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Management of Systemic Sclerosis: The First Five Years

David Roofeh[1], **Dinesh Khanna**[1]

[1]Department of Internal Medicine, Division of Rheumatology, Scleroderma Program, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Purpose of review: This review provides a risk stratified and evidence-based management for subsets of systemic sclerosis (SSc) patients in the first five years from disease onset.

Recent findings: Cardio-pulmonary disease remains the primary cause of mortality in SSc patients. Morbidity and mortality in SSc-associated pulmonary arterial hypertension has improved with combination treatment, in either an upfront or sequential treatment pattern. Traditional therapies for interstitial lung disease (SSc-ILD) have targeted those with clinically significant and progressive ILD with immunosuppression. New data suggest a possible paradigm shift, introducing immunosuppressive therapy to patients before they develop clinically significant or progressive ILD. 2019 saw the approval of the first FDA-approved therapy for SSc-associated interstitial lung disease, using an anti-fibrotic agent previously approved for idiopathic pulmonary fibrosis. To date only autologous hematopoietic stem cell transplant has demonstrated a mortality benefit for SSc-ILD, albeit in a narrow spectrum of SSc-ILD patients.

Summary: SSc is a highly heterogeneous autoimmune disease typified by varying clinical trajectories. Its management may be stratified within the first five years by sub-classifying patients based on factors that have important prognostic significance: skin distribution and auto-antibody status.

Keywords

Systemic Sclerosis; Management; Treatment

I. INTRODUCTION

Systemic Sclerosis

Systemic sclerosis (SSc) is a chronic, heterogeneous autoimmune disease characterized by a triad of immune dysregulation, vasculopathy, and overproduction of collagen leading to skin and internal organ fibrosis[1]. This clinical heterogeneity may be codified into disease subsets, a critical insight allowing the provider to anticipate internal organ involvement and disease progression. Classification based upon the distribution of affected skin areas and autoantibody status informs the management of disease-related complications.

Corresponding Author: Address correspondence to Dr. Roofeh., Division of Rheumatology/Department of Internal Medicine, 300 North Ingalls St., Suite 7C13, Ann Arbor, Michigan 48109-5422, USA., davroofe@umich.edu, Phone: 734-936-5561, Fax: 734-936-3695.

This article focuses on disease stratification and management in the first five years from onset of SSc. We support algorithmic approaches to management of disease subsets using recently published data.

II. EARLY SYSTEMIC SCLEROSIS

Early Disease

The majority of internal organ involvement in SSc will occur within the first two to five years from the disease onset (typically defined as the appearance of the first non-Raynaud's phenomenon symptom). Classifying SSc patients into an early disease subset allows for tailored screening and management strategies, with an aim to institute therapeutic intervention to prevent irreversible organ damage.

Classification

Patients with SSc may be classified based on the extent of skin involvement: limited cutaneous (affected skin is distal to the elbows and knees, and may include the face), diffuse cutaneous (affected skin is both distal and proximal to the elbows and knees, and may include the face, chest, trunk, and thighs), or absent (SSc sine scleroderma). The 2013 ACR/EULAR classification criteria improved upon the performance of the 1980 classification criteria in terms of recognition of the disease, especially in limited disease and the early stages when skin fibrosis is less advanced: the sensitivity improved (91%, from 75%), as well as the specificity (90%, from 72%)[2].

Patients may also be classified based on autoantibody status: antibodies are detected in more than 95% of patients with SSc, rarely found in healthy populations, and are mutually exclusive (the presence of one generally precludes the presence of another). These serological markers precede the onset of symptoms and are useful in making an early diagnosis[3]. Table 1 provides an overview of the likelihood of clinical feature development of SSc stratified by auto-antibody status. Anti-centromere antibody has a high specificity for limited cutaneous SSc, (95%) [4,5]. Anti-SCL-70 (anti- topoisomerase I antibody) is typically associated with diffuse cutaneous SSc, however up to one third of patients with anti- topoisomerase I antibodies may have limited cutaneous SSc[6]. Commercially available ELISA based assays for this antibody have been associated with high false positivity[7]. Anti-RNA polymerase III antibodies are associated with diffuse cutaneous SSc (90%)[8].

Prognostication

Factors present in the first five years of disease are predictive of development of major outcomes in SSc (e.g., development of interstitial lung disease, pulmonary hypertension, scleroderma renal crisis, death)[9–15].

Patients with limited cutaneous SSc typically have a burden of non-lethal signs and symptoms, notably a longstanding course of Raynaud's phenomenon, digital ulcerations, gastrointestinal involvement, and later-stage development of pulmonary arterial hypertension. Compared to patients with diffuse cutaneous SSc, they have a lower mortality rate and incidence of developing severe interstitial lung disease[16,17]. Those with diffuse

cutaneous SSc, particularly in the early stage, will have rapid progression of skin thickening, musculoskeletal involvement, higher frequency of clinically-significant interstitial lung disease, renal disease, and mortality.

Autoantibody status has better predictive value, compared to the extent of skin distribution, in predicting scleroderma organ involvement[6,18]. Patients with anti-centromere antibody positivity have a favorable prognosis compared to those with anti-SCL-70 antibody; they are more likely to develop ulcerations, gangrene, and tuft resorption of the digits, calcinosis, and are lower risk for arthritis or myositis. This antibody is associated with a higher risk for pulmonary arterial hypertension[19,20]. Patients with anti-SCL-70 antibody have a higher prevalence of arthritis, tendon friction rubs, severe pulmonary fibrosis, severe cardiac disease, and scleroderma renal crisis. The risk of interstitial lung disease in anti-SCL-70 positive patients is similar independent of the extent of skin involvement[21]. RNA polymerase III antibody positive patients have a high prevalence of scleroderma renal crisis (25%)[22].

III. MANAGEMENT

Table 2 provides a screening strategy for internal organ involvement by skin and auto-antibody status, noting areas of high priority.

Interstitial Lung Disease

All patients should be screened with HRCT and routine use of pulmonary function testing for monitoring purposes. The majority (55–65%) of scleroderma patients will have HRCT positive interstitial lung disease; that number increases to 96% of those with abnormal pulmonary function testing[23,24]. Routine pulmonary testing (spirometry and DLco), especially in the first 5 years, is to identify those patients developing progressive interstitial lung disease[25,26]. Patients with only minor impairment in the forced vital capacity (FVC) after more than 5 years of disease duration are much less likely to develop severe fibrotic lung disease later in their disease course. Reduced FVC within 4 years of the onset of symptoms is an important predictor of the eventual development of severe lung disease (FVC ≤ 50%)[4]. The greatest risk of progression for SSc ILD appears to be early in the disease course, particularly in those with diffuse SSc, male gender, African-American race, and positive anti-SCL-70 antibodies[27].

Traditional management focuses on treating those with significant baseline impairment in FVC, extensive involvement on HRCT, or evidence of progressive disease. Proposed definitions identifying those with clinically-significant disease include an FVC less than 70%, and extensive ILD on baseline HRCT of greater than 20%, and a decline of FVC by ≥ 5–10 percent and/or DLco of >10–15% within a 12 month period[28,29]. The goal of treatment is disease attenuation and retardation of progression with the use of cyclophosphamide or mycophenolate mofetil, as demonstrated in the Scleroderma Lung Study I and II trials[30,31]. Importantly, SLS-II demonstrated that mycophenolate mofetil with a target dose of 3g/day was comparable in efficacy to 1 year of oral cyclophosphamide, was better tolerated with fewer adverse hematological events. In patients with early diffuse SSc, a recent open-label

single-institution study showed promising evidence of lung and skin benefit with rituximab therapy[32].

The landscape of treatment is showing signs of changing in terms of targeted populations and mechanisms of action. Within the last year, clinical trials in SSc-ILD have shown data to suggest benefit of tocilizumab in reducing the rate of FVC decline compared to placebo in those with mild impairment on pulmonary function testing in early diffuse SSc patients, with elevated inflammatory markers and positive SCL 70 antibody[33,34]. A landmark phase III, randomized, double-blind, placebo-controlled trial showed an anti-fibrotic medication, nintedanib, to slow the rate of decline in FVC decline in SSc-ILD[35]. This medication has demonstrated efficacy in those with progressive fibrotic lung disease despite being on immune suppression and those with a UIP pattern deriving significant benefit from anti-fibrotic therapy[36].

There are no universally agreed-upon treatment algorithms at this time, but several have been proposed[34,37,38]. A recent European consensus statement, achieved through a modified Delphi process, yielded a clinical management algorithm for SSc-ILD. Nintedanib may be appropriate for treatment initiation or escalation, and used as monotherapy or in combination with mycophenolate mofetil 3g/day[39,31,35]. We recommend stratifying based on disease severity (subclinical vs. clinical ILD) and tailoring therapy based on risk of progression and the burden of disease (e.g., if lung predominant or multi-organ involvement). Figure 1a outlines a recommended treatment strategy based on this approach.

The use of autologous hematopoietic stem cell transplantation should be reserved for those with early diffuse scleroderma, less than 65 years of age, with severe visceral organ involvement (e.g., SSc-ILD) but without cardiac disease[40]. The experience of the treating medical team is considered to be of high importance when considering this modality[41]. Lung transplant should be considered in patients with progressive ILD despite aggressive medical therapy.

Pulmonary Arterial Hypertension

All patients with SSc are risk for developing of pulmonary arterial hypertension (PAH), however there is increased risk in those with longer disease duration, male gender, the number of telangiectasias, reduced capillary nail fold density, and anti-centromere antibody positivity. It is important to differentiate between pre-capillary pulmonary hypertension (due to PAH vs. PH-ILD) and post-capillary PH. PAH accounts for 17–30% of deaths among SSc patients[42,43]. Early detection and prompt initiation of therapy for PAH is essential; those with early diagnosis have more pronounced benefit with therapy[44,45]. In 2018 a revised definition of PH was proposed, lowering the threshold of right heart catheterization-derived mean pulmonary arterial pressure from ≥25mmHg to >20mmHg[46]. This shift was in accord with data showing those with an elevated mPAP have an increased risk for morbidity and mortality compared to normal mPAP[47,48]. Its implementation did not significantly impact the diagnosis of PH of those in two different screening cohorts [49].

Patients with longer duration of disease and limited cutaneous involvement are more likely to develop this complication[50,51], however patients within their first five years[52] and

those with diffuse cutaneous involvement may also be affected, largely due to PH-related ILD. A recent single-center review of SSc showed a high rate of co-existing interstitial lung disease (>20% extent of lung involvement) and WHO Group III PH[53]. As a result, all patients should receive EKG, pulmonary function testing, echocardiography, and NT-proBNP screening for this complication at the time of diagnosis. A screening algorithm, as proposed by recent 6TH World Symposium on Pulmonary Hypertension, should be performed annually[54]. Any new symptoms or signs should prompt consideration for referral for right heart catheterization.

Treatment for patients with PAH includes use of PDE5 inhibitors (e.g., sildenafil, tadalafil), endothelin receptor antagonists (e.g., bosentan, macitentan, ambrisentan), and prostacyclins (iloprost, epoprostenil, and treprostinil), with a goal to achieve NYHA functional class II or higher (mild shortness of breath) and slight limitation during ordinary activity[55]. Recent data from 3 large clinical trials (AMBITION, SERAPHIN, GRIPHON) suggest benefit of targeting multiple pathways in treatment of PAH[56–58]. The AMBITION trial showed Ambrisentan and Tadalafil combination therapy was superior to monotherapy for either medication[59]. The SERAPHIN trial showed the addition of macitentan (compared to placebo) and patients in the GRIPHON study receiving the addition of selexipag to combination therapy reduced the risk of morbidity/mortality [56,57,60,61]. Treatment of PH-ILD includes management of underlying ILD and 02 therapy, although many patients may have an overlap for PAH and PH-ILD[53].

Scleroderma Heart Involvement

The majority of cardiac involvement in early SSc is subclinical[62–64]. Cardiac involvement may be separated into fibrotic disease that can affect any component of the heart (pericardium, myocardium, conduction system, and less commonly the valves) and secondary involvement due to other sites of SSc involvement (e.g., PAH, SSc-ILD, renal disease)[65,66]. Myocardial involvement may present in early disease; it presents more commonly with diastolic (rather than systolic) dysfunction as heart failure with preserved ejection fraction[67–69].

Cardiac assessment should include considerations of myocardial fibrosis, coronary artery disease, co-occurring pulmonary hypertension, arrhythmias, and myocarditis. Hung et al., provide a diagnostic algorithm that includes an initial work-up of cardiac involvement including electrocardiogram, chest x-ray, transthoracic echocardiogram, troponin, CK-MB, and NT-proBNP measurements[66]. If abnormal or symptomatic, an appropriate work up should include a Holter monitor and appropriate referral to Cardiology should be made. Speckle tracking echocardiography is a technique recently shown to detect LV and RV dysfunction not detected by conventional 2D echo[70]. Cardiac MRI is a noninvasive, radiation-free, operator independent technique for identifying myocardial fibrosis and perfusion defects even in early disease. Those patients with modifiable risk factors for coronary artery disease (e.g., hypertension, dyslipidemia, diabetes, smoking) should be counseled.

Scleroderma Renal Crisis

Scleroderma renal crisis is the new onset of accelerated arterial hypertension and/or rapidly progressive oliguric renal failure during the course of scleroderma[71]; this is significantly more likely in diffuse SSc (12%) compared to limited SSc (2%)[72]. Features predictive of scleroderma renal crisis include disease symptoms less than 4 years, diffuse cutaneous skin involvement, rapid progression of skin thickening, the presence of anti-RNA polymerase III antibody, new anemia, new pericardial effusion or congestive heart failure, and antecedent high-dose corticosteroids.

Providers should become concerned for renal crisis if the SSc patient has an elevated BP of >150/85mmHg or if there is an increase of ≥20mmHg from baseline systolic blood pressure on two occasions in a 24-hour period[73]. These patients should be directed to the emergency department immediately. A decline in renal function (increase of 50% from baseline creatinine or an absolute increase of 0.3mg/dL, even if within normal range) and/or presence of proteinuria (>2+) and/or hematuria 1+ should prompt initiation of an ACE inhibitor[74]. A small proportion of patients may develop normotensive renal crisis, especially in those with background ACE inhibitor. Supportive features of this diagnosis include a microangiopathic hemolytic anemia, retinopathy typical of an acute hypertensive crisis, new onset of urinary red blood cells, flash pulmonary edema, and oliguria/anuria[71,73]. Clinical features include dyspnea, headache, blurred vision, encephalopathy, and seizures.

Management includes education for those at high risk regarding the importance of routine blood pressure monitoring, and close communication of new symptom development (headache, dyspnea, dizziness, syncope). Patients with scleroderma renal crisis should be hospitalized and prompt initiation of angiotensin converting enzyme inhibitor with close monitoring to avoid hypotensive nephropathy[75]. Other antihypertensive agents may be used if the blood pressure remains unacceptably high, with the exception of beta blockers. The use of ACE inhibitors in a prophylactic role has been found to be detrimental; and one study, exposure to ACE inhibitors prior to the onset of scleroderma renal crisis was associated with a greater than twofold increased risk of mortality[76].

Gastrointestinal Disease

GI involvement is the most common site of internal organ involvement, and may affect anywhere in the tract: gastroesophageal reflux disease, dysphagia due to altered contractility of the esophagus, delayed gastric emptying, delayed motility with resulting postprandial bloating and small intestinal bacterial overgrowth, chronic constipation, and vascular complications like gastric antral vascular ectasia[77].

Management is based on symptom development. Immunosuppression and stem cell transportation has not demonstrated correction of the underlying gastrointestinal dysmotility associated with SSc. Education about silent aspiration and precautions to avoid choking should be instituted early on. We recommend conservative measures like remaining upright during meals, using liquids between swallowing solid foods, and avoiding recumbency for at least 4 hours following a meal to allow gravity to facilitate bolus transit.

Treatments include proton pump inhibitor for esophageal reflux disease, serial esophageal dilatation for persisting dysphasia, nutritional supplementation for those with a restricted diet and/or malabsorption, antibiotics for bacterial overgrowth, and photocoagulation for those patients with GAVE. We recommend co-management with a gastroenterologist when considering use of promotility agents or Botox injections into the esophagus. There are data to suggest sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement[78]. Use of phosphodiesterase inhibitors and calcium channel blockers can impair the lower esophageal sphincter from functioning, and make esophageal reflux worse. Care should be taken to avoid pill esophagitis with common culprits (e.g., bisphosphonates, doxycycline), and consider common infections like candida as a source of esophageal discomfort.

Musculoskeletal/Cutaneous Involvement

SSc may affect several structures of the musculoskeletal system. Inflammatory arthritis (occurring in 16% (1,191 of 7,286) of a large European registry) and tendon friction rubs (occurring in 11% of patients (802 of 7,7286)) are commonly found in dcSSc, affecting the hands, wrists, elbows, knees, and ankles[79]. In addition to skin thickening, cutaneous disease involves the presence of calcinosis, occurring in 20–40% of SSc patients and seen more frequently in those with limited SSC with positive anti-centromere antibody positivity. Pruritus results as a consequence of small fiber neuropathy.

Patients with inflammatory arthritis may be treated similarly to those with rheumatoid arthritis[80]. Use of nonsteroidal anti-inflammatory drugs should be conducted with caution, given the risk of gastroesophageal abnormalities, GAVE in a small subset of patients, and those with impaired renal function. Low dose corticosteroids (less than 10 milligrams/day) may have value for symptomatic treatment of inflammatory arthritis. Providers should be cautious not to give doses above 15 milligrams/day to those patients with early diffuse SSc and especially those with RNA polymerase III positivity for fear of induction of scleroderma renal crisis. RA approved therapies may be considered, including abatacept and tocilizumab for treatment-refractory arthritis, although this recommendation is based on expert opinion[81].

Treatment options for skin involvement appear to have modest benefit; efficacy in treatment is confounded by a treatment-independent regression of skin thickening (typically by five years past the first non-Raynaud’s phenomenon onset). Treatments include methotrexate, mycophenolate mofetil, with recent trials of tocilizumab and abatacept failing to show significant differences in modified Rodnan skin score compared to placebo, but significant improvements in global assessment of disease with abatacept[82]. The role of intravenous immunoglobulin therapy on skin manifestations in SSc remain unclear, but promising[83]. Hematopoietic stem cell transplant may be an option for a narrow spectrum of patients with early, rapidly progressive diffuse SSc with poor prognosis but an absence of advanced organ involvement.

Hand therapy includes paraffin wax treatments, resistance training, home therapy exercises as directed by an occupational therapist, and splinting[84]. Hand surgery is reserved for those with severe fixed deformities with functional limitations, ulcerations, and calcinosis

refractory to treatment. The focus of surgery is to reposition digits and fuse the joints, immobilizing them to reduce pain and further digital complications of severely flexed PIP joints.

The efficacy of treatment of calcinosis remains disappointing. To date, there are little data to support the use of calcium channel blockers, bisphosphonates, minocycline, warfarin, and elective surgical excision. Gabapentin may have therapeutic role in treating small-fiber neuropathic pruritus.

Screening for Malignancy

There are data to suggest that SSc may be a paraneoplastic syndrome[85,86]. Maria et al. provide a comprehensive review of the subject to date[87]. In one cohort of 2,383 patients with scleroderma, 205 or 8.6% had a diagnosis of cancer. Patients with RNA polymerase III antibody positivity had a standardized incidence ratio of 2.84 (95% confidence interval 1.89–4.10); those who did not have scleroderma specific auto antibody positivity had a standardized incidence ratio of 1.83 (95% confidence interval 1.1–2.86). Those who were anti-centromere antibody positive had a lower risk of cancer during follow-up, with a standardized incidence ratio of 0.59 (95% confidence interval 0.44–0.76)[88].

IV. APPROACH TO CLINICAL CARE

Management of early SSc

For patients with early SSc, we begin by counseling and educating the patient on his/her disease, the expected distribution and severity of organ involvement based on their skin and auto-antibody profile, and reinforce the varied trajectories of clinical outcomes depending on development of disease progression. Figures 1a and 1b outline the general management of early SSc.

All patients should be screened for cardiac disease, interstitial lung disease, and pulmonary arterial hypertension; we recommend baseline EKG, echocardiogram, pulmonary function testing, and HRCT for all patients. Pulmonary arterial hypertension is rare to develop within the first five years, but the onset of shortness of breath is insidious and a screening algorithm such as the DETECT algorithm[89] is advocated; echocardiogram is insufficient as a screening tool for PAH. High resolution chest CT is the gold standard in diagnosing ILD. Those patients with clinically-significant ILD, high risk for progression, or evidence of progressive disease should be initiated on immunosuppressive or anti-fibrotic therapy[34]. It is unclear if mild or subclinical ILD with limited SSc and anti-centromere antibody should be offered therapy. For those with positive anti-SCL-70 antibody status or elevated CRP levels in the setting of mild ILD on HRCT and mild deficits on FVC % predicted, we recommend initiation of tocilizumab or mycophenolate mofetil[33] as these patients are at an increased risk of progression. For those with symptomatic ILD, mild-to-severe ILD on HRCT, FVC% predicted or DLco% predicted less than the lower limit of normal and/or clinically meaningful decline in FVC or DLco (if >1 PFT is available) accompanied by desaturation on oximetry during hall walk, we recommend mycophenolate mofetil. For those with progressive disease or non-tolerability to MMF, we add/replace with nintedanib

[31,90]. Those with extensive skin, musculoskeletal, and lung disease receive mycophenolate mofetil, cyclophosphamide, or rituximab[30,31,91].

Nearly all patients will have gastrointestinal symptoms at the time of initial contact with rheumatology; patients should institute reflux/aspiration precautions, increase the frequency and decrease food consumption size per meal, and initiate proton pump inhibitor for GERD symptoms. Symptoms of small intestinal bacterial overgrowth should be screened for at each visit; we administer UCLA SCTC GIT 2.0 to every patient to assess for symptoms and severity of GI involvement (https://umich.qualtrics.com/jfe/form/SV_3eBP4A4umBwnSvj). We refer patients to gastroenterology who continue to have symptoms despite pharmacologic therapy.

Inflammatory arthritis and advancing skin thickening may simultaneously be treated with escalating immune suppressive therapy[33,82,92], but continues to lead to considerable morbidity and remains a focus in the unmet needs of this subset of patients[93]. Patients with dcSSc and anti-SCL-70 antibody positivity are more likely than others to develop digital ulcerations; vasodilation, pain management, and prevention of/treatment for osteomyelitis remain a top priority[94,95]. Patients should be evaluated for the severity and frequency of Raynaud's phenomenon, with particular attention paid to the presence and monitoring of digital ulcerations; tobacco abstinence should be a top priority for several health benefits, in addition to its detrimental vasoconstriction effect[96].

Those with RNA Polymerase III antibody positivity should be counseled as above for risk of renal crisis. Those patients, and those with triple-negative antibody screening (negative anti-centromere, SCL-70, and RNA Polymerase III) should achieve up-to-date age-appropriate cancer screening[88].

Finally, enrollment in clinical treatment trials provides an option for investigational use of medications not yet approved by the FDA for SSc. Clinical research trials are advancing the goal of improving outcomes for SSc patients and stratifying therapies for SSc subsets[97].

V. CONCLUSIONS

Systemic sclerosis is a highly heterogeneous autoimmune disease, with varying clinical trajectories. Identifying patients within the first five years and sub-classifying patients based on skin distribution and auto-antibody status allows practitioners the best opportunity to intervene before advanced fibrosis sets in and cannot be reversed. Patients should be educated on the challenges ahead, limitations to treatment, and empowered to optimize their participation in maintaining their health. We encourage all our patients to explore their disease and management options at www.selfmanagescleroderma.com and scleroderma.org. Depending on the patient's SSc subset, risk stratification allows for timely follow-up and close monitoring for the development of and response to therapy.

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Key Points

1. Identifying patients within the first five years and sub-classifying patients based on skin distribution and auto-antibody status allows practitioners the best opportunity to intervene before advanced fibrosis sets in and cannot be reversed.
2. All patients should be screened with HRCT for SSc-ILD and routinely monitored for the development of dyspnea, cough, or exercise limitation alongside pulmonary function testing.
3. Early detection and prompt initiation of therapy for PAH is essential.
4. Those with RNA Polymerase III antibody positivity should be counseled for risk of renal crisis and remain up-to-date on age-appropriate cancer screening.
5. Enrollment in clinical treatment trials provides an option for investigational use of medications not yet approved by the FDA for SSc.

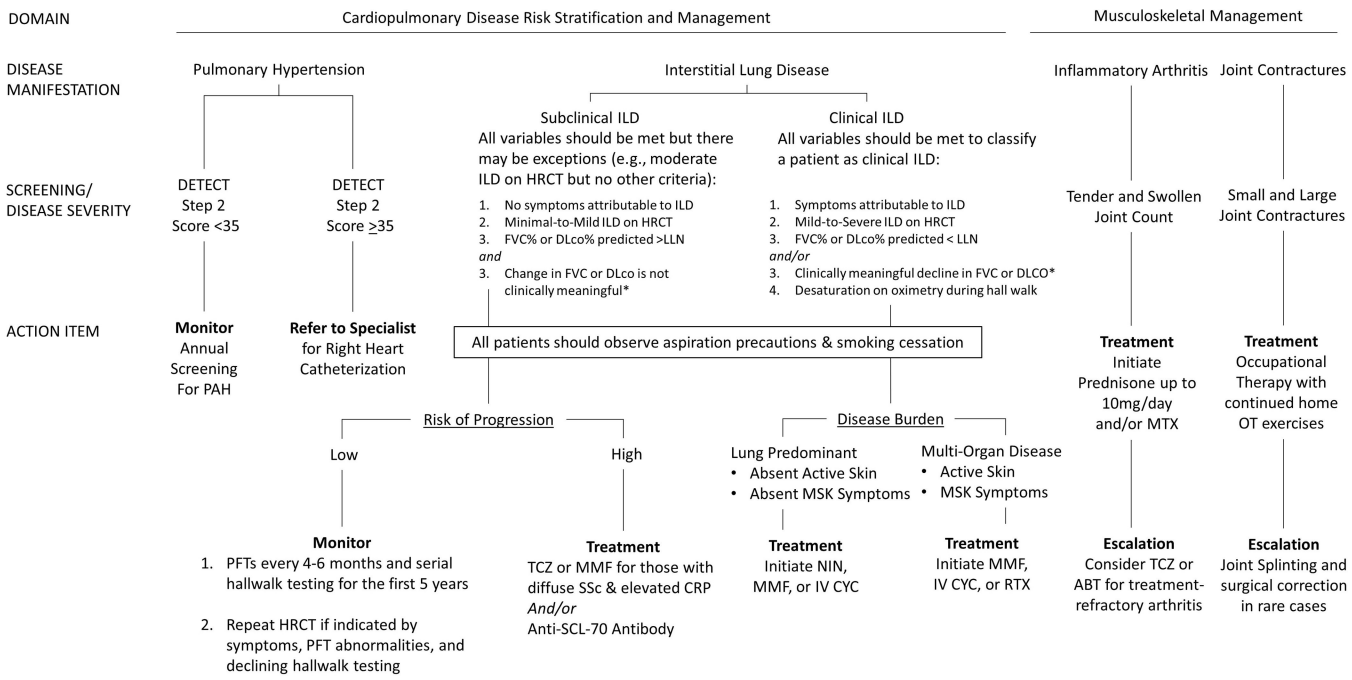

Figure 1a:

General management of early systemic sclerosis

Clinically Meaningful Change:

*if >1 PFT available, a clinically meaningful decline is defined as FVC levels of >10% from baseline or decline in FVC >5% to <10% and >15% relative decline in DLCO.

Medication/Treatment Acronyms

ABT: Abatacept

CYC: Cyclophosphamide

MMF: Mycophenolate Mofetil

MTX: Methotrexate

NIN: Nintedanib

OT: Occupational Therapy

RTX: Rituximab

TCZ: Tocilizumab

Testing Acronyms

Anti-SCL-70: Anti-Topoisomerase I Antibody

CRP: C-Reactive Protein

DLco: Diffusion Capacity of Carbon Monoxide

FVC: Forced Vital Capacity

HRCT: High Resolution Chest CT

LLN: Lower Limit of Normal

PFT: Pulmonary Function Testing

Disease Acronyms

ILD: Interstitial Lung Disease

MSK: Musculoskeletal

SSc: Systemic Sclerosis

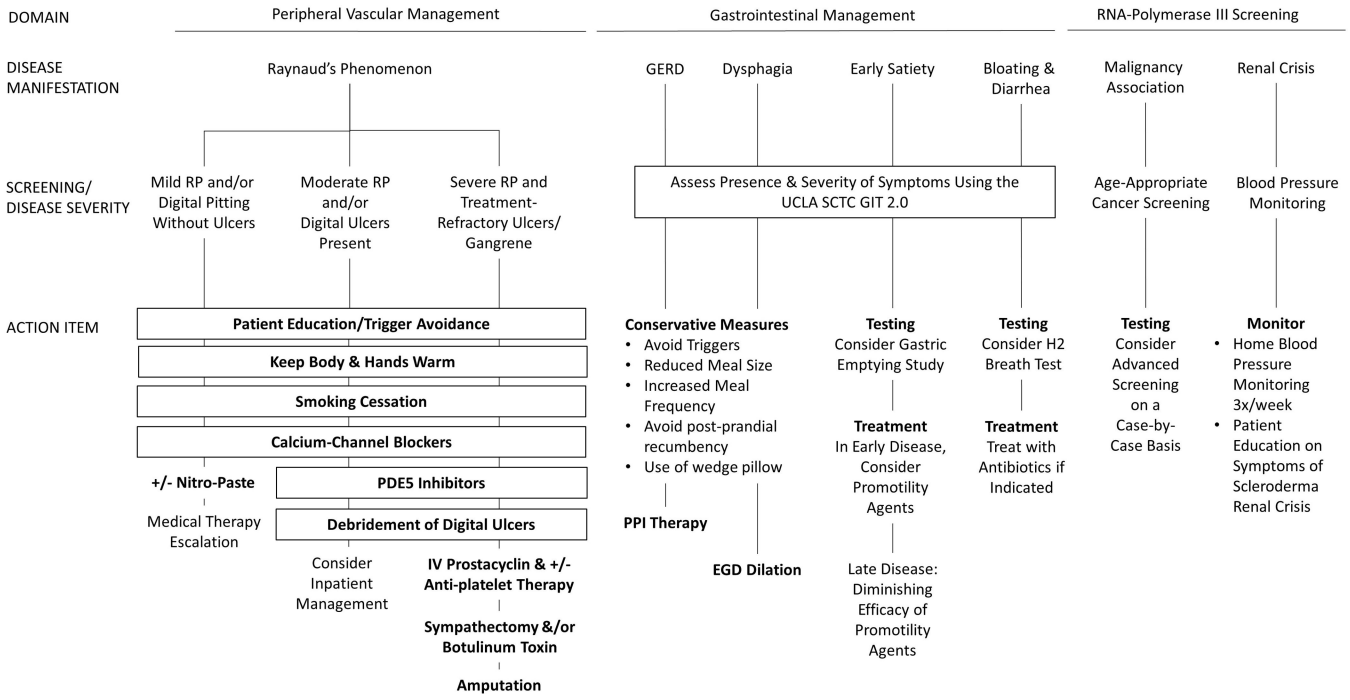

Figure 1b:

General management of early systemic sclerosis

Medication/Treatment Acronyms

EGD: Esophagogastroduodenoscopy

PDE5: Phosphodiesterase 5

PPI: Proton Pump Inhibitor

Testing Acronyms

H2: Hydrogen

UCLA SCTC GIT 2.0: UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Questionnaire

Disease Acronyms

GERD: Gastroesophageal Reflux Disease

RP: Raynaud's Phenomenon

Table 1:

Organ Involvement Within the First Five Years, Stratified by Auto-Antibody Status

	Anti-Centromere	Anti-SCL-70	Anti-RNA Polymerase III	ANA Positive, ENA Negative
Skin				
Limited Cutaneous	++	+	+	Unclear
Diffuse Cutaneous	−	+++	+++	Unclear
Cardiopulmonary				
Pulmonary Arterial Hypertension	+*	+/−	+	+
Clinically Significant Interstitial Lung Disease	+/−	+++	++	++
Cardiomyopathy	+/−	+	+/−	+
Renal				
Scleroderma Renal Crisis	+/−	+	+++	++
Malignancy				
Presence	−	+	+++	Unclear

− Very Rare

+/− Rare

+* Rare within the first 5 years

+ Less Common

++ Common

+++ More Common

Table 2:

Screening Stratified by Skin Involvement and Auto-Antibody Status

	Limited SSc		Diffuse SSc		
	Anti-Centromere	**Anti-SCL-70**	**Anti-SCL-70**	**Anti-RNA Polymerase III**	**ANA Positive, ENA Negative**
Screening					
Cardiopulmonary Involvement					
Electrocardiogram	++	++	++	++	++
Transthoracic Echocardiogram	++	++	++	++	++
Pulmonary Function Testing	++	++	++	++	++
High Resolution Chest CT	+	++	++	++	++
Blood Pressure Monitoring for Scleroderma Renal Crisis	+	+	+	++	+
Age-appropriate Cancer Screening	+	+	+	++	+

+ Routine Clinical Care

++ High Priority