Best of ACR 2023

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Topics

- Systemic Sclerosis
- Interstitial lung
- diseasesIgG4 related diseases
- Myopathies

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ACR Convergence
Where Rheumatology Meets
#ACR23

"Systemic Sclerosis Screening for Organ Involvement"

Francesco Boin, MD
Professor of Medicine
Director, Division of Rheumatology
Kao Multispecialty Scleroderma Program
Cedars Sinai Medical Center
Los Angeles, CA

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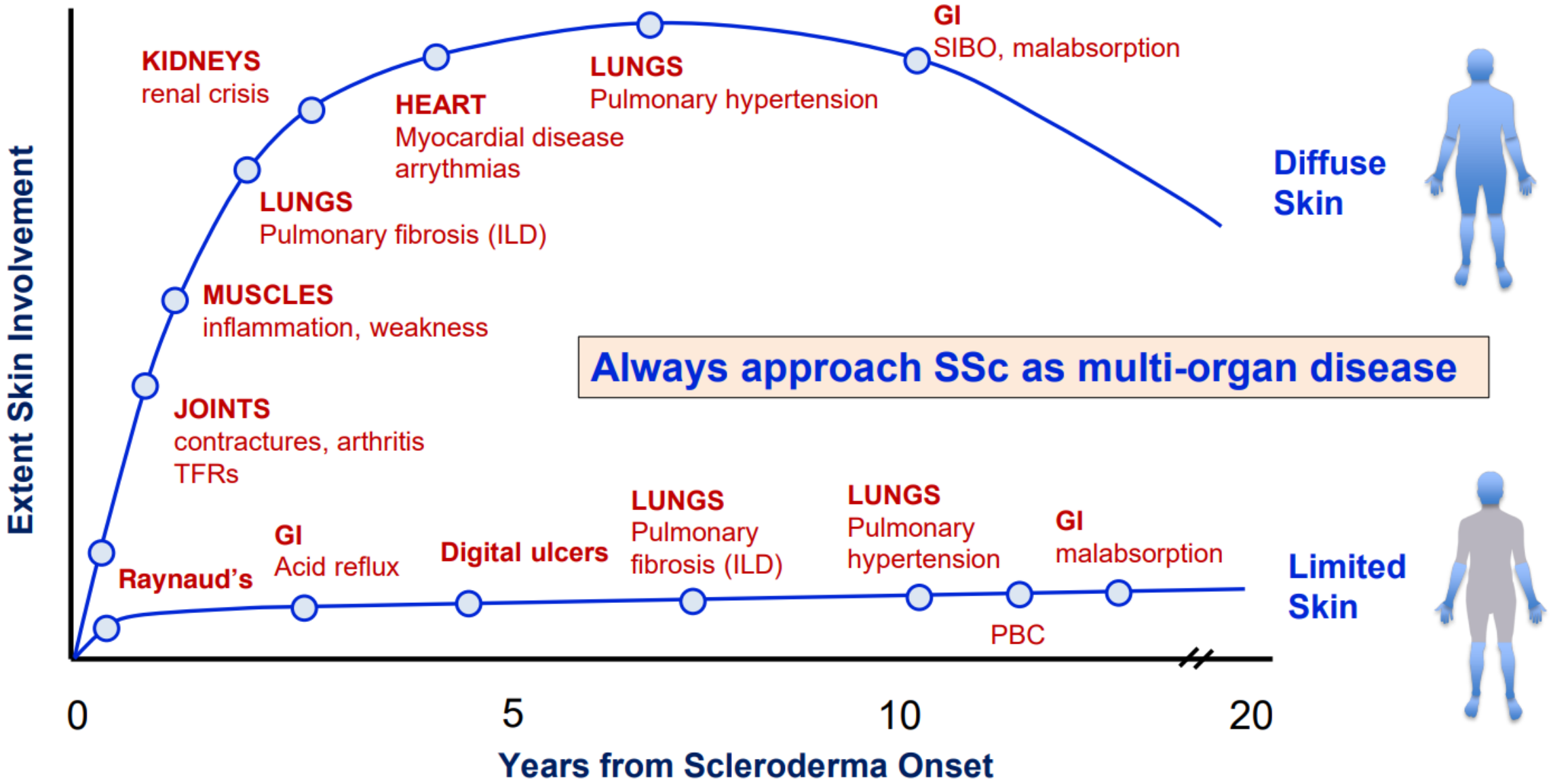
Systemic Sclerosis Screening for Organ Involvement

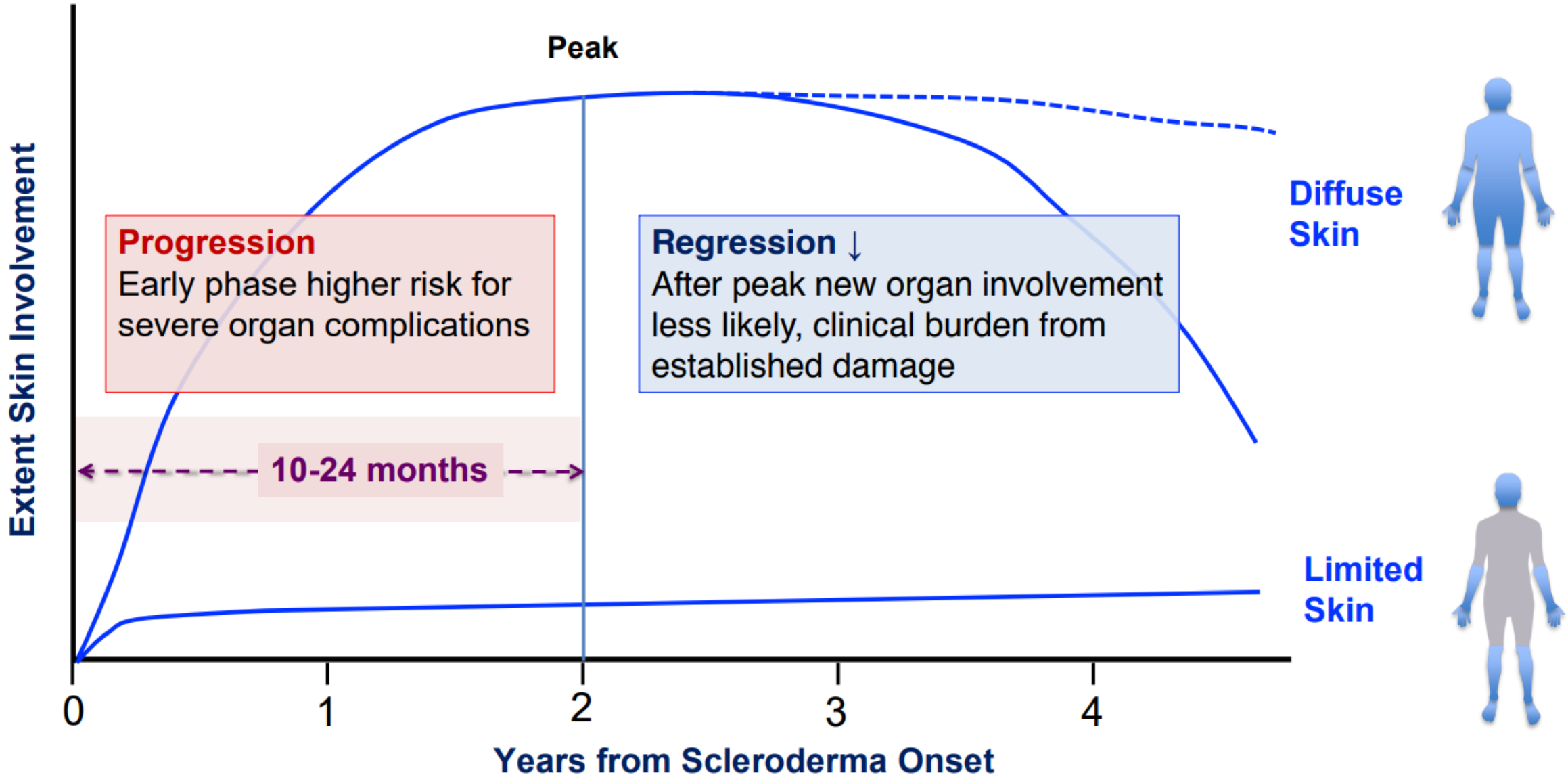
Outline

- Scleroderma: a multi-organ disease
- Autoantibodies: specificity for SSc organ-involvement
- Approach to cardiopulmonary assessment
- Scleroderma Renal Crisis
- Myocardial involvement (primary)

Timing of Skin and Organ Involvement In Scleroderma

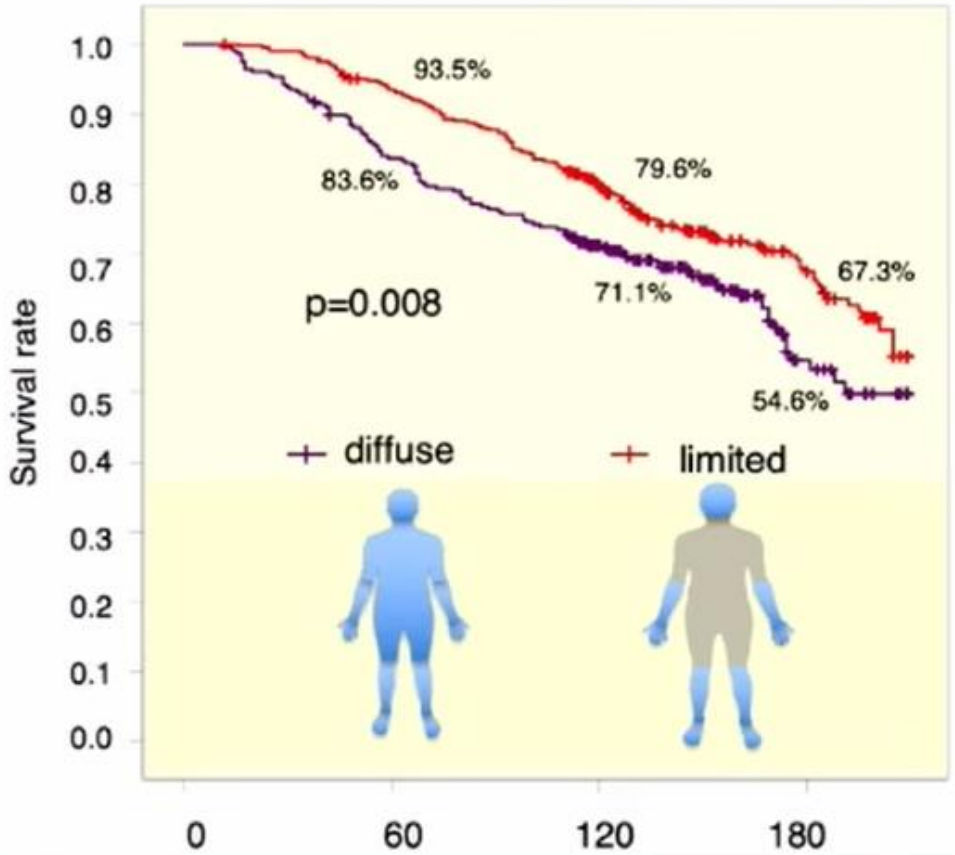


Timing of Skin and Organ Involvement In Scleroderma

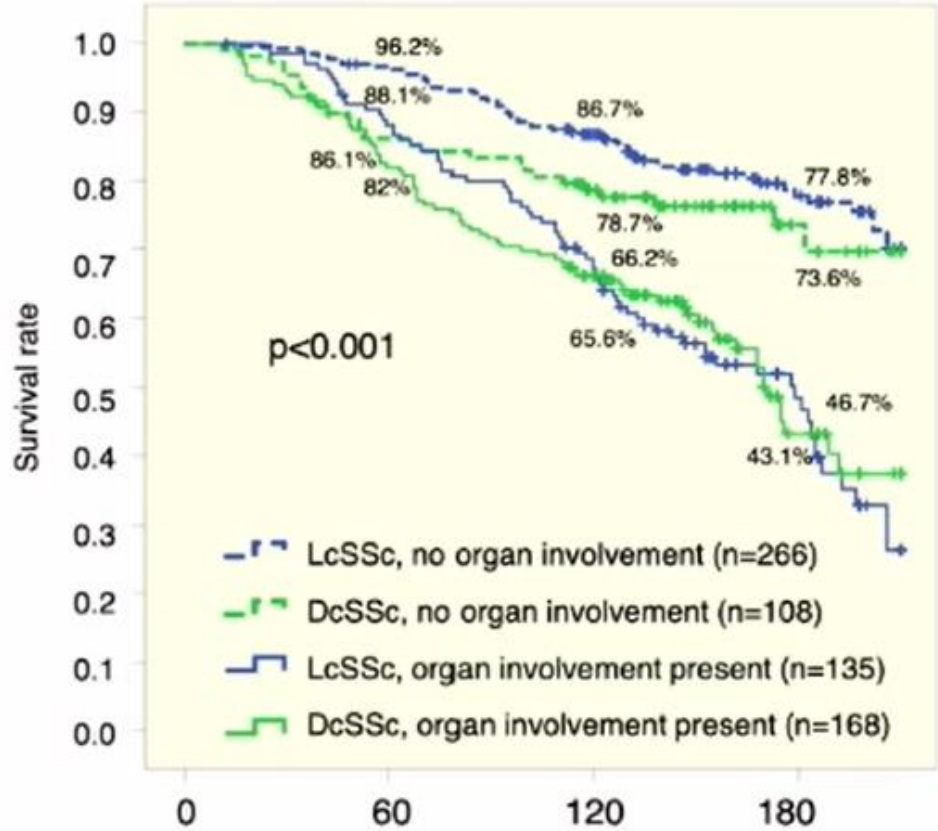


Survival in Systemic Sclerosis is Determined by Subset and Organ-based Manifestations

Impact of disease subset on survival



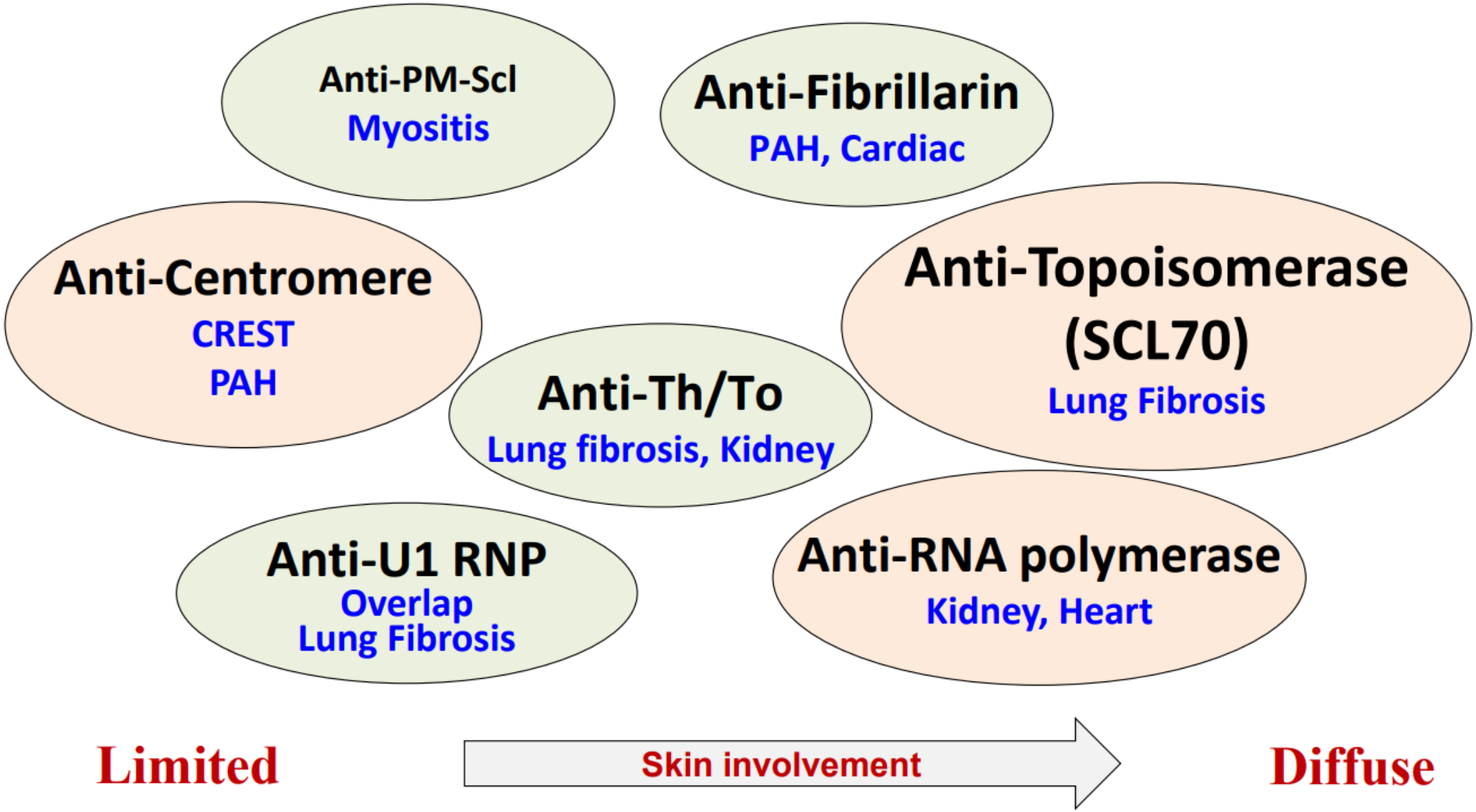
Impact of organ-based complications

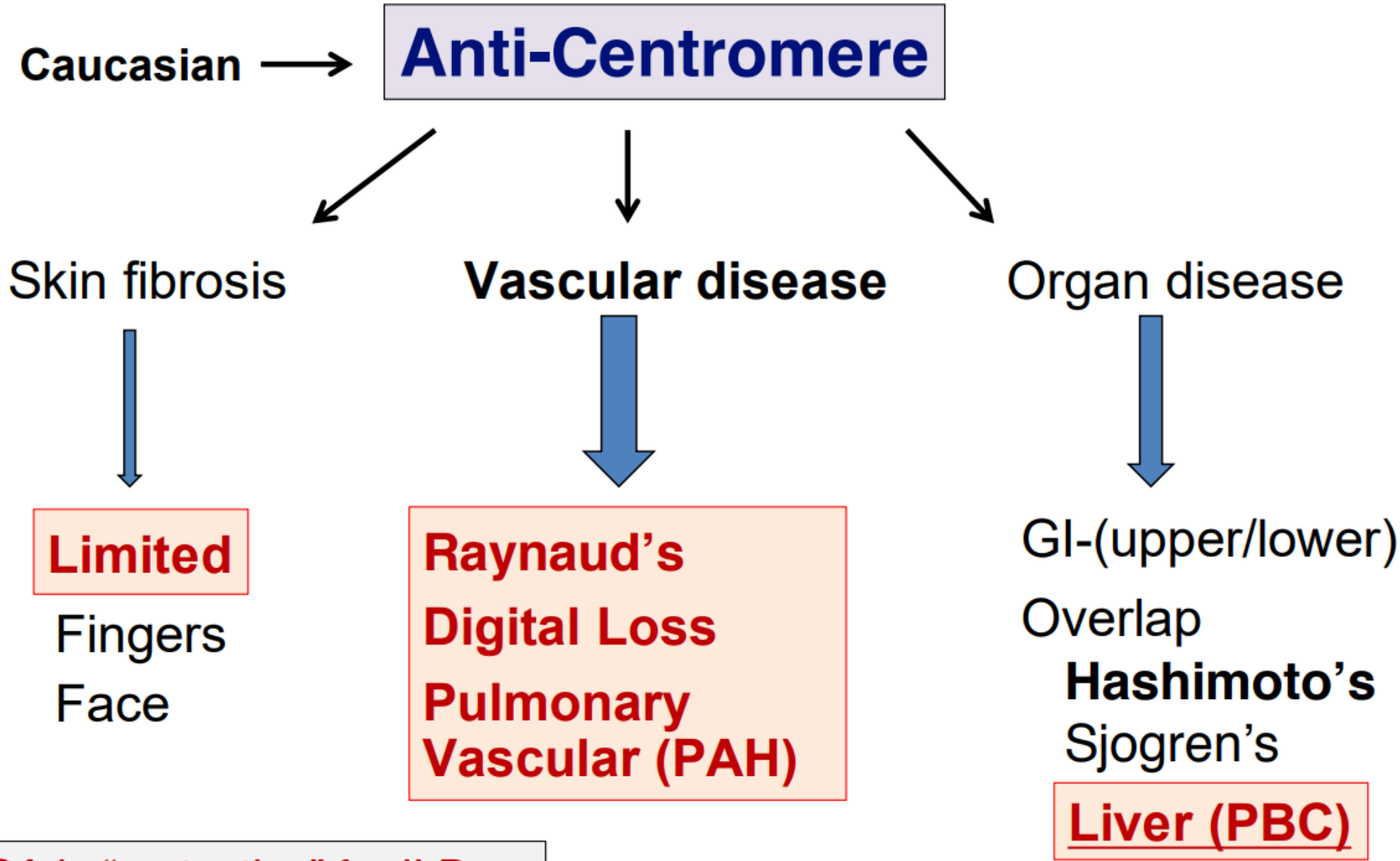


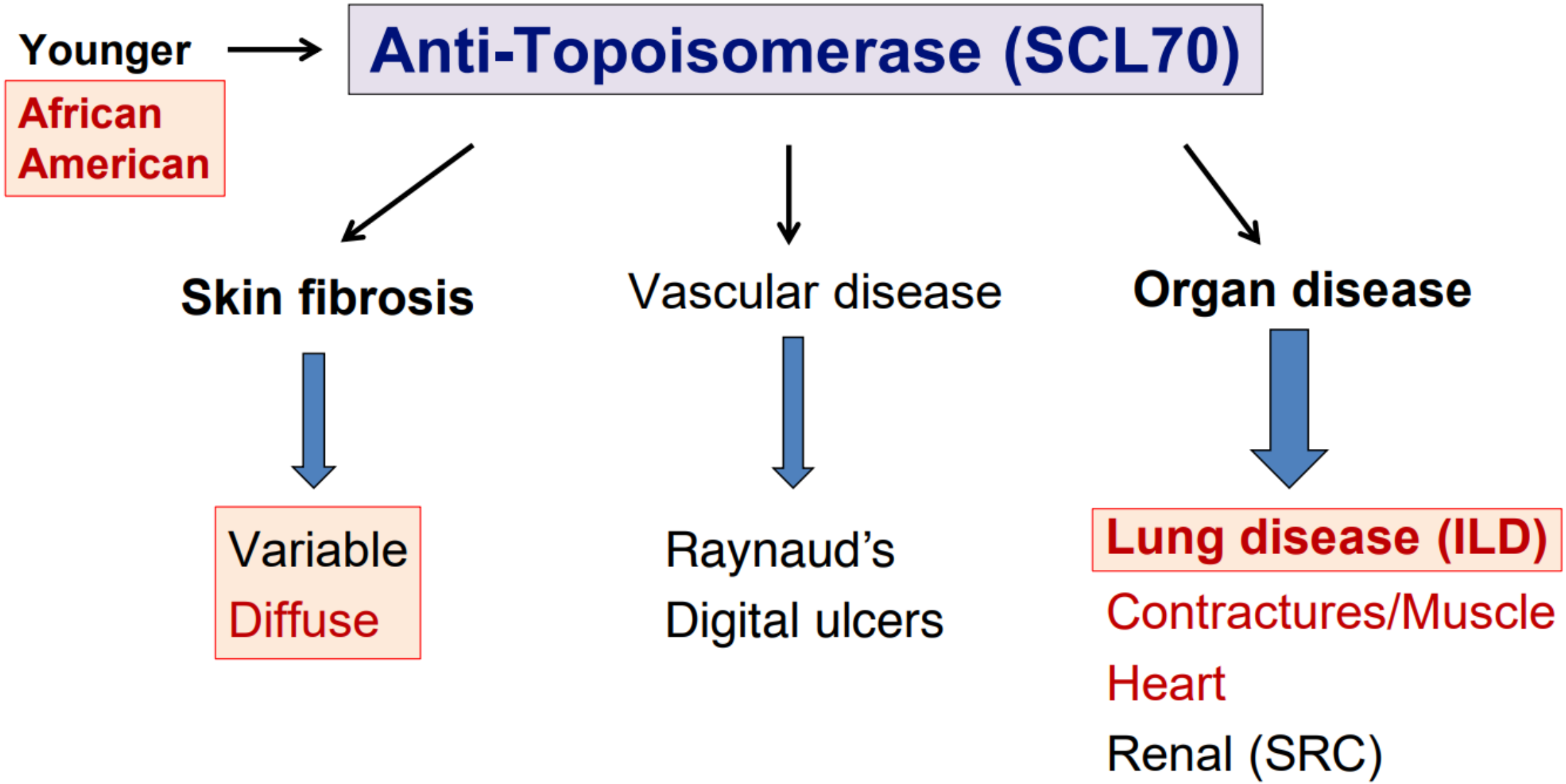
Screening for major complications: cornerstone of global and effective management!

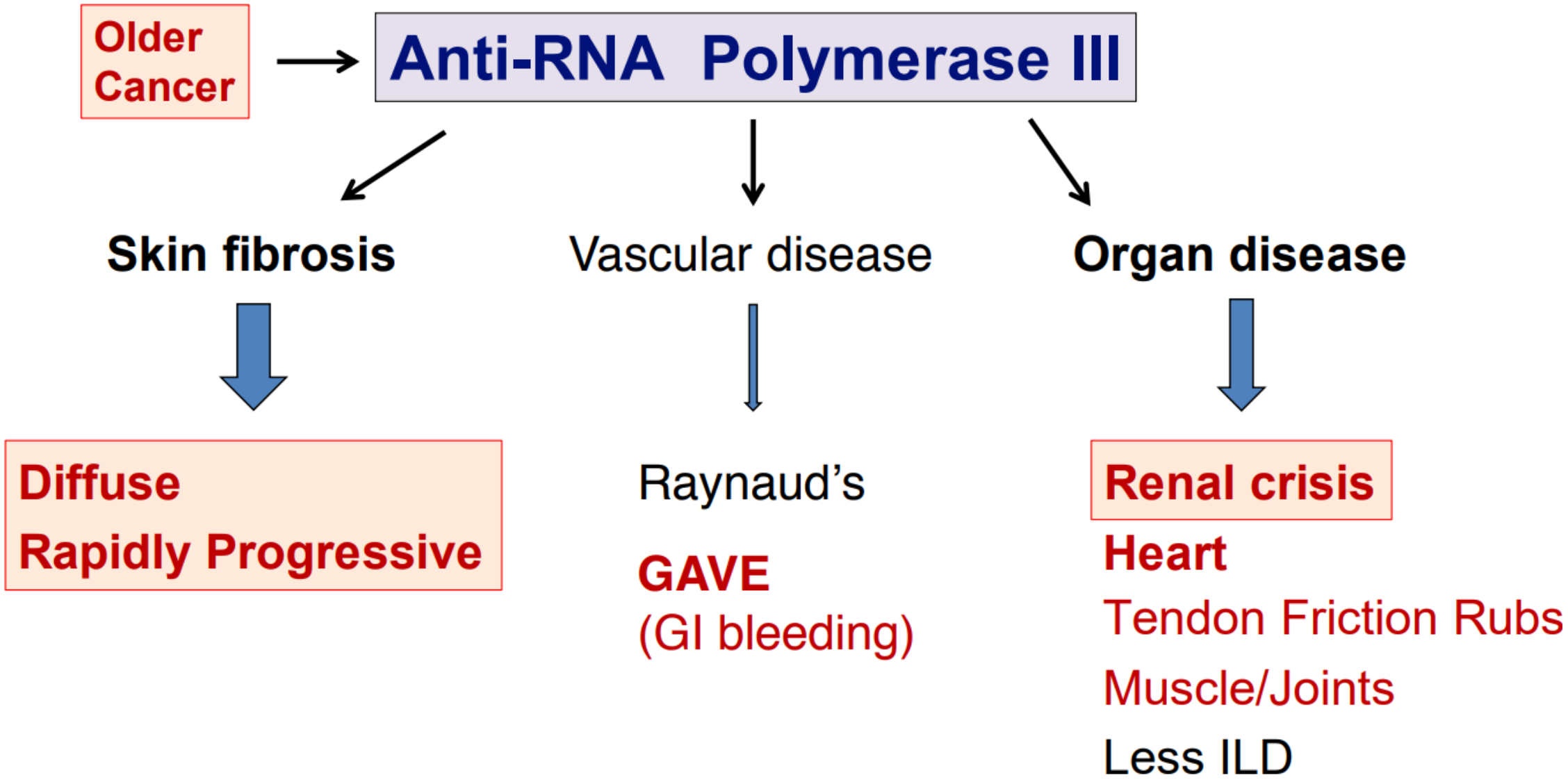
Nihtyanova Arthritis Rheum 2014

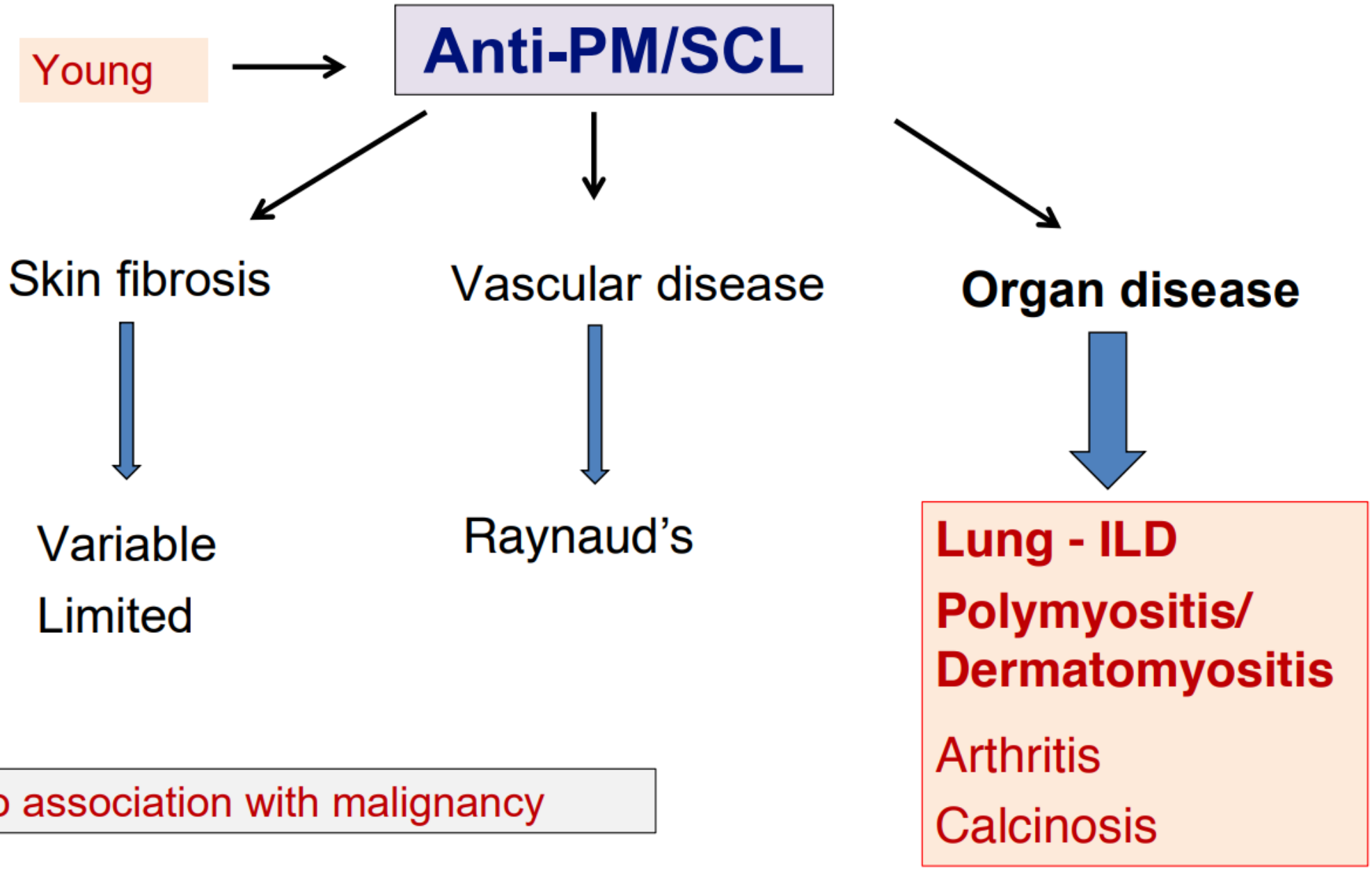
Scleroderma-Specific Autoantibodies

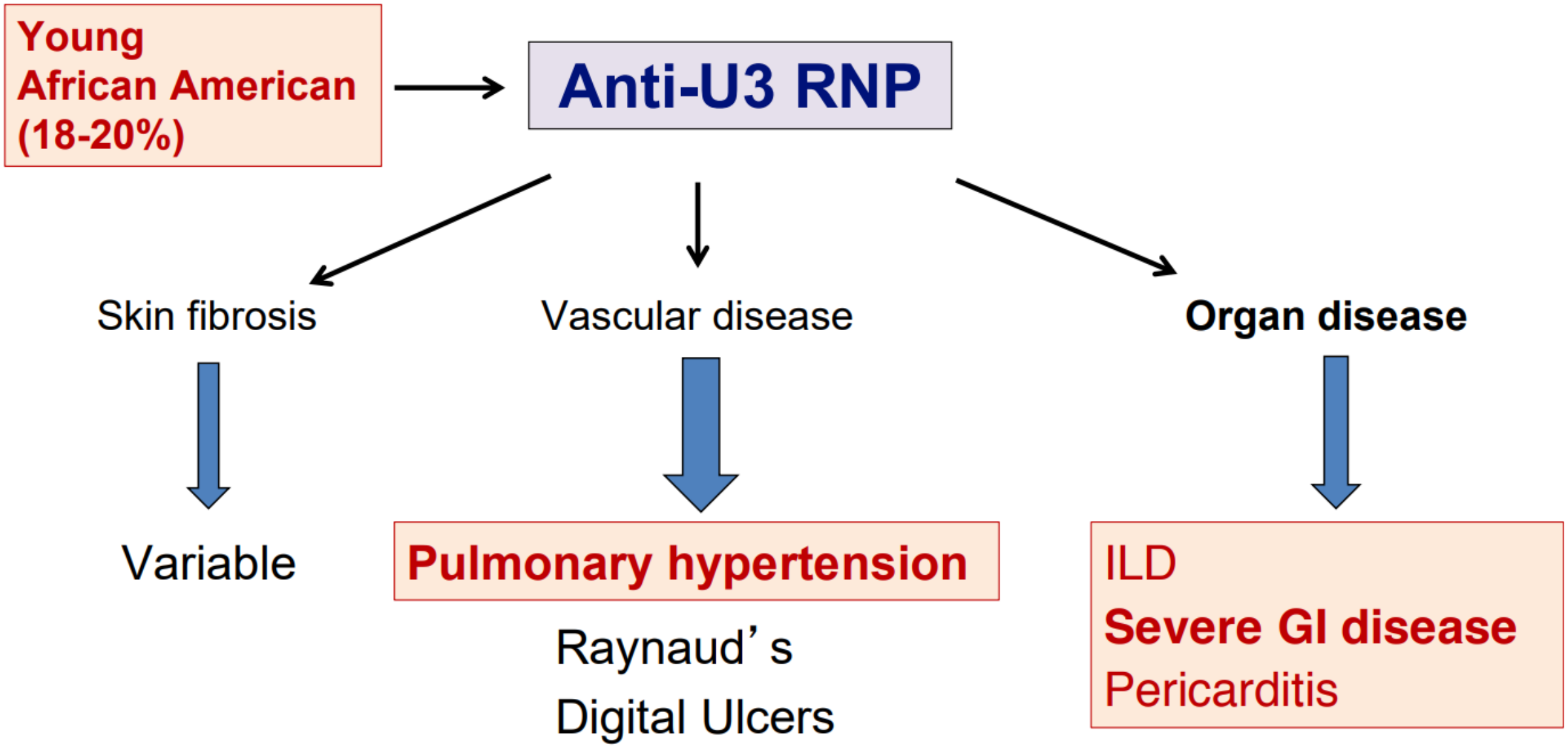



Caucasian
Anti-Centromere
Skin fibrosis
Vascular disease
Organ disease
Limited
Fingers
Face
Raynaud's
Digital Loss
Pulmonary Vascular (PAH)
GI-(upper/lower)
Overlap
Hashimoto's
Sjogren's
Liver (PBC)
ACA is "protective" for ILD


Younger
African American
Anti-Topoisomerase (SCL70)
Skin fibrosis
Vascular disease
Organ disease
Variable
Diffuse
Raynaud's
Digital ulcers
Lung disease (ILD)
Contractures/Muscle
Heart
Renal (SRC)


Older Cancer
Anti-RNA Polymerase III
Skin fibrosis
Vascular disease
Organ disease
Diffuse
Rapidly Progressive
Raynaud's
GAVE
(GI bleeding)
Renal crisis
Heart
Tendon Friction Rubs
Muscle/Joints
Less ILD


Young
Anti-PM/SCL
Skin fibrosis
Vascular disease
Organ disease
Variable
Limited
Raynaud's
Lung - ILD
Polymyositis/
Dermatomyositis
Arthritis
Calcinosis
No association with malignancy


Young
African American
(18-20%)
Anti-U3 RNP
Skin fibrosis
Vascular disease
Organ disease
Variable
Pulmonary hypertension
Raynaud's
Digital Ulcers
ILD
Severe GI disease
Pericarditis

Systemic Sclerosis Pulmonary Fibrosis - ILD

SSc-ILD: Who is at risk for disease onset and progression?

- **Diffuse SSc (70-80%) > Limited SSc (15-25%)**
- **Early disease** - Majority of lung function decline in first 2-4 years
- **Severe gastro-esophageal reflux**
- **Advanced age**
- **Racial/Ethnic background** - African American
- **Elevated acute phase reactants** - ESR, CRP
- **Autoantibodies**

Increased risk: **anti-SCL70 (70%)**, **Pm/Scl (70%), Th/To (50%), U1-RNP (40%),** U3-RNP

Decreased risk: anti-Centromere

Nihtyanova Arthritis Rheumatol 2014
Richardson Sem Arthritis Rheum 2016
Gelber Ann Rheum Dis 2014
Cottrell Ann Rheum Dis 2013
Kuawana Ther Adv Musculoskel Dis 2021

Diagnostic Evaluation of SSc Pulmonary Fibrosis - ILD

- Clinical Assessment
- Laboratory
- Cardiac Studies
- Pulmonary Function Test (PFTs)
- Imaging

LABORATORY

- **Autoantibodies**
  - SCL70
  - U1-RNP
  - Pm/Scl
  - U3-RNP
  - Centromere
- **Comorbidities**
  - CBC
  - CPK/Aldolase
  - NT-proBNP
  - Troponin

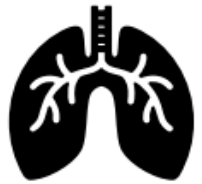
CARDIAC STUDIES

- **ECHO**
- **ECG**

Diagnostic Evaluation of SSc Pulmonary Fibrosis - ILD

- Clinical Assessment
- Laboratory
- Cardiac Studies
- Pulmonary Function Test (PFTs)
- Imaging

PULMONARY FUNCTION TESTS (PFTs)



- **Not a Screening Tool**
  False-negative rate > 60%
- **Establish Baseline**
  ILD Severity, prediction
- **Assess Progression**
  Change over time
- **Suspect Comorbidities**
  Myopathy: ⇩FVC, normal DLCO

  Pulmonary hypertension:
  ⇩DLCO isolated, ⇧FVC/DLCO

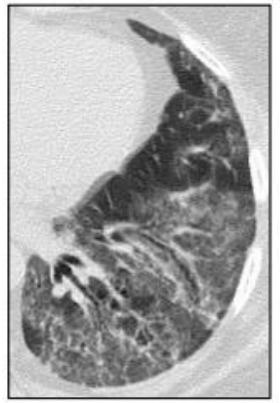
Diagnostic Evaluation of SSc Pulmonary Fibrosis - ILD

- Clinical Assessment
- Laboratory
- Cardiac Studies
- Pulmonary Function Test (PFTs)
- Imaging

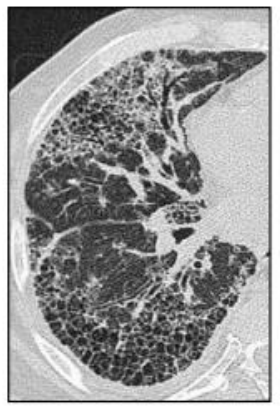
IMAGING

- **HRCT Chest**
  - Gold standard
  - Anatomical Distribution
  - Severity, prediction
  - Subsets (NSIP/UIP)
- **Atypical Features**
  - Infections
  - Masses/nodules
  - Emphysema/cystic changes
  - Pulmonary vascular
  - BO/BOOP

NSIP 75-80%
Early Inflammatory



UIP 20-25%
Fibrotic Late

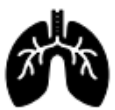


Diagnostic Evaluation of SSc Pulmonary Fibrosis - ILD

Clinical Assessment

Laboratory

Cardiac Studies



Pulmonary Function Test (PFTs)

Imaging

Bronchoscopy/BAL
Lung Biopsy

- Atypical presentation
- Infections
- Malignancy

GENETIC TESTING

- SNPs (i.e. telomerase)

Exhaled Breath Analysis

- i.e. eNose

New Imaging Modalities

- Low-dose CT
- Ultrasound
- MRI (lung protocol)

Should every Newly Diagnosed SSc patient be screened with HRCT?

The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements

Anna-Maria Hoffmann-Vold*, Toby M Maher*, Edward E Philpot, Ali Ashrafzadeh, Rafic Barake, Simone Barsotti, Cosimo Bruni, Paolo Carducci, Patricia E Carreira, Ivan Castellvi, Francesca Del Galdo, Jörg H W Distler, Ivan Foeldvari, Paolo Fraticelli, Peter M George, Bridget Griffiths, Alfredo Guillén-Del-Castillo, Abdul Monem Hamid, Rudolf Horváth, Michael Hughes, Michael Kreuter, Florentine Moazzen, Suman Paul, Cinzia Rotondo, Manuel Rubio-Rivas, Andrei Seferian, Michal Tomčík, Yurdagül Uzunhan, Ulrich A Walker, Oliver Distler

Expert Consensus (Delphi)

"Patients with systemic sclerosis **should be screened** for SSc-associated ILD using HRCT, **particularly if they are showing one or more risk factors**"

Hoffmann-Vold AM et al. Lancet Rheumatol 2020

Expert consensus on the management of systemic sclerosis-associated interstitial lung disease

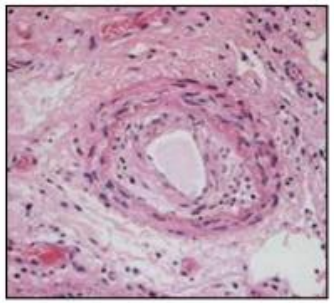
Franck F. Rahaghi[1*], Vivien M. Hsu[2], Robert J. Kaner[3], Maureen D. Mayes[4], Ivan O. Rosas[5], Rajan Saggar[6], Virginia D. Steen[7], Mary E. Strek[8], Elana J. Bernstein[9], Nitin Bhatt[10], Flavia V. Castelino[11], Lorinda Chung[12], Robyn T. Domsic[13], Kevin R. Flaherty[14], Nishant Gupta[15], Bashar Kahaleh[16], Fernando J. Martinez, Lee E. Morrow[17], Teng Moua[18], Nina Patel[6,19], Oksana A. Shlobin[20], Brian D. Southern[21], Elizabeth R. Volkmann[6] and Dinesh Khanna[14*]

"All patients with SSc **should be screened**, with **greater agreement for patients with respiratory symptoms and those at high risk**"

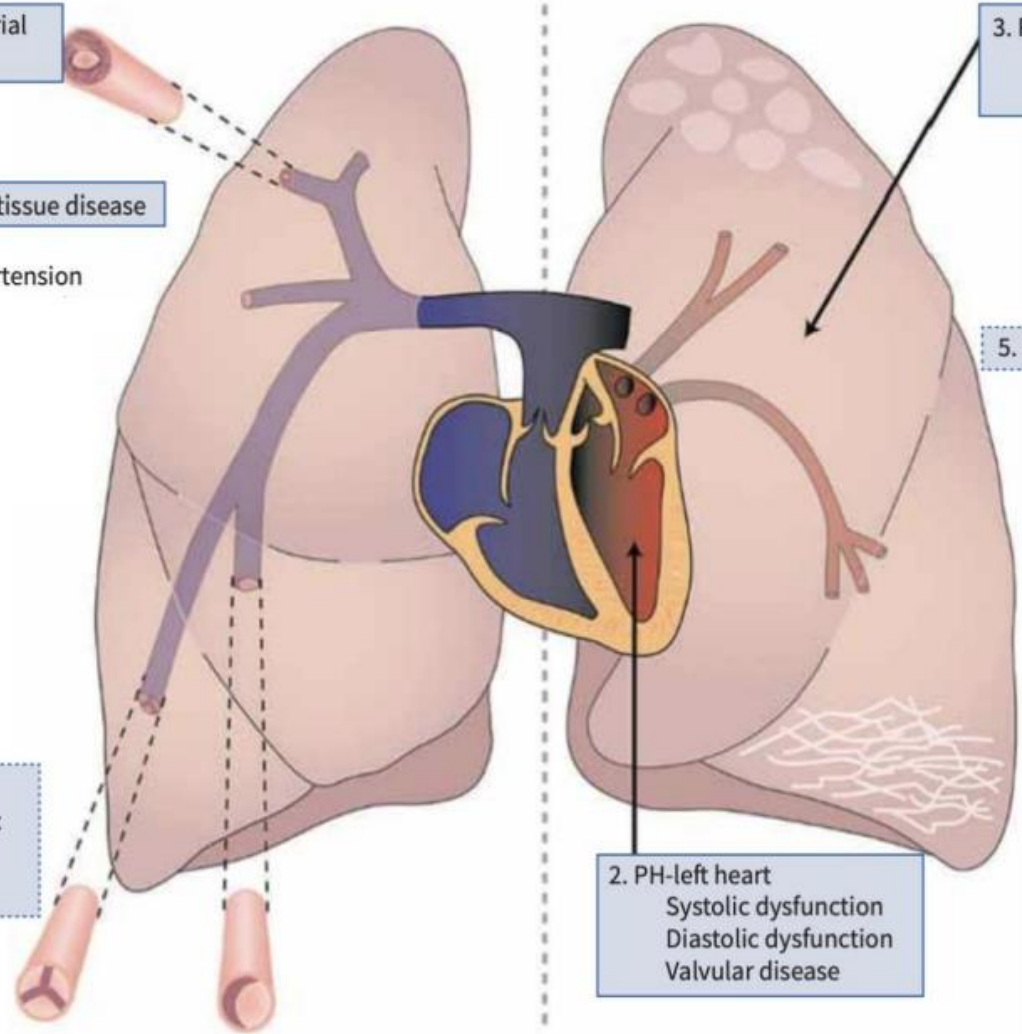
Rahaghi FF ET al. Respir Res. 2023

Pulmonary Hypertension in Scleroderma

WHO Group 1

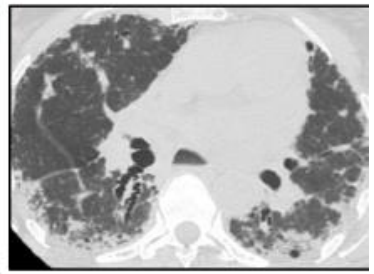


1. Pulmonary arterial hypertension
   - Idiopathic
   - Heritable
   - Drugs
   - Connective tissue disease
   - HIV
   - Portal hypertension



3. PH-lung disease/hypoxia
   - COPD
   - Interstitial lung disease
   - Sleep disorder
   - Alveolar hypoventilation

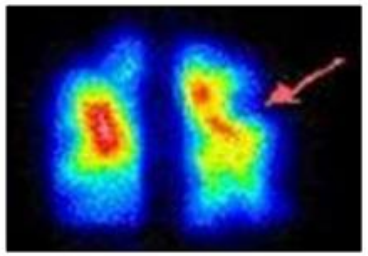
WHO Group 3



5. Multifactorial/unclear

WHO Group 5

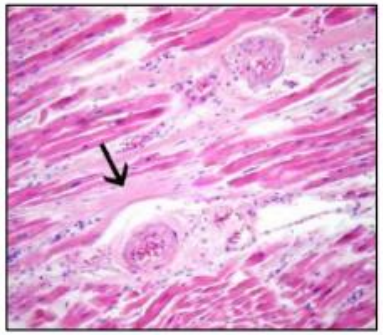
WHO Group 4



4. Chronic thromboembolic pulmonary hypertension

2. PH-left heart
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

WHO Group 2



Adapted from Haque Eur Respir Rev 2021

Diagnostic Evaluation of SSc Pulmonary Hypertension (PAH)

Clinical Assessment

- Risk factors
- History/Symptoms
- Physical exam

Laboratory

- Autoantibodies
- BNP/NT-proBNP

Functional Assessment

- O2 saturation
- 6MWD, CPET

Cardiac Studies

- Echocardiogram
- EKG

Pulmonary Function

- PFT

Screening Algorithms

- **DETECT**
- **ERS/ECS**
- **ASIG**

Establish Probability of Pulmonary Arterial Hypertension

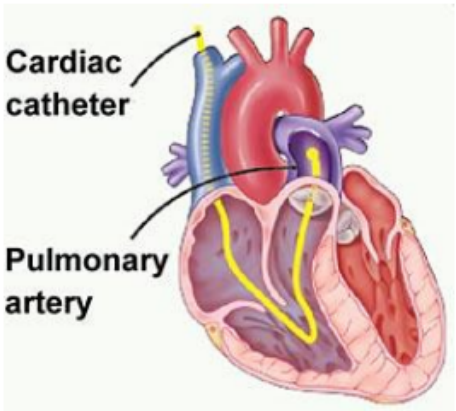
Referral

RIGHT HEART CATHETERIZATION

Gold standard for DIAGNOSIS

Pulmonary Hypertension Definition

2022 ESC/ERS Guidelines for Pulmonary Hypertension



Hemodynamic definition Precapillary PH (i.e. PAH)

- **Mean PAP ≥ 20 mmHg**
- Pulmonary capillary wedge pressure [PCWP] ≤15 mmHg
- Pulmonary vascular resistance **(PVR) > 2 Wood units**

Humbert M Eur Respir J 2022

PAH in Scleroderma
Risk Factors and Predictors

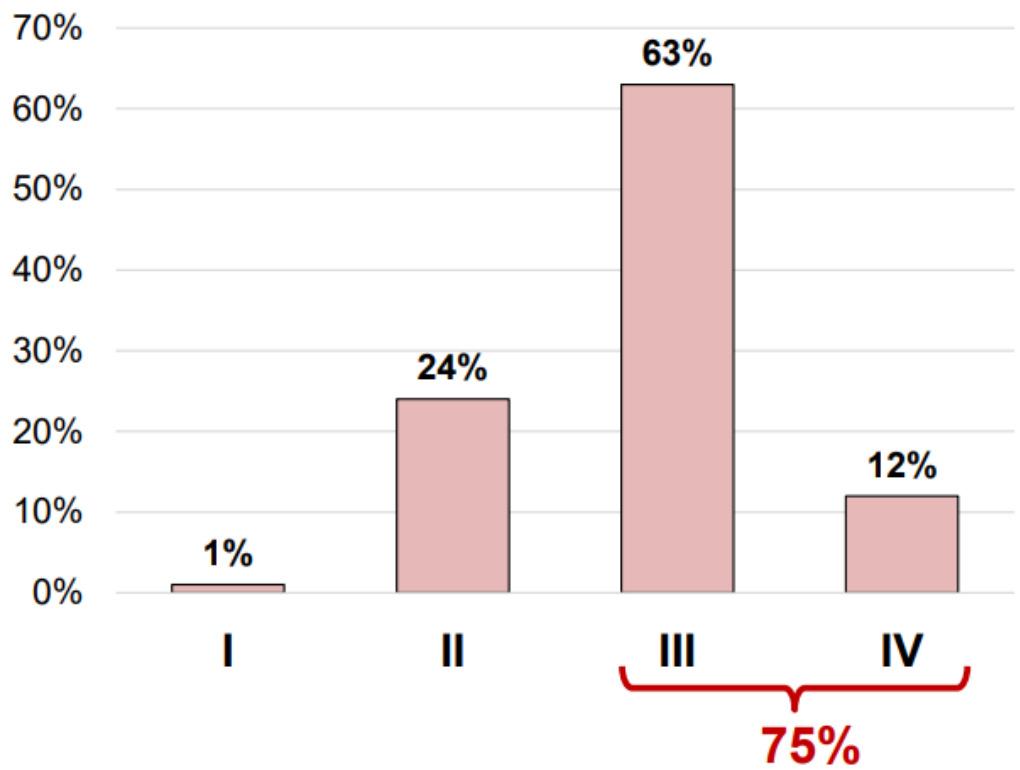
- Late age onset of scleroderma
- Longer disease duration (> 8 years)
- Limited scleroderma
- Severe Raynaud's phenomenon
- Numerous and prominent telangiectasias

- Low Diffusing Capacity (DLCO <55%, FVC%/DLCO% >1.6)
- NT-pro BNP elevation (together with low DLCO, HR=47.2)
- Autoantibody associations:
  - Anti-Centromere, U1-RNP, U3 RNP, Th/To

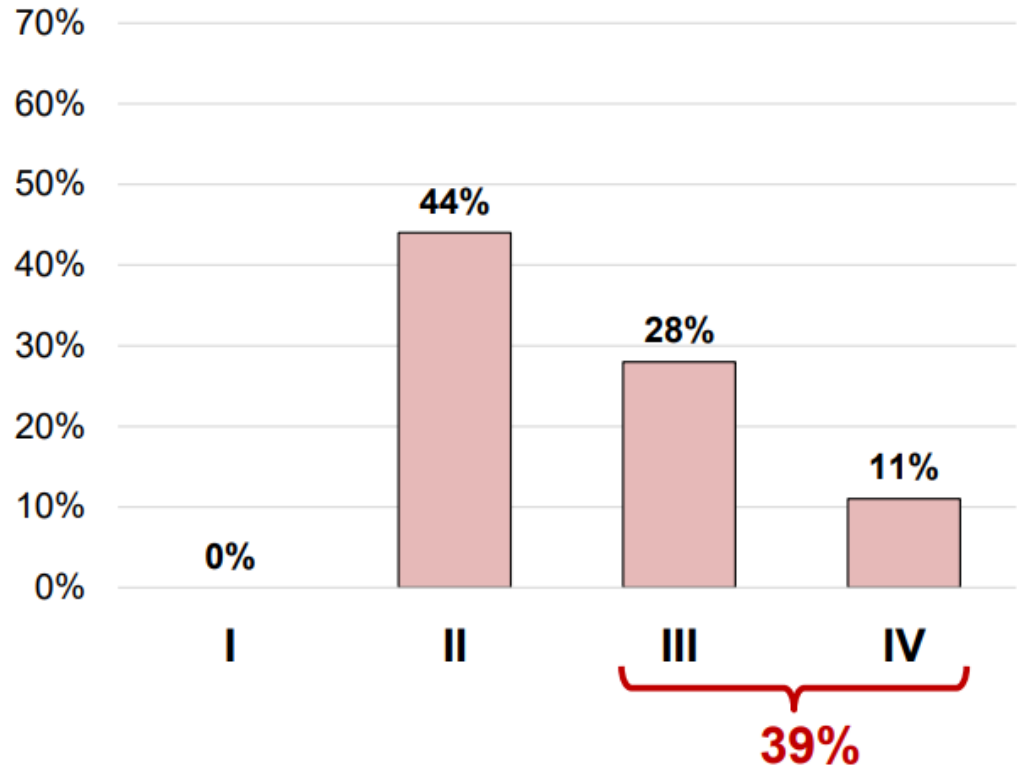
Allanore Arthritis Rheum 2008
Shah J Rheumatol 2010
Hesselstrand Rheumatology 2003

Screening Helps Diagnosing PH at Earlier Stage

NO SCREENING



SCREENING



Humbert M Am J Resp Crit Care Med 2006
Hachulla E Chest 2009

Scleroderma Renal Crisis

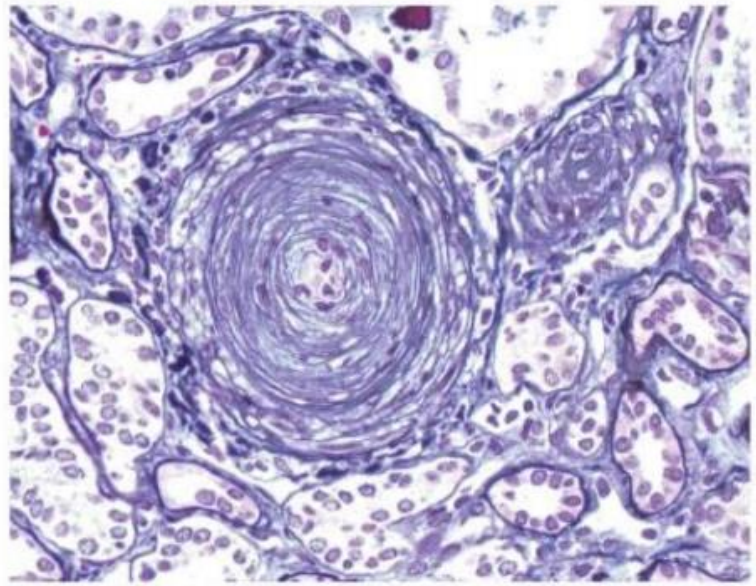
RISK FACTORS

- **Early diffuse skin disease**
  - 2-3 years from SSc onset, median 8 months
- **Anti-RNA polymerase III** (60%)
- **Use of corticosteroids**
  - >15 mg/d or low doses for longer time

KEY FACTS

- **Can mark SSc onset or precede SSc diagnosis**
  - 20% no skin involvement

Prevalence 12-20%



Penn Q J Med 2007
Teixeira Ann Rheum Dis 2008
Guillven Rheumatology 2012
Batal Int J Rheumatol 2010

Scleroderma Renal Crisis (SRC): Clinical Presentation

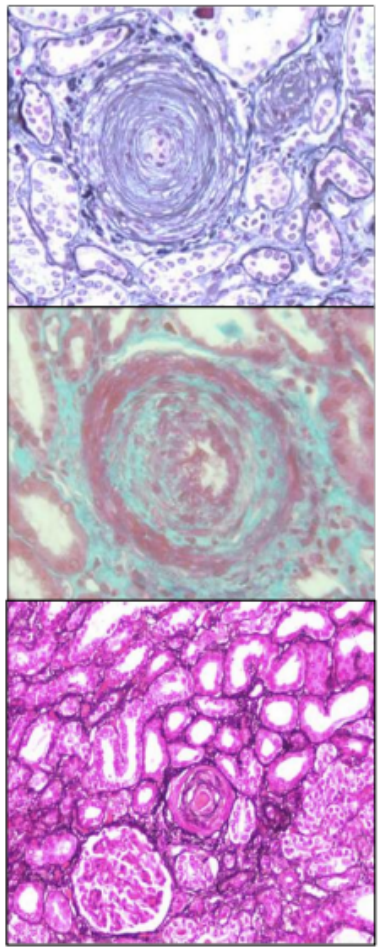
SRC Typical Features

- **Very high blood pressure**
  increase >20mmHg over "usual" blood pressure (i.e. 160/90)
- **Sudden renal failure**
  raising creatinine, proteinuria
- **Malignant hypertension**
  flash pulmonary edema, headache, retinopathy, encephalopathy
- **Hemolytic anemia and/or thrombocytopenia**
  thrombotic microangiopathy, schistocytes

SRC Atypical Features

- → Without renal failure (**early phase**)
- → Without hypertension (**10%**)
- → Asymptomatic pericardial effusion, arrhythmias

Kidney Biopsy in Scleroderma Renal Crisis (SRC)



Time is of the essence

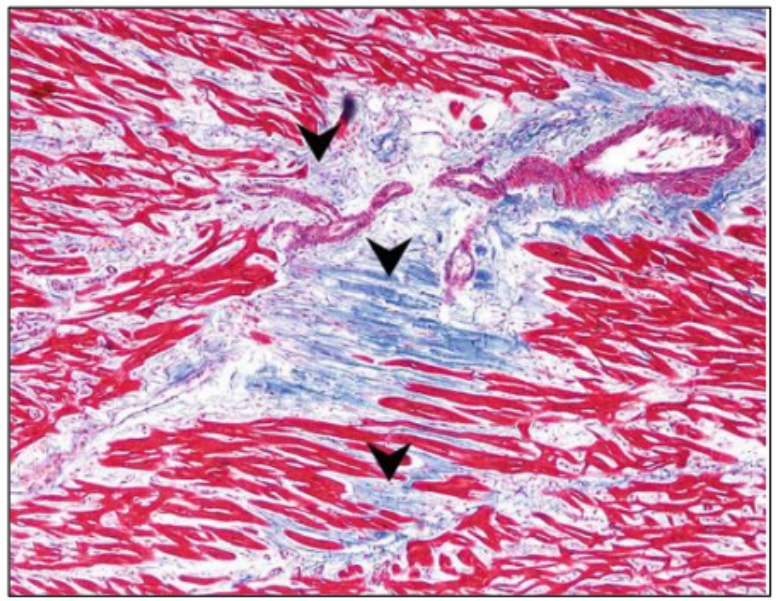
- Confirm diagnosis

  - DDx: pauci-immune GNF (ANCA+), interstitial nephritis, FSGS

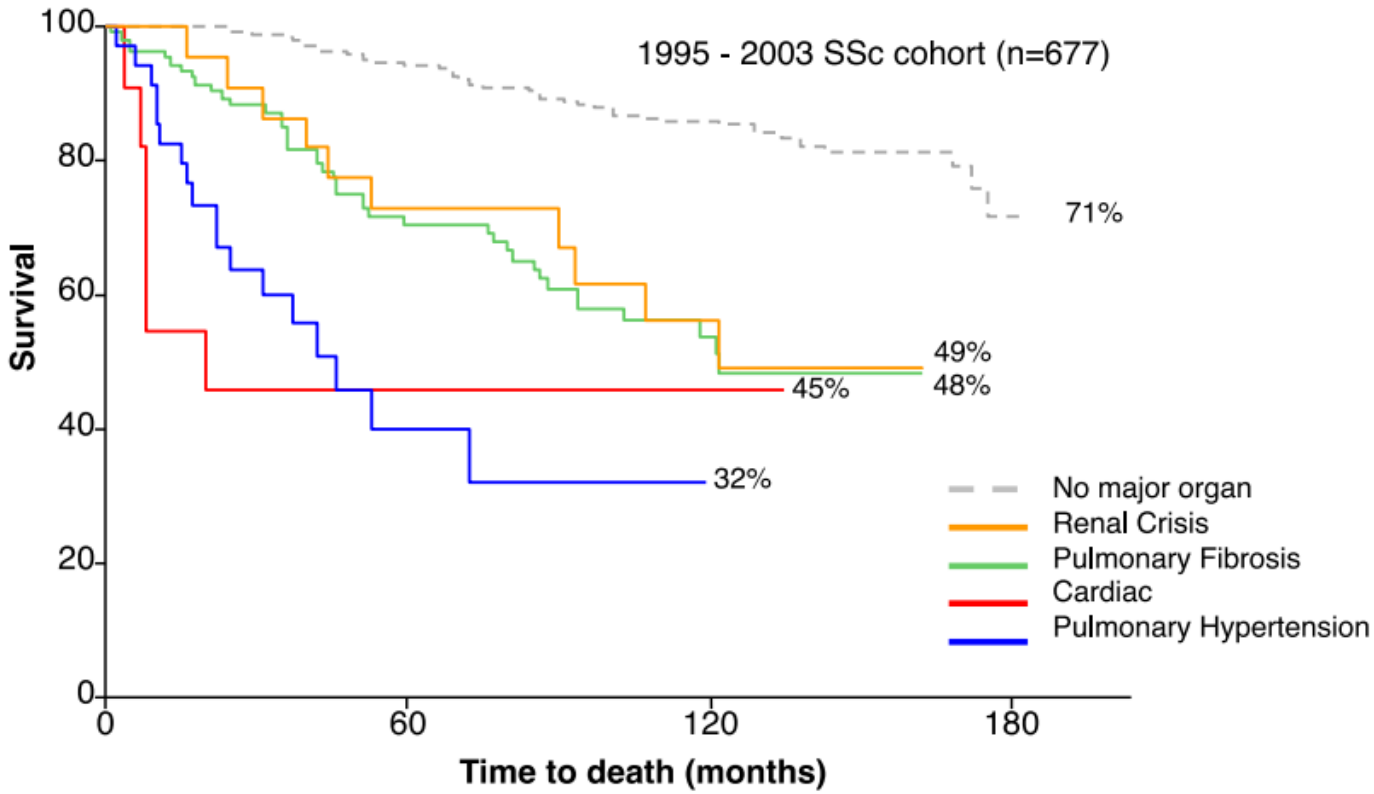
- Define extent of damage, identify irreversible renal involvement
- Establish prognosis, help setting long-term goals and patient expectations

Penn Q J Med 2007
Teixeira Ann Rheum Dis 2008
Guillven Rheumatology 2012
Batal Int J Rheumatol 2010

SSc Myocardial Involvement Drives Early Mortality



- Small vessel ischemia
- Myocardial inflammation



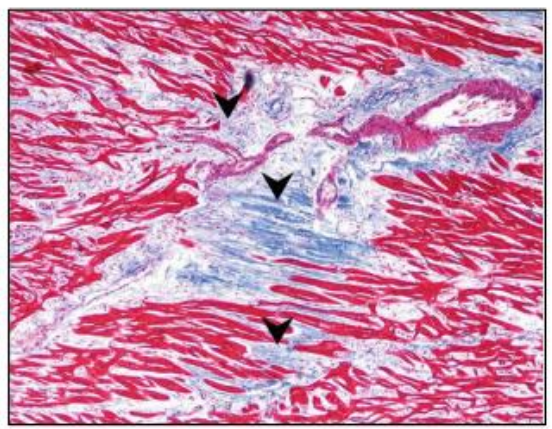
Increased risk of sudden death

Nihtyanova Arthritis Rheum 2014

Scleroderma Primary Cardiac Involvement - Risk Factors

Demographic features

- Older age at SSc onset
- Male gender
- Black/African American



SSc Clinical Phenotype

- Diffuse skin disease
- **Early disease, rapidly progressing**
- **Inflammatory myositis**
- **Inflammatory arthritis**
- **Tendon Friction Rubs**
- Late pattern on capillaroscopy
- Lung Involvement
- Anti-SCL70, **RNA Pol III**, U3-RNP

Bissel Rheumatology 2017
Allanore Ann Rheum Dis 2010
Ross Diagnostics 2021

Evaluation of Heart Involvement in SSc

All SSC Patients Yearly

- **Functional Assessment**
- **EKG**
- **Echocardiogram**
- **PFTs**
- **Blood Tests**

  Troponin, CK
  BNP, NTproBNP
  Lipids, HbA1C

New Symptoms Abnormal Findings

- Unexplained dyspnea
- Palpitations
- Syncope or pre-syncope
- Chest pain
- Dependent edema

- Troponin elevation
- BNP elevation
- LV dysfunction, ↓LVEF
- Ischemic changes
- Arrythmia, conduction defects

Cardiology Referral

- **Cardiac MRI**
- **Stress test**
- **Coronary angiogram**
- **Right heart catheterization**
- **Holter Event recorder**
- **Cardiac Electrophysiology**

AICD may save lives!

Ross Diagnostics 2021 Bissel Rheumatology 2017 Bernardo J Rheum 2011

General Principles for Evaluation of Organ Involvement in SSc

- Evaluate every patient for organ involvement (exp. lung and heart)
- Recognize associated factors and stratify risk
- Screen early - do not await for symptoms development
- Accurate physical examination can be very helpful
- Assess for comorbidities

- PFTs and ECHO should be obtained annually or sooner with new symptoms
- Screening algorithms and high yield testing (HRCT) indicated
  - patients at risk, early phases, new symptoms

- Early and accurate diagnosis = earlier intervention = more effective therapies

ACR Convergence
Where Rheumatology Meets
#ACR23

Developing the ACR Systemic Autoimmune Rheumatic Disease-ILD Guidelines

Elana J. Bernstein, MD, MSc
Florence Irving Associate Professor of Medicine
Director, Columbia/NewYork-Presbyterian Scleroderma Center
Columbia University Irving Medical Center

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EGYSIR

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ACR Convergence
Where Rheumatology Meets
#ACR23

Presentation of the systemic autoimmune rheumatic disease-ILD screening, monitoring and treatment guidelines

Endorsed by ACR and CHEST

Sindhu Johnson MD PhD
Director, Toronto Scleroderma Program
Director, Clinical Epidemiology Program, Dalla Lana School of Public Health
Professor of Medicine, University of Toronto

Guideline Development Process

Adapted from https://rheumatology.org/clinical-practice-guidelines

2 guideline summaries available online
3 manuscripts currently under peer review:
- Screening/Monitoring
- Treatment
- Patient Panel

Anticipate publication by Spring 2024 in *A&R* and *AC&R*

Core Team

- Sindhu R. Johnson (PI)
- Elana J. Bernstein
- Marcy B. Bolster
- Jonathan H. Chung
- Sonye K. Danoff
- Michael D. George
- Dinesh Khanna
- Reza D. Mirza
- Gordon Guyatt (GRADE expert)
- Ilya Ivlev (Co-lit review lead)
- Stacey Uhl (Co-lit review lead)

6 rheumatologists
1 pulmonologist
1 thoracic radiologist
1 GRADE expert
2 literature review experts

Patient Panel

- 21 people with systemic autoimmune rheumatic diseases (SARDs)
  - 4 (19%) at risk for interstitial lung disease (ILD); 17 (81%) with ILD
  - 16 (71%) women
  - Median age 53 (range 33-73) years
  - 14 (67%) White, 7 (33%) Black or multiracial; 2 (10%) Hispanic

PICO: Population of Interest

- Age ≥ 17 years
- SARDs with a high risk of ILD: SSc, RA, IIM, MCTD, SjD

- *Excluded: pediatric SARDs, SLE, ANCA-associated vasculitis, sarcoidosis, ankylosing spondylitis, undifferentiated connective tissue disease, interstitial pneumonia with autoimmune features, unclassifiable ILD*

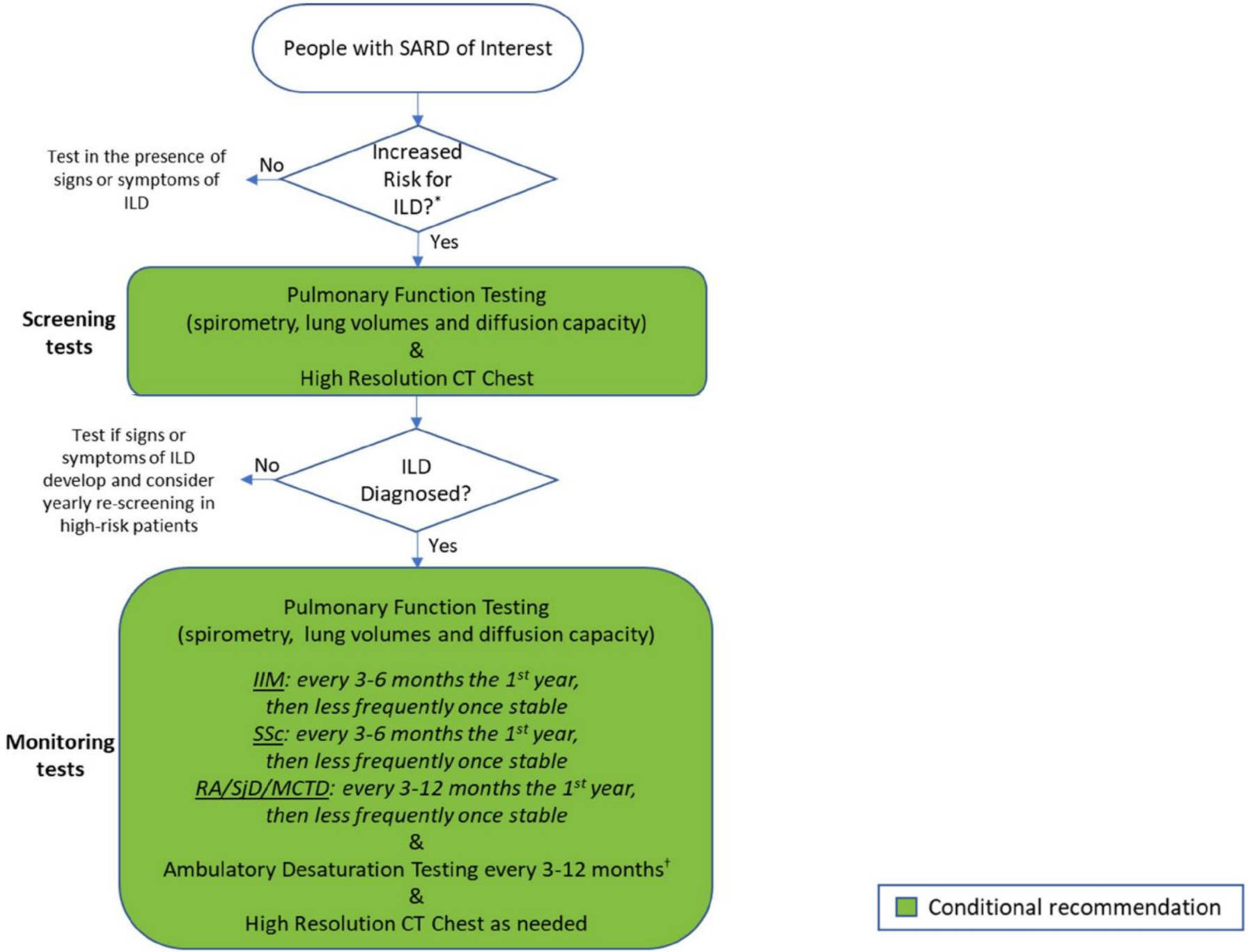
Who should be screened?

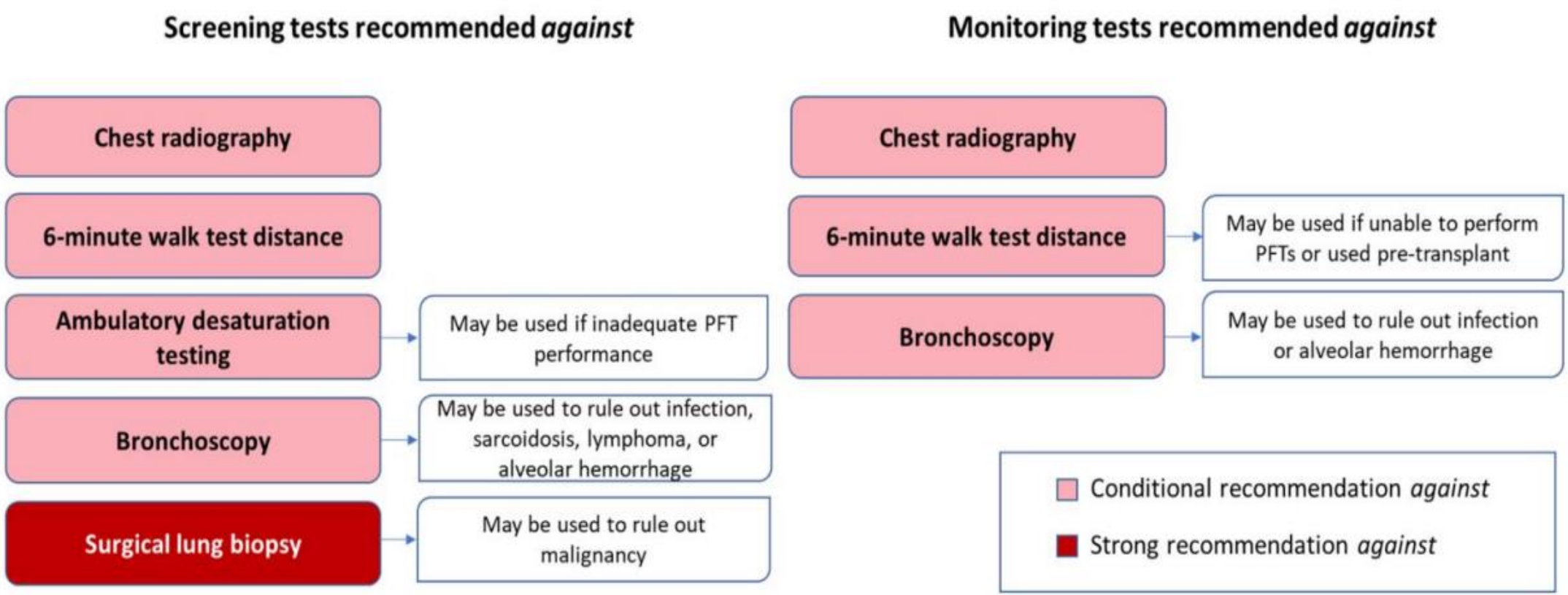
American College of Rheumatology
Empowering Rheumatology Professionals

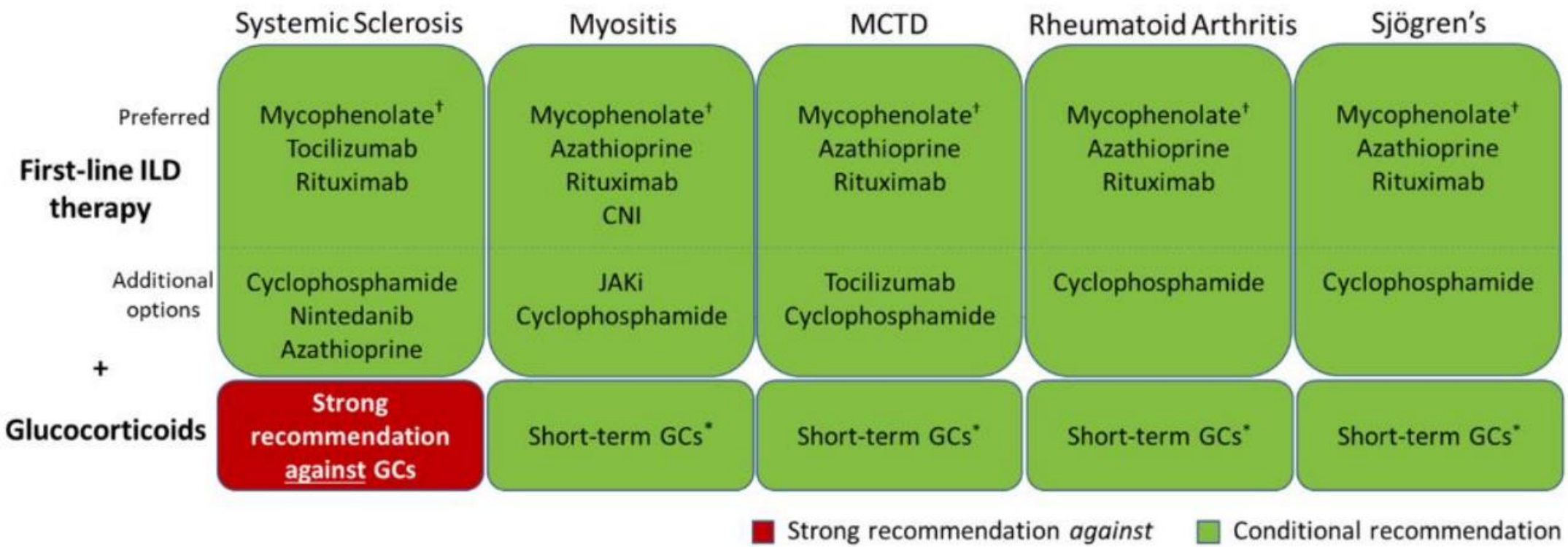
RA, SSc, IIM, MCTD, and SjD all confer an increased risk of developing ILD compared to the general population.

However, risks of developing ILD and ILD progression vary between and within these diseases.

Disease	Risk Factors
Systemic sclerosis	• Scl-70, ANA with nucleolar pattern • Diffuse subtype, male sex, African-American race • Early disease (first 5-7 years after onset) • Elevated acute phase reactants
Rheumatoid arthritis	• High titer RF, high titer anti-CCP • Smoking, older age at RA onset, high disease activity • Male sex, higher BMI
Idiopathic inflammatory myopathies	• Jo-1, PL7, PL12, EJ, OJ, KS, Ha, Zo, Ku, Pm/Scl, Ro52 • Anti-MDA5 • Mechanic's hands, arthritis/arthralgia, ulcerating lesions
Mixed connective tissue disease	• Dysphagia, Raynaud phenomenon, • Other SSc clinical or laboratory features
Sjögren's disease	• Anti-Ro52 antibody, ANA • Raynaud phenomenon, older age, lymphopenia


People with SARD of Interest
Increased Risk for ILD?*
No
Test in the presence of signs or symptoms of ILD
Yes
Screening tests
Pulmonary Function Testing
(spirometry, lung volumes and diffusion capacity)
&
High Resolution CT Chest
Test if signs or symptoms of ILD develop and consider yearly re-screening in high-risk patients
No
ILD Diagnosed?
Yes
Monitoring tests
Pulmonary Function Testing
(spirometry, lung volumes and diffusion capacity)
IIM: every 3-6 months the 1st year, then less frequently once stable
SSc: every 3-6 months the 1st year, then less frequently once stable
RA/SjD/MCTD: every 3-12 months the 1st year, then less frequently once stable
&
Ambulatory Desaturation Testing every 3-12 months†
&
High Resolution CT Chest as needed
Conditional recommendation


Screening tests recommended *against*
Chest radiography
6-minute walk test distance
Ambulatory desaturation testing
May be used if inadequate PFT performance
Bronchoscopy
May be used to rule out infection, sarcoidosis, lymphoma, or alveolar hemorrhage
Surgical lung biopsy
May be used to rule out malignancy
Monitoring tests recommended *against*
Chest radiography
6-minute walk test distance
May be used if unable to perform PFTs or used pre-transplant
Bronchoscopy
May be used to rule out infection or alveolar hemorrhage
Conditional recommendation *against*
Strong recommendation *against*


Systemic Sclerosis
Myositis
MCTD
Rheumatoid Arthritis
Sjögren's
First-line ILD therapy
Preferred
Mycophenolate†
Tocilizumab
Rituximab
Mycophenolate†
Azathioprine
Rituximab
CNI
Mycophenolate†
Azathioprine
Rituximab
Mycophenolate†
Azathioprine
Rituximab
Mycophenolate†
Azathioprine
Rituximab
Additional options
Cyclophosphamide
Nintedanib
Azathioprine
JAKi
Cyclophosphamide
Tocilizumab
Cyclophosphamide
Cyclophosphamide
Cyclophosphamide
+
Glucocorticoids
Strong recommendation against GCs
Short-term GCs*
Short-term GCs*
Short-term GCs*
Short-term GCs*
Strong recommendation against
Conditional recommendation

Progression of ILD

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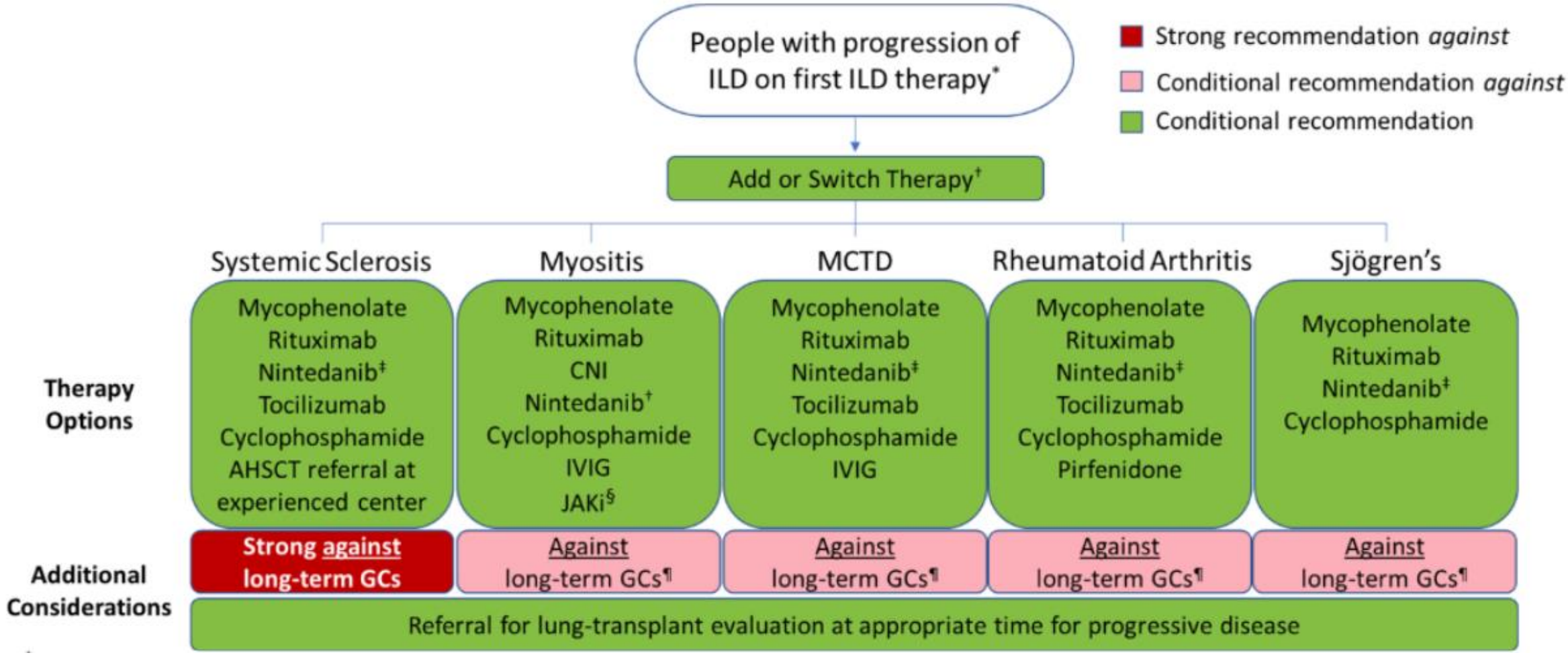
Progression was defined using the INBUILD trial criteria

- ✓ a relative decline in the FVC of at least 10% of the predicted value,
- ✓ a relative decline in the FVC of 5% to <10% of the predicted value and worsening of respiratory symptoms, or an increased extent of fibrosis on high-resolution CT
- ✓ worsening of respiratory symptoms and an increased extent of fibrosis

all within 24 months.

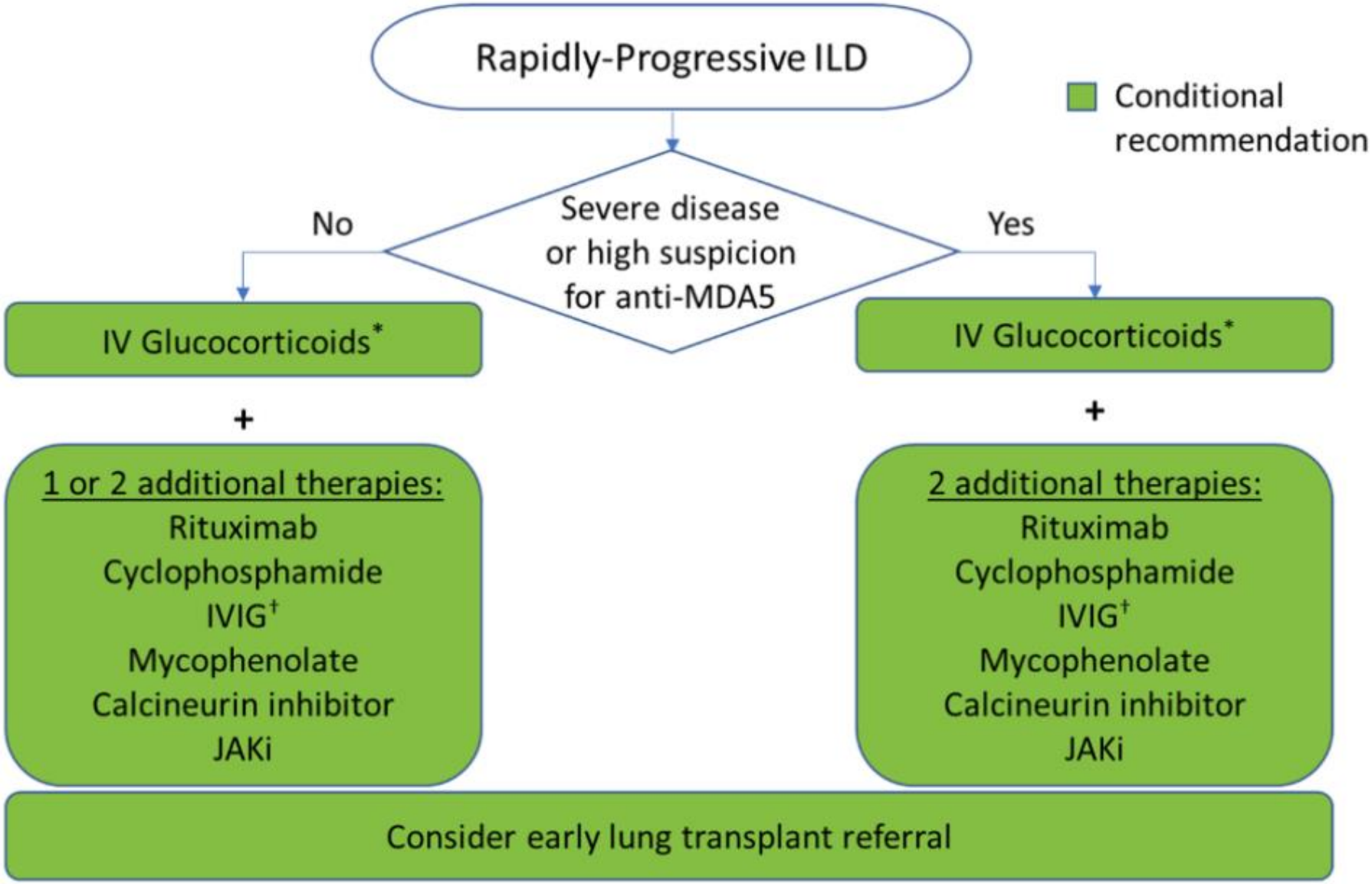
Flaherty KR et al. *N Engl J Med.* 2019;381(18):1718-1727.


People with progression of ILD on first ILD therapy*
Strong recommendation against
Conditional recommendation against
Conditional recommendation
Add or Switch Therapy†
Systemic Sclerosis
Myositis
MCTD
Rheumatoid Arthritis
Sjögren's
Therapy Options
Mycophenolate
Rituximab
Nintedanib‡
Tocilizumab
Cyclophosphamide
AHSCT referral at experienced center
Mycophenolate
Rituximab
CNI
Nintedanib†
Cyclophosphamide
IVIG
JAKi§
Mycophenolate
Rituximab
Nintedanib‡
Tocilizumab
Cyclophosphamide
IVIG
Mycophenolate
Rituximab
Nintedanib‡
Tocilizumab
Cyclophosphamide
Pirfenidone
Mycophenolate
Rituximab
Nintedanib‡
Cyclophosphamide
Additional Considerations
Strong against long-term GCs
Against long-term GCs¶
Against long-term GCs¶
Against long-term GCs¶
Against long-term GCs¶
Referral for lung-transplant evaluation at appropriate time for progressive disease

Rapidly Progressive ILD (RP-ILD)

A subpopulation of ILD characterized by a

- rapid progression from no oxygen or a patient's baseline oxygen requirement to a high oxygen requirement or intubation
- within days to weeks
- without a documented alternative cause (e.g., infection, heart failure)


Rapidly-Progressive ILD
Conditional recommendation
Severe disease or high suspicion for anti-MDA5
No
Yes
IV Glucocorticoids*
+
1 or 2 additional therapies:
Rituximab
Cyclophosphamide
IVIG†
Mycophenolate
Calcineurin inhibitor
JAKi
IV Glucocorticoids*
+
2 additional therapies:
Rituximab
Cyclophosphamide
IVIG†
Mycophenolate
Calcineurin inhibitor
JAKi
Consider early lung transplant referral

Cautionary note

These guidelines should not be used by insurers to mandate a specific order of prescribing

Clinicians must retain the latitude to prescribe medications based on individual patient's factors & preferences

Interventions	Examples
Integrative	
Exercise	Aerobic, resistance training, yoga, tai chi
Palliative care	Symptom treatment (cough, pain, air hunger), end of life planning
Physiotherapy	Chest physiotherapy, airway clearance, incentive spirometry
Pulmonary Rehabilitation	Cardiopulmonary rehabilitation, resistance training
Supplemental oxygen	Oxygen administration by nasal prongs
Pharmacologic	
Gastroesophageal reflux management	Proton pump inhibitors, H2 blockers
Pneumocystis jirovecii pneumonia prophylaxis	Trimethoprim sulfamethoxazole
Promotility agents	Domperidone
Vaccines	Measles, mumps, rubella, influenza, Covid-19, pneumococcus, zoster, RSV

Defining Clinical Phenotype in IgG4-RD: Lessons from ACR/EULAR Classification Criteria


Arthritis & Rheumatology
Vol. 72, No. 1, January 2020, pp 1–3
DOI: 10.1002/art.41149
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EDITORIAL

Classification of IgG4-Related Disease: A Medical Marvel of Our Time

Sindhu R. Johnson[1] and Arthur Bookman[2]

John H. Stone, M.D., M.P.H.
Professor of Medicine, Harvard Medical School
The Edward A. Fox Chair in Medicine
Massachusetts General Hospital

B Cells, T Cells, and Immune-Mediated Fibrosis in IgG4-related Disease

Cory A. Perugino, D.O.
Assistant Professor of Medicine
Harvard Medical School
Principal Investigator
Massachusetts General Hospital
Center for Immunology and Inflammatory Diseases

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ACR Convergence
Where Rheumatology Meets
#ACR23

Treatment and Monitoring of IgG4-related disease

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Arthritis & Rheumatology
Vol. 72, No. 1, January 2020, pp 7–19
DOI 10.1002/art.41120

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SPECIAL ARTICLE

The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease

Zachary S. Wallace,[1] Ray P. Naden,[2] Suresh Chari,[3] Hyon Choi,[1] Emanuel Della-Torre,[4] Jean-Francois Dicaire,[5] Phil A. Hart,[6] Dai Inoue,[7] Mitsuhiro Kawano,[8] Arezou Khosroshahi,[9] Kensuke Kubota,[10] Marco Lanzillotta,[11] Kazuichi Okazaki,[12] Cory A. Perugino,[1] Amita Sharma,[1] Takako Saeki,[13] Hiroshi Sekiguchi,[3] Nicolas Schleinitz,[14] James R. Stone,[1] Naoki Takahashi,[3] Hisanori Umehara,[15] George Webster,[16] Yoh Zen,[17] and John H. Stone,[1] for the American College of Rheumatology/European League Against Rheumatism IgG4-Related Disease Classification Criteria Working Group

8 Weighted Inclusion Domains

- Serum IgG4
- Histopathology
- Immunostaining
- Glandular enlargement
- Chest & thoracic aorta
- Pancreas & biliary tree
- Kidney
- Retroperitoneum

Each domain had 3-4 weighted items contributing to the overall score

THRESHOLD: 20 total points

- Sensitivity: 86.5%
- Specificity: 98.5%

Lesson 2: Classification Criteria work in practice, too

- MITIGATE
  - Inebilizumab in IgG4-RD
- INDIGO
  - Obexelimab in IgG4-RD
- AIG01
  - Elotuzumab in IgG4-RD
- Rilzabrutinib

- Many other trials & studies

The criteria do have blind spots.

- Meaning of hypocomplementemia
- Fibrotic disease

ACR/EULAR Criteria favor:

- Multi-organ disease
- Elevated serum IgG4
- Organs accessible to biopsy

Unknowns

- Biologic plausibility?
- Stability of proposed phenotypes

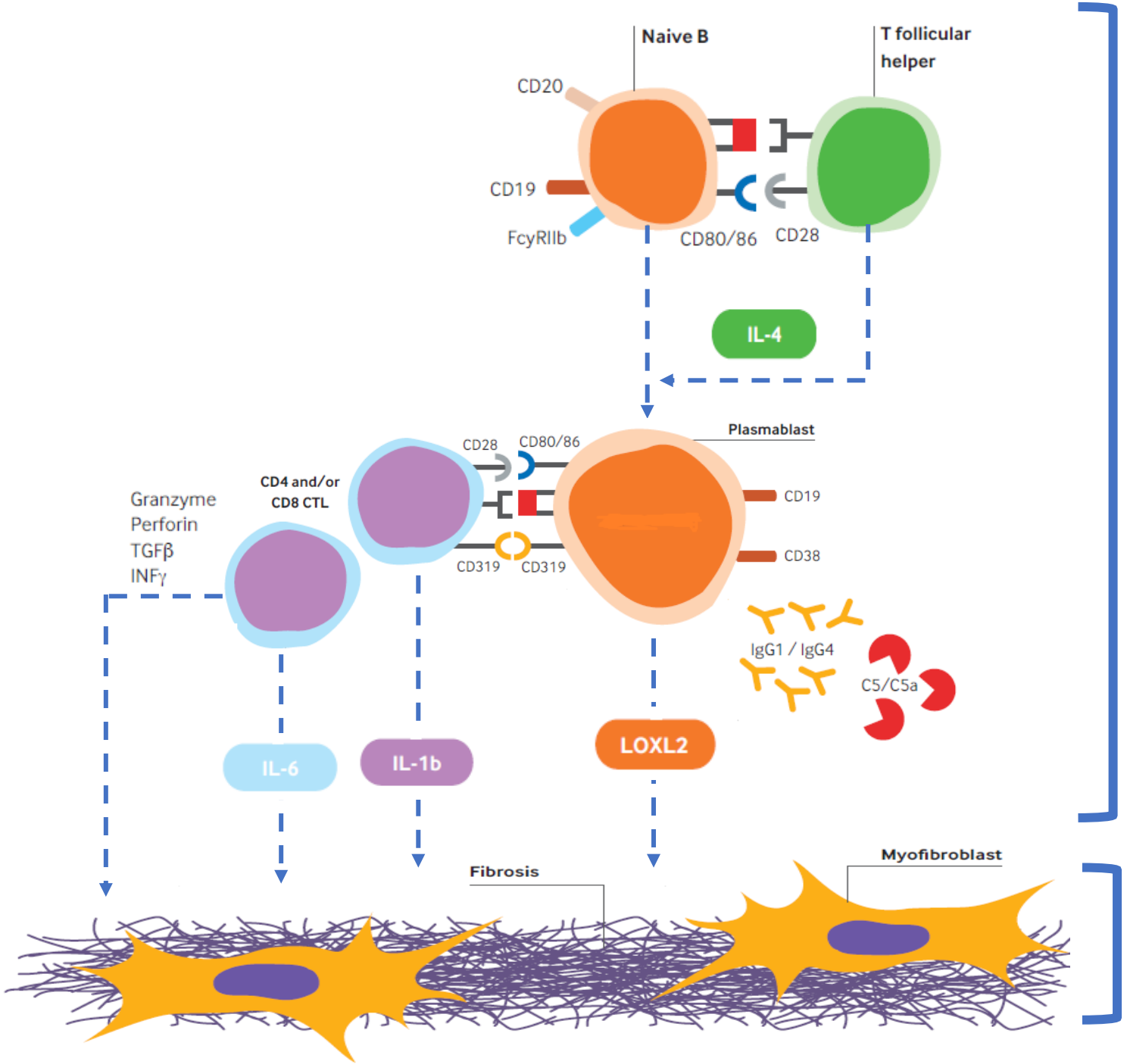
Pathophysiology

Antigen presented on class II major histocompatability complex

T cell receptor

Complement molecules

LOXL2: Lysyl Oxidae Homologue 2



Lanzillotta et al., BMJ 2020;369:m1067

Treatment – Overarching Principles

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SPECIAL ARTICLE

International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease

A. Khosroshahi,[1] Z. S. Wallace,[2] J. L. Crowe,[3] T. Akamizu,[4] A. Azumi,[5] M. N. Carruthers,[6] S. T. Chari,[7] E. Della-Torre,[8] L. Frulloni,[9] H. Goto,[10] P. A. Hart,[11] T. Kamisawa,[12] S. Kawa,[13] M. Kawano,[14] M. H. Kim,[15] Y. Kodama,[16] K. Kubota,[17] M. M. Lerch,[18] M. Löhr,[19] Y. Masaki,[20] S. Matsui,[21] T. Mimori,[16] S. Nakamura,[22] T. Nakazawa,[23] H. Ohara,[24] K. Okazaki,[25] J. H. Ryu,[7] T. Saeki,[25] N. Schleinitz,[26] A. Shimatsu,[27] T. Shimosegawa,[28] H. Takahashi,[29] M. Takahira,[14] A. Tanaka,[30] M. Topazian,[7] H. Umehara,[31] G. J. Webster,[32] T. E. Witzig,[7] M. Yamamoto,[33] W. Zhang,[32] T. Chibu,[34] and J. H. Stone[2]

- SYMPTOMATIC/ ASYMPTOMATIC
- URGENT CASES
- COMORBIDITIES
- “REVERSIBLE” vs “NOT-REVERSIBLE” fibrosis
- RELAPSING REMITTING COURSE

Kosroshahi et al. Arthritis Rheum

Treatment – First Line | Glucocorticoids

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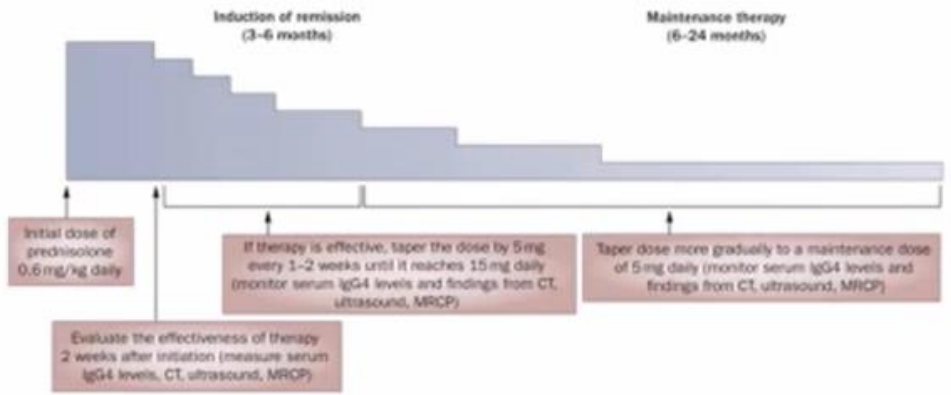
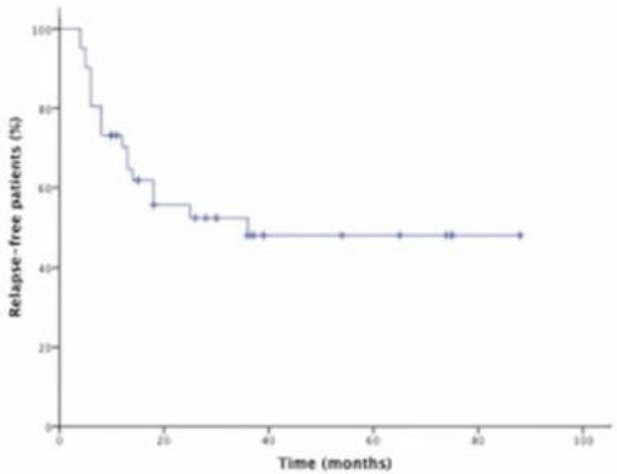
GLUCOCORTICOIDS

0.6-1 mg/Kg oral prednisone (equivalents)



Treatment – Disease Flare



Risk of IgG4RD relapse
25% within 1 year
46% within 2 years
50% within 3 years

Predictors of relapse
Multiorgan disease
Elevated IgG4 at baseline
Elevated IgE at baseline

Campochiaro et al, Scand J Rheumatol
Wallace et al, Rheumatology

Treatment – Maintenance | DMARDs

Disease Modifying Antirheumatic Drugs

Table 2 | Available therapeutic strategies for inducing and maintaining remission of IgG4 related disease (IgG4-RD)

Drug	Initial dose	Tapering	Maintenance	Study design
Glucocorticoids[111 137 150]	po PDN 0.6 mg/kg/day (2-4 weeks)	5 mg/1-2 weeks (2-6 months)	2.5-10 mg/day (6-36 months)	Retrospective cohort studies
	po PDN 30-60 mg/day (2-4 weeks)	5 mg/1-2 weeks (2-6 months)	2.5-10 mg/day (6-36 months)	
	iv MPDN 250-500 mg/day (3-5 days) → switch po	-	-	
	po PDN 0.5 v 1 mg/kg/day (4 weeks)	5-10% every 2 weeks	7.5-10 mg/day (24 weeks)	RCT
	po PDN 0.6 mg/kg/day (2-4 weeks)	(12 weeks)	5-7.5 mg/day v 0 mg/day (36 months)	RCT
DMARDs:				
Azathioprine[125]	po 0.5-2.5 mg/kg/day*	-	0.5-2.5 mg/kg/d† (median 29-60 months)	Case series
Methotrexate[45 132 151]	po/sc 15-20 mg/week*	-	15-20 mg/week sc† (median 15-60 months)	Case series
Leflunomide[131]	po 10-20 mg/day*	-	10-20 mg/day† (mean 12 months)	Case series
Mycophenolate mofetil[43 61 122 127]	po 1-1.5 g/day* (6 months)	po 0.5-1.0 g/day† (6 months)	po 0.5-1.0 g/day† (19±6 months)	RCT
	po 1-2 g/day*	-	1-2 g/day† (15-47 months)	Retrospective cohort studies
Cyclophosphamide[123]	po 50-100 mg/day* (3 months)	-	50 mg/day or maintain starting dose† (>9 months)	Prospective cohort study
Ciclosporin[113]	po 100 mg/day*	-	100 mg/day†	Case series
Tacrolimus[124 130]	po 1-2.5 mg/day*	-	1-2.5 mg/day†	Case series
6 Mercapto-purine[120]	po 0.7-2.6 mg/kg/day*	-	0.7-2.6 mg/kg/day†	Case report
Iguratimod[118 119]	po 50 mg/day*	-	50 mg/day*	Prospective cohort study

Lanzillotta et al, British Medical Journal

Treatment – Second Line | B-cell depletion

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RITUXIMAB (2 iv 1gr infusions 15 days apart)

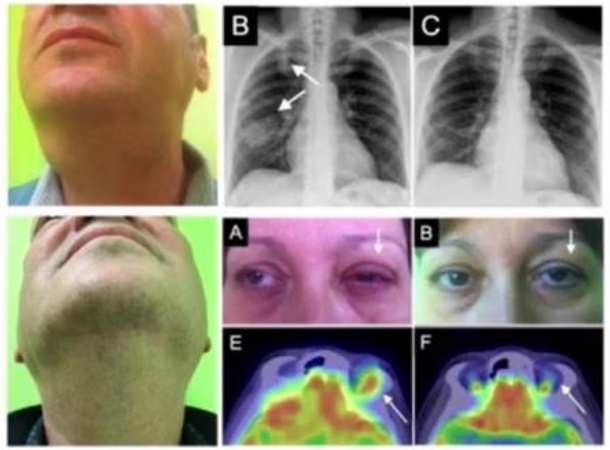

Table 2 Primary and secondary outcomes

Outcome	Proportion of participants (%)
Primary outcome	23/30 (77%)
Disease response (6 months)	29/30 (97%)
Sustained disease response	22/30 (73%)
Complete remission (6 months)	14/30 (47%)
Complete remission (6 months), exclusive of serum IgG4	18/30 (60%)
Complete remission (any time point)	18/30 (60%)
Complete remission (any time point), exclusive of serum IgG4	20/30 (67%)
Relapses occurring before month 6	3
Relapses occurring between months 6 and 12	4
Time to endpoint	**Duration (days)**
Time to disease response (mean±SD)*	43±37
Time to complete remission (mean±SD)*	198±87
Time to relapse (mean±SD)	210±105
Treatment	
Total prednisone dose equivalent (mg) administered in the 28 days prior to the 6 month study visit (mean, range)	15 (0–280)
Retreatment with RTX for relapses during the 12 months after enrolment	4/30 (13%)

*The time to disease response and time to complete remission measures overestimate the speed required to achieve these measures because an in-person visit was required for these measures.
RTX, rituximab.

Carruthers et al. Ann Rheum Dis

Treatment – Maintenance | B-cell depletion

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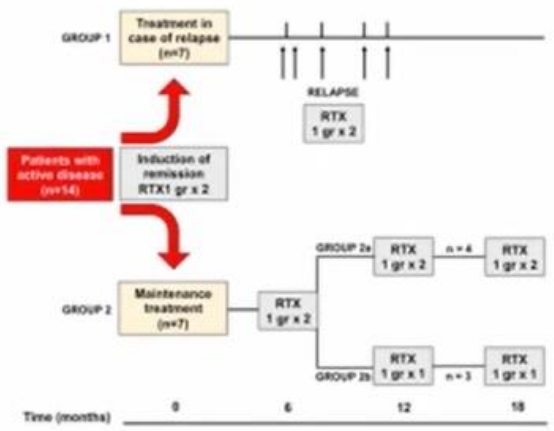
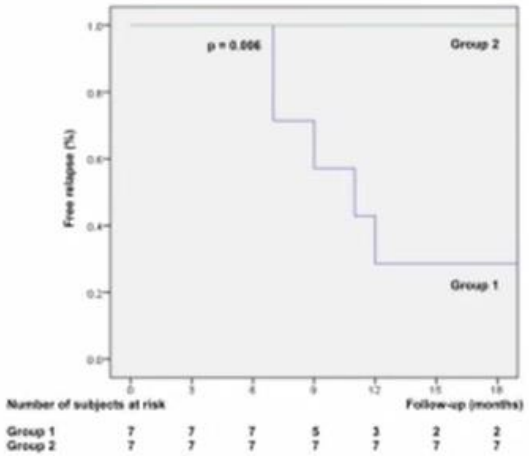
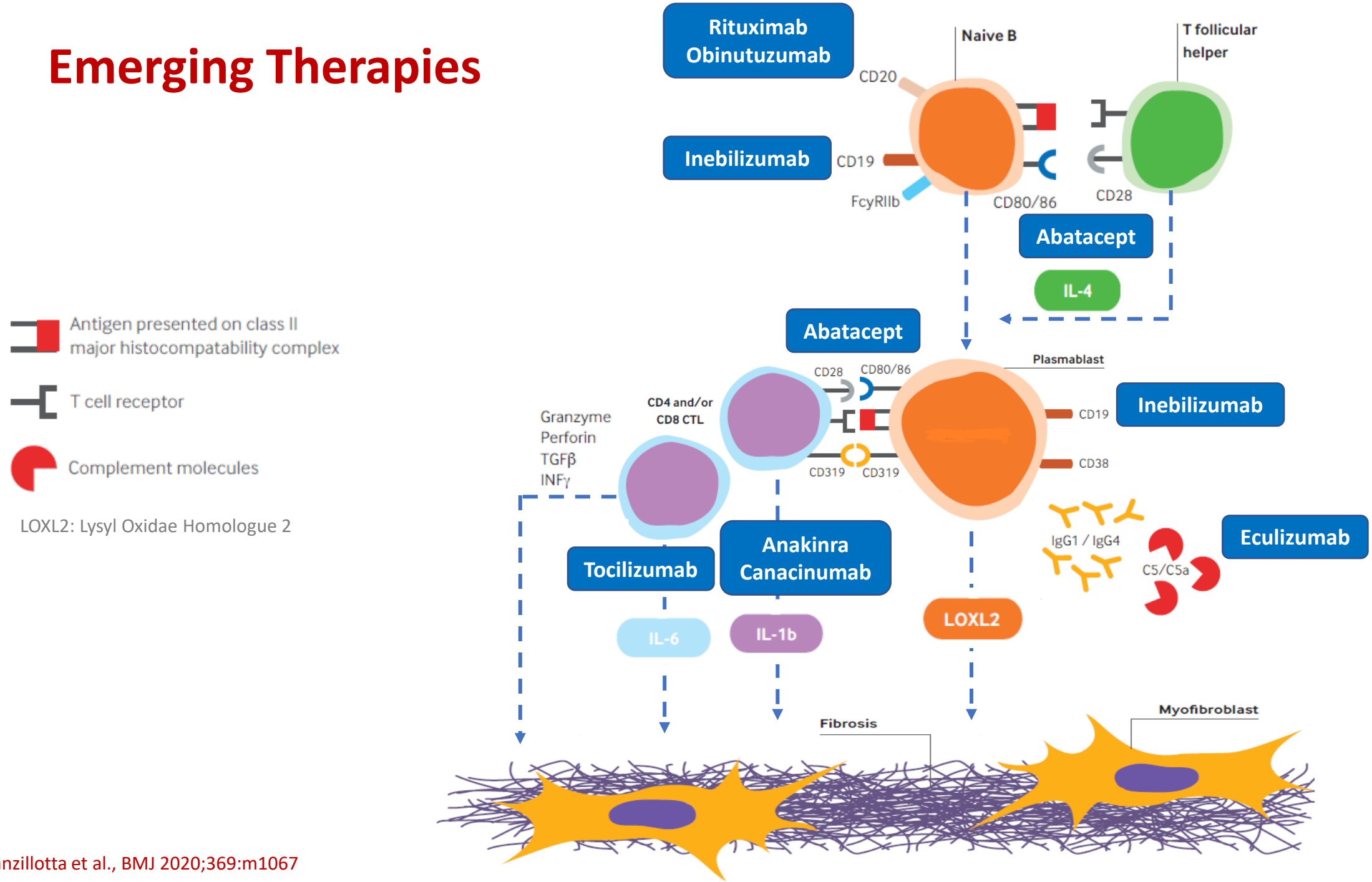




Della-Torre et al, EJIM

Emerging Therapies



LOXL2: Lysyl Oxidae Homologue 2

Lanzillotta et al., BMJ 2020;369:m1067

Treatment – Comorbidities

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SPECIAL ARTICLE

International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease

1. **Pancreatic** involvement: replacement of pancreatic enzymes / insulin / nutritionist
2. **Biliary tract** involvement: ursodeoxycholic acid / biliary stents / prophylactic antibiotics
3. **Urinary tract** involvement: ureteral stents
4. **Kidney** involvement: ace-inhibitors
5. **Retroperitoneal** involvement: pain killers
6. **Osteoporosis**: bisphosphonates

Khosroshahi et al. Arthritis Rheum

Monitoring – Serum IgG4 level

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Strenghts	Limitations
Elevated in 55-70%	Elevation may occur in a number of mimickers
Correlate with organ involvement	Do not normalize after glucocorticoids in up to 63% of cases
Widely available assay	Do not rise again at disease flare in nearly 10% of cases
Decline with clinical improvement in most patients	
Baseline elevation predicts relapse	

Carruthers, Annals of Rheumatic Diseases, 2014
Khosroshahi, Medicine, 2012

Monitoring – Clinically relevant biomarkers

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Type and subclass of biomarker	Examples	Comments
Disease activity	Serum IgG4, IgE, and eosinophils	Decrease with disease response to treatment. May not normalize at disease remission in patients presenting with marked elevation at diagnosis. Mild oscillation should not prompt additional investigations. Marked (>twofold) increase after remission should raise possibility of disease flare
	Serum IgG4/IgG ratio	Decreases with disease response to treatment
	CSF IgG4 indices	Decrease with disease response to treatment
	Plasmablasts and plasma cells	Decrease with disease response to treatment and increase at flare
	Serum ESR/CRP	More often correlate with disease activity in case of retroperitoneal and aortic involvement
	Serum C3, C4	May normalize in case of remission and decrease during flares, especially in case of renal involvement
	^{18}FDG-PET	Reduced ^{18}FDG uptake in response to treatment. Caution is needed when interpreting lymph node uptake because IgG4-RD lymphadenopathy is indistinguishable from reactive lymph nodes
Predictors of relapse	Serum IgG4, IgE, and eosinophils	The higher the baseline values, the greater the risk of relapse and the shorter the time to relapse
Fibrosis	-	-

Lanzillotta M, British Medical Journal, 2020

Monitoring – Proposed biomarkers

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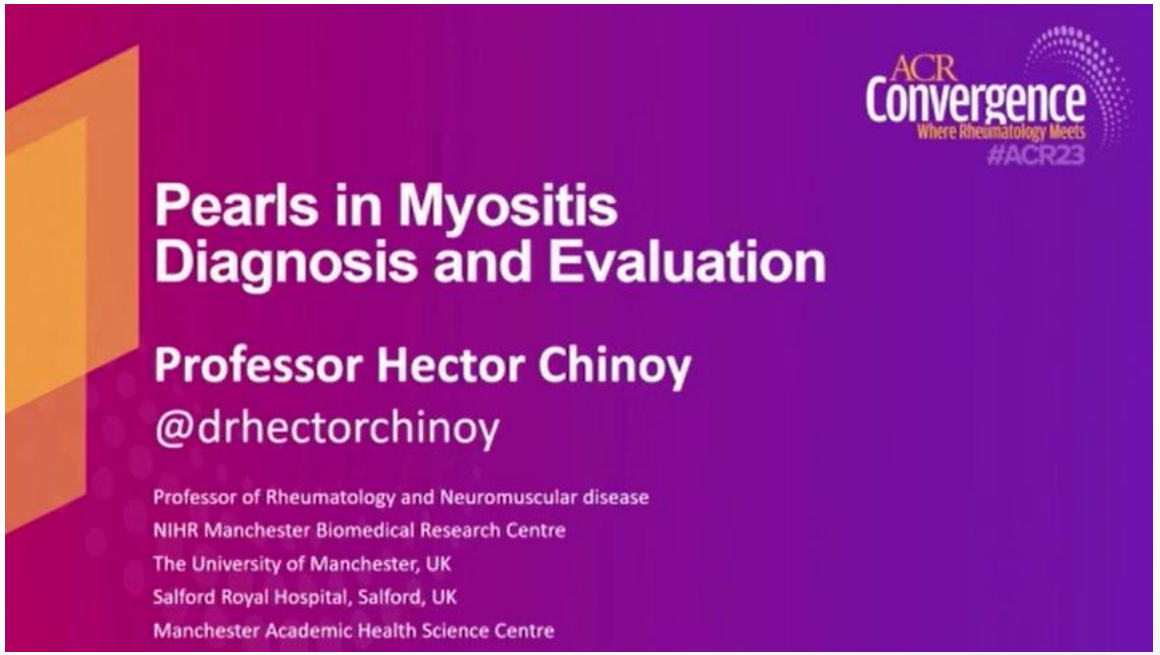
	Biomarker	Clinical relevance	Reference
Immunoglobulins	IgG2	Elevated in IgG4-related orbital disease compared to non-IgG4 orbital inflammation	Chan 2017 (26)
	IgG4	Elevated in 55-97% of patients, correlates with disease burden, decrease after treatment in the majority of patients, increased baseline levels predict refractory or relapsing disease	Ohara 2013 (8), Yu 2015 (9), Wallace 2016 (70), Hao 2016 (20), Kawa 2017 (12), Moon 2017 (13), Tanaka 2017 (14), Tan 2018 (15), Qi 2018 (16), Maritati 2019 (17), Aydemir 2019 (19)
	IgG4/IgG mRNA ratio	Elevated in active disease, superior diagnostic accuracy in IgG4-associated cholangitis/autoimmune pancreatitis, decreases with disease response to treatment	Doorenspleet 2016 (22)
	IgE	Increased serum levels in IgG4-RD, correlate with IgG4 levels, associated with a higher risk to relapse during follow-up, potential predictor of extraocular muscle enlargement in IgG4-related ophthalmic disease	Wallace 2016 (70), Culver 2017 (27), Tsubota 2020 (57)
	IgA	Relapsed IgG4-RD patients had significantly lower levels at baseline	Sasaki 2018 (71)
	sFLC	κ sFLC and κ/λ ratio correlated positively with the number of involved organs and IgG4-RD RI, κ sFLC and λ sFLC increased in renal involvement	Martin-Nares 2021 (28), Ikemune 2021 (29)

Iaccarino L, Clin Exp Rheumatol, 2022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Where Rheumatology Meets
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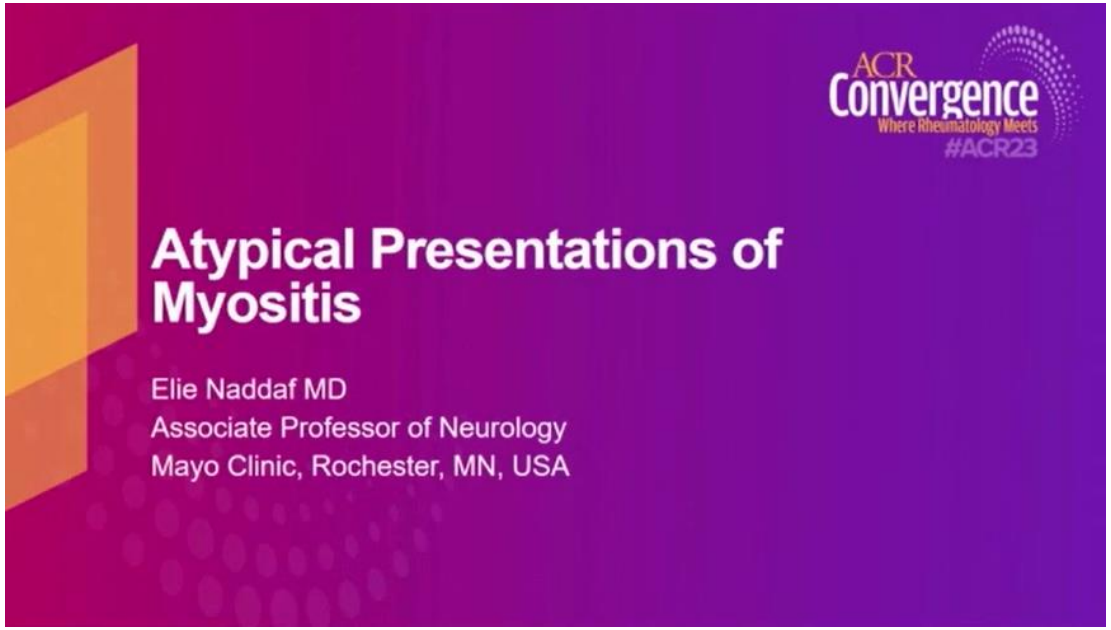
Pearls in Myositis
Diagnosis and Evaluation
Professor Hector Chinoy
@drhectorchinoy
Professor of Rheumatology and Neuromuscular disease
NIHR Manchester Biomedical Research Centre
The University of Manchester, UK
Salford Royal Hospital, Salford, UK
Manchester Academic Health Science Centre


ACR Convergence
Where Rheumatology Meets
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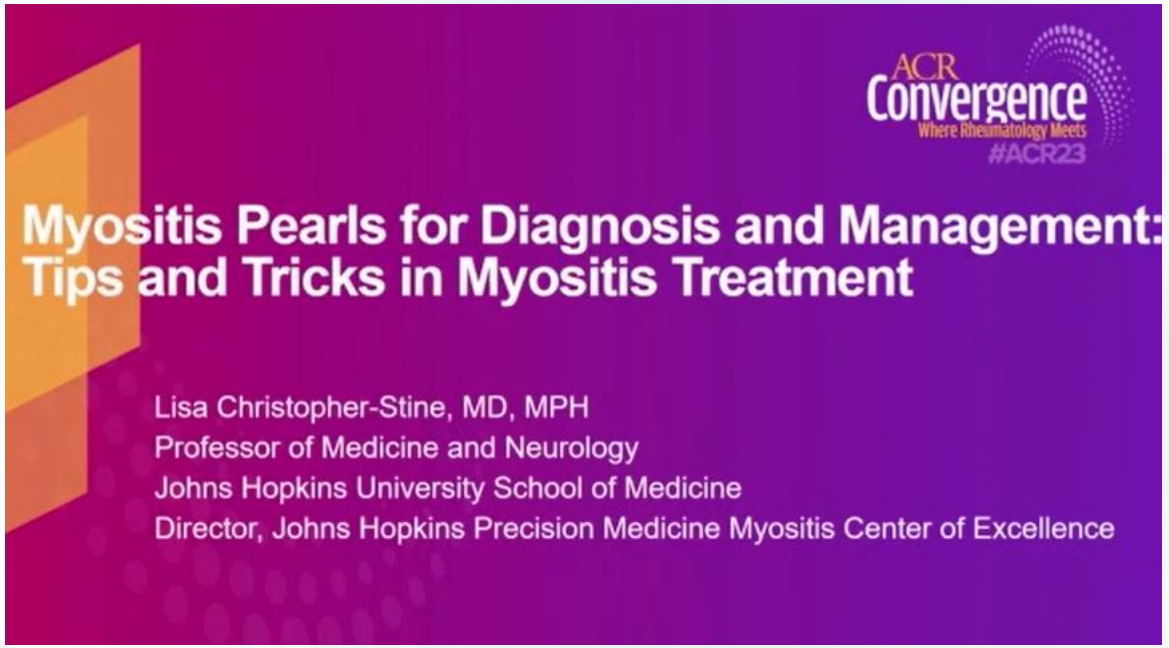
Atypical Presentations of
Myositis
Elie Naddaf MD
Associate Professor of Neurology
Mayo Clinic, Rochester, MN, USA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Where Rheumatology Meets
#ACR23
Myositis Pearls for Diagnosis and Management:
Tips and Tricks in Myositis Treatment
Lisa Christopher-Stine, MD, MPH
Professor of Medicine and Neurology
Johns Hopkins University School of Medicine
Director, Johns Hopkins Precision Medicine Myositis Center of Excellence

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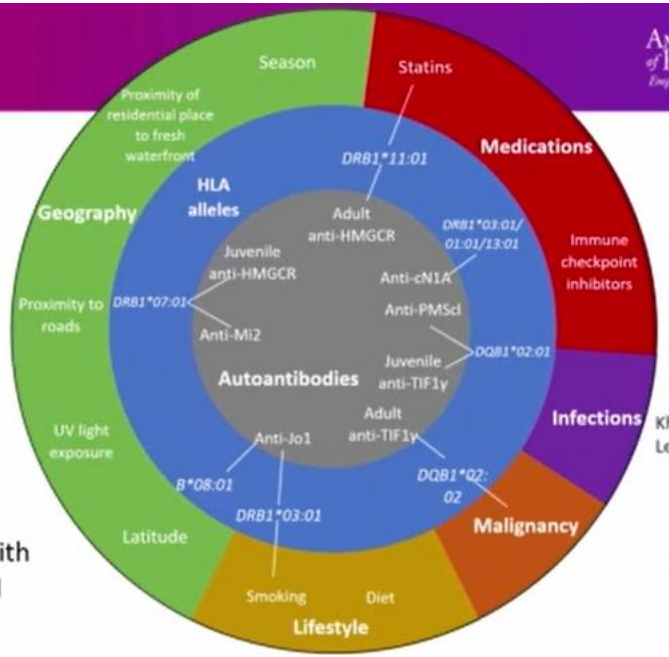
"What caused my condition Doctor?"

Interaction of environmental and genetic risk factors with autoantibodies in IIM patients



Khoo T, Lilleker JB, Thong BY, Leclair V, Lamb JA, Chinoy H. Epidemiology of the idiopathic inflammatory myopathies. Nat Rev Rheumatol. 2023 doi: 10.1038/s41584-023-01033-0. PMID: 37803078.

The Changing Landscape of Myositis

Polymyositis

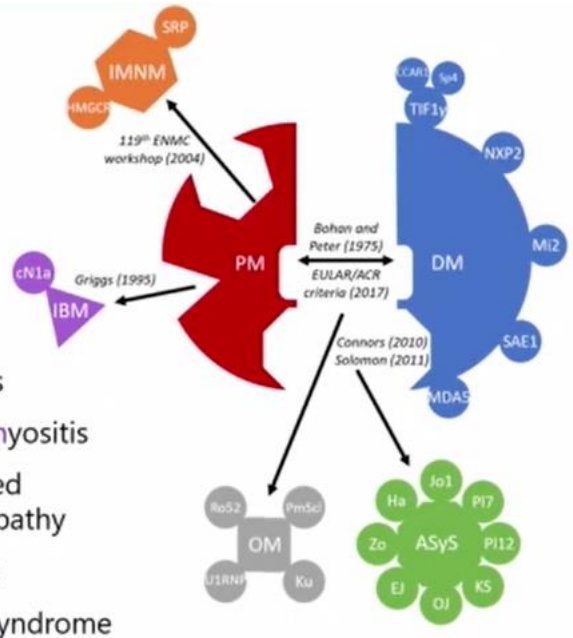
Dermatomyositis

Inclusion body myositis

Immune mediated necrotising myopathy

Overlap myositis

Antisynthetase syndrome



Khoo T, Lilleker JB, Thong BY, Leclair V, Lamb JA, Chinoy H. Epidemiology of the idiopathic inflammatory myopathies. Nat Rev Rheumatol. 2023 Oct 6. doi: 10.1038/s41584-023-01033-0. Epub ahead of print. PMID: 37803078.

The Spectrum of Statin-Associated Myotoxicity

		Spectrum of statin-related muscle side effects		Incidence (/100,000 person-years)[1]	Disease features	CK elevation	HMGCR Ab
Early after statin commencement	Fully resolves with statin cessation	Myalgia without CK elevation	Asymptomatic CK elevation	190	Myalgia / asymptomatic	Normal / <4x ULN	Anti-HMGCR not present
		Myopathy		5	Myalgia +/- weakness	>4x <10x ULN	
	Resolution depends on muscle damage	Rhabdomyolysis		0.1-8.4	Myalgia and/or weakness AKI	>10x up to 50x ULN	
Delayed onset after statin commencement (median 38 months)[2]	Does not resolve with statin cessation	Immune-mediated necrotising myopathy (IMNM)		0.2/100,000 person-years	Muscle weakness +/- pain	>10x ULN	Anti-HMGCR present

[1]Derived from Alfirevic, A. *et al.* Phe... for statin-induced myotoxicity. C...

[2]Basharat, P. *et al.* Statin-Induced A... Myopathy. *J Am Coll Card...*

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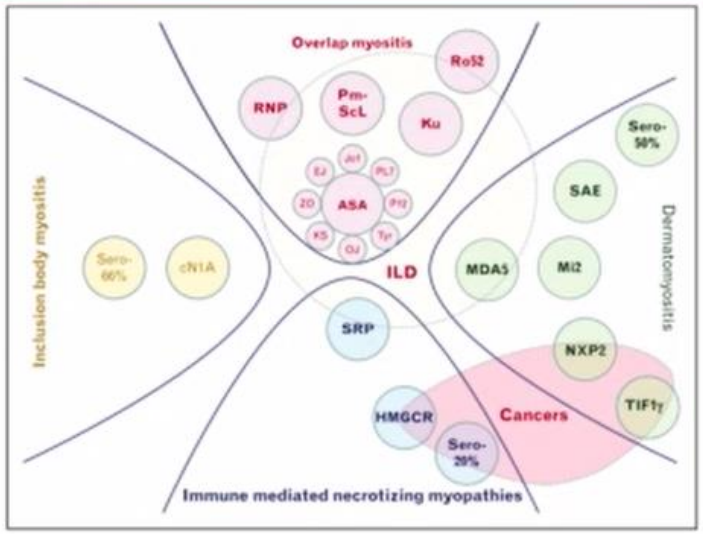


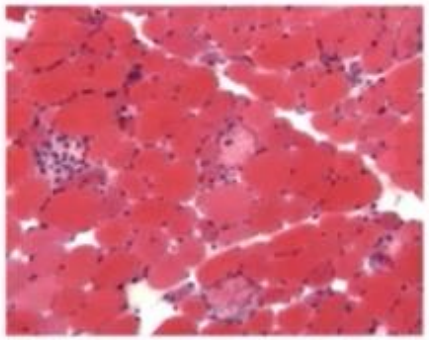
What about muscle biopsy?

- generally unnecessary if +ve myositis antibody detected which fits with clinical phenotype
- still carried out in IBM
- provides valuable information about pathological processes

Benveniste O, Stenzel W, Allenbach Y. Advances in serological diagnostics of inflammatory myopathies. Curr Opin Neurol. 2016 Oct;29(5):662-73. doi: 10.1097/WCO.0000000000000376. PMID: 27538058.

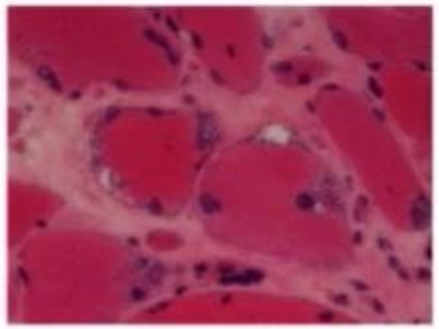
Chameleons - conditions masquerading as non-IIM

Immune-mediated necrotizing myopathy



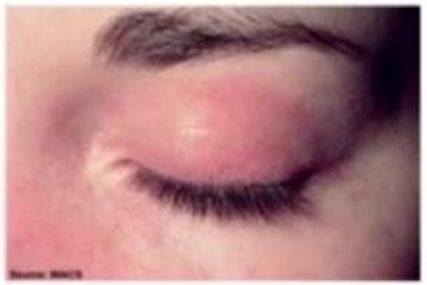
- ↑ ↑ CK
- Lack of inflammation on muscle biopsy
- Indolent forms may resemble LGMD

Inclusion body myositis



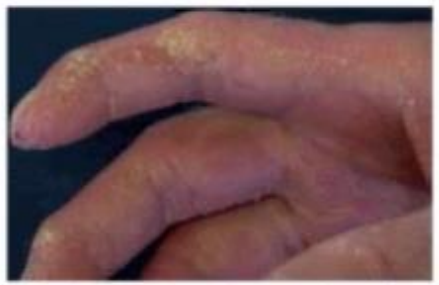
- "Unusual" pattern of muscle weakness (distal upper limb, proximal lower limb)
- ↑ age onset (>45)
- Treatment resistant

Dermatomyositis



- *Sine* myopathy
- *Sine* dermatitis
- *Sine* antibody

Anti-synthetase syndrome



- Manifestations may be extramuscular
- (pulmonary, arthritis, Raynaud's, mechanic's hands)

Chinoy H, Lilleker JB. Pitfalls in the diagnosis of myositis. Best Pract Res Clin Rheumatol. 2020 Feb;34(1):101486. PMID: 32063440.

Slides courtesy of IMACS, Dr DuPlessis, Prof Oddis & McHugh

How do we assess disease activity?

- Not just by using CK
- Requirement to test more than one muscle group to assess strength, and also to quantify the result

1. Sultan SM, Allen E, Oddis CV, Kiely P, Cooper RG, Lundberg IE, Vencovsky J, Isenberg DA. Reliability and validity of the myositis disease activity assessment tool. Arthritis Rheum. 2008 Nov; 58(11):3593-9.
2. Rider LG, Koziol D, Giannini EH, Jain MS, Smith MR, Whitney-Mahoney K, Feldman BM, Wright SJ, Lindsley CB, Pachman LM, Villalba ML, Lovell DJ, Bowyer SL, Plotz PH,

Manual Muscle Testing - 8

Muscle Groups	Right (0 – 10)	Left (0 – 10)	Axial (0 – 10)
Axial Muscles (0 – 10)			
Neck flexors	X	X	0-10
Proximal Muscles (0 – 100)			
Deltoid	0-10	0-10	X
Biceps	0-10	0-10	X
Gluteus maximus	0-10	0-10	X
Gluteus medius	0-10	0-10	X
Quadriceps	0-10	0-10	X
Distal Muscles (0 – 40)			
Wrist extensors	0-10	0-10	X
Ankle dorsiflexors	0-10	0-10	X
MMT- 8 score (0 – 150)	0-70	0-70	0-10
Muscle Groups	**Right (0 – 10)**	**Left (0 – 10)**	**Axial (0 – 10)**

Unilateral Score = 80; Bilateral score = 150

Slide courtesy of Rohit Aggarwal

Six Core Set Measures: Validated and Reliable

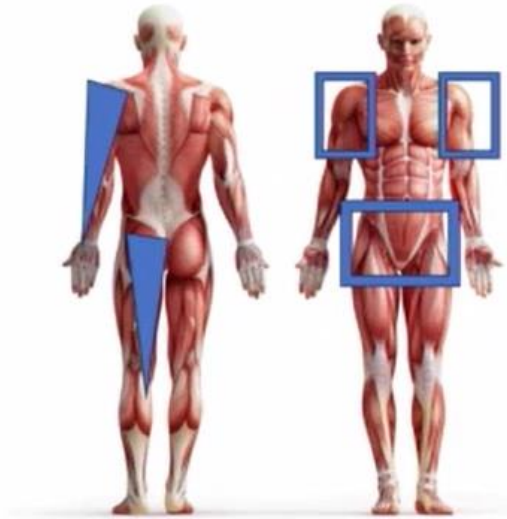
Domain	Core Set Measure	Range
Physician Global Activity	Physician global VAS (10 cm scale)	0-10
Patient Global Activity	Patient/Parent global VAS (10 cm scale)	0-10
Muscle Strength	Composite score of 8 muscle groups (MMT-8)	0-80
Physical Function	Health Assessment Questionnaire (HAQ) score	0-3
Laboratory Enzymes	Most abnormal enzyme among CK, LDH, AST, ALT, Aldolase	**Depends on muscle enzymes**
Extramuscular Disease Activity	Global extramuscular disease activity VAS (10 cm): constitutional, cutaneous, articular, GI, pulm, cardiac	0-10

International Guideline for IIM-Associated Cancer Screening (Abstract 2575 – Wed Nov 15th Abstract Session)

	'High risk' factors	'Intermediate risk' factors	'Low risk' factors
IIM subtype	☐ Dermatomyositis	☐ CADM ☐ Polymyositis ☐ IMNM	☐ ASSD ☐ CTD-associated IIM
MSA and MAA	☐ Anti-TIF1-γ antibodies ☐ Anti-NXP2 antibodies	☐ Anti-SAE1 antibodies ☐ Anti-HMGCR antibodies ☐ Anti-Mi2 antibodies ☐ Anti-MDA5 antibodies	☐ Anti-SRP antibodies ☐ Anti-Jo1 antibodies ☐ Non-Jo1 ASSD antibodies ☐ MAA[a]
Clinical features	☐ Age >40 years at IIM onset ☐ Persistent high disease activity despite therapy ☐ Dysphagia (moderate to severe) ☐ Cutaneous necrosis	☐ Male sex	☐ Raynaud phenomenon ☐ Inflammatory arthropathy ☐ Interstitial lung disease

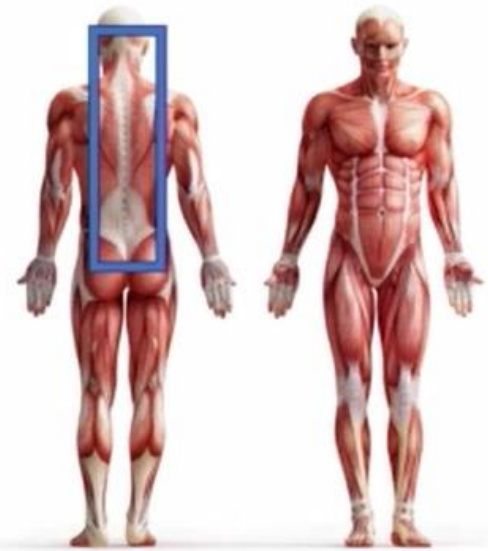
Oldroyd AGS, Callen JP, Chinoy H, Chung L, Fiorentino D, Gordon P, Machado PM, McHugh N, Selva-O'Callaghan A, Schmidt J, Tansley SL, Vleugels RA, Werth VP; International Myositis Assessment and Clinical Studies Group Cancer Screening Expert Group; Aggarwal R. International Guideline for Idiopathic Inflammatory Myopathy-Associated Cancer Screening: an International Myositis Assessment and Clinical Studies Group (IMACS) initiative. Nat Rev Rheumatol. 2023 Nov 9. doi: 10.1038/s41584-023-01045-w. Epub ahead of print. PMID: 37945774.

Typical clinical phenotype



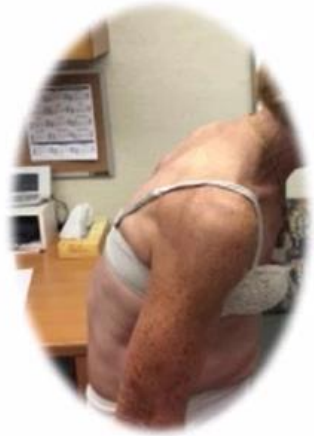
Fror

Atypical presentation 1: Axial myopathy



Clinical syndromes

- Dropped head



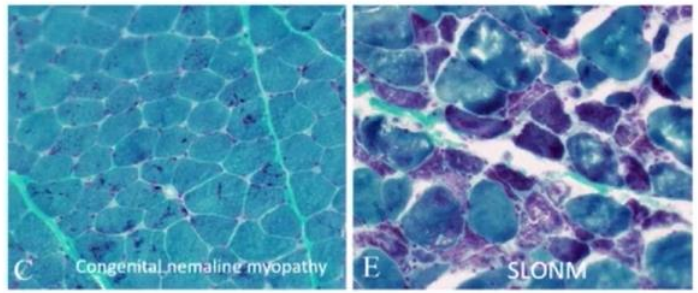
- Camptocormia

Ivanovski et al. 2021

Myopathies presenting with head drop

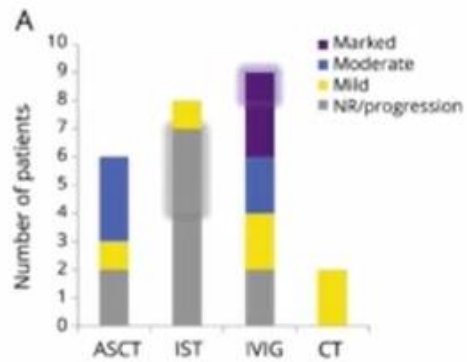
IDIOPATHIC INFLAMMATORY MYOPATHIES	OTHER IMMUNE-MEDIATED MYOPATHIES	Non-immune etiologies
• Overlap myositis/scleroderma • IBM • Dermatomyositis • NAM	• Sporadic late-onset nemaline myopathy • GVHD myositis	• Radiation induced • Inherited • Toxic (hydroxychloroquine, MEK inhibitors)

Sporadic late-onset nemaline myopathy



Naddaf et al. *Ann Clin Trans Neurol* 2022

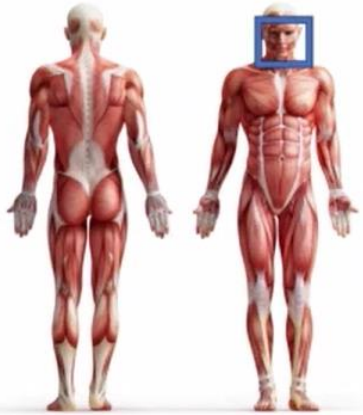
Sporadic late-onset nemaline myopathy

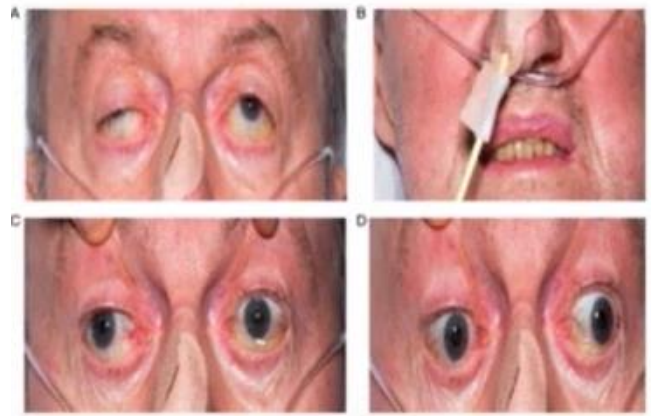


- 5th-9th decade of life
- 64% males
- 61% have an associated monoclonal protein (always IgG or light chain only)
- Presentation: head drop, camptocormia, proximal weakness, respiratory failure
- Half of patients have a rapidly progressive course
- 93% of patients have a **normal CK level**.
- Treatment: IVIG, ASCT for patients with a monoclonal protein who fail IVIG

Naddaf et al. *Neurology* 2019

Atypical presentation 2: Craniopharyngeal muscles



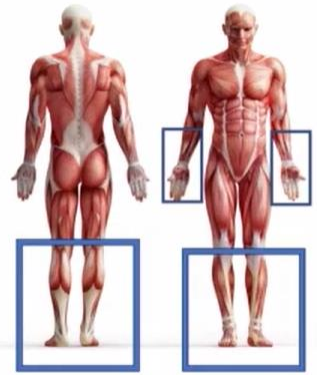


Haddox et al. Ann Oncol 2017

Craniopharyngeal muscles

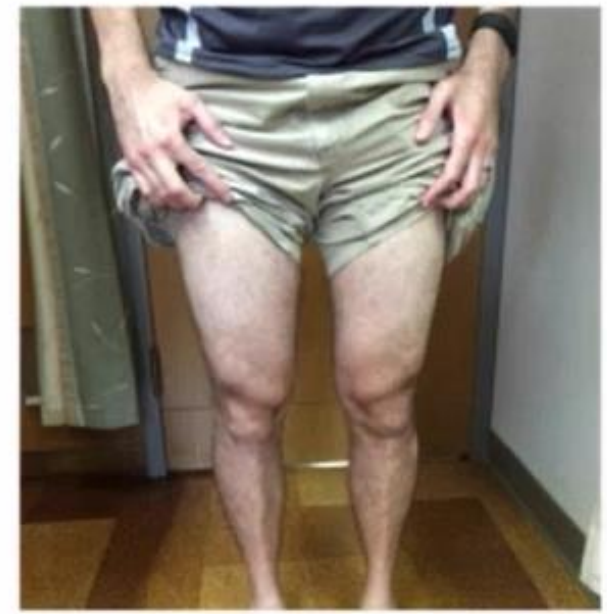
- Symptoms: Dysphagia >>> dysarthria, facial weakness, diplopia
- The most common IIM to present with bulbar symptoms is, by far, IBM.
- Other IIM can rarely present with a bulbar myopathy (e.g Dermatomyositis with NXP2 seropositivity)
- Other immune mediated myopathies: SLONM, GVHD, Check point inhibitors myositis
- Top differential diagnosis: Amyotrophic lateral sclerosis, myasthenia gravis.

Atypical presentation 3: Distal myopathy



Distal myopathies

- Always consider IBM
- Other inflammatory myopathies can very rarely present with distal weakness (myositis NOS, granulomatous/sarcoid myositis, focal myositis)
- Outside IBM, distal myopathies are most commonly inherited myopathies.
- To make things more complicated, one of the most common distal myopathy due to mutations in *DYSF* commonly has inflammation on biopsy.



Timeline

- Typically, weakness develops over a few months, except in IBM.

Differential diagnosis

Hyperacute/acute

- Rhabdomyolysis
- Toxic myopathy
- Viral myositis/myopathy

Chronic

- Inherited myopathy (muscular dystrophy, congenital myopathy etc.)

Case 1:

A 44 year-old man with anti-Tif-1+ **dermatomyositis** with **cutaneous** and **muscle** symptoms has been treated with *methotrexate* (now discontinued due to lack of efficacy) , *mycophenolate mofetil(MMF)* with partial muscle response and complete cutaneous response.

Most recently 3 courses of rituximab (1000 mg day 0 and 14) Q 6 months was added to MMF. He develops two episodes of thick green drainage, postnasal drip, cough, and facial pain beneath his eyes.

His sinus symptoms are most likely due to:

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1. A direct consequence of dermatomyositis known to occur in anti-Tif-1 gamma positive patients
2. A side effect of the Mycophenolate mofetil
3. An infectious process unrelated to his treatment regimen
4. Low immunoglobulins secondary to rituximab

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AAAAI Work Group Report

American Academy of Allergy Asthma & Immunology

Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees

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San Francisco, Calif; Buffalo and Great Neck, NY; Durham and Chapel Hill, NC; Cincinnati, Ohio; St Petersburg, Fla; Denver, Colo; Dallas, Tex; and Boston, Mass

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Growing evidence shows that iatrogenic secondary hypergammaglobulinemia (SHG) is seen in myositis with use of BCTT.

In addition to sinus cultures, antibiotics, and possible referral to otolaryngology, this patient needs:

- ✓ Institution of IgG replacement therapy (IgG-RT)
- ✓ Rituximab dose/frequency adjustment or discontinuation
- ✓ Possibly IgG-RT while allowing rituximab to be continued without adjustment/discontinuation
- ✓ RCTs needed to demonstrate the equivalency of SCIG to IVIG

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Antibody defects may be observed in autoimmune and hematologic/oncologic conditions before initiation of immunosuppressive treatment.

Screening at time of diagnosis and before initiation of B-cell targeted therapies (BCTT) with at least a serum IgG level is recommended.

Extrapolating from RA, IgG level screening is recommended before starting RTX. Subsequent monitoring is recommended 4 to 6 months after RTX infusions and before re-treatment, particularly in patients with low baseline IgG levels.

Otani IM,. J Allergy Clin Immunol. 2022 May;149(5):1525-1560

Case 2:

62 year-old woman with **anti-MDA5+ amyopathic dermatomyositis** with minimal **ground glass opacities** on Chest CT and normal pulmonary function tests has concomitant bilateral **synovitis** of small joints of the hands and wrists and severe **calcinosis** of both hip areas that has been unresponsive to diltiazem, probenecid and topical sodium thiosulfate. Concomitant therapies have included *corticosteroids*, *methotrexate* and *mycophenolate* which have helped to control cutaneous symptoms of rash and mechanic's hands but not the calcinosis.

What therapeutic agent may be helpful in this instance? How can you get insurance approval for it?

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1. Tofacitinib
2. Azathioprine
3. IVIG
4. Topical steroids

Tofacitinib treatment was associated with clinical improvement in the treatment of DM cutaneous and muscle symptoms, as well as improvement in calcinosis.

While the mechanism of calcinosis is not fully understood, there are hypotheses that dysregulated mitochondrial calcium storage and release mediated by the STAT 3 pathway may be contributing to the pathogenesis.

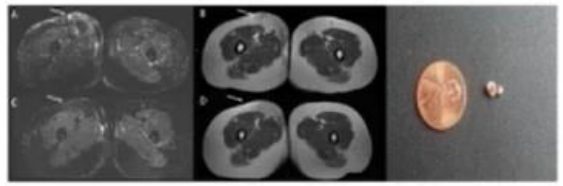

FIG. 1 Patient 1 – a 50-year-old woman with dermatomyositis and calcinosis

Axial STIR (A) and T1-weighted images (B) through the bilateral thighs using myositis protocol performed at baseline reveal bilateral asymmetric right greater than left lower extremity skin thickening and reticular elevated STIR signal and confluent T1-hypointense signal in the right anteromedial thigh to the greatest extent (arrows). Note the close proximity of signal abnormality in the right anterior thigh to the skin surface. Superficial calcific masses can ulcerate and extrude calcium as seen in this patient. Axial STIR (C) and T1-weighted images (D) through the bilateral thighs using myositis protocol performed 3 months after treatment reveal decrease in subcutaneous signal abnormalities in both legs (arrows). Photograph (E) demonstrates the extruded calcium deposit from patient 1's leg after treatment with tofacitinib.

SabbaghS.BrainJNeurol2019; 142:e59

Shneyderman M. Rheumatology (Oxford). 2021 Nov 3;60(11):e387-e388

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JAK inhibitors may play a pivotal role in not only inflammatory arthritis/seronegative rheumatoid arthritis but also calcinosis related to dermatomyositis.

Given that this patient has a seronegative rheumatoid arthritis picture and is at high risk for interstitial lung disease due to anti-MDA5 autoantibodies, TNF inhibitors are relatively contraindicated, so a safer biologic option to start is tofacitinib.

Shneyderman M. Rheumatology (Oxford). 2021 Nov 3;60(11):e387-e388

Case 3:

A 64 year-old woman with a history of hypercholesterolemia, diabetes mellitus, and coronary artery disease (CAD) status post cardiac stent x 3 is found to have anti-HMGCR+ myositis 3 years after being placed on atorvastatin for lipid control and secondary prevention.

Regarding her long-term strategies for secondary CAD prevention you advise her to speak to her cardiologist about which of the following:

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1. Restart another statin other than atorvastatin.
2. Suggest that she try red yeast rice or ezetimibe as a statin alternative.
3. Suggest that she be started on a PCSK9 inhibitor monotherapy in the absence of a statin.
4. Advise against all lipid lowering therapies and hope for the best.

Among 122 anti-HMGCR-positive patients, 8 patients identified were receiving PCSK9 inhibitors (alirocumab and evolocumab) for hyperlipidemia.

Patients followed up for an average of 1.5 years (range 3-37 months), and none exhibited reduction in muscle strength.

The mean ± SD CK level prior to the initiation of PCSK9 inhibitors was 956 ± 1,137 IU/liter, which was reduced to 419 ± 393 IU/liter at their last visit. Anti-HMGCR antibody titers followed a similar trend.

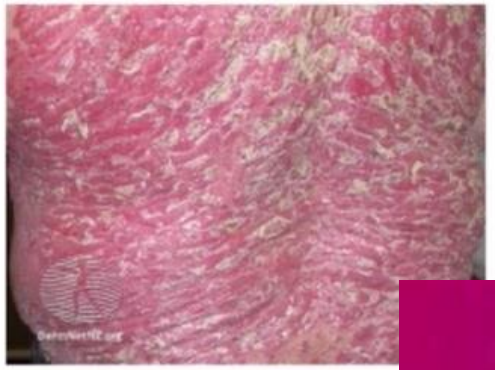
In 2 patients, the initiation of the lipid-lowering medication was followed by unanticipated spontaneous clinical improvement and reduction in immunosuppression.

PCSK9 inhibitors appear to be safe for long-term use as a cholesterol-lowering agent in patients with statin-associated IMNM.

Tiniakou E, Arthritis Rheumatol. 2019 Oct;71(10):1723-1726

Case 4:

A 24 year-old woman with new-onset anti-SAE+ dermatomyositis is started on hydroxychloroquine and corticosteroids. Two weeks after starting these therapies, she develops a worsening exfoliating dermatitis.



You should:

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1. Discontinue the hydroxychloroquine, continue the corticosteroids and add another steroid-sparing agent like methotrexate or mycophenolate after assuring that there is no secondary skin infection present.
2. Continue hydroxychloroquine but discontinue the corticosteroids.
3. Discontinue the hydroxychloroquine and the corticosteroids.
4. Continue both agents, as erythroderma is a consequence of the dermatomyositis, and it will take longer for the hydroxychloroquine to start working.

111 DM patients included; 23 (20.7%) developed a hydroxychloroquine-associated skin eruption

Skin eruptions approximately 3 times more common in patients with anti–SAE-1/2 autoantibodies (7 of 14 [50.0%]) compared with those without the autoantibody (16 of 97 [16.5%])

None of 15 patients with anti–MDA-5 autoantibodies had skin eruption vs 23 of 96 (24.0%) of those without the autoantibody.

Wolstencroft PW, JAMA Dermatol. 2018 Oct 1;154(10):1199-1203

Case 5:

73 year-old woman presents with a 3-month worsening of muscle weakness in the setting of a 2-year history of progressive muscle weakness. No rash , ILD, or articular symptoms.

She noted difficulty going up and down stairs associated with the sensation of lower extremity weakness.

CK was elevated to 444, aldolase was elevated at 14.8.

Her NT5C1A antibody testing is positive. All other myositis specific antibody testing was negative.

Her physical exam is notable for asymmetric muscle involvement, with notable finger flexor weakness, and knee extensor greater than hip flexor weakness.

Her MRI shows muscle atrophy, suggestive of a chronic myopathy, with evidence of edema suspicious for active inflammation.

Her EMG is notable for irritable myopathy.

Muscle biopsy was consistent with "polymyositis with mitochondrial myopathy"/PM-Mito.

You offer her the following therapeutic options:

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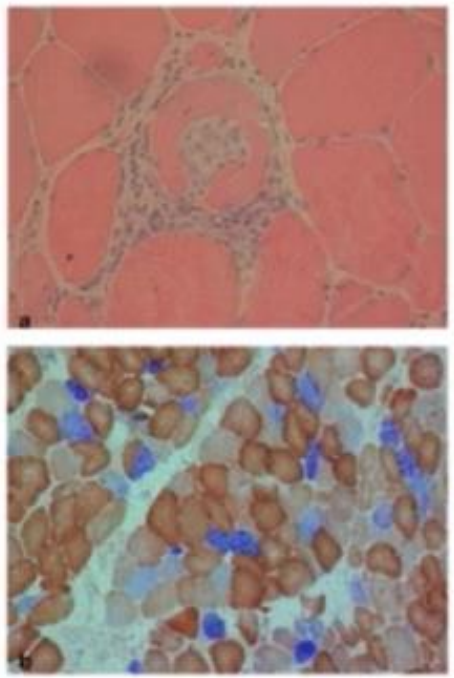
1. Physical therapy and occupational therapy only
2. No immunosuppression as PM-Mito is just an early form of inclusion body myositis
3. Trial of methotrexate and corticosteroids
4. Trial of immunosuppression or IVIG with physical therapy and occupational therapy



PM-Mito is characterized by the symptoms of inclusion body myositis (IBM) and by the myopathological findings of polymyositis (PM) except for an increase of muscle fibers with insufficient mitochondrial cytochrome C(Cox negative fibers)

PM-Mito has more slowly progressive weakness than IBM and rarely has TDP-43 or SMI-31 staining aggregates in muscle fibers.

Theoretically, if PM-Mito is considered an intermediate form between PM and s-IBM, it could be expected that treatment may occasionally be benefcial and probably inversely related to the extent of the degenerative component and the chronicity of the disease.

Muscle biopsy sections stained with H&E,showing endomysial infiltrates and inflammatory cells invading a non-necrotic muscle fber and COX-SDH staining (×40), b revealing many COX-deficient muscle fibers (×20)

Papadimas G.Rheumatology International (2019) 39:1459–1466

Case 6:

55 year-old previously healthy marathon runner diagnosed with high titer anti-HMGCR + necrotizing myopathy (225 CU where normal is <20 CU) complicated by respiratory failure due to neuromuscular weakness one month after initial diagnosis.

He received endotracheal intubation and PEG placement with high dose steroids, azathioprine (stopped due to elevated LFTs), and IVIG. His disease progresses in spite of this.

What is the therapeutic option with the best chance of rapid response?

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1. Add rituximab to the current regimen.

2. Add another steroid sparing regimen such as mycophenolate or methotrexate.

3. Trial Plasmapheresis/Plasma exchange (PLEX), 5 treatments every other day x 10 days followed by rituximab and continue IVIG.

4. Change IVIG to weekly dosing and continue monotherapy.

Six patients (median age at diagnosis 52.5 years, IQR 35.8-64.5 years, four male/two female) underwent a median of 7.5 (IQR: 5-10) PLEX procedures with 5% albumin as replacement.

All patients exhibited a **statistically significant reduction in CK** level from pre-PLEX baseline (range: 43.0%-58.7% reduction).

Responses in this cohort were **best in patients with antibodies** targeting **HMGCR** (3 patients) and **SRP** (1 patient), which are most strongly associated with Necrotizing autoimmune myopathy (NAM).

These results compare favorably to a literature review of NAM patients (n = 19) treated with PLEX, who also exhibited positive clinical and laboratory responses across varying treatment lengths.

Kruse RL. J Clin Apher. 2022 Jun;37(3):253-262.

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Rituximab (one course of 1 g x 2 only) and plasmapheresis/PLEX (one course) instituted in addition to the IVIG.

Patient regained strength, anti-HMGCR autoantibody fell but did not normalize, and patient has been able to be maintained on IVIG 2g/kg, now at every 8 weeks, two years out from his diagnosis.

Some evidence PLEX can be helpful in severe refractory myositis cases, especially NAM and with high titer autoantibodies that are believed to be potentially pathogenic.

A course of rituximab following PLEX may also be helpful and may not need to be continued long-term.

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Samah El-Bakry