Egyptian Rheumatology and Rehabilitation

RESEARCH

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Egyptian evidence-based consensus on clinical practice recommendations for the management of systemic sclerosis

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Abstract

Background This work aims to develop clinical practice recommendations for the management of systemic sclerosis (SSc).

Results Fourteen expert panels had completed the two rounds of surveys. After the end of round 2, recommendations were released and distributed on 11 domains. The percentage of the agreement on the recommendations was 92.3% to 100%. All 11 key questions were answered at the end of the second round with agreement.

Conclusion This guideline tried to tackle the gaps in research that limit treatment options. Stratifying the patients according to their disease domains has helped to set up sequential management pathways for each domain.

Keywords Systemic sclerosis, SSc, Guidelines, Recommendations, Multidisciplinary, ILD, Renal crisis, Scleroderma, Egyptian Academy of Rheumatology

Background

Systemic sclerosis (SSc) is a rare autoimmune rheumatic disease [1] characterized by skin fibrosis, vasculopathy as well as internal organs affection. Due to its diverse, complex, and multi-systemic nature, the lack of a specific diagnostic test, and how the disease might initially present itself, there is a delay in the diagnosis process associated with a high degree of uncertainty regarding what complications may arise and how to manage it [2]. Consequently, this represents a challenge for both the patients and the physicians. In comparison to all the other autoimmune rheumatic diseases, SSc has the highest mortality, with approximately 70% of the affected patients eventually dying due to the illness itself or a result of its systemic complication [3].

In a trial to tackle the mosaic nature of the disease and following the consideration of early SSc definition [4], the American College of Rheumatology (ACR) and The

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European Alliance of Associations for Rheumatology (EULAR) jointly proposed guidelines for Systemic Sclerosis classification [5]. Such criteria facilitate the earlier diagnosis of the disease, at stages when the illness might potentially be amenable to therapy. In fact, such advances in understanding the disease's pathognomonic features, evolving criteria for early diagnosis and newer therapeutic modalities provide a new ray of hope in this disease.

With imperative new drug trials and evidence-based therapies for the management of SSc, together with changes in medical care policies in Egypt and the introduction of the national insurance strategy; it was important to provide a practical roadmap for the treatment of SSc. Therefore, the aim of this work is to develop a guideline that builds upon the previously published management guidelines and incorporates recent developments in evidence-based medical therapies as well as increased knowledge about the evaluation, classification, and investigations of systemic sclerosis.

Methods

Design

The study design was developed through a qualitative synthesis of consensus and scientific evidence, using both clinical experience and currently available scientific evidence. The "Clinical, Evidence-based, Guidelines" (CEG) initiative procedure was followed in this multi-step process, which sought to establish an actionable clinical gold standard for Treat-to-Target management of rheumatic and bone diseases. The manuscript's evidence-based section complied with the recommended reporting items for systematic reviews and the meta-analyses reporting requirements for systematic reviews [6]. The Egyptian Academy of Rheumatology spearheaded the effort.

Development stages

Core team

It is formed of three experts with established experience in rheumatology, particularly SSc. The core team coordinated and supervised the teamwork, and assisted in the development of the project scope and setting up of the initial Patient/Population, Intervention, Comparison, and Outcomes (PICO) [7] clinical questions. The team has also helped in reaching a consensus on the key questions to be included in the guideline nominating the expert panel and drafting the manuscript.

Literature review team

Led by 1 methodologist and 2 experienced specialists in review of the literature with the base of key research questions, were identified. The task was to carry out review of the literature [8] focussing on SSc diagnosis and treatment. The period covered by the article search was January 2000–July 2023.

Data sources and search strategies

The Key clinical questions (Table 1) were used to conduct the literature search. The bibliographic research was carried out until July 2023, to find studies that met the criteria for inclusion in the MEDLINE, EMBASE, and Cochrane Library databases. For pragmatic reasons, the language was limited to English. The search strategies were designed to be broad to have high sensitivity for identifying relevant literature.

This systematic review was conducted following the specific Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) methodological guidelines [6] and the PICO question model for the definition of the inclusion criteria: P (population): "systemic sclerosis patients"; I (intervention): "treatment", "treatment with biologic medications"; C (comparison): "same conditions with placebo, sham therapy or no intervention or pre-/post-comparison data group"; O (outcomes): "Skin disease (modified Rodnan scale value [mRSS]); pulmonary function test (forced vital capacity [FVC] and carbon monoxide diffusing capacity [DLCO]); and health status (Health Assessment Questionnaire [HAQ] Disability Index [DI] → HAQ-DI Scale). These parameters were included as outcomes as they are commonly assessed in health biomarker studies and in SSc research [9].

Bibliographic search terms included a mix of medical subject headings (MeSH) and free text words for key concepts related to SSc: scleroderma, systemic sclerosis, scleroderma diffuse, diffuse cutaneous systemic sclerosis, guidelines, consensus, recommendation, best practice, therapeutics, biologic therapy, rituximab, nintedanib, ofev, tocilizumab, azathioprine, biological therapy,

Table 1 The key clinical questions

1. What is the aim of this guideline?
2. Who are the targeted audience?
3. What is the classification of scleroderma?
4. What are the benefits of classification or stratification of Systemic Sclerosis?
5. How to evaluate and follow-up systemic sclerosis patient?
6. How to screen for organ involvement in SSc?
7. What are the general recommendations in the management of early SSc?
8. How to manage organ-specific affection in SSC?
9. What is the non-pharmacological management of systemic sclerosis?
10. What is the risk of malignancies in systemic sclerosis patient?
11. What are the serious complications and prognosis of systemic sclerosis?

SSC Systemic sclerosis

DMARDs, antibodies, and monoclonal (monoclonal antibodies); all linked using the Boolean operators OR and AND.

Electronically, duplicate screening of the findings of the literature search was done. By looking through the reference lists of studies found using the database search methodologies that satisfied the inclusion requirements, further pertinent research was found. Following the revision, each of the experts responsible for the literature review provided recommendations regarding each section based on evidence, when that was available, or on their own experience.

Level of evidence

Levels of evidence are assigned to studies based on the research design, quality of the study, and applicability to patient care. The level of evidence was determined for each section using the Oxford Centre for Evidence-based Medicine (OCEBM) system (Supplement Table S2) [10]. Higher levels of evidence have less risk of bias.

Study selection

By using inclusion and exclusion criteria for the literature that was found using the search methodologies, the pertinent studies were chosen.

Inclusion criteria

The included articles were observational studies, case–control, cohort, and cross-sectional studies; systematic reviews; uncontrolled trials; and randomized controlled trials (RCTs). When multiple publications reported data from the same study, the publication with the most complete data was included whereas publications reporting duplicate data were excluded. Studies were reviewed for inclusion or exclusion in two stages—first, titles and abstracts were assessed, and then studies identified as possibly relevant by title/abstract screen received full-text review.

Exclusion criteria

Editorials, conference abstracts, commentary, and narrative/personal reviews that lack supporting data were not included.

Study selection and data extraction

All reports were independently screened for inclusion by two reviewers. A third expert was consulted in the event that there was a dispute. Every report's year of publication, study design, number of patients, kind, severity, and duration of the SSc, dosage and/or dosing schedule, duration of treatment, definition of effective treatment, outcome, side effects, and the number of dropouts and their causes were noted.

Expert panel

Fourteen members were nominated by the core leadership team. Their selection criteria included being actively involved in scientific research on SSc and having at least 10 years of experience in their specialty (rheumatology, dermatology, cardiovascular, pulmonology, gastroenterology, or nephrology). Information on the project's objective and the Delphi approach were included in the invitation that was sent to the experts. The experts who accepted this invitation were informed that in order to take part in the next rounds of ratings, they had to reply to the first round. The expert panel participated in the project's scope development, helped to improve the PICO questions, and submitted votes on the recommendations.

Key questions used to develop the guideline

The target population, classification criteria, intervention or exposure under investigation, comparison(s) used, outcomes used to measure efficacy, effectiveness, or risk, and the timing of introducing the appropriate management are all defined by a set of structured key questions that served as the basis for this guideline. The following procedures were followed in order to collect the evidence needed to respond to the clinical questions: developing the clinical questions, organizing the questions, searching for evidence, critically evaluating and choosing the evidence, presenting the findings, and making recommendations. These inquiries, as indicated in Table 1, serve as the basis for the systematic literature search and, subsequently, the clinical care standards.

Developing the clinical care standards framework

Based on the answers to the structured key questions and the literature research, a structured template was developed to assist in the standardized identification of the recommendation components. It has been determined what format each component's information and recommendations would be retrieved and presented in.

Delphi process

Thus, the Delphi method's aim is to generate consensus recommendations from a panel of experts through an organized, iterative process. The two main characteristics of this approach are participant anonymity and regulated feedback [11–13].

Consensus process

From 4 to 27 October 2023, to reach a consensus, there were two Delphi rounds. Following the identification of the main aspects of this strategy, a working group

with the scientific committee determined which components should be included in the surveys. The structured Delphi method, which is particularly useful for geographically disparate centers like Egypt, guarantees that participant perspectives are taken into equal consideration. Online questionnaires were used to carry out the Delphi process. Two rounds were used as this is seen to be the best way to achieve consensus and allows for sufficient reflection on group responses [14]. Additionally, free-text answers from round 1 could be added to round 2 surveys in two rounds as new statements. There were 11 domains in the initial electronic questionnaire round.

Voting process

Voting was conducted in two time-limited rounds via live online distribution. Every task force member received an invitation to participate and advance notice of the start and end times of each voting session. Votes were collected and processed anonymously, and special access links were distributed. During the voting process, feedback on possible ambiguity, unidentified overlaps, and rephrasing of each statement was received. Voting on the statements was restricted to task force members alone.

Rating

Every statement received a score ranging from 1 to 9, where 1 represented "complete disagreement" and 9 represented "complete agreement." In general, the numbers 1–3, 4–6, and 7–9 stand for disagreement, uncertainty, and agreement, in that sequence. If a member feels that a statement is outside of their area of competence, they are advised to abstain. Consequently, "inconvenience about the accuracy of the recommendation" is represented by a "uncertainty" vote. Following each voting round, comments that were examined by the scientific committee are permitted for all statements. Members were also encouraged to offer comments in each voting round when they disagreed with a decision. This will enable the panel to identify cases of misinterpretation of statements and nullify the vote on those specific statements.

Definition of consensus

An agreement-based definition was created before any data was analyzed. It was discovered that consensus would be formed if at least 75% of participants achieved agreement (score 7–9) or disagreement (score 1–3) [8, 11, 12]. A statement was retired if its mean vote fell below three or it had a "low" degree of agreement. Statements that scored between 4 and 6 on the uncertainty scale had their rates changed in light of the feedback. Each recommendation statement's levels of agreement were classified as "high" if, following the second round of voting, every vote fell inside the agreement bracket (7–9) [13, 15, 16]. When replies varied by less than 10% between round groups, stability of consensus was deemed to have been attained [17].

Chronogram of Delphi rounds

The first round ran for 9 days, from October 4–12, 2023. In consideration of the feedback, the elements on which respondents were unable to reach consensus in the first round were changed and included in the second. The second round was held from October 20–27, 2023, for 8 days, 1 week after the first round.

Ethical aspects

The Helsinki Declaration was followed in the conduct of this study. This involved a series of steps that adhered to the "Clinical, Evidence-based, Guidelines" (CEG) initiative protocol (Tanta University's ethical board, ethical approval code: 34,842/8/21). The process' objective was to establish a practical clinical gold standard for Treat-to-Target management of bone and rheumatic diseases.

Results

Literature research and evidence selection

Nine hundred forty-five records were found during the search; 714 of those were reviewed after duplicates were eliminated (231). We were able to obtain the complete text of 115 possible papers after screening. The literature review contained 24 papers. The findings were compiled, summarised, and developed into suggestions for the care of SSc patients. After that, they were debated, changed, and put to a vote. Supplementary Figure S1 displays this process's flowchart.

Expert panel characteristics

The Delphi form was sent to the expert panel ($n=14$) all the panels completed the two-round survey. The participants were one from Europe and 13 from Africa (Egypt).

Delphi round 1

Eleven topics, all of which addressed clinical questions addressed in later rounds, made up the round devoted to the major clinical questions. Every domain and question was accepted (all respondents strongly agreed or agreed), and no questions were removed from the list.

Delphi round 2

Using the data from round 1, a list of 11 sectioned recommendations was produced based on the literature search. The experts' panel received 100% of the responses for round 2. Changes in wording were proposed for eight domain statements. The claims were updated and changed. There was agreement on every point (more than

80% of respondents strongly agreed or agreed). The ratings given by medical professionals and patients did not differ much. The gastrointestinal and vascular domains were the focus of the primary modification.

Statements and grade of recommendations (GOR) for the management of SSc

The following is a list of the recommendations made in order to address the main clinical questions. Under each section are the following: the mean degree of agreement among the expert panel members, the percentage of agreement, the level of evidence (LOE), and the grades of recommendations. Table 2 shows the overarching principles for these recommendations.

There are 11 domains to answer the 11 key questions.

1 What is the aim of this guideline? level of agreement: *Mean + SD: 8.92 ± 0.28, percentage of agreement: 100%, Level of agreement: High.*

The purpose of the guideline is to support medical professionals who treat and care for individuals with systemic sclerosis in all of its clinical manifestations. Patients and those in charge of procuring systemic sclerosis patient care in the National Health Service should find the guideline to be a useful resource.

2. Who are the targeted audience? *level of agreement: Mean + SD: 8.85 ± 0.55, percentage of agreement: 100%, Level of agreement: High*

Management of SSc should occur within the framework of a multidisciplinary team. Therefore, this recommendation is for rheumatologists, dermatologists, pulmonologists, cardiologists, and other physicians who are involved in the management of SSc patients.

3. What is the classification of Systemic Sclerosis/localized scleroderma? level of agreement: Mean + SD: 8.61 ± 0.5, percentage of agreement: 100%, Level of agreement: High

When SSC is suspected clinically by the expert physician; ANA and capillaroscopy should be done for early diagnoses and management, then cardiopulmonary consultation could be done. SSc are classified according to Systemic Sclerosis 2013 ACR/EULAR classification criteria. Clinical presentation can be either localized scleroderma or systemic sclerosis according to the clinical presentation and the visceral involvement. Localized scleroderma is limited to fibrotic involvement of the skin and subcutaneous tissues (morphea or linear scleroderma), while SSc affects also internal organs which is classified as limited cutaneous or diffuse cutaneous type (Diffuse proximal skin involvement is defined as involving the skin of the trunk or proximal limbs). Rarely SSc could be presented as SSc sine scleroderma in the absence of cutaneous sclerosis.

It is important to identify those with overlap disease so that SSc can be administered concurrently with the overlap features.

4. What are the benefits of classification or stratification of systemic sclerosis? *level of agreement: Mean + SD: 8.85 ± 0.53, percentage of agreement: 100%, Level of agreement: High*

Table 2 Overarching principals

1) Always approach systemic sclerosis as a multi-organ disease
2) Chronological involvement of the skin and organ involvement in both systemic sclerosis (Fig. 1) as well as scleroderma (Fig. 2) is important as it might have therapeutic implications and prophylactic impact
3) Systemic Sclerosis (SSc) has the highest mortality of any of the autoimmune rheumatic diseases, with approximately half of the people affected by SSc eventually dying as a direct result of the disease or a related complication(s)
4) Timely diagnosis of SSc is vital and delays in diagnosis should be minimized
5) Once a confirmed diagnosis is established, all patients can be designated as either lcSSc or dcSSc subset based upon the extent of skin thickening
6) Proximal skin involvement, involving the skin of the trunk or proximal limbs, is designated diffuse
7) Of people with SSc, 1 in 5 develop overlap connective tissue diseases, therefore, cases with overlap disease should be identified so that overlap features may be treated concurrently with SSc
8) All patients require symptomatic treatment, and both limited and diffuse cases should be treated for vascular manifestations
9) Active, early dcSSc requires immunosuppressive treatment
10) In all cases of SSc, watchful follow-up to determine significant organ-based complications is mandatory
11) Patient-reported outcomes can be of help to monitor the individual patient's disease activity status, the development of organ affection, identify his/her targets, and set up self-management programs
12) Shared decision-making should be the base for all management strategies offered to the patient

SSC systemic sclerosis, *lc* limited cutaneous, *dc* diffuse cutaneous

It's important to distinguish between localized scleroderma and systemic sclerosis, as they differ in their management approaches. SSc should also differentiated into limited cutaneous and diffuse cutaneous types; as they are different in their specific autoantibodies, associated with different presentations in internal organ manifestations, and differ in prognosis and outcomes. Also, classification helps to differentiate SSc from scleroderma mimics.

5. How to evaluate and follow-up systemic sclerosis patient? *Level of evidence: 4C, level of agreement: Mean+SD: 8.85 ± 0.38, percentage of agreement: 100%, Level of agreement: High*

- Baseline organ-specific evaluation and monitoring should be done when any organ or system affection is suspected.
- Follow-up examinations are essential for screening and monitoring the complications and visceral damage, disease activity and severity, and monitoring the treatment effect, tolerability, and adverse effects.
- Monitoring of SSc patients differs according to organ affection, type of complication, and severity of disease. Unless there is an emergency or life-threatening condition, follow-up should be done every 3 months, especially in the first 5 years of onset of the disease then every 6 months.

6. How to screen for organ involvement in SSc? Level of evidence: 3C, level of agreement: Mean + SD: 8.85 ± 0.38, percentage of agreement: 100%, Level of agreement: High

- For early evaluation of SSc; capillaroscopy should be done which has diagnostic, prognostic, and disease activity assessment roles.
- Laboratory assessment is crucial in classification and prognostic values of SSc (Fig. 3), such that:

  – Anti-Scl-70 (anti-topoisomerase) antibody is associated with dcSSc, and a higher risk for the development of progressive interstitial lung disease (ILD),
  – Anticentromere antibody (ACA) is associated with lcSSc, the risk for pulmonary artery hypertension (PAH), and primary biliary cirrhosis.
  – Positive RNA polymerase III antibody is at the highest risk of developing scleroderma renal crisis (SRC), and heart affection.
  – Anti-fibrillin is associated with PAH and cardiac affection, and anti-U1RNP is associated with overlap, mixed connective tissue disease (MCTDs), and lung fibrosis. Anti-PM-Scl is associated with myositis

- Cardiopulmonary evaluation [pulmonary function tests (PFTs), high-resolution CT (HRCT) chest, ECHO cardiography, or even cardiac catheterization] should be done as early as possible when suspected cardiopulmonary affection in SSC patients.

7. What are the general recommendations in the management of early SSc? *Level of evidence: 3C, level of agreement: Mean + SD: 8.69 ± 0.48, percentage of agreement: 100%, Level of agreement: High.*

  – Early recognition and diagnosis of dcSSc is a priority, with referral to a specialist SSc center
  – Early and accurate diagnosis = earlier intervention = more effective therapies
  – Evaluate every patient for organ involvement
  – Recognize associated factors and stratify risk
  – Screen early: Do not wait for symptoms to develop
  – Accurate physical examination can be very helpful
  – Assess for comorbidities
  – D-Penicillamine is not recommended.
  – Autologous hemopoietic stem cell transplant ASCT may be considered in some cases, particularly where there is a risk of severe organ involvement, balancing concerns about treatment toxicity.

8. How to manage organ-specific affection of systemic sclerosis?

General principles for evaluation of organ involvement in SSc

- Evaluate every patient for organ involvement
- Recognize associated factors and stratify risk
- Screen early—do not await for symptoms development
- Accurate physical examination can be very helpful
- Assess for comorbidities

Management of each system or organ in SSc is mentioned in detail in Table 3. The approach to Raynaud's phenomenon and Digital Ulcer management is summarized in Table 4.

9. What is the non-pharmacological management of systemic sclerosis? Level of evidence: 4D, level of agreement: Mean + SD: 8.69 ± 0.48, percentage of agreement: 100%, Level of agreement: High

- Non-pharmacological therapies are recommended in all cases of SSC to avoid disability.
- SSC patients must stop smoking and should do regular exercise as tolerated
- Avoidance of cold exposure and protection against microtrauma is important for the management of Raynaud's phenomena (RP-SSC).
- Salt-reduced diet should be followed in patients with PAH and peripheral edema
- Physiotherapy and rehabilitation modalities for the musculoskeletal system, pulmonary and cardiac rehabilitation
- Occupational therapy is important, especially in patients with extensive hand affection.
- Consultation with a dietitian and food modification are essential, especially in GIT affection.
- Psychotherapy and social support are essential for SSC patients.

10. What is the risk of malignancies in systemic sclerosis patient? (LOE 1 b) Level of evidence: 2B, level of agreement: Mean + SD: 8.61 ± 0.65, percentage of agreement: 100%, Level of agreement: High

- All patients with new onset SSC should have a comprehensive physical examination and age-, sex- and risk factor-based cancer screening tests.
- Scleroderma patients with positive RNA polymerase III and anti-topoisomerase I antibodies are at higher risk for malignancy.
- Long-standing lung fibrosis is considered a lung cancer risk factors
- Some patients with SSc and chronic GERD develop Barrette's esophagus, which can progress to dysplasia, which is a risk factor for esophageal adenocarcinoma.
- Exposure to cyclophosphamide is linked to bladder cancer.

11. What are the serious complications and prognosis of systemic sclerosis? Level of evidence: 4C, level of agreement: Mean + SD: 8.85 ± 0.37, percentage of agreement: 100%, Level of agreement: High

- The prognosis of SSC differs widely according to depending on the type of cutaneous affection and the type and degree of visceral affection.
- Diffuse cutaneous type is the worst prognosis and rapidly progressive type of SSc especially in the first 3–5 years from disease onset. The most common associated complications are musculocutaneous complications, diffuse infiltrative lung disease, and/or cardiac symptoms, renal crisis, and gastrointestinal disorders (Fig. 1).
- The most common complications associated with limited cutaneous SSc are PAH and digestive affection, other visceral affections are less common than diffuse type (Fig. 2).
- The mortality rate is higher in the diffuse than limited cutaneous form of the disease.
- Life-threatening conditions in SSc depend on the extent of major complications such as gastric antral vascular ectasia, intestinal pseudo-obstruction, SRC, ILD, PAH, and myocardial dysfunction.

Discussion

Systemic sclerosis represents, likely, a group of closely related systemic pathologies that share features of autoimmunity, vasculopathy, and fibrosis. Over the past decades, there has been an unmet need for clinical practice guidelines in the management of several domains in affected SSc patients. Consequently, it was paramount to provide a comprehensive management approach to SSc. The aim of this work was to develop a holistic standard clinical guideline valid to ensure the delivery of high-quality and homogeneous care for the management of SSc patients.

The developed guidelines provided global management of SSc, and in the meantime endorsed the patients' stratification according to their risk. The guideline was grouped into 11 domains regarding assessment and management. This includes eight disease domains: Raynaud's phenomenon and digital ulcers, skin, musculoskeletal, cardio-pulmonary, interstitial lung disease, gastrointestinal, renal, and neurological affection. Consequently, it suggested sequential treatment of SSc organ-based complications. The developed guideline endorsed also the awareness of the treating healthcare professionals regarding the high-risk probability of their patients developing organ-specific damage such as renal crisis or interstitial lung disease. Appropriate screening and treatment practices should be implemented to ensure long-term benefits. This is in line with recently published guidelines including the published EULAR recommendations [9, 18], the British Society for Rheumatology (BSR) guideline (2016) [19], the European Dermatology Forum Guideline

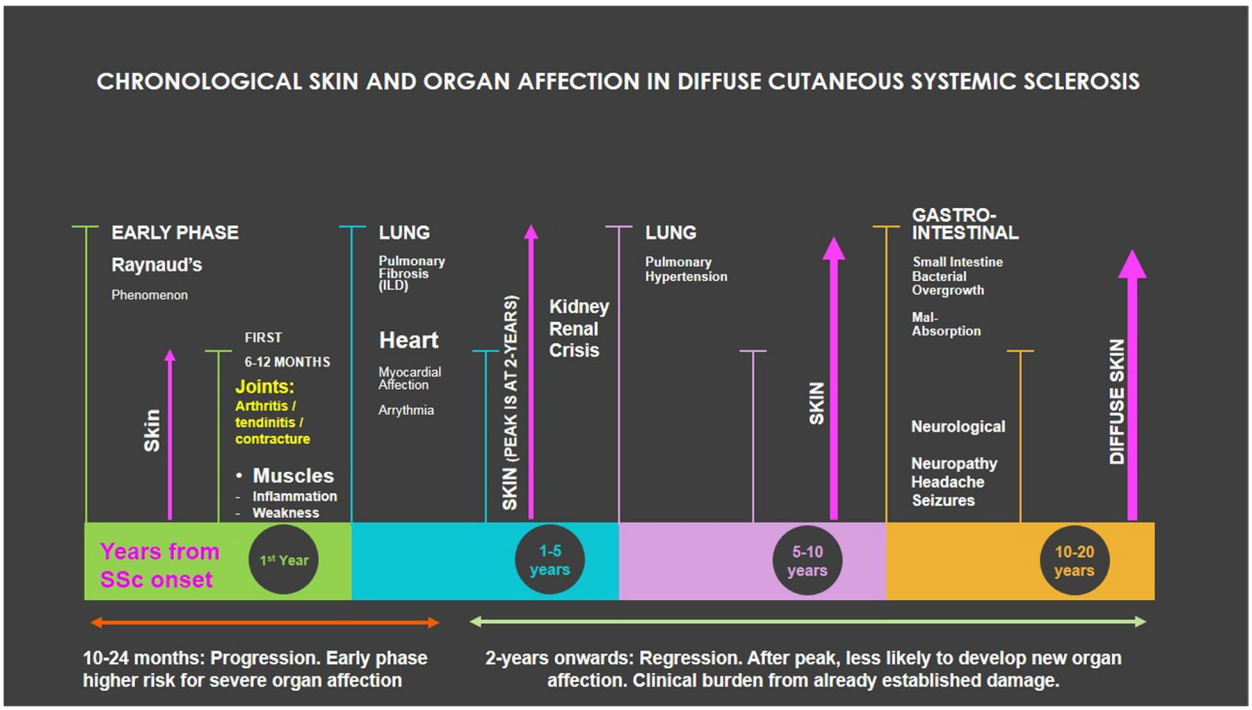

Fig. 1 Chronological affection of skin and organ affection in diffuse cutaneous systemic sclerosis

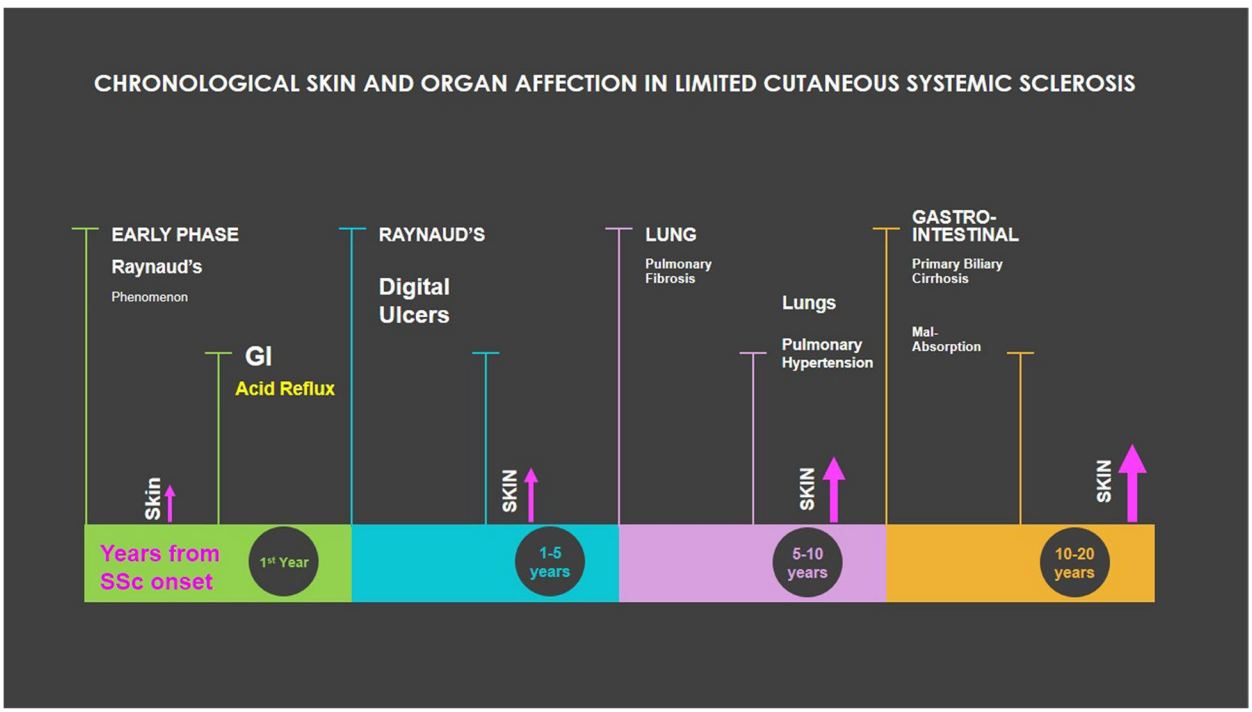

Fig. 2 Chronological affection of skin and organ affection in limited cutaneous systemic sclerosis

Diagnostic Algorithm for ANA testing														
History and clinical assessment suggestive of Connective tissue disease														
ANA Blood test														
ANA Negative		**ANA Positive**												
Re-assess clinical manifestations		**Assess clinical manifestations and the degree of ANA positivity (1:40-1:80) or> 1:160**												
Possibility of CTD	**CTD unlikely**	**Assess ENA**												
		Clinically Possible SLE		**Clinically SSc Or inflammatory myositis (check the pattern/ENA)**										**Sjogren**
Repeat ANA	Repeat ANA whenever indicated clinically	**Positive Anti-DNA; Anti-Sm**		**Centromere**	**Nucleolar / Scl-70**	**RNA polymerase III**	**U3-RNP**	**Th/To**	**U11/U12 RNP**	**Ku**	**Pm/Scl**	**U1RNP**	**Jo 1**	**SSA SSB**
Negative	**Positive**	ANA 1:80 ? Incomplete SLE, ? early SLE	ANA >1:160	Limited cutaneous SSc (CREST)	dcSSc	dcSSc	lcSSc dcSSc	lcSSC	dcSSC/ lcSSc	SSc / Overlap	SSc/ overlap	SSc/ Overlap	Inflammatory myositis	
				Associated pathophysi-ology pattern: Skin fibrosis: limited (fingers/ face) Vascular: RP, Digital loss, PAH Organ: GI (upper/ lower), Overlap, Hashimoto's, Sjogren, Liver (PBC)	Associated pathophysi-ology pattern: Skin fibrosis: Variable / diffuse Vascular: RP, DU Organ: ILD Joint/ Muscles Heart Kidney: SRC	Associated pathophysi-ology pattern: Skin fibrosis: Diffuse, Rapidly progressive Vascular: RP, GAVE (GI bleeding) Organ: SRC Heart Tendon friction, Muscle/ joints, less ILD	Associated pathophysi-ology pattern: Skin fibrosis: Variable Vascular: PAH, RP, DU Organ: ILD, Severe GI disease, Pericarditis				Associated pathophysi-ology pattern: Skin fibrosis: Variable, limited Vascular: RP Organ: IID, Polymyositis, dermatomyositis, Arthritis calcinosis	Associated pathophysi-ology pattern: Skin fibrosis: variable, limited Vscular: RP, PAH Organ: ILD, overlap, myositis, lupus feature, RA		
Repeat Clinical Assessment	**Follow the positive result scheme**	Follow up 6-12 months	SLE	**Possible systemic affection**										
CTD Likely	CTD unlikely			Eosophageal disease, PAH, consider monitoring for ILD and scleroderma renal crisis	ILD, Internal organ involvement, Renal crisis	Higher risk of renal crisis	Inflammatory myositis PHA GI disease	ILD PAH	ILD	Inflammatory myositis, Arthritis Monitoring/ prophylaxis for digital ulcers	Inflammatory myositis Arthritis ILD Digital ulcers	Overlap syndromes / MCTD		
?ANA negative CTD variant	Repeat ANA whenever indicated clinically													

Fig. 3 Diagnostic algorithm for ANA testing

[20], UK Scleroderma Study Group (UKSSG) best practice recommendations [21–24] and the single hub and access point for pediatric rheumatology in Europe recommendations on juvenile SSc [25].

The guidelines considered the role played by the disease pathophysiologic features in setting up the management pathway. An example is the recommendation of a similar medical therapy protocol for Raynaud's, digital ulcers as well as pulmonary arterial hypertension, three well-known vascular manifestations of SSc, which in turn reflect the unified vascular phenotype in systemic sclerosis. This also raises the attention to the potential prophylactic impact of starting early treatment for one disease phenomenon which might benefit another belated one. This is important time-wise as pulmonary hypertension usually develops several years (around 10 years) after the first symptom (Fig. 1), so by treating Raynaud's phenomena and digital ulcers, pulmonary hypertension may be prevented. This is supported by the available longitudinal studies, though they are few. Yet the more robust data from the EUSTAR [26] cohort suggest worse outcomes when a history of digital ulcers is present. Such therapeutic strategies pave the way to 'widen' the still very narrow 'window of opportunity'.

The developed guideline endorsed also the use of targeted synthetic and biological therapies as disease-modifying medications for SSc key fibrotic manifestations. Mycophenolate mofetil has been recommended for the treatment of skin fibrosis. For SSc-associated interstitial lung disease, mycophenolate mofetil, Rituximab, tocilizumab as well as nintedanib have been suggested. On another front, phosphodiesterase-5 (PDE-5) inhibitors and endothelin receptor antagonist [ERA] monotherapy have also been recommended for up-front combination use for digital ulcers and pulmonary hypertension. Though these were present in 2017, recent clinical trials have discussed and confirmed the benefit of nintedanib, rituximab, or tocilizumab in SSc-associated interstitial lung disease [27, 28].

This guideline was developed with the best evidence and consensus across a range of expert opinions. Current management is essentially centered on the specialty of rheumatology with appropriate engagement and cross-referral to other specialties including

Table 3 Management of organ-specific affection of systemic sclerosis

Organ-specific affection	Recommendations and LOE	Mean rate ± SD	Percentage and level of agreement
Raynaud's phenomenon (RP) and digital vasculopathy/digital ulcers (more details are represented in supplement 1)	Recommendations for RP in SSc • The aim of RP treatment is to decrease its severity, at least a moderate reduction in the intensity of attacks, and prevent RP complications as prevention of tissue loss and digital ulceration • Patient education and lifestyle modification to maintain body warmth and avoid other triggers for RP, discontinuing all tobacco products, and avoiding the precipitating factors and drugs which exacerbate RP are essential in RP management • First-line treatments are calcium channel blockers (1,A) and angiotensin II receptor antagonists (2,C) • Calcium channel blockers (CCB) (with gradually increasing dose) are the first line of treatment for RP to decrease the severity and frequency of incidence of RP.(2,C) • In cases that do not respond adequately to a CCB alone, add or substitute either a phosphodiesterase 5 (PDE 5) inhibitor or a topical nitrate. (The combination of PDE type 5 inhibitors and topical nitrates should be avoided due to the increased risk of hypotension). (3, C) • In severe/resisted or complicated cases, Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine at 20 mg/day), and prostacyclin analogs may be used. (3,C) • Oral antiplatelet and anticoagulant agents, pentoxifylline, and statins may be used in certain conditions as supplementary treatment. (4,D) Recommendations for digital ulcers in SSc • DUs require integrated management by a multidisciplinary team; management includes local and systemic treatment (3, C) • Digital ulcers must be cleaned, and mechanical debridement of hyperkeratotic covering should be done (3, C) • Oral vasodilator treatment should be optimized, analgesia optimized and any infection promptly treated (3, C) • Sildenafil should now be used before considering i.v. prostanoids and bosentan (1, A) • In severe active digital ulceration, patients should receive i.v. prostanoid (1, B). In patients with recurrent, refractory DUs, a phosphodiesterase type 5 inhibitor (1, B) or i.v. prostanoid (1, B) and an endothelin receptor antagonist (including bosentan; 1, B) should be considered • In severe and/or refractory digital ulcers: Digital (palmar) sympathectomy (with or without botulinum toxin injection/ hyperbaric oxygen therapy) may also be considered (3, D)	8.38 ± 0.7	100% High
Skin affection	• Treatment of skin thickening, assessed by modified Rodnan skin score, is central to the management of dcSSc treatment, and pruritus is common and troublesome in early-stage disease. (3, B) • Patients with early dcSSc should be offered an immunosuppressive agent (3, C) • Using low-dose corticosteroids at edematous cutaneous SSc should be individualized and evaluated case by case due to fear of SSc renal crisis (SRC) precipitation. (3, B) • Local softening and moisturizing cream or lotion should be applied to the patient's skin (3, C) • Methotrexate is the first line of treatment of cutaneous manifestations of SSc with moderate effect, MMF or CYC could be used as alternative therapy (2, C) • Rituximab may be an option in refractory severe cutaneous affection in SSc.(4, C) • Tocilizumab, IVIG, and HSCT may be alternative options in refractory severe cutaneous SSc.(3, C) • Pruritus could be treated with anti-histaminics or low-dose corticosteroids for a short period.(1, C) • Current treatment options for telangiectasia include skin camouflage and laser or intense pulsed light therapy (3, C) **Calcinosis in SSc:** (3, C) • There is no effective treatment for calcinosis, colchicine may be tried with mild effect in inflammatory lesions • Surgical excision can be proposed to promote healing and avoidance of secondary infection • Calcinosis complicated by infection should be recognized early and treated with appropriate antibiotic therapy • Surgical intervention should be considered for severe, refractory calcinosis, which is severely impacting upon functional ability and quality of life	8.92 ± 0.3	100% High

Table 3 (continued)

Organ-specific affection	Recommendations and LOE	Mean rate ± SD	Percentage and level of agreement
Musculoskeletal disease	• Musculoskeletal involvement includes tendinopathy, joint contractures and, in some cases, overlap arthritis. (3, C) • NSAIDs and short period of low-dose corticosteroids may be enough for mild arthralgia and early tenosynovitis.(3, D) • Methotrexate is used for the treatment of inflammatory arthritis • Rituximab and tocilizumab might be an alternative option in the failure of methotrexate and low-dose corticosteroids(3, C) • TNFi should be avoided in SSc due to fear of fatal exacerbation of fibrosing alveolitis.(2, C) • In cases of overlap between SSc and inflammatory myositis; corticosteroids (dose not exceed 0.5 mg/kg/d for fear of SRC) and MTX may be added to the conventional treatment of SSc, with MMF, and rituximab may be considered as alternative options.(2, B) • Osteoporosis should be expected in patients with SSc and should be properly assessed and managed	8.77 ± 0.4	100% High
Cardiopulmonary complications	(PAH) (3, C) • Early diagnosis and management are essential for improving the outcome of SSc-PAH • Diagnostic evaluation: - Clinical assessment: risk factors, history/symptoms, physical examination - Lab: auto-antibodies, BNP/NT, proBNP - Functional assessment: O2 saturation, cardiopulmonary exercise test (CPET) - Cardiac: Echo, ECG - Pulmonary functions: Pulmonary function tests/DLCo • When to suspect: - Asymptomatic phase - Early symptoms: Shortness of breath with activity, palpitation - Late symptoms: Feeling tired (fatigue), signs of right heart failure (legs and ankles edema), arrhythmia, exertional chest pain/pressure, dizziness/syncope) • An expert cardiologist should be involved with the rheumatologist in the management of SSc-PAH • The best predictor for PAH development in SSc is declining DLCo, and Echocardiography should be done annually on all the patients. Rt heart catheterization is the gold standard test for the diagnosis of PH • Pulmonary hypertension definition: - Mean pulmonary artery pressure (PAP: ≥ 20 mmHg - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg - Pulmonary vascular resistance (PVR) > 2 wood units • Risk factors and predictors: - Late age onset of scleroderma - Longer disease duration (> 8 years) - Limited scleroderma - Severe Raynaud's phenomenon - Numerous and prominent telangiectasia - Low diffusion capacity (DLCo < 55%, FVC/DLC0 > 1.6) - NT-pro BNP elevation (together with low DLCo) - Auto-antibody association: anti-centromere, U1-RNP, Th/To • Staging and risk stratification: Treatment of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) is guided by risk stratification, which uses information from clinical assessments and imaging • Risk is graded using the REVEAL 2.0 calculator (involving 14 variables): a REVEAL score ≤ 6 corresponds with a low risk, a score of 7 or 8 corresponds to an intermediate risk and a score ≥ 9 indicates a high risk • Risk factors and predictors ■ Late age onset of scleroderma ■ Longer disease duration (> 8 years) ■ Limited scleroderma ■ Severe Raynaud's phenomenon ■ Numerous and prominent telangiectasia ■ Low Diffusing Capacity (DLCO < 55%, FVC%/DLCO% > 1.6) ■ NT-pro BNP elevation (together with low DLCO, HR = 47.2) ■ Autoantibody associations: - Anti-Centromere, U1-RNP, U3 RNP, Th/To • Four groups of pulmonary hypertension-specific therapies can be considered in the treatment of SSc-PAH: endothelin receptor (ETR) antagonists, phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase (sGC) stimulators, and prostacyclin analogs and receptor agonists	8.61 ± 0.5	100% High

Table 3 (continued)

Organ-specific affection	Recommendations and LOE	Mean rate ± SD	Percentage and level of agreement
	• Low or intermediate risk: Oral combination therapy with ETR antagonist and PDE5 inhibitor Monotherapy with either an ETR antagonist or PDE5 inhibitor if: – Very mild PAH (e.g., WHO functional class I, (Pulmonary vascular resistance) PVR 3–4 WU, mPAP < 30 mmHg, normal right – ventricle at echocardiography) – PAH with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis – Long-term-treated historical PAH in patients on stable monotherapy (> 5–10 years) with a low-risk profile – Combination therapy is unavailable or contraindicated (e.g., because of severe liver disease) • High risk: Combination therapy including - Intravenous prostacyclin analogue - Consider referral for lung transplantation • Refractory cases: - Sequential combination therapy between two or three (endothelin-receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclin) is recommended - Lung-heart transplantation is the last option in the management of SSc-PAH Monitoring: serial PFT and repeat HRCP to determine progression and need for treatment Risk assessment after 3–6 months: – Low risk: structured follow-up – Intermediate or high risk: triple combination therapy with an ETR antagonist, PDE5 inhibitor, and prostacyclin analog ––––––––––––––––––		
	(Pericarditis) (1, B) • NSAIDs and colchicine are the first line of treatment of pericarditis • High-dose corticosteroids and/or pericardial drainage should be considered in severe cases ––––––––––––––––––		
	Arrhythmia (2, B) • Use anti-arrhythmic drugs should be used (beta blockers usually are contraindicated due to their negative effects on RP and digital ulcers) • Anti-coagulants should be considered in certain conditions of supraventricular tachycardia • Pacemaker may be considered for severe conduction disorders ----------		
	Cardiac affection • Evaluation of heart involvement in systemic sclerosis: All SSc patients should be assessed annually for new symptoms/abnormal findings: - Unexplained dyspnea - Palpitation - Syncope or pre-syncope - Chest pain - Dependent edema - Troponin elevation - BNP elevation - Left ventricular dysfunction (low LVEF) - Ischemic changes - Arrhythmia, conduction defects • Cardiology referral: - Cardiac MRI - Stress Test - Coronary angiogram - Right heart catheterization - Holter/even recorder - Cardiac electrophysiology Heart failure - Systolic heart failure i. Consider immunosuppression with or without a pacemaker (4, D) ii. Consider the potential benefit of an implantable cardioverter defibrillator (3, D) iii. Angiotensin-converting enzyme inhibitors and carvedilol. Selective β-blockers may be considered, but consider aggravation of RP (4, D)		

Table 3 (continued)

Organ-specific affection	Recommendations and LOE	Mean rate ± SD	Percentage and level of agreement
	Diastolic heart failure with preserved left ventricular ejection fraction i. Diuretics, including spironolactone and furosemide (4, D) ii. Calcium channel blockers have been shown to reduce the frequency of systolic heart failure in SSc with investigational evidence of cardiac abnormalities (3, D)		
Pulmonary complications (interstitial lung disease (ILD))	• All SSc cases should be assessed for lung fibrosis. Up to 80% of SSc will develop ILD, but this might be mild and stable Early diagnosis and management are essential for improving the outcome of SSc-ILD • When to suspect: - It can be silent: no symptoms - Shortness of breath (also consider anemia, deconditioning, muscle weakness, aspiration, cardiac disease) - Chronic cough: Also acid reflux, post-nasal discharge - Fatigue: also deconditioning, anemia, depression - Weight loss: also GI disease, malabsorption • Diagnostic Evaluation: - Clinical assessment - Lab: Auto-antibodies (ENA). Comorbidities: FBC, CK/ Aldolase, NT-proBNP, Troponin - Cardiac studies: ECHO, ECG - Pulmonary function tests (not screening tool, establish baseline [ILD severity, prediction], assess progression [change over time], suspect comorbidities [Myopathy: low FVC, normal DLCo/ Pulmonary hypertension: isolated DLCo, high FVC/DLCo] - Imaging: Gold standard. It shows the anatomical distribution, severity, prediction, subsets [NSIP/UIP] • Risk factors for SSc-ILD onset and progression: – Diffuse SSc (70–80%) > Limited SSc (15–25%) – Early disease: the majority of lung function declines in first 2–4 years – Severe gastro-esophageal reflux – Advanced age – Racial/Ethnic background (African American) – Elevated acute phase reactants-ESR, CRP – Autoantibodies: Increased risk: [anti-SCL70 (70%), Pm/Scl (70%), Th/To (50%), U1-RNP (40%), U3-RNP]. Decreased risk: (anti-Centromere) • All patients with SSc should be screened for SSc-associated ILD using HRCT, particularly if they are showing respiratory symptoms or have one or more risk factors • Diffusion lung capacity (DLCo): sensitive but not specific. Decreases in obstructive, restrictive, anemia, and pulmonary vascular disease • An expert pulmonologist should be involved with the rheumatologist in the management of SSc-ILD • The decision to initiate ILD-directed therapy must be made on a case-by-case based on the extent and severity of ILD • Initial therapy: cyclophosphamide (CYC) or mycophenolate mofetil (MMF) are the drugs of choice for patients with progressive SSc-ILD, (MMF is safer and better tolerated). (3, C) • Tocilizumab and rituximab could be used as initial therapy for SSc-ILD in patients who are not able to take MMF or CYC.(4, C) • Maintenance treatment is continued for at least 2 years and often several years, according to the disease course (the treatment should continue till sustained disease stability.(4, C) • MMF or azathioprine are recommended as maintenance therapy for SSc-ILD. (3, C). Tocilizumab also might be considered for maintenance therapy. (4, C) • In refractory cases, the addition of rituximab or antifibrotic agents such as nintedanib to the ongoing therapy is recommended.(4, C) • Hematopoietic Stem Cell Transplantation (HSCT) should be reserved for patients who failed all previous therapies. (5, D) • Lung transplantation may be considered in severe respiratory failure if the patient is fit for operation.(3, B) • Adjuvant corticosteroids are reserved for patients with extrapulmonary affection.(4, D) • Adding prophylactic vaccination for pneumococcal, influenza, and COVID-19 infections is recommended before starting ILD treatment with immunosuppressants.(3, B)	8.31 ± 0.9	100% High

Table 3 (continued)

Organ-specific affection	Recommendations and LOE	Mean rate ± SD	Percentage and level of agreement
Gastrointestinal tract disease	Oropharyngeal disease (3, B) • Regular dental hygiene is necessary for preventing dental caries Gastro-esophageal disease (3, C) • Avoidance of eating 2 h before sleep and dietary modification is recommended • It is better to confirm eradication of H. Pylori before starting long-standing anti-inflammatory drugs or corticosteroids as its presence increases peptic ulcer complications • GERDs are treated with proton pump inhibitors, histamine H2 receptor antagonists, and HCL antisecretory drugs • Prokinetic dopamine antagonists may be used for dysphagia and reflux • Injectable octreotide may be considered, and endoscopic injection of botox into the pyloric sphincter has been used for resistant cases of GERD • iron replacement therapy and red blood cells transfusion may be used for gastric antral vascular ectasis (GAVE) treatment • argon plasma coagulation or laser therapy are effective for GAVE treatment Intestinal (3, C) • Intermittent broad-spectrum oral antibiotics (e.g. ciprofloxacin) are recommended for intestinal overgrowth, and rotational regimes may be helpful • Parenteral nutrition should be considered in severe malabsorption and deteriorated general condition refractory to enteral supplementation • Anti-diarrhoeal agents (e.g., loperamide) or laxatives may be used for symptomatic management of diarrhea or constipation that often alternate as clinical problems • Rifaximine is a locally acting anti-microbial and recommended in cases of small intestinal bacterial overgrowth as it works locally with no systemic complications	8.69 ± 0.5	100% High
Renal complications	• Patients at risk of scleroderma renal crisis (SRC), should be followed closely and their blood pressure monitored at least weekly (3, C) • Risk Factors: ■ Early diffuse skin disease: 2–3 years from SSc onset, median 8 months ■ Anti-RNA polymerase III (60%) ■ Use of corticosteroids > 15 mg/day or low doses for longer time • Avoidance of corticosteroids (dose > 20 mg/day) is important to avoid scleroderma renal crisis (SRC), as this might precipitate its incidence(2, B) • The onset of SRC usually occurs in early diffuse scleroderma (the first 1–4 years after diagnosis) (2, C) • SRC can mark SSc onset or precede SSc diagnosis (20% no skin involvement) • SRC is a medical emergency in which the patient should be hospitalized • SRC typical clinical presentation - Very high blood pressure (> 20 mmHg over usual blood pressure) - Sudden renal failure (rising creatinine, proteinuria) - Malignant hypertension (flash pulmonary edema, headache, retinopathy, encephalopathy) - Hemolytic anemia and/or thrombocytopenia (thrombotic microangiopathy, schistocytes) • The aim of treatment is to decrease systolic blood pressure by 20 mmHg within the first 24 h • The first line of treatment is ACE inhibitor (3, C), a long-acting ACEi is most used but short-acting agents might be recommended in cases with hemodynamic compromise • Calcium channel blockers may be considered as a second line of treatment for the management of refractory hypertension in conjunction with an angiotensin-converting enzyme inhibitor in SRC (3, C) • There is no evidence about using ACE inhibitors in SRC prophylaxis, using ACE inhibitors may prevent early diagnosis of SRC in some patients by modulating hypertension • Renal dialysis and renal transplantation may be required in resisted SRC patients.(4, C) • ACE inhibitors should be continued even in patients who have progressed to dialysis, as renal dialysis may be temporary if renal functions improve	8.62 ± 0.5	100% High

Table 3 (continued)

Organ-specific affection	Recommendations and LOE	Mean rate ± SD	Percentage and level of agreement
Neurological complications	• Neuropathy is common in the first 10 years after SSc onset • Compression neuropathies can be treated with decompression surgery. (4, C) • Non-compression peripheral neuropathy in SSc may occur secondary to traumatic injury, ischemia, metabolic sequelae, or adverse effects of medication. (3, C) • Treatment of non-compressive peripheral neuropathies included corticosteroids, CYC, amitriptyline, gabapentin, methotrexate, and anticonvulsants. (3, D)	8.15 ± 1.6	92.3% High

ACA anticentromere antibody, *CYC* cyclophosphamide, *ds.SSC* diffuse cutaneous systemic sclerosis, *DLCo* diffusion lung capacity, *GAVE* gastric antral vascular ectasis, *HSCT* hematopoietic stem cell transplantation, *HRCT* high-resolution CT, *ILD* interstitial lung disease, *lc.SSC* limited cutaneous systemic sclerosis, *MCTDs* mixed connective tissue disease, *MMF* mycophenolate mofetil, *PDE5*phosphodiesterase 5, *PAH* pulmonary artery hypertension, *PFTs* pulmonary function tests, *PVR* pulmonary vascular resistance, *RCTs* randomized controlled trials, *RP* Raynaud's phenomena, *SRC* scleroderma renal crisis, *SSc* systemic sclerosis

respiratory medicine, dermatology, nephrology, gastroenterology, cardiology, and others. There are also important shared care links with other specialists. The expert panel that was shared in this work covered all these specialties including 9 rheumatologists, 1 methodologist, 1 respiratory medicine, 1 dermatologist, 1 cardiologist, 1 nephrologist, and 1 gastroenterologist. This was necessary to establish auditable criteria and guarantee that the care is coordinated. This agrees with the approach adopted in a series of best practice recommendations published earlier [18–25].

Such methodology has helped to harmonize management across expert healthcare professionals. The multidisciplinary strategy endorsed in this guideline is expected also to tackle another challenge that faces healthcare professionals managing SSc patients. This includes SSc patients presenting with a major organ-based complication such as renal crisis, interstitial lung disease, pulmonary artery hypertension, or thrombotic microangiopathy who have not yet been diagnosed with SSc although they may fulfill the 2013 ACR/EULAR classification criteria [5].

Limitations of the guideline

The guideline's lack of comparative evidence to assist therapy selection and its low number of longitudinal studies, albeit reflecting the best available data at the time the report was created, are two of its weaknesses. The main comparative benefit/efficacy and harms evidence is incorporated here. The fact that we limited our search to works written in English is another drawback. When evaluating the data, care should be taken because the findings of more research may need to change the report's conclusions or suggestions. In the best interests

Table 4 Approach to Raynaud's phenomenon and Digital Ulcer management

Management	Raynaud phenomenon	Digital ulcers in SSc
First line	Calcium Channel blockers	Calcium channel blockers
Second line	PDE5 inhibitor, or IV prostacyclin analogs	For the prevention of new ulcers: bosentan For healing or prevention of new ulcers: PDE5 inhibitor, intravenous prostacyclin analogs
Third line	Prostacyclin analogs or PDE5 inhibitor	Prostacyclin analogs
Supplementary	Nitroglycerin	Digital sympathectomy analgesics, atorvastatin
	Angiotensin II receptor blocker, aspirin, botulinum toxin, fluoxetine, Pentoxifylline, Hyperbaric oxygen	botulinum toxin, fat grafting
	Digital sympathectomy, anticoagulation, fat grafting	
General suggestions:	• Avoid cold and trauma • Wear proper clothing • Smoking cessation	
Selected situations:	Infection: • Consider antibiotics, wound care, and pain management in the case of infection • Oral antibiotics to be used in digital ulcer treatment only if an infection is suspected • In the event of an abscess or osteomyelitis, surgical debridement should be considered • Digit or limb amputation might be warranted if gangrene is present	

of particular patients and unique situations, it can be required—even desirable—to deviate from the recommendations. Deviation from guidelines should not always be considered negligent, just as following them may not be sufficient to defend against a claim of carelessness.

Conclusion

There is a vascular as well as fibrotic disease continuum in systemic sclerosis. This guideline tried to tackle the gaps in research that limit treatment options. Stratifying the patients according to their disease domains has helped to set up sequential management pathways for each domain. This has also facilitated the recognition of common pathogenic pathways, which paved the way for identifying similar management patterns for different organ manifestations. Putting this recommendation into routine practice will hopefully result in better care for SSc patients as long as data support best practices in management. The consensus panel's wide representation would help to spread the findings of this research to the many medical professionals who care for persons with schizophrenia, increasing the likelihood that the guidelines will be adopted and followed.

Abbreviations

ACR	American College of Rheumatology
ACA	Anticentromere antibody
BSR	British Society for Rheumatology
ds.SSC	Diffuse cutaneous systemic sclerosis
HRCT	High-resolution CT
ILD	Interstitial lung disease
lc.SSC	Limited cutaneous systemic sclerosis
MCTDs	Mixed connective tissue disease
CEBM	Oxford Centre for Evidence-based Medicine
PAH	Pulmonary artery hypertension
PFTs	Pulmonary function tests
RCTs	Randomized controlled trials
RP	Raynaud's phenomena
SRC	Scleroderma renal crisis
SSc	Systemic Sclerosis
CEG	The Clinical, Evidence-based, Guidelines
EULAR	The European Alliance of Associations for Rheumatology
LOE	The level of evidence
UKSSG	UK Scleroderma Study Group

Supplementary Information

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Additional file 1. The flow chart for the selection process of the study.

Additional file 2. Levels of evidence.

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Authors' contributions

Conceptualization and design: Yasser El Miedany, Mohammed Hassan Abu-Zaid, and Waleed Hassan. Acquisition of data: Yasser El Miedany and Mohammed Hassan Abu-Zaid. Formal analysis: Maha El Gaafary. Investigation: Yasser ElMiedany Methodology: all authors. Writing—original draft: Yasser El Miedany, Mohammed Hassan Abu-Zaid, and Samar Tabra. Final approval of the version to be submitted: all authors.

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Availability of data and materials

The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Helsinki Declaration. This was a multistep process that followed the "Clinical, Evidence-based, Guidelines" (CEG) initiative protocol (ethical approval code: 34842/8/21, ethical board Tanta University) aiming at setting up an actionable clinical gold standard for Treat-to-Target management of rheumatic and bone diseases.

Consent for publication

Not applicable.

Competing interests

The authors declare that Mohammed Hassan Abu-Zaid is the associate editor of the Egyptian Rheumatology and Rehabilitation, and Waleed Hassan, Mohammed Mortada, and Yasser El Miedany are from the editorial board of the journal.

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