Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome: a preliminary study

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Abstract. – OBJECTIVES: Aims of the study were to assess the effects of rifaximin treatment on small intestinal bacterial overgrowth (SIBO) prevalence and gastrointestinal symptoms.

STUDY DESIGN: Fifty (50) irritable bowel syndrome (IBS) children were consecutively enrolled. All subjects underwent lactulose hydrogen/methane breath test (LBT) to assess SIBO before and one month after the treatment with rifaximin 600 mg daily for one week. All IBS patients filled out a Visual Analogic Scale (VAS) to assess and score gastrointestinal symptoms (abdominal pain, constipation, diarrhoea, bloating, flatulence) at baseline and one month after treatment.

RESULTS: The prevalence of abnormal LBT in patients with IBS was 66% (33/50). LBT normalization rate was 64% (21/33). Compliance was excellent, and no relevant side-effects were observed during treatment. VAS score was significantly higher in IBS patients with abnormal LBT than SIBO negatives, and strongly improved after successful treatment.

CONCLUSIONS: Rifaximin was effective and safe in SIBO treatment and IBS symptoms improvement in childhood. Double blind placebo-controlled interventional studies are warranted to verify the real impact of SIBO on gastrointestinal symptoms in children with IBS.

Key Words:
Small intestinal bacterial overgrowth, Irritable bowel syndrome, Rifaximin, Lactulose breath test, Children.

Introduction

Irritable bowel syndrome (IBS) is common in children presenting to tertiary care clinics in Western countries[1]. Pathophysiology of IBS is currently focused on the interplay of visceral hy-persensitivity, emotional factors and stress[2]. Visceral hypersensitivity may be related to microbial agents' effect, inflammation and altered gut motility[2,3].

Among microbial agents, mutual gut microflora's dysregulation and certain intestinal pathogens might contribute to the onset and/or maintenance of IBS[3-4]. Small intestinal bacterial overgrowth (SIBO) is a clinical syndrome characterized by an abnormally high bacterial population level in the small bowel, exceeding 10^5 organisms/milliter, whose symptoms are similar to those observed in IBS[5].

The culture of intestinal aspirate is the gold standard test for the diagnosis of SIBO at present. However, it is too invasive, expensive and difficult to be applied to the clinical setting, especially in the case of epidemiological studies in childhood[5,6]. Breath tests using as substrates the carbohydrates glucose and lactulose has been proposed as a surrogate of the culture of intestinal aspirate, since they are cheap, simple, reproducible and their accuracy is acceptable for clinical studies in children when compared to the gold standard[5-8]. The glucose breath test seems to be more specific but less sensitive than lactulose breath test (LBT) since this substrate is rapidly absorbed[9]. Furthermore, the lactulose palatability is greater than glucose one. For this reason, the LBT is commonly used in childhood for SIBO diagnosis[7].

Dysregulation of the gut microbiota and symptoms overlapping led to the hypothesis that SIBO may play a role in IBS in adults[10]. Recent interventional studies on adults confirmed that successful SIBO treatment significantly improves IBS symptoms[11,12].

Antibiotic therapy is the cornerstone in SIBO treatment. As long as SIBO may occur either by a mix of aerobic and anaerobic flora or by purely

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aerobic flora the most effective antibiotic regimens generally include broad spectrum antibiotics, that are associated with several side-effects[5-13].

Rifaximin is a semi-synthetic, rifamycin-based non-systemic antibiotic, with a low gastrointestinal absorption and a good antibacterial activity. Its antimicrobial action is based on its property to bind to the beta-subunit of bacterial DNA-dependent RNA polymerase inhibiting, thereby, the bacterial RNA synthesis[14]. It takes action toward Gram-positive and Gram-negative organisms, both aerobes and anaerobes[14]. So far rifaximin has become an important therapeutic agent in several organic and functional gastrointestinal diseases in adults, such as hepatic encephalopathy, small intestine bacterial overgrowth, inflammatory bowel disease and colonic diverticular disease. Rifaximin has the advantage of low microbial resistance, good tolerability and safety in all patient populations, including children[14].

Our previous research demonstrated a significant association between IBS and SIBO in childhood[15]. To date no literature data are available concerning the treatment of SIBO in children affected by IBS. Aim of the present study was to assess the effects of rifaximin treatment on SIBO prevalence and gastrointestinal symptoms in children affected by IBS.

Patients and Methods

Study Design

This prospective trial was conducted between March 2009 and May 2010 in consecutive outpatients affected by IBS, according to the pediatric Rome II criteria, from the Gastroenterology Pediatric Unit of *Gemelli* Hospital, Catholic University of the Sacred Heart, Rome.

Patients were sent by pediatric practitioners of Rome and surrounding area affiliated with our centre for further evaluation about chronic gastrointestinal symptoms.

They were enrolled after parents' informed consent, according to the rules of the Ethical Committee of our University.

All the patients underwent a lactulose breath test (LBT) and on the same day their gastrointestinal symptoms were evaluated with a validated VAS questionnaire. Subsequently only the patients with an abnormal LBT underwent antibiotic treatment with rifaximin. The patients repeated the LBT together with the VAS questionnaire one month after the end of treatment.

Methods

Symptoms were assessed by a validated visual analogic scale (VAS) questionnaire investigating abdominal pain/discomfort, constipation, diarrhoea, bloating, and flatulence. The score ranged from 0 to 10. The questionnaire was administered to the relatives of children younger than 10 years and directly to the patients if older[15].

Patients were classified into the three bowel habit subtypes according to the Rome II criteria: (1) diarrhoea-predominant (IBS-D); (2) constipation-predominant (IBS-C); (3) alternating bowel habit (IBS-A)[1]. In addition patients were defined as carrying post-infectious IBS (PI-IBS) according to their clinical history (IBS developing after an infectious illness characterized by 2 or more of the following: fever, vomiting, acute diarrhoea, and positive stool culture)[1].

Exclusion criteria were: use of antibiotics within the previous 2 months; history of diabetes, thyroid disease, intestinal surgery, connective tissue disease; positive stool culture; hypersensitivity to rifaximin.

All patients underwent a hydrogen (H_2)/methane (CH_4) LBT under standard conditions[5,6]. No patients should have received laxatives in the 30 days preceding the test. Subjects were asked to have a carbohydrate-restricted dinner on the day before the test and to be fasting for at least 12 hours, to minimize basal H_2 excretion. Physical exercise was not allowed for 30 minutes before and during the test. End-alveolar breath samples were collected immediately before lactulose ingestion. Then a dose of 10 g of lactulose in 20 ml solution was administered and samples were taken every 15 minutes for 4 hours using a two bag system. The two-bag system is a device consisting 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 samples were aspirated from the bag into a plastic syringe. Samples were analyzed immediately for H_2 and CH_4 using a model DP Quintron Gas Chromatograph (Quintron Instrument Company, Milwaukee, WI, USA). The results were expressed as parts per million (p.p.m.). A normal LBT was defined as the absence of an early rise in H_2 and/or CH_4 excretion of > 20 p.p.m. within the first 90 minutes[5,6].

In order to assess the gas production of both patients and controls the area under the H_2 time curve (AUC) was calculated using the trapezoidal rule[16].

Patients with evidence of LBT positivity underwent treatment by oral suspension of rifaximin (*Normix®*, Alfa-Wassermann; 200 mg t.i.d. for 7 days).

Side-effects were defined as the occurrence of: (1) abnormalities in the main laboratory parameters; (2) "adverse experiences", considered as clinical findings or patient complaints that were not present in the 24 hours immediately before the enrolment in the trial.

As concerning laboratory parameters, total blood cell count, liver and kidney function were evaluated in all patients at enrolment and 3 days after the end of the treatment.

Parents were asked to fulfill daily dairy cards in order: (1) to record and graduate (1 mild; 2 moderate; 3 severe) any patient's 'adverse experience' during the treatment period; (2) to record every time the patient did not assume the prescribed doses (in order to assess the compliance to rifaximin treatment). They were asked to return the daily cards at the post-treatment interview. Low compliance was defined as more than 20% of prescribed doses not assumed.

Statistical Analysis

The statistical analysis was performed using STATA 6.0 (Stata Corporation, University of Texas, College Station, TX, USA). Differences among groups were assessed by the following tests when appropriate: χ^2, Mann-Whitney, Fisher, ANOVA. Results were expressed as mean and standard error of the mean (SEM). A *p*-value of < 0.05 was considered to be statistically significant.

Results

A total of 50 IBS patients were enrolled. Demographics of the enrolled patients and prevalence of IBS subtypes are summarized in Table I.

SIBO prevalence as suggested by abnormal LBT was 66% (33/50). H_2 and CH_4 producers were 28 and 5 respectively. No significant difference was observed concerning either the prevalence of abnormal LBT or the gas pattern excretion (H_2 and/or CH_4) among the three bowel habit subtypes, and between PI-IBS and patients without (data not shown).

No drop-outs were observed. Compliance to rifaximin treatment was excellent. More than 95% of patients took the prescribed doses for the 7-days treatment.

No abnormalities in the tested laboratory parameters (total blood cell count, liver and kidney function) were registered. Adverse events were registered in 2 cases (constipation, both mild).

LBT normalized in 21 out of 33 IBS patients (64%). BMI did not affect the rifaximin efficacy.

Pre-treatment total AUC values observed in IBS children with abnormal LBT were significantly higher than patients with normal LBT (3718 ± 678 versus 1779 ± 317 ppm/min, $p < 0.05$) according to a significant difference in gas production in the small bowel (60-120 min time window: 1328 ± 269 versus 436 ± 93, $p < 0.05$) (Figure 1a). Total AUC significantly decreased in patients with post-treatment LBT normalization (3718 ± 678 versus 1898 ± 322 ppm/min; ANOVA, $p < 0.005$) according to a reduction of gas production in the small bowel (1328 ± 678 versus 487 ± 91 ppm/min, ANOVA, $p < 0.005$) (Figure 1b).

Patients with abnormal LBT showed a trend toward a worse VAS score with respect to IBS children without SIBO; a significant difference was observed for bloating and flatulence (Table II).

IBS patients with persistence of abnormal LBT after rifaximin treatment showed a trend toward a worse VAS score with respect to children with successful SIBO therapy, with a significant higher prevalence of both bloating and flatulence. Successfully treated patients had an improvement of VAS scores for abdominal pain, bloating and flatulence (ANOVA, $p < 0.005$) (Figure 2). No significant difference was observed in gastrointestinal symptoms in cases of persistently abnormal LBT before and after treatment (data not shown).

Table I.

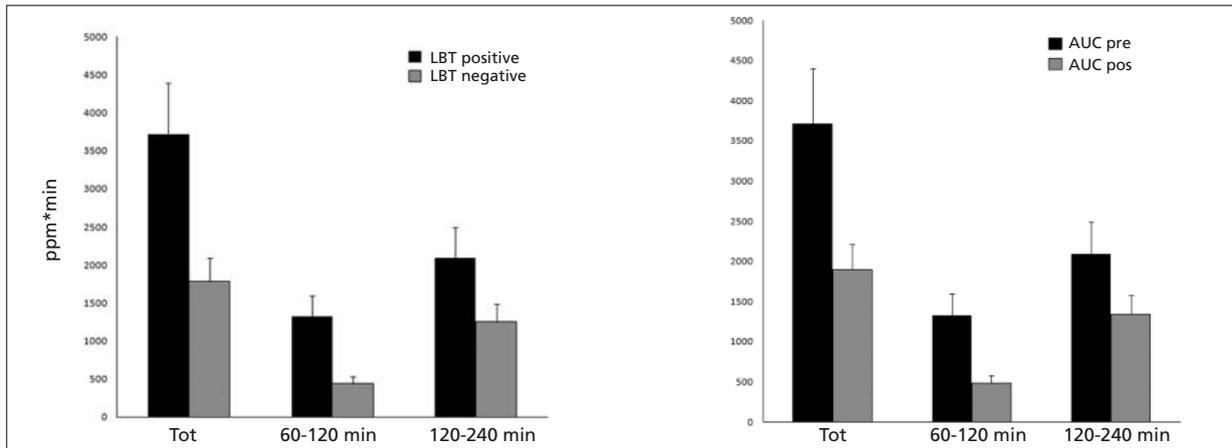|	Patients (n = 50)
Age (years)	9.9 ± 3.7
Range	3.2-15
Males	39.9% (20/50)
BMI (kg/m^2)	20 ± 0.1
IBS-D	38% (19/50)
IBS-C	24% (12/50)
IBS-A	38% (19/50)
PI-IBS	22% (11/50)

Figure 1. *A*, Pre-treatment AUC values in IBS children with and without abnormal LBT. *B*, AUC values in IBS children after rifaximin treatment.

Table II.

	IBS-SIBO pos	IBS-SIBO neg
Abdominal	6.2 ± 1.2	5.3 ± 1.1 cm
Constipation	6.3 ± 1.1	4.4 ± 1.0 cm
Diarrhoea	5.9 ± 1.2	4.4 ± 1.3 cm
Bloating	6.0 ± 1.0	3.5 ± 1.5* cm
Flatulence	5.4 ± 0.9	3.2 ± 1.2* cm

*$p < 0.05$.

Discussion

Data on adults showed that SIBO is highly prevalent in IBS patients and successful gut microflora remodulation improves gastrointestinal symptoms, suggesting that SIBO may play a role in this syndrome[10,11,17-20].

To date many features of SIBO management in children with IBS remain unknown. Concerning SIBO prevalence, a recent case-control study by
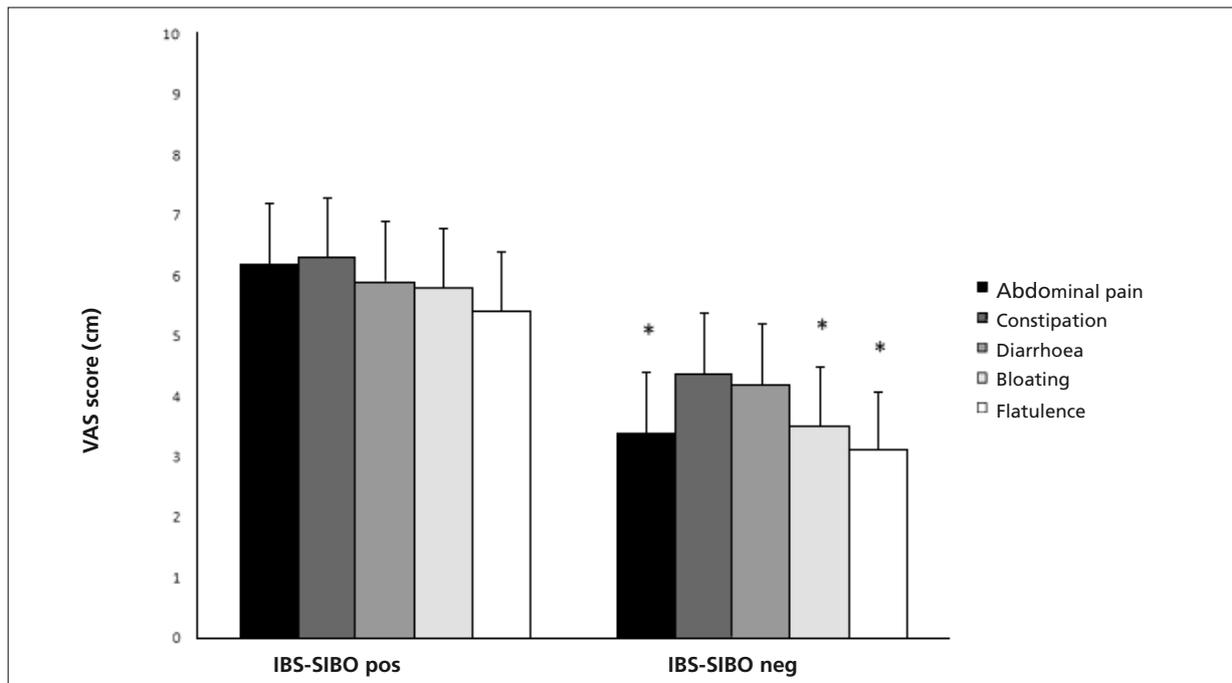

Figure 2. VAS score in IBS children after rifaximin treatment.

our group found an epidemiological association between SIBO and IBS in childhood as seen in adults[15]. However, no consistent literature data are available on SIBO treatment in IBS children.

At the best of our knowledge, this was the first interventional study assessing the effects of the antibiotic rifaximin in a specific population of SIBO-positive IBS children. It showed that 1 week-600 mg-rifaximin treatment was effective in achieving SIBO treatment since it was associated to LBT normalization in 64% of SIBO patients. A consensual improvement of gastrointestinal symptoms was observed only in successfully treated patients; no significant modification of VAS score occurred in IBS cases with persistence of abnormal LBT.

The present data suggest several considerations. The finding that successful SIBO therapy was associated to IBS improvement suggests that SIBO may play a pathophysiologic role in IBS in children as in adults, nonetheless a definitive demonstration of a causal link will be given by double blind placebo-controlled trials.

Concerning the potential mechanisms behind the suggested association, the excessive intestinal gas production in the small bowel, as a result of abnormal fermentation by SIBO-related unbalanced intestinal microflora, may affect the generation of IBS-like symptoms[21]. This speculation fits with our findings that the symptoms improvement correlated with a significant decrease of gut gases' production in successfully treated children. Furthermore, the strong SIBO-related quantitative and qualitative modification of gut microbiota may induce a dysfunction of the intestinal mucosa: mucosal barrier defects leading to increased gastrointestinal permeability, activation of host mucosal immunity, and low-grade intestinal inflammation. These changes may contribute to visceral hypersensitivity and gut motility dysfunction, that are the two most plausible mechanisms behind IBS physiopathology[21-23].

Rifaximin treatment at the dosage and duration used in our study was not only effective but also safe and well tolerated. Empirical courses of broad-spectrum absorbable antibiotics (amoxicillin-clavulanic acid, metronidazole, fluoroquinolones among others) are widely used for SIBO treatment in adults since few well-conducted trials are available testing the best antibiotic regimen[24]. However, they are commonly associated with several side-effects[5,25]. Safety and tolerability of an antibiotic treatment are crucial as its efficacy, especially in children and in the presence of

a benign disorder like SIBO, associated to an high recurrence rate requiring repeated antibiotic cycles. The non-absorbable antibiotic rifaximin, able to act against bacteria topically within the gut lumen, is candidate to become the treatment of choice for SIBO[14]. In fact, according to the literature on adult's studies, rifaximin showed both good efficacy and low side effects incidence in the treatment of SIBO[11,12,14,19,20,26,27]. The therapeutic schemes used in different studies were extremely variable concerning dosage (600-1600 mg/day) and duration (7-12 days). Different breath tests' normalization rates were reported, generally directly proportioned to the increase of dosage and duration, but all trials agreed for the high safety/tolerability of the rifaximin treatment[11,14,19,20,26,27].

So far scarce literature data are available concerning the use of rifaximin for SIBO therapy in childhood. A previous study by Collins et al[28] on chronic abdominal pain (CAP) children has showed no efficacy of rifaximin 550 mg t.i.d. for ten days in LBT normalization as well as for the symptoms improvement. Results' differences between this and our study may arise from: the different criteria used for the definition of LBT positivity[6]; the composition of the study population, including exclusively IBS subjects in our but not in the cited study where the subjects were also dyspeptic, functional abdominal pain (FAP); the different mean age of the subjects, older in the Collins' study thus justifying a different intestinal microbial composition and drugs' response although different from those of adults.

Based on the most common rifaximin schemes used in adults, it can be reasonably extrapolated that the dose of 600 mg/day for 7 days used with young children in this study was sufficient to achieve a comparable drug exposure in the intestinal tract. LBT normalization rate observed in the present study was similar to that reported for the 1-week 1200 mg scheme administered to SIBO-positive adults affected by IBS[26,27]. However, since a single-dosing regimen of rifaximin for a fixed duration was used in the present study, a dose-response effect was not be specifically studied. It could be interesting to test rifaximin at different dosages and treatment durations, in order to assess the best scheme in terms of efficacy, safety and tolerability for SIBO treatment in IBS in childhood. Muniyappa et al[29] studied the effect of rifaximin treatment at different dosages in children affected by inflammatory bowel disease. Their data showed that the use of higher dosages

in the range of 1200 mg/day gave significant improvement in abdominal pain, without affecting safety and tolerability[28]. On the other hand Collins et al[28] has shown no significant effect on SIBO prevalence and symptoms amelioration in children with CAP using a 1600 mg oral dosage of rifaximin but these differences can be explained by the different dishomogenous population notherless by the different LBT positivity criteria used in this latter study.

Major limits of this study were the abscence of a control group and placebo treatment useful in order to verify our preliminary results.

Conclusions

This was a preliminary open label trial showing that 1 week course of rifaximin 600 mg/day is either effective or safe and tolerable when used for SIBO treatment in IBS children. Furthermore, it found that successful SIBO therapy is associated to improvement of IBS symptoms as already found for adults. Randomized double-blind placebo-controlled interventional trials are necessary to definitively confirm the efficacy of rifaximin on SIBO-IBS symptoms in childhood.

Conflict of Interest

None to declare.

References

1) RASQUIN A, DI LORENZO C, FORBES D, GUIRALDES E, HYAMS JS, STAIANO A, WALKER LS. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006; 130: 1527-1537.

2) MAYER EA, COLLINS SM. Evolving pathophysiologic models of functional gastrointestinal disorders. Gastroenterology 2002; 122: 2032-2048.

3) MALINEN E, RINTTILA T, KAJANDER K, MÄTTÖ J, KASSINEN A, KROGIUS L, SAARELA M, KORPELA R, PALVA A. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. Am J Gastroenterol 2005; 100: 373-382.

4) GASBARRINI A, LAURITANO EC, GARCOVICH M, SPARANO L, GASBARRINI G. New insights into the pathophysiology of IBS: intestinal microflora, gas production and gut motility. Eur Rev Med Pharmacol Sci 2008; 12(Suppl 1): 111-117.

5) GASBARRINI A, LAURITANO EC, GABRIELLI M, SCARPELLINI E, LUPASCU A, OJETTI V, GASBARRINI G. Small intestinal bacterial overgrowth: diagnosis and treatment. Dig Dis 2007; 25: 237-240.

6) GASBARRINI A, CORAZZA GR, GASBARRINI G, MONTALTO M, DI STEFANO M, BASILISCO G, PARODI A, USAI-SATTA P, VERNIA P, ANANIA C, ASTEGIANO M, BARBARA G, BENINI L, BONAZZI P, CAPURSO G, CERTO M, COLECCHIA A, CUOCO L, DI SARIO A, FESTI D, LAURITANO C, MICELI E, NARDONE G, PERRI F, PORTINCASA P, RISICATO R, SORGE M, TURSI A; 1ST ROME H2-BREATH TESTING CONSENSUS CONFERENCE WORKING GROUP. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther 2009; 29(Suppl 1): 1-49.

7) MENDOZA E, CRISMATT C, MATOS R, SABAGH O, CAMPO M, CEPEDA J, VILLANUEVA D. Diagnosis of small intestinal bacterial overgrowth in children: the use of lactulose in the breath hydrogen test as a screening test. Biomedica 2007; 27: 325-332.

8) GASBARRINI G. Breath tests. Eur Rev Med Pharmacol Sci 2004; 8:1.

9) KHOSHINI R, DAI SC, LEZCANO S, PIMENTEL M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci 2008; 53: 1443-1454.

10) CARRARA M, DESIDERI S, AZZURRO M, BULIGHIN GM, DI PIRAMO D, LOMONACO L, ADAMO S. Small intestine bacterial overgrowth in patients with irritable bowel syndrome. Eur Rev Med Pharmacol Sci 2008; 12: 197-202.

11) PIMENTEL M, CHOW EJ, LIN HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2003; 98: 412-419.

12) PIMENTEL M. Review of rifaximin as treatment for SIBO and IBS. Expert Opin Investig Drugs 2009; 18: 349-358.

13) DI STEFANO M, MICELI E, MISSANELLI A, CORAZZA GR. Treatment of small intestine bacterial overgrowth. Eur Rev Med Pharmacol Sci 2005; 9: 217-222.

14) OJETTI V, LAURITANO EC, BARBARO F, MIGNECO A, AINORA ME, FONTANA L, GABRIELLI M, GASBARRINI A. Rifaximin pharmacology and clinical implications. Expert Opin Drug Metab Toxicol 2009; 5: 675-682.

15) SCARPELLINI E, GIORGIO V, GABRIELLI M, LAURITANO EC, PANTANELLA A, FUNDARÒ C, GASBARRINI A. Prevalence of small intestinal bacterial overgrowth in children with irritable bowel syndrome: a case-control study. J Pediatr 2009; 155: 416-420. Epub 2009 Jun 16.

16) CAPPELLERI JC, BUSHMAKIN AG, ZLATEVA G, SADOSKY A. Pain responder analysis: use of area under the curve to enhance interpretation of clinical trial results. Pain Pract 2009; 9: 348-353. Epub 2009 Jun 22.

17) Lupascu A, Gabrielli M, Lauritano EC, Scarpellini E, Santoliquido A, Cammarota G, Flore R, Tondi P, Pola P, Gasbarrini G, Gasbarrini A. Hydrogen glucose breath test to detect small intestinal bacterial overgrowth: a prevalence case-control study in irritable bowel syndrome. Aliment Pharmacol Ther 2005; 22: 1157-1160.

18) Carrara M, Desideri S, Azzurro M, Bulighin GM, Di Piramo D, Lomonaco L, Adamo S. Small intestine bacterial overgrowth in patients with irritable bowel syndrome. Eur Rev Med Pharmacol Sci 2008; 12: 197-202.

19) Majewski M, McCallum RW. Results of small intestinal bacterial overgrowth testing in irritable bowel syndrome patients: clinical profiles and effects of antibiotic trial. Adv Med Sci 2007; 52: 139-142.

20) Cuoco L, Salvagnini M. Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin. Minerva Gastroenterol Dietol 2006; 52: 89-95.

21) Lin HC, Pimentel M. Bacterial concept in irritable bowel syndrome. Rev Gastroenterol Disord 2005; 5(Suppl 3): 3-9.

22) Shulman RJ, Eakin MN, Czyzewski DI, Jarrett M, Ou CN. Increased gastrointestinal permeability and gut inflammation in children with functional abdominal pain and irritable bowel syndrome. J Pediatr 2008; 153: 646-650. Epub 2008 Jun 9.

23) Di Lorenzo C, Youssef NN, Sigurdsson L, Scharff L, Griffiths J, Wald A. Visceral hyperalgesia in children with functional abdominal pain. J Pediatr 2001; 139: 838-843.

24) Lauritano EC, Gabrielli M, Scarpellini E, Ojetti V, Roccarina D, Villita A, Fiore E, Flore R, Santoliquido A, Tondi P, Gasbarrini G, Ghirlanda G, Gasbarrini A. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. Eur Rev Med Pharmacol Sci 2009; 13: 111-116.

25) Quigley EM, Quera R. Small intestinal bacterial overgrowth: Roles of antibiotics, prebiotics and probiotics. Gastroenterology 2006; 130 (2 Suppl 1): 78-90.

26) Lauritano EC, Gabrielli M, Lupascu A, Santoliquido A, Nucera G, Scarpellini E, Vincenti F, Cammarota G, Flore R, Pola P, Gasbarrini G, Gasbarrini A. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther 2005; 22: 31-35.

27) Scarpellini E, Gabrielli M, Lauritano CE, Lupascu A, Merra G, Cammarota G, Cazzato IA, Gasbarrini G, Gasbarrini A. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther 2007; 25: 781-786.

28) Collins BS, Lin HC. Double-blind, placebo-controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. J Pediatr Gastroenterol Nutr 2011; 52: 382-386.

29) Muniyappa P, Gulati R, Mohr F, Hupertz V. Use and safety of rifaximin in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2009; 49: 400-404.