

Small Intestinal Bacterial Overgrowth in Rosacea: Clinical Effectiveness of Its Eradication

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Background & Aims: To better understand the role of small intestinal bacterial overgrowth (SIBO) in rosacea, we aimed to assess the presence of SIBO in patients with rosacea and the clinical effectiveness of its eradication. **Methods:** We enrolled 113 consecutive rosacea ambulatory patients (31 M/82 F; mean age, 52 ± 15 years) and 60 healthy controls who were sex- and age-matched. Patients and controls underwent lactulose and glucose breath tests (BTs) to assess the presence of SIBO. Patients positive for SIBO were randomized to receive rifaximin therapy (1200 mg/day for 10 days) or placebo. A group of patients with negative BTs were also treated with rifaximin. Eradication was assessed 1 month after the end of therapy. Two dermatologists, unblinded on therapy, evaluated rosacea patients before and after treatment on the basis of an objective scale. **Results:** The prevalence of SIBO was higher in patients than controls (52/113 vs 3/60, $P < .001$). After eradication, cutaneous lesions cleared in 20 of 28 and greatly improved in 6 of 28 patients, whereas patients treated with placebo remained unchanged (18/20) or worsened (2/20) ($P < .001$). Placebo patients were subsequently switched to rifaximin therapy, and SIBO was eradicated in 17 of 20 cases. Fifteen had a complete resolution of rosacea. After antibiotic therapy, 13 of 16 patients with negative BTs for SIBO remained unchanged, and this result differed from SIBO-positive cases ($P < .001$). **Conclusions:** This study demonstrated that rosacea patients have a significantly higher SIBO prevalence than controls. Moreover, eradication of SIBO induced an almost complete regression of their cutaneous lesions and maintained this excellent result for at least 9 months.

Rosacea is characterized by a chronic inflammation of the central facial area and the eyes that causes social discomfort and greatly reduces the quality of life. It is a quite common disease, ranking fifth among the most common dermatologic diagnoses.^{1,2}

In fact, rosacea is a multiphase disease that includes 4 phases^{2,3}: flushing, erythrosis, papulopustules, and phymata. Whereas flushing and erythrosis are common to most patients, the papulopustular and phyma phases occur, often on an erythrotic background, only in a minority of patients, suggesting that diverse etiopathogenetic factors, specific for each phase, are at work.^{3,4}

Although etiopathogenesis is far from being clear, gastrointestinal disorders are often reported by the patients. Dyspepsia,

meteorism, bloating, flatulence, abdominal pain, and alteration of intestinal habits have been described,^{5,6} and many cases associating rosacea with ulcerative colitis,⁷ Crohn's disease,⁸ celiac disease,⁹ hypochlorhydria, *Helicobacter pylori* (Hp) gastritis,^{5,10} alteration of intestinal mucosa, and lipase deficiency^{5,6} can be found in the literature. Cutaneous lesions, furthermore, are well-known to improve with the administration of systemic drugs as chemically different as metronidazole, tetracyclines, macrolides, and even chloramphenicol and neomycin,² but no sound explanation of their mechanism of action has ever been produced. A recent report of the improvement of rosacea with the reduction of gut transit time¹¹ drew attention to the possibility that intestinal bacteria and their products might contribute to the development of cutaneous lesions, as it was assumed for Hp infection,^{5,10} providing as well a possible explanation of the beneficial effect of the systemic administration of antibiotics.

Small intestinal bacterial overgrowth (SIBO) is defined as an unexpected microbial concentration ($>10^5$ colony-forming units/mL) in the jejunal aspirate culture and is caused by numerous predisposing disorders, including the reduction of gastric acid secretion, intestinal motor and anatomic abnormalities, and immune function impairment.^{12–14} SIBO shows a wide clinical spectrum, varying from a completely asymptomatic status to symptoms similar to those of irritable bowel syndrome and also to a severe malabsorption syndrome characterized by steatorrhea, multiple nutritional deficiencies, and weight loss.^{14–19} Moreover, extraintestinal disorders are not infrequent in SIBO patients, and associations with fibromyalgia²⁰ and nonalcoholic steatohepatitis (NASH)^{21,22} have also been described.

The gold standard test for the diagnosis of SIBO is the jejunal aspirate culture, but this is a too complex and invasive technique to be used routinely in clinical practice. Lactulose and glucose H₂/CH₄ breath tests (LH-BT, G-BT) represent, instead, noninvasive, cheap, and validated diagnostic tools.^{17–19,23}

Aims of this study were to assess the prevalence of SIBO in patients with rosacea and the effects of its eradication on rosacea lesions.

Abbreviations used in this paper: BT, breath test; GA, global assessment; G-BT, glucose breath test; GSS, global symptomatic score; Hp, *Helicobacter pylori*; LH-BT, lactulose breath test; NASH, nonalcoholic steatohepatitis; OCTT, orocecal transit time; SIBO, small intestinal bacterial overgrowth; UBT, urea breath test.

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Table 1. Baseline Assessment of Rosacea Lesions According to SIBO and Hp Infection and the Clinical Effectiveness of SIBO Eradication in Clearing Each Type of Lesion

Patients with	Total	SIBO +	Hp +	SIBO eradicated	With lesions cleared	SIBO noneradicated	With lesions cleared
Flushing	2	2	1	2	2	—	—
Flushing + erythrosis	27	0	16	—	—	—	—
Papules	8	6	0	5	4	1	0
Flushing + papules	34	11	2	9	9	2	0
Flushing + erythrosis + papules	8	7	2	6	3	1	0
Papules + pustules	7	4	0	4	4	—	—
Flushing + papules + pustules	16	13	2	11	8	2	0
Flushing + erythrosis + papules + pustules	11	9	1	8	5	1	0
Total	113	52	24	45	35	7	0

Methods

Patients and Controls

This is a prospective study involving 113 consecutive rosacea patients (82 women, 31 men; mean age, 52 ± 15 years) recruited in an academic dermatologic department and 60 healthy, sex- and age-matched controls (40 women, 20 men; mean age, 49 ± 11 years). Two patients had flushing, 27 had erythrosis, and 84 had papulopustules. Two patients with papulopustular rosacea exhibited also phymata. Most patients associated 2 or more phases (Table 1).

Dermatologic Assessment

Two independent dermatologists (F.D., A.P.) evaluated the clinical features of patients and the outcome after treatment. The kappa agreement between them was calculated. The overall assessment of inflammatory lesion severity was expressed as a 7-point static score, ranging from 0 (clear) to 6 (severe), according to an investigator's global assessment (GA) (Table 2).²⁴ Recovery was defined as a complete resolution of inflammatory lesions (score, 0), whereas minimal residual lesions (score, 1) were considered as a significant improvement. Moreover, cutaneous lesions were documented with a picture taken before and after 1 month of therapy in each patient.

Diagnostic Procedures

All patients completed an interview questionnaire, taking into account 11 variables (diarrhea, upper and lower ab-

dominal pain/discomfort, bloating, abdominal tenderness, nausea, emesis, dysuria, tenesmus, fever, general illness), scored from 0 (no symptoms) to 3 (severe). A global symptomatic score (GSS),²⁵ calculated as the sum of all symptom scores, was assigned to each patient (maximum score, 33). It was aimed at assessing the effect of antibiotic therapy for SIBO on the overall severity of the various symptoms. Controls were selected on the basis of clinical history among healthy subjects without gastrointestinal symptoms, and so they did not complete the GSS questionnaire, because they were supposedly free from the symptoms listed above.

All patients had their baseline biochemical and stool analyses performed, and Hp status was determined by means of 75-mg urea breath test (UBT).²⁶

As for LH-BT and G-BT, all subjects were studied after an overnight fasting, having been instructed during the 24 hours preceding the examination to avoid foods likely to generate hydrogen. The preparation diet was based on nonseasoned boiled rice, meat cooked on a hot plate or boiled fish, and no sparkling water. Breath testing started between 8:30 and 9:30 AM after thorough mouth washing with 40 mL of 1% chlorhexidine solution. Smoking and physical exercise were not allowed for 1 hour before and throughout the test.

In LH-BT, the H₂/CH₄ breath concentration, in parts per million, was measured by gas chromatography (Quintron MicroLizer model DP plus; Milwaukee, WI) in basal conditions and every 15 minutes for at least 4 hours after the administra-

Table 2. Investigator's Global Assessment of Rosacea: 7-Point Static Score

Numeric score	Definition	Description
0	Clear	Almost no rosacea (ie, no papules and/or pustules); no or residual erythema; mild to moderate degree of telangiectasia may be present.
1	Minimal	Rare papules and/or pustules; residual to mild erythema; mild to moderate degree of telangiectasia may be present.
2	Mild	Few papules and/or pustules; mild erythema; mild to moderate degree of telangiectasia may be present.
3	Mild to moderate	Distinct number of papules and/or pustules; mild to moderate erythema; mild to moderate degree of telangiectasia may be present.
4	Moderate	Pronounced number of papules and/or pustules; moderate erythema; mild to moderate degree of telangiectasia may be present.
5	Moderate to severe	Many papules and/or pustules, occasionally with large inflamed lesions; moderate erythema; moderate degree of telangiectasia may be present.
6	Severe	Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate to severe erythema; moderate to severe degree of telangiectasia may be present.

tion of an oral loading dose of lactulose (10 g in 120 mL of water). Alveolar air samples were collected in a 750-mL bag equipped with a "T" with a nozzle and connected to a bag for the collection of air coming from the respiratory dead space.

The test was considered positive for SIBO in the presence of 2 distinct peaks of H_2/CH_4 excretion (>10 ppm compared with the basal value).^{19,27} The SIBO eradication was defined as the disappearance of the double peak profile. Orocecal transit time (OCTT) is defined as the time the lactulose bolus reaches the cecum. We have considered as OCTT measurement the beginning of the first peak rising branch in SIBO-negative subjects and the beginning of the second peak rising branch in SIBO-positive ones.^{27,28}

G-BT was performed 1 week after LH-BT, following the same preparation, H_2/CH_4 breath concentration by gas chromatography in basal conditions and every 15 minutes for at least 2 hours after the administration of an oral loading dose of glucose (50 g in 250 mL of water). A single H_2/CH_4 peak higher than 10 ppm was considered positive for SIBO. The SIBO eradication was defined as the disappearance of the H_2/CH_4 peak.²⁹

Therapeutic Interventions

Patients with Hp infection were treated with rabeprazole 20 mg twice a day, clarithromycin 500 mg twice a day, and metronidazole 500 mg twice a day for 7 days, and 1 month after the end of therapy they underwent a second UBT and dermatologic visit.

Patients positive for SIBO were randomized to receive rifaximin 400 mg every 8 hours ($n = 32$) or placebo ($n = 20$) for 10 days, following a computer-generated sequence with a ratio 3:2. They underwent a second LH-BT or G-BT 1 month after stopping therapy to assess the eradication of SIBO. At the same time, all patients completed a second symptom questionnaire and underwent an additional dermatologic visit. Patients treated with placebo were subsequently switched to rifaximin therapy. Moreover, SIBO-negative patients, who did not obtain any significant improvement after topical therapy, received the same scheme of therapy with rifaximin and underwent an additional dermatologic visit 1 month after the end of therapy to rule out a possible influence of antibiotic treatment on colonic microflora.

Patients presenting both SIBO and Hp were treated first for SIBO and then for Hp infection at 1-month interval from each other.

The study was approved by our local Ethical Committee, and each subject gave his/her consent to take part in it.

Statistical Analysis

Data were statistically analyzed by SPSS software, version 12 for Windows (SPSS Inc, Chicago, IL). The quantitative variables were expressed as median and interquartile range, and the Mann-Whitney test was used to compare data between patients and controls. Chi-square test was performed to evaluate SIBO prevalence in all studied groups.

Results

Baseline blood and stool analyses were normal in all patients and controls.

A significantly increased prevalence of SIBO was found in patients with rosacea compared with controls (52/113 vs 3/60,

respectively; $P < .001$). In 40 of 52, both LH-BT and G-BT were positive, whereas G-BT only was positive in the remaining 12 cases.

Seven patients presented both SIBO and Hp infection. When stratified for cutaneous lesions, 42 of 98 patients with flush and/or erythrosis were SIBO-positive versus 10 who had papulopustules ($P = .149$), whereas flushing patients (24/98) were more often Hp-positive than the remaining patients (0/15) ($P = .069$). Patients with papulopustules had SIBO significantly more often (50/84) than those without papulopustules (2/29) ($P < .001$). Conversely, the latter were more often Hp-positive (17/29) than those with papulopustules (7/84) ($P < .001$) (Table 1).

Eradication of SIBO was achieved in 28 of 32 patients (87.5%) in the rifaximin-treated arm, and this was associated with a significant decrease of the median GSS score (6, 25th-75th percentiles 4-8 vs 2, 25th-75th percentiles 0-4.75, respectively; $P = .020$). In 20 (71.4%) of the 28 patients with eradicated SIBO, cutaneous lesions cleared (GA score, 0). In 6 (21.4%), papules and papulopustules were markedly reduced in number (GA score, 1). Only 2 patients did not present any improvement. The interobserver agreement between the 2 dermatologists was very high ($\kappa = 0.97$). Four patients did not respond to rifaximin therapy, and their clinical features improved only partially (GA score, 4).

Pictures of some rosacea patients before and after SIBO eradication are displayed in Figure 1 and confirm the complete resolution of skin lesions.

Among patients treated with placebo, 18 of 20 (90%) had their lesions unchanged, and 2 (10%) were even worse. Therefore, the dermatologic assessment after treatment was highly different between the rifaximin- and placebo-treated groups ($P < .001$) (Figure 2).

The 20 placebo-treated patients were subsequently switched to rifaximin, and 17 of them proved to have SIBO eradicated. After 1 month of active therapy, cutaneous lesions cleared in 15 patients with eradicated SIBO (GA score, 0) and a relevant improvement in the 2 remaining cases (GA score, 1), whereas only a partial improvement (GA score, 3) was achieved in patients with noneradicated SIBO. The interobserver agreement between the 2 dermatologists was again excellent ($\kappa = .98$).

Altogether, the eradication of SIBO was obtained in 45 of 52 (86.5%) of SIBO-positive rosacea patients treated with rifaximin. Complete recovery of cutaneous lesions was achieved in 35 (78%) and relevant improvement in 8 patients (17.7%) (Table 1). The median GA scores before and after treatment were 5 (25th-75th percentiles, 4-5) and 0 (25th-75th percentiles, 0-0), respectively ($P < .001$).

A group of 16 patients with BTs negative for SIBO (5 with erythrosis, 11 with papulopustules) who did not obtain any significant improvement after topical therapy were nonetheless treated with rifaximin therapy. A partial improvement of lesions (GA score, 2) was observed only in 3 patients, whereas the remaining ones were unchanged. The dermatologic assessment after treatment with rifaximin was, therefore, highly different between SIBO-positive and SIBO-negative groups ($P < .001$) (Figure 3).

All SIBO-eradicated patients have been followed up for at least 9 months. Cutaneous lesions were kept in remission without any other therapy in all of them but two, in whom papulopustules recurred after several months when they proved to be



Figure 1. Cutaneous lesions of some patients with SIBO before and after treatment with rifaximin. All patients had complete resolution of cutaneous lesions after normalization of BTs.

G-BT positive again. After SIBO eradication, rosacea lesions cleared.

OCTT proved significantly more delayed in patients with SIBO (150 minutes; 25th-75th percentiles, 142.5-165) than in controls (105 minutes; 25th-75th percentiles, 90-135) ($P < .001$).

Last, in 7 patients with both SIBO and Hp infection, cutaneous lesions fully cleared after rifaximin administration before commencing the anti-Hp therapy.

Discussion

This study demonstrates that rosacea patients have a significantly higher SIBO prevalence than controls, and, more

importantly, that the eradication of SIBO induces an almost complete regression of the cutaneous lesions in rosacea patients and maintains this excellent result for at least 9 months. In fact, in 78% of our patients, skin lesions fully cleared and in 17.7% improved greatly 1 month after interrupting rifaximin therapy. Moreover, all rosacea patients who remained unchanged with placebo treatment and were switched to the antibiotic arm showed the same rapid dramatic improvement of their lesions. Last, rosacea was kept in remission in 96% patients followed up for at least 9 months, and this remarkable finding contrasts with the frequent relapse observed with the traditional therapies.^{2,3} The 2 patients in whom papulopustules relapsed proved again to be SIBO-positive, and the eradication of their intestinal

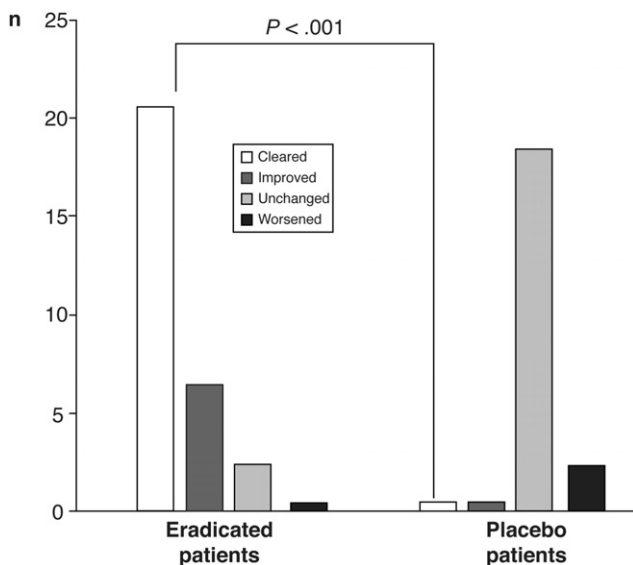


Figure 2. Clinical outcome in SIBO-positive patients treated with rifaximin (eradicated patients) or placebo.

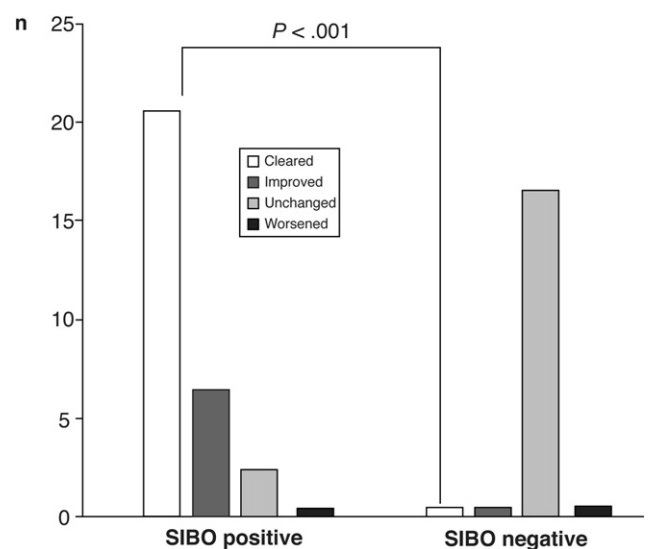


Figure 3. Clinical outcome in SIBO-positive and SIBO-negative patients treated with rifaximin.

contamination achieved a further remission of skin lesions, thus confirming the etiologic role of SIBO in at least 50% of rosacea patients.

Our findings strongly support the pathogenetic role of intestinal bacteria in the development of cutaneous lesions of rosacea, especially those with papulopustules. In addition, they provide an explanation of the well-known and so far obscure activity of several antibiotics on rosacea lesions. How SIBO might lead to skin lesions is unclear. However, other associations between SIBO and extraintestinal diseases, such as fibromyalgia²⁰ and NASH,^{21,22} have an unclear pathogenesis. The hypersensitivity in fibromyalgia has been related to a high endotoxemia or bacterial translocation that might occur in SIBO and the hepatic damage of NASH to an increased endotoxemia and tumor necrosis factor- α levels. Likewise, we speculate that an increased intestinal permeability caused by SIBO develops also in SIBO-positive rosacea patients,³⁰ favoring the translocation into the blood of bacterial products and proinflammatory cytokines, such as tumor necrosis factor- α , which in turn might be held responsible for cutaneous inflammation.

Systemic antibiotics such as tetracyclines or metronidazole, however beneficial in rosacea, do not guarantee a prolonged period of remission.³¹ They have been shown to be effective in eradicating SIBO as well,³² possibly explaining their activity in rosacea. However, because of their systemic activity, they could be beneficial on skin lesions through several other mechanisms, for example, their activity on the cutaneous microflora. Rifaximin, instead, is poorly absorbable and well-known to be effective in controlling SIBO,³³ as is confirmed by the improvement of the intestinal symptoms in our patients with eradicated SIBO. Therefore, it is reasonable that its efficacy in clearing rosacea lesions is somehow due to its activity on the intestinal bacteria, with small if any interference on cutaneous microflora. Moreover, rifaximin therapy failed to improve skin lesions in 16 SIBO-negative patients, ruling out its possible activity on the colonic microflora and confirming that the small intestine contamination is the target of treatment.

The delayed OCTT in our rosacea patients with SIBO could explain the higher prevalence of this condition in them compared with controls. Intestinal hypomotility is, in fact, a well-recognized functional disorder that might favor the bacterial overgrowth.¹²⁻¹⁴ Only 12 of 52 SIBO-positive patients were taking benzodiazepines, which could theoretically explain the delayed OCTT. The most frequent medications in both SIBO-positive and SIBO-negative patients were antihypertensive drugs (angiotension-converting enzyme inhibitors or Ca antagonists), but there was no difference between the 2 groups.

For a better understanding of the possible interactions between SIBO and other possible etiologic factors, we studied also the role of Hp infection, which remains controversial. As previously suggested,⁵ Hp seems to play a relevant role only in flushing/erythrotic patients, possibly through the release of angiogenic and vasomotor agents (nitric oxide, gastrin, tumor necrosis factor- α). Conversely, the higher and significant prevalence of SIBO in papulopustular rosacea suggests that different etiologic agents might be involved in each subtype of disease, overlapping in some cases.

Six of our 113 patients reported a previous Hp infection that had been successfully treated, with only a temporary remission of skin lesions. All these patients had a positive hydrogen BT and experienced a complete remission of cutaneous lesions

after SIBO eradication. Their previous anti-Hp therapy containing metronidazole might have decreased the intestinal bacterial concentration, determining at the same time the short-lasting improvement of their cutaneous lesions, erroneously attributed to Hp eradication. In fact, all of the 7 patients with both SIBO and Hp infection had their skin lesions cleared after SIBO eradication, despite the persistence of the Hp infection. Alternatively, one might speculate that Hp eradication might have improved the erythrotic component, whereas SIBO eradication would have completed the rosacea clearance.

This study has 2 limitations. First, we used diagnostic tools for SIBO detection that are associated with lower rates of accuracy than jejunal culture.^{23,34} However, the jejunal aspirate culture is an invasive procedure and is difficult to perform in routine clinical practice. Conversely, LH-BT and G-BT are non-invasive and inexpensive techniques, which have been shown to assess the bacterial contamination in the small intestine with sufficient accuracy. In addition, LH-BT evaluates also the bowel transit time, although indirectly.²⁸

Second, our study was not blind. However, the assessment of rosacea severity was based on an objective score,²⁴ and 2 independent dermatologists evaluated patients and scored the severity of lesions before and after therapy, with a very high interobserver agreement ($\kappa = 0.97$). This is mostly because the lesions disappeared almost completely after treatment in virtually all patients, preventing any difficulty in scoring. It is unlikely, therefore, that the lack of blindness affected our results in a relevant way.

In conclusion, this study demonstrated a significantly higher prevalence of SIBO in patients with papulopustular rosacea than in controls. The clearance of cutaneous lesions in almost all rosacea patients after its eradication strongly suggests that SIBO plays a significant pathogenetic role in rosacea, especially in its papulopustular component. Although the underlying mechanisms linking SIBO to the cutaneous lesions of rosacea need to be elucidated, we believe that our findings represent paramount progress in the clinical management of those frustrated patients.

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