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BSR and BHPR guideline for the treatment of systemic sclerosis

- full guideline for on-line publication as supplement to executive summary

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Key words: scleroderma, systemic sclerosis, management, Raynaud's phenomenon, lung fibrosis, pulmonary hypertension, digital ulcers

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Introduction

Background

Systemic sclerosis (SSc) is a heterogeneous autoimmune rheumatic disease that falls within the SSc spectrum of disorders. It is characterized by fibrosis of the skin and internal organs together with vascular manifestations including secondary Raynaud's phenomenon, digital ischemia, pulmonary arterial hypertension and renal crisis. Within UK, SSc has an annual incidence of 3.7/million and a prevalence of 31-88/million with a peak age of onset of 40-50 years. Recent classification criteria have been developed and major disease subsets are recognized, notably limited or diffuse cutaneous subsets [1]. It can occur in overlap with other autoimmune rheumatic diseases.

Need for guidelines

SSc is a complex, multi-organ disease associated with a high morbidity and mortality and a comprehensive multidisciplinary guideline is therefore required. This guideline will therefore provide advice and rationale for health professionals in making choices and decisions in managing this disease. European League against Rheumatism (EULAR) has published a summary of evidence-based recommendations for management of SSc [2].

Target audience

The target audience is rheumatologists, dermatologists, general physicians and organ based specialists treating complications of SSc including nephrologists, cardiologists, gastroenterologists, respiratory physicians, cardiologists as well as trainees, specialist nurses and other healthcare professionals.

Methodology

This guideline was developed in accordance with the current BSR Standards Audit and Guidelines working group (SAGWG) protocol for developing evidence based guidelines. A comprehensive literature review was undertaken using the PUBMED and MEDLINE databases for English-language papers (up to and including 30th June 2014) using the search terms "systemic sclerosis" or "scleroderma" in combination with additional terms according to each topic within the guideline. Further relevant papers were identified from the reference lists of retrieved articles. Two reviewers independently extracted information from each study.

The literature reviews were used to inform and underpin discussion during a series of face to face meetings and telephone conference calls as the guideline was developed and drafted. Designated

members of the group took the lead on each section of the guideline which was then refined and approved by consensus. An associated executive summary represents a summary of the full guideline document. The recommendations were graded for level of evidence and strength by the working party according to the Royal College of Physicians' Concise Guidance to Good Practice (<http://www.rcplondon.ac.uk/resources/clinical-resources/concise-guidance-good-practice>). Based on the level of evidence and the strength of the recommendation, each recommendation was subjected to a vote and a minimum 75% agreement was considered as consensus.

It is expected that the guideline will be updated after 5 years or earlier if there is significant development in key areas in management of SSc.

Eligibility and exclusion criteria

Patients are classified as having a diagnosis SSc based on current classification criteria (ACR/EULAR 2013 [1]) including those with overlap with other connective tissue diseases including inflammatory arthritis, systemic lupus erythematosus (SLE), myositis and vasculitis. The statements made in this guideline should therefore be considered in conjunction with the guidelines on management of these other associated diseases. Localised SSc, juvenile SSc and SSc mimics (e.g. scleroedema, scleromyxoedema, nephrogenic systemic fibrosis and eosinophilic fasciitis) were not included in this document. Care of children with SSc below 16 years of age should be led by a Paediatric Rheumatology service, who may wish to involve adult Rheumatology colleagues as needed for guidance. From 16 years of age cases should be transitioned into adult SSc clinics and the present guideline applies for treatment.

Part A: General approach to SSc management

The heterogeneous nature of SSc is an important consideration in management since the timing and frequency of the development of specific features of SSc varies. Operationally the key issues are the diagnosis of SSc, the classification into major subsets based upon the extent of skin sclerosis, the potential use of other criteria to subgroup patients with SSc in meaningful ways and the definition of onset of the disease which has relevance especially for clinical research and trial recruitment. SSc can be divided into distinct subsets of disease. The major subsets of limited and diffuse cutaneous SSc based upon the extent of skin thickening. Overlap SSc cases that account for up to 20% of cases in many published cohorts and can be classified as limited or diffuse SSc but more often fit into the limited skin subset. **Figure 1** summarises a general approach to management of SSc that is informed

by this guideline and the 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) must occur within the framework of a multidisciplinary team and this permits broad approach, education and medical and non-medical aspects of the disease to be addressed. In general there needs to be a baseline assessment of internal organ function and attention to symptomatic treatment of common or universal symptoms such as Raynaud's phenomenon, gastro-oesophageal reflux and pruritus. Most important though is consideration of initiation of immunosuppressive therapy that may modify skin and internal organ manifestations. Any patient with dcSSc of less than 3 years duration should be considered for treatment with a broad-spectrum immunosuppressive agent, although the evidence base for this approach is weak [2]. The currently used agents include mycophenolate (MMF), methotrexate (MTX) and cyclophosphamide (CYC). There is some evidence base to support the use of these agents but few controlled trials and other agents are under evaluation. Observational cohort studies and retrospective case series have been published. Outcome assessment is confounded by natural history of dcSSc and this is variable. However it is clear that there is substantial capacity for spontaneous improvement in skin disease as this has been observed in many patients enrolled into the placebo arm of randomised controlled trials [3]. Early identification of suspected cases of dcSSc is important and all of these patients should be seen in a specialist SSc centre although shared care with local specialists is usually the most appropriate strategy and this is central to the long-term management plan of these patients.

Recommendations in management of early systemic sclerosis:

- Early recognition and diagnosis of dcSSc is a priority with referral to a specialist SSc centre. Patients with early dcSSc should be offered an immunosuppressive agent [4]: MTX, MMF or intravenous cyclophosphamide (CYC) (III/C) Final consensus 90%. Some cases might later be candidates for autologous haemopoietic stem cell transplant (ASCT) ([5] see below). D-penicillamine is not recommended (IIa/C) [6] Final consensus 100%.
- The choice of agent and route of administration depend upon careful clinical assessment to detect internal organ involvement and risk of adverse effects. Final consensus: 100%.
- Skin involvement may be treated with either MTX (II,B) [7] or MMF (III,C) Final consensus 100%. 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) Final consensus 90%.

- Azathioprine or MMF should be considered after CYC to maintain improvements in skin sclerosis and/or lung function (III,C) Final consensus 90%.

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

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

RP is characterized by vasospasm affecting the extremities on exposure to change in ambient temperatures or emotional stressors leading to acral ischaemia [8]. The attacks typically present with triphasic colour changes, initially with pallor due to vasoconstriction evolving to the cyanotic blue phase and finally the painful reactive hyperaemic phase [9]). It is clinically important to differentiate primary RP (PRP) in which there is no underlying medical condition from RP secondary to another disease (SRP). Among the rheumatic diseases, SSc has the highest frequency of RP and it often precedes the onset of other features of SSc. The interval between RP and onset of other SSc-specific symptoms is generally longer for limited cutaneous SSc than dcSSc [10].

Digital ulcers typically occur as a result of poor tissue perfusion over the digital pulps, around the nailfold and on extensor surfaces of the fingers or toes (in particular over the small joints) but may also occur in relation to calcinosis. Around half of patients with SSc [11] report a history of digital ulceration, often occurring within the first year of the disease [12]. Digital ulcers are associated with significant impact on function and quality of life [13] and impact negatively on occupation [14] with greater requirement for paid and unpaid help [15]. Severe DU are those causing or threatening tissue destruction or when 3 or more occur in one year. These need advanced therapy such as sildenafil.

Recommendations for Raynaud's phenomenon in systemic sclerosis

- Although there is no evidence base to support 'general measures', most clinicians believe that patient education, specifically general/lifestyle measures including keeping warm, the avoidance of cold ambient environments and smoking cessation, are key aspects of management. Final consensus: 100%.
- First line treatments are calcium channel blockers (Ia,A) and angiotensin II receptor antagonists (Ib,C) Final consensus 100%.

- Other treatments that may be considered if these are either ineffective or not tolerated are: selective serotonin reuptake inhibitors, alpha-blockers and statin therapy (III,C) Final consensus 100%.
- 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) Final consensus 100%.

Recommendations for digital ulcers (DU) in systemic sclerosis

- Digital ulcers require integrated management by a multidisciplinary team: management includes local and systemic treatment. Final consensus: 100%.
- Oral vasodilator treatment should be optimized and (for those patients progressing to DU) analgesia should be optimised and any infection promptly treated (III, C) Final consensus: 100%.
- 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).
- 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 (Final consensus 100%).
- Digital (palmar) sympathectomy (+/- botulinum toxin injection) may also be considered in severe and/or refractory cases (III,D). Final consensus 90%.

Lung fibrosis

Pulmonary complications are the commonest cause of death related to SSc [16]. SSc-ILD may affect patients with diffuse or limited cutaneous SSc in equal frequency. Those with certain subtype antibodies including anti-Scl70 antibodies, anti-U11/U12 ribonucleoprotein (RNP) antibodies or anti-Th/To RNP antibodies are more likely to develop ILD. Up to 80% of SSc patients will develop ILD and it is clinically significant in approximately a third of patients. Deterioration in lung function tends to occur early in the disease i.e. within 5 years of the first non-Raynaud's manifestation. Steen et al found in their historical cohort that after 3 years more than 50% of patients with SSc had developed a FVC of less than 55% predicted [17].

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) Final consensus 90%
- Cyclophosphamide by IV infusion is recommended (I, A/B) and MMF may also be used as an alternative or following cyclophosphamide (II, B) Final consensus 90%.

Pulmonary arterial hypertension

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure (PAP) \geq 25mm Hg with a pulmonary capillary wedge pressure of < 15 mm Hg. Over the last fifteen years there have been significant advances in the treatment of PAH. Several classes of drugs have shown a beneficial effect in RCTs for the treatment of PAH, including prostaglandins (e.g. iloprost, epoprostenol), ERAs (bosentan [ERA and ERB blocker], ambrisentan [selective ERA blocker]) and PDE-5 inhibitors (sildenafil, tadalafil). In the UK these therapies are approved for the treatment of SSc-PAH provided the patient fulfils the specified criteria defined by the NHS. The process varies slightly between the devolved nations. For patients living in England, the 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 PH in adults (NHS England/A11/P/b and NHSCB/A11/P/a). Patients should also receive supportive medical treatment e.g. diuretic therapy including a loop diuretic and/or spironolactone, and oxygen (if they are hypoxic with a Pa O₂ < 8 kPa or experience exertional desaturation). Routine anticoagulation with warfarin is not recommended in patients with PH and SSc unless the underlying aetiology is thrombo-embolic. Sometimes patients with SSc-PH will also have other manifestations of disease such as lung fibrosis or features of overlap connective tissue disease such as SLE and may benefit from immunosuppressive therapy e.g. IV cyclophosphamide or MMF.

Recommendations for pulmonary arterial hypertension in systemic sclerosis:

- All SSc patients should be evaluated for possible PH in line with current recommendations from the UK Pulmonary Hypertension Centres and referred for specialist management (I,A) Final consensus 100%.
- 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). Final consensus 100%

- Therapies licensed for PAH based upon pivotal clinical trials that included a significant proportion of SSc associated PAH should be used in line with current practice within the UK Pulmonary Hypertension Centres taking account of the agreed commissioning policies for PAH therapy (I,A/B) Final consensus 100%.

Gut disease

The gastrointestinal (GI) tract is the most frequent internal organ system affected by SSc and is responsible for substantial morbidity. This guideline focuses on the evidence for the drug treatment of gut disease and not its screening, investigation or overall management (which is covered by the UKSSG consensus best practice recommendation on gastrointestinal involvement [18]).

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 maintenance therapy (III, C) Final consensus 100%
- Prokinetic dopamine agonists may be used for dysphagia and reflux (III, C) Final consensus 90%.
- Parenteral nutrition should be considered for patients with severe weight loss refractory to enteral supplementation (III, C) Final consensus 100%
- Intermittent broad spectrum oral antibiotics (e.g. ciprofloxacin) are recommended for intestinal overgrowth and rotational regimes may be helpful (III, C) Final consensus 100%
- Anti-diarrhoeal agents (e.g. loperamide) or laxatives may be used for symptomatic management of diarrhoea or constipation which often alternate as clinical problems (III, C) (Final consensus 100%).

Renal complications

SSc renal crisis (SRC) is a severe and life-threatening complication of SSc, estimated to affect 5–10% of all patients [19], predominantly in the diffuse subset [20]. Several studies identified a number of risk factors that predict the occurrence of SRC [21, 22]. Among these are SSc duration < 4 years, diffuse and rapidly progressive skin thickening, new anaemia, new cardiac events (e.g., pericardial effusion or congestive heart failure), anti-RNA-polymerase III antibodies and corticosteroid therapy (prednisone >15 mg/d)(III,C) Final consensus 80%[19].

Recommendations for treatment of scleroderma renal crisis:

- Patients at risk of SRC should be followed closely and their blood pressure monitored at least weekly.
- Prompt recognition of SRC and initiation of therapy with an ACE inhibitor offers the best opportunity for a good outcome (III, C) Final consensus 90%.
- Other anti-hypertensive agents may be considered for managing refractory hypertension in conjunction with ACEi in SRC (III, C) Final consensus 90%.

Cardiac disease

Clinically evident cardiac involvement is associated with a poor prognosis [23,24] and a large proportion of SSc-related fatalities are attributable to cardiac causes [25, 26]. Whilst fibrosis is a central feature of SSc, clinical and pathological evidence suggests microvascular dysfunction is a primary process and one of the earliest features of disease. Myocardial fibrosis can affect the endocardium, myocardium and pericardium explaining the varied clinical presentations [27, 28]. Of note, these recommendations relate to primary myocardial involvement as opposed to right heart involvement and pulmonary hypertension that are discussed elsewhere in this guideline.

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) Final consensus 90%
- Consider the potential benefit of Implantable Cardio Defibrillator (ICD) (III,D)Final consensus 90%
- ACE inhibitors and carvedilol. Selective beta-blockers may be considered but consider aggravation of RP (IV, D) Final consensus 90%

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

- Diuretics including spironolactone and furosemide (IV,D) Final consensus 100%
- Calcium channel blockers have been shown to reduce the frequency of systolic heart failure in SSc with investigational evidence of cardiac abnormalities (III,D) Final consensus 90%

Skin manifestations

Management of skin disease is an intrinsic aspect of management of SSc. Pruritus is a common and particularly troublesome in early stage diffuse cutaneous SSc and becomes less intrusive once the disease plateaus. Cutaneous telangiectasia may be widespread especially over the hands and face and may present as a major cosmetic problem [29, 30]. Immunosuppression that aims to modify the disease is also likely to impact on skin involvement but it is also important to consider the evidence based management for cutaneous manifestations of SSc per se. The evidence base and treatment options for individual skin manifestations are outlined below.

Recommendations for skin manifestations in systemic sclerosis:

- Practical approaches in particular maintaining adequately moisturised skin is essential, especially moisturisers that are lanolin-based. It is strongly recommended to avoid frequent bathing with harsh deodorants soaps and non-soap cleansers should be used where possible (III, C) Final consensus 100%.
- Antihistamines are often used for itch (III,C). Final consensus 90%.
- Current treatment options for telangiectasia include skin camouflage and laser or intense pulsed light therapy [31, 32] (III,C) Final consensus 100%.

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 and none of the therapies listed below have positive trial data to support routine use making this a key area in need of research [33].

Recommendations for treatment of calcinosis in systemic sclerosis

- Superadded infection of calcinosis should be recognised early and treated with appropriate antibiotic therapy (III,D) Final consensus 100%.
- Surgical intervention should be considered in severe, refractory calcinosis, which is severely impacting upon functional ability and quality of life (III,D) Final consensus 90%.
- Therapeutic options which have been tried include aluminium hydroxide, bisphosphonates, calcium channel blockers, colchicine, infliximab, intravenous immunoglobulin, minocycline [33], rituximab and warfarin (III,D) Final consensus 80%.
- Interventional options include extracorporeal shock wave lithotripsy, intralesional steroid and laser therapy (III,D) Final consensus 80%.

Musculoskeletal manifestations

Musculoskeletal complications in SSc are common and debilitating and can occur either as a primary manifestation of the condition or as a result of an overlap disorder with another autoimmune rheumatic disease (ARD). For the latter, a recent study from a single-centre cohort showed that a fifth of patients with SSc have a coexisting ARD: a third had rheumatoid arthritis and another 40% had myositis [34]. Primary involvement occurs due to deformity and restricted movement of joints, tendon or soft tissue contractures and fibrosis or inflammatory changes in or around tendons and joints and involvement of skeletal muscle.

There is limited evidence to support specific treatment of musculoskeletal involvement but it is likely that these manifestations will benefit from treatments given for skin or other manifestations especially as the agents used are in widespread use for treatment of other forms of inflammatory musculoskeletal disease.

Recommendations for musculoskeletal manifestations in systemic sclerosis:

- Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other aspects of the disease such as skin (III, C) Final consensus 100%.
- When arthritis or myositis 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 (III, C) Final consensus 100%.

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

The principle of autologous ASCT in autoimmune diseases is the ablation of an aberrant or self-reactive immune system using high-dose chemotherapy and/or lymphoablative antibodies or total body irradiation (TBI) and regeneration of a new immune system from hematopoietic stem cells [35]. The combination of high dose CYC and anti-thymocyte globulin (ATG) is considered a non-myeloablative ASCT, leaving bone marrow stem cells intact, whereas the use of TBI and chemotherapeutic agents such as busulfan renders conditioning myeloablative, depending on the doses used. Haematopoietic stem cells transplant registry data, several case reports and pilot studies in the USA [36, 37] and Europe [38,39] involving patients with dcSSc demonstrated a rapid clinical improvement of functional performance, skin thickening and stabilisation of major organ function, but at the cost of high treatment-related toxicity and mortality [40]. To understand the effect of ASCT on SSc patients three randomised controlled trials have been designed to date. Efficacy, safety and long-term side effects of autologous ASCT in SSc have been studied.

The ASSIST study was an open label, randomised phase 2 trial to compare autologous non-myeloablative ASCT with monthly pulse CYC [41] and 19 subjects were enrolled on the study. All patients who underwent ASCT showed significant clinical improvement within 12 months compared with none from the control group. No deaths were recorded during the study which may reflect selection of patients with mild disease, small sample size and relatively short follow-up [42]. The Autologous Stem cell Transplantation International Scleroderma trial (ASTIS) was a multinational prospective randomised controlled phase 3 trial, comparing safety and efficacy of ASCT versus CYC in patients with early progressive dcSSc patients with disease duration of a) 4 years or less and evidence of organ involvement or b) of 2 years or less and evidence of systemic inflammation with or without major organ involvement [43]. 156 patients were recruited and 79 patients were randomized to the transplant arm. The primary endpoint was event-free survival (EFS), defined as time from randomization until the occurrence of death or development of major organ failure.

With a median follow-up 5.8 years 53 events had occurred: 22 in the HSCT group (19 deaths and irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures). Eight deaths (10%) in the HSCT group were considered treatment-related by the independent data monitoring committee and none died from treatment related causes in the control group, most deaths in the last group occurred due to progressive disease.

Despite 10% treatment-related mortality, long term event-free survival and overall survival were significantly better in the HSCT group than in the group treated with IV pulse cyclophosphamide. The “Scleroderma: Cyclophosphamide Or Transplantation” (SCOT) randomized, controlled phase III trial in North America is ongoing (see [ClinicalTrials.gov \(NCT00114530\)](https://clinicaltrials.gov/ct2/show/study/NCT00114530)).

Recommendation for autologous stem cell transplantation in systemic sclerosis:

- Current evidence support the use of ASCT in poor prognosis diffuse SSc that does not have severe internal organ manifestations that render the treatment highly toxic (Ib, B) Final consensus 80%.
- Definitive statements regarding relative safety and efficacy compared with other immunosuppressive strategies and definition of appropriate cases for ASCT will require further data (III,C) Final consensus 90%.

Non-drug interventions

Although the main focus of this guideline is pharmacological treatment for SSc it is clear that other approaches to management are also used and that these may be complementary to drug therapy. There is evidence to support the use of physical therapy and connective tissue massage and also other formal programmes to increase exercise capacity. These may be delivered in the hospital setting or within the community. Although the formal evidence base is quite limited there was strong feeling from patient representatives and those professionals involved in delivering such interventions that they have merit and are generally well tolerated.

Recommendation for non-drug interventions in systemic sclerosis:

- Although there are very few studies the opinion of the group was that non-drug interventions may be helpful in SSc and are generally not detrimental.
- 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) Final consensus 100%.

Part C. Service organization and delivery within NHS England

Systemic sclerosis must be diagnosed promptly, investigated appropriately and managed within an integrated system of primary, secondary and tertiary level care. Within secondary care it is important to have involvement of appropriate organ-based specialists and also relevant surgical disciplines including plastic surgery, orthopaedics and lower GI surgeons. In addition there should be input from allied healthcare professionals including clinical nurse specialists, physiotherapy, podiatry, occupational therapy and psychological support. Care should be delivered as close to a patient's home as possible but include the essential level of SSc expertise. The principle of excellent and equitable specialist care is a goal of NHS England and SSc requires integrated care from a managed network that may include outreach clinical services from specialist SSc centres. Education, clinical nurse specialist-led clinic for rapid access and availability of telephone helplines form part of a recommended template for high quality care of SSc. Additional support including self-management advice and social support should also be offered through liaison with patient-based organisations such as the Raynaud's and the Scleroderma Association and Scleroderma Society. Any system that support patients with SSc need to tailor to their needs and respond promptly as uncontrolled disease can lead to accrual organ damage and in some cases, these crises may be life-threatening. Such systems may be available at different levels in primary or secondary care, provided by clinical nurse specialists or consultants as appropriate. Some services that are required are

already commissioned within specialist centres including pulmonary hypertension, home parenteral nutrition, haemopoietic stem cell transplantation and dialysis services for renal failure. These provide a template for delivery of care but it is important that specialist centres are familiar with the particular challenges posed by SSc and its multisystem nature and high burden of complications and co-morbidity.

Quality standards and audit tool

SSc is an uncommon condition and the heterogeneous nature of the disease with multisystem involvement pose significant challenges in management of these patients. This guideline aimed to focus on key elements in assessment and treatment of both specific complications and general aspects of the disease. The quality standards and audit tool therefore relate to these core elements of patient care and service delivery.

Key quality standards

- i. Suspected systemic sclerosis (SSc) cases should be assessed by a specialist physician to confirm diagnosis and classify disease subset
- ii. All SSc cases should have baseline assessment of internal organ function including cardio-respiratory, renal, gastrointestinal tract and musculoskeletal and skin manifestations
- iii. People with SSc require access to a multi-disciplinary team either based locally or as part of a regional network. A shared care approach with easy access to specialized centre is key to management of these patients.
- iv. Patients with SSc should have an individualized comprehensive care plan that outlines advice about sudden complications and long term approaches to living with the disease including patient support groups and specialist nurse advice. Patients should be empowered to be involved in self –management and access to specialized helplines or local support groups should be made available for discussions and advice throughout their course of disease.
- v. Patients should have access to full range of treatments including specialist treatments covered by NHS England policies following specific treatment pathways relevant to SSc.
- vi. There should be opportunity to participate in clinical research projects, registries specific to specialized treatments and clinical trials to improve quality of care and help others in the future.

Mechanism for audit of the guideline

This guideline offers opportunity for audit to assess management practice and to monitor quality of services. The individual measures that comprises the audit tool is congruent with the metric definition set out in the Specialised Services Quality Dashboard for connective tissue disease. The following are some topics that may be audited:

Service delivery

- i. Time to assessment in a specialist SSc clinic after referral – 6 weeks first referral, 18 weeks specialist scleroderma review. Standard 100%.
- ii. Nominated lead clinician for each patient. Standard 100%
- iii. Access to multi-disciplinary team. Standard 100%
- iv. Availability of full range of SSc-specific ANA testing and screening investigations (Echo and lung function). Standard 100%
- v. Access to intravenous prostanoids for critical digital ischemia or severe digital ulcer disease. Standard 100%
- vi. Defined referral pathway for ASCT therapy. Standard 100%

Patient specific

- i. Documented management plan for each patient. Standard 100%
- ii. Documentation of explanation of risks of immunosuppressive and other SSc therapies for child-bearing in appropriate cases. Standard 100%
- iii. Proportion of patients having PDE5 (e.g. sildenafil)for digital ulcer disease. Standard 10%-50%.
- iv. Proportion of patients referred for invasive investigation for pulmonary hypertension. Standard 10-40%.
- v. Proportion of patients who meet the criteria for Bosentan for DU as per NHS England policy receives the treatment with appropriate monitoring of efficacy. Standard 100%
- vi. Assessment and treatment of specific complication including use of licensed therapies for digital ulcer disease.
- vii. Proportion of cases enrolled into observational clinical studies of interventional clinical trials.
- viii. Proportion of cases enrolled into registries (DUO for digital ulcer) or BILAG registry (lupus overlap connective tissue diseases)

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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.