Consensus Best Practice pathway of the UK Scleroderma Study Group: gastrointestinal manifestations of systemic sclerosis

N. Hansi[1], N. Thoua[2], M. Carulli[3], K. Chakravarty[4], S. Lal[5], A. Smyth[6], A. Herrick[7], O. Ogunbiyi[1], J. Shaffer[5], J. McLaughlin[5], C. Denton[8], V.H Ong[8], A.V. Emmanuel[8], C.D. Murray[1]

[1]Royal Free Hospital, London, UK;
[2]Homerton University Hospital, London;
[3]Imperial College, London, UK;
[4]Queens Hospital, Romford, Essex, UK;
[5]Salford Royal NHS Foundation Trust, UK;
[6]Ulster Hospital, Belfast, UK;
[7]University of Manchester, UK;
[8]University College London, London, United Kingdom.

Navjyot Hansi, MBBS, MRCP
Nora Thoua, PhD, MRCP
Maresa Carulli, MSc, FRCP
Kuntal Chakravarty, FRCP
Simon Lal, MD, PhD, FRCP
Anita Smyth, MD, FRCP
Ariane Herrick, MD, FRCP
Olagunju Ogunbiyi, MD, FRCS
Jon Shaffer, MD, FRCP
John McLaughlin, PhD, FRCP
Christopher Denton, PhD, FRCP
Voon H. Ong, PhD, MRCP
Anton Emmanuel, MD, FRCP
Charles Murray, PhD, FRCP

Please address correspondence to:
Dr Charles Murray,
Consultant Gastroenterologist,
Centre for Gastroenterology,
Royal Free Hospital,
Pond Street,
London NW3 2QG, United Kingdom.
E-mail: charlesmurray1@nhs.net

Received on May 22, 2014; accepted in revised form on October 9, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 86): S214-S221.

Key words: systemic sclerosis, practical guidelines, scleroderma

Competing interests: none declared.

ABSTRACT

Systemic sclerosis is an autoimmune connective tissue disorder, which can be progressive with multisystem involvement. Guidance on the management of complications is based on a limited data set and practice amongst clinicians can vary. The UK Scleroderma study group set up several working groups to agree some consensus pathways for the management of specific complications. Approximately nine out of ten patients with systemic sclerosis will have involvement of the gastrointestinal system and in this review article we explore the management of these complications in a symptom-based approach. The algorithms are a useful tool for clinicians, which we hope, will be a point of reference and highlight the need for further research in these areas.

Introduction

Systemic sclerosis (SSc) is an autoimmune mediated connective tissue disorder. The aetiology of the disease process is still undetermined but is characterised by fibrosis, inflammation and proliferative vascular lesions of the skin and internal organs (lungs, heart, kidneys and gastrointestinal tract). Prevalence in the UK is estimated at 8 per 100,000 of the population (1-3). It can affect all ethnic groups but is twice as common in afrocaribbeans as caucasians, more predominant in women at a ratio of 4:1 and the peak age of onset is between 30 to 50 years of age (4, 5). Based on the extent of skin involvement there are two subsets; diffuse cutaneous and limited cutaneous. Those in the latter group will have skin involvement in areas distal to elbows and knees, but the face can be affected in either group. The importance of this classification system is that the associated natural history, organ involvement, antibody profile and prognosis vary (6). Involvement of the gastrointestinal tract (GIT) can be in either group, affecting over 90% of patients (7, 8). It is associated with a high morbidity and poorer outcome depending on the severity of GIT involvement (9, 10).

The management of specific complications of systemic sclerosis is often centered in tertiary referral centres with variation in practice outside these units. The European League Against Rheumatism (EULAR) have published guidance on the management of these complications based on the limited data available (11). In order to achieve some standardisation of therapy, especially outside of tertiary centres, the UK Scleroderma study group set up several working groups to agree some consensus pathways for the management of specific complications. The working group on gastrointestinal complications produced the pathways discussed here and this group consisted of rheumatologists, gastroenterologists, surgeons, nurses and importantly patient representatives. Following discussion, the group decided to explore management in a symptom based, rather than anatomical approach, since it was felt this was more helpful to the practicing clinician managing these patients.

The symptom-based groupings were:

- Gastro-oesophageal symptoms
- Abdominal pain and distension
- Weight loss and nutritional issues
- Diarrhoea
- Incontinence
- Constipation

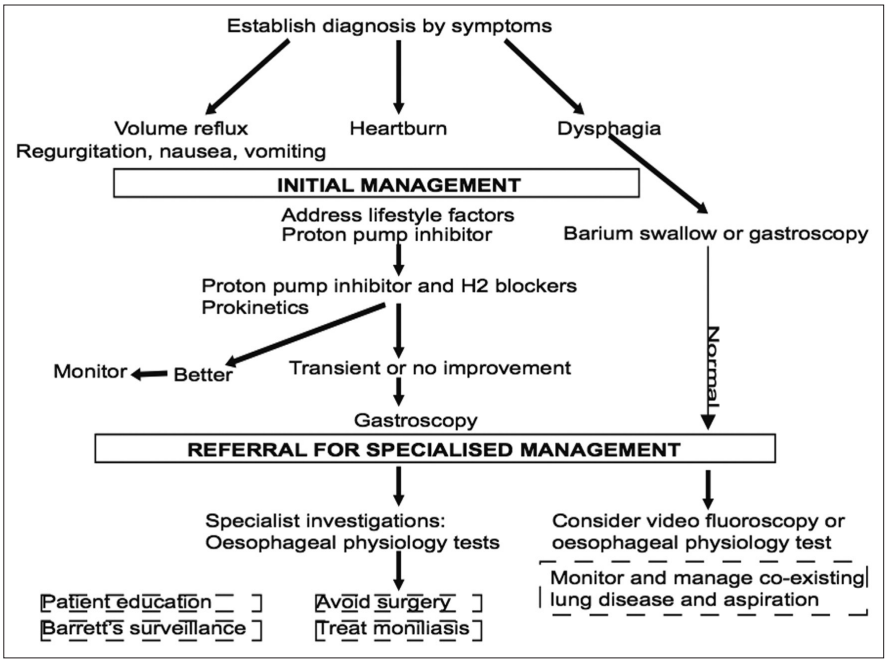

Fig. 1A. Algorithm for management of GORD (Gastro-oesophageal reflux disease.

Gastro-oesophageal symptoms
(Fig. 1A)

The oesophagus is the most commonly affected part of the GI tract and oesophageal manifestations dominate in up to 90% of patients who may describe symptoms of heartburn, regurgitation and dysphagia. The large European League Against Rheumatism Scleroderma Trails and Research (EUSTAR) multicenter collaboration cohort analysis of 7655 patients described more manifestations of upper compared with lower GIT symptoms (12).

Pathophysiology

There is smooth muscle atrophy (preferentially of the inner circular layer of the muscularis propria) and fibrosis affecting the distal two thirds of the oesophagus but sparing of the proximal part. Roberts *et al*. conducted a case control study of 74 scleroderma cases with matched controls and examined the oesophageal tissue to determine possible causes of atrophy. The pathological findings were inconsistent with ischaemia or an inflammatory process and they concluded that the dysfunction could be related to loss of normal neural function not observable by light microscopy or the lesion is due to a primary smooth muscle disease process (13).

In patients with SSc typical findings on manometry are a reduction in amplitude of contractions and peristalsis of the oesophageal body in conjunction with an incompetent lower oesophageal sphincter (LOS). The reduced LOS pressure predisposes to gastro-oesophageal reflux disease. Progression of the disease results in absence of peristalsis and impaired coordination between the distal oesophageal body and LOS (14). Defective excitatory innervation may partially explain the mechanism behind ineffective peristaltic action (15, 16). There is some evidence to suggest *H. pylori* infection correlates with severity of multisystem involvement in SSc patients however data is lacking and it is not clear whether *H. pylori* is merely a bystander or has a more important role in the pathogenesis of SSc and can provide prognostic information as well (17).

Diagnostics

Acid reflux can cause oesophagitis which may lead to further complications if left untreated such as ulceration, Barrett's oesophagus and benign strictures. Interstitial lung disease is a major cause of death in patients with SSc (18) and there is an increasing awareness that GI reflux may be a causative factor in the development of interstitial lung disease in some patients with SSc, as it can be in non-SSC patients (19), underscoring the importance of aggressive and early treatment (20).

The first line investigation for oesophageal symptoms, especially dysphagia, is upper GI endoscopy. It is also useful in investigating iron deficiency anaemia, and evaluating for candidiasis and gastric antral vascular ectasia (GAVE) (21). GAVE has a unique endoscopic appearance, sometimes called 'watermelon stomach', with prominent multiple red vessels in a stripe pattern radiating from the pylorus to the antrum. The aetiology remains unknown but is commonly reported to be associated with autoimmune disorders, systemic sclerosis one of the most frequently linked. Marie *et al*. published a case series of 264 patients in whom 5.7% (15 patients) had GAVE (22). Treatment options range from conservative PPI and iron therapy as well as endoscopic and surgical approaches.

If Barrett's oesophagus is present patients may require regular surveillance as per national guidelines. A prospective study of 50 patients with Barrett's in SSc confirmed a slightly higher incidence of oesophageal cancer (0.7% per year) (23, 24) but previous studies have suggested no increased risk of adenocarcinoma with chronic reflux in SSc compared with other patient groups. Wang *et al*. suggested a baseline endoscopy in all newly diagnosed SSc patients and a further study with a larger cohort of patients (25). Barium swallow used to be the investigation of choice but this has largely been replaced by upper GI endoscopy (OGD). If OGD or barium swallow are normal but symptoms persist then referral for more specialised investigations such as oesophageal physiology studies should be considered.

Therapeutics

Lifestyle modifications such as not eating a certain number of hours before bedtime, head of bed elevation, and avoidance of exacerbating food groups (*e.g*. spicy food) are often suggested first but patients often need intensive treatment with proton pump inhibitors (PPI) to control symptoms. We suggest titrating the dose to patient symptoms. PPI has reduced the incidence of pep-

tic strictures significantly which used to be seen in up to a third of patients with SSc (26) and the efficacy of PPI in GORD in the general population is well documented in meta-analyses of randomised controlled trials despite there being a lack of randomised control trials in the efficacy of PPI in SSc. Using prokinetics as adjuncts has not been found to be beneficial except in patients who have reflux due to delayed gastric emptying (27). Use of ranitidine at night-time to reduce nocturnal acid breakthrough has not been shown to have a consistent effect on patient symptoms (28).

In SSc surgical procedures such as fundoplication are avoided as they provide little benefit and can lead to complications such as severe dysphagia (29). A recent retrospective review of 23 SSc patients undergoing surgery for reflux disease compared fundoplication, roux-en-y gastric bypass and oesophagectomy. The patients selected for antireflux surgery were those who had failed medical therapy with persistence of reflux symptoms or evidence of severe oesophagitis or stricturing disease despite optimal therapy. The group who underwent oesophagectomy were associated with significant morbidity but those who underwent roux-en-y gastric bypass had statistically significant reduction in dysphagia and improved control of reflux symptoms compared with those who had fundoplication (30).

Abdominal pain and distension

(Fig. 1B)

Up to 50% of patients will report gastric dysfunction symptoms of early satiety, nausea, bloating, and abdominal discomfort (31, 32).

Pathophysiology

The pathophysiology of gastric involvement is not clear but studies suggest possible lymphocyte activation playing an important role (33). Smooth muscle atrophy and collagen deposition with severe ultrastructural alterations of smooth muscle cells and nerve fibres are the pathological hallmarks found in SSc (34, 35). Gut dysfunction is thought to relate to a neuropathic process in SSc patients, with similar abnormalities observed in patients with diabetic neuropathy (36). Autonomic dysfunction in the stomach causes impaired gastric accommodation and compliance. In a study of SSc patients, those with higher scores of autonomic dysfunction showed greater impairment of gastric compliance compared with patients with normal autonomic scores (37). This abnormality can delay gastric emptying and induce more dyspeptic symptoms and bloating. On ultrasonography no significant difference in gastric wall motility has been observed, but gastric empting was delayed in the fundus and antrum (38). Small intestinal motility is abnormal in SSc, with a neuropathic pattern observed early in the disease (39). The small bowel absorptive surface in SSc is normal unless there is co-existing coeliac disease and previous reports have indicated increased or normal intestinal permeability (40).

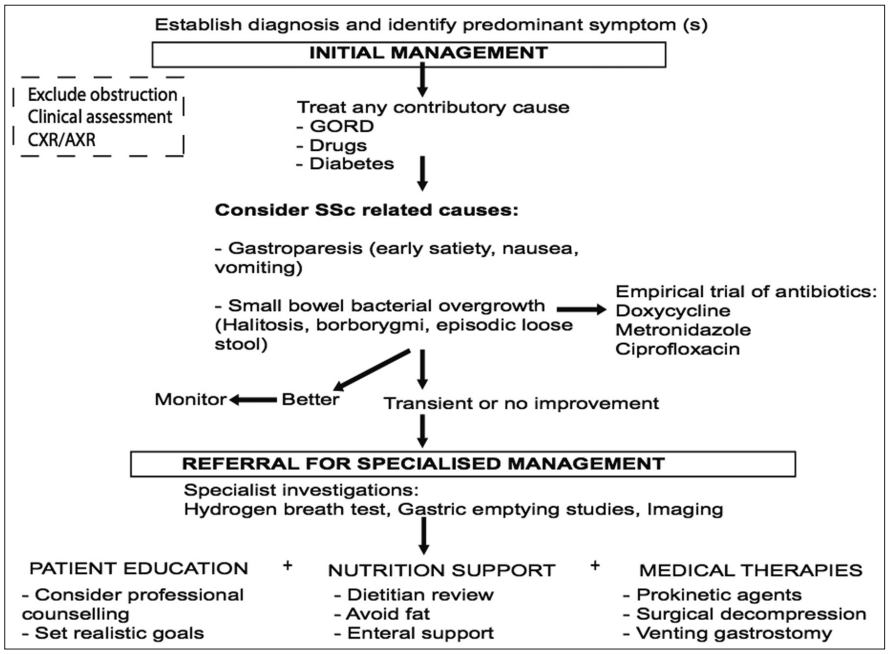

Fig. 1B. Algorithm for management of abdominal pain and distension.

Diagnostics

Imaging of the small bowel can determine the presence and severity of involvement, giving the radiological appearance of thickened valvulae conniventes (41). Hypomotility, poor intestinal clearance and also reduced gastric acid secondary to acid suppressant therapy often lead to small intestinal bacterial overgrowth (SIBO) and malabsorption. Symptoms are more often reported in diffuse cutaneous SSc rather than limited cutaneous SSc (42).

Assessment of delayed emptying would include a gastroscopy initially to rule out gastric outlet obstruction and the patient may warrant further investigation such as gastric emptying studies and ultrasonography.

SIBO can be diagnosed with hydrogen breath testing or from jejunal aspirates. A trial of empirical antibiotics for bacterial overgrowth may be started as per local guidelines such as ciprofloxacin or metronidazole, but cyclical courses may be needed. Studies of Rifaximin use in the general population have shown significant improvement in its eradication of SIBO (43) and can be administered at high doses of 800mg twice daily (44).

Therapeutics

Clinical management of gastric motility disorders can be difficult because of a poor correlation between symptoms and gastric motility studies. Dietary modification with use of a prokinetic as an adjunct is often the mainstay of treatment. Probiotics may be useful in some patients (45). Use of metoclopramide has been found to improve gastric motility and motor activity (46, 47)but the studies involved small numbers

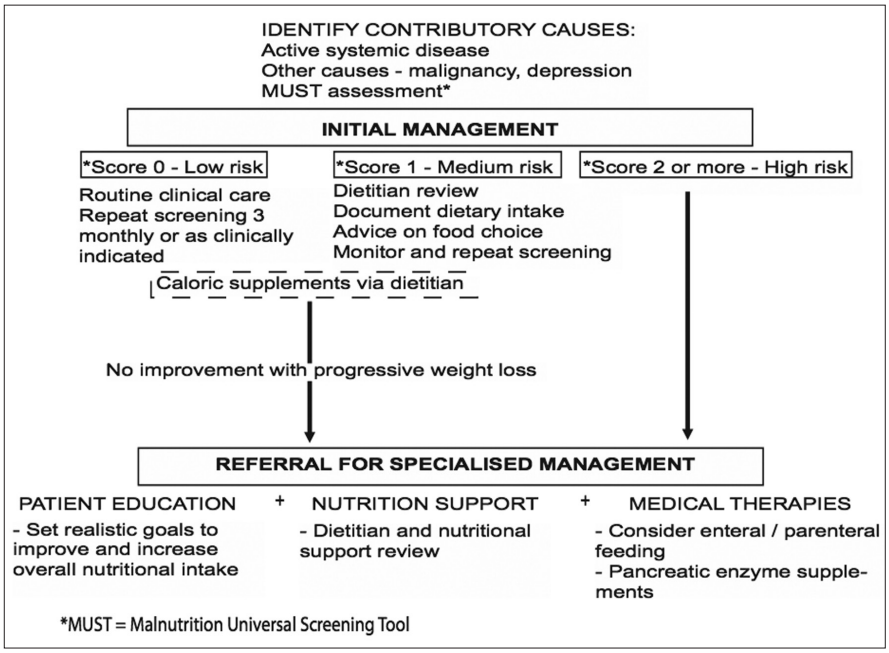

Fig. 2A. Algorithm for management of weight loss and nutritional problems.

and the drug has extrapyramidal side effects. There is no published data for domperidone in SSc. There is limited evidence from the 1990s advocating erythromycin (48, 49) and cisapride was withdrawn from the market due to its association with cardiotoxicity and prolonged QT syndrome. Mosapride, has been shown to accelerate gastric emptying in a study of 60 patients who were randomized to receiving mosapride or nothing, however there is no data for its use in SSc (50). Somatostatin analogues such as octreotide have also been used to induce contractile activity throughout the bowel (51). Octreotide with erythromycin has been found useful in patients with abdominal discomfort associated with pseudo-obstruction (52). Octreotide does have its own disadvantages with increased risk of cholelithiasis, with inhibitory effects on gastric emptying, pancreatic secretions and gallbladder contractions and we would not advocate its use routinely.

Weight loss and nutritional problems (Fig. 2A)

Up to 18% of patients with SSc are reported to be at high risk of malnutrition (53), Malnutrition is multifactorial and common in SSc outpatients, but prospective studies are needed to determine whether there is a significant association with disease activity (54). Due to perioral sclerosis, oesophageal dysmotility and abdominal discomfort SSc patients often eat less bulky, difficult to chew foods. Gut dysmotility, stasis and the associated SIBO can result in persistent and debilitating symptoms of nausea, vomiting and early satiety (55). Contractures can make preparing and eating meals arduous. Poor appetite can also be a consequence of depression and low mood. Other contributory factors that should be excluded include cholestasis resulting in vitamin deficiency and fat malabsorption. There is a slightly increased prevalence of Primary Biliary Cirrhosis (PBC) in SSc; one series of 817 patients reporting a prevalence of 2% (56). In addition, untreated pancreatic insufficiency can cause malabsorption and weight loss but the pathophysiology of exocrine pancreatic insufficiency associated with SSc is poorly understood (57, 58).

Diagnostics

Recognition of malnutrition in patients with SSc is extremely important, as it is thought that increasing weight loss can help differentiate between mild (5.0–9.9 kg) to end-stage (20+ kg) disease (59). BMI and serum albumin, alone are not good indicators and gastrointestinal screening instruments are a useful tool for guiding further diagnostic investigations and follow up.

The malnutrition universal screening tool (MUST) is a five-step screening tool that identifies risk based on baseline BMI, unplanned weight loss in 3-6 months and if person is acutely ill with no oral intake for more than 5 days. The final score identifies the level of risk for the patient. A single-centre prospective cohort involving 160 outpatients found MUST significantly predicts mortality (60). This screening instrument is advocated by BAPEN (British Association of Enteral and Parenteral Nutrition) and NICE (National Institute of Health and Clinical Excellence) but it is limited in its use in chronic and progressive disorders because as a scoring tool it is weighted towards rapid weight loss and acute disease effect. There are other tools such as the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0), which is a validated, quality of life instrument that also assesses GIT severity in SSc. It is a 34-item instrument that has seven subscales: reflux, distention/bloating, diarrhoea, faecal soilage, constipation, emotional well being, and social function and a total GI score. It can be used in the outpatient clinic setting but does not capture physical examination findings of malnutrition or weight change. Bae *et al*. assessed GIT 2.0 in 55 patients compared with objective (barium swallow with small bowel follow through, gastric emptying study, lactulose breath test, endoscopy, esophageal manometry, HRCT of the chest) and laboratory tests, concluding that the GIT 2.0 instrument complements objective tests for assessment of the upper GI tract (61).

The subjective global assessment (SGA) assesses nutritional status based on history and physical examination. Murtaugh *et al*. evaluated the nutritional assessment of MUST and SGA with GIT 2.0 in 24 patients and found the GIT 2.0 gastrointestinal symptom questionnaire a complementary tool in assessment of SSc patients (62).

Therapeutics

Management of weight loss and malnutrition is a multidisciplinary team ap-

proach (63). The role of dietician, nutrition specialists and ward nursing staff is crucial. The timing and route of enteral or parenteral support is contentious but efforts should be made to institute nutritional support early, with the aid of nutritional status screening instruments included in the clinical work up of SSc patients, rather than waiting for intestinal failure when the reported outcomes are poor. Patients with severe or refractory symptoms may need jejunostomies or a gastrostomy tube for venting. Enteral support may be necessary but its success is limited, so parenteral nutrition may be initiated (64). Intestinal failure is a marker of poor long-term outcome, though adequate nutritional support may improve this (64).

Diarrhoea (Fig. 2B)
Diarrhoea can affect up to 50% of patients (65).

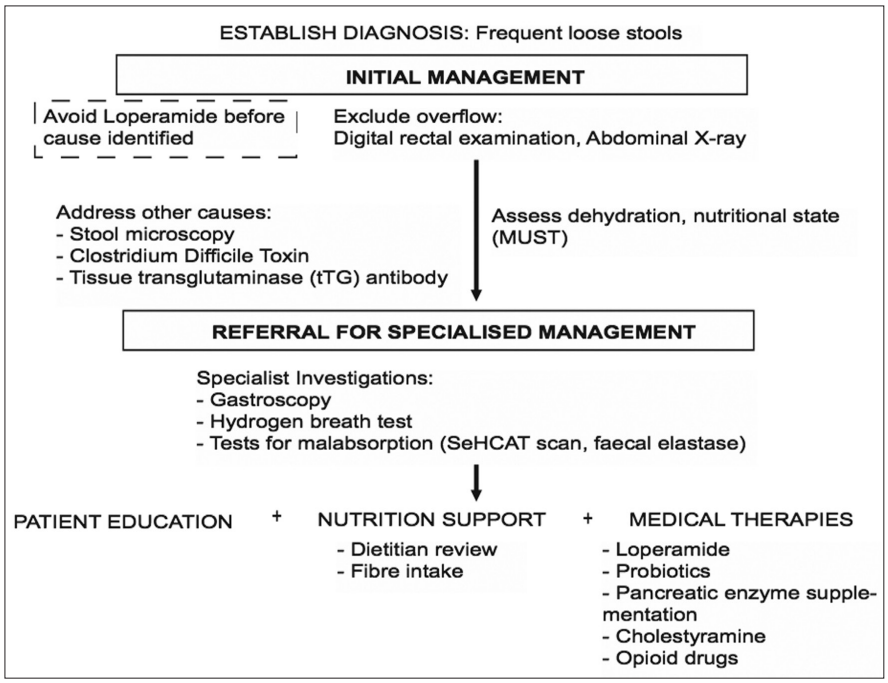

Fig. 2B. Algorithm for management of diarrhoea.

Diagnostics
It is important that patients are fully assessed since the causes of loose stool in SSc are multifactorial. Before instigating other therapies faecal impaction should be ruled out since this can lead to overflow. Screening tests include stool microscopy, testing for clostridium difficile, and initial tests to check for malabsorption such as hydrogen breath testing for SIBO, faecal elastase testing to exclude pancreatic exocrine insufficiency, coeliac serological testing (anti-tissue transglutaminase (tTG) antibodies and immunoglobulins) and SeHCAT scan for bile acid malabsorption.

Therapeutics
Once contributory causes for malabsorption have been investigated symptomatic approaches such as dietary measures to increase stool consistency, and use of loperamide to inhibit peristalsis and secretion can be trialled. However, caution needs to be used to avoid pseudo obstruction. Cholestyramine or other bile salt acid sequestrants may be helpful.

Incontinence (Fig. 3A)
After the oesophagus, the colon and anorectum are the second most common areas of the GI tract to be affected (32).

Pathophysiology
Faeces and air arrive at the rectum and maintenance of continence is an elaborate interaction dependent on voluntary and involuntary coordination between anal and colorectal activity. When the rectum is distended, the internal anal sphincter (IAS) relaxes reflexively and the external anal sphincter (EAS) will contract voluntarily to maintain continence. The EAS will relax during defecation. Suggested pathophysiological mechanisms of neuronal dysfunction (66, 67), smooth muscle atrophy and fibrosis affecting the IAS (as seen on anal ultrasound and manometry studies) culminate in anorectal dysfunction reported in as many as 50 to 70% of SSc patients. Faecal urgency can ensue due to reduced rectal compliance and capacity from collagen deposition.

Diagnostics
Management involves patient education, with advice on diet and fluid intake modification, review of medications that may be resulting in faecal incontinence, and prescribing anti diarrhoeal drugs. If the patient remains symptomatic they may have to be referred for specialist investigations such as anorectal manometry, endoanal ultrasound or MR pelvis.

Therapeutics
Faecal incontinence has a significant negative impact on the quality of life of patients with SSc (68). Practical specialist management such as biofeedback, bowel retraining and pelvic floor muscle training can be offered although evidence base is limited. It is important not to forget simple practical tips regarding continence products and address the emotional and psychological aspects. Surgical approaches can be considered such as sacral nerve stimulation (69) and sphincter augmentation with a bioprosthetic device. The former has shown a significant benefit in the medium term for patients but more long-term data in a larger study set are required. For some a defunctioning stoma may provide relief. Surgical repair of the anal sphincter has been done but long term outcomes suggest worsening of continence following repair (70) and this approach is not advocated.

Constipation (Fig. 3B)
It has been reported that colonic involvement occurs in 20–50% of patients (32).

Pathophysiology
In the normal gut, post-prandially the

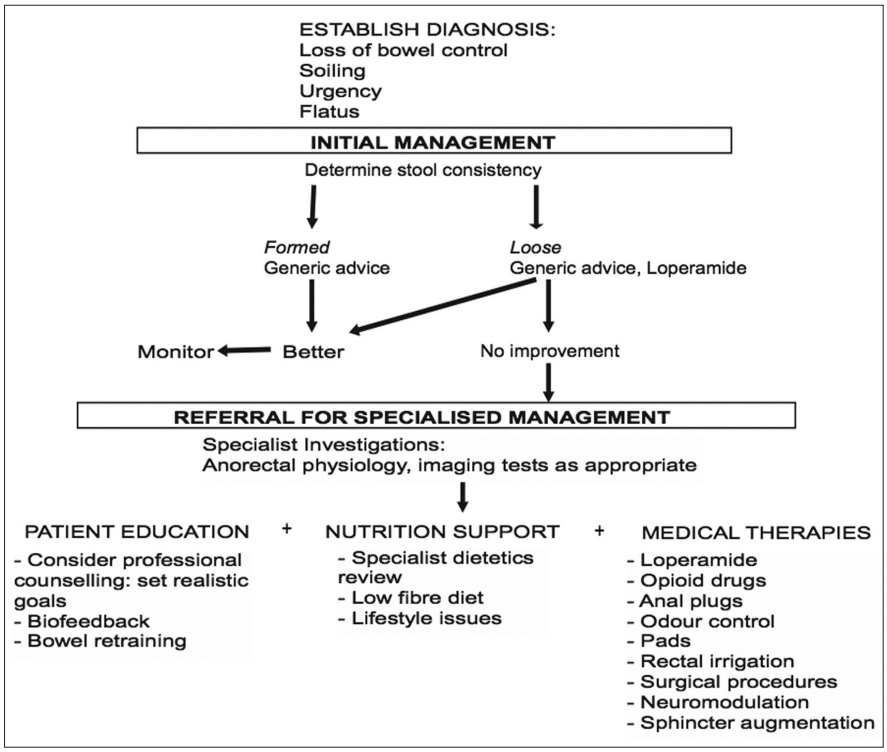

Fig. 3A. Algorithm for management of incontinence.

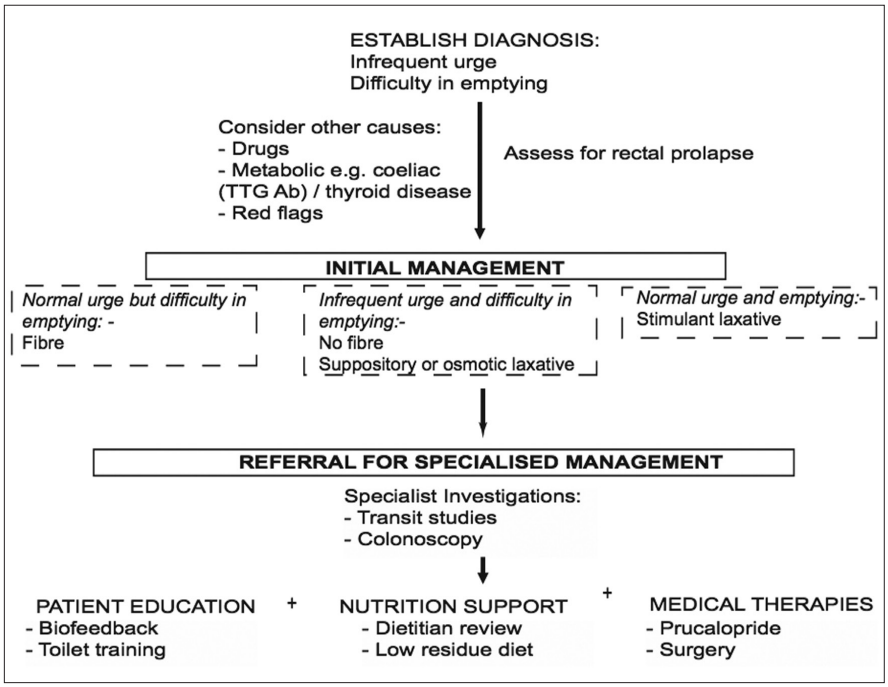

Fig. 3B. Algorithm for management of constipation.

colonic motor activity rises sharply for 30-60 minutes; this constitutes the gastrocolic response and is mediated by a cholinergic pathway (71). This is often absent in SSc, colonic motility is reduced and there is prolonged colonic transit (72, 73).

Diagnostics

Any constipating medications should be stopped and structural causes for constipation excluded (*e.g.* rectal prolapse, rectocele or anal fissure). Contributory factors such as metabolic and endocrine causes should be assessed. It may be necessary for colonic imaging or direct visualisation with colonoscopy if history highlights red flags for malignancy.

Therapeutics

Unfortunately, often laxatives offer little benefit and have a variable effect as stimulant laxatives particularly rely on contact with the bowel mucosa, which is unpredictable, and osmotic laxatives can aggravate bloating and discomfort. Prucalopride, a 5HT4 receptor agonist has been shown to accelerate colonic transit, the results have been promising but only published in case reports (74). Opioid antagonists such as methylnaltrexone do not appear to be very beneficial in patients with SSc due to the nature of their bowel dysmotility. Biofeedback training is a useful therapy in idiopathic constipation but has not been studied in SSc (75). There is no published data for the effect of sacral nerve stimulation (SNS) in SSc on constipation although it has been demonstrated to be useful in idiopathic constipation (76). The drawbacks of SNS are that it is an expensive, invasive procedure associated with risks of infection, lead migration and pain. There is not much data for surgery for intractable constipation in SSc, but the multiple organ involvement of patients with SSc often makes surgery a high-risk intervention. Intestinal pseudo-obstruction is a rare gastrointestinal manifestation of SSc with limited data existing as to clinical course and mortality. Often spontaneous resolution occurs whilst managing conservatively with intravenous hydration and bowel rest, but some patients may require lengthier periods of hospitalization needing surgical intervention, and prolonged total parenteral nutrition (TPN) (77).

Within the algorithms we touch on the subject of professional patient counselling. Depressive symptoms have been reported to be involved with GIT involvement in SSc patients (78). The treating gastroenterologist should take an overall holistic approach to the patient and explore quality of life, functional status and depressive symptoms whilst treatment interventions for SSc are limited.

Conclusion

Although the GI system is the second most frequently involved organ system (with skin being first) amongst this group of patients and a major determinant of quality of life, there is little published evidence available to guide clinicians on the best management for these patients. The guidance and algorithms described in this article are a pragmatic approach reflecting opinions and experience based with limited data.

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