Systemic Sclerosis

Myanmar National Guideline

Myanmar Rheumatology Society

jointly organised by Dermatology Society, Internal Medicine and Clinical Pharmacology

"The members of the guideline development group had critically appraised many available papers and evidences to get the consensus guidance for Myanmar doctors to help systemic sclerosis patients most effectively in most understandable format."

-Prof. Chit Soe

Title: Systemic Sclerosis, Myanmar National Guideline

Effective Date: August 7, 2020

Version: First

Organization: Myanmar Rheumatology Society

Purpose: to provide a comprehensive guideline for management of systemic sclerosis

Intended Users: General Practitioners, Internists, Rheumatologists and Dermatologists

Target Populations: Patients with Systemic Sclerosis

Funding Source: Myanmar Rheumatology Society

Update Plan: Every Five Years and as needed

Number of Copies: 1000

Note: The following indicate the intended target users

- Rheumatologist
- Internist
- Primary Health Care

Foreword

I am happy to write a forward for another Myanmar National Guideline, for this time "Systemic Sclerosis". Although systemic sclerosis is not very common and actually it can be labeled as one of the neglected disease, it is a chronic and disfiguring disease causing a huge burden for the patient and the family. Since the number of patients all over is not large, the number of RCT research evidence is rationally small. The available investigations and management tools are different in Myanmar from Europe and US. Eastern studies are more relevant to Myanmar in many ways.

The members of the guideline development group had critically appraised many available papers and evidences to get the consensus guidance for Myanmar doctors to help systemic sclerosis patients most effectively in most understandable format.

I would like to mention the appreciation words for inputs from UM1, UM2, UM Mandalay rheumatologists, internists and not the least, from pharmacology department.

I believe it will be useful not only for rheumatologist, but also for internal medicine specialist as well as for general practitioners.

Professor Chit Soe
President
Myanmar Rheumatology Society

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Chapter 1.

Diagnosis of Systemic Sclerosis

Diagnosis of systemic sclerosis should be based upon 2013 ACR/EULAR Classification criteria for Systemic Sclerosis. (1)

This classification includes

one definitive criteria which is sufficient to make diagnosis of SSc and

seven criteria with point system which are used if definitive criteria is not fulfilled.

Note: Morphea will be a subclass of systemic sclerosis and will be managed differently.

Skin biopsy can be done when suspect a scleroderma like disorder (e.g, eosinophilic fascitis)

Definition of items in ACR/EULAR classification

Skin Thickening — Skin Thickening or hardening not due to scarring after injury, trauma, etc.

Puffy fingers — Swollen digits- a diffuse, usually non-pitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.

Fingertip ulcers or pitting scars — Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes.

Telangiectasia — Telangiectasia are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasia in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.

Abnormal nailfold capillary pattern consistent with systemic sclerosis — Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nail fold, may be seen on the cuticle

Pulmonary arterial hypertension — Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions

Interstitial lung disease — Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of “Velcro” crackles on auscultation, or not due to another cause such as congestive heart failure

Raynaud’s phenomenon — Self-reported or reported by a physician, with at least a 2-phase color change in finger (s) and often toe(s) consisting of pallor, cyanosis and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor

Scs-Related autoantibodies — Anticentromere antibody or centromere pattern seen on anti-nuclear antibody testing, anti-topoisomerase I antibody (also known as anti-Scl-70 antibody) or anti-RNA polymerase III antibody. Positive according to local laboratory standards

Table: 2013 ACR/EULAR classification criteria for Systemic Sclerosis

ITEM	SUBITEM	WEIGHT/ SCORE
skin thickening of the fingers of both hands extending proximal to MCP joints	**(sufficient criteria)**	**9**
Skin thickening of the fingers (only count the higher score)	**Puffy fingers**	**2**
	Sclerodactyly of fingers (distal to the MCP joints, proximal to the PIP joints)	**4**
Fingertip lesions (only count the higher score)	**Digital tip ulcers**	**2**
	Fingertip pitting scars	**3**
Telangiectasia		**2**
Abnormal nailfold capillaries		**2**
Pulmonary arterial hypertension and/or interstitial lung disease		**2**
Raynaud's phenomenon		**3**
SSc related auto-antibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III)		**3**

Chapter 2.

Referral and Shared Care in Systemic Sclerosis

A. Shared Care in Systemic Sclerosis (Primary Health Care Level)

1. When to suspect Systemic Sclerosis

a. suspect systemic sclerosis if there is Raynaud's phenomenon which is likely to be secondary and puffy fingers or generalised swelling (sclerodema) (see the figure; VEDOSS criteria) for early diagnosis

b. any cases presenting with skin tightening (either localised or generalised) or skin dyspigmentation (such as salt and pepper skin changes)

2. What to do when Systemic Sclerosis is suspected

The general practitioner should refer the patients to **Internists** or **Rheumatologists** if suspected case of systemic sclerosis to confirm diagnosis by NFC and Laboratory tests (as in the figure - VEDOSS) or any cases with definite systemic sclerosis to evaluate the organ involvement such as ILD, myositis, pulmonary hypertension and kidney damage.

3. Monitoring and Indications for refer back to Rheumatologist

Monitoring should be done with CP, ESR, ALT, Creatinine at least every 3 months and as symptoms suggested at follow-up (see the details in the Chapter 4; monitoring)

Refer back to Rheumatologist if

a. when there is the complication of treatment with DMARDs
b. when the patient has family planning or become pregnant
c. when there is suspect of existing organ progression or new organ involvement e.g Scleroderma renal crisis or new critical digital ischaemia with gangrene or severe infection or FHS decline

4. Continued care at primary health care level for the minor infections such as acute gastroenteritis without features of sepsis, upper respiratory tract infection, lower urinary tract infection or minor skin infections such as herpes or fungal infection.

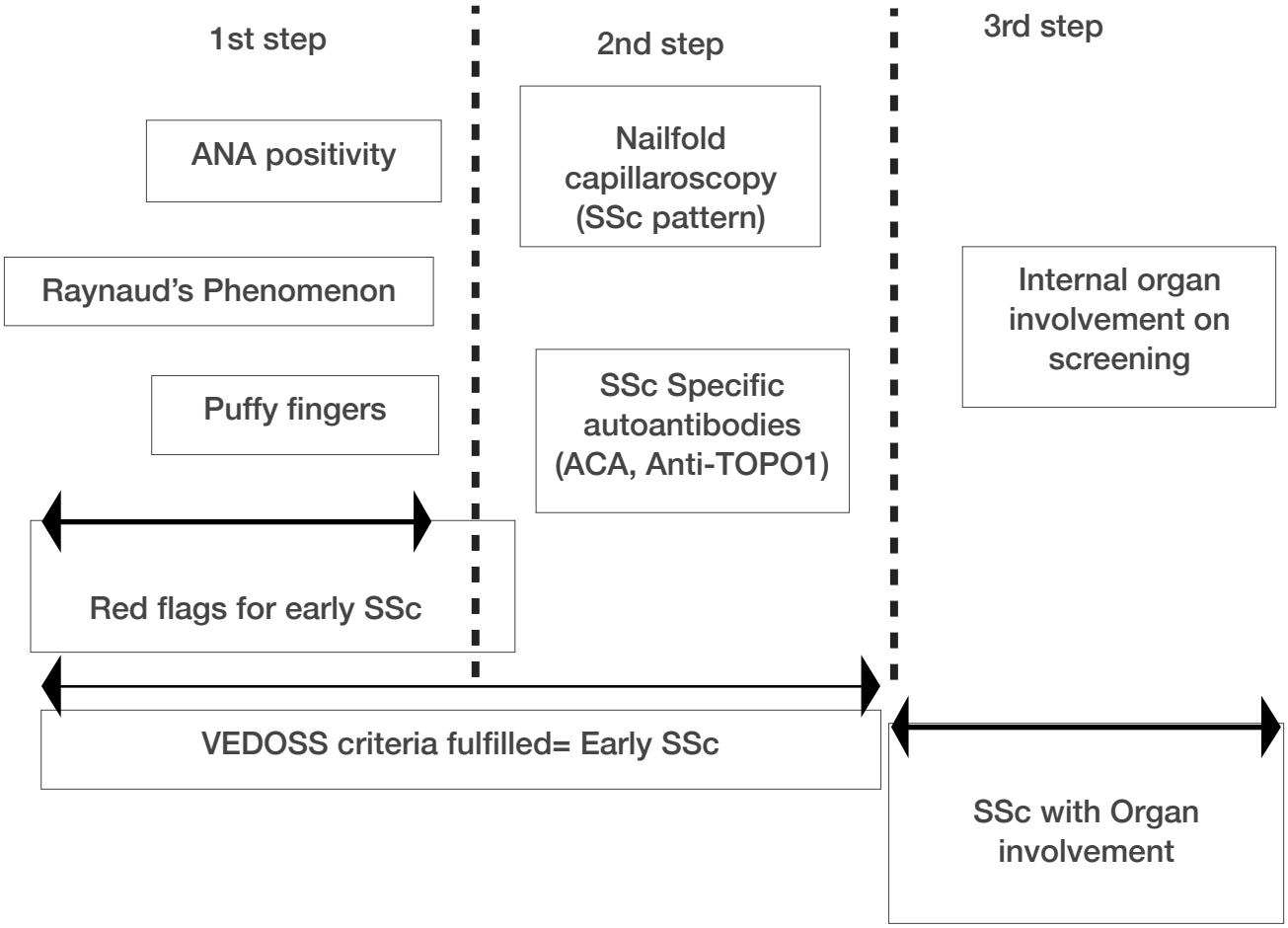
B. The internist/Dermatologist should refer the patients with systemic sclerosis to Rheumatologist if

1. When the first diagnosis of systemic sclerosis is being made
2. When the patient with systemic sclerosis has been detected for systemic involvement (ILD, Pulmonary hypertension or Scleroderma renal crisis)
3. when there is the complication of treatment with DMARDs
4. when the patient is pregnant

C. The rheumatologist should refer the patients with systemic sclerosis to Dermatologists if

1. if the patients has extensive skin sclerosis and severe acrosclerosis (role of PUVA/UVB?)
2. calcinosis or pigmentary changes
3. severe telangiectasis with local complication (bleeding) (?Laser therapy)

Very Early Disease Onset of Systemic Sclerosis (VEDOSS diagnostic criteria) (Algorithm)



Chapter 3.

Assessment of the patients suspected to have systemic sclerosis on first clinic visit

The initial assessment should be done at Specialist Centre designated to be responsible for caring patients with systemic sclerosis (**preferably by Rheumatologist or if not available by Internists).**

The following should be evaluated in patients to confirm the diagnosis of systemic sclerosis;

Thorough history taking and physical examination is the core part of the assessment. Apart from the routine assessment, the following should be emphasised on history and physical examination.

History:

- Duration of first clinical symptom and its progression,
- the presence of Raynaud's symptom and its complications, respiratory or cardiac symptoms suggestive of ILD and pulmonary hypertension, and GI (such as GERD)
- the presence of features of other autoimmune disorder such as arthritis, malaria rash, photosensitivity to exclude overlap or mixed connective tissue disorder.
- Vaccination status and obstetric and gynecology history in patients of reproductive age

Physical examination:

- Assessment of skin thickening by modified Rodnan skin Score
- digital ulcer and critical digital ischaemia
- Clinical signs of ILD and pulmonary hypertension
- presence of muscle weakness or pain suggestive of myositis
- Other features of auto-immune disorder: synovitis, oral ulcer, malar rash, alopecia.

Investigations

Nail-fold Capillaroscopy to detect active and early capillary changes in early systemic sclerosis (by Rheumatologists) ; VEDOSS criteria

Report of Nailfold Capillaroscopy finding

The following parameters should be reported –

Morphology: normal shapes, hairpin;

Nonspecific changes: tortuosities and crossing (once or twice),

Neo-angiogenesis;

Density;

Dimensions: normal, ectasia or giants and

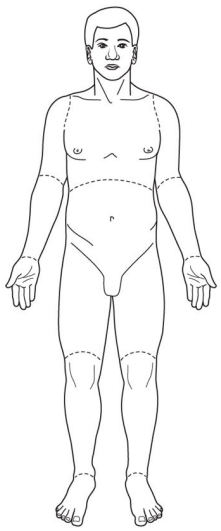
The presence or absence of haemorrhages

Figure: mRSS scoring format

Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____

Date of Examination: _____



	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								

Key: *0 – No Thickening* *1 – Mild Thickening* *2 – Moderate Thickening* *3 – Severe Thickening*

Notes:

Examiner:

Printed Name: _____

Signature: _____ Date: _____

How to score skin thinkening by mRSS (2) (Rheumatologist/internist)

Assessment of mRSS can be done by using index finger and thumb or two thumbs to measure thickness.

mRSS =0 where there is no appreciable skin thickness
mRSS =1 where there is mild skin thickness
mRSS =2 where there is moderate skin thickness
mRSS =3 where there is severe skin thickness

Laboratory investigations:

- Routine: RBS, ECG, Complete Blood Count, Systemic inflammatory markers such as ESR and CRP, Urea, Creatinine and electrolytes, Liver function assessment for baseline before starting DMARDs,
- Infection screening: HBV (combo), HCV and HIV serological screening
- Immunology: ANA, ANA profile or ANA (Scleroderma) profile,
- Others: CK and myositis profile for co-existing myositis

Imaging:

- CXR: to detect ILD and other abnormality such as presence of Koch's lung
- HRCT (chest) in suspected case of ILD,
- Echocardiogram (to confirm pulmonary hypertension)
- Lung function tests if available to assess ILD severity and for monitoring

Chapter 4.

Monitoring of the patients with Systemic sclerosis

Monitoring at regular interval at primary health care level monthly or 3 monthly for stable patients on oral medication and at Specialist centre for at least once a year

A. Monitoring at primary health care level or specialist centre

- Worsening of Clinical signs and symptoms such as digital ulcer, gangrene and 6 min walking distance for breathlessness at every visit
- CBC: RBS: Liver enzymes, Creatinine, urea and electrolytes, urine RE, cholestrol, CK (if myopathy presence)
- Eye examination: cataract due to long-term steroid use
- Pregnancy screening in reproductive age females

B. Monitoring at Specialist Centre (preferably rheumatologists or internists if not available)

- Progress of skin tightening by mRSS (Internists and Rheumatologist)
- Lung function test - yearly or when FHS decline
- HRCT (chest) if symptom suggest ILD and not done initially
- ECHO - yearly or if symptom arise or progress
- BMD testing for age over 50 or risk of OP

Chapter 5.

Management

5.a SSc-Related Skin Involvement (9)

Treatment choice

- Methotrexate or Leflunomide
- Mycophenolate mofetil (if failure to respond to MTX)
- Cyclophosphamide in generalised skin involvement with rapid progression
- Rituximab in refractory cases

Note: Low dose steroid in short term is optional.

5.a SSc-related Digital Vasculopathy

First Step:

- exclude the other causes and
- Remove the precipitating cause

General measures:

- to educate the patient to avoid/minimize common precipitating factors, such as cold temperature, stress, and nicotine.
- Medications associated with RP (ie, ergot derivatives, b-blockers) should be discontinued if clinically possible.

Dosages of drugs (5)

- Nifedipine: 10 mg BD - 40 mg BD,
- Amlodipine: 5 mg OD - 10 mg OD
- Diltiazem: 60 mg BD - 120 mg BD
- Losartan: 25 mg OD - 100 mg OD
- Fluoxetine: 20 mg OD
- Prazosin: 500 mg BD - 2 mg BD
- Sidenafil: 20 mg/25 mg TDS - 50 mg TDS
- Tadalafil: 10 mg AD - 20 mg OD

Pharmacological Treatment

Raynaud's treatment:

- First line- CCB (Nifedipine) or PDE5 inhibitors(sidenafil or tadalafil): other choices: ARBs (losartan), GTN patch,
- SSRI (Fluoxetine), a blockers (prazocin)
- Monitoring: Frequency and severity of Raynaud's

Digital Ulcer Treatment:

- First line- CCB and PDE5 inhibitors
- Second line- IV prostanoids
- Third line- Bosentan
- Refractory- digital sympathetomy
- Supportive therapy- Aspirin and Atorvastatin, Infection control

- Monitoring: healing, presence of secondary infection, new ulcer, signs of critical ischaemia

Critical digital ischaemia or gangrene treatment:

- Treat precipitating cause: Large vessel disease, Vasculitis, Coagulopathy, Thromboembolism, Smoking
- Analgesia, Antiplatelet, Statin, Antibiotics
- First line: IV prostanoid, PDE5 inhibitor optimization,
- Second line: Digital sympathetomy or Surgical intervention if necessary, short term anticoagulation (optional)

5. b SSc-Related inflammatory Arthritis (3)

- Initial Choice: Methotrexate
- If not controlled well, low dose oral steroid can be added
- HCQ and leflunomide can be added if still not controlled.
- IV Rituximab or Tocilizumab or TNF can be considered if the above agents failed or if overlap with other autoimmune disease
- NSAIDs to be added to the above treatment while symptomatic.

5. c Systemic Sclerosis with ILD

When to start treatment

if the patients with systemic sclerosis presents with dyspnoea preferably within 5 years of diagnosis

- If the lungs involvement is > 20% in HRCT or
- FVC < 70% if HRCT lung involvement is between 15 and 20%,
- or >10% decline of FVC in serial monitoring.

Monitoring after treatment: Lung function test (6-12 monthly)

Note: If lung function test shows FVC >70%, serial monitoring with lung function test is recommended. Treatment with oral drugs should be started as in skin involvement.

Induction: Duration: 6 months

- First line: MMF or IV CYC
- Alternative: Rituximab, HSCT, TCZ

Maintenance: MMF, Azathioprine, MTX or leflunomide or 3 monthly IV CYC

NOTE:

HRCT staging at five levels:: 1) Origin of great vessels 2)Main carina 3)Pulmonary venous confluence 4) halfway between the third and fifth section 5) Immediately above the right hemi-diaphragm

Four Variables: 1) Total disease extent 2) extent of a reticular pattern 3) the proportion of ground-glass 4) coarseness of reticular disease

Grade 0= Ground glass attenuation alone

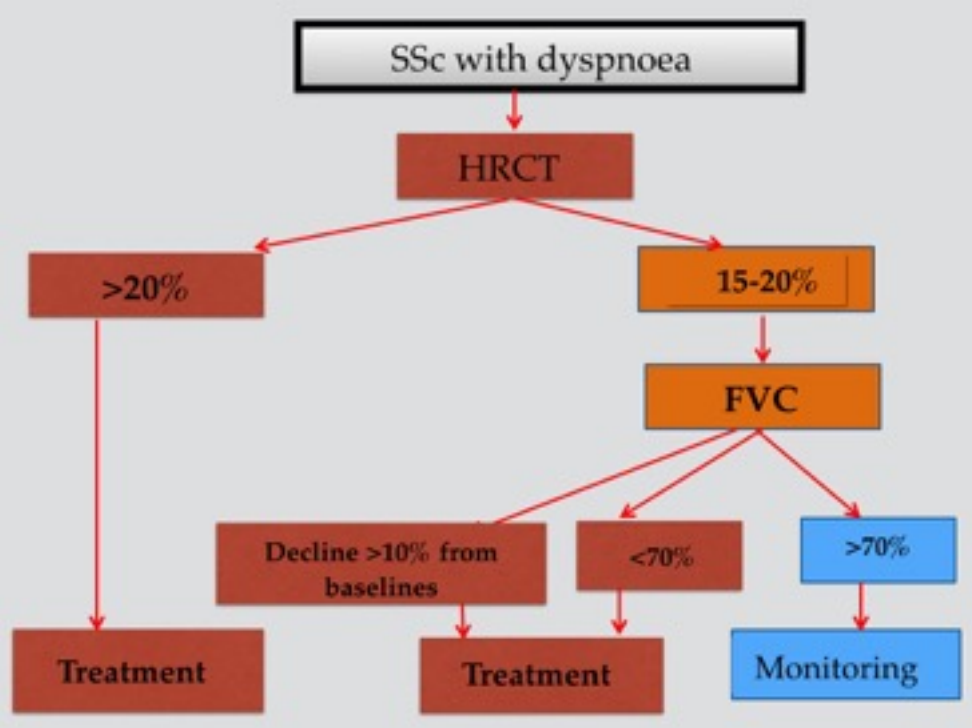
Grade 1= fine intralobular fibrosis

Grade 2=microcystic honeycombing (air spaces less than or equal to 4 mm in diameter

Grade 3= macrocystic honeycombing (air spaces greater than 4 mm in diameter)

Total coarseness score= sum for all five levels (0-15)

Algorithm for ILD Management



Protocol for Induction (IV CYC) in PSS-ILD

Initial 6 months therapy (Total Six cycles)
IV Cyclophospamide 0.4 mg/m2 body surface area + NS 100 ml (infusion over 1 hour) monthly for six months
(Same dose of IV mesna- will also be given)

PO Steroid (prednisolone)
0.8 mg/kg/day for 1 month,
then 5 mg of prednisolone will be reduced every week until the dose reach to 10 mg
then maintain on 10 mg of prednisolone until end of six months
No more IV methylprednisolone will be given together with IV cyclophosphamide

Method to calculate body surface area (Mosteller method)

$$\text{Body Surface area (m2)} = \frac{\text{Height(cm)} * \text{weight (kg)}}{3600}$$

Qx med application can also be downloaded and BSA be calculated by using this app

Maintenance oral immunosuppressant treatment
First Choice: Mycophenolate mofetil, leflunomide
Others: azathioprine, methotrexate, tacrolimus

Note: beware of SRC if prednisolone dose >20 mg/day

Other supportive treatment such as Calcium+ Vitamin D supplement, CCB for Raynaud's phenomenon, Statin and Antiplatelet for Digital ulcer, PPI for GERD , Sidenafil for co-existing pulmonary hypertension or digital vasculopathy will also be considered in personalised treatment decision

5. d SSc related Pulmonary Hypertension

Screening

- All patients with SSc should be screened for clinical signs and symptoms of pulmonary hypertension
- Echocardiography if available
- Monitoring
- Annual Echocardiography should be considered for monitoring

Treatment Indications

- Echocardiography with WHO functional class > 2

First choice- PDE5 Inhibitor

Second choice- Bonsentan

- Routine anticoagulation is not recommended
- Associations with ILD or overlap with other CTD may benefit from immunosuppressive therapy

Note: refer to cardiologists if necessary.

5. e Scleroderma Renal Crisis (SRC) (7)

suspect SRC in patients with systemic sclerosis

- if new onset BP >150/85 mmHg or increase >=20 mmHg from usual systolic BP
- AKI stage 1 or higher: >50% increase in Serum creatinine from stable baseline or absolute increase of 265 umol/l

Plus supporting evidences (organ damage by HT)

- MAHA on blood film, Thrombocytopenia and other biochemical findings consistent with hemolysis
- Features of accelerated hypertension such as hypertensive retinopathy
- Oliguria or anuria
- Microscopic hematuria on Urine dipstick or RBCs on urine microscopy
- Flash pulmonary oedema

Risks for SRC

- dcSSc
- Older age
- Males
- Use of GC (>20 mg/day)
- RNAP III or ANA speckled pattern
- Tendon Friction Rub
- Pericardial effusion

In high risk patients: Home BP monitoring weekly is recommended

if SBP >140/90 or rise in >30 mmHg (SBP) and >20 mmHg(DBP), review with Rheumatologist or internist

“SRC is a medical emergency”

Early Treatment:

Initial Treatment: ACE-I (preferably)+additional antihypertensive treatment (CCB, ARB, Alpha-blockers) as necessary (avoid beta-blockers)

Target BP: 10% reduction in SBP and/or DBP per day

Optimise supportive care

When to refer to nephrologist: rapidly rising creatinine

ICU or Intensive care if presence of

- Pulmonary oedema
- Hypertensive encephalopathy
- MAHA
- Tachyarrhythmia
- Severe AKI needing RRT

Long-term Treatment

- continue ACE-I and taper glucocorticoids
- in patients needing regular RRT after 12 months, renal transplant should be considered.

5. f SSc-related Cardiac involvement (3)

The patients with systemic sclerosis can present with cardiac manifestation such as myocarditis, pericarditis, ischemic cardiomyopathy or arrhythmias.

Treatment choice in myocarditis

- MMF or IV CYC or IV Rituximab + high dose Steroids
- plus standard treatment for heart failure

Treatment choice for pericarditis

- First line: Low dose steroids, NSAIDs, colchicine, HCQ
- Second line: MTX or MMF
- Third line: Pericardiocentesis if impending tamponade

Ishemic cardiomyopathy or arrhythmia:

- as per standard protocol for cardiac problems

Note: Refer to cardiologist if necessary

5. g SSc-Related GI involvement (3)

Treatment options

Lifestyle modification

- Smoking cessation,
- eating smaller portions more often,
- eating the last meal of the day earlier, and
- elevation of the head of the bed.
- Dietary interventions: modifying the texture of food, such as purees or scrambled eggs.
- Yogurt may be recommended
- avoidance of exacerbating food groups, such as spicy food.

Drugs: Proton pump inhibitors, Histamine blockers, prokinetics: metochlorphramide/ domeridone, antibiotics

Treatment of

A. **GERD**: lifestyle modification, PPI, H2 blockers
B. **Oesophageal dysmotility**: buspirone 20 mg daily
C. **Dysphagia**: Domperidone 10 to 20 mg up to 4 times a day 30 minutes before meals
D. **Gastroparesis**: Dietary modifications, metochlorpramide/domperidone, IVIG in resistant cases,Selective 5HT4 receptor agonists, such as prucalopride
E. **Small bowel bacterial overgrowth**: dietary modification, antibiotics, pro-motility drugs,rifaximin
F. **Constipation due to Colonic hypomotility**: dietary modification, stool softeners, laxatives
G. **Fecal incontinence:** biofeedback, anorectal feedback

Note: refer to gastroentrologists in selective cases as necessary e.g., refractory GERD cases, chronic diarrhoea

Chapter 6.

Minimal Care

Minimal Care in Systemic Sclerosis includes

1> Management of disease related organ involvement and complication (as in previous chapters)

2> Management of Complication of treatment (e.g glucocorticoid induced osteoporosis prevention and management)

3> CVD prevention and Infection (CVD risk stratification and Vaccination)

4> Social and Family Planning, Lactation

6. a Bone protection (8)

All adults taking prednisone at a dose of 2.5 mg/day for 3 months

- Optimize calcium intake (1,000–1,200 mg/day) and vitamin D intake (600–800 IU/day) and
- lifestyle modifications
  - balanced diet,
  - maintaining weight in the recommended range,
  - smoking cessation,
  - regular weight-bearing or resistance training exercise,
  - limiting alcohol intake to 1–2 alcoholic beverages/day)

In Adults age >= 40 years at moderate to high risk of major fracture,

- an oral bisphosphonate is prefer to IV bisphosphonates, teriparatide, denosumab, or raloxifene

6. b Nutrition

- Advice on optimal nutritional intake and explain the impact from taboo
- Balance diet with carbohydrate, protein, fat and trace elements as well as vitamins

6. c CVD risk stratification and prevention

- regular screening of Hypertension, Diabetes, dyslipidemia, ischemic heart disease, gout, chronic renal impairment and adequate treatment to control them if present (antiplatelet, statin, antihypertensive)

6. d Vaccination and infection screening

- HBV: double dose of HBV i.e, 2 vials at 0,1,2 or 0,1,6 regime. Booster dose in those already vaccinated
- Flu vaccine yearly
- Pneumococcal vaccine every 5 years if available
- Avoid live vaccines
- have low threshold for infection screening especially Koch's lung which can re-activate or re-infected or co-existing in patients with chronic lung disease such as ILD.

6. e Family planning and lactation (6)

Family planning

Every patients of reproductive age should be counselled for family planning and pregnancy before starting treatment

Their partners also need to be counselled.

Avoid pregnancy if

- Sever ILD (FVC <50%)
- Moderate to severe pulmonary hypertension
- while on immunosuppressant

***Refer to OGs before planned pregnancy and during pregnancy for proper AN care.**

***csDMARDs which are compatible with pregnancy**

- hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus

***csDMARDs which are teratogenic and must be stopped before bregnancy**

- methotrexate, mycophenolate mofetil, leflunomide, cyclophosphamide
- Biologics such as rituximab, tocilizumab, abatacept should be replaced before pregancy

Postphone pregancy (use the contraceptive) till

- 2 years after leflunomide
- 6 months after the last dose of methotrexate or MMF or rituximab
- 1 year after cyclophospamide

Pregnant while on DMARDs

Elimination procedure for leflunomide:

- cholestyramine 8 G PO TDS*11 days

During lactation,

- the following drugs should be continued : HCQ, CQ, SSZ, AZA, Ciclosporin, TAC, Colchicine, prednisolone, Immunoglobin, non-selective COX inhibitors and celecoxib
- the following drugs should be avoided: methotrexate, MMF, CYC, leflunomide, tofacitinib, COX II inhibitors apart from celecoxib
- Biologics: infliximab, adalimumab, etanercept and certolizumab can be continued due to low transfer to breast milk

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