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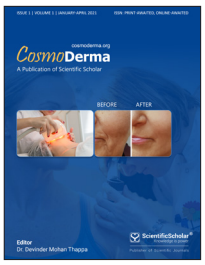

Resident Forum

Simplified guidelines for the management of systemic sclerosis

Pariyaram Veetil Midhuna[1], Devinder Mohan Thappa[1]

[1]Department of Dermatology, Venerology and Leprology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India.

***Corresponding author:**
Pariyaram Veetil Midhuna, Department of Dermatology, Venerology and Leprology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

drmidhuna20@gmail.com

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INTRODUCTION

Systemic sclerosis (SSc) is a multisystem disorder, which can affect skin, blood vessels, lungs, heart, kidney, gastrointestinal (GI) tract, and musculoskeletal systems. It is characterized by autoimmunologic processes, vascular endothelial injury, inflammation, and extensive activation of fibroblasts.

The European League against Rheumatism and European Scleroderma Trials and Research group have updated their recommendations on management of SSc. The use of phosphodiesterase type-5 (PDE-5) inhibitors for the treatment of SSc-related Raynaud phenomenon (RP) and digital ulcers (DU), and riociguat for the treatment of pulmonary arterial hypertension (PAH) have been stressed upon.

Due to wide spectrum of disease manifestations and multiple organ involvement in SSc, management is tailored to individual patient. Hence, heterogenicity and clinical complexity of SSc make the treatment challenging and will need a multidisciplinary approach.[1] Therefore, a clear guidance on organ-based symptomatic therapy and choice of drugs that are supported by best clinical evidence is of utmost importance in appropriate management of outcomes of SSc.

MANAGEMENT

Initial management of SSc should begin with counseling and education of the patient about his/her disease condition, expected distribution, severity of organ involvement, and reinforcement of various outcomes as the disease progression happens.

Raynaud's phenomenon in SSc

RP is an exaggerated vascular response to cold temperature or emotional stress manifested as sharply demarcated color changes of skin of digits which gets complicated by ischemia and ulceration. The therapy for RP should be aimed at improving quality of life and to prevent tissue loss such as ulceration and gangrene. Early detection of RP cases and identification of cases who are at risk of progression to connective tissue diseases can be done by Raynaud's provocation test, nailfold capillaroscopy, or antinuclear antibody levels. Simple but important recommendations for decreasing the frequency of Raynaud attacks include educating the patient on measures like use of warm clothing for digits as well as for whole body, avoiding precipitating

factors such as cold exposure, smoking, caffeine, vibratory tools, emotional stress, and vasoconstrictive drugs such as nasal decongestants, amphetamines, ephedra, ergotamine, and sumatriptan. Raynaud attacks can be terminated by few general measures like placing hands under warm water or in warm place (like axilla) or rotating arms in whirling or windmill pattern.

Among pharmacological measures, calcium channel blockers (CCBs) remain the first-line therapy in view of good safety profile and long-term experience [Figure 1].[2] Dihydropyridine CCBs commonly used are nifedipine (30–120 mg/day) and amlodipine (5–20 mg/day). The drug is started at a lower dose and gradually titrated according to response and tolerance to maximum of 120 mg/day. Systemic blood pressure monitoring should be serially done during titration of the CCB. If these drugs are ineffective at highest tolerated dose, then other substitutes such as nicardipine, felodipine, nimodipine, and isradipine are used. Major side effects include hypotension, headache, dizziness, flushing, tachycardia, and peripheral edema.

Those patients who do not satisfactorily respond to CCBs or in patients with severe RP are started on PDE-5 inhibitors such as sildenafil (25–50 mg twice or thrice daily) or tadalafil (20 mg every other day).[2] Adverse effects that may occur include hypotension, peripheral edema, palpitations, tachycardia, hearing loss, and visual disturbances.

For severe SSc-RP, intravenous prostanoids like iloprost administered for a course of 3–5 consecutive days, at a dose of 0.5–2 ng/kg/min (titrated to maximum dose tolerated by the patient) reduce the frequency and severity of RP attacks. Selective serotonin reuptake inhibitors like fluoxetine (20 mg daily) used as an alternative in patients with SSc who cannot tolerate or do not respond to vasodilators.

Approximately 11% of patients with SSc will develop critical limb ischemia during the course of their disease (within the first 5 years), and 18% of all SSc patients have DU and signal a severe disease, including internal organ involvement. In SSc, DUs usually occur on fingertips and dorsal aspect of hand. DUs should be addressed by following the hierarchical principles which include[3]

1. Exclusion of all other underlying diseases leading to DU-like ulcerations independent of SSc
2. Multidisciplinary team should be involved in care of DUs and patient education regarding use of skin protection (gloves and creams), skin hydration, adequate nutrition, rehabilitation, and importance of cessation of smoking needs to be emphasized
3. Analgesic therapy to ameliorate nocturnal pain may be used and optimized
4. Rehabilitation in the form of physiotherapy and occupational therapy to increase blood flow should be adapted as a preventive strategy
5. Local wound management to be combined with systemic treatment form vasodilation. As vasodilatory therapies, PDE5 inhibitors may be used for wound healing. Endothelin receptor antagonists (ERAs) like bosentan are recommended in patients with multiple DUs despite treatment with CCBs, PDE-5 inhibitors, and iloprost to prevent development of new DU.

SSc-related PAH

Lung involvement in SSc is an important cause of mortality and morbidity and can present as three major forms:

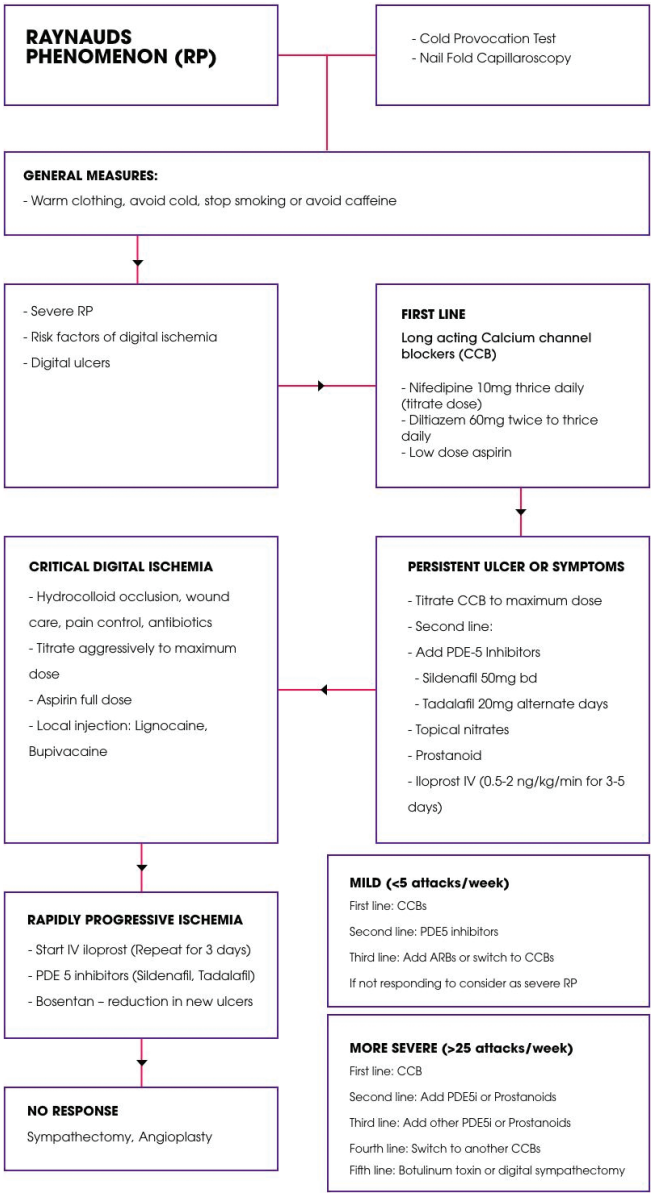

Figure 1: Flow diagram for Raynaud's phenomenon.

Interstitial pneumonitis, bronchiolitis, and pulmonary vascular disease.[4] Common symptoms and signs of PAH are exertional dyspnea, fatigue, loud pulmonic second heart sound (P2), exertional chest pain, and syncope as it progresses to the right heart failure. Individuals with SSc and cardiopulmonary symptoms need further evaluation with pulmonary function tests, echocardiography, 6 min walk test, and high-resolution CT (HRCT). Impaired diffusion capacity of the lung for carbon monoxide (DLCO ≤75%) is found to be an early marker of both lung fibrosis and PAH. Interstitial lung involvement is determined by the presence of subpleural localized opacities and subpleural cysts with "honeycomb" formations in HRCT or thoracic radiography. PAH can be detected by non-invasive procedure like transthoracic Doppler echocardiography, but invasive diagnostic procedure like right heart catheterization is indeed gold standard. PAH is defined as a mean pulmonary artery pressure of ≥25 mmHg at rest together with pulmonary capillary wedge pressure of ≤15 mmHg as determined by right heart catheterization.

Early detection and prompt initiation of therapy for PAH is essential; those with early diagnosis have more pronounced benefit with therapy [Figure 2]. ERA (ambrisentan, bosentan, and macitentan), selective PDE-5 inhibitors (sildenafil and tadalafil), and riociguat have been approved for treatment of SSc-related PAH.[5] Based on overall risk-to-benefit considerations, experts recommend intravenous epoprostenol as treatment of choice in severe, therapy-resistant SSc-PAH.

Skin and lung disease

Skin involvement is usually a universal feature of SSc characterized by variable extent and severity of skin thickening. Edematous change and erythema may precede skin induration and sclerosis commonly involving fingers, hands, and face. Assessment of skin involvement includes semi-quantitative estimation of skin thickness, hardness, and fixation to underlying structures (tethering). Commonly used outcome measure is modified Rodnan skin score (MRSS) which rates the severity from 0 (normal) to 3 (most severe) in 17 distinct areas of body. MRSS can also be used to titrate the treatment for cutaneous involvement in SSc. Experts agreed use of methotrexate (MTX) and mycophenolate mofetil (MMF) as first line and second line, respectively, in MRSS of 24. For a MRSS of 32, first-through fourth-line treatments suggested were MMF, MTX, IV cyclophosphamide, and hematopoietic stem cell transplantation (HSCT), respectively.[6]

Treatment options for skin involvement unfortunately demonstrate only a modest benefit. MTX (target dose of 15–25 mg weekly) may be considered for the treatment of skin manifestations if early diffuse SSc, ideally initiated within 3 years of disease onset, and has been found to improve skin score [Figure 3]. Cyclophosphamide should be considered for the treatment of SSc-related interstitial lung disease (ILD), in particular for patients with SSc with progressive ILD. Dose and duration of treatment to be tailored individually depending on the clinical condition and response. HSCT has shown improvement of skin involvement and stabilization of lung function in patients with SSc and hence recommended in rapidly progressive SSc at risk of organ failure.

Calcinosis cutis can manifest in 20–40% of patients with SSc which is reported by the patients as lumps over pressure points such as fingers, extensor aspect of elbows, forearm, and knee

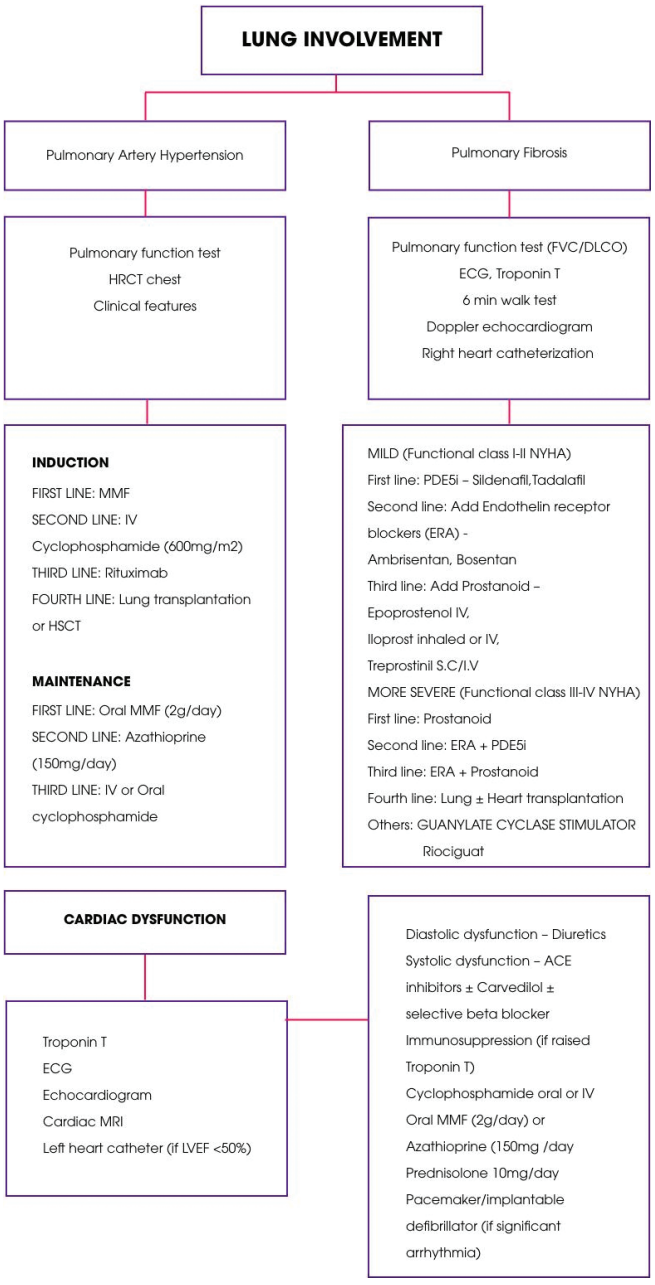

Figure 2: Flow diagram for lung/cardiac involvement.

which turn painful as it enlarges and ulcerates with extrusion of toothpaste like material. This can be easily visualized on plain radiography or ultrasound and appropriate treatment can be initiated which includes general measures such as antibiotics and analgesics and in case of failure to respond to consider surgical debridement for debulking. Treatment with warfarin, colchicine, diltiazem, minocycline, and bisphosphonates has attracted interest in past. Intralesional corticosteroid injection, IV immunoglobulins, topical and intravenous sodium thiosulfate, and carbon dioxide laser have also been tried.

Pruritus is also seen in up to 60% of patients with SSc and is considered to correlate with disease severity. This could be

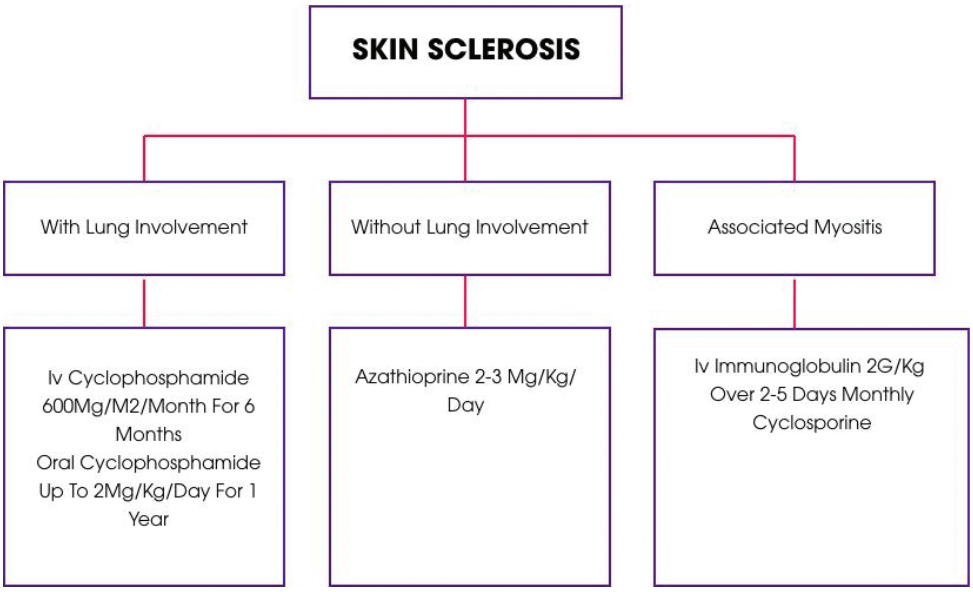

Figure 3: Flow diagram for skin involvement.

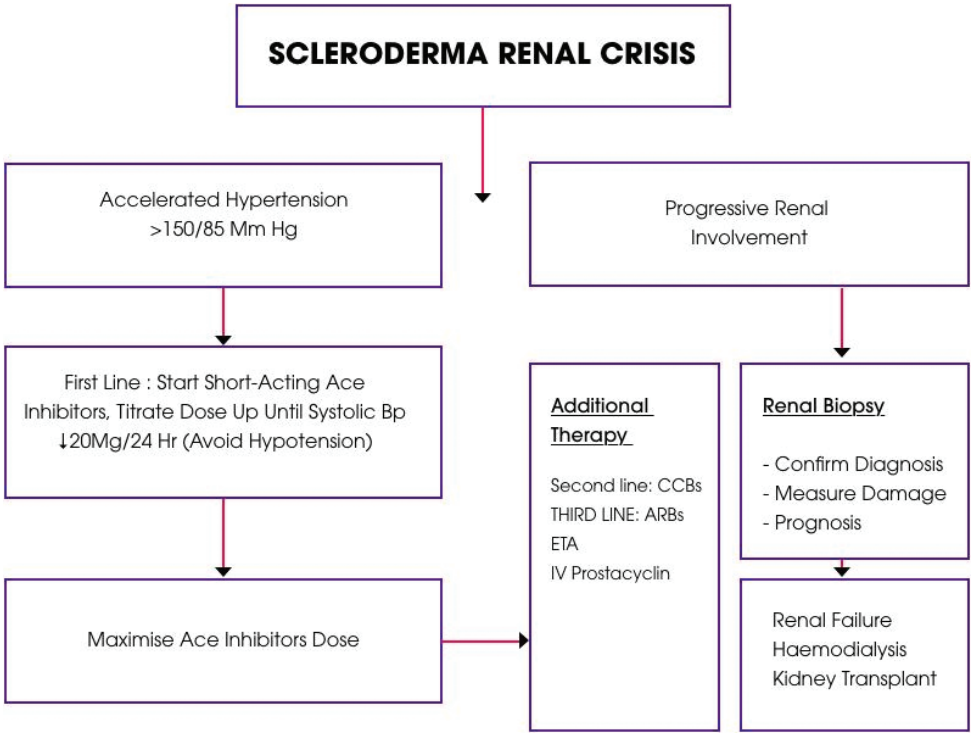

Figure 4: Flow diagram for scleroderma renal crisis.

directly associated with skin diseases or can be secondary to internal organ involvement. The exact pathomechanism of itch in SSc still needs to be elucidated. The probable major factors that contribute to skin xerosis and itch include inflammatory process in dermis, the subsequent loss of skin appendages by the fibrotic process in combination with the loss of the ability to synthesize appropriate amounts of "endogenous lipids and emollients." Furthermore, entrapping of sensory nerve fibers can also lead to pruritus.

Adequate symptomatic treatment of itch is an important component of multimodal therapy in SSc patients as it can significantly affect quality of life, disturb sleep, and contribute to mood disorders and depression. As a first step, patients should be advised about frequent application of moisturizers, keeping room temperature stable and avoidance of frequent showers.[7] Topical therapy will be the mainstay of initial treatment and hence emollients containing urea (3–10%), lactic acid (1–5%), and a higher percentage of glycerol (up to 20%) should be recommended. Other modalities of treatment include antihistamines, gabapentin, pregabalin, and UV-based therapy.

Scleroderma renal crisis (SRC)

SRC is found to be a life-threatening complication of scleroderma and presents with the abrupt onset of severe hypertension accompanied by rapidly progressive renal failure, hypertensive encephalopathy, congestive heart failure, and/or microangiopathic hemolytic anemia. Hence requires close monitoring for progression to SRC during first 4–5 years of SSc. Greatest risk is encountered among patients with early stage diffuse cutaneous disease, rapidly progressive

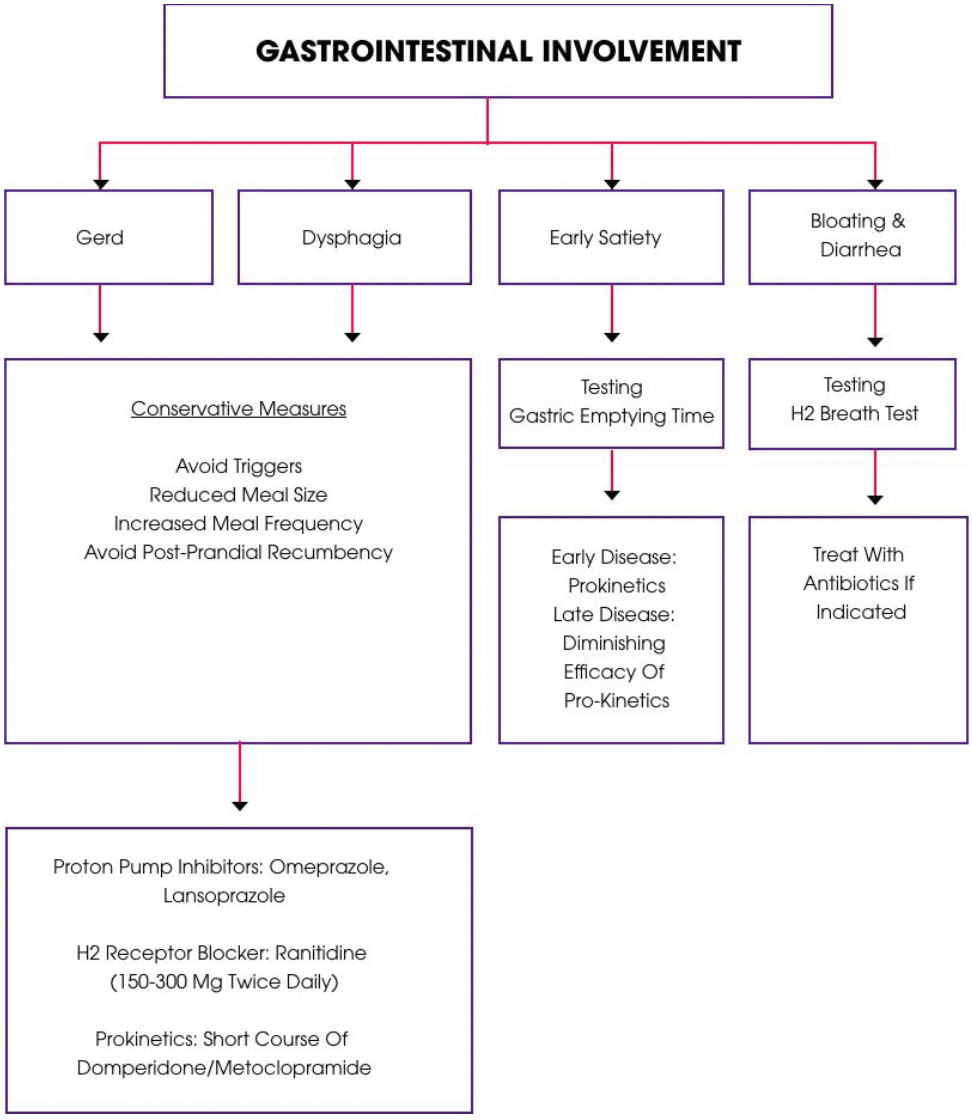

Figure 5: Flow diagram for gastrointestinal involvement.

cutaneous involvement, or autoantibodies to RNA polymerase III. Another important risk factor for SRC as suggested by retrospective studies is use of antecedent high-dose corticosteroids. As a result of this close monitoring of blood pressure and renal function for early detection of SRC becomes essential in SSc patients on glucocorticoids. Renal crisis should be of concern if SSc patient has an elevated blood pressure of more than 150/85 mm Hg or if there is an increase of at least 20 mmHg from baseline systolic blood pressure on two occasions in a 24 h period. A decline in renal function (increase of 50% from baseline creatinine or absolute increase of 0.3 mg/dl, even if within normal range) and/or presence of >2+ proteinuria and/or hematuria should prompt appropriate management.[8]

The optimal antihypertensive recommended by expert in SRC is an ACE inhibitor like captopril preferred over enalapril or ramipril [Figure 4]. ACE inhibitors have shown to have greater antihypertensive efficacy, better preservation of renal function, and improved survival in patients with SRC. However, preventive use of ACE inhibitors to reduce the risk of development or improve outcome of SCR is found to be ineffective.[2]

GI disease

Involvement of GI tract is common in SSc and may involve any or all parts from mouth to anus. The patient can present with gastroesophageal reflux disease (GERD), dysphagia due to altered esophageal contractility, delayed gastric emptying, delayed motility resulting in postprandial bloating and small intestinal bacterial overgrowth, chronic constipation, and vascular complications like gastric antral vascular ectasia.

Treatment is mainly instituted for amelioration of symptoms and is largely supportive. Conservative measurements such as sitting upright during meals, using liquids between swallowing solid foods, and avoiding recumbency for at least 4 h following a meal to facilitate bolus transmit are advised. Proton-pump inhibitors (PPIs) are most effective for the treatment of GERD and peptic ulcer disease in SSc and should be used in symptomatic patients [Figure 5].

Those who fail to respond to twice-daily PPI therapy are supplemented with H2 blockers at bedtime. Prokinetics drugs such as metoclopramide, cisapride, and domperidone are administered to relieve symptoms of esophageal dysmotility. The use of intermittent or rotating antibiotics to treat symptomatic small intestinal bacterial overgrowth is also recommended.

CONCLUSION

SSc being a highly heterogeneous and complex autoimmune disease needs involvement of multiple experts from different specialties in early diagnosis and intervention before advanced fibrosis sets in and cannot be reversed. An updated recommendation and concise management guidelines can help improve care of patients with SSc in an evidence-based way.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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