RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Scleroderma

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Faculty Disclosures

Jessica Farrell, PharmD:

- Speaker: Abbvie, Pfizer
- Consultant: Boehringer Ingelheim

Christina Starks, MPA, PA-C

- Speaker: Horizon, Abbvie, Amgen
- Advisory Board: Sanofi, Abbvie

Objectives

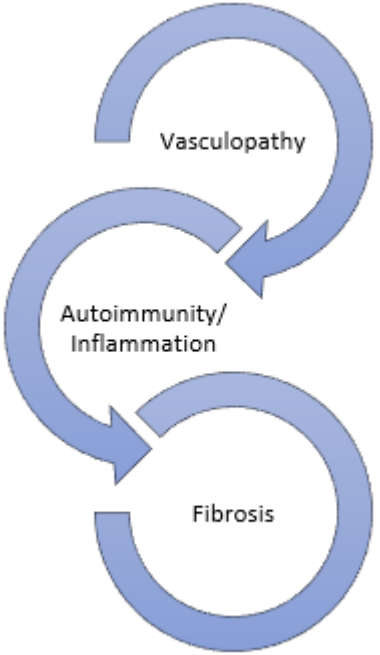
1. Review pathophysiology of scleroderma/systemic sclerosis (SSc) and common clinical presentations.

2. Discuss management of various clinical presentations associated with scleroderma/ systemic sclerosis.

3. List monitoring parameters associated with treatments and disease manifestations in patients with scleroderma.

Overview - Scleroderma

- Sclero (hard), derma (skin)
- Rare, complex, autoimmune disease hallmarked by vasculopathy, autoimmunity/inflammation, and fibrosis which affects connective tissue systemically.
- Classification
  - Localized = skin only involvement
  - Generalized = systemic involvement



Epidemiology

Rare disease and varies greatly

- Low incidence and prevalence
  - -- 8 to 56 new cases/million/year.
  - -- 38 and 341 total cases/million.
- Female > Male by 4:1
- Age 25 to 65
  - younger in African American women
  - Pediatric population

Scleroderma		
Disease	Prevalence	# in US
Osteoarthritis	12%	27 million
Rheumatoid arthritis	0.6 – 0.8%	1.5 – 2.0 million
Lupus	< 0.1%	240,000
Systemic sclerosis	< 0.025%	50,000

Ingegnoli F, Ughi N, Mihai C. Update on the epidemiology, risk factors, and disease outcomes of systemic sclerosis. Best Pract Res Clin Rheumatol. 2018 Apr;32(2):223-240. doi: 10.1016/j.berh.2018.08.005. Epub 2018 Sep 14. PMID: 30527428.

Geoepidemiology

Varies globally

- Higher rates in Europe, Sweden, North America.

Clustering

- Choctaw Natives in Oklahoma
  - highest disease prevalence in US
- Burrows of London, England near airports
- Woodstock, Ontario, Canada
- Western Victoria Australia, rural Italy

Scleroderma Classification

Localized/Morphea (Cutaneous)			Generalized (Systemic Sclerosis – SSc)		
Plaque	**Linear**	**Deep**	**Limited Cutaneous lcSSc**	**Diffuse Cutaneous dcSSc**	**SSc Sine Scleroderma ssSSc**
Circumscribed Guttate Keloidal Nodular Superficial Bullous Atrophoderma	Linear bands of skin thickening - arms, legs, face - **en coup de sabre**	Poorly circumscribed, bound down sclerotic plaques involving fascia "cobblestone"	Limited thickening to face, neck, and **distal to elbow and knees**	Diffuse thickening **proximal to elbow or knees** with trunk involvement	Internal organ involvement **without e/o skin thickening** some consider subtype of lcSSc
Oval/round Trunk, neck Hyper- and hypopigmented -37% pediatric morphea -most common adult morphea	Single tight bands Can involve subcutaneous fat, muscle, bone Children ≤ 10 yo: -32% pediatric morphea (non facial) -17% en coup de sabre	- Eosinophilic fasciitis - Pansclerotic disabling morphea	Slow onset Long standing Raynaud's, GERD, CREST **Scl-70 → ILD** **ACA → PAH** **SRC rare**	Fast onset, Puffy hands, Raynaud's, arthritis, rapid skin **progression ILD** **RNA pol3 → SRC**	+ SSc Abs: Scl-70 ACA RNA pol3

Varga, J., Denton, C. P., & Wigley, F. M. (2012). Scleroderma. Springer Science & Business Media.

CREST Syndrome

- Somewhat outdated term
  - May give impression it is distinct from SSc or represent a category of SSc

C – Calcinosis

R – Raynaud's

E – Esophageal dysmotility

S – Sclerodactyly

T - Telangiectasia

West, S. G., & Kolfenbach, J. (2019). Rheumatology Secrets. 4th Ed. Elsevier Health Sciences. 163.

Pathophysiology

Pathophysiology

Etiology unknown.

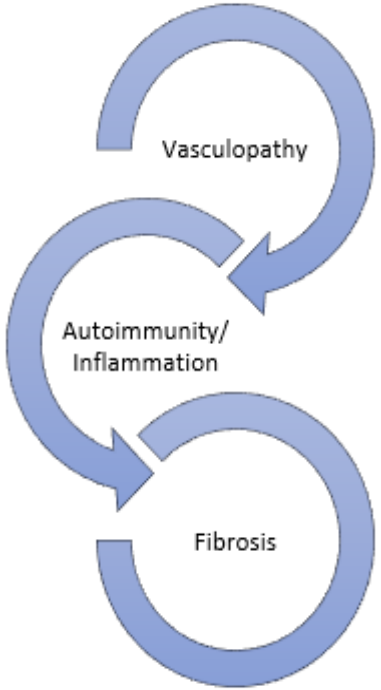
- Multifactorial, complex, incompletely understood.

Genetics vs Environment

- No single gene or environmental trigger is alone to blame.

Main processes:

- Vasculopathy
- Immune dysfunction/inflammation
- Fibrosis

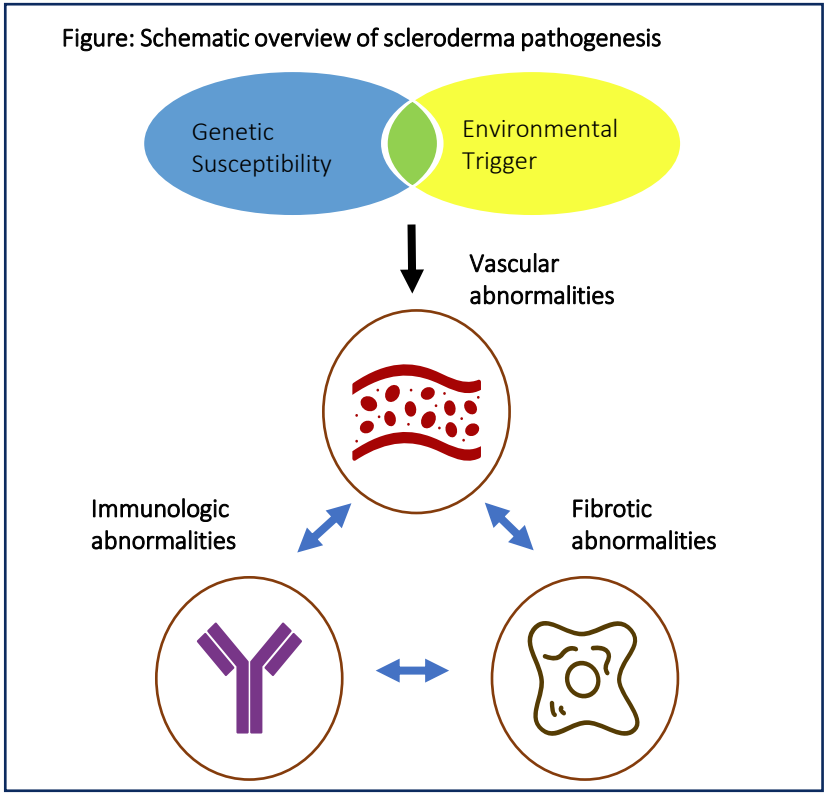


Vascular injury & Endothelial damage

- Likely the primary events.
- Which leads to activation of the innate and adaptive immune systems.
- Further contributes to fibrosis.

Pathophysiology

- 3 distinct pathophysiological processes:
  - Diffuse microangiopathy:
    - Endothelia cell activation
    - Leukocyte attraction and adhesion
    - Vascular Occlusion
    - Tissue Hypoxia
  - Inflammation and autoimmunity
    - Macrophage activation
    - T lymphocyte activation
    - B lymphocyte activation (autoantibody production)
    - Cytokine and chemokine production
  - Visceral and vascular fibrosis
    - Fibroblast activation
    - Myofibroblast activation
    - Excessive accumulation of extracellular matrix (ECM)



Adapted from Katsumoto et al., 2011

Clinical Presentation

History

- History and presentation can vary depending on form and will differ among patients.
- Common early findings:
  - Raynaud's, may be present for years
  - Nailfold capillary changes
  - Puffy/swollen fingers
  - Tight, shiny skin
  - Pruritus
  - GERD

Presentation

Classic presentation of **Limited** Cutaneous Systemic Sclerosis

Limited Cutaneous Systemic Sclerosis - lcSSc Centromere positive		
Year 0	**Years ~5-10**	**Years ~10-20**
Raynaud's	Puffy/swollen fingers Sclerodactyly GERD/Reflux Telangiectasia Calcinosis ILD	Pulmonary Arterial Hypertension

Presentation

Classic presentation of Diffuse Cutaneous Systemic Sclerosis

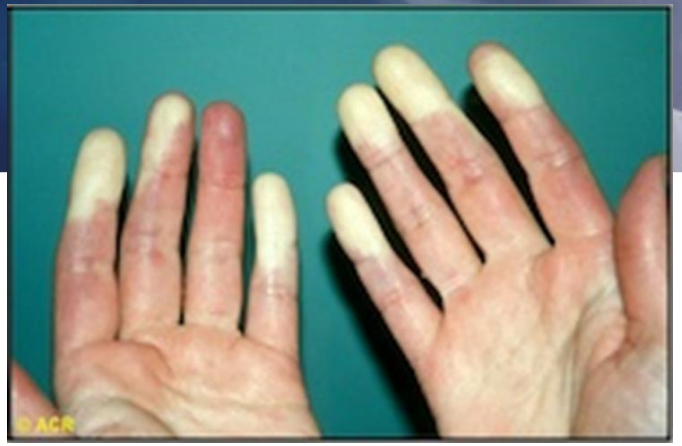
Diffuse Cutaneous Systemic Sclerosis - dcSSc		
Year 0-1	**Years ~1-5**	**Years +5**
Raynaud's Progressive skin thickening Tendon friction rub GI involvement Arthritis Fatigue Scl-70 or Nucleolar ANA	ILD Renal crisis	Pulmonary Arterial Hypertension Pulmonary Hypertension

Exam

Cutaneous Manifestations

Raynaud's	Fat atrophy
Puffiness/swelling in fingers	Loss of sweat glands and hair in areas of thickened skin
Pruritus	Telangiectasias
Tight shiny skin	Fingertip pitting or digital ulcers
Skin thickening	Loss of wrinkles
Morphea	Lip thinning/oral aperture changes
Skin contractures (late finding)	
Pigmentation changes – salt 'n pepper	

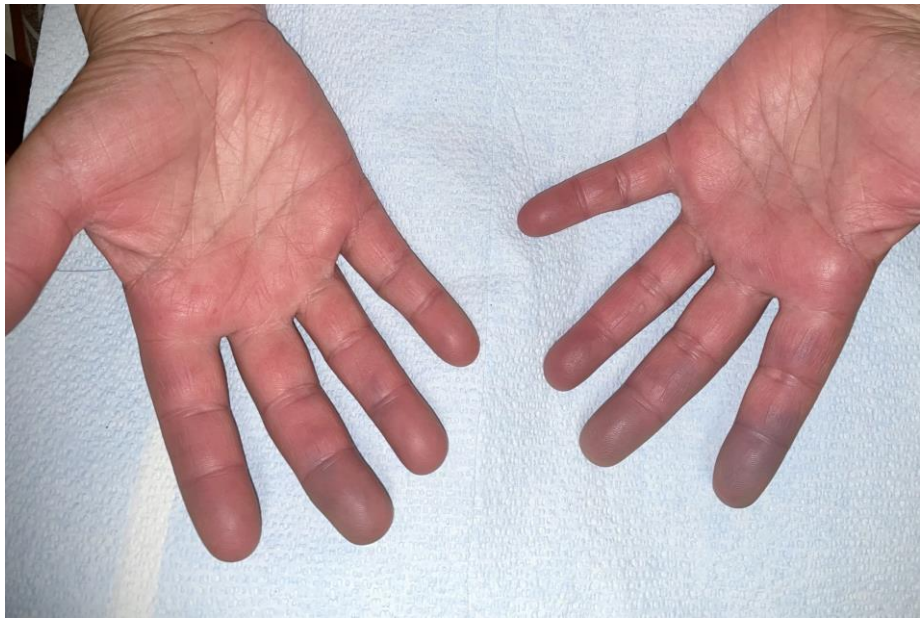
Exam

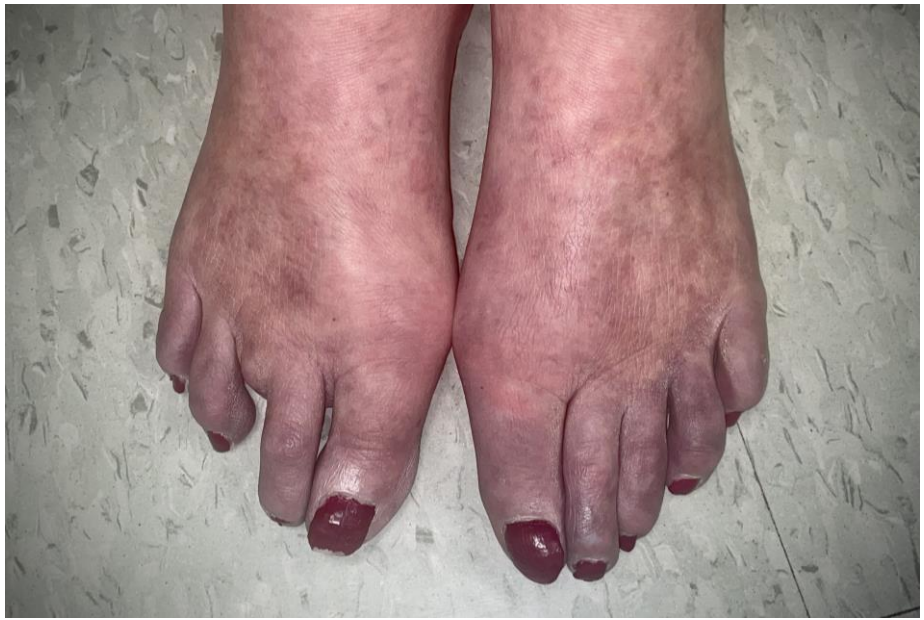


Raynaud's phenomenon

- **Common early finding**
- May be present for years
- In SSc it is thought that the underlying vasculopathy disrupts the thermoregulatory vessels beyond vasospasm
- Progressive narrowing of the vessels that can lead to digital ischemia
- Pitting, digital ulcers, autoamputation

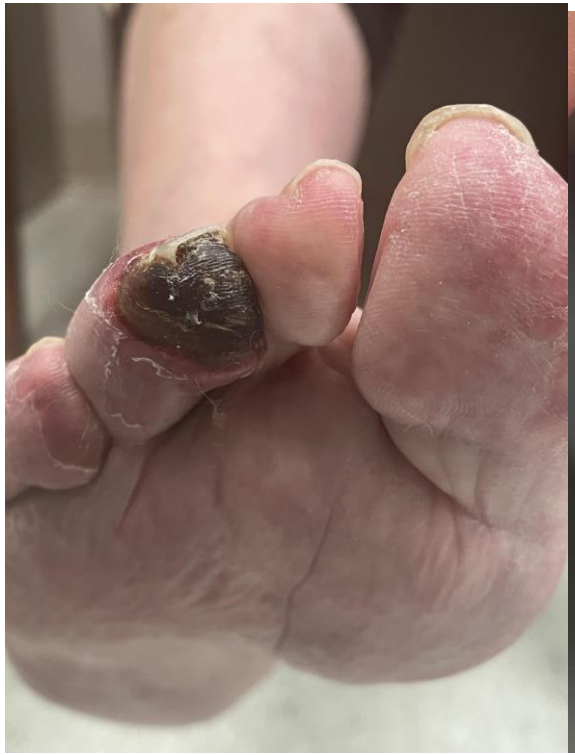
Raynaud's

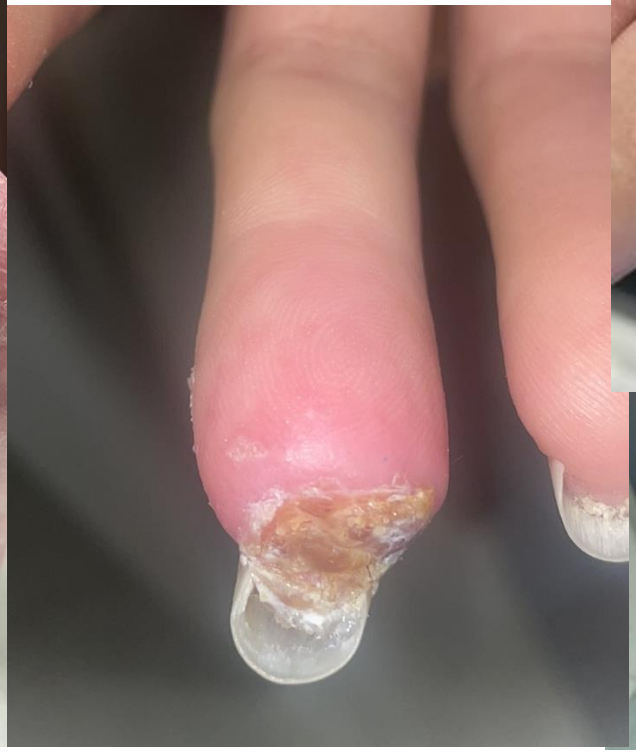


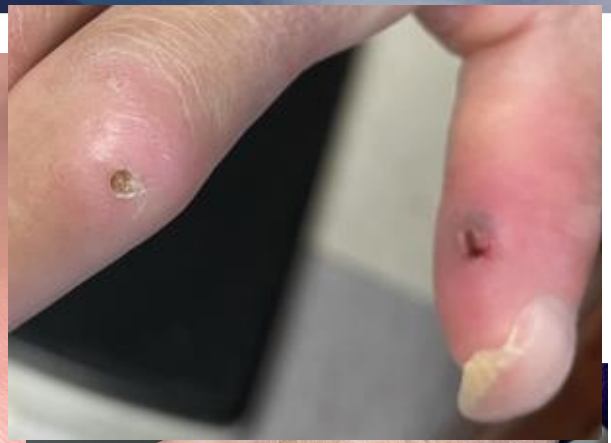


C.Starks photo -uwp

Digital ulcers





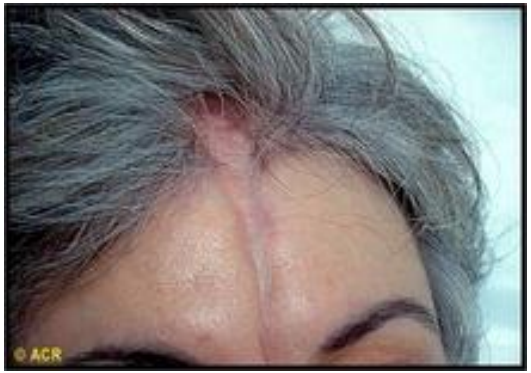


C.Starks photo -uwp

Exam

Morphea

- Localized skin thickening
- Subtypes:
  - circumscribed, linear, generalized, deep, pansclerotic, mixed
- En coup de sabre
  - linear induration on forehead/scalp
  - *The blow of a sword*



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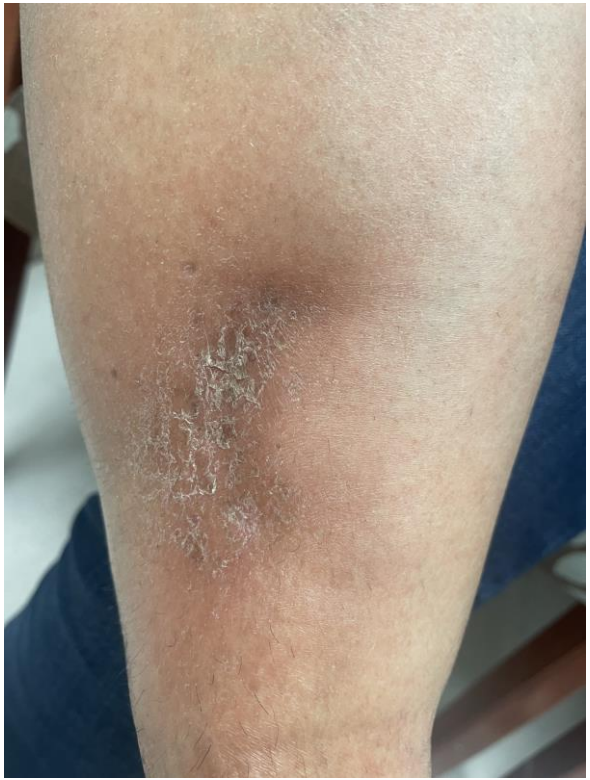
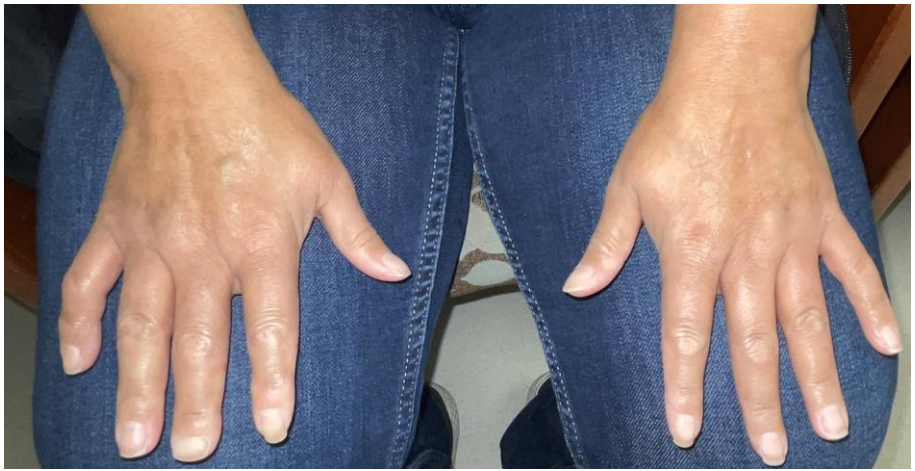


C.Starks photo -uwp

Exam

Skin Thickening

- Starts distal in the fingers, toes
- Limited SSc skin thickening does not pass elbows/knees
- Degree of skin thickening varies among patients
- Most will soften or atrophy over 3-10 years with no intervention

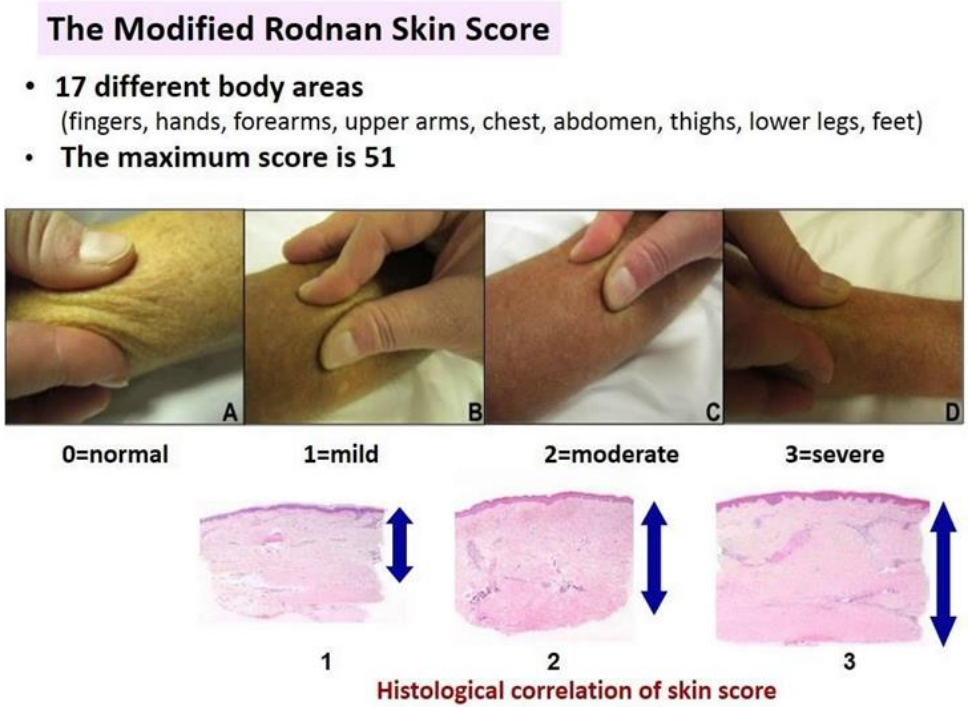


C.Starks photo -uwp

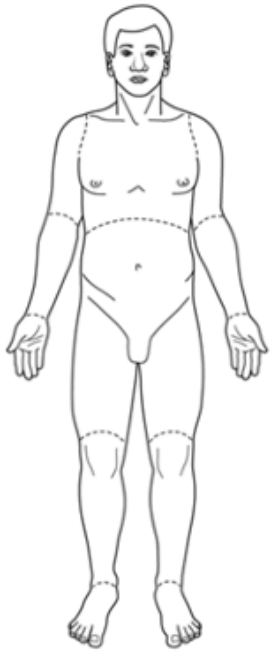
Exam

Modified Rodnan skin score (mRSS)

- Tool to assess skin involvement
- 0 to 3 grading based on degree of thickness
- Used clinically and for research
- Skin score over 15-20 and rapid progression indicate severe thickening



Modified Rodnan Skin Score mRSS



	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*

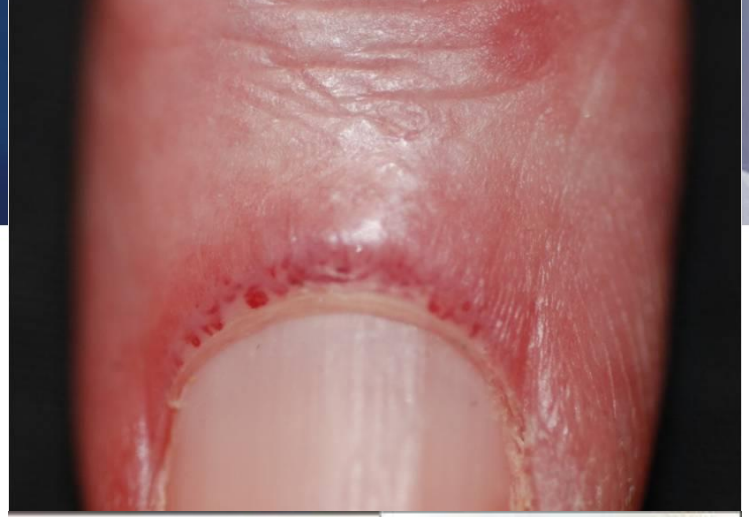
Notes:

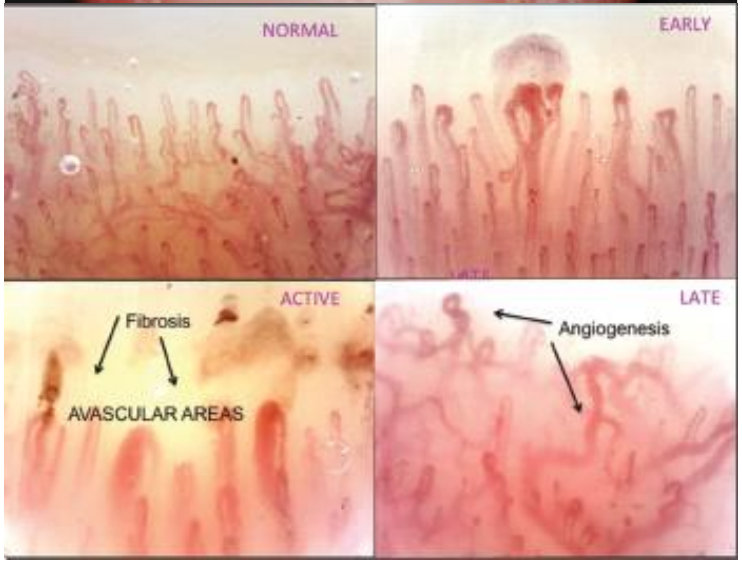
Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, Distler O, Foeldvari I, Kuwana M, Matucci-Cerinic M, Mayes M, Medsger T Jr, Merkel PA, Pope JE, Seibold JR, Steen V, Stevens W, Denton CP. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017 Jan-Apr;2(1):11-18. doi: 10.5301/jsrd.5000231. PMID: 28516167; PMCID: PMC5431585.

Exam

Nailfold changes

- Abnormalities in nailfold capillaries are an early sign
- Dilation, hemorrhage, giant capillaries, capillary loss can be seen under magnification
  - video capillaroscopy
  - dermatoscope
  - ophthalmoscope



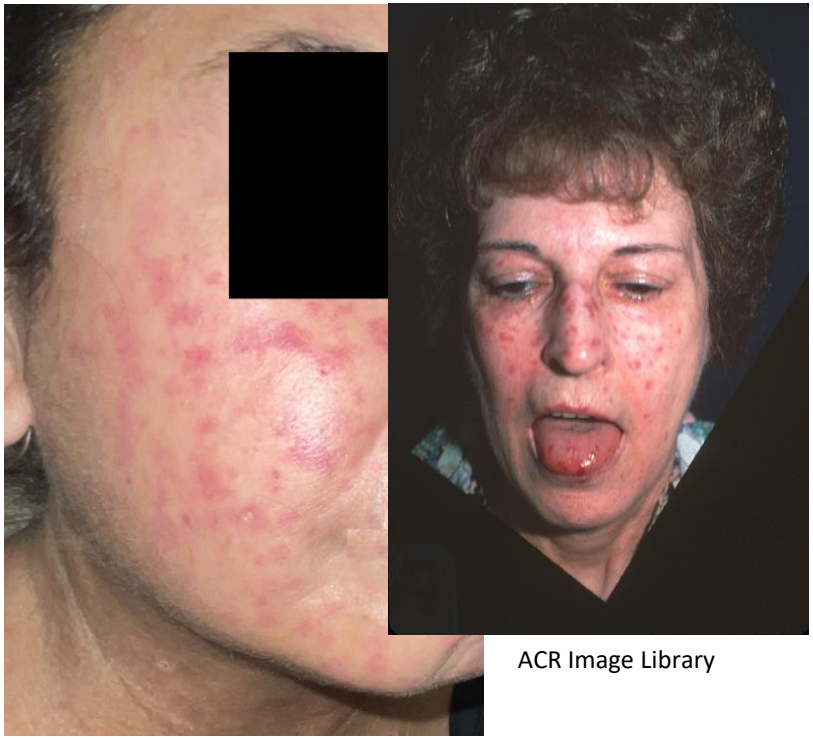


ACR Image Bank

Exam

Telangiectasias

- Hallmark of SSc skin disease
- Seen in limited and diffuse
- Early - fingers, palm, face, mucous membranes.
- Late - arms, trunk



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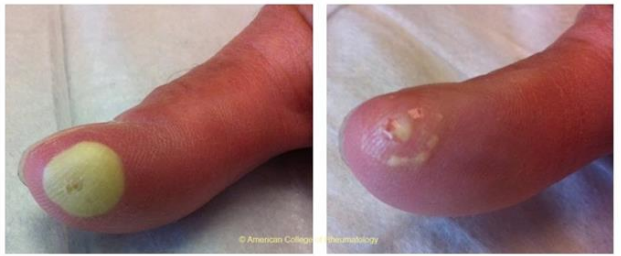
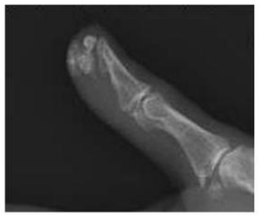
Exam

Calcinosis

- Calcium phosphate crystals form in the skin
- Fingers, arms, elbows
- Whitish papules, nodules
- Can be painful, mimic infection, or become infected





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Exam

MSK findings

- Arthralgias
  - 12-65% initial manifestation
  - 46-97% eventual manifestation
  - Predominantly hands, wrists, ankles
  - Presence of synovitis may represent RA overlap
- Carpal Tunnel Syndrome from swelling and fibrotic changes
- **Tendon friction rubs** - leathery crepitus or rubbery sensation
- Bursitis

Steen, V D, and T A Medsger. "The Palpable Tendon Friction Rub: An Important Physical Examination Finding in Patients with Systemic Sclerosis." Arthritis & rheumatism. 40.6 (1997): 1146–1151.
Doré, Adam et al. "Significance of Palpable Tendon Friction Rubs in Early Diffuse Cutaneous Systemic Sclerosis." Arthritis care and research : the official journal of the Arthritis Health Professions Association. 65.8 (2013): 1385–1389.

Diagnostic Criteria

Item	Sub-item	Score
Skin thickening of fingers of both hands extending proximal to metacarpophalangeal (MCP) joints		9
Skin thickening of fingers (only count the highest score)	Puffy fingers Sclerodactyly of the fingers, distal to MCP, proximal to IP	2 4
Fingertip lesions (only count the highest score)	Digital tip ulcers Pitting scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease		2
Raynaud's phenomenon		3
Scleroderma-related antibodies (any of anti-centromere, anti-topoisomerase I [anti-Scl 70], anti-RNA polymerase III)	Anticentromere Anti-topoisomerase I (Scl-70) Anti-RNA polymerase III (RNA-Pol III)	3
Patients with a total score of ≥9 are classified as having definite systemic sclerosis (sensitivity 91%, specificity 92%) (Other SSc-minims and potential causes of skin thickening must be excluded.)		

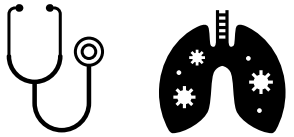
(From Hoogen F, Khanna D, Fransen J, et al (2013). 2013 Classification criteria for systemic sclerosis. Arthritis Rheum 65: 2737-2747)

van den Hoogen, Frank et al. "2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative." Arthritis & rheumatism. 65.11 (2013): 2737–2747. Web.

Pulmonary manifestations

Pulmonary

- ILD and PAH
- Largest cause of disease mortality
- Driven by vasculopathy - PAH 10% all SSc
- Lung function decline typically slow but can be rapid
- Scl-70 common
- ACA uncommon
- Diagnostics
  - Chest XR, High resolution Chest CT (HRCT), PFTs, 6 minute walk test



Hx/Findings

- Often non-specific history
- DOE, SOB, dry cough
- Fatigue
- Poor exercise tolerance
- Fine crackles at bases
- Digital clubbing and cyanosis (advanced)

Cardiac manifestations

Cardiac

- SSc cardiac involvement prevalence varies.
- SSc can affect any cardiac structure.
- Poor prognosis when symptomatic.
- Early screening is key.

Symptoms	Cardiac complication
Exertional lightheadedness, dizziness, syncope	Pulmonary arterial hypertension Right ventricular dysfunction Arrhythmias
Lethargy, abdominal fullness, early satiety, leg swelling	Right-sided heart failure Pericardial disease
Chest pain, shortness of breath, overt left-sided heart failure	Late stage myocardial disease
Sudden worsening Raynaud's (digital necrosis)	Severe cardiac microvascular dysfunction

Renal manifestations

Scleroderma Renal Crisis

- Acute kidney injury marked by new onset of arterial hypertension (>150/90)
  - Associated with oliguria, pericardial effusion, retinopathy, microproteinuria, thrombocytopenia, microangiopathic hemolysis (schistocytes; 50%), elevated renin
- Risk Factors for SRC (10% of SSc)
  - RNA pol III
  - Early in disease (75% occur first 4 years)
  - Early diffuse skin thickening (20-25% dcSSc)
  - Tendon friction rubs
  - Corticosteroids (prednisone >20mg/day)
  - NSAIDs
  - Cyclosporine

ACE inhibitors

- Treat promptly to avoid renal failure

- No data to support prophylactic use

Diagnostics

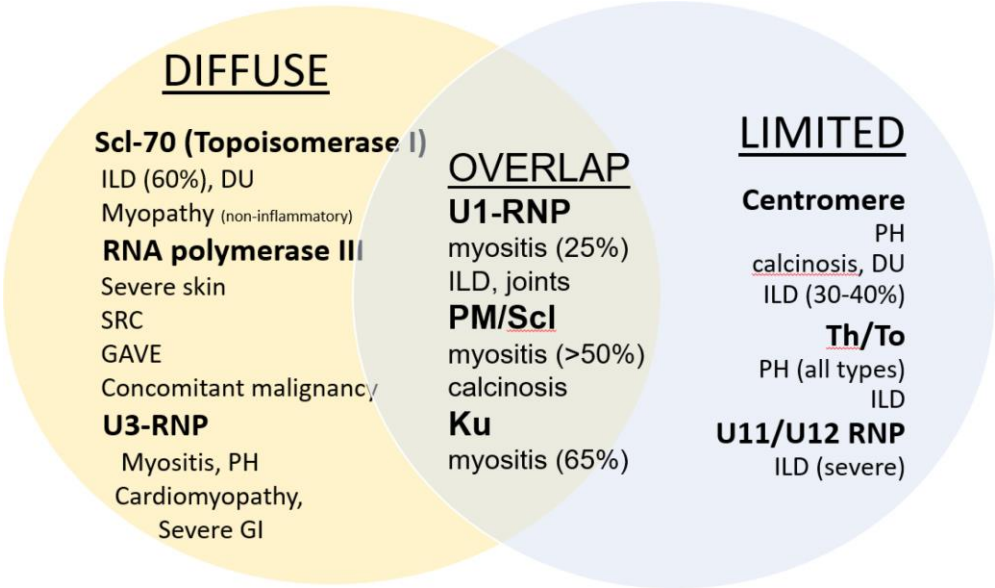
Diagnostics

Labs

SSc-specific autoantibodies:

- Anticentromere (ACA)
- Anti-topoisomerase I (Scl-70)
- Anti-RNA polymerase III (RNA pol III)
- Others: U3 RNP, U1 RNP, PM-Scl, Th/To, Anti-U11/U12, Anti-Ku

ACA	**lcSSc**	PH, esophageal disease, "protection" from ILD/renal
Scl-70	**dcSSc**	ILD, isolated PH is less likely
RNA pol III	**dcSSc**	Renal Crisis (SRC), severe skin, malignancy, GAVE



Saketkoo LA et al. *Best Pract Res Clin Rheumatol*. 2021;35(3):101707. Published online 2021 Sep 15. doi: 10.1016/j.berh.2021.101707

Diagnostics

Cardiopulmonary

- PFTs, HRCT, 6 minute walk,
- EKG, Echo, ?PAH→Cath

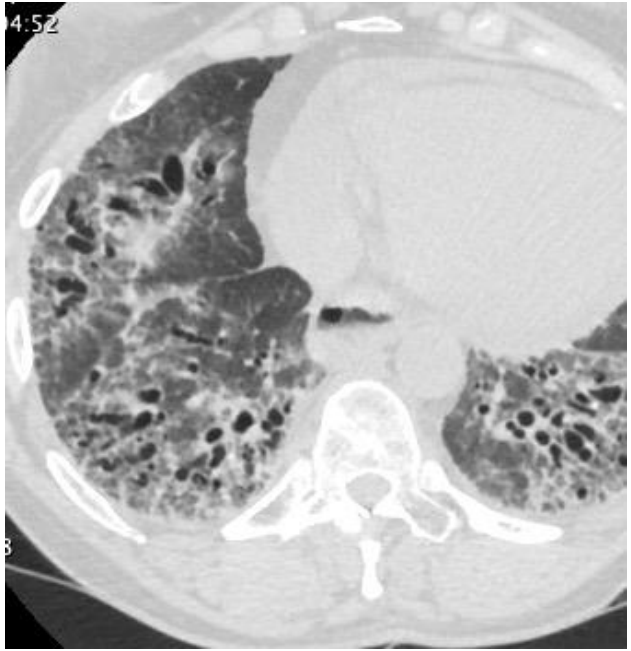
GI

- EGD for upper GI involvement
- Barium swallow - patulous esophagus
- Esophageal manometry - lower esophageal involvement

Treatment & Management

Goals of Treatment

- Reduce or prevent end organ involvement & improve quality of life
- No single drug therapy has been found to treat all aspects of scleroderma
- Targeted at treating inflammation, autoimmunity, vascular disease, and tissue fibrosis
- **Major causes of death**
- **PAH affects 10-15%:**
  - Anti-centromere, LcSsc, telangiectasia burden, duration RP>8y, DLCO<60 without ILD
- **Pulmonary Fibrosis affects 40%:**
  - anti-SCL70
- Does skin involvement predict internal organ involvement?



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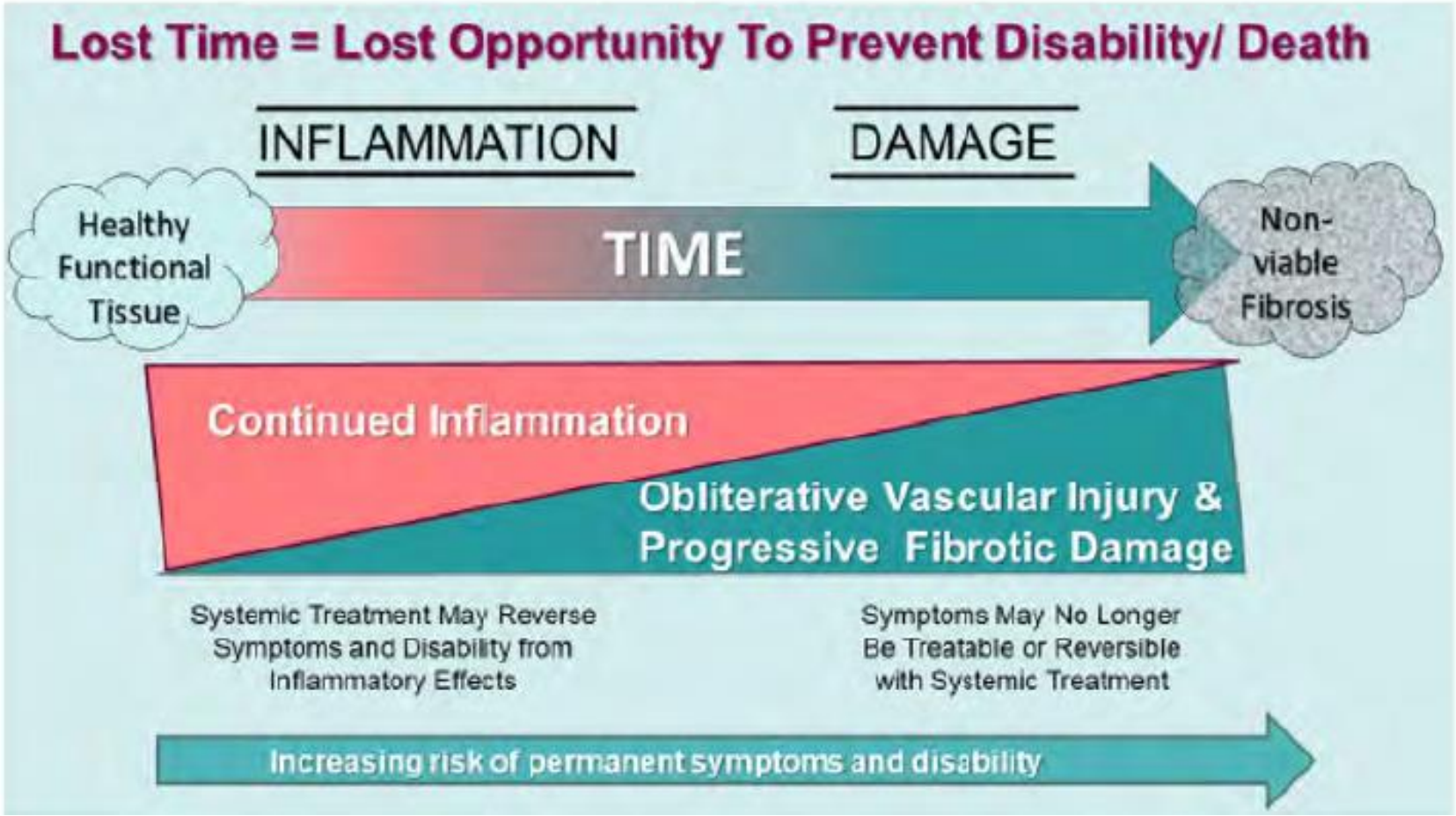

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Raynaud's Phenomenon

Drug Class	Drug Names	General Side Effects/Monitoring
Calcium Channel Blocker (CCB)	nifedipine, amlodipine	Hypotension, flushing, dizziness, peripheral edema
Angiotensin Receptor Blocker (ARB)	Losartan, valsartan	Dizziness, diarrhea, hypotension, muscle cramps, and headache
Alpha Blockers	Prazosin	Hypotension, dizziness, drowsiness
Nitrates	Topical Nitroglycerin 2%	Rash, headache, facial flushing, dry mouth, hypotension, tachycardia
Phosphodiesterase-5 Inhibitors (PDE-5i)	Sildenafil Tadalafil	Blurred vision, flushing, headache, hypotension, visual impairment, tachycardia

Raynaud's & Digital Ulcers

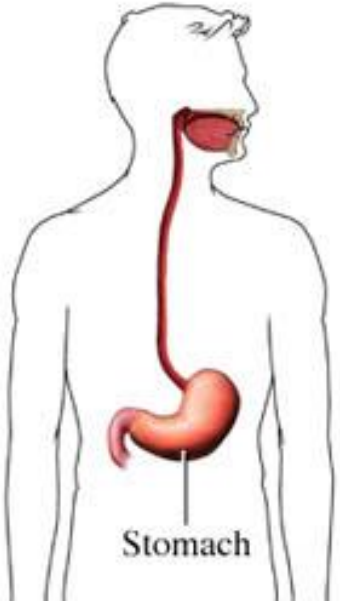
Drug Class	Drug Names	General Side Effects/Monitoring
Phosphodiesterase-5 Inhibitors	Sildenafil Tadalafil	Blurred vision, flushing, headache, hypotension, visual impairment, tachycardia
Prostacyclin/ prostacyclin analog	Epoprostenol Treprostinil Iloprost	Hypotension, dizziness, muscle cramps, peripheral edema, headache *Administration concerns
Endothelial Receptor Blockers	Bosentan Ambrisentan	Liver injury, headache, flushing, leg swelling, fatigue, hypotension, itching, and weight gain *REMS program

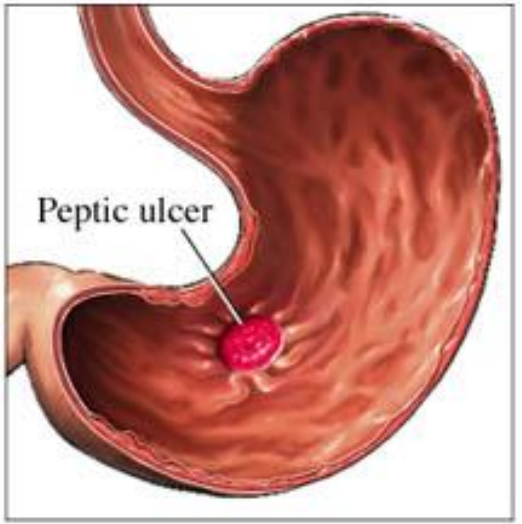
Raynaud's: Agents to Avoid

- NICOTINE!
- Caffeine
- Amphetamine
- Beta-blockers (propranolol, metoprolol, atenolol)
- Pseudoephedrine (includes combo products!)
- Migraine meds
- Clonidine

Pain Management: Concerns in Scleroderma

- NSAIDS (ibuprofen, naproxen, etc)
  - Esophageal concerns
  - Gastritis (damage to GI lining)
- Steroids
  - Risk for renal crisis
    - Caution/Avoid if RNA- Polymerase 3 antibody
- Opioid Pain Meds
  - Decreased motility in GI tract
    - Constipation in general population → may be exaggerated in scleroderma patients
  - Risk of respiratory depression
  - May require a multimodal approach





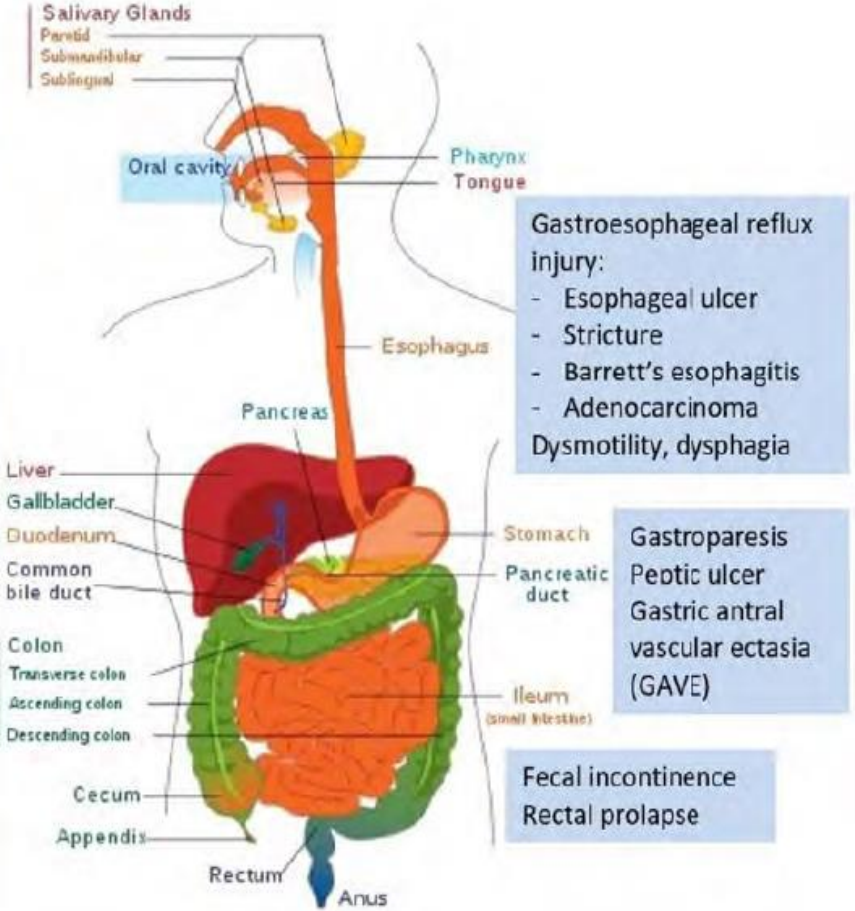
Steen VD, Medsger TA Jr. *Arthritis Rheum*. 1998; 41:1613.

Gastrointestinal Tract in SSc

Oropharyngeal structural changes:
- Small oral aperture
- Dental shifting
- Tooth loss

Sicca
Dysphagia
Gastroesophageal reflux related damage to:
- Teeth
- Mucosal lining
- Vocal cords

Pseudo-obstruction
Small intestine bacterial overgrowth (SIBO)
Dysmotility
Malabsorption
Malnutrition
Colonic inertia
Diverticuli
Megacolon



Gastroesophageal reflux injury:
- Esophageal ulcer
- Stricture
- Barrett's esophagitis
- Adenocarcinoma

Dysmotility, dysphagia

Gastroparesis
Peptic ulcer
Gastric antral vascular ectasia (GAVE)

Fecal incontinence
Rectal prolapse

Saketkoo LA et al. *Best Pract Res Clin Rheumatol*. 2021;35(3):101707.

PPI's: Safety

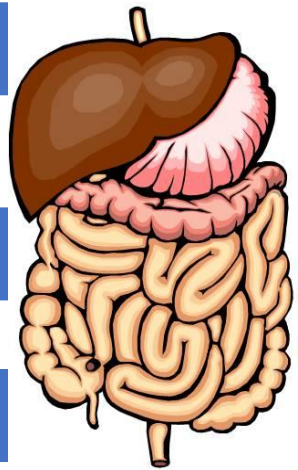
- **Common side effects:**
  - Nausea, diarrhea, headache (minimal)
- **Possible decreased absorption of vitamins:**
  - Calcium, Magnesium, Vitamin B12, Iron
- **Drug interactions:**
  - Decreased absorption of other drugs?
- **Rare long term effects:**
  - Osteoporosis, GI infections (*Salmonella, C. difficile*), pneumonia(?), polyps, liver problems, acute/chronic kidney disease, dementia (?)
- **Watch for combination products**
  - Vimovo *(naproxen/esomeprazole)* Duexis *(famotidine/ibuprofen)*
  - OTC's
- **Long-term/Life-time Use**
  - Large placebo-controlled trial confirms safety of proton pump inhibitors (PPIs). American Gastroenterological Association. Published June 6, 2019.

Carlson et al. Curr Rheumatol Rep 2015; 17:475
Moayyedi et al. *Gastroenterology*. 2019;157(3):682-691.e2.

GI Treatments

Small Bowel Bacterial Overgrowth/Diarrhea

- Cyclic antibiotic therapy
- Octreotide



Antiemetics

- Ondansetron (prolongs GI transit, headache, cardiac arrhythmia)

Promotility Agents

- Metoclopramide (long term use – movement disorders)
- Prucalopride/Cisapride
- Domperidone (not available in US)
  - Risk of heart problems/potential drug interactions
- Risk vs Benefits

TEAM APPROACH:
MD & Pharmacist!

Saketkoo LA et al. *Best Pract Res Clin Rheumatol*. 2021;35(3):101707.
Foocharoen et al. *Rheumatology (Oxford)*. 2017;56(2):214-222.

GI Symptoms: Agents to Avoid

⇩ GI Movement

- Narcotic pain meds
- Tricyclic antidepressants
  - Amitriptyline/Nortriptyline
- Iron supplements
- Anti-Parkinson's meds
- Verapamil
- Anti-histamines
  - Diphenhydramine

⇧ GI Movement

- Laxatives
- Erythromycin
- Orlistat
- Muscle relaxants
- Risperidone
- Colchicine
- Magnesium

*** Not an all-inclusive list***

Renal Crisis

SCLERODERMA RENAL CRISIS PREVENTION

<< Please fill out this card and keep it with you. >>

- You have been identified as a person at risk of RENAL CRISIS, a preventable problem.
- Warning signs: New onset headaches, blurred vision, shortness of breath, confusion, abrupt elevation of blood pressure.
- Monitor your blood pressure and know and record your usual readings _____
- Call Dr. _____ if BP is greater than _____or seek urgent care.

Show any treating physician this card.

SCLERODERMA RENAL CRISIS: PREVENTION AND TREATMENT

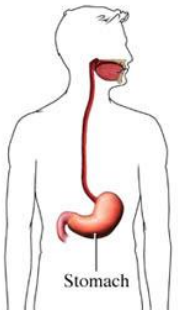
- This is a patient at risk of scleroderma renal crisis.
- If hypertensive or blood pressure is acutely increased, ACE INHIBITORS are the only drugs predictably effective at aborting renal crisis.
- If unable to administer orally, give I.V. enaprilat.
- Check creatinine as renal failure may occur abruptly.
- Please call this patient's rheumatologist,
  Dr. _____
  Phone # _____

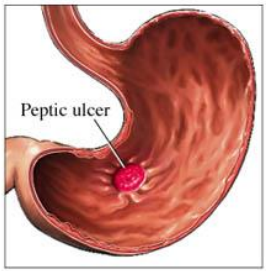
Shapiro et ak, Ann Rheum Dis 2015;74(Suppl 2):1136.

Immunosuppressants and Biologics

Corticosteroids

- Prednisone, methlyprednisone
- Route: PO, IV, pulse, pre-medication for infusions
- ADRs: immunosuppression, insomnia, psychiatric, glucose,
- Concerns in SSc
  - Esophageal concerns/ gastritis if used with NSAIDs
  - Risk for renal crisis
    - **Caution/Avoid if RNA- Polymerase 3 antibody**!!!!!
  - Added risk for osteoporosis





Steen VD, Medsger TA Jr. *Arthritis Rheum*. 1998; 41:1613.

Conventional DMARDs & Immunosuppressants in SSc

Drug	Use in SSc	ADRs	Monitoring/Counseling	Medication Errors
Methotrexate	Diffuse cutaneous Inflammatory arthritis Inflammatory myopathy	N/D, hepatotox, stomatitis, alopecia, SOB, myelosuppression (MYL)	CBC, Scr, LFTs q 4-8 weeks, signs of infection; pregnancy Concomitant use of folic acid, avoid alcohol, use of contraception	WEEKLY dosing, dose adjustments, drug interactions, lab monitoring
Mycophenolate mofetil (Cellcept) **Mycophenolic acid (Myfortic)**	Interstitial lung disease Diffuse cutaneous	GI (DIARRHEA), increased risk of infection, headache, elevated liver enzymes, peripheral edema, leukopenia, thrombocytopenia	CBC, serum electrolytes, liver enzymes, kidney function; drug interactions; **REMS (pregnancy)**	**REMS**, do not crush, PPI interactions
Azathioprine (Imuran)	Diffuse cutaneous Inflammatory myopathy	GI upset, myalgia, leukopenia, thrombocytopenia, risk of infection, elevated hepatic enzymes, alkaline phosphatase and bilirubin	Signs of bleeding, sx of jaundice, change in color of stool; TPMT deficiency, drug interactions	Community high-alert med, error prone abbreviations (AZT for zidovdine), dose reductions
Cyclophosphamide (Cytoxan)	Interstitial lung disease Diffuse cutaneous Inflammatory myopathy	Hair loss, GI upset, decreased appetite, stomatitis, amenorrhea, myalgia, nail discoloration, interstitial cystitis, infertility, oligospermia/azoospermia, Stevens-Johnson syndrome, increased risk of bladder cancer	CBC, urinalysis (monthly if on IV therapy)	Look-alike/sound alike-cyclosporine, community high-alert med; do not crush list, error prone abbreviations

https://www.ismp.org.

Biologics Used in SSc

Drug	Use in SSc	ADRs	Monitoring
Abatacept *T-cell Costimulation Modulator*	Inflammatory arthritis	Injec.site rxn, HA, dizziness, cough, nasopharyngitis	Screen for TB, Signs of infection, respiratory w/ COPD pts. **infection risk clinically lower than other biologics
Rituximab *B-cell Modulator*	Interstitial lung disease Diffuse cutaneous Inflammatory myopathy	Infusion rxn (rash, N, SOB, urticaria, HA, fever, chills) Methylpred 100mg 30 min prior & diphenhydramine	Signs of infection, post infusion rxn, Progressive multifocal leukoencephalopathy (PML)- neurology s/sx
Tocilizumab *IL-6 inhibitor*	Interstitial lung disease Diffuse cutaneous	Infus. rxn, ↑ risk of infection, anemias, ↑ lipids/ liver enzymes, GI sx	↑ risk of infection ANC, LFTs, platelets, lipids, GI symptoms; **drug intx**

N/V/D=nausea, vomiting, diarrhea; HA=headache; TB=tuberculosis; ANC=absolute neutrophil count

Immunoglobulin Therapy
IVIG VS. SCIG Therapy

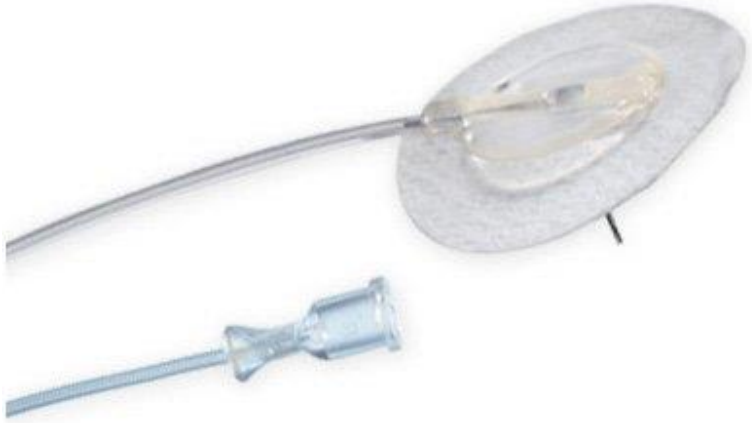
IVIG	SCIG

○ Administered via IV infusion
○ Administration typically every 3-4 weeks
  ○ Greater peak and lower trough concentrations → increased propensity of systemic AE's
○ Typical dosage is 1-2 g/kg administered over 1-5 days
○ Side Effects: headache, flushing, myalgias, fever, nausea, infusion reactions
○ Serious AE's: aseptic meningitis, clot, leukopenia serum sickness
○ Pretreat with APAP and diphenhydramine or hydrocortisone sodium succinate (Solu-Cortef) and by slowing the rate of infusion
○ Infusion started at 30 mL/hr and increased to a max of 250 mL/hr
	○ Administered via infusion under the skin, into the subcutaneous layer of the abdomen, thighs or outer buttocks at one or multiple sites, depending on the volume being infused
	○ Administered more frequently (biweekly, weekly or daily)
	  ○ Steady state concentrations with fewer fluctuations in Ig plasma levels
	○ Typical starting dose is between 400 to 600 mg/kg/month
	○ Total monthly dosing is calculated by the prescriber then divided according to the interval between infusions
	○ SCIG vs fSCIG
	○ Fewer systemic AE's
	○ Most common side effect is injection site reactions

Immunoglobulin (IG) Replacement Therapy [Internet]. Towson (MD): Immune Deficiency Foundation; 2022

Considerations When Choosing a Route of Administration

	IVIG	SCIG (Conventional)
Frequency of Dosing	Every 3-4 weeks	From daily to every 14 days
IgG Level	Achieves initial high concentration that ↓ gradually over 21 days	No variation in IgG level once steady state is achieved
Access	Requires IV access (NOT a port)	Does not require IV access. Individual can do their therapy independently once trained
Needle Sticks	Usually, one	One to four, or more depending on dose/preference
Time of Infusion	Usually, 3 to 4 hours	Rapid (less than 30 minutes)
Ancillary People	Requires healthcare professional to establish IV access and monitor infusion	Individuals can do their own SCIG infusion once trained
Systemic Side Effects	Possible chills, BP changes, N&V, aches	Usually none
Pre-medication	Sometimes necessary	No
Local Side Effects	Not usually unless, IV infiltrates	Sometimes itching and burning
Post-infusion Side Effects	Systemic side effects possible	Redness and swelling
Cost	Cost for drug and nursing/infusion center	Cost for drugs and supplies



Pulmonary Manifestations in SSc and Therapies Used

Immunosuppressants

- Mycophenolate mofetil, cyclosphosphamide, rituximab, tocilizumab

Phosphodiesterase-5 Inhibitors:

- Sildenafil (Revatio), and tadalafil (Adcirca)

Prostacyclin Agonists:

- Epoprostenol (Flolan)
- Treprostinil (Remodulin)
- Iloprost (Ventavis)

Interstitial fibrosis

- Earlier manifestation

Pulmonary Arterial Hypertension (PAH)

- Late manifestation

- Endothelial Receptor Blockers:
  - Bosentan (Tracleer)
  - Ambrisentan (Letairis)
  - Macitentan (Opsumit)
- Soluble Guanylate Cyclase (sGC) Stimulator
  - Riociquat (Adempas)
- Anti-fibrotic
  - Nintedinib

Pulmonary Disease in SSc: How Do You Choose Therapy?

Drug	Type of SSc-ILD
Mycophenolate mofetil	All ILD
Cyclophosphamide	Rapidly progressive disease
Rituximab	Inflammatory disease with ILD, Overlap myositis or Sjogren's
Tocilizumab	Inflammatory disease with ILD
Nintedanib	Progressive ILD
Azathioprine	2nd line agent for patients with contraindications to other therapies and/or low intensity treatment

Drug Interactions

- Importance of a good medication history
  - Supplements, OTC's, infusions/injections
- Oftentimes dose-dependent
  - Ex: methotrexate and NSAIDs, antidepressants combinations
- May be able to manipulate schedule to avoid interaction
  - Spacing medications apart (ex: levothyroxine, omeprazole, mycophenolate mofetil)

SSc Disease State Monitoring

Modified Rodnan Skin Score (mRSS)

- 17 areas: 0 (no involvement) 3 (severe involvement).
  - Total possible score=51.
- Scores 15 -20 and rapid progression (1st year) = severe skin thickening.
- Does not measure extent of functional disability of patient

SHAQ-DI: HAQ-DI modified for patients with scleroderma

SSPRO: Systemic sclerosis patient reported outcome (skin-related)

DON'T FORGET:

- CXR/CT/PFT (ILD)
- Echo/RHC (PAH)
- GI work up (GERD/Hypomotility)
- Renal crisis- patient education!
- Eye exam (SRC)- cotton wool/papilledema/retinopathy

Early Diffuse Systemic Sclerosis Case Study

History

- 30-year-old white female presents with a 11-month history of general fatigue, bilateral hand stiffness, and swelling of fingers which has required her to remove her wedding ring. She also reports a 4-week history of bilateral ankle swelling and generalized itching of her chest, abdomen, and upper thighs. She reports bilateral pain in the hands and wrists along with heartburn, both worse at night, similar to when she was pregnant. Additionally, she experiences intermittent blanching of her fingers especially when she goes outside in the cold.

Physical Exam

- Afebrile, BP 140/90 mmHg
- Puffy hands and wrists with loss of skin creases; puffy skin around ankles; periungual redness; indurated, tight, and excoriated erythematous skin over chest and abdomen
- Mask-like facial features with reduced oral aperture
- mRSS score 19/51

Early Diffuse Systemic Sclerosis Case Study

- Puffy fingers, unable to fully extend fingers and elbows
- Nailfold capillary microscopy shows widened cuticles with capillary loop drop out with areas of hemorrhage
- Bilateral fine crepitations at lung base; normal S1 and S2 heart sounds with no murmurs

Laboratory Studies

- CBC: Hgb 10.5 g/dL; MCV 72 fL; creatine kinase slightly elevated; C-reactive protein 14 mg/L
- Urinalysis: 1+ protein; no blood
- ANA: positive (1:640) with specked pattern on staining
- Rheumatic factor negative

Early Diffuse Systemic Sclerosis Case Study

Imaging

- Soft tissue swelling around wrists; no joint erosions and normal joint spaces
- Normal lung and heart findings on Xray and echocardiogram

Pulmonary function test (PFT)

- Slight reduction in DLCO and FEV1/FVC ratio

Diagnosis

- Presence of proximal scleroderma, new-onset Raynaud's phenomenon, proximal skin involvement, facial findings, and positive ANA is suggestive of diffuse cutaneous systemic sclerosis

Early Diffuse Systemic Sclerosis Case Study

Treatment

- Education on her condition, advice on exercises and skin care; details of support groups
- Advice about regular blood pressure monitoring (3x a week) and monthly urinalysis
- Nifedipine 10 mg po bid for Raynaud's phenomenon
- Lansoprazole 15 mg po qd for heartburn and loratadine 10 mg po qd for urticaria

Follow Up Visit

- First follow up visit 6 weeks later
- MMF started (after pulm consult): 500 mg po bid x 5 days, increasing by 250 mg bid increments every 5 days until 1-1.5g po bid maintenance dose reached (ILD)
- Follow up visits: 3-monthly clinical evaluation; PFT as often a s q 6 mon; annual echocardiogram

Emerging Treatments

Inebilizumab: demonstrated improvement in skin thickness but not lung outcomes (phase I trial)

Dabigatran: demonstrated improvement in skin thickness but not lung outcomes (phase I trial)

Romilkimab: appeared to improve lung function, Raynaud's, pain, and quality of life (phase II trial)

Tofacitinib: demonstrated a trend towards skin and lung clinical improvement (phase I/II trial)

Lenabasum: significant improvement in CRISS scores compared to placebo (phase II)

Abatacept: clinically meaningful improvement in the mRSS was observed in both the abatacept and PBO groups when patients transitioned to abatacept (phase II)

Pirfenidone: Scleroderma Lung Study III where pirfenidone is used in combination with MMF

Campochiaro et al. *Arthritis Res Ther*. 2021;23(1):155.

Questions?

Additional References

Katsumoto TR, et al. The pathogenesis of systemic sclerosis. Annu Rev Pathol. 2011;6:509-37.

Hachulla E, et al; Collaborators. French recommendations for the management of systemic sclerosis. Orphanet J Rare Dis. 2021;16(Suppl 2):322.

Spierings J, et al. PASTUL questionnaire: a tool for self-assessment of scleroderma skin during the COVID-19 pandemic. Ann Rheum Dis. 2021:annrheumdis-2020-219775.

Campochiaro C, et al. An update on targeted therapies in systemic sclerosis based on a systematic review from the last 3years. Arthritis Res Ther. 2021 Jun 1;23(1):155.

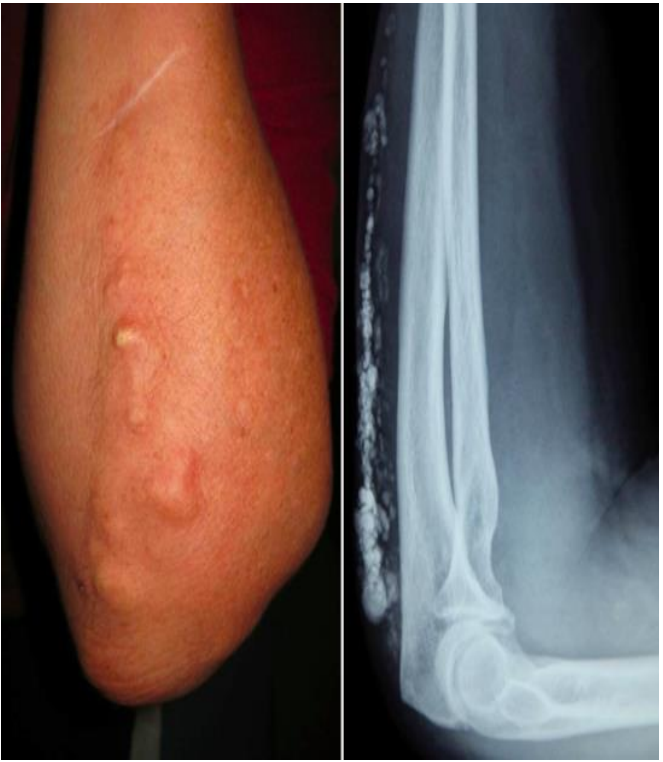
Zhu JL, et al. Emerging treatments for scleroderma/systemic sclerosis. Fac Rev. 2021 May 5;10:43.

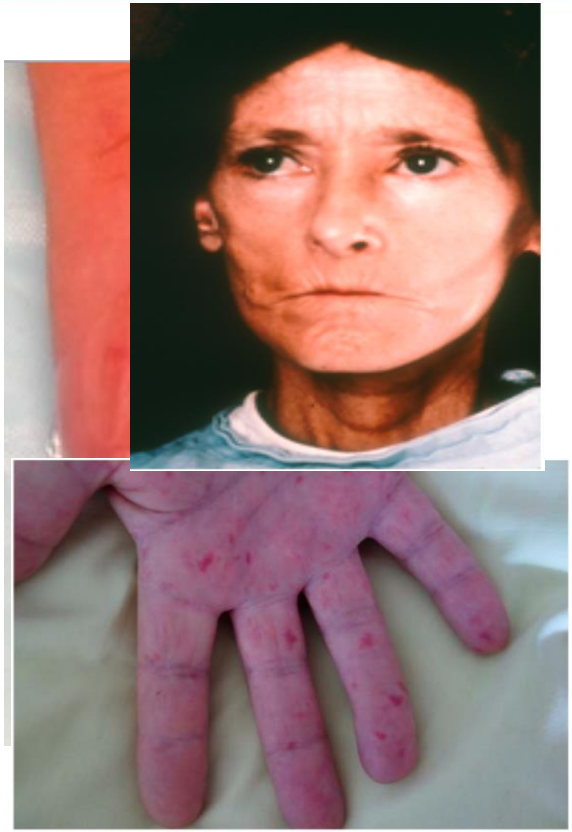
Varga, J. Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 18, 2023.)

Varga, J., Denton, C. P., & Wigley, F. M. (2012). Scleroderma. Springer Science & Business Media.

Extra Slides

Clinical Features to Remember





Scleroderma Overview

- Characterized by indurated skin.
    - Vascular and immune dysfunction → fibrosis
- Incidence in the US: ~ 20 cases/million population
- Black population have a higher incidence compared with other ethnicities
- Incidence ratio is 4-9 times greater in women than in men
- Affecting people 35-64 yo but other age ranges cases have been documented

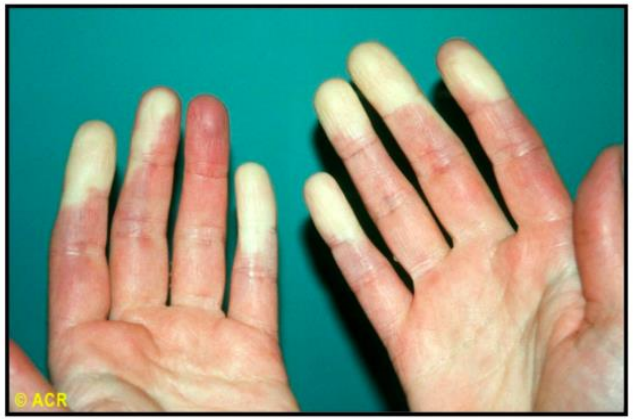
Incidence Ratio 4:1 greater

Americas & Europe > Asia

Early Clinical Features

- Raynaud's phenomenon
- Nail-fold capillary changes
- Diffuse edema of feet/hands

Pearl:
65% of patients with RP + abnormal capilaroscopy and/or specific antibodies develop SSc in 5 years



Autoantibody	Type of SSc	Manifestation
Anti-topoisomerase I (Scl-70)	dcSSc	Pulm, digital ulcers
Anti-RNA polymerase III	dcSSc	Renal crisis/?neoplastic
Anti-U3RNP (fibrillarin)	dcSSc	Less common
Anti-Th/To	lcSSc	Less common
Anti-U1-RNP	lcSSc	
Anti-PM-Scl	Overlap syndrome	
Anti-centromere	lcSSc	Pulm Fibrosis and PAH
Anti-hUBF (NOR 90)	lcSSc	

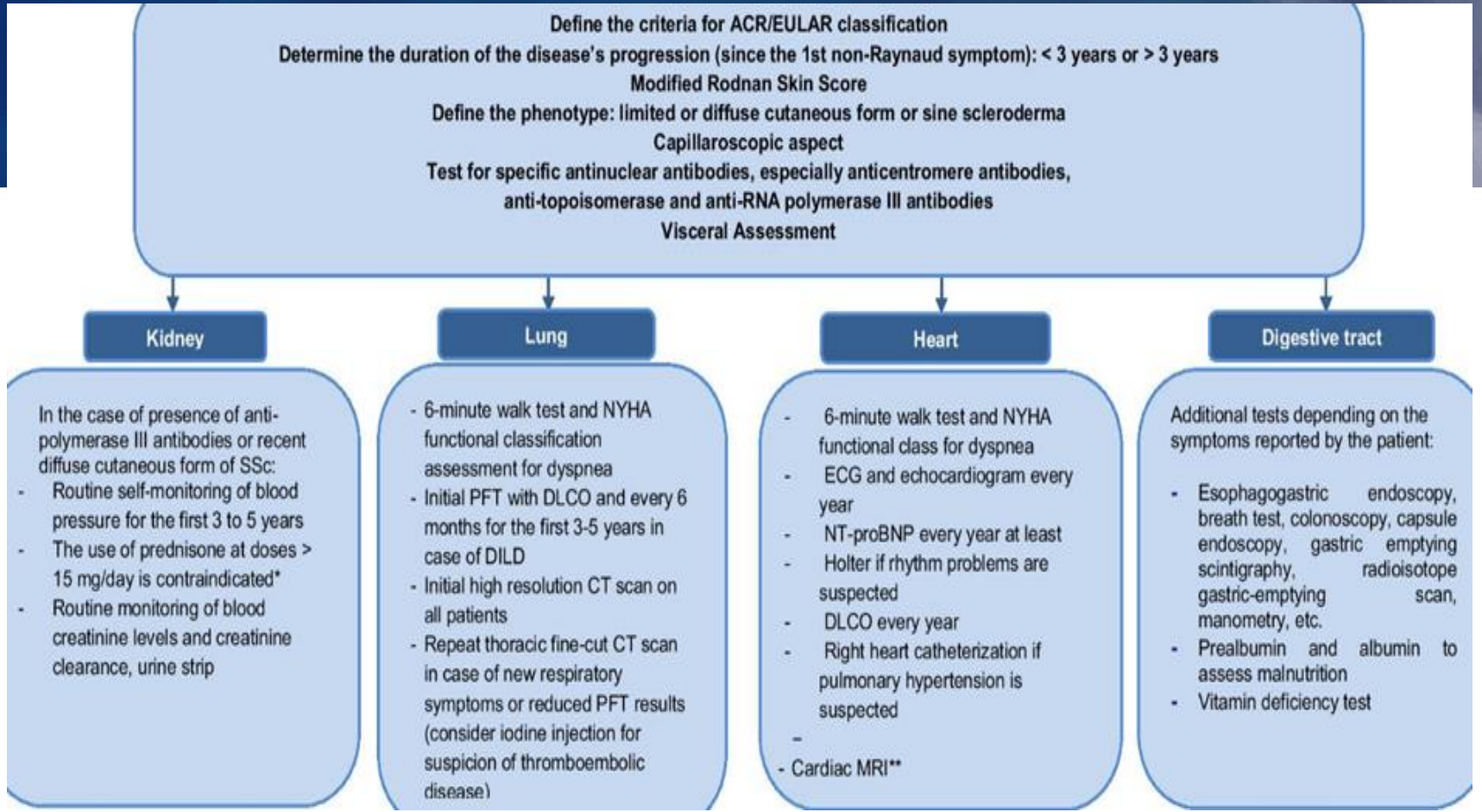
Sobolewski et al. *Reumatologia*. 2019;57(4):221-233.

Interstitial Lung Disease

- **<u>Baseline testing is very important</u>**
  - Thoracic HRCT
  - Complete PFTs (lung volume, spirometry, Dlco
  - Six minute walk test for oxygen desaturation
- HRCT – findings of **NSIP and UIP consistent with ILD in SSc**
  - Lung biopsy is not indicated
  - > 20 % lung involvement = poor prognosis (5 year survival 60%)
- Serial FVC and Dlco quantify respiratory impairment and provide information about coexistent PAH
- **Progressive** disease by PFT:
  - **Decline > 10 % predicted FVC or > 15 % predicted DLco**
  - FVC < 70% = poor prognosis (5 year survical 60-65%)

Scleroderma Renal Crisis

- **IMPORTANT!** This is a medical emergency
  - If untreated, ESRD may occur within 1-2 months, high mortality within 1 year
- Occurs in 5-20% of diffuse cutaneous SSc
- Onset most always within 5 years of the diagnosis
- 3 Major features
  - Abrupt onset of marked hypertension
  - Acute onset renal failure, usually in absence of prior renal disease
  - Urinalysis typically normal or reveals only mild proteinuria
- Risk Factors
  - + RNA Polymerase Ab
  - extensive skin involvement, tendon/friction rubs present



Recent dcSSc greater risk of renal crisis and severe pulm fibrosis.

Hachulla, E., Agard, C., Allanore, Y. *et al.* French recommendations for the management of systemic sclerosis. *Orphanet J Rare Dis* **16,** 322 (2021).

Treatment

Skin damage

- Short course corticosteroids and antihistamines
- DMARDs: CYC, MMF, methotrexate
- autologous hematopoietic stem cell transplantation (HSCT)

Renal crisis (5%)

- 1st ACE inhibitors (not prophylactically)
- 2nd CCB
- 3rd ARB
- Dialysis- 50-60%
  - ½ recover enough to come off

Peripheral vascular damage/Raynaud's

- 1st Line- CCBs
- angiotensin-receptor blockers
- antiadrenergic agents (prazosin)
- topical nitrates
- PDE5 inhibitors (sildenafil)
- PhospEndothelin-1 receptor antagonist
  - ex) Tracleer- (reduces risk of new ulcers)

Digestive damage

- Proton pump inhibitors/ H2 bloackers
- Motility agents: metoclopramide or erythromycin (early disease)
- Refractory-GI dysmotility: injectable octreotide

Treatment

Musculoskeletal damage

- Non-steroidal antiinflammatory drugs (NSAIDs)
- Corticosteroids (caution)
- Methotrexate
- Biologics for refractory arthritis
  (rituximab, abatacept, tocilizumab)

Interstitial Lung Disease (ILD)

- Immunosuppressants
  (MMF, cyclophosphamide, azathioprine)
- Corticosteroids
- Rituximab
- Tocilizumab (2021)
- Oxygen therapy
- Lung transplantation

Cardiovascular damage

- ACE/ARB blockers
- Calcium channel blockers
- Prostacyclin receptor agonists
- Heart transplant/heart–lung transplant

Pulmonary arterial hypertension

- Phosphodiesterase 5 inhibitors (Sildenafil)
- Prostacyclins (Iloprost)
- **Endothelin receptor antagonists (Tracleer)**

IG Mechanism of Action in Different Disease States

- Primary Humoral Immunodeficiency: Restores abnormally low IgG levels to the normal range and thus helping in preventing infections
- Autoimmune Thrombocytopenia: Fc portion of the IVIG binds the Fc receptor on reticuloendothelial cells blocking the removal of antibody coated cells
- Kawasaki's Disease: IVIG reduces the expression of adhesion molecules on endothelial cells, binds cytokines that cause inflammation, reduces the number of activated T cells and binds staphylococcal toxin superantigens
- Dermatomyositis and Polymyositis: The Fc portion of IVIG can bind to C3b and C4b, decreasing complement activation

West ST. Rheumatology secrets. 3rd ed

Immunoglobulin Therapy

- Ig replacement for people with primary and secondary immunodeficiencies that affect antibody production or patients receiving highly immunosuppressive therapies
  - Common Variable Immune Deficiency (CVID), X-linked Agammaglobulinemia (XLA), Kawasaki's disease, dermatomyositis, polymyositis, juvenile dermatomyositis and thrombocytopenia in SLE patient's
  - **SSc relevant: Hypogammaglobinemia, Sjogren's syndrome, myositis, polyneuropathy**
- Prepared from a pool of immunoglobulins from the plasma of thousands of healthy donors
  - Generally, about 15,000 donors
  - FDA mandates a minimum of 1,000 donors
- Given intravenously (IVIG) or subcutaneously (SCIG)

Immunoglobulin (IG) Replacement Therapy [Internet]. Towson (MD): Immune Deficiency Foundation; 2022
Ness ST. Intravenous and subcutaneous immunoglobulin treatment options. AJMC. 2019 Jun 28;25(6)

Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease

Slower rate of decline in lung function over 1 year versus placebo

Sensitivity analyses failed to show a significant difference, though there was still a trend towards better outcomes with nintedanib

Does NOT seem to affect skin involvement or other disease manifestations

Role in therapy is emerging; may be best to reserve for patients failing Cellcept until more data are available

- 48.8% of patients were on mycophenolate mofetil at baseline

Most common adverse effects were diarrhea (occurring in 75.7% of patients in this clinical trial)

Other adverse events included nausea, vomiting, fatigue, and weight loss

No major difference in serious ADEs was observed

Distler O et al. *N Engl J Med*. 2019;380(26):2518-28.