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Guidelines

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Consensus-based recommendations for the management of juvenile systemic sclerosis

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Abstract

Juvenile systemic sclerosis (JSSc) is a rare disease of childhood and currently no international consensus exists with regard to its assessment and treatment. This SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative, based on expert opinion informed by the best available evidence, provides recommendations for the assessment and treatment of patients with JSSc with a view to improving their outcome. Experts focused attention not only on the skin assessment but also on the early signs of internal organ involvement whose proper treatment can significantly affect the long-term outcome. A score for disease severity is proposed in order to perform a structured assessment of outcome over time but a validation in a wider patient population is recommended. Finally, a stepwise treatment approach is proposed in order to unify the standard of care throughout Europe with the aim to reduce morbidity and mortality in this disease.

Key words: scleroderma, juvenile systemic sclerosis, assessment, recommendations, treatment, severity score, outcome

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Introduction

In 2012, a European project called Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases [1]. As no international or European consensus currently exists regarding diagnosis and treatment of juvenile rheumatic diseases, the definition of clear guidelines has been one of the most important aims of SHARE. In this paper, we focus on juvenile systemic sclerosis (JSSc) consensus-based recommendations.

Methods

An international committee of 16 experts in paediatric rheumatology was established to develop consensus-based recommendations for juvenile systemic sclerosis [2]. EULAR standard operating procedures for developing best practice were used [3]. Ten experts were part of the SHARE consortium; the other six experts were asked to take part in the project due to their great clinical experience in management of juvenile scleroderma. The methodology was similar to that performed in the recently published recommendations for juvenile localized scleroderma (JLS) [4].

Systematic literature search

The electronic databases PubMed/MEDLINE, Embase and Cochrane were searched in August 2013. All synonyms of JSSc were searched in MeSH/Emtree terms, title and abstract. Reference tracking was performed in all included studies (full search strategy in Supplementary Fig. S1, available at *Rheumatology* online). Two non-voting fellows (R.C., F.S.) and two experts (F.Z., I.F.) selected relevant papers for validity assessment (inclusion and exclusion criteria shown in Supplementary Fig. S1, available at *Rheumatology* online): 37 out of 1415 papers were selected. All full-text scored papers are listed in Supplementary Data S1, available at *Rheumatology* online.

Validity assessment

Two experts, who extracted data using a predefined scoring form separately for assessment and therapeutic studies, have independently assessed every relevant paper for methodological quality. Disagreement were resolved by the opinion of a third expert. Adapted classification tables for assessment, therapeutic and epidemiological studies were used to determine the level of evidence and strength of each recommendation.

Recommendation development

As part of the EULAR standard operating procedure [3], experts assessed validity and level of evidence and described the main results and conclusions of each paper. These data were examined by two experts (F.Z., I.F.) and used to formulate 11 provisional recommendations. These drafted recommendations were first presented to the expert committee in an online survey (100% response rate) and subsequently revised accordingly to responses. The derived recommendations were then presented to an expert committee formed by 16 paediatric rheumatologists with consolidated experience in managing patients with JSSc, and discussed using Nominal Group Technique [5] in two face-to-face meetings coordinated by S.J.V. who acted as non-voting facilitator. Recommendations were accepted when ≥80% of the experts agreed. At the first meeting, held in Genova, 9 out of 11 recommendations were accepted by the committee and two were discarded. Because of publication of new relevant papers in the meantime, at the second consensus meeting in Barcelona seven further recommendations, based on those recent evidences, were formulated and five were finally approved.

Results

The literature search yielded 1415 papers; after the application of inclusion/exclusion criteria, title/abstract and full text screening, 37 papers (21 for assessment and 16 for treatment) were selected and sent to the expert committee for validity assessment. Following a consensus-based methodology, the scleroderma working group of SHARE formulated 14 recommendations for the management of JSSc. In total, one overarching principle, five recommendations on assessment and eight on treatment were accepted with ≥80% agreement among the experts. Topics include assessment of skin, vascular and internal organ involvement and treatment suggestions at disease onset and in refractory disease.

In the following section, we describe the recommendations and present the supporting literature. Tables 1 and 2 summarize the recommendations for JSSc, the corresponding level of evidence, recommendation strength and percentage of agreement between experts. Of note, one recommendation derived from a controlled study without randomization (strength of recommendation B and level of evidence 2 A, modified adding evidences from another controlled study published after the literature search) (Table 2). The remaining recommendations derive from descriptive or case-control studies (strength of recommendation C-D, level of evidence 3) or from the expert committee opinion (strength of recommendation D, level of evidence 4).

Overarching principle

Juvenile systemic sclerosis is a rare multisystemic disease characterized by inflammation, vascular abnormalities and fibrosis that affects the skin and various internal organs [6]. Onset of the disease occurs mainly in adults, but onset during childhood is reported in about 10% of cases with a mean age at onset of 8 years [7]. The incidence, reported in a UK study, is 0.27 per million children per year [8] and a prevalence of 1 in 1 000 000 children from the USA claim database [9]. Given the rarity of the disease, the expert group agreed that all patients with

Table 1 JSSc – recommendations regarding assessment

		L	S	Agreement %
1	*Overarching principle* All children with suspected JSSc should be referred to a specialized paediatric rheumatology centre for multi-disciplinary care.	4	D	100
2	*Vascular involvement* All patients with isolated RP should have a nailfold capillary assessment and ANA testing. If capillaroscopy is abnormal and/or ANA are positive, then regular follow-up is recommended.	3	C	80
3	*Cutaneous involvement* A standardized skin score tool should be used for clinical assessment in JSSc. The modified Rodnan skin score is suitable, but needs to be adapted and validated for use in childhood.	4	D	100
4	*Internal organ involvement* The Juvenile Systemic Sclerosis Severity Score (J4S) can be used as a severity assessment tool in JSSC, but needs to be validated.	4	D	100
5	Pulmonary function tests, including DLCO, and HRCT in children with JSSc are sensitive tools to detect presence and severity of interstitial lung disease. Pulmonary function tests are also indicated for the respiratory function monitoring.	3	C	100
6	Patients with JSSc should have assessment of pulmonary function tests with DLCO, cardiac echo, renal function and modified Rodnan skin score at least every 6 months.	4	D	90

DLCO: diffusing capacity for carbon monoxide; HRCT: high resolution computed tomography; JSSc: juvenile systemic sclerosis; L: level of evidence; S: strength of recommendation.

Table 2 JSSc – recommendations regarding treatment

		L	S	Agreement %
1	*Skin involvement* Systemic corticosteroids, in combination with a DMARD, are useful in the active inflammatory phase of JSSc.	4	D	100
2	At the time of diagnosis of JSSc, a systemic immunomodulatory treatment, like methotrexate, should be considered.	4	D	100
3	In case of non-response to methotrexate an additional immunomodulatory agent (i.e. MMF) should be considered.	3	D	90
4	*Pulmonary involvement* Cyclophosphamide may be used to treat cardiac and/or pulmonary involvement.	4	D	100
5	*Vascular involvement* Iloprost may be used to treat ischaemic digits and digital ulcerations.	3	C	90
6	In New York stage II pulmonary hypertension, and/or digital ulcerations refractory to other therapies, bosentan should be considered.	3	D	100
7	*Experimental treatment* Biological agents, in particular tocilizumab or rituximab, should be considered in severe or refractory cases.	4	D	100
8	Autologous stem cell transplantation may be an option to treat patients with JSSc with progressive disease refractory to immunosuppressive therapy.	2a 2b	B	100

JSSc: juvenile systemic sclerosis; L: level of evidence; S: strength of recommendation.

suspected juvenile systemic sclerosis should be referred to a specialized paediatric rheumatology centre for clinical assessment and treatment.

Disease assessment

RP is often the presenting symptom and one of the most common clinical features in jSSc [7]. Nailfold Capillaroscopy (NFC) is a useful test to assess patients with RP [10] and the so-called 'scleroderma NFC pattern' has been demonstrated to be significantly associated with the development of connective tissue diseases (systemic sclerosis, dermatomyositis, overlap syndrome with signs of systemic sclerosis and mixed connective tissue disease) [11, 12]. In a cohort of 153 patients with JSSc, RP was the first clinical sign of the disease in ∼70% of cases [13].

ANA, with title over 1:80, are positive in over 80% of patients with JSSc [13, 14]. In the setting of an isolated RP, they are sensitive predictors of an underlying connective tissue disease; in particular, JSSc in presence of SSc-specific autoantibodies [15].

Based on these evidences and clinical practice, the expert group agreed that all patients with isolated RP should have an NFC assessment and ANA testing. If capillaroscopy is abnormal and/or ANA are positive (titer >1:80), then regular follow-up for identification of signs or symptoms of JSSc is recommended.

Skin induration is the second most frequent clinical manifestation in patients with JSSc during the course of the disease [13]. Quantification of the severity of skin involvement is important as an indicator of severity of the disease and as an outcome measure to monitor the response to treatment. A standardized skin score tool should be used for clinical assessment in JSSc; however, at present, no validated scoring system for JSSc is available. The modified Rodnan Skin Score (mRSS) is a simple and useful tool to assess cutaneous involvement that considers the extension of skin involvement and the degree of skin thickness [16]. It is widely used as an assessment tool in adult SSc and it shows correlation with survival [17]. However, it has been reported that median values of mRSS appear to be higher in the healthy paediatric population than in adults [18]. Therefore, for this measure to be useful in evaluating JSSc skin involvement, it will need to be adapted and validated for use in childhood.

Internal organ involvement, including pulmonary, cardiac, gastrointestinal, renal and nervous system, although rarer in JSSc than in adult forms of SSc, has shown to be associated with poorer outcome [19]. Respiratory and gastrointestinal systems are more frequently affected, while cardiac, renal and nervous system diseases are uncommon. In 2012, a new severity assessment tool for JSSc, the Juvenile Systemic Sclerosis Severity Score (J4S), was developed [20]. The J4S is a scoring system that includes indices of nine organ systems, each scored on a scale ranging from 0 to 4 according with the severity of each organ involvement. The J4S has been shown to be very effective and reliable in detecting change in disease severity. The expert group suggested the application of J4S into daily practice, although awaiting its validation in a large cohort of patients.

Pulmonary disease has been shown to be the most frequent internal organ involvement in patients with JSSc [13]. The most common presentation is that of progressive interstitial lung disease (ILD), whose most common symptoms are cough, dysponea and respiratory failure. Radiologic signs of ILD can be detected by chest X-ray only in the advanced phase and should be more properly evaluated and quantified using high resolution computed tomography scan (HRCT), which is the current gold standard of imaging. Pulmonary function tests (PFTs) should be used for detecting a reduction in forced vital capacity (FVC) and/or diffusing capacity for carbon monoxide (DLCO). These are sensitive and non-invasive tools to monitor the presence and severity of pulmonary involvement in paediatric patients aged older than 6–7 years. The correlation between PFTs, particularly FVC, and severity of changes on HRCT scan in JSSc patients with ILD has been shown to be quite good [21].

There is a general consensus on the need for a periodic follow-up of JSSc patients, that includes at least mRSS, NFC and musculoskeletal and internal organ assessment with pulmonary, cardiac, renal function tests. The time interval for these checks depends upon the disease status but should not be less than six months.

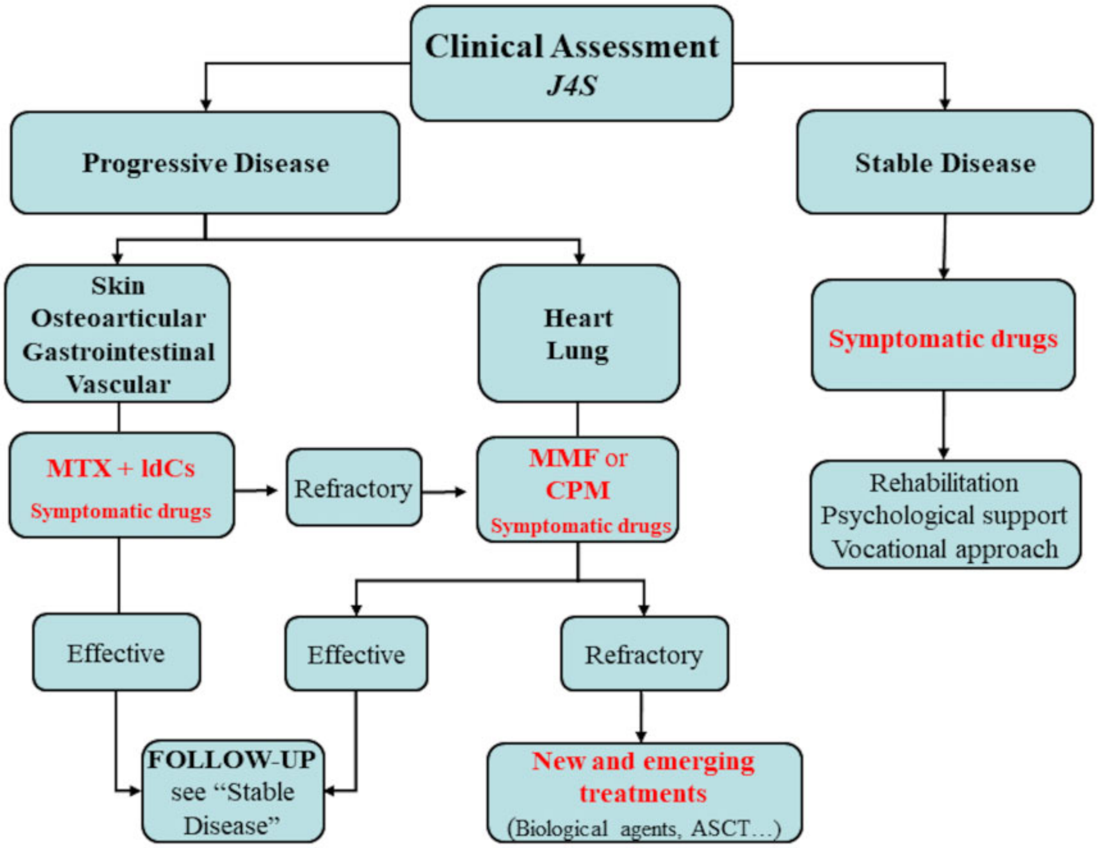
As compared with the adult form, JSSc appears to be less severe, involving internal organs less frequently, particularly at the time of diagnosis [13]. However, data from a descriptive study underlined the presence of a subset of patients with rapidly progressive disease characterized by early signs of widespread internal organ involvement. This severe course is associated with poorer outcome and higher mortality rate, suggesting the need for a more aggressive treatment [19].

Treatment

Published data regarding systemic sclerosis treatment in children are rare and mostly consist of case reports; therefore, the therapeutic strategy is often based on published data and guidelines for adult patients [22, 23]. The expert group agreed on the importance of developing age-specific treatment guidelines for patients with JSSc.

Corticosteroid treatment should be started at the time of diagnosis of JSSc, to reduce the inflammatory component as quickly as possible. Although the literature is lacking in evidence for the use of corticosteroids in JSSc, there is a general consensus on its indication for the active inflammatory phase, especially when myositis or arthritis are present. However, no consensus has been reached about dosage and administration regimens. Because scleroderma renal crisis in children is very rare [13], experts agree that corticosteroid treatment should be started early; of course, with close patient monitoring, including blood pressure and renal function check. Methotrexate or an alternative DMARD should also be commenced at the time of diagnosis. The EULAR guidelines for adult patients recommend methotrexate as treatment for scleroderma-related skin involvement [21]. Again, there is a paucity of literature relating to the effectiveness of methotrexate in treating cutaneous involvement or other organ manifestations of JSSc. However, low-dose methotrexate (15 mg/m^2/week) is widely used in juvenile localized scleroderma [24, 25] and other connective tissue diseases in childhood and has a good safety profile [26, 27]. Therefore, expert experience suggests the early use of MTX in JSSc, especially when cutaneous, articular, vascular and/or gastrointestinal involvement are present (Fig. 1).

Fig. 1 Flow chart for the treatment of patients with juvenile systemic sclerosis according to disease severity



ASCT: autologous stem cell transplantation; biological agents: rituximab, tocilizumab, abatacept; CPM: cyclophosphamide;J4S: Juvenile Systemic Sclerosis Severity Score; ldCs: low dose corticosteroids; symptomatic drugs: calcium channel blockers, phosphodiesterase type 5 inhibitor, angiotensin converting enzyme inhibitors, proton pump inhibitors, prokinetics.

If the disease is resistant to MTX (J4S score worsening by at least 6 months of MTX therapy), addition or switching to MMF should be considered. EULAR guidelines regarding MMF in adult forms of scleroderma are poor [22, 23] although data from the recent literature report positive effects on cutaneous and pulmonary involvement with good tolerability [28, 29].

As compared with adults, children with JSSc have better outcomes, related to a lower mortality [19]. Morbidity is a major issue for JSSc, with most patients having multi-organ manifestations [30]. In a recent North American cohort of 64 JSSc patients, 38% were found to have more than four organ systems involved [14]. In addition, 36% of them were found to have impaired function (ACR functional scores >1). Poorer quality of life scores were found to be associated with gastrointestinal symptoms, arthritis and pulmonary diseases and this was confirmed in another recent study [29]. These findings underline the importance of a holistic approach to the treatment of internal organ involvement.

Given the lack of evidence for the use of immunosuppressive therapy in JSSc, we currently rely on the published literature in adult patients. The EULAR guidelines for adults, taken from two Randomized Controlled Trials (RCT), suggest a positive role of cyclophosphamide in SSc-related interstitial lung disease [31, 32]. Despite its known toxicity, clinical practice experience in European paediatric scleroderma centres also supports the indication for cyclophosphamide in case of pulmonary and/or cardiac involvement; therefore, its use should be considered in this group of patients but carefully thought out.

Vascular involvement, frequent both in adult SSC and in JSSc mainly manifests as RP and digital ulceration. Pulmonary arterial hypertension is also described, although rarer in JSSc than in the adult forms [13]. Vasodilator agents are often used in adult patients with SSc [22]. The use of vasodilators in JSSc is rather common as well, especially for the treatment of vasospastic phenomena of the extremities. The most widely used vasodilators are calcium channel blockers (CCBs) and among them, nifedipine is the most common. An alternative to CCBs are the phosphodiesterase type 5 inhibitors (PDE-5i), such as sildenafil [22]. Experts suggested that iloprost, an analogue of natural prostacyclin (PGI2), may be used to treat severe refractory RP or digital ulcerations [33, 34]. When digital ulcerations are refractory to CCB and prostanoids or in case of New York stage II pulmonary hypertension, bosentan should be considered. In adults, bosentan is also recommended for preventing digital ulcerations [22, 35].

In the presence of rapidly progressive or refractory disease, treatment with selected categories of biological agents could be considered, despite poor evidences in the paediatric population. Literature data regarding anti-CD20 (rituximab) or anti-IL6 (tocilizumab) treatment in adult forms of SSc support their efficacy and relative safety, particularly for skin and respiratory involvement [36–39]. However, unfortunately no data on these agents had been published, at the time of the search, in children with JSSc; therefore, their use is suggested only on the basis of more recent case reports [40].

Novel therapeutic approaches could target specific inflammatory or profibrotic chemokines and cytokines that have been shown to be overexpressed in SSc [41]. Recent reports show promising results of haematopoietic stem cell transplantation (HSCT) in adult-onset SSc and encourage optimism for this therapeutic approach in children, who may have less organ damage when disease is recognized [13].

Literature provides data on both adult and paediatric patients, on HSCT in autoimmune diseases [42, 43]. Preliminary data suggest that a careful selection of the patients to undergo HSCT is crucial. However, the lack of consensus about the transplant technique and the high risk of transplant-related morbidity and mortality suggest the need for further studies to assess the efficacy and safety of this procedure in the paediatric population. Based on consensus recommendations, a flow chart to guide the treatment of JSSc was eventually proposed (Fig. 1).

Discussion

The scleroderma working group of SHARE has formulated a total of 14 recommendations for the management of JSSc, based on a systematic literature review and consensus procedure. Topics include assessment of skin and internal organ involvement and the use of systemic treatment options. In total, one overarching principle, five recommendations on clinical assessment and eight on therapy were accepted with $\geq$80% agreement among the experts.

Close monitoring of patients' disease status and well-being by an experienced multidisciplinary and interdisciplinary team with expertise in JSSc is essential for a good clinical outcome. As in patients with juvenile localized scleroderma, all experts agree on the importance of managing JSSc in specialized centres [4]. In addition, international sharing of patients' data in larger studies, such as registries and biobanks, will provide evidence to improve standards of care.

Research agenda

All experts agreed that a future research agenda should include the prospective validation of J4S score, the role of HRCT in the assessment and monitoring of ILD and, among possible biomarkers, scleroderma-specific autoantibodies and cardiopulmonary markers, such as NT-pro-BNP and serum Krens von den Lugen 6 (KL-6). This is a mucin-like glycoprotein expressed on type II pneumocytes in alveoli and epithelial cells of bronchioles that resulted elevated in adults and children with severe interstitial lung disease [44, 45]. As for treatment, the future research agenda should include the evaluation of safety and efficacy of MMF, biological agents and newly discovered anti-fibrotic agents.

One of the limits of this work is that, being the literature search performed in 2013–2014, new evidences have been published in the meantime. In light of new data available, relevant changes to the recommendations were made only after being discussed, voted on and approved by the expert group. Another limitation is that the literature search did not provide relevant data regarding gastrointestinal assessment in JSSc. Therefore, this topic was mentioned but not elaborated on during the consensus meetings.

To conclude, this SHARE initiative, based on expert opinion informed by the best available evidence, provides recommendations for the assessment and treatment of patients with JSSc, with a view to improving their outcome in Europe. We anticipate that physicians outside Europe caring for JSSc patients will also likely adopt these guidelines. It is now important to disseminate these recommendations, test their reliability in the international scientific community and update them as new data become available.

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Data availability statement

Additional unpublished data from the study are available by just sending an email to F.Z. (francescozulian58@gmail.com).

Supplementary data

Supplementary data are available at *Rheumatology* online.

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