

# Scleroderma, an overview

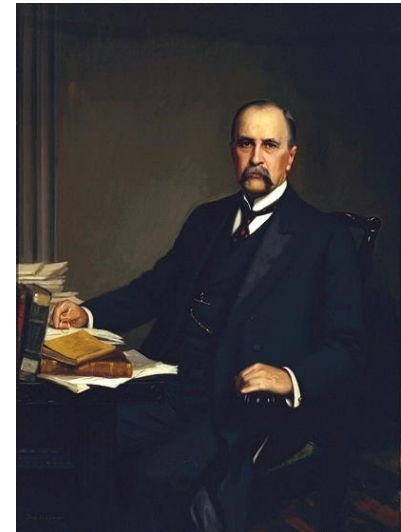
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# History

- ▶ 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.“



- ▶ Sir William Osler (1849 - 19 19) noted:
- ▶ In its more aggravated forms diffuse scleroderma is one of the most terrible of all human ills. Like Tithonus, to “wither slowly,” and like him to be “beaten down and marred and wasted” until one is literally a mummy, encased in an evershrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern



# So what is scleroderma?

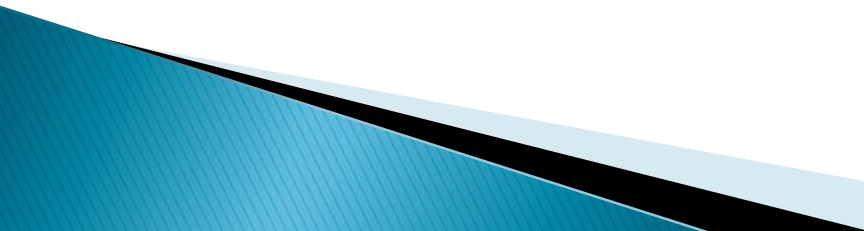
- ▶ The word “scleroderma” comes from two Greek words:
- ▶ “sclero” meaning hard
- ▶ “derma” meaning skin



- ▶ The disease has been called “progressive systemic sclerosis”
- ▶ Cause is unknown
- ▶ No cure



# 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 ?

- ▶ A genetic basis for the disease has been suggested
- ▶ The genetic basis, although intensely studied, remains unclear and there are no definitive genome-wide association studies published
- ▶ In rare cases systemic scleroderma runs in families
- ▶ **Choctaw Native American ancestry** is a risk factor (prevalence reported as high as 659 cases/million)
- ▶ HLA haplotype identified



# Environmental

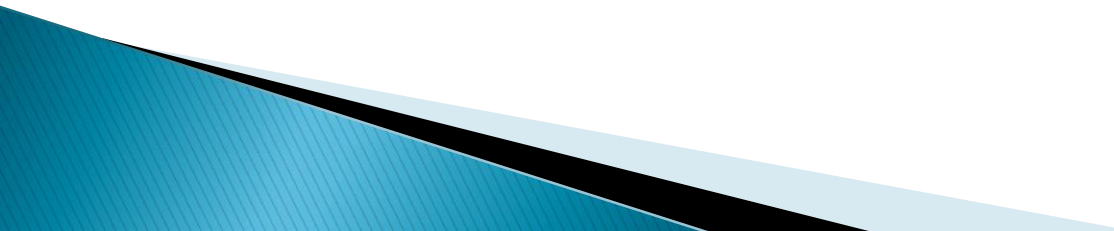
- ▶ Infection, especially Viruses
- ▶ Studies from Europe suggest that localized scleroderma (morphea) may be associated with *Borrelia burgdorferi* infection
- ▶ **Noninfectious environmental factors**
  - silica dust
  - silicone exposure?

# Environmental

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

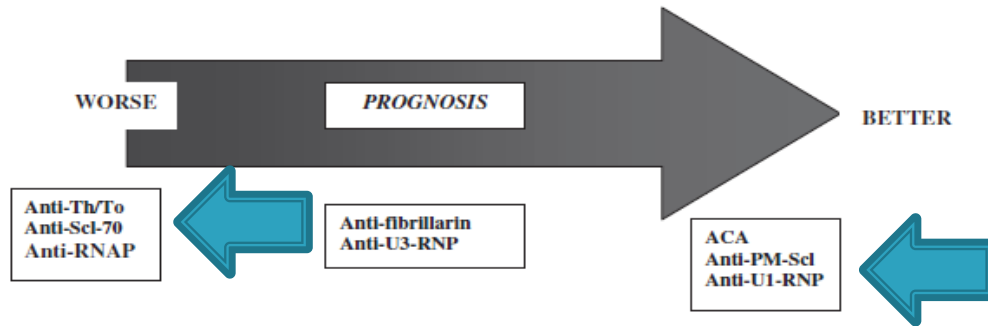


# Negative prognostic factors

- ▶ Older age of onset
  - ▶ Male sex
  - ▶ Scleroderma renal crisis
  - ▶ Pulmonary fibrosis
  - ▶ Pulmonary arterial hypertension
  - ▶ Cancer
  - ▶ **Antitopoisomerase antibodies**
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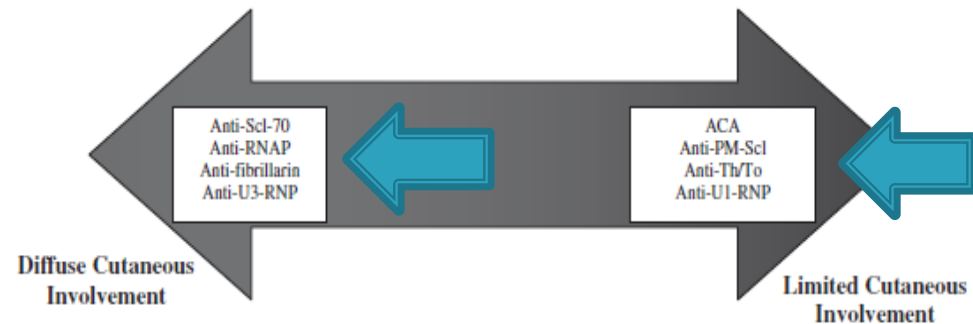
# Antibodies

Figure 1



Prognosis and systemic sclerosis-associated autoantibodies.

Figure 2



Skin involvement and autoantibody subset of systemic sclerosis.

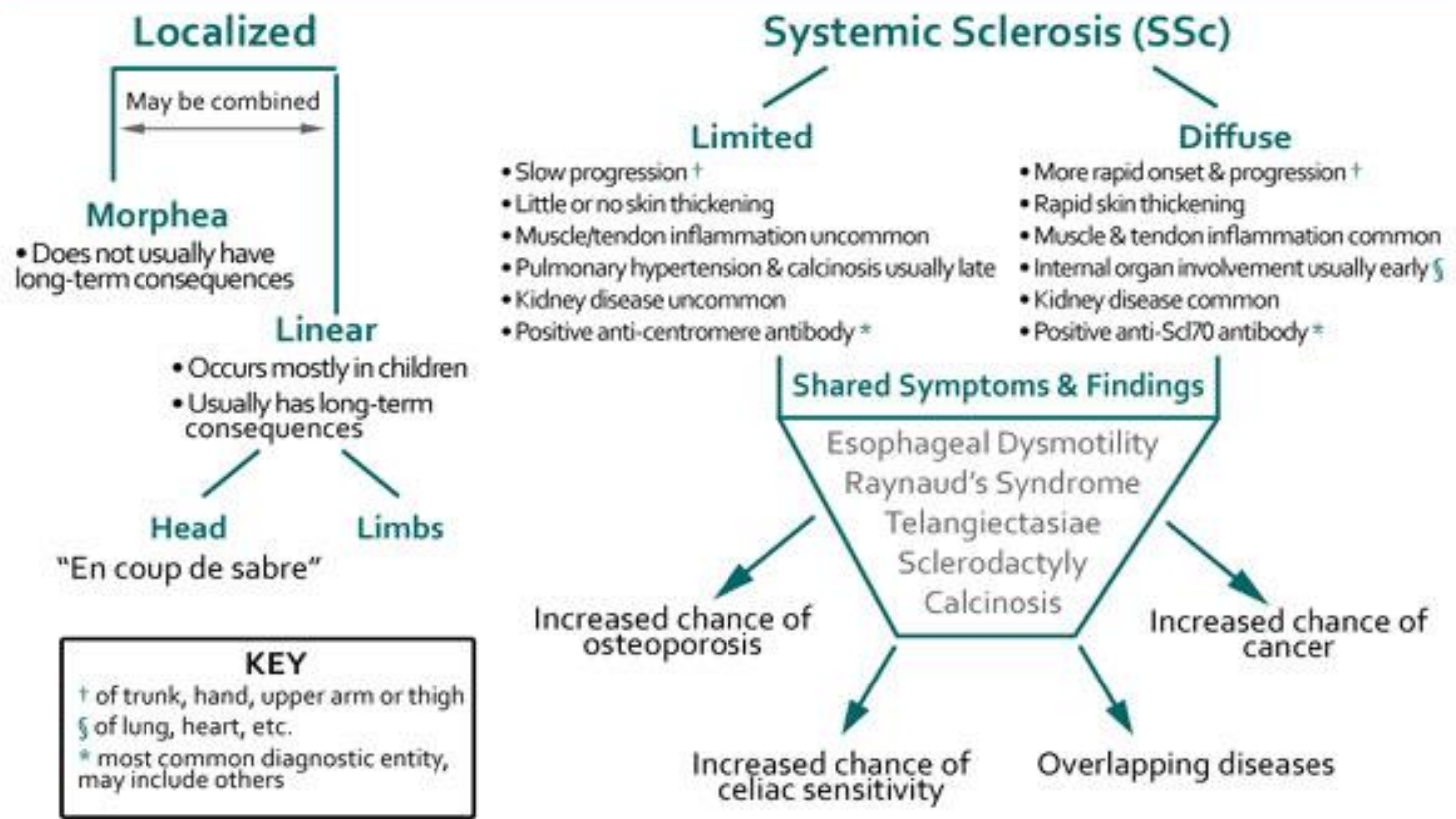
# SCLERODERMA

Unknown causes

Environmental

Genetic

Overlapping diseases



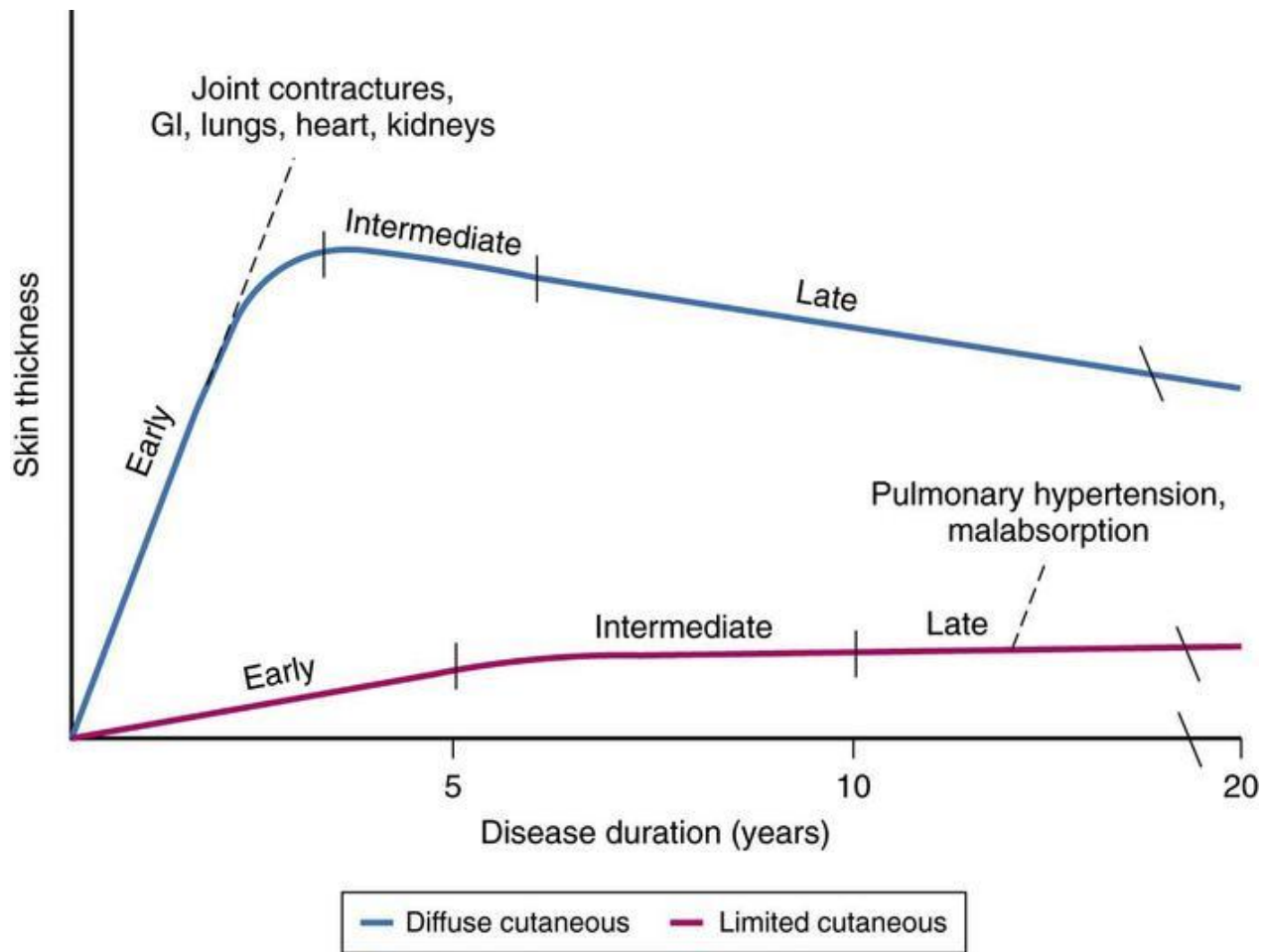
**Table 1. Organ involvement in diffuse versus limited scleroderma.**

Organ involvement	Diffuse	Limited
Interstitial lung disease	35–60% (severe in 15%)	35% (severe in 15%)
Pulmonary arterial hypertension	5–10%	10–15%
Renal crisis	12–15%	1–2%
Tendon friction rubs	65%	5%
Myopathy*	20%	10%
Esophageal dysmotility	75%	75%

\*Includes benign myopathy and inflammatory myositis.

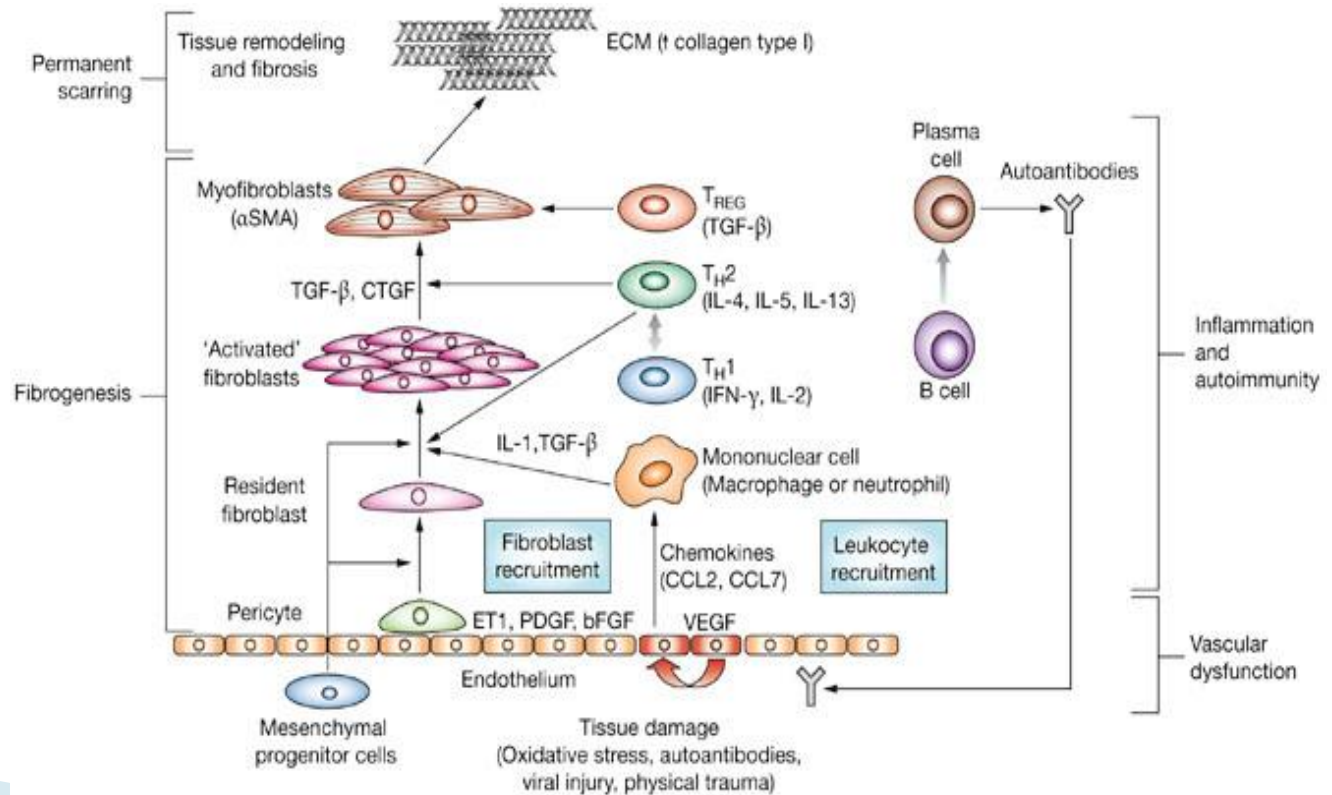
Image courtesy of Remedica Journals

<http://www.remedicajournals.com/International-Journal-of-Advances-in-Rheumatology/BrowseIssues/Volume-8-Issue-2/Article-Scleroderma-and-Fibrosing-Disorders>



# Pathology

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



# Clinical manifestations and treatment





## Clinical manifestations of scleroderma

- A, Generalized morphea
- B, Diffuse edema of hands
- C, Firm, thickened skin
- D, Flexion contractures
- E, Raynaud's phenomenon





**Clinical manifestations of scleroderma.**

F, Ischemic digital ulcer

G, Telangiectasias on the face (a),  
dorsum of the hand (b),  
mucosa (c)

H, Calcinosis cutis

# Symptoms

- ▶ **Joints**-can swell and become painful and stiff, especially hands\*
- ▶ **Muscles**-can become weak, and tendons can become abnormally thick, causing pain and limited joint motion

\*

- ▶ **Fatigue**



# Treatment

- ▶ Arthralgias/joint pains

- Nsaids

- Tylenol

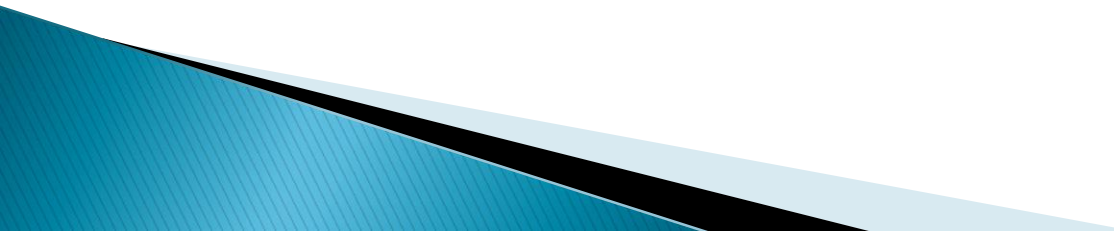
- Low dose glucocorticoids for a few weeks

- Plaquenil

- Methotrexate

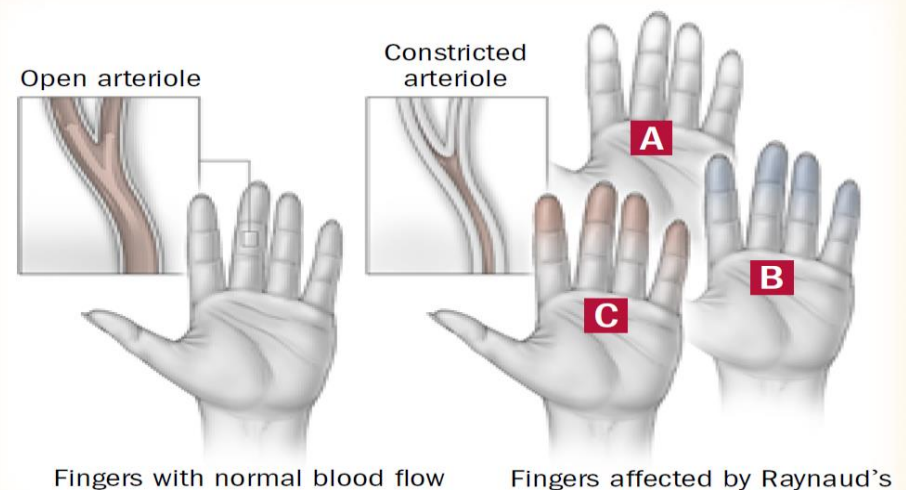
- Physical therapy

# 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
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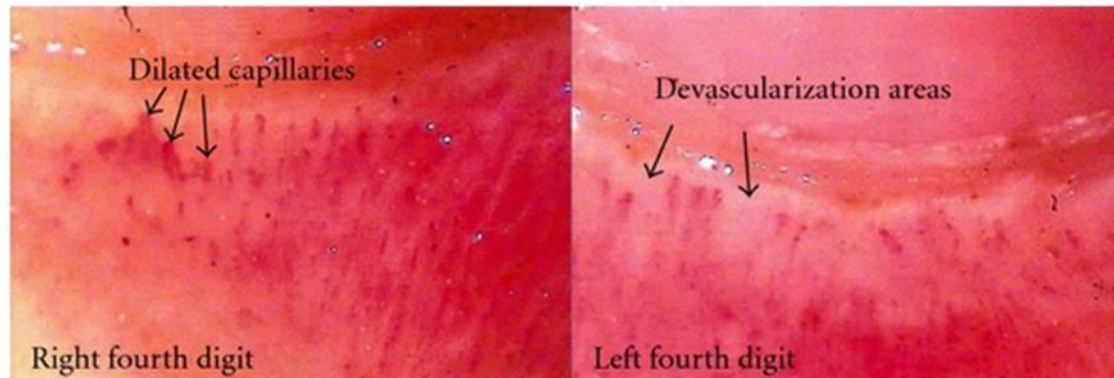
# Raynauds phenomenon

- ▶ Blood vessels in the fingers or toes, and sometimes in the tips of the nose and ears, suddenly constrict
- ▶ The area turns white or blue and becomes cold and numb. This is followed by a flush of redness as the area warms up again, often together with pain or tingling
- ▶ Raynaud's phenomenon can be triggered by exposure to cold or vibration or by emotional stress



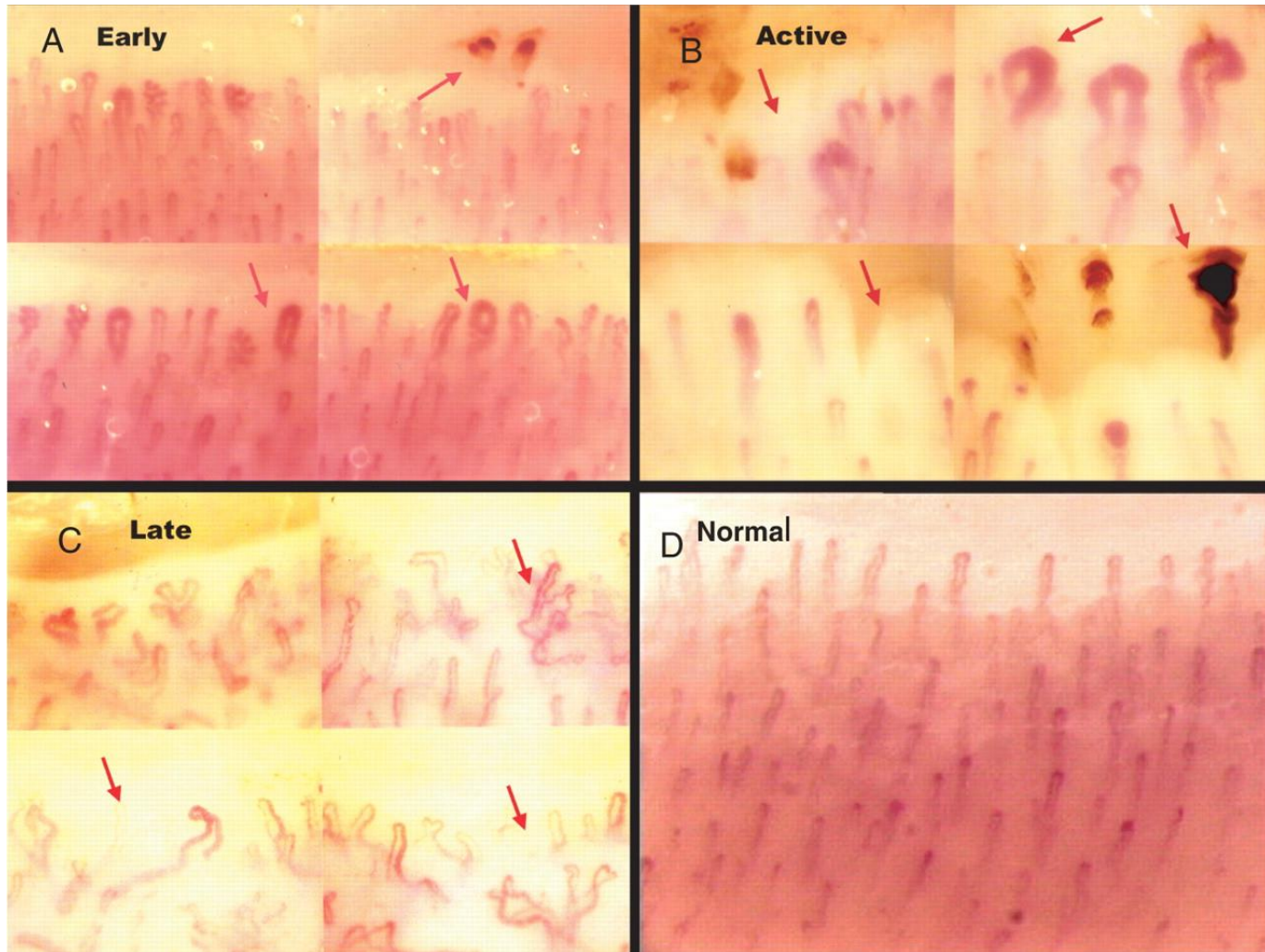
# Nailfold capillaroscopy

- ▶ This technique allows nailfold capillaries (the small blood vessels of the nailfold) to be visualised under the microscope
- ▶ Useful tool for the early selection of those patients who are potential candidates for developing SSc spectrum disorders





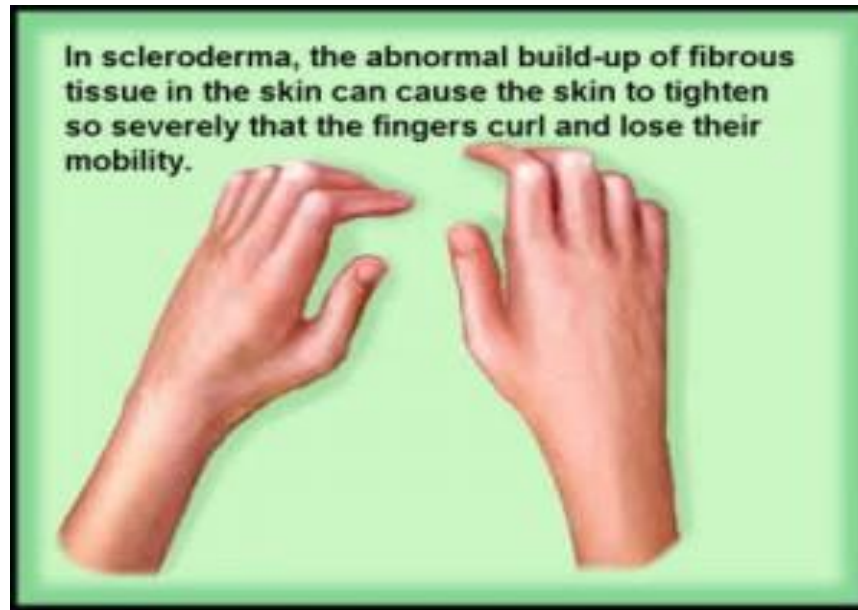
**A, early SSc pattern; B, active SSc pattern; C, late SSc pattern and D, normal pattern (magnification 200×).**



**M. Cutolo et al. Rheumatology 2006;45:iv43-iv46**

# Skin symptoms

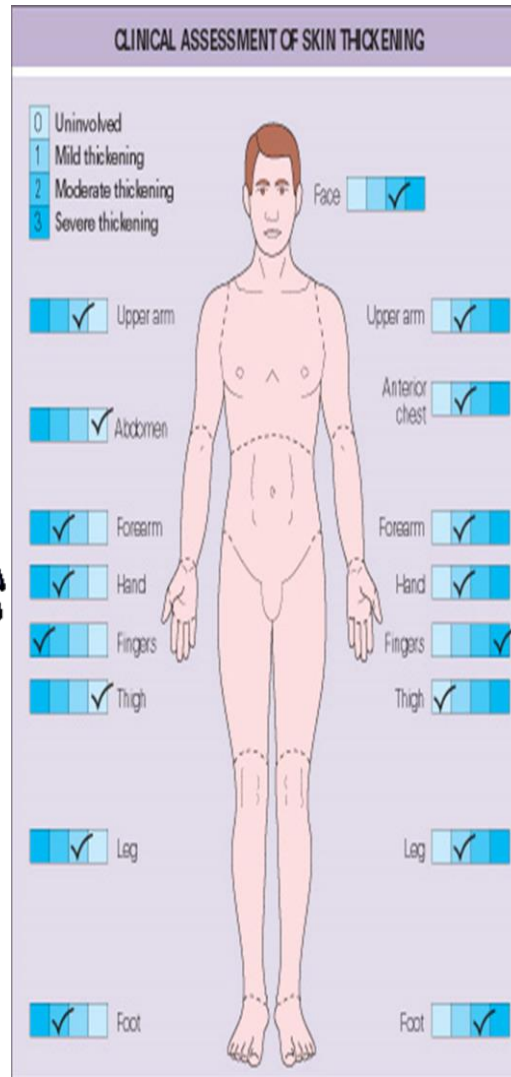
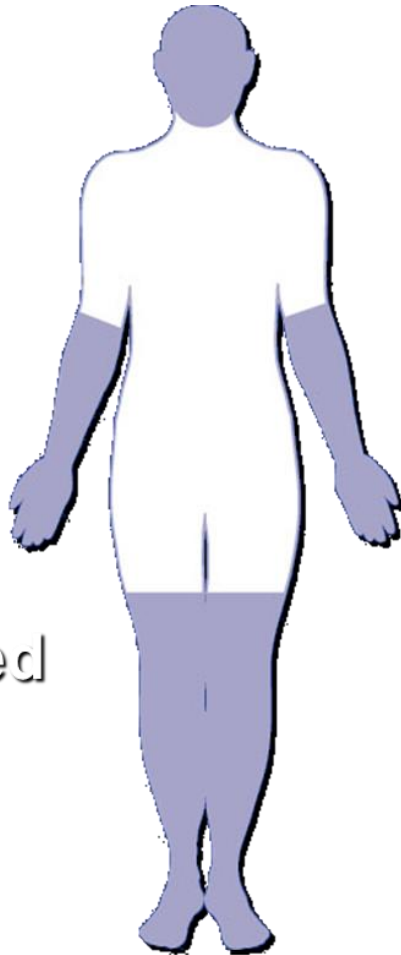
- ▶ There can be swelling of the fingers, hands, forearms and face and sometimes the feet and lower legs. This is followed by a skin thickening and tightness that can limit body movement.





# Distribution

Limited



Diffuse



# Skin

- ▶ Skin ulcers
- ▶ 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

-Allogeneic bone marrow transplantation

-UVA Phototherapy

(Nitroglycerin ointment also dovonex)

# Treatment

## ▶ Pruritis-

- Antihistamines
- Lubricating creams
- Low dose oral steroids

## ▶ Calcinosis-

- Surgery
- Minocycline

## ▶ Telengectasias

-?

# Digestive system

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

\*

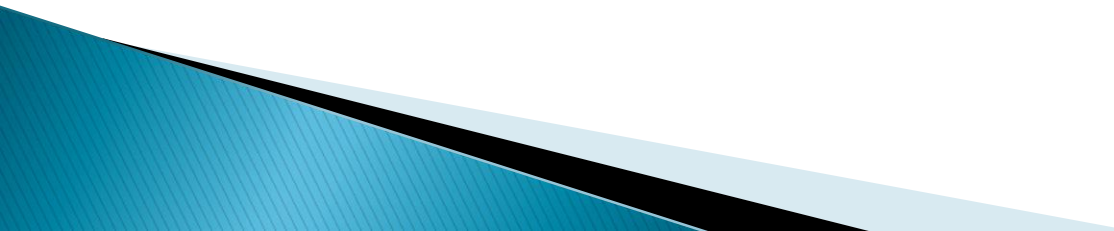


\*\*



# 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 the supine position within three hours of eating
- Cessation of smoking and reduction of alcohol intake if excessive
- Antisecretory agents(H-2 blockers and Proton Pump Inhibitors)

## ▶ 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

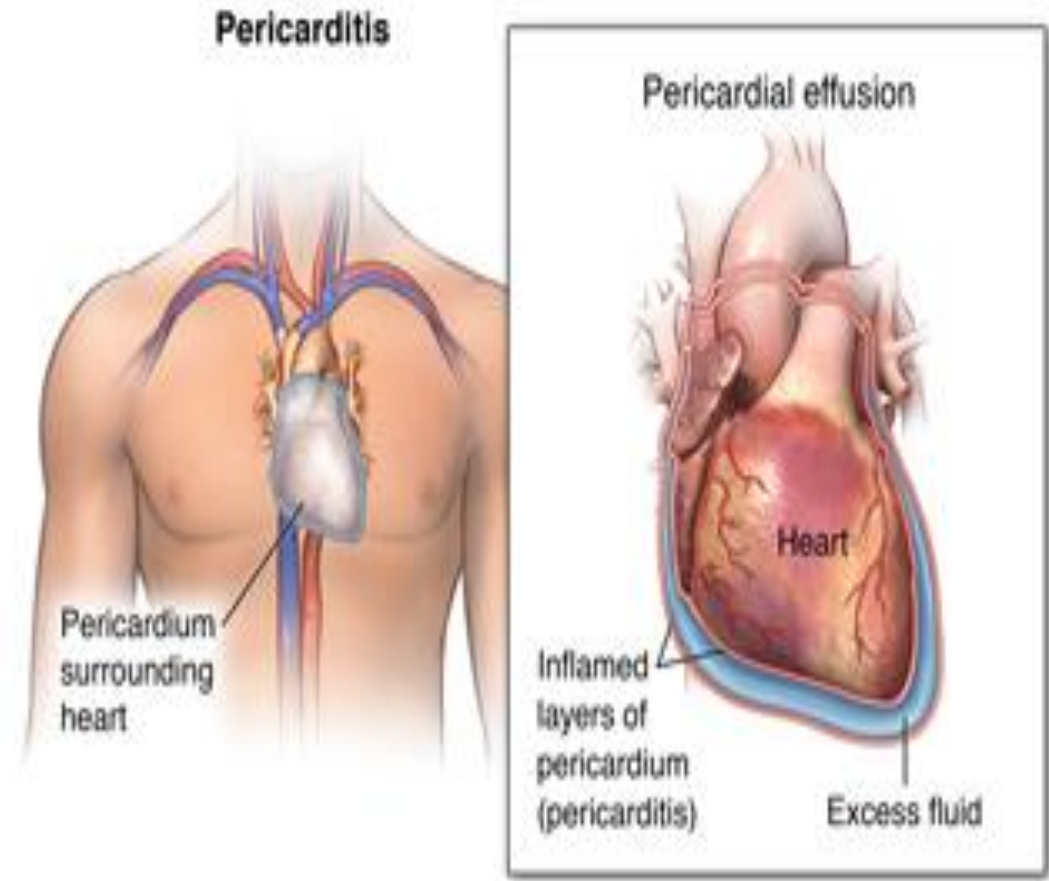
Take a daily probiotic supplement and/or eat yogurt with active cultures

Increase fluid intake

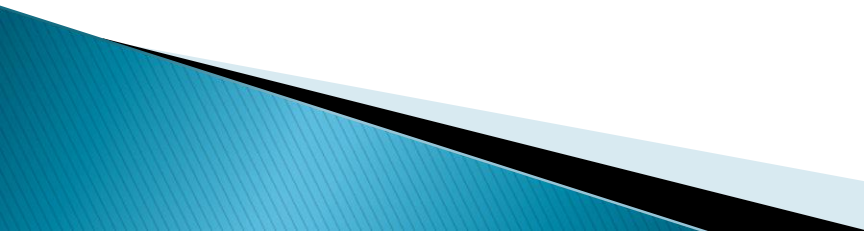


# Cardiac

- ▶ Congestive heart failure
- ▶ Pericarditis
- ▶ Pericardial effusion
- ▶ Arrhythmias
- ▶ Myocardial fibrosis

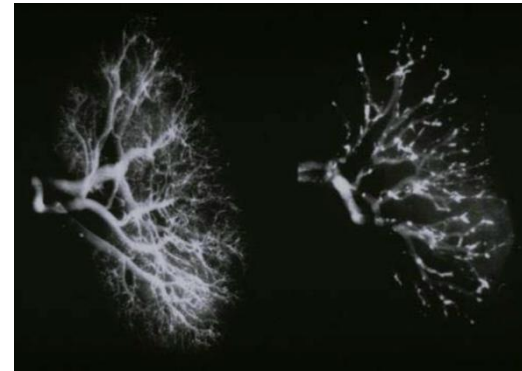


# Treatment

- ▶ Nonsteroidal anti-inflammatory drugs or low-dose corticosteroids can be used for symptomatic pericarditis
  - ▶ If myocarditis is identified clinically or by endomyocardial biopsy, high-dose glucocorticoid therapy should be tried
  - ▶ Digitalis and diuretics are the mainstay of therapy
  - ▶ Progressive left ventricular failure caused by myocardial fibrosis is unaffected by any therapy and may lead to cardiac transplantation
  - ▶ Serious arrhythmias are treated in the standard way
- 

# 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

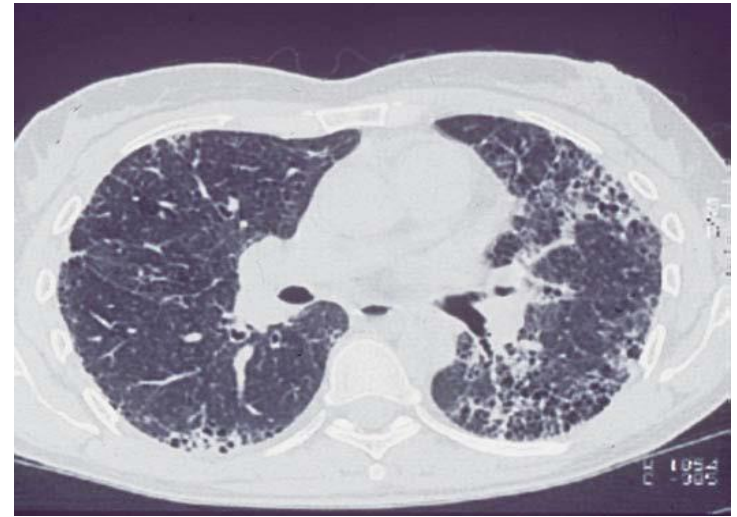
- Neoplasm

- Aspiration pneumonia

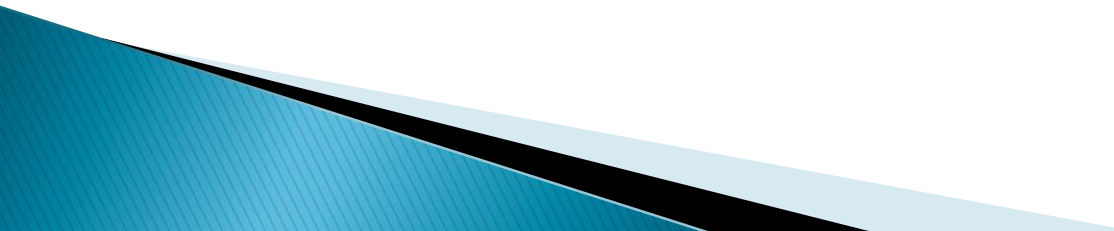
- ▶ **Pulmonary htn** the leading cause of death

- ▶ The prevalence of PAH is 8–12% in patients with SSc

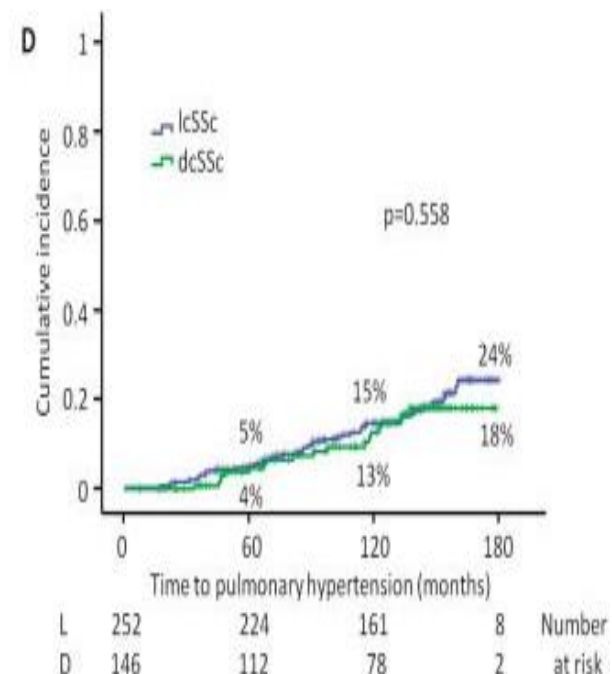
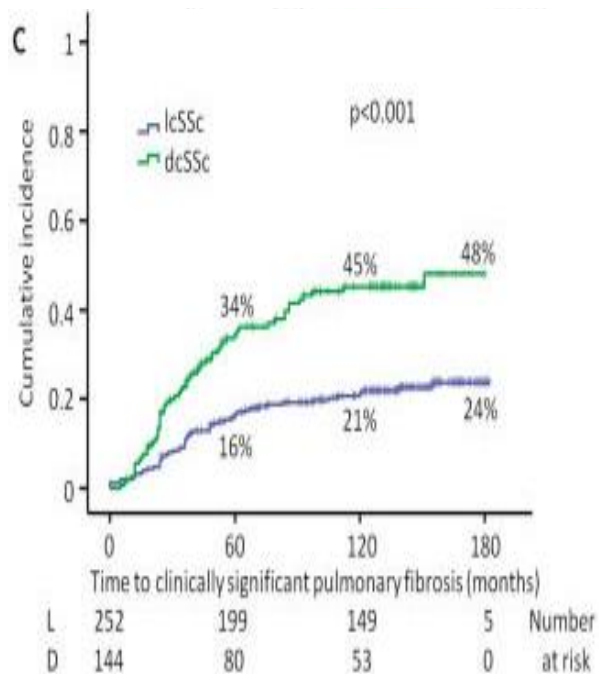
- ▶ PAH is responsible for almost 30% of SSc related deaths



# 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 and PFTs should be performed annually on all patients with SSc
  - ▶ The full screening panel should be performed as soon as any new signs or symptoms are present
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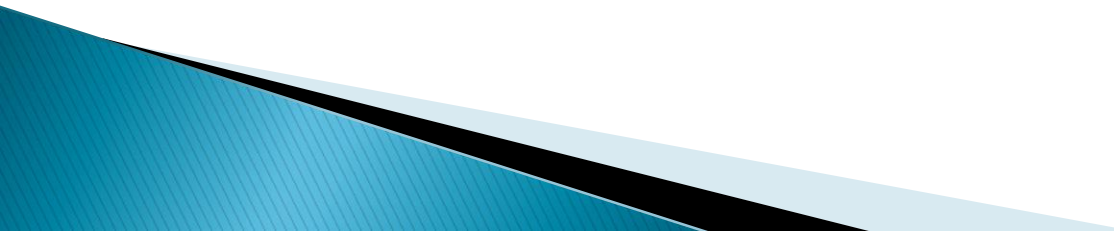
# Prediction of Pulmonary Complications and Long-Term Survival





# Treatment

- ▶ **Interstitial Lung Disease with active inflammation-**
  - ▶ Mycophenolate
  - ▶ Azathioprine
  - ▶ Cytoxan - IV
  - ▶ Steroids
- 
- ▶ **Pulmonary Hypertension-**
  - ▶ Vasodilators: bosentan, sildenafil, epoprostenol, treprostinil, iloprost
  - ▶ Lung Heart Transplant

- ▶ Disease-modifying treatment aims at inhibiting tissue fibrosis and vascular and immune system alterations, which are the three crucial components of disease pathogenesis
  - ▶ The US Food and Drug Administration (FDA) has not approved any disease-modifying therapies for systemic sclerosis
- 

## 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	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

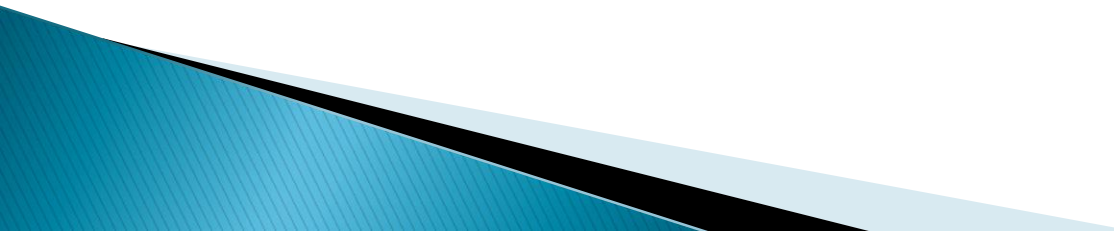
\* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, 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  $\geq 9$  are classified as having definite scleroderma.**

# Good news!

- ▶ Steen and Medsger reported the 10-year cumulative survival rate in their longitudinal Pittsburgh cohort
- ▶ Improvement in survival from 54% in 1970s to 66% in the 1990s
- ▶ Presently the percentage is in the 70s
- ▶ **The prognosis and functionality has improved**

# Why?

- ▶ The prognosis and functionality has improved....
  - ▶ Less infections
  - ▶ Earlier detection of pulmonary htn
  - ▶ Improved diagnosis and treatment of renal crisis
  - ▶ Symptomatic treatments of individual organ pathologies
  - ▶ Overall, patients with ISSc without renal, cardiac or pulmonary involvement for 3 years after the disease onset, and negative for antitopoisomerase have a survival similar to the general population
- 

**Therapies targeting the immune system**

- Cyclophosphamide
- Methotrexate
- Rituximab
- Infliximab
- Intravenous immunoglobulins
- Cyclosporin

**Therapies targeting underlying vascular disease**

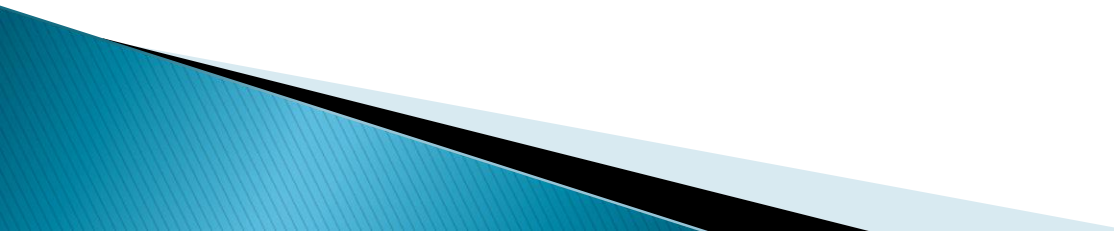
- Selective endothelin A receptor and nonselective endothelin A/B receptor antagonists (e.g. sitaxentan, bosentan)
- Phosphodiesterase-type-5 inhibitors (e.g. sildenafil)
- Prostacyclins (e.g. iloprost)
- Calcium-channel blockers
- Angiotensin-converting-enzyme inhibitors
- Angiotensin-receptor inhibitor (e.g. losartan)
- Topical nitroglycerin formulations (e.g. glycerin trinitrate)
- Statins (e.g. atorvastatin)

**Prospective therapies targeting established fibrosis**

- Inhibitors of the tyrosine kinase c-Abl (e.g. imatinib)
- PDGF-receptor inhibitor
- Anti-TGF- $\beta$  monoclonal antibody or small-molecule inhibitors of TGF- $\beta$ -receptor

Abbreviations: PDGF, platelet-derived growth factor; SSc, systemic sclerosis; TGF- $\beta$ , transforming growth factor  $\beta$ .

# Scleroderma Clinic

- ▶ So why start a scleroderma clinic?
  - ▶ Scleroderma is a multi-organ disease
  - ▶ Clinically heterogeneous
  - ▶ Needs multi- specialty approach to maintain good QOL and overall improve outcomes
  - ▶ Limited exposure and knowledge among physicians regarding nuances of Scleroderma
- 



# Effects and challenges of scleroderma

- ▶ Appearance and self esteem
- ▶ Caring for oneself
- ▶ Family relationships
- ▶ Currently no medications to slow down progression of scleroderma
- ▶ More cases diagnosed

-Prevalence figures from Australia reveal incidence increased from **45 per million in 1975**, to 86/million in 1988, and **233 cases/million for 1999**

-3 recent US studies(1989-2002) reported similar prevalence figures of around **300 cases/million**

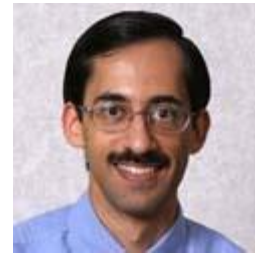


# Multidisciplinary clinic

- ▶ Rheumatology-Ali Ajam and Brian Lameroux



- ▶ Pulmonary/ILD-Namita Sood Nitin Bhatt



- ▶ Gastroenterology-Jon Walker Marty Meyer Royce Groce



- ▶ Vascular-Steven Dean

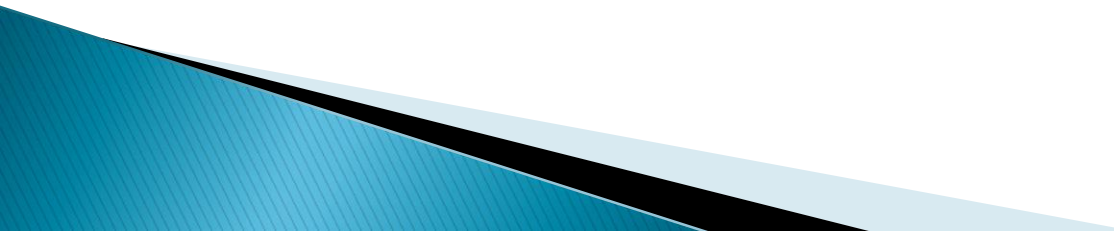


# Aspects of the program

- ▶ Clinic in shared space in MMMP every Monday morning
- ▶ Streamlined referral process to GI and Vascular Disease
- ▶ Bimonthly multidisciplinary meeting
  - 3<sup>rd</sup> Tuesday every 2 months
  - Next meeting August 18<sup>th</sup> at 7.30 AM

NIH sponsored Trial : Rituximab in PAH associated with SCI

# Goals and objectives

1. To provide state of the art, multidisciplinary care
  2. Easier/Faster access for patients
  3. Proactively identify complications
  4. To provide access to new therapies via clinical trials
  5. Develop a Protocol driven approach
  6. Develop a repository containing data and blood and tissue samples from patients who chose to participate in clinical studies
  7. Reach out to the columbus community and provide education/lectures to scleroderma patients
  8. Incorporate scleroderma awareness via use of social media
  9. Become a scleroderma center!
- 

# Resources

- [www.scleroderma.org](http://www.scleroderma.org) -- Scleroderma Foundation
  - [www.srfcure.org](http://www.srfcure.org) -- Scleroderma Research Foundation
  - [www.arthritis.org](http://www.arthritis.org) -- The Arthritis Foundation
  - [www.niams.nih.gov](http://www.niams.nih.gov) -- National Institute of Arthritis and Musculoskeletal and Skin Diseases
  - [www.rheumatology.org](http://www.rheumatology.org) -- American College of Rheumatology
  - [www.sclero.org](http://www.sclero.org) -- International Scleroderma Network
  - [www.sctc-online.org](http://www.sctc-online.org) -- Scleroderma Clinical Trials Consortium
  - [www.phassociation.org](http://www.phassociation.org) -- Pulmonary Hypertension Association
  - [www.thoracic.org](http://www.thoracic.org) -- American Thoracic Society
- 

THANK YOU!

