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Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Systemic Sclerosis

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A B S T R A C T

Background: Systemic Sclerosis (SSc) or Scleroderma is a systemic autoimmune rheumatic disease characterized by dysregulation of the immune system, fibrosis of the skin and visceral organs and vasculopathy. The global prevalence of SSc reaches 17.6 per 100,000 population and the incidence reaches 1.4 per 100,000 people per year. The prevalence and incidence of SSc in Asia reaches 6.8 per 100,000 and 0.9 per 100,000, which is lower than other continents. Women have a prevalence and incidence of SSc five times higher than men. The prevalence and incidence of SSc depends greatly on the results of the study. There has not been much research on the epidemiological studies of SSc in Indonesia.
Methods: Twelve selected rheumatologists from the Indonesian Rheumatologist Association (IRA) made recommendations based on key questions formed by a steering committee from IRA. These recommendation materials were taken from several online databases such as PubMed, Science Direct, and Google Scholar. Level of evidence and grades of recommendation were then assigned, and every member of the panelist team will assign a score for level of agreement.
Results: A total of 50 recommendations that discussed the diagnosis, pharmacological and non-pharmacological therapy, and prognosis for SSc were made.
Conclusion: These recommendations can be used to help clinicians correctly diagnose and choose the most suitable therapy for SSc patients. All recommendation statements were created with the consideration of Indonesia's clinical setting, facility, and drug availability.

1. Introduction

Systemic Sclerosis (SSc) or Scleroderma is a systemic autoimmune rheumatic disease characterized by dysregulation of the immune system, fibrosis of the skin and visceral organs and vasculopathy. Immune system disorders are characterized by an imbalance in cytokine expression, autoantibody production, and abnormalities in progenitor cells and/or effector cells in the blood.[1,2]

The global prevalence of SSc reaches 17.6 per 100,000 population and the incidence reaches 1.4 per 100,000 people per year.[1-3] The prevalence and incidence of SSc in Asia reaches 6.8 per 100,000 and 0.9 per 100,000, which is lower than other continents. Women have a prevalence and incidence of SSc five times higher than men.[1] The prevalence and incidence of SSc is highly dependent on study results, but there has not been much research on the epidemiological studies of SSc in Indonesia.[4,5]

The ratio of men and women affected by SSc is 1:3, but in the young population SSc is much more common in women with a ratio of 1:7.[4-5] Data from Indonesia shows that the peak age of SSc patients in West Java, Indonesia is 30-40 years and almost all the patient was female (the male:female ratio was 1:56).[6] Considering that so far there is no recommendations on diagnosis and management of SSc in Indonesia and with different healthcare landscape in Indonesia in

terms of diagnostic capacity and treatment choices compared to other countries, the objectives of this recommendations are to provide guidance on diagnosis and management of SSc for healthcare provider in Indonesia.

2. Methods

The recommendation team was assembled by The Indonesian Rheumatologist Association (IRA). The recommendation team, consisting of six rheumatologists, was in charge of formulating key questions for diagnosis, therapy, and monitoring of SSc. There was also a team of steering committee consisting of six core members from IRA. The panelist team consisted of 51 rheumatologists from various branches of IRA and institutions in Indonesia, with at least five years of working experience as a rheumatologist. Each member of the panelist team provided independent opinions regarding the level and strength of recommendation that was issued by the recommendation team. No delegation from the pharmacy industry was involved in the process of composing this recommendation.

A total of 9 key questions were formed to determine the recommendations for diagnosing and managing SSc in Indonesia:

1. How to diagnose SSc?
2. What are the examinations needed to diagnose SSc?
3. What are the comprehensive treatments for SSc patients?
4. What are the non-pharmacologic treatments for SSc patients?
5. What are the pharmacologic treatments for SSc patients?
6. What are the educations for SSc patients??
7. What are the comorbidities or complications in SSc?
8. How to monitor disease activity and management in SSc?
9. When to refer SSc patients?

Literature searching was done online using PubMed, Science Direct, Google Scholar, and other databases, using these keywords: Systemic Sclerosis, diagnosis, management, and monitoring. The literature was limited to published English meta-analysis, systematic review, clinical trial, randomized controlled trial (RCT), and observational study. The literature was also limited to studies published within 2011 to 2023.

Recommendations were then issued based on the 9 key questions above. The recommendation team then assigned the level of evidence (LoE) and grades of recommendation (GoR) based on the criteria listed in Table 1.[7] The recommendations were then reviewed by the steering committee. In the final step, the panelist team members were asked to give a score of 0-10 for each recommendation, to determine the level of agreement (LoA). A score of 0 means complete disagreement and 10 means complete agreement. The panelist member would be asked for comments should a score below 8 was issued. Each recommendation with an average score below 8 were then rediscussed by the recommendation team to be revised and then reassessed for determining the LoA from the panelist team.

Table 1. Level of Evidence and Grades of Recommendations

Level of evidence (LoE)		Grades of recommendation (GoR)	
I	High quality meta-analysis or systematic review of RCTs, or individual RCTs with low risk of bias	A	Strong recommendation: referring to level I studies
II	High quality systematic review of observational studies (case control or cohort), or individual observational studies	B	Moderate recommendation: referring to level II studies or extrapolation of level I studies
III	Non-analytic studies (case report or case series)	C	Weak recommendation: referring to level III studies or extrapolation of level II studies
IV	Non-analytic low quality studies (case report or case series)	D	Consensus recommendation: expert opinion or based on limited evidence

3. Results

Based on the discussion, 50 recommendations were agreed by the recommendation team, steering committee, and the panelist team. Summary of these recommendations can be seen in Table 2.

Table 2. Summary of Recommendations for Diagnosis and Management of Ssc
INITIAL ASSESSMENT OF SYSTEMIC SCLEROSIS PATIENTS

No	Recommendation	LoE	GoR	LoA
1.	Systemic sclerosis needs to be suspected in patients with clinical manifestations of fibrosis such as skin thickening and/or pulmonary fibrosis and/or vascular abnormalities such as ulcers/gangrene and/or pulmonary hypertension, especially in women without evidence of other causes.	IV	D	9.6
2.	Patients suspected of having SSc need further examination or referral to a specialist in internal medicine, a subspecialist in rheumatology or another subspecialist according to organ involvement.	IV	D	9.5
3.	The diagnosis of SSc is made based on clinical findings and supporting examinations and requires review by an experienced specialist doctor.	I	A	9.7
4.	The 2013 ACR/EULAR SSc Classification Criteria can be used to aid the diagnosis.	I	A	9.7
5.	Every patient with SSc requires an assessment of organ involvement to determine an appropriate treatment plan.	I	A	9.9
6.	Additional supporting examinations are required according to suspected organ involvement and to screen for comorbidities.	IV	D	9.6
7.	The ANA test needs to be carried out on every patient suspected of having SSc and if possible, SSc-specific autoantibodies can be done to predict the possibility of organ involvement and prognosis.	I	A	9.6
8.	Skin thickening needs to be evaluated in every patient with SSc using *Modified Rodnan Skin Score* (mRSS).	I	A	9.5
9.	Evaluation of mRSS carried out at least every three months and changes that are considered significant are a change of at least 5 points or at least 15-25% from baseline.	I	B	9.6
10.	Treatment options for skin thickening in systemic sclerosis are			
	a. Methotrexate (MTX), or	II	C	9.6
	b. Mycophenolate mofetil (MMF)	II	C	9.8
	c. Cyclophosphamide can be used in systemic sclerosis patients with progressive skin fibrosis or with internal organ manifestations.	II	C	9.6
	d. In SSc conditions with progressive skin manifestations accompanied by internal organ involvement, Rituximab (RTX) can be considered.			
11.	Every SSc patient needs to be evaluated in detail to determine the presence of finger vascular disorders in the form of Raynaud's Phenomenon (RP), ulcers, or gangrene.	IV	C	9.6
12.	Lifestyle changes is effective to control RP, including wearing warm clothes, smoking cessation, protecting hands/feet from microtrauma, avoid triggering factors such as cold and vasoconstrictive medications.	II	C	9.6
13.	In SSc patients with RP, calcium antagonists (including nifedipine) can be used as the first line treatment.	I	A	9.5
14.	In SSc patients with RP who do not respond or are intolerant to calcium antagonists, the prostanoid and/or a PDE-5 antagonist can be given or added.	I	A	9.3
15.	In SSc patients with finger ulcers or gangrene, bosentan can be added to prevent the formation of new finger ulcers which is given at the same time as drugs for RP.	I	B	9.2
16.	Antiplatelet drugs may be considered in the management of vasculopathy in SSc.	III	C	9.4
17.	Statins may be considered in the management of vasculopathy.	III	C	9.6
18.	ACE inhibitors and ARBs may be considered in the treatment of SSc-associated finger ulcers.	II	C	9.7

19.	Treatment of finger ulcers requires multidisciplinary management, such as local and systemic therapy, including oral vasodilators, analgesia, and treatment of possible complications.	III	C	9.5
20.	Every patient with SSc needs to be evaluated for musculoskeletal involvement including arthritis, myopathy, and tendinopathy.	IV	D	9.7
21.	Treatment options for arthritis, myopathy, and tendinopathy are NSAIDs or oral corticosteroids in combination with methotrexate.	IV	D	9.6
22.	Every patient with SSc needs to be evaluated for lung involvement and management of Interstitial Lung Disease need to be given from the initial diagnosis of the disease.	II	A	9.6
23.	Pulmonary function examination (*forced vital capacity* [FVC] or *diffusing capacity of carbon monoxide* [DLCO]) needs to be carried out periodically for screening and diagnosis of Interstitial Lung Disease.	III	B	9.7
24.	*High Resolution CT (HRCT) scan thorax* is the gold standard for ILD screening, it can be carried out from the beginning of SSc diagnosis to screen for ILD diagnosis and repeated to assess disease progression.	II	B	9.5
25.	Multidisciplinary collaboration is needed for non-pharmacological and pharmacological therapy for the management of ILD in SSc.	IV	B	9.3
26.	First-line treatment with Mycophenolate mofetil or Cyclophosphamide is the pharmacological therapy of choice for ILD cases, especially in patients with NSIP features (*ground glass opacity*) on HRCT.	I	A	9.5
27.	Nintedanib, an anti-fibrosis, can be used as second-line therapeutic option in progressive SSc-ILD or with UIP on HRCT.	I	A	9.3
28.	Indications for starting pharmacological treatment in Interstitial Lung Disease needs to consider the severity of the disease and risk factors for progression.	I	A	9.5
29.	For patient with *Progresive Pulmonary Fibrosis* phenotype, the treatment options are Mycophenolate mofetil or Cyclophosphamide in combination with Nintedanib.	I	A	9.3
30.	Every patient with SSc needs to be evaluated for cardiac involvement.	IV	D	9.6
31.	Diagnosis of cardiac involvement in SSc was made with multidisciplinary collaboration after ruling out other heart diseases based on clinical and supporting evaluation	IV	D	9.4
32.	Management of cardiac involvement in SSc is decided according to clinical manifestations based on expert opinion and multidisciplinary collaboration.	IV	D	9.5
33.	Initial screening for Pulmonary Arterial Hypertension (PAH) needs to be carried out in all SSc patients from the beginning of diagnosis.	II	B	9.7
34.	Multidisciplinary collaboration is needed for diagnosis and therapy for management of PAH in SSc.	I	B	9.6
35.	Echocardiography and/or biomarkers NT-proBNP and/or PFP can help identify PAH patients.	II	B	9.4
36.	PAH therapy options in SSc are as follows:			9.3
	Endothelin Receptor Antagonist (ERA: ambrisentan, bosentan and macitentan), *Phosphodiesterase type 5 inhibitor (PDE-5 inhibitor:* sildenafil, tadalafil).	I	B	9.3
	Phosphodiesterase type 5 inhibitor (PDE-5 inhibitor: sildenafil, tadalafil)	I	B	9.3
	Riociguat	I	B	9.3
	Epoprostenol intravenous	I	B	9.3
	Prostacycline analogues (iloprost, treprostinil, beraprost)	I	B	9.3
37.	Vigilance on *scleroderma renal crisis* (SRC) needs to be considered if hypertension or impaired kidney function is found, especially in steroid users with a dose equivalent to prednisone >15 mg/day.	1	C	9.5
38.	Diagnosis of SRC in SSc if found 1. New onset of hypertension 2. Impaired kidney function Accompanied by 1. Hematuria 2. Lung oedema 3. Oligouria/anuria	1	A	9.5

	4. *Microangiopathic hemolytic anemia*			
39.	Recommendations for SRC management are:			9.6
	ACE blockers as first choice	I	C	9.6
	CCB as a second choice	II	D	9.6
	ARB is an alternative therapy in conditions of ACE blocker intolerance	II	C	9.6
	ACE blockers have not been recommended as prophylactic therapy for SRC	I	B	9.6
	Dialysis can be considered if needed	I	C	9.6
40.	Be aware of gastrointestinal disorders in SSc if there are complaints of dysmotility such as swallowing disorders, bloating and constipation.			9.6
41.	Lifestyle modification is recommended to treat upper gastrointestinal complaints in SSc.	1	C	9.3
42.	A small-repeated diet is recommended for the management of gastrointestinal dysmotility.	2	D	9.5
43.	Antibiotics are recommended under circumstances of *intestinal bacterial overgrowth.*	1	D	9.3
44.	The following prokinetic preparations are recommended to improve gastrointestinal dysmotility in SSc:			9.3
	Metoclopramide is the first choice	2	B	
	Domperidone as a second choice	1	B	
	Octreotide as an alternative therapy for small intestinal dysmotility	2	B	
45.	Proton pump inhibitors are recommended for the treatment of GERD in SSc.	1	A	9.4
46.	Pregnancy in SSc patients is recommended when the clinical condition of the disease is stable according to the assessment of the treating specialist/subspecialist.	II	B	9.6
47.	SSc patients with pregnancy require monitoring of the condition of the mother and fetus during pregnancy by the relevant specialist doctor.	II	B	9.6
48.	The use of drugs in SSc patient needs to be considered during the period of conception, pregnancy, lactation.	II	B	9.7
49.	SSc patients require special perioperative preparation regarding medications and evaluation of the risk of perioperative complications.	II	B	9.7
50.	SSc patients need to receive vaccinations according to indications, taking into account the benefits and risks	II	B	9.6

Recommendation 1-5: Initial Assessment of Systemic Sclerosis Patients

Visceral organ involvement in SSc.[9-18]

The clinical manifestations of SSc involve almost all organ systems as follows:

a. Constitutional manifestations/symptoms

Manifestations/constitutional symptoms of SSc include fever (without evidence of infection), excessive fatigue, malaise, decreased appetite and weight.

b. Skin manifestations

Skin manifestations in the form of skin hardening are a characteristic feature of SSc. The initial symptom that follows Raynaud's phenomenon is edema/swelling of both hands (puffy hands). Puffy hands in SSc resemble edema due to heart failure or venous obstruction. Puffy hands will then turn into non-pitting edema and then the edema on the skin turns into hardening of the skin and sclerodactyly forms. Other skin involvement is itching/pruritus, blackening of the skin, and the appearance of white spots including (hyper and hypo-pigmented spots/salt and pepper appearance). Facial skin hardens, skin wrinkles disappear, the mouth puckers up, and there is a limitation in opening the mouth (pursed lip appearance). Reddish spots on the face (telangiectasia), calcinosis, and contractures of the fingers due to hardening of the skin can be found in SSc patients.

c. Peripheral vascular manifestations:

Raynaud's phenomenon can appear before other symptoms appear in SSc, namely

vasospasm/vasoconstriction of blood vessels when exposed to cold or under stress.

d. Musculoskeletal manifestations:

Musculoskeletal manifestations in the form of arthralgia, arthritis, joint contractures with limited joint movement, myopathy and myositis can be found in SSc.

e. Pulmonary manifestations:

Data from the European Scleroderma Trials and Research (EUSTAR) shows that pulmonary fibrosis contributes to 35% of disease-specific mortality and 20% of overall mortality. All compartments of the respiratory system can be abnormal in SSc. The lung disorders most frequently found in SSc are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension occurs in 15% of SSc patients and is one of the main causes of death besides interstitial lung disease. The extent of telangiectasia on the skin is known to be associated with the incidence of pulmonary arterial hypertension.

f. Cardiac manifestations

Cardiac manifestations in SSc vary depending on the definition used. Various cardiac manifestations recorded in several studies are arrhythmia, decreased systolic ejection fraction, or chest pain due to pericarditis.

g. Gastrointestinal manifestations

Gastrointestinal manifestations are common in SSc and can occur throughout the gastrointestinal tract. The most common gastrointestinal complaints are meteorism, cough/hoarseness and heartburn. Oropharyngeal manifestations can include reduced ability to open the mouth.

h. Renal manifestations

The most important renal manifestation in SSc is renal crisis or scleroderma renal crisis (SRC).

i. Hematological manifestations

There are no specific hematological manifestations in SSc.

Systemic Sclerosis Disease Activity

Evaluation of skin involvement in SSc is one way to assess the degree of disease activity. The Rodnan skin score is a tool for assessing skin thickening in SSc created by Gerald Rodnan. The Rodnan score assesses skin thickening with a score of 0–4 at 26 locations. Clements et al. then made a modification of the Rodnan score to calculate skin involvement in SSc to only 17 locations. Calculation of the Rodnan modification score divides skin thickness into a score of 0-3, namely 0 if normal (fine skin wrinkles are still visible), 1 if skin hardening is minimal/equivocal, 2 if skin hardening is moderate so fine wrinkles are no longer visible on the skin, 3 if the hardening skin is heavy so the skin is difficult to pinch. Calculations were carried out on 17 skin areas so that the total score ranged from 0–51.[12-14]

Recommendation 6-7: Supporting Examination in Systemic Sclerosis.[11-18]

a. Basic Laboratory Examination

Routine peripheral blood tests can reveal anemia due to chronic diseases or hematological disorders related to immunosuppressant therapy. Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP) levels can be used for monitoring therapy. Renal function examination is needed to detect early renal crisis in SSc. Liver function tests are needed to monitor side effects of the drugs given. In patients who will receive immunosuppressants, screening tests for hepatitis B, hepatitis C, HIV and TB infections need to be carried out. Urine examination may show proteinuria as a manifestation of SSc renal crisis.[11-18]

b. Specific Autoantibodies Examination

One sign that SSc is an autoimmune disease is the discovery of various autoantibodies such as ANA and various other specific autoantibodies. ANA examination is found in 95% of SSc but ANA positive is not specific for SSc.

In SSc serum, autoantibodies against specific intracellular antigens can be detected. Each

specific autoantibody is associated with its own clinical manifestations, disease course and severity. SSc has very diverse clinical manifestations, information about these autoantibodies is very valuable to help establish the diagnosis and predict the patient's prognosis.[13] The three main specific autoantibodies in the diagnosis of SSc are Anti Topoisomerase Antibodies (ATA) I, Anti Centromere Antibodies (ACA) and Anti RNAP-III Antibodies, all three of which are listed in the 2013 ACR/EULAR classification criteria.[7,8,15]

c. Other supporting examinations

Barium esophagography examination to see esophageal dysmotility; Esophageal manometry with 24-hour pH measurement can detect reflux of stomach acid into the esophagus. Upper gastrointestinal endoscopy is needed to detect blood loss in gastric antral vascular ectasia (GAVE), and gastritis. The endoscopic appearance of GAVE is referred to as a watermelon stomach.[11]

In SSc patients, pulmonary complications in the form of pulmonary arterial hypertension (PAH), pulmonary fibrosis, and interstitial lung disease are the main causes of death. Lung evaluation is necessary in every SSc patient. Chest x-ray examination showed basilar pulmonary fibrosis. Examination with a high resolution CT scan (HRCT) provides a ground glass image showing an inflammatory process or alveolitis, advanced interstitial lung disease on CT scans in the form of honeycombing or bonchiectasis. To assess respiratory function, spirometry or diffusing capacity for carbon monoxide (DLCO) examination can be performed. In patients with features of interstitial lung disease >20% of all lungs or with forced vital capacity (FVC) based on spirometry or DLCO <70% predictor values according to age and gender are an indication for aggressive treatment of interstitial lung disease.[4,16]

Echocardiography is used to determine the presence of pericardial effusion and measure pulmonary artery pressure in patients with suspected pulmonary arterial hypertension.

Nailfold capillaroscopy examination using a capillaroscopy tool can assess abnormalities in the patient's capillary blood vessels.[13,14]

Recommendation 8-10: Skin Involvement In Systemic Sclerosis. [3,4,7,13,14]

Manifestations and Clinical Evaluation of Skin Involvement in Systemic Sclerosis (SSc)

Skin manifestations are found in almost all systemic sclerosis patients.[3,4,7,13,14]

Cutaneous manifestations of systemic sclerosis take several forms. Skin manifestations in systemic sclerosis patients can include:

1. **Skin Thickening**

   Systemic sclerosis will cause diffuse thickening and induration of the skin accompanied by loss of skin elasticity and tightness. On palpation, the skin will feel rough and hard like wood or a board. The skin will be difficult to pinch with the thumb and index finger. This can occur due to the spread of fibrosis into the subcutaneous area to the attachment of the dermis to the fascia. The distribution of skin thickening on the body can help classify the type of SSc into one of the subtypes: in limited type SSc there is thickening of the skin on the hands, extremities distal to the elbows, and face with slow progression; whereas in the diffuse type of SSc there is thickening of the skin in the proximal extremities, so that it can involve the whole body with rapid progression.[9,13,14]

2. **Puffy hands**

   Swelling in the fingers is an early diagnostic sign, so it is one of the red flags of systemic sclerosis.

3. **Telangiectasia**

   Dilation of blood vessels that occur in the nail folds is one of the early signs of SSc which can be seen using capillaroscopy.

4. **Calcinosis**

   Deposits of insoluble calcium salts on the skin and subcutaneous tissue usually occur at pressure

points. Calcinosis is more common in limited type SSc.

Recommendation 8. Evaluation of skin thickening in Systemic Sclerosis is carried out by examining the Modified Rodnan Skin Score.[12-14]

Skin evaluation in systemic sclerosis is carried out clinically by assessing the Modified Rodnan Skin Score (mRSS) by assessing the degree of skin thickening in 17 areas of the body including the face, upper arms, forearms, back of the hands, fingers, anterior chest, abdomen, thighs, calves and feet.

Recommendation 10.a. The treatment option to reduce skin thickening in Systemic Sclerosis is Methotrexate (MTX).[20-24]

A double-blind randomized clinical trial study by Van Den Hoogen et al. which compared administration of methotrexate 15 mg/week intramuscularly with a placebo control showed that over the 24 weeks of the study, as many as 53% of the group of subjects receiving methotrexate therapy produced a clinical improvement in skin response (compared to 10% in the placebo group) without causing additional organ disorders despite therapy was continued for 48 weeks. However, conflicting results were obtained in the study by Pope et al. with a double-blind randomized clinical trial method in early diffuse systemic sclerosis that compared administration of methotrexate 10 mg/week which was then increased to 15 mg/week with placebo which showed no significant difference in skin improvement. The ESOS observational study by Herrick et al. which looked at changes in mRSS scores in patients with various treatment modalities showed that there was a significant decrease in mRSS scores in patients who received methotrexate for 12 months by −4.0 (−5.2 to −2.7) compared to the initial score although there was no difference significantly compared to groups receiving cyclophosphamide, MMF, or not receiving immunosuppressants.[20-24]

Recommendation 10.b. The treatment option for skin thickening in Systemic Sclerosis is Mycophenolate mofetil (MMF).[21,22]

A prospective observational study by Derk et al. which was carried out on early-stage diffuse type SSc patients, the results were that in the first 6 months there was an improvement in the mRSS score from initially 22.4 to 13.6 until the end of the study at 8.4. In this study, MMF was given at an initial dose of 1000 mg/day which was increased gradually to 3000 mg/day. In the Scleroderma Lung Study II, oral cyclophosphamide and MMF both reduced mRSS scores at the end of the study compared to baseline, but there was no difference in the reduction of mRSS. between cyclophosphamide and MMF.

Recommendation 10.c. Cyclophosphamide can be used in Systemic Sclerosis patients with Progressive Skin Fibrosis or with internal organ manifestations. [22-25]

There are several studies examining the effect of cyclophosphamide on skin thickening in systemic sclerosis patients. Macedo et al. administered intravenous cyclophosphamide at a dose of 500 mg/m2 to 1000 mg/m2 body surface area per month for 12-18 months in nine diffuse systemic sclerosis patients with mRSS of at least 30.[23]

There was a decrease in MRSS in oral and intravenous cyclophosphamide but there was no significant difference in the two groups, however side effects were found to be higher in the intravenous cyclophosphamide group.

Side effects of cyclophosphamide that may occur include bone marrow suppression, teratogenicity, reproductive failure and hemorrhagic cystitis.[10] Cyclophosphamide is only recommended for cutaneous manifestations in patients who have progressive skin involvement or have not responded to other immunosuppressants or have other indications such as interstitial lung disease and should be carefully monitored for adverse drug effects. [22-25]

Recommendation 10.d. In SSc conditions with progressive skin manifestations accompanied by internal organ involvement, Rituximab (RTX) can

be considered.[26,27]

1. Rituximab (RTX)

There are several studies examining the effects of rituximab in systemic sclerosis and these studies generally prescribe rituximab due to internal organ involvement but the effects on the skin were also assessed.

Management of Calcinosis in Systemic Sclerosis.[28-30]

1. General management and supportive therapy
   Patients are advised to maintain blood flow by avoiding trauma, stress, or exposure to cold temperatures. Antibiotics may be given if superinfection of calcinotic lesions is suspected. To relieve pain, acetaminophen, NSAIDs or opioids can be given.
2. Medical management
   The following drugs have been proven to treat calcinosis through various studies, namely as follows:
   - Calcium channel blocker (CCB) (240 – 480 mg/day for 1 – 12 years)
   - Colchicine (1 mg/day)
3. Surgery

Recommendation 11-19: Vascular involvement of the fingers (Raynaud's phenomenon and finger ulcers) in Systemic Sclerosis.[12-14]

SSc patients can experience a wide spectrum of finger vascular disorders, ranging from the most common being Raynaud's phenomenon (RP), finger ulcers, and more rarely to ischemia. RP occurs in >90% of SSc patients, is often the earliest manifestation of SSc, can even occur years before a diagnosis of SSc is made.

RP is a vasospasm of blood vessels when exposed to cold or under stress. There are three phases of skin color change in RP when exposed to cold temperatures, namely starting from pale, then bluish, and reactive hyperemia will occur. Apart from color changes, sometimes patients can feel tingling, discomfort, or loss of feeling in the discolored area. These symptoms are most often found on the fingers rather than the toes, as well as on the nose, ears and even the tongue. An episode of RP usually lasts 15-20 minutes after exposure to cold temperaturesend.

The diagnosis of Raynaud's phenomenon in SSc can be seen in Table 3 below:

Table 3. History and examination of patients with Systemic Sclerosis with Raynaud's phenomenon.[12-14,30-33]

Anamnesis	A complete history includes complaints related to SSc, organ involvement, family history, use of diseases and medications, and occupation.
Physical examination	A systematic physical examination needs to be carried out to look for organ involvement. It is necessary to pay attention to the extent of skin lesions in SSc. The hands and feet area need to be paid more attention to see if there are any *puffy finger* (swollen fingers), sclerodactyly and/or proximal skin thickening, ulcers on the fingers or at the tips of the fingers (*digital ulceration/digital pitting scars*). Peripheral pulses should also be checked.
Investigation	Minimum examination in the form of complete blood count, ESR or CRP, ANA test, and so on *nail fold capillaroscopy*. Liver function, kidney function, electrolytes and chest x-rays need to be done. Specific autoantibodies related to the underlying disease of SSc also need to be performed.

Finger (hand and foot) ulcers are a serious manifestation of vasculopathy in SSc. Ulcers commonly occur on the fingertips or on the extensor side of the hand and may also be associated with calcinosis. Approximately 50% of SSc patients have a history of finger ulcers, often occurring in the early stages of the disease. These finger ulcers have the potential to cause pain and disability, interfere with

work, reduce quality of life, and are even associated with higher mortality in SSc patients.

Risk factors for finger ulcers in SSc include: onset of the disease at a young age, extensive skin thickening (high mRSS score), positive anti-topoisomerase-I or anti-Scl-70, smoking, duration of the disease and RP longer duration, presence of finger joint contractures, history of previous finger ulcers, ESR and HAQ-DI score (*Health Assessment Score – Disability Index)* high levels, involvement of internal organs, and delay in vasodilator therapy are risk factors for finger ulcers from various studies. SSc patients with positive anti-Scl-70 will have an increased risk of developing finger ulcers 2.23–7.9 times compared to that negative.[31-33]

The spectrum of ulcers on the fingers of SSc patients can be seen in the image following:

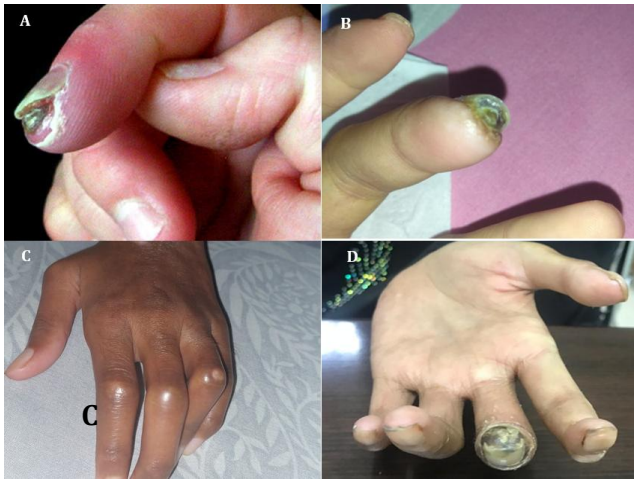

Figure 1. Ulceration of the Finger and Ischemia of the Finger Systemic Sclerosis
(A, B) Ulcers on the tips of the fingers (C) Multiple finger ulcers on the extensors (D) Gangrene of the fingers

The Digital Ulcer Clinical Assessment Score (DUCAS) is currently still in preliminary studies to clinically assess the condition of finger ulcers, including the number of ulcers, the formation of new ulcers, the presence of gangrene, the need for surgery, the presence of infection, the need for hospitalization, and the analgesics needed to controlpainful.

Recommendation 12. Lifestyle changes are one effective way to control Raynaud's Phenomenon (RP), including wearing warm clothes, stop smoking, protecting hands/feet from microtrauma, avoiding trigger factors such as cold and vasoconstrictor medication.[37-39]

Certain conditions can worsen RP such as cold air, drugs that cause vasoconstriction, atherosclerosis, excessive caffeine consumption, and smoking. Drugs that can precipitate or exacerbate RP include migraine drugs (ergotamine derivative sumatriptan, *methysergide*), hyperprolactinemia therapy (bromocriptine, *cabergolin*), interferon-α andβ, cocaine, local or systemic nasal decongestants (ephedrine, pseudoephedrine, phenylephrine, phenylpropanolamine), adrenaline, amphetamine derivatives, certain chemotherapy (bleomycin, cysplatin), clonidine, cyclosporin, anti-parkinson drugs, *pergolide*, and the most common are the inhibitorsβ which is non-selective.

Recommendation 13. In SSc patients with RP as first therapy, calcium antagonists (including nifedipine) can be used.[36-39]

Nifedipine is said to reduce the frequency and severity of RP in SSc patients. Dihydropyridine-type calcium antagonists such as oral nifedipine are the first line of therapy for SSc-associated RP.

Recommendation 14. In SSc patients with RP who do not respond or are intolerant to calcium antagonist administration, the prostanoid iloprost and/or a PDE-5 antagonist can be given or added.[40-44]

PDE-5 inhibitors (*phosphodiesterase type-5*) is given to SSc patients with severe RP and/or unresponsiveness to calcium antagonists.

Prostanoids are potent vasodilators and also have the effect of inhibiting platelet aggregation and vascular smooth muscle cell proliferation. Intravenous iloprost can reduce the frequency and severity of RP attacks in SSc, its use is recommended for severe RP after failure of oral therapy with calcium antagonists or PDE-5 inhibitors. Iloprost is administered intravenously at a dose of 0.5–2 ng/kg/min for 3–5

days in a row or given orally with a dose of 50–150 mcg every 12 hours.

Recommendation 15. In SSc patients with finger ulcers or finger gangrene, bosentan can be added to prevent the formation of new finger ulcers which is given together with drugs for RP.[41-44]

The results of studies on bosentan as an endothelin-1 receptor antagonist are quite varied. This preventive effect of bosentan has also been proven in various meta-analyses. Side effects of bosentan include hepatotoxicity, teratogenicity, and reduced hormonal contraceptive effects due to interactions with cytochrome enzymes P450.

Recommendation 16. Antiplatelet drugs may be considered in RP therapy in SSc. [41-44]

Research on the use of antiplatelets in SSc vasculopathy consists of case reports with varying results. The use of cilostazol provides an improvement in RP after 4 weeks of administration.

Recommendation 17. Statins may be considered in the management of finger vasculopathy. [41-44]

A RCTs prove that statins are more effective in reducing pain and the degree of RP and finger ulcers associated with SSc than placebo. Another study with lower levels using atorvastatin 40 mg showed a reduction in the number of new finger ulcers.

Recommendation 18. ACE inhibitors and ARBs may be considered in the treatment of SSc-associated finger ulcers.[35-39]

Multicenter RCT showed that there was no inhibition of the formation of new ulcers or improvement in the frequency and severity of RP in SSc after quinapril therapy. Another RCT using losartan showed improvement in primary RP therapy, but not in associated RP in SSc patients.

Recommendation 19. Handling of finger ulcers requires multidisciplinary management, namely local and systemic therapy including oral vasodilators, analgesia, and dealing with possible infections. [40-44]

Fluoxetine as an inhibitor *reuptake-serotonin*

Recommendation 20-21: Musculoskeletal Involvement in Systemic Sclerosis. [46-47]

Musculoskeletal Manifestations in Systemic Sclerosis

Musculoskeletal (MSK) manifestations are often experienced by SSc patients (ranging between 40-80%) and especially in diffuse type SSc patients in the early stages.

Recommendation 20. Every patient with SSc needs to be evaluated for musculoskeletal involvement including arthritis, myopathy, and tendinopathy. [46-47]

The diagnosis of arthritis in SSc is made based on clinical findings and supporting examinations. Clinical symptoms, namely arthralgia, stiffness and mild pain, are common features of joint involvement, but can also be accompanied by severe joint inflammation. The onset may be acute or insidious, and the pattern of joint involvement may be oligoarticular or polyarticular. Almost all joints can be affected, but most often the joints in the fingers (especially the MCP and PIP joints), wrists and ankles.

Recommendation 21. Treatment options for arthritis, myopathy, and tendinopathy are NSAIDs or oral corticosteroids in combination with methotrexate. [46-47]

There have been no studies with randomized controlled trials regarding the management of musculoskeletal involvement in SSc.

- Arthralgia and arthritis can be treated with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for the short term, with monitoring of kidney function and gastrointestinal risks.
- Oral corticosteroids are given with an initial dose equivalent to prednisone between 10-15

mg/day, for long-term use a dose of less than 10 mg/day is recommended in cases of arthritis involvement.

- High-dose corticosteroid therapy can be given specifically in cases of symptomatic inflammatory muscle involvement proven by MRI imaging or muscle biopsy results showing inflammatory infiltration.

Recommendation 22-29: Interstitial Lung Disease in Systemic Sclerosis (SSc-ILD).[49-51]

Recommendation 22. Every patient with SSc needs to be evaluated for pulmonary involvement and ILD treatment carried out from the initial diagnosis of the disease. [49-51]

Most patients with SSc-ILD are asymptomatic, especially in the early phase of the disease and when the patient's mobility is limited due to other non-pulmonary manifestations of SSc. The most frequently reported symptom is shortness of breath/*dyspnea* (initially during activity, then also felt at rest), non-productive dry cough, and fatigue (*fatigue*). A physical examination was obtained *velcro-like crackles* on auscultation.

In SSc, suspicion of ILD on chest x-ray should be considered if a typical reticular picture is found at the basal periphery of the lung or there is a picture of reticulonodular opacity. At the beginning of the diagnosis of SSc, a normal chest x-ray can be found. Newly diagnosed SSc patients are recommended for pulmonary function examination with spirometry or DLCO as an initial ILD screening and can be repeated for disease monitoring and treatment response every 3-6 months for the next 3-5 years.

Recommendation 23. Pulmonary function examination *(forced vital capacity [FVC] or diffusing capacity of carbon monoxide [DLCO])* needs to be carried out periodically for diagnostic screening and monitoring therapy of SSc-ILD. [49-51]

Demographic factors associated with ILD in SSc are male gender, African American race, diffuse type SSc. ILD in SSc is also more frequently found in patients with capillary abnormalities in the nail bed (*nailfold capillary*), digital ulcers, patients with long disease duration, and the presence of pulmonary arterial hypertension on echocardiography. ILD in SSc is also more often found in patients who have anti-topoisomerase antibodies but is less common in patients with anti-centromere antibodies.[86] Several other auto antibodies were also found to be associated with the appearance of ILD, including antibody es*anti-neutrophil cytoplasmic*, *anti-cardiolipin*, *anti U11/U12, anti Th/To, anti PM-Scl, anti Ro52*, and*anti-NOR90.*

Recommendation 24. *High Resolution CT (HRCT) scan thorax* as the gold standard, it can be carried out from the beginning of SSc diagnosis to screen for ILD diagnosis and repeated to assess disease progression. [49-51]

On pulmonary function examination (PFE) based on spirometry, restrictive lung abnormalities were found. Restrictive lung abnormalities in SSc can be found due to extrapulmonary abnormalities such as extensive skin involvement (hardening of the skin) on the chest wall or respiratory muscle weakness due to concomitant myopathy. In the initial phase of ILD, PFE can be found within normal limits.

Recommendation 25. Multidisciplinary collaboration is needed for non-pharmacological and pharmacological therapy for the management of SSc-ILD). [49-51]

HRCT should be performed early in the diagnosis as*baseline* and repeated when there is a significant decrease in lung function or new symptoms related to ILD appear.[87] Lung interstitial tissue abnormalities in SSc patients are found in up to 80% on HRCT examination and 90% on autopsy, but only 30-40% of patients experience ILD clinically, with*10-year mortality* reached 40%.

Recommendation 26. First-line treatment with Mycophenolate mofetil or Cyclophosphamide is

the pharmacological therapy of choice for ILD cases, especially in patients with NSIP features (*ground glass opacity*) on HRCT.[51-57]

- Mycophenolate mofetil and cyclophosphamide are effective therapies in SSc-ILD.
- Glucocorticoid monotherapy is not effective for SSc-ILD.

Recommendation 27. Second-line treatment with Nintedanib which is an antifibrosis can be a therapeutic option in progressive SSc-ILD or with UIP on HRCT.[58,59]

- SSc patients with ILD in the early and stable stages or patients with mild symptoms are routinely monitored and initiation of therapy begins if worsening occurs.
- SSc-ILD therapy can be started in patients with extensive disease (ILDε 20% on HRCT, or 10-30% and FVC < 70% predicted) or limited disease (ILD < 20% on HRCT, or 10-30% and FVCε 70% prediction) accompanied by progressive risk factors.

Recommendation 28. Indications for initiating pharmacological treatment for ILD consider the severity of the disease and risk factors for progression. [58,59]

Recommendation 29. In the Progressive Pulmonary Fibrosis phenotype, the treatment options are Mycophenolate mofetil or Cyclophosphamide in combination with Nintedanib. [58,59]

Nintedanib, an *inhibitor tyrosine kinase* which has been FDA approved as an antifibrotic therapy for ILD in SSc. Nintedanib is given in ILD with HRCT imaging of UIP or in progressive cases (see Recommendation 30). Nintedanib as monotherapy or in combination with Mycophenolate mofetil can be used as initiation therapy or escalation therapy. Nintedanib in the SENSCIS study was found to provide significant benefits on FVC values. In a double-blind clinical trial of 576 ILD-SSc patients for 52 weeks who received Nintedanib 2 x 150 mg or placebo. There was a lower reduction in progression in the Nintedanib group compared to placebo. The change in FVC value was -52.4 ml per year in the Nintedanib group compared to -93.3 ml per year in the placebo group.

PPF is defined if 2 of the following 3 criteria are obtained in the last year without any explanation of other alternative causes:

1. Worsening of respiratory symptoms.
2. Physiological evidence of worsening of the disease (one of the following signs):
    a. Absolute decrease in FVCε 5% predictions in the last 1 year *follow up*.
    b. Absolute decrease in DLCO (corrected and predicted in the last 1 year of follow up.
3. Radiological evidence of worsening of the disease (one or more found):
    a. Increased extent and severity of traction bronchiectasis and bronchiectasia
    b. *Ground glass opacity* with new traction bronchiectasis
    c. *Fine reticulation* new
    d. Increased extent and severity of reticular abnormalities
    e. Improvement or discovery *honeycomb*.
    f. Increased lung volume loss.

If Mycophenolate mofetil and cyclophosphamide do not provide good results, other options are:

- Nintedanib is recommended to be added to PPF patients receiving standard therapy for SSc-ILD (MMF or cyclophosphamide).

In cases that do not respond to the above therapies, the following therapies can be considered:

- Rituximab[61-64] and Tocilizumab[65-66] as *rescue therapy* in that case.
- *Autologous haemopoietic stem-cell transplantation* (ASCT) and lung transplantation are effective in a subset of SSc patients. EULAR has made recommendations for the use of cyclophosphamide or ASCT in patients with progressive ILD.[60]

The study by Daoussis et al. in SSc-ILD patients for 7 years, patients in the Rituximab group had a %FVC value that was higher than the initial value (*baseline*); the control group showed a decrease in %FVC compared to the initial value (*baseline*). In this study, 33 SSc patients were given two or more cycles of Rituximab (each cycle consisted of 4 infusions of 375 mg Rituximab/m^2 body surface area once a week and repeated every 6 months), and compared with 18 SSc patients with conventional therapy (MTX, Azathioprine or MMF). Both cohort groups showed improvement in skin (lower mRSS), but the Rituximab group showed improved lung function significant.[61-65]

Double-blind study involving 87 SSc patients; 43 received Tocilizumab, 44 placebo for 48 weeks; The Tocilizumab group experienced improved mRSS compared to placebo and fewer experienced a decrease of 10% or more in FVC. Improvements in mRSS scores and more stable lung function were obtained in the group Tocilizumab.[65,66]

Recommendation 30-32: CARDIAC INVOLVEMENT IN SYSTEMIC SCLEROSIS.[68-76]

Recommendation 30. Every patient with SSc should be evaluated for cardiac involvement.[68-70]

Cardiac involvement in SSc is often found with varied clinical manifestations and if symptomatic indicates a poor prognosis. Cardiac abnormalities in SSc can occur primary (direct cardiac involvement due to the SSc disease process), or secondary due to pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), or due to kidney disease in SSc patients.

Recommendation 31. It is a diagnosis of cardiac involvement in SSc *by exclusion*, after ruling out other heart defects based on clinical and supporting evaluation with multidisciplinary collaboration. [71-74]

Diagnosis of primary cardiac involvement in SSc remains a challenge today. Primary cardiac involvement in SSc clinically can include acute heart failure, fulminant myocarditis, and asymptomatic conduction disorders.

The course of primary heart disease in SSc generally has a poor prognosis characterized by a slow disease course *intractable* leading to end-stage heart failure and death, or manifesting as *sudden cardiac death*. Until now there hasn't been one *disease-modifying therapy* for cardiac manifestations in SSc. It is important to identify patients with primary cardiac involvement in SSc before the onset of non-specific heart failure. Treatment and evaluation of cardiac abnormalities in SSc requires careful screening, requiring a multidisciplinary approach involving rheumatologists, cardiologists and radiologists.

Pathological changes occurring in all cardiac structures are found in SSc patients. SSc can cause damage to all parts of the heart, causing myocardial abnormalities (myocardial fibrosis, left ventricular systolic and diastolic dysfunction), coronary microvascular ischemia, pericardial disease, conduction abnormalities (brady-tachycardia), and valvular abnormalities. The characteristic feature of primary cardiac involvement in SSc is complete fibrosis in both ventricles but not involving the coronary vessels. Extensive fibrosis was found in SSc patients with intact coronary vessels.

Recommendation 32. Management of cardiac involvement in SSc is given according to clinical manifestations based on expert opinion and multidisciplinary collaboration. [72-76]

Routine checks such as heart rate, blood pressure, echocardiography, etc. *Transthoracic echocardiography* (TTE) is performed to exclude other cardiac abnormalities besides primary cardiac involvement in SSc.

Diagnostic examination and *imaging* specifics such as: echocardiography, *ECG, CPET*, right heart catheterization, angiography, endomyocardial biopsy, *CMR, SPECT* need to collaborate with an experienced cardiologist and radiologist.

There is no specific therapy for heart defects in SSc.

Recommendation 33-36: PULMONAL ARTERY HYPERTENSION IN SYSTEMIC SCLEROSIS.[77-80]

Recommendation 33. Initial screening for Pulmonary Arterial Hypertension (PAH) needs to be carried out in all SSc patients from the beginning of diagnosis.

Pulmonary Hypertension (PH) is a syndrome characterized by increased pulmonary pressure which causes an increase in pulmonary vascular resistance (PVR/*Pulmonary Vascular Resistance*) which causes right ventricular dysfunction, heart failure and death. PH is hemodynamically defined as an increase in mean pulmonary artery pressure/*mean arterial pressure (mPAP)* ≥20 mmHg on right heart catheterization examination. PH can occur due to various diseases. PH can occur due to primary processes outside the pulmonary vasculature, such as in the heart, lung parenchyma, liver, kidneys, as well as due to processes in the pulmonary vasculature itself directly such as thromboembolism. Patients with connective tissue diseases such as systemic sclerosis are at high risk for PH.

Recommendation 34. Multidisciplinary collaboration is needed for diagnosis and therapy for management of PAH SSc.[77-80]

Approach to Diagnosis of PAH

The diagnosis of PAH is often delayed in SSc patients. PAH can occur at any time in SSc, on average it occurs at 6.3 (±6.6) years after SSc diagnosis. Early-onset PAH (<5 years after SSc diagnosis) is found in approximately half of SSc patients, both diffuse and limited types.

It should be noted that not all PHs in SSc are PAHs (group 1). SSc patients often experience other types of PH besides PAH.

Pulmonary Artery Hypertension (PAH) Screening/Filtering

Several non-invasive tests can be used to screen for PAH in SSc. This screening test must be confirmed by right heart catheterization (*Right Heart Catheterization*/RHC) which is the gold standard for PAH.

Non-invasive examination for PAH screening in SSc:

1. Pulmonary Function Examination (PFE) FVC/DLco ratio < 1.6 and/or DLco < 60% predictive, indicating the patient is at risk of developing PAH SSc.
2. Right heart echocardiography
3. Elevated NT-proBNP indicates myocardial dysfunction

Recommendation 35. Echocardiography and/or NT-pro BNP and/or PFE biomarkers can help identify PAH patients.[77-80]

One method that is widely used is the DETECT algorithm: a two-step algorithm that includes pulmonary function test parameters, serum biomarkers, clinical characteristics (presence of Telangiectasia), and findings on ECHOCARDIOGRAPHY examination (right atrial enlargement, TR jets ≥2.5 m/s) which determines whether echocardiography or right heart catheterization is necessary.

Right heart catheterization is the gold standard. RHC measures blood pressure in the heart and pulmonary arteries so it is recommended in cases of connective tissue disease PAH to confirm the diagnosis, assess the severity of the disease, and rule out left heart disease. Regular screening and early diagnosis can improve the outcome of PAH SSc patients.

Recommendation 36. PAH therapy options in SSc[81-84]

The latest therapy guidelines (ESC/ERS), recommend therapy for SSc-PAH following the therapy guidelines in *Idiopathic Pulmonary Arterial Hypertension* (IPAH). A number of *Endothelin Receptor Antagonist (ERA)* namely ambrisentan, bosentan and macitentan; *Phosphodiesterase type 5 inhibitor (PDE-5 inhibitor)* namely sildenafil, tadalafil; and riociguat has

been approved as a therapy for SSc-PAH. Intravenous epoprostenol may be considered in severe SSc-PAH (grades III and IV). Other prostacyclin analogues such as treprostinil (intravenous, subcutaneous and inhalation) and iloprost (inhalation), oral beraprost also approved for PAH in connective tissue diseases. A combination of different classes of PAH-specific drugs can be given for SSc PAH, especially in severe and progressive cases.

Recommendation 37-39: KIDNEY INVOLVEMENT IN SYSTEMIC SCLEROSIS.[18,85-86]

Recommendation 37. Vigilance *scleroderma renal crisis* (SRC) needs to be considered if hypertension or impaired kidney function is found, especially in steroid users with a dose equivalent to prednisone > 15mg/day. [18,85-86]

A significant consequence of arterial damage and vasospasm is renal involvement. However, renal involvement is often subclinical until the advanced phase of SSc. Cannon et al. found that approximately 50% of asymptomatic patients had clinical markers of renal dysfunction such as proteinuria, increased serum creatinine levels, or hypertension.[181] Autopsy studies show that 60-80% of SSc patients have kidney abnormalities.

The most common renal involvement is *scleroderma renal crisis* (SRC). Other renal manifestations that may be present are hypertension, ANCA-associated vasculitis, decreased renal function, and proteinuria (in the absence of renal crisis). SRC is defined as new onset *accelerated arterial hypertension* and *rapidly progressive oliguric renal failure* in SSc patients.

Recommendation 38. Diagnosis of SRC in SSc if new onset of hypertension and impaired renal function are found accompanied by hematuria, pulmonary edema, oliguria/anuria, and*microangiopathic hemolytic anemia.* [85-86]

Diagnosis of SRC is based on an increase in blood pressure >150/85 at least 2 measurements within 24 hours or an increase in systolic blood pressure >30 mmHg or diastolic blood pressure >20 mmHg above baseline blood pressure; and a decrease in kidney function of at least 10% of eGFR or kidney function <90 ml/minute/1.73m^2; often accompanied by new onset hematuria (rule out other causes), pulmonary edema, oliguria/anuria, *microangiopathic hemolytic anemia* (hemolytic anemia with *coombs test* negative, thrombocytopenia, schistocytes/erythrocyte fragmentation in blood smear).

The presence of organ dysfunction such as acute hypertensive retinopathy, hypertensive encephalopathy, seizures, visual disturbances, acute heart failure, and pericarditis; and renal biopsy consistent with SRC (proliferation *onion skin* in the tunica interna arteries and arterioles, fibrinoid necrosis, and reduced number of glomeruli) would strengthen the diagnosis of SRC.

SRC can occur in normotensive SSc patients so this condition will require measurement of plasma renin levels. High plasma renin activity will support the diagnosis of SRC and if possible be supported by renal pathology data (biopsy is not mandatory in the diagnosis of SRC). Normotensive SRC patients are reported to have a worse prognosis.

Considering the high mortality of SRC, identification of predictive factors for SRC is necessary. Several conditions that have an important role in SRC occurring are as follows:

1. *Rapid progressive skin thickening*
2. Diffuse SSc
3. Anti RNA polymerase III (anti-RNAP III)
4. Anti topoisomerase I
5. Proteinuria
6. Hypertension

Other risk factors that have been reported are anemia, thrombocytopenia, new cardio involvement, large joint contractures, *digital pitting scars*, and myalgia/myopathy. Users of cocaine, cyclosporine A, and glucocoticoids (prednisone doses >15 mg/day) also increase the risk of SRC.

Recommendation 39. Recommendations for the management of SRC are ACE blockers as the first choice, CCB as the second choice, ARB is an alternative therapy in conditions of intolerance to ACE blockers, ACE blockers have not been recommended as prophylactic therapy for SRC, and dialysis can be considered if necessary. [85-86]

The key to managing SRC is early detection and aggressive administration of ACE blockers. The target for reducing blood pressure is blood pressure≤120-130 mmHg and <70-80 mmg within 72 hours after initiation of therapy. ACE blockers are the first choice in treating hypertension in SRC and if necessary can be added with *calcium channel blocker* as a second choice or diuretics and alpha blockers as a third choice. Usage *angiotensin II receptor blocker* indicated in patients who are intolerant to ACE blockers. In some cases with systemic complement activation and resistance to conventional therapy, the use of eculizumab, a humanized recombinant monoclonal antibody against C5, may be considered. There is currently no research to support use *plasma exchange*, eculizumab as first choice.

In conditions of systolic blood pressure ≥180 and/or diastolic ≥110 mmHg, efforts are made to reduce MAP (*mean arterial pressure)* by 10–20% in 1 hour using intravenous preparations (such as nicardipine or urapidil) allowing dose titration. If systolic blood pressure is ≤180 and diastolic ≤110 mmHg, efforts are made to reduce systolic blood pressure by 20 mmHg and systolic blood pressure by 10 mmHg per day. Prioritize usage *intermediate-acting* ACE blockers such as ramipril and enalapril, and uses *short-acting* such as captopril, especially in unstable hemodynamic conditions.

Risk factors for poor prognosis in SRC are serum creatinine levels >3 mg/dl, male gender, poor blood pressure control, late initiation of antihypertensive therapy, congestive heart failure, normotensive SRC and features of arteriolar fibrinoid necrosis, *severe glomerular ischemic collapse*, and severe interstitial fibrosis/tubular atrophy on renal biopsy. However, there is no evidence to support the use of ACE blockers for prophylaxis. Some SRC patients who experience worsening kidney function will develop kidney failure, requiring dialysis or a kidney transplant.

Recommendation 40-45: GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS. [87-90]

Recommendation 40. Be alert for gastrointestinal disorders in SSc if there are complaints of dysmotility such as swallowing disorders, bloating and constipation. [87-90]

Gastrointestinal involvement is a common problem in SSc, reaching up to 90% of patients. There is no difference in frequency between limited type SSc and diffuse SSc, can even appear in *SSc sine scleroderma*.

GI manifestations can occur along the GI tract from the mouth to the anus and the area most frequently affected are the esophagus and anorectal tract. Dysmotility is the main cause of GI disorders although vascular disorders also occur.

- Oropharynx: Microstomia, salivary hypofunction, increased risk of periodontal disease, swallowing disorders, and changes in the shape of the lower jaw (mandibular). Microstomia causes disruption of the chewing process (mastication) and worsens oral hygiene.
- Esophagus: Esophageal involvement is the most common GI manifestation in SSc, can reach 90%, and occurs more frequently in limited type SSc. Esophageal motility dysfunction can occur especially in the distal part, with clinical manifestations such as dysphagia, cough, *heartburn*, regurgitation, and dyspepsia. Esophageal dysphagia causes swallowing disorders that occur in 4.35% of SSc patients. GERD is the most common manifestation, reaching 70% of SSc patients with possible complications including esophageal stenosis, Barrett's esophagus, cough, bronchospasm and laryngospasm. Esophageal involvement also plays a role in its occurrence *interstitial lung disease* (ILD).
- Stomach: About 50% of cases of SSc will experience stomach disorders. Manifestations that often occur

are delayed gastric emptying time and *gastric antral vascular ectasia* (GAVE or *watermelon stomach*). Clinical manifestations include abdominal distension/pain, bloating, **satiety quickly (most often) and nausea *postprandial*. However, the severity of the complaint is not related to the degree of gastric involvement.**

- Small intestine: Complications of SSc to the small intestine are quite frequent and the duodenum is the part most frequently affected (40-88%).
- Colon: Colon involvement reaches 20-50% in SSc patients, usually in the form of constipation, diarrhea, or fecal incontinence.
- Anorectal: Anorectal complaints occur in 50-70% of patients and affect the internal anal sphincter resulting in fecal incontinence, constipation and rectal prolapse. Fecal incontinence associated with *long standing* SSC where there is a decline *resting pressure* and atrophy of the internal anal sphincter, while constipation and rectal prolapse are caused by impaired relaxation and distension restriction.
- Liver and pancreas: Liver disease in SSc is very rare (1.5%) and most often in the form *primary biliary disease* (PBC). Manifestations in limited type SSc are more common than diffuse type SSc. Usually asymptomatic while pancreatic involvement is suspected if symptoms such as Small Intestinal Bacterial Overgrowth (SIBO) are present but do not respond adequately to therapy.

Recommendation 41. Improving lifestyle is recommended to treat upper gastrointestinal complaints in SSc.[88-90]

Treatment that can be given to SSc patients with GI manifestations is as follows:

- Oropharynx:
  Maintaining hydration and using artificial saliva
- Esophagus:
  - Lifestyle modifications such as sleeping with your head elevated (pillow height around 15 cm
  - Avoid stimulating foods (coffee, tea, chocolate), avoid eating ≤ 3 hours before bed, and eat small portions repeatedly
  - Avoid cigarettes and alcohol
  - Control gastric acid production with Proton Pump Inhibitors (PPI) and/or H2 receptor antagonists.

Recommendation 42. A small-repeated diet is recommended for the management of gastrointestinal dysmotility. [88-90]

- Stomach:
  - Lifestyle modifications and good diet management.
  - Management of GAVE includes supportive therapy with iron supplementation and monitoring for bleeding that requires endoscopic intervention.
- Small intestine:
  - Conservative management consists of: *bowel rest*, fluid resuscitation, correction of electrolyte disturbances, and antibiotics if necessary. If there is no improvement with conservative methods, prokinetics can be given, especially in the early phase of SSc.
  - Surgical intervention is avoided as much as possible and sometimes a decompression procedure is necessary.
- Colon:
  Symptomatic treatment with stimulant laxatives and prokinetic drugs can be added.
- Anorectal:
  Dietary modification will improve the clinical course; Be careful when using anti-diarrhea because they can cause constipation and induce rectal prolapse.
- Liver and pancreas:
  Ursodeoxycholic acid (UDCA) is the primary therapy for PBC and transplantation is an option in advanced cases. Prednisone/budesonide has good results in early cases but there are no long-term studies. Pancreatic insufficiency requires pancreatic enzyme supplementation.

Recommendation 43. Antibiotics are recommended under circumstances *intestinal bacterial overgrowth.* [90-91]

Small intestinal bacterial overgrowth (SIBO) is a condition of delayed transit time in the intestine resulting in stasis of intestinal contents which causes migration and colonization of bacteria from the colon and overgrowth of these bacteria occurs. Typically SIBO manifests with postprandial bloating, nausea, diarrhea, excessive farting, and weight loss. Vitamin B12 and iron deficiencies may also occur.

With limited interpretation of *breath test*, experts recommend giving empirical antibiotic therapy and rotating the choice of antibiotics used. Probiotics have also been reported to improve patient complaints. Diet modification and nutritional supplementation are highly recommended to improve the patient's nutritional status.

Recommendations 44. The following prokinetic preparations are recommended to correct gastrointestinal dysmotility in SSc: Metoclopramide is the first choice, domperidone is the second choice, octreotide is an alternative therapy for small intestinal dysmotility. [89-91]

Prokinetic agents can improve dysmotility complaints in SSc, especially in the early phase. Domperidone and metoclopramide are prokinetic drugs that are often used.

Recommendation 45. Proton Pump Inhibitors (PPI) are recommended for the treatment of GERD in SSc. [89-91]

The use of proton pump inhibitors (PPI) is recommended in SSc. RCT conducted by Pakozdi et al. reported that lansoprazole administration could suppress GI complaints in the short term although it did not show satisfactory results after 12 months and also reported no improvement in GI motility. No improvement in motility despite improvement in esophagitis was also reported by Nagaraja et al. Creamer et al. reported that giving omeprazole 20-80 mg for up to 5 years provided significant improvement, also reported that administration of omeprazole 20 mg per day can provide adequate protection against reflux while Nagaraja et al. stated that SSc patients often require PPI doses 2–4 times the standard dose to get satisfactory results.

Recommendation 46-50: MANAGEMENT OF SPECIAL CIRCUMSTANCES IN SYSTEMIC SCLEROSIS

Recommendation 46. Pregnancy in SSc patients is recommended when the clinical condition of the disease is stable according to the assessment of the treating specialist/subspecialist. [92-93]

Fertility (Fertility)

Fertility is not reduced in women with SSc. However, pregnancy may be delayed due to conditions in the early stages of the disease or active disease conditions. SSc disease has a significant psychosocial impact on women due to changes in body and facial appearance.

Contraception

The use of contraception in women with SSc such as estrogen can be considered in SSc patients with negative anti-phospholipid antibodies and non-smokers; Apart from that, intrauterine devices (IUDs) and contraception *barrier* can also be used.

Pre-Pregnancy Counseling

Optimizing pregnancy planning before conception, as well as careful management and monitoring during pregnancy, are essential to obtain good clinical outcomes during pregnancy.

Recommendation 47. SSc patients with pregnancy require monitoring of the condition of the mother and fetus during pregnancy by the relevant specialist doctor. [92-93]

During the pregnancy period, monthly obstetric examinations are recommended as well as fetal biometric, uterine and umbilical Doppler

examinations. The goal is to find out signs of progression of disease activity. Clinical examinations recommended every month are:

- Check for symptoms and signs of dyspnea, heart failure, and progression of skin disorders
- Blood pressure measurement, urinalysis (screening for preeclampsia or kidney crisis)
- Laboratory tests: Creatinine, liver function (SGOT, SGPT), blood sugar levels (KGD), platelets, hemoglobin
- Routine fetal ultrasound examination (at 12, 22 and 32 weeks of gestation); Additional periodic monitoring is required in patients with diffuse SSc and/or severe systemic involvement, or if there is a history of obstetric complications. Additional ultrasound with uterine and umbilical doppler starting from 22 weeks of gestation.

Recommendation 48. The use of drugs in SSc patients needs to be considered during the period of conception, pregnancy, lactation. [92-93]

The choice of delivery method in SSc patients must consider the presence of mechanical restrictions due to contracture and hardening of the skin, the risk of poor wound healing and postoperative ileus. In SSc female patients with PAH involvement, the option of elective caesarean section may be recommended while taking into account the risks and benefits of each delivery modality. Regional anesthesia, especially epidural *block* is recommended because it is useful for peripheral vasodilation in the lower extremities and reduces the risk of peripheral ischemia. Ergometrine and bolus oxytocin should be avoided, especially in SSc with PAH, as they can lead to increased peripheral vascular resistance and hypotension. Slow infusion of oxytocin or misoprostol is a safe alternative, which has no effect on pulmonary or systemic vasculature.

Effect of pregnancy on SSc disease activity

Pregnancy does not appear to influence the course of SSc. [92-93]

Recommendation 49. SSc patients require special perioperative preparation regarding medications and evaluation of the risk of perioperative complications. [94-95]

SSc patients who are planned for elective surgery require routine medication adjustments to be made to avoid intraoperative and postoperative complications. DMARD dose adjustment in SSc patients before surgery. Regular consumption of glucocorticoids can suppress the hypothalamus-pituitary-adrenal axis in producing cortisol.

SSc patients have a greater risk of difficult or failed intubation, increased GERD symptoms, and aspiration. Early anesthesia consultation is recommended before surgery for SSc patients whose mouths are difficult to open wide to anticipate difficulties with orotracheal intubation.

Recommendation 50. SSc patients need to receive vaccinations according to indications taking into account the benefits and risks. [96-98]

There is an increase in morbidity and mortality caused by infection in autoimmune rheumatism patients.[11] Increased risk of infection is associated with high disease activity and disease duration, comorbidities, immunosuppressant drugs such as corticosteroids, conventional synthetic DMARDs (csDMARDs), biologic agents (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Prevention of infection is very important in the management of autoimmune rheumatic patients. Vaccination aims to prevent infection by inducing and/or increasing protective immunity. Vaccination is expected to reduce the rate of hospital admissions related to infectious diseases and treatment in emergency rooms.

4. Discussion

For these recommendations, IRA assembled a team of rheumatologists from various cities and region as well as various level of health facilities ranging from local, regional, and national referral hospital to ensure the consideration of healthcare capabilities on all

levels. The key questions were formulated based on the most relevant questions when a clinician encounter a patient with SSc. The key questions on the treatment for SSc patients were then being broken down and described in details into each manifestation namely skin, vasculopathy, musculoskeletal, lung, cardiac, renal, and gastrointestinal manifestation.

For the diagnosis of SSc patients, 2013 ACR/EULAR classification criteria was used on this recommendations as a tool for diagnosis of SSc. Although the purpose of the classification criteria is largely for research purpose, the use of classification criteria as diagnostic tool can help to standardize diagnosis in different health care centers especially when there is no rheumatologist. SSc autoantibodies may help in in the diagnosis and also useful for predicting progression of very early SSc cases however this recommendation stated that SSc autoantibodies can be done if possible. There is slight difference of recommendations from IRA with French recommendation,[37] and the difference is due to the consideration that SSc autoantibodies is not easily accessible in Indonesia.

The recommendations on the management of skin manifestations slightly differed from EULAR and French Recommendation.[39] Both EULAR dan French recommendation did not stated Rituximab for skin manifestations while our recommendation did not state HSCT as treatment modality for skin manifestations in SSc. Our recommendation, however, is consistent with Japanese guideline on SSc which stated Rituximab as one of the options for skin thickening in SSc but Japanese guideline also included HSCT as an option. HSCT is not included in our recommendation due to the consideration that until now HSCT is not yet available in Indonesia.

The recommendations of the management of SSc-ILD generally consistent with previous guidelines.[49-51] Mycophenolate mofetil, cyclophosphamide, and nintedanib was listed as treatment options for SSc-ILD whis were similar to EULAR and French recommendation.[37,39] However, our recommendation did not include Tocilizumab and HSCT as treatment options for SSc-ILD due to HSCT and subcutaneous Tocilizumab are not available in Indonesia. Rituximab can also be given for ILD although the recommendation on the use of rituximab was stated on the part concerning the skin. Recommendations on vascular, cardiac and gastrointestinal manifestation were consistent with previous published recommendations.

This recommendations is the first published recommendations on the diagnosis and management of SSc in Indonesia. This recommendations also covered several aspects on the diagnosis and management of SSc. Efforts have been made that all recommendations were made through evidence-based methods. However, there are several issues on which the scientific evidence is unclear therefore some recommendations were formulated through expert consensus. This recommendations may provide as guidance but the clinical decision should be made according to individual patient and taking into account the clinical autonomy of the treating physician.

5. Conclusion

There were 50 recommendations on the diagnosis and management of systemic sclerosis in Indonesia. These recommendations are all created with the consideration of Indonesia's clinical setting, facility, and drug availability.

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