# BSR and BHPR guideline for the treatment of systemic sclerosis – executive summary

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## Introduction

### *Scope and purpose*

Systemic sclerosis (SSc) is a complex, multi-organ disease requiring a comprehensive multidisciplinary guideline. This is a short summary of the guideline, which is available in full as supplementary material at Rheumatology Online (www.oxfordjournals.org).

### *Eligibility and exclusion criteria*

Patients are classified as having SSc based on current classification criteria (ACR/EULAR 2013 [1]). Other scleroderma spectrum diseases are not included in this document.

## Part A: General approach to SSc management

**Figure 1** summarises a general approach to management of SSc. Key source references and internet links are summarised for individual classes of treatment in **Table 1**.

### Importance of early diffuse SSc – current priorities and approach

Management of early diffuse cutaneous SSc (dcSSc) should occur within the framework of a multidisciplinary team.

### *Recommendations in management of early systemic sclerosis*

- Early recognition and diagnosis of dcSSc is a priority with referral to a specialist SSc centre (III C)
- Patients with early dcSSc should be offered an immunosuppressive agent: MTX, MMF or intravenous cyclophosphamide (CYC) (III/C), although the evidence base is weak. Some might later be candidates for autologous haemopoietic stem cell transplant (ASCT) ( see below)
- D-penicillamine is not recommended (IIa/C)
- Autologous haemopoietic stem cell transplant (ASCT) may be considered in some cases particularly where there is risk of severe organ involvement, balancing concerns about treatment toxicity (IIa/C)
- Skin involvement may be treated with either MTX (II,B) or MMF (III,C). Other options include CYC (III,C), oral steroid therapy (in as low a dose as possible to suppress symptoms, and with close monitoring of renal function; III,C) and possibly rituximab (III,C)
- Azathioprine or MMF should be considered after CYC to maintain improvement in skin sclerosis and/or lung function (III,C).

**Part B. Key therapies and treatment of organ-based disease**

**Raynaud's phenomenon (RP) and digital ulcers (DU)**

RP is almost universal and can be treated by vasodilators but benefit must be balanced against side effects. Around half of patients with SSc report a history of digital ulceration that reflects more structural vasculopathy. Severe DU are those causing or threatening tissue destruction or when 3 or more occur in one year. These should be considered for advanced therapy such as sildenafil, iloprost or bosentan [2].

***Recommendations for Raynaud's phenomenon in systemic sclerosis***

- First line treatments are calcium channel blockers (Ia,A) and angiotensin II receptor antagonists (Ib,C)
- Other treatments that may be considered are: selective serotonin reuptake inhibitors, alpha-blockers, and statin therapy (III,C)
- Phosphodiesterase-type 5 (PDE-5) inhibitors are being used increasingly for SSc-related RP (IIa,C)
- Intravenous prostanoid (e.g. iloprost) (Ia,B) and digital (palmar) sympathectomy (+/- botulinum toxin injection) should be considered in severe and/or refractory cases (III,D).

***Recommendations for digital ulcers (DU) in systemic sclerosis***

- Digital ulcers require integrated management by a multidisciplinary team: management includes local and systemic treatment (III,C)
- Oral vasodilator treatment should be optimized and analgesia should be optimised and any infection promptly treated (III, C)
- Sildenafil should now be used before considering intravenous prostanoids and bosentan in line with the current NHS England Clinical Commissioning policy (h[3] (I,A)
- In severe active digital ulceration, patients should receive intravenous prostanoid (Ia,B). In patients with recurrent, refractory digital ulcers, a PDE-5 inhibitor (IIa,B), or IV prostanoid (Ia,B), an endothelin receptor antagonist (ERA including bosentan) (Ia,B) should be considered
- Digital (palmar) sympathectomy (+/- botulinum toxin injection) may also be considered in severe and/or refractory cases (III,D).

**Lung fibrosis**

Up to 80% of SSc patients will develop ILD but this may be mild and stable. Immunosuppression should be considered when extensive or progressive disease is confirmed.

***Recommendations for lung fibrosis in systemic sclerosis***

- All SSc cases should be evaluated for lung fibrosis. Treatment is determined by extent and severity and likelihood of progression to severe disease (I, A)
- Cyclophosphamide by IV infusion is recommended (I, A/B) and MMF may also be used as an alternative or after cyclophosphamide (II, B).

**Pulmonary arterial hypertension**

For patients living in England, treatments are initiated through a designated Pulmonary Hypertension Centre (see NHS England A11/S/a) according to the national commissioning policy for treatment of PH (NHS England/A11/P/b and NHSCB/A11/P/a) reflecting expert recommendations [4].

***Recommendations for pulmonary arterial hypertension in systemic sclerosis:***

- Diagnosis should be based upon results of full evaluation of PH including right heart catheterisation and evaluation of concomitant SSc related cardiac or lung disease (I,A)
- Therapies licensed for PAH should be used in the UK Pulmonary Hypertension Centres taking account of the agreed commissioning policies (I,A/B).

**Gut disease**

Gastro-oesophaeal reflux is near universal and needs treatment. Other GI manifestations include constipation, bloating, small intestinal bacterial overgrowth, altered bowel habit and anorectal incontinence (overall management covered elsewhere [5]).

***Recommendations for gastrointestinal manifestations in systemic sclerosis***

The following therapeutic approaches and drugs are considered by experts to be of value in treatment of GI tract complications of SSc:

- Proton pump inhibitors and Histamine H2 receptor antagonists are recommended for treatment of gastro-oesophageal reflux and dysphagia and may require long term administration (III, C)
- Prokinetic dopamine agonists may be used for dysphagia and reflux (III, C)
- Parenteral nutrition should be considered for patients with severe weight loss refractory to enteral supplementation (III, C)

- Intermittent broad spectrum oral antibiotics (e.g. ciprofloxacin) are recommended for intestinal overgrowth and rotational regimes may be helpful (III, C)
- Anti-diarrhoeal agents (e.g. loperamide) or laxatives may be used for symptomatic management of diarrhoea or constipation that often alternate as clinical problems (III, C).

**Renal complications**

SSc renal crisis (SRC) causes severe hypertension, acute kidney injury and without treatment is often lethal. It affects 5–10% of SSc , predominantly the diffuse subset.

***Recommendations for treatment of scleroderma renal crisis:***

- Patients at risk of SRC should be followed closely and their blood pressure monitored at least weekly (III C)
- Prompt recognition of SRC and initiation of therapy with an ACE inhibitor offers the best opportunity for a good outcome (III, C)
- Other anti-hypertensive agents may be considered for managing refractory hypertension in conjunction with ACEi in SRC (III, C).

**Cardiac disease**

Clinically evident cardiac involvement includes diastolic or systolic heart failure, arrhythmia and conduction disturbances and has a significant mortality.

***Recommendations for treatment of cardiac manifestations of systemic sclerosis:***

Although the published evidence base is limited, experts have recommended the following treatment approach for cardiac complications of SSc.

**Systolic heart failure**

- Consider immunosuppression +/- pacemaker (IV,D)
- Consider the potential benefit of Implantable Cardio Defibrillator (ICD) (III,D)
- ACE inhibitors and carvedilol. Selective beta-blockers may be considered but consider aggravation of RP (IV, D).

**Diastolic heart failure – with preserved left ventricular ejection fraction (LVEF)**

- Diuretics including spironolactone and furosemide (IV,D)

- Calcium channel blockers have been shown to reduce the frequency of systolic heart failure in SSc with investigational evidence of cardiac abnormalities (III,D).

**Skin manifestations**

Treatment of skin thickening, assessed by modified Rodnan skin score, is central to management diffuse cutaneous SSc treatment and pruritus is common and troublesome in early stage disease.

***Recommendations for skin manifestations in systemic sclerosis:***

- Practical approaches to ensure adequately moisturised skin are essential, especially moisturisers that are lanolin-based (III, C).
- Antihistamines are often used for itch (III,C).
- Current treatment options for telangiectasia include skin camouflage and laser or intense pulsed light therapy (III,C).

**Calcinosis in SSc**

There is a very limited evidence base (mainly case reports and small series) to guide clinicians on the management of calcinosis in patients with SSc.

***Recommendations for treatment of calcinosis in systemic sclerosis***

- Calcinosis complicated by infection should be recognised early and treated with appropriate antibiotic therapy (III,D).
- Surgical intervention should be considered for severe, refractory calcinosis, which is severely impacting upon functional ability and quality of life (III,D).

**Musculoskeletal manifestations**

Musculoskeletal involvement includes tendinopathy, joint contractures and in some cases overlap arthritis.

***Recommendations for musculoskeletal manifestations in systemic sclerosis:***

- Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other complications such as skin disease (III, C).
- When arthritis or myositis are more severe, generally in the context of an overlap SSc syndrome, management is in line with similar clinical conditions occurring outside the context of SSc (III, C).

**Autologous stem cell transplantation (ASCT) as a treatment for poor prognosis early dcSSc**

Haematopoietic stem cells transplant registry data, several case reports and pilot studies in the USA and Europe in dcSSc demonstrated a rapid clinical improvement, but with important treatment-related mortality [6].

***Recommendation for autologous stem cell transplantation in systemic sclerosis:***

- Current evidence supports use of ASCT in poor prognosis diffuse SSc where patients do not have severe internal organ manifestations that render this treatment option highly toxic (Ib, B).

**Non-drug interventions**

Although the evidence base is limited non-drug interventions may have merit and are well tolerated.

***Recommendation for non-drug interventions in systemic sclerosis:***

- Specialist experience of SSc cases is likely to make non-drug interventions more effective and these approaches are popular with patients and can be expected to impact positively on the disease. More research is needed in this area (III, D).

**Part C. Service organization and delivery within NHS England**

Systemic sclerosis should be diagnosed promptly, investigated appropriately and managed within an integrated system of primary, secondary and tertiary level care.

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**Figure 1. Overview of management of systemic sclerosis**