



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Vasculitis / GCA / PMR

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 - Clinical focus: vasculitis
 - Research focus: clinical trials

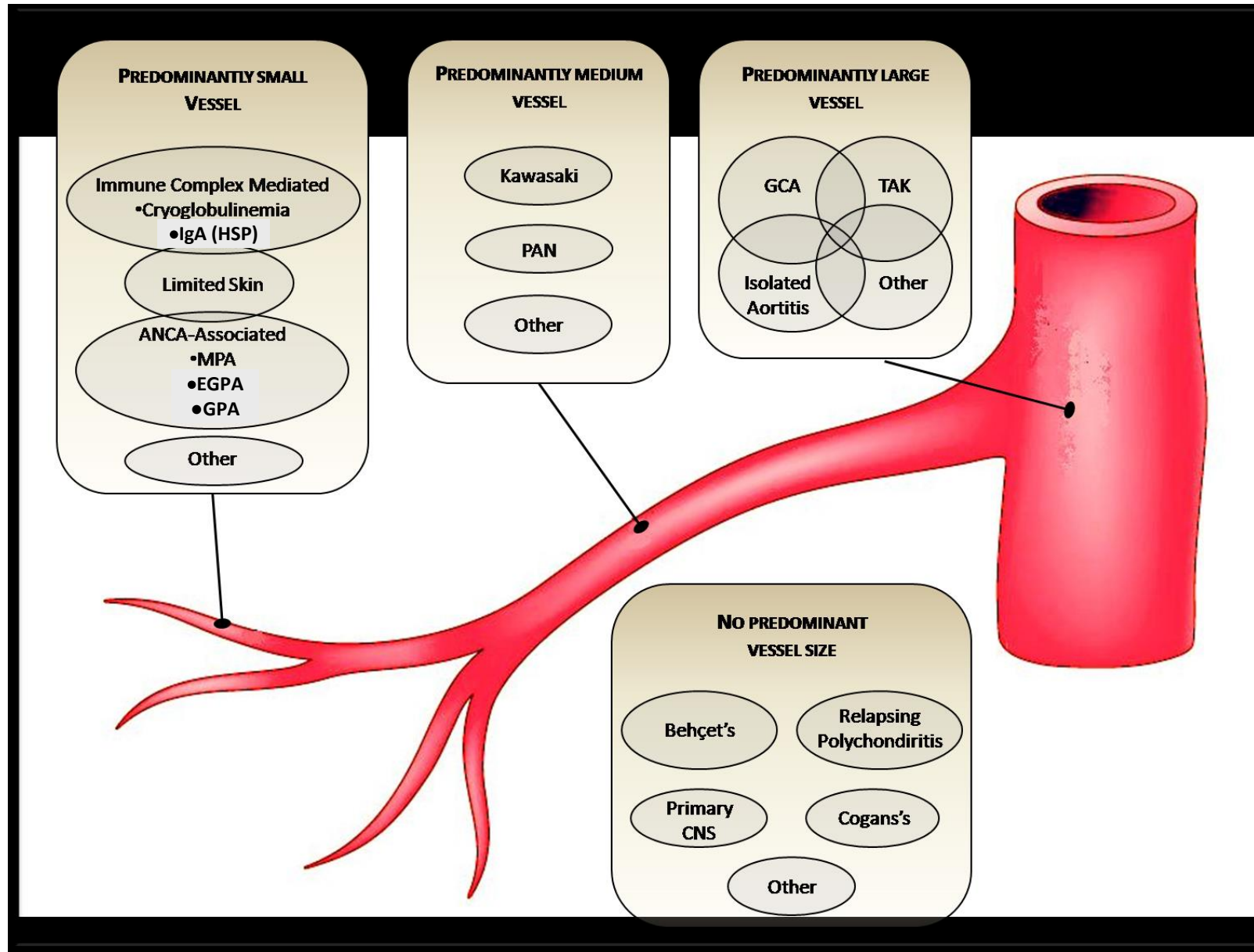
Disclosures

- Bristol-Myers Squibb: investigator in previous trials of abatacept
- ChemoCentryx, Genentech, GlaxoSmithKline: investigator in previous trials of avacopan, rituximab, and mepolizumab
- Consulting: ChemoCentryx, Hi-Bio

Objectives

- Review the clinical features of and diagnostic tests for the major vasculitides
- Summarize approaches to treatment of the vasculitides

Classification of Vasculitis



Vasculitis – big picture

- **Shared feature = Inflammatory destruction of blood vessel walls**
 - Small vessel: neutrophilic, necrotizing → healing +/- re-vascularization
 - Medium vessel: neutrophilic, necrotizing → mononuclear → resolution
 - Large vessel: mononuclear, non-necrotizing, sparing endothelium
- **Symptoms**
 - Tissue ischemia and infarction
 - Varies with organ system (+/- pain, dysfunction, repair +/- restored function)
 - Local and systemic inflammation
- **Syndromes**
 - Named multi-organ syndromes / diseases
 - In setting of other autoimmune diseases, drug exposure, malignancy
 - Idiopathic single-organ and otherwise unclassifiable

Diagnosing vasculitis

	Biopsy	(CT/MR) Angio	Specific Labs	History, exam, non-specific tests
Immune Complex	+++		+	++
ANCA-associated	+		+++	++
PAN	++	+		++
GCA	++	+		++
Takayasu's		+++		++

How rare is rare?

	1: 100	1: 1000	1: 10,000	1: 100,000
GCA	+ + +			
Behcet's	+ (endemic)		+ (other)	
IgA (HSP)	+ (pediatric)			+ (adult)
GPA (Wegener's)			+ + +	
MPA				
EGPA (Churg-Strauss)				
PAN				+
Takayasu			+ +	
Single-organ	+ (skin)			+ (other)

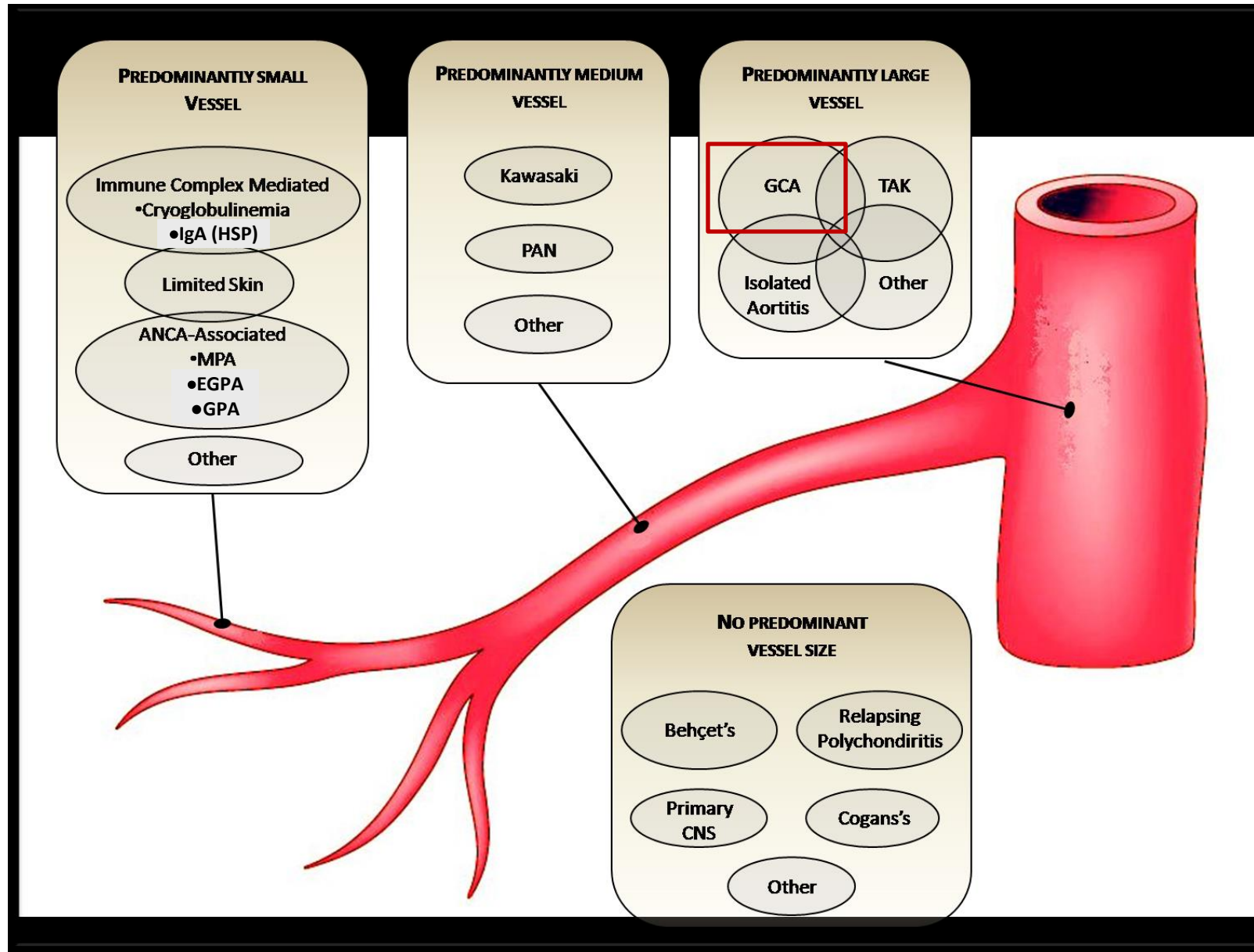
Treatment - evidence

- Even the most common vasculitides have many questions not assessed in studies
- Evidence from multiple randomized trials
 - ANCA-associated vasculitis: GPA (Wegener's), MPA
 - GCA, Kawasaki
- A few trials, many gaps
 - EGPA (Churg-Strauss), Cryo, Takayasu
- Mostly uncontrolled trials and case series
 - IgAV (HSP), PAN, CNS

Treatment principles

- Some syndromes are mild, self-limited (cutaneous especially)
- **Glucocorticoids**
 - Wide variation in dose and duration
 - Syndrome and severity don't predict response perfectly
- **Non-steroid drugs (across diseases)**
 - Mildest cases (small/medium vessel): colchicine, dapsone, hydroxychloroquine
 - Moderate: methotrexate, azathioprine, mycophenolate, leflunomide, cyclosporine
 - Severe (mostly small/medium vessel): cyclophosphamide (temporarily)
- **Biologics (more disease specific)**
 - Rituximab (anti-CD20, depletes B cells)
 - Tocilizumab, sarilumab (anti-IL6R)
 - Mepolizumab, benralizumab (anti-IL5, anti-IL5R)

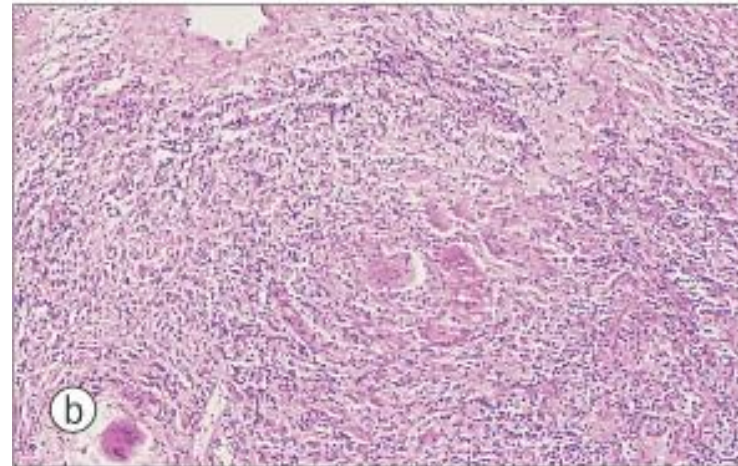
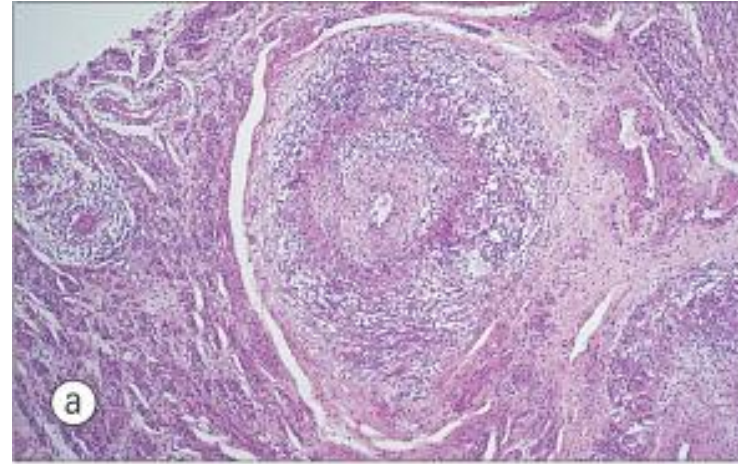
Classification of Vasculitis



Giant cell arteritis (GCA)

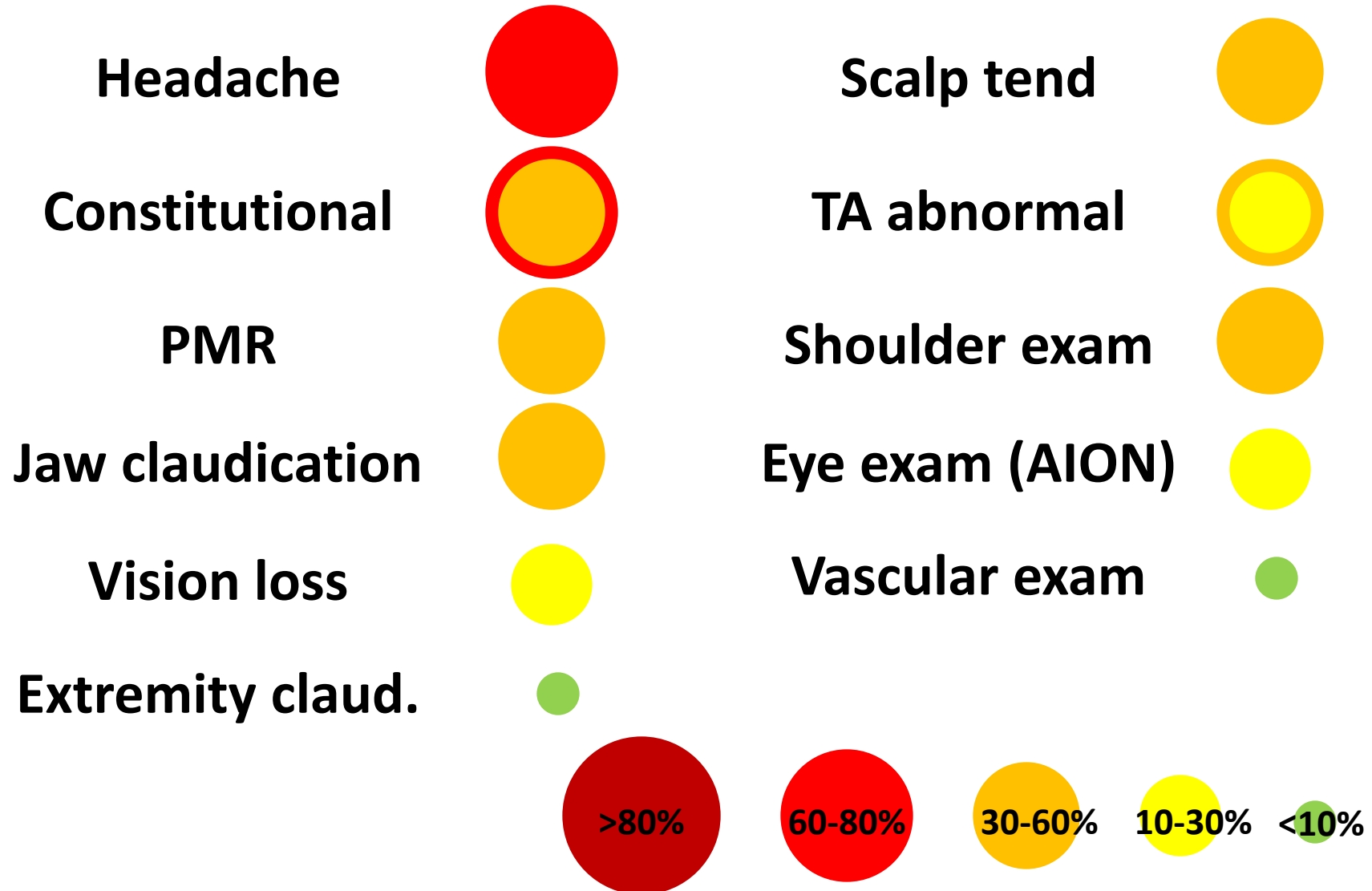


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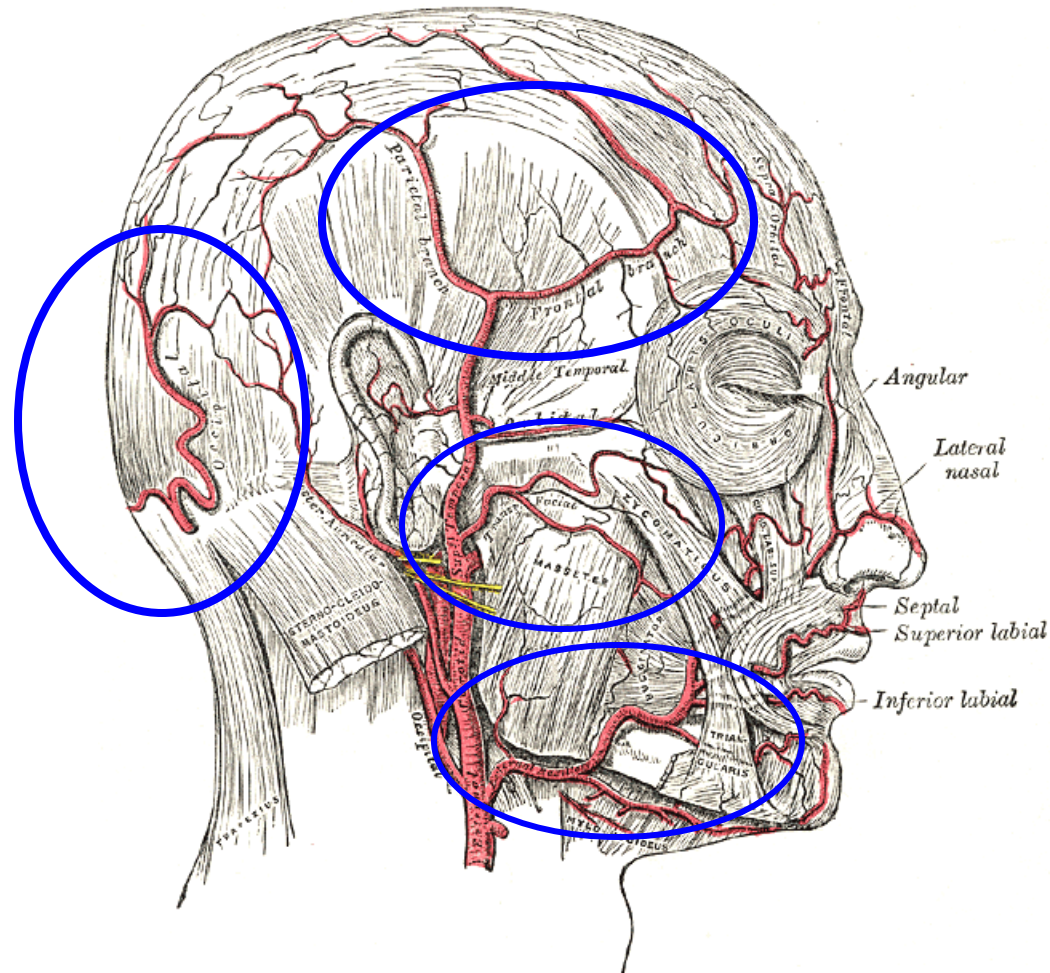


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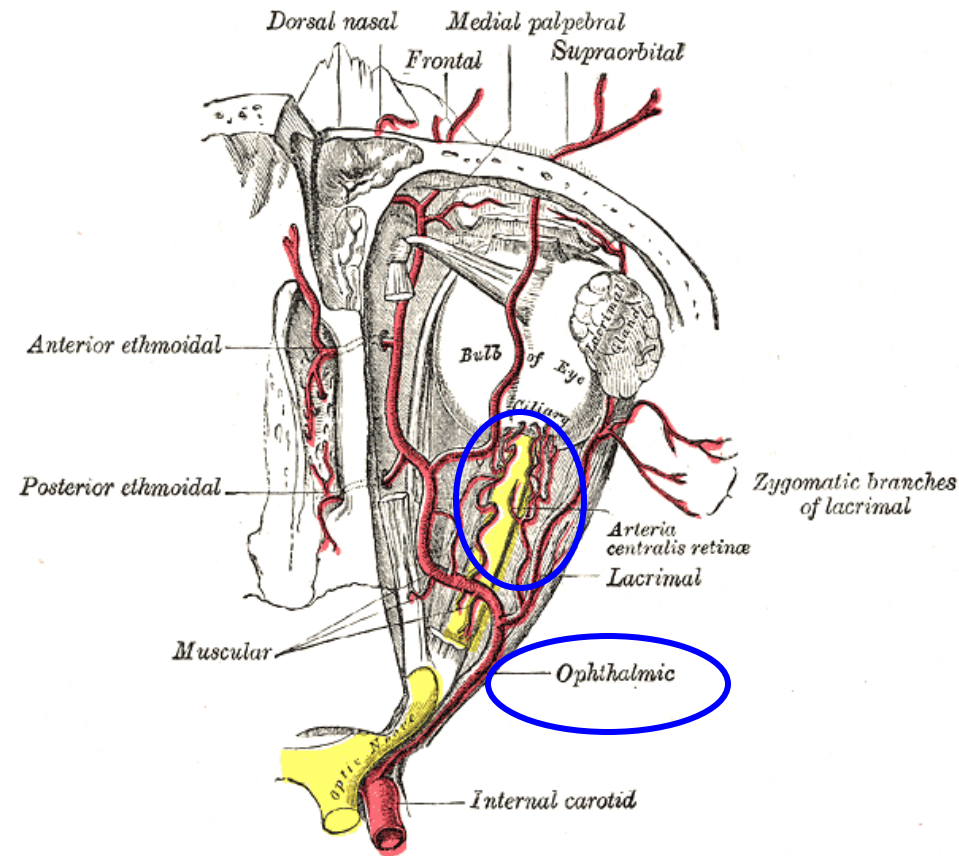
Symptoms and signs in GCA



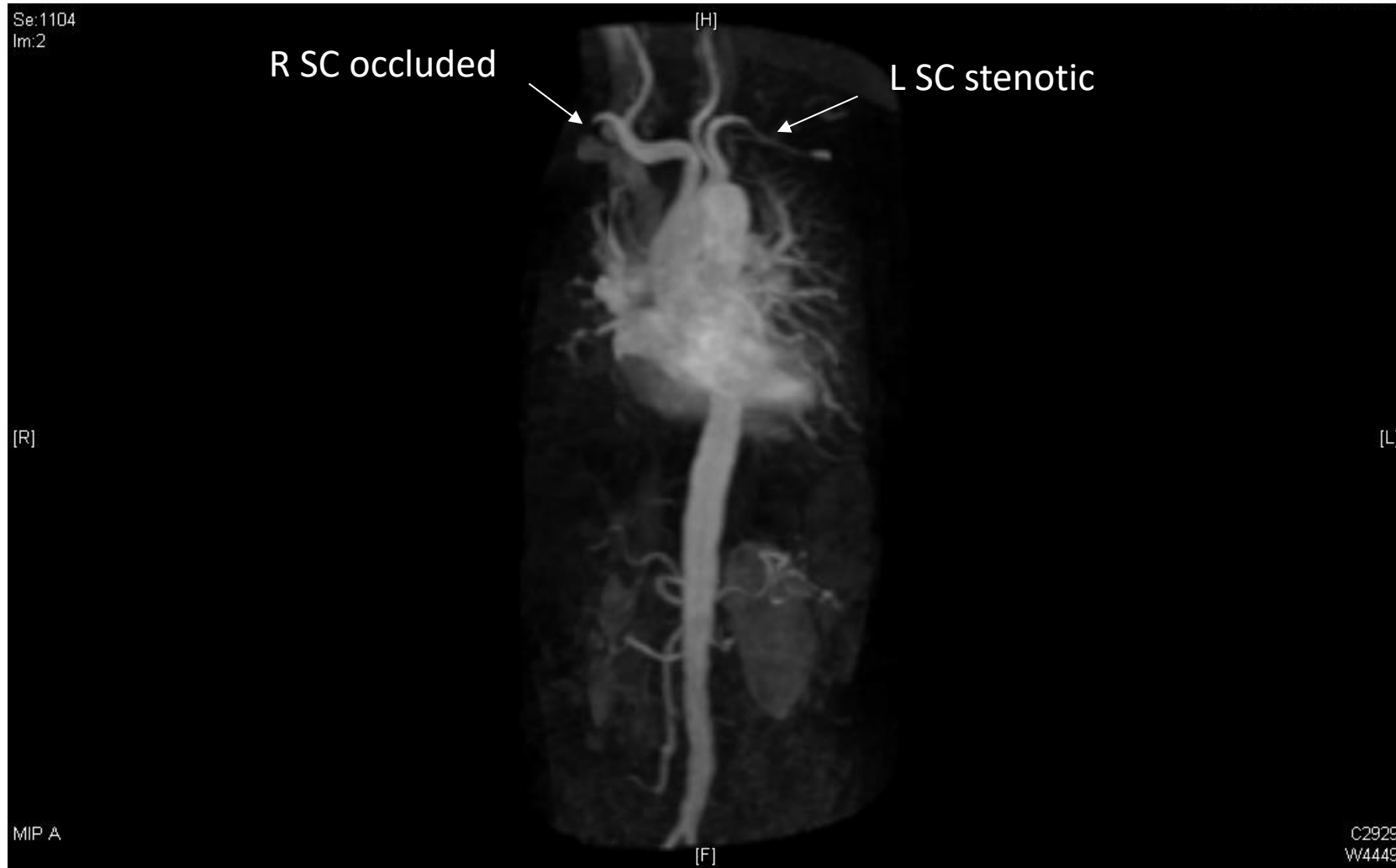
Explaining the symptoms of GCA



Why the eye is at risk in GCA



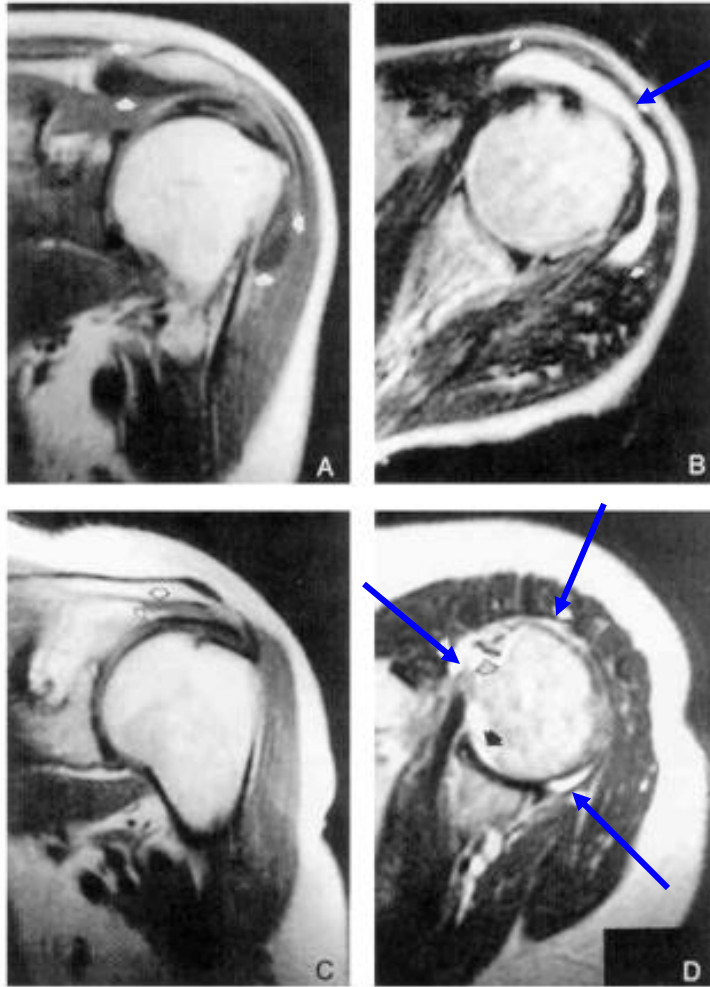
Large-vessel vasculitis in GCA



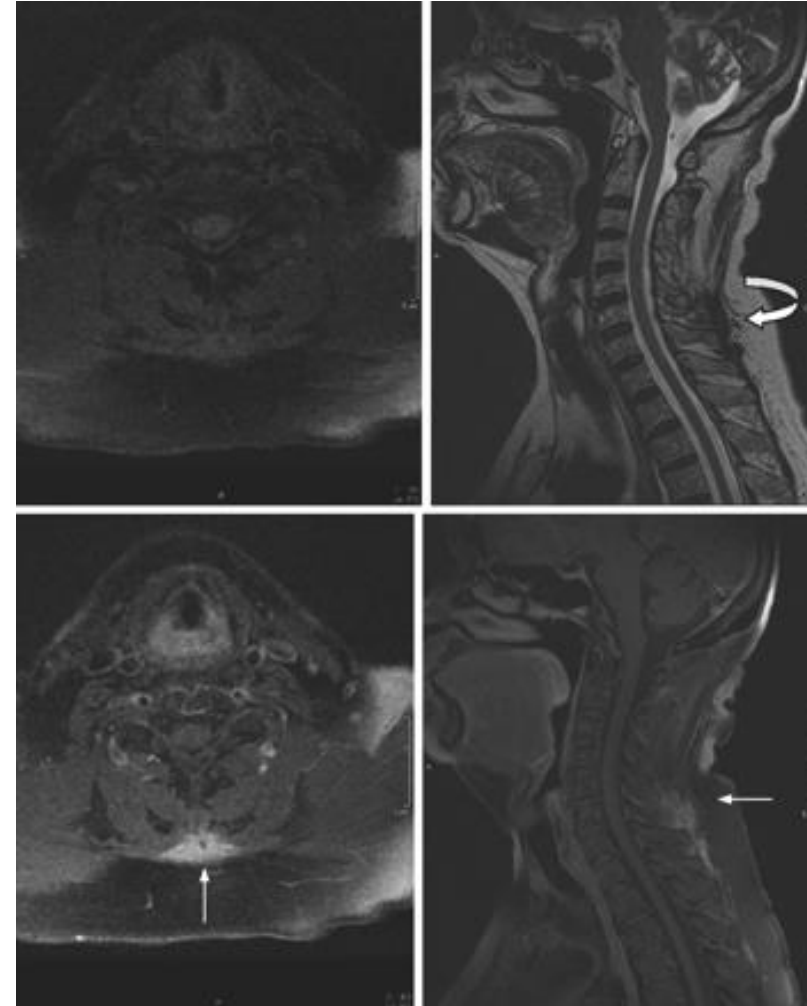
Polymyalgia rheumatica

- **Inflammatory arthritis, bursitis, and tenosynovitis**
(usually a combination)
 - Negative for RF and CCP antibodies
 - No specific lab or imaging finding, just inflammation
- **Clinical syndrome**
 - Bilateral shoulder pain in great majority
 - Hip girdle > neck > widespread pain common
 - Peripheral arthritis in 10%
 - Peripheral arthritis without shoulder pain is not PMR
 - Constitutional symptoms common

Explaining the symptoms of PMR



Salvarani, Ann Int Med 1997



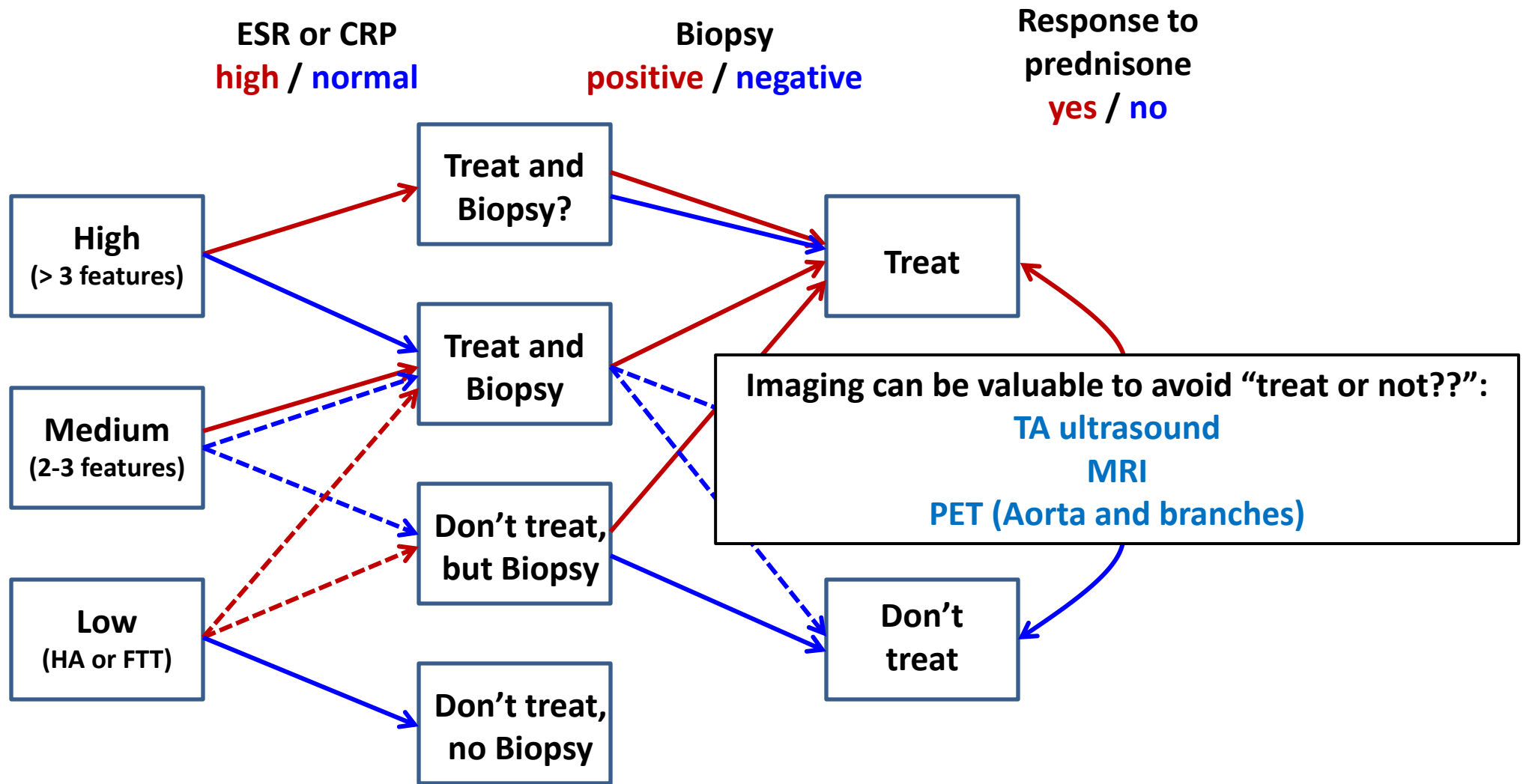
Salvarani, Ann Rheum Dis 2008

GCA and PMR: epidemiology

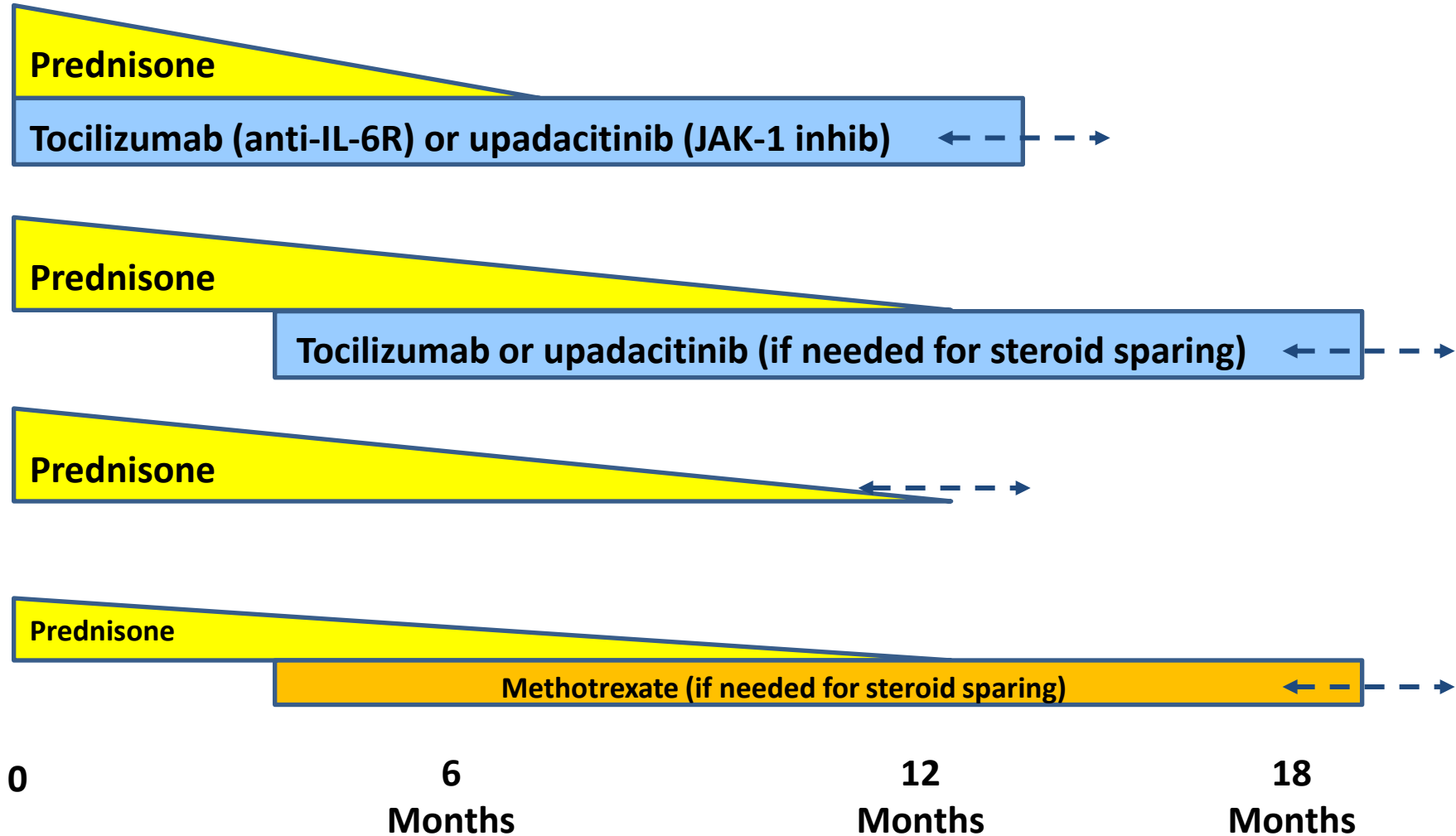
- **Age:** > 50 and usually much older
 - Rare in 50's, relatively common by age 80
 - Younger people **do not** get GCA or PMR
- **Sex:** 70% female
- **Ethnic background**
 - Usually **European (especially northern) descent**, but this is not absolute
 - Black/African-American and Hispanic/Latino patients **do** get GCA, just not as often
 - Very rare in East Asians and South Asians?

GCA – making the diagnosis

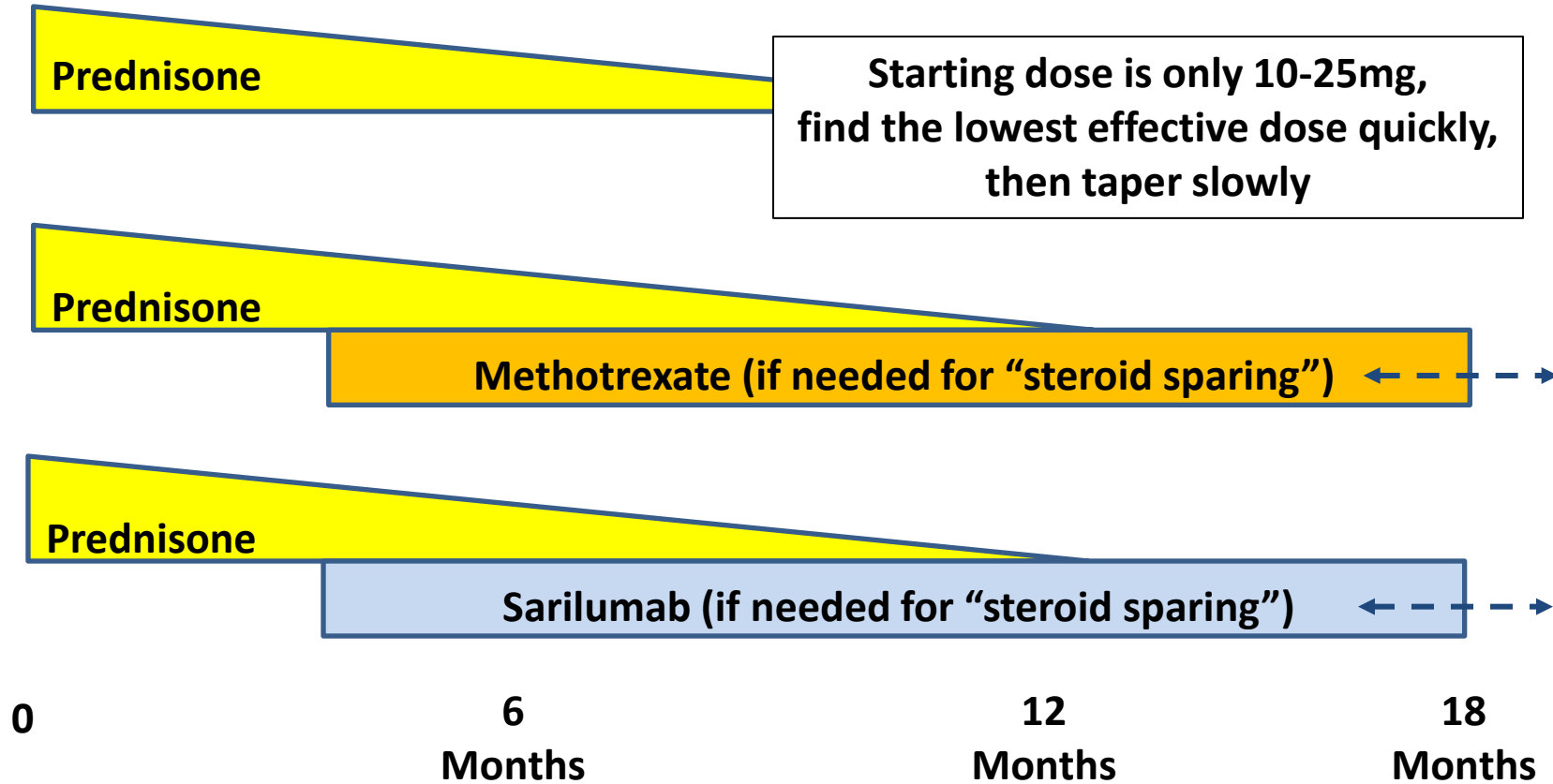
- **ESR and CRP – send both**
 - Each alone 80-85% sensitive, together 96%
- **Temporal artery biopsy**
 - More is better (length, bilateral vs unilateral)
 - Ongoing arguments about how much better, and what to do
 - Only ~80% sensitive (“gold standard” problem...)
- **Imaging?** (mostly at expert centers and research studies)
 - Ultrasound – in the right hands 80% sensitive
 - MRI – with the right sequences 80% sensitive
 - PET/CT – 60% positive aorta, lower in major branches



Common Approaches to GCA



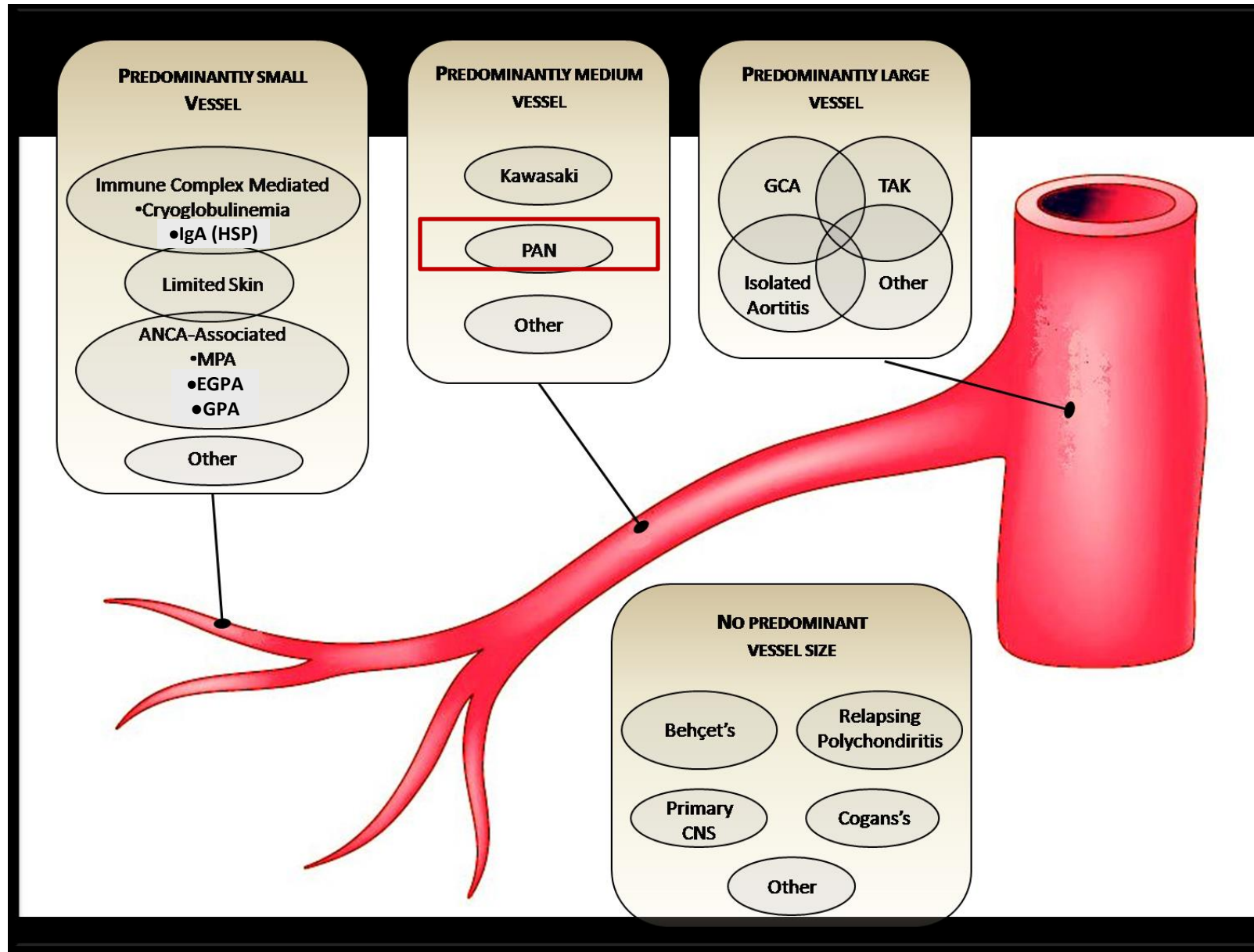
Common Approaches to PMR



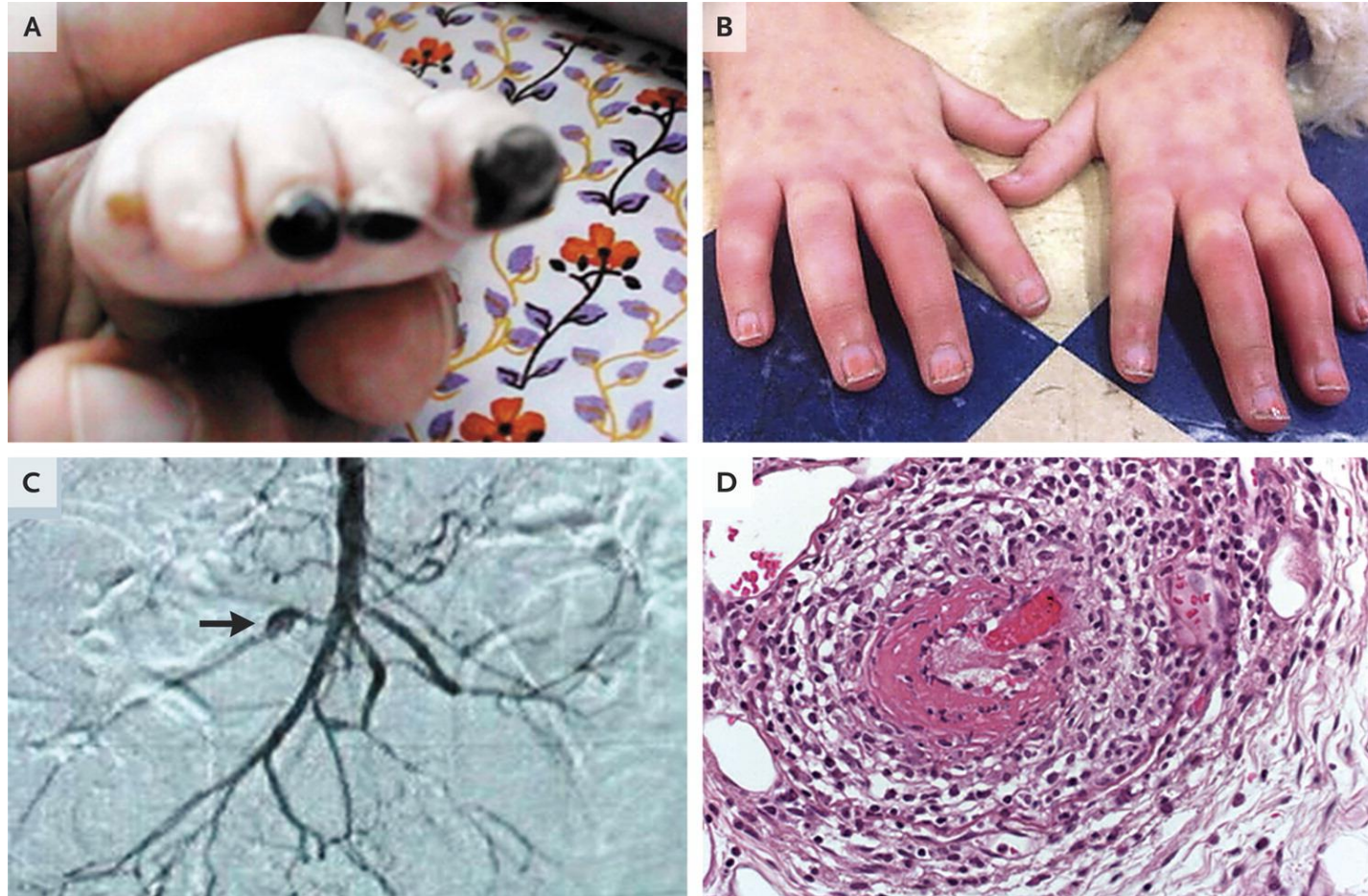
GCA and PMR follow-up

- **Early and often**
 - Max follow-up time (weeks) = 120 / prednisone dose (mg)
 - Typical disease course is gradually decreasing steroid dose over 1-3 years
- **ESR and CRP**
 - We all check these in GCA and get nervous about them, but...
 - Consensus is to NOT increase steroids for asymptomatic rise in ESR/CRP (usually...)
- **Screening for steroid side-effects**
 - BMD, hemoglobin A1c, BP, weight, etc...
- **Screening for large-vessel involvement** (method?)
 - Risk of thoracic aortic aneurysm 6%, usually many years later

Classification of Vasculitis

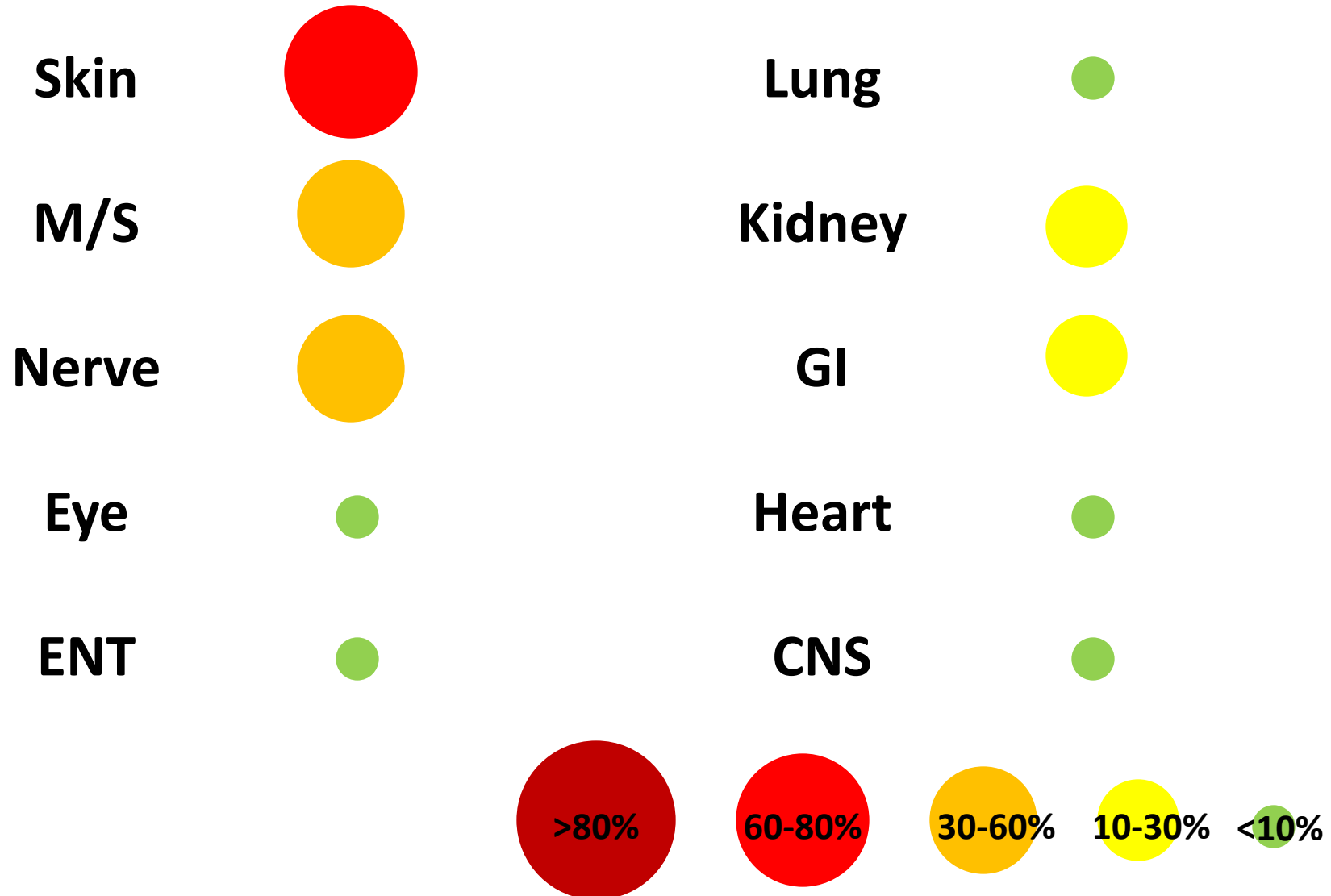


Polyarteritis Nodosa

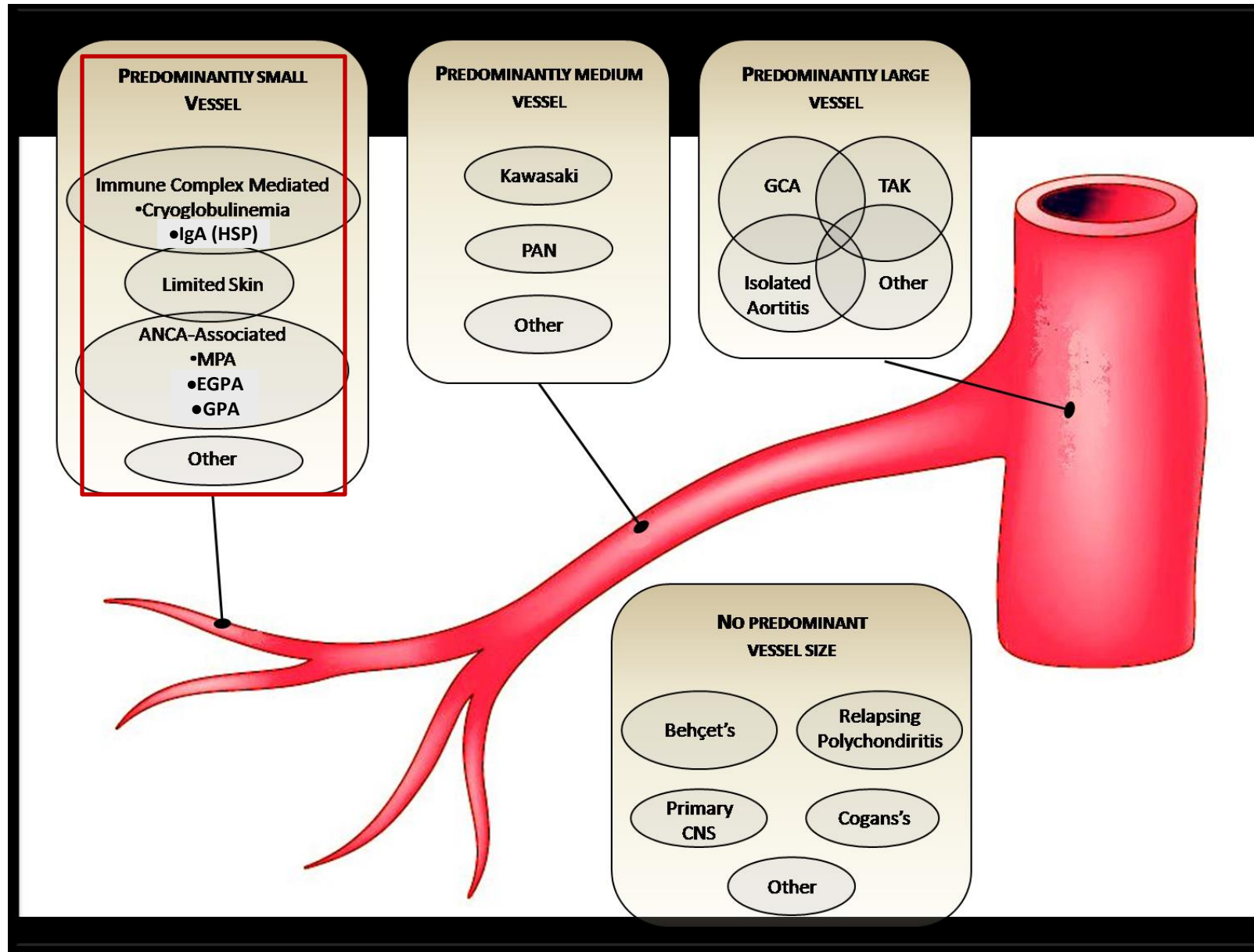


Navon Elkan, N Engl J Med 2014
(these pictures from a case of PAN caused by mutations in ADA2)

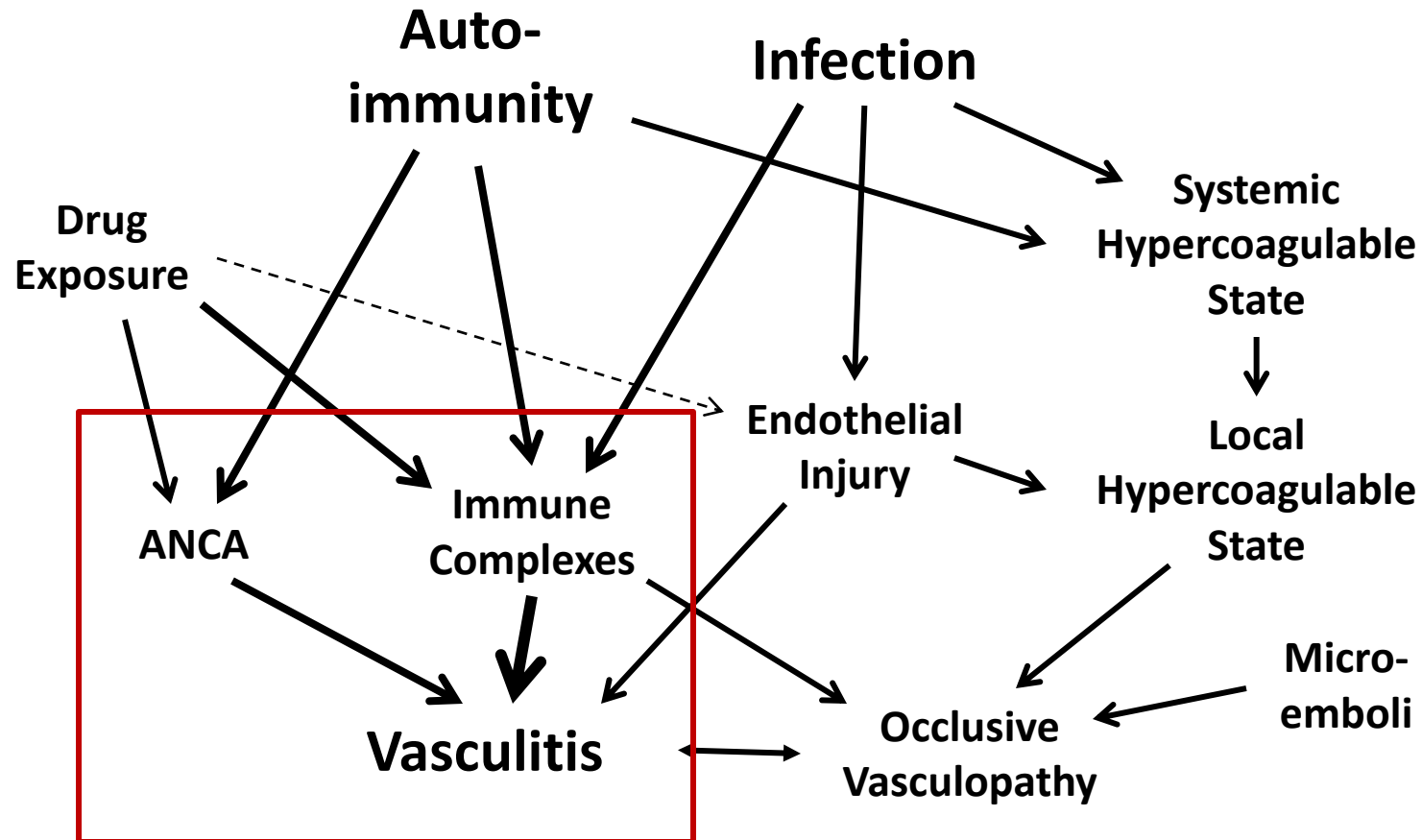
Organ systems in PAN



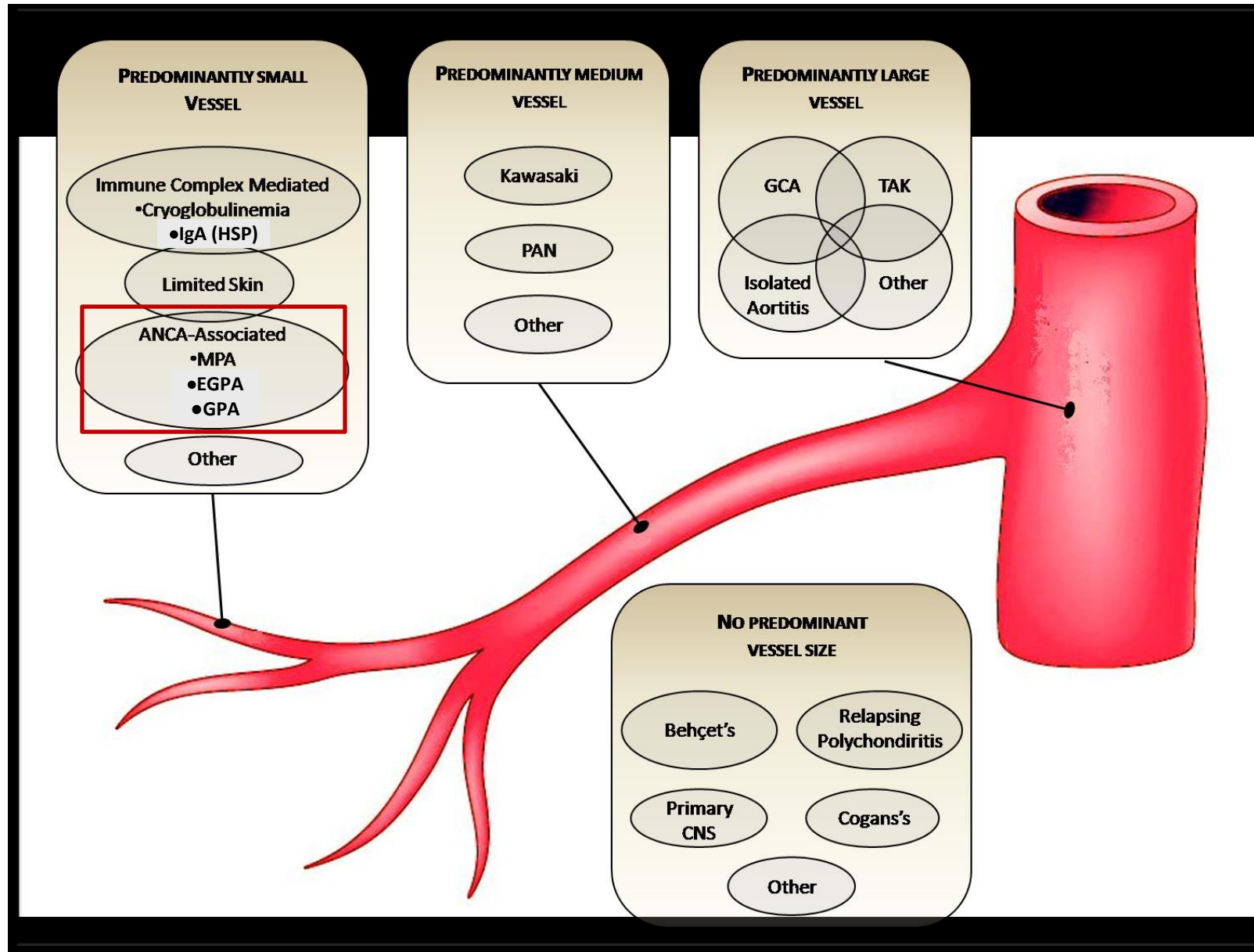
Classification of Vasculitis



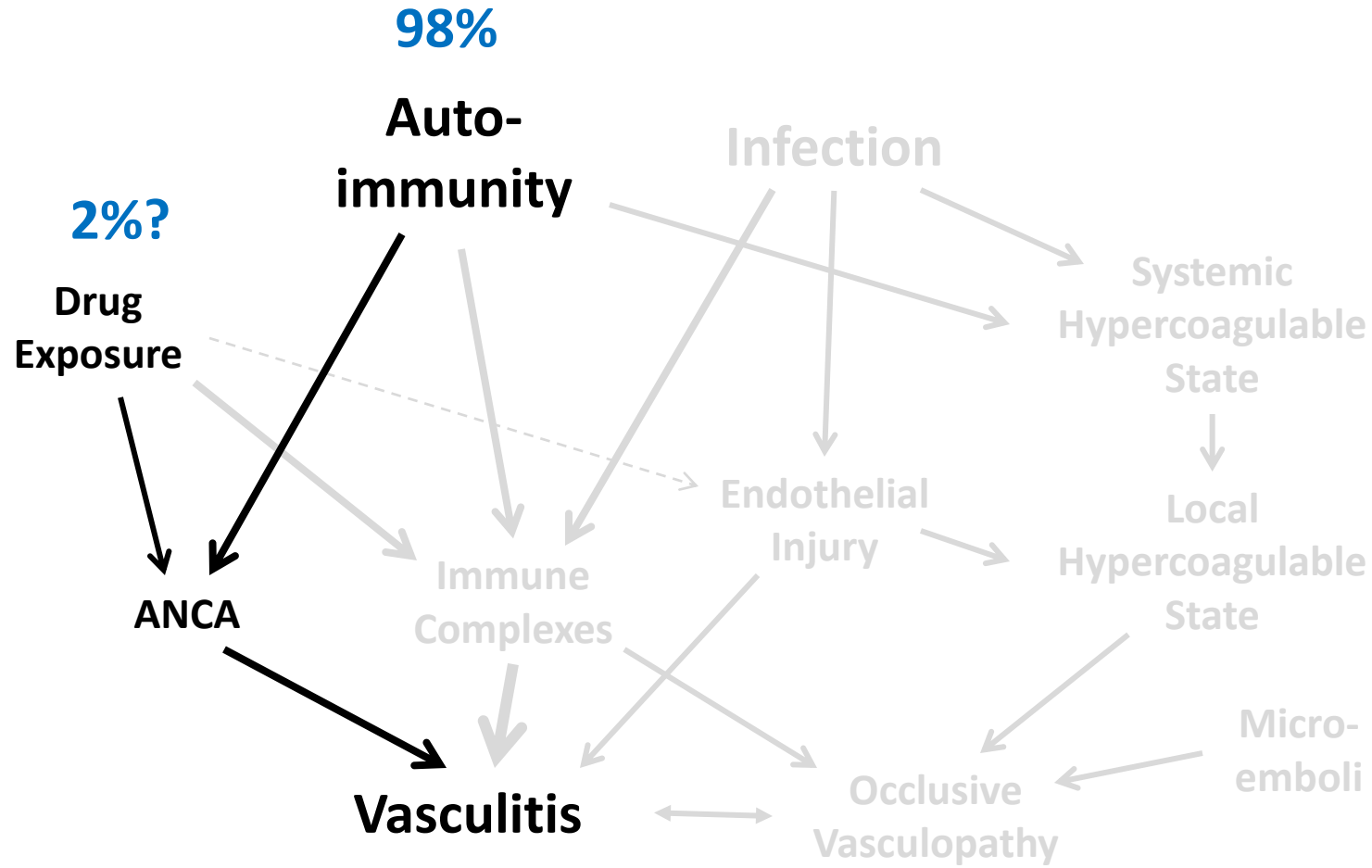
Causes of Vasculitis or Vasculopathy in Small Vessels



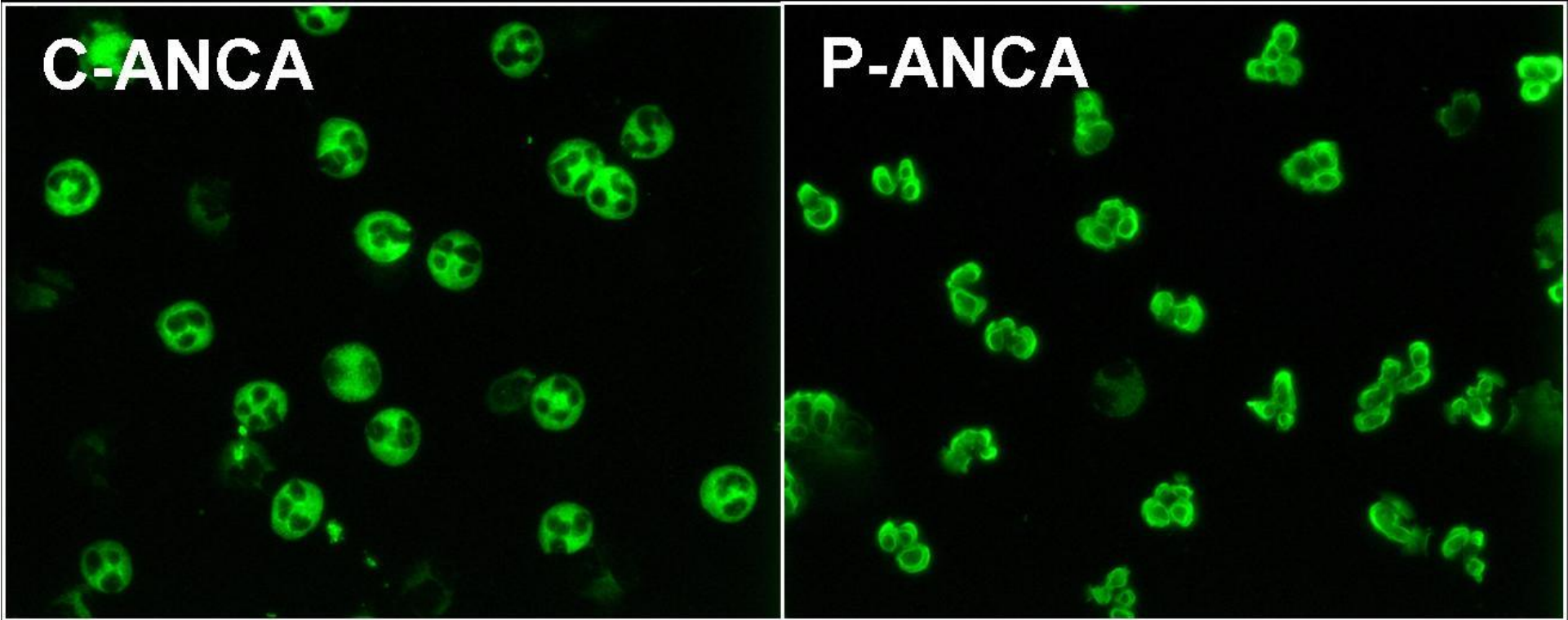
Classification of Vasculitis



Causes of Vasculitis or Vasculopathy in Small Vessels



Antineutrophil-cytoplasmic antibodies (ANCA)



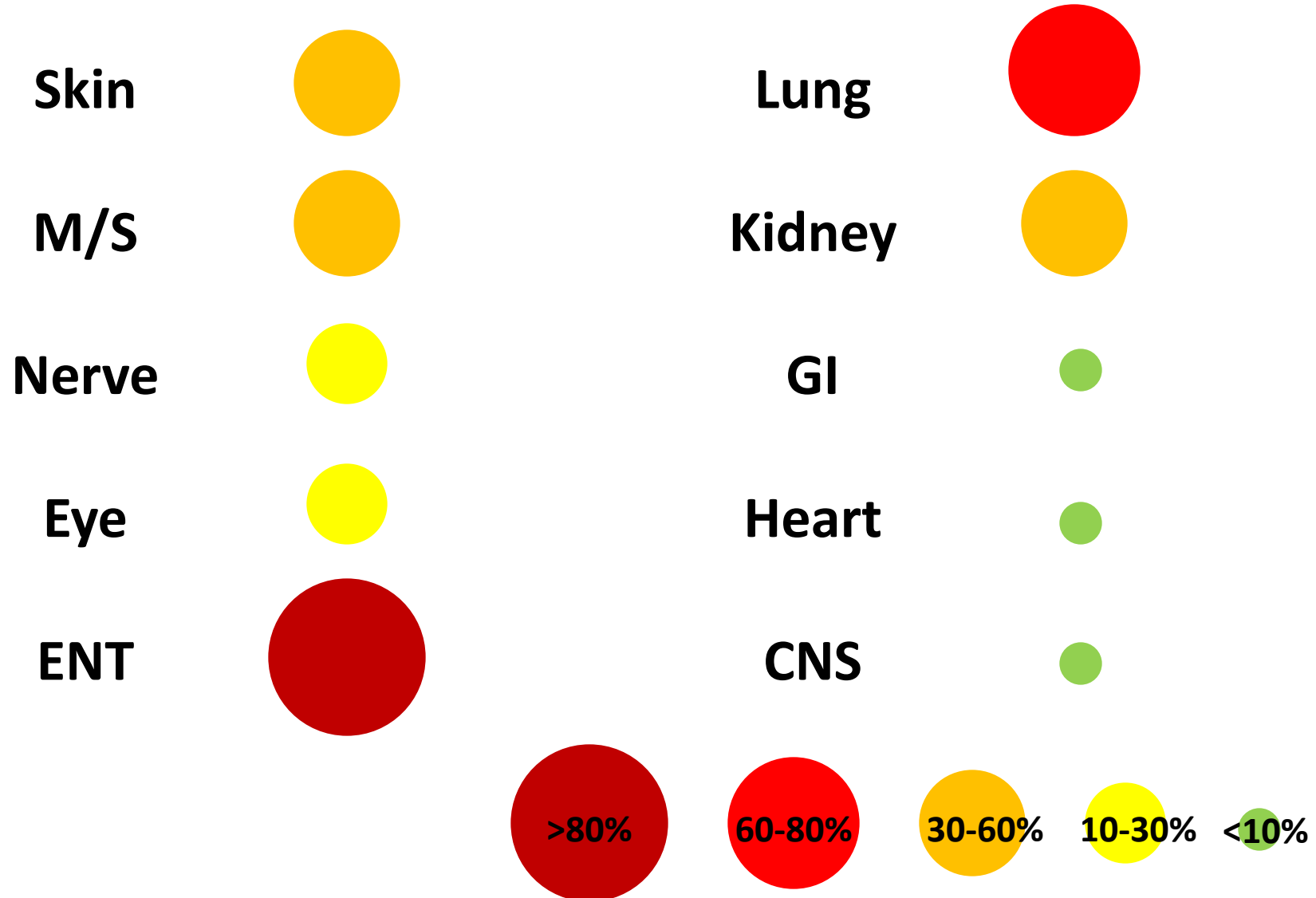
Antigen = Proteinase-3 (PR3)

Antigen = Myeloperoxidase (MPO)

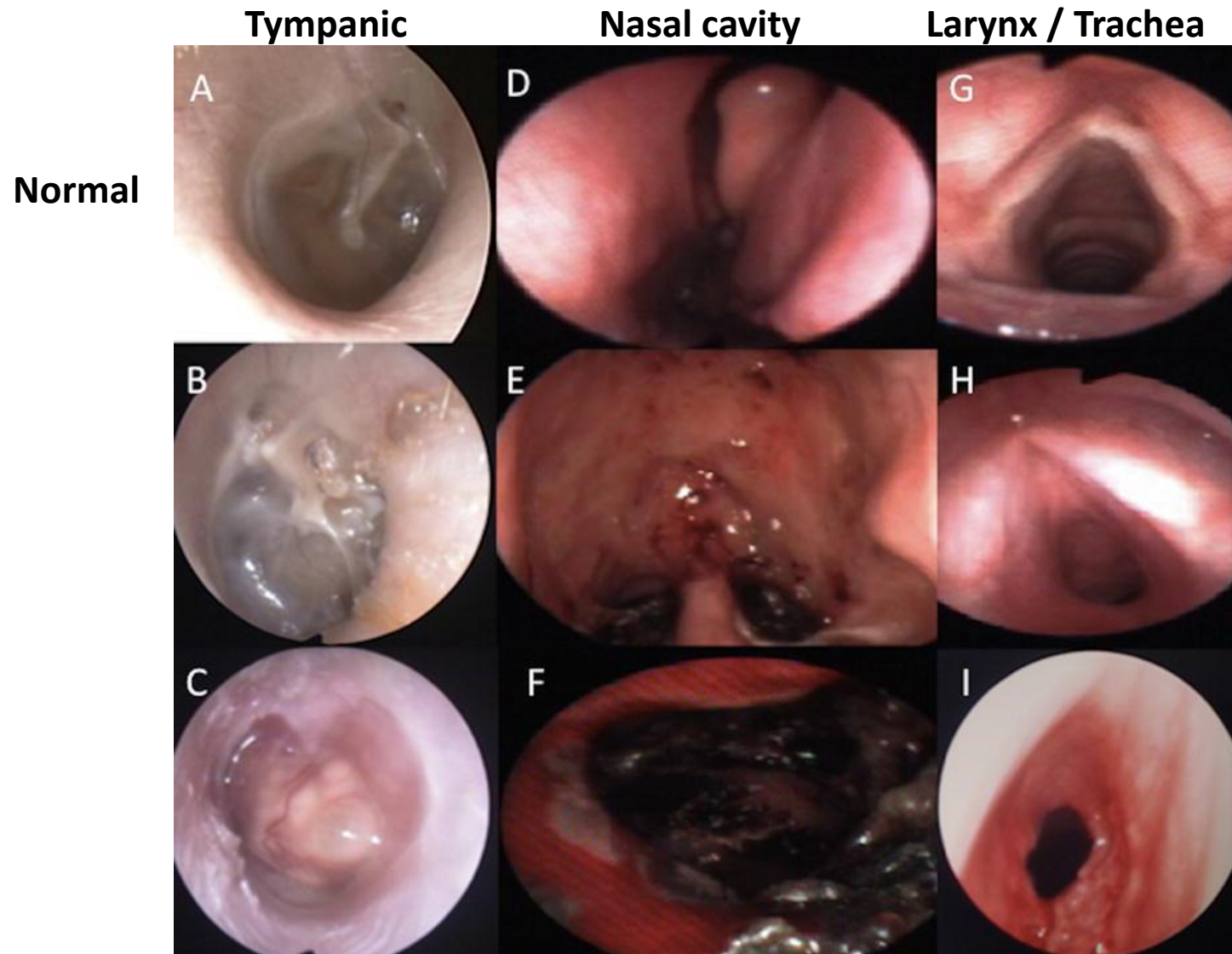
ANCA-associated vasculitis: clinical and laboratory features

- **Microscopic polyangiitis (MPA)**
 - Small-vessel necrotizing vasculitis
 - Associated with **MPO-ANCA >90%**
- **Granulomatosis with polyangiitis (GPA, Wegener's)**
 - Small-vessel necrotizing vasculitis
 - Additional features of **necrotizing granulomatous inflammation** in upper airway, lungs, skin, elsewhere
 - Associated with **PR3-ANCA ~80%, MPO-ANCA 10%**
- **Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss)**
 - Small-vessel necrotizing vasculitis
 - **Hypereosinophilia, asthma**, eosinophilic inflammation
 - Associated with **MPO-ANCA 40%**

Organ systems in GPA (Wegener's)



GPA (Wegener's)



GPA

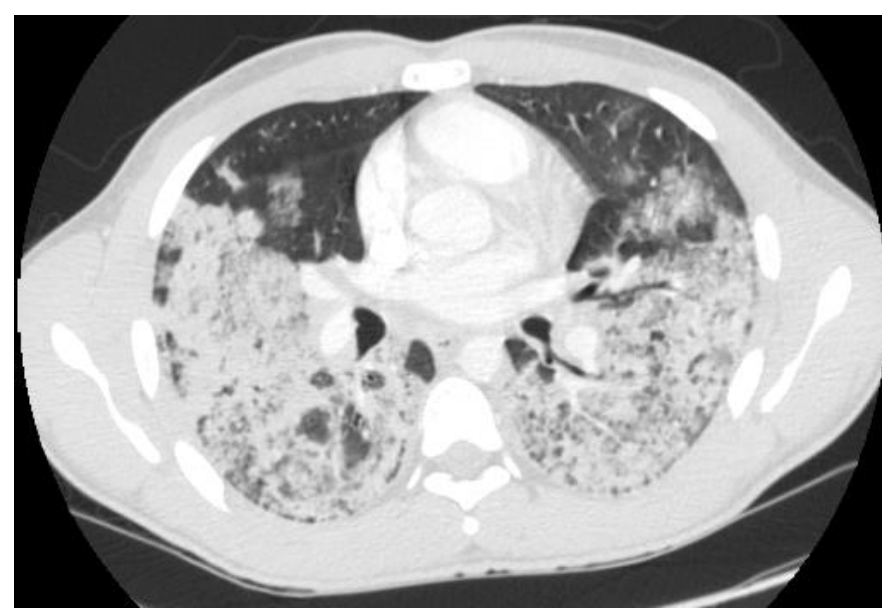
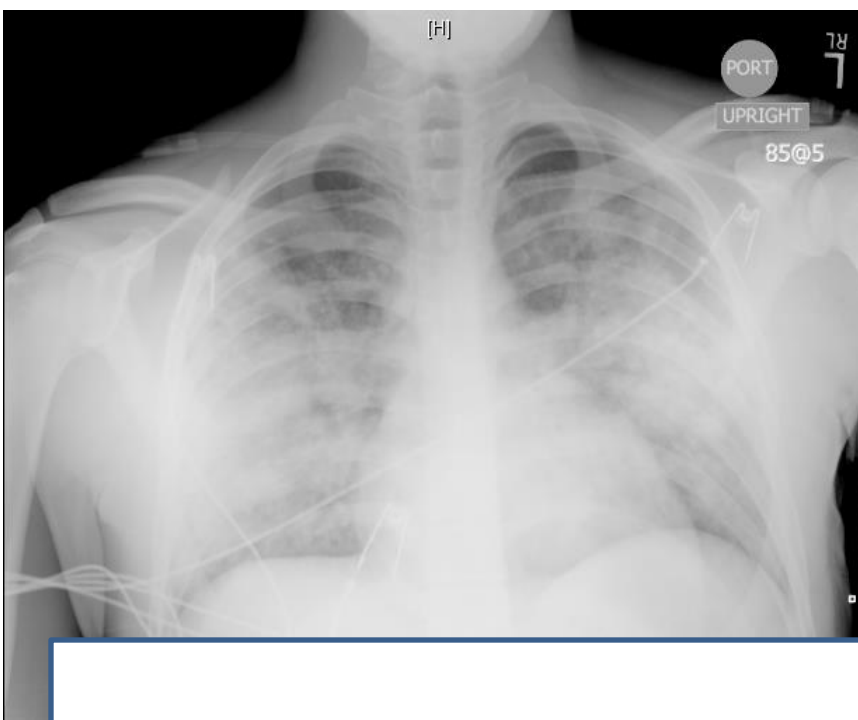
Saddle-nose deformity



Scleritis



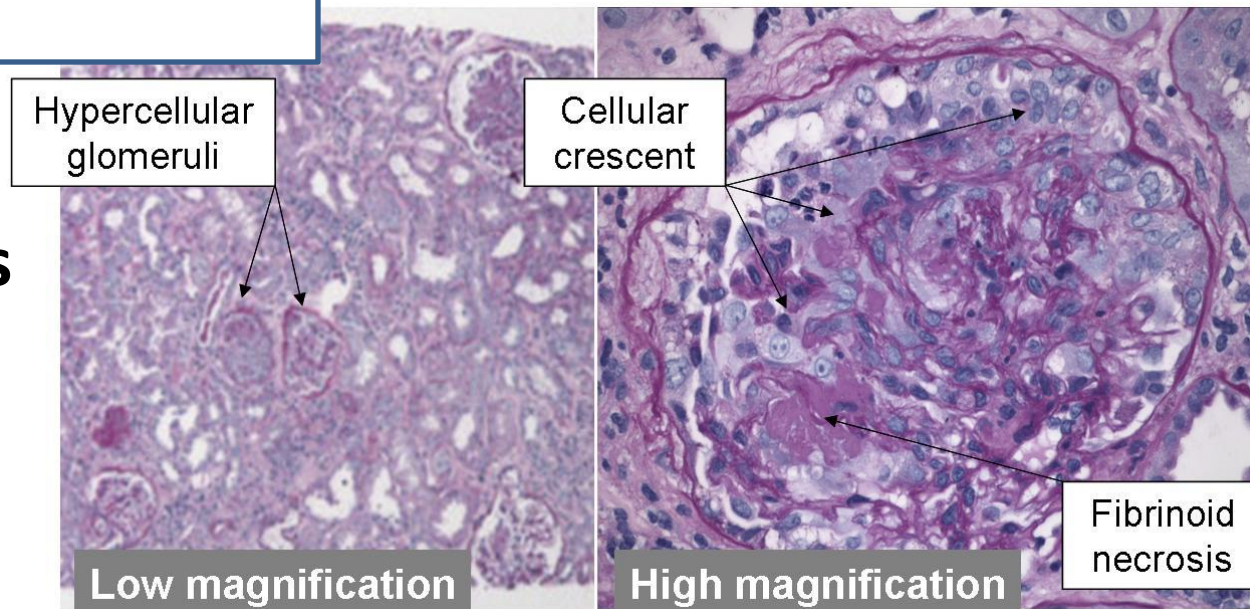
Hochberg, *Rheumatology*, 6th ed.



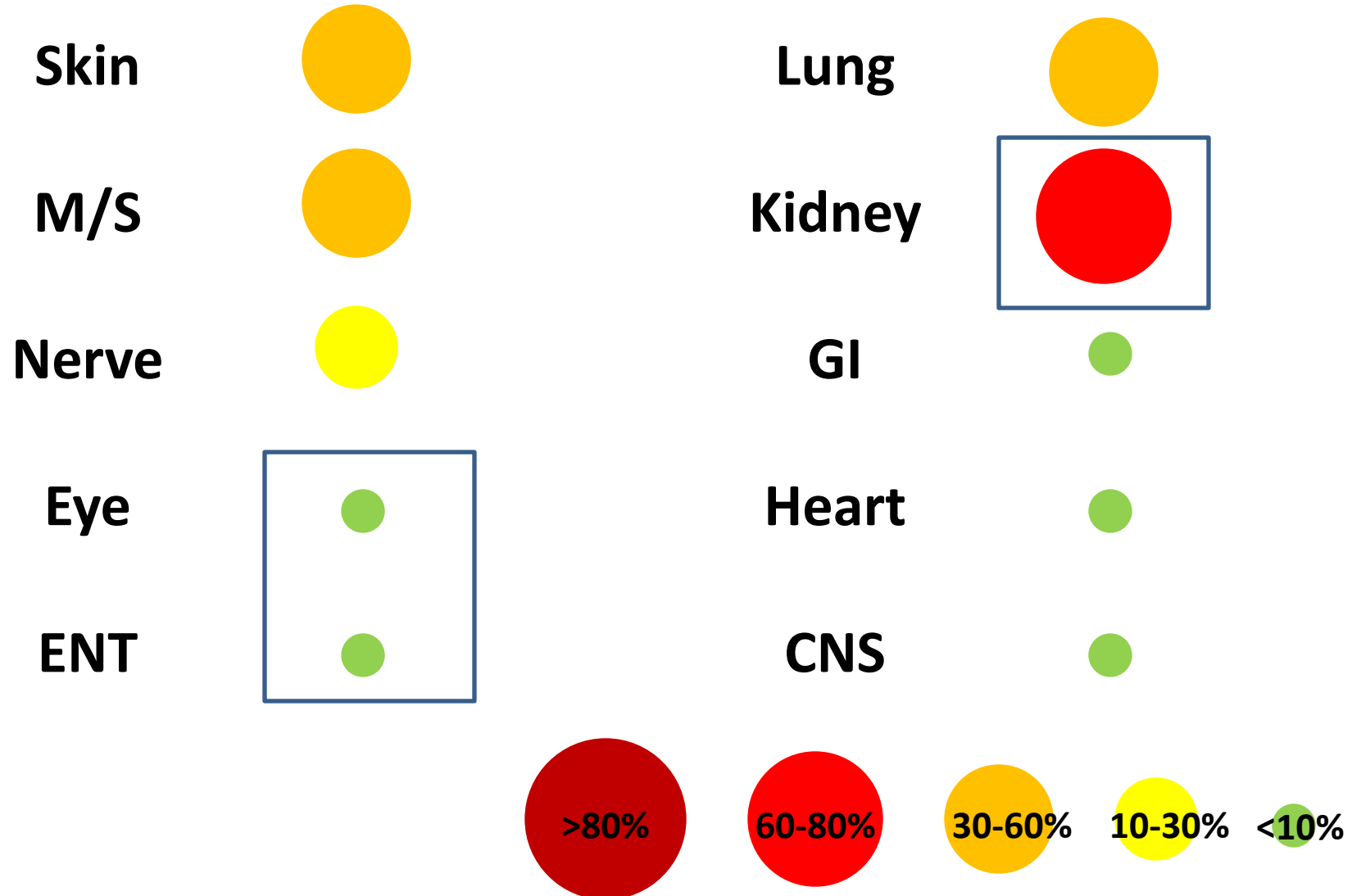
GPA or MPA

Alveolar hemorrhage

**Glomerulonephritis
(often crescentic)
“Pauci-immune” on IF**



Organ systems in MPA

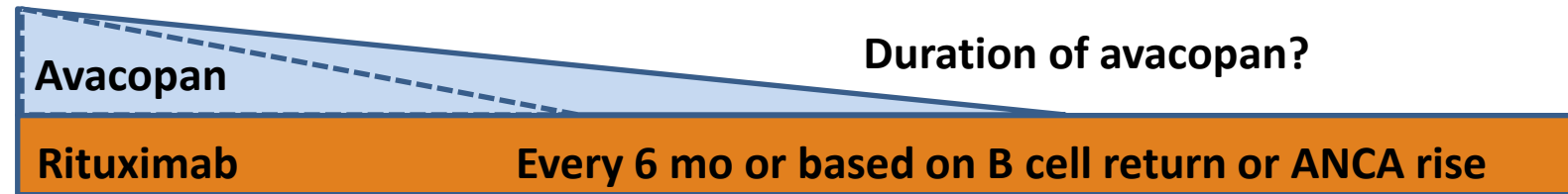


Approaches to a first episode of severe GPA or MPA

Consider PEXIVAS low-dose regimen →



Usually with initial very short course of steroids →

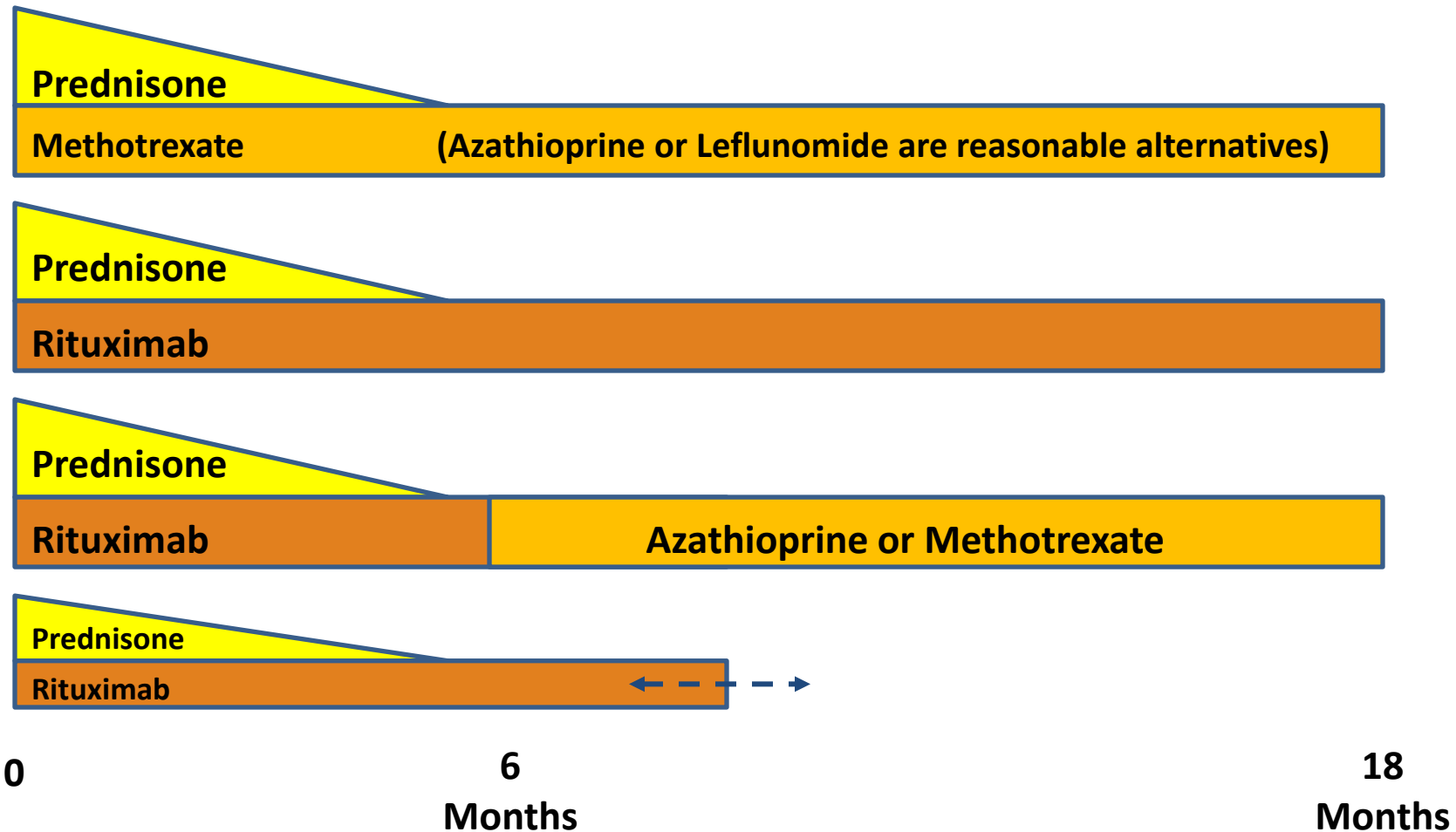


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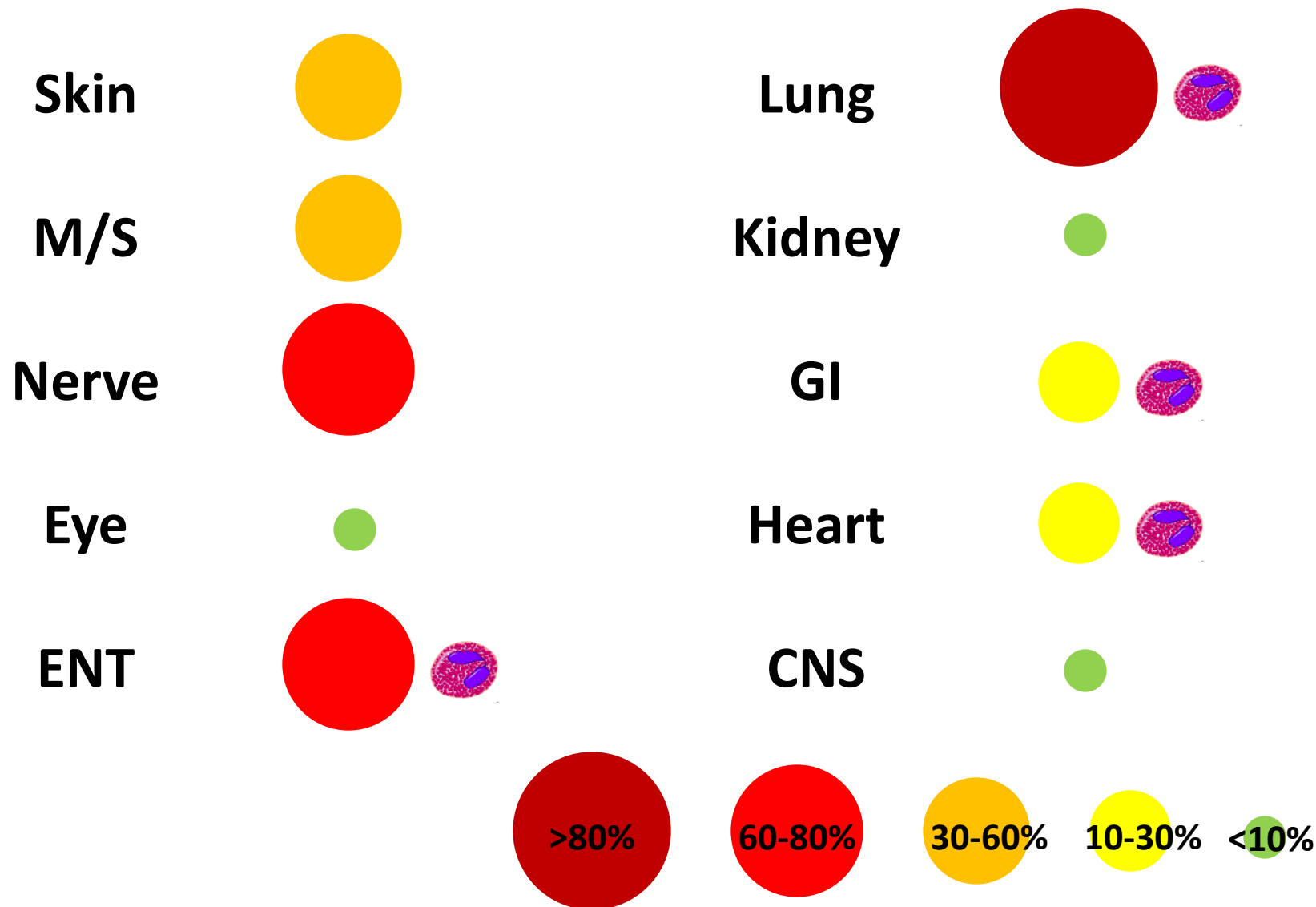
6
Months

18
Months

Approaches to a first episode of limited GPA or MPA: an under-studied area

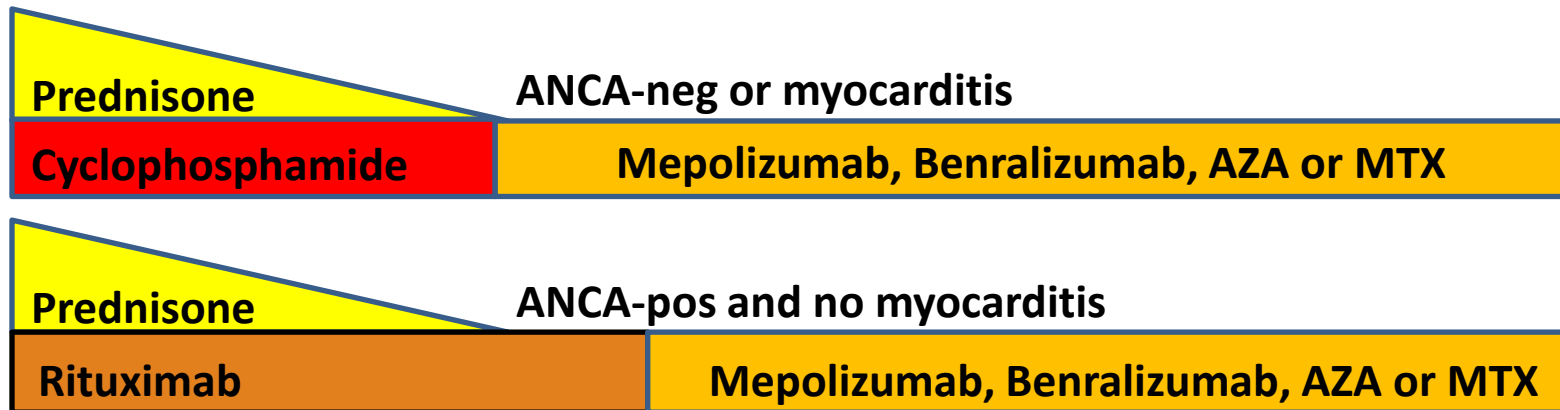


Organ systems in EGPA (Churg-Strauss)

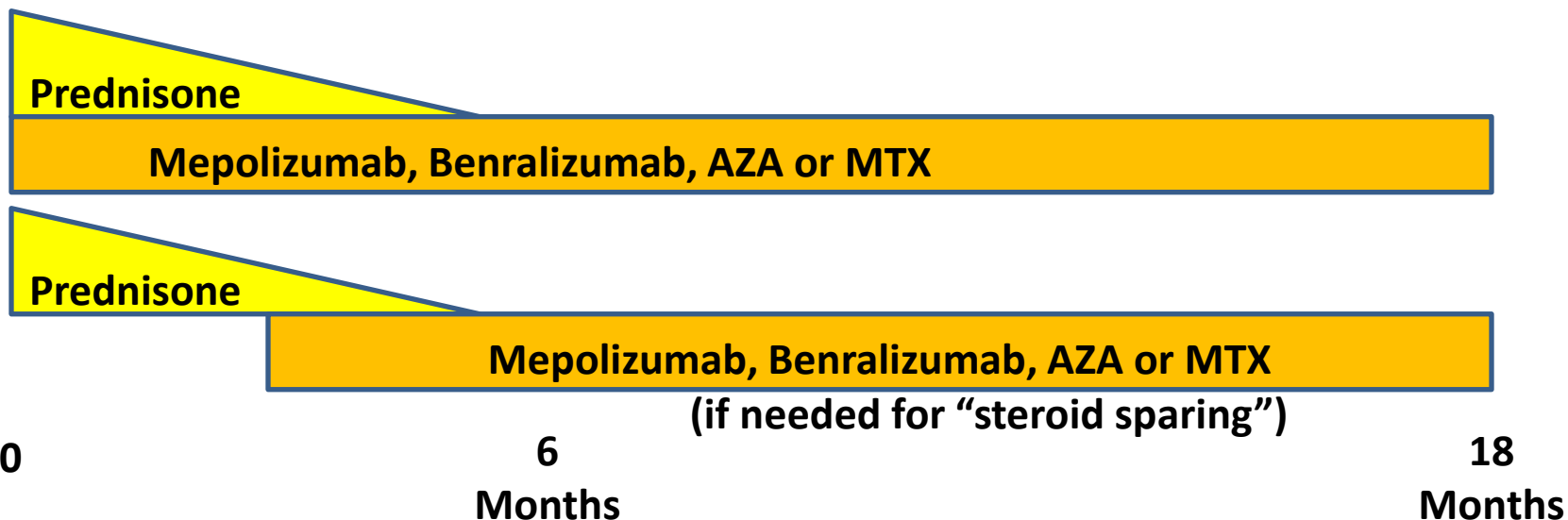


Approaches to a first episode of EGPA

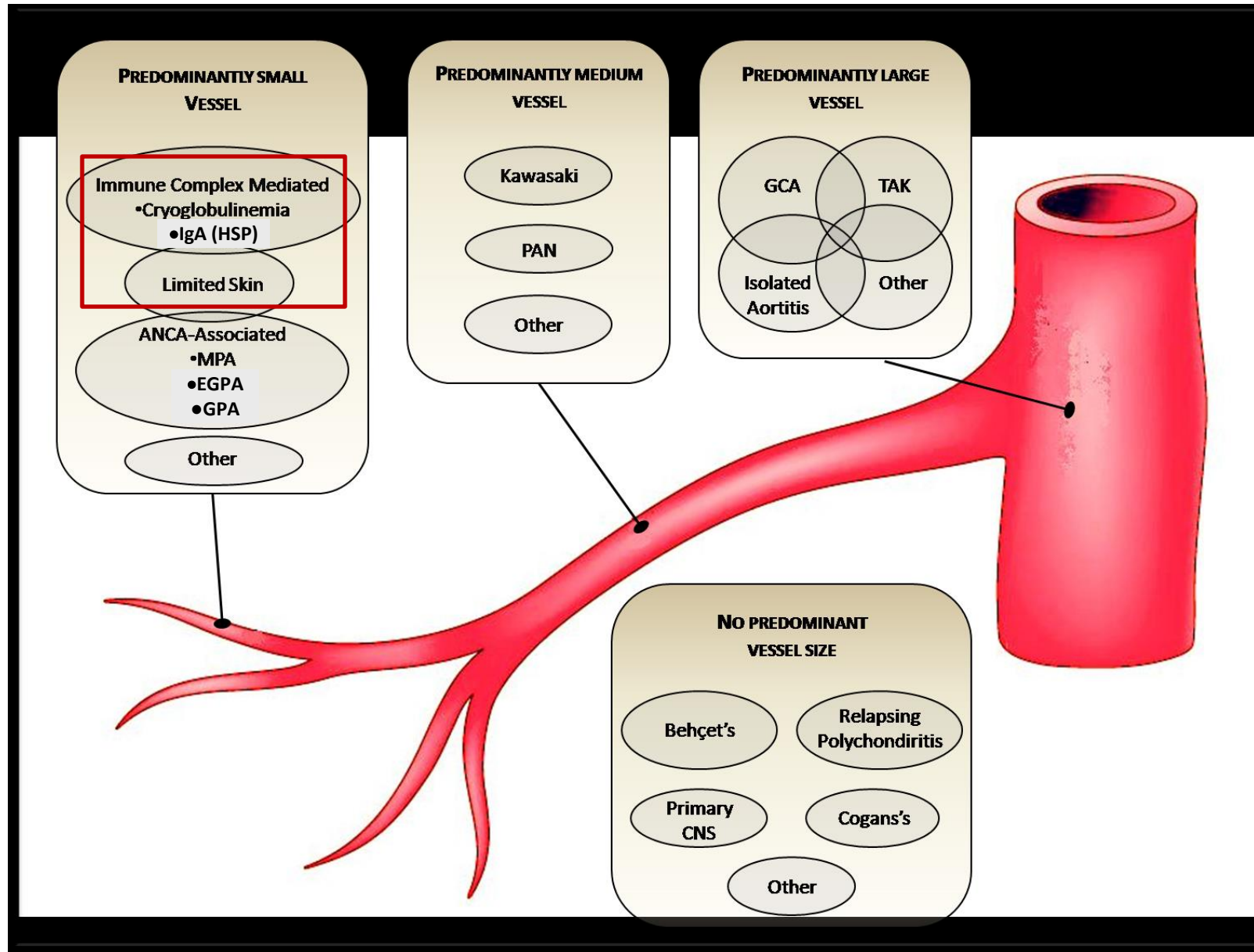
Severe



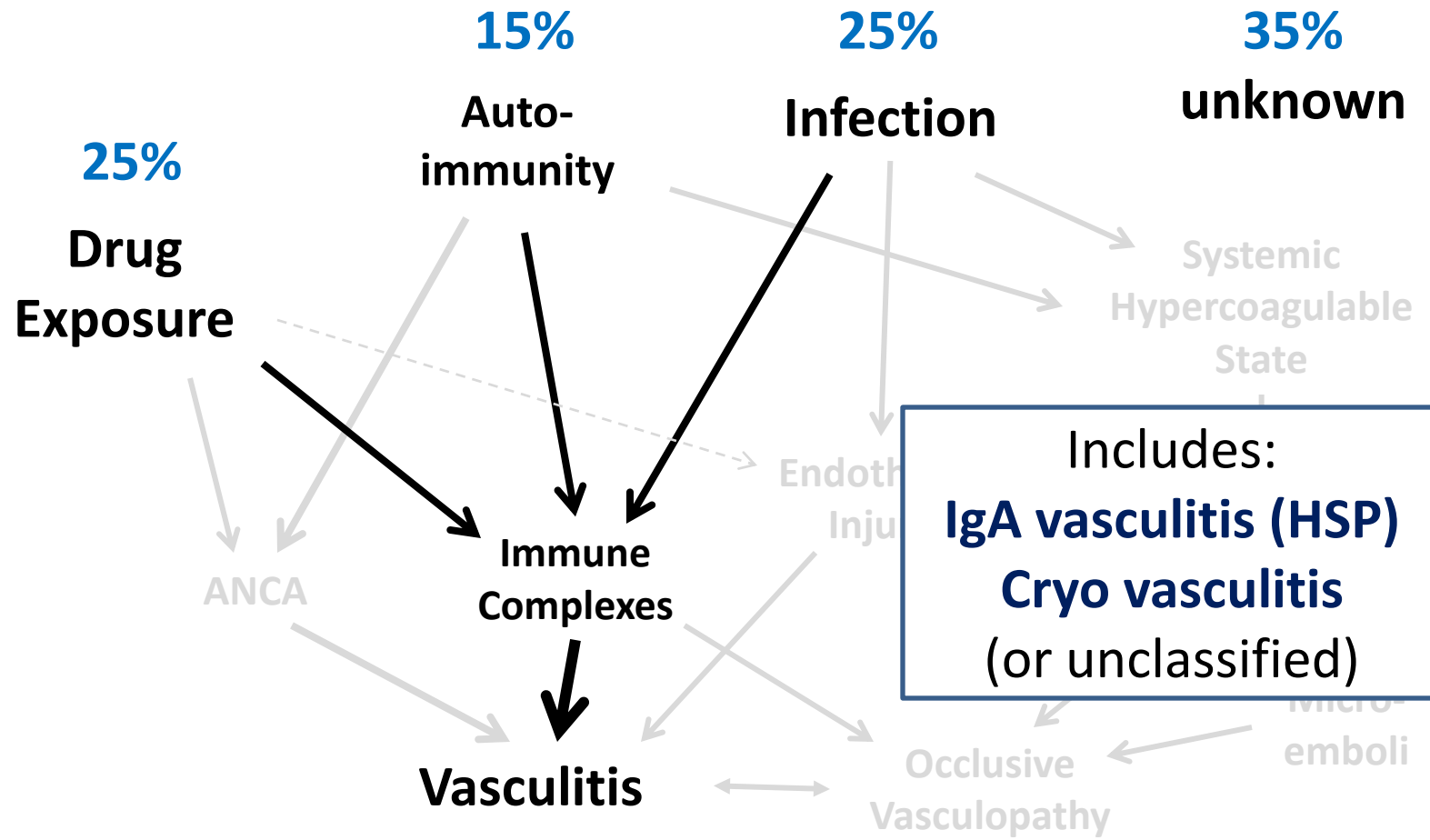
Non-severe



Classification of Vasculitis



Causes of Vasculitis or Vasculopathy in Small Vessels



Summary / MOC

- The vasculitides all feature inflammatory destruction of blood vessels but otherwise have diverse mechanisms
- Diversity is present within as well as between diseases
- Diagnosis begins with recognizing a plausible clinical syndrome, then proceeds to biopsy, imaging, and/or a small number of specific blood tests
- Vasculitis is highly treatable but requires immune-suppressive drugs, especially glucocorticoids initially
- Advances in treatment are identifying drugs that treat some vasculitides but not others, e.g. (FDA approved):
 - Rituximab, avacopan (AAV); mepolizumab or benralizumab (EGPA); tocilizumab or baricitinib (GCA); sarilumab (PMR)
- Reducing exposure to and toxicity of glucocorticoids remains a key goal

Review Question 1

67F with no significant PMH developed diffuse myalgias, arthralgias and fatigue starting 2 months ago, then numbness in the right foot 2 weeks ago. She became short of breath starting 3 days ago and now seeks urgent medical attention. Exam shows increased work of breathing, oxygen saturation 88%, absent sensation on the lateral aspect of the right foot, and no other abnormalities. Work-up shows hematocrit 33, eosinophils 3% (absolute count 400), albumin 3.3, creatinine 1.6 mg/dL, ESR 75, CRP 31 mg/L, urinalysis with 3+ blood and trace protein, chest X-ray with diffuse infiltrates bilaterally.

Which is the most likely diagnosis?

- A. Systemic lupus erythematosus
- B. Microscopic polyangiitis
- C. Polyarteritis nodosa
- D. Granulomatosis with polyangiitis (Wegener's)

Review Question 1

67F with no significant PMH developed diffuse myalgias, arthralgias and fatigue starting 2 months ago, then numbness in the right foot 2 weeks ago. She became short of breath starting 3 days ago and now seeks urgent medical attention. Exam shows increased work of breathing, oxygen saturation 88%, absent sensation on the lateral aspect of the right foot, and no other abnormalities. Work-up shows hematocrit 33, eosinophils 3% (absolute count 400), albumin 3.3, creatinine 1.6 mg/dL, ESR 75, CRP 31 mg/L, urinalysis with 3+ blood and trace protein, chest X-ray and CT with diffuse infiltrates bilaterally.

Which is the most likely diagnosis?

- A. Systemic lupus erythematosus. Although the presentation is compatible with lupus, pulmonary hemorrhage and acute peripheral neuropathy are uncommon, and common features such as rash, inflammatory arthritis, and significant proteinuria are absent.
- B. Microscopic polyangiitis. The organ systems involved (lung consistent with pulmonary hemorrhage, kidney, nerve) and non-specific musculoskeletal and constitutional symptoms are commonly affected in ANCA-associated vasculitis. The absence of features of granulomatous disease in the upper or lower airway makes the probable diagnosis MPA rather than GPA.
- C. Polyarteritis nodosa. Although most of the symptoms and laboratory tests are compatible with PAN (including renal insufficiency with non-specific urinalysis), lung involvement is very rare.
- D. Granulomatosis with polyangiitis (Wegener's). The absence of features on history or exam suggesting granulomatous disease argues against GPA.

Review Question 2

In a patient with GCA, what evaluation is most important to follow even in a patient who remains asymptomatic long after completing prednisone treatment.

- A. Imaging to rule out thoracic aortic aneurysm
- B. Bone mineral density
- C. ESR and CRP
- D. Hemoglobin A1c

Review Question 2

In a patient with GCA, what evaluation is most important to follow even in a patient who remains asymptomatic long after completing prednisone treatment?

- A. **Imaging to rule out thoracic aortic aneurysm.** About 6% of patients with GCA will develop a thoracic aortic aneurysm large enough to consider surgical repair. 60% of patients have evidence of aortitis by PET scan at diagnosis. The extent to which PET scan results at diagnosis (or later) determine risk of future aneurysm is unknown. The most appropriate method to monitor is unclear, considering accuracy and cost-effectiveness.
- B. Bone mineral density. After prednisone treatment is completed, the rate in decline of bone density returns to baseline. Repeat testing should be based on guidelines derived from the FRAX score.
- C. ESR and CRP. Although it seems wise to monitor inflammatory markers for about a year after completing treatment, this recommendation is not based on evidence, and clinically significant flare of GCA more than a year off of treatment is very uncommon.
- D. Hemoglobin A1c. Elevation of blood sugar is directly related to glucocorticoid dose, so completion of treatment brings the risk back to baseline. Patients who have gained a lot of weight during treatment may continue to be at higher risk than they were before diagnosis of GCA.

Supplemental References

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