

## Management of gastrointestinal manifestations in systemic sclerosis (scleroderma)

Gastrointestinal (GI) manifestations are often seen in patients with systemic sclerosis (SSc), although in previous years it has not received the same emphasis as other organ systems affected by this disease. In the past 5 years there has been a higher emphasis on these manifestations and more work is being carried out to identify and describe them, and to also formulate therapeutic strategies to deal with them. SSc can involve almost all parts of the GI tract, with some manifestations greatly diminishing quality of life for these patients. As esophageal manifestations are the most common GI manifestation of SSc, they have been the subject of a lot of research, and successful treatment of gastroesophageal reflux disease has been shown to reverse damage. Managing bacterial overgrowth and malnutrition in these patients, while difficult, has improved and patients are having better outcomes and improved quality of life. The research needs for this particular aspect of SSc are still very high, although the increased quality of work in this field over recent years is helping us to answer some of the questions.

**KEYWORDS:** bacterial overgrowth ■ esophageal dysmotility ■ gastric antral vascular ectasia ■ gastrointestinal ■ intestinal pseudo-obstruction ■ primary biliary cirrhosis ■ scleroderma ■ systemic sclerosis

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### Learning objectives

Upon completion of this activity, participants should be able to:

- Describe esophageal and gastric involvement in SSc, based on a review
- Describe small intestine involvement and malabsorption in SSc, based on a review
- Describe large intestine involvement in SSc, based on a review

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The vast majority of patients with systemic sclerosis (SSc) develop gastrointestinal (GI) involvement during their disease course and approximately 50% of patients will have GI symptoms [1]. GI manifestations are only second in frequency to the skin manifestations of this disease [2], and almost every part of the GI tract can be involved [3]. GI involvement is often diagnosed after severe complications have already occurred and management can be difficult [4]. Early diagnosis and treatment are important to delay or prevent complications [4]. Histopathological changes appear to have similarities throughout the GI tract [2,5] and both diffuse and limited cutaneous SSc patients can be affected [6,7]. The presence of GI involvement adversely affects mortality and quality of life [8], and although severe GI manifestations in SSc (defined as malabsorption, repeated episodes of pseudo-obstruction or severe problems requiring hyperalimination) are uncommon (8%), only 15% of such patients survived after 9 years of their diagnosis [9].

### Pathogenesis & pathophysiology

The pathophysiology of the different GI manifestations of SSc is not well understood [10]. In a review by Sjogren, the author proposed that the GI involvement in SSc follows a sequence beginning with a neuronal dysfunction triggered by vascular changes in the vasonervosum of the neuronal myenteric plexus, followed by smooth muscle atrophy and finally muscle fibrosis [11]. The early neuronal dysfunction/injury theory stemmed from an observation that abnormal motility has been detected in patients without any clear evidence of muscular involvement

(FIGURE 1) [12]. While in most cases fibrosis is the most common reason for the severe GI manifestations [13], in some cases fibrosis was not found [12,14]. This observation has been further supported by the detection of antibodies to myenteric neurons in a significant proportion of SSc patients. Antibodies directed against the muscarinic-3 acetylcholine receptors (M3R) in the neuronal myenteric plexus of the GI tract of SSc patients, thought to be related to GI dysmotility, were detected more frequently in scleroderma patients who had severe GI tract involvement (defined as malabsorption or pseudo-obstruction) compared to early SSc cases without severe GI manifestations or healthy controls [15]. Targeting of these antibodies through removal or neutralization may have a potential therapeutic benefit [10,16].

### Esophageal involvement

The esophagus is the most commonly involved organ of the GI tract in SSc [4], and in the early stages of SSc, esophageal manometry studies show low amplitude peristaltic contractures, a low lower esophageal sphincter (LES) pressure and failure of the LES to relax [11]. In mid-stage SSc, the decreased peristaltic amplitude progresses into absent peristalsis of the lower two-thirds of the esophagus [11], and myoelectrical activity between swallows are absent [17]. In late stages, LES is almost completely absent [11] and the function of the upper third of the esophagus may also be involved, which may lead to even worse consequences due to loss of the last barrier that prevents aspiration [11].

Gastroesophageal reflux disease (GERD) is a major clinical finding in scleroderma patients.

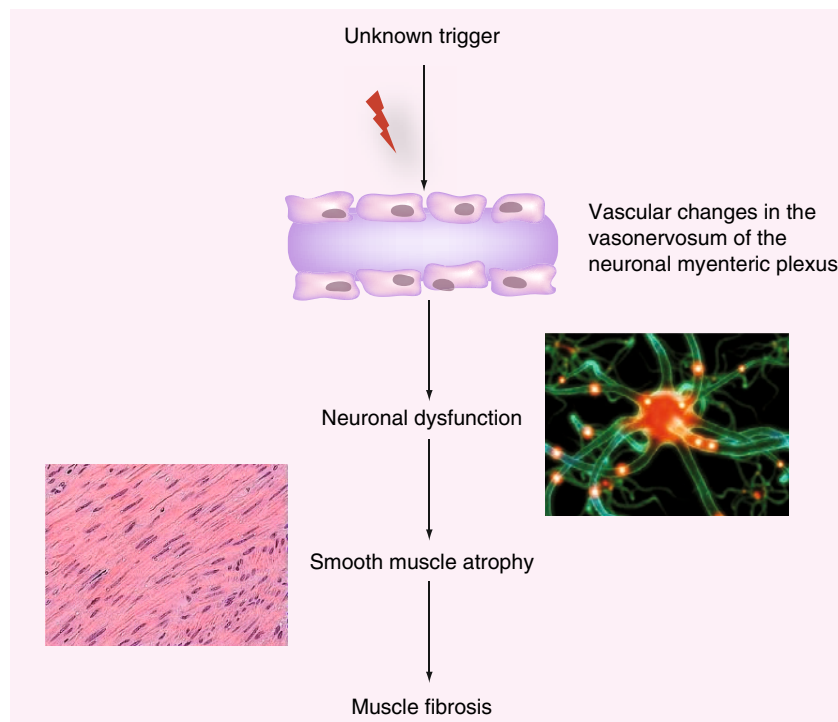
The reflux of gastric content into the esophagus and the resultant mucosal injury is not only facilitated by a lower LES pressure, but also by the inability of the lower esophagus muscle peristalsis to effectively clear the esophageal content [17,18]. The latter mechanism may be the main contributor to esophageal injury from acid exposure in SSc patients [18].

Patients with GERD complain of dysphagia, odynophagia, heartburn and regurgitation. Prolonged GERD may lead to erosive esophagitis, esophageal ulceration and stricture of the distal esophagus, and in the worse cases Barrett's esophagus that can lead to esophageal cancer [4]. Not all patients with GERD are symptomatic. Endoscopic studies showed that a significant proportion of patients with SSc have evidence of esophagitis in the absence of any symptoms [19], which highlights the importance of early screening for GERD in this population.

The management of GERD in systemic sclerosis incorporates pharmacological therapy and lifestyle modifications [20]. Patients are advised to elevate the head of the bed, avoid going to bed for 3–4 h following a meal, lose weight, stop smoking and minimize alcohol use. Patients are also encouraged to avoid using beverages or medications that can further lower the LES pressure such as caffeine-containing drinks, chocolate, calcium channel blockers and nitrates. Patients should be given strict instructions when prescribed medications that can cause esophageal irritation (bisphosphonates, tetracyclines, iron and NSAIDs), such as to avoid lying down or bending for 1–2 h after use and to take them with a full glass of water. In some cases, these medications should be avoided altogether.

Proton pump inhibitors (PPIs) play a major role in the management of GERD in scleroderma patients. Omeprazole has been shown to heal esophagitis [21] and may even reverse esophageal fibrosis [22]. The use of a higher than standard dose has been shown to control symptoms in most patients without major side effects [21]. In a recent randomized, placebo-controlled trial involving 24 patients, lansoprazole, at a standard dose of 30 mg daily was effective in controlling the symptoms of GERD in SSc patients in the first 6 months of therapy, but not after 1 year. The authors concluded that inadequate response may be the result of inadequate dosing [23]. Starting PPIs in all SSc patients early in the course of the disease should be considered [10,24]. Physicians should explain to patients that PPI use is lifelong [20].

In the PPI era, H<sub>2</sub>-blockers may still have some role when used in conjunction with PPI,



**Figure 1. Hypothesis of pathophysiological mechanisms that lead to gastrointestinal manifestations in systemic sclerosis.**

particularly if nocturnal symptoms are present despite maximal PPI therapy [20]. Prokinetic agents, such as cisapride, work by increasing the LES pressure, improving peristalsis and esophageal clearance, and by increasing gastric emptying, thus improving symptoms [25,26]. There is a paucity in the literature about the exact role of prokinetic agents use in conjunction with acid suppressive therapy for the esophageal manifestations of SSc, although some authors advise this combination when concomitant gastroparesis is present [20].

More recent work has focused on GABA[B] agonists, and metabotropic glutamate receptor antagonists (mGluR), both of which have been shown to increase basal LES pressure. Baclofen, the prototypic GABA(B) agonist was used at a dose of 40 mg, 90 min before a meal and it inhibited reflux episodes in up to 40–60% of healthy volunteers [27], although CNS side effects may limit its use. A proof-of-concept study has recently also looked at mGlu R modulator ADX10059. During 24 h of esophageal pH monitoring, 250 mg of baclofen given three-times daily reduced esophageal acid exposure from 7.2 to 3.6 % of the total monitoring time in healthy volunteers [28]. Neither of these agents has been looked at in SSc-GERD.

The incidence of *Candida* esophagitis is increased in SSc patients with GERD, particularly those on chronic acid suppressive therapy [11,29],

and although therapy for 2–4 weeks with fluconazole is effective in eradicating the infection, it recurred in almost all of the patients [29].

In general, surgical antireflux therapy should be approached with caution in scleroderma patients with severe GERD since the procedure may itself further worsen the emptying capacity of an already-damaged distal esophagus [20]. Nevertheless, fundoplication has been shown to reduce GERD in SSc patients [30], while esophageal strictures are managed by endoscopic dilatation of the involved area.

#### ■ Barrett's esophagus

Chronic GERD can lead to metaplasia of the lower esophageal mucosa, whereby normal squamous epithelium is replaced by columnar and goblet cells, and this is characterized as Barrett's esophagus (BE). In total, 5–15% of patients develop BE due to chronic GERD regardless of etiology [31,32]. One report estimated that 12.7% of SSc patients with GERD developed BE over a 2-year follow-up while on a PPI [33]. BE can frequently lead to dysplasia and these patients are at increased risk for adenocarcinoma [34], while specific recommendations for the best endoscopic follow-up strategy in SSc-related GERD patients needs to be assessed in future studies, patients with GERD and BE should undergo endoscopy every 2–3 years. If low-grade dysplasia is diagnosed, a yearly endoscopy is recommended and every 3 months if high-grade dysplasia is present [32].

#### ■ Lung involvement due to esophageal dysfunction

A new distinct pattern of interstitial lung disease (ILD) has been described in SSc patients called centrilobular fibrosis (CLO) [35] and has been linked to GERD. This is a pathologically different pattern than other ILD patterns described in SSc patients (nonspecific interstitial pneumonia and usual interstitial pneumonia), and thus aggressive management of GERD may result in better pulmonary outcome [10,36].

A recent study using pH impedance monitoring in SSc patients off PPI therapy compared acid reflux in patients who had ILD on their high-resolution CT of the chest versus patients who did not have ILD, and they showed that patients with ILD were more likely to have acid and nonacid reflux episodes and a higher number of reflux episodes reaching the proximal esophagus [37]. In another study, six patients with SSc-ILD possibly related to GERD who were treated with anti-reflux therapy showed stability after 12 months [38].

#### Gastric involvement

Delayed gastric emptying, or gastroparesis, is the most common gastric manifestation in SSc patients leading to nausea, vomiting and postprandial fullness [4,20], and is an important contributing factor to the development of GERD [4,39]. Radionuclide gastric emptying studies are used for diagnosis and should be carried out when GERD symptoms are intractable [20], although at times an initial endoscopy may be required to rule out mechanical causes.

Initial therapy should be dietary modification, which should include more liquid-based meals, and the intake of fats and nondigestible fiber should be reduced. Small portion meals spread throughout the day or in more severe cases, liquid or homogenized meals with vitamin supplementation should be used. If dietary modification alone is not successful then treatment options include metoclopramide, domperidone or cisapride, although the last two agents are not readily available in the USA owing to concerns of prolonged QT interval. Metoclopramide can be used at a dose of 5–10 mg every 8 h. Erythromycin, a motilin receptor agonist, has been successfully used in small doses in prokinetic-resistant, severe delayed gastric emptying [40].

Metoclopramide is the only the US FDA-approved agent for gastroparesis and domperidone is available although investigation programs in the USA. Erythromycin also has risks for QT prolongation and it lacks the antiemetic properties that the other two agents have. Medically resistant cases can be treated with endoscopic injection of botox into the pyloric sphincter, causing paralysis of the muscle [41].

Gastric antral vascular ectasia (GAVE) is an uncommon [42], yet well-recognized source of subtle, as well as frank, upper GI bleeding in SS patients [20]. It has a characteristic appearance on endoscopy known as 'watermelon' stomach [43,44]. Histologically it is characterized by mucosal capillary dilatation containing fibrin thrombi, fibromuscular hyperplasias and reactive epithelial changes. Therapy includes iron supplementation, blood transfusions and antrectomy in severe cases [45]. Yttrium aluminium garnet laser treatment (applied during endoscopy) is another effective therapy for chronic blood loss anemia in SSc patients with GAVE [46]. A newer technique, argon plasma coagulation (APC) has been shown to be effective and an inexpensive modality in treating GAVE [47].

The role of immunosuppressive therapy for GAVE needs to be further explored. A case report [45] and a case series of three patients [48]

suggested that cyclophosphamide may play a role in the management of GAVE refractory to conventional therapies [49].

### Diseases of the small intestine

After the esophagus, the small intestine is the most common GI target involved in systemic sclerosis. The small intestine is involved in 17–57% of patients, with clinical manifestations including: bacterial overgrowth, malabsorption, intestinal pseudo-obstruction, pneumatosis cystoides intestinalis and arteriovenous malformations [50]. Symptoms of small bowel involvement are often nonspecific and include nausea, vomiting, abdominal discomfort and altered bowel habits.

### Bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is a frequent problem seen in 33–40% of patients with systemic sclerosis [51,52]. Defined as bacterial counts of  $\geq 10^5$  organisms/ml of jejunal fluid, reduced peristalsis results in stasis and pooling in the small bowel, and eventually an imbalance of the intestinal microbiome. In the healthy individual, a pattern of cyclic contractile activity, also known as the migrating motor complex (MMC), occurs approximately every 90 min during the fasting state [53]. The MMC function is to clear up remnants of food, bacteria and secretions from the preceding meal and it serves as the ‘house keeper’ of the small intestine. In scleroderma, there is absent or abnormal MMC activity and a reduced amplitude of contractions.

Symptoms of bacterial overgrowth include bloating, flatulence, abdominal pain, discomfort, diarrhea, and in more severe cases, weight loss, steatorrhea and malabsorption [54]. The gold standard for diagnosis of bacterial overgrowth is small bowel aspiration and direct culture of jejunal contents. However, this is both an expensive and invasive procedure that may need to be repeated owing to regrowth. The glucose and lactulose  $H_2/CH_4$  breath tests are noninvasive, low-cost tests useful in clinical practice [55]. Limitations, however, include lack of standardization, low specificity and lack of bacterial resistance sensitivities.

Bacterial overgrowth responds in most cases to repeated courses of rotating antibiotics and prokinetic drugs. Norfloxacin (400 mg two-times/day), amoxicillin-clavulanic acid (500 mg three-times/day), rifamixin (1200 mg/day), metronidazole (250 mg three-times/day), ciprofloxacin (250 mg two-times/day), neomycin (500mg, four-times/day)

and trimethoprim–sulfamethoxazole (one double-strength tablet, two-times/day) have all proven effective in SIBO, although no trials exist regarding comparative efficacy of the different regimens [56]. If SIBO is suspected irrespective of a positive breath test a 10-day or in some cases an initial 21-day course of antibiotics can be tried and if the patient has a good response then they can use a 10-day course of antibiotics as needed. If the patient has a quick relapse it is then recommended that the antibiotic is used for the first 10 days of 4 consecutive months and in those who are still relapsing then the patient should be potentially placed on continued antibiotics [57]. Obtaining jejunal aspirate for culture is reasonable in patients who have resistance to rotating antibiotics and diarrhea that is difficult to control with empiric antibiotics.

### Malabsorption

Patients with scleroderma are also at risk for malabsorption, which is commonly due to intestinal stasis with subsequent bacterial overgrowth. The mechanism of bacterial involvement causing impaired absorption is not well understood, although one hypothesized mechanism is that bacterial deconjugation and dehydroxylation of conjugated bile salts results in decreased micellar formation and esterification of fatty acids [58,59]. Malabsorption is a poor prognostic sign in scleroderma and has been associated with a 50% mortality rate at 8.5 years [5]. Patients with malabsorption often suffer from deficiencies of fat soluble vitamins A, D, E and K, vitamin B12 and folic acid. They must be monitored for symptoms of these vitamin deficiencies, including fatigue, weakness, easy bruising, bleeding and bone loss. Some recommend serum quantification of  $\beta$  carotene as a screening test for patients with malabsorption [60].

If bacterial overgrowth is suspected as the cause of malabsorption, treatment with a regimen of oral antibiotics is indicated. After a course of antibiotic has been tried, the addition of probiotic therapy may be considered [61]. In refractory cases, octreotide can be used to stimulate small bowel motility [62]. Patients with persistent symptoms may eventually require parenteral nutrition or enteral nutrition via a jejunostomy.

### Intestinal pseudo-obstruction

Scleroderma is a common cause of intestinal pseudo-obstruction, although the association

with other connective tissue disorders, hypothyroidism, Chagas' disease, diabetes, Parkinson's disease and the use of narcotics or drugs with anticholinergic properties are known [63]. In this disorder, patients manifest with symptoms of intestinal obstruction in the absence of a mechanical blockage. The lack of contractile activity at regular intervals results from atrophy and fibrosis of the muscularis layer of the small bowel. Symptoms of nausea, vomiting, abdominal pain and distention, and altered bowel habits are often chronic and recurrent.

Plain radiographs of the abdomen show dilated loops of the small bowel with air fluid levels although this cannot exclude mechanical obstruction as a cause. A more characteristic sign of scleroderma intestinal pseudo-obstruction is a 'hide-bound' or 'accordion-like' appearance produced by closely packed valvulae resulting from excessive collagen deposition. This characteristic mucosal fold pattern is uniquely seen in scleroderma [64]. Biopsy shows fibrosis and atrophy of the smooth muscle with preferential involvement of the circular layer of the muscularis propria [65].

Patients with intestinal pseudo-obstruction are placed on *nil per os* status with parenteral nutrition support. Prokinetic drugs such as metoclopramide, erythromycin, domperidone, cisapride and octreotide are the treatments of choice [62]. In resistant cases, octreotide can go from once a day to twice a day subcutaneously, or erythromycin can be added to a daily dose of octreotide [66]. A small study of seven patients looked at the use of intramuscular long-acting-release octerotide on a monthly basis, which seemed to limit the quick relapse of pseudoobstruction [67].

### **Pneumatosis cystoides intestinalis**

Pneumatosis cystoides intestinalis (PCI) is a rare complication of scleroderma and is characterized by the presence of multiple gaseous cysts in the bowel wall on x-ray or computed tomography [68]. The development of PCI is dependent on the severity of GI tract involvement from scleroderma rather than on overall disease duration [69]. One theory is that PCI may be caused by an excess of hydrogen-producing bacteria in the intestine altering the partial pressure of nitrogen in the intestinal wall resulting in gas accumulation [70]. Patients may be asymptomatic or complain of nausea, vomiting, abdominal pain, appetite loss and diarrhea or constipation [71]. PCI is considered a 'benign' condition although bowel ischemia, perforation and peritonitis are

rare complications that have been reported [72]. Treatment of PCI is nonsurgical and largely symptomatic, consisting of bowel rest, antibiotics, oxygen therapy, parenteral nutrition and prokinetic agents.

### **Arteriovenous malformations**

Arteriovenous malformations (AVMs) can be seen cutaneously as well as throughout the GI tract, including the stomach, small bowel and colon. They may be a source of GI bleeding and iron deficiency anemia in patients with scleroderma and reports of massive hemorrhage from these telangiectasias have occurred [73]. Identification of AVMs are best made by endoscopy, although initial endoscopy may be nondiagnostic and require repeating. Mesenteric angiography is another useful tool in locating the source of bleeding in patients with AVMs. Thermal ablation with endoscopic guidance is the treatment of choice in patients with focal lesions, whereas patients with large, diffuse lesions often require hormonal therapy with estrogen-progesterone.

### **Diseases of the large intestine**

Colonic disease occurs in 10–50% of patients with systemic sclerosis, with the anorectum being the most frequently affected area [11]. Patients will often report of constipation, diarrhea and/or fecal incontinence. Constipation, defined as less than two stools per week, is commonly due to slow colonic transit, whereas diarrhea is caused by bacterial overgrowth. Both constipation and diarrhea can be associated with fecal incontinence. The presence of wide-mouthed diverticuli and rectal prolapse are other colonic complications seen in patients with scleroderma.

### **Fecal incontinence**

Normal fecal continence is maintained through a complex interplay involving the anal sphincter muscles, rectal wall properties, colorectal transport and anorectal sensation [74]. In scleroderma, the internal anal sphincter (IAS), which is responsible for the anal resting tone, may be fibrosed and atrophied, resulting in reduced anal resting pressure and fecal leakage. Impaired rectal capacity and wall compliance may further contribute to fecal incontinence [75]. Anal manometry will frequently show a reduction or loss of the rectoanal inhibitory reflex [76]. A more recent study looking at 64 SSc patients, 24 with fecal incontinence, 20 asymptomatic and 20 incontinent controls, showed that the

recto-anal inhibitory reflex was absent in more SSc patients with fecal incontinence and much less frequent in asymptomatic SSc patients and fecal incontinent controls, suggesting that fecal incontinence in SSc may be more related to a neuropathy rather than sphincter atrophy and rectal fibrosis [77].

Fecal incontinence is a debilitating symptom that can be disruptive to a patient's daily activities and is frequently under-reported. In a study investigating lower GI symptoms on quality of life, fecal incontinence negatively impacted both patients' general wellbeing and social life [78]. Treatments include biofeedback, sacral nerve stimulation and surgical repair. Loperamide or other antidiarrheal agents can be used cautiously although they may adversely affect GI motor function. Cholestyramine, a bile acid sequestrant, is another therapeutic option for some patients but must be used with caution in patients with renal impairment as it can cause hypochloremic acidosis [79].

### Diverticuli

Atrophy and thinning of the muscular wall in scleroderma leads to dilatation and development of 'wide-mouth' or 'fish-mouth' diverticuli with loss of haustral markings in the colon and more seldom in the rectum. These diverticuli involve all layers of the intestinal wall and are considered 'true' diverticuli. Rare complications include ulceration from fecal impaction, diverticulitis and rupture. With progression of scleroderma and increased rigidity of the intestinal wall, these diverticuli may eventually disappear [80]. Management is similar to that of diverticulosis and diverticulitis in non-SSc patients with the avoidance of foods that could cause impaction of the diverticuli and treatment with antibiotics when diverticulitis symptoms occur.

### Rectal prolapse

Rectal prolapse is a treatable complication in patients with systemic sclerosis, which worsens anal sphincter dysfunction and may aggravate fecal incontinence. Patients with a prolapsed rectum may complain of pain during bowel movements, leakage of mucus or blood, incontinence, or a sense of incomplete evacuation. Treatment includes management of constipation, but recurrent rectal prolapse often requires surgical correction for definitive management.

### Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune liver disorder that has been seen in

association with rheumatic disorders such as systemic sclerosis, Raynaud's and Sjogren's syndrome. Up to 10% of patients with PBC have a concomitant diagnosis of systemic sclerosis [81,82]. Anti-mitochondrial antibodies are a serological marker for this disease and can be seen in up to 90–95% of patients [83]. The prevalence of PBC in systemic sclerosis patients has been estimated to be approximately 2.5% [84]. The association of PBC and systemic sclerosis was first described by Telfer Reynolds in 1971 and at times this association has been described as Reynold's syndrome [85].

PBC is characterized by inflammation and subsequent fibrosis, and destruction of the interlobular and septal bile ducts, which leads to chronic cholestasis and biliary cirrhosis, which in turn can lead to portal hypertension and liver failure. It is often discovered incidentally on blood tests where the patient has an elevated alkaline phosphatase and the diagnosis should be considered, especially in the presence of an antimitochondrial antibody (AMA) in the serum. A liver biopsy can confirm the diagnosis and also give a sense of the severity of the disorder. Early clinical symptoms are pruritus, fatigue and abdominal pain and discomfort in the right upper quadrant. With more advanced disease the patient can develop jaundice, darkening of the urine, pedal edema and cirrhosis [86].

The only therapy that has been shown to slow the progression of this disease is ursodeoxycholic acid, a bile acid that helps to move bile through the bile ducts. Typically this agent is more successful in patients with early disease and it is considered a disease-modifying drug. It has been shown to improve the biochemical liver tests, delays histological progression and prolongs liver transplant free survival [87]. It is believed to exert its benefit by stimulating hepatobiliary secretion, protecting hepatocytes from cell death and protecting cholangiocytes from the cytotoxic effects of bile acids. The recommended dose of ursodeoxycholic acid is 13–15 mg/kg/day although it is recommended that the dose is slowly titrated to this level because of the potential of exacerbation of pruritus when initiating it at full dose. Other agents that have been tried in this disease, although they have had suboptimal responses, have been methotrexate, cyclosporine, azathioprine, thalidomide and sulindac. Corticosteroids have also been used and have been shown to improve liver biochemistries and histology, and budenoside has been specifically studied in this disease

[86]. Another class of drugs being looked at, the fibrates, have an effect on bile acids before they reach the liver [87].

Fatigue can be seen in 40–80% of patients with PBC and has a major effect on quality of life and it does not appear to correlate with the severity of the disease. Modafinil has been studied and shown to benefit these patients at 400 mg/day [88]. Pruritus an equally debilitating symptom of this disease is seen in up to 80% of patients and while antihistamines are the first line of therapy, other agents such as cholestyramine have to be used sometimes. Osteoporosis has been seen in approximately 35% of these patients and while the treatment of this would typically be an increase in calcium and vitamin D intake in conjunction with an oral bisphosphonate, patients with systemic sclerosis often have esophageal and gastric problems that makes intravenous formulations of bisphosphonates the preferred agents. Fat soluble vitamins have to be supplemented and hyperlipidemia treated, both of which are prevalent in PBC.

When the disease progresses it leads to portal hypertension, esophageal varices, cirrhosis and peritoneal ascites, all of which can be treated the same as in patients with other causes of cirrhosis. Patients who advance to decompensated cirrhosis have to be evaluated for a

liver transplant, which has a 1-year and 5-year survival of 83 and 72%, respectively [89].

**Conclusion**

Systemic sclerosis is a heterogeneous and debilitating disorder for which no universally acceptable therapy exists. It affects the GI system, causing significant morbidity. Early screening for the GI manifestations of systemic sclerosis is important to prevent long-term complications. PPIs have been shown to prevent complications from GERD and potentially could also slow down the progression of ILD that may be affected by chronic micro-aspiration. Intestinal dysmotility has to be evaluated and differentiated from intestinal bacterial overgrowth because it is treated with prokinetic agents, while the later requires antibiotic therapy. Signs of slowly progressing anemia should alert the physician to a potential diagnosis of gastric antral vascular ectasia. Weight loss and signs of malabsorption need to be addressed early and promptly treated, while liver enzyme elevations and increasing pruritus should alert the clinician to a potential autoimmune liver process (TABLE 1). While fecal incontinence is seen in up to 20% of these patients, this often goes undiagnosed and untreated either because of the patient not reporting the symptoms or because the physician has not asked.

**Table 1. Therapeutic management of gastrointestinal manifestations of systemic sclerosis.**

Part of GI tract	Manifestation	Therapeutic options
Esophageal dysfunction	Gastroesophageal reflux	Diet modification
	Barrett’s esophagus	H2 blockers
	Centrilobular interstitial lung disease	Proton pump inhibitors Prokinetic agents GABA(B) agonists (baclofen)
Gastric involvement	Gastroparesis	Prokinetic agents Botox injection into pyloric sphincter
	Gastric antral vascular ectasia	Laser therapy Immunomodulatory therapy
Small intestine	Bacterial overgrowth	Antibiotics Prokinetic agents
	Malabsorption	Antibiotics Enteral and parenteral nutrition Prokinetic agent
	Pseudoobstruction	<i>Nil per os</i> Intravenous hydration Prokinetic agents
Large intestine	Large diverticuli	Diet modification
	Anorectal sphincter dysfunction	Biofeedback Sacral nerve stimulation Surgical repair
Biliary	Primary biliary cirrhosis	Ursodeoxycholic acid



### Future perspective

As compared to other organ systems, the GI system has not been extensively studied in patients with SSc. While hypotheses of the potential pathogenesis of this disease have been around for many years, work to confirm this has not been substantial. The theory of an initial vascular event that leads to neuronal dysfunction, smooth muscle atrophy and muscle fibrosis can form the basis for further research although

the fact that anti-M3R antibodies have been detected in patients with GI symptoms, but not muscle fibrosis, leads us to believe that a potential immunomodulatory treatment could have an effect in SSc-GI disease, as has recently been seen in a small case series of GAVE patients. Trials looking at immunomodulatory agents for the treatment of SSc-GI manifestations will soon be forthcoming and may lead us to a completely different approach of such patients.

### Executive summary

#### Esophageal & gastric involvement

- Acid suppressive therapy continues to be the mainstay of therapy for these manifestations, although better understanding, especially of the neurological component of this disease, will lead to unique new therapies. The potential association of gastroesophageal reflux disease and interstitial lung disease in systemic sclerosis patients presents a unique chance for intervention.

#### Small intestine involvement & malabsorption

- This is a leading cause of diminished quality of life in systemic sclerosis patients, and better therapeutic options beyond antibiotic therapy and nutritional support are needed.

#### Large intestine involvement

- While often a less-reported symptom from the patients of this article, it needs to be more actively addressed and the potential neurological versus structural pathogenesis for this process may lead to better therapies targeting the neurological component of this disease.

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- of interest
- of considerable interest

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## Management of gastrointestinal manifestations in systemic sclerosis (scleroderma)

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### Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 37-year-old female with systemic sclerosis (SSc) reporting heartburn-like symptoms. Based on the review by Dr. Noaiseh and colleagues, which of the following statements about esophageal and gastric involvement in SSc is most likely correct?

- A Esophageal manifestations are the least common gastrointestinal manifestations of SSc
- B Acid suppressive therapy is ineffective for esophageal symptoms
- C Chronic micro-aspiration may affect interstitial lung disease (ILD)
- D Proton pump inhibitors play no role in treatment of ILD

2. Based on the review by Dr. Noaiseh and colleagues, which of the following statements about small intestine involvement and malabsorption in SSc is most likely correct?

- A Small intestine involvement and malabsorption do not significantly affect quality of life in SSc patients
- B Prokinetic agents are of no value in treating intestinal dysmotility
- C Slowly progressive anemia always reflects malabsorption due to small intestine involvement
- D Liver enzyme elevations and increasing pruritus may suggest a potential autoimmune liver process

3 Based on the review by Dr. Noaiseh and colleagues, which of the following statements about large intestine involvement in SSc would most likely be correct?

- A Colonic disease occurs in about three quarters of patients with SSc
- B The anorectum is the most frequently affected area in patients with large intestine involvement
- C Fecal incontinence is a rare complication of SSc
- D Wide-mouthed diverticuli have not been reported