Small Intestinal Bacterial Overgrowth is Associated to Symptoms in Irritable Bowel Syndrome. Evidence from a Multicentre Study in Romania. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome

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Background and Aims. Small intestinal bacterial overgrowth (SIBO) is involved in the pathogenesis of irritable bowel syndrome (IBS). It has been suggested that by treating SIBO in IBS, symptoms may be improved. The aim of this study was to evaluate the prevalence of SIBO in patients with IBS compared with healthy volunteers (HV), to assess the effect of an intestinal antibiotic in eradicating SIBO and on the symptoms, in patients with IBS.

Methods. Design: a cross-sectional multicentre study with cohort comparison performed in 6 medical centers from Romania. 331 consecutive patients diagnosed with IBS according to Rome III criteria and 105 HV were screened for SIBO using glucose hydrogen breath test (GHBT). Positive patients received 7 days therapy with the antibiotic rifaximin 1200 mg/day and were retested 1 week after completing the treatment. The IBS symptoms were assessed before and after treatment. The group was controlled with 20 age and sex matched IBS patients who did not receive any antibiotic therapy for their condition (control patients).

Results. SIBO was found in 105 patients with IBS (31.7%) and in 7 HV (6.6%) (OR= 6.5, $p < 0.0001$). Patients with IBS have been classified according to Rome III criteria into 4 groups: IBS-constipation, IBS-diarrhea, IBS-mixed (alternation of constipation/and diarrhea) and IBS-unclassified. Diarrhea and mixed symptoms were found to be predictive for SIBO (OR= 2.5 for IBS-diarrhea and OR = 2.23 for mixed). Among patients with SIBO, 85.5% were found negative after treatment ($p = 0.0026$). SIBO patients showed an important relief of their symptoms, with complete improvement in 46.6% and partial in 31.4%.

Conclusions. This study is the first to estimate the prevalence of SIBO in IBS patients from Romania (31.7%). SIBO was present in nearly half of the IBS-D patients (45.7%). Rifaximin is effective in treating SIBO in IBS patients and controlled trials are warranted.

Key words: Irritable bowel syndrome (IBS), Small Intestinal bacterial overgrowth (SIBO), Glucose hydrogen breath tests (GHBT), Rifaximin.

Irritable bowel syndrome (IBS), one of the most common disorders diagnosed all over the world, has a complex pathogenesis [1]. The main factors involved in the occurrence of IBS are the disturbances of the brain-gut axis, abnormal gastro-intestinal motor function, visceral hypersensitivity, autonomic dysfunction, mucosal immune activation, psychosocial factors [2, 3]. Over the past years, there has been a considerable amount of studies suggesting that gut flora plays an important role in the occurrence of symptoms and possibly in the pathogenesis of IBS [3, 4].

The small intestinal bacterial overgrowth (SIBO) is a clinical condition caused by an increased number of abnormal types of bacteria in the small bowel which may result in nutrient malabsorption and intestinal inflammation [5]. A bacterial count greater than 10^5 colony-forming units/ml (CFU/ml) by small bowel culture is considered the cut-off for the assessment of SIBO [6].

SIBO is characterized by abdominal pain, diarrhea, bloating, symptoms that may be associated with excessive gas in the small intestine, due to the presence of a large number of hydrogen producing bacteria [7].

The hydrogen breath test (HBT) is currently the most important diagnostic tool for SIBO.

Taking into account that over the past decade, there has been an accumulation of data suggesting that gut flora has a role in IBS, [5, 8, 9] new IBS treatment concepts involving the use of antibiotics have been proposed [8, 10]. Rifaximin, a semi-synthetic, antibacterial, rifampicin derivative with virtually no systemic absorption and a favorable side-effect profile is such an antibiotic [10].

Prevalence of SIBO in IBS is differently reported in different parts of the world [3, 8], and in our area there are only a few single center studies [11].

Aim. The first aim of this study was to look for the prevalence of SIBO in patients with IBS, compared with healthy volunteers (HV) in Romania. The second aim was to assess the effect on symptoms in IBS by eradicating SIBO, using rifaximin.

MATERIAL AND METHODS

STUDY DESIGN

A prospective multicentre study performed in 6 medical centers from Romania was designed. Two groups were investigated: a group of IBS patients and a group of healthy volunteers.

PATIENTS

Inclusion criteria: Patients with IBS diagnosed according to Rome III criteria [12] and in which any organic or biochemical diagnosis was ruled out according to a comprehensive work-out including colonoscopy, testing for malabsorption, hyper-thyroidism and any other confounding conditions.

Exclusion criteria: any organic disorder with similar symptoms or comorbidities: intestinal tumors, inflammatory bowel disease, coeliac disease, diabetes, cirrhosis; on therapy able to change gastrointestinal motility. Other reason for exclusion from the study was the intake of antibiotics 4 weeks before the breath test, or if the patients have undergone colonoscopy or barium study less than one month before the breath test.

All subjects included in the study, after signing an informed consent, answered to a questionnaire containing information on baseline demographics, severity (using a Likert scale) and type of IBS symptoms, previous medical and surgical history.

Controls: Two groups of controls were created: an age and sex matched group of healthy volunteers and an age and sex matched group of IBS patients who were not included in the inter-vention.

Protocol. All IBS patients referred to the participating centers (all tertiary centers) during 6 months have been submitted to the SIBO invest-tigation using glucose hydrogen breath test (GHBT). The patients presented with diarrhea (IBS-D): n = 105, constipation (IBS-C): n =101, unclassified symptoms (IBS-U): n = 90 and alternation constipation/diarrhea (IBS-M): n = 35 (Fig. 1).

SIBO testing. The fermentable substrate is represented by 50 g of glucose dissolved in 250 ml water. Patients are fasting in the morning, after one day diet free of fermentable sugars. After a baseline sample of expired air, patients drink the substrate and start collecting breath samples at 15-min interval up to 120 min. The test is considered positive if there is a clear H2 peak, exceeding 20 ppm before the 120 minutes have passed [13] (Fig. 2).

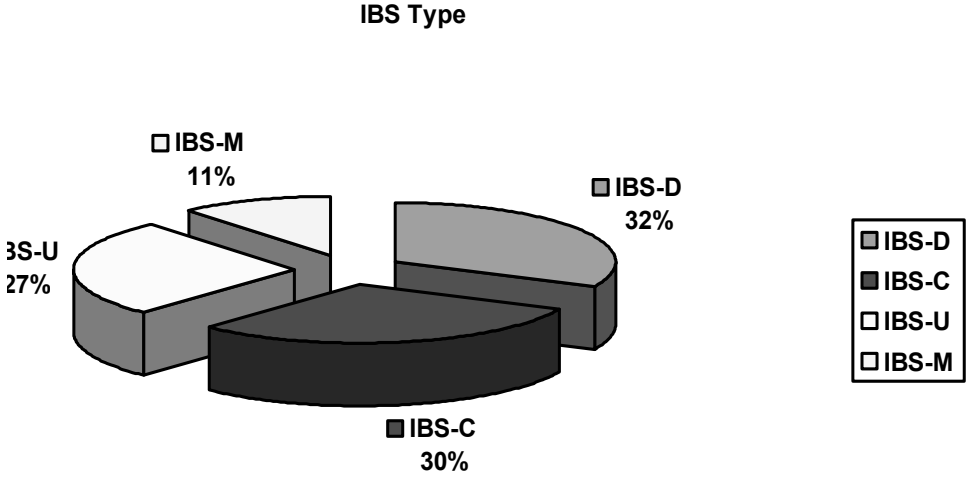

Figure 1. IBS groups repartition according to symptoms.

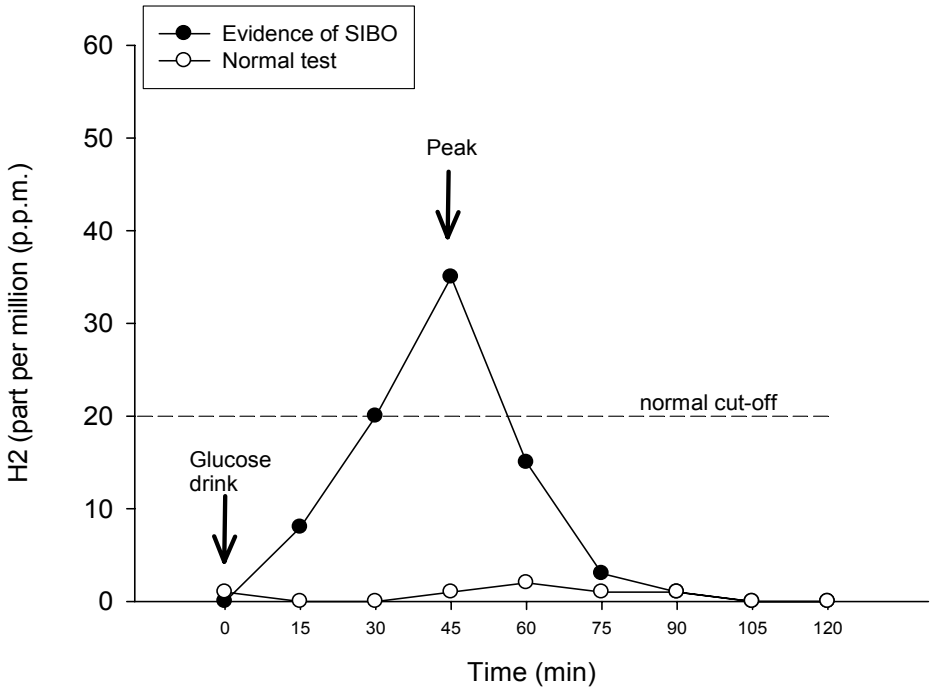

Figure 2. Example of a positive GHBT (adapted from Portincasa P.).

Patients were not allowed to chew gum, smoke and perform any kind of physical exercise 2 hours before and during the test (hyperventilation can cause changes in breath H2 content). Just before the test, subjects were asked to brush their teeth and disinfect their moth with chlorhexidine. Vitamins and laxatives were forbidden at least in the 24 hr before the GHBT.

Subjects were excluded from the protocol if the fasting level of H2 was greater than 10 ppm, a number of 10 patients have been excluded because of this.

Intervention. Patients who were positive for SIBO have been treated for 7 days with rifaximin 1200 mg/day. Patient's symptoms were assessed before and after the end of the treatment using a 5 points Likert scale for pain, stool ,bloating (no improvement 1, little improvement 2, partial improvement 3, almost complete 4, complete improvement 5).

One week after the end of treatment, patients were retested for the presence of SIBO. Patients with a negative test stopped treatment; those with a persistent positive test have been retreated with rifaximin for one more week and retested 1 week after the end of treatment. Patients with persistent positive test for SIBO have been reevaluated clinically in order to determine if they have taken correctly the treatment, if they have respected the diet (at least one day of low fiber) before the test or if there is another underlying disease (Fig. 3).

A control group of 105 healthy volunteers were tested as well for the presence of SIBO and positive subjects received rifaximin treatment.

The group was controlled with 20 age and sex matched IBS control patients (CP) that received conventional therapy for the same interval of 7 days and have been evaluated for symptoms after this interval using Likert scale.

Response to rifaximin was considered positive if the GHBT became negative and IBS symptoms improved from baseline.

ETHICAL ISSUES

The study was approved by the institutional review board of coordinating institution.

STATISTICS

Categorical and continuous data were analyzed using a commercially available statistical package.

RESULTS

CHARACTERISTICS OF THE GROUPS

The study included a group of 331 IBS patients, 208 females (62.8%) and 123 males (37.1%), a group of 105 healthy volunteers (HV), 70 females (66.6%) and 35 males (33.3%) and 20 age and sex matched IBS patients (Table I).

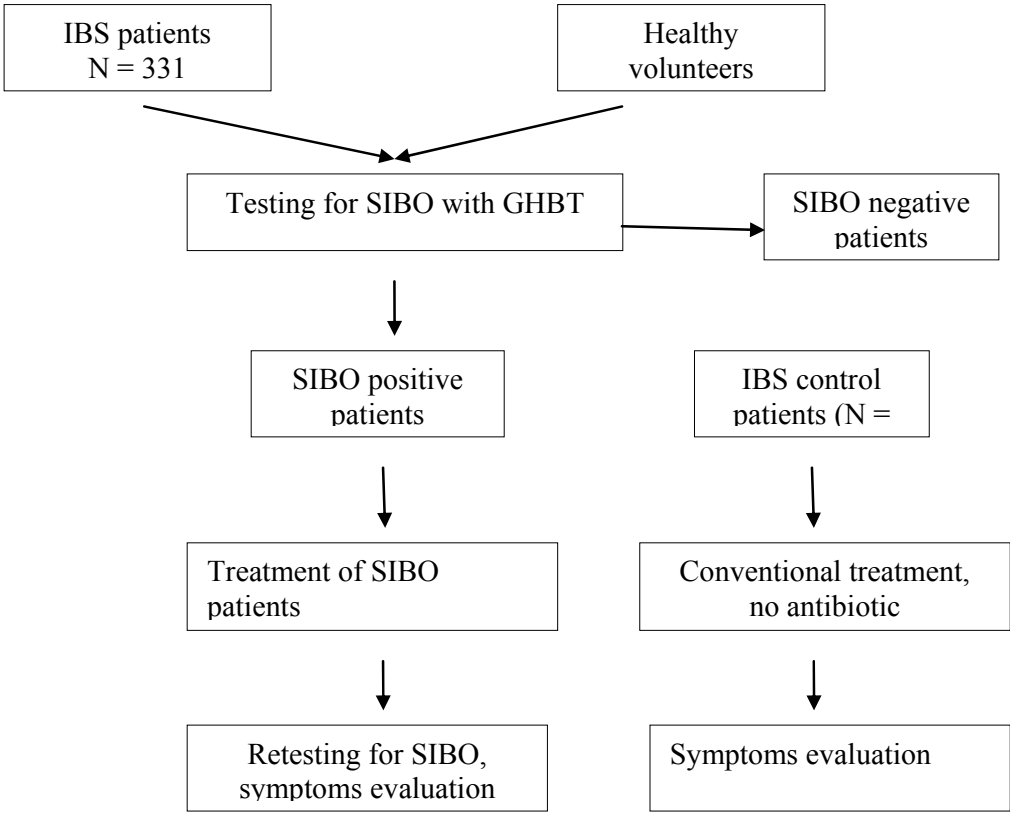

Figure 3. Flow chart of the protocol.

Table I
Gender and age repartition of patients

	IBS patients	Healthy volunteers	Control patients	P value
Gender repartition	208 females 123 males	70 females 35 males	12 females 8 males	P = 0.83
Mean age	54,5 ± 12.3	59 ± 13	53 ± 12.7	P = 0.64

After testing for SIBO using the GHBT, 105 out of 331 initial IBS patients were positive (31.7%) and 7 patients out of 105 HC (6.6%) [105/331 (31.7%) *vs.* 7/105 (6.6%); OR = 6.5, P < 0.0001]. Demographic, clinical and laboratory parameters of the study subjects have been compared. There was no statistical difference between patients with IBS and HC regarding age and gender (p = ns).

Out of 105 positive patients, 48 were part of the IBS-D group (45.7%), 21 of the IBS-C (20%) group, 19 IBS-M (18.1%) and the last 17 part of the IBS-U (16.2%) (Fig. 4).

Among patients with SIBO, 29 positive patients did not come to be re-checked and were considered dropped out.

SIBO was more frequent in the IBS-D patients then non- IBS-D [48/105 *vs*. 57/226 (OR = 2.5, p = 0.0002)] and among the IBS-M group then non IBS-M [19/35 *vs*. 88/296 (OR = 2.23, p = 0.02)].

Constipation and unspecified symptoms are not predictive for SIBO (OR =0.45) between IBS-C and non IBS-C patients, OR = 0.48 and between IBS-U and non IBS-U patients.

A number of 7 patients out of 105 HV, presented with positive GHBT (6.6 %).

All positive patients for SIBO have been treated with rifaximin 1200 mg (400 mg × 3/day) for 7 days. One week after the end of treatment 76 out of 105 SIBO patients and 5 patients out of the HV group have been retested to reassess the efficacy of the treatment (negative GHBT and relief of symptoms). Only 11 patients (14.4%) were still positive for SIBO from the IBS group and none from HV group. All positive patients showed a negative GHBT after another 7 days cure of antibiotic (Fig. 5).

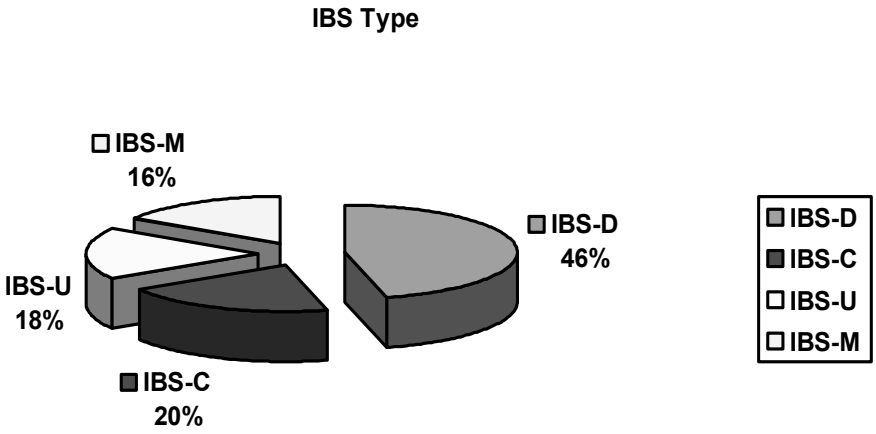

Figure 4. IBS group patients with SIBO.

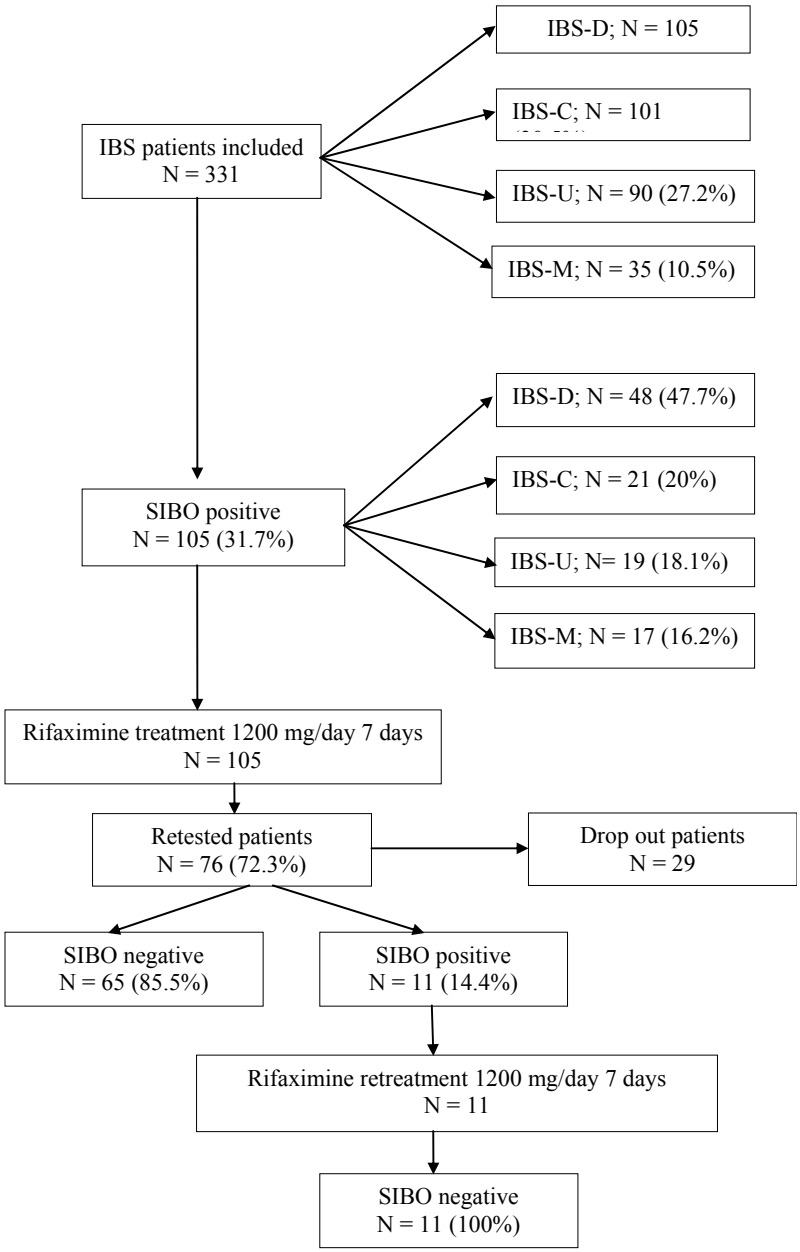

Figure 5. Flow-chart of the study.

EVOLUTION OF SYMPTOMS

A questionnaire regarding symptoms improvement has been given to each patient from the SIBO group after the end of treatment. After completing the questionnaire, a number of 49 patients (46.6%) showed a complete response to treatment, 27 patients from the IBS-D group (56.2%), 9 IBS-M (52.9%), 7 IBS-U (36.9%) and 6 patients part of the IBS-C group (28.5%). There were 33 patients (31.4%) that showed a partial response to treatment when evaluated using Likert scale, 17 part of the IBS-D group (35.4%), showing a diminution of the stool number, an increase in consistence, 6 part of the IBS-M group (35.3%), 5 IBS-U group (26.3%) and 5 IBS-C group (23.8%). A number of 23 patients showed no improvement after the end of treatment (22%).

The IBS control group (20 age and sex matched IBS patients) has been treated for 7 days using conventional treatment (antispasmodic, gas absorber, laxatives etc.) with symptoms evaluated using Likert scale, before and after the end of treatment. A number of 7 patients showed a partial improvement (35%) and 1 complete improvement (5%), all the rest showed no improvement in their symptoms (60%) (Tabel II). There is a significant difference between the number of patients with complete improvement in the rifaximin group and the number of patients with conventional therapy ($p = 0.0005$) and the number of patients not responding to treatment ($p = 0.0005$).

Table II
Repartition of patients according to symptoms improvement

Patients	Gender	Age	Complete response	P value	Partial response	P value	No response	P value
IBS-SIBO (105)	60 females 45 males	54.1 ± 12	49 patients (46.6%)	P = 0.0005	33 patients (31.4%)	P = 0.7	23 patients (22%)	P = 0.0005
IBS control (20)	12 females 8 males	53 ± 12.7	1 patient (5%)		7 patients (35%)		12 patients (60%)	

DISCUSSIONS

The focus regarding the pathogenesis of IBS has been traditionally put on alterations of gastrointestinal motility and visceral hypersensitivity. More recent studies have considered the role of inflammation, alterations in fecal flora, and bacterial overgrowth. The etiopathogenesis of IBS has not yet been satisfactorily clarified [14]. Symptoms of SIBO and IBS overlap to a large degree [15, 16].

We have evaluated the presence of SIBO in 331 patients diagnosed with IBS according to Rome III criteria and 105 HV from 6 Romanian medical tertiary centers. In our study, 31.7% of the IBS patients have been diagnosed with SIBO and 6.6% out of the HV group. In the recent literature there are a lot of controversial studies on the etiopathogenic role of SIBO in IBS. Using LHBT, Pimentel *et al*. [17] found abnormal breath test results in 93/111 (84%) patients with IBS. Since that SIBO has been proposed as an etiologic factor in IBS. A study performed on 65 IBS patients and 102 controls found a positive glucose breathe test in 31% and 4% respectively [9]. Almost the same results (35% positive GHBT) were obtained in the study of Reddymasu [18]. A recent study performed on 50 IBS children using LHBT showed a 66% abnormal test results (33 patients/50) [19].

Studies that found a small prevalence of SIBO among IBS patients exist as well. In a study performed in India that included 225 consecutive patients with IBS according to Rome II criteria and 100 controls, SIBO was found in 25 of 225 (11.1%) and 1of 100 (1%) [20].

Because breath tests indirectly measure bacteria and are associated with relatively low sensitivity and specificity, many consider direct bacterial assessment of intestinal aspirate cultures a better method of detecting SIBO [5, 21]. Clinical studies employing direct sampling of jejunal aspirates detected SIBO in 4% to 12% of patients with IBS, a lower prevalence compared with results of breath testing [22]. Differences in the geographical origin of the studied population, criteria for diagnosis of IBS, methods for diagnosis of SIBO and methods of breath tests, might explain the variation in prevalence of SIBO in different studies.

In our study we have found a large proportion of patients with SIBO from the IBS-D group (48 patients out of 105, 45.7%), data that coincide with the literature. In a study performed on 204 IBS patients that met ROME II criteria for IBS (170F & 34M; mean age 46.4; range 18–88) and underwent GBT, 93 (46%) had a positive GBT. 68 (73%) of these 93 IBS were IBS-D, 12 (13%) were IBS-C and 13 (14%) IBS with alternating bowel pattern

[23]. There are currently no recommendations guiding clinicians on whether they should routinely test for SIBO in their IBS patients. However, the body of evidence suggests that, particularly for IBS patients with diarrhea, the role of SIBO remains potentially important [23].

Regarding the treatment of SIBO, this study shows that a 7-days treatment with rifaximin determined a negative GHBT in 85.5% of treated patients and a significant improvement in symptoms, data sustained by other experiences reported in the most recent literature [24]. A study was performed on 97 patients fulfilling the Rome II criteria diagnosed with SIBO using lactulose. Patients with positive test received rifaximin 1200 mg/d for 7 d; 3 wk after the end of treatment, the LHBT was repeated. Based on the LHBT results, SIBO was present in about 56% of IBS patients. 1-wk treatment with rifaximin turned the LHBT to negative in about 50% of patients and significantly reduced the symptoms [25]. Another recent study comprised 106 of 150 patients with IBS (71%) who were LBT positive and treated with rifaximin. Assessment at week 4 following commencement of therapy showed that rifaximin provided significant improvement of the following IBS-associated symptoms: bloating, flatulence, diarrhea, pain [26]. In the study performed by Scapellini *et al*. [19], there was a significant percentage (64%) normalization of LHBT and symptom improvement after rifaximin treatment. The advantage to use antibiotics is their rapid effect and the persistence of the effect after the end of therapy. The disadvantage is that these drugs could potentially change the gut flora developing resistant organisms [27]. Even if there is accumulating evidence pointing towards the benefit of a short course of treatment with rifaximin in the global improvement of patients with IBS, larger, well-designed trials are necessary to better elucidate the role of rifaximin in the treatment of this disorder.

CONCLUSIONS

A significant percentage (31.7%) of patients with IBS were found positive for SIBO, the great majority (47.7%) being part of the IBS-D group, as compared with the HV group (6.6% positive for SIBO), suggesting the association of SIBO in the pathogenesis of IBS.

Treatment with rifaximin has normalized the GHBT in 85.5% of patients. Eradicating SIBO improved IBS symptoms with complete improvement in 46.6% of patients and 31.4% partial improvement.

Acknoknowledgement: This study was supported by the company Alfa-Wasserman who supplied the consumable materials for the study, but did not intervene in collecting, analyzing and publishing the data.

Scopul studiului. *Suprapopularea bacteriană intestinală (SIBO) este implicată în patogeneza sindromului de intestin iritabil (IBS). S-a vehiculat ideea conform căreia tratând SIBO, simptomele IBS se pot ameliora. Scopul acestui studiu a fost de a evalua prevalența SIBO la pacienții cu IBS comparativ cu voluntarii sănătoşi (HV) şi de a evalua efectul unui antibiotic în eradicarea SIBO şi asupra simptomelor, la pacienții cu IBS.*

Metoda. *Design: Studiu multicentric cu grup de cohortă, efectuat în 6 centre medicale din România. 331 de pacineți diagnosticați cu IBS conform criteriilor Roma III şi 105 HV au fost evaluate pentru prezența SIBO utilizând testul respirator cu glucoză (GHBT). Pacienții cu test pozitiv au fost tratați timp de 7 zile cu un antibiotic – rifaximina 1200 mg/zi şi retestați la o săptămână de la încheierea tratamentului. Simptomele de IBS au fost evaluate la începutul şi la sfârşitul tratamentului. A existat un grup de control format din 20 de pacienți IBS comparabili din punct de vedere al vârstei şi sexului cu celelalte grupuri de pacienți, care nu au urmat tratament antibiotic (grup de control).*

Rezultate. *SIBO a fost diagnosticat la 105 patienți cu IBS (31,7%) şi la 7 HV (6,6%) (OR = 6,5, p < 0,0001). Pacienții cu IBS au fost divizați comform criteriilor Roma III în 4 grupuri: IBS – constipație, IBS – diaree, IBS – mixt (alternanța costipație/diaree) şi IBS – neclasificat. Diareea şi simptomele mixte au fost predictive positive pentru diagnosticul SIBO (OR = 2,5 pentru IBS – diaree şi OR = 2,23 mixt). Din rândul pacienților diagnosticați cu SIBO, după tratament 85,5% au fost negativi (p = 0,0026). Pacienții cu SIBO au prezentat o ameliorare semnificativă a simptomelor, cu ameliorare totală la 46,6% şi parțială la 31,4%.*

Concluzii. *Acest studiu este primul care estimează prevalența SIBO în rândul pacienților cu IBS din România (31,7%). SIBO a fost diagnosticat aproape la jumătate dintre pacienții cu IBS-D (45,7%). Rifaximina este eficientă în tratamentul SIBO la pacienții cu IBS dar acesta este un aspect de trebuie încă studiat.*

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