent findings suggest that SIBO is highly prevalent in patients with IBS and that SIBO decontamination is associated to a significant improvement of IBS symptoms[3-5].

The culture of jejunal aspirates, regarded by many as the gold standard for the SIBO diagnosis, has several limitations such as the potential for contamination by oropharyngeal bacteria during intubation, and the fact that SIBO may be patchy and thus missed by a single aspiration. In addition, it is too much invasive, expensive and difficult and too little reproducible to be proposed as a routine diagnostic test for SIBO in the clinical practice, especially for patients with non-specific symptoms or those requiring repeated testing[1,2].

The GBT is considered a simple tool for SIBO diagnosis, since it is non invasive, highly reproducible and inexpensive when compared to the culture of jejunal aspirates. In addition, the specificity and the sensitivity of GBT are acceptable for screening studies (77-100% and 67-98% respectively)[6-8]. The $H_2$ produced in the human body after glucose ingestion derives entirely

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from intestinal bacterial fermentation. The appearance of an early increase in breath $H_2$ concentration suggests the presence of SIBO[6-8].

An effective antibiotic decontamination regimen should include one or more drugs with activity against both aerobic and anaerobic bacteria since SIBO may occur either by a mix of aerobic and anaerobic flora or by purely aerobic flora in a minority of cases[1,2,9-11]. Empirical courses of broad-spectrum antibiotics are widely used at present for SIBO decontamination, since few well-conducted trials have been performed up today to verify which is the best antibiotic regimen[1,2,11,12].

Metronidazole is effective against Gram-negative and Gram-positive anaerobic bacteria such as *Bacterioides*, *Fusobacterium* and *Peptostreptococci*[13]. These characteristics make it potentially useful for the treatment of small bowel bacterial overgrowth as confirmed by literature data[14].

Rifaximin is a rifamycin derivative with antibacterial activity caused by inhibition of bacterial synthesis of RNA[15]. It is active against gram-positive and gram-negative bacteria, including both aerobes and anaerobes[15-17]. Less than 0.1% of the oral dose is absorbed[16]. Rifaximin at a dosage of 1200 mg per day for 1 week is associated to a significant gain in terms of therapeutic efficacy in SIBO contamination without increasing the incidence of side-effects with respect to lower dosages (600 and 800 mg per day for the same treatment period)[18].

The aim of the present study was to assess the efficacy, safety and tolerability of the non-absorbable antibiotic rifaximin with respect to the systemic antibiotic metronidazole in patients affected by SIBO.

## Material and Methods

This prospective parallel-group randomized trial was conducted between February 2005 and August 2007 in consecutive out-patients from the Gastroenterology and Internal Medicine Departments of the Catholic University of Rome, Italy.

### Inclusion/Exclusion Criteria

Patients referring to our centre for the presence of gastrointestinal symptoms (bloating, abdominal pain, flatulence and diarrhoea) since ≥ 6 months were evaluated.

Major organic gastrointestinal disorders were ruled out on the basis of: history collection; full physical examination; laboratory tests (total blood count, erythrocyte sedimentation rate, reactive C protein, stool examination for occult blood, ova and parasites, anti-transglutaminase antibodies); abdominal ultrasonography and colonoscopy when alarm symptoms were present (fever, gastrointestinal bleeding, weight loss, anemia, abdominal mass).

The Rome II criteria were used to verify the diagnosis of IBS or other functional bowel disorders[19].

The exclusion criteria were: previous antibiotic treatment associated to SIBO diagnosis; age <18 years; use of antimicrobial agents within the previous 3 months; hypersensitivity to the antibiotics used in the present study; pregnancy or breast-feeding; evidence of major concomitant diseases (including tumours and hepatic and/or renal insufficiency).

Exclusion criteria were: age <18 years; hypersensitivity to the antibiotics; pregnancy or breast-feeding; evidence of major concomitant diseases (including tumours and hepatic and/or renal insufficiency). Consecutive patients with positive GBT were included in the present study after informed consent.

The procedures followed were in accordance with with the Helsinki Declaration of the World Medical Association.

### Laboratory Parameters

Total blood cell count, liver and kidney function were assessed in all patients at enrolment and 3 days after the end of the treatment.

### Breath $H_2$ Testing

GBT was performed under standard conditions. In the month preceding the test patients should not have received antibiotics or laxatives. To minimize basal $H_2$ excretion, patients were asked to follow a carbohydrate-restricted dinner on the day before the test and to fast for at least 12 hours. On the day of testing, patients did a mouthwash with 20 ml of chlorhexidine 0.05%. Smoking and physical exercise were not allowed for 30 minutes before and during the test. End-alveolar breath samples were collected immediately before glucose ingestion. A dose of 50 g of glucose in the form of iso-osmotic solution was administered and samples were taken every 10 min for 2 hours respectively using a two-bag system. The two-bag system is a device consist-

ing of a mouthpiece, a T valve and two collapsible bags, the first one collects dead space air, the second one collects alveolar air. The breath sample was aspirated from this bag into a 20 ml plastic syringe. Samples were analyzed immediately using a model Quintron Gas Chromatograph (Quintron Instrument Company, Milwaukee, WI).

The test was considered as indicative of the presence of SIBO when the peak, that is the increase over the baseline of $H_2$ levels, was >12 p.p.m.[7].

The GBT was repeated 1 month after the end of therapy to assess GBT normalization.

### Outcomes

The primary outcome of the present study was the GBT normalization rate using rifaximin or metronidazole.

Secondary outcomes were patient's compliance and incidence of side-effects in the two therapeutic schemes.

Compliance was assessed by an interview (administered by a trained physician) performed after the end of the therapy and by a pill count of the drugs boxes returned at the same interview. Low compliance was defined as more than 20% of pills returned.

At enrolment the patients were informed on the common side-effects expected from the studied therapies. Side effects were defined as the occurrence of: a) abnormalities in the main haematochemical parameters considered; b) "adverse experiences", considered as clinical findings or patient complaints that were not present in the 24 hours immediately before the enrolment in the trial. All patients were asked to fill in a validated questionnaire (modified DeBoer) in order to report therapy related adverse experiences (diarrhoea, taste disturbance, nausea, bloating, loss of appetite, vomiting, abdominal pain, constipation, headache, skin rash)[20]. Each symptom was graded from absent (0) to severe (interruption of treatment, 3) based on the intensity. The questionnaire was administered at enrolment and the patients were asked to complete diary cards in the same format (Likert scales) during the treatment period and to return them at the post-therapy interview.

### Randomization

Using a computer-generated number sequence, generated by a statistician, the patients were randomly assigned to one of the two 7-day treatment groups:

1. Rifaximin 1200 mg/day (2 tablets tid; group 1: n=71)
2. Metronidazole 750 mg/day (1 tablet tid; group 2: n=71).

### Data Analysis

For the purpose of the analysis, the incidence of side-effects was considered as a binomial variable (present/absent). To detect differences in GBT normalization rates and the incidence of side-effects, the $X^2$ or Fisher's exact tests were used. Odds Ratio (OR) for achieving GBT normalization with 95% confidence intervals (95% CI) was calculated. The statistical analysis was performed using STATA 6.0.

## Results

### Patients Characteristics and Overall Compliance

A total of 142 patients were enrolled. Characteristics of the study groups are summarized in Table I. Groups were similar for sex, age, body mass index and the prevalence of irritable bowel syndrome (IBS) and of the other subtypes of functional bowel disorders.

The overall compliance of the present study was excellent: 135 of 141 completed the studied therapeutic regimens. However the incidence of drop-outs was higher in the group of patients

**Table I.** Demographic and clinical characteristics of SIBO positive patients included in the two treatment groups (group 1=rifaximin; group 2=metronidazole). BMI, body mass index; IBS, irritable bowel syndrome; FAD, functional abdominal disorder.

| Characteristics | Group 1 (n = 71) | Group 2 (n = 71) | P |
|---|---|---|---|
| Age (years) | 34 ± 9 | 35 ± 11 | ns |
| Males (%) | 35% | 40% | ns |
| BMI (kg/m$^2$) | 22 ± 6 | 22 ± 7 | ns |
| IBS | 45% | 39% | ns |
| Functional abdominal bloating | 21% | 25% | ns |
| Functional abdominal pain | 15% | 14% | ns |
| Unspecified FAD | 19% | 22% | ns |

treated with metronidazole with respect to those treated by rifaximin. In fact, 5 drop-outs occurred in the metronidazole group (one for the inability to maintain appointments and 4 for the occurrence of side-effects), with respect to 1 in the rifaximin group (for the inability to maintain appointments).

### GBT Normalization Rate

The glucose breath test normalization rate was significantly higher in the rifaximin with respect to the metronidazole group in intention-to-treat analysis (63.4%, 45/71 versus 43.7%, 31/71; $p<0.05$; OR 1.50, 95% CI 1.14-4.38). No significant differences were found between groups in per protocol analysis.

### Side-Effects Profile

No abnormalities in the tested laboratory parameters were observed in the two groups at the control performed three days after the end of the treatment. Details on the incidence of adverse events during the study period are reported in Table II. The overall incidence of adverse events was 15.5% (22/142). The overall incidence of adverse events was significantly higher in the metronidazole with respect to the rifaximin group (22.5%, 16/71 versus 8.5%, 6/71; OR 1.59, 95% CI 1.15-8.61).

In the metronidazole group, 3 patients reported adverse events graduated as moderate and 4 patients abandoned the study because of the occurrence of severe adverse events. The 6 adverse experiences observed in the rifaximin group were all mild.

**Table II.** Adverse events during the study period in the two treatment groups (group 1=rifaximin; group 2=metronidazole).

| Adverse events | Group 1 (n=71) | Group 2 (n=71) |
|---|---|---|
| Skin rush | 0 | 1 |
| Taste disturbance | 0 | 3 |
| Bloating | 2 | 2 |
| Abdominal pain | 0 | 2 |
| Nausea/vomiting | 1 | 3 |
| Diarrhoea | 0 | 2 |
| Constipation | 3 | 1 |
| Weakness | 0 | 0 |
| Loss of appetite | 0 | 2 |
| Others | 0 | 0 |
| Overall | 6 | 16 |

## Discussion

Empirical courses of broad-spectrum antibiotics are widely used at present in the clinical setting for SIBO decontamination[1,2,10-12]. This occurs for several reasons. Few literature data are available on the bacterial population contaminating the small bowel and its antibiotic sensitivity patterns[1,2,9]. On the other hand, although ideally the choice of antimicrobial agent should reflect in vitro susceptibility testing, this usually is impractical in the case of SIBO because many different bacterial species, with different antibiotic sensitivities, typically coexist[1,2,9]. In addition, few well-conducted clinical trials has been performed in order to assess the most effective and safe antibiotic regimen for SIBO decontamination[1,2].

Metronidazole may be suitable for SIBO treatment since it is effective against Gram-negative and Gram-positive anaerobic bacteria such as *Bacteroides, Fusobacterium* and *Peptostreptococci*[13,14]. Castiglione et al[14]showed a good therapeutic efficacy of both metronidazole and ciprofloxacin in terms of breath test normalization rate in patients affected by Crohn's disease and evidence of SIBO.

However, all systemic antibiotics, also if endowed with a satisfactory efficacy profile, are associated to several side-effects such as diarrhoea, constipation, dizziness, weakness, skin rush and dyspepsia. The safety and tolerability of an antibiotic treatment are as important as its efficacy, especially in a disease as SIBO that is characterized by high recurrence rate and necessity of repeated antibiotic courses.

Non-absorbable antibiotics such as neomycin and rifaximin, both able to act against bacteria topically within the gut lumen, have been proposed for treatment of SIBO in order to minimize the potential side-effects of systemic antibiotics.

The neomycin treatment achieved the normalization of lactulose breath test in 20% of patients carrying SIBO with respect to 2% in the placebo group; no relevant side-effects and no drop-out were observed during the study[21]. The high binding (about 90%) of neomycin with faeces could explain the limited *in vivo* activity[21].

Rifaximin has a broad-spectrum antibiotic efficacy, especially against anaerobic intestinal bacteria, such as *Bacteroides*, *Lactobacilli* and *Clostridia*, bacteria frequently responsible for metabolic alterations observed in SIBO patients[15-17]. Its toxicity is very low since it is not

absorbed by the gut[16]. In a double-blind controlled trial Di Stefano et al. compared the efficacy of rifaximin (1200 mg/die) with respect to chlortetracycline in the short-term treatment of SIBO. GBT normalized in 70% of patients treated with rifaximin with respect to 27% of chlortetracycline group. No side-effect occurred, thus confirming that rifaximin is a safe drug for SIBO treatment[22]. In a recent study by our group, higher doses of rifaximin (1200 mg/day) led to a significantly higher therapeutic efficacy in terms of SIBO contamination with respect to doses of 600 and 800 mg per day. Moreover, at the tested doses, rifaximin was associated to uncommon, mild, transient side-effects and no drop-out was registered[18]. Another advantage of rifaximin concerns antibiotic resistance: it has been demonstrated that resistant strains rapidly disappear from the gut thus allowing cyclic administration of rifaximin[15,16].

In the present study we tested efficacy, safety and tolerability of rifaximin with respect to a systemic antibiotics such as metronidazole for SIBO decontamination. Rifaximin showed an higher decontamination rate compared to the absorbable antibiotic metronidazole, both with a significant gain in terms of tolerability.

In conclusion, the present data, both with available previous literature evidencies, suggest that rifaximin may represent a good option for SIBO decontamination in consideration of its good GBT normalization rate, null toxicity, high tolerability. Future studies should be addressed to the management of SIBO patients refractory to the current rifaximin decontamination scheme and to verify its efficacy in the re-treatment of patients with SIBO recurrence.

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