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# Treatment Algorithms for Systemic Sclerosis According to Experts

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***Objective.*** **There is a lack of agreement regarding treatment for many aspects of systemic sclerosis (SSc). We undertook this study to generate SSc treatment algorithms endorsed by a high percentage of SSc experts.**

***Methods.*** **Experts from the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research group (n = 170) were asked whether they agreed with SSc algorithms from 2012. Two consensus rounds refined agreement; 62, 54, and 48 experts (36%, 32%, and 28%, respectively) completed the first, second, and third surveys, respectively.**

***Results.*** **For treatment of scleroderma renal crisis, 81% of experts agreed (first-, second-, and third-line treatments were angiotensin-converting enzyme inhibitors, then adding calcium-channel blockers [CCBs], then adding angiotensin receptor blockers [ARBs], respectively). For pulmonary arterial hypertension (PAH), 81% of experts agreed (for mild PAH, treatments were phosphodiesterase 5 [PDE5] inhibitors, then endothelin receptor antagonists plus PDE5 inhibitors, then prostanoids, respectively; for severe PAH, prostanoids were first-line treatment). For mild Raynaud's phenomenon (RP), 79% of experts agreed (treatments were CCBs, then adding PDE5 inhibitors, then ARBs or switching to another CCB, respectively; after the third line of treatment, mild RP was deemed severe). For severe RP, the first- through fourth-line treatments were CCBs, then adding PDE5 inhibitors or prostanoids, then adding PDE5 inhibitors (if not added as second-line treatment) or prostanoids (if not added as second-line treatment), then switching to another CCB, respectively. For active treatment of digital ulcers, 66% of experts agreed (first- and second-line treatments were CCBs and PDE5 inhibitors, respectively). For interstitial lung disease, 69% of experts agreed (for induction therapy, treatments were mycophenolate mofetil [MMF], intravenous cyclophosphamide [IV CYC], and rituximab, respectively; for maintenance, first-line treatment was MMF). For skin involvement, 71% of experts agreed (for a modified Rodnan skin thickness score [MRSS] of 24, first- and second-line treatments were methotrexate [MTX] and MMF, respectively; for an MRSS of 32, first- through fourth-line treatments were MMF, MTX, IV CYC, and hematopoietic stem cell transplantation, respectively). For inflammatory arthritis, 79% of experts agreed (first- through fourth-line treatments were MTX, low-dose glucocorticoids, hydroxychloroquine, and rituximab or tocilizumab, respectively). Algorithms for cardiac and gastrointestinal involvement had ≥75% agreement.**

***Conclusion.*** **Total agreement for SSc algorithms was considerable. These algorithms may guide treatment.**

Systemic sclerosis (SSc; scleroderma) is an autoimmune connective tissue disease characterized by autoantibodies, fibrosis, and microvascular injury and endothelial cell activation that result in vascular damage. Vascular injury induces both innate and acquired immune responses, resulting in fibroblast activation and organ fibrosis (1). SSc may target multiple organs, including the skin, lungs, heart, vascularization, kidneys, gastrointestinal tract, and musculoskeletal structures (2). Mortality among scleroderma patients is significant, with a standardized mortality ratio (SMR) of 3.5 in studies of prevalent cases (3). This mortality may be

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increased in the early years of the disease, reaching an SMR of 4 in a multinational inception cohort (4). In general, treatment strategies target involved organs as early as possible to avoid damage. Many treatment options are available for each manifestation, but evidence with respect to the order of treatment is scarce. Current management guidelines have some gaps regarding second-line treatment, combinations, and proposed algorithms (5).

In 2012, several algorithms for SSc treatment were developed by a consensus of international experts (6). The goal was to provide a consensus for treatment options in SSc management in usual practice. Since new therapeutic advances have been developed, we intended to review and update the previous expert-assessed algorithms.

## METHODS

The surveys were conducted between August 2016 and September 2017. A complete list of SSc experts participating in the Scleroderma Clinical Trials Consortium (SCTC) and/or in the Canadian Scleroderma Research Group (CSRG) was obtained. All the participants received the first survey in 2 separate e-mails (Figure 1). All those who answered the previous survey were invited to complete the next one, and so on. The collaborators who completed the 3 surveys were listed as authors in the Scleroderma Algorithm Group. A list of Scleroderma Algorithm Group authors is provided in Appendix A.

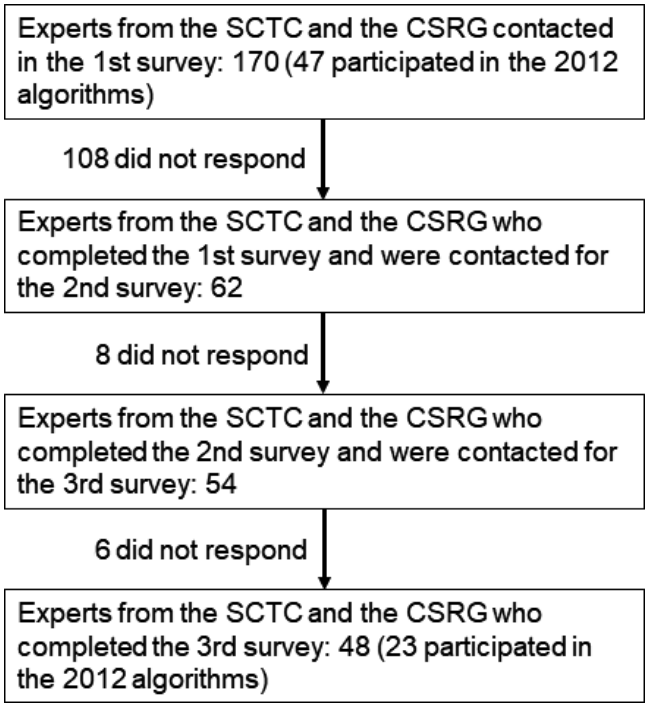


**Figure 1.** Flow chart of the systemic sclerosis algorithm surveys. For the 2012 algorithms, see ref. 6. SCTC = Scleroderma Clinical Trials Consortium; CSRG = Canadian Scleroderma Research Group.

We designed 3 consecutive surveys using Google forms. The first survey was based on the previous 2012 algorithms (6). Experts were questioned on demographics (age, sex, specialty, years of practice, practice setting, management of SSc patients, number of SSc patients in their practice, number of SSc referrals per year) and if they agreed (yes/no/minor modifications) with each of the 2012 organ-based SSc treatment algorithms. In case they did not agree, spaces for free text were provided for each line of treatment to provide their treatment preferences. The SSc algorithms included scleroderma renal crisis (SRC), pulmonary arterial hypertension (PAH), Raynaud's phenomenon (RP), interstitial lung disease (ILD), gastrointestinal (GI) involvement, skin involvement, and inflammatory arthritis. No previous algorithm was available for cardiac involvement; therefore, each respondent stated what he or she would use as first-line, second-line, and further treatment for various cardiac scenarios (such as treatment for pericardial involvement, myocardial dysfunction, and conduction alterations).

The second survey provided the frequencies with which respondents from the first survey agreed, along with suggested modifications (represented in a modified algorithm if the number of experts who disagreed was higher than the number of those who agreed; otherwise, the suggested changes were reflected in a notation to the previous algorithm). Experts were asked if they would add the next treatment or just switch to the next treatment for second- to fifth-line treatments depending on each algorithm. A semiquantitative approach was used to ask questions regarding dosing for prednisone and nifedipine (chosen as the most representative drugs of their respective classes). The GI involvement algorithm was completely redesigned after suggestions from the participants to cover distinct manifestations. This new algorithm was included in the second survey. Experts were asked to rate their agreement, and some extra open questions were added regarding likely modifications and use of prokinetics.

A third survey was conducted to show the likely final configuration of the algorithms, open to minor modifications. Minor modifications were made to pool different treatment options with similar agreement rates in the same line of treatment to increase the agreement rate among participants. Unfortunately, due to database design issues (missing identification in the first survey), we were unable to link the demographic information collected at the first survey with some experts who completed the 3 surveys.

There were no definitions for each organ involved. Algorithms were provided by experts asking which treatment they would use first, then which second treatment, and so on, under the assumption that there was no contraindication to treatment. Grading agreement was not predetermined.

## RESULTS

**Percentages of experts responding to surveys.** One hundred seventy SSc experts received the survey. Sixty-two, 54, and 48 experts completed the first, second, and third surveys, respectively. Thirty-six percent of the experts responded to the first survey, 87% of those who responded to the first survey responded to the second survey, and 89% of those who responded to the second survey responded to the third survey. The demographic

and practice characteristics of the respondents are summarized in Table 1. The final percentages of agreement for the 2012 and 2017 algorithms are shown in Table 2.

**SRC.** The initial agreement after the first survey was 69%. The algorithm was simplified, but no major changes were made (Figure 2A). Eighty-one percent of the experts agreed with this algorithm after the third survey. It is important to mention that before every new add-on to the treatment, the previous antihypertensive medication should have been well tolerated and should have had some benefit. The blood pressure (BP) goals were 140/85 mm Hg for 39% of respondents or ≤120/80 mm Hg for 37% of respondents; only 9.3% of respondents would target a higher BP (150/90 mm Hg). The time to obtain the target BP was <24 hours for 15% of respondents, 24–48 hours for 44%, 48 hours to 1 week for 33%, and >1 week for 7%. Approximately half of respondents (36 of 62) would not prescribe angiotensin-converting enzyme (ACE) inhibitors during pregnancy.

**Table 1.** Characteristics of the respondents comparing the first and final rounds*

| | First survey (n = 62) | Third survey (n = 32)† |
|---|---|---|
| Practice | | |
| Community based | 2 (3) | 1 (3) |
| University based | 59 (95) | 30 (94) |
| Other | 1 (2) | 1 (3) |
| Sex | | |
| Female | 32 (52) | 14 (45) |
| Male | 30 (48) | 17 (55) |
| Specialty | | |
| Rheumatology | 55 (90) | 26 (84) |
| Pediatric rheumatology | 1 (2) | 1 (3) |
| Internal medicine | 4 (7) | 3 (10) |
| Other | 1 (2) | 1 (3) |
| Years in practice | | |
| <5 | 2 (3) | 0 (0) |
| 5–10 | 7 (11) | 5 (16) |
| 11–15 | 12 (20) | 6 (19) |
| 16–20 | 3 (5) | 2 (7) |
| >20 | 37 (61) | 18 (59) |
| SSc patients per year | | |
| <30 | 2 (3) | 2 (7) |
| 31–50 | 5 (8) | 2 (7) |
| 51–100 | 18 (29) | 7 (23) |
| 101–200 | 10 (16) | 6 (19) |
| 201–300 | 12 (19) | 7 (23) |
| 301–400 | 9 (14) | 3 (10) |
| >400 | 6 (10) | 4 (13) |
| New SSc patients per year | | |
| <10 | 8 (13) | 4 (13) |
| 11–25 | 22 (35) | 12 (39) |
| 26–50 | 19 (31) | 9 (29) |
| 51–100 | 9 (14) | 3 (10) |
| >100 | 4 (6) | 3 (10) |

* Values are the number (%). SSc = systemic sclerosis.
† Forty-eight experts responded to the third survey, but data for 16 of them were not identifiable due to database design problems.

**Table 2.** Comparison of agreement on treatment guidelines from the previous report with agreement obtained in the current study*

| Algorithms for SSc treatment | Agreement in 2012, %† | Agreement in 2017, % |
|---|---|---|
| Scleroderma renal crisis | 69 | 81 |
| Pulmonary arterial hypertension | 45 | 81 |
| Raynaud's phenomenon | 66 | 79 |
| Digital ulcers | 58 | 66 |
| Interstitial lung disease | 64 | 69 |
| Gastrointestinal involvement | NA | 77 |
| Skin involvement | 56, 40, 36‡ | 71 |
| Inflammatory arthritis | 45 | 79 |
| Cardiac involvement | NA | 75 |

* Agreement is the percentage of experts who agreed to the algorithm. SSc = systemic sclerosis; NA = not applicable.
† See ref. 6.
‡ For modified Rodnan skin thickness scores of 10, 24, and 32, respectively.

ACE inhibitors are used for first-line SRC treatment. Experts proposed adding calcium-channel blockers (CCBs) only after first-line treatment to gain rapid control of hypertension. Regarding CCBs, initial doses of nifedipine at 30 mg extended release once daily (37% of respondents) or 10 mg 3 times daily (30% of respondents) were the preferred options. Doses of 30 mg extended release twice daily and 20 mg 3 times daily accounted for 11% and 22%, respectively, of the experts.

**PAH.** The original algorithm for mild PAH had a 45% acceptance rate in the first survey, while that for severe PAH had 64% agreement. In mild PAH, phosphodiesterase 5 (PDE5) inhibitors replaced endothelin receptor antagonists (ERAs) as the first-line treatment (Figure 3B). As an alternative, the initial combination of ERAs and PDE5 inhibitors was proposed by 23% of the experts. ERAs were second-line treatment and prostanoids stayed as third-line treatment. Provided that the previous treatment was well tolerated, adding treatment was the most common practice if the PAH target was not achieved. In severe PAH, 27% of the experts would advocate for the combination of ERAs and PDE5 inhibitors as first-line treatment. Lung transplantation with or without heart transplantation was incorporated as a fourth line of treatment. Overall, after the third survey, the final agreement rate was 81%. The use of oral anticoagulants in SSc patients for PAH was infrequent (6% of experts for always, 28% for occasionally, 30% for rarely, and 37% for never). If anticoagulation was used for PAH, 60% would use warfarin, 7% would use direct action anticoagulants, and 31% would use either class of anticoagulant.

**RP.** Fifty-two percent of the experts agreed with the old algorithm for mild RP, and 66% agreed with the severe RP algorithm. After the third line of treatment,

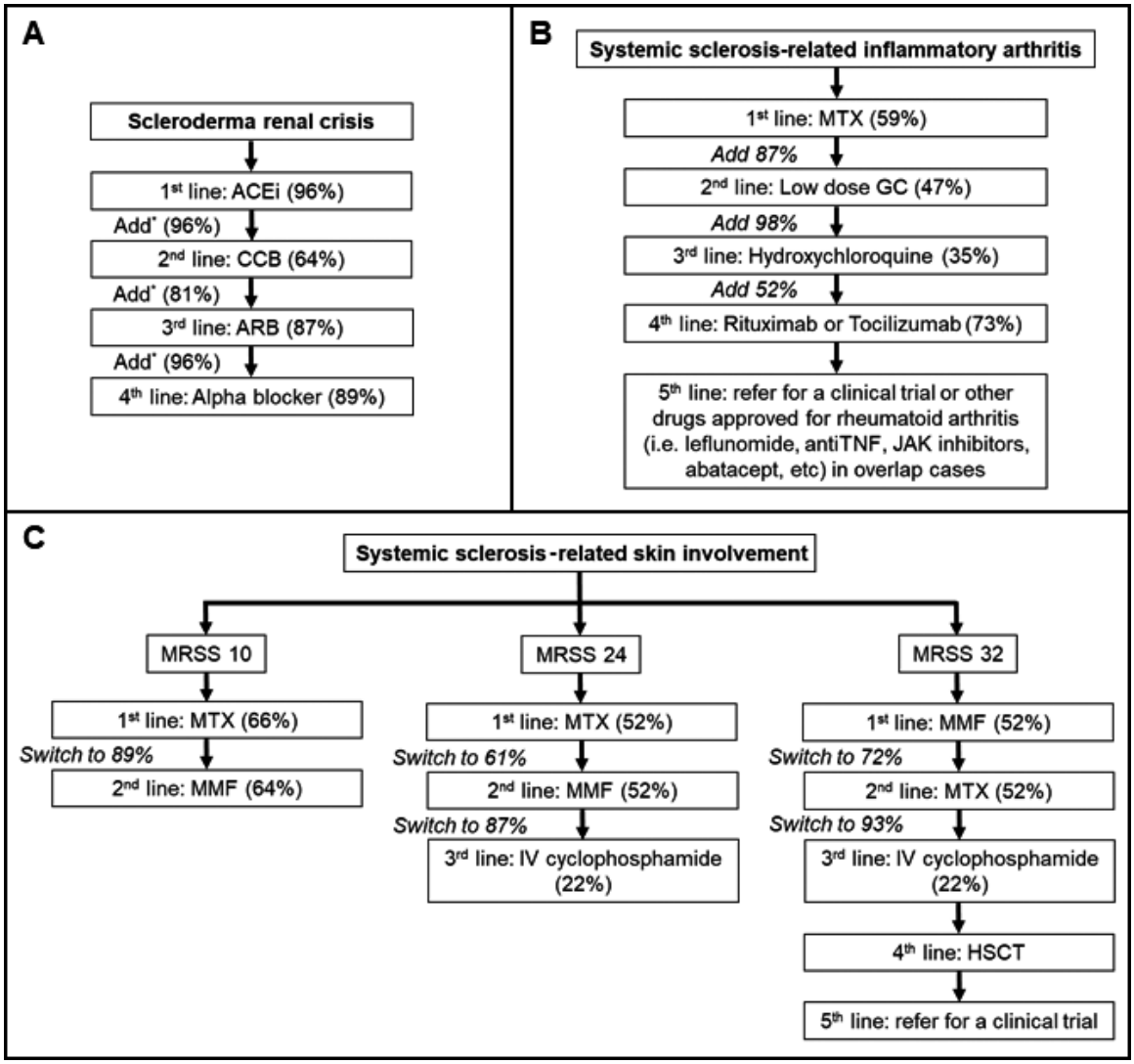


**Figure 2.** Algorithms for the treatment of systemic sclerosis (SSc) renal crisis (**A**), SSc-related inflammatory arthritis (**B**), and SSc-related skin involvement (**C**). ACEi = angiotensin-converting enzyme inhibitor; CCB = calcium-channel blocker; ARB = angiotensin receptor blocker; MTX = methotrexate; GC = glucocorticoid; anti-TNF = anti–tumor necrosis factor; MRSS = modified Rodnan skin thickness score; MMF = mycophenolate mofetil; IV = intravenous; HSCT = hematopoietic stem cell transplantation. * = only if the previous drug was tolerated and gave some benefit.

mild RP was deemed severe (Figure 3C). Digital sympathectomy and botulinum toxin infiltrations were included as a fifth line of treatment, although this was more controversial. Only 44% of the experts occasionally recommended digital sympathectomy. Recommendations for other potential RP treatment varied (58% of experts), including aspirin (75% of experts), statin (29%), fluoxetine (21%), and pentoxifylline (7%). Respondents were asked about use of topical nitrates; 54% said they would consider their use, mostly as topical paste (62%) applied in the interdigital areas. The modified algorithm resulted in 79% agreement.

**Digital ulcers.** Agreement with the 2012 algorithm was 58% for digital ulcer prevention and 40% for active treatment of digital ulcers. The prevention algorithm was simplified without major changes (Figure 3D). The active treatment scheme incorporated prostanoids as third-line treatment. The final overall expert agreement increased to 66%, although 34% suggested minor modifications.

**ILD.** Only 24% of the participants agreed with the previous ILD induction therapy algorithm, while 64% agreed with the maintenance proposal. Mycophenolate mofetil (MMF) replaced intravenous cyclophosphamide (IV CYC) as first-line induction therapy (Figure 3A).

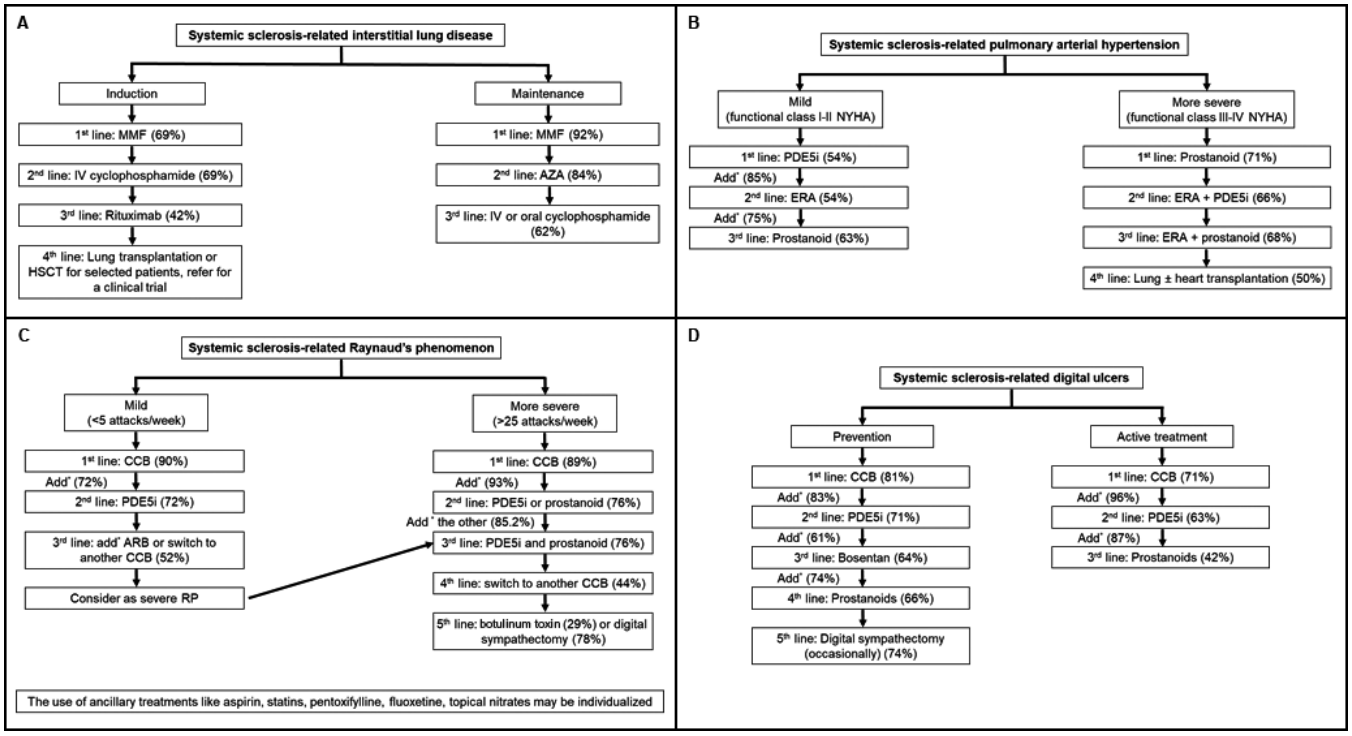


**Figure 3.** Algorithms for the treatment of systemic sclerosis–related interstitial lung disease (**A**), pulmonary arterial hypertension (**B**), Raynaud's phenomenon (RP) (**C**), and digital ulcers (**D**). Note that in some countries or regions, certain drugs (i.e., prostanoids or bosentan) may have prescription restrictions or may not be available. MMF = mycophenolate mofetil; IV = intravenous; HSCT = hematopoietic stem cell transplantation; AZA = azathioprine; NYHA = New York Heart Association; PDE5i = phosphodiesterase 5 inhibitor; ERA = endothelin receptor antagonist; CCB = calcium-channel blocker; ARB = angiotensin receptor blocker. * = only if blood pressure is not low and previous drug was tolerated and gave some benefit.

Rituximab was added as the third option, and the possibility of hematopoietic stem cell transplantation (HSCT) in selected cases or for clinical trial referral was open for nonresponding patients. Maintenance treatment for ILD did not show significant changes in agreement. In the final survey, 69% of the experts agreed with the modified algorithm.

Use of glucocorticoids (GCs) in ILD induction therapy was not common (11% of experts would use them always, 28% sometimes, 24% occasionally, and 37% never). Among the experts who would use GCs in ILD induction therapy, 41% would treat with prednisone at <7.5 mg/day, 46% at 7.5–20 mg/day, and 13% at >20 mg/day. GC treatment would be prescribed for <3 months by 42%, for 3–6 months by 33%, and for >6 months by 8%.

**GI involvement.** The original algorithm was redesigned to cover more GI manifestations. The new algorithm had 77% agreement (Figure 4A). Agreement among experts varied for first-line promotility agents (metoclopramide 44%, domperidone 31%, erythromycin 15%, octreotide 15%) and for antibiotics (metronidazole 60%, ciprofloxacin 60%, rifaximin 35%, doxycycline 23%).

**Skin involvement.** Agreement rates with the 2012 algorithms for SSc skin involvement in 3 different patient scenarios were 56% for patients with a modified Rodnan skin thickness score (MRSS) (7) of 10, 40% for those with an MRSS of 24, and 35% for those with an MRSS of 32. The skin score scenarios were to mimic mild, moderate, and severe skin disease activity. The final results for first-line treatments were close (Figure 2C), especially for an MRSS of 24 (agreement of 52% for methotrexate [MTX] and 48% for MMF) and an MRSS of 32 (agreement of 52% for MMF and 48% for MTX). Most of the experts would switch from one treatment to the next. For an MRSS of 32, IV CYC was considered third-line treatment and HSCT was considered fourth-line treatment, while nonresponding patients or those eligible for HSCT would be candidates for a clinical trial. Agreement reached 71%.

Experts were questioned about the concomitant use of GCs for skin treatment. Thirteen percent prescribed them always, 19% sometimes, 33% occasionally, and 35% never. Among the experts who would use GCs, 49% would suggest prednisone at <7.5 mg/day, and 51% would suggest prednisone at 7.5–20 mg/day.

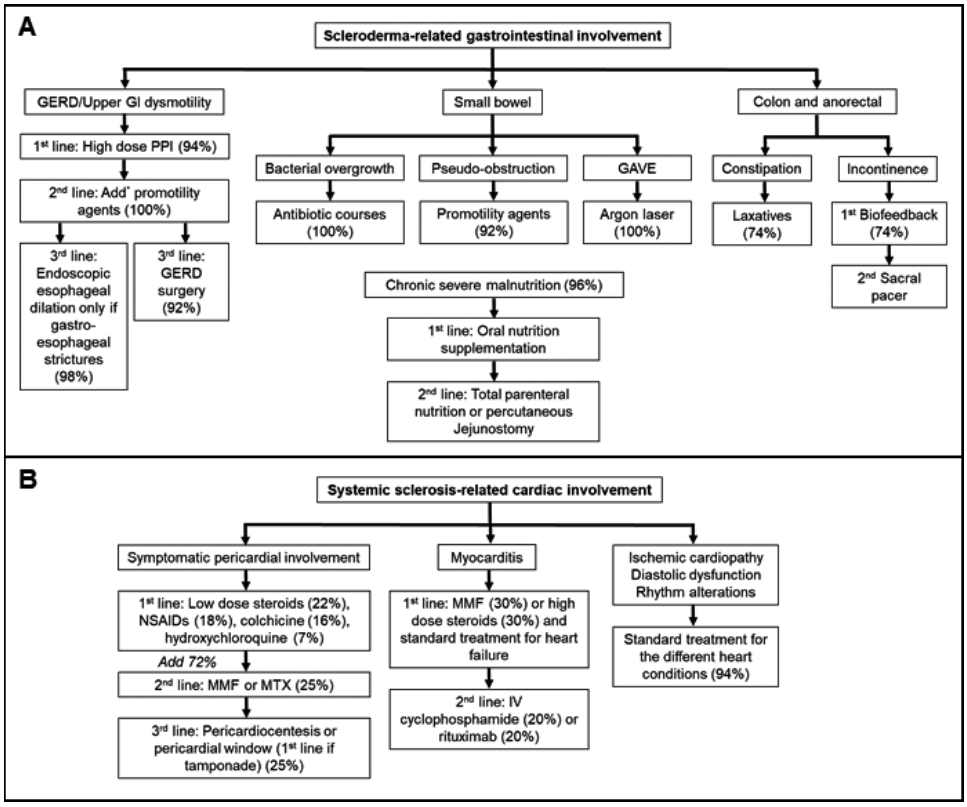


**Figure 4.** Algorithms for the treatment of systemic sclerosis (SSc)–related gastrointestinal (GI) involvement (**A**) and SSc-related cardiac involvement (**B**). GERD = gastroesophageal reflux disease; PPI = proton-pump inhibitor; GAVE = gastric antral vascular ectasia; NSAIDs = nonsteroidal antiinflammatory drugs; MMF = mycophenolate mofetil; MTX = methotrexate; IV = intravenous. * = only if the previous drug was tolerated and gave some benefit.

**Inflammatory arthritis.** Forty-five percent of the experts agreed with the initial algorithm for inflammatory arthritis. Multiple first-line treatment options were used by the participants, but MTX was the most commonly used (59%), followed by hydroxychloroquine (27%). GCs might be prescribed by 75% of the experts and nonsteroidal antiinflammatory drugs by 77%, if these were not contraindicated or if there were no safety concerns. GCs in low doses (54% would treat with prednisone at <7.5 mg/day and 41% at 7.5–20 mg/day) for a short period (67% would prescribe for <3 months, 8% for 3–6 months, and 25% for >6 months) were part of second-line treatment for inflammatory arthritis. Biologic agents (rituximab and tocilizumab) were introduced into the algorithm for fourth-line treatments, and other advanced treatments for patients with features of rheumatoid arthritis (RA) were left as fifth-line treatments. Most participants (79%) agreed with the algorithm (Figure 2B).

**Cardiac involvement.** No previous algorithm was available. The main conditions included were symptomatic pericardial involvement, myocarditis, ischemic cardiopathy, diastolic dysfunction, and rhythm/conduction alterations (Figure 4B). Specific expert recommendations were made for symptomatic pericardial involvement and myocarditis. The final agreement was 75%.

## DISCUSSION

The low prevalence of SSc (8) and the limited treatment algorithms available, especially after first-line treatments have failed, may lead to variations in SSc management. The main causes of death among SSc patients are PAH, ILD, cardiac involvement, and cancer (8). Most of the treatments available are organ-based therapies that were originally indicated for other conditions, but multiple new drugs are currently in the pipeline (9). Treatment may modify the natural history of SSc (10). The heterogeneous features of SSc may make trials challenging (11). The current guidelines for treatment of SSc are those of the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) (12) and the updated European League Against Rheumatism (EULAR) recommendations (13), published in 2016 and 2017, respectively. The treatment algorithms are not

meant to contradict SSc or other organ-specific guidelines. The suggestions by experts for therapy reported herein intend to provide consensus in SSc where there is uncertainty regarding therapy and to provide information about current practice using the drugs available. Many clinical trials do not provide treatment after first- or second-line standard therapy has failed.

In the present study, we updated the 2012 algorithms according to experience of experts in SSc. Algorithms include those for SRC, PAH, RP, ILD, GI involvement, skin involvement, inflammatory arthritis, and cardiac involvement. In general, the agreement has remained the same for many organ treatment algorithms, but some, such as that for treatment of PAH, have improved. Some new trends and advances in SSc treatment are reflected in the evolution of the algorithms. These recommendations may help clinicians in dealing with situations in which evidence supporting one treatment versus another is weak and guidelines fall short.

The rate of response to the first survey was modest. Most of the 62 experts who responded to the first survey responded to the subsequent surveys. Given the similarity of the expert panel composition between the first and third surveys, dropouts did not seem to diminish the global expertise. We did not define agreement rates a priori, but we thought that they were mostly fair to good (69–82%).

Differences in practice have been described between SSc experts and general rheumatologists who occasionally see SSc patients (14). Even among experienced centers, practices vary by center size (15). Experienced clinicians who contributed to the algorithms were mainly at university centers, where only 15% see fewer than 50 SSc patients annually. The characteristics of the respondents are comparable to those of the respondents who participated in the 2012 study (6).

SRC algorithms did not change substantially over time. The present algorithm is simpler because the drugs used for both severe and mild SRC were the same and agreement improved from 66% to 81%. No major changes to SRC treatment have been reported since the introduction of ACE inhibitors (16). Rapid control of BP should be a target with the addition of other antihypertensive agents to ACE inhibitors. In the present survey, CCBs replaced angiotensin receptor blockers as the second line of treatment (to be added to the first line). Although ACE inhibitors may increase the risk of fetal malformations in pregnancy, 40% of the experts would keep using them if a patient had previous SRC due to the chance of recurrence with discontinuation of ACE inhibitors. Consensus might be improved if there was universal access to drugs and if the experts had a face-to-face meeting to further discuss points of view where differences exist.

PAH treatment algorithms have evolved since the 2012 study. Previously, after monotherapy failed, a combination of drugs was accepted for severe PAH (9). In 2017, the AMBITION study, a phase III/IV double-blind randomized clinical trial that evaluated the use of combined ambrisentan and tadalafil as an initial treatment for class II/III PAH (including SSc patients), demonstrated more improvement in the combination arm (17). This combination (or other combinations of ERAs and PDE5 inhibitors) could potentially replace prostanoids as the first option in severe PAH. Riociguat, a guanylate cyclase stimulator, has been approved to treat PAH and connective tissue disease–related PAH (18). Only a minority of experts recommended riociguat (possibly due to incomplete access to the drug and less experience with it), but its use may increase in the future. Finally, lung transplantation (occasionally along with heart transplantation), which appears to be a valid treatment option for selected patients with end-stage PAH or ILD (19), was included as a fourth-line treatment for severe ILD.

Treatment for RP has remained without major changes. Ancillary treatments for RP may be introduced along with the treatments in the algorithms. An important consideration is that side effects are fewer and financial costs are lower in comparison with more advanced treatments like PDE5 inhibitors or prostanoids.

Prevention of digital ulcers was simplified in comparison with the previous algorithm. Macitentan was not effective in preventing digital ulcers (20), so only bosentan was included in the algorithm. Regarding active treatment of digital ulcers, prostanoids were third-line treatment, although a meta-analysis only showed a trend toward significance in digital ulcer healing with IV iloprost (21). Use of prostanoids to treat digital ulcers also appears in SSc guidelines (12,13).

Management of ILD induction therapy has changed considerably. After the Scleroderma Lung Studies (SLS 1 and SLS 2) (22), experts have changed their first-line preference from CYC to MMF. Oral CYC was used in the SLS studies, but the majority of experts said that if they used CYC, it would be mostly IV. There are more adverse events with oral CYC than with IV CYC. Some experts suggested the use of oral CYC either if IV CYC was not feasible or due to the severity of the disease. The use of rituximab as a rescue therapy is also increasing, with some observational data supporting its effectiveness in this context (23). Tocilizumab was only occasionally suggested, and this could be due to results of a phase III trial not yet being available along with a lack of experience and access currently in routine practice (24). The fourth line of treatment may include referral for ongoing clinical trials and HSCT for selected patients (25). Experts may have less experience

with this last option due to high treatment-related morbidity, requirement of specialized teams, and uncertain benefits for ILD. Some experts (60%) may prescribe GCs to patients with ILD (possibly those with fast-progressing lung fibrosis), using moderate-to-low doses often for <6 months.

Multiple treatments for GI involvement were used by experts in their daily practice for dysmotility/gastroesophageal reflux disease and bacterial overgrowth. Randomized clinical trial data are lacking for the best treatment approach in SSc for various GI complications.

The use of GCs among experts was not high in our study; however, they have been used more frequently in some trials (22). Experts incorporated MMF (as first-line treatment) and IV CYC (as third-line treatment) to treat SSc patients with high MRSS scores. There is weak evidence favoring the use of immunosuppression in early diffuse cutaneous SSc (dcSSc) (26). Experts have incorporated the possibility of performing HSCT (25). In skin involvement, randomized clinical trials show a clear benefit of HSCT versus IV CYC, but it is only a later line of treatment due to its risks (27). Recruitment for clinical trials may be an option given the lack of consistently effective treatment in early dcSSc.

Treatment for inflammatory arthritis was similar to treatment for RA, such as disease-modifying antirheumatic drugs, low-dose GCs, and biologic agents, as suggested in the BSR and BHPR guideline (12). Advanced treatments like tocilizumab, abatacept, and rituximab might have a role for refractory arthritis or patients with overlapping RA (28).

There is no randomized clinical trial evidence for treatment of cardiac involvement in SSc. Many cardiac manifestations, such as congestive heart failure, are treated similarly to other causes of heart failure. Pericarditis and myocarditis in SSc seemed to be treated by experts as inflammatory complications. Small pericardial effusions often accompany other serious organ involvement such as SRC or PAH, and in these cases they are usually not inflammatory and not treated, but they may be a poor prognostic marker (due to the other organs involved).

Expert practices may differ in the treatment options available according to geographic and socioeconomic restrictions. There was a predominance of North American (n = 27) and European (n = 17) experts, reflecting the composition of the SCTC and CSRG. The initial response rate was 36% in those surveyed, but it may be that 62 SSc experts provide enough variation in opinions with respect to treatment. However, we don't know if results would differ if the response rate was higher. After the first questionnaire, those who responded were invited to participate further in the study and their retention was good. Moreover, experts in respirology, cardiology, gastroenterology, nephrology, or other specialties were not consulted. The treatments reported are what are currently being prescribed for SSc patients, and they may or may not reflect what is being prescribed by other specialists. A limitation is that some treatment is based on expert opinion. For instance, the use of CCBs as first-line treatment for digital ulcers differs from the EULAR recommendations (13). Delphi exercises can get close to consensus, but total agreement is not likely.

A strength of our study is that there was a large sample of experts reflecting a broad range of opinions, and agreement was still frequently high. These algorithms may be superseded by specific situations such as drug intolerance, treatment failure, drug access, and clinical judgment, so they can serve as a guide to treatment in SSc. The latest PAH guidelines make some recommendations that are not immediately available for most of the regional health care systems due to financial and approval issues. It is possible that treatment recommendations for PAH (such as ambrisentan, selexipag, and riociguat) have not yet been incorporated for all patients.

In conclusion, we have updated our previous algorithms for treatment of SSc, reaching a higher level of overall agreement and providing therapeutic options for real-world situations, especially where high-quality evidence is not available.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Pope had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Fernández-Codina, Walker, Pope.
**Acquisition of data.** Fernández-Codina, Walker, Pope.
**Analysis and interpretation of data.** Fernández-Codina, Walker, Pope.

## REFERENCES

1. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, et al. Systemic sclerosis. Nat Rev Dis Prim 2015;1:15002.
2. Denton CP, Khanna D. Systemic sclerosis. Lancet (London) 2017;56:912–21.
3. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012;51:1017–26.
4. Hao Y, Hudson M, Baron M, Carreira P, Stevens W, Rabusa C, et al. Early mortality in a multinational systemic sclerosis inception cohort. Arthritis Rheumatol 2017;69:1067–77.
5. Pellar RE, Pope JE. Evidence-based management of systemic sclerosis: navigating recommendations and guidelines. Semin Arthritis Rheum 2017;46:767–74.
6. Walker KM, Pope J. Treatment of systemic sclerosis complications: what to use when first-line treatment fails–a consensus of systemic sclerosis experts. Semin Arthritis Rheum 2012;42:42–55.
7. Clements P, Lachenbruch P, Seibold J, White B, Weiner S, Martin R, et al. Inter and intraobserver variability of total skin thickness

score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281–5.
8. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897–905.
9. Lee JJ, Pope JE. Diagnosis and management of systemic sclerosis: a practical approach. Drugs 2016;76:203–13.
10. Khanna D, Distler JH, Sandner P, Distler O. Emerging strategies for treatment of systemic sclerosis. J Scleroderma Relat Disord 2016;1:186–93.
11. Gordon JK, Domsic RT. Clinical trial design issues in systemic sclerosis: an update. Curr Rheumatol Rep 2016;18:38.
12. Denton CP, Hughes M, Gak N, Vila J, Buch MH, Chakravarty K, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford) 2016;55:1906–10.
13. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.
14. Pope JE, Ouimet JM, Krizova A. Scleroderma treatment differs between experts and general rheumatologists. Arthritis Rheum 2006;55:138–45.
15. Harding S, Khimdas S, Bonner A, Baron M, Pope J, Canadian Scleroderma Research Group. Best practices in scleroderma: an analysis of practice variability in SSc centres within the Canadian Scleroderma Research Group (CSRG). Clin Exp Rheumatol 2012;30 Suppl 71:S38–43.
16. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis 2007;66:940–4.
17. Coghlan JG, Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Ann Rheum Dis 2017;76:1219–27.
18. Humbert M, Coghlan JG, Ghofrani HA, Grimminger F, He JG, Riemekasten G, et al. Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. Ann Rheum Dis 2017;76:422–6.
19. Shah RJ, Boin F. Lung transplantation in patients with systemic sclerosis. Curr Rheumatol Rep 2017;19:23.
20. Khanna D, Denton CP, Merkel PA, Krieg T, Le Brun FO, Marr A, et al. Effect of macitentan on the development of new ischemic digital ulcers in patients with systemic sclerosis: DUAL-1 and DUAL-2 randomized clinical trials. JAMA 2016;315:1975–88.
21. Tingey T, Shu J, Smuczek J, Pope J. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. Arthritis Care Res (Hoboken) 2013;65:1460–71.
22. Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, et al. Mycophenolate mofetil versus placebo for systemic sclerosis–related interstitial lung disease: an analysis of scleroderma lung studies I and II. Arthritis Rheumatol 2017;69:1451–60.
23. Daoussis D, Melissaropoulos K, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum 2017;46:625–31.
24. Khanna D, Denton CP, Lin CJ, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). Ann Rheum Dis 2017;387:2630–40.
25. Eyraud A, Scouppe L, Barnetche T, Forcade E, Lazaro E, Duffau P, et al. Efficacy and safety of autologous haematopoietic stem cell transplantation in systemic sclerosis: a systematic review of the literature. Br J Dermatol 2018;178:650–8.
26. Herrick AL, Pan X, Peytrignet S, Lunt M, Hesselstrand R, Mouthon L, et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). Ann Rheum Dis 2017;76:1207–18.
27. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. N Engl J Med 2018;378:35–47.
28. Elhai M, Meunier M, Matucci-Cerinic M, Maurer B, Riemekasten G, Leturcq T, et al. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. Ann Rheum Dis 2013;72:1217–20.

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