Clinical Pearls In

Connective Tissue Disease and Systemic Vasculitis

For the Internal Medicine Resident Board Examination

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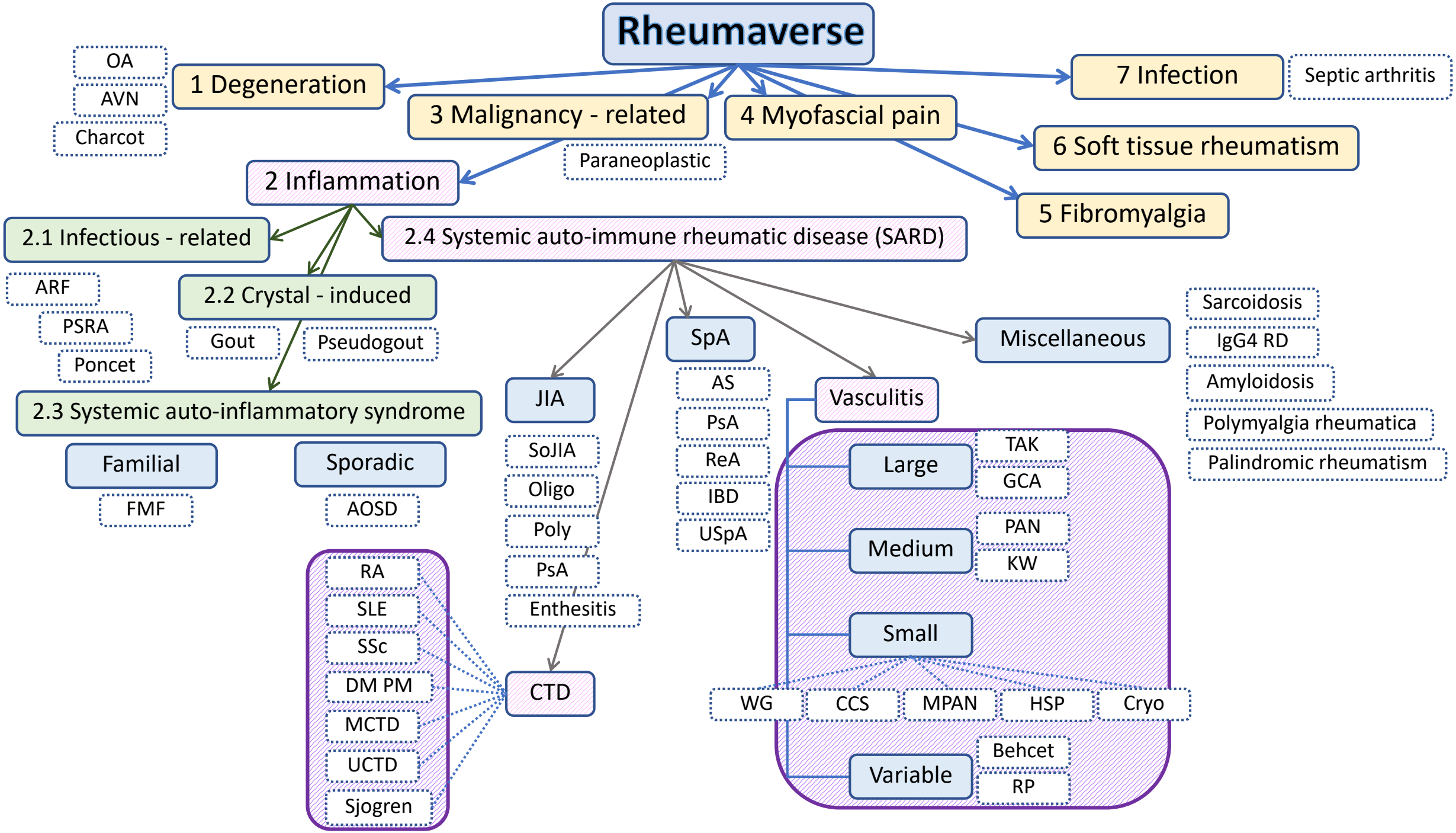

Rheumaverse
1 Degeneration
OA
AVN
Charcot
2 Inflammation
3 Malignancy - related
Paraneoplastic
4 Myofascial pain
5 Fibromyalgia
6 Soft tissue rheumatism
7 Infection
Septic arthritis
2.1 Infectious - related
ARF
PSRA
Poncet
2.2 Crystal - induced
Gout
Pseudogout
2.3 Systemic auto-inflammatory syndrome
Familial
FMF
Sporadic
AOSD
2.4 Systemic auto-immune rheumatic disease (SARD)
JIA
SoJIA
Oligo
Poly
PsA
Enthesitis
SpA
AS
PsA
ReA
IBD
USpA
Vasculitis
Large
TAK
GCA
Medium
PAN
KW
Small
WG
CCS
MPAN
HSP
Cryo
Variable
Behcet
RP
Miscellaneous
Sarcoidosis
IgG4 RD
Amyloidosis
Polymyalgia rheumatica
Palindromic rheumatism
RA
SLE
SSc
DM PM
MCTD
UCTD
Sjogren
CTD

The Family of Connective Tissue Diseases

CTDs	Prevalence	Age onset	Female : Male
1. RA	1: 100	45 – 55	5:1
2. SLE	1: 1,000	<16 and 20S – 40S	9:1 (adult)
3. SSc	1: 10,000	30S – 40S	5:1
4. DM/PM	<1: 10,000	<16 and 40S – 60S	5:1 (adult)
5. MCTD	<1: 10,000	30S – 40S	9:1
6. UCTD	<1: 10,000	30S – 40S	9:1

Neighbor

Sjogren syndrome	<1: 10,000	35 – 60	5-9:1

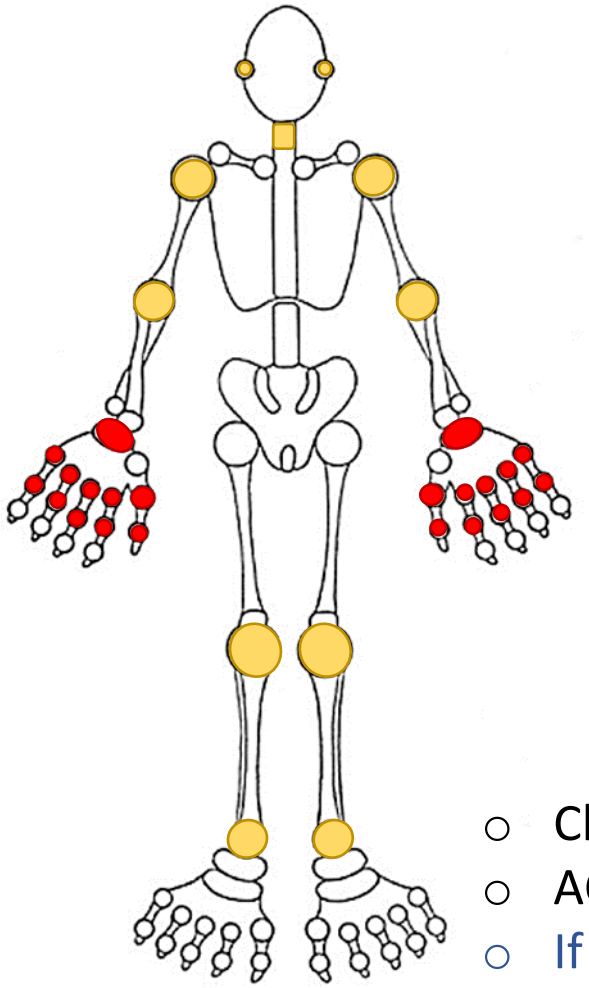
The Family of Connective Tissue Diseases

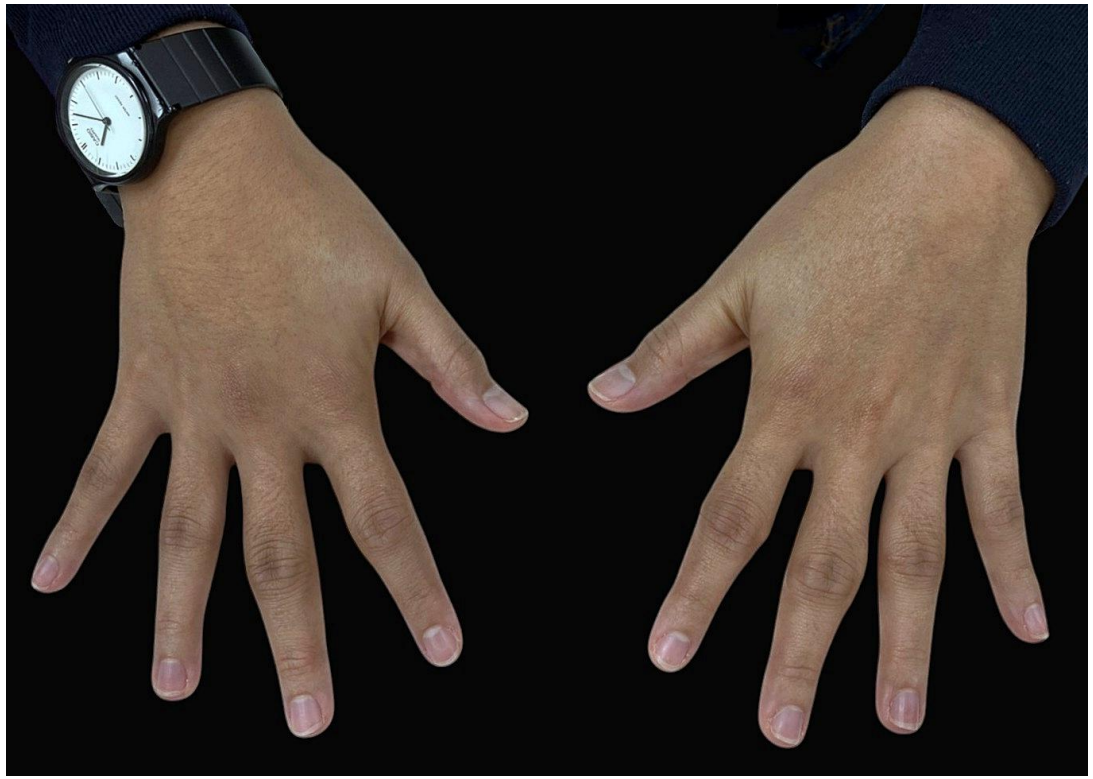
CTDs	Classic presentations	
1. RA	Chronic symmetrical arthritis of hand (PIPs, MCPs, wrists) joints	
2. SLE	Fever, RA-like arthritis, Rashes, Nephritis, Blood dyscrasia	
3. SSc	Raynaud's	Puffy fingers, sclerodactyly, scleroderma, GERD, ILD, Digital ulcers
4. DM/PM	Proximal muscle weakness of LE → UE → Neck → Trunk → Heart/ Diaphragm	
5. MCTD	Raynaud's	Puffy fingers, sclerodactyly, RA-like arthritis, Pulmonary vasculitis
6. UCTD	Raynaud's	Puffy fingers, sclerodactyly, RA-like arthritis

Neighbor

Sjogren	Xerostomia, xerophthalmia, Raynaud's, RA-like arthritis, ILD, Interstitial nephritis

Rheumatoid arthritis





Disease that has positive RF	
Autoimmune	RA, SLE, SjS, SSc, DM, PM, sarcoidosis
Infection	IE, TB, Leprosy, Syphilis, Lyme, parasite
Virus	HIV, EBV, CMV, HBV, HCV, Influenza, Rubella
Lung disease	Chronic bronchitis, ILD, Silicosis
Liver disease	PBC, AIH
Vasculitis	Cryoglobulinemia

The disease that has RA – liked arthritis	
Virus	HIV, HBC, HCV, EBV, CMV, Influenza, COVID, Chikungunya, Dengue
Bacteria	Salmonella
Reaction	ARF, PSRA, Poncet disease
CTD & SpA	AOSD, SLE, MCTD, SSc, PsA, AS
Vasculitis	AAV, Cryoglobulinemia, HSP
Malignancy	Leukemia, Lymphoma

- Chronic symmetrical polyarthritis of PIP, MCP, wrist
- ACD, ↑WBC, ↑Plts., ↑ESR, ↑CRP
- If Raynaud +ve → MCTD, SLE, anti-synthetase syndrome
- RF: Sn 69%, Sp 85%
- ACPA: Sn 67%, Sp 95%
- Long-standing RA: C1-2 subluxation, UIP
- Px RA-UIP: MMF, AZA, RTX

RA hands

RA hands w/ bilat. CTS

Scleroderma hands

Dermatomyositis hands

Puffy hands – MCTD

SLE hands

DGI hands

Strep. agalactiae hands

OA hands

Gout hands

Psoriatic hands

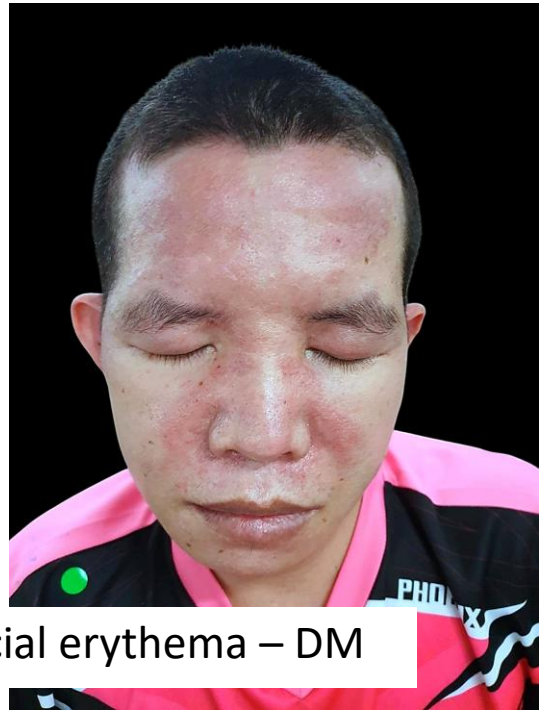
D/Dx Early Arthritis in CTD & Sjogren

CTDs	RA-liked Arthritis	RP	Puffy	Distinctive Hand Features
1. RA	Boggy swelling	5-10%	N	Rheumatoid nodule (<5% - early RA)
2. SLE	Mild swelling	20-40%	N	Discoid LE, Inter-knuckle erythema
3. SSc	Mild swelling	85-95%	Y	Digital pitting scars, Sclerodactyly
4. DM/PM	Mild swelling	10-20%	N	Gottron papules/ signs, Peri-ungual telangiectasia
5. MCTD	Boggy swelling	80-95%	Y	—
6. UCTD	Mild swelling	40-60%	Y	—
Neighbor				
Sjogren	Mild swelling	10-20%	N	—

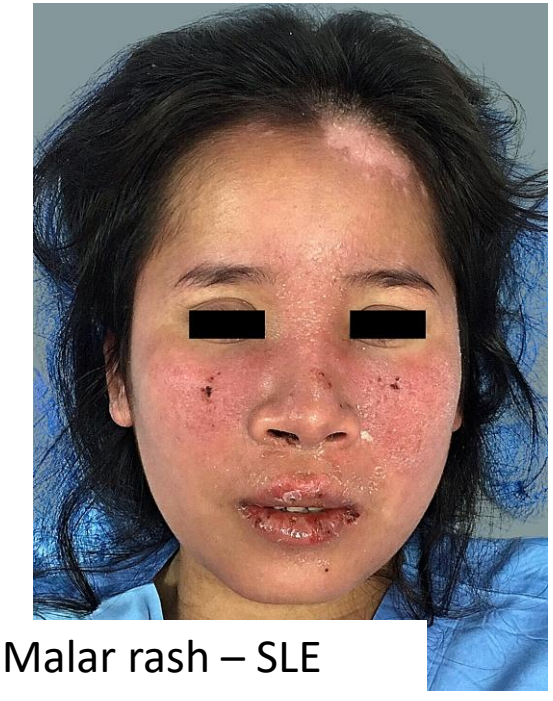
*Boggy = Rubbery or Spongy, and Compressible

Distribution of skin lesions in CTD

- SLE
  - Malar rash, Photosensitivity
  - Annular Polycyclic, Psoriasiform
  - Discoid Lupus erythematosus
- SSc
  - Poikiloderma (salt & pepper skin)
- Dermatomyositis
  - Facial erythema
  - Heliotrope
  - V sign, Shawl sign, Holster sign
- MCTD
  - Photosensitivity



Facial erythema – DM



Malar rash – SLE

Systemic Lupus Erythematosus




DLE lesions

- Flat or slightly elevated, well-demarcated, red-purple macules or papules with scaly surface
- Commonly evolve into larger, coin-shaped erythematous plaques *covered by* prominent adherent scale that extend into dilated hair follicles
- Scales accumulate in dilated hair follicle openings

Dermatomyositis

Pathognomonic rashes

Heliotrope rash

- Violaceous discoloration of eyelids, often with periorbital edema
- Associated with classic dermatomyositis & active disease

- This picture shows
  - ∗ Heliotrope (pathognomonic)
  - # Facial erythema
  - § V sign (**characteristic rashes**)

Gottron papules

- Violaceous papules over MCP/ PIP joints
- Associated with classic dermatomyositis & active disease
- There is inter-knuckle erythema, as well as a nonspecific SLE rash

Dermatomyositis

Characteristic rashes

V sign: rash over the anterior chest
Association: photosensitivity

Shawl sign: rash over the upper back/ shoulders/ posterior neck
Association: photosensitivity

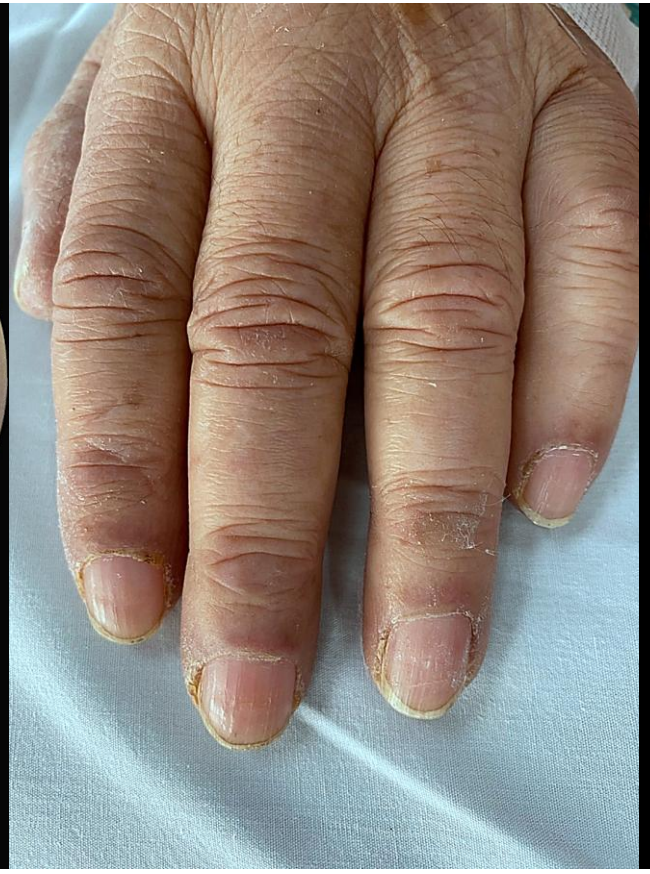
Holster sign: rash over the lateral thighs
Association: dermatomyositis

Photo distributed dermatomyositis rash: rash over the extensor upper arms
Association: dermatomyositis

Dermatomyositis

Characteristic rashes

PVA: **P**oikiloderma **V**asculare **A**trophican
Poikiloderma = Salt and Pepper skin
Vasculare = Telangiectasia
Atrophicans = Skin (appendages) atrophy



Cuticular Overgrowth (ragged cuticle) associated w/ DM and **Periungual Telangiectasia** associated w/ active disease & microangiopathy

Mechanic's hands = Hyperkeratosis, fissuring, and rough skin over lateral fingers
– Very strongly associated with **ILD**
– Strong association with **anti-synthetase**
– commonly associated with **RP, arthritis**

Dermatomyositis

Characteristic rashes of anti-MDA5 (amyopathic DM with RP-ILD)

C: Inverse Gottron papules
F, G: Ulcerated Gottron papules

Ischemic ulcerations of the skin and digital pulps & tips

Palmar papules and lateral nail fold ulceration

Cleveland Clinic Journal of Medicine. 2025; 92 (10): 627-637.
Journal of Rheumatology. 2017; 44 (3): 319-325.
BMJ Case Reports CP 2022;15:e246192.

Idiopathic Inflammatory Myopathy

1. Overlap Myositis (OM)				2. DM	3. NAM			4. PM	5. IBM
1.1 ASS	**1.2 Anti-MDA5**	**1.3 OM + ANA**	**1.4 OM + DM**		**3.1 Anti-HMGCR**	**3.2 Anti-SRP**	**3.3 Sero neg.**		
PM (amyopathic)	**DM** (amyopathic)	**PM**	**DM**	**DM**	**PM**	**PM**	**PM**	**PM**	Finger Wrist Quadriceps
ILD (50%) RP-ILD (10%)	ILD (50%) RP-ILD (50%)	Depend on primary CTDs							
Mechanic's Raynaud Arthritis Fever	Skin ulcers Palmar papule Inverse Gottron	Pre-existing RA, SLE, SSc, MCTD As an Overlap syndrome		Heliotrope Gottron papules	Less severe Myositis	Severe Myositis	Classic Myositis	Classic Myositis	Distal > Proximal Muscle weakness
<5% cancer	<5% cancer	Unlikely		≥50%	Cancer (statin naïve)	No	Yes	No	No
Anti-Jo1 Anti-PL7, 12	Anti-MDA5	ANA panels		Anti-Mi2 Anti-TIF1γ Anti-NXP2	Anti-HMGCR	Anti-SRP			Anti-5'-nucleotidase 1A

Renal Involvement

CTDs	Typical	Clinical Pearls
1. **RA**	Usually none	**Rare**: AA amyloidosis
2. SLE	LN (class I – VI)	Immune complex GN, Full-house IF (class III, IV)
3. SSc	Classic SRC, Normotensive (TMA)	**Rare**: overlap anti-MPO ANCA
4. **DM/PM**	Generally, none	**Rare**: Rhabdomyolysis → AKI
5. MCTD	Mild nephropathy	Usually, Mesangial/ Membranous GN
6. **UCTD**	Usually none	If exists → evolution to SLE or MCTD

Neighbor

Sjogren	Tubulo-interstitial nephritis	Distal RTA (Type I)*, MPGN (from 2^{o}cryoglobulinemia)

*Type I distal RTA = hypo K, nephrocalcinosis, kidney stones

Hematological Involvement

	RBC	WBC	Platelets	APS
1. RA	ACD (classic)	↑; if ↓N → Felty syndrome	↑	No
2. SLE	ACD, AIHA (20%)	↓ (usually lymphopenia)*	↓	Lab 30-40%, clinical 15-20%
3. SSc	No	No	No	Very rare (~1%)
4. DM/PM	Mild ACD	No	No	Rare
5. MCTD	Mild ACD/ AIHA	↓	↓	Rare
6. UCTD	No	↓	No	Rare; unless evolving to SLE
Neighbor				
Sjogren	Mild ACD	↓	↓	No

*Leucopenia usually precedes other SLE features

Pulmonary Involvement

	Serosa	Parenchyma-acute	Parenchyma-chronic	Airways
1. RA	Effusion – rare	DAH – very rare (AOSD)	**UIP** (+RF, +ACPA)	Bronchiolitis/ ectasis
2. SLE	Pleuritis – 20%	Pneumonitis/ DAH	Mild NSIP	Rare
3. SSc	Very rare	Very rare	**NSIP** (>70%), UIP (10%) (+anti-Scl70)	Mild bronchiolitis
4. DM/PM	Rare	**Anti-MAD5 (50%)** – anti-MDA5 **Anti-synthetase (10%)** – anti-PL7/12, anti-EJ	NSIP, **OP**	Rare
5. MCTD	Occasional	Rare	NSIP	Mild bronchiolitis
6. UCTD	Rare	Rare	Mild NSIP possible	Rare
Neighbor				
Sjogren	Rare	Rare	NSIP (>50%), UIP (20-30%), **LIP** (10%), OP (<10%) Anti- (+Ro52 or Anti-Ro60/SSA)	Bronchiolitis/ ectasis

Cardiac Involvement

	Pericardium	Myocardium	Endocardium	Pulmonary HT
1. RA	Seropositive	Rare	Rheumatoid nodule (Rare)	PH – ILD
2. SLE	Common	Occasionally myocarditis	**Libman-Sachs endocarditis**	CTEPH, PAH
3. SSc	Mild	Myocardial fibrosis	Conduction defects	PH-ILD, PAH, PH-LHD
4. DM/PM	Rare	Occasionally myocarditis	Conduction defects	PH-ILD
5. MCTD	Mild	Mild myocarditis	Rare	**PAH** (Late/ common)
6. UCTD	Rare	Rare	Rare	PAH occasionally
Neighbor				
Sjogren	Rare	Rare	Rare	PH-ILD (Rare)

Gastro-Intestinal-Hepatobiliary Involvement

	Esophagus	Stomach	Small bowel	Large bowel	Hepato-Biliary
1. RA	—	—	—	—	
2. SLE	—	—	**Mesenteric vasculitis**	Ischemic colitis	Lupus hepatitis **Overlap AIH**
3. SSc	**Dysmotility** **GERD**	**GAVE**	**Pseudo-obstruction** **Bacterial overgrowth**	**Constipation**	**Overlap PBC**
4. DM/PM	Oro-pharyngeal Dysphagia	—	—	—	—
5. MCTD	Dysmotility GERD	—	—	—	—
6. UCTD	—	—	—	—	—
Neighbor					
Sjogren	Sicca Dysphagia	Atrophic gastritis	—	—	**Overlap PBC**

Neurological Involvement

	Leptomeninges	Cranial N.	Central	Peripheral N.	Vessel
1. RA	Rare	Rare	C1-2 subluxation	Carpal-Tunnel Syndrome	Rare vasculitis
2. SLE	**Aseptic meningitis**	**II, VII, X**	**Seizure, Psychosis**	**Peripheral Neuropathy**	**Stroke (APS)**
3. SSc	—	Trigeminal Neuralgia	—	Peripheral Neuropathy	—
4. DM/PM	—	—	—	—	—
5. MCTD	—	Trigeminal Neuropathy	Encephalopathy	Peripheral Neuropathy	—
6. UCTD	—	—	—	—	—
Neighbor					
Sjogren	—	Trigeminal Neuropathy	Cognitive Dysfunction	Sensory Neuropathy	—

SSc disease evolution

Matucci-Cerinic M, et al. Ann Rheum Dis. 2009; 68: 1377-80.
Koenig M, et al. Arthritis Rheum. 2008; 58: 3902-12.
Valentini G, et al. Rheumatology 2011; 50: 317-23.
Avouac J, et al. Ann Rheum Dis. 2010; 69: 128.
Sakkas L, et al. Clin Rheumatol. 2015; 34: 1327-31.

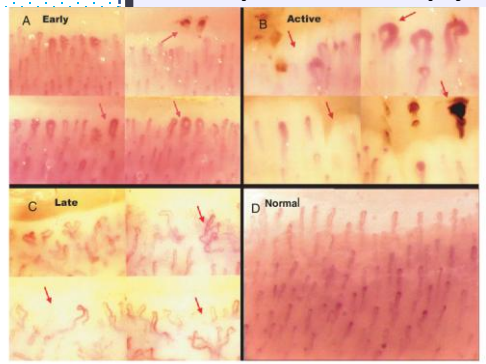
mRSS

*ACR/EULAR 2013

Auto Ab only
1 SSc specific Ab
(Non-disease)

Very early SSc
1 Raynaud
2 SSc specific Ab
3 Capillaroscopy

Early SSc
1 Raynaud
2 SSc specific Ab
3 Capillaroscopy
4 Puffy fingers
5 Arthritis



การตรวจพบหลัก	การตรวจพบรอง	คะแนนการวินิจฉัย
Proximal scleroderma		9
Sclerodactyly (นับข้อที่มีคะแนนสูงสุด)	1. Puffy fingers 2. Sclerodactyly	2 4
Fingertip lesions (นับข้อที่มีคะแนนสูงสุด)	1. Digital tip ulcers 2. Fingertip pitting scars	2 3
Telangiectasia		2
SSc-pattern nailfold capillaroscopy		2
Pulmonary arterial hypertension and/or interstitial lung disease (คะแนนสูงสุดเท่ากับ 2)	1. Pulmonary arterial hypertension 2. Interstitial lung disease	2 2
Raynaud's phenomenon		3
SSc-related autoantibody (คะแนนสูงสุดเท่ากับ 3)	1. Anti-centromere 2. Anti-topoisomerase-I (Scl-70) 3. Anti RNA polymerase III	3

Digital ulcers
Scleroderma
Interstitial lung
Renal crisis
GERD

PAH

dcSSc

lcSSc

Disease flare

Disease flare

edematous *fibrotic* *atrophic*

Yr.

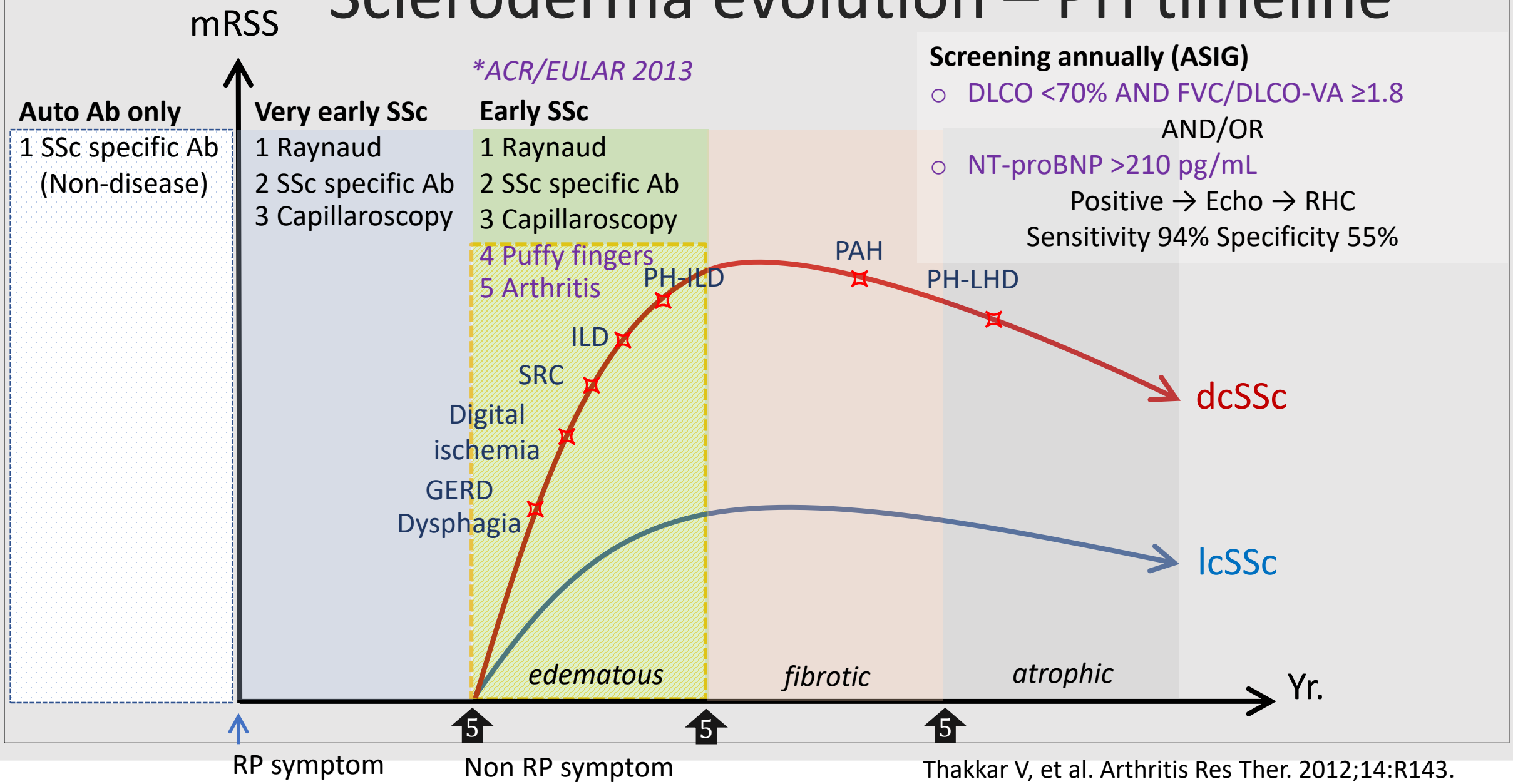
5 5 5

RP symptom

Non RP symptom

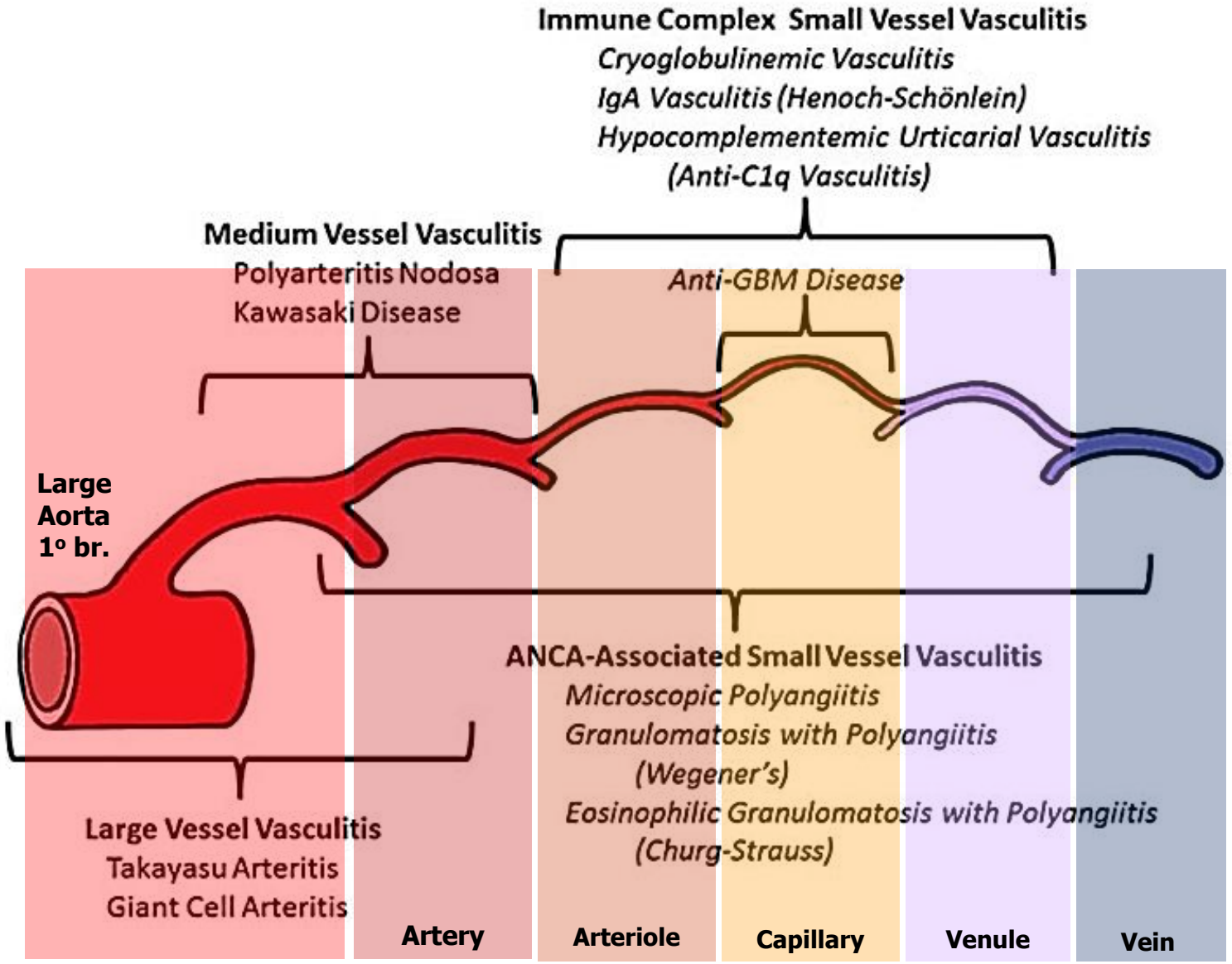
Other disease subsets
Sine SSc = RP, DU, PAH, and SSc specific Ab
SSc overlap

Scleroderma evolution – PH timeline



Thakkar V, et al. Arthritis Res Ther. 2012;14:R143.

Systemic Vasculitis



The Great & Large vessel vasculitis

CTDs	Prevalence	Age onset	Female : Male
1. TAK	1:100,000	<40 years (15 – 35)	9:1
2. GCA	1:10,000	>50 years (70 – 80)	3:1

The Medium vessel vasculitis

CTDs	Prevalence	Age onset	Female : Male
1. PAN	1:100,000	40 – 60	1:1
2. KW	1:5,000	<5 years	1:1.5

The Variable vessel, including aorta vasculitis

CTDs	Prevalence	Age onset	Female : Male
1. Behcet disease	1:10,000	35 – 45	1:1

Presenting symptoms

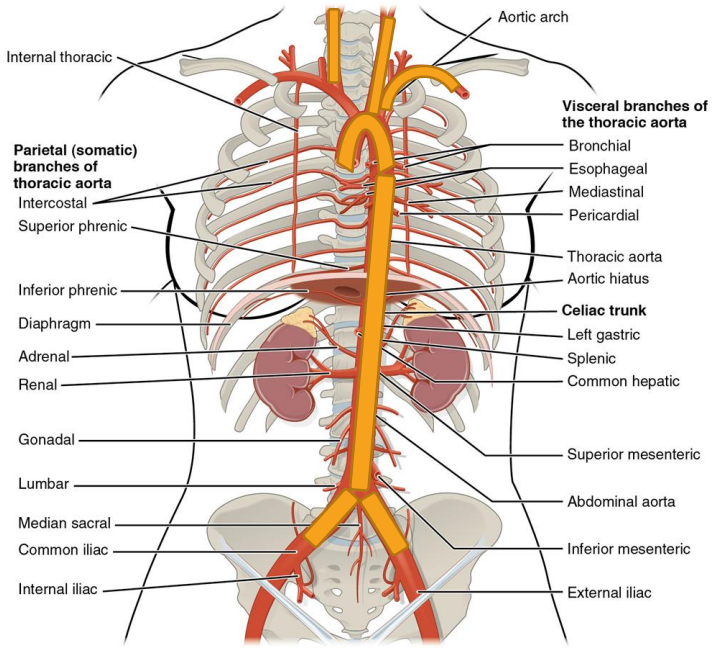
TAK

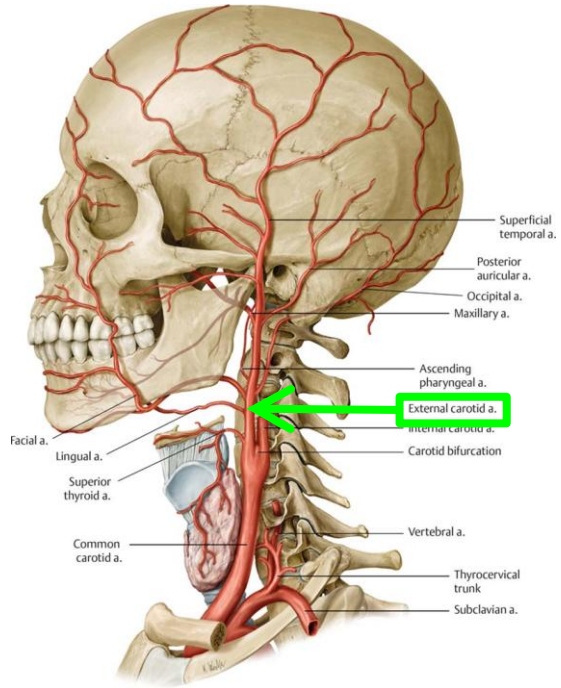
- Young female w/ found pulseless (10%)
- Fever, Wt. loss, Carotidynia, Erythema nodosum, pyoderma gangrenosum (30%)
- Renovascular HT, Limb claudication, Aortic regurgitation, Carotid stenosis (ischemic stroke/ arterial-to-arterial embolism – Anterior Cir.), CRAO (60%)

GCA

- An Elderly with
  - Constitutional symptoms, PMR
  - Ischemic claudication of
    - Temporal/ Scalp/ Jaw/ Tongue/ Orbit
    - Ophthalmic a.
      - Central retinal a. (CRAO)
      - Anterior ischemic optic neuropathy
  - ACD, ↑ESR, ↑CRP
  - Vertebral/Basilar a. stroke (Posterior Cir.)

Key word: vasculitis of the Aorta & its primary extra-cranial branches = carotid, subclavian (Lt. > Rt.), pulmonary a., superior mesenteric a., and renal a.



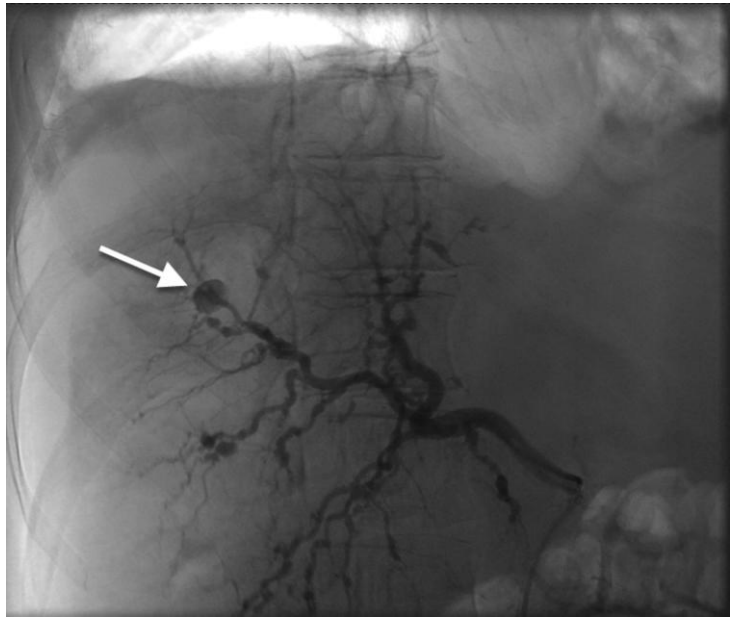


Presenting symptoms

PAN

Key word: Medium-vessel necrotizing vasculitis (no ANCA, no glomerulonephritis, no alveolitis)

- Fever, Constitutional symptoms
- Mononeuritis multiplex (Nerve)
- Mesenteric ischemia (GI)
- Renal infarct (↑Cr, Ø urine sediment)
- Skin ulcers/ nodules, Livedo reticularis (Skin)



Angiography of the hepatic artery. Microaneurysms and stenoses are visible. The largest aneurysm shows signs of active bleeding (arrow).
J Rheum. 2013; 40(1): 87-88.

Behcet

Key word: Variable-vessel vasculitis

- Painful oral ulcer (>5 lesions, >5 attacks, 100%)
- Painful genital ulcer (70%)
- Papulopustular lesions (>60%), Erythema nodosum (50%)
- Pathergy reaction (30%)
- Pan-uveitis (50%) – recurrent, bilaterally
- Non-erosive oligoarthritis of LE
- Aortitis, Thrombophlebitis, DVT, CVST
- Ileum ulceration (around IC valve) (10%)
- Neuro-Behcet: pons, midbrain, BG (abscess – liked) (10%)

Prolonged fever with aortitis

Aortitis

D/Dx depends on clinical background.

Infectious

Staphylococcus aureus
Salmonella spp.
Streptococcus pneumoniae
Treponema pallidum (Syphilitic)
Mycobacterium tuberculosis
Others (rare):
- Escherichia coli
- Haemophilus influenzae
- Nocardia asteroids
- Burkholderia pseudomallei
- Listeria monocytogenes
- Pasteurella multocida

Virus: HIV
Fungal: candida, Aspergillus, Cryptococcus

Non-Infectious

Systemic vasculitis

Large vessel:
- **Takayasu arteritis (TAK)**
- Giant cell arteritis (GCA)

Medium-to-Small vessels:
GPA (Wegener granulomatosis)
EGPA (Churg-Strauss syndrome)
Variable vessels:
- **Behcet disease**
- Relapsing polychondritis
- Cogan's syndrome

Clinically isolated aortitis (CIA)

CTD

Rheumatoid arthritis (RA)
Systemic lupus erythematosus

Idiopathic

IgG4 related disease
Sarcoidosis

Spondyloarthropathy

Ankylosing spondylitis (AS)

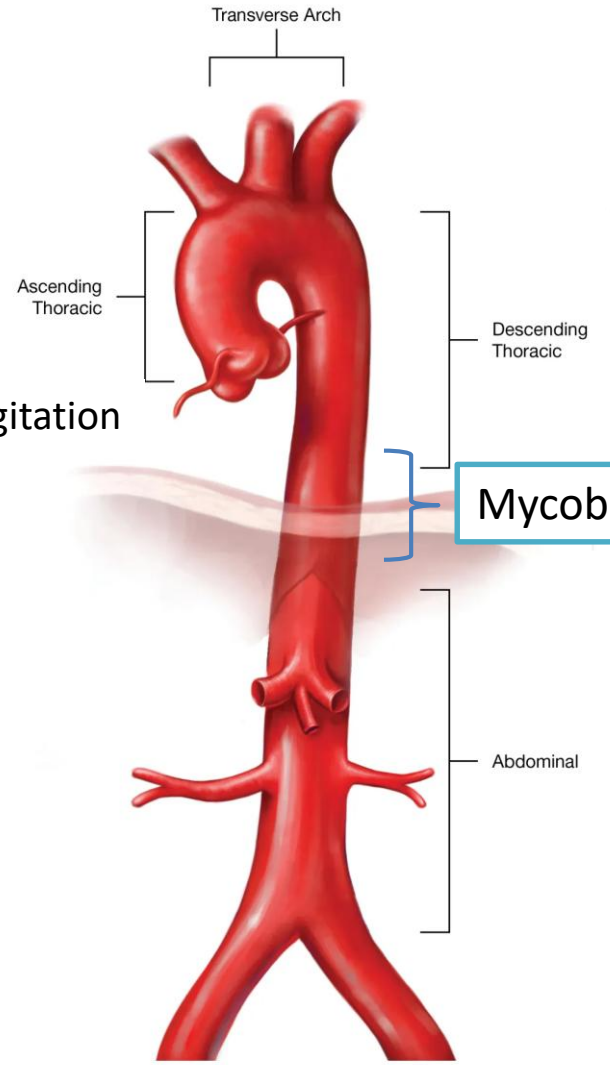
External cause

Drug-induced:
- Ergot alkaloids
- Dopaminergic drugs
- Methysergide
- GCSF
- Immune checkpoint inhibitor

Radiation aortitis

Anatomical approach

Note:
Atherosclerotic aortopathy (aneurysm)
Usually occurs at the arch and abdominal aorta near renal arteries bifurcations



Root – Arch – Thoracic – Abdominal aorta

Takayasu arteritis (TAK): prefers ascending, arch, abdominal
Steno-occlusive aortitis with hypertrophic adventitia
Aneurysm is less common (post-stenotic or RAS w/ 2º HT)
Giant cell arteritis (GCA): prefers arch > ascend.> abdominal
Extensive medial aortitis w/ necrosis and skipped lesion
Aneurysm is common
Behcet: whole aorta

Aortic root & AoV

→ Aortic regurgitation

Ankylosing spondylitis (AS)
Behcet
Relapsing polychondritis

Aortic Valve & annulus

Cogan's syndrome
(keratitis, conjunctivitis, aortitis)
RA, SLE

Coronary artery

Behcet
GPA
RA
IgG4 RD

Mycobacterium tuberculosis

Abdominal aorta

Salmonella
Syphilitic
Behcet
IgG4 RD +peri-aortitis
GPA, EGPA
Drugs

Thoracic - Abdominal aorta

Staphylococcus
Streptococcus
Other infectious aortitis
Behcet (saccular pseudoaneurysm)
GPA, EGPA
RA (rare)
SLE (rare)
Sarcoidosis

https://www.uabmedicine.org/specialties/aortic-aneurysm/

D/Dx Pan–aortitis

	TAK	GCA	Behcet disease
Racial difference	Asian	Caucasian (northern European heritage)	latitudes 30° and 45°N in Asian and Eurasian populations (silk road)
Age @presentation	< 40 yr.	> 50 yr. (max. prev. @70 yr.)	35-45 yr.
Gender, female: male	9:1	3:2	Nearly 1:1
Histopathology	Granulomatous pattern w/ or w/o giant cells		Mixed pattern
Aortic anatomy	Ascend/ Arch/ Ab	Arch > Ascend > Ab	Root to abdominal
Aneurysm formation	Less	More common/ skipped lesion	Saccular pseudoaneurysm
Coronary a. involvement	No	No	Yes
Pulmonary a. involvement	Yes	No	Yes
Distinguish features	RAS w/ 2° HT	Temporal arteritis	Oral/Genital ulcer/ Uveaitis Artery & Vein involvement

The Small-Medium to Arteriole & Venule Systemic Vasculitis

ANCA-associated systemic vasculitis (AAV)

CTDs	Prevalence	Age onset	Female : Male
1. GPA	1:10,000	40 – 60	1:1
2. EGCA	1:50,000	40 – 50	1:1
3. MPA	1:10,000	50 – 65	1:1
Differential diagnosis closely to AAV			
1. Cryoglobulin	1:50,000	45 – 65	2-3:1
2. IgA (Henoch Schoenlein)	1:100,000	20 – 60	1:1
3. Hypersensitivity	1:5,000	adulthood	1:1
4. Urticarial (anti-C1q)	1:100,000	30 – 50	2-3:1

Presenting symptoms

Pauci-immune vasculitis

Immune complex vasculitis

	GPA	EGPA	MPA	Cryoglobulin	IgA vasculitis	HSV	Urticarial
Constitution	✓	✓	✓	✓	✓	✓	—
Key	**ENT**	**Asthma, ↑Eo**	No ENT	**Very low C4**	**↓C3, ↔C4**	**↓C3 & C4**	**↔ to ↓**
Pulmonary	Cavitary Lung	Infiltrations	**DAH**	—	—	—	Less
Renal	**RPGN**	Less/ Mild	**RPGN**	**MPGN**	Nephritis	Less	Less
Cutaneous	Less	Less	**Purpura**	**Purpura Generalized**	**Purpura LE > UE**	**Purpura Generalized**	Urticaria >1D
Neuro	Less	**Mononeuritis**	Less	**Neuropathy**	—	—	—
GI	—	Mucosal vas.	Rare	—	Mucosal vas.	Rare	—
Myocarditis	—	✓	—	—	—	—	—

Key features:

- Upper airway destruction + cavitary lung + GN → **GPA**
- Pulmonary – Renal without ENT → **MPA**
- Asthma/ Eosinophilia first, vasculitis later → **EGPA**

Key features:

- Purpura + Nephritis + normal complement → **IgA**
- New drug + purpura only → **HSV**
- Purpura + Neuropathy + very low C4 → **Cryoglobulin**
- Hives >24 hr. & leave marks → **Urticarial vasculitis/ SLE**

Immune complex (IC) vasculitis

Mechanism
- Circulating IC
- Deposition in postcapillary venules
- Complement activation

Hemodynamic principle
- High hydrostatic pressure
- Low blood flow
- Dependent distribution

IgA	IgM, IgG
IgA vasculitis: **LE > UE**	HSV: **LE predominant** but more generalized
	Cryoglobulinemia: **LE predominant** but more diffuse

Pauci-immune vasculitis

Mechanism: Neutrophil activation
Microvascular pressure & flow >> **LE > UE**

Differential Diagnosis

Platelets: petechiae, diffuse incl. trunk, mucosal
Coagulopathy: ecchymosis, hematoma
DIC: purpura, acral/generalized, critically ill

Palpable Purpura

IgA vasculitis (HSP)
- LE predominant
- Symmetry
- Abdominal pain
- Renal
- Gr. B Strep

ANCA vasculitis
- LE predominant
- Pulmonary
- Renal

Hypersensitivity vasculitis
- LE predominant
- Wide spread
- Hx Drugs

Cryoglobulin
- LE predominant
- More diffuse
- Skin Ulcer
- Neuropathy
- Very low C4

Approach to systemic vasculitis

Clinical presentations of vasculitis

	Large vessel	Medium vessel	Small vessel
	Constitutional symptoms (ไข้ เบื่ออาหาร น.น.ลด อ่อนเพลีย), Symmetrical polyarthritis		
	Renovascular HT ○ Refractory HT ○ HT in the young **Limb claudication** **Central retinal a. occlusion** ○ Painless visual loss **Stroke in the young** **Aortic regurgitation** (aortitis)	**Mononeuritis multiplex** Cutaneous ulcer Palpable purpura with ulceration Digital(s)/ Toe(s) gangrene	**Petechial rashes** **Palpable purpura** (leukocytoclastic vasculitis, LCV) Glomerulonephritis Diffuse alveolar hemorrhage (Nodules, Cavitation) Uveitis, Retinitis
	Could it be vasculitis mimics? (apply Virchow triads)		
1. Vessel wall	**Atherosclerotic stenosis/ emboli** Thrombotic emboli Thromboangiitis obliterans	**Vasospasm (Cafe got)** Raynaud's disease (Primary RP) Embolism	Livedo reticularis
2. Cellular		**RBC** (PV), **WBC** (CML, CLL, ALL), **Platelets** (ET or ↓platelets)	
3. Plasma		**APS**, **DIC**, coumadin-induced skin necrosis, calciphylaxis	

Approach to systemic vasculitis

Clinical presentations of vasculitis

	Large vessel	Medium vessel	Small vessel
	Could it result from other secondary causes?		
1. Infection	Staphylococcus spp. Streptococcus spp. Salmonella spp. Tertiary syphilis Mycobacterium Tuberculosis Pythium insidiosum		Streptococcus group A Coxiella Parvovirus B19 Rubeola Mumps Hepatitis B/C, HIV
2. Inflammation	Behcet aortitis Ankylosing spondylitis aortitis IgG4 related disease	Behcet, Relapsing polychondritis CTD (RA, SLE, Dermatomyositis, Polymyositis, MCTD, Sjogren)	
			Henoch-Schoenlein Purpura Cryoglobulinemic vasculitis
3. Tumor		Paraneoplastic systemic vasculitis	
4. Drugs		Drug-induced hypersensitivity vasculitis	
Primary	**Takayasu arteritis** **Giant cells arteritis**	ANCA-associated vasculitis (**AAV**): GCA, MPA, EGPA	
		Polyarteritis nodosa Kawasaki vasculitis	

Clinical Glucocorticoid Pharmacology

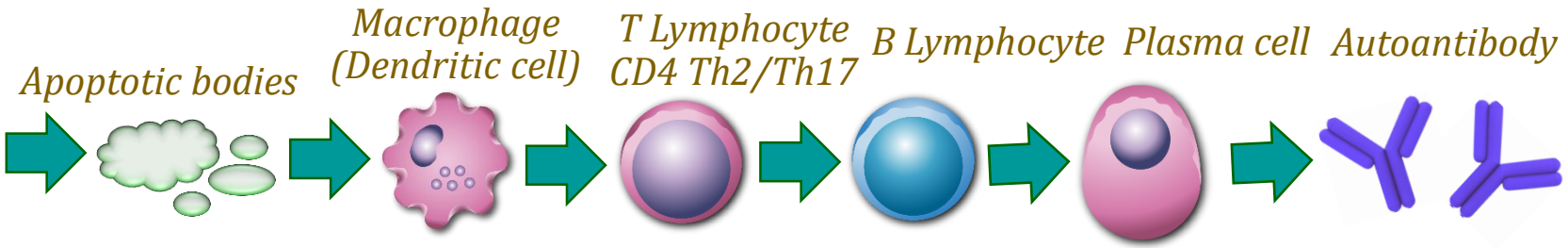
Dose	Prednisolone (mg/day)		Clinical effect	Mechanism	Immune effect	Clinical Use
Physiologic	< 7.5		Maintenance	Physiologic	Slight cytokine suppression	Adrenal insufficiency
Low	< 10	< 0.5 MKD	Anti-inflammatory	Genomic (onset in many hours)	Inhibit NF-kB, STAT path. • ↓IL1, IL2, IL6, TNFα, COX2 • → T cell suppression	
Medium	10 – 30					Minor Organ
High	30 – 100	≥ 0.5 MKD	Immunosuppressive	Genomic and Non-genomic (onset in minutes)	Steroids ≡ GR • Inhibit MAPK, TCR signaling • Lymphocyte proliferation & expansion & apoptosis • ↓Neutrophil adhesion • Ag presentation • Complement-mediated inflammation	Major Organ
Very high	> 100		Rapid immune shutdown			
Pulse	≥ 250 IV MP		Cytokine storm suppression	Non-genomic (dominant)		Life-Threatening

Adverse effects:

- Osteoporosis: ≥2.5 mg prednisolone ≥3 months
- AVN is associated with a high peak dose
- Myopathy: HDGC ≥2 wk
- Wound dehiscence: HDGC >1 wk
- Psychosis: ≥HDGC within 2-6 wk

Buttgereit F. Ann Rheum Dis. 2002
Buttgereit F. Rheum. 1998
Rhen T, Cidlowski JA. N Engl J Med. 2005
Barnes PJ. Clin Sci. 1998.

SLE Treatment



Triggers

UVB
Virus
Bacteria
Drugs

Correct

Autoimmunity → Tissue injury ±Damages

Stop immune – mediated tissue inflammation

Prednisolone (5)
3 x 2 pc x 4 wk.
3-0-2 pc 1 wk.
2-0-2 pc 1 wk.
3 x 1 pc 2 wk. → 2½ x 1 2 wk.
2 x 1 2 wk. → 1½ x 1 2 wk.
1 x 1 2 wk. → ½ x 1 2 wk.
½ x 1 AD 2 wk. → off

Induction Px

Minor organ (non life-threatening): Fever, malar rash, arthritis, serositis

: NSAIDS 2 – 4 wks.

: Prednisolone ≤0.5 MKD 2 – 4 wks. → Taper off

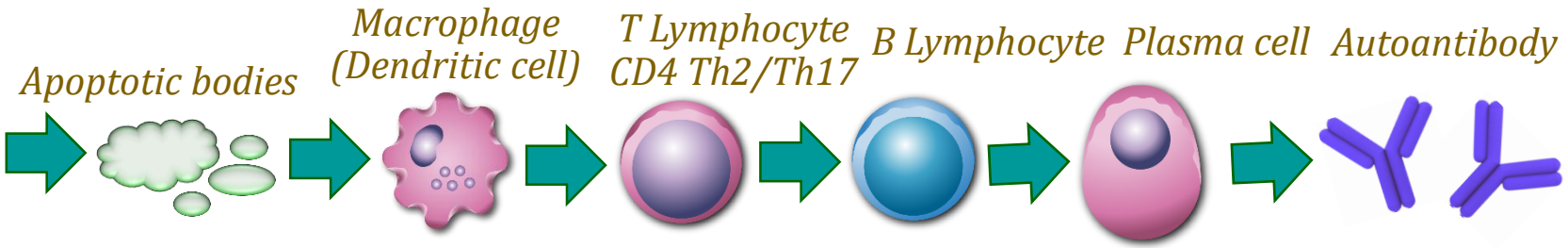
Prevention of (relapse) further damages

Maintenance Px

: Chloroquine 3 MKD [250 mg/tab ½ tab po OD] or Hydroxychloroquine 5 MKD [200 mg/tab OD]
If inadequate control, add Methotrexate (2.5) 2 tab po weekly titrate to (max) 8 tab po weekly [+ folic acid 5 mg/day]
Or Azathioprine 0.5 – 1 MKD Or (add) Leflunomide (20) 1 tab po weekly to 1 x 1
Or (change to) MMF max 3 g/D or Cyclosporine 0.5 – 2.5 MKD

Fanouriakis A, et al. Ann Rheum Dis 2020;79:713–723.

SLE Treatment



Triggers

UVB
Virus
Bacteria
Drugs

Correct

Autoimmunity | Tissue injury ±Damages

Stop immune – mediated tissue inflammation

Prednisolone (5)
↓ 5-10 mg/d q 1–2 wk to 40 mg/d
↓5 mg/d q 1–2 wk to 20 mg/d
↓1 – 2.5 mg/d q 2 wk
To off

Induction Px

Major organ: *AIHA Hb <8 g/dL, ITP <50K, Bleeding, LN type 3, 4, 5, Nervous system*

: Prednisolone 1 MKD 4 - 8 wks. Or Dexamethasone in an equivalent dose Or

: Methylprednisolone 1 g in NSS 100 ml IV drip in 1 hr. 3 – 5 d → Prednisolone 0.5 MKD 4 – 8 wk.
(life-threatening condition: RPGN, DAH, Seizure)

: Cyclophosphamide

NIH regimen: 0.5 – 0.75/BSA (m^2) in NSS 100 mL drip in 1 hr. q 1 month x 6 (total 6 months) [LN W/ AKI, LN 5]

EURO Lupus regimen: 0.5 g in NSS 100 mL drip in 1 hr. q 2 wk. x 6 (total 3 months) [LN 3, 4, ±5 W/O AKI]

: Mycophenolate mofetil 2 – 3 g/day x 6 months [LN 3, 4, 5 W/O AKI]

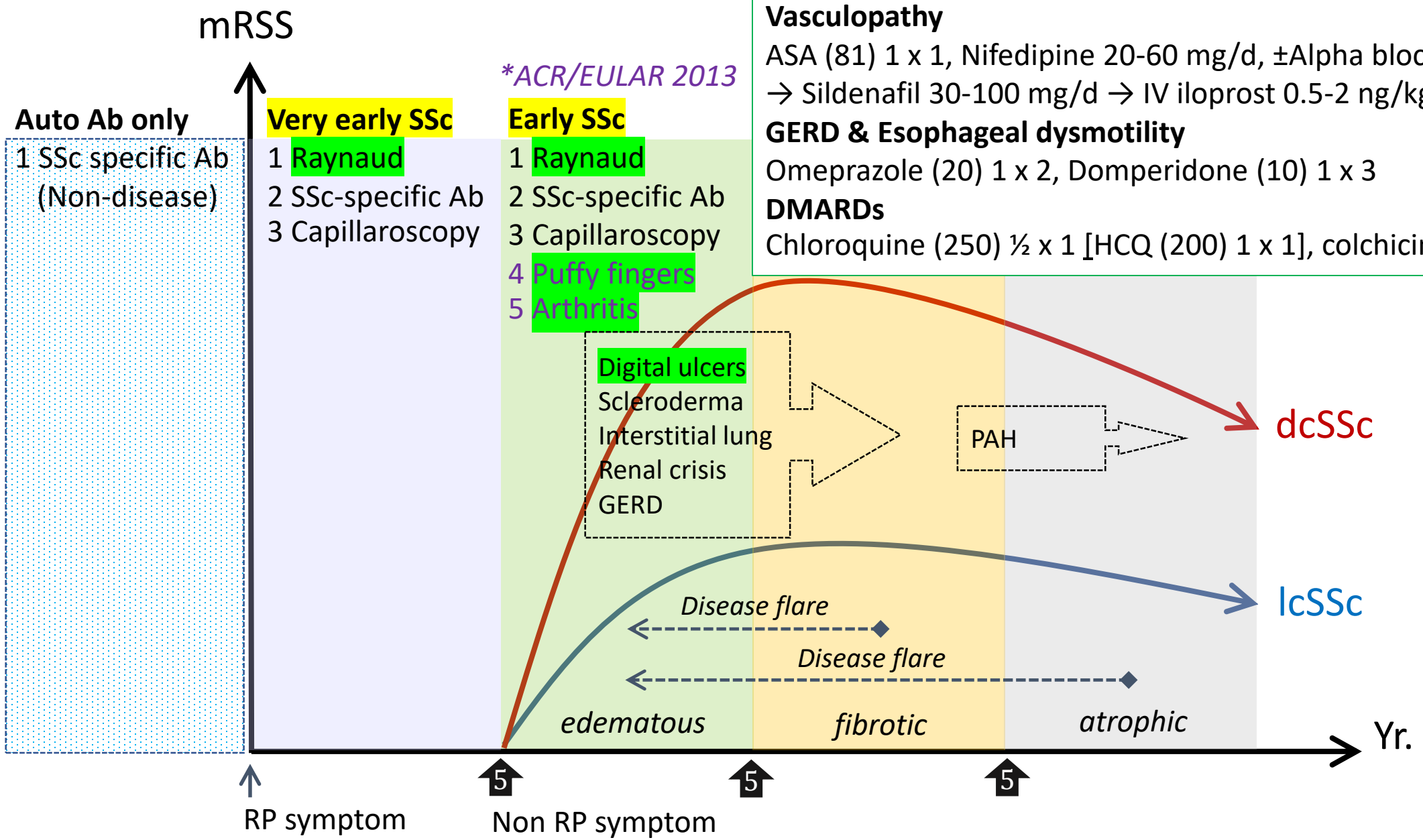
: MMF 1 – 2 g/day + TAC 2-3 g/day x 6 months [LN V] or TAC 0.08 MKD [LN 5]

Prevention of (relapse) further damages

Maintenance Px

: CQ (3 MKD) + Azathioprine 1 – 2 MKD OR Mycophenolate mofetil 1 – 1.5 g/day x 6 months

SSc Px in very early & early SSc

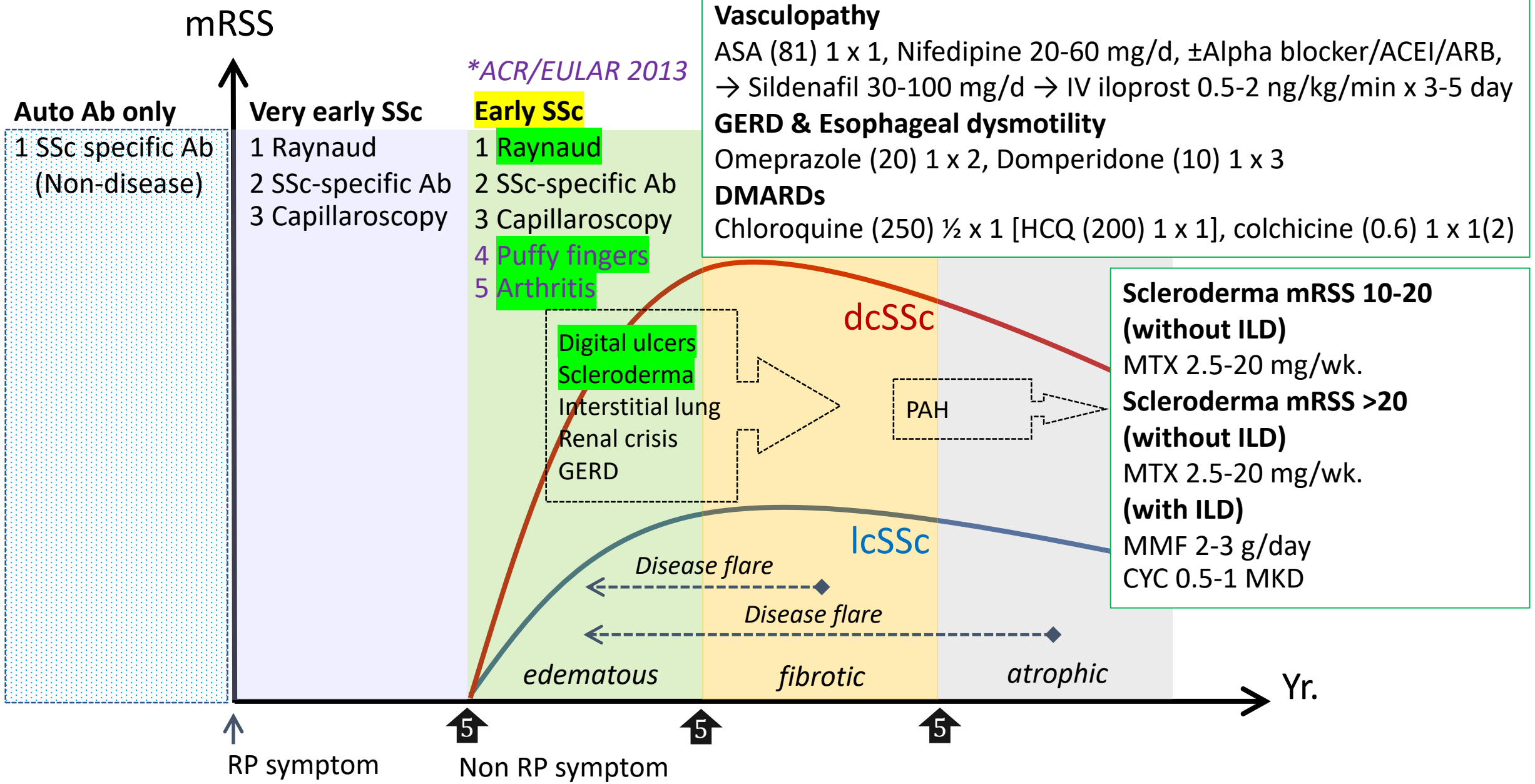


Vasculopathy
ASA (81) 1 x 1, Nifedipine 20-60 mg/d, ±Alpha blocker/ACEI/ARB, → Sildenafil 30-100 mg/d → IV iloprost 0.5-2 ng/kg/min x 3-5 day

GERD & Esophageal dysmotility
Omeprazole (20) 1 x 2, Domperidone (10) 1 x 3

DMARDs
Chloroquine (250) ½ x 1 [HCQ (200) 1 x 1], colchicine (0.6) 1 x 1(2)

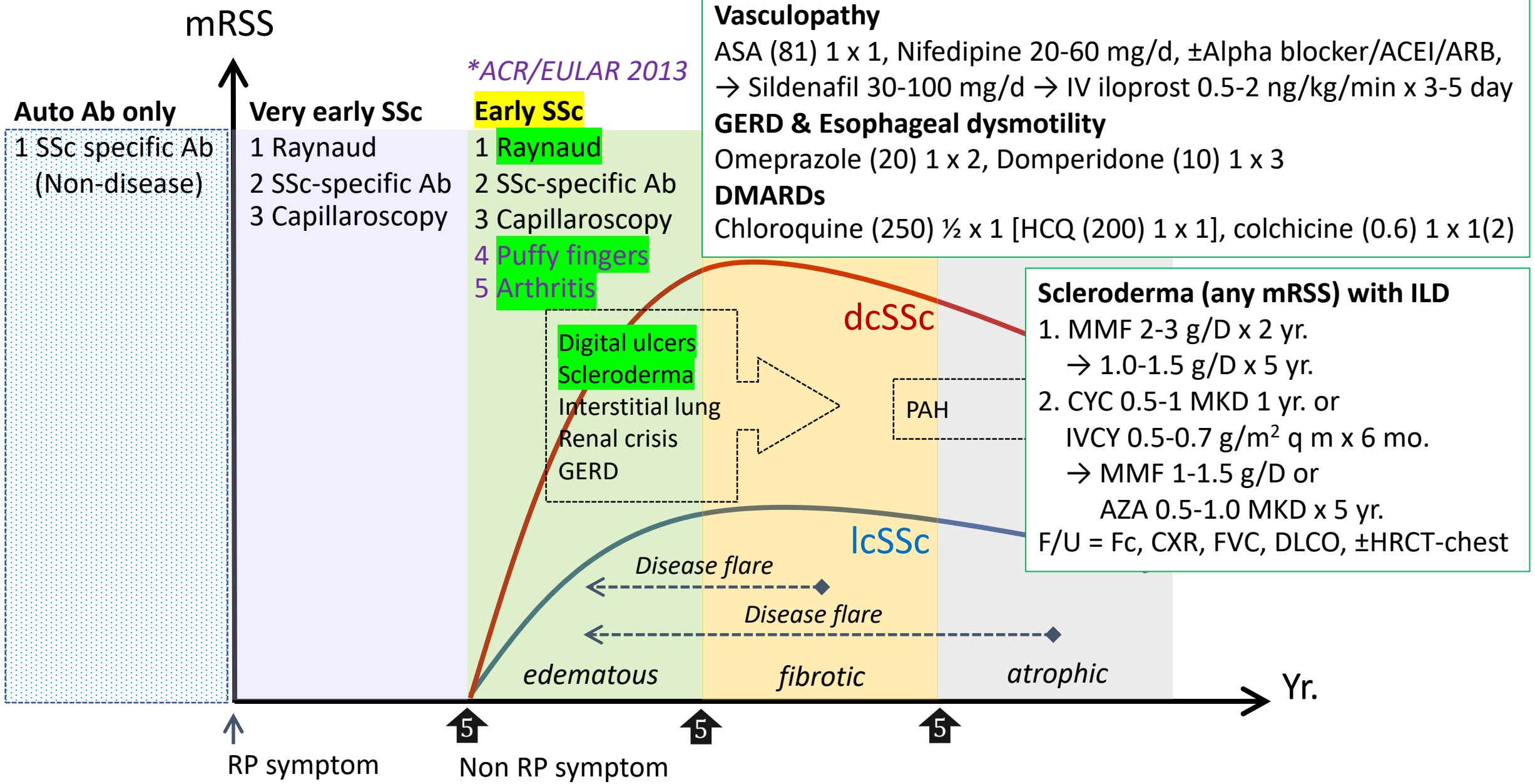
SSc Px in early SSc to establish SSc



Vasculopathy
ASA (81) 1 x 1, Nifedipine 20-60 mg/d, ±Alpha blocker/ACEI/ARB, → Sildenafil 30-100 mg/d → IV iloprost 0.5-2 ng/kg/min x 3-5 day
GERD & Esophageal dysmotility
Omeprazole (20) 1 x 2, Domperidone (10) 1 x 3
DMARDs
Chloroquine (250) ½ x 1 [HCQ (200) 1 x 1], colchicine (0.6) 1 x 1(2)

Scleroderma mRSS 10-20 (without ILD)
MTX 2.5-20 mg/wk.
Scleroderma mRSS >20 (without ILD)
MTX 2.5-20 mg/wk.
(with ILD)
MMF 2-3 g/day
CYC 0.5-1 MKD

SSc Px in early SSc to establish SSc



Vasculopathy
ASA (81) 1 x 1, Nifedipine 20-60 mg/d, ±Alpha blocker/ACEI/ARB,
→ Sildenafil 30-100 mg/d → IV iloprost 0.5-2 ng/kg/min x 3-5 day

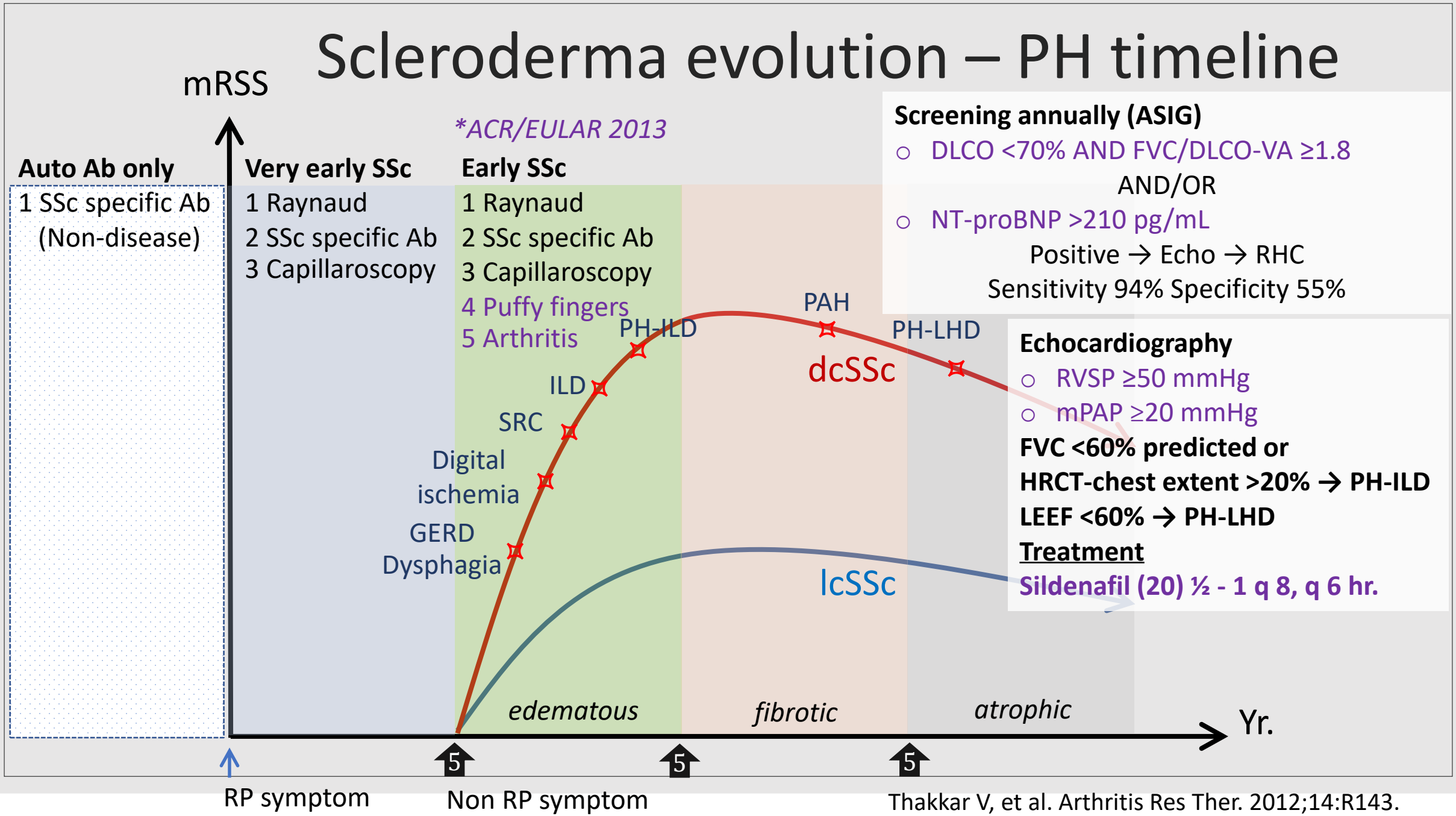
GERD & Esophageal dysmotility
Omeprazole (20) 1 x 2, Domperidone (10) 1 x 3

DMARDs
Chloroquine (250) ½ x 1 [HCQ (200) 1 x 1], colchicine (0.6) 1 x 1(2)

Scleroderma (any mRSS) with ILD
1. MMF 2-3 g/D x 2 yr.
   → 1.0-1.5 g/D x 5 yr.
2. CYC 0.5-1 MKD 1 yr. or
   IVCY 0.5-0.7 g/m^2 q m x 6 mo.
   → MMF 1-1.5 g/D or
   AZA 0.5-1.0 MKD x 5 yr.

F/U = Fc, CXR, FVC, DLCO, ±HRCT-chest

Scleroderma evolution – PH timeline



Screening annually (ASIG)

- DLCO <70% AND FVC/DLCO-VA ≥1.8

AND/OR

- NT-proBNP >210 pg/mL

Positive → Echo → RHC

Sensitivity 94% Specificity 55%

Echocardiography

- RVSP ≥50 mmHg
- mPAP ≥20 mmHg

FVC <60% predicted or

HRCT-chest extent >20% → PH-ILD

LEEF <60% → PH-LHD

Treatment

Sildenafil (20) ½ - 1 q 8, q 6 hr.

Thakkar V, et al. Arthritis Res Ther. 2012;14:R143.

Treatment for DM/PM

	Induction	Maintenance
General measures	Strengthening exercise	
Modulators	CQ (250) ½ x 1 or HCQ (200) 1 x 1	
Muscle & Skin	Prednisolone 1 MKD 4 – 8 wk.	MTX 2.5 mg/wk. → 20 mg/wk. *Rescue Px* Change to AZA 0.5 – 1.0 MKD (OD) Add on Cyclosporine 0.5 – 2.5 MKD (bid.) MMF 1.0 – 3.0 g/D (bid.) Tacrolimus 0.075 MKD (bid.)
Dysphagia or Severe myopathy	IV MP 0.5 – 1.0 g/D x 3 – 5 D then Prednisolone 0.5 – 1 MKD 4 – 8 wk. with *Options* 1. IV CYC 0.5 – 0.7 g/m2 IV q mo. x 6 2. IVIG 1 g/kg divided over 1-2 D q mo. x 1 – 6 mo. 3. RTX 1 g at D1 – D15 q 6 mo.	*Options* AZA 0.5 – 1.0 MKD (OD) Cyclosporine 0.5 – 2.5 MKD (bid.) MMF 1.0 – 3.0 g/D (bid.) Tacrolimus 0.075 MKD (bid.)

2021 ACR management for TAK

Active TAK vasculitis

Prednisolone (1 MKD) at least 4 wks. plus
Methotrexate 2.5 – 15 mg/wk. OR
Azathioprine 1 – 2 MKD

- Active TAK – cranial or vertebrobasilar involvement → ASA
- F/U ESR, CRP + regularly scheduled noninvasive vascular imaging
- Px of renovascular HT: ACEI/ARB (F/U Cr., electrolyte), CCB
- Vascular intervention during the remission period

Maz M, et al. Arthritis Rheumatol. 2021 Aug;73(8):1349-1365.

2021 ACR management for GCA

Very major: 1. visual loss 2. critical cranial ischemia

Methyl prednisolone 1 g in NSS 100 ml IV drip in 1 hr. x 3 – 5 days then
Prednisolone (or equivalent 0.5 – 1 MKD) (at least 4 wks.) plus
+ Tocilizumab 8 mg/kg (or 162 mg/wk.) IV or SC q 4 wk. (x 18 wks. then taper) OR
+ Methotrexate 2.5 – 15 mg/wk.

Major: extracranial large vessel involvement

Prednisolone (or equivalent 1 MKD) (at least 4 wks.) plus
+ Tocilizumab 8 mg/kg (or 162 mg/wk.) IV or SC q 4 wk. (x 18 wks. then taper) OR
+ Methotrexate 2.5 – 15 mg/wk.

Maz M, et al. Arthritis Rheumatol. 2021 Aug;73(8):1349-1365.

2021 ACR management for GPA/MPA

Active severe GPA/MPA (DAH, RPGN, MN, digital ischemia)

Induction

BW 50-75 kg
MP 1 g NSS 100 ml IV 1 hr. x 3D
Prednisolone 60 mg/D x 1 wk.
Prednisolone 30 mg/D x 1 wk.
Prednisolone 25 mg/D x 2 wk.
Prednisolone 20 mg/D x 2 wk.
Prednisolone 15 mg/D x 2 wk.
Prednisolone 12.5 mg/D x 2 wk.
Prednisolone 10.0 mg/D x 2 wk.
Prednisolone 7.5 mg/D x 2 wk.
Prednisolone 5.0 mg/D x 10 wk.

Rituximab
375 mg/m^2 IV q 4 wk. OR
1 g IV on D1, D15
OR
Cyclophosphamide
1-2 MKD 3-6 mo. OR
15 mg/kg IV q 2 wk. x 3 doses
then q 3 wk. x 3 doses

← No need of plasma exchange!
← Reduced dose GC regimen

Maintenance

Rituximab 500 mg IV q 6 mo. OR 1 g IV q 4 mo.
Methotrexate 2.5-25 mg/wk. OR
Azathioprine 1-2 MKD OR
Leflunomide 20 mg/D

Chung SA, et al. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.

2021 ACR management for GPA/MPA

Active nonsevere GPA/MPA (mild constitutional symp., LCV, arthritis)

Induction

Prednisolone 1 MKD 2-4 wk.

Methotrexate 2.5-25 mg/wk. OR
Rituximab 375 mg/m^2 IV q 4 wk. OR 1 g IV on D1, D15 OR
Cyclophosphamide 1-2 MKD 3-6 mo. OR 15 mg/kg IV q 2 wk. x 3 then q 3 wk. x 3 OR
Azathioprine 1-2 MKD or
Mycophenolate mofetil 2-3 g/D

Maintenance

Methotrexate 2.5-25 mg/wk. OR
Azathioprine 1-2 MKD OR
Mycophenolate mofetil 2-3 g/D
Rituximab 500 mg IV q 6 mo. OR 1 g IV q 4 mo.

Chung SA, et al. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.

2021 ACR management for EGPA

	Active severe	Active nonsevere
Induction	IV MP 1 g IV x 3 days OR Prednisolone 1 MKD	Prednisolone 1 MKD
	Rituximab 375 mg/m^2 IV q 4 wk. OR 1 g IV on D1, D15 OR **Cyclophosphamide** 1-2 MKD 3-6 mo. OR 15 mg/kg IV q 2 wk. x 3 then 15 mg/kg IV q 3 wk. x 3	**Methotrexate** 2.5-25 mg/wk. OR **Azathioprine** 1-2 MKD or **Mycophenolate mofetil** 2-3 g/D **Rituximab** 375 mg/m^2 IV q 4 wk. OR 1 g IV on D1, D15
Maintenance	**Methotrexate** 2.5-25 mg/wk. OR **Azathioprine** 1-2 MKD or **Mycophenolate mofetil** 2-3 g/D **Rituximab** 500 mg IV q 6 mo. OR 1 g IV q 4 mo.	

Chung SA, et al. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.

2018 EULAR management for Behcet

Minor lesions

Papulopustular lesion (acne-like lesion): 0.1% TA cream bid.
Genital/ Oral ulcer, Erythema nodosum, arthritis: colchicine (0.6) 1 x 2

Major lesions: uveitis, deep vein vasculitis (DVT), pulmonary vasculitis, CVST

Prednisolone (or equivalent 1 MKD) (at least 4 wks.) plus
+ Azathioprine 1 – 2 MKD (uveitis, DVT, IBD, CNS)
+ Cyclosporine A (uveitis, DVT)
+ Cyclophosphamide (DVT, pulmonary arteritis, aortitis, arteritis)

Hatemi G, Christensen R, Bang D, et al. Ann Rheum Dis 2018;77:808–818.