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

ANDREA PARODI,* STEFANIA PAOLINO,‡ ALFREDO GRECO,* FRANCESCO DRAGO,‡ CARLO MANSI,* ALFREDO REBORA,‡ AURORA PARODI,‡ and VINCENTO SAVARINO*

*Department of Internal Medicine, Gastroenterology Unit, and ‡Department of Endocrine and Medical Sciences, Dermatology Unit, University of Genoa, Genoa, Italy

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 phases3-5: 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 deficiency5,6 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,5 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.
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 abdominal 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 administration of 13C urea and 13C alanine, as described elsewhere.25

### 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

<table>
<thead>
<tr>
<th>Patients with Total</th>
<th>SIBO +</th>
<th>Hp +</th>
<th>SIBO eradicated With lesions cleared</th>
<th>SIBO noneradicated With lesions cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Flushing + erythrosis</td>
<td>27</td>
<td>0</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Papules</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Flushing + papules</td>
<td>34</td>
<td>11</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Flushing + erythrosis + papules</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Papules + pustules</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Flushing + papules + pustules</td>
<td>16</td>
<td>13</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>52</td>
<td>24</td>
<td>45</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Numeric score</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
<td>Almost no rosacea (ie, no papules and/or pustules); no or residual erythema; mild to moderate degree of telangiectasia may be present.</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
<td>Rare papules and/or pustules; residual to mild erythema; mild to moderate degree of telangiectasia may be present.</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Few papules and/or pustules; mild erythema; mild to moderate degree of telangiectasia may be present.</td>
</tr>
<tr>
<td>3</td>
<td>Mild to moderate</td>
<td>Distinct number of papules and/or pustules; mild to moderate degree of telangiectasia may be present.</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>Pronounced number of papules and/or pustules; moderate erythema; mild to moderate degree of telangiectasia may be present.</td>
</tr>
<tr>
<td>5</td>
<td>Moderate to severe</td>
<td>Many papules and/or pustules, occasionally with large inflamed lesions; moderate erythema; moderate degree of telangiectasia may be present.</td>
</tr>
<tr>
<td>6</td>
<td>Severe</td>
<td>Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; severe erythema; moderate to severe degree of telangiectasia may be present.</td>
</tr>
</tbody>
</table>
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 H₂/CH₄ excretion (>10 ppm compared with the basal value). 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.

G-BT was performed 1 week after LH-BT, following the same preparation, H₂/CH₄ 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 H₂/CH₄ peak higher than 10 ppm was considered positive for SIBO. The SIBO eradication was defined as the disappearance of the H₂/CH₄ peak.

**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 rifaximin therapy. A partial improvement of lesions (GA score, 3) was achieved in 6 (21.4%) 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.

**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
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.

The 2 patients in whom papulopustules relapsed proved again to be SIBO-positive, and the eradication of their intestinal
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 fibromyalgia, 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 or bacterial translocation that might occur in SIBO as well, possibly explaining their activity in controlling SIBO, as is confirmed by the improvement of skin lesions in our patients with eradicated SIBO. Therefore, it is reasonable that its efficacy in clearing 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.

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.

References


Address requests for reprints to: Vincenzo Savarino, MD, Professor of Gastroenterology, University of Genoa, Department of Internal Medicine, Viale Benedetto XV, 6, Genova 16132, Italy. e-mail: vsavarin@unige.it; fax: 3.90E+11.
Prof Aurora Parodi and Prof Vincenzo Savarino are supported by the Italian Ministry of University.