HHS Public Access

Author manuscript

*Curr Treatm Opt Rheumatol*. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

*Curr Treatm Opt Rheumatol*. 2015 March 1; 1(1): 82–105. doi:10.1007/s40674-014-0005-0.

# Management of gastrointestinal involvement in scleroderma

**Vivek Nagaraja, MD**[1,*], **Zsuzsanna H. McMahan, MD MHS**[2,*], **Terri Getzug, MD**, and **Dinesh Khanna, MD MS**[4]

[1]Division of Rheumatology, University of Toledo, Toledo, Ohio [2]Division of Rheumatology, John Hopkins University, Baltimore, Maryland [3]Division of Gastroenterology, UCLA, Los Angeles, California [4]Division of Rheumatology, University of Michigan, Ann Arbor, Michigan

## Abstract

Gastrointestinal tract (GIT) commonly affects patients with systemic sclerosis (SSc). The GI involvement is quite heterogeneous varying from asymptomatic disease to significant dysmotility causing complications like malabsorption, weight loss and severe malnutrition. This review focuses on the management of GI involvement in SSc and has been categorized based on the segment of GIT involved. A brief discussion on the role of patient reported outcome measures in SSc-GI involvement has also been incorporated.

Corresponding author: Dinesh Khanna, MD, MSc Associate Professor of Medicine Director, University of Michigan Scleroderma Program Division of Rheumatology/Dept. of Internal Medicine Suite 7C27 300 North Ingalls Street, SPC 5422 Ann Arbor, MI 48109 khannad@med.umich.edu Phone: 734.647.8173 Fax: 734.763.5761.

Other author information:

Vivek Nagaraja, MD Assistant professor, Division of Rheumatology Division of Rheumatology / Department of Internal Medicine University of Toledo Medical center 3000 Arlington Ave, mailstop 1186 Toledo, OH 43614 Vivek.Nagaraja@utoledo.edu Phone: 419 383 4271 Fax 419 383 6197

Zsuzsanna H. McMahan, MD, MHS Assistant Professor of Medicine Johns Hopkins University Division of Rheumatology 5501 Hopkins Bayview Circle Baltimore, MD 21224 zmcmaha1@jhmi.edu Phone: 410-550-7715 Fax: 410-550-1363

Terri Getzug, MD Clinical Professor of Medicine Division of Digestive Diseases David Geffen School of Medicine at UCLA 100 UCLA Medical Plaza Ste 303 Los Angeles, CA 90095 tgetzug@mednet.ucla.edu Phone: 310-206-6279

*Co-first authors

General

Compliance with Ethics Guidelines

Conflict of Interest

Vivek Nagaraja reports that he has no conflict of interest.

Terri Getzug reports that she has no conflict of interest.

Zsuzsanna H. McMahan reports funding from the Rheumatology Research Foundation.

Dinesh Khanna reports grants from EMD SERONO, BRISTOL-MEYERS SQUIBB, BAYER, GILEAD, InterMune, NIH/NI AMS, Actelion, Astra-Zenica, Scleroderma Foundation and Pulmonary Hypertension Association; personal fees from Actelion, Astra-Zenica, Bayer, Biogen Idec, BRISTOL-MEYERS SQUIBB, Genentech/ Roche, Glaxo SmithKline, InterMune, EMD Serono, Sanofi-Aventis/Genzyme, Takeda, Lycera, Cytori; other from Actelion, Astra-Zeneca, Biogen Idec, Bristol Myers Squibb, Genentech/ Roche, GlaxoSmithKline, InterMune, EMD Serono, Sanofi-Aventis/Genzyme, and Takeda during the conduct of the study

Human and Animal Rights and Informed Consent

Human studies done by authors (but no animal studies)

This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

**Keywords**

Gastrointestinal tract; systemic sclerosis; scleroderma; gastroesophageal reflux; dysphagia; gastroparesis; gastric antral vascular ectasia; bacterial overgrowth; intestinal dysmotility; nutrition; constipation; diarrhea

## Introduction

Gastrointestinal (GI) disease is a major cause of morbidity and mortality in systemic sclerosis (SSc) [1-3]. Gastrointestinal involvement occurs early in SSc and most patients (up to 90%) are affected [4-6]. In SSc, gastrointestinal disease is heterogeneous, clinically ranging from asymptomatic disease to significant dysmotility, and the time course may vary from indolent to rapidly progressive. While the entire GI tract (GIT) may be involved, the predominantly affected region of dysmotility within the GIT often varies among patients further contributing to the complexity of management [5, 7].

Optimizing therapies to improve gastrointestinal function in patients with SSc is critical as symptoms of dysmotility significantly impact quality of life. Nausea, vomiting, diarrhea, weight loss, severe constipation, and fecal incontinence, all may culminate in severe malnutrition [8-10]. This review discusses the approach to gastrointestinal disease management in SSc and is divided into sections addressing targeted therapies for different GI complications. A summary of the GI management in SSc can be found in Table 1, and a list of common medications used can be found in Table 2.

### Approach to Treatment of Esophageal Complications of Systemic Sclerosis

The esophagus is involved early in SSc and is the most frequently involved portion of the GIT affecting approximately 80% of patients [6, 11]. While the majority of patients are symptomatic, the absence of symptoms does not exclude esophageal dysfunction [11-13].

### Gastroesophageal Reflux Disease (GERD)

Gastroesophageal Reflux Disease (GERD) in SSc is often multifactorial and related to a combination of esophageal and/or gastric dysmotility as well as a normal, weak, or incompetent LES [14, 15].

GERD management aims to provide symptom relief and prevent erosions, strictures, and pre-malignant transformation (e.g. Barrett's) [15-17]. Several studies suggest that uncontrolled GERD is associated with micro-aspiration, possibly contributing to the presence and progression of interstitial lung disease [18-21] although the causal association has not been determined.

**Lifestyle modification and non-prescription medications—**GERD management involves a multi-pronged approach. Lifestyle modification is an important initial step and includes the avoidance of (1) aggravating foods (2) eating more than 3 hours before bed, and (3) avoidance of alcohol and smoking tobacco products [22, 23]. Elevating the head of the bed at night by 6 inches with a wedge pillow or cinder blocks may also help alleviate

symptoms. Ingestion of multiple small meals throughout the day rather than three large meals is recommended [24, 25]. Over the counter antacids may be used for mild disease on an as-needed basis, although they are not generally enough to prevent complications of GERD.

**Proton pump inhibitors—**Proton pump inhibitors (PPI) may be prescribed as a single or double dose in moderate to severe GERD. Although objective data supporting double dose PPI is limited and some studies suggest no significant improvement in esophageal acid exposure or symptom control, the treatment options for severe GERD are limited and some patients may benefit [26]. Risks associated with prolonged PPI use are important to consider and include osteoporosis, risk of C.difficile infection, pneumonia and interaction with anti-platelet agents. These risks should be discussed at the time of drug initiation [27-30]. These associations are noted in large cohort studies in the general population and in the authors' view, the benefits of PPIs outweigh the risks. Of the six available PPI's, the traditional delayed release PPI's include omeprazole, lansoprazole, pantoprazole, and rabeprazole. They are prodrugs that are activated upon exposure to the acidic environment of the secretory canaliculus. With these drugs, synchronizing ingestion of the drug with meal-stimulated acid secretion optimizes acid suppression. Therefore, these PPI's should be ingested 15-60 minutes prior to a meal, which may negatively affect compliance [31]. Given differences in bioavailability and efficacy between PPI's, switching to an alternative PPI (e.g. from older to newer) may be effective. An oral dissolving PPI such as lansoprazole can also be used in patients with esophageal stasis.

If symptoms of GERD persist despite twice daily PPI, H2 receptor antagonists (H2RA) may be prescribed at night or further evaluation with esophageal pH testing can be tried. Testing may be performed while on therapy in combination with pH impedance testing in such patients. This approach helps to clarify the efficacy of the prescribed PPI therapy by defining pathological acid vs. non-acid exposure [23]. Esophageal manometry in refractory GERD is of limited value and not recommended. Its use is primarily for accurate placement of trans-nasal pH impedance probes and to rule out severe hypomotility (e.g. severe scleroderma esophageal dysfunction) or achalasia prior to anti-reflux surgery [23].

**H2 Receptor antagonists & combination therapy—**The H2RA (nizatidine, famotidine, cimetidine, ranitidine) may also be used independently from or in combination with the PPI's to control GERD [32]. As nocturnal acid secretion is largely dependent on histamine secretion, it is more refractory to PPI's. As a result, H2RAs are often added in the evening for overnight symptom control [33, 34].

Baclofen, a gamma-aminobutyric acid receptor type B (GABA-B) agonist, also suppresses acid reflux. It inhibits transient LES relaxations, augmenting LES pressure and length, and may suppress reflux through a "flap valve" mechanism [35]. It is used in GERD symptom management, although no trials have formally evaluated its use in scleroderma. Sucralfate is an alternative agent, in cases of erosive esophagitis, although it may aggravate constipation in patients and data supporting benefit is limited.

**Prokinetics—**In the acute setting, esophageal dysmotility may culminate in GERD and erosive esophagitis, and when untreated may cause strictures, and Barrett's esophagus [7, 16]. Prokinetic agents are reported to improve GERD symptoms in SSc, by improving gastric emptying [13, 36], although limited benefit has been demonstrated in clinical trials [37]. Combination therapy with prokinetic agents and acid blocking agents may improve symptoms and reduce the risk of tissue damage in early disease but will have little to no impact in later stages where smooth muscle atrophy is prominent [13, 38]. Both metoclopramide and erythromycin contribute to GERD control through increasing LES tone and gastric emptying [39-41]. Other agents (e.g. cisapride and domperidone) are reported to improve symptoms but associated toxicities resulted in strict regulation [36, 42, 43].

**Endoscopic anti-reflux procedures—**Upper endoscopy to disrupt strictures is used for symptomatic patients, although no controlled studies are available in SSc. Other more invasive surgical procedures are potential interventions in SSc GERD, and include fundoplication as well as antrectomy with Roux-en-Y anastomosis[44]. While these interventions may benefit some [45], patients with SSc are at increased risk of associated complications, especially worsening dysphagia, thus they are reserved for selected patients [7, 46]. If absolutely required, experienced cardiothoracic surgeons should perform the surgery.

**Novel therapies—**Acupuncture was evaluated in a non- SSc population for GERD control. Double dose PPI was compared to adding acupuncture to regular dose PPI and was found to be more effective in controlling GERD[47]; however, it is unclear if the effects of acupuncture on SSc skin would yield similar results. Application of TENS for dysmotility was suggested as efficacious in a SSc population although more data is needed [48]. Several novel pharmacological targets are under investigation for the management of GERD including nitrous oxide synthase, CCK receptors, cannabinoid receptors, gherlin, muscarinic receptors, and opioid receptors aim at treating GERD via reduction of the transient lower esophageal sphincter relaxation (TLESR). The efficacy and safety of these agents are still being determined.

**Key recommendations for management of gastro-esophageal reflux disease—**In summary, SSc patients are at high risk for refractory GERD and may require aggressive symptom management. Lifestyle modifications including head of the bed elevation, and avoidance of meals 3 hours before bedtime are recommended for nocturnal GERD. Avoidance of aggravating foods is important. Traditional delayed release PPI's are given 30-60 minutes prior to meals for maximal pH control, though this is less important for the newer PPI's. For patients who fail daily PPI's, a reminder conveying the recommended PPI dosing time and compliance should be communicated. If the patient is compliant, then a different PPI may be tried (e.g. pantoprazole to omeprazole) and BID dosing may subsequently be implemented if there is no significant change with alternative drugs. Patients refractory to twice daily PPI's, may add H2 receptor antagonists at night and/or see a gastroenterologist for upper endoscopy, and esophageal pH testing and impedance. If these tests confirm persistent acid reflux, nightly H2RA should be added. Interventions for GERD, outside of acid-suppression (e.g. prokinetics, baclofen) should not be implemented prior to

diagnostic testing. Surgical intervention in patients with severe GERD and scleroderma should be avoided except in the most extreme cases where no other alternatives exist. Collaborative care between rheumatology and an experienced gastroenterologist for patients with refractory disease is important for long-term management.

## Strictures

Esophageal strictures are complications of chronic, poorly controlled GERD. They result during healing of erosive esophagitis and lead to a narrowed esophageal lumen as a consequence of excess collagen deposition and fibrosis. Strictures are suspected with complaints of difficulty passing solid foods through the esophagus. Stricture formation is seen in up to 29% of scleroderma patients, and [15]. Barium esophagogram or endoscopy may be used for evaluation [15]. Treatment of SSc esophageal strictures involve optimizing GERD therapy to reduce risk of stricture recurrence [49]. If the patient is experiencing dysphagia, endoscopic dilation is indicated [50]. Complicated strictures (asymmetry, diameter <12 mm or inability to pass an endoscope) may require repeated sessions. Refractory lesions may be treated with steroid injection although data is limited. Empiric dilation is not well studied in scleroderma, but in the absence of stricture, dilation is not recommended due to the risk of esophageal perforation [51].

## Barrett's esophagus

Barrett's esophagus is a change from the normal squamous epithelium of the esophagus to specialized columnar-lined epithelium. It is a complication of longstanding uncontrolled GERD and esophagitis, and is therefore a risk for patients with SSc.

Importantly, Barrett's is the major risk factor for esophageal adenocarcinoma and patients should be screened regularly with endoscopic biopsies to evaluate for malignant progression. One European study evaluated outcomes of Barrett's and estimated the esophageal adenocarcinoma risk in SSc prospectively over 3-years [52]. During the 3-year follow-up, there was a 3% per year risk of conversion from Barrett's to high-grade dysplasia/EAC.

The frequency of endoscopic screening for Barrett's in patients at risk is dependent on the presence or absence of dysplasia and on the degree of dysplasia if present [53]. In the absence of dysplasia, screening every 3-5 years is recommended, whereas for low grade and high-grade dysplasia, more frequent screening endoscopies with biopsy are advised (6-12 months and every 3 months, respectively).

Optimizing management of GERD in observational studies prevents metaplastic progression to high grade dysplasia, which is attributed to chronic gastric acid exposure and resultant DNA damage in Barrett's metaplastic cells [54-56]; however, as this has not been demonstrated in a prospective, long-term controlled trial, the American Gastroenterology Association (AGA) recommends against using a PPI solely to reduce progression to dysplasia or cancer.

Until recently, the treatment of choice for early stage lesions in Barrett's was surgery; however, interventional endoscopy now plays an important role [57]. The AGA

recommends radiofrequency ablation, photodynamic therapy, or endoscopic resection with the aim of endoscopic eradiation for patients with high-grade dysplasia over surveillance.

## Approach to Treatment of Gastric Complications of Systemic Sclerosis

**Gastric Antral Vascular Ectasia—**Gastric Antral Vascular Ectasia (GAVE), also known as "watermelon stomach," is an endoscopic finding where dilation of gastric submucosal vessels appear in a spoke-like pattern from the pylorus into the antrum [58]. Anemia, a consequence of acute or chronic gastric bleeding, is the primary complication. While GAVE is not specific for SSc, it is seen more frequently in this population [59].

**Supportive therapies:** Management of GAVE in SSc is initially supportive with iron supplementation and involves monitoring and managing the anemia and endoscopic intervention. Intravenous fluids and blood products are important in the setting of an acute bleed.

**Endoscopic therapies:** Endoscopic therapies are a mainstay for the management of GAVE if conservative therapy has failed. The most common of these interventions include laser photocoagulation and argon plasma coagulation (APC). Laser or argon plasma coagulation are both commonly accepted as the first-line endoscopic procedures for the management of GAVE [60-64]. The efficacy of Nd:YAG laser therapy is well-established in the treatment of GAVE, although multiple treatment sessions are often required [65-68]. Argon plasma coagulation is an alternative endoscopic approach which utilizes targeted argon gas to deliver highly controlled currents which penetrate target tissues [69]. It is also a well-recognized intervention in the management of GAVE [63, 70, 71] and multiple sessions may also be required for optimal bleeding control [72, 73]. APC is considered by many to be superior to Nd:YAG laser when considering cost, convenience, and complication rates [63, 74].

Some data supports a role for endoscopic band ligation in GAVE management, however data is from small or retrospective studies with variable outcome reporting and there are no studies in SSc [75, 76]. Data on other endoscopic procedures used to manage GAVE (e.g. sclerotherapy, cryotherapy, heater probe) is limited [77, 78]

Given the currently available therapies and the high morbidity and mortality, surgery (e.g. antrectomy) in the management of SSc -associated GAVE would only be considered in severe refractory cases where all other strategies fail [79].

**Gastroparesis—**Gastroparesis is defined by abnormal gastric motility and prolonged gastric emptying in the absence of a mechanical obstruction [80]. Gastroparesis affects approximately 50% of SSc patients [60, 81]. Abnormal gastric findings in SSc relative to normal controls include decreased size of the gastric fundus and antrum at basal evaluation. Liquid emptying studies demonstrate reductions in gastric filling after liquid bolus ingestion and delays in gastric emptying from both the fundus and antrum [82]. As functional dyspepsia may mimic gastroparesis, documentation of delayed gastric emptying is recommended prior to initiating prokinetic agents [14].

**Non-pharmacological interventions:** Dietary and lifestyle modification are important components of gastroparesis management. In the acute setting, restoration of fluids and electrolytes, and nutritional support are recommended. In the longer term, optimizing hydration, avoidance of fatty foods and foods high in soluble fiber is important. Consumption of small frequent meals is recommended. Optimizing GERD management is also critical, as gastroparesis will often exacerbate acid reflux. Medications should be evaluated and those that may contribute to delayed gastric emptying should be minimized or discontinued if possible.

**Prokinetics:** Prokinetics and anti-emetics are the mainstay for the pharmacological management of gastroparesis. Prokinetics are recommended when evidence of gastroparesis is noted on objective testing and/or patients have persistent symptoms of GERD, dysphagia, nausea, and vomiting despite lifestyle modification and optimization of acid control. Early satiety and unintentional weight loss may also occur. Improvement in symptoms rather than repeated gastric emptying studies, determines response to medications, as symptom control does not correlate well with accelerations in gastric emptying [83, 84]. These medications are more effective in early disease, prior to the onset of smooth muscle atrophy. Efficacy, availability, and side-effect profile all must be considered when selecting medications.

Metoclopramide is the first line prokinetic therapy in gastroparesis [14]. It acts through antagonism of the 5-HT4 and D2 receptor and directly stimulates smooth muscle contraction. As it penetrates the blood-brain barrier, it also acts on the D2 receptor in the brainstem and antagonism of vagal and brainstem 5HT3 receptors [80]. It has been shown to improve gastric emptying in a case series of patients with scleroderma [41] and it is known to be effective in improving the delay in gastric emptying associated with gastroparesis complicating other conditions [85]. While it is more commonly administered orally, intramuscular and intravenous formulations are available as well. To facilitate absorption 30 – 60 minutes before a meal, it should be prescribed in the liquid formulation at the lowest effective dose [14]. The development of medication tolerance may be a problem with prolonged use. It must be used cautiously in patients at risk for dysrhythmia as it may prolong the QT interval and result in serious arrhythmias. An EKG should be done at baseline, prior to initiating the drug [86, 87]. Its anti-dopaminergic effects in the CNS may result in tardive dyskinesia, neuroleptic malignant syndrome, acute dystonia, and other serious toxicities so caution must be used with administration and patients should be monitored closely for early neurological effects of the medication with discontinuation of the medication in the setting of involuntary muscle movements. Prolonged use increases risk of the irreversible extrapyramidal complications [88].

Domperidone, a peripheral D2 receptor antagonist, is recommended in patients who are unable to use metoclopramide [14]. It is comparable in efficacy to metoclopramide but the CNS side effects are reduced, as it does not cross the blood brain barrier. However, due to associated cardiac arrhythmias it is not widely available in the United States.

Macrolide antibiotics are motilin receptor agonists and have a role in stimulating gastric emptying [89-92]. Erythromycin may be used in the short term using the oral suspension (200 mg/5mL) or intravenous formulation, however long term use is limited due to

tachyphylaxis, which may result in the setting of down-regulated motilin receptors. Additional risk associated with this drug involves sudden cardiac arrest [93]. An EKG should also be checked prior to the administration of this drug due to risk of QT prolongations.

Cisapride, a drug with strong 5HT4 receptor and weak 5HT3 receptor antagonism was previously used for gastroparesis, however it is no longer recommended in light of the risk of sudden cardiac death associated with this drug [94].

Pyridostigmine is a cholinesterase inhibitor that may also have a role in stimulating gastric motility by increasing acetylcholine levels and increasing gastric contractions. This drug was reported in a case report to be efficacious in a patient with gastroparesis secondary to autoimmune disease although there is no data available for its use in SSc [95].

Other alternative interventions were recently reported as possible therapies of gastroparesis in SSc. Ghrelin, a neuro-hormonal transmitter secreted by the stomach was demonstrated to enhance gastric emptying and improve symptoms in patients without SSc [96, 97]. One recent randomized, double blind placebo controlled crossover study showed that an infusion of ghrelin (5 micrograms/Kg) significantly accelerated gastric emptying in SSc suggesting it may be a novel therapy worthy of further study in this population [98]. There are several other therapies under investigation for gastroparesis but further discussion of these novel agents is beyond the scope of this review.

Non-pharmacological interventions for the treatment of gastroparesis are being studied in SSc and have included acupuncture-based modalities. These interventions are hypothesized, in part to act by enhancing vagal activity through peripheral nerve stimulation. A systematic review recently found self-reported and physiologic evidence for improvement in GI symptoms or functioning in patients with SSc [99].

**Anti-emetic therapy:** In patients with gastroparesis, treatment of nausea and vomiting with anti-emetics is important. A variety of medications are available to treat nausea related to gastroparesis, including serotonin 5HT3 antagonists (e.g. ondasetron, granisetron transdermal), antihistamines (e.g. meclizine), and the serotonin 5HT2/alpha-2 adrenergic receptor antagonist, mirtazapine. Long-term efficacy among patients with SSc is variable. Dronabinol may play an increasing role, as it is now more widely available.

**Management of refractory gastroparesis:** In patients with gastroparesis refractory to medical management, oral intake should continue for as long as the patient is able to maintain their nutritional status. If the patient is unable to tolerate solid food, a dietician should be consulted to assist in guiding the consumption of pureed or liquid nutrient-dense meals [14]. If oral intake is insufficient, (e.g. patient loses 10% or more of their usual body weight in a 3-6 month time period or they are repeatedly hospitalized for recurrent symptoms), supplemental feeds through a jejunostomy tube should be considered if they have a functioning lower bowel [14]. If the small bowel is not functional or the patient does not tolerate enteral tube feeds, parenteral nutrition may be required. There is no data to support the use of gastric stimulators in scleroderma. Surgical interventions such as venting

gastrostomy or gastrectomy carries a high risk of associated complications in our patient population and should be reserved for refractory cases where all other therapies have failed or avoided altogether [100].

**Key recommendations for the management of gastroparesis:** Patients with SSc who have symptoms suggestive of gastroparesis should have a gastric emptying study done to confirm delayed gastric emptying, prior to the initiation of medications. Initial management of gastroparesis includes dietary modification and optimizing hydration. In patients with persistent symptoms, prokinetics and anti-emetics may be required. Prokinetics are more effective in early disease where smooth muscle atrophy is minimal. Liquid formulations may increase absorption. Metoclopramide is the first line therapy, although patients should be monitored closely for signs of neurotoxicity, and the medication should be discontinued at the earliest symptom. Domperidone and erythromycin may be considered in cases where metoclopramide intolerance or efficacy is an issue. An EKG should be done at baseline to evaluate for a prolonged QT interval prior to the initiation of these drugs. Pyridostigmine, a reversible cholinesterase inhibitor may also have a role in the management of refractory disease. Parenteral nutrition may be required in severe cases with excessive weight loss or recurrent hospitalizations. Gastrectomy is associated with a high risk of complications and should be only be used in the most severe refractory cases when all other therapies have failed.

## SMALL INTESTINAL INVOLVEMENT

About 40% to 90% of patients with SSc are reported to have intestinal dysmotility [101, 102]. A decrease in the intestinal peristalsis can lead to stasis and dilatation causing bacterial overgrowth; rarer complications include intestinal pseudo-obstruction, and pneumatosis cystoides intestinales [7].

**Approach to treatment of small intestinal bacterial overgrowth (SIBO)—**Stasis of intestinal contents result in migration and colonization of bacteria from the colon and leading to their overgrowth [36]. Patients usually complain of post-prandial bloating, nausea, vomiting, abdominal pain, diarrhea, excessive flatulence, and inability to maintain body weight despite good oral intake. Malabsorption eventually ensues with deficiency of fat-soluble vitamins, vitamin-B12 and iron. As an initial screening test, serum carotene (a marker of vitamin A absorption), serum B12, 25-hydroxy-vitamin D, iron and pro-thrombin time readings can be obtained. Breath tests (lactulose hydrogen, glucose hydrogen) have been used to assess for SIBO; however these tests have a poor sensitivity ranging from 65% - 70% despite good specificity [103]. Further, it has been proposed that breath tests are unable to detect overgrowth in the more distal reaches of the small intestine [104]. Thus, accurate diagnosis of SIBO continues to pose a number of challenges in clinical practice. The aim of treatment is to relieve the symptoms, prevent complications and avoid any nutritional deficiencies.

**Antibiotic therapy:** Due to the poor yield and difficulty with interpretation of breath tests, the approach by most clinicians is to empirically treat with broad-spectrum antibiotics. The objective of antibiotic therapy in SIBO is to modify the bacterial flora in a manner that

results in symptomatic improvement rather than eradicate it [105]. Antibiotic therapy has been shown to significantly improve symptoms in SSc patients with SIBO [106]. Effective antibiotic therapy must cover both aerobic and anaerobic enteric bacteria given the wide variety of gut flora in different parts of the intestine.

A trial of antibiotics despite being an appealing alternative to most clinicians lacks standardization with regards to the choice of antibiotics, dosing, duration of the regimen and measurement of outcome. Recently, a meta-analysis was performed to compare the clinical effectiveness of antibiotic therapies in the treatment of symptomatic patients with SIBO [107]. Of the ten studies that met the inclusion criteria, antibiotics were more effective than placebo (effectiveness ratio: 2.55; 95% confidence interval: 1.29–5.04). Rifaximin was the most commonly used antibiotic. The clinical response was quite variable and ranged from 62% to 91% for those who were successfully eradicated as determined by breath test normalization.

The authors recommend 2 weeks trial of antibiotics followed by assessment of symptoms; if there is subjective improvement, the patients can be monitored closely for recurrence of symptoms; if not, some proceed with cyclical course of 2 – weeks on antibiotics and 2 – weeks off, or continuous rotation every 2 – weeks. Some antibiotics that have been used include amoxicillin, ciprofloxacin, metronidazole, doxycycline, neomycin, trimethoprim-sulfamethoxazole, tetracyclines, levofloxacin and rifaximin. Patients with recurrence of SIBO or when SIBO co-exists other complications like malabsorption or intestinal failure, rotating antibiotic regimens are recommended to prevent the development of resistance.

**Probiotics:** Probiotic therapy may have a role in the treatment of bacterial overgrowth syndrome especially in case of resistant cases when used in conjunction with antibiotics. Data to support their use is scant and primarily from open labeled studies in patients with irritable bowel syndrome [108]. In a pilot study, patients with SIBO and chronic abdominal distension were randomized to receive either a probiotic or metronidazole [109]. A statistically significant difference in symptomatic response was reported favoring the use of probiotic ($P = 0.036$). In another study, the use of probiotics was shown to significantly improve patient reported outcomes in the distention / bloating, reflux and emotional well-being scales which were measured using the University of California, Los Angeles, Scleroderma Clinical Trials Consortium Scleroderma Gastrointestinal scale 2.0 (GIT 2.0) [110]. Double blind randomized controlled trials are needed in the future to assess clinical effectiveness. The authors recommend the use of yogurt with live-active cultures to be taken everyday because it provides 15% to 20% of daily-required calcium and lacks side effects. However, there have been small studies suggesting that SIBO increases the likelihood of lactose intolerance in patients with chronic functional diarrhea probably as a consequence of lactose fermentation in the small intestine [111].

**Dietary modification, nutritional supplementation and support:** A diet consisting of poorly absorbed but fermentable oligo-, di- and mono-saccharides and polyols (FODMAPs) was developed and shown to be effective in reducing functional gastrointestinal symptoms in patients with irritable bowel syndrome [112]. The FODMAP diet alters the gut microbiata composition an (higher fecal pH, reduced bacterial abundance and greater microbial

diversity) [113]. The FODMAP studies are confined to a single center and have not been studied in patients with SIBO or SSc; however, it does offer as a less invasive and potential cheaper intervention and needs multi-center studies. The authors recommend multivitamin replacement as guided by laboratory testing. If SIBO progresses to malabsorption with ongoing weight loss despite adequate therapy, total parenteral nutrition needs to be considered.

**Key treatment recommendations for SIBO:** When there is a clinical suspicion for SIBO, it is acceptable to proceed with a therapeutic trial of antibiotics without further diagnostic testing. The regimen and duration of therapy is based on severity of symptoms, clinical response and any recurrence of symptoms. Rotating antibiotics are generally required. An assessment for nutritional deficiencies is important early on in the treatment course to guide appropriate supplementation. In resistant cases complicated by malabsorption, total parenteral nutrition (TPN) may be required.

**Approach to treatment of intestinal pseudo-obstruction—**Intestinal pseudo-obstruction is a clinical syndrome characterized by obstructive symptoms despite the absence of a mechanical etiology; it is due to a disorder in the intestinal propulsion seen in patients with SSc [114]. It can be either acute or chronic. Until recently, there was scant data on the demographics, clinical course and outcomes except for case reports. A single center case control study specifically looked into demographics, clinical course, outcomes, and mortality in SSc patients admitted with acute intestinal pseudo – obstruction [115]. The most common symptoms were nausea and abdominal pain. As expected, an abdominal radiograph and / or computer tomography scan of the abdomen was performed in most patients to exclude a mechanical cause. Of these cases, 70% had spontaneous resolution with conservative measures of intravenous hydration and bowel rest, 9% underwent surgical resection, and 25% required prolonged TPN. There was a 16% patient mortality in this population; mortality was higher in male patients ($p = 0.014$), patients with low hemoglobin ($p = 0.00008$), and those with a low serum albumin ($p = 0.001$) at presentation.

**Initial management:** Patients with intestinal pseudo – obstruction need to be hospitalized for further evaluation to exclude mechanical causes and management. The management is aimed to relieve symptoms due to dysmotility and likely associated SIBO, The initial treatment includes bowel rest, intravenous fluids, broad-spectrum antibiotics, and correction of electrolyte imbalances.

**Nutritional support:** Patients with intestinal pseudo-obstruction often have difficulty maintaining normal oral nutrition and their body weight [116]. Due to the insidious onset of disease and delay in recognition, the problems with nutrition are often present for many months to years. Up to two-thirds of the patients have nutritional deficiencies and almost half of them need some form of nutritional support [116, 117]. An evaluation by nutrition experts early in the hospitalization is vital as they consider several factors (intestinal absorptive function, electrolyte imbalances, weight, body mass index, dietary history) prior to prescribing the appropriate nutritional support. Patients with intestinal failure need long-termTPN.

**Prokinetics:** Prokinetic agents usually improve gastrointestinal propulsive activity. There is lack of good evidence in the use of these agents. However, prokinetics are used in conjunction with antibiotics to decrease the bacterial load in the small intestine. Various case series have reported the effectiveness of metoclopramide, cisapride, and domperidone in relieving pseudo-obstruction; erythromycin has no effect on intestinal dysmotility in patients with SSc [118]. Octreotide, a somatostatin analogue has been best studied in SSc patients with pseudo-obstruction and shown to have favorable results by improving intestinal motility [119-121]. It is effective in doses of 50 to 200 micrograms administered as a subcutaneous injection in divided doses. Long acting preparations are also available and have been shown to be quite effective in relieving symptoms and improving motility [119]. However, it is important to exclude bowel obstruction prior to starting octreotide. The authors recommend starting subcutaneous octreotide at 50 micrograms twice daily during an acute attack; and ensuing clinical improvement is usually seen within 2 – 3 days. In the event that a satisfactory response is not seen, the dose may be increased upto 200 micrograms per day. In recurrent cases, 50 micrograms of subcutaneous octreotide can be given at bedtime; alternatively long acting preparations are available which can be given once a month. In resistant cases, a combination of erythromycin and octreotide can be tried, especially in patients with gastroparesis [122]. In these patients, octreotide can decrease gastric emptying and make gastroparesis worse.

**Surgical options:** In SSc-associated small intestine dysmotility, surgical resection of the involved tissue is usually discouraged due to the risk of prolonged post-surgical ileus and diffuse GIT involvement [123]. However, surgery might be considered in severe cases of intestinal pseudo-obstruction that have failed conservative / medical therapies, for the sake of venting (decompression to relieve symptoms) and feeding, and to exclude intestinal obstruction.

**Key treatment recommendations for intestinal pseudo-obstruction:** The diagnosis of pseudo-obstruction has to be made after carefully excluding for any mechanical cause of obstruction. The authors use broad-spectrum antibiotics to treat co-existent SIBO. The key aspects of medical management include – bowel rest, nutritional support, correcting any electrolyte imbalances, and use of prokinetics. A dietician needs to be involved early in the treatment course as adequate nutritional support is vital alongside other measures. The authors prefer using subcutaneous octreotide at doses of 50 to 200 micrograms per day. Surgical resection of the intestine is usually discouraged.

**Approach to treatment of malnutrition—**SSc patients with GI involvement are at risk for malnutrition; various causes exist including malabsorption from SIBO, dysmotility in various segments of the GIT and the resultant nausea and vomiting that may affect oral intake [124, 125]. In a Canadian study using the malnutrition universal screening tool (MUST), up to 18% of SSc patients were at high risk of malnutrition; it was associated with shorter disease duration, markers of GI involvement, and disease severity [126]. Hence, screening for malnutrition is recommended in all SSc patients.

**Screening for malnutrition:** A set of basic laboratory tests should be obtained including hemoglobin (may indicate nutritional deficiency such as iron, folic acid or vitamin B12), serum carotene (indicative of fat malabsorption), serum folate (elevated in bacterial overgrowth). Serum albumin is neither sensitive nor specific for malnutrition, unless it falls below 3.5 mg/dL [127]. Measurement of pre-albumin is better (due to long-term protein stores) than albumin (has a quick turnover). In patients with suspected malabsorption (like SIBO), additional tests should be performed to assess for micro- or macro-nutrient deficiency. Patients who screen positive for malnutrition should be referred to a dietitian for a more detailed evaluation. These patients may require temporary or long-term home TPN.

**Pneumatosis cystoides intestinalis—**Pneumatosis cystoides intestinalis or air in the bowel wall has been reported in SSc. It is usually of no consequence, but sometimes can be life threatening in the event of a pneumoperitoneum [128]. Usually these cysts do not require surgery; yet, it is important to be aware of this rare condition.

## COLON AND ANORECTAL DISORDERS

Colonic involvement is seen in 20 to 50% of SSc patients and usually presents as constipation or diarrhea. The early phases of colonic involvement are associated with constipation from delayed intestinal transit. As the small intestinal dysmotility sets in, the luminal dilatation leads to bacterial overgrowth and diarrhea from malabsorption [129]. In addition to SIBO, diarrhea can occur due to fibrosis of lymphatic drainage system and chronic intestinal ischemia affecting the small bowel [7]. Diarrhea with co-existent fecal incontinence, make the symptoms more apparent and affect quality of life.

The anorectum is affected in 50% to 70% of patients with SSc and over 20% develop fecal incontinence [130, 131]. Thinning and atrophy of the internal anal sphincter (IAS) has been implicated as the cause of the incontinence [132]. A recent study utilizing a novel method (functional lumen imaging probe and endoanal ultrasound) to assess for biomechanical abnormality revealed, that the middle anal canal (IAS and external sphincter) of SSc patients was thinned out and easily distensible compared to controls [133]. Patients usually present with chronic diarrhea, fecal incontinence and rectal prolapse.

**Approach to treatment of constipation—**As with management of any chronic constipation, existent constipating medications should be stopped and structural causes should be excluded [4]. Lifestyle modifications should be advised – liberal ingestion of fluids and ensuring adequate (but not excessive) fiber intake. Fiber based laxatives are usually helpful in patients with episodic constipation who form hard stools (due to lack of water) or in those with difficulty in expelling stools from the rectum. Some SSc patients may find it hard to tolerate the increased fiber intake due to SIBO. Osmotic laxatives such as senna, bisacodyl, and polyethylene glycol (Miralax ®) are helpful in fecal impaction and in those with slow transit; lactulose can make the bloating and flatulence significantly worse. These laxatives exert their effects primarily via alteration of electrolyte transport by the intestinal mucosa, and by increasing intestinal motor activity. Stool softeners are effective when used in combination with stimulant laxatives. Patients are advised to take their

laxatives every 2 – 3 days to maintain a healthy bowel regimen. The regimen may be tailored to the individual patient's needs.

**Approach to treatment of diarrhea—**Dietary measures to improve stool consistency should be attempted. Alternative causes for diarrhea need to be considered – infections, celiac disease, amyloidosis, microscopic colitis (patients with immune mediated disorders are at increased risk). A rotational antibiotic regimen is used to treat SIBO. Anti-diarrheal agents such as loperamide can be used to inhibit peristalsis and secretion, but must be weighed against the risk of inducing pseudo-obstruction. In cases of fat malabsorption from SIBO, bile acid sequestrants can be used [4].

**Approach to treatment of fecal incontinence—**The treatment should focus on appropriate management of diarrhea and utilization of behavioral therapies like anorectal biofeedback training and pelvic floor exercises.

Sacral nerve stimulation has been shown to be a safe and effective intervention to treat fecal incontinence in SSc patients [134, 135]. An implantable pulse generator is inserted under local anesthesia by a surgeon. The short-and long-term effects have been very encouraging, with a decrease in episodes of fecal incontinence and marked improvement in quality of life. The procedure is associated with minimal morbidity.

**Key treatment recommendation for colon and anorectal involvement:** A work-up for constipation should include exclusion of structural causes. Lifestyle modifications should be instituted alongside medications. Pharmacologic management should be individualized based on the nature of constipation and the presence of other GI symptoms. Diarrhea is often multifactorial and should be accordingly managed after carefully identifying the causes. Optimal management of diarrhea is an important aspect of treating fecal incontinence. Biofeedback and sacral nerve stimulation can be helpful.

## PATIENT-REPORTED OUTCOME MEASURES

Most patients with SSc often have multiple types and anatomical segments of GIT involvement. Often, the correlation between histologic and physiologic severity and GIT symptoms is poor [7, 36]. The symptoms often precede laboratory or anatomical abnormality. All these factors make it challenging to quantify the GIT involvement in SSc, stressing the need for a validated patient-reported instrument or outcome (PRO). PROs capture the patients' illness experience in a structured format and may help providers understand symptoms from the patients' perspective [136]. There are two well-validated PRO instruments to assess the GI burden due to SSc.

**The University of California, Los Angeles, Scleroderma Clinical Trials Consortium Scleroderma Gastrointestinal scale 2.0 (GIT 2.0)—**GIT 2.0 is a shortened version of GIT 1.0, which was originally developed to capture GIT involvement in patients with SSc [137, 138]. It has been validated for use to capture the GI burden due to SSc. GIT 2.0 is a 7–multi-item scale with areas of reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning and has been shown to have a good test–retest reliability. Symptom scales were able to discriminate subjects with

corresponding clinical GI diagnoses. The total GIT 2.0 score, developed by averaging 6 of 7 scales (excluding constipation), was reliable and provided greater discrimination between mild, moderate, and severe self-rated GI involvement than individual scales. The authors routinely use this scale in clinical care of all patients with SSc to screen for any GI involvement and it has been translated into many languages. It is available free of charge at http://uclascleroderma.researchcore.org/.

**National Institute of Health Patient Reported Outcomes Measurement Information System (PROMIS®) gastrointestinal (GI) symptom measures (PROMIS-GI)—**Recently, the PROMIS-GI instrument was developed to have a standardized, rigorously developed, electronically administered set of PROs that span the breadth and depth of GI symptoms, and that could be used across all GI disorders for clinical and research purposes [139]. PROMIS-GI has 60 items and assesses 8 domains: gastroesophageal reflux, disrupted swallowing, diarrhea, bowel incontinence/soilage, nausea and vomiting, constipation, belly pain, and gas /bloating /flatulence. It utilizes a computer adaptive testing and hence the questions can be customized to the patient's responses based on the available items. PROMIS-GI was shown to have content and cross-sectional construct validity when used in diverse GI patient population and specifically in SSc patients [139, 140].

## Conclusion

GI involvement in SSc is common and is quite varied in presentation; it can be potentially disabling and is associated with poor health related quality of life. Early recognition is important. The management is mainly aimed at alleviating the symptoms and preventing complications.

## Ackowledgement

Dr. Khanna was supported by NIH/NIAMS K24 AR063120

## References

1. Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Seminars in arthritis and rheumatism. 2010; 39(4):269–77. [PubMed: 18706680]

*2. Bodukam V, Hays RD, Maranian P, Furst DE, Seibold JR, Impens A, et al. Association of gastrointestinal involvement and depressive symptoms in patients with systemic sclerosis. Rheumatology. 2011; 50(2):330–4. [PubMed: 20884655] [This reference highlights the burden of GI involvement in patients with SSc.]

3. Omair MA, Lee P. Effect of gastrointestinal manifestations on quality of life in 87 consecutive patients with systemic sclerosis. The Journal of rheumatology. 2012; 39(5):992–6. [PubMed: 22467930]

4. Butt S, Emmanuel A. Systemic sclerosis and the gut. Expert review of gastroenterology & hepatology. 2013; 7(4):331–9. [PubMed: 23639091]

5. Jaovisidha K, Csuka ME, Almagro UA, Soergel KH. Severe gastrointestinal involvement in systemic sclerosis: report of five cases and review of the literature. Seminars in arthritis and rheumatism. 2005; 34(4):689–702. [PubMed: 15692963]

6. Thonhofer R, Siegel C, Trummer M, Graninger W. Early endoscopy in systemic sclerosis without gastrointestinal symptoms. Rheumatology international. 2012; 32(1):165–8. [PubMed: 20711592]

7. Sallam H, McNearney TA, Chen JD. Systematic review: pathophysiology and management of gastrointestinal dysmotility in systemic sclerosis (scleroderma). Alimentary pharmacology & therapeutics. 2006; 23(6):691–712. [PubMed: 16556171]
8. Caporali R, Caccialanza R, Bonino C, Klersy C, Cereda E, Xoxi B, et al. Disease-related malnutrition in outpatients with systemic sclerosis. Clinical nutrition. 2012; 31(5):666–71. [PubMed: 22417677]
**9. Harrison E, Herrick AL, McLaughlin JT, Lal S. Malnutrition in systemic sclerosis. Rheumatology. 2012; 51(10):1747–56. [PubMed: 22850183] [A review on approach to recognition and management of malnutrition in SSc.]
10. Recasens MA, Puig C, Ortiz-Santamaria V. Nutrition in systemic sclerosis. Reumatologia clinica. 2012; 8(3):135–40. [PubMed: 22197834]
11. Roman S, Hot A, Fabien N, Cordier JF, Miossec P, Ninet J, et al. Esophageal dysmotility associated with systemic sclerosis: a high-resolution manometry study. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2010
*12. Bae S, Allanore Y, Furst DE, Bodukam V, Coustet B, Morgaceva O, et al. Associations between a scleroderma-specific gastrointestinal instrument and objective tests of upper gastrointestinal involvements in systemic sclerosis. Clinical and experimental rheumatology. 2013; 31(2 Suppl 76):57–63. [PubMed: 23910611] [Patient reported outcomes measures complement objective testing in SSc-GI involvement.]
13. Clements PJ, Becvar R, Drosos AA, Ghattas L, Gabrielli A. Assessment of gastrointestinal involvement. Clinical and experimental rheumatology. 2003; 21(3 Suppl 29):S15–8. [PubMed: 12889216]
14. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of G. Clinical guideline: management of gastroparesis. The American journal of gastroenterology. 2013; 108(1): 18–37. quiz 8. [PubMed: 23147521]
15. Ebert EC. Esophageal disease in scleroderma. Journal of clinical gastroenterology. 2006; 40(9): 769–75. [PubMed: 17016130]
16. Cameron AJ, Payne WS. Barrett's esophagus occurring as a complication of scleroderma. Mayo Clinic proceedings. 1978; 53(9):612–5. [PubMed: 682690]
17. Halpert RD, Laufer I, Thompson JJ, Feczko PJ. Adenocarcinoma of the esophagus in patients with scleroderma. AJR American journal of roentgenology. 1983; 140(5):927–30. [PubMed: 6601435]
18. Zhang XJ, Bonner A, Hudson M, Canadian Scleroderma Research G. Baron M, Pope J. Association of gastroesophageal factors and worsening of forced vital capacity in systemic sclerosis. The Journal of rheumatology. 2013; 40(6):850–8. [PubMed: 23547215]
19. Savarino E, Bazzica M, Zentilin P, Pohl D, Parodi A, Cittadini G, et al. Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. American journal of respiratory and critical care medicine. 2009; 179(5):408–13. [PubMed: 19096004]
20. Marie I, Dominique S, Levesque H, Ducrotte P, Denis P, Hellot MF, et al. Esophageal involvement and pulmonary manifestations in systemic sclerosis. Arthritis and rheumatism. 2001; 45(4):346–54. [PubMed: 11501722]
21. Christmann RB, Wells AU, Capelozzi VL, Silver RM. Gastroesophageal reflux incites interstitial lung disease in systemic sclerosis: clinical, radiologic, histopathologic, and treatment evidence. Seminars in arthritis and rheumatism. 2010; 40(3):241–9. [PubMed: 20494406]
22. Rose S, Young MA, Reynolds JC. Gastrointestinal manifestations of scleroderma. Gastroenterology clinics of North America. 1998; 27(3):563–94. [PubMed: 9891698]
23. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. The American journal of gastroenterology. 2013; 108(3):308–28. quiz 29. [PubMed: 23419381]
24. Abu-Shakra M, Guillemin F, Lee P. Gastrointestinal manifestations of systemic sclerosis. Seminars in arthritis and rheumatism. 1994; 24(1):29–39. [PubMed: 7985035]
25. McMahan ZH, Hummers LK. Systemic sclerosis--challenges for clinical practice. Nature reviews Rheumatology. 2013; 9(2):90–100.

26. Orlando RC, Liu S, Illueca M. Relationship between esomeprazole dose and timing to heartburn resolution in selected patients with gastroesophageal reflux disease. Clinical and experimental gastroenterology. 2010; 3:117–25. [PubMed: 21694855]
27. Corleto VD, Festa S, Di Giulio E, Annibale B. roton pump inhibitor therapy and potential long-term harm. Current opinion in endocrinology, diabetes, and obesity. 2014; 21(1):3–8.
28. Ghebremariam YT, LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation. 2013; 128(8):845–53. [PubMed: 23825361]
29. Hendel L, Hage E, Hendel J, Stentoft P. Omeprazole in the long-term treatment of severe gastro-oesophageal reflux disease in patients with systemic sclerosis. Alimentary pharmacology & therapeutics. 1992; 6(5):565–77. [PubMed: 1420748]
30. Maggio M, Lauretani F, Ceda GP, De Vita F, Bondi G, Corsonello A, et al. Use of proton pump inhibitors is associated with lower trabecular bone density in older individuals. Bone. 2013; 57(2): 437–42. [PubMed: 24076021]
31. Dutta U, Armstrong D. Novel pharmaceutical approaches to reflux disease. Gastroenterology clinics of North America. 2013; 42(1):93–117. [PubMed: 23452633]
32. Rackoff A, Agrawal A, Hila A, Mainie I, Tutuian R, Castell DO. Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2005; 18(6):370–3.
33. Leite LP, Johnston BT, Just RJ, Castell DO. Persistent acid secretion during omeprazole therapy: a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. The American journal of gastroenterology. 1996; 91(8):1527–31. [PubMed: 8759655]
34. Wang Y, Pan T, Wang Q, Guo Z. Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough. The Cochrane database of systematic reviews. 2009; (4):CD004275. [PubMed: 19821323]
35. Curcic J, Schwizer A, Kaufman E, Forras-Kaufman Z, Banerjee S, Pal A, et al. Effects of baclofen on the functional anatomy of the oesophago-gastric junction and proximal stomach in healthy volunteers and patients with GERD assessed by magnetic resonance imaging and high-resolution manometry: a randomised controlled double-blind study. Alimentary pharmacology & therapeutics. 2014
36. Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis and rheumatism. 1994; 37(9):1265–82. [PubMed: 7945489]
37. Richter JE. American College of Gastroenterology: a pyramid of strength for the practitioner, educator, and clinical investigator. The American journal of gastroenterology. 1996; 91(4):632–6. [PubMed: 8677922]
38. Lock G, Holstege A, Lang B, Scholmerich J. Gastrointestinal manifestations of progressive systemic sclerosis. The American journal of gastroenterology. 1997; 92(5):763–71. [PubMed: 9149182]
39. Ramirez-Mata M, Ibanez G, Alarcon-Segovia D. Stimulatory effect of metoclopramide on the esophagus and lower esophageal sphincter of patients of patients with PSS. Arthritis and rheumatism. 1977; 20(1):30–4. [PubMed: 319806]
40. Mercado U, Arroyo de Anda R, Avendano L, Araiza-Casillas R, Avendano-Reyes M. Metoclopramide response in patients with early diffuse systemic sclerosis. Effects on esophageal motility abnormalities. Clinical and experimental rheumatology. 2005; 23(5):685–8. [PubMed: 16173247]
41. Johnson DA, Drane WE, Curran J, Benjamin SB, Chobanian SJ, Karvelis K, et al. Metoclopramide response in patients with progressive systemic sclerosis. Effect on esophageal and gastric motility abnormalities. Archives of internal medicine. 1987; 147(9):1597–601. [PubMed: 3632168]
42. Cubeddu LX. Iatrogenic QT Abnormalities and Fatal Arrhythmias: Mechanisms and Clinical Significance. Current cardiology reviews. 2009; 5(3):166–76. [PubMed: 20676275]
43. Tonini M, De Ponti F, Di Nucci A, Crema F. Review article: cardiac adverse effects of gastrointestinal prokinetics. Alimentary pharmacology & therapeutics. 1999; 13(12):1585–91. [PubMed: 10594392]

44. Poirier NC, Taillefer R, Topart P, Duranceau A. Antireflux operations in patients with scleroderma. The Annals of thoracic surgery. 1994; 58(1):66–72. discussion -3. [PubMed: 8037562]
45. Kent MS, Luketich JD, Irshad K, Awais O, Alvelo-Rivera M, Churilla P, et al. Comparison of surgical approaches to recalcitrant gastroesophageal reflux disease in the patient with scleroderma. The Annals of thoracic surgery. 2007; 84(5):1710–5. discussion 5-6. [PubMed: 17954091]
46. Henderson RD, Henderson RF, Marryatt GV. Surgical management of 100 consecutive esophageal strictures. The Journal of thoracic and cardiovascular surgery. 1990; 99(1):1–7. [PubMed: 2294341]
47. Dickman R, Schiff E, Holland A, Wright C, Sarela SR, Han B, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. Alimentary pharmacology & therapeutics. 2007; 26(10):1333–44. [PubMed: 17875198]
48. McNearney TA, Sallam HS, Hunnicutt SE, Doshi D, Chen JD. Prolonged treatment with transcutaneous electrical nerve stimulation (TENS) modulates neuro-gastric motility and plasma levels of vasoactive intestinal peptide (VIP), motilin and interleukin-6 (IL-6) in systemic sclerosis. Clinical and experimental rheumatology. 2013; 31(2 Suppl 76):140–50. [PubMed: 23406616]
49. Standards of Practice C. Egan JV, Baron TH, Adler DG, Davila R, Faigel DO, et al. Esophageal dilation. Gastrointestinal endoscopy. 2006; 63(6):755–60. [PubMed: 16650533]
50. Lew RJ, Kochman ML. A review of endoscopic methods of esophageal dilation. Journal of clinical gastroenterology. 2002; 35(2):117–26. [PubMed: 12172355]
51. Kaplan M, Mutlu EA, Jakate S, Bruninga K, Losurdo J, Losurdo J, et al. Endoscopy in eosinophilic esophagitis: “feline” esophagus and perforation risk. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2003; 1(6): 433–7. [PubMed: 15017642]
52. Wipff J, Coriat R, Masciocchi M, Caramaschi P, Derk CT, Hachulla E, et al. Outcomes of Barrett's oesophagus related to systemic sclerosis: a 3-year EULAR Scleroderma Trials and Research prospective follow-up study. Rheumatology. 2011; 50(8):1440–4. [PubMed: 21415021]
53. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ, American Gastroenterological A. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011; 140(3):e18–52. quiz e13. [PubMed: 21376939]
54. El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. The American journal of gastroenterology. 2004; 99(10):1877–83. [PubMed: 15447744]
55. Kastelein F, Spaander MC, Steyerberg EW, Biermann K, Valkhoff VE, Kuipers EJ, et al. Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013; 11(4):382–8. [PubMed: 23200977]
56. Zhang HY, Hormi-Carver K, Zhang X, Spechler SJ, Souza RF. In benign Barrett's epithelial cells, acid exposure generates reactive oxygen species that cause DNA double-strand breaks. Cancer research. 2009; 69(23):9083–9. [PubMed: 19920191]
57. Dubecz A, Stein HJ. Endoscopic versus surgical therapy for early cancer in Barrett's esophagus. Gastrointestinal endoscopy. 2009; 70(4):632–4. [PubMed: 19788980]
58. Jabbari M, Cherry R, Lough JO, Daly DS, Kinnear DG, Goresky CA. Gastric antral vascular ectasia: the watermelon stomach. Gastroenterology. 1984; 87(5):1165–70. [PubMed: 6332757]
59. Gyger G, Baron M. Gastrointestinal manifestations of scleroderma: recent progress in evaluation, pathogenesis, and management. Current rheumatology reports. 2012; 14(1):22–9. [PubMed: 22105546]
60. Marie I, Ducrotte P, Antonietti M, Herve S, Levesque H. Watermelon stomach in systemic sclerosis: its incidence and management. Alimentary pharmacology & therapeutics. 2008; 28(4): 412–21. [PubMed: 18498445]
61. Ripoll C, Garcia-Tsao G. Management of gastropathy and gastric vascular ectasia in portal hypertension. Clinics in liver disease. 2010; 14(2):281–95. [PubMed: 20682235]

62. Ripoll C, Garcia-Tsao G. The management of portal hypertensive gastropathy and gastric antral vascular ectasia. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2011; 43(5):345–51.
63. Rosenfeld G, Enns R. Argon photocoagulation in the treatment of gastric antral vascular ectasia and radiation proctitis. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2009; 23(12):801–4. [PubMed: 20011731]
64. Selinger CP, Ang YS. Gastric antral vascular ectasia (GAVE): an update on clinical presentation, pathophysiology and treatment. Digestion. 2008; 77(2):131–7. [PubMed: 18391491]
65. Liberski SM, McGarrity TJ, Hartle RJ, Varano V, Reynolds D. The watermelon stomach: long-term outcome in patients treated with Nd:YAG laser therapy. Gastrointestinal endoscopy. 1994; 40(5):584–7. [PubMed: 7988823]
66. Kar P, Mitra S, Resnick JM, Torbey CF. Gastric antral vascular ectasia: case report and review of the literature. Clinical medicine & research. 2013; 11(2):80–5. [PubMed: 23262190]
67. Gostout CJ, Ahlquist DA, Radford CM, Viggiano TR, Bowyer BA, Balm RK. Endoscopic laser therapy for watermelon stomach. Gastroenterology. 1989; 96(6):1462–5. [PubMed: 2785467]
68. Calamia KT, Scolapio JS, Viggiano TR. Endoscopic YAG laser treatment of watermelon stomach (gastric antral vascular ectasia) in patients with systemic sclerosis. Clinical and experimental rheumatology. 2000; 18(5):605–8. [PubMed: 11072602]
69. Dumot JA, Greenwald BD. Argon plasma coagulation, bipolar cautery, and cryotherapy: ABC's of ablative techniques. Endoscopy. 2008; 40(12):1026–32. [PubMed: 19065487]
70. Klump B, Schneider GA, Fierlbeck G, Hoeft S, Gregor M, Porschen R. Argon plasma coagulation in endoscopic therapy of CREST syndrome associated upper gastrointestinal hemorrhage. Zeitschrift fur Gastroenterologie. 1997; 35(6):469–76. [PubMed: 9281240]
71. Kwan V, Bourke MJ, Williams SJ, Gillespie PE, Murray MA, Kaffes AJ, et al. Argon plasma coagulation in the management of symptomatic gastrointestinal vascular lesions: experience in 100 consecutive patients with long-term follow-up. The American journal of gastroenterology. 2006; 101(1):58–63. [PubMed: 16405534]
72. Thonhofer R, Siegel C, Trummer M, Gugl A. Clinical images: Gastric antral vascular ectasia in systemic sclerosis. Arthritis and rheumatism. 2010; 62(1):290. [PubMed: 20039398]
73. Shibukawa G, Irisawa A, Sakamoto N, Takagi T, Wakatsuki T, Imamura H, et al. Gastric antral vascular ectasia (GAVE) associated with systemic sclerosis: relapse after endoscopic treatment by argon plasma coagulation. Internal medicine. 2007; 46(6):279–83. [PubMed: 17379994]
74. Swanson E, Mahgoub A, MacDonald R, Shaukat A. Medical and endoscopic therapies for angiodysplasia and gastric antral vascular ectasia: a systematic review. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2014; 12(4):571–82. [PubMed: 24013107]
75. Sato T, Yamazaki K, Akaike J. Endoscopic band ligation versus argon plasma coagulation for gastric antral vascular ectasia associated with liver diseases. Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society. 2012; 24(4):237–42. [PubMed: 22725108]
76. Wells CD, Harrison ME, Gurudu SR, Crowell MD, Byrne TJ, Depetris G, et al. Treatment of gastric antral vascular ectasia (watermelon stomach) with endoscopic band ligation. Gastrointestinal endoscopy. 2008; 68(2):231–6. [PubMed: 18533150]
77. Watson M, Hally RJ, McCue PA, Varga J, Jimenez SA. Gastric antral vascular ectasia (watermelon stomach) in patients with systemic sclerosis. Arthritis and rheumatism. 1996; 39(2): 341–6. [PubMed: 8849390]
78. Cho S, Zanati S, Yong E, Cirocco M, Kandel G, Kortan P, et al. Endoscopic cryotherapy for the management of gastric antral vascular ectasia. Gastrointestinal endoscopy. 2008; 68(5):895–902. [PubMed: 18640673]
79. Sebastian S, O'Morain CA, Buckley MJ. Review article: current therapeutic options for gastric antral vascular ectasia. Alimentary pharmacology & therapeutics. 2003; 18(2):157–65. [PubMed: 12869075]
80. Waseem S, Moshiree B, Draganov PV. Gastroparesis: current diagnostic challenges and management considerations. World journal of gastroenterology : WJG. 2009; 15(1):25–37. [PubMed: 19115465]

81. Domsic R, Fasanella K, Bielefeldt K. Gastrointestinal manifestations of systemic sclerosis. Digestive diseases and sciences. 2008; 53(5):1163–74. [PubMed: 17934861]
82. Cozzi F, Parisi G, Ciprian L, Bullo A, Cardarelli S, Rizzo M, et al. Gastric dysmotility after liquid bolus ingestion in systemic sclerosis: an ultrasonographic study. Rheumatology international. 2012; 32(5):1219–23. [PubMed: 21258796]
83. Sturm A, Holtmann G, Goebell H, Gerken G. Prokinetics in patients with gastroparesis: a systematic analysis. Digestion. 1999; 60(5):422–7. [PubMed: 10473966]
84. Talley NJ. Diabetic gastropathy and prokinetics. The American journal of gastroenterology. 2003; 98(2):264–71. [PubMed: 12591039]
85. Parkman HP, Hasler WL, Fisher RS, American Gastroenterological A. American Gastroenterological Association medical position statement: diagnosis and treatment of gastroparesis. Gastroenterology. 2004; 127(5):1589–91. [PubMed: 15521025]
86. Tung A, Sweitzer B, Cutter T. Cardiac arrest after labetalol and metoclopramide administration in a patient with scleroderma. Anesthesia and analgesia. 2002; 95(6):1667–8. table of contents. [PubMed: 12456435]
87. Ellidokuz E, Kaya D. The effect of metoclopramide on QT dynamicity: double-blind, placebo-controlled, cross-over study in healthy male volunteers. Alimentary pharmacology & therapeutics. 2003; 18(1):151–5. [PubMed: 12848637]
88. Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Archives of internal medicine. 1993; 153(12):1469–75. [PubMed: 8512437]
89. DiBaise JK, Quigley EM. Efficacy of prolonged administration of intravenous erythromycin in an ambulatory setting as treatment of severe gastroparesis: one center's experience. Journal of clinical gastroenterology. 1999; 28(2):131–4. [PubMed: 10078820]
90. Fiorucci S, Distrutti E, Bassotti G, Gerli R, Chiucchiu S, Betti C, et al. Effect of erythromycin administration on upper gastrointestinal motility in scleroderma patients. Scandinavian journal of gastroenterology. 1994; 29(9):807–13. [PubMed: 7824860]
91. Fiorucci S, Distrutti E, Gerli R, Morelli A. Effect of erythromycin on gastric and gallbladder emptying and gastrointestinal symptoms in scleroderma patients is maintained medium term. The American journal of gastroenterology. 1994; 89(4):550–5. [PubMed: 8147358]
92. Hara T, Ogoshi K, Yamamoto S, Kameya T, Kenmochi T, Kise Y, et al. Successful treatment of severe reflux esophagitis with erythromycin in a patient with progressive systemic sclerosis and proximal gastrectomy. The Tokai journal of experimental and clinical medicine. 2006; 31(2):70–2. [PubMed: 21302226]
93. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. The New England journal of medicine. 2004; 351(11): 1089–96. [PubMed: 15356306]
94. Abell TL, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, et al. Treatment of gastroparesis: a multidisciplinary clinical review. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2006; 18(4):263–83. [PubMed: 16553582]
95. Pasha SF, Lunsford TN, Lennon VA. Autoimmune gastrointestinal dysmotility treated successfully with pyridostigmine. Gastroenterology. 2006; 131(5):1592–6. [PubMed: 17101331]
96. Murray CD, Martin NM, Patterson M, Taylor SA, Ghatei MA, Kamm MA, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. Gut. 2005; 54(12):1693–8. [PubMed: 16085693]
97. Tack J, Depoortere I, Bisschops R, Verbeke K, Janssens J, Peeters T. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. Alimentary pharmacology & therapeutics. 2005; 22(9):847–53. [PubMed: 16225494]
98. Ariyasu H, Iwakura H, Yukawa N, Murayama T, Yokode M, Tada H, et al. Clinical effects of ghrelin on gastrointestinal involvement in patients with systemic sclerosis. Endocrine journal. 2014; 61(7):735–42. [PubMed: 24739333]

99. Sallam HS, McNearney TA, Chen JD. Acupuncture-based modalities: novel alternative approaches in the treatment of gastrointestinal dysmotility in patients with systemic sclerosis. Explore. 2014; 10(1):44–52. [PubMed: 24439095]
100. Oiwa H, Ikemoto Y, Mandai K, Koide K, Nishida T, Tabe Y. A case of systemic sclerosis sine scleroderma associated with perforation of an afferent loop after subtotal gastrectomy with Billroth 2 anastomosis for its severe gastrointestinal involvement. Modern rheumatology / the Japan Rheumatism Association. 2005; 15(5):371–3. [PubMed: 17029097]
101. Marie I, Ducrotte P, Denis P, Hellot MF, Levesque H. Outcome of small-bowel motor impairment in systemic sclerosis--a prospective manometric 5-yr follow-up. Rheumatology. 2007; 46(1):150–3. [PubMed: 16782730]
102. Savarino E, Mei F, Parodi A, Ghio M, Furnari M, Gentile A, et al. Gastrointestinal motility disorder assessment in systemic sclerosis. Rheumatology. 2013; 52(6):1095–100. [PubMed: 23382360]
103. Ghoshal UC, Srivastava D, Ghoshal U, Misra A. Breath tests in the diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome in comparison with quantitative upper gut aspirate culture. European journal of gastroenterology & hepatology. 2014; 26(7):753–60. [PubMed: 24849768]
104. Quigley EM. Small intestinal bacterial overgrowth: what it is and what it is not. Current opinion in gastroenterology. 2014; 30(2):141–6. [PubMed: 24406476]
105. Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology. 2006; 130(2 Suppl 1):S78–90. [PubMed: 16473077]
106. Parodi A, Sessarego M, Greco A, Bazzica M, Filaci G, Setti M, et al. Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. The American journal of gastroenterology. 2008; 103(5):1257–62. [PubMed: 18422815]
107. Shah SC, Day LW, Somsouk M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. Alimentary pharmacology & therapeutics. 2013; 38(8):925–34. [PubMed: 24004101]
108. Barrett JS, Canale KE, Gearry RB, Irving PM, Gibson PR. Probiotic effects on intestinal fermentation patterns in patients with irritable bowel syndrome. World journal of gastroenterology : WJG. 2008; 14(32):5020–4. [PubMed: 18763284]
109. Soifer LO, Peralta D, Dima G, Besasso H. Comparative clinical efficacy of a probiotic vs. an antibiotic in the treatment of patients with intestinal bacterial overgrowth and chronic abdominal functional distension: a pilot study. Acta gastroenterologica Latinoamericana. 2010; 40(4):323–7. [PubMed: 21381407]
110. Frech TM, Khanna D, Maranian P, Frech EJ, Sawitzke AD, Murtaugh MA. Probiotics for the treatment of systemic sclerosis-associated gastrointestinal bloating/ distention. Clinical and experimental rheumatology. 2011; 29(2 Suppl 65):S22–5. [PubMed: 21586214]
111. Zhao J, Fox M, Cong Y, Chu H, Shang Y, Fried M, et al. Lactose intolerance in patients with chronic functional diarrhoea: the role of small intestinal bacterial overgrowth. Alimentary pharmacology & therapeutics. 2010; 31(8):892–900. [PubMed: 20132150]
112. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology. 2014; 146(1):67–75. e5. [PubMed: 24076059]
113. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut. 2014
114. Ebert EC. Gastric and enteric involvement in progressive systemic sclerosis. Journal of clinical gastroenterology. 2008; 42(1):5–12. [PubMed: 18097282]
115. Mecoli C, Purohit S, Sandorfi N, Derk CT. Mortality, Recurrence, and Hospital Course of Patients with Systemic Sclerosis-related Acute Intestinal Pseudo-obstruction. The Journal of rheumatology. 2014
116. Stanghellini V, Cogliandro RF, De Giorgio R, Barbara G, Cremon C, Antonucci A, et al. Natural history of intestinal failure induced by chronic idiopathic intestinal pseudo-obstruction. Transplantation proceedings. 2010; 42(1):15–8. [PubMed: 20172271]

117. Lindberg G, Iwarzon M, Tornblom H. Clinical features and long-term survival in chronic intestinal pseudo-obstruction and enteric dysmotility. Scandinavian journal of gastroenterology. 2009; 44(6):692–9. [PubMed: 19308797]
118. Folwaczny C, Laritz M, Meurer M, Endres SP, Konig A, Schindlbeck N. Effects of various prokinetic drugs on gastrointestinal transit times in patients with progressive systemic scleroderma. Zeitschrift fur Gastroenterologie. 1997; 35(10):905–12. [PubMed: 9432812]
119. Nikou GC, Toumpanakis C, Katsiari C, Charalambopoulos D, Sfikakis PP. Treatment of small intestinal disease in systemic sclerosis with octreotide: a prospective study in seven patients. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2007; 13(3):119–23. [PubMed: 17551375]
120. Perlemuter G, Cacoub P, Chaussade S, Wechsler B, Couturier D, Piette JC. Octreotide treatment of chronic intestinal pseudoobstruction secondary to connective tissue diseases. Arthritis and rheumatism. 1999; 42(7):1545–9. [PubMed: 10403284]
121. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. The New England journal of medicine. 1991; 325(21):1461–7. [PubMed: 1944424]
122. Verne GN, Eaker EY, Hardy E, Sninsky CA. Effect of octreotide and erythromycin on idiopathic and scleroderma-associated intestinal pseudoobstruction. Digestive diseases and sciences. 1995; 40(9):1892–901. [PubMed: 7555439]
123. Lindsey I, Farmer CR, Cunningham IG. Subtotal colectomy and cecosigmoid anastomosis for colonic systemic sclerosis: report of a case and review of the literature. Diseases of the colon and rectum. 2003; 46(12):1706–11. [PubMed: 14668600]
124. Brown M, Teubner A, Shaffer J, Herrick AL. Home parenteral nutrition--an effective and safe long-term therapy for systemic sclerosis-related intestinal failure. Rheumatology. 2008; 47(2): 176–9. [PubMed: 18084002]
125. Lundberg AC, Akesson A, Akesson B. Dietary intake and nutritional status in patients with systemic sclerosis. Annals of the rheumatic diseases. 1992; 51(10):1143–8. [PubMed: 1332633]
126. Baron M, Hudson M, Steele R, Canadian Scleroderma Research G. Malnutrition is common in systemic sclerosis: results from the Canadian scleroderma research group database. The Journal of rheumatology. 2009; 36(12):2737–43. [PubMed: 19833750]
127. Baron M, Bernier P, Cote LF, Delegge MH, Falovitch G, Friedman G, et al. Screening and therapy for malnutrition and related gastro-intestinal disorders in systemic sclerosis: recommendations of a North American expert panel. Clinical and experimental rheumatology. 2010; 28(2 Suppl 58):S42–6. [PubMed: 20576213]
128. Balbir-Gurman A, Brook OR, Chermesh I, Braun-Moscovici Y. Pneumatosis cystoides intestinalis in scleroderma-related conditions. Internal medicine journal. 2012; 42(3):323–9. [PubMed: 22432985]
129. Forbes A, Marie I. Gastrointestinal complications: the most frequent internal complications of systemic sclerosis. Rheumatology. 2009; 48(Suppl 3):iii36–9. [PubMed: 19487222]
130. Franck-Larsson K, Graf W, Ronnblom A. Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. European journal of gastroenterology & hepatology. 2009; 21(2):176–82. [PubMed: 19212206]
131. Mawdsley AH. Patient perception of UK scleroderma services--results of an anonymous questionnaire. Rheumatology. 2006; 45(12):1573. [PubMed: 17043046]
132. Thoua NM, Schizas A, Forbes A, Denton CP, Emmanuel AV. Internal anal sphincter atrophy in patients with systemic sclerosis. Rheumatology. 2011; 50(9):1596–602. [PubMed: 21504990]
133. Fynne L, Luft F, Gregersen H, Buntzen S, Lundby L, Lundager F, et al. Distensibility of the anal canal in patients with systemic sclerosis: a study with the functional lumen imaging probe. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2013; 15(1):e40–7. [PubMed: 23067109]
134. Hetzer FH, Hahnloser D, Clavien PA, Demartines N. Quality of life and morbidity after permanent sacral nerve stimulation for fecal incontinence. Archives of surgery. 2007; 142(1):8–13. [PubMed: 17224495]

135. Kenefick NJ, Vaizey CJ, Nicholls RJ, Cohen R, Kamm MA. Sacral nerve stimulation for faecal incontinence due to systemic sclerosis. Gut. 2002; 51(6):881–3. [PubMed: 12427794]

136. Spiegel BM. Patient-reported outcomes in gastroenterology: clinical and research applications. Journal of neurogastroenterology and motility. 2013; 19(2):137–48. [PubMed: 23667745]

137. Khanna D, Hays RD, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis and rheumatism. 2009; 61(9):1257–63. [PubMed: 19714600]

138. Khanna D, Hays RD, Park GS, Braun-Moscovici Y, Mayes MD, McNearney TA, et al. Development of a preliminary scleroderma gastrointestinal tract 1.0 quality of life instrument. Arthritis and rheumatism. 2007; 57(7):1280–6. [PubMed: 17907224]

**139. Spiegel BM, Hays RD, Bolus R, Melmed GY, Chang L, Whitman C, et al. Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) Gastrointestinal Symptom Scales. The American journal of gastroenterology. 2014 [Patient reported outcome measurement in assessing the gastrointestinal burden due to SSc.]

140. Nagaraja V, Hays RD, Khanna PP, Spiegel BM, Chang L, Melmed GY, et al. Construct validity of the Patient Reported Outcomes Measurement Information System (PROMIS(R)) gastrointestinal symptom scales in systemic sclerosis. Arthritis care & research. 2014

**Table 1**

Summary of management of gastrointestinal involvement in scleroderma

| Gastrointestinal Complication | Initial Intervention/testing | Subsequent interventions | Additional modifications |
|---|---|---|---|
| Gastroesophageal reflux disease (GERD) | Dietary and lifestyle modification; Daily PPI | Ensure PPI (if traditional) is taken 30 minutes to one hour prior to eating; consider trial on alternative PPI and/or may increase to twice daily dosing; if still not controlled may add H2 blocker at night; if still not controlled with high dose and or combination therapy consider GI referral for pH monitoring, impedance testing, and endoscopy | Small meals throughout the day, more food earlier in the day, walking after eating, sleeping on an incline/wedge, avoidance of aggravating foods |
| Barrett's esophagus | Optimize GERD regimen and continue close monitoring with gastroenterologists with regular upper endoscopy | Radiofrequency ablation (RFA) may have benefit in low-moderate grade dysplasia and is indicated in high grade dysplasia | |
| Stricture | Optimize GERD therapy | If dysphagia is persistent, may require endoscopic dilation | |
| Gastroparesis | Management may include prokinetics or gastric emptying study to confirm delayed gastric emptying | Modify diet and optimize fluid intake; if symptoms persist check EKG for prolonged QT; Add promotility agent (e.g. metoclopramide); if normal QT and no drug interactions may use domperidone or erythromycin; treat nausea | Small meals, walking after eating |
| Gastric antral vascular ectasia (GAVE) | Endoscopy to confirm the diagnosis; Argon plasma therapy in patients with active bleeding; supportive care in the acute setting | Repeated sessions of argon plasma therapy may be required; alternative approach is laser therapy. Immunosuppression may play a role in patients who have other indications requiring such drugs | |
| Small intestinal bacterial overgrowth (SIBO) | Breath tests have poor sensitivity; tests for underlying malabsorption. Therapeutic trial of antibiotics (metronidazole, ciprofloxacin, neomycin, rifaximin, amoxicillin, doxycycline) | In recurrent cases, cyclic antibiotic therapy; probiotics can be used in conjunction; in cases of malabsorption, simultaneous oral or parenteral nutritional support. FODMAP diet can also be considered. | |
| Intestinal pseudo-obstruction | Clinical evaluation; imaging to exclude mechanical cause of obstruction (abdominal radiograph, CT scan of the abdomen); patients need to be hospitalized and initial supportive treatment | Nutritional support, prokinetic agents (such as subcutaneous octreotide), and broad-spectrum antibiotics; in severe cases that have failed conservative therapies, surgery can be considered for the sake of decompression | |
| Malnutrition | Screening and early detection is vital; BMI should be evaluated at each visit. Screening tools like MUST and laboratory test to identify nutritional deficiencies | Total parenteral nutrition is needed in severe cases; a selected group of patients need percutaneous feeding tubes | |
| Constipation | Good bowel hygiene and trial of stimulant laxatives and stool softeners | Osmotic laxatives | Liberal ingestion of fluids and ensuring adequate fiber intake in daily diet |
| Diarrhea | Identified the cause as cause is multifactorial | Identification and management of the etiology is important (dysmotility, SIBO, fat malabsorption) | |
| Fecal incontinence | Optimize the management of diarrhea and SIBO; biofeedback, pelvic floor exercises | Sacral nerve stimulation for resistant cases. | |

## Table 2

Medications to treat gastrointestinal manifestations in systemic sclerosis

| |
|---|
| **Proton pump inhibitors**<br>• Omeprazole 20-40 mg 1 to 2 times per day<br>• Lansoprazole 15-30 mg 1 to 2 times per day<br>• Pantorazole 40 mg 1 to 2 times per day<br>• Esomeprazole 20-40 mg 1 to 2 times per day<br>• Dexlansoprazole 30-60 mg once per day |
| **Histamine-2 receptor blockers**<br>• Famotidine, Cimetidine, Ranitidine, Nizatidine at night (or twice daily) and as needed if on maximum doses of proton-pump inhibitors |
| **Pro-motility agents**<br>• Metoclopramide 10 mg 3 to 4 times per day<br>• Erythromycin 250 mg 3 to 4 times per day<br>• Domperidone 10-20 mg 3 to 4 times per day<br>• Octreotide 50 - 200 mcg, 1 to 2 times per day, subcutaneous injection |
| **Antibiotics for small intestinal bacterial overgrowth**<br>• Amoxicillin 500 mg 3 times per day<br>• Amoxicillin/ Clavulanate 500/125 or 875/125 mg 2 times per day<br>• Ciprofloxacin 500 mg 2 times per day<br>• Metronidazole 500 mg 3 times per day<br>• Doxycycline 100 mg 2 times per day<br>• Bactrim® Double Strength 1 tablet 2 times per day (trimethoprim-sulfamethoxazole)<br>• Rifaximin 400 mg up to 3 times per day<br>• Neomycin 500 mg 2 to 4 times per day |
| **Laxatives**<br>• Docusate sodium 100 mg 1 to 2 times per day<br>• Lactulose 15-30 ml 1 to 2 times per day (watch for increase in gas / distention)<br>• Milk of magnesia 30-60 ml once per day or Magnesium tablets (magnesium oxide)<br>• Sennosides 1 capsule 1 to 2 times per day<br>• Polyethylene glycol 17 grams, 1 to 2 times daily<br>• Linaclotide 145 – 290 micrograms once daily 30 minutes after breakfast<br>• Lubiprostone 8 – 24 micrograms, 2 times daily |