Best clinical practice in the treatment of juvenile systemic sclerosis: expert panel guidance - the result of the International Hamburg Consensus Meeting December 2022

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ABSTRACT

Introduction: Juvenile systemic sclerosis (jSSc) is an orphan disease with a prevalence of 3 in 1,000,000 children. Currently there is only one consensus treatment guideline concerning skin, pulmonary and vascular involvement for jSSc, the jSSc SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) initiative, which was based on data procured up to 2014. Therefore, an update of these guidelines, with a more recent literature and expert experience, and extension of the guidance to more aspects of the disease is needed.

Areas covered: Treatment options were reviewed, and opinions were provided for most facets of jSSc including general management, some of which differs from adult systemic sclerosis, such as the use of corticosteroids, and specific organ involvement, such as skin, musculoskeletal, pulmonary, and gastroenterology.

Expert opinion: We are suggesting the treat to target strategy to treat early to prevent cumulative disease damage in jSSc. Conclusions are derived from both expert opinion and available literature, which is mostly based on adult systemic sclerosis (aSSc), given shared pathophysiology, extrapolation of results from aSSc studies was judged reasonable.

1. Introduction

1.1. Why we need a best practice proposal?

Juvenile-onset systemic sclerosis (jSSc) is defined as youth, children and young adults meeting the SSc ACR/EULAR 2013 diagnostic criteria with the onset of Raynaud's or non- Raynaud's manifestations <18 years old. JSSc is rare, with an incidence of jSSc is 0.27 per million children and estimated prevalence around 3 in a million children [1]. Rare and com- plex diseases such as systemic sclerosis (SSc) are a particular challenge for clinicians because cases occur infrequently in everyday practice and clinical management is necessarily

varied according to the diversity of presentation and organ- based complications. This leads to potential variability in prac- tical aspects of treatment, confused or disjointed treatment across subspecialties and consequent detrimental impact on clinical outcome. However, through collaboration and iterative discussion between experts, there is substantial opportunity to apply principles of management from commoner organ-based diseases that have parallels with SSc, such as arthritis, myositis, lung fibrosis, and gastrointestinal dysmotility that are more familiar to pediatric specialists.

In this article, we consider the development of consensus best practice approaches for the major clinical aspects of jSSc.

Article highlights

- A diverse group of international jSSc experts propose treatment recommendations for juvenile systemic sclerosis (jSSc), both general guidance and regarding specific organ systems.
- Many recommendations are extrapolated from adult systemic scler- oderma (SSc) data with a pediatric context.
- Both supportive care measures and medical therapies recommended for jSSc are described.
- The goal is to provide a standardized comprehensive treatment approach, which is both multidisciplinary and interdisciplinary for best care for jSSc patients.
- Implementation of recommendations should lead to overall better outcomes in jSSc.
- The pediatric rheumatology 'treat to target' concept should be applied to jSSc.

This approach has proven valuable in adult SSc practice and complements more formal evidence-based guidelines and recommendations such as those endorsed by EULAR [2,3] or BSR [4]. By adopting an expert consensus approach, informed by published SSc literature, personal experience, and evi- dence-based treatment of related conditions in pediatric prac- tice, it is feasible to develop management strategies that can be applied more broadly. These can provide a template for care that ensures the most important aspects of treatment are prioritized.

The Hamburg Symposium is an annual international pedia- tric scleroderma conference of scleroderma and content experts, providing an established platform to achieve consen- sus. Invited participants are pediatric and adult rheumatologists, dermatologists, pediatric pulmonologists, pediatric nephrologists, pediatric gastroenterologists, and pediatric cardiologists, physiotherapists, and patient representatives to envelop the different aspects. The December 2022 meeting was dedicated to discussion and voting on best current treat- ment options for jSSc. Background material prepared ahead of time was presented on Day 1 by individuals from workgroups regarding different organ systems, physiotherapy, and overall management, based on current knowledge and clinical prac- tice for jSSc. Most of the data in jSSc are dependent, to a large extent, on case reports and case series. Therefore, adult SSc recommendations have been extrapolated to jSSc, with the recognition that jSSc has some unique aspects, such as the majority of patients having diffuse subset, more overlap fea- tures (myositis), and different impact on growth parameters
[5] and psychosocial development, though with a shared pathophysiology with adult onset SSc. The consensus meeting was held on Day 2, where ≥ 80% agreement among voting members present had to be reached for consensus, as defined a priori, using the nominal group technique. The consensus meeting was moderated by Dan Furst, an experienced adult SSc rheumatologist. These recommendations represent good clinical care based on updated review of the literature com- bined with expert opinion.

The current article fills an important gap between current rather variable practice, especially outside expert centers, and the future development of more formal evidence-based recommendations or guidelines for jSSc that can be disseminated and updated.

2. Development of the guidance for best practice in treatment for juvenile systemic sclerosis using the framework of the 15th Hamburg Symposium on Juvenile Scleroderma, December 2022, Hamburg, Germany

*2.1. Overarching principal of treatment (**Table 1**)*

2.1.1. "All children with jSSc should be referred to a specialized pediatric clinical care center familiar with scleroderma with access to multidisciplinary care" (18/18 voted Yes)

The group agreed to adopt the overarching principle of the previous SHARE guideline [6] for juvenile systemic sclerosis. It cannot be emphasized enough that children with jSSc need physicians experienced in jSSc care. The care team should be a multidisciplinary arrangement, aiming for an interdisciplinary approach, as the disease involves multiple organ systems at the same time, so the patient needs access to several specia- lists, who coordinate the treatment for the one patient. It is very important that patient and family unit are involved in therapy decisions and undertaking.

2.1.2. "Aim to get disease under control so the child can continue to grow and develop; Improve quality of life and prevent damage to organs" (18/18 voted Yes).

The aim of therapy in jSSc is to achieve inactive disease to enable the child a normal somatic and psychosocial development.

2.1.3. "Standardized outcomes should be used when measures are available " (18/18 voted Yes)

The group discussed and emphasized that if pediatric out- comes exist they should be applied to assess the response to therapy. The group recently published proposed outcome measures for a 12-month trial in juvenile systemic scleroderma based on the 11th Hamburg consensus meeting in 2018 [7].

3. DOMAIN – General treatment concepts

The group agreed to discuss overarching treatment concepts for jSSc, which have an effect on several organ systems, before engaging organ-specific treatment and guidance (Table 1).

3.1. Corticosteroids

3.1.1. "Systemic corticosteroids, in combination with a Disease Modifying Antirheumatic Drug (DMARD), are useful in the active inflammatory phase of jSsc" (18/18 voted Yes)

The group agreed univocally to adopt the concept of corti- costeroid treatment of the jSSc SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) consen- sus recommendations regarding treatment [6], which denotes 'systemic corticosteroids (CS), in combination with a DMARD, are useful in the active inflammatory phase of jSSc.' In the SHARE recommendation it was suggested for skin involvement, but it can be extrapolated for patients with overlap features with myositis. CS treatment is consid- ered as a bridging therapy, until the initiated disease-

modifying antirheumatic drug (DMARD) has a more sustained effect. In a recent ACR abstract, an international jSSc registry, the Inception cohort, found that 52% of the patients were on CS at first study visit [8]. This is not in tandem with adult SSc guidelines and is unique for jSSc. The main concern regard- ing CS treatment in the adult recommendations [2] is the occurrence of scleroderma renal crisis (SRC). Renal crisis rarely occurs in the pediatric patients and has not been documented in the more recent large jSSc cohorts [5], likely due to the absence of comorbidities, such as hypertension (0.4% in the inception cohort), atherosclerosis, and smoking, and lack of RNA Pol III positivity in jSSc.

3.2. Initiation of DMARDs

3.2.1. "Initiation of treatment with DMARD and physical therapy should not be delayed" (18/18 voted Yes)

Disease should be treated as early as possible based upon organ symptoms and severity of the organ involvement to prevent organ damage, or at least progression of the damage if already present. Nearly a quarter of jSSc patients have a significant delay in their first pediatric rheumatology consult, supported by a CARRA study demonstrating 23% of children had a two-year or greater delay between symptoms onset and their first pediatric rheumatology assessment [9]. The extrapo- lation of the 'therapeutic window' concept from other pedia- tric rheumatologic diseases, like juvenile idiopathic arthritis, was discussed and supported, but unfortunately because of the delay in the diagnosis and referral to the specialized centers, a true therapeutic window is often missed.

Parallel to medications, supportive care should be consid- ered in all cases. Supportive care includes nursing support, physical therapy, occupational therapy, and psychological services. Physical therapy includes physiotherapy, occupational, hand, and respiratory therapy [10–12]. A detailed assessment to provide guided treatment recommendations should be completed as soon as the diagnosis is made and should include assessment of range of movement (ROM), with differ- entiating between joint contracture and/or muscle or skin tightness, muscle strength, respiratory function, fatigue, phy- sical function (e.g. activities of daily living) and mobility.

3.2.2. DMARDs commonly used to treat jSSc include Methotrexate, Mycophenolate, and Cyclophosphamide (18/ 18 voted Yes)

The first-line DMARD for jSSc treatment in general discussed among the group was Methotrexate (MTX) or Mycophenolate Mofetil (MMF), seen as equivalent, this differs slightly from the SHARE recommendations in which MTX was considered the only first-line DMARD, with using MMF only after MTX non- response [6]. This was based on mostly for treatment guided at skin manifestations but can be considered for many organ manifestations in jSSc.

A recent data analysis of jSSc medication use from the ongoing juvenile scleroderma inception cohort, which was presented at the 2022 American College of Rheumatology meeting, demonstrates MTX as the most commonly used DMARD at the time of the inclusion in the cohort (51% of the patients) and at the 12 months follow-up visit (50% of the patients) [8]. As for juvenile idiopathic arthritis, for jSSc Methotrexate is started at 15 mg/m2 body surface area, reach- ing 1 mg/kg per week, with maximum 25 mg/week. This start- ing dose is significantly higher compared to adult SSc studies [13,14], and higher than the maintenance MTX dose of 10 mg/ week for adult SSc, which was used by Pope et al [14].

MMF was the second most commonly used DMARD in the inception cohort and was prescribed to 26% of the jSSc patients at the time of the inclusion and 44% at the 12 months

visit [8]. In jSSc we suggest MMF dosing similar to adults, with a range of 1000–1500 mg/m^2/day divided twice a day, with an average dosing of 600 mg/m^2/dose, with a maximum dose of 1500 mg twice a day. An advantage of MMF in small children is it has an easy liquid form of 200 mg/1 mL concentrations in some countries, most young children then can be on a few mL twice daily. Not uncommonly, pediatric rheumatologists agree to use these medications, MTX and MMF, in tandem as in juvenile localized scleroderma [15], to gain better control of disease. It was observed that 12% of the jSSc inception cohort were on both MTX and MMF at baseline study visit [8]. There are no pediatric studies regarding either MTX or MMF for jSSc treatment. The efficacy of MTX and MMF therapy is extrapo- lated from the adult studies [13,14,16,17] and juvenile loca- lized scleroderma [15].

Historically, cyclophosphamide (CYC) has been used in jSSc as an effective medication. Cyclophosphamide is an option for patients with severe interstitial lung disease [16] or cardiac invol- vement, according SHARE [6]. Among the group, CYC could be considered for severe cases of skin and musculoskeletal disease, refractory to DMARDs. Cyclophosphamide was prescribed in 12% of the patients at the time of the inclusion in the inceptions cohort and 2% at the 12-month follow-up visit [8]. The dosing is extrapolated from pediatric systemic lupus erythematosus treatment of 500–1000 mg/m^2 monthly intravenously, typically for 3 to 6 months, not exceeding 1000 mg/dose.

3.2.3. "In case of insufficient response to therapy, change or additional therapy is recommended" (18/18 voted Yes)

The treat to target concept [18] was discussed and accepted. Therefore, if there is insufficient response or partial response after 3 to 6 months of therapy [19] with a conventional DMARD [20] in a jSSc patient, a combination of MTX with MMF could be considered, or adding a biologic DMARD [20], like Tocilizumab [19,21] or Rituximab [22] should be consid- ered. In the inception cohort TCZ was used in 2% at time of inclusion in the cohort and 10% at the 12-month visit, most often in combination with a conventional DMARD. Rituximab was used in 2% at the time of inclusion and 4% at 12 months [8]. Treatment with a small molecule [20], like a JAK inhibitor seems to be promising for SSc [23–25].

3.2.4. "ASCT could be considered an option to treat patients with jSSc with progressive disease refractory to DMARD therapy" (18/18 voted Yes)

Two large multicenter trials examining the potential benefit and treatment-related risks of autologous stem cell transplant (ASCT) in adult SSc patients conducted between 2001 and 2011 helped establish ASCT as a treatment option for early diffuse SSc, the Autologous Stem Cell Transplantation International Trial (ASTIS) trial in Europe [26] and the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial in the US [27]. Both were open-label, randomized, parallel- group trials which found significant increased event-free sur- vival benefit at 5 years in the ASCT compared to IV CYC group, and more tolerable transplant-related mortality (6%) com- pared to prior studies. Both ASCT studies included high-dose CYC and antithymocyte globulin (ATG) immunoablation followed by infusion of CD34+ autologous stem cells [26,27]. Total body irradiation (TBI) was an additional step in the conditioning protocol in the SCOT protocol [27]. Although the mortality rate in SSc ILD appears improve following ASCT, there remains significant initial transplant-related mor- tality (6%). Thus, ASCT should be reserved for primarily rapidly progressive cases or secondarily to refractory cases.

Including Dr. Torok's recent abstract from Pittsburgh's ASCT jSSc cases (n = 5) [28,29], there are currently 15 reported cases of ASCT in jSSc (12 females, 3 males), median age of 12.5 years (range 9–21 years), all with established lung disease (14 with ILD and 1 with MSK respiratory insufficiency) and refractory to a variety of DMARDs [29–33]. Conditioning included cyclopho- sphamide in 13 of the 15 cases, either alone (n = 1), with Alemtuzumab (n = 5), or with ATG (n = 5) and TBI (n = 4) [29– 33]. General outcomes at 6 months demonstrate initial clinical remission (CR) in 14 out of the 15 patients and 1 with partial remission (PR). Later follow-up at approximately 2–3 years includes majority of patients in remission (11/15), with catch- up linear growth and weight along with increased general well-being, 1 in partial remission, and 3 that had initial CR relapse between 9 and 15 months post-transplant. These case reports along with recent efficacy and safety results from adult-onset SSc ASCT regimens [26,27,34] provide reasoning to utilize ASCT as a viable therapy for refractory jSSc. Patients should be advised to pursue ASCT only at large centers with high expertise in the management of this intervention. This is further supported by the SHARE consensus statement regard- ing ASCT [6].

4. Organ specific treatment (**Table 1**)

4.1. DOMAIN – Skin

4.1.1. "First line treatment of jSSc skin involvement is Mycophenolate or Methotrexate ± combination with low dose systemic corticosteroid" (19/19 voted Yes)

According SHARE treatment recommendations [6] systemic CS, in combination with a DMARD, are useful in the active inflammatory phase of jSSc (recommendation 1) and at the time of diagnosis of jSSc, a systemic immunomodulatory treat- ment, like MTX, should be considered (recommendation 2). Additionally, SHARE recommendations suggest in case of non- response to MTX an additional immunomodulatory agent (i.e. MMF) should be considered (recommendation 3). In the cur- rent discussion, the SHARE recommendations 1 and 2 regard- ing treatment were confirmed. The third recommendation was modified, as MTX and MMF were considered as equally effec- tive by the experts, this is reflected in the medication use in the inception cohort [8] and it reflects the recent practice pattern in adults [35].

4.1.2. *"In case of insufficient response to first line jSSc skin treatment, the addition of tocilizumab or rituximab to treatment should be considered. Additional agents that can be considered are abatacept, cyclophosphamide, Jaki and IVIG" (19/19 voted Yes)*

In the SHARE treatment recommendation 7 it is suggested that biological agents, in particular tocilizumab or rituximab should be considered in severe or refractory cases. This recom- mendation is in line with a current expert opinion [25], which describe good efficacy of both agents on SSc skin involve- ment. In the phase 3 tocilizumab(TCZ) trial for adult SS [21], patients in the combination group of MMF and TCZ, had an additional positive effect on the response. The SSc EUSTAR clinical study and the Japanese double-blind, randomized, placebo-controlled trial study with Rituximab demonstrate significant improvement in the modified Rodnan Skin score (mRSS) [36,37]. A small case series of jSSc patients found rituximab combined with MMF to be effective across several clinical outcomes, including skin [38].

There are also studies suggesting effectiveness of abata- cept on skin involvement in SSc. A EUSTAR cohort study demonstrated decrease of the mRSS from 9.2 to 4.4 ($p < 0.05$) after one year [39]. This finding was not confirmed in the abatacept Phase 2 trial [40]. Therefore, we suggested that abatacept should be considered. Cyclophosphamide was considered in a recent systematic review only as a third line treatment for skin involvement [41]. JAK inhibition seems to be promising [23–25].

4.1.3. *"Physical therapy, massage, emollients, skin care and other supportive therapy should be started in tandem with first line therapy" (19/19 voted Yes)*

It is important to start passive and dynamic stretches and therapeutic massage to the affected areas of skin and joints as soon as possible [12,42]. The use of emollients including hot wax baths is highly recommended to make these treatments more effective. Stretches and massage need to be supported by strengthening [43] and active range of movement (ROM) exercises to ensure the treatments are maintained and pro- gressed. Hot wax baths [44] are very useful for hand and feet therapy and teaching self-stretches also empowers the patient with positive input into their care. It is important to educate the patient and their family that not only is therapeutic exer- cise safe, but it is also very important in the effective manage- ment of this condition. These physical therapies need to be completed at least daily for them to be effective.

4.1.4. *"Topical pharmacological treatments ± phototherapy should be considered as adjunctive therapy" (19/19 voted Yes)*

Topical therapies and/or phototherapy should not be used alone, but in combination with systemic treatments and may contribute to symptom relief and skin softening in SSc. There are no large RCTs of topical therapies in SSc. Evidence is largely low level from small case series or comparative studies in localized scleroderma. Regular once or twice daily use of moisturizers containing 5–10% urea or an anti-pruritic agent (e.g. menthol, polidocanol, calamine) can improve skin hydra- tion, reduce transepidermal water loss, stabilize the skin bar- rier function, and relieve itch. Topical pharmacological treatments including potent or ultrapotent topical corticoster- oids [45], topical tacrolimus ointment (0.03% or 0.1%) [46], topical 5% imiquimod [47,48], and topical vitamin D analogues [49], are only useful in the early active stages to help reduce pruritus, inflammation, and edema-related indura- tion. Application should be limited to up to 4 weeks for

ultrapotent and 3 months for potent topical corticosteroids [45]. A non-corticosteroid preparation may be used for 3 months thereafter. These treatments are unlicensed in jSSc and use is limited by potential side effects including skin atrophy, infection and delayed wound healing (corticoster- oids), burning sensations, pruritus, erythema, and photosensitivity (tacrolimus); flu-like symptoms, skin ulceration (imiquimod), hypercalcemia, and nephrolithiasis (Vitamin D analogues).

Phototherapy may be considered in early disease with limited skin involvement, but in a guarded fashion in jSSc [45]. Uncontrolled studies have indicated a beneficial effect on skin thickening, skin elasticity, pruritus, and inflamma- tion in adults [50,51]. However, the long-term risks of skin cancer development [52], skin atrophy, and photocarcino- genesis risk with concomitant use of phototherapy (nbUVB and PUVA) with oral ciclosporin, azathioprine, tacrolimus, or mycophenolate dampen any enthusiasm to use routi- nely for jSSc [53]. Consequently, light therapy before pub- erty is a therapeutic option that should only be used in exceptional cases [54].

Matt-like telangiectasis at high-impact cosmetic sites can appear early in disease and have a profound impact on self-confidence and wellbeing. Effective treatment is available with vascular lasers (pulsed dye) and intense pulsed light (IPL) [55]. IPL should be avoided in patients with overlap syndrome and potential photosensitivity (Pm-Scl, Ro, SSA antibody positivity).

5. DOMAIN – Musculoskeletal

5.1. "First line jSSc associated arthritis treatment is MTX and/or Tocilizumab, ± in combination low dose systemic CS. Additional agents to consider are abatacept, rituximab, TNFi, Jaki, IVIG and HCQ" (19/19 voted Yes)

Musculoskeletal (MSK) involvement is strongly associated with functional impairment, pain, and poorer quality of life in adults with SSc [56]. MSK involvement is more common in jSSc (61.5%) than adult SSc (39%), with arthritis a key contributor (32.5%, 16.9%, respectively) [57]. Different SSc arthropathy patterns have been reported, including erosive arthritis, enthe- sitis, sacroiliitis, and inflammatory back pain, tenosynovitis, calcinosis, osteophytosis, and fibrous arthropathy [56,58–61].

There have been no clinical trials focused on MSK involve- ment, so no MSK-specific recommendations were generated by EULAR. The jSSc consensus SHARE recommendations, based upon a literature review to 2013, suggest methotrexate with or without low-dose corticosteroids for jSSc-associated arthritis or skin involvement treatment [6]. For refractory patients, mycophenolate mofetil or cyclophosphamide, then biologic agents or autologous hematopoietic stem cell trans- plant was recommended [6]. Surveys of adult SSc experts showed high agreement on methotrexate as first-line therapy, with refractory patients treated with a brief course of low dose corticosteroids, then hydroxychloroquine, then rituximab or tocilizumab [16]. A European prospective observational cohort study of early diffuse cutaneous SSc found hand function improved more in methotrexate treated than untreated patients [62]. Several case series, including one of a jSSc patient, sup- port the safety and efficacy of tocilizumab for arthropathy/ arthritis [63–65]. A 2013 analysis of the EUSTAR registry reported that both tocilizumab and abatacept reduced the number of tender and swollen joints, morning stiffness duration, and DAS28 scores [66], with a more recent EUSTAR analysis confirming the efficacy and safety of aba- tacept for arthritis treatment at 12 months [39]. Case series of other biologics (TNFi, rituximab, IVIG) and JAK inhibitors have also reported SSc-associated arthritis improvement [24,67–71].

5.2. "First line jSSc associated myositis treatment is MTX, MMF, and/or IVIG, ± in combination with low dose systemic CS. Additional agents to consider are Rituximab, Abatacept, Jaki, TNFi, cyclophosphamide and hydroxychloroquine" (19/19 voted Yes)

Myopathy typically results in symmetric proximal weakness and muscular atrophy, with weakness found in 20−32% of jSSc patients [56]. The pathophysiological process leading to SSc-associated myopathy is complex and includes microangio- pathy, interstitial fibrosis and inflammatory infiltrate in about half of the cases. Myositis is more common in the overlap SSc subtype, and presents similar to juvenile dermatomyositis, including muscle and electromyographic features, although with only a moderate elevation of muscle enzymes and MRI signal abnormalities.

There are no specific recommendations regarding myositis treatment in the jSSc SHARE [6] or adult SSc EULAR [2] recommendations. The British Society of Rheumatology guideline [4] for SSc treatment recommends that patients with severe myo- sitis receive treatment in line with similar clinical conditions occurring outside the context of SSc (level of evidence III, strength C), so recommendations often follow strategies used for inflammatory myositis. Methotrexate, mycophenolate mofetil, IVIG, corticosteroids, rituximab, and cyclophospha- mide are all suggested treatment options for juvenile derma- tomyositis in the SHARE recommendation [72]. In a EUSTAR observational study with tocilizumab or abatacept patients with SSc-myopathy, after a follow-up of 18 months, myopathy tended to improve, but the results were not statistically sig- nificant [66]. There have been small case reports of improve- ment in SSc-myopathy with IVIG [71] and rituximab [38].

5.3. "Physical therapy should be started in tandem with first line therapy for jSSc associated MSK issues" (19/19 voted Yes)

Physical therapy (occupational and physiotherapy) [11,12,43] is required as a first-line treatment to resolve issues of loss of strength, range of motion (ROM) and fatigue. It is also important to minimize deterioration of mobility and function or progres- sion

of the disease. Accurate assessment of specific joint ROM, muscle strength (using standardized assessments) and function will assist monitoring disease progression and help focusing the treatment goals. Families may not be aware of worsening of specific physical function but may notice an increase in fatigue or a loss of enthusiasm and ability in doing usual activities. Treatment needs to have a biomechanical focus to ensure that joint range of movement and muscle length [43] is regained and maintained and stretches and exercises will support this. The use of splinting may also have a role to play in certain joints, though this needs to be used with care to avoid stiffening and loss of strength and function. Maintaining soft and flexible skin is an important consideration for maintaining range and enabling muscle to work effectively.

Strengthening exercises should initially focus upon specific muscles using a progressive, resisted, and high repetition focus. Careful reestablishment of normal movement patterns is important and aiming for individually strong muscles to support and protect joints is vital. Progression to sport and other physical activity will be more successful if the biomechanics of movement, strength, and function are optimal.

6. DOMAIN – Renal

6.1. "Renal crisis is extremely rare in jSSc. If it occurs, management should follow adult SSc guidelines" (19/19 voted Yes)

Scleroderma renal crisis is a life-threatening complication. Patients should be immediately admitted to the hospital and referred to a well-trained team [73]. The EULAR recommenda- tions [2] suggest immediate use of angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors should be continued long-term if there is potential for additional kidney function improvement. ACE inhibitors are not recommended to pre- vent renal crisis [73]. These recommendations are based on several case reports [74]and uncontrolled studies [75]. In one cohort [75] of 108 adults with SSc, ACE inhibitors significantly improved the survival of patients with renal crisis (1-year survival: 15% without and 76% with ACE inhibitors; $p < 0.001$). As association between treatment with steroids and a higher risk of renal crisis has been established in adults with SSc [76]. The risk of a renal crisis in children and adolescents is significantly lower when compared to adults. Nevertheless, when treated with steroids jSSc patients should be carefully monitored, including evaluation of blood pressure and renal function [6].

6.2. "Systemic hypertension should be treated" (13/14 voted Yes)

Blood pressure should be evaluated at every clinic visit. Hypertension should be diagnosed if there is persistent systolic and/or diastolic blood pressure ≥ 95th percentile for sex, age, and height of the child [77]. These cutoffs are used regardless of if a patient is already on a calcium channel blocker or other vasodilator for their Raynaud's. Lifestyle modifications, if needed, should be recommended and treatment with anti-hypertensive drugs should be started. It is recommended that a pediatric nephrologist and/or a pediatric cardiologist be involved in the care of jSSc patients with hypertension.

The treatment is according to the combined pediatric nephrology and cardiology guidelines of general management of high blood pressure in children [77]. If there is an abrupt onset of moderate to marked hypertension it is essential to include a scleroderma renal crisis in the differential diagnosis.

7. DOMAIN – Raynaud's phenomenon (RP) and Digital Ulcers (DU)

7.1. "Education about self-management and lifestyle strategies are key, and include keeping core body warm, hand warmers and avoidance of environmental triggers" (19/19 voted Yes)

The group were unanimous in recommending education around self-management and lifestyle strategies which should be age-appropriate. Examples of strategies to keep core and peripheral body warm include layers of clothing, electric gloves and socks, hand and feet warmers. Patients and families should be aware of the environmental triggers, such as cold weather but also cold environments (such as air-conditioning, refriger- ated sections of supermarkets) and vasoactive agents (including caffeine, ADHD medications, and nicotine-containing products (both tobacco and e-cigarettes).

7.2. "First line jSSc RP treatment are Calcium channel blockers. Additional agents to consider are topical nitrates, ARBs, PDE5, fluoxetine, ERA, prostacyclin, and other" (19/19 voted Yes)

Management of SSc-RP should always consider potentially modifi- able aggravating factors (such as low BMI, anti-phospholipid syndrome) and patients should be counseled on effective methods for self-management [78]. There have been no RCTs evaluating efficacy of treatments for SSc-RP or primary RP in children. Data from the jSSc Inception cohort show that calcium channel blockers (CCB) are commonly used in jSSc 55% (122/222) with phospho- diesterase type 5 (PDE-5) inhibitors being prescribed in up to 24% of the cohort and endothelial receptor antagonists (ERA) in up to 9%. IV prostanoids were not prescribed for this group. The SHARE consensus-based recommendations [6] did not include a recommendation on treatment of RP in jSSc but suggested that CCBs were commonly used in clinical practice and alternatives include PDE-5 inhibitors, such as sildenafil. A case series of 15 children (6 with jSSc) [79] describes the use of IV iloprost for digital ischemia and severe RP refractory to CCB. Normal digital blood flow was achieved in

74%. A retrospective case series of 42 pediatric patients with RP [80] (of which 3 had jSSc) showed use of CCBs, amlodipine, and nifedipine, was most common and topical nitrites were also used. All 3 jSSc patients required IV iloprost [80]. A case report of bosentan in jSSc-PAH showed improved peripheral circulation measure by thermography [81]. The adult SSc EULAR recommendations for SSc-RP state that CCB, usually oral nifedipine, should be considered first-line therapy and PDE-5 inhibitors should also be considered [2]. Meta-analysis of RCTs on CCBs [82] and PDE-5 inhibitors [83] have indicated a modest net benefit of these treatments on diary-based approaches to quantifying RP attack characteristics, although there is strong consensus among specialists that such treatments are useful for SSc-RP [78]. IV iloprost was also recommended for SSc-RP after oral therapy based on meta-analysis of RCTs [84].

Given the paucity of data in jSSc and the common use of vasodilatory treatments in jSSc clinical practice, the group agreed that the vasculopathy in jSSc is similar to adult SSc and thus it is reasonable to extrapolate evidence from adult SSc-RP and DU studies where pediatric dosing and safety was established for other indications, e.g. sildenafil for PAH. While CCB are relatively well tolerated in children, side- effects include dizziness, flushing, headaches, and less com- monly peripheral edema. Concerns have been raised about the potential for CCBs to reduce lower esophageal sphincter pressure which could aggravate GERD symptoms. Pediatric dosing is available for the PDE-5 inhibitor sildenafil but not currently for tadalafil or vardenafil. Other agents to be con- sidered in jSSc-RP include topical nitrites, angiotensin II recep- tor blockers and fluoxetine [78]. The role of digital sympathectomy, botox, anti-platelet therapies, statins, and fat transfer are yet to be defined in the pediatric population but may play a role in severe refractory SSc-RP symptoms.

7.3. "All jSsc with DU should have rapid access to specialized expert wound care management" (19/19 voted Yes)

SSc-DU significantly impacts on quality of life due to pain, functional impairment, and delayed healing. Relative contribu- tions of small vessel vasculopathy, trauma, and large vessel disease to ulceration should be evaluated. Patients are best managed by a multidisciplinary team with wound care exper- tise including dermatologists, vascular surgeons, and trained nurses. Removal of necrotic tissue, treatment of infection, and maintenance of the correct moisture balance with appropriate dressings are key in promoting ulcer healing [85,86]. A distinction should be made between exudative and infected ulcers which require alginates and antimicrobials to dry them, versus dry, non-granulating wounds which require hydrocol- loids and hydrogels to wet them to promote healing. Treatments are based on standard wound care regimens and should be used in combination with the other supportive and systemic measures described herein [87]. The exact role and benefits of tissue debridement (both scalpel and autolytic, topical glyceryl trinitrate or nitroglycerin, low-level light ther- apy, and local botulism toxin injection in SSc-DU require further study in larger cohorts [86,88–91].

7.4. "First line jSSc DU treatment is PDE-5 and/or ERAs. Additional agents to consider are prostacyclins, Botox injections, sympathectomy" (19/19 voted Yes)

Treatment of digital ulcers should always address modifiable risk factors such as cryoglobulinemia, vasculitis and secondary APS [78]. Skin protection advice may avoid repeated micro- trauma and superadded infection. Clinicians should consider the need for antibiotics to treat infection that may complicate SSc-DU disease. The SHARE consensus-based recommenda- tions [6] for jSSc state that iloprost may be used to treat ischemic digits and digital ulcerations. Adult SSc EULAR recommendations [2] also suggest the consideration of IV iloprost for treatment of digital ulcers (DU) based on 2 RCTs [92,93]. EULAR guidelines also recommend PDE-5 inhibitors to improve healing of DU and possibly in preventing develop- ment of new DU [2]. Bosentan, an endothelin receptor antago- nist (ERA), has shown efficacy in reducing the number of new DU and should be considered in patients with multiple DU despite CCB, PDE5 inhibitors, or iloprost therapy [2,94,95].

The group agreed that extrapolation of the efficacy of PDE- 5 inhibitors and ERA from adult studies was appropriate to recommend these agents in jSSc-DU where pediatric dosing is available. In refractory cases, combination of ERA and PDE-5 inhibitors should be considered, but dosing may need to be modified to minimize side effects. Liver function monitoring is required for patients receiving ERA therapy. Local treatments, such as digital sympathectomy, may have a role in patients experiencing adverse effects of traditional vasodilator medica- tions, or in patients with refractory ulceration affecting one or more digits.

7.5. "Critical ischemia is a medical emergency which almost always requires hospitalization with maximization of vasodilation with IV prostacyclins, pain management and wound care. Additional agents to consider are antibiotics anti-platelet therapeutics." (16/16 voted Yes; *to note 3 members had to depart from the original 19)*

Critical ischemia (with necrosis) of digits is rare in SSc but should be considered a medical emergency and requires urgent admission to hospital for IV prostacyclin analog, like iloprost. Aggravating factors such as secondary APS, vasculitis and cryo- globulinemia should be excluded. It is frequently complicated by pain which may require opioids and secondary infection which requires careful wound care and antibiotics [78].

8. DOMAIN – Interstitial lung involvement

8.1. "First line therapy in jSSc ILD is MMF or Cyclophosphamide ± in combination the systemic CS. MMF is preferred over cyclophosphamide due to better safety profile. Additional agents to consider are Tocilizumab, Rituximab and Ninetadanib" (16/16 voted Yes)

Interstitial lung disease (ILD) is common in jSSc with a prevalence of 30–50%, similar to adults [96]. The develop- ment of ILD is more common early in the disease course [97], can be rapid and progressive [98], and once present, is gen- erally irreversible. High-resolution chest computed tomogra- phy (HRCT) is the gold standard for diagnosis [99] as pulmonary function tests are inadequate for diagnosis [100]. For example, a study in the Inception cohort found reliance on forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO) would have missed ILD in almost 2/3rd of HRCT confirmed cases [100]. As such, in agreement with adult guidelines [97], all children with jSSc should receive a screening HRCT and pulmonary function tests (PFT) at the time of diagnosis [96]. As HRCT requires radiation exposure, PFT are currently preferred for ongoing routine monitoring, which should be at a least every 6 months in those without and every 3–6 months for those with ILD [99].

Although there is no known cure for jSSc-ILD, effective therapies are available and mostly extrapolated from adult studies [101]. Cyclophosphamide was the first immunosup- pressive agent to demonstrate stabilization of ILD in the Scleroderma Lung Study (SLS I) [102], with mycophenolate demonstrating non-inferiority in the SLS II trial [17]. Mycophenolate is often preferred over cyclophosphamide owing to side effect and safety profiles [97]. More recently, tocilizumab demonstrated reduction of FVC decline in adults with early active disease [103], supporting treatment of early ILD. In the SENSCIS trial, nintedanib demonstrated reduction of FVC decline compared to placebo, both in participants who did and did not receive mycophenolate [104]. In subsequent SENCSIS analyses, nintedanib slowed FVC decline irrespective of the extent of fibrosis [105]. The InPedILD clinical trial, the only trial in children although nonspecific to jSSc-ILD, evalu- ated the dose exposure and safety of nintedanib in fibrosing ILD and found responses similar to adults, demonstrating safety for usage in children [106]. The RECITAL trial found rituximab to be not superior, though relatively equivalent, to cyclophosphamide in adults with connective tissue-ILD, including SSc-ILD [107], with more recent adult algorithms supporting too the consideration for rituximab in cases refrac- tory to first-line therapies [19]. Corticosteroids are not recom- mended as monotherapy and not included in adult guidelines [99], although extrapolation to jSSc may be less clear given the comparative rarity of renal crises [96].

8.2. "Physical therapy should be started in tandem with first line therapy, minimizing GERD and avoiding environmental triggers to promote lung health." (16/16 voted Yes)

Learning appropriate deep breathing exercises focusing on diaphragmatic movement is important in maximizing lung function and volume. Inspiratory muscle training can aid in both pulmonary function and controlling gastro-esophageal reflux disease (GERD), training the lower esophageal sphincter [108]. Other respiratory techniques such using 'positive expira- tion pressure' (i.e. bubblepep) can also help improve respira- tory muscle flexibility and strength. The role of movement and aerobic exercise should also be considered.

Positioning after food and drink is important and sleeping with a wedge or with the head of the bed elevated to avoid lying completely flat can also help avoid silent aspiration from GERD and esophageal dysfunction. This also assists the effi- ciency of breathing when asleep.

9. Domain – Cardiac

9.1. Pulmonary Arterial Hypertension

9.1.1. "First line jSSc associated PAH treatment are PDEi and ERA medications. In high-risk patients, from extrapolation from adults SSc PAH data, patients should be also treated with prostanoids." (16/16 voted Yes) Pulmonary hypertension in SSc typically resides in Group 1, also known as pulmonary arterial hypertension (PAH), the subtype associated with connective tissue disease. Overall, guidelines and algorithms from the cardiology and respiratory specialty socie- ties for idiopathic PAH (IPAH) are followed for SSc-associated PAH [109], though there are some subtle nuances. Decisions for the care of patients with SSc-PAH should involve discussion

among multi-disciplinary specialties including pulmonary vascu- lar, cardiology, and rheumatology experts, and the patient [16]. Similar to patients with IPAH, PAH-directed therapy in patients with SSc is individualized according to the World Health Organization (WHO) functional class, the degree of sever- ity/dysfunction. Treatment of PAH is directed toward three path- ways that alter vascular tone and/or remodeling: nitric oxide (NO) pathway via cyclic guanosine monophosphate (cGMP) enhan- cers (phosphodiesterase inhibitors (PDEi) and guanylate cyclase stimulants), endothelin pathway via endothelial receptor antago- nists (ERAs), and prostacyclin pathway via prostacyclin agonists, and most often, combinations of these agents [110,111]. These includeagents used for more severe Raynaud's and digital ulcers discussed above, such as bosentan and iloprost.

For SSc patients with mild-moderate PAH (WHO class II-III) initial combination oral therapy, typically with an ERA and PDEi, such as ambrisentan and tadalafil, is recommended. And those with more moderate-severe PAH (WHO class II rapid/progressive and class IV) are typically treated with a parenteral prostanoid along with two oral agents from different vascular pathways/ targets [112]. Differing from IPAH guidelines is the lack of support for high-dose CCB therapy since vasodilator-responsive PAH is a very rare occurrence in SSc patients (<5%) and unlike patients with IPAH, the response is unlikely to be sustained [2]. In general, with the exception of high-dose CCB, the principles of agent selection mirror those of the IPAH population.

The role of immunosuppressants in SSc-PAH is unclear, though all agree immunomodulation should be maximized since there is strong evidence for immune dysregulation and fibrosis in the pathogenesis of SSc and SSc-PAH. Rituximab is a DMARD that seems promising for SSc-PAH, although not significant, there does seem to be an impact on the 6-minute walk test performance, and could serve as adjunctive immu- notherapy in SSc-PAH [113].

PAH is rare in pediatric SSc, with a frequency of 2% and 5% reported in recent North American [9] and international [5] prospective juvenile SSc cohorts, respectively. Therefore, the group agreed to extrapolate the general treatment guidelines outlined for adult SSc-associated PAH.

9.2. Other cardiac involvement

Three other categories of cardiac involvement in SSc: myocardi- tis, arrythmia, and pericarditis were briefly discussed, though due to scare data for pediatric jSSc and limited treatment algorithms for adult SSc for these topics, we did not vote on specific gui- dance points and moved on to the gastrointestinal tract in SSc.

10. Domain Gastrointestinal involvement

10.1. 'Nutritional issues, poor growth, and failure to thrive are common in jSSc. Nutritional management includes patient education, nutritional support, potentially enteral/parental feeding and supplementation' (14/14 voted Yes; to note 2 members had to depart from the 16)

Gastrointestinal (GI) tract involvement is documented in 42– 74% of jSSc patients and has been associated with malnutrition, poor quality of life and interstitial lung disease [5,9,114–116]. It is important to recognize children often do not complain of overt gastro-esophageal reflux (GER) or dys- phagia symptoms, and more often self-limit portions and amount of food, causing weight loss and crossing into lower percentiles on their growth curve trajectory [117]. Vasculopathy and inflammation leading to fibrosis can man- ifest in the entire gastrointestinal tract, from mouth to anus. The most common GI problem encountered in jSSc and adult SSc is esophageal dysmotility, which causes poor weight gain and very low BMI (from nausea, dysphagia, and stasis), GERD with acid sequela, and silent aspiration of GI contents [5,100,118]. Esophageal involvement was also recently cap- tured from the patients' viewpoint in a prospective assess- ment of the National Registry of Childhood Onset Scleroderma (NRCOS) cohort (n = 54) who completed the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA-GIT 2.0; GIT), one of the most widely used and validated PRO for severity of GI involvement in adult- onset SSc [119,120]. The jSSc patients median Total GIT score and subscale scores were similar to those reported in adult SSc [121,122], with greatest impact of GI issues to be from Reflux and Distention and domains [123].

Routine assessment of nutritional status and referral to a nutritionist is beneficial in growing children with SSc, especially those with low BMI, with the additional concern of low muscu- larity and sarcopenia also contributing to low BMI. Medical treat- ment is directed at the level of GI disease (*see sections below*). The goals are to improve quality life through relieving symptoms, and to protect the GI tract from damage leading to strictures, dysmotility, aspiration, erosions, bleeding, and malignant trans- formation. Surgical interventions should be avoided, as they are of high risk in patients with SSc, who are prone to perforation and post-surgical strictures. Immunosuppressive therapy has not been demonstrated to treat or prevent the gastrointestinal man- ifestations of SSc, although GI outcomes have not been routinely reported in clinical trials.

10.2. "In jSSc patients general oral health includes regular dental care, maintaining oral hygiene and mouth hydration, and supportive oral physiotherapy" (14/14 voted Yes)

Oral manifestations of SSc are best treated prophylactically [124]. Skin tightening over the face, lips and mouth, leading to microstomia and poor mouth opening, tight skin over fingers and hands all contribute to making oral hygiene more challenging for patients with SSc. Ensuring the skin is effectively softened with emollients and massage is helpful. A dry

mouth (xerostomia) can lead to cavities and odynopha- gia and require treatment. Over-the-counter saliva substitutes, toothpastes, and mouthwashes containing xylitol, carboxy- methylcellulose or hydroxyethyl cellulose are recommended. Gingival and tooth care are important and may require devices to aide in flossing (flossers with toothbrush-like handles) and brushing (rechargeable oscillating, rotating toothbrushes) to improve oral hygiene for patients with significant difficulty with mouth opening or upper extremity joint contractures. Referral to a physical therapist should be considered for patients with microstomia, dysphagia, or aspiration for orofa- cial exercise therapy, specifically active and passive stretches and strengthening the mastication muscles, and safe food recommendations [125–127].

10.3. 'GERD is extremely common in jSSc. Management includes patient education, lifestyle modification, PPIs ± H2 blocker' (14/14 voted Yes)

Gastroesophageal reflux disease (GERD) is prevalent in jSSc, between 75–90% when full screening is applied (i.e. esopha- geal, pH probe, endoscopy), but only captured by symptoms in approximately 50% of the patients [123]. Many clinicians feel GERD must be treated even in asymptomatic patients. This is mainly due to concern for both silent damage to the esophagus with risk for cellular transformation as well as to help control acid to avoid chemical pneumonitis from silent chronic microaspiration, associated with ILD in adults and children [100,118]. In jSSc, the association between esopha- geal dysfunction and lung disease was underscored by the correlation between abnormal esophageal peristalsis and/or bolus clearing and decreased FVC on PFTs [118].

GERD is managed in part by lifestyle and dietary changes, including nighttime routine to avoid chronic microaspiration while sleeping, which consists of raising the head of the bed by 6 inches/15.2 cm and avoiding meals 3 hours before bed to reduce the gastric contents and help avoid nighttime aspiration [128].

Proton pump inhibitors (PPIs) are the mainstay of GERD therapy and should be given 30 minutes prior to meals, because they are activated by gastric acid [129,130]. Twice a day dosing is recommended for those on once-a-day dosing who are still symptomatic or have findings of esophagitis on endoscopy or significant reflex with pH probe. Adult SSc EULAR treatment guidelines recommend that a "PPI should be used for the treatment of SSc-related GERD to prevent ulcers and strictures" [2]. The pediatric SHARE jSSc guidelines did not address GI treatment [6]. From a practical standpoint, lansoprazole specifically can be dissolved, and thus easier to take for younger patients and those with esophageal dysmo- tility hindering swallowing. Acid secretion at night is depen- dent on histamine; therefore, refractory disease can be controlled by adding an evening dose of a H2 receptor antagonist, as supported by adult SSc guidelines for "PPI- partial responders" [128]. Additional symptomatic therapy for esophagitis includes sucralfate to coat the esophagus and stomach. To note, calcium channel blockers (taken for RP) relax the distal gastroesophageal sphincter, and clinicians should be mindful of alternative RP therapies in those with problematic GERD, or to screen for GERD symptoms after increasing CCB dose. Evaluation and co-management with a pediatric gastroenterologist, specifically a motility expert if available, is encouraged for all patients, especially given the general lack of overt symptoms or complaints in jSSc patients.

10.4. "Esophageal and gastric dysmotility in jSSc should be treated with a prokinetic agent" (14/14 voted Yes)

Esophageal dysmotility is as common as GERD in jSSc identi- fied by esophagram and symptomatically by upper (throat) and lower (mid-chest) dysphagia [123]. It compounds the issues of GERD attributing to poor appetite and weight gain. A similar phenomenon occurs in the stomach with gastropar- esis identified by delay in gastric emptying study and symp- toms of early satiety, nausea and regurgitation. A trial of prokinetic agent is warranted if these findings are present, especially in the setting of failure to thrive or low BMI. In jSSc, erythromycin or cyproheptadine are the preferred agents to begin due to good safety profile [29]. Low-dose erythromy- cin 2 to 3 times a day lowers esophageal pressure and increases gastric contractions to move food through the eso- phagus, whereas cyproheptadine assists in gut motility, gastric accommodation, and appetite stimulation, commonly used in pediatrics for different failure to thrive conditions. Metoclopramide is a useful prokinetic agent that increases esophageal sphincter pressure, improving peristalsis and gas- tric emptying, but has a more involved side-effect profile including tardive dyskinesia and prolonged QTc. Promotility agents are most effective if taken before meals 3 times daily and at bedtime. There are several other promotility agents used in adult SSc GI dysmotility, that could be considered in jSSc, but are not frequently used, mostly due to disease effect profile: prucalopride, pyridostigmine, mirtazapine, cisapride and domperidone [130]. Other non-pharmacologic methods to assist with GI motility in SSc are under investigation and include transcutaneous electroacupuncture and transcuta- neous auricular vagal nerve stimulation, both of which have shown decrease in symptoms and GI patient reported out- come measures in small studies [130,131].

10.5. "Esophageal surgical intervention for jSSc- associated GERD is not recommended" (14/14 voted Yes)

A gastric fundoplication for GERD is relatively contraindicated in patients with SSc due to the high incidence of post-operative dysphagia from underlying esophageal dysmotility which is not corrected by the surgery [132]. Esophageal strictures, on the other hand, would require mechanical dilatation via endoscopy to allow for swallowing in jSSc as in adult disease [133]. Treatment of Barrett's esophagus, as in adult SSc, includes radiofrequency ablation, photodynamic therapy, or endoscopic resection followed by close monitoring [134]. The group agreed that surgical intervention in children for better nutrition, such as a placement of a gastrostomy or jejunostomy tube, is comple- tely acceptable in the case of poor weight gain and failure to thrive

despite nutritional and medical therapy.

10.6. 'Treatment of SIBO in jSSc is helpful, and includes rotating antibiotics, promotility agents, and supplements' (14/14 voted Yes)

The frequency of small intestinal bacterial overgrowth (SIBO) is not clear in jSSc, but the symptoms reflect those of adult SSc, with diarrhea, bloating, and crampy abdominal pain. This is seen in jSSc in those with more advanced GI involve- ment. The mainstay of SIBO treatment is antibiotics, with varying length of treatment, typically a 7- to 10-day course, either once or on a more continual manner based on symptoms, with an "antibiotic"holiday every few weeks. Antibiotic choice is empirical and includes rifaximin (advan- tage of not being systemically absorbed), amoxicillin with clavulanate, gentamicin, and fluoroquinolones [135]. In refractory cases, metronidazole can be added for 5–7 days to treat anaerobic flora. Gut dysbiosis with alterations in the gut microbiome in SSc support a possible role for probiotics to aid in restoring balance to bacterial flora. Small studies, specifically with *Saccharomyces boulardii*, which has the advantage of being resistant to antibiotics being used in tandem for SIBO, show improvement bloating and disten- tion [136]. Treating the dysmotility contributing to the SIBO is also recommended, using prokinetic drugs, especially ear- lier in the process before the muscularis propria is atrophic and/or fibrotic. Octreotide is the main agent used, as in adult SSc, followed by prucalopride and pyridostigmine
[130] The use of intravenous immunoglobulin (IVIG) as an adjunct in SSc treatment for GI dysmotility has been shown to significantly improve patients GI symptoms (including GIT scores significantly) in observational case series, and could be considered as additional therapy in jSSc patients with small bowel gut dysmotility [137]. Lastly, malabsorption can occur secondary to SIBO and poor GI absorption, and may require supplementation of fat- and water-soluble vitamins, such as B12 and vitamin D3, along with dietary modifica- tions to help absorption, such as a lactose-free diet and low dietary long-chain fatty acids [138].

10.7. 'Treatment of jSSc associated constipation includes fiber, increased physical activity, osmotic, stimulative and/or secretory laxatives' (14/14 voted Yes)

Slow transit constipation due to colonic sclerosis is best trea- ted with hydration, dietary fiber, and regular exercise. Polyethylene glycol is a commonly used osmotic laxative, though should be used in moderation as these laxative can cause uncomfortable bloating. A secretory agent is typically next prescribed, such as linaclotide or prucalopride. Significant improvement in patient-reported GIT score with a moderate to more-than-moderate effectiveness documented in SSc patients taking prucalopride, a selective, high-affinity seroto- nin (5-HT_4) receptor agonist with marked gastrointestinal pro- kinetic activity [139].

10.8. 'Treatment of jSSc associated fecal incontinence includes bulking agents and pelvic floor exercises' (14/14 voted Yes)

Fecal incontinence must be screened for in teens and young adults since many do not offer this information by using patient reported outcome instruments, such as the GIT. The NRCOS cohort administered the GIT to 58 jSSc patients and identified that 12% (7/58) ranked either '1–2 days' or '3–4 days' on the GIT question #13, regarding 'accidentally soil (dirty) your underwear before getting to the bathroom' [123], while none of these patients offered this information during the routine clinical visit. Referral to a pediatric gastroenterologist is advised with encouragement of bulking agents to improve stool consistency, pelvic floor exercises, biofeedback and sacral nerve stimulation [140].

"Pseudo-obstruction in jSSc requires urgent medical evaluation and frequently requires in-patient management" (14/14 voted Yes)

Intestinal pseudo-obstruction in jSSc is treated by guidelines developed by adult SSc experts, which is typically inpatient admission for the evaluation to exclude mechanical obstruc- tion (i.e. abdominal imaging) and supportive care with bowel rest [128]. This regimen includes IV hydration, nutritional sup- port (total parenteral nutrition when indicated) with electro- lyte balance, prokinetic agents (such as subcutaneous octreotide), and broad-spectrum antibiotics for co- management of existing SIBO. Nasogastric tubes for decom- pression reasonable option but surgery is relatively contra- indicated and should be avoiding unless a severe case in which there is a failure of conservative therapies to decom- press the bowel.

11. Conclusion

Consensus for the best practices approach for jSSc patients was established with overarching principles of treatment across 8 domains with 29 total recommendations. This is a landmark study since it is an expansion beyond the first set of consensus recommendations by the SHARE initiative, which was based upon literature up to 2013, covered 8 treat- ment recommendations, and limited to European pediatric rheumatologists. Whereas the current consensus meeting encompasses literature to 2023, and diverse expertise and perspectives from pediatric and adult rheumatologists, pedia- tric pulmonologists, dermatologists, physical therapists, and patient representatives who participated in voting, capturing a true

multidisciplinary and international approach to jSSc management. These consensus recommendations can provide a template for care that ensures the most important aspects of jSSc treatment are prioritized, with the goal of elevating the standard of care internationally for jSSc patients. This standard of care should also enable patients to transition more smoothly to adult rheumatology care when age appropriate.

12. Expert opinion

This publication covers most facets of jSSc with overarching principle of treatment and covering 8 domains and 29 recommendations (Table 1). Therapeutic guidance is derived from both expert opinion and available literature, which is mostly based on adult systemic sclerosis (aSSc). Given shared patho- physiology of adult and juvenile systemic scleroderma, extrapolation of results regarding treatment from aSSc studies was judged reasonable. The more direct extrapolation from adult data is only possible for a particular therapy if a pediatric dosing exists, even if that is derived from a different pediatric indication, like for the treatment of arthritis or myositis.

We strongly suggest an early referral of jSSc patients to a specialized scleroderma center, to be able to introduce and practice the concept of therapeutic window and the treat to target strategy, which is proposed for the first time officially for the treatment of jSSc. The 'therapeutic window' aims to treat early to prevent cumulative disease damage in pediatricrheumatologic conditions. To reach this target, there needs to be more of a proactive movement to send the children early to as specialized center to receive multidisciplinary care to address and manage all aspects of the disease. The 'treat to target' concept covers an escalation the immunomodulatory treatment until remission of the disease is accomplished. We suggest starting MTX or MMF at the occurrence of the first sign of skin involvement or other non-Raynaud involvement. If after 3 to 6 months no improvement occurs or there is any significant deterioration, we propose combining their baseline DMARD (i.e. MMF or MTX) with biologic DMARDs, like tocilizu- mab or rituximab. If there is still no improvement or a decline in outcomes over the next 3 to 6 months, we suggest starting a different biologic DMARD or JAK inhibitor to find the right combination for each patient. We are suggesting considering autologous stem cell transplantation in the case of progressive disease in jSSc, such as an increase in mRSS with 5 points in 6 months or decrease in FVC with 10% or DLCO with 10% in 6 months. Historically, ASCT has been performed as individual cases or small case series for patients that have failed numer- ous medications and, therefore, have already accumulated damage. Given the advancement in safety of ASCT, we are hopeful patients with signs of progressive or severe disease undergo ASCT early in their disease path. We are hopeful that these treatment recommendations (Tables 1 and 2) will be adopted internationally into clinical practice. In the future we plan to compare national and inter- national jSSc registry outcomes and treatment practices in the 10 years prior to this publication in comparison to the follow- ing 10 years' practices. Collected in these data would be unique aspects of pediatrics, like growth and psychosocial development, as well as patient reported outcomes to include the patient's perspective. Importantly would be following jSSc cohort patients into their late teens and early adulthood to understand overall outcomes and potential impact in change in therapeutic strategy.

It is extremely important to include jSSc patients in the phase II or III studies of emerging drugs and cellular therapies to be able to assess these new treatments quite early and make them available for our patients. Most jSSc patients do not have traditional adult comorbidities, such as hypertension, coronary artery disease, hyperlipidemia or smoking, therefore; they are able to tolerate most drugs and cellular therapies significantly better then adult patients. Higher or more effec- tive doses of this drugs could be used.

We emphasize the involvement of the patients and care- givers into the treatment process, practicing 'shared decisions' in a patient centered care model.

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