Prevalence and predictors of small intestinal bacterial overgrowth in systemic sclerosis patients with gastro-intestinal symptoms

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ABSTRACT

Objective. There is a paucity of data available on small intestinal bacterial overgrowth (SIBO) in systemic sclerosis (SSc). The objectives of the study were to estimate the prevalence of SIBO in SSc patients exhibiting intestinal symptoms and identify patients at risk of SIBO regarding clinical and biological presentations and gastrointestinal symptoms captured by standardised questionnaires.

Methods. Between 2011 and 2012, patients exhibiting intestinal complaints underwent glucose H2/CH4 breath tests (BT) and blood assays. They were interviewed using the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0 (UCLA SCTC GTI) and the Short Form-36 (SF-36). For patients diagnosed with SIBO, BT was repeated 1 to 4 months after the end of antibiotics.

Results. Among 120 consecutive patients, 37 patients (29 women) exhibiting intestinal complaints were included (median age: 60 years). Fourteen patients (38%) were diagnosed with SIBO; patients from this subset had a longer disease duration (p=0.02), a significant weight loss within the past 6 months (p=0.03) and a higher total UCLA SCTC GTI score (p=0.03). The SF-36 assessment was not discriminant. Among the 14 patients treated for SIBO, 6 had a negative control BT, 4 remained positive, 2 failed to repeat the test and 2 patients died due to severe chronic malabsorption.

Conclusion. SIBO is a not uncommon, late onset, severe and not easy to treat complication of SSc. Higher UCLA SCTC GTI score and weight loss appeared to be strongly associated with SIBO.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterised by early-generalised microangiopathy and massive deposits of collagen and other matrix substances in the connective tissue (1). It is defined by increasing thickness of the skin and the connective tissue of internal organs. Within the targets of the disease, the gastrointestinal (GI) tract is very frequently affected (2-7). As such, it is a source of morbidity and even increased mortality (8), but it must be emphasised that it is also a major cause of patient dissatisfaction (7, 9). The pathogenesis of GI involvement is not well known but it is thought to relate to early vaso-nervorum impairment of the nerves supplying the GI tract (3). Subsequent effects lead to ineffective function with reduced contractility and progressive fibrosis of the GI musculature. A recent histological analysis of the gastric wall has revealed a pronounced deposition of collagen, the presence of myofibroblasts, and increased expression of several profibrotic factors, including TGF-β and endothelin-1 (10). The most commonly affected part of the GI tract is the gastro-oesophagus, which is affected in up to 90% of patients (11-14). In the EUSTAR registry, the prevalence of oesophageal symptoms was 67.3% in 2012 (66.4% in patients with the limited cutaneous subset and 69.5% in patients with the diffuse) (6). The anorectum is affected in 50 to 70% (15) and the colon in 10 to 50% of patients (16). In addition, although few studies have been performed, small intestinal function is not uncommonly affected and is suspected to be compromised in 40% of patients (17). Moreover, intestinal symptoms have been recorded in 23.5% of SSc patients in the EUSTAR database (6) and were

of high frequency in the German network of the systemic sclerosis (DNSS) (7). Small bowel disease can present as chronic intestinal pseudo-obstruction with distended loops of small intestine and bacterial overgrowth, which can lead to impaired absorption and progressive development of nutritional deficiencies.

Small intestinal bacterial overgrowth (SIBO), defined as an increase in the number ($\geq 10^5$ bacteria) and/or alteration in the type of bacteria in the upper intestinal tract (18), is part of such involvement. It can compromise the patient quality of life and lead to severe outcomes with malnutrition and high infectious risk. Although the gold standard for diagnosing SIBO remains microbial investigation of jejunal aspirates, non-invasive hydrogen and methane breath tests are most commonly used. However, the prevalence of SIBO in patients suffering from SSc (ranging from 21 to 63%) (4, 19-23) is not well established and predictors remain poorly known.

The objectives of the current study were to estimate the prevalence of SIBO in patients with SSc exhibiting intestinal symptoms and to identify subsets of patients at risk of SIBO regarding clinical or biological presentations and GI symptoms captured by standardised questionnaires.

Material and methods

Between January 2011 and December 2012, patients with SSc exhibiting intestinal complaints (abdominal pain, diarrhoea, bloating, and/or constipation) or weight loss ($\geq 5\%$ of the total body weight) underwent glucose hydrogen (H2) and methane (CH4) breath test (BT). Intestinal symptoms were ascertained by asking the patients themselves at the intake. Patients with any of the aboved mentioned symptoms were subjected to breath test but the majority of them (approximately 80%) displayed at least 2 symptoms. The principles and methods of H2/CH4 breath test (BreathTracker SC Quintron apparatus) were described in detail elsewhere (24). Briefly, after a 12 h fasting and a 48 h residue-free diet, H2/CH4 breath concentration, in parts per million (ppm),

was measured by gas chromatography in basal conditions and every 15 min for at least 3 h after the administration of an oral loading dose of glucose (50 g in 250 mL of water). Alveolar air samples were collected and connected to a bag for the collection of air coming from the respiratory dead space. After the glucose challenge, 2 consecutive H2 and/or CH4 increases ≥ 20 ppm or 3 consecutive increases ≥ 12 ppm compared to basal value were considered as a positive result for SIBO. None of the patients was allowed to take antibiotics or probiotics during the 4 weeks before the BT. The following blood tests were also performed at the time of the BT: C-reactive protein, ferritin, vitamin D, plasmatic folic acid and vitamin B12, serum albumin, calcium, phosphate, prothrombin and lipid profile. Moreover, patients were asked to fulfill 2 questionnaires: the Medical Outcomes Study Short Form Health Survey-36 (SF-36) (25) and the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0 (UCLA SCTC GTI) (26, 27).

SSc patients diagnosed with SIBO were given successive antibiotic administrations as recommended by the European League Against Rheumatisms (EULAR): amoxicillin (500mg 3 times a day *per os*, during the first month), followed by ciprofloxacin (500mg twice a day *per os*, during the second month) and metronidazole (500mg 3 times a day *per os*, during the third month). Patients were asked to repeat glucose BT 1 to 4 months after the end of the rotating antibiotic therapy. The local ethics committee approved the study and all the subjects gave written informed consent. Statistical analyses were made using chi-square test for group comparison involving binary data. Comparisons involving continuous data were performed using the non-parametric Mann-Whitney U-test. The results were considered as significant when the *p*-value was less than 0.05.

Results

Prevalence of SIBO

During a period of time of 2 years, among 120 consecutive SSc patients

seen in the department, 37 exhibited intestinal symptoms and were included in the study. Fourteen patients (38%) had a positive BT and were diagnosed with SIBO giving a prevalence of 38% (14/37) in SSc patients with GI symptoms and a supposed prevalence of 12% (14/120) in SSc (see discussion section). Of note, no patient had a high baseline value >20ppm on the BT.

Epidemiological characteristics of the patients included in the study and comparison between patients with and without SIBO

Among the 37 patients included, 29 patients were women (78%), with a median age of 60 years (range: 35-80 years). Median disease duration was 9 years (range: 1-35 years), 14 patients (38%) had the diffuse cutaneous subset whereas 23 had the limited form of the disease. All SSc patients were receiving proton pump inhibitors before entering the study. Patients with SIBO showed a longer disease duration (median: 11 years, range: 1–29 years) *vs*. 7 years (range: 3–35 years), *p*=0.02); a lower frequency of anti-topoisomerase-I antibodies (1/14, 7% *vs*. 9/23, 39%, *p*=0.04) and a higher frequency of pulmonary arterial hypertension confirmed by right heart catheterisation (3/14, 21% *versus* 0/23, 0%, *p*=0.04) (Table I). Median age (61.5 *vs*. 59 years, *p*=0.5) and cutaneous subset (36% *vs*. 39% patients with the diffuse subset, *p*=0.9) did not differ between SSc patients with and without SIBO. Of the most interest, significant weight loss within the past 6 months ($\geq 5\%$ of total body weight) was observed in patients with a positive BT (6/14, 43% *vs*. 2/23, 8%, *p*=0.03). Logistic regression analysis did not identify any disease characteristic independently associated with SIBO.

Biological characteristics of SSc patients with SIBO

Despite normal median values, calcium (*p*=0.03), phosphate (*p*=0.03) and triglycerid levels (*p*=0.04) were lower in patients with SIBO compared to patients without SIBO. No difference was found considering C-reactive protein, serum albumin, ferritin, folic acid or 25(OH)-vitamin D concentrations (Table I).

Correlates between UCLA SCTC GTI 2.0 and SF-36 questionnaires and SIBO

Focusing on gastro-intestinal manifestations, it is of note that the total UCLA SCTC GTI score was higher in patients suffering from SIBO (0.79 (0.21-2.22) *vs*. 0.31 (0.04-1.30), *p*=0.03). No difference was found considering the distention/bloating (*p*=0.9) and diarrhoea (*p*=0.1) items or each of the 5 other multi-item scales separately (reflux, fecal soilage, constipation, emotional well-being, and social functioning). Besides, the SF-36 assessment either on mental or physical composite score was comparable between the 2 groups (Table II).

SIBO outcomes after antibiotic administration

Fourteen patients diagnosed with SIBO received the rotating scheme antibiotic therapy. The treatment was well tolerated in all patients. Among them, 6 had a negative control BT after the antibiotic treatment, 4 remained positive and 2 failed to repeat the test. Two patients died due to intestinal involvement with severe chronic malabsorption. The first patient was a 72 year-old man with the diffuse SSc cutaneous subset, complicated with a severe interstitial lung dis-ease (stage III NYHA dyspnea, restrictive pattern at spirometry and strikingly reduced carbon monoxide diffusing capacity) and gastro-esophageal impairment (oesophagitis and gastroparesia). The second patient was a 67 year-old woman with the diffuse SSc cutaneous subset (anti-topoisomerase-I antibodies positive), complicated with severe PAH (associated with pericardial effusion). At the time of SIBO diagnosis, both patients complained about diarrhoea, abdominal pain and bloating. Besides, they showed major impaired general condition with a 16% and 19% weight loss respectively in the last year prior to death. Moreover, the second patient presented with a biological signature of malabsorption/maldigestion (microcytic hypochromic anaemia with iron deficiency, vitamin D deficiency), which surprisingly was not the case for the first one. Several courses of rotating antibiotic therapy (as described above), dietary measures with high protein supplement foods, vitamin D and iron supplies and finally intravenous nutrition (using central port-a-catheters) failed to improve patients' advanced intestinal failure. Moreover, the antibiotic therapy was complicated by a pseudomembranous colitis due to *Clostridium Difficile* in the second patient. Because of their impaired general health condition and the concurrent aggravation of their pulmonary complications, glucose BT were not controlled in these 2 cases, who subsequently died from sepsis.

Overall, bad outcome was observed in 6 out of the 14 patients (43%) diagnosed with SIBO (2 deaths and 4 patients not cured).

Discussion

GI involvement is frequent in SSc patients (5-7). As assessed in a recent study performed by Savarino and colleagues, oesophagus (with 70% of reduced lower oesophageal sphincter pressure and ineffective oesophageal motility pattern) and small bowel (with delayed oro-caecal transit time (160 min versus 105 min in healthy controls, *p*<0.01) and 46% of SIBO) are frequently impaired (4). In our series, the prevalence of SIBO was 38% of SSc patients displaying intestinal symptoms and 12% among 120 consecutive SSc patients seen in our department in a 2 years period. The prevalence of 12% (14/120) can only be supposed. Indeed, it does not include patients who have no GI symptoms but may have a positive BT. Therefore it is the lowest rate expected according to the number of patients who underwent BT. Nevertheless, the prevalence

Table 1. Epidemiological, clinical and biological characteristics of the patients included in the study.

	SSc Patients with SIBO (n=14)	SSc patients without SIBO (n=23)	Monovariate *p*-value
Median age (years)	61.5, range: 42-80	59, range: 35-79	0.5
Female gender: n (%)	10/14 (71.4)	19/23 (82.6)	0.9
Median SSc duration (years)	11 (range: 1-29)	7 (range: 3-35)	0.02
SSc subset: n (%) of dcSSc	5/14 (36)	9/23 (39)	0.9
Anti-Scl70 Ab: n(%)	1/14 (7)	9/23 (39)	0.04
Anti-centromeres Ab: n (%)	8/14 (57)	7/23 (33)	0.3
ILD: n (%)	6/14 (43)	10/23 (43)	0.8
PAH: n (%)	3/14 (21)	0/23 (0)	0.04
Active or past digital ulcers: n (%)	9/14 (64)	7/23 (30)	0.08
Serum albumin (g/l)	39.2 (range: 35-44)	40 (range: 33-45)	0.2
Vitamin B12 (pmol/l)	322 (range: 166-697)	373 (range: 232-488)	0.1
Folic acid (nmol/l)	7.9 (range: 4.5-13.3)	12.4 (range: 5-54)	0.09
Ferritin (µg/l)	51.9 (range: 10-147)	63.6 (range: 10-170)	0.07
Calcium (mmol/l)	2.27 (range: 2.14-2.41)	2.33 (range: 2.22-2.47)	0.03
Phosphore (mmol/l)	1.05 (range: 0.83-1.35)	1.21 (range: 0.94-3.32)	0.03
Triglycerids (mmol/l)	0.96 (range: 0.66-1.24)	1.51 (range: 0.64-3.32)	0.04
25-OH-vitamin D (nmol/l)	30.6 (range: 7-86.2)	45.8 (range: 12.5-111)	0.1
Prothrombin rate (%)	101.3 (range: 82-123)	106.8 (range: 81-130)	0.07
CRP (mg/l)	3.7 (range: 1-13)	6.5 (range: 0-22)	0.2

Ab: antibodies; CRP: C-reactive protein; dcSSc: diffuse cutaneous systemic sclerosis; F: females; ILD: interstitial lung disease; M: males; PAH: pulmonary arterial hypertension.

Table II. UCLA assessment among the patients included in the study.

	SSc Patients with SIBO (n=14) Median (range)	SSc patients without SIBO (n=23) Median (range)	Monovariate *p*-value
Reflux	0.43 (0.0-3.0)	0.37 (0.00-2.00)	0.7
Distension/bloating	1.0 (0.0-2.0)	0.75 (0.0-3.0)	0.9
Feacal soilage	0.0 (0.0-3.0)	0.0 (0.0-2.0)	0.5
Diarrhoea	0.25 (0.0-2.0)	0.0 (0.0-1.5)	0.1
Social functionning	0.42 (0.0-2.83)	0.17 (0.0-1.67)	0.6
Emotional well being	0.61 (0.0-3.0)	0.44 (0.0-2.22)	0.7
Constipation	0.62 (0.0-2.0)	0.75 (0.0-2.0)	0.9
Total UCLA score	0.79 (0.21-2.22)	0.31 (0.04-1.30)	0.03

of 38% is lower than ones reported in previous publications. Indeed, Marie *et al*. (22), Parodi *et al*. (23) and Savarino *et al*. (4) found a point prevalence of 43.1% (22/51), 55.5% (30/54) and 46% (47/99) of unselected SSc patients, respectively. No data was available about SIBO prevalence among the subgroup of SSc patients complaining about intestinal symptoms or presenting a significant weight loss in these studies but it was however available in few other studies and ranged from 21 to 63% (19-21, 28). Clinical characteristics of SSc patients included in our series such as age, gender, disease duration and cutaneous subset were broadly comparable with the cohorts described by Marie *et al*. (22) and Savarino *et al*. (4) (these data were not available in Parodi's publication (23)). It also must be pointed out that the BT used to assess SIBO were different. Indeed, Savarino *et al*. (4) and Parodi *et al*. (23) utilised lactulose BT and even if Marie *et al*. (22) managed their study with glucose BT, positive criteria for SIBO were less stringent (H2 and/or CH4 increase >20 ppm above basal value or >10 ppm on 2 consecutive measurements or >10 ppm between minimal and maximal values after glucose ingestion in their patient *versus* 2 H2 and/or CH4 increases ≥20 ppm or 3 increases ≥12 ppm compared to basal value in our study). These observations underscore that assessment of SIBO needs standardisation. However, we cannot exclude the possibility that the difference in prevalence in previous publications as compared with our study may be mainly explained by the fact that the other studies included unselected SSc patients whereas our deals with symptomatic patients.

This study and the aforementioned might be criticised about the use of BT as diagnostic tool for SIBO detection. BT is associated with lower rates of accuracy than jejunal culture. However, although jejunal aspirate culture is the gold standard analysis for the diagnosis of SIBO, it has several limitations such as the potential for contamination by oropharyngeal bacteria during intubation and the fact that SIBO may be missed by a single aspiration (the distribution of bacterial overgrowth may be irregular or restricted to a particular, difficult to access area of the small bowel (18)). In addition, intubation methods may be regarded as cumbersome and invasive for patients with non-specific symptoms or for those who may require repeated testing. The glucose breath test has, in fact, been shown to have a sensitivity of 62.5% and a specificity of 82% (diagnostic accuracy of 72%). Moreover, Kaye and colleagues found a high correlation rate between direct and indirect methods for detecting SIBO in SSc patients (29). BT has also some drawbacks with possible false results (18) and has the disadvantage that subsequent antibacterial therapy cannot be specific as bacterial species, antibiotics sensitivity and resistance are unknown (30). Nevertheless, in clinical practice, glucose and lactulose breath tests represent non-invasive, non-toxic, easily available and cheap valid diagnostic tools. Of the most interest, the present study enabled the identification of a subset of SSc patients at risk of developing SIBO. Long disease duration was found as associated factor with SIBO. It is difficult to conclude on pulmonary arterial hypertension because of

the small sample sizes. Conversely, the absence of anti-topoisomerase-I antibodies was highlighted in patients without SIBO. These findings may suggest that long disease duration is a predisposing factor while the lack of anti-topoisomerase-I antibodies is protective against SIBO in SSc. These results have to be confirmed by larger and prospective studies.

Besides, we took advantage of the newly validated tools available to assess GI involvement in SSc. Interestingly, the UCLA SCTC GTI was recently used to assess that GI manifestations, especially fecal incontinence, have a negative influence on the quality of life of patients with SSc (31). In the series reported by Omair and colleagues (31), patients who responded positively to the reflux, distension, diarrhoea, and constipation domains had lower scores in the well-being and social domains. To our knowledge, the present study is the first using the UCLA SCTC GTI to investigate patients at risk of SIBO in SSc. Higher total UCLA SCTC GTI score appeared to be strongly associated with SIBO. Interestingly, minimally important differences (MID) — smallest changes in score that patients perceive as beneficial or detrimental— for the UCLA SCTC GIT 2.0 have been recently estimated in a longitudinal observational cohort (32). MID estimates provide a benchmark for interpretation of results by helping researchers and clinicians understand whether Health-related Quality Of Life-score differences between two treatment groups are meaningful. If we extrapolate these findings to our study, the MID estimates for the total score being about 0.12, the difference of 0.48 observed between SIBO positive and SIBO negative patients should be meaningful. Furthermore, apart from the UCLA score, weight loss (>5% of total body weight within the past 6 months) was significantly correlated with SIBO. No difference was found considering each of the 7 multi-item scales separately: reflux, distention/bloating, diarrhoea, fecal soilage, constipation, emotional well-being, and social functioning. The SF-36 assessment, a widely used generic measure failed to show differenc-

es about SIBO-related quality of life. Moreover, multivariate analysis did not identify any item independently associated with SIBO probably because of the small size of our cohort.

No biological feature such as, ferritin, 25(OH)-vitamin D, albumin, calcium, phosphate or prothrombin rates, that could underscore malabsorption, helped to discriminate patients with and without SIBO. However, patients with SIBO showed a trend to have lower, albeit in normal ranges, calcium, phosphate and triglycerid levels.

With 2 deaths and a high percentage of weight loss in SIBO+ patients, our series illustrates the severe course that may have SIBO in SSc. Indeed, the mortality rate attributable to GI or small intestinal involvement is reported to be 4% (8) and 8.5% (33) respectively. Nevertheless, the specific mortality rate due to SIBO in SSc is still unknown. Obvious clinical and laboratory signs of SIBO may have late-onset in patients with SSc and we know that even though malnutrition is common, traditional markers of nutritional status including Body Mass Index and serum albumin do not seem to be good indicators of malnutrition in SSc (34). These data highlight the importance of an early screening in order to initiate the appropriate treatment for SIBO.

In our series, severity and difficulty to treat SIBO were illustrated by the fact that 6 out of 14 patients (43%) had a bad outcome (2 deaths and 4 uncured) and only 43% of them were healed after antibiotic therapy. The antibiotic failure seems to be high. Indeed, Marie and colleagues (22) obtained eradication of SIBO in only 31.8% of cases after a first course of rotating alternative antibiotic therapy based on norfloxacin and metronidazole for 3 months. Moreover, Lauritano and colleagues found a relapse rate of SIBO in 44% of patients nine months after successful treatment with rifaximin (35). Rifaximin is a broad-range, gastrointestinal-specific antibiotic that also demonstrated improvement in global symptoms and eradication of SIBO (36). Unfortunately, rifaximin is not worldwide available especially in France and in many other European countries mak-

ing difficult any comparison of it with other antibiotic therapies.

Recurrence has not yet been evaluated after cyclical gastrointestinal selective antibiotics therapy. Apart from the basic underlying disease, further risk factors for recurrence of SIBO have been identified including long-term treatment with proton pump inhibitors (OR 3.5) (35) which concerns about 90% of SSc patients and may partially explain absence of SIBO healing in SSc. Besides, in their series, Savarino (4) and colleagues found that proton pump inhibitors consumption was associated with a higher occurrence of SIBO.

Because SIBO shows a clinical spectrum varying from a completely asymptomatic status to severe malabsorption syndrome, the first point that may be criticised in our study could be the lack of systematic BT in SSc patients admitted in our department regardless their symptomatic status. Selecting patients for BT might have lowered the prevalence of SIBO in SSc. We deliberately decided to screen the only patients displaying intestinal symptoms or weight loss in order to enhance the strategy of routine medical care. Another substantial limitation is that our study was not focused on the evolution of UCLA SCTC GTI and SF-36 scores after SIBO treatment. This point might be developed in a different work in order to determine if SIBO healing is actually associated with a meaningful reduction in the total UCLA SCTC GTI score. Another limitation is the absence of correction for multiple comparisons using the Bonferroni method. However, this method is known to be sometimes inappropriate, as it is highly conservative and may miss real differences (37). The present study shows a high prevalence of SIBO in symptomatic patients (38%) and highlights the fast and simple investigations that need to be performed in such patients. In addition to clinical intestinal symptoms, weight loss and a high UCLA score are helpful to risk stratify the patients to refer for BT. The severity of SIBO is also underscored, together with the difficulty to cure the bacterial overgrowth. The acute management still needs more data to be clarified.

References
1. LEROY EC, BLACK C, FLEISCHMAJER R et al.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
2. POIRIER TJ, RANKIN GB: Gastrointestinal manifestations of progressive systemic scleroderma based on a review of 364 cases. *Am J Gastroenterol* 1972; 58: 30-44.
3. SJÖGREN RW: Gastrointestinal motility disorders in scleroderma. *Arthritis Rheum* 1994; 37: 1265-82.
4. SAVARINO E, MEI F, PARODI A et al.: Gastrointestinal motility disorder assessment in systemic sclerosis. *Rheumatology* (Oxford) 2013; 52: 1095-100.
5. WALKER UA1, TYNDALL A, CZIRJÁK L et al.: Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007; 66: 754-63.
6. MEIER FM1, FROMMER KW, DINSER R et al.: Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis* 2012; 71: 1355-60.
7. SCHMEISER T1, SAAR P, JIN D et al.: Profile of gastrointestinal involvement in patients with systemic sclerosis. *Rheumatol Int.* 2012; 32: 2471-8.
8. ELHAI M, MEUNE C, AVOUAC J, KAHAN A, ALLANORE Y: Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2012; 51: 1017-26.
9. OMAIR MA, LEE P: Effect of gastrointestinal manifestations on quality of life in 87 consecutive patients with systemic sclerosis. *J Rheumatol* 2012; 39: 992-6.
10. MANETTI M, NEUMANN E, MILIA AF et al.: Severe fibrosis and increased expression of fibrogenic cytokines in the gastric wall of systemic sclerosis patients. *Arthritis Rheum* 2007; 56: 3442-7.
11. COHEN S: The gastrointestinal manifestations of scleroderma: pathogenesis and management. *Gastroenterology* 1980; 79: 155-66.
12. AKESSON A, WOLLHEIM FA: Organ manifestations in 100 patients with progressive systemic sclerosis: a comparison between the CREST syndrome and diffuse scleroderma. *Br J Rheumatol* 1989; 28: 281-6.
13. KAHAN A, MENKES CJ: Gastrointestinal involvement in systemic sclerosis. *Clin Dermatol* 1994; 12: 259-65.
14. TURNER R, LIPSHUTZ W, MILLER W, RITTENBERG G, SCHUMACHER HR, COHEN S: Esophageal dysfunction in collagen disease. *Am J Med Sci* 1973; 265: 191-9.
15. HAMEL-ROY J, DEVROEDE G, ARHAN P, TETREAULT L, DURANCEAU A, MENARD HA: Comparative esophageal and anorectal motility in scleroderma. *Gastroenterology* 1985; 88: 1-7.

16. HARPER RA, JACKSON DC: Progressive systemic sclerosis. *Br J Radiol* 1965; 38: 825-34.

17. D'ANGELO WA, FRIES JF, MASI AT, SHULMAN LE: Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med* 1969; 46: 428-40.

18. BURES J, CYRANY J, KOHOUTOVA D *et al*.: Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010; 16: 2978-90.

19. COBDEN I, AXON AT, GHONEIM AT, McGOLDRICK J, ROWELL NR: Small intestinal bacterial growth in systemic sclerosis. *Clin Exp Dermatol* 1980; 5: 37-42.

20. GOUGH A, ANDREWS D, BACON PA, EMERY P: Evidence of omeprazole-induced small bowel bacterial overgrowth in patients with scleroderma. *Br J Rheumatol* 1995; 34: 976-7.

21. KAHN IJ, JEFFRIES GH, SLEISENGER MH: Malabsorption in intestinal scleroderma. Correction by antibiotics. *N Engl J Med* 1966; 274: 1339-44.

22. MARIE I, DUCROTTÉ P, DENIS P, MENARD JF, LEVESQUE H: Small intestinal bacterial overgrowth in systemic sclerosis. *Rheumatology* (Oxford) 2009; 48: 1314-9.

23. PARODI A, SESSAREGO M, GRECO A *et al*.: Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. *Am J Gastroenterol* 2008; 103: 1257-62.

24. GASBARRINI A, CORAZZA GR, GASBARRINI G *et al*.: Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. A*liment Pharmacol Ther* 2009; 29 (Suppl. 1): 1-49.

25. KHANNA D, FURST DE, CLEMENTS PJ *et al*.: Relaxin Study Group; Scleroderma Clinical Trials Consortium. Responsiveness of the SF-36 and the Health Assessment Questionnaire Disability Index in a systemic sclerosis clinical trial. *J Rheumatol* 2005; 32: 832-40.

26. KHANNA D, HAYS RD, MARANIAN P *et al*.: Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Arthritis Rheum* 2009; 61: 1257-63.

27. BAE S, ALLANORE Y, COUSTET B, MARANIAN P, KHANNA D: Development and validation of French version of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Clin Exp Rheumatol* 2011; 29: S15-21.

28. VANDERHOOF JA, YOUNG RJ: Etiology and pathogenesis of bacterial overgrowth. Clinical manifestations and diagnosis of bacterial overgrowth. Treatment of bacterial overgrowth. UpToDate online, vol 18.1; Wellesley, 2010.

29. KAYE SA, LIM SG, TAYLOR M, PATEL S, GILLESPIE S, BLACK CM: Small bowel bacterial overgrowth in systemic sclerosis: detection using direct and indirect methods and treatment outcome. *Br J Rheumatol* 1995; 34: 265-9.

30. PARODI A, CAPURSO G, PERRI F, CUOCO L, LAURITANO EC: H2- breath testing for small-intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2009; 29 (Suppl. 1): 18-22.

31. OMAIR MA, LEE P: Effect of gastrointestinal manifestations on quality of life in 87 consecutive patients with systemic sclerosis. *J Rheumatol* 2012; 39: 992-6.

32. KHANNA D, FURST DE, MARANIAN P *et al*.: Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *J Rheumatol* 2011; 38: 1920-4.

33. SCUSSEL-LONZETTI L, JOYAL F, RAYNAULD JP *et al*.: Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine* 2002; 81: 154-67.

34. KRAUSE L, BECKER MO, BRUECKNER CS *et al*.: Nutritional status as marker for disease activity and severity predicting mortality in patients with systemic sclerosis. *Ann Rheum Dis* 2010; 69: 1951e7.

35. LAURITANO EC, GABRIELLI M, SCARPELLINI E *et al*.: Small intestinal bacterial overgrowth recurrence after antibiotic therapy. *Am J Gastroenterol* 2008; 103: 2031-5.

36. PIMENTEL M: Review of rifaximin as treatment for SIBO and IBS. *Expert Opin Investig Drugs* 2009; 18: 349-58.

37. BLAND JM, ALTMAN DG: Multiple significance tests: the Bonferroni method. *BMJ* 1995; 310: 170.