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BSR Guidelines

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The 2024 British Society for Rheumatology guideline for management of systemic sclerosis—executive summary

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Abstract

This guideline was developed according to the British Society for Rheumatology Guidelines Protocol by a Guideline Development Group comprising healthcare professionals with expertise in SSc and people with lived experience, as well as patient organization representatives. It is an update of the previous 2015 SSc guideline. The recommendations were developed and agreed by the group and are underpinned by published evidence, assessed by systematic literature review and reinforced by collective expert opinion of the group. It considers all aspects of SSc including general management, treatment of organ-based complications, including cardiopulmonary, renal and gastrointestinal tract manifestations, as well as broader impact of disease. Whilst it is focused on adults with SSc we expect that the guideline will be relevant to people of all ages and expert input and review by paediatric rheumatologists and other relevant specialists considered where the guideline was, or may not be, applicable to young people with SSc and juvenile-onset disease. In addition to providing guidance on disease assessment and management the full guideline also considers service organization within the National Health Service and future approaches to audit of the guideline. The lay summary that accompanies this abstract can be found in Supplemental information 1.

Keywords: scleroderma, systemic sclerosis, interstitial lung disease, guideline, management.

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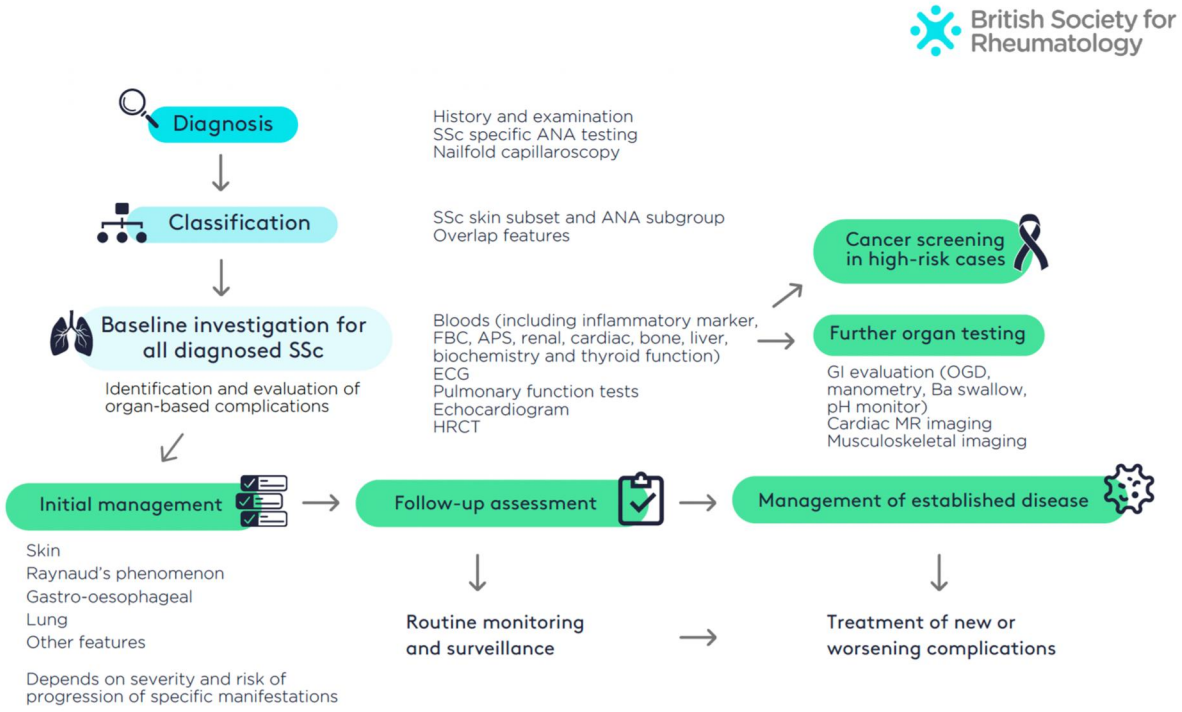
Graphical abstract



This guideline was developed in line with the British Society for Rheumatology (BSR)'s Guidelines Protocol [1].

Need for guideline

Updating the BSR SSc guideline was required to reflect important changes in management of organ-based complications together with changes in National Health Service (NHS) England prescribing policies (e.g. digital ulcers) that now mean that the 2015 guideline no longer reflects current best practice and does not reflect all the available high-quality evidence that can underpin management of SSc [2]. The updated guideline includes consideration of all ages of people affected by SSc, with specific consideration of the relevance to children and adolescents with SSc including transition into adult services [3].

Objectives of the guideline

This guideline offers systematic and evidence-based recommendations to support UK clinicians in management of SSc across the whole life course, based upon systematic literature review [4] and expert consensus. Strength of recommendation (1 or 2), quality of supporting evidence/level of evidence (A, B, C) and strength of agreement (SoA) across the guideline working group (percentage) is provided for each statement.

Target audience

The target readership is clinicians involved in management of people with SSc. It will also be relevant to primary care clinicians, allied health professional involved in the management of SSc and all people with SSc.

Areas the guideline does not cover

Diagnosis, classification and investigation of localized scleroderma (morphoea) and of 'scleroderma-like' conditions (e.g. scleroedema, scleromyxeodema, fasciitis, nephrogenic systemic fibrosis) will not be considered in this guideline.

Guideline structure

I. Early diagnosis, classification and stratification of risk

What is the best approach to early diagnosis and classification?

Recommendation for diagnosis and classification of SSc:

i) Clinical diagnosis of SSc should be guided by validated classification criteria (**1A**, 96%).
ii) Skin subset and SSc associated autoantibody subset should be used to stratify for risk of specific organ-based complications (**1B**, 97%).
iii) Assessment of nailfold microcirculation (capillaroscopy) should be performed as part of initial SSc assessment and when a diagnosis of SSc is suspected (**2C**, 96%).

II. Global management of SSc

Overarching principles of management of all cases of SSc

A comprehensive approach to global management for the current updated guideline is presented in Fig. 1. This covers early diagnosis and stratification for follow-up. Early-stage dcSSc deserves particular attention because of the high risk

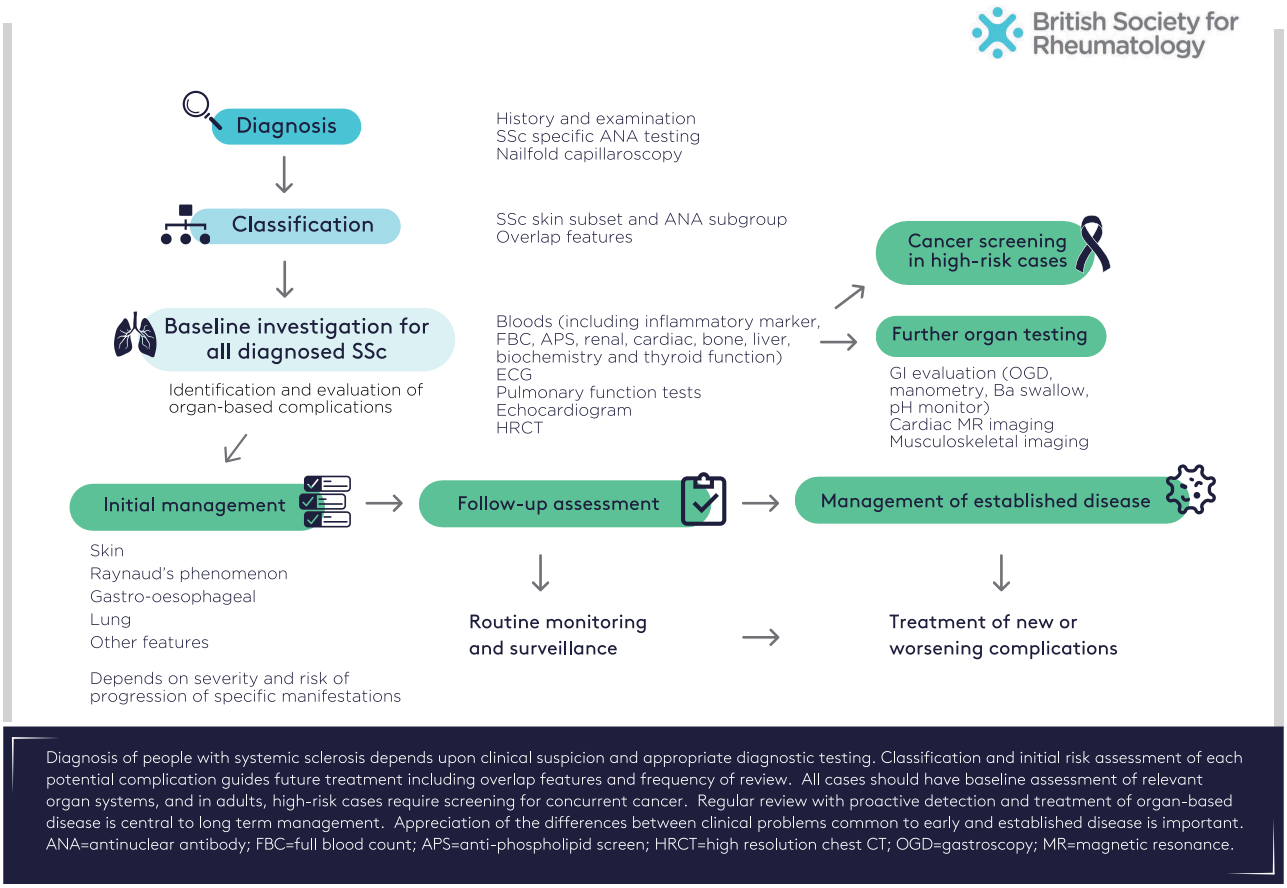


Figure 1. Overarching principles for management of SSc

of early progression and development of organ-based complications.

What are the best treatments for early dcSSc?

Recommendation for treatment of early dcSSc:

i) Early dcSSc is defined by disease duration from first non-RP manifestation of <3 years, although cases may show improvement in skin from 18 months, and some have clinical features of skin worsening and progression over >5 years (**2C**, 94%).
ii) All early dcSSc cases should be considered for immunosuppression with MMF as treatment for skin fibrosis. Alternatively, MTX may be used for skin fibrosis (**1C**, 96%).
iii) Multi-disciplinary and multi-speciality care should be available. All early dcSSc cases should be assessed in a specialist centre for consideration of clinical trials and specialized treatments including biological agents such as rituximab or tocilizumab and autologous haematopoietic stem cell transplant (AHSCT) (**2B**, 97%).
iv) All paediatric SSc should be managed in a tertiary paediatric rheumatology service with multi-disciplinary and multi-speciality input (**1C**, 99%).

Cancer screening in SSc

When and how should people with SSc be screened for malignant disease?

It is now well established that some cases of SSc are associated with concurrent malignancy. However, risk is low overall and so a patient-specific approach to screening or investigation for cancer is suggested by the expert group.

Recommendation for cancer screening in adults with SSc:

i) Cases over 65 years or with a clinical phenotype of paraneoplastic SSc [overlap DM; anti-RNA polymerase III (ARA), palmar fibrosis; red flag symptoms of malignancy] should have baseline screening with breast examination, lymphoreticular assessment, fecal immunochemical testing (FIT) and endoscopy if indicated (**2C**, 95%).
ii) In addition, chest, abdomen and pelvis (CAP) CT scan with contrast, and/or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT scanning should be considered on an individual basis (**2C**, 95%).
iii) Follow-up screening should be guided by clinical suspicion and in high-risk cases with history of Barrett's oesophagus or previous treatment with high cumulative dose of CYC (**2C**, 94%).

III. Treatment of organ-based complications of SSc

Key therapies and treatment of organ-based disease in SSc

For all people diagnosed with SSc there should be a focus on identification and treatment of specific complications and organ-based disease [5]. The following section summarizes guidance for managing common aspects of SSc. The topics

are informed by key questions defined during the scoping of this guideline underpinned by the results of associated systematic literature reviews.

Cardio-pulmonary complications

Cardiorespiratory manifestations are critical in managing SSc, accounting for most SSc-related deaths as well as major morbidity [6]. There has been progress in management of all three aspects since the previous BSR guideline.

Interstitial lung disease (lung fibrosis)

What is the best management for interstitial lung disease in SSc?

Recommendation for screening and monitoring of interstitial lung disease in SSc (SSc-ILD):

i) All SSc cases should be screened for ILD with baseline chest high-resolution CT (HRCT) and pulmonary function tests (PFTs; including spirometry and gas transfer) (**1B**, 97%).
ii) In confirmed SSc-ILD, PFTs should be repeated every 3–6 months in recently diagnosed SSc (first 3–5 years) and considered every 6–12 months thereafter (**1B**, 96%).
iii) Chest HRCT should be repeated to evaluate ILD progression if worsening symptoms/PFTs and to exclude alternative causes of worsening. Consider repeating chest HRCT to compare with baseline after 1–3 years, or pre-treatment changes (**2B**, 97%).

Recommendation for treatment of SSc-ILD:

i) Treatment is determined by risk factors associated with extensive or progressive ILD including recent SSc diagnosis, diffuse skin disease, raised inflammatory markers, ATA positive, CT extent and lung function impairment together with longitudinal behaviour. Informed choice should be considered in selecting treatment (**1B**, 99%).
ii) MMF is recommended as first-line treatment. Rituximab and/or CYC by i.v. infusion may be used as an alternative (**1B**, 97%).
iii) Consider tocilizumab as first-line treatment in early dcSSc with raised inflammatory markers and ATA positivity, independent of the extent of ILD on CT (**1A**, 92%).
iv) Consider adding rituximab or tocilizumab to background treatment with MMF or other immunosuppressant, as rescue immunomodulatory therapy (**2C**, 96%).
v) Nintedanib is recommended in progressive pulmonary fibrosis despite immunosuppressant treatment, dependent on tolerability, and may be considered as first-line treatment in combination with MMF in extensive fibrosis (**1B**, 98%).
vi) Consider reducing/stopping immunosuppression in severe fibrosis experiencing recurrent infections particularly if elderly/frail. Consider nintedanib as sole treatment in extensive fibrosis (extensive traction bronchiectasis/bronchial dilatation and/or honeycombing) and with recurrent infections on immunosuppressants (**2C**, 95%).
vii) Supportive treatment is important including pulmonary rehabilitation and management of infection, gastro-oesophageal reflux, nutrition, resting hypoxaemia or severe exertional hypoxaemia (long-term oxygen and/or ambulatory oxygen therapy) (**1C**, 99%).
viii) Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza, *Streptococcus pneumoniae* and herpes zoster (using a non-live vaccine) is recommended and consider antibiotic prophylaxis for recurrent infections and *Pneumocystis jirovecii* pneumonia (PJP) prevention—especially on RTX and with combination immunosuppression (**2B**, 99%).
ix) Referral for lung transplantation is appropriate in some cases although comorbidity, particularly oesophageal involvement, may limit eligibility (**2C**, 96%).

Pulmonary hypertension

What is the best management for pulmonary hypertension in SSc?

Recommendation for screening and management of SSc pulmonary arterial hypertension (SSc-PAH):

i) Screening for PAH should be undertaken in all people with SSc on an annual basis. This would typically comprise PFTs, echocardiography, N-terminal pro B-type natriuretic peptide (NTproBNP) and use DETECT tool in appropriate people (**1B**, 98%).
ii) In children, need for right heart catheterization for diagnosis of PAH is made on a case-by-case basis. Diagnosis and treatment initiation should be through the designated paediatric Pulmonary Hypertension Centre (**1C**, 99%).
iii) Several classes of drugs have shown a beneficial effect in randomized controlled trials for the treatment of Group I precapillary PAH with mean pulmonary artery pressure $\geq$25 mmHg and this is generally used as the threshold for initiation of PAH drug therapy (**1A**, 94%). PAH therapies should be initiated and monitored by a designated PH centre.
iv) The following classes of drug are used to treat PAH-SSc: phosphodiesterase type 5 inhibitors (PDE5i) (tadalafil, sildenafil), endothelin receptor antagonists (ambrisentan, macitentan, bosentan), prostaglandins (e.g. inhaled iloprost, i.v. epoprostenol, s.c. or inhaled treprostinil), prostacyclin receptor agonist (selexipag) and riociguat (sGC stimulator). Combining riociguat and any PDE5i is contraindicated due to risk of hypotension (**1A**, 99%).
v) For adults living in England, the diagnosis must be made by right heart catheter and treatments are initiated through one of the designated Pulmonary Hypertension Centres (see NHS England A11/S/a) and according to the national commissioning policy for targeted therapies for the treatment of PAH in adults (NHS England/A11/P/b and NHSCB/A11/P/a) (**1B**, 99%).
vi) People should also receive supportive medical treatment, such as diuretic therapy, specialist input for management of arrhythmia, correction of iron deficiency, supervised exercise training, oxygen (long-term oxygen for at least 15 h a day if they are hypoxic at rest with an arterial partial pressure of O_2 <8 kPa (SaO_2 <92%) and/or ambulatory oxygen if they experience exertional desaturation (SpO_2 $\leq$88% on a six-minute walk test), vaccination against SARS-CoV-2, influenza and *S. pneumoniae*, contraception and pregnancy counselling for women of child-bearing age, and psychosocial support (**2B**, 99%).
vii) Anticoagulation with warfarin is not recommended in SSc-PAH (**1B**, 98%).

SSc cardiac involvement

What is the best management for cardiac involvement in SSc?

Cardiac involvement is recognized as an important cause of morbidity and mortality in people with SSc. Differentiation of primary cardiac involvement from SSc is important. Management of cardiac failure with reduced or preserved left ventricular ejection fraction is summarized in Supplementary Data S1, available at *Rheumatology* online.

Recommendation for screening and diagnosis of SSc primary heart involvement (SSc-pHI):

i) A multi-speciality team should inform the management and treatment of possible SSc-pHI and other cardiovascular pathology should be excluded (**1C**, 100%).
ii) Screening for pHI (in asymptomatic individuals) should be undertaken in all people with SSc on an annual basis. This would typically comprise ECG, echocardiography and serum troponin (ideally, I or T) and NTproBNP (or BNP in renal disease) (**2C**, 96%).
iii) Where pHI is suspected, diagnostic work up should include cardiovascular magnetic resonance (CMR). Endomyocardial biopsy should only be considered in selected cases, after exclusion of coronary artery disease. Holter monitor should be performed to detect arrhythmic burden (**2C**, 96%).
iv) Screening with CMR (or other sensitive cardiovascular imaging) may be considered in high-risk individuals (male gender, diffuse cutaneous skin subset, anti-topoisomerase I, early disease, presence of interstitial lung disease, peripheral myositis and other inflammatory manifestations) (**2C**, 95%).
v) In juvenile SSc (jSSc) with suspected pHI, a formal assessment by a paediatric cardiologist is recommended (**1C**, 100%).

Recommendations on the use of immunosuppressive treatment of SSc-pHI:

i) Immunosuppression with MMF should be considered in SSc-pHI when investigation suggests myocardial inflammation. Glucocorticoid may also be added to MMF [although risk of scleroderma renal crisis (SRC) in adults should warrant caution] (**2C**, 95%).
ii) Other biological DMARDs (rituximab, tocilizumab) may be added to MMF therapy if appropriate, and/or CYC (**2C**, 89%).
iii) Immunosuppression with MMF may be considered for SSc-pHI with evidence of myocardial fibrosis, although robust studies are lacking. Evidence of myocardial fibrosis may support additional treatment as indicated in (ii) (**2C**, 92%).

AHSCT as a treatment for SSc

Which people with SSc should be considered for AHSCT?

The efficacy of AHSCT in dcSSc is well shown but studies have also defined potential treatment-related toxicity and mortality and this, together with the invasive and intense nature of the procedure and resource requirements, limits applicability [7].

Recommendation for AHSCT in SSc:

i) AHSCT may be considered in selected dcSSc where benefit is likely to be greater than treatment-related risk. Severe internal organ disease precludes AHSCT and should be carefully evaluated before considering this treatment in adults (**1B**, 96%).
ii) AHSCT should be delivered within an experienced specialized centre for both adults and children (**1B**, 98%).
iii) Use of AHSCT in adults with later-stage dcSSc and in lcSSc requires further data and is not recommended (**2C**, 90%).
iv) AHSCT may be considered in children and young people with SSc who have severe or refractory disease, regardless of disease subset (**2C**, 92%).

Digital vasculopathy

Digital vasculopathy leads to Raynaud's and digital ischaemia with development of complications of severe vasculopathy including gangrene, ulceration, and infection of superficial and deep tissues [8]. In children, similar approaches used to adults but consider availability of jSSc dosing and pharmacokinetic data.

What is the best management for digital ulceration in SSc?

Recommendation for digital ulcers (DU) in SSc:

i) Severe digital vasculopathy with new tissue necrosis or critical ischaemia is an emergency requiring urgent clinical assessment (preferably within 48 h) (**1C**, 95%).
ii) Sildenafil (or tadalafil) is recommended as first line agent in DU healing and secondary prevention and bosentan as second-line treatment in line with NHS England policy 210302P [1911] (**1C**, 99%).
iii) I.v. prostanoids may be considered to promote DU healing (1C, 98%).
iv) Consider anti-platelet therapy in DU disease (particularly if local necrosis) (**2C**, 94%).
v) Digital (palmar) sympathectomy (with or without botulinum toxin injection) may be considered in those intolerant to systemic vasodilator meds and recurrent DU at a single site (**2C**, 95%).
vi) Debridement of DU may promote healing (**2C**, 93%).
vii) There should be access to SSc/CTD specialist wound care services to prevent and treat skin ulcers (**1C**, 98%).

What is the best management for RP?

Guideline recommendation for RP in SSc:

i) Although therapeutic benefits appear modest, calcium channel blockers and other vasodilators should be considered in management of SSc-RP (**1B**, 100%).
ii) PDE5i (e.g. sildenafil, tadalafil) and i.v. prostanoids are effective as second-line agent for refractory SSc-RP (**1B**, 99%).
iii) Consider anti-platelet therapy (aspirin, clopidogrel) and statins in refractory SSc-RP given strong therapeutic rationale despite limited evidence (**2C**, 93%).
iv) For rescue therapy in severe SSc-RP, i.v. prostanoids may be considered (**1C**, 99%).
v) Digital (palmar) sympathectomy (with or without botulinum toxin injection) which may be considered in severe and/or refractory cases of SSc-RP—particularly if systemic vasodilator therapies poorly tolerated, e.g. low basal blood pressure (**2C**, 93%).

Gastrointestinal tract disease

What is the best management for gastrointestinal complications of SSc?

Gastrointestinal (GI) tract manifestations are the most frequent organ-based complication of SSc. The following recommendations represent components of current best practice approaches for GI SSc.

Recommendation for GI manifestations in SSc:

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

i) Optimize and ensure compliance to general/lifestyle measures in SSc with oesophageal symptoms (e.g. gastro-oesophageal reflux) (**1C**, 99%).
ii) Proton pump inhibitors and/or histamine H2 receptor antagonists are recommended for treatment of symptomatic gastro-oesophageal reflux and dysphagia (**1C**, 99%).
iii) Promotility agents including prokinetic dopamine antagonists may be used for dysphagia and reflux (**1C**, 98%).
iv) In refractory gastro-oesophageal reflux disease, consider examination of upper GI tract structure and motility, and confirmation of acid reflux (e.g., pH testing) (**2C**, 96%).
v) Parenteral nutrition should be considered for those with severe weight loss and/or malnutrition (including high risk), which is refractory to enteral supplementation (**1B**, 97%).
vi) In jSSc, nutrition, growth and pubertal status should be actively assessed, monitored and pro-actively managed if faltering growth is noted which includes liaison with tertiary paediatric gastroenterology and paediatric dietetic expertise (**1C**, 99%).
vii) Intermittent broad-spectrum oral antibiotics (e.g. ciprofloxacin) are recommended for symptomatic small intestinal bacterial overgrowth, and rotational regimes may be helpful. Rifaximin may be an effective alternative in refractory cases (**2B**, 95%).
viii) Anti-diarrhoeal agents (e.g. loperamide) or laxatives may be used for symptomatic management of diarrhoea or constipation, which often alternate as clinical problems, and non-SSc causes should be excluded (**1C**, 96%).
ix) Surgical intervention for GI complications of SSc should generally only be considered when essential and no alternative (**1C**, 97%).
x) Pelvic floor physiotherapy including anorectal biofeedback training may be considered in selected cases with incontinence (**2C**, 91%).

Renal complications

What is the best management for SRC?

The most serious renal complication of SSc is SRC with thrombotic microangiopathy with acute kidney injury in the context of SSc, generally associated with significant new-onset hypertension [9].

Recommendation for treatment of SRC:

i) Angiotensin-converting enzyme inhibitor should be initiated or continued in all cases of diagnosed SRC and up titrated to maximum therapeutic dose (**1A**, 100%).
ii) Other antihypertensive drugs are often required to control hypertension and can be added based on clinical need (**1B**, 99%).
iii) In adults, glucocorticoid treatment should be minimized in SSc due to association with increased SRC (**1A**, 96%).
iv) When required, renal replacement therapy should initially use the least haemodynamically demanding approach (e.g. haemofiltration or peritoneal dialysis) (**1C**, 99%).
v) Renal biopsy should be considered when diagnosis is uncertain (especially if substantial proteinuria, ANCA+, overlap serology SLE, etc.) (**1C**, 99%).
vi) Referral for renal transplantation may be considered after 12 months in cases without features suggesting significant renal recovery (**1B**, 99%).

Skin complications

What is the best management for non-fibrotic skin manifestations in SSc?

As well as skin thickening and fibrosis, there are many other dermatological aspects of SSc, and these require expert management.

Recommendation for non-fibrotic skin manifestations in SSc:

i) Practical approaches, maintaining adequately moisturized skin, are essential. It is strongly recommended to avoid frequent bathing with harsh deodorant soaps, and emollients should be used as soap substitutes where possible (**2C**, 97%).
ii) Itch is associated with disease activity and so other disease targeted treatment may result in improvement. Antipruritic moisturizers and antihistamines are often used for itch, and the sedative effects of the latter agents may be beneficial at night-time. In adults, expert opinion suggests low-dose opioid antagonists, e.g. naloxone and naltrexone, and other options including gabapentin and pregabalin, and low-dose antidepressants such as mirtazapine, may be considered (**2C**, 89%).
iii) Current management options for telangiectasia include (green) skin camouflage and injected sclerosing agents or thermocoagulation methods such pulsed dye laser or intense pulsed light therapy (**2C**, 95%).
iv) Consider autologous fat transfer for facial fat loss (**2C**, 89%).

Musculoskeletal disease

What is the management for musculoskeletal manifestations of SSc?

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

Recommendation for musculoskeletal manifestations in SSc:

i) Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other complications, such as skin disease (**1C**, 95%).
ii) When arthritis or myositis (or non-inflammatory musculoskeletal pain) is 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 (**1C**, 93%).

Calcinosis in SSc

What is the management for calcinosis in SSc?

There is a very limited evidence base to guide clinicians on the management of calcinosis in patients with SSc, but practical approaches are considered important to mitigate impact. This is a key area for the research agenda (see full guideline).

Recommendation for management of calcinosis in SSc:

i) Superadded infection of calcinosis should be recognized early and treated with appropriate antibiotic therapy (**1C**, 99%).
ii) Surgical intervention should be considered in severe, refractory calcinosis, which is severely impacting upon functional ability and quality of life (**1C**, 95%).

Fatigue, and quality of life

What are the best interventions for general impact of SSc on health status and quality of life, including fatigue?

Recommendation for fatigue and quality of life in SSc:

i) Consider the impact of diagnosis and disease on health-related quality of life in all people with SSc (**2C**, 99%).
ii) Physical and occupational therapy are recommended for the management of musculoskeletal impairment in SSc to improve function and may have a role in improving quality of life, pain and fatigue (**2C**, 99%).

Neurological complications

What is the best management for neurological complications of SSc?

A range of neurological complications of SSc have been reported. Cranial nerve involvement is well recognized and includes trigeminal neuropathy as well as trigeminal neuralgia.

Recommendation for neurological complications in SSc:

i) Neurological complications of SSc require multi-speciality management with careful exclusion of other relevant causes (**1C**, 97%).
ii) Peripheral nerve abnormalities occur in SSc including CTS, peripheral neuropathy and cranial nerve dysfunction that can be neuralgia or neuropathy, most often affecting the trigeminal nerve (**1C**, 97%).
iii) Peripheral sensory neuropathy of the feet is common and disabling in adults with SSc and investigation should be prompted by clinical suspicion (**2C**, 93%).

Pregnancy and reproductive health

What is the management for pregnancy and reproductive health in SSc?

SSc has a major impact on reproductive health. There is substantial unmet need related to sexual dysfunction in male and female patients [10].

Recommendation for pregnancy and reproductive health in SSc:

i) Sexual dysfunction should be sensitively discussed with engagement of specialist gynaecology, urology and sexual health clinical services (**1C**, 98%).
ii) When considering planned pregnancy in SSc it is important to identify any significant renal, cardiac or lung complications, as well as to discontinue medication that may be harmful and replace with safer alternatives (e.g. AZA) if necessary (**1C**, 99%).
iii) SSc should be judged stable and pregnancy management should occur within the context of robust medical support and integrated multi-disciplinary care (**2C**, 100%).

IV. Organization of services for SSc within the NHS

Service organization and delivery within NHS England and UK devolved nations including paediatric and transitional services

The working group recognizes that there are challenges delivering high quality equitable care for SSc across England and the devolved nations. It is important to ensure that adult services link to paediatric, adolescent and transitional services for SSc. All children with jSSc should be managed by tertiary paediatric services with multi-disciplinary and multi-specialist expertise. Given the rarity of jSSc, close links with adult SSc centres has benefits for sharing expertise and allowing smooth transition of paediatric patients to adult services. Transition from paediatric to adult services should be carefully planned and in line with National Institute for Health and Care Excellence guideline.

Approaches to audit of the guideline

Potential audit approaches and standards are included in the Full Guideline.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

No new data were generated in support of this work.

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