

Scleroderma, an overview

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Assistant Professor

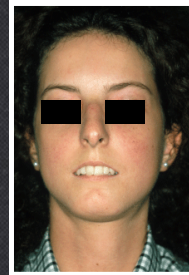
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Learning objectives

- Define scleroderma
- Describe the epidemiology and pathophysiology of systemic sclerosis (SSc)
- Antibodies
- Understand the typical disease presentation ,clinical findings, and complications of SSc
- Differences between limited cutaneous disease (lcSSc) and diffuse cutaneous disease (dcSSc)
- Outline the approach to treating and monitoring patients with SSc, focusing on pulmonary complications

So what is scleroderma?

- The word “scleroderma” comes from two Greek words:
 - “**sclero**” meaning hard
 - “**derma**” meaning skin
- The disease has been called “progressive systemic sclerosis”
- Cause is unknown
- No cure



History

- Cases of skin disease similar to scleroderma may be found in the writings of Hippocrates as far back as 460–370 B.C
- Hippocrates recorded patients in whom “the skin is stretched, and parched and hard, the disease terminates without sweat.”
- He treated a patient from Athens whose skin was so hard that “it was not possible to raise it in folds.”

So what is scleroderma?

- Scleroderma is classified as an autoimmune disease
- In an autoimmune disease, the immune system mistakes a person's own tissues as foreign invaders and sets up a protective attack that backfires to cause problems
- Chronic, rheumatic disease that affects the body by **hardening connective tissue**
- In scleroderma, cells start making collagen as if there were an injury that needs repairing. The cells do not turn off as they should and end up making too much collagen. The **extra collagen in the tissues** can prevent the organs from functioning normally

Pathology

- Disease process in scleroderma involves three primary features:
 - **1.an overproduction of collagen**
 - **2.an autoimmune process**
 - **3.blood vessel damage**

Epidemiology

- 3-24 per 100,000 population
- About 75,000 to 100,000 people in the U.S. have this disease
- Females > Males (most are women between 30 and 50)
- African-Americans have earlier onset and more severe disease
- Appears to be higher in North America and Australia as compared to Europe and Japan

Genetic?

- The genetic basis remains unclear
- In rare cases systemic sclerosis runs in families
- **Choctaw Native American ancestry** is a risk factor (prevalence reported as high as 659 cases/million)
- HLA haplotype identified

Environmental

- Infection, especially Viruses
- Noninfectious environmental factors
 - silica dust
 - silicone exposure?

SSc like disorder:

L-tryptophan:

Eosinophilia Myalgia syndrome

Environmental

- Vinyl chloride
- Epoxy resins
- Petroleum based products
- Contaminated rapeseed oil
- L-Tryptophan
- Drugs
 - Bleomycin

Antibodies in scleroderma

- **ANA**-found in 95% of patients with scleroderma. Typically of nucleolar, homogenous, or anticentromere pattern
- **Anti Scl70(antitopoisomerase-1)** -99% specific and sensitivity varies between 20-40%(pts usually have diffuse cutaneous involvement, pulmonary fibrosis, cardiac involvement, PVD)
- **Anticentromere** (more common with limited scleroderma-CREST, has a higher association with digital ischemic loss), also pulmonary htn

Antibodies

- **Anti RNA Polymerase3**-Renal crisis, diffuse cutaneous involvement
- **Anti U3RNP(antifibrillarin)**-95% specific for diffuse cutaneous involvement. African Americans. Low sensitivity limits their utility
- **Anti U1RNP**-Found in MCTD commonly, common in raynauds, pulmonary fibrosis
- **Anti TH/TO**- Typically indicates limited cutaneous involvement
- **Anti Polymyositis/Scl**-Diffuse or limited. Myositis. Calcinosis.

We can order the scleroderma antibody panel in IHIS. Its not a miscellaneous send out order. Goes to quest lab I believe.

The panel includes RNAP3, ACA, TH/TO, U1and U3 RNP, also PM/Scl.

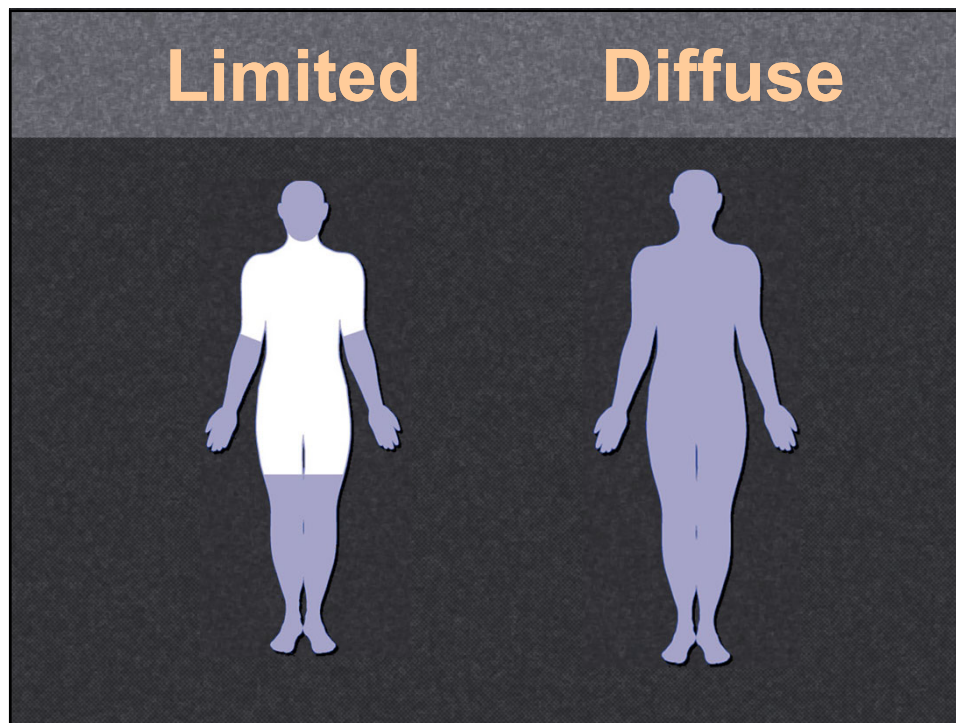
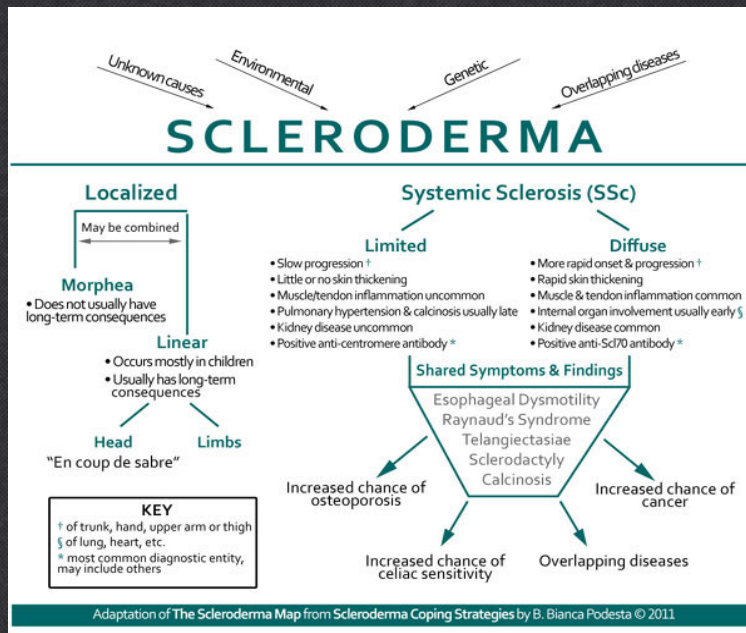
2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)*

Item	Sub-items(s)	Weight/score [†]
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (<i>sufficient criterion</i>)	-	9
Skin thickening of the fingers (<i>only count the higher score</i>)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (<i>only count the higher score</i>)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (<i>maximum score is 2</i>)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) (<i>maximum score is 3</i>)	Anticentromere 3 Anti-topoisomerase I Anti-RNA polymerase III	3

* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

[†] The total score is determined by adding the maximum weight (score) in each category.
Patients with a total score of ≥ 9 are classified as having definite scleroderma.

Clinical manifestations and treatment



Clinical signs and symptoms

- Skin
- Joints
- Gastrointestinal
- Renal
- Pulmonary
- Cardiac

Symptoms

- **Fatigue**(in 75% of patients)
- **Joints**-can swell and become painful and stiff
- **Worst in hands.Sclerodactyly. Acroosteolysis**
- **Muscles**-can become weak, and tendons can become abnormally thick, causing pain and limited joint motion
- **In diffuse cutaneous systemic sclerosis, tendon inflammation can result in an audible sound upon movement of involved structures (most commonly the fingers and wrists) known as a tendon friction rub. This finding is a marker of aggressive disease and puts patients at higher risk of serious organ involvement**

General measures

- **Fatigue-**
- Eat small, frequent meals to provide continuous energy
- Increase fluid intake
- Participate in 30-60 minutes of moderate daily exercise such as walking, bike riding, pool exercise, pilates, yoga, or tai chi
- Sleep for 7-8 hours each night
- If iron levels are low, which is typical of someone with chronic disease, discuss additional iron supplementation

- **Gastric antral vascular ectasia(watermelon stomach)**
- Treatment-
- Blood transfusion and iron supplementation
- More recent reports have suggested that endoscopic laser ablation can be effective in as many as 75% of cases
- APC(argon plasma coagulation)

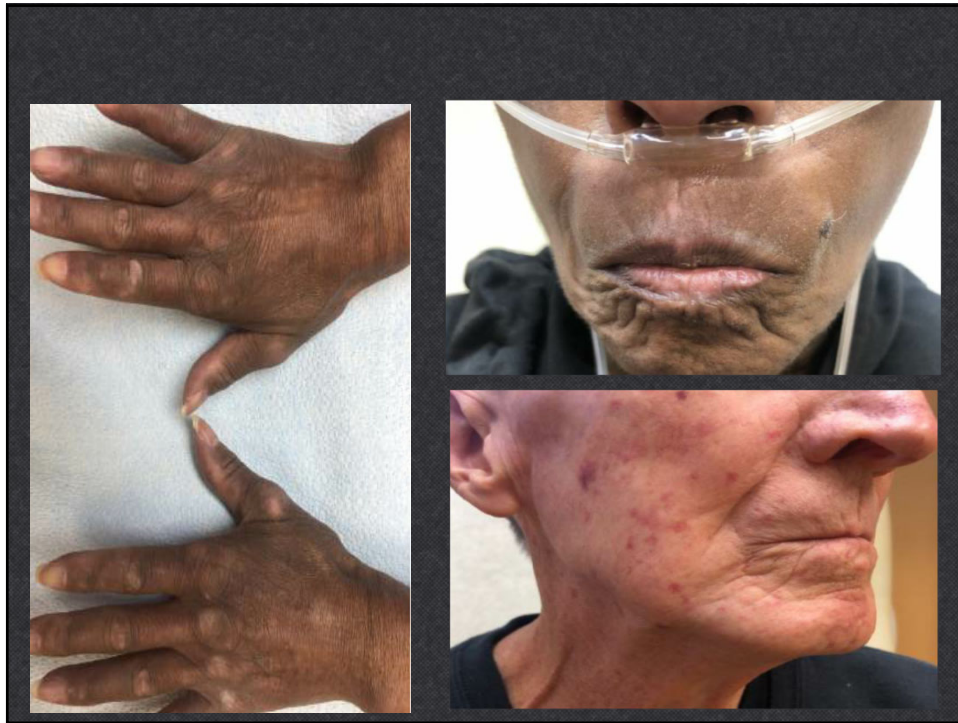
Treatment

- **Arthralgias/joint pains**

- Nsaid
- Tylenol
- Low dose glucocorticoids for a few weeks
- Plaquenil
- Methotrexate
- Physical therapy

Skin

- Skin ulcers
- Skin thickening
- Loss of hair
- Abnormal skin dryness, including vaginal dryness
- Calcium deposits in the skin (subcutaneous calcinosis)*
- Small red spots caused by localized swelling of tiny blood vessels (telangiectasias)
- Pruritis



Treatment

- **Tight skin-**
- **General measures-**

Eat foods rich in vitamin E such as nuts, seeds, wheat germ, and canola, olive, and peanut oils; consider taking 5 mg (5000 mcg) biotin supplement, which may help skin and nails

Treatment

- **Skin Fibrosis-**
 - D-penicillamine
 - Methotrexate
 - Mycophenolate mofetil
 - Cyclophosphamide
 - Tocilizumab
 - Allogeneic bone marrow transplantation
 - UVA Phototherapy
 - (Nitroglycerin ointment, also dovonex)

Treatment

- **Pruritis-**
 - Antihistamines
 - Lubricating creams
 - Low dose oral steroids
- **Calcinosis-**
 - Coumadin
 - Colchicine
 - Bisphosphonates
 - Diltiazem
 - Minocycline
 - Aluminum hydroxide
 - Surgical excision
- **Telengectasias**
 - ?

Digital ulcers

- Digital ulcers (DUs) are a major clinical problem in patients with **limited or diffuse SSc, occurring in 30 and 58 percent of patients, respectively.**
- DUs are considered a marker for disease severity.
- DUs can appear on the fingers or toes and are located usually on the tips or the finger creases and they are secondary to ischemic tissue injury.
- Disability

Treatment

- **Digital ulcers-**
 - Local wound care
 - Pain relief
 - Sympathectomy
 - Botulin toxin
 - Calcium channel blockers
 - Prostacyclin analogues
 - PDE5 inhibitors
 - Endothelin receptor antagonists

Digestive system

- Small oral aperture(microstomia)
- Heartburn
- Dysphagia
- Bloating
- Constipation
- Lower abdominal pain
- Malabsorption

Treatment

- **Oral manifestations**
 - Supportive
 - Tight skin treated with facial exercises
 - Dental hygiene
 - Artificial saliva
 - Mucosal advancement

- **Heartburn**
 - Establishment of normal weight
 - Elevation of the head of the bed
 - Multiple small meals
 - Avoidance of supine position within 3 hours of eating
 - Cessation of smoking and reduction of alcohol intake
 - Antisecretory agents(H-2 blockers and PPIs)
- **Malabsorption**
 - Antibiotics

- **Decreased GI motility/constipation**
- Prokinetic agents
 - metoclopramide
 - cisapride
 - erythromycin

Exercise, such as walking, helps move food through the digestive tract

Eat a high fiber diet with 100% whole grains, fruits and vegetables

Take a daily probiotic supplement or eat yogurt with active cultures

Increase fluid intake

Fecal incontinence can be evaluated with anorectal manometry to see if biofeedback therapy is warranted

Scleroderma renal crisis

- Abruptly developing severe hypertension
- Rise in SBP by > 30 mmHg, DBP by > 20 mm Hg
- **One of the following:** Inc. serum creatinine by 50%, Hematuria, Thrombocytopenia < 100
- Can cause headache, encephalopathy, seizures, LV failure
- 90% with blood pressure > 150/90
- Can occur also with lower blood pressures < 140/90

Risk factors and treatment

- Rapidly progressive skin thickening within the first 2-3 years
- Steroid use (prednisone > 15 mg)
- Anti-polymerase III Ab
- Pericardial Effusion
- **Treatment**
- Medical Emergency: generally with admission
- Initiation of ACE inhibitors; lifelong treatment with ACE inhibitors*
- Dose escalation of captopril

* Prior to ACEI- >90% mortality within a year
After ACEI- >60% after 10 years

Lung

- Usually the most serious complications of systemic scleroderma
 - ILD
 - Pulmonary hypertension
 - Pleural disease
 - Neoplasm
 - Aspiration pneumonia
- **Pulmonary htn** the leading cause of death
- PAH is responsible for almost 30% of SSc related deaths

Physical exam

- Whereas exertional dyspnea and fatigue can be suggestive of pulmonary hypertension, dry cough is mostly seen in conjunction with interstitial changes in the lungs.
- Dry “velcro” crackles at lung bases is a common physical exam finding.
- Clubbing can be seen in patients with long standing hypoxia.

ILD

- Can be silent
- Dyspnea
- Chronic cough
- Fatigue
- The 5-year mortality for patients with systemic sclerosis and ILD have a survival of 82-90% in 5 years
- Prospective studies of lung biopsies in patients with ILD-scl suggest that the pathological pattern was more frequently **NSIP than UIP**
- **NSIP** typically manifests on CT scan as ground-glass opacity (GGO) i.e, increased lung attenuation in the absence of architectural distortion.
- **UIP** is associated with reticular opacities and honeycomb cystic fibrosis on HRCT scan

Investigations

- HRCT
- Pulmonary function tests
- **FVC and DLCO (Greater than 10% change in FVc in 6 months is consistent with progression of ILD**
- **Forced vital capacity (FVC) or total lung volume (TLC) less than 80% of predicted suggest restrictive lung disease pattern. Combination of reduced DLCO and reduced lung volumes suggest ILD.**
- **An isolated reduction in DLCO with normal lung volumes can be seen in early asymptomatic disease or in pulmonary hypertension. Similarly, a FVC/DLCO ratio of 1.6 or greater suggests pulmonary hypertension.**
- Lung biopsy(not used widely, histology of little prognostic value, 75-80% NSIP)
- BAL
- 6 MWT

- Pulmonary disease can even occur in SSc with no skin involvement (an entity known as scleroderma sine scleroderma).
- These patients can be misclassified as having idiopathic ILD and the presence of telangiectasias, Raynaud's phenomenon, reflux, a nucleolar-antinuclear antibody test should alert the clinician to the possibility of scleroderma sine scleroderma

Pulmonary htn

- The prevalence of pulmonary arterial hypertension (PAH) is around 10%
- PAH survival is still poor with a median survival time of 3 years
- SSc-PAH patients are most often less responsive than patients with idiopathic PAH
- The definition of PH is a mean pulmonary artery pressure ≥ 25 mmHg.
- PAH is diagnosed if PAWP is ≤ 15 mmHg and pulmonary vascular resistance is >3 Wood units (WU) in the absence of another cause of pre-capillary PH, such as chronic thromboembolic PH (CTEPH) or PH due to chronic lung disease

Screening for PAH

- All patients with SSc should be screened for PAH
- Initial evaluation in pts with SSc and scleroderma spectrum disorders-
- Screening PFTs(spirometry with lung volumes) with DLCO
- Transthoracic echocardiogram
- Measurement of N-terminal (NT-proBNP)
- TTE should be performed annually on all patients with SSc.
- PFTS recommended every 4-6 months.
- The full screening panel should be performed as soon as any new signs or symptoms are present.

Treatment

- ▶ Interstitial Lung Disease with active inflammation-
- ▶ Mycophenolate
- ▶ Azathioprine
- ▶ Cyclophosphamide
- ▶ Steroids
- ▶ Tocilizumab
- ▶ Rituxamab
- ▶ Pulmonary Hypertension-
- ▶ Vasodilators:
- ▶ Endothelin receptor antagonists-bosentan
- ▶ Phosphodiesterase 5 inhibitors-sildenafil
- ▶ Prostacyclin analogues-epoprostenol, iloprost
- ▶ Lung Heart Transplant

Take home points

- Scleroderma is a heterogeneous condition, and requires a multidisciplinary approach
- GI, skin, lung tend to be most commonly and severely affected organs
- Delineating between limited and diffuse subsets of scleroderma is important, and made primarily on extent of skin involvement rather than pattern/extent of organ involvement
- Screening for pulmonary htn as well as ILD is of paramount importance
- Scleroderma, regardless of which organ is involved, is wholly treatable

**Should every patient
be treated with
medications?**

Scleroderma prognosis

Vascular Complications of Scleroderma

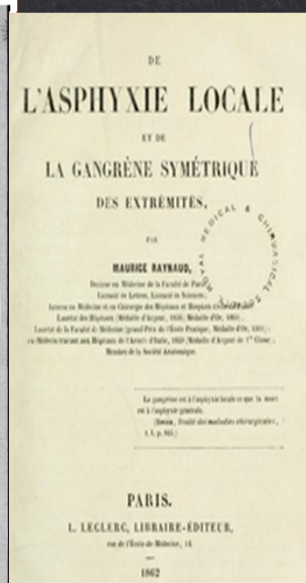
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Maurice Raynaud

1862

“De l’asphyxie locale
et de la gangrene
symétrique des
extrémités”

25 cases: one with
scleroderma



What happens in Raynaud phenomenon with Scleroderma?

Reversible vasospasm



**Digital artery fibrosis
with in-situ thrombosis**

“Vasculopathy”

Severity of Raynaud phenomenon

1. No Raynaud phenomenon
2. Raynaud phenomenon without skin lesions
3. Digital pits
4. Active digital ischemic ulceration(s)
5. Dry gangrene
6. Amputation



Raynaud phenomenon and its complications are universal features of Scleroderma affecting > 95% of patients!



Raynaud Phenomenon: Clinical Features

Only a *minority* of patients display the classic *triphasic* color change!

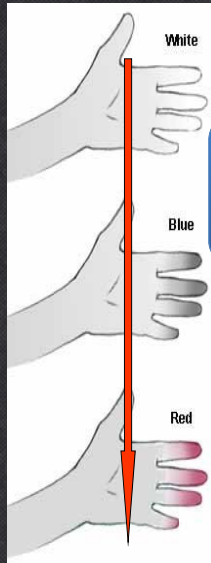


Figure 1. The usual stages of an attack of Raynaud's phenomenon. It is often accompanied by pain and tingling.



Raynaud phenomenon: Digital pits



**HARD
SKIN**

Scleroderma Digital Ulcers

- Occur in roughly **1 in 2** patients with scleroderma
- Can occur at tips of digits, over the to fingers, or over fingers creases
- Sometimes complicate calcinosis
- *Painful* and heal slowly
- Complications :
 - Functional disability and immobility
 - Scarring and loss of distal tissue (ie, fingertip)
 - Infection (skin and osteomyelitis)
 - Can progress to gangrene



Scleroderma Digital Ulcers

Risk Factors

- Male sex
- Presence of pulmonary arterial hypertension
- Severe involvement of the esophagus
- Diffuse skin involvement (only when PAH present)
- Young age at onset of RP
- Elevated sedimentation rate

Scleroderma Digital Ulcers

Multiple causes:

- Vasospasm (Raynaud's)
- Vasculopathy
- Calcinosis
- Repeated trauma
- Tight skin overlying joints



Fingertips (most common)



Extensor Digital Ulcerations



Calcinosis



Dry gangrene

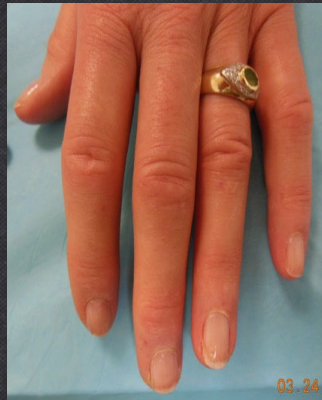


Amputations



Additional Cutaneous Manifestations of Scleroderma

Telangiectasias



“Salt & Pepper” Appearance



Livedo Reticularis



Source: S. M. Dean, B. Sabiani, W. T. Abraham: Color Atlas and Synopsis of Vascular Diseases
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Diagnosis of Raynaud Phenomenon

What about
“Cold Immersion”
Testing?



Diagnosis of Raynaud Phenomenon

“It is not necessary to perform a provocative test [immersion of the patient’s hand in ice water] to make a definitive diagnosis”

The diagnosis of Raynaud Phenomenon is a **clinical diagnosis** and **should not be made** on the basis of a non invasive vascular laboratory test!

*Wigley F. NEJM 2002;347:1001-1008

Cold Stimulation Test

Do not let your
doctor dunk
your hands in
ice water to
test for
Raynaud's!
*It is painful,
unnecessary
and possibly
even
dangerous!*

**Acute
ischemic
crisis**



**Sclero.org*

Treatment

Management principles can be considered
in three groups including :

- 1) **Nonpharmacological** behavioral Rx
- 2) **Pharmacological** treatment, and
- 3) **Interventional** - surgical
procedures.

Non pharmacological Treatment

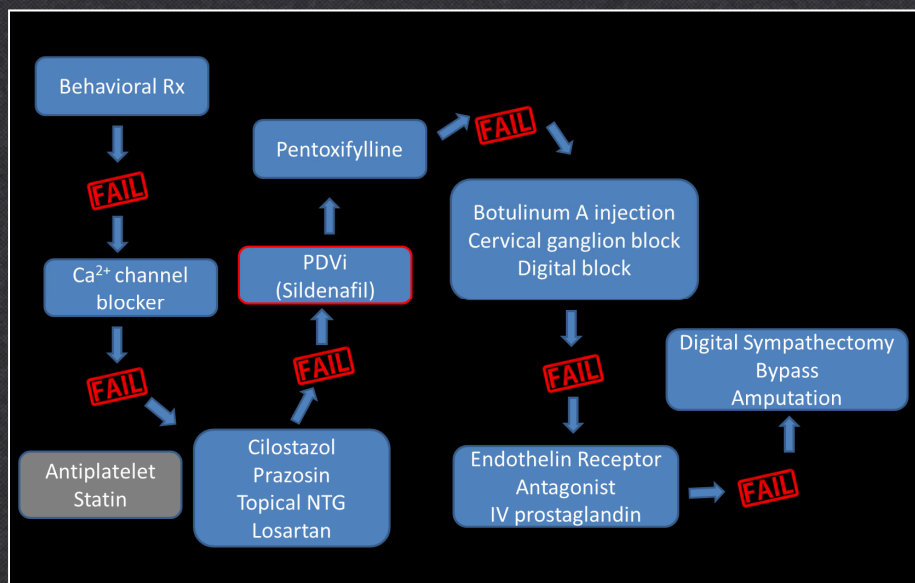
- Keep whole body warm
 - NOT just hands and feet
- Keep gloves everywhere
 - Kitchen
 - Car
 - Work
- Extra layers of clothing
 - Air conditioning can trigger
- Space heater
- Car warmed up



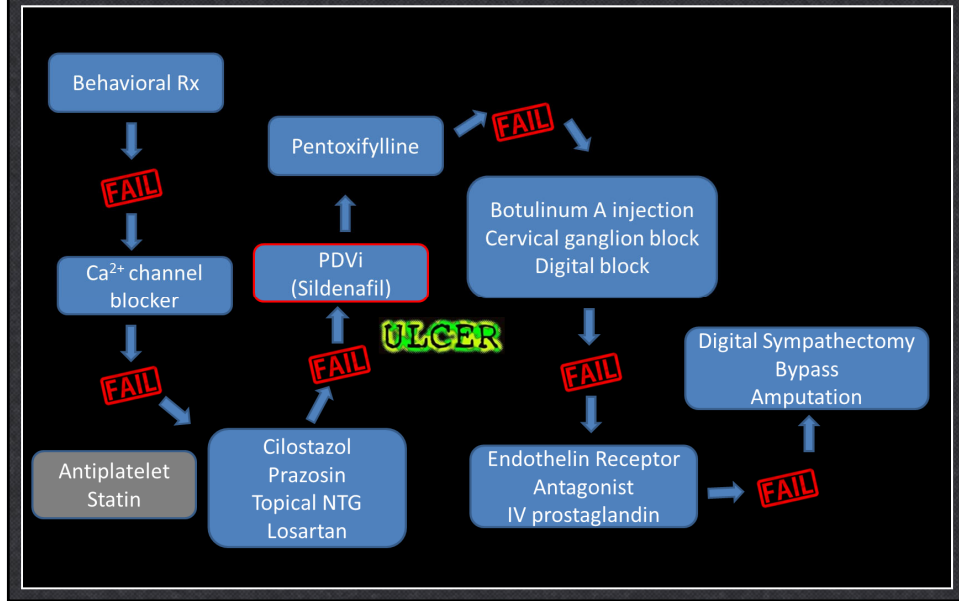
Beta-Blockers



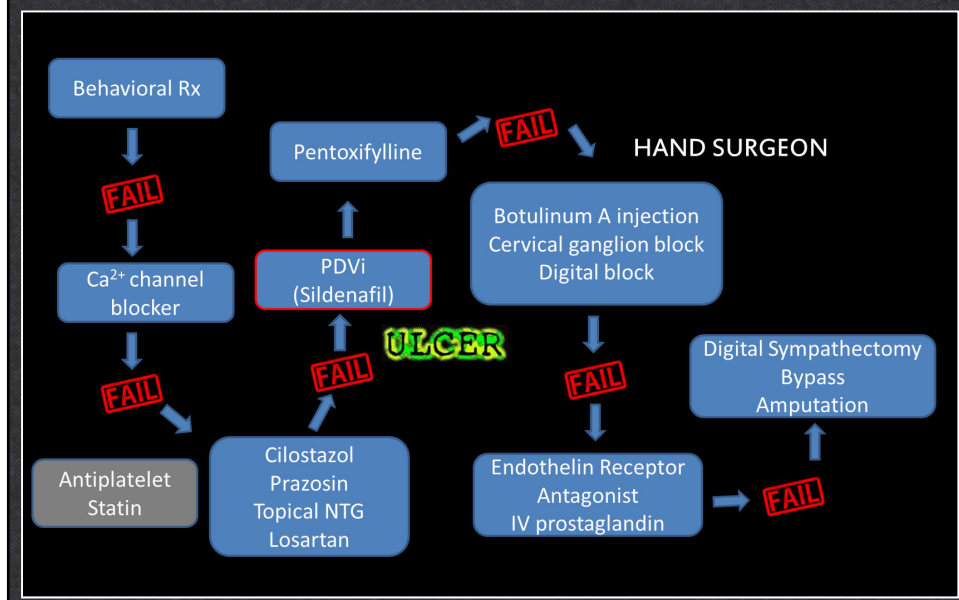
Treatment Pathway for RP in Scleroderma



Treatment Pathway for RP in Scleroderma



Treatment Pathway for RP in Scleroderma



Lipodermatosclerosis

- Fat & skin inflammation with fibrosis (scarring) – usually seen with CVI yet also complicates autoimmune diseases (especially **scleroderma**)
- Cause in scleroderma is unknown
- “Bound down” skin
- Isolated or diffuse (calf)



That's all Folks!