Esophageal manifestation in patients with scleroderma

Theodoros A Voulgaris, Georgios P Karamanolis

Abstract
The esophagus is the most commonly affected part of the gastrointestinal system in patients with systemic sclerosis (SSc). Esophageal involvement may lead to a significant reduction in patient quality of life. The exact pathophysiology is complex and not yet fully elucidated. Ultimately, esophageal smooth muscle becomes atrophied and replaced by fibrous tissue leading to severe motility disturbance of the distal esophagus. Symptoms are mainly attributed to gastroesophageal reflux disease and to esophageal dysmotility. Compelling evidence has correlated esophageal involvement to the severity of pulmonary disease. No formed guidelines exist about the diagnostic modalities used to assess esophageal disease in patients with SSc, though upper gastrointestinal endoscopy is the first and most important modality used as it can reveal alterations commonly observed in patients with SSc. Further exploration can be made by high resolution manometry and pH-impedance study. Proton pump inhibitors remain the mainstay of treatment, while prokinetic agents are commonly used as add-on therapy in patients with symptoms attributed to gastroesophageal reflux disease not responding to standard therapy as well as to motility disturbances. Gastroesophageal reflux disease symptoms in patients with SSc are frequently difficult to manage, and new therapeutic modalities are emerging. The role of surgical treatment is restricted and should only be preserved for resistant cases.

Key Words: Systemic sclerosis; Esophagus; Gastroesophageal reflux disease; Esophageal dysmotility; Proton pump inhibitors

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
nearly 90% of the systemic sclerosis population. Among the gastrointestinal tract, the esophagus is the most commonly affected. In this review, we will present the current understanding of the pathophysiologic mechanisms of systemic sclerosis, the clinical presentation and diagnosis of esophageal involvement. Finally, we highlight the latest developments in the management of this disease.

INTRODUCTION

Systemic sclerosis (SSc) is an uncommon immune-mediated multisystemic disease that leads to a significant reduction in patient quality of life and has a high mortality rate [1]. Its global prevalence is estimated to be around 1 in 10000 people, whereas the estimated annual incidence is of less than 10 per 100000 individuals, both in Europe and in the United States. SSc is found to be four times higher in women compared to men[2-4].

Five-year survival in SSc largely depends on the subtype of the disease and is reported to be 80% in diffuse and 90% in limited phenotypes. Almost 9 out of 10 patients with SSc will develop at some point during the course of their disease a gastrointestinal (GI) manifestation, though severe involvement leading to increased morbidity and mortality will arise in only 8%. The reported survival of SSc patients with GI involvement is calculated to be 15% at 9 years[5].

SSc can affect any segment of the GI tract from mouth to anus, though the esophagus is the most commonly involved portion of the GI tract followed by the anorectum and the small bowel[6]. Up to 90% of patient will manifest esophageal symptoms and dysfunction[7,8]. Symptoms of esophageal dysfunction may not occur in up to half of the affected patients until severe tissue damage takes place[9,10].

PATHOPHYSIOLOGY OF ESOPHAGEAL DISEASE IN SSC

SSc is temporarily considered as an orphan disease, and its origin has not been yet fully elucidated. It is assumed that a combination of environmental factors alongside genetic susceptibility as well as other factors, such as epigenetics, leads to a deregulation of the repairing mechanism of connective tissue in response to injury[11].

Originally a tripartite pathogenesis (vascular injury, autoimmunity and inflammation, fibrosis) has been hypothesized to be the basis of SSc development. However, current data point out that the epithelium, blood-derived cells and disturbances in the wound healing process also possess a critical role in the pathogenesis of SSc[12]. An initial trigger leads to vascular injury due to autoimmunity and/or environmental influences that due to the existence of altered endothelial cells and pericytes/vascular smooth muscle cells steers to impaired vascular remodeling[13,14]. The initially observed disturbed peripheral circulation and activation of endothelial cells, pericytes/vascular smooth muscle cells and fibroblasts induces the production of cytokines, growth factors and chemokines, which in turn promotes in the affected organ the accumulation and activation of different immune cells such as macrophages, mast cells, B and T cells and plasmacytoid dendritic cells.

According to recent data, esophageal inflammation and fibrosis is in a significant manner mediated by Th17 cells. In a recent study focusing on cytokine analysis presenting in the gastric juice from patients with esophageal dysmotility, profibrotic endothelin-1 and the proinflammatory cytokines interleukin (IL)-17, IL-6, IL-1β, IL-9 and IL-2 were significantly increased in patients with esophageal dysmotility, which is known to be associated with atrophy and fibrosis of the smooth muscle layer. These data and especially the increased levels of IL-17 led the researchers to the conclusion that Th17 cells possess a crucial role in the pathogenesis of esophageal fibrosis, a finding compatible with previous studies in SSc patients with skin and lung disease [15]. The end product of this not fully elucidated cascade is the overproduction of
extracellular matrix (ECM) by interstitial fibroblasts of different origin, transited to myofibroblasts due to the abovementioned vascular and inflammatory reactions. ECM accumulation in tissues affected by scleroderma is derived grossly by transforming growth factor (TGF)-β, connective tissue growth factor, plasminogen activator inhibitor-1, fibronectin 1 and other cytokines, though the principal mediator of tissue fibrosis in SSc is thought to be TGF-β\(^\text{[16,17]}\).

A new insight in our understanding of the role of TGF-β in excessive production and collagen deposition in patients with SSc has been recently revealed. TGF-β acts through binding to its receptors and phosphorylation of SMAD2 and SMAD3 proteins. TGF-β action is facilitated by its connection to TGF-β-binding proteins. TGF-β-binding proteins are structural components of the ECM and are involved in the deposition of TGF-β in the ECM and are implicated in TGF-β secretion and regulation of TGF-β activation\(^\text{[18,19]}\).

A recent study has postulated the fact that patients with SSc and esophageal involvement overexpress TGF-β-binding protein-4 in parallel to the observed TGF-β increase\(^\text{[20]}\). It seems that the above complex mechanism affecting esophageal smooth muscle, nerves and connective tissues contributes to fibrosis and ultimately to esophageal dysfunction\(^\text{[21-23]}\). Progressively the esophageal smooth muscle becomes atrophied and replaced by fibrous tissue leading to severe motility disturbance of the distal esophagus\(^\text{[24,25]}\).

### CLINICAL PRESENTATION

SSc can manifest with various clinical presentations. Symptoms originate from both structural and functional changes such as a reduced lower esophageal sphincter (LES) pressure, low or absent peristalsis and sicca syndrome. Symptoms such as heartburn, regurgitation, chronic cough and hoarseness are attributed to gastroesophageal reflux disease (GERD) or to esophageal dysmotility when symptoms such as dysphagia, odynophagia and chest pain are present\(^\text{[26,27]}\). Symptoms related to GERD are the most common in patients with SSc with a prevalence of around 35%, whereas dysphagia occurs rarer in about 4% of patients\(^\text{[21]}\).

The presence of Barrett’s esophagus (BE) and adenocarcinoma has also been reported to be increased in patients with SSc, though screening patients with SSc and esophageal disease for esophageal adenocarcinoma (EAC) does not seem to be cost effective\(^\text{[26-29]}\).

Esophageal disease may remain asymptomatic for a long period of time. Even in the absence of symptoms, up to three quarters of patients may show esophageal dilatation on chest tomography and esophageal abnormalities on endoscopy\(^\text{[24,30,31]}\). This is of special interest due to the fact that recent data point out that esophageal disease in SSc, even among asymptomatic patients, is linked to the development of interstitial lung disease, and patients with more active reflux disease ultimately develop more advanced interstitial lung disease\(^\text{[32]}\). Even if no causative association between esophageal involvement and pulmonary disease is proven, it is hypothesized that in the setting of unopposed acid reflux in patients with SSc the tracheobronchial aspiration of gastric secretions over time leads to pulmonary fibrosis\(^\text{[24,32-35]}\). This hypothesis is also based in experimental data coming from a study in a rodent model. According to the researchers, when recurrent gastric fluids were added to rodent lungs, inflammatory cells and cytokines in the lungs were observed, suggesting that GERD and aspiration triggers an inflammatory response, which ultimately may lead to pulmonary fibrosis\(^\text{[36]}\). Additionally, it has been postulated that the wider the esophagus caliber becomes the greater the diffusing capacity for carbon monoxide and forced vital capacity are\(^\text{[37]}\).

### DIAGNOSIS

There is no gold standard examination for the detection and the assessment of esophageal involvement in patients with SSc. Due to the various esophageal symptoms, usually the first examination undertaken is an upper GI endoscopy. When patient presents with symptoms referring to a motility disorder then additional information can be obtained by high resolution manometry. When the primary complaint of the patient is attributed to GERD, an esophageal pH monitoring with or without impedance may be undertaken.
Endoscopy
There are no specific guidelines suggesting a mandatory baseline upper GI endoscopy for patients with SSc[38]. Furthermore, there are no specific endoscopic findings for diagnosing SSc, though gastroscopy is a very useful tool in assessing patients' symptoms such as dysphagia or heartburn. The most common endoscopic finding among patients with SSc is erosive esophagitis, which is revealed in one out of two patients[34,39,40]. It must be stated that endoscopic findings of esophagitis may be present in an even larger portion of asymptomatic patients. Thonhofer et al[31] revealed findings of erosive esophagitis in 77% of asymptomatic patients with SSc[31]. Moreover, endoscopy can show GERD complications such as benign peptic stenosis, BE and EAC. Patients with SSc tend to have an increased incidence of BE, which can be up to 10.1%[32,34,40]. The increased incidence of BE in patients with SSc is not accompanied with an increase in the incidence of EAC in patients with SSc and BE. A study that followed patients with SSc and BE for up to 3 years reported a yearly rate of EAC in patients with high dysplasia rating up to 4%, which is comparable to the yearly rate of progression to EAC among patients with BE and high grade dysplasia without SSc[41].

HRM
After its development HRM has substituted conventional manometry as the ideal study for assessing esophageal motility disorders. Although there are no specific recommendations for the role of HRM in clinical practice, it may add substantially significant information about esophageal involvement in SSc[42]. SSc typical manometric presentation consists of a reduced LES resting pressure in combination with diminished amplitude or aperistalsis[27,43,44]. It should be underlined that data regarding the prevalence of the typical manometric presentation, as it is assessed by HRM, are still inconsistent ranging from one out of three patients to one out of two patients[45-47].

An interesting finding in SSc patients with esophageal motility abnormality is the phenomenon of abnormal peristaltic reserve, defined as the absence of contraction and abnormal peristaltic augmentation after multiple rapid swallows[45]. Moreover, Roman et al[47] concluded that in the initial phase of esophageal involvement, the middle and not the distal esophagus is first involved, as the mean amplitude of middle esophageal body contractions (but not distal contractions) was significantly decreased in patients with hypotensive peristalsis compared to patients classified with normal peristalsis[47].

However, it should be stressed that there is a discordance regarding the correlation between manometric findings and patient symptoms. Multiple studies have failed to prove such a correlation[48-50], whereas studies using well defined and validated questionnaires, such as the University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0) or Gastrointestinal Symptoms Severity Index Scores, support the idea of a correlation between patient symptoms and manometric findings of esophageal involvement[45,51,52].

In any case, we should keep in mind that asymptomatic patients tend to show a great proportion of manometric abnormalities that are compatible with esophageal involvement in HRM. Indeed, Vettori et al[53] found that almost 84% of asymptomatic SSc patients had esophageal motility abnormalities in an HRM study. They also concluded that baseline impaired esophageal motility was an independent risk factor of progression to symptomatic upper GI involvement, and therefore HRM may have a role as a predicting tool for early diagnosis of esophageal involvement among patients with SSc[53].

Esophageal pH monitoring, with or without impedance
As stated above, GERD is the most common clinical presentation of esophageal involvement in SSc patients. The utility of performing an esophageal pH monitoring is graded for patients with typical GERD symptoms that did not respond to proton pump inhibitor (PPI) therapy. Thus, a 24 h pH monitoring combined with impedance is the preferred test in order to confirm the presence of persistent abnormal acid exposure of the esophagus and/or presence of weak acid reflux.

In a large recent study including SSc patients with GERD, PPI partial response was observed in 53.9%[54]. These nonresponders to PPI SSc patients showed on pH-monitoring higher acid exposure times (AETs) than non-SSc patients matched for PPI formulation and dose GERD (61% vs 18%, respectively), significantly longer AETs, longer median bolus clearance, lower nocturnal impedance values but lack of increased reflux episodes[55].
Previous studies have shown that abnormal pH monitoring is seen in up to 85% of SSc patients without treatment\[48,56,57\]. Moreover, a study including GERD patients with or without SSc, revealed that SSc patients tend to have worse GERD symptoms and more severe reflux esophagitis\[58\].

**Computed tomography scan**

Thoracic computed tomography scan can access the existence of pulmonary involvement. It is of special interest that critical information about esophageal involvement could also be drained. It is known that esophageal dilation in computed tomography will be associated to symptomatic esophageal disease in patients with SSc \[59\]. A study evaluating esophageal abnormalities in SSc patients found that in high-resolution computed tomography with radionuclide transit a ≥ 9 mm threshold for esophageal dilation could accurately predict esophageal dysmotility with a sensitivity of 83.1% and a specificity of 94.1%\[60\].

**MANAGEMENT**

**General principles**

Treatment of esophageal involvement in SSc is supportive as no disease specific therapy is available. Treatment focuses on alleviation of each patient’s specific symptoms.

**Medical treatment**

The management of GERD includes, at the first stage of the disease, dietary and lifestyle interventions such as avoidance of aggravating foods, having meals within three hours before bedtime, head of bed elevation, weight reduction, smoking cessation, alcohol drinking reduction and small and frequent meal consumption. However, the mainstream treatment option includes drug administration, mainly PPIs \[61,62\]. PPIs should be administered 30–60 min before a meal, beginning initially once daily before breakfast. Even though studies using once daily PPIs dosage in patients with SSc showed symptom alleviation and healing of esophagitis in a percentage of patients, a substantial number of patients were characterized as partial or nonresponders\[63-66\]. Thus, in such patients, adjustment to twice daily dosing should be considered. According to recent data, the response rate of GERD treatment among SSc patients was less than 50% after taking omeprazole 20 mg twice daily for 4 wk, a percentage significantly lower than that reported for patients without SSc\[54,55,67-69\]. Authors found that the presence of dysphagia was the only predictor of PPI-partial response GERD in those patients\[54\].

In another study among patients with SSc and GERD treated with high PPI dose, 60% of those still had a total AET ≥ 4.5%, and 55% had an AET > 6% when evaluated with pH-impedance study\[55\]. However, the accurate strategy for the treatment of partial or nonresponders to PPIs is not fully elucidated. Vonoprazan is a first-in-class PPI that unlike conventional PPIs functions in the absence of an acidic environment and leads to a more consistent acid suppression compared to other PPIs. Thus, it could be an alternative therapeutic option as it has been proven efficient in the treatment of GERD refractory to traditional PPIs\[70,71\]. Indeed, a recent study stated that Vonoprazan was efficient in patients with SSc and refractory GERD. Vonoprazan was given to 15 patients among whom 14/15 suffered from PPI-refractory GERD, and the authors found that vonoprazan in the dose of 20 mg offered symptom relief in 83.4% of patients and achieved long term symptom control (≥ 2 years)\[72\].

PPIs act as an acid suppressor, but it has no effect on esophageal motility and/or LES pressure, which could be a putative GERD mechanism in SSc. So, esophageal dysmotility might explain the fact of the higher prevalence of PPI-partial response GERD in SSc compared to non-SSc patients. Prokinetic agents have a mechanism of action on the esophageal motility by facilitating esophageal motility and increasing LES pressure\[73,74\]. Therefore, it is rational to hypothesize that they can improve reflux control in patients who have failed PPI treatment. Foocharoen et al\[67\] investigated the role of add-on therapy with either domperidone or aglycone in SSc patients. The authors enrolled SSc patients, 59.4% of whom had a partial response after an initial 4 wk trial of omeprazole 20 mg twice a day. Then they were randomly assigned to take omeprazole plus either domperidone or aglycone for 4 wk. Only 13% of patients in the domperidone group and 22% of patients in the aglycone groups did not respond to the additional therapy. Moreover, quality of life was improved in SSc patients treated with domperidone or aglycone\[67\]. Therefore, the authors suggested that in
Table 1: Studies assessing per os pharmacotherapy in patients with systemic sclerosis and esophageal involvement

| Ref. | Patients (n) | Treatment | Treatment duration | Response to treatment |
|------|--------------|-----------|--------------------|----------------------|
| Hendel et al [63], 1992 | 25 | Omeprazole 20-80 mg (adjustments of the maintenance dose of omeprazole) | Mean time of 40 mo | Healing of esophagitis in almost 50% patients |
| Marie et al [34], 2006 | 133 | Omeprazole 20-40 mg | Mean duration of 6 yr from treatment initiation | Heartburn (n = 103; 77.4%), dysphagia (n = 19; 14.3%) Improvement of heartburn: (77.4%) Improvement of dysphagia: (14.3%) Esophagitis healing: 32.3% |
| Pakozdi et al [64], 2009 | 21 | Lansoprazole 30 mg | 12 mo | Short-term (6 mo) efficacy in decreasing frequency of symptoms in No long-term benefit |
| Muro et al [65], 2009 | 84 | Rabeprazole 10 mg | 8 wk | Effective for the symptom control |
| Foocharoen et al [67], 2017 | 148 | Omeprazole 20 bid | 4 wk | 40.1% responded to omeprazole |
| Pakozdi et al [64], 2009 | 88 | Omeprazole + domperidone (n = 38)/aglycon (n = 37) | | Domperidone and aglycon are equally effective treatments when used in combination with omeprazole 17% of patients were nonresponsive |
| Stern et al [55], 2018 | 38 | Twice daily different PPIs (rabeprazole, dexlansoprazole, esomeprazole, omeprazole, lansoprazole, pantoprazole)-variable dosing schedules | Treatment duration not given | Despite PPIs high-dose: 61% of SSc patients had an AET ≥ 4.5% 55% of SSc patients had an AET > 6% |
| Foocharoen et al [54], 2020 | 243 | Omeprazole 20 mg bid | 4 wk | PPI-partial response: 53.9% |
| Tabuchi et al [72], 2021 | 15 (14/15 with PPI-partial response) | Vonoprazan 10-20 mg | > 2 yr | Symptom relief in 83.4% Long-term symptom control in 87% |
| Johnson et al [77], 1987 | 12 | Metoclopramide 10 mg X 2 | 1 wk from treatment initiation | Significant reduction of reflux events: in 91.6% All but 2 patients attained LES pressure values that fell in the normal range after metoclopramide treatment |
| Karamanolis et al [84], 2016 | 22 | Buspirone 20 mg | 4 wk | Improvement in the severity of heartburn: 70% Improvement in the severity of regurgitation in 58% Improvement in dysphagia in 50% and in chest pain in 25% |

AET: Acid exposure times; bid: Twice a day; LES: Lower esophageal sphincter; PPIs: Proton pump inhibitors; SSc: Systemic sclerosis.

PPI-partial responder patients, a trial of adding domperidone to PPIs can be administered, whereas in patients suffering from side effects due to prokinetic administration, aglycon in combination with PPI can be a favorable therapeutic option.

Besides domperidone, other prokinetic drugs, such as metoclopramide, erythromycin and cisapride, have also been evaluated among SSc patients. It is thought that they could contribute to GERD control through increasing LES tone and gastric emptying, and they might also improve symptoms originating from esophageal motility disturbance such as dysphagia[33,75-77]. Unfortunately, there are scarce data about their use in SSc patients even if they are frequently used in clinical practice[78]. Moreover, their chronic use is withheld due to additional toxicities[79] (Table 1).

In patients with SSc, stricture formation, due to GERD, may occur in up to 29% of them[25], and in such cases esophageal balloon dilatation is advised[80]. It is of special note for the clinician to keep in mind that dysphagia in patients with SSc may also be due to candida esophagitis, as fungal cultures from the esophagus of patients with SSc...
were positive in 38%[26]. In cases of esophageal candidiasis, systemic antifungal therapy is always required. The recommended treatment in patients who can tolerate oral therapy is oral fluconazole 200–400 mg (3–6 mg/kg) daily or intravenous fluconazole 400 mg (6 mg/kg) daily in patients who cannot tolerate oral treatment for 14–21 d[81].

**Novel therapies**

Studies in healthy volunteers evaluating the effect of buspirone, an orally available 5-hydroxytryptamine receptor agonist, in LES have proven its ability to increase LES residual pressure and increase esophageal motility[82]. This beneficial effect has been evaluated in a pioneer study in patients with SSc and esophageal involvement[83]. According to the study findings, a single 10 mg buspirone dose led to a significant increase in the LES resting pressure in up to 80% of SSc patients and showed a trend to increase the amplitude of esophageal body motility. Based on these findings, a 4 wk open-label trial of 20 mg of oral buspirone in 22 SSc patients with esophageal involvement indeed verified the beneficial effect of buspirone in increasing the LES resting pressure. This effect was translated to an improvement in patient symptom severity of heartburn and regurgitation, though no improvement in chest pain or dysphagia was observed[84].

**Surgery**

Generally, in patients with well documented long-standing GERD, antireflux surgery is an option[61]. Unfortunately, Nissen fundoplication results were suboptimal in SSc patients, possibly due to concomitant esophageal dysmotility. Even though amelioration in the severity of reflux symptoms was observed, postoperative dysphagia was observed in up to 71% of patients[85-87]. However, a recent study including SSc patients showed improved long-term (mean follow-up of 36 wk) postoperative results after minimally invasive fundoplication, such as Toupet and Dor. The authors reported that 41% of patients had no symptoms, 56% had reduced symptoms, and persistent dysphagia was noted in only 11.7% of patients[88].

Besides fundoplication, Roux-en-Y gastric bypass (RYGBP) has also been evaluated as a viable surgical alternative for GERD patients with complete aperistalsis. It is thought that the small gastric pouch has minimal acid content, as the acid-producing mucosa of the fundus is excluded, and the roux limb prevents biliary reflux into the pouch and the esophagus. In an interesting study comparing RYGBP vs fundoplication, the authors found a statistically lower incidence and severity of postoperative dysphagia in the RYGBP group as well as an improved reflux control[89]. Adding to this study, Yan et al[90] showed GERD symptom resolution or improvement in all patients with RYGBP, while only 50% of the fundoplication group reported partial improvement[90]. It should be mentioned that RYGBP predisposes to bacterial overgrowth, which especially in patients with SSc and possible impaired intestinal motility may further deteriorate a patient’s clinical status. Other surgical alternatives tested in patients with SSc include biliary/duodenal diversion and esophagectomy with either gastric or colon with variable success and increased mortality[91].

**CONCLUSION**

Esophageal involvement is very common among patients with SSc, grossly affecting patient quality of life. Upper GI endoscopy is the primary and most often used diagnostic modality evaluating patient symptoms and possible complications, while useful information can be drawn by esophageal HRM and/or pH impedance study, depending on patient symptoms. PPIs remain the cornerstone in esophageal involvement treatment, even if a significant percentage of patients partially or not fully respond to them. In such cases, a trial of prokinetic agents may alleviate patient symptoms, while promising data have arisen using buspirone, an orally available 5-hydroxytryptamine 1A receptor agonist. Surgical treatments should be preserved for well documented, poorly responding to pharmacological modalities cases due to suboptimal results.

**REFERENCES**

1. McFarlane IM, Bhamra MS, Kreps A, Iqbal S, Al-Ani F, Saladini-Aponte C, Grant C, Singh S,
Awall K, Koci K, Saperstein Y, Arroyo-Mercado FM, Laskar DB, Atluri P. Gastrointestinal Manifestations of Systemic Sclerosis. *Rheumatology (Oxford)* 2018; 8 [PMID: 30057856 DOI: 10.4172/2161-1149.1000235]

2 **Barnes J**, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012; 24: 165-170 [DOI: 10.1097/BOR.0b013e32834f2e8]

3 **Chifflet H**, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum* 2008; 37: 223-235 [PMID: 17692364 DOI: 10.1016/j.semarthritis.2007.05.003]

4 **Bergamasco A**, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. *Clin Epidemiol* 2019; 11: 257-273 [PMID: 31114386 DOI: 10.2147/CLEP.S191418]

5 **Ponge T**, Bruley des Varannes S. [Digestive involvement of scleroderma]. *Rev Prat* 2002; 52: 1896-1900 [PMID: 12532866]

6 **Sjogren RW**. Gastrointestinal motility disorders in scleroderma. *Arthritis Rheum* 1994; 37: 1265-1282 [PMID: 7945489 DOI: 10.1002/art.1780370902]

7 **Notoumazios SK**, Vouglari PV, Potsis K, Koutis E, Tsifetaki N, Assimakopoulos DA. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. *Semin Arthritis Rheum* 2006; 36: 173-181 [PMID: 17045829 DOI: 10.1016/j.semarthritis.2006.08.002]

8 **Carlson DA**, Hinchcliff M, Pandolfino JE. Advances in the evaluation and management of esophageal disease of systemic sclerosis. *Curr Rheumatol Rep* 2015; 17: 475 [PMID: 25475597 DOI: 10.1007/s11926-014-0475-x]

9 **Savino E**, Bazzica M, Zentlini P, Pohl D, Parodi A, Cittadini G, Negrini S, Indiveri F, Tutuian R, Savarino V, Ghio M. Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. *Am J Respir Crit Care Med* 2009; 179: 408-413 [PMID: 19096004 DOI: 10.1164/rccm.200808-1359OC]

10 **Lock G**, Holstege A, Lang B, Schölmerich J. Gastrointestinal manifestations of progressive systemic sclerosis. *Am J Gastroenterol* 1997; 92: 763-771 [PMID: 9149182]

11 **Denton CP**, Khanna D. Systemic sclerosis. *Lancet* 2017; 390: 1685-1699 [PMID: 28413064 DOI: 10.1016/S0140-6736(17)30933-9]

12 **Titremault MP**, Kahrilas P. GI Manifestations With a Focus on the Esophagus: Recent Progress in Understanding Pathogenesis. *Curr Rheumatol Rep* 2019; 21: 42 [PMID: 31270707 DOI: 10.1007/s11926-019-014-074-7]

13 **Sgouros R**, Gruschwitz MS, Boeck G, Sepp N, Gruber J, Wick G. Endothelial cell apoptosis in systemic sclerosis is induced by antibody-dependent cell-mediated cytotoxicity via CD95. *Arthritis Rheum* 2000; 43: 2550-2562 [PMID: 11083280 DOI: 10.1002/1529-0131(200011)43:11<2550::AID-ANR2-3.0.CO;2-H>]

14 **Kahaleh MB**, Fan PS, Otsuka T. Gammadelta receptor bearing T cells in scleroderma: enhanced interaction with vascular endothelial cells in vitro. *Clin Immunol* 1999; 91: 188-195 [PMID: 10227311 DOI: 10.1006/clim.1999.4694]

15 **Nicola S**, Rolla G, Bucca C, Geronazzo G, Roldofi I, Ferraris A, Fusaro E, Peroni CL, Dughiera L, Brussino L. Gastric Juice Expression of Th-17 and T-Reg Related Cytokines in Scleroderma Esophageal Involvement. *Cells* 2020; 9 [PMID: 32947843 DOI: 10.3390/cells90902106]

16 **Gasse P**, Mary C, Guenon I, Noulin N, Charron S, Schnyder-Candrian S, Schnyder B, Akina S, Quensiaux VF, Lagente V, Ryffel B, Couillin I. IL-1R1/MyD88 signaling and the inflammasome are essential in pulmonary inflammation and fibrosis in mice. *J Clin Invest* 2007; 117: 3786-3799 [PMID: 17992263 DOI: 10.1172/JCI32285]

17 **Algedik R**, Algedik S, Karamanlo H, Uysal S, Bozkurt B, Ozol D, Armutcu F, Yıldırım Z. Effect of resveratrol on treatment of bleomycin-induced pulmonary fibrosis in rats. *Inflammation* 2012; 35: 1732-1741 [PMID: 22707284 DOI: 10.1007/s10753-012-9491-6]

18 **Kantola AK**, Ryyrönen MJ, Lhotá F, Keski-Oja J, Koli K. Independent regulation of short and long forms of latent TGF-beta binding protein (LTBP)-4 in cultured fibroblasts and human tissues. *J Cell Physiol* 2010; 223: 727-736 [PMID: 20175115 DOI: 10.1002/jcp.22092]

19 **Zülbérg L**, Todoric V, Dabovic B, Horugusi M, Couroussis T, Sakai LY, Rifkin DB. Specificity of latent TGF-β binding protein (LTBP) incorporation into matrix: role of fibrillins and fibronecin. *J Cell Physiol* 2012; 227: 3828-3836 [PMID: 22495824 DOI: 10.1002/jcp.20494]

20 **Lu J**, Liu Q, Wang L, Tu W, Chu H, Ding W, Jiang S, Ma Y, Shi X, Pu W, Zhou X, Jin L, Wang J, Wu W. Increased expression of latent TGF-β-binding protein 4 affects the fibrotic process in scleroderma by TGF-β/SMAD signaling. *Labor Investigat* 2017; 97: 591-601 [DOI: 10.1038/Labinvest.2017.20]

21 **Alastal Y**, Hammad TA, Renno A, Khalil B, Pierre J, Kwaah B, Khudar SA, Nawras A. Gastrointestinal manifestations associated with systemic sclerosis: results from the nationwide inpatient sample. *Ann Gastroenterol* 2017; 30: 498-503 [PMID: 28845104 DOI: 10.20524/aog.2017.0171]

22 **Braun-Moscovici Y**, Brun R, Braun M. Systemic Sclerosis and the Gastrointestinal Tract-Clinical Approach. *Rambam Maimonides Med J* 2016; 7 [PMID: 27824553 DOI: 10.5041/RMMJ.10258]

23 **Gyger G**, Baron M. Systemic Sclerosis: Gastrointestinal Disease and Its Management. *Rheum Dis Clin North Am* 2015; 41: 459-473 [PMID: 26210129 DOI: 10.1016/j.rdc.2015.04.007]

24 **Lock G**, Pfeifer M, Straub RH, Zeuner M, Lang B, Schölmerich J, Holstege A. Association of
esophageal dysfunction and pulmonary function impairment in systemic sclerosis. Am J Gastroenterol 1998; 93: 341-345 [PMID: 9517636 DOI: 10.1111/j.1572-0241.1998.00341.x]

25 Orringer MB, Dabich L, Zarafonetis CJ, Sloan H. Gastroesophageal reflux in esophageal scleroderma: diagnosis and implications. Ann Thorac Surg 1976; 22: 120-130 [PMID: 9916 DOI: 10.1016/0003-4975(76)90720-0]

26 Zamost BJ, Hirschberg J, Ippoliti AF, Furst DE, Clements PJ, Weinstein WM. Esophagegitis in scleroderma. Prevalence and risk factors. Gastroenterology 1987; 92: 421-428 [PMID: 3491774 DOI: 10.1016/S0016-5085(79)90137-5]

27 Weston S, Thumshirn M, Wiste J, Camilleri M. Clinical and upper gastrointestinal motility features in systemic sclerosis and related disorders. Am J Gastroenterol 1998; 93: 1085-1089 [PMID: 9672335 DOI: 10.1111/j.1572-0241.1998.00334.x]

28 Katzka DA, Reynolds JC, Saul SH, Plotkin A, Lang CA, Ouyang A, Jimenez S, Cohen S. Barrett's metaplasia and adenocarcinoma of the esophagus in scleroderma. Am J Med 1987; 82: 46-52 [PMID: 3799692 DOI: 10.1016/0002-9343(87)90376-7]

29 Segel MC, Campbell WL, Medsger TA Jr, Roumm AD. Systemic sclerosis (scleroderma) and esophageal adenocarcinoma: Is increased patient screening necessary? Gastroenterology 1985; 89: 485-488 [PMID: 3926590 DOI: 10.1016/0016-5085(85)90440-8]

30 Bhalla M, Silver RM, Shepard JA, McLeod TC. Chest CT in patients with scleroderma: prevalence of asymptomatic esophageal dilatation and mediastinal lymphadenopathy. AJR Am J Roentgenol 1993; 161: 269-272 [PMID: 8333359 DOI: 10.2214/ajr.161.2.8333359]

31 Thonhofer R, Siegel C, Trummer M, Graninger W. Early endoscopy in systemic sclerosis without gastrointestinal symptoms. Rheumatol Int 2012; 32: 165-168 [PMID: 20711592 DOI: 10.1007/s00296-010-1595-y]

32 Marie I, Dominique S, Levesque H, Ducrotte P, Denis P, Hellot MF, Courtoir H. Esophageal involvement and pulmonary manifestations in systemic sclerosis. Arthritis Rheum 2001; 45: 346-354 [PMID: 11501722 DOI: 10.1002/1529-0131(200108)45:4<346::AID-ART347>3.0.CO;2-L]

33 Johnson DA, Drane WE, Curran J, Cattau EL Jr, Ciarleglio C, Khan A, Cotelingam J, Benjamin SB. Pulmonary disease in progressive systemic sclerosis. A complication of gastroesophageal reflux and occult aspiration? Arch Intern Med 1989; 149: 589-593 [PMID: 2919934]

34 Marie I, Ducrotte P, Denis P, Hellot MF, Levesque H. Oesophageal mucosal involvement in patients with systemic sclerosis receiving proton pump inhibitor therapy. Aliment Pharmacol Ther 2006; 24: 1593-1601 [PMID: 17206947 DOI: 10.1111/j.1365-2036.2006.03180.x]

35 Ebert EC. Esophageal disease in scleroderma. J Clin Rheumatol 2006; 40: 769-775 [PMID: 17016130 DOI: 10.1097/01.rhe.0000225549.19127.90]

36 Appel JZ. 3rd, Lee SM, Hartwig MG, Li B, Hsieh CC, Cantu E 3rd, Yoon Y, Lin SS, Parker W, Davis RD. Characterization of the innate immune response to chronic aspiration in a novel rodent model. Respir Res 2007; 8: 87 [PMID: 18042282 DOI: 10.1186/1465-9921-8-87]

37 Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J, Cuttica MJ, Dematte JD, Chang RW, Hinrichs ME. Esophageal dilatation and interstitial lung disease in systemic sclerosis: A cross-sectional study. Semin Arthritis Rheum 2016; 46: 109-114 [PMID: 27033049 DOI: 10.1016/j.semarthrit.2016.02.004]

38 Smith V, Scirià CA, Talarico R, Airo P, Alexander T, Allarone Y, Bruni C, Codullo V, Dalm V, De Vries-Bouwstra J, Dell Rossa A, Distler O, Galetti I, Lanay D, Lepri G, Mathiow, A, Moutheon L, Ruaro B, Sulli A, Tincani A, Van de Casteele E, Vanhaecke A, Vantuynne M, Van den Hoogen F, Van Vollenhoven R, Vorisky AE, Zanatta E, Bombardiere S, Burmester G, Eurico FJ, Frank C, Hachulla E, Houssiau F, Mueller-Ladner U, Schneider M, van Laar JM, Vieira A, Cutolo M, Mosca M, Mattucci-Cerinic M. Systemic sclerosis: state of the art on clinical practice guidelines. RMD Open 2018; 4: e000782 [PMID: 30402270 DOI: 10.1136/rmdopen-2018-000782]

39 Lahcene M, Oumnia N, Matougui N, Boudjella M, Tebaibia A, Touchene B. Esophageal involvement in scleroderma: clinical, endoscopic, and sonographic features. ISRN Rheumatol 2011; 2011: 325826 [PMID: 22389793 DOI: 10.5402/2011/325826]

40 Petcu A, Ghilb LJ, Grad SM, Popovici C, Rogojan L, Rednic NV, Rednic S. Upper gastrointestinal involvement in systemic sclerosis: Findings in a real-life setting. Exp Ther Med 2019; 18: 5095-5100 [PMID: 31798729 DOI: 10.3892/etm.2019.8125]

41 Wipff J, Coriat R, Masciocchi M, Caramaschi P, Derk CT, Hachulla E, Riccieri V, Mouton L, Krasowska D, Ananyeva LP, Kahan A, Matuscini-Cerinic M, Chaussade S, Allarone Y. Outcomes of Barrett's oesophagus related to systemic sclerosis: a 3-year EULAR Scleroderma Trials and Research Initiative follow-up study. Rheumatology (Oxford) 2011; 50: 1440-1444 [PMID: 21415021 DOI: 10.1093/rheumatology/ker110]

42 Schutyser W, Cruyt L, Vulpsteke JB, Lenaerts JL, De Langhe E. The role of high-resolution manometry in the assessment of upper gastrointestinal involvement in systemic sclerosis: a systematic review. Clin Rheumatol 2020; 39: 149-157 [PMID: 31709478 DOI: 10.1007/s10067-019-04794-w]

43 Al-Amri SM. The pattern of esophageal manometry in progressive systemic sclerosis. J Clin Med 2003; 24: 68-71 [PMID: 12590279]

44 Savarino E, Mei F, Parodi A, Ghio M, Furnari M, Gentile A, Berdini M, Di Sario A, Bendia E, Bonazzi P, Scarpellini E, Laterza L, Savarino V, Gasbarrini A. Gastrointestinal motility disorder assessment in systemic sclerosis. Rheumatology (Oxford) 2013; 52: 1095-1100 [PMID: 23382360 DOI: 10.1093/rheumatology/kes429]

45 Crowell MD, Umar SB, Griffing WL, DiBaise JK, Lacy BE, Vela MF. Esophageal Motor
Abnormalities in Patients With Scleroderma: Heterogeneity, Risk Factors, and Effects on Quality of Life. *Clin Gastroenterol Hepatol* 2017; 15: 207-213. e1 [PMID: 27613260 DOI: 10.1016/j.cgh.2016.08.034]

46 Ogliali C, Piazza O, Sed N, Vecchi M. High Resolution Manometry in Scleroderma Patients. *Clin Gastroenterol Hepatol* 2017; 15: 1640-1641 [PMID: 28552803 DOI: 10.1016/j.cgh.2017.05.030]

47 Roman S, Hot A, Fabien N, Cordier JF, Miousser P, Ninet J, Mion F. Rseau Sclerodermie des Hospices Civils de Lyon. Esophageal dysmotility associated with systemic sclerosis: a high-resolution manometry study. *Dis Esophagus* 2011; 24: 299-304 [PMID: 21166734 DOI: 10.1111/j.1442-2050.2010.01150.x]

48 Raja J, Ng CT, Sujau I, Chin KF, Sockalingam S. High-resolution oesophageal manometry and 24-hour impedance-pH study in systemic sclerosis patients: association with clinical features, symptoms and severity. *Clin Exp Rheumatol* 2016; 34 Suppl 100: 115-121 [PMID: 26843456]

49 Arana-Guajardo AC, Barrera-Torres G, Villarreal-Alarcen MA, Vega-Morales D, Esquivel-Valerio JA. Esophageal symptoms and their lack of association with high-resolution manometry in systemic sclerosis patients. *Reumatol Clin* 2019; 15: 165-169 [PMID: 29258705 DOI: 10.1016/j.reuma.2017.09.005]

50 Kimmel JN, Carlson DA, Hinchcliff M, Carns MA, Aren KA, Lee J, Pandolfino JE. The association between systemic sclerosis disease manifestations and esophageal high-resolution and esophageal-resolution manometry parameters. *Neurogastroenterol Motil* 2016; 28: 1157-1165 [PMID: 26921101 DOI: 10.1111/nmo.12813]

51 de Carlan M, Lescoat A, Brochard A, Coiffier G, Cazalets C, Ropert A, Jigo P. Association between Clinical Manifestations of Systemic Sclerosis and Esophageal Dysmotility Assessed by High-Resolution Manometry. *J Scler Rel Dis* 2017; 2: 50-56 [DOI: 10.5301/jsr.5000233]

52 Abozaid HSM, Imam HMK, Abdelaziz MM, El-Hammady DH, Fathi NA, Forst DE. High-resolution manometry compared with the University of California, Los Angeles Scleroderma Clinical Trials Consortium GIT 2.0 in Systemic Sclerosis. *Semin Arthritis Rheum* 2017; 47: 403-408 [PMID: 28624173 DOI: 10.1016/j.semarthrit.2017.05.005]

53 Vettori S, Tolone S, Capocotta D, Chieffo R, Giaco V, Valentini G, Docimo L. Esophageal high-resolution impedance manometry alterations in asymptomatic patients with systemic sclerosis: prevalence, associations with disease features, and prognostic value. *Clin Rheumatol* 2018; 37: 1239-1247 [PMID: 29442260 DOI: 10.1007/s10067-018-4026-1]

54 Foocharoen C, Chumleeithi K, Mairipang P, Mahakanakrua A, Suwannaraj S, Namvijit S, Wantha O, Nanagara R. Prevalence and predictors of proton pump inhibitor partial response in gastroesophageal reflux disease in systemic sclerosis: a prospective study. *Sci Rep* 2020; 10: 769 [PMID: 31964957 DOI: 10.1038/s41598-020-57636-0]

55 Stern EK, Carlson DA, Falmagne S, Hoffmann AD, Carns M, Pandolfino JE, Hinchcliff M, Brenner DM. Abnormal esophageal acid exposure on high-dose proton pump inhibitor therapy is common in systemic sclerosis patients. *Neurogastroenterol Motil* 2018; 30 [PMID: 29910377 DOI: 10.1111/nmo.12474]

56 Arif T, Masood Q, Singh J, Hassan I. Assessment of esophageal involvement in systemic sclerosis and morphea (localized scleroderma) by clinical, endoscopic, manometric and pH metric features: a prospective comparative hospital based study. *BMC Gastroenterol* 2015; 15: 24 [PMID: 25888470 DOI: 10.1186/s12876-015-0241-2]

57 Weber P, Ganser G, Froisch M, Roth J, Höskamp G, Zimmer KP. Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease. *J Rheumatol* 2000; 27: 2692-2695 [PMID: 11093455]

58 Matsuda R, Yamamichi N, Shimamoto T, Sumida H, Takahashi Y, Minatsuki C, Kodashima S, Ono S, Nimi K, Tsuji Y, Sakaguchi Y, Saito I, Kataoka Y, Asada-Hirayama I, Kikimoto H, Yakabi S, Takeuchi C, Matsumoto Y, Tamaki Z, Fujishiro M, Asano Y, Sato S, Koike K. Gastroesophageal Reflux Disease-Related Disorders of Systemic Sclerosis Based on the Analysis of 66 Patients. *Digestion* 2018; 98: 201-208 [PMID: 30045036 DOI: 10.1159/000489848]

59 Karamanolis GP, Denaxas K, Panopoulos S, Bournia K, Zorbala A, Kamberoglou D, Schizas D, Ladas SD, Sifkakis PP. Severe oesophageal disease and its associations with systemic sclerosis. *Clin Exp Rheumatol* 2017; 35 Suppl 106: 82-85 [PMID: 28869413]

60 Pietrz E, Bredemeier M, Xavier RM, Capobianco KG, Restelli VG, Vieira MV, Ludwig DH, Brenol JG, Furtado AP, Fonseca LM, Guifilen B. Oesophageal dysmotility in systemic sclerosis: comparison of HRCT and scintigraphy. *Br J Radiol* 2006; 79: 719-724 [PMID: 16885178 DOI: 10.1259/bjr/17000205]

61 Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108: 308-328; quiz 329 [PMID: 23419381 DOI: 10.1038/ajg.2012.444]

62 Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med* 2008; 359: 1700-1707 [PMID: 18923172 DOI: 10.1056/NEJMcp0804684]

63 Hendel I, Hage E, Hendel J, Stentoff P. Omeprazole in the long-term treatment of severe gastrooesophageal reflux disease in patients with systemic sclerosis. *Aliment Pharmacol Ther* 1999; 6: 565-577 [PMID: 14207484 DOI: 10.1111/j.1365-2036.1999.tb00571.x]

64 Pakozdi A, Wilson H, Black CM, Denton CP. Does long term therapy with lansoprazole slow progression of oesophageal involvement in systemic sclerosis? *Clin Exp Rheumatol* 2009; 27: 5-8 [PMID: 19796554]
Voulgaris TA et al. Esophageal manifestation in patients with scleroderma

65 Muro Y, Sugira K, Nitta Y, Mitsuma T, Hoshino K, Usuda T, Hayashi K, Murase Y, Shimizu M, Matsuo H. Scoring of reflux symptoms associated with scleroderma and the usefulness of rabeprazole. *Clin Exp Rheumatol* 2009; 27: 15-21 [PMID: 19796556]

66 Shreiner AB, Murray C, Denton C, Khanna D. Gastrointestinal Manifestations of Systemic Sclerosis. *J Scleroderma Relat Disord* 2016; 1: 247-256 [PMID: 28133631 DOI: 10.5301/jsrd.5000214]

67 Foucaroen C, Chunletriith K, Mairiang P, Mahakkanukrauh A, Suwanmaro S, Namvijit S, Wantha O, Nanagara R. Effectiveness of add-on therapy with domperidone vs alginic acid in proton pump inhibitor partial response gastro-esophageal reflux disease in systemic sclerosis: randomized placebo-controlled trial. *Rheumatology (Oxford)* 2017; 56: 214-222 [PMID: 27179107 DOI: 10.1093/rheumatology/kew216]

68 Hussain ZH, Henderson EE, Maradey-Romero C, George N, Fass R, Lacy BE. The Proton Pump Inhibitor Non-Responder: A Clinical Conundrum. *Clin Transl Gastroenterol* 2015; 6: e106 [PMID: 26270485 DOI: 10.1038/ctg.2015.32]

69 Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastrointestinal reflux disease. *Am J Gastroenterol* 2011; 106: 1419-1425; quiz 1426 [PMID: 21537361 DOI: 10.1038/ajg.2011.146]

70 Hoshino S, Kawami N, Takenouchi N, Umezawa M, Hanada Y, Hoshikawa Y, Kawagoe T, Sano H, Hoshihara Y, Nomura T, Iwakiri K. Efficacy of Vonoprazan for Proton Pump Inhibitor-Resistant Reflux Esophagitis. *Digestion* 2017; 95: 156-161 [PMID: 28190016 DOI: 10.1159/000456072]

71 Akazawa Y, Fukuda D, Fukuda Y. Vonoprazan-based therapy for *Helicobacter pylori* eradication: experience and clinical evidence. *Therap Adv Gastroenterol* 2016; 9: 345-352 [PMID: 27083739 DOI: 10.1177/17562831X16668093]

72 Tabuchi M, Minami H, Akazawa Y, Ashida M, Hara T, Ichinose K, Kitayama M, Hashiguchi K, Matsushima K, Yamaguchi N, Takeshima F, Kondo H, Kawakami A, Nakao K. Use of vonoprazan for management of systemic sclerosis-related gastrointestinal reflux disease. *Biomed Rep* 2021; 14: 25 [PMID: 33408859 DOI: 10.3892/br.2020.1401]

73 Ramirez-Mata M, Ibanez G, Alarcon-Segovia D. Stimulatory effect of metoclopramide on the esophagus and lower esophageal sphincter of patients with PSS. *Arthritis Rheum* 1977; 20: 30-34 [PMID: 319806 DOI: 10.1002/art.1780200105]

74 Di Martino N, Ingrasso M, Fei L, Maffettone V, Landolfi V, Del Genio A. [Behavior of the lower esophageal sphincter after intravenous administration of domperidone in normal subjects]. *Minerva Med* 1985; 76: 1411-1417 [PMID: 4022433]

75 Wehrenmann T, Caspary WF. [Effect of cisapride on esophageal motility in healthy probands and patients with progressive systemic sclerosis]. *Klin Wochenschr* 1990; 68: 602-607 [PMID: 2198381 DOI: 10.1007/BF01660958]

76 Sallam H, McNearney TA, Chen JD. Systematic review: pathophysiology and management of gastrointestinal dysmotility in systemic sclerosis (scleroderma). *Aliment Pharm Ther* 2006; 23: 691-712 [PMID: 1655617 DOI: 10.1111/j.1366-2036.2006.02804.x]

77 Johnson DA, Drane WE, Curran J, Benjjamin SB, Chobanian SJ, Karvelis K, Cattau EL Jr. Metoclopramide response in patients with progressive systemic sclerosis. Effect on esophageal and gastric motility abnormalities. *Arch Intern Med* 1987; 147: 1597-1601 [PMID: 3632168]

78 Nagaraja V, McMahan ZH, Geituz T, Khanna D. Management of gastrointestinal involvement in scleroderma. *Curr Treatm Opt Rheumatol* 2015; 1: 82-105 [PMID: 26005632 DOI: 10.1007/s40674-014-0005-0]

79 Tonini M, De Ponti F, Di Nucci A, Crema F. Review article: cardiac adverse effects of gastrointestinal prokinetics. *Aliment Pharm Ther* 1999; 13: 1585-1591 [PMID: 10594392 DOI: 10.1046/j.1365-2036.1999.00655.x]

80 Hansi N, Thoua N, Carulli M, Chakraverty K, Lal S, Smyth A, Herrick A, Ogunbiyi O, Shaffer J, Mclaughlin J, Denton C, Ong V, Emmanuel AV, Murray CD. Consensus best practice pathway of the UK scleroderma study group: gastrointestinal manifestations of systemic sclerosis. *Clin Exp Rheumatol* 2014; 32: S-214 [PMID: 25372804]

81 Pappas PG, Kaufman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 62: e1-50 [PMID: 26679628 DOI: 10.1093/cid/ciw933]

82 Blonski W, Vela MF, Freeman J, Sharma N, Castell DO. The effect of oral buspirome, pyridostigmine, and bethanecol on esophageal function evaluated with combined multichannel esophageal impedance-manometry in healthy volunteers. *J Clin Gastroenterol* 2009; 43: 253-260 [PMID: 18987553 DOI: 10.1097/MCG.0b013e3181868989]
Orringer MB, Orringer JS, Zarafonetis CJ. Combined Collis gastroplasty--fundoplication operations for scleroderma reflux esophagitis. *Surgery* 1981; 90: 624-630 [PMID: 7281001]

Mansour KA, Malone CE. Surgery for scleroderma of the esophagus: a 12-year experience. *Ann Thorac Surg* 1988; 46: 513-514 [PMID: 3190323 DOI: 10.1016/0003-4975(88)90516-1]

Goldberg MB, Abbas AE, Smith MS, Parkman HP, Schey R, Dempsey DT. Minimally Invasive Fundoplication Is Safe and Effective in Patients With Severe Esophageal Hypomotility. *Innovations (Phila)* 2016; 11: 396-399 [PMID: 27922988 DOI: 10.1097/MII.0000000000000315]

Kent MS, Luketich JD, Irshad K, Awais O, Alvelo-Rivera M, Churilla P, Fernando HC, Landreneau RJ. Comparison of surgical approaches to recalcitrant gastroesophageal reflux disease in the patient with scleroderma. *Ann Thorac Surg* 2007; 84: 1710-5; discussion 1715 [PMID: 17954091 DOI: 10.1016/j.athoracsur.2007.06.025]

Yan J, Strong AT, Sharma G, Gabbard S, Thota P, Rodriguez J, Kroh M. Surgical management of gastroesophageal reflux disease in patients with systemic sclerosis. *Surg Endosc* 2018; 32: 3855-3860 [PMID: 29435755 DOI: 10.1007/s00464-018-6115-2]

Bakhos CT, Petrov RV, Parkman HP, Malik Z, Abbas AE. Role and safety of fundoplication in esophageal disease and dysmotility syndromes. *J Thorac Dis* 2019; 11: S1610-S1617 [PMID: 31489228 DOI: 10.21037/jtd.2019.06.62]
