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REVIEW

Systemic Sclerosis—Recent Advances in Diagnosis and Management

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Abstract

Systemic sclerosis is a multisystem connective tissue disease which can present to a broad range of medical specialities. It carries significant morbidity and mortality, but substantial advances have been made in recent years. Recent advances include autologous haematopoietic stem cell transplantation for early diffuse disease (for highly selected patients), the increasing use of phosphodiesterase type 5 inhibitors and of bosentan for digital ulceration, a better understanding of the use of different immunosuppressant therapies for interstitial lung disease (and which patients are likely to benefit from antifibrotic therapy), and the increasing early use of combination therapies for pulmonary arterial hypertension (PAH). Ongoing clinical trials investigating new therapeutic approaches should lead to further advances in the next 10 years. This review provides a broad overview of the condition with a focus on recent progress in specific areas: early diffuse cutaneous disease, digital vasculopathy, interstitial lung disease, and PAH.

Key words: systemic sclerosis; scleroderma; digital vasculopathy; interstitial lung disease; pulmonary hypertension; pulmonary arterial hypertension

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Introduction

Systemic sclerosis (SSc), sometimes termed ‘scleroderma’ (meaning hard skin) is a multisystem connective tissue disease with high morbidity, and high mortality due to internal organ involvement (Elhai et al, 2017; Volkmann et al, 2023). SSc can present to a number of different specialties, either before or after diagnosis (Saketkoo et al, 2021).

This review focuses on four aspects of SSc where there have been important recent advances for the general physician: early diffuse cutaneous disease, digital vasculopathy (Raynaud’s phenomenon and digital ulcers), interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Yet despite these advances, these all remain areas of unmet clinical need.

SSc presents many other challenges and, although it is outside the scope of this review to discuss them in detail, we begin with brief descriptions of epidemiology, the two major subtypes of SSc (limited cutaneous and diffuse cutaneous disease)

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and of autoantibody associations for context. We then outline differential diagnosis, the importance of early diagnosis (another area of recent advance), and tabulate a general overview of the investigation and management of the different clinical features of this heterogeneous disease.

It is worth highlighting that the clinical features of SSc result primarily from a combination of fibrosis and vascular abnormalities: SSc is not primarily an inflammatory disease, although inflammation can occur in certain situations for example in early diffuse cutaneous SSc and in overlap syndromes. This has major implications for management. For example, corticosteroids are seldom used and are relatively contra-indicated due to corticosteroids being a risk factor for scleroderma renal crisis (Steen and Medsger, 1998; Griffiths-Jones et al, 2023). Increased understanding of the complex pathophysiology of SSc, which involves interplay between vascular abnormalities, fibrosis, and immune dysfunction, holds promise for new approaches to therapies: many clinical trials are ongoing.

Epidemiology

SSc is rare. Prevalence estimates vary, but approximately 100–250 per million are affected, with an incidence of approximately 10–20 per million (Nikpour et al, 2010). Higher prevalence rates have been reported in North America than in Europe (Nikpour et al, 2010; Bairkdar et al, 2021), with recent studies reporting higher prevalences than earlier ones (Bairkdar et al, 2021), probably due to more sensitive criteria, and increased availability of modern diagnostic tools including specific autoantibody testing and nailfold capillaroscopy. Females are more frequently affected than males (5:1) (Bairkdar et al, 2021).

Limited and Diffuse Cutaneous Subtypes, and Autoantibody Associations

The two major subtypes of SSc are defined on the basis of the extent of skin involvement (LeRoy et al, 1988): limited cutaneous (when skin involvement is confined to the extremities, face and neck) and diffuse cutaneous (when skin involvement progresses proximal to the elbow and/or knee, or involves the trunk). Rarely SSc can occur without skin involvement, when it is termed ‘SSc sine scleroderma’. The two major subtypes have different natural histories, autoantibody associations and prognoses as described below, and both subtypes can occur in overlap with other connective tissue diseases (Denton and Khanna, 2017).

Limited Cutaneous SSc (lcSSc)

This is the more common subtype and usually presents with Raynaud’s phenomenon, that can precede the diagnosis by several years (Denton and Khanna, 2017). In the past, there has often been a misconception that limited cutaneous SSc is a ‘mild’ form of SSc. This is untrue: internal organ involvement can occur, and late mortality from PAH can occur as well. In the past, the term ‘CREST’ was sometimes used to describe this subtype (LeRoy et al, 1988), but it is no longer used except as an acronym for five of the clinical features of SSc which occur

Table 1. The more common systemic sclerosis-specific autoantibodies and their associations.

Specific autoantibody	Phenotypic associations
Anticentromere	Limited cutaneous subtype Severe digital ischaemia Pulmonary arterial hypertension Telangiectasias
Anti-topoisomerase I (anti-Scl 70)	Diffuse cutaneous subtype Interstitial lung disease
Anti-RNA polymerase III	Diffuse cutaneous subtype Scleroderma renal crisis May be associated with underlying malignancy
Anti-polymyositis-scleroderma (PM-Scl)	Myositis overlap Calcinosis
Anti-U1-ribonucleoprotein (U1-RNP)	Overlap syndromes
Anti-Th/To	Interstitial lung disease Pulmonary arterial hypertension

in either subtype (Calcinosis, Raynaud's, Esophageal involvement, Sclerodactyly [scleroderma of the fingers], Telangiectasias). The 2013 classification criteria for SSc (van den Hoogen et al, 2013) are more sensitive than previous criteria in identifying patients with lcSSc and this probably contributes to the rising prevalence mentioned above. For example, a patient with Raynaud's phenomenon, 'puffy fingers', a positive anticentromere antibody and abnormal nailfold capillaries would score 10 (9 required) of the 2013 criteria but would not have fulfilled earlier criteria (Masi et al, 1980).

Diffuse Cutaneous SSc (dcSSc)

This has a very different onset from lcSSc, often with painful, swollen fingers (sometimes initially misdiagnosed as inflammatory arthritis) followed by rapid development of skin thickening and early internal organ involvement as described below. The skin may be very itchy and painful, and finger (and often elbow) flexion contractures are common (Herrick et al, 2022).

Autoantibodies

Most patients with SSc are antinuclear antibody (ANA) positive, but ANA is non-specific, and it is important to check for SSc-specific autoantibodies. The different specific autoantibodies associate with different disease trajectories/phenotypes, as shown in Table 1, and help to predict prognosis (Nihtyanova et al, 2020).

Differential Diagnosis

Conditions other than SSc can cause skin thickening (scleroderma) (Orteu et al, 2020), with the main differential diagnoses being localised scleroderma (mor-

phoea), which can be very extensive but is not associated with internal organ involvement, eosinophilic fasciitis, and (very rarely) scleromyxoedema, nephrogenic systemic fibrosis or scleroedema. Histological features on skin biopsy can be helpful in diagnosis (Orteu et al, 2020). A key differentiating factor between these 'other' conditions and SSc is that, in these conditions, the fingers are often spared (in SSc, the fingers are usually the first affected) and the nailfold capillaries are normal (in SSc they are usually abnormal) (Orteu et al, 2020).

Early Diagnosis

Most patients with SSc present with Raynaud's phenomenon, which provides a window of opportunity for early diagnosis. The Very Early Diagnosis of SSc (VEDOSS) study (Bellando-Randone et al, 2021) confirmed the following as predictive of the development of SSc in patients presenting with Raynaud's phenomenon: puffy fingers, an SSc-specific autoantibody, and abnormal nailfold capillaries (Fig. 1). Therefore, these should always be looked for, especially when Raynaud's commences after the age of 40 years. Conversely, a negative ANA is a strong negative predictor for development of SSc in the patient presenting with Raynaud's (Bellando-Randone et al, 2021). Early diagnosis allows early identification and treatment of internal organ involvement, which can be life-threatening, and of digital ulcers.

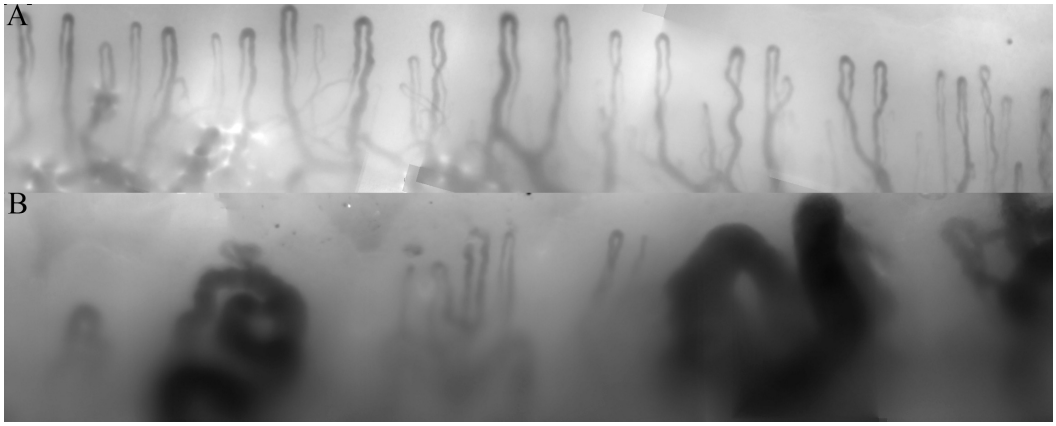

Fig. 1. Nailfold capillaroscopy images in health and disease. (A) Normal nailfold capillaries as seen in healthy control subjects or in patients with primary Raynaud's phenomenon. (B) Structurally abnormal nailfold capillaries with enlarged capillaries and reduced capillary density with areas of avascularity: these appearances are consistent with SSc. Permission has been obtained. SSc, systemic sclerosis.

Table 2. The clinical features of SSc with some of the key points in investigation and management.

Clinical problem/organ system	Key symptoms and signs (or specific clinical entity)	Key elements of investigation and treatment
Early diffuse cutaneous disease		
Diffuse cutaneous disease within 5 years of disease onset (carries a high risk of early internal organ involvement)	Progressive skin thickening, contractures	1. Early referral to a specialist centre. 2. Close monitoring of blood pressure, and warning patients to seek urgent medical advice if they develop any new symptoms which could be indicative of renal crisis (e.g., sudden onset of breathlessness, headache, flu-like symptoms). 3. Multidisciplinary team input including physiotherapy and occupational therapy. 4. Immunosuppression, e.g., with mycophenolate mofetil. 5. Consider autologous haematopoietic stem cell transplantation (highly selected cases only, taking the benefits versus the risks of treatment into account). 6. Being vigilant for development of internal organ disease, including with pulmonary function testing and echocardiography.
Digital vasculopathy		
Raynaud's phenomenon	Discoloured, painful fingers on cold exposure	1. 'Non-drug' measures, e.g., wearing warm gloves and socks. 2. Vasodilator therapy — first line calcium channel blocker, second line phosphodiesterase type 5 inhibitor.
Digital ulceration	Ulcers of fingers or toes	1. Advise patient to seek medical advice as soon as an ulcer develops. 2. Local wound care +/– debridement. 3. Antibiotics if ulcer(s) infected. 4. Analgesia. 5. Optimise treatment of Raynaud's phenomenon.

Table 2. Continued.

Clinical problem/organ system	Key symptoms and signs (or specific clinical entity)	Key elements of investigation and treatment
		6. Bosentan (an endothelin receptor antagonist) in patients with recurrent ulcers. 7. Consider intravenous prostanoid therapy (e.g., iloprost) in an acute situation or in patients with more chronic ulcers not responding to other measures.
Internal organ involvement		
Gastrointestinal (both upper and lower gastrointestinal dysmotility can occur)	Symptoms of gastro-oesophageal reflux disease, dysphagia	1. Dietary advice (small, frequent meals, avoid eating late in evening). 2. Avoid lying flat. 3. Proton pump inhibitor +/– H2 receptor antagonist. 4. Consider prokinetic drugs for gastrointestinal dysmotility.
	Symptoms of anaemia — suspect gastric antral vascular ectasia (GAVE)	Gastric antral vascular ectasia (GAVE) may be asymptomatic, but always suspect this in patients with iron deficiency anaemia.
	Symptoms of malabsorption (usually due to small bowel bacterial overgrowth), e.g., weight loss, diarrhoea	1. Antibiotic therapy (often rotational antibiotics) if breath testing suggests small bowel bacterial overgrowth, or if high index of suspicion. 2. Address any nutritional issues 3. Enteral or parenteral nutrition may be required in patients with severe disease.
	Constipation	1. High fibre diet. 2. Laxatives.
	Faecal incontinence	1. Regulate bowel habit. 2. Consider biofeedback.

Table 2. Continued.

Clinical problem/organ system	Key symptoms and signs (or specific clinical entity)	Key elements of investigation and treatment
Interstitial lung disease	Breathlessness, cough, basal crackles	1. Imaging – chest radiograph and high resolution computed tomography. 2. Monitor lung function (including forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (TLCO)). 3. Immunosuppression – mycophenolate mofetil usually first line, other options include cyclophosphamide, rituximab and tocilizumab. 4. Consider antifibrotic treatment (nintedanib). 5. Lung transplantation may be an option in highly selected patients.
Pulmonary arterial hypertension	Breathlessness, loud second heart sound at pulmonary area, right heart failure in advanced cases	1. Echocardiography allows estimation of the pulmonary arterial systolic pressure. 2. Electrocardiogram (ECG) may show right ventricular strain pattern in advanced cases. 3. Monitor lung function — the TLCO may be disproportionately reduced compared to the FVC. 4. Right heart catheterisation is the diagnostic test of choice. 5. Treatment with vasoactive therapy (often combination therapy) including phosphodiesterase type 5 inhibitor, endothelin receptor antagonist, prostanoid therapy. 6. Lung transplantation may be an option in highly selected patients.
Scleroderma renal crisis	A sudden rise in blood pressure (accompanied by a decline in renal function). Rarely normotensive renal crisis can occur	1. This is a medical emergency necessitating urgent hospital admission. 2. A microangiopathic haemolytic anaemia can occur. 3. Angiotensin converting enzyme (ACE) inhibition (often in association with other vasodilator therapies) is the cornerstone of management. 4. At-risk patients (e.g., those with early diffuse disease, especially if anti-RNA polymerase III positive or on corticosteroids) should be advised to monitor their blood pressure regularly. 5. Prophylactic ACE inhibition is not generally recommended.

Table 2. Continued.

Clinical problem/organ system	Key symptoms and signs (or specific clinical entity)	Key elements of investigation and treatment
Cardiac involvement	Breathlessness, palpitations	1. Treatment depends on the nature of the involvement (i.e., arrhythmia, heart failure). 2. Immunosuppression may be indicated for myocarditis.
Nervous system involvement	Carpal tunnel syndrome (in early diffuse systemic sclerosis) Trigeminal neuralgia Peripheral neuropathy Autonomic neuropathy	1. Symptomatic treatment. 2. Optimising treatment of underlying disease.
Musculoskeletal manifestations		
Arthritis	Joint pain and swelling	If a patient has a concomitant inflammatory arthritis, this should be treated accordingly.
Myositis	Muscle weakness Pharyngeal dysphagia	1. Check the creatine kinase and consider other investigations, e.g., magnetic resonance imaging, neurophysiology testing. 2. Corticosteroids may be indicated but should be used with caution. 3. Consider immunosuppression.
Contractures	Finger contractures, elbow contractures, reduced movement at other joints due to skin thickening	Physiotherapy and occupational therapy.
Cutaneous/subcutaneous manifestations (other than scleroderma)		
Calcinosis (subcutaneous lumps of calcium containing salts)	Palpable lumps, most commonly at pressure points, e.g., fingers, extensor aspects of elbows and knees	Current management comprises early treatment of superadded infection, and (in selected cases) surgical debulking.
Telangiectasias	Occur mainly on the face (including lips), anterior chest wall and upper limbs	1. Consider pulsed dye laser therapy (or intense pulsed light). 2. Camouflage techniques. 3. Recognition of distress these cause to patients.

General Overview

It is not possible within a short article to describe in detail all the clinical features of SSc, but Table 2 lists the most important ones, with some key points regarding assessment and management (Denton and Khanna, 2017; Saketkoo et al, 2021; Volkmann et al, 2023; Herrick and Samaranayaka, 2024). Fig. 2 summarises the principles of management, which involves input from allied health professionals as well as from different medical and surgical specialists. Detailed treatment guidelines/recommendations have been published by the British Society for Rheumatology and the European Alliance of Associations for Rheumatology (Del Galdo et al, 2025; Denton et al, 2024). SSc is a disfiguring as well as a disabling and painful disease: some of the characteristic abnormalities of the face and hands are shown in Figs. 3,4.

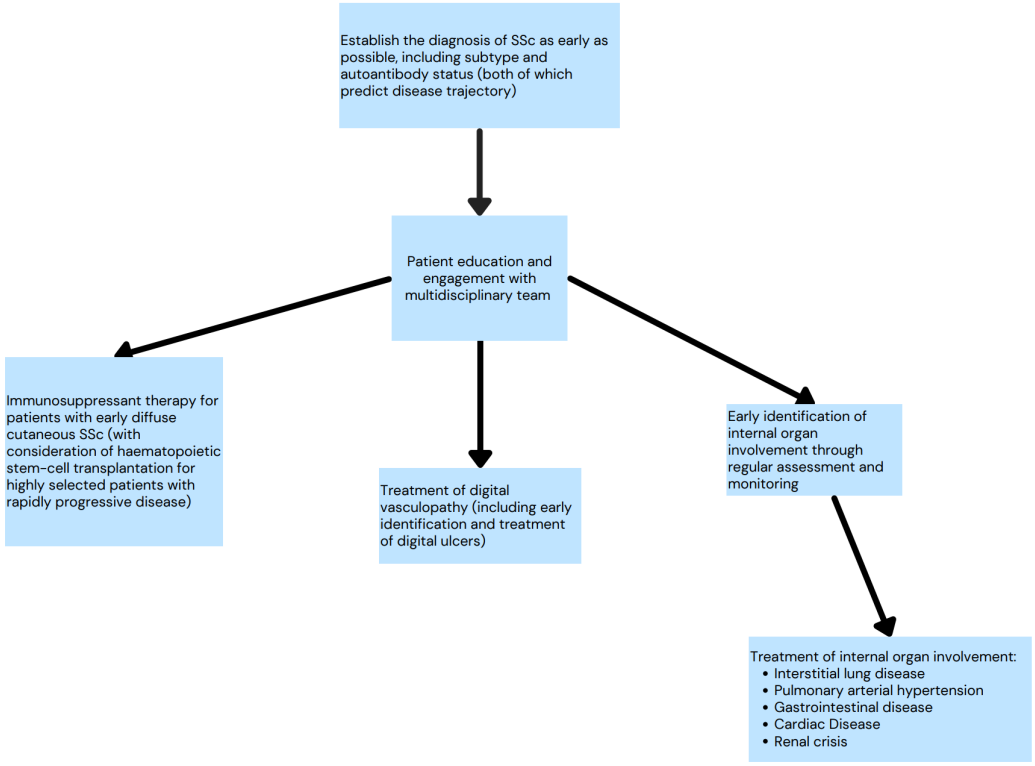

Fig. 2. The broad principles of management of SSc. Figure drawn with Canva software (2024, Personal access, Scotland, UK).

Early Diffuse Cutaneous Disease

Background

Early dcSSc is associated with high morbidity and mortality and affected patients often have significant functional impairment (with high levels of hand disability) (Peytrignet et al, 2018) mainly due to painful, thickened skin causing contractures. The extent of skin thickening can be measured using the modified Rodnan

Fig. 3. Typical facial appearances in SSc. (A) 'Beaking' of the nose (B) telangiectasias (including of the lips) and reduced mouth opening. Images copyright of Northern Care Alliance NHS Foundation Trust. Permission has been obtained.

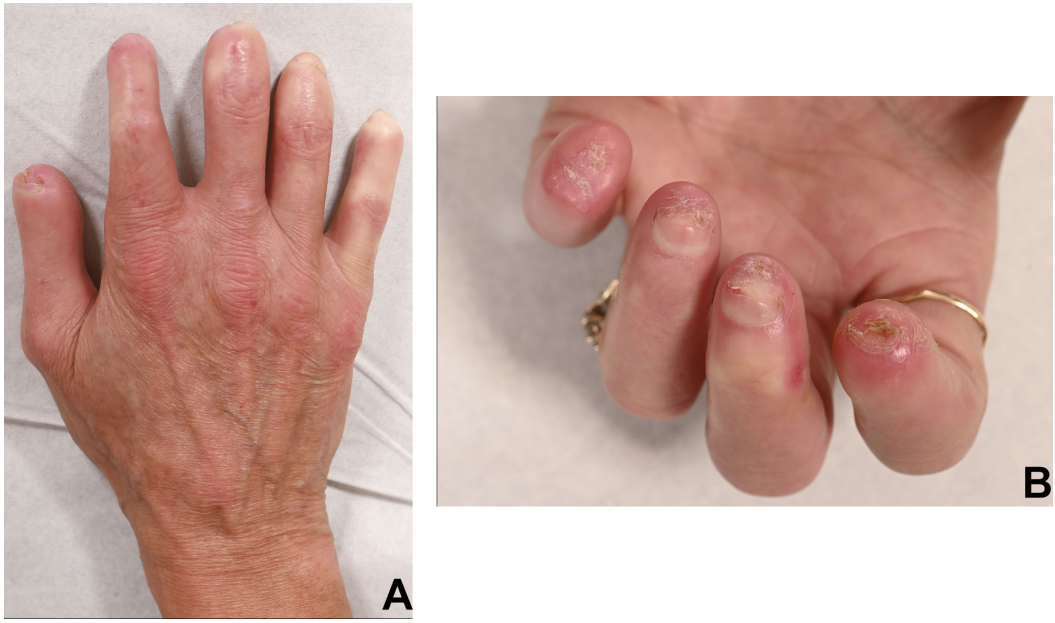

Fig. 4. Finger abnormalities in systemic sclerosis. (A) Finger contractures with amputation of the tip of the middle finger (B) ischaemic changes of the fingertips, including a healing ulcer of the index finger. Images copyright of Northern Care Alliance NHS Foundation Trust. Permission has been obtained.

skin scoring system (mRSS, 17 body sites, maximum score 51) (Khanna et al, 2017). The higher the mRSS, the higher the mortality. Internal organ involvement tends to occur early: patients require close monitoring especially during the first 5 years of the disease. This includes blood pressure monitoring due to the risk of renal crisis in early diffuse disease.

Treatment

'General measures' include analgesia (skin involvement is painful) and input from the multidisciplinary team. Physiotherapy is essential to preserve/optimise range of movement, and occupational therapy will help to minimise the impact of hand disability. Standard practice is to recommend immunosuppression, such as with mycophenolate mofetil (MMF). Cyclophosphamide and methotrexate are other options. Autologous haematopoietic stem cell transplantation (AHSCT) has been shown to confer benefit in three clinical trials (reviewed by Khanna et al, 2023) and should be considered in highly selected patients with rapidly progressive disease. Whenever possible, patients should be offered the opportunity to enroll in a clinical trial for one of the many new approaches to treatment currently being investigated, including cell-based therapies such as mesenchymal stem cells and chimeric antigen receptor T cell-based therapy (Khanna et al, 2023). All patients with early dcSSc should be referred to a specialist centre, so that these options can be considered and delivered.

Digital Vasculopathy

Background

The spectrum of SSc-related digital vasculopathy comprises Raynaud's phenomenon (in which the fingers classically turn white, then blue, then red in response to cold exposure or emotional stress), digital ulceration and critical digital ischaemia.

Almost all patients with SSc experience Raynaud's phenomenon, which can be very severe and progress to digital ulceration in approximately 50% of patients (Hughes et al, 2020). A minority of patients develop critical ischaemia and gangrene. SSc-related Raynaud's can progress to irreversible tissue injury because vascular abnormalities are structural as well as functional, leading to poor perfusion of the fingers and toes.

Treatment of Raynaud's Phenomenon

All patients should be educated on the importance of keeping warm and avoiding triggering factors. Most patients with SSc will require drug treatment for their Raynaud's, although currently available vasodilators tend to provide only modest (if any) benefit (Khouri et al, 2019). Calcium channel blockers are generally considered first line. A sustained release preparation is usually recommended, starting at a low dose and then gradually up-titrating to the maximum possible dose. Phosphodiesterase type 5 inhibitors (PDE5i, e.g., sildenafil) are now generally considered second line and can be used in combination with a calcium channel blocker. Other vasodilators may also be tried albeit with little evidence base (Khouri et al, 2019), although this lack of evidence may be (at least in part) due to the complexities and challenges of clinical trials of treatment for Raynaud's phenomenon.

Treatment of Digital Ulceration

Many ulcers become infected and require antibiotic therapy. If underlying osteomyelitis is suspected, magnetic resonance imaging (MRI) should be considered to detect this at an early stage. The pain from digital ulcers can be excruciating, and so adequate analgesia (sometimes with opiates in the short-term) is a key aspect of management, together with local wound care. Treatment of Raynaud's phenomenon should be optimised and a PDE5i added if the patient is not already on this. Bosentan (an endothelin receptor antagonist) is indicated for patients with recurrent ulcers (NHS England, 2021). Patients with refractory (or acute) ulceration may require hospital admission for intravenous (IV) prostanoid treatment (usually iloprost) (Wigley et al, 1994; NHS England, 2021). Some ulcers require surgical debridement. Digital (palmar) sympathectomy should be considered for patients who do not respond to all other measures. Other approaches which have attracted recent interest are botulinum toxin injections and autologous fat grafting (Herrick and Philobos, 2023).

Treatment of Critical Ischaemia

This is along similar lines to that of digital ulceration. Critical ischaemia is always a medical emergency, and the patient must be hospitalised. It is important always to check for contributory causes, e.g., large vessel disease, or coagulopathy. Intravenous prostanoid therapy should be considered although some patients will require amputation of part or all of the affected digit.

Interstitial Lung Disease (ILD)

Demographics and Risk Factors

ILD is very common in SSc and is the leading cause of SSc-related deaths (35% of all disease-related mortality) (Tyndall et al, 2010). It can appear early in the disease, with most volume loss in severe ILD occurring in the first four years (Nikpour et al, 2010). All patients with SSc and respiratory symptoms should be evaluated for ILD, but male patients and African Americans are at increased risk of severe disease (Nikpour et al, 2010). ILD is more commonly associated with dcSSc but can also occur in lcSSc. Auto-antibody profile also affects risk (Table 1) (Hoffmann-Vold et al, 2020; Nihtyanova et al, 2020).

Investigation

At the point of diagnosis of SSc, a minimum set of pulmonary investigations should be performed. This includes (in addition to history, clinical examination, and a SSc antibody panel), pulmonary function testing (PFT) (spirometry and gas transfer), and high resolution computerised tomography of the chest (HRCT). Typically, the radiographic pattern seen in SSc-ILD is non-specific interstitial pneumonia (NSIP) pattern fibrosis (Fig. 5A), however usual interstitial pneumonia (UIP) pattern fibrosis (Fig. 5B) can also be seen. Prone imaging can be helpful to ensure dependent basal change is not interpreted as ILD. Other parameters such as a 6-minute walk distance (6MWD), WHO functional class and severity of exertional

desaturation are additional useful means of assessing functional disease progression (Hoffmann-Vold et al, 2020; Rahaghi et al, 2023; Raghu et al, 2024).

Monitoring frequency is influenced by initial findings, together with symptom progression, but a 6 monthly clinical review and PFT in early disease (first 3–5 years) and yearly PFT thereafter is often a reasonable minimum (Denton et al, 2024). Frequency of HRCT should be guided by the clinical picture rather than at fixed intervals to minimise radiation exposure but is generally considered to be a more definitive assessment of ILD progression. It should be prompted in cases of clinical or PFT deterioration (Hoffmann-Vold et al, 2020). The role of lung ultrasound in ILD screening is under exploration with promising results (Song et al, 2016) and hyperpolarised Xenon MRI has also been used experimentally to assess gas exchange (Montesi and Caravan, 2019). There are also a number of experimental biomarkers for ILD risk (e.g., Krebs von den Lungen-6 (KL-6), Interleukin (IL)-6, Chemokine Ligand (CCL) 18, Chemokine (CXC Motif) Ligand 4, CCL2 and surfactant protein D) that may have a future role in clinical practice.

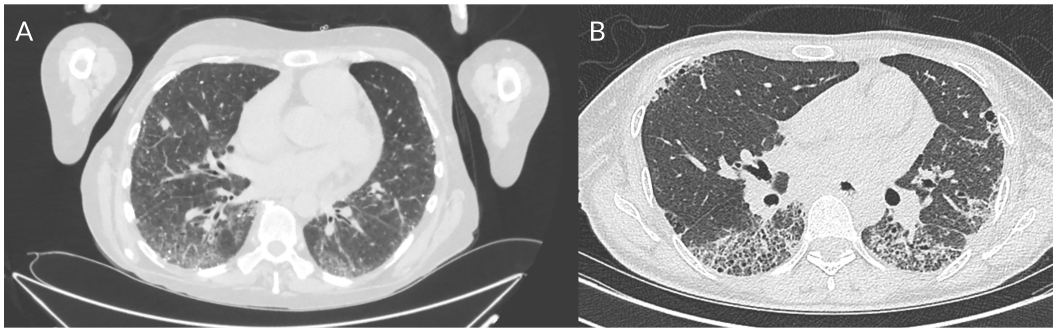

Fig. 5. HRCT slices demonstrating. (A) Systemic sclerosis interstitial lung disease with moderate severity non-specific interstitial pneumonia pattern fibrosis characterised by relatively fine homogenous reticulation and inflammatory change. (B) Systemic sclerosis interstitial lung disease with subpleural cyst formation, extensive reticulation, traction bronchiectasis typical of usual interstitial pneumonia pattern fibrosis. Permission has been obtained. HRCT, high resolution computerised tomography of the chest.

Treatment

There is no absolutely defined pathway for SSc-ILD currently with variation in clinical practice reflected in differences across British Society for Rheumatology/American Thoracic Society/European Respiratory Society guidelines. An approach to management is suggested in Fig. 6.

The traditional approach is immunosuppression, however anti-fibrotic therapies have an increasingly recognised role. Initial evidence of improvement in lung function came with cyclophosphamide but now MMF is typically preferred as first line therapy based on the results of the Scleroderma Lung Study II (Tashkin et al, 2016). This demonstrated no significant difference in efficacy between MMF and cyclophosphamide but a better side effect profile with MMF (Tashkin et al, 2016). Cyclophosphamide (oral or intravenous) is typically considered second line though rituximab is an alternative where there is evidence of disease progression on estab-

lished therapy. Evidence for tocilizumab use is predominantly in early SSc with ILD where there is evidence of an acute phase response (Khanna et al, 2020; Rahaghi et al, 2023). The emerging role of anti-fibrotic agents such as nintedanib is less defined. In many guidelines, it is seen as a second line agent, particularly where a progressive fibrotic picture predominates. However, there is some data to support use upfront with MMF, especially where the presenting picture is markedly fibrotic (Denton et al, 2024). Pirfenidone, another licensed antifibrotic therapy in IPF, does not have a clear evidence base in SSc-ILD though trials as an adjunctive therapy are ongoing (NCT04928586, NCT05505409). Steroids are largely avoided as already mentioned.

Treatment response is generally measured by the same parameters as disease progression (forced vital capacity [FVC], diffusing capacity of the lungs for carbon monoxide [DLCO], clinical symptoms with or without 6MWD, exertional desaturation, HRCT when indicated). Treatment de-escalation is generally considered after prolonged periods of stability (>2 years) and would generally be performed gradually under close monitoring.

For patients with aggressive disease not responding to immunosuppressive and antifibrotic therapies, lung transplantation should be considered (Denton et al, 2024). Detailed discussion is beyond the scope of this review but clearly mortality risks of transplant must be carefully balanced against disease prognosis. Lung transplantation can be significantly complicated by the multi-system nature of SSc with oesophageal dysmotility a frequent barrier to consideration for transplantation in a limited donor pool, due to elevated risk of post-transplantation bronchiolitis and chronic lung allograft dysfunction (Denton et al, 2024).

Other general measures such as vaccinations against respiratory infections are encouraged, and supplemental oxygen should be supplied if indicated. Pulmonary rehabilitation can be of significant benefit, but musculoskeletal disease sequelae may preclude this. Special consideration should be given to gastro-oesophageal reflux disease (GORD). When severe, GORD is linked to increased risk of disease progression in SSc-ILD and is generally aggressively medically managed (Silver and Silver, 2015).

The diagnosis and management of SSc-ILD is evolving and there are a number of consensus statements now defining the diagnostic pathway and the immunosuppressive and anti-fibrotic elements of treatment (Hoffmann-Vold et al, 2020; Rahaghi et al, 2023; Denton et al, 2024; Raghu et al, 2024).

Pulmonary Arterial Hypertension

Pulmonary hypertension (PH) represents a haemodynamic disease of the pulmonary circulation with a mean pulmonary artery pressure of over 20 mmHg at right heart catheterisation. PAH represents a distinct pathological subtype of PH characterised by pulmonary vascular remodelling and vasculopathy (Humbert et al, 2022). PAH has a high prevalence of between 5 and 19% in SSc cohorts and is the second most common cause of death in SSc, accounting for 26% of all SSc mortality (Tyndall et al, 2010). Whilst PAH will be the focus of this section, it

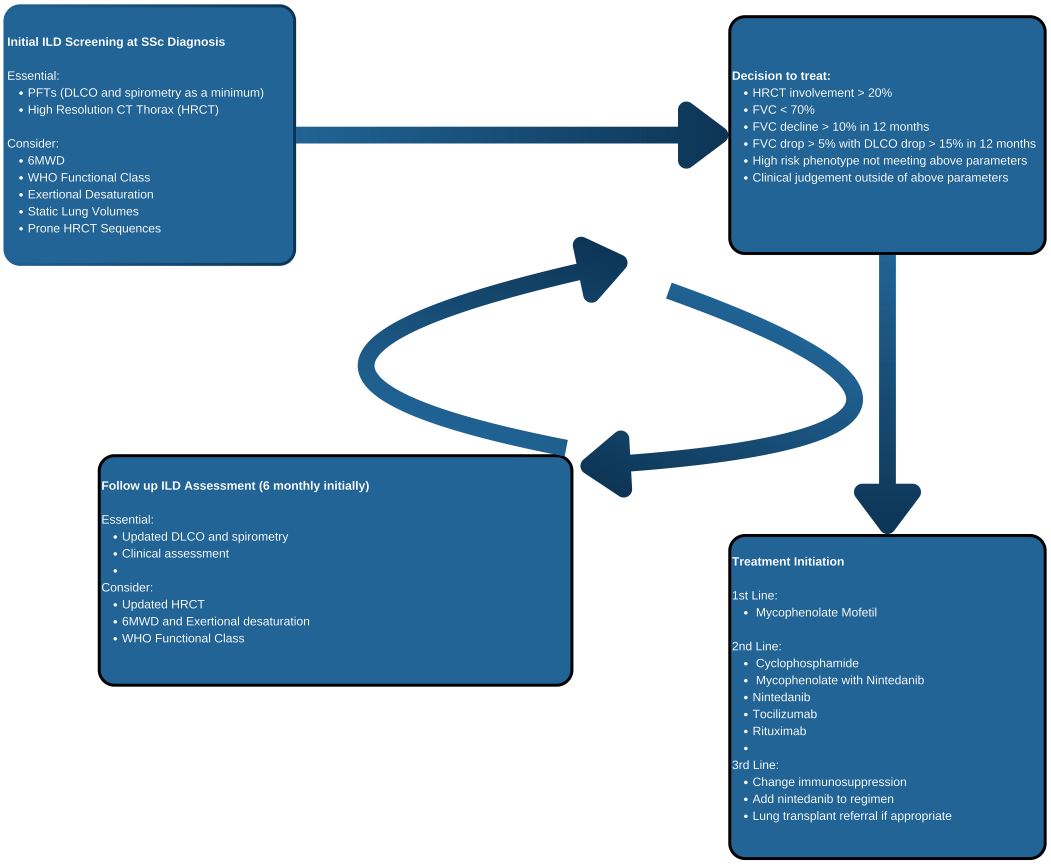

Fig. 6. Flow chart detailing an approach to screening and management of SSc-ILD based on British, European and US consensus statements (Hoffmann-Vold et al, 2020; Rahaghi et al, 2023; Denton et al, 2024; Raghu et al, 2024). 6MWD, 6-minute walk test; AHSCT, autologous haematopoietic stem cell transplant; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; PFT, pulmonary function test; ILD, interstitial lung disease. Figure drawn in Canva software (2024, Personal access, Scotland, UK).

should be noted patients with SSc carry increased risk of developing other forms of PH. This includes, as defined by expert consensus, Group 2 (pulmonary venous hypertension), Group 3 (hypoxic lung disease related) and Group 4 (due to chronic thromboembolic disease) disease (Humbert et al, 2022; Kovacs et al, 2024).

Demographics and Risk Factors

Increasing age, disease duration and African heritage increase risk of developing SSc-PAH. Presence of digital ulceration and specific antibodies (Table 1) also increases risk (Walker et al, 2007; Jiang et al, 2020).

Screening and Diagnosis

A high index of suspicion should be maintained for the development of SSc-PAH, particularly in those with dyspnoea, low DLCO but no (or only mild) interstitial changes on CT scanning. Early diagnosis is important in this at-risk population and has been linked to less severe haemodynamic impairment and improved survival (Humbert et al, 2011).

All patients with SSc should undergo PH screening. Physical examination may demonstrate signs of raised pulmonary pressure, or right ventricular (RV) failure and routine electrocardiogram (ECG) may show signs of right heart disease whilst N-terminal pro-B-type natriuretic peptide (NT-proBNP) and FVC%: DLCO% (with a ratio >1.5 being suggestive of PH) can be used in initial screening also.

Echocardiography has the major role in screening. There are a number of parameters including RV systolic pressure estimation (based on tricuspid regurgitant jet velocity), RV size and function and pulmonary valve acceleration time that combine to give a risk stratification for PH with those at intermediate or high risk recommended for further assessment (see ERS/ESC guidelines (Humbert et al, 2022) for further details). Current guidance recommends screening for PAH in SSc including echocardiography yearly (Humbert et al, 2022). Other imaging modalities including computed tomography pulmonary angiogram (CTPA) and cardiac MRI (Fig. 7) also demonstrate characteristic appearances in PAH. Both modalities may demonstrate dilatation of the right sided chambers and main pulmonary artery or a pericardial effusion (reflecting raised right atrial pressures). CTPA may also demonstrate contrast reflux into a, typically dilated, inferior vena cava. Cardiac MRI may show right ventricular systolic impairment with reduced ejection fraction as well as tricuspid and/or pulmonary valve regurgitation and septal flattening in systole (reflecting raised right ventricular systolic pressure).

Several multimodality algorithms have attempted to increase the specificity of detection in screening. For example, the "DETECT algorithm" can be applied to asymptomatic patients with SSc diagnosed >3 years and DLCO <60% (i.e., a cohort with an increased baseline risk), with a two-stage process to guide both when to echo and when to perform right heart catheterisation (Coghlan et al, 2014). Patients with a clinical suspicion of PH based on screening investigations should always be discussed with a specialist centre for consideration of right heart catheterisation which remains the diagnostic test of choice (Humbert et al, 2022).

Therapies

Several treatment options are available for SSc-PAH. Pulmonary vasodilation remains the mainstay of therapy with three classes of medications currently available that target distinct signalling pathways: PDE5i or guanylate cyclase stimulator (riociguat) which target the nitric oxide – cyclic guanylate monophosphate pathway; endothelin receptor antagonists (ERA, e.g., ambrisentan) acting on the endothelin pathway; and prostacyclin analogues (e.g., epoprostenol) or a prostacyclin receptor agonist (selexipag) acting on the prostacyclin pathway. Current guidance on initial treatment is to initiate low and intermediate risk patients on dual therapy with ERA and PDE5i whilst in high-risk patients a combination of medications from all three classes, including a parenteral prostanoid, is recommended (Humbert et al, 2022). There are a number of emerging therapies of interest in PAH targeting novel pathways including ones which may reverse the pulmonary vascular remodelling. Activin signalling inhibitors have shown efficacy in the treatment of PAH and are now licensed in the USA for treatment (Hoeper et al, 2023). Other particular areas

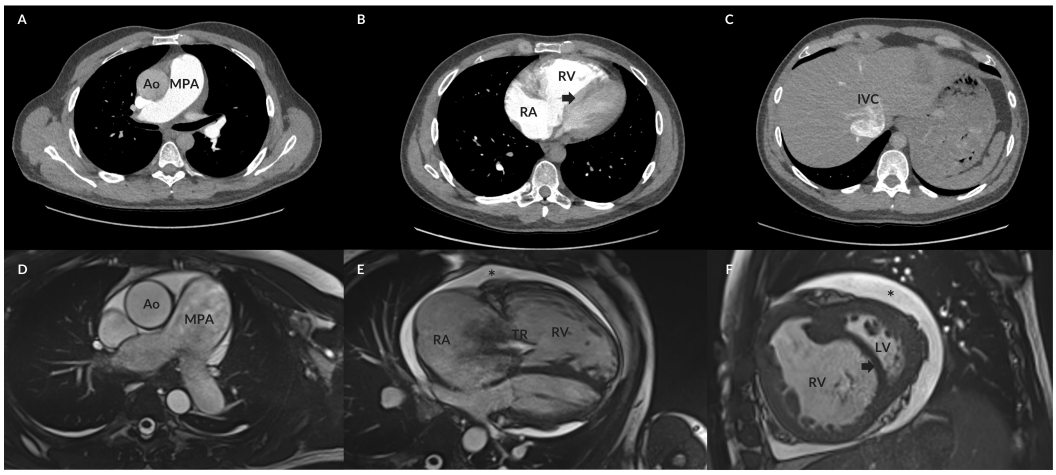

Fig. 7. Representative CTPA (row 1) and cardiac MRI (row 2) slices from a patient with group 1 pulmonary hypertension. (A) Enlargement of the MPA relative to the aorta at the same level. (B) Marked RA and RV dilatation with septal flattening. (C) Contrast reflux into dilated IVC and hepatic veins. (D) Marked MPA dilatation. (E) Gross RV and RA dilatation with severe TR, small global pericardial effusion. (F) Very severe RV dilatation, mild RVH, septal bowing in systole. Ao, Aorta; IVC, Inferior Vena Cava; MPA, Main pulmonary artery; RA, Right atrium; RV, Right Ventricle; RVH, Right Ventricular Hypertrophy; TR, Tricuspid regurgitation; CTPA, computed tomography pulmonary angiogram; *, pericardial effusion; →, interventricular septum. Permission has been obtained.

of interest include novel tyrosine kinase inhibitors (with imatinib being used off licence in end stage PAH) and monoclonal antibodies targeting other points in the activin/bmp pathway (Sommer et al, 2021).

Routine anticoagulation has now been shown to cause harm and is no longer recommended outside of other specific indications (e.g., pulmonary thromboembolism). In contrast to some other connective tissue diseases (systemic lupus erythematosus, mixed connective tissue disease) there is no evidence that immunosuppression alters the disease course of PAH in SSc (Humbert et al, 2022).

Once established on therapy, monitoring of response is generally through a composite score (Compera 2.0) utilising NT-ProBNP, 6MWD and WHO functional class. Interval reassessment with echocardiography, cardiac MRI, cardiopulmonary exercise testing or repeat right heart catheterisation is important especially if the patient is deteriorating despite therapy. Ongoing care is delivered under the supervision of specialist centres. As in SSc-ILD, SSc-PAH patients should be considered for lung transplant referral where appropriate and prompt referral is critical.

Conclusion

There have been recent advances in early diagnosis, identification of internal organ involvement, monitoring and treatment of SSc. This review has focused on early dcSSc, digital vasculopathy, ILD and PAH, but advances are also being made in the diagnosis and treatment of other aspects of the disease, as described in recently published national and international guidelines/recommendations. The key message for the general physician is that patients with SSc can present to any

specialty, and that there is now a great deal which can be done to improve quality of life and to reduce morbidity and mortality.

Key Points

- SSc is a multisystem connective tissue disease characterised by vascular abnormality, fibrosis, and immune dysfunction.
- The two major subtypes of SSc (limited cutaneous and diffuse cutaneous) are defined on the basis of the extent of the skin involvement, and have different natural histories, autoantibody associations and prognoses.
- The different SSc-specific autoantibodies (in addition to disease subtype and degree of internal organ involvement) help to predict disease trajectory and prognosis.
- Most patients present with Raynaud's phenomenon, which provides a window of opportunity for early diagnosis.
- There have been recent treatment advances, especially in the management of early diffuse cutaneous disease, digital vasculopathy (Raynaud's phenomenon and digital ulcers), interstitial lung disease and pulmonary arterial hypertension.
- Best practice management involves a multidisciplinary team, and involvement of different medical and surgical specialists.

Availability of Data and Materials

Not applicable.

Author Contributions

AH conceived the review topic and structure. AC, AH and WK conducted the literature search and analysis. Different sections were initially drafted by AC, AH and WK and the manuscript was compiled by WK. All authors contributed to important editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work and have read and approved the final manuscript.

Ethics Approval and Consent to Participate

Informed consent has been obtained from the patients.

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Conflict of Interest

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