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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 for selected patients where there is not severe early organ involvement leading to 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, angiotensin converting enzyme (ACE) inhibitors 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 (https://www.engage.england.nhs.uk/consultation/specialised-services-policies/user_uploads/bosntn-sildnfl-syst-sclerosis-pol.pdf) (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 in some cases 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 [3].

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[4]).

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 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 [5].

Recommendation for autologous stem cell transplantation in systemic sclerosis:

- Current evidence supports the 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.

Disclosure statement: All other authors have completed declaration of conflict of interest in accordance with the BSR guideline policy and these are available via BSR secretariat.

References

1. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737-47
2. Hughes M, Ong VH, Anderson ME, Hall F, Moinzadeh P, Griffiths B, Baildam E, Denton CP, Herrick AL. Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. Rheumatology. 2015 Jun 26. pii: kev201. [Epub ahead of print] PubMed PMID: 26116156.
3. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; Authors/Task Force Members. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2015 Aug 29. pii: ehv317. [Epub ahead of print] PubMed PMID: 26320113.
4. Hansi N, Thoua N, Carulli M, Chakravarty K, Lal S, Smyth A, Herrick A, Ogunbiyi O, Shaffer J, Mclaughlin J, Denton C, Ong V, Emmanuel AV, Murray CD. Consensus best practice pathway of the UK scleroderma study group: gastrointestinal manifestations of systemic sclerosis. Clin Exp Rheumatol. 2014 Nov-Dec;32(6 Suppl 86):S-214-21.
5. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, Schuerwegh AJ, Marijt EW, Vonk MC, Schattenberg AV, Matucci-Cerinic M, Voskuyl AE, van de Loosdrecht AA, Daikeler T, Kötter I, Schmalzing M, Martin T, Lioure B, Weiner SM, Kreuter A, Deligny C, Durand JM, Emery P, Machold KP, Sarrot-Reynauld F, Warnatz K, Adoue DF, Constans J, Tony HP, Del Papa N, Fassas A, Himsel A, Launay D, Lo onaco A, Philippe P, Quéré I, Rich É, Westhovens R, Griffiths B, Saccardi R, van den Hoogen FH, Fibbe WE, Socié G, Gratwohl A, Tyndall A; EBMT/EULAR Scleroderma Study Group. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014 Jun 25;311(24):2490-8.

Figure Legend

Figure 1. Overview of management of systemic sclerosis

The principles of current management of systemic sclerosis (SSc) are summarized. Once a confirmed diagnosis is established all patients can be designated as either limited (lcSSc) or diffuse (dcSSc) subset based upon the extent of skin thickening. Proximal skin involvement involving skin of trunk or proximal limbs is designated diffuse. Cases with overlap disease should be identified so that overlap features may be treated concurrent with SSc. All patients require symptomatic treatment and both limited and diffuse cases should be treated for vascular manifestations. Active, early dcSSc requires immunosuppressive treatment. In all cases of SSc vigilant follow up to determine significant organ based complications is mandatory.

Table 1. Evidence summary for drugs included in this guideline with specific recommendation for use in systemic sclerosis (SSc)

Drug class	Examples of agents	Mechanism of action	Indication	Comments	Summary of published evidence [text citation indicated]	Links to policies and recommendations
Immunosuppressive	Cyclophosphamide	Alkylating agent targeting DNA replication – broad spectrum immunosuppressive	Lung fibrosis Severe skin involvement	Usually given by monthly intravenous infusion. High doses used in ASCT protocols	Tashkin et al 2006 [44] Hoyles et al 2006 [45] van Laar et al 2014 [43] Kowal-Bielecka et al 2009 [2]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html
Immunosuppressive	Mycophenolate mofetil	Inhibits de novo purine pathway for DNA synthesis in lymphocytes	Lung fibrosis Severe skin involvement	Used for skin and lung fibrosis based upon cohort studies and small trials	Nihtyanova et al, 2007 [46] Mendoza et al, 2012 [47]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html
Immunosuppressive	Methotrexate	Inhibits folic acid metabolism for de novo thymidine synthesis and inhibits DNA, RNA and protein metabolism	Musculoskeletal and skin involvement	Two randomized trials and cohort studies suggest benefit for skin disease in SSc	Van den Hoogen et al, 1996 [48] Pope et al 2001 [49] Kowal-Bielecka et al 2009 [2]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html
Proton pump inhibitor	Lansoprazole, omeprazole etc.	Inhibits the final step in gastric acid secretion by parietal cells	Gastro-oesophageal reflux	Strong evidence base outside SSc but few disease specific studies. Generally immediate symptomatic benefit.	Pakozdi et al, 2009 [50]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html
ACE inhibitor	Ramipril, captopril quinapril, etc.	Inhibits renin-angiotensin system by blocking conversion of angiotensin I to II.	Scleroderma renal crisis	Case control study and cohort analysis confirm unequivocal benefit for SRC with improved survival. No evidence of prophylactic benefit for SRC or benefit for Raynaud's phenomenon	Steen et al 1990 [20] Steen et al 2000 [51] Hudson et al 2014 [52]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html
Selective PDE5 inhibitor	Sildenafil, tadalafil	Facilitates nitric oxide vasodilator activity by inhibiting cGMP breakdown by phosphodiesterase	Pulmonary arterial hypertension Digital ulcers	Licensed therapy for PAH based on pivotal trial including SSc cases. Emerging support for treatment of digital ulcers and Raynaud's. Included in NHS England SSc digital ulcer policy	Avouac et al. 2008 [53] Galie et al, 2005 [54] Badesch et al 2007 [55] Tingey et al 2013 [56] Galiè et al. 2013 [57]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html

		5				NHS England SSc DU policy: bosntn-sildnfl-syst-sclerosis-pol.pdf
Endothelin receptor antagonist	Bosentan, Ambrisentan, Macitentan	Blocks endothelin 1 signaling by inhibiting specific cell surface receptors	Pulmonary arterial hypertension Digital ulcers	Licensed therapy for PAH based on pivotal trials including SSc cases. Bosentan licensed for prevention of new digital ulcers in SSc	Liu et al, 2009 [58] Avouac et al. 2008 [53] Denton et al, 2009 [59] Denton et al, 2006 [60] Pulido et al, NEJM, 2013 [61] Korn et al 2004 [62] Mattuci et al 2011 [63] Galiè et al. 2013 [57]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html Galiè et al. J Am Coll Cardiol. 2013;62:D60-72. http://www.pulmonaryhypertensioncentres.co.uk/book/index.html NHS England SSc DU policy: bosntn-sildnfl-syst-sclerosis-pol.pdf
Prostacyclin analogue	Iloprost, Epoprostenol, Treprostinil	Stimulates prostanoid signaling via IP receptor and raises cAMP levels in target cells	Pulmonary arterial hypertension Digital ulcers and vasculopathy	Licensed therapy for PAH based on pivotal trial including SSc cases. Support for treatment of digital ulcers and Raynaud's. Included in NHS England SSc digital ulcer policy	Badesch et al, 2010 [64] Tingey et al 2013 [56] Galiè et al. 2013 [57]	EULAR SSc recommendations http://ard.bmj.com/content/68/5/620 UKSSG best practice recommendations http://www.scleroderma-royalfree.org.uk/UKSSG.html Galiè et al. J Am Coll Cardiol. 2013;62:D60-72. http://www.pulmonaryhypertensioncentres.co.uk/book/index.html NHS England SSc DU policy: bosntn-sildnfl-syst-sclerosis-pol.pdf
Soluble guanylate cyclase agonists	Riociguat	Increases cGMP synthesis intracellularly, cGMP is a downstream mediator of NO actions	Pulmonary arterial hypertension	Licensed therapy for PAH based on pivotal trial including SSc cases.	Ghofrani et al, 2013 [65] Galiè et al. 2013 [57]	Galiè et al. J Am Coll Cardiol. 2013;62:D60-72. http://www.pulmonaryhypertensioncentres.co.uk/book/index.html

Please see full guideline text for citation details for references listed above. The guideline is available as supplementary material at Rheumatology Online (www.oxfordjournals.org)

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