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# Prevalence of Small Intestine Bacterial Overgrowth Diagnosed by Quantitative Culture of Intestinal Aspirate in Celiac Disease

**Alberto Rubio-Tapia, MD**[*], **Susan H. Barton, MD**[*], **Jon E. Rosenblatt, MD**[†], and **Joseph A. Murray, MD**[*]

[*]*Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN.*

[†]*Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN.*

## Abstract

**Background and Aim:** A recent study using lactulose hydrogen-breath testing suggests that small intestine bacterial overgrowth (SIBO) is a common cause of nonresponsive celiac disease (CD). The prevalence of SIBO in CD diagnosed by quantitative culture of intestinal aspirate is unknown. The aim of this study is to evaluate the prevalence and significance of SIBO in CD based on the results of quantitative culture of intestinal aspirate.

**Methods:** We studied patients with CD in whom culture of intestinal aspirate was evaluated for the presence of anaerobes and aerobes. Bacterial overgrowth was diagnosed if culture demonstrated > $10^5$ colony forming units/mL. The causes of nonresponsive CD were investigated.

**Results:** We included 149 biopsy-confirmed CD patients. The intestinal aspirate was collected in 79 (53%) patients with nonresponsive CD, 47 (32%) as initial work-up for malabsorption, and in 23 (15%) asymptomatic treated CD. SIBO was diagnosed in 14 (9.3%). Nine (11%) with nonresponsive CD, 5 (11%) at initial work-up for malabsorption, and 0 in asymptomatic treated CD. Patients with a positive culture had evidence of worse malabsorption. A coexistent disorder was found in 67% of patients with both nonresponsive CD and bacterial overgrowth.

**Conclusions:** The prevalence of SIBO diagnosed by quantitative culture of intestinal aspirate was 9.3% in patients with CD. Patients with symptomatic treated or untreated CD were affected. SIBO may coexist with other disorders associated with nonresponsive CD.

### Keywords

small intestine bacterial overgrowth; celiac disease; gluten-free diet

Celiac disease (CD), also known as gluten-sensitive enteropathy or celiac sprue, is defined as a permanent intolerance to ingested gluten (the storage protein components of wheat, barley, and rye) that damages the small intestine characteristically inducing crypt hyperplasia and villous atrophy, which resolves with removal of gluten from the diet.[1]

Nonresponsive CD can be described in terms of the clinical scenario of a lack of initial response to a prescribed gluten-free diet (GFD), or the recurrence of gastrointestinal (GI) symptoms despite maintenance of GFD in a patient who responded initially to GFD.[2] The prevalence of nonresponsive CD is unknown, but chronic diarrhea can be present in as many as 17% of the

Reprints: Joseph A. Murray, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (e-mail: murray.joseph@mayo.edu)..

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patients with CD after gluten withdrawal.[3] Gluten contamination is the leading reason for nonresponsive CD, but other causes have been identified including small intestine bacterial overgrowth (SIBO).[2-5]

SIBO is a condition caused by an abnormal number of bacteria in the small intestine.[6] The stomach and proximal small bowel normally contain relatively small numbers of bacteria in adults. The intestine, however, contains 300 to 500 different species of bacteria.[7] The concentration of gut flora increases from $10^{0-4}$ colony forming units/mL (CFU/mL) in the duodenum and the jejunum, to $10^{0-5}$ in the proximal ileum, $10^{5-8}$ in the terminal ileum, and $10^{10-12}$ CFU/mL in the cecum.[8,9] Symptoms related to bacterial overgrowth are diarrhea, bloating, weight loss, anemia, and malabsorption. SIBO is especially common among the elderly, patients with previous GI surgery (Billroth II or small intestine anastomosis), decreased gastric acid secretion, intestinal diverticulosis, and motor disorders.[10] To date, there is no general agreement as to which test should be preferred for the diagnosis of SIBO, but culture of intestinal aspirates is usually considered the standard for detecting bacterial overgrowth.[6,7,11-13] SIBO has been suggested to be associated with a large number of different GI conditions, such as cirrhosis, chronic pancreatitis, and irritable bowel syndrome.[14-16] However, in most cases the diagnosis of SIBO has been established by the use of hydrogen-breath tests ($H_2$-BT), as a noninvasive alternative to quantitative culture of small intestinal aspirate. Data obtained from breath testing need a cautious interpretation, because the results vary significantly even with minor modifications to the used technique, and the definition of normal and abnormal varies in the literature.[17,18] This test-to-test and center-to-center variability may explain the contradictory results obtained after comparing breath testing with other diagnostic test (specifically with quantitative culture of intestinal aspirate) or even among researchers using the same breath test for assessment of the frequency of SIBO in a particular disease.[19]

The lactulose $H_2$-BT is an indirect test for SIBO, based on the fact that lactulose passes unabsorbed through the small bowel into the colon. The original definition of a positive lactulose test was an early hydrogen peak ( > 20 ppm), due to the presence of small intestine bacteria, occurring at least 15 minutes before the later prolonged peak secondary to colonic fermentation (double-peak criterion).[18,20] However, in a study that examined and compared the diagnostic value of the lactulose $H_2$-BT and of a scintigraphic orocecal transit study, with that of culture of intestinal aspirate, showed a poor sensitivity (16.7%) and specificity (70%) of the lactulose $H_2$-BT for SIBO, when the definition of an abnormal test was based on the occurrence of the double-peak criterion. The combination with scintigraphy increased specificity to 100%, but sensitivity was only 38.9%.[21] In another study, using the double-peak criterion, 20% of healthy volunteers showed a positive lactulose $H_2$-BT.[19] Other studies demonstrated the poor reliability of lactulose $H_2$-BT for SIBO diagnosis as compared with culture of intestinal aspirate.[6,13]

A recent study using lactulose $H_2$-BT as diagnostic tool suggested that SIBO was present in 66% of patients with CD and persistent GI symptoms after gluten withdrawal.[4]

The prevalence of SIBO in patients with CD based on the result of culture of proximal small intestinal aspirate is not known.

The aim of this study is to evaluate the prevalence and clinical significance of SIBO in patients with CD based on the result of culture of proximal small intestinal aspirate.

# MATERIALS AND METHODS

## Patients

We included biopsy-confirmed CD patients. All enrolled cases underwent quantitative culture of intestinal aspirate that was evaluated for the presence of anaerobic and aerobic microorganisms. Culture of intestinal aspirate was taken (1) as part of the initial work-up for malabsorption, (2) because of nonresponsive CD despite a GFD of at least 6 months duration, and (3) in asymptomatic treated CD. The study was approved by the Institutional Review Board of the Mayo Foundation.

## Diagnostic Criteria

CD was supported by positive serology and histologic findings. Nonresponsive CD was considered when patients with CD presented persistent or relapsing symptoms despite a GFD.[2] Good adherence to a GFD was defined when no source of gluten contamination was identified by the dietitian interview associated to negative celiac serology and absence of intestinal atrophy in the biopsy. SIBO was diagnosed if culture demonstrated > $10^5$ CFU/mL.[6-9,18,22] Mildly elevated count of bacteria in the culture of small intestine aspirate was defined as the presence of ≥ $10^3$ CFU/mL but ≤ $10^5$ CFU/mL. Culture of intestinal aspirate with < $10^3$ CFU/mL was considered negative.

## Clinical and Laboratory Data

Demographic data, presence/absence of GI symptoms (diarrhea, abdominal pain), body mass index, and the following blood tests: hemoglobin, leukocyte, platelet concentration, β-carotene, albumin, zinc, cooper, cobalamin, folate, immunoglobulin (Ig) A, IgG, IgM, IgA/IgG antigliadin antibodies, IgA antitissue transglutaminase antibodies, and IgA antiendomysial antibodies, were recorded at the time of SIBO diagnosis.

## Quantitative Culture Technique

Small bowel aspirate for bacteriologic culture was obtained endoscopically. A disinfected gastroscope and a sterile catheter were used for the collection of aspirate in all patients. Briefly, after the endoscope had been introduced into the GI tract, no suction was applied until the desire area of aspiration in the distal part of the duodenum was reached. When the tip of the endoscope reached the distal duodenum (in a region distal to the ampulla of Vater), an aspirating sterile catheter 240-cm long and 2.3-mm width (Hobbs Medical, Inc, CT) was introduced through the working channel of the endoscope and advanced to the distal part of the duodenum. Suction was applied with a sterile 30-mL syringe until at least 2 mL of the intestinal fluid were obtained. The intestinal aspirate was transferred immediately to aerobic and anaerobic ("vacuum containing $CO_2$") sterile tubes, and sent to the Microbiology Laboratory.

## Microbiologic Analysis

Collected intestinal fluid was processed and incubated immediately after it was obtained. For quantitative determination of bacteria, the following prepared culture media (BBL, Becton Dickinson and Company) were used for anaerobic culture: CDC anaerobe blood agar, CDC anaerobe laked blood agar with kanamycin and vancomycin, and phenylethyl alcohol agar with 5% sheep blood. The media used for aerobic culture were trypticase soy agar with 5% sheep blood and Levine eosin methylene blue agar. An aliquot (0.01 mL) of the specimen was inoculated into each media using a calibrated loop. Anaerobic plates were examined after 48 hours at 37°C in an anaerobic atmosphere. Aerobic plates were examined after 24 hours of incubation at 37°C with 5% to 10% $CO_2$. After incubation, different colony types were counted. The agar plates were reviewed for bacterial growth every day for 48 hours for aerobic bacteria

and for 7 days for anaerobic bacteria. For anaerobic bacteria, only colonic-type bacteria (eg, *Bacteroides fragilis*) were considered true positive to decrease the possibility of a false positive owing to contamination with oropharyngeal flora during endoscope insertion. The microbiologic result was based on the quantitative analysis of the number of CFU/mL of intestinal fluid as follows: < 10 colonies = $< 10^3$ CFU/mL; 10 to 1000 colonies = $10^3$ to $10^5$ CFU/mL; and > 1000 colonies $\geq 10^5$ CFU/mL.

### Histologic Analysis

Duodenal mucosal biopsy specimens taken during the same endoscopy when the small intestinal aspirate was collected were stained with hematoxylin-eosin and evaluated for the presence or absence and grade of intestinal atrophy as well as count of intraepithelial lymphocytes (IELs) according to the modified Marsh's classification.[23] The number of IELs was calculated by counting the number of IELs per 100 epithelial cells.

### Statistics

Clinical and microbiology data are expressed as mean ± SD. The Mann-Whitney *U* test, $\chi^2$ test, or Fisher exact test were used when necessary as significance tests for comparison between culture positive and negative groups. A *P* value of < 0.05 was considered statistically significant.

## RESULTS

### Patients

We included 149 patients who had biopsy confirmed CD (115 female, 34 male; mean age 55 ± 16 y, range 22 to 94 y).

The intestinal aspirate was collected from 79 patients with nonresponsive CD, in 47 patients as part of the initial work-up for malabsorption wherein CD was diagnosed, and in 23 asymptomatic treated CD patients who undergone upper GI endoscopy for CD follow-up.

Culture of the intestinal aspirate demonstrated > $10^5$ microorganisms/mL in 14 (9.3%), ≥ $10^3$ CFU/mL but ≤ $10^5$ CFU/mL in 17 (11.4%), and < $10^3$ CFU/mL in 118 (79.1%) patients.

SIBO was present in 9 (11%) patients with nonresponsive CD, 5 (11%) at initial work-up, and 0 in asymptomatic treated CD (Fig. 1). The clinical characteristics of all patients with SIBO are shown in Table 1.

Mildly elevated counts of bacteria were present in 10 (13%) patients with nonresponsive CD, 5 (11%) at initial work-up, and 2 (9%) in asymptomatic treated CD.

### Coexistent Disorders in Patients With Nonresponsive CD and SIBO

Six (67%) of 9 patients with SIBO and nonresponsive CD had a coexistent disorder (2 refractory sprue, 3 microscopic colitis, and 1 enteropathy-associated T-cell lymphoma). No patients with SIBO had diabetes mellitus, were on prescription proton-pump inhibitor for more than 1 month (although we cannot exclude over-the-counter use), or had previous GI surgery (including bowel resection). No patient with recent use of antibiotics (within 1 mo of the time of intestinal aspirate), known motility disorders, or common variable immunodeficiency was included.

### Nonresponsive CD Patients With Good Adherence to a GFD

Twenty-two (28%) of the 79 patients with nonresponsive CD had good adherence to GFD. The mean age was 52.2 ± 16 years and the female:male ratio was 3:1. Fifteen (68%) demonstrated a negative intestinal fluid culture. Three (14%) cases showed SIBO, 1 with coexistent

microscopic colitis, and 1 with intestinal lymphoma (cases 12 and 14 in Table 1). Four patients (18%) had mildly elevated counts of bacterial.

### Clinical Features in Patients With SIBO

Patients with SIBO were older, and had lower level of hemoglobin, β-carotene, and albumin than those without SIBO. A higher amount of fat in stool (g/24 h collection) was found in patients with SIBO Table 2.

No differences where found in microminerals (zinc and copper), iron, folate, or cobalamin levels between celiacs with or without SIBO.

### Celiac Serology

No differences were found in levels of IgG antigliadin (25.6 ± 35 vs. 27.7 ± 38 Units, $P = 0.82$) and IgA antigliadin (70.1 ± 98 vs. 56.7 ± 86.3 Units, $P = 0.78$) between patients with SIBO and those without SIBO. Serum levels of antitissue transglutaminase antibodies (13.8 ± 8.8 vs. 40 ± 54.6 Units, $P = 0.12$) tended to be different among patients with CD and SIBO than those without SIBO.

### Histopathology

All the patients had villous atrophy (Marsh type 3 lesion) at the time of initial diagnosis of CD, but 45 (44.1%) of the 102 treated CD showed normal histology (classified as "Marsh 0") after GFD was started. The duration of a GFD was at least 6 months in all patients. SIBO was assessed after 6 months on GFD in 7 (6.9%), 12 months in 35 (34.3%), and 24 months or more in 60 (58.8%) patients. The histologic spectrum of the duodenal mucosa after GFD was Marsh 0 in 45 (44.1%), Marsh 1 in 12 (11.8%), Marsh 3a in 14 (13.7%), Marsh 3b in 16 (15.7%), and Marsh 3c in 15 (14.7%). Sixty-nine (67.6%) subjects showed improvement on histology (decrease of ≥ 1 degree on the modified Marsh scale). Treated CD patients who were asymptomatic at follow-up had a tendency to have more frequent histologic improvement than those who were symptomatic after gluten exclusion (82.6% vs. 63.2%, $P = 0.08$). The frequency of abnormalities and distribution of degree of intestinal damage on histology between CD with or without SIBO was similar (data not shown).

No significant difference was found in the number of IELs per 100 epithelial cells among CD patients with or without SIBO (72 ± 20 vs. 68 ± 20; $P = 0.79$).

## DISCUSSION

This study yielded 2 major findings: firstly, we demonstrated a low prevalence of SIBO diagnosed by quantitative culture of aspirate of the proximal intestine in a large cohort of patients with CD, even in the group with nonresponsive CD. Secondly, SIBO does not seem to be the only factor involved in persistence of symptoms in the majority of our patients with a positive culture.

The low frequency of SIBO in patients with nonresponsive CD in this study differ from that found in a previous study in which the diagnosis of SIBO was based on lactulose $H_2$-BT.[4] However, our results are consistent with the previous work in the fact that SIBO was present in those patients with symptomatic CD. What is(are) the reason(s) for the discrepancy in prevalence of SIBO among studies? $H_2$-BT is far from the ideal test to establish SIBO diagnosis. Studies that compared the $H_2$-BT with quantitative culture of intestinal aspirates suggest that it has a low sensitivity and a high frequency of false positive results.[13,20,21] Definitions of normal and abnormal results on $H_2$-BT are more variable than for cultures.[6, 18] Even more, in a recent study that included symptomatic patients with clearly defined risk

factors for SIBO, the reliability of lactulose $H_2$-BT was very poor as compared with quantitative culture of small bowel aspirate for diagnosis of SIBO.[21] Moreover, patients with untreated CD demonstrated higher fasting hydrogen levels than healthy volunteers and treated CD.[24] Thus, the lactulose $H_2$-BT may be unreliable for SIBO diagnosis in patients with nonresponsive CD because intentional and/or inadvertent gluten contamination is a major issue in this clinical scenario.[2,3] Other breath tests (eg, 80-g glucose-$H_2$BT and 1-g $^{14}$C-xylose) have a much higher sensitivity (65% to 70%, >95%; respectively) and specificity (83%, >95%; respectively) equivalent to the culture of small bowel aspirate obtained from a single site.[10,11,17,18,20]

Quantitative culture of intestinal aspirate is regarded by many as the most effective method for the diagnosis of SIBO, but may have some limitations. The main difficulty with culture of intestinal aspirate is the potential risk of contamination by microflora in the oropharynx. To decrease that risk in our study, the small intestinal aspirate was performed under direct vision and a sterile catheter for fluid aspiration was used. Additionally, for anaerobes, only colonic-type bacteria were considered clinically relevant. We do not believe that contamination by oropharyngeal microflora was a major pitfall in our study, but certainly, even with the precautions to avoid it, we cannot completely excluded that issue. However, if that was the case, thus our results overestimate the frequency of SIBO, further supporting our observation of a low prevalence of SIBO in patients with CD. Another limitation of the quantitative culture technique is the issue that the sample collection is restricted to the proximal small bowel. What is the impact of taking the intestinal fluid beyond the mid-small bowel in SIBO prevalence? The answer to this important question cannot be addressed with the present study design, and there is no practical device that allows us to routinely collect intestinal fluid beyond the area commonly reached by the standard endoscope. Even more important, currently SIBO is defined by the number of CFU/mL of intestinal fluid aspirated from the proximal intestine by standard endoscopy.[6-9,18,22] Finally, evidence of the existence of culture proven ileal bacterial overgrowth with normal number of bacteria in the proximal intestine is lacking.[19]

An additional novel finding in this study is that SIBO does not seem to be the only factor involved in the persistence of GI symptoms in the majority of our patients with nonresponsive CD and a positive culture, 67% had a coexistent disorder that may explain the lack of response to gluten exclusion. Thus, in our population even if SIBO is diagnosed, additional work-up is necessary, principally to unmask refractory sprue or microscopic colitis. It should be noted that the observed prevalence of SIBO in nonresponsive CD patients may be particular to patients like ours who were referred for investigation for symptoms unresponsive to a GFD. Whether this equally applies to unreferred community-based patients who have chronic diarrhea, despite a GFD, is unknown but deserving of study.

Nonetheless, recognition of SIBO is important because (1) SIBO could be the cause of and/or contributory factor in a small subset of nonresponsive CD patients and (2) celiacs with SIBO have evidence of worse malabsorption as reflected by increased amount of fat in stool (steatorrhea) and lower levels of hemoglobin, β-carotene and albumin. However, it is not clear whether the underlying disorder (present in 67% of nonresponsive CD patients) or bacterial overgrowth worsened the malabsorption but certainly both factors may have a negative synergistic effect.

Interestingly, we found 5 cases of SIBO diagnosed in patients with untreated CD. The reasons for this association are not clear, but seem to be related to gluten ingestion as reflected by the fact that none of our patients received specific treatment for SIBO with antibiotics, and the clinical evolution was favorable after gluten exclusion. The detection of SIBO at the time of initial diagnosis suggests that SIBO could result from damage to the epithelium that could be the result of rather than the cause of epithelial damage. Motility disorders associated with "active" CD, specifically delayed orocecal transit could lead to SIBO in these cases.[25]

However, this explanation remains speculative, because we did not assess the intestinal motility before and after gluten exclusion in our patients. Another plausible explanation for the presence of SIBO in untreated CD is related to the significantly older age demonstrated in our patients with positive culture. Thus, the well-described associated risk factors for SIBO in older people cannot be excluded as a possible explanation for SIBO presentation at the time of the diagnosis of CD.[26,27] It is possible that SIBO present at the time of CD diagnosis may persist after starting the GFD and prolong symptoms despite good adherence to GFD, but prospective (follow-up) studies are needed to test this hypothesis.

Finally, a similar proportion of symptomatic and asymptomatic CD patients had mildly elevated counts of bacteria in the small bowel; however, the clinical significance of these findings are unclear, and the possible pathogenic role of mildly elevated counts of bacteria in the small intestine of a subset of patients with CD is uncertain.

Strengths of our study are (1) we based our results in the diagnosis of SIBO by quantitative culture of intestinal aspirate, and (2) large sample size. The results of this study justify a prospective evaluation of the prevalence of bacterial overgrowth in patients with CD.

In conclusion, we demonstrated a low prevalence of SIBO in patients with CD using for diagnosis the quantitative culture of intestinal aspirate. SIBO may coexist with other disorders associated with nonresponsive CD. The combination of CD and SIBO was found to be associated with worse malabsorption.

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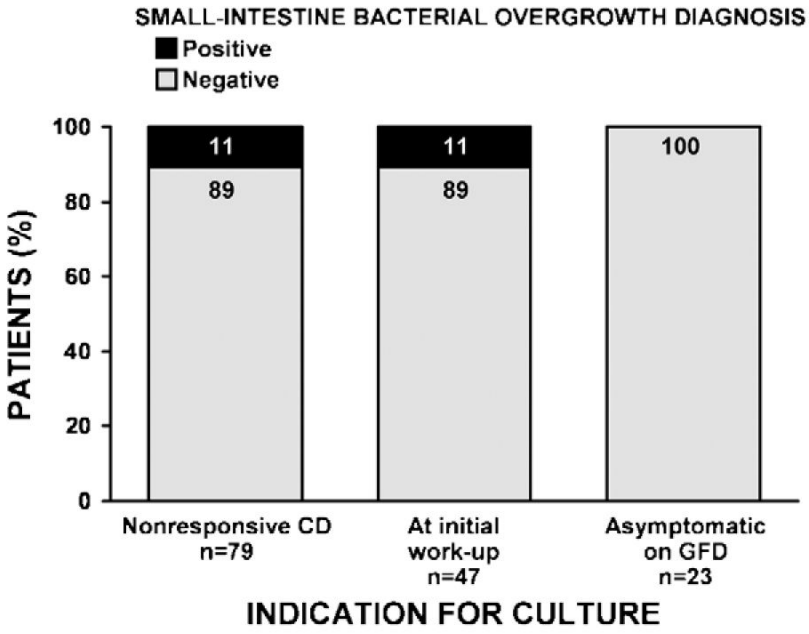


**FIGURE 1.**
Indication for collection of intestinal fluid and result of the culture.

**TABLE 1**

Clinical Features in Patients With Small Bowel Bacterial Overgrowth

| Patient No.* | Age (y)/Sex | Celiac Serology | | | Intestinal Biopsy | | |
|---|---|---|---|---|---|---|---|
| | | IgG AGA | IgA AGA | tTGA | Atrophy | iIELs | Associated Disorder |
| 1 | 44/F | + | + | ND | Yes | Yes | No |
| 2 | 59/M | + | + | + | Yes | Yes | No |
| 3 | 71/F | − | − | − | Yes | Yes | No |
| 4 | 53/M | − | − | + | Yes | Yes | No |
| 5 | 69/M | − | − | − | Yes | Yes | No |
| 6 | 62/F | ND | ND | + | Yes | Yes | No |
| 7 | 73/F | − | − | − | Yes | Yes | No |
| 8 | 55/F | + | + | ND | Yes | Yes | No |
| 9 | 79/F | − | − | ND | Yes | Yes | Type 1 RS |
| 10 | 74/M | − | − | − | Yes | Yes | Type 1 RS |
| 11 | 49/F | ND | ND | − | Yes | Yes | LC |
| 12 | 76/M | − | − | ND | No | No | LC |
| 13 | 64/F | − | − | − | Yes | Yes | CC |
| 14 | 77/M | − | − | ND | No | No | Lymphoma |

AGA indicates antigliadin; CC, collagenous colitis; LC, lymphocytic colitis; ND, not determinate; RS, refractory sprue; tTGA, antitissue transglutaminase; +, positive; −, negative.

*SIBO was diagnosed at initial work-up for malabsorption in 5 (patients 1 to 5) and in 9 patients with nonresponsive CD (patients 6 to 14).

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**TABLE 2**

Differentially Distributed Clinical and Laboratory Data in Patients With CD With or Without SIBO

| Variable | Nonbacterial Overgrowth (n=135) | Bacterial Overgrowth (n=14) | *P** |
|---|---|---|---|
| Age, y | 53.6±15.5 | 64.6±14 | 0.007 |
| Hemoglobin, g/dL | 13±1.4 | 11.8±1.6 | 0.01 |
| β-carotene, mg/dL | 155.2±79.5 | 53.4±71.3 | 0.001 |
| Albumin, g/dL | 3.7±0.6 | 3.3±0.6 | 0.003 |
| Fecal fat, g/24 h | 14.5±11.3 | 43.3±30.4 | 0.01 |

* Mann-Whitney *U* test.