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Advances in the Evaluation and Management of Esophageal Disease of Systemic Sclerosis

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Abstract

Symptoms of heartburn and dysphagia, as well as objective findings of abnormal esophageal acid exposure and esophageal dysmotility are common in patients with systemic sclerosis (SSc). Treatments for SSc esophageal disease are generally limited to gastroesophageal reflux disease (GERD) treatment with proton pump inhibitors. Progresses made in esophageal diagnostic testing offer the potential for improved clinical characterization of esophageal disease in SSc that may help direct management decisions. In addition to reviewing GERD management in patients with SSc, present and potential uses of endoscopy, reflux monitoring, manometry, impedance planimetry, and endoscopic ultrasound are discussed.

Keywords

Systemic sclerosis; GERD; esophageal reflux monitoring; manometry; impedance

Introduction

Esophageal symptoms and disease are common in patients with systemic sclerosis (SSc): heartburn and dysphagia, and objective findings of esophageal dysfunction have been reported in 50–90% of patients [1, 2]. Thus, the esophagus is second only to the skin as the most commonly affected organ in SSc. Despite its prevalence, the understanding of the pathogenesis of esophageal dysfunction in SSc remains relatively poor; mechanisms involving vascular injury and ischemia, neurodegeneration, and collagen deposition causing muscular atrophy and fibrosis are considered [3–5]. Various SSc clinical manifestations including disease subtype, serum autoantibodies, skin findings, and Raynaud's phenomenon have been found to be associated with increased prevalence of SSc esophageal disease [6–

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8]. The most notable association, however, is interstitial lung disease which is the primary cause of mortality in SSc [9–14].

Symptoms are poorly correlated with objective findings of esophageal disease in patients with SSc [7, 8]. Common abnormalities in gastrointestinal function include weak or absent distal esophageal peristalsis and hypotensive lower esophageal sphincter (LES) pressure, a pattern often termed scleroderma esophagus (even in the absence of SSc). Gastroparesis can also develop. These functional abnormalities impair esophageal acid clearance and predispose patients to gastroesophageal reflux disease (GERD) and its potential complications. Proton pump inhibitors (PPI) are effective at controlling GERD manifestations, though little progress has been made in the prevention and treatment of SSc esophageal dysmotility. Innovative diagnostic modalities in esophageal diagnostic testing have been implemented into both research and clinical practices over the past decade, such as esophageal impedance and high resolution manometry. Application of existing and new technologies in patients with SSc may be utilized to better define and classify esophageal disease that may facilitate development of more tailored and effective management strategies.

Treatment of GERD in Systemic Sclerosis

Proton pump inhibitors are the primary treatment for reflux esophagitis and frequent GERD symptoms. While the various available PPIs vary in potency (see Table 1), no clear advantage of one PPI over another has been demonstrated in clinical studies. Thus any agent (usually the most affordable) is an acceptable choice for first line therapy. To optimize gastric acid suppression, PPIs should be taken 30–60 minutes before meals. Use of twice daily PPI (e.g. lansoprazole 15mg taken before breakfast and dinner) can increase and prolong gastric acid suppression more effectively than an equivalent dose taken once daily (e.g. lansoprazole 30mg daily) [15]. Large scale, randomized, controlled trials of PPI use in SSc patients are lacking. A study that randomized 24 SSc [19 limited cutaneous (lc)SSc, 5 diffuse cutaneous (dc)SSc] to daily lansoprazole or placebo reported significant symptomatic improvement at 6, but not 12 months [16]. In this study, lansoprazole did not prevent progression of esophageal dysmotility as assessed by scintigraphy. A study of SSc patients with esophageal dysmotility and erosive esophagitis has demonstrated that daily omeprazole alleviated GERD symptoms and promoted healing of esophagitis [17]. Another study evaluating SSc patients treated with rabeprazole (10mg daily) showed symptomatic improvement at 4 and 8 weeks [18]. However, not all patients will have a satisfactory response to treatment with PPIs and the likelihood of treatment success depends on the GERD manifestation being treated (see Figure 1) [19].

When patients have persistent GERD symptoms or primary nocturnal symptoms despite PPI treatment, increasing to twice daily dosing or switching to a more potent PPI, such as esomeprazole or rabeprazole, should be considered. Dexlansoprazole employs a modified release formulation (the drug is initially absorbed in the proximal small intestine, then the distal small intestine several hours later) to increase the duration of acid suppression [20]. Thus, dexlansoprazole is an option for treating breakthrough and/or nocturnal acid reflux with once daily dosing. Head of bed elevation using blocks or a wedge pillow, should be

recommended for all patients with nocturnal reflux symptoms [21]. Addition of a histamine-2 receptor antagonist (H2RA) at bedtime to daily or twice daily PPI has demonstrated short-term (generally 5–7 days) effectiveness for treatment of nocturnal breakthrough acid reflux [22]. However, tachyphylaxis generally occurs after 1–2 weeks of H2RA use. Not surprisingly, other studies of longer-term H2RA treatment (> 4 weeks), including a cross-over study that followed 14 SSc patients (9 dcSSc, 5 lcSSc) for 6 week treatment periods, have not demonstrated sustained improvement in nocturnal acid suppression [23, 24].

Though PPIs are generally safe medications, recent studies have described associations with PPI use and infection (*Clostridium difficile* and pneumonia), osteoporosis, and small intestinal bacterial overgrowth (SIBO). Meta-analyses of observational studies of patients receiving PPIs have report increased pooled-relative risks of approximately 1.7 and 1.34 for developing *Clostridium difficile* and community-acquired pneumonia, respectively [25–27]. Proton pump inhibitor use has inconsistently been associated with a slight increased risk of hip and vertebral fractures, but a decline in bone mineral density was not associated with PPI use [28–31]. The association of SIBO and PPI use has also been inconsistently observed (though possibility due to variation in SIBO testing method), but appears to be independent of intestinal dysmotility [32, 33]. Thus our practice is to wean patients' PPI use to the lowest effective dose needed to control symptoms and heal esophagitis.

Few pharmacologic therapies are directed toward improving esophageal motility. Metoclopramide use in SSc patients appears to improve LES pressure and inconsistent stimulation of esophageal body pressure waves have been observed [34–37]. However, these studies only assessed experimental, not clinical settings (i.e. single intravenous dose before and after esophageal functional testing). Furthermore, the development of neurologic side effects, including potentially irreversible tardive dyskinesia, is associated with long-term metoclopramide use. Cisapride, which is not readily available in the United States due to the potential association with cardiac arrhythmias, may increase LES pressure, but has generally not shown beneficial effects on esophageal peristalsis [38]. Prucalopride, a 5-HT4 agonist that is available in Europe (but not presently in the United States) for the treatment of chronic constipation, has been shown to decrease esophageal acid exposure time and increase gastric emptying (without having any significant effects on esophageal motor function) in healthy controls, and warrants study in SSc patients with GERD [39].

Anti-reflux surgery, such as gastric fundoplication, is sometimes considered for refractory reflux; however, SSc is considered a relative contraindication. Although anti-reflux surgery in SSc patients has been reported to reduce reflux symptoms and improve esophageal acid exposure [40, 41], a study involving 20 SSc patients demonstrated development of reflux esophagitis in all patients at an average of 4 years after surgery [42]. Furthermore, postoperative dysphagia developed in 38–71% of patients that underwent fundoplication in various studies [40–43]. A more recent retrospective review of SSc patients undergoing surgical management of GERD (23 patients; 3 esophagectomy, 8 Roux-en-Y gastric bypass, and 10 fundoplication) reported better post-operative GERD-related quality of life and less dysphagia in patients undergoing Roux-en-Y than fundoplication and esophagectomy at a median follow-up interval of 21 months [43]. However, given the possibility of small

intestinal dysmotility and bacterial overgrowth in SSc patients, Roux-en-Y should also be pursued with caution. Over the past decade, several endoscopic anti-reflux procedures and a novel device consisting of magnetic beads that is laparoscopically placed around the esophagogastric junction (EGJ) that attempt to augment EGJ pressure to prevent GERD have been developed [44–49]. However clinical studies of these devices to date have excluded patients with SSc and significant esophageal dysmotility, thus their potential effectiveness and safety in SSc patients requires further study.

Endoscopy

Esophagogastroduodenoscopy (EGD) is usually pursued in evaluation of GERD-associated symptoms (heartburn, regurgitation, non-cardiac chest pain, and sometimes extra-esophageal symptoms of cough, hoarseness, throat clearing, etc) if there is an inadequate response to once or twice daily PPI therapy or if an alternative diagnosis (such as Candida esophagitis) or GERD complications (esophageal strictures) are suspected. The initial diagnostic modality for the work-up of dysphagia in all patients is EGD as it offers both diagnostic as well as therapeutic potential (e.g. identification and dilation of a peptic stricture). Discovery of erosive esophagitis and/or Barrett's esophagus is essentially diagnostic of GERD, though both findings carry a low sensitivity [50, 51]. A recent retrospective analysis of 13 PPI-naïve asymptomatic patients with early SSc disease suggests that EGD may be useful in this population [52]. Low grade erosive esophagitis was demonstrated on EGD in 77% and was suggestive of esophageal dysmotility in 85% of patients [53]. Patients with esophagitis were initiated on PPI (dose and schedule not reported) and all patients that underwent follow-up EGD demonstrated complete healing of esophagitis. Due to the high prevalence and poor association of symptoms to objective findings of esophageal disease in SSc patients, PPI use has been recommended for all SSc patients [7, 8, 54]. In spite of long-term daily omeprazole (median treatment duration 6 years, range 1–38 years) initiated at SSc diagnosis in 133 patients, the development of esophagitis and Barrett's esophagus (BE) was still identified in 32% and 7%, respectively [55]. Thus endoscopy remains essential in the evaluation of patients with SSc and may be considered even in asymptomatic patients.

Barrett's esophagus is intestinal metaplasia of the normal esophageal squamous mucosa and has been identified as a pre-cursor lesion to esophageal adenocarcinoma. However, the risk of progression of non-dysplastic BE to cancer is low (0.1–0.6%/year) [56, 57]. Use of EGD for routine screening for BE in GERD patients remains controversial, but consideration is recommended for individuals at increased risk for BE and esophageal adenocarcinoma. Risk factors include male sex, age greater than 50, obesity, Caucasian race, and long-standing (often defined as >5 years) GERD [58–60]. A study that followed 50 European SSc patients (56% lcSSc, mean (standard deviation) disease duration of 12.2 (10.3) years since first non-Raynaud's phenomenon symptom) with BE (10/50 with dysplasia) reported an overall 0.7%/year rate of progression to adenocarcinoma [61]. Though the rate of progression of BE to adenocarcinoma in SSc patients is not dramatically greater than the general population, it is noteworthy that the SSc population is demographically different than typical BE patients, comprised mostly of young, slender woman. Furthermore, given that SSc has been associated with an increased risk for esophageal cancer, SSc should be considered another risk factor to guide individualized medical decision making in BE screening [62].

Reflux monitoring

Progress in ambulatory reflux monitoring over the past decade includes the use of a wireless pH sensor (Bravo pH monitoring system, Given Imaging, Yoqneam, Israel) and the incorporation of impedance monitoring with pH sensors. Reflux monitoring is typically employed if symptoms are not responsive to high-dose acid-suppressive therapy (such as twice daily PPI), if the diagnosis of GERD is questioned, such as for atypical reflux symptoms (e.g. cough, laryngitis), and/or prior to consideration of any anti-reflux surgery.

Traditional pH monitoring employed a transnasal catheter to position a pH-sensor in the distal esophagus to measure intraesophageal acid exposure. Use of the wireless pH sensor offers several advantages over catheter-based assemblies such as improved patient tolerance [63–65], possible greater test sensitivity due to longer testing periods (48–96 hours, compared with 24 hours for catheter-based testing) [64, 66–68], and lack of disruption of normal activity and diet during the testing period [63, 64, 69]. One drawback of wireless pH sensors is placement during endoscopy is typically required.

Reflux monitoring with pH-impedance utilizes a transnasally-placed catheter-based assembly. Impedance probes can measure the composition of intraesophageal contents (liquid, gas, or mixed) and thus when combined with pH-sensors, can detect weakly acid and non-acid reflux events. Because PPIs effectively increases gastric pH, the yield of pH-monitoring (without impedance) for the detection of acid reflux while remaining on PPI is low in the general GERD population [70]. This topic has not been studied in patients with SSc specifically. In contrast, reflux monitoring with pH-impedance while *on PPI* can offer some additional insight into the etiology of PPI-refractory symptoms by detecting weakly acidic reflux, in addition to breakthrough acid reflux. However, retained fluid in the esophagus can cause low baseline impedance measurements that can make study interpretation difficult or not possible. For instance, a study of 2809 pH-impedance studies found that 38 patients had uninterpretable exams due to low baseline impedance. Esophageal manometry demonstrated absent peristalsis in 10.5% (4/38) and ineffective esophageal motility in 37% (14/38), both common manometric patterns of esophageal dysmotility in SSc. Thus, the utility of pH-impedance testing may be limited in SSc patients with significant esophageal dysfunction.

Reflux monitoring may provide additional prognostic information in patients with SSc and interstitial lung disease. A retrospective study of 10 patients with severe SSc who underwent esophageal functional testing during lung transplant evaluation, found that severe reflux, measured via a composite score of esophageal pH testing was a comparable, if not better, predictor of survival than pulmonary function testing metrics [71]. While GERD-induced aspiration pneumonitis is a commonly cited contributor to SSc interstitial lung disease, SSc-related pulmonary disease could also induce GERD by exaggerated decreases in intrathoracic pressure due to increased respiratory effort. Data regarding the effectiveness of anti-acid and/or anti-reflux treatment in SSc patients with interstitial lung disease are scarce and GERD treatment has not demonstrated consist benefits in other pulmonary diseases including asthma [72, 73]. An exception may be anti-reflux surgery around the time of lung transplant. A retrospective evaluation of lung transplant patients with GERD (symptomatic

and/or positive pH test) demonstrated improved survival with fundoplication accompanying transplant [74]. While anti-reflux surgery post lung transplantation was reported to preserve lung function in a small cohort of SSc patients (N=6) [75], as discussed above, fundoplication should be considered high risk in patients with SSc.

Esophageal manometry

The typical manometric pattern of esophageal dysmotility seen in SSc involves absent or ineffective distal esophageal peristalsis and hypotensive LES pressurization [76, 3]. Manometry is typically utilized for non-obstructive dysphagia or pre-operative anti-reflux surgery evaluations. It is performed by placing a catheter with pressure sensors transnasally into the stomach and measuring esophageal pressures during a series of swallows. Conventional manometry utilizes pressure sensors positioned at the lower esophageal sphincter (LES) and at various intervals (often 5cm) along the esophagus to produce pressure measurements in the form of line tracings (Figure 2A). High-resolution manometry (HRM) utilizes a catheter with multiple sensors spaced 1 cm apart spanning from the hypopharynx to the stomach. Computer software interpolates pressure output to create a space-time-pressure plot called esophageal pressure topography (EPT, Figure 2B). Analysis of EPT utilizes various modality-specific metrics of esophageal peristaltic and sphincter function that have been incorporated into a diagnostic classification system for esophageal motility disorders [77, 78]. Increased sensor number and decreased spacing interval in HRM/EPT compared to conventional line tracings enhances esophageal peristaltic and sphincter function characterization and theoretically improves diagnostic accuracy.

One study of esophageal motility defined utilizing HRM in 51 patients with SSc found that most (83%) patients had hypotensive basal LES pressures and a substantial proportion also had ineffective distal esophageal motility (47% with absent peristalsis, 20% with weak peristalsis) [8]. In this series, all patients with esophagitis and/or circumferential Barrett's esophagus had absent peristalsis and hypotensive LES pressures. Another study utilizing HRM in 28 SSc patients with absent distal peristalsis on manometry reported smaller peristaltic pressure wave amplitudes in patients with (mean+/− standard deviation 0.5 +/− 2.3 mmHg) than without (10.8 +/− 18.4 mmHg) Raynaud's phenomenon [79]. While this association with Raynaud's phenomenon may support a vasospastic and/or ischemic mechanism to SSc esophageal dysfunction, the clinical significance of the small absolute difference in wave amplitudes is questionable.

Impedance sensors, which assess fluid bolus presence, can also be combined with esophageal manometry to potentially enhance the diagnostic evaluation by detecting esophageal bolus clearance (Figure 2C) [80]. In addition to assessing bolus clearance, high-resolution impedance manometry (HRIM) allows additional assessment of esophageal function and potentially symptom development by providing the ability to apply new metrics such as the bolus flow time, which assess bolus flow across the LES, and the bolus impedance height, which measures the amount of retained fluid in the esophagus [81, 82]. While the bolus impedance height provides similar functional information as a timed barium esophagram, unlike an esophagram, it does not require radiation [82]. Furthermore, HRIM can be used to measure intrabolus pressures during identified distinct functional phases of

esophageal peristalsis. Extrapolating intrabolus pressure measurements as a marker of esophageal wall states may offer additional insight into the role of esophageal *wall* properties (instead of previously focused-upon intraesophageal pressures) on esophageal function and symptom development [83].

Inclusion of multiple rapid swallows (MRS), a provocative maneuver included in manometry study protocols, may offer another method to help direct management of esophageal disease. An analysis of conventional manometry using MRS demonstrated that approximately half the patients with manometric ineffective esophageal motility displayed increased distal esophageal peristaltic contraction amplitudes following an MRS protocol (a finding also seen in normal controls) [84]. They concluded that assessing esophageal body response to MRS may represent subsets of patients with ineffective esophageal motility that may help predict a response to pro-motility agents, though this theory remains to be systematically studied.

Functional Luminal Imaging Probe

Another novel diagnostic tool for esophageal functional assessment is the functional luminal imaging probe (FLIP; Crospon, Inc. Galway, Ireland). Placed per-orally during endoscopy, FLIP is a balloon-tipped catheter that measures esophageal cross-sectional areas using high-resolution impedance planimetry and pressures during volumetric distension of the balloon. Thus, distensibility of the esophagogastric junction (EGJ) and esophageal body are assessed [85]. This device has primarily been used to assess patients with achalasia and eosinophilic esophagitis. In both patient groups, FLIP has been demonstrated to provide useful prognostic information regarding clinical outcomes and response to treatment [86, 87]. It also may permit assessment of EGJ distensibility as it pertains to GERD risk, as well as a potential tool to help monitor and direct anti-reflux procedures [85,88]. A study utilizing FLIP demonstrated that GERD patients exhibit larger cross-sectional area at lower pressures during segmental volumetric distension (i.e. greater EGJ distensibility) than asymptomatic controls [85]. Impedance planimetry has been used in the evaluation of SSc patients with esophageal dysfunction and has demonstrated some regional differences in esophageal distensibility between normal controls and SSc-disease subtypes [89]. Use of impedance planimetry has also been reported in the assessment of 11 patients with SSc (5 lcSSc, 6 dcSSc); median, range SSc disease duration: 11 years, 3–35 years) and absent or impaired esophageal peristalsis [90]. By applying principles of pressure-volume work loops during evoked secondary peristalsis by distension of the esophageal body, they were able to document increased esophageal stiffness and impaired esophageal body muscle function.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) offers evaluation of the wall of the gastrointestinal tract and the adjacent extraluminal space. A recent study demonstrated that EUS use in 62 patients with esophageal motility disorders identified clinically relevant findings in 15%, however most demonstrated esophageal motility patterns associated with esophageal obstruction, such as achalasia [91]. EUS evaluation of 25 patients with SSc (14 dcSSc, 11 lcSSc) and dysphagia demonstrated thickened esophageal, antral, and duodenal walls, most prominently

in the submucosa and muscularis, compared with 25 non-SSc, control patients [92]. Subgroup analysis demonstrated that differential thickening of the esophageal and gastroduodenal walls was not seen in 11/25 SSc patients without dysphagia compared with controls. Thus, the association of wall thickness and dysphagia in SSc patients may offer some insight into pathophysiology and/or the mechanism of symptom development.

Conclusions

Despite the high prevalence of esophageal disease and symptoms in patients with SSc, the pathologic mechanisms remain uncertain. PPIs are effective in controlling GERD symptoms in SSc patients. Treatment options directed toward esophageal dysfunction are limited and complicated by potential adverse events. While anti-reflux surgery remains a possibility in refractory GERD cases, caution needs to be exercised due to the frequency of cardiopulmonary comorbidities and significant chance of worsened post-operative esophageal function. Established technologies including endoscopy and manometry, may lead to early identification of patients with SSc esophageal dysfunction. Application of evolving technologies, such as reflux monitoring and high-resolution impedance manometry, may better characterize clinically relevant SSc esophageal disease subtypes. Functional luminal imaging probes and EUS provide additional esophageal functional information in SSc, but more study using these technologies is needed to demonstrate the clinical relevance and utility of their findings. With continued utilization and critical appraisal of the known, evolving, and emerging esophageal diagnostics, disease mechanisms, clinical phenotypes and insights into pathogenesis may be elucidated providing groundwork for novel therapies.

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Abbreviations

BE	Barrett’s esophagus
dcSSc	diffuse cutaneous systemic sclerosis
EGD	Esophagogastroduodenoscopy
EGJ	esophagogastric junction
EPT	esophageal pressure topography
HR(I)M	high resolution (impedance) manometry
lcSSc	limited cutaneous systemic sclerosis
LES	lower esophageal sphincter
MRS	multiple rapid swallows
GERD	gastroesophageal reflux disease

PPI	proton pump inhibitor
SIBO	small intestinal bacterial overgrowth
SSc	systemic sclerosis
UES	upper esophageal sphincter

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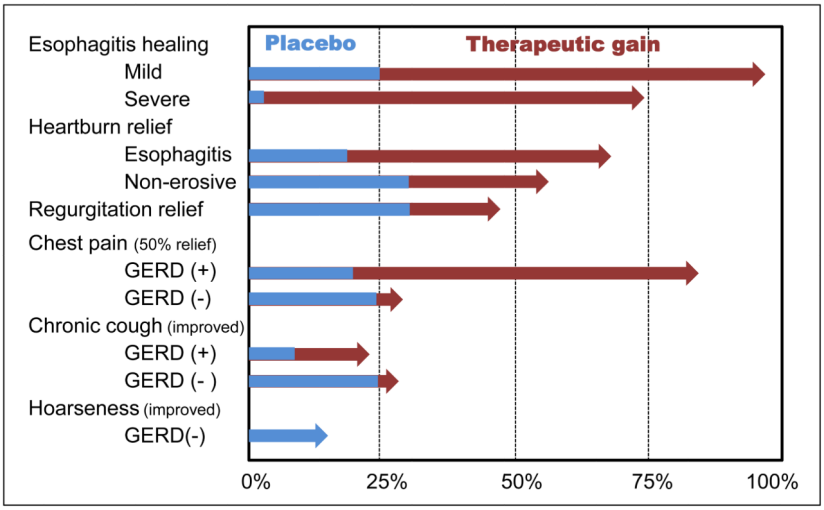
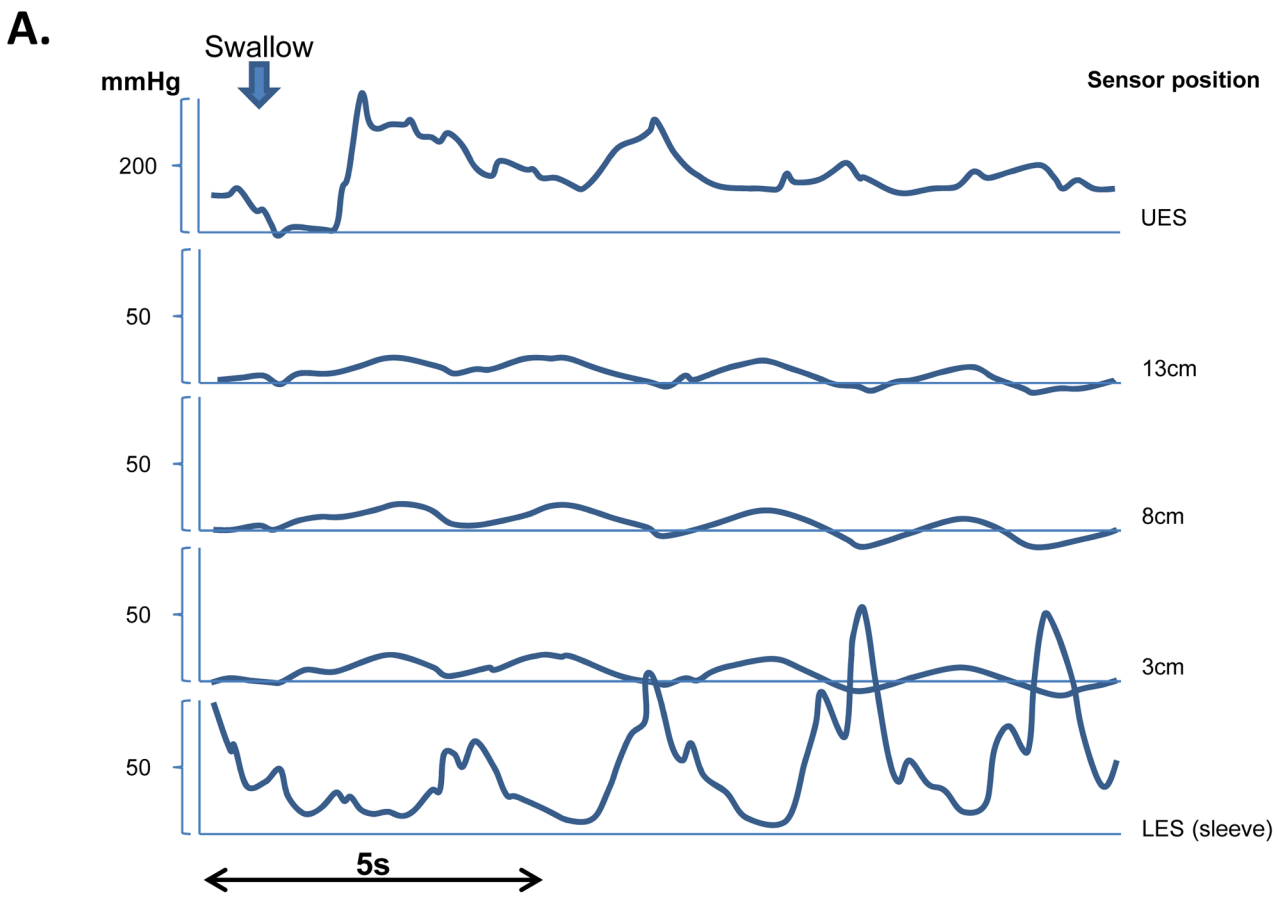
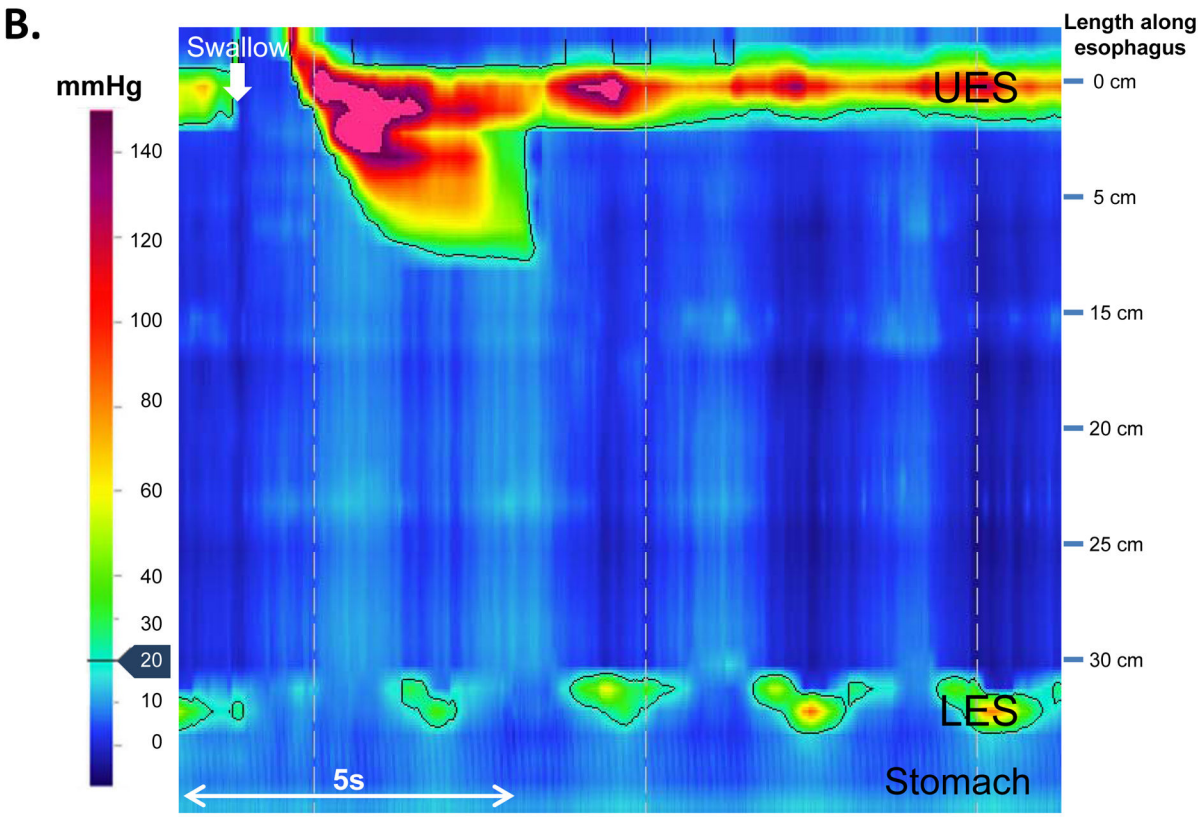


Figure 1. Efficacy of PPIs based on GERD manifestation

Adapted from Reference #19, estimates of placebo response (blue) and therapeutic gain of PPI use (red) are based on pooled data of randomized control trials. Data are grouped in terms of brand and dose for simplicity. GERD (+) or (−) is based on EGD findings or results of esophageal pH testing. As demonstrated, PPIs are efficacious for healing of esophagitis, but have decreasing efficacies when used for heartburn, regurgitation, cough, and hoarseness. It is noteworthy that none of the included trials specifically included patients with SSc. Reproduced with permission [19].





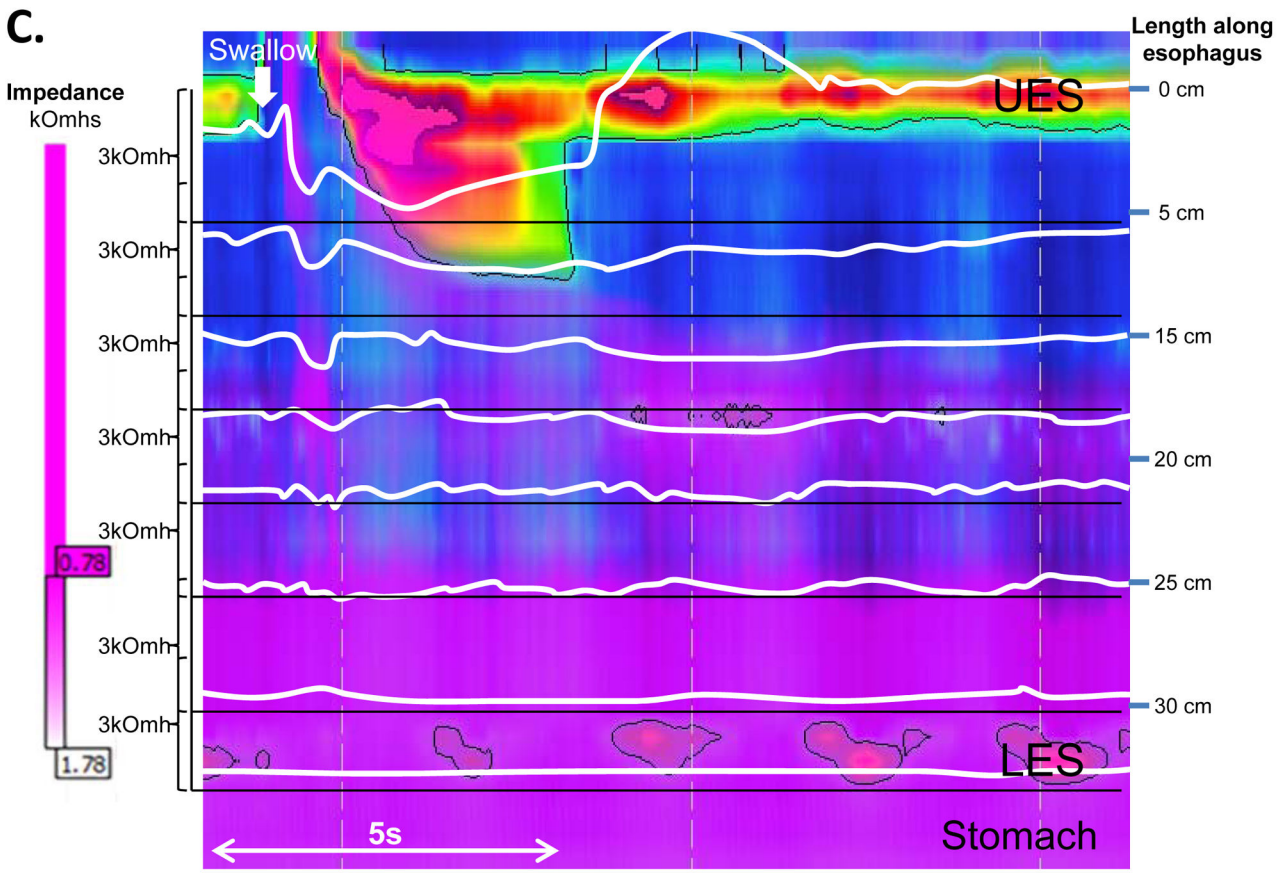


Figure 2. Conventional manometry (A) and Esophageal pressure topography with (B) and without (C) impedance of a patient with systemic sclerosis

A typical pattern, often termed *scleroderma esophagus*, involving absent peristalsis and low LES pressures is depicted. Incorporation of multi-channel impedance, displayed both by line tracings (white lines) and topography (purple color) demonstrates incomplete liquid bolus clearance. Bolus presence is indicated on line tracings by a bolus entry at a 50% decrease in impedance from baseline and bolus passage by 50% recovery from nadir to baseline. The bolus appears to be retained about 12 cm above the LES. UES – upper esophageal sphincter. Used with permission from the Esophageal Center at Northwestern.

Table 1

Relative potencies of equivalent doses and compared to omeprazole on the effect of 24-hour gastric pH are based on a meta-analysis of clinical studies [15]. Studies evaluating dexlansoprazole were not included in the meta-analysis. However a cross-over study comparing gastric pH in healthy subjects receiving 60mg dexlansoprazole and 40mg esomeprazole demonstrated a higher gastric pH over 24 hours with dexlansoprazole, but equivalent gastric pH between the two agents at 0–12 hours [20]. Combining omeprazole with sodium bicarbonate (*Zegerid)*, allows for more rapid PPI absorption and onset of action.

Drug	Trade name	Relative potency	Standard doses (mg)
Rabeprazole	Aciphex	1.82	20
Esomeprazole	Nexium	1.6	20, 40
Omeprazole	Prilosec, Zegerid	1.0	20, 40
Lansoprazole	Prevacid	0.9	15, 30
Dexlansoprazole	Dexilant		30, 60
Pantoprazole	Protonix	0.23	20, 40