ANCA-Associated Vasculitis

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Aug 15th 2024

Tehran


Conflict
of
Interest


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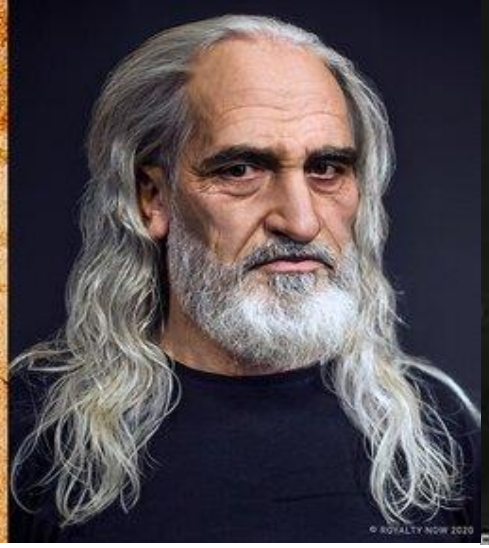
tere


Anthony S. Fauci, M.D.

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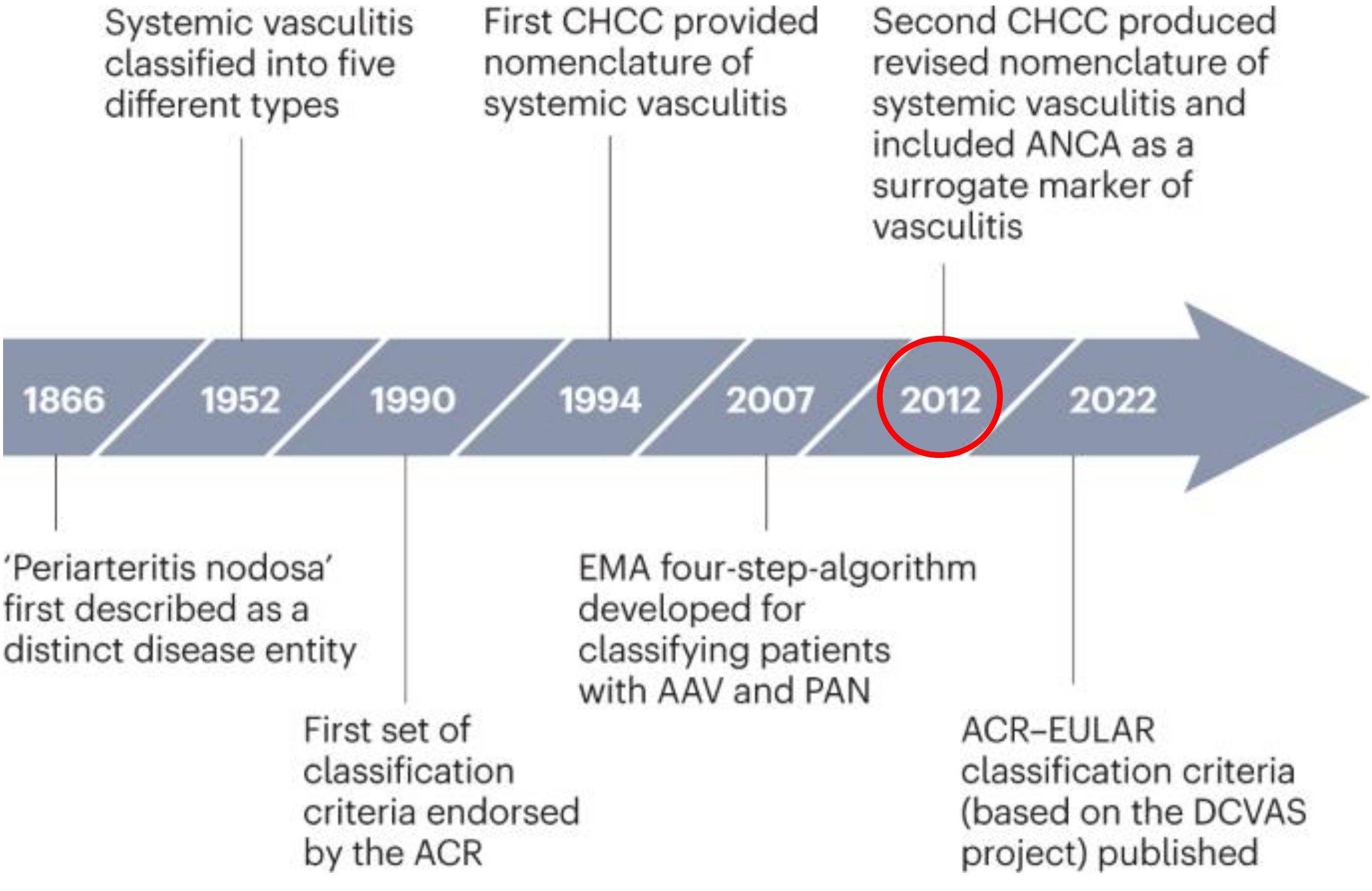
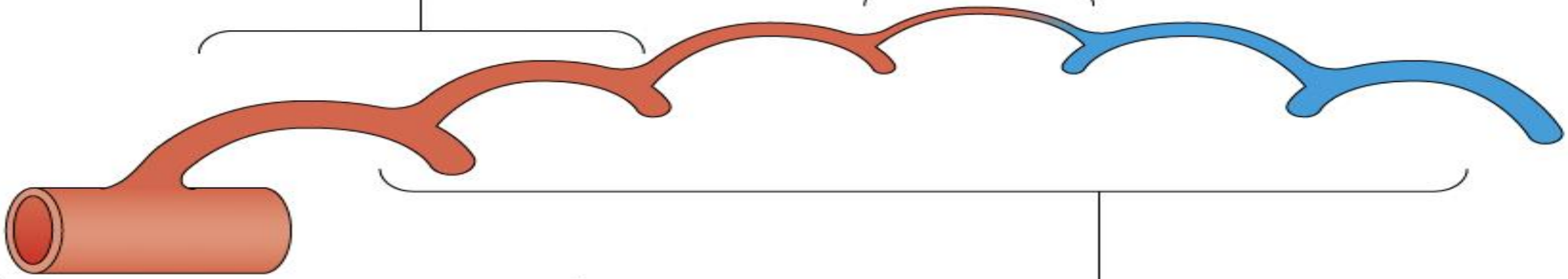

Systemic vasculitis classified into five different types
First CHCC provided nomenclature of systemic vasculitis
Second CHCC produced revised nomenclature of systemic vasculitis and included ANCA as a surrogate marker of vasculitis
1866
1952
1990
1994
2007
2012
2022
'Periarteritis nodosa' first described as a distinct disease entity
First set of classification criteria endorsed by the ACR
EMA four-step-algorithm developed for classifying patients with AAV and PAN
ACR–EULAR classification criteria (based on the DCVAS project) published

a

Medium vessel vasculitis
- Polyarteritis nodosa
- Kawasaki disease

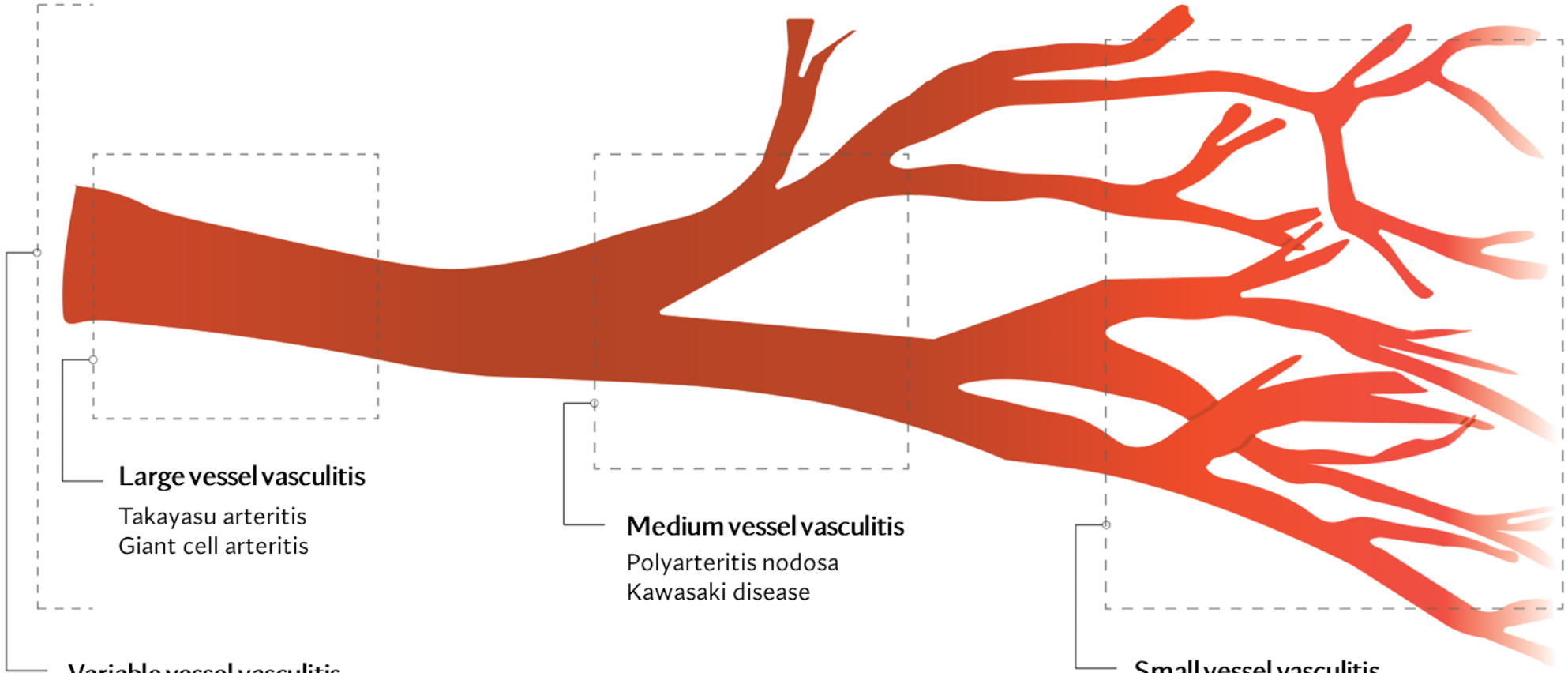
Immune complex small vessel vasculitis
- Cryoglobulinaemic vasculitis
- IgA vasculitis (Henoch–Schönlein purpura)
- Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis)

Anti-GBM disease



Large vessel vasculitis
- Takayasu arteritis
- Giant cell arteritis

ANCA-associated small vessel vasculitis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis



Large vessel vasculitis

Takayasu arteritis
Giant cell arteritis

Medium vessel vasculitis

Polyarteritis nodosa
Kawasaki disease

Variable vessel vasculitis

Behçet's disease
Cogan's syndrome

Small vessel vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA) – associated vasculitis

Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis

Immune complex-mediated vasculitis

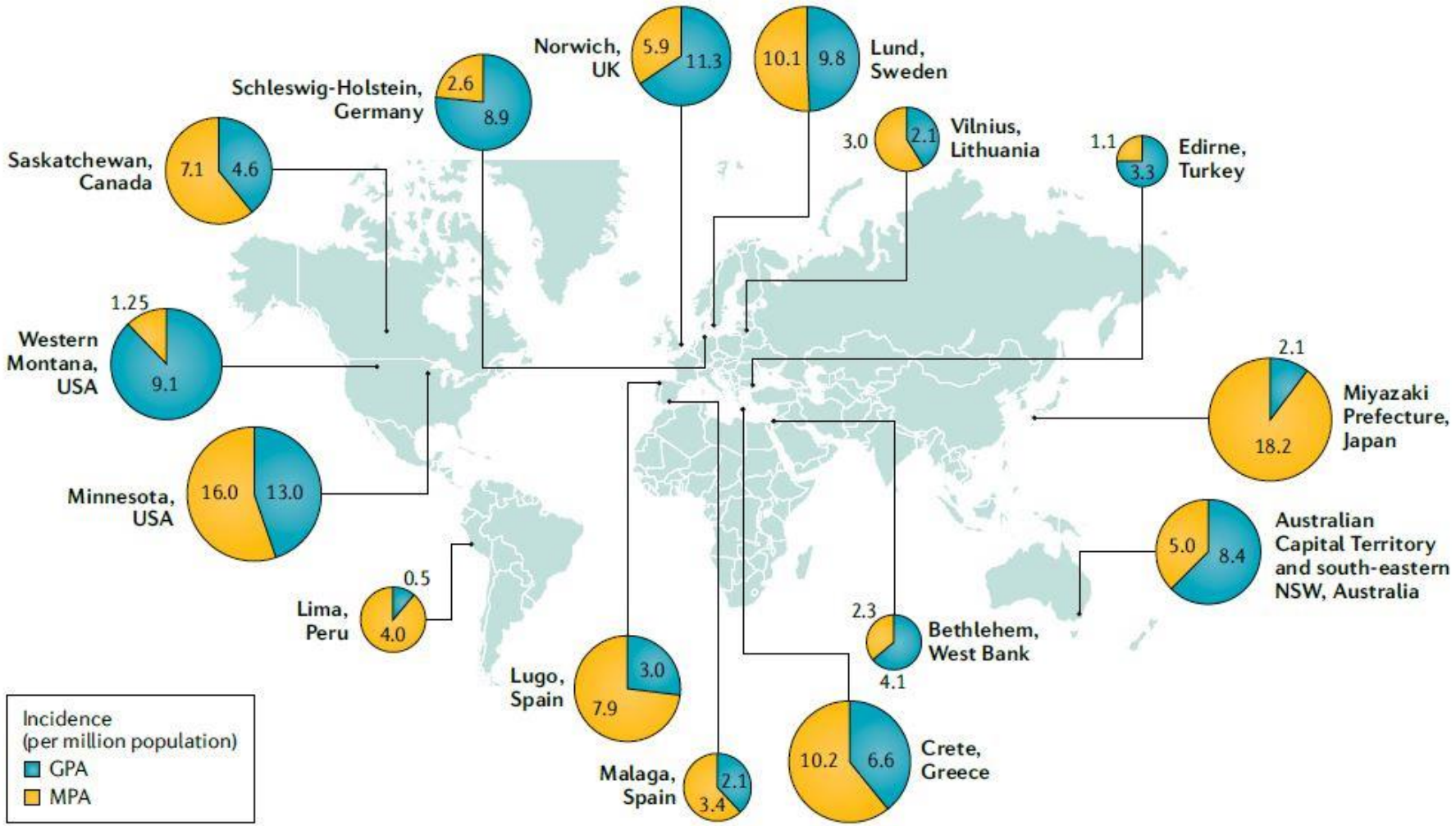
Anti-glomerular basement membrane (GBM) disease
Cryoglobulinemic vasculitis
IgA vasculitis
Hypocomplementamic urticarial (anti-C1q) vasculitis

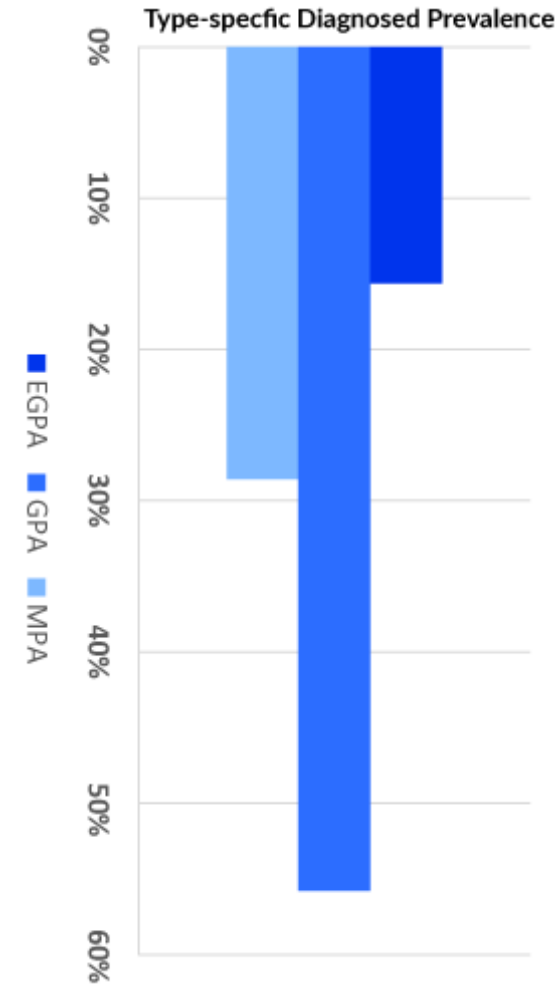
Other types of vasculitis:

- **Single-organ vasculitis**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- **Vasculitis associated with systemic disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- **Vasculitis associated with probable etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Everyone's opinions about things change over time. Nothing is constant. Everything changes. And to hold onto some dogged idea forever is a little rigid and maybe naive.

— Frida Kahlo —


Norwich, UK
5.9
11.3
Lund, Sweden
10.1
9.8
Schleswig-Holstein, Germany
2.6
8.9
Vilnius, Lithuania
3.0
2.1
Edirne, Turkey
1.1
3.3
Saskatchewan, Canada
7.1
4.6
1.25
Western Montana, USA
9.1
2.1
Miyazaki Prefecture, Japan
18.2
Minnesota, USA
16.0
13.0
Australian Capital Territory and south-eastern NSW, Australia
5.0
8.4
0.5
Lima, Peru
4.0
2.3
Bethlehem, West Bank
4.1
Lugo, Spain
3.0
7.9
Crete, Greece
10.2
6.6
Malaga, Spain
2.1
3.4
Incidence (per million population)
GPA
MPA


Type-specfic Diagnosed Prevalence
0%
10%
20%
30%
40%
50%
60%
EGPA
GPA
MPA

Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis (AAV)

Background

Despite advances in diagnosis and treatment, patients with AAV have a poor prognosis, and the predicative factors are not well categorized. Evaluation of long-term outcomes in major European RCTs and identifying prognostic factors.

Methods

Multicenter
74 centers, 17 countries in Europe

848 patients
Enrolled 1995–2012 in 7 EUVAS (European Vasculitis Society) randomized clinical trials

- Newly diagnosed with AAV
- Compared to matched background population

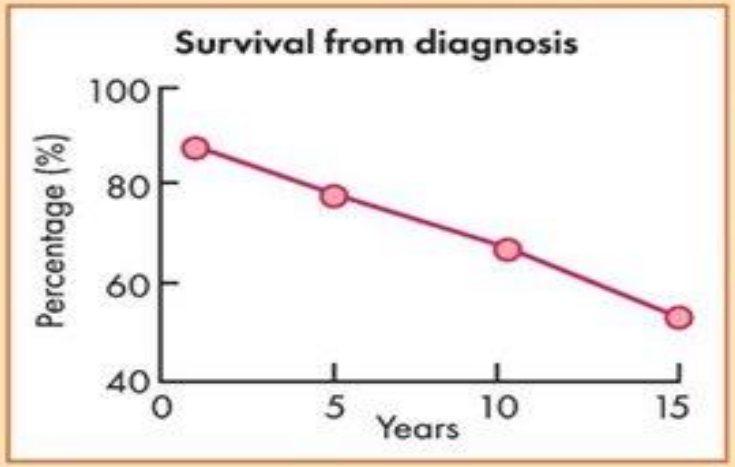
GPA 56% | MPA 44%

Median long-term follow-up
8 years (IQR: 2.9–13.6)

→ Survival
Causes of death
Prognostic factors

Results

Median survival from diagnosis: 17.8 years
*95% CI 15.7–20 years



Excess mortality compared to general population

14% at 1 year
20% at 10 years
29% at 15 years

Main causes of death


Infection


Cardiovascular disease


Malignancy

Negative prognostic factors:

Advanced age 
Male sex 
Low eGFR 
Low platelet count 

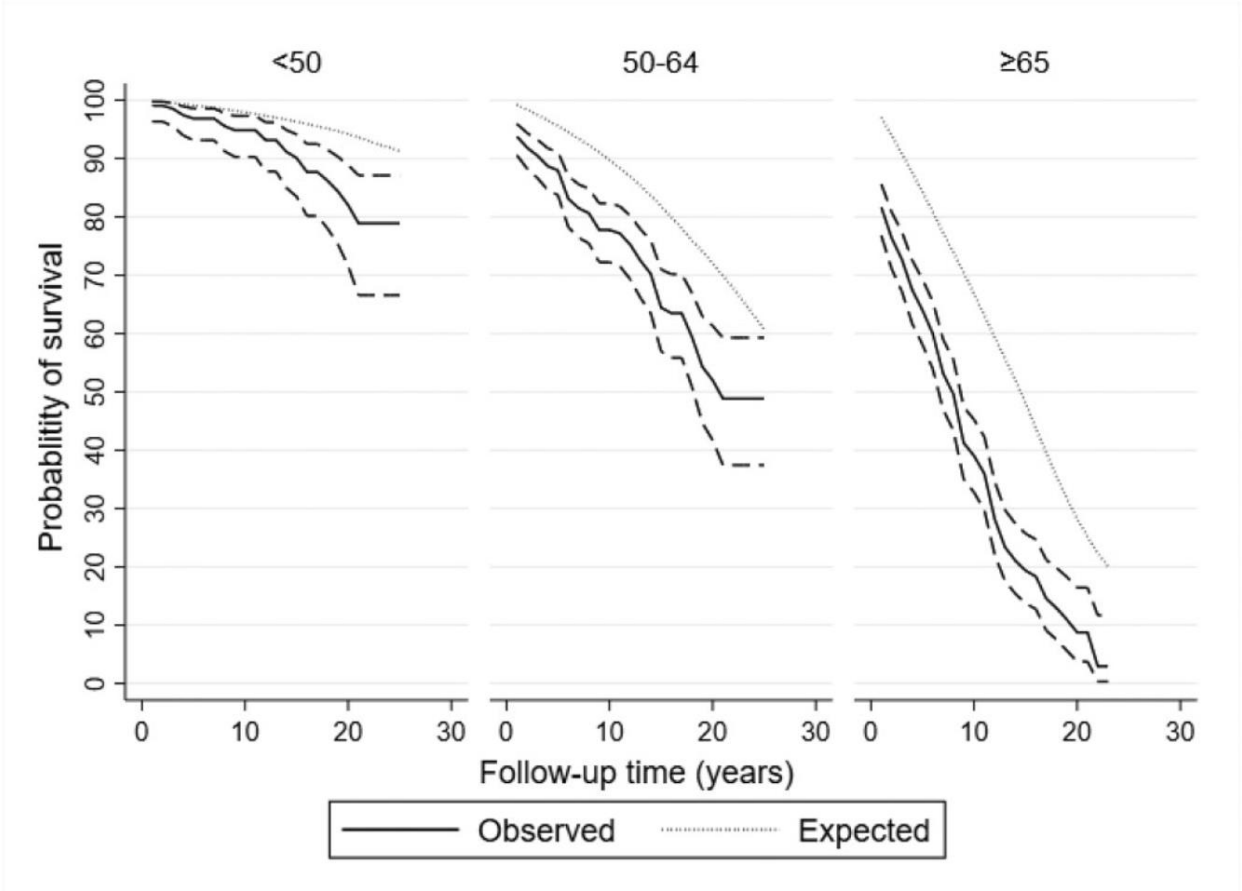
Conclusion

Patients with AAV have an increased risk of mortality compared to the general population. Treatment complications and organ damage are the main causes of limited survival. Infections are the leading cause of death.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

Sánchez Álamo B., Moi L. et al., on the behalf of the EUVAS. NDT (2022)
@NDTSocial

Pt survival grouped by age



	Granulomatosis with polyangiitis*	Microscopic polyangiitis*	PR3-ANCA-associated vasculitis†	MPO-ANCA-associated vasculitis‡
General	77·7%	85·8%	81%	91·7%
Body temperature ≥38°C	30·7%	35·4%	44·3% (≥38·5°C)	..
Fatigue	56·4%	68·0%	-	..
Weight loss ≥2 kg	34·7%	43·1%	46·7% (>3 kg)	..
Arthralgia	54·5%	31·7%	56·4%	..
Myalgia	22·1%	24·3%	26·2%	..
Cutaneous	34·7%	29·5%	33·9%	16·7%
Petechiae or purpura	16·8%	9·5%	17·9%	..
Mucous membranes or eyes	38·3%	12·9%	28·2%	10·4%
Scleritis or episcleritis	13·5%	0·6%	4·9% (scleritis) and 10·4% (episcleritis)	..
Ear, nose, and throat	82·3%	25·8%	81·0%	2·1%
Respiratory	63·1%	62·8%	68·1%	50·0%
Haemoptysis or diffuse alveolar haemorrhage	21·1%	19·4%	17·8%	22·2%
Cardiovascular	10·7%	15·1%	15·9%	6·3%
Abdominal	18·7%	22·2%	11·2%	3·5%
Renal	58·6%	82·2%	57·7%	79·2%
Neurological	31·2%	36·6%	30·0%	38·9%
Neuropathy	11·9%	25·8%	20·7%	20·8%
Mononeuritis multiplex	4·9%	8·6%	..	..
Sensory neuropathy	11·1%	21·2%	..	..

Granulomatosis with Polyangiitis

Systemic Symptoms 30-97%
Fever, weight loss, myalgia, arthralgia

CNS 6-13%
Pachymeningitis, pituitary gland involvement, cranial nerve palsies CNS vasculitis

Eye 14-58%
Conjunctivitis, scleritis, keratitis, uveitis, optic neuropathy, oculomotor nerve palsy, retinal vasculitis, orbital granuloma

ENT 75-98%
Rhinosinusitis with possible nasal septum perforation and saddle-nose deformity; chronic otitis media; sensorineural hearing loss; "strawberry" gingival hyperplasia; subglottic stenosis

Heart 2-13%
Pericarditis/pericardial effusion, cardiomyopathy, coronary artery disease, valvular disease, arrhythmia

Lung 45-94%
Nodules with cavities, pulmonary infiltrates; alveolar hemorrhage, pleuritis with pleural effusions

Gastrointestinal 1-11%
Abdominal pain, bleeding, diarrhea, organ perforation, rarely pancreatitis

Kidney 18-60%
Rapidly progressive glomerulonephritis (pauci-immune necrotizing GN)

PNS 15-41%
Multiple mononeuropathy; symmetric polyneuropathy

Skin 13-50%
Palpable purpura, nodules, papules, ulceration/necrosis, livedo reticularis

Microscopic Polyangiitis

Systemic Symptoms 73-92%
Fever, weight loss, myalgia, arthralgia

CNS 0-18%
CNS vasculitis, cranial nerve palsies, less commonly ischemic events or intracranial hemorrhage

Eye 0-30%
Conjunctivitis, scleritis, keratitis, uveitis, optic neuropathy, oculomotor nerve palsy, retinal vasculitis, etc.

ENT 19-30%
Mild, non-granulomatous, non-erosive, and non-specific sinus inflammation; sensorineural hearing loss

Heart 9-18%
Pericarditis/pericardial effusion, cardiomyopathy, heart failure, valvular disease, arrhythmia

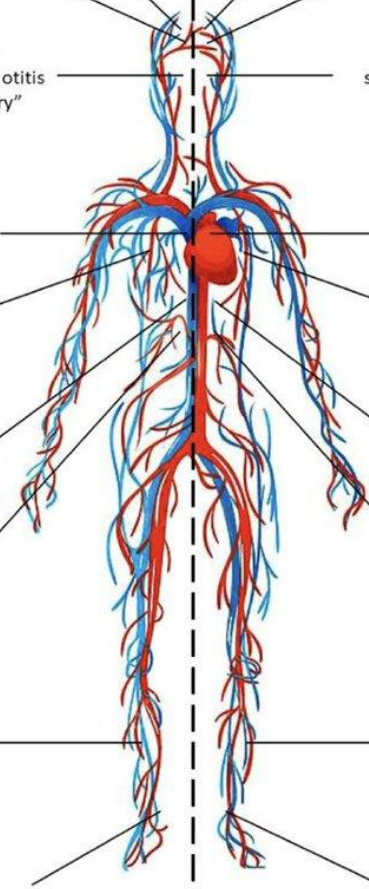
Lung 22-55%
Diffuse alveolar hemorrhage, pulmonary infiltrates, interstitial pneumonitis/pulmonary fibrosis

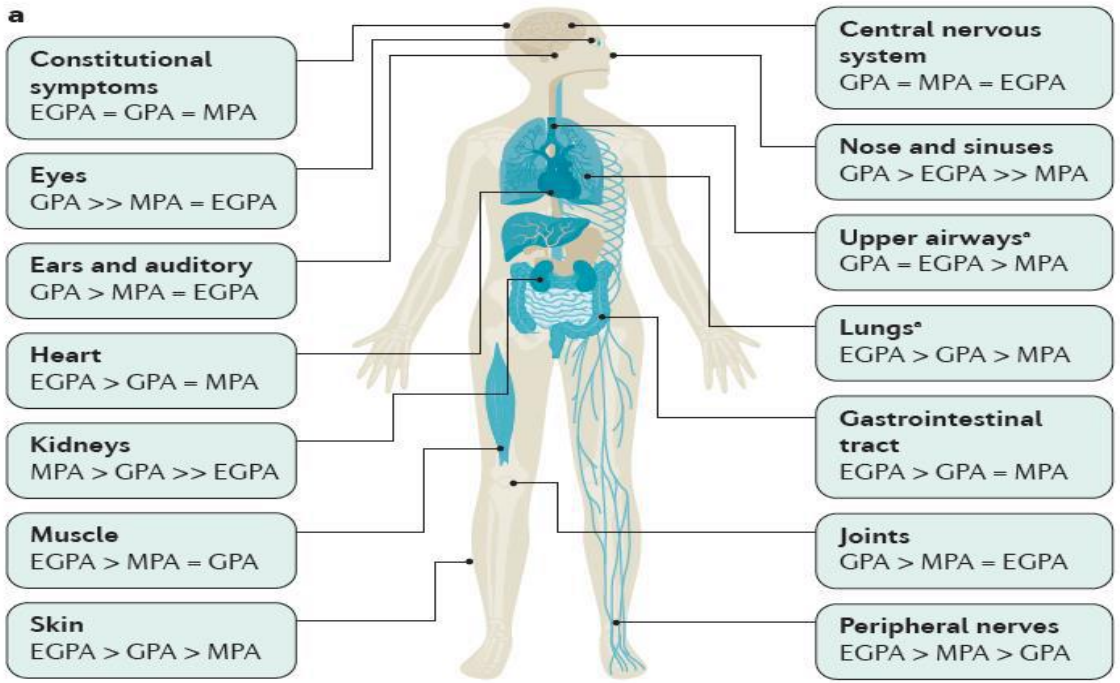
Gastrointestinal 30-56%
Abdominal pain, bleeding, diarrhea, abnormal liver tests, hepatomegaly, pancreatitis, organ perforation, cholecystitis, appendicitis

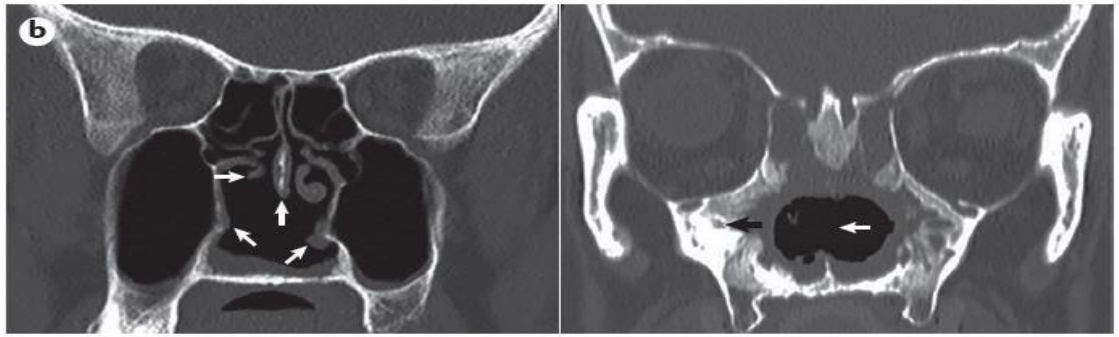
Kidney 73-100%
Rapidly progressive glomerulonephritis (pauci-immune necrotizing GN)

PNS 14-58%
Multiple mononeuropathy; symmetric polyneuropathy

Skin 30-56%
Palpable purpura, livedo reticularis, nodules, urticarial lesions, ulceration/necrosis, bullae, plaques




a
Constitutional symptoms
EGPA = GPA = MPA
Eyes
GPA >> MPA = EGPA
Ears and auditory
GPA > MPA = EGPA
Heart
EGPA > GPA = MPA
Kidneys
MPA > GPA >> EGPA
Muscle
EGPA > MPA = GPA
Skin
EGPA > GPA > MPA
Central nervous system
GPA = MPA = EGPA
Nose and sinuses
GPA > EGPA >> MPA
Upper airways*
GPA = EGPA > MPA
Lungs*
EGPA > GPA > MPA
Gastrointestinal tract
EGPA > GPA = MPA
Joints
GPA > MPA = EGPA
Peripheral nerves
EGPA > MPA > GPA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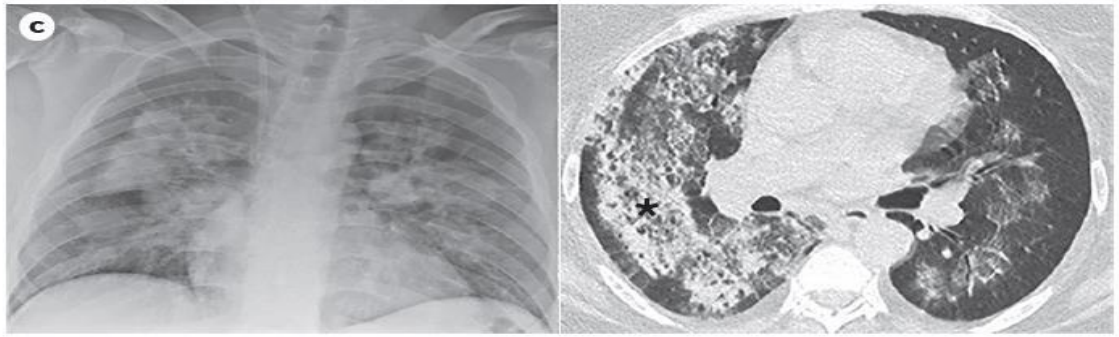
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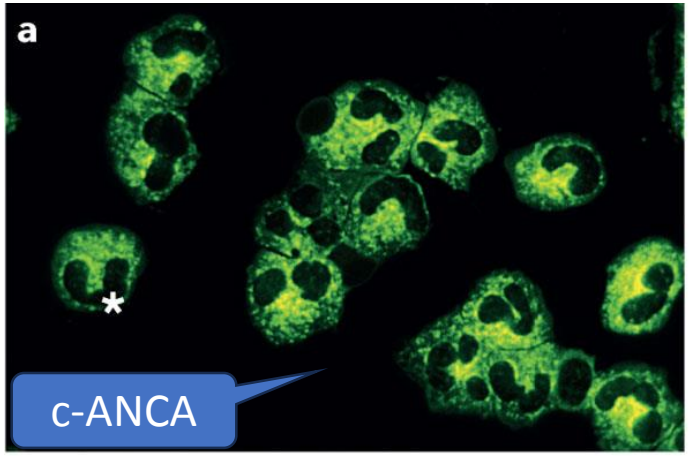
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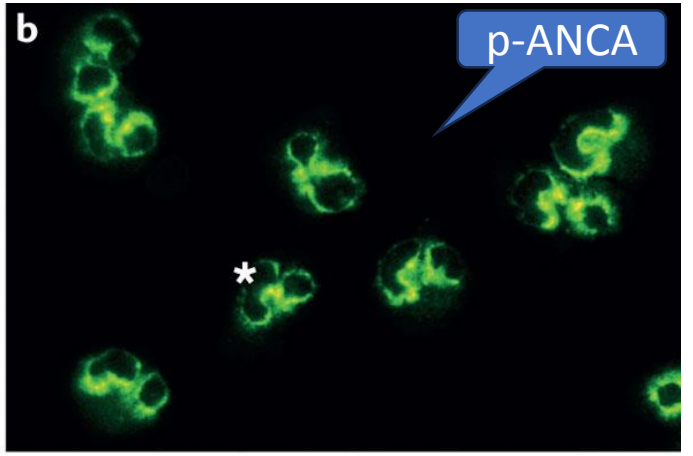
c-ANCA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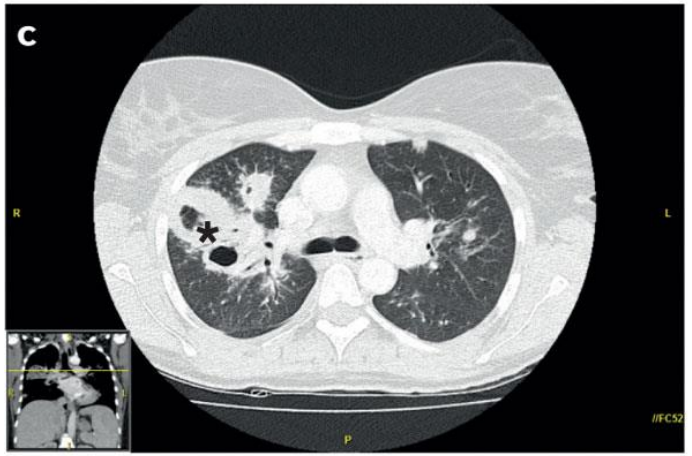
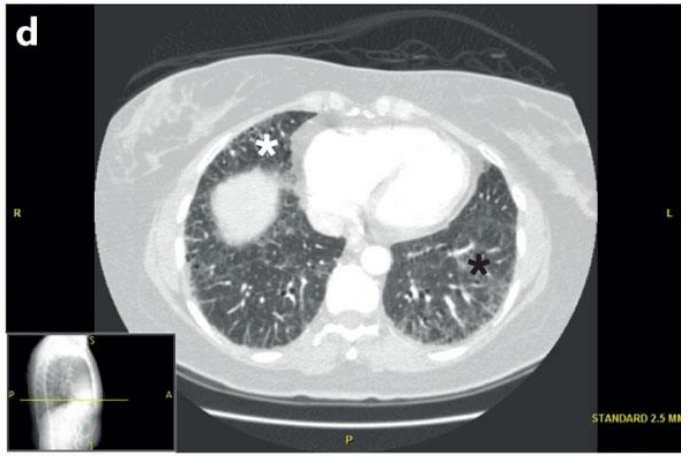
p-ANCA


c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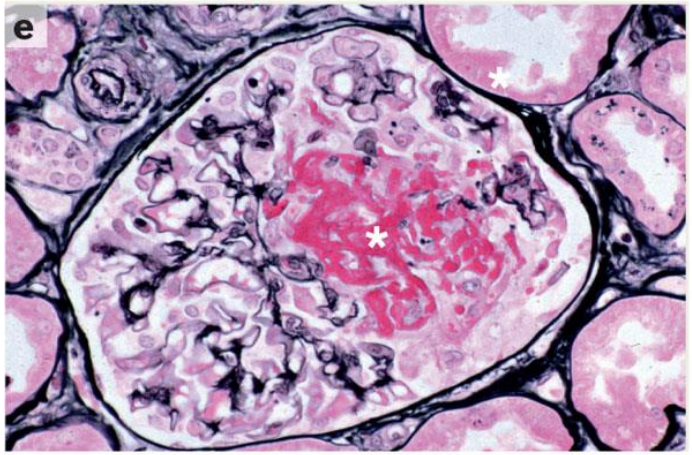
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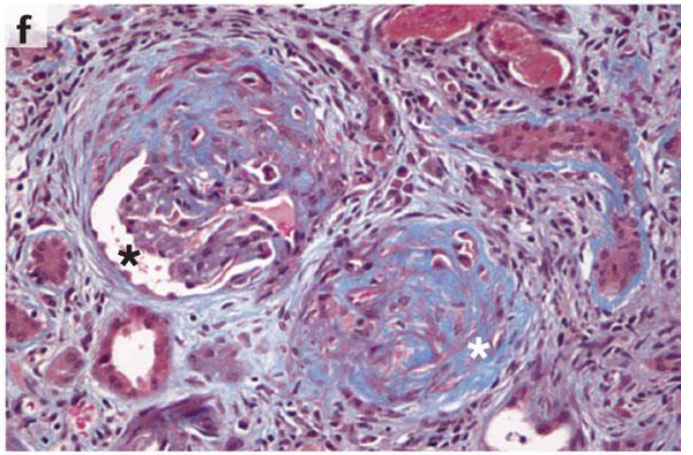
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Presentations

EASY

- 1- **RPGN**
- 2- DAH
- 3- Skin
- 4- Hyper-Eos

- **Dx earlier**

HARD

- 1- **slow burn presentation**
  a- older pts w/ **CKD (only minor U/A abnormalities)**
- 2- **ANCA –ve**

- Dx **Delayed Nephritis**

Generally these conditions are Dx by the presence of ANCA in the blood

ANCA-Mediated Vasculitis

What is taught to happening…

Mechanism of ANCA-associated vasculitis

. (A) Priming and activation of neutrophils,

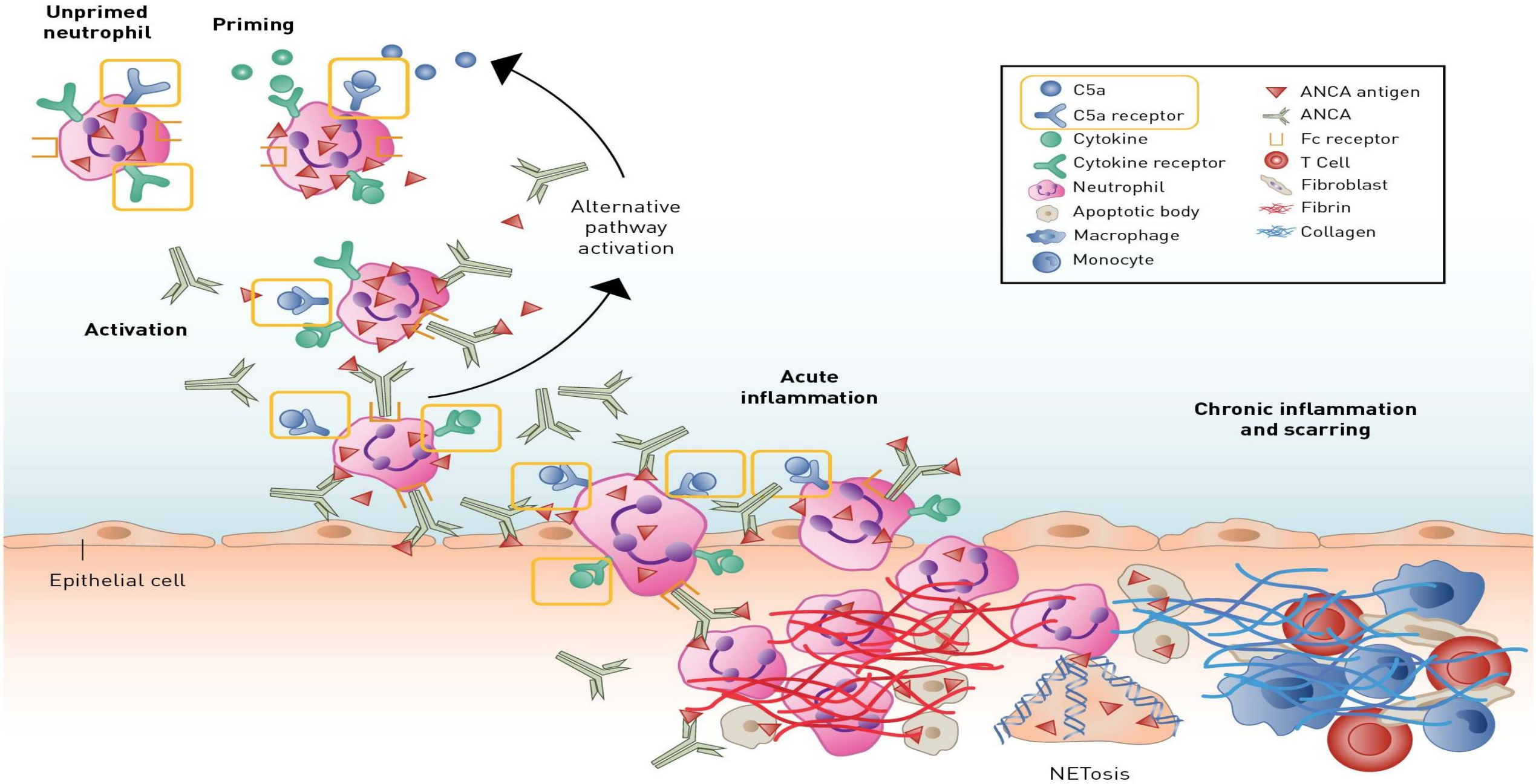
(B) expression of adhesion molecule on endothelial cells,

(C) binding of pathogenic ANCA to ANCA-antigens,

(D) interaction between neutrophils and endothelial adhesion molecules, leading to extravasation of neutrophils,

(E) production of reactive oxygen radicals and degranulation of neutrophils,

(F) a **loop of complement activating** factors to C5a fragment.


Unprimed neutrophil
Priming
Alternative pathway activation
Activation
Acute inflammation
Chronic inflammation and scarring
Epithelial cell
NETosis
C5a
C5a receptor
Cytokine
Cytokine receptor
Neutrophil
Apoptotic body
Macrophage
Monocyte
ANCA antigen
ANCA
Fc receptor
T Cell
Fibroblast
Fibrin
Collagen

Testing in ANCA vasculitis

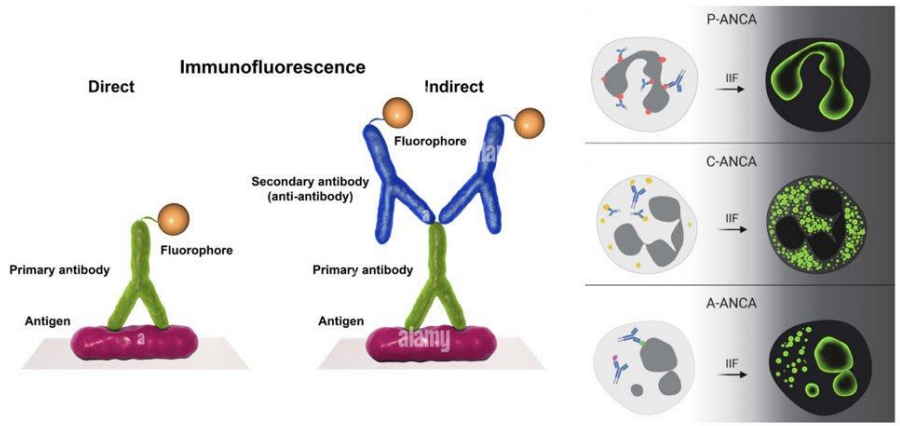
Anti Neutrophilic Cytoplasmic Antibody

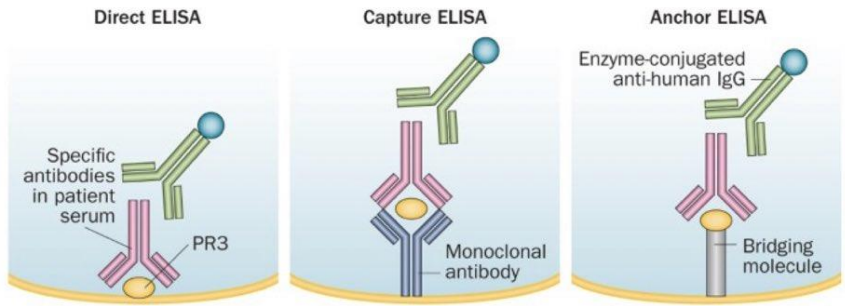
Against Proteinase 3 (PR3)

Against Myeloperoxidase (MPO)

Indirect Immuno florescence

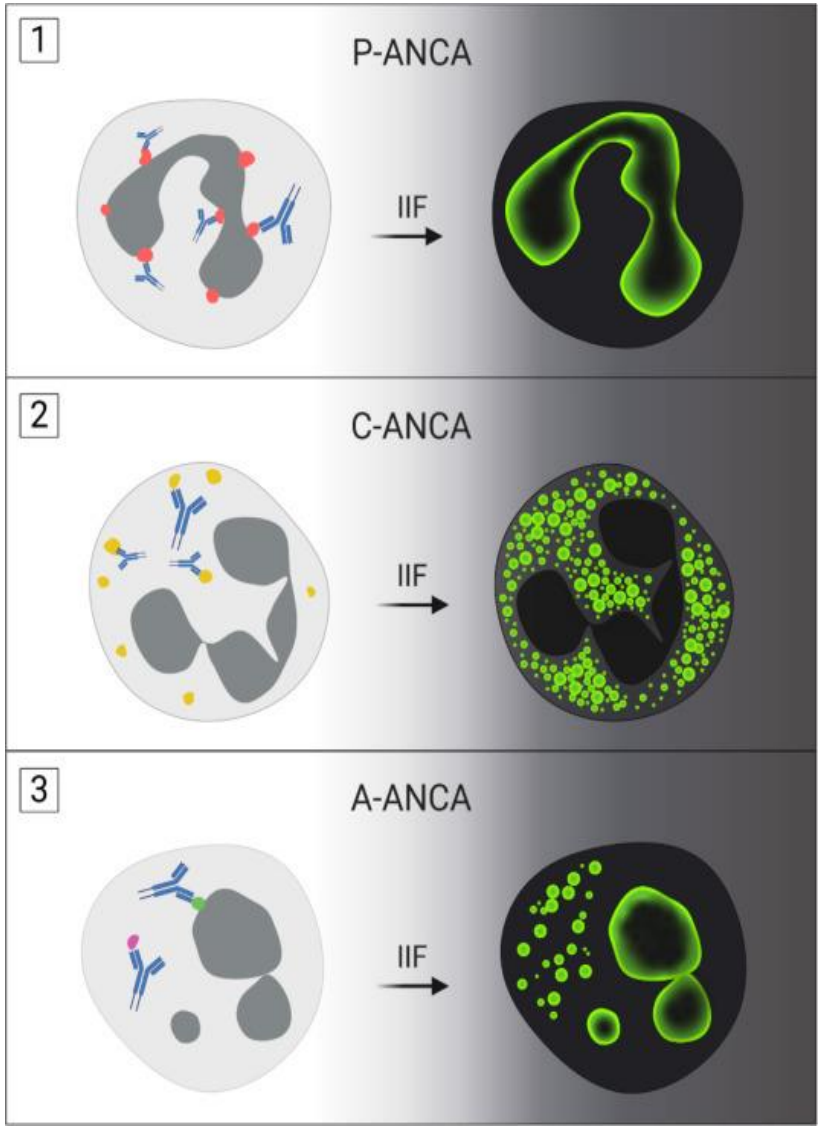
Antigen specific assays

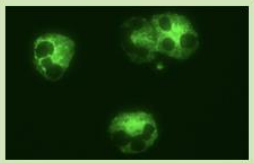
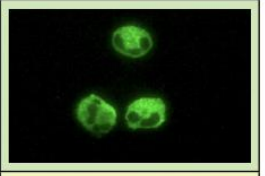
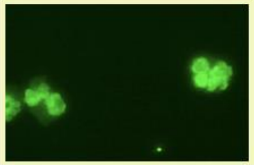
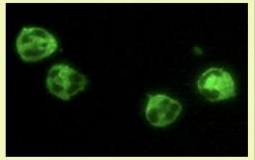
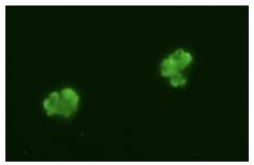
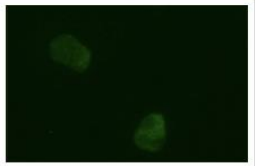


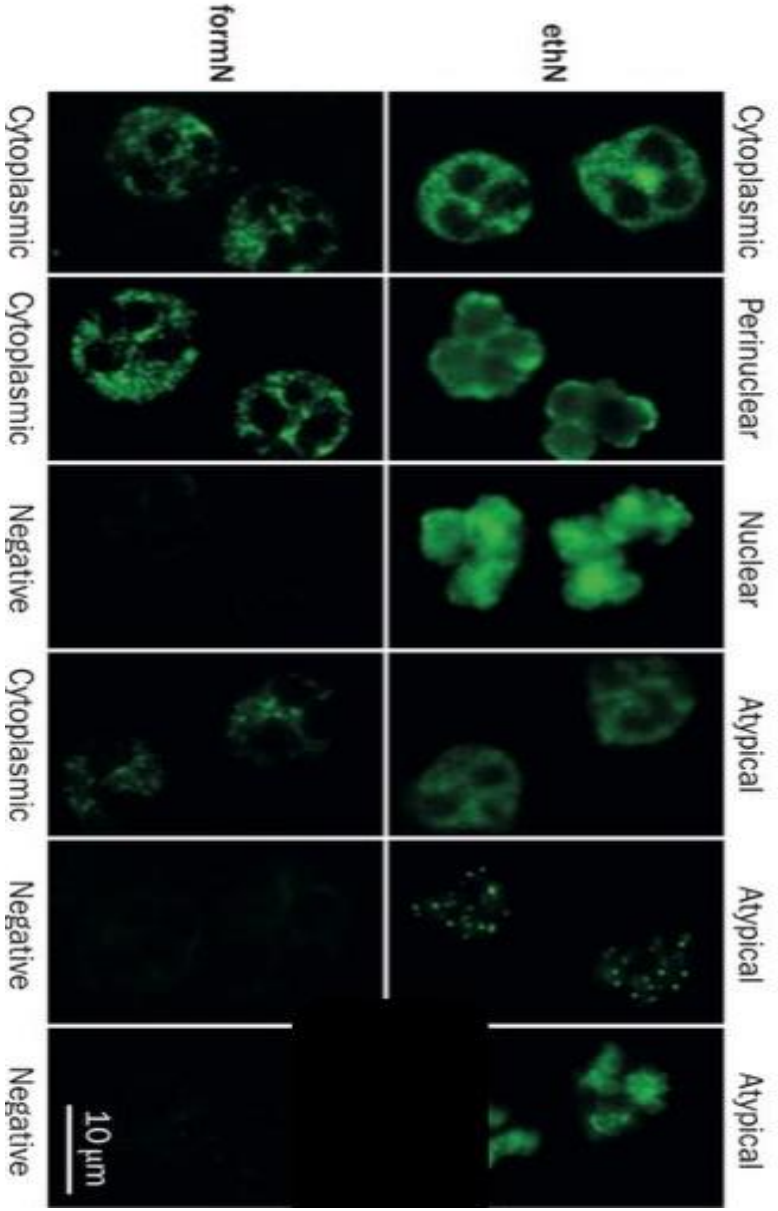


P ANCA - MPO - Microscopic Polyangiitis
C ANCA - PR3- Granulomatosis Polyangiitis

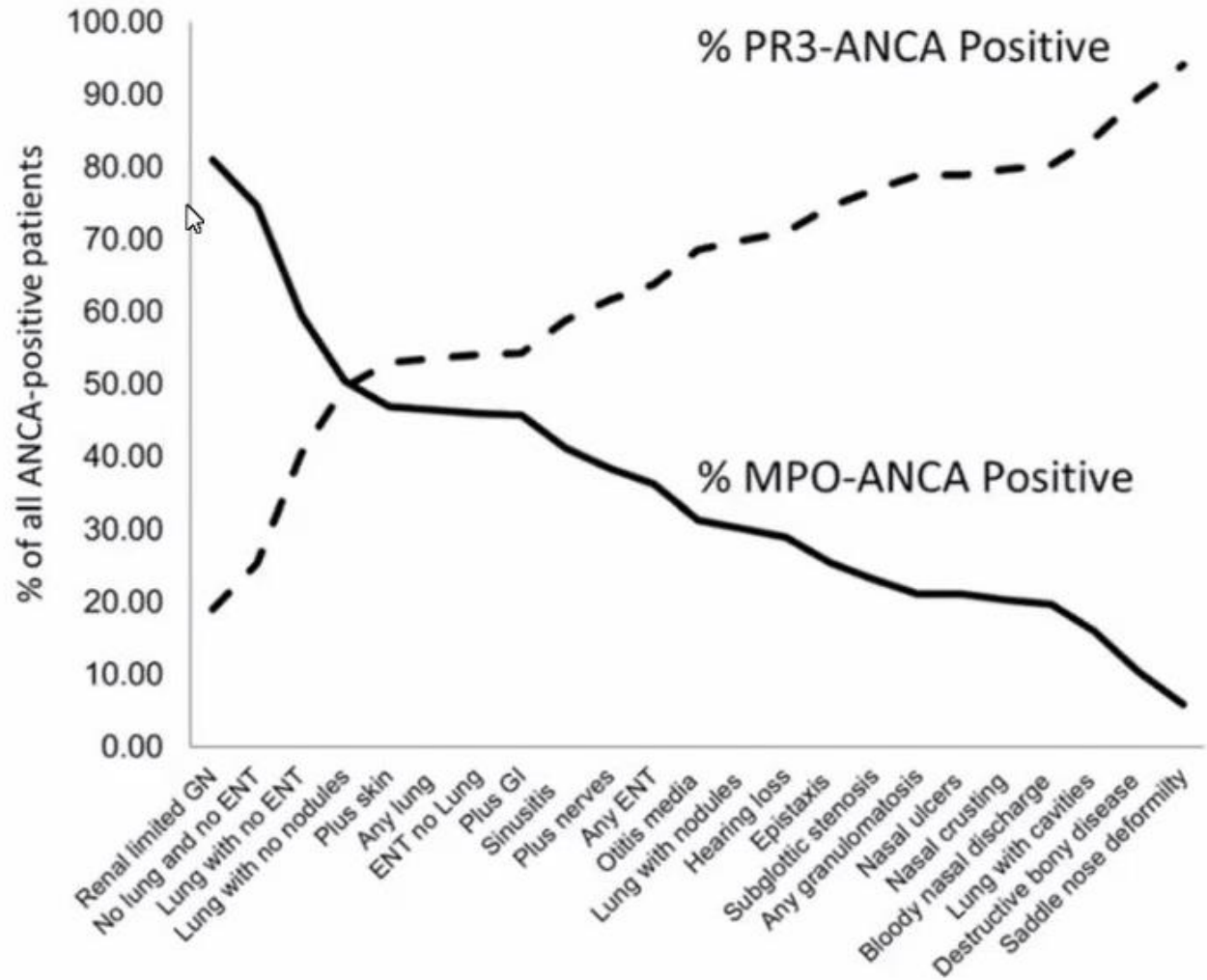
ANCA Patterns



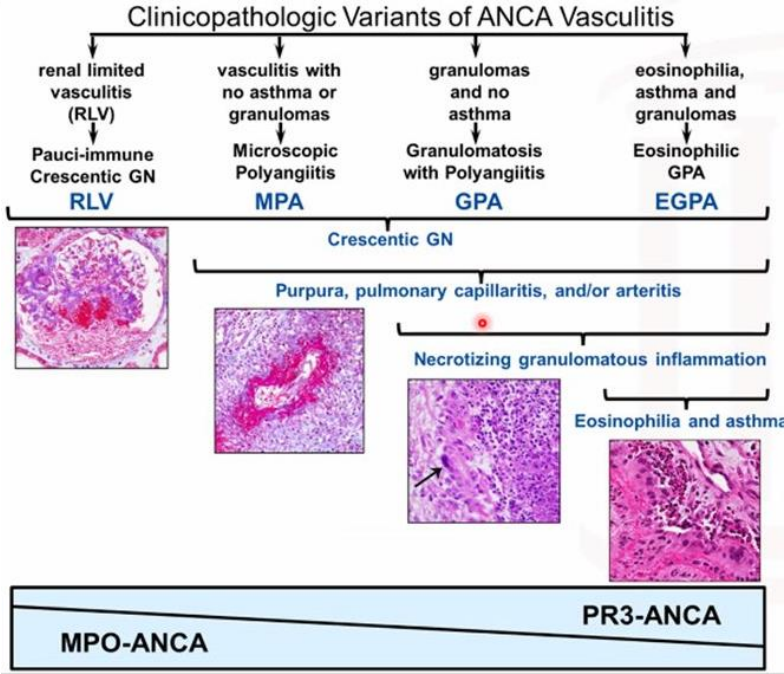
	ANCA-Ethanol	ANCA-Formalin
cANCA positive		
pANCA positive		
ANA positive		



Clinical Manifestations of PR-3 (GPA) vs MPO (MPA) ANCA -Jennette, Nachman, *CJASN* 12, 2017




NORTHERN EUROPE
PR3-AAV: 61.2%
MPO-AAV: 24.6%
ANCA (-)-AAV: 14.2%
SOUTHERN EUROPE
PR3-AAV: 37%
MPO-AAV: 40.7%%
ANCA (-)-AAV: 22.2%
CHINA
PR3-AAV: 21.2%
MPO-AAV: 45.4%
ANCA (-)-AAV: 33.3%
JAPAN
PR3-AAV: 2.1%
MPO-AAV: 81.3%
ANCA (-)-AAV: 16.7%
MIDDLE EAST
PR3-AAV: 50%
MPO-AAV: 32.9%
ANCA (-)-AAV: 17.1%

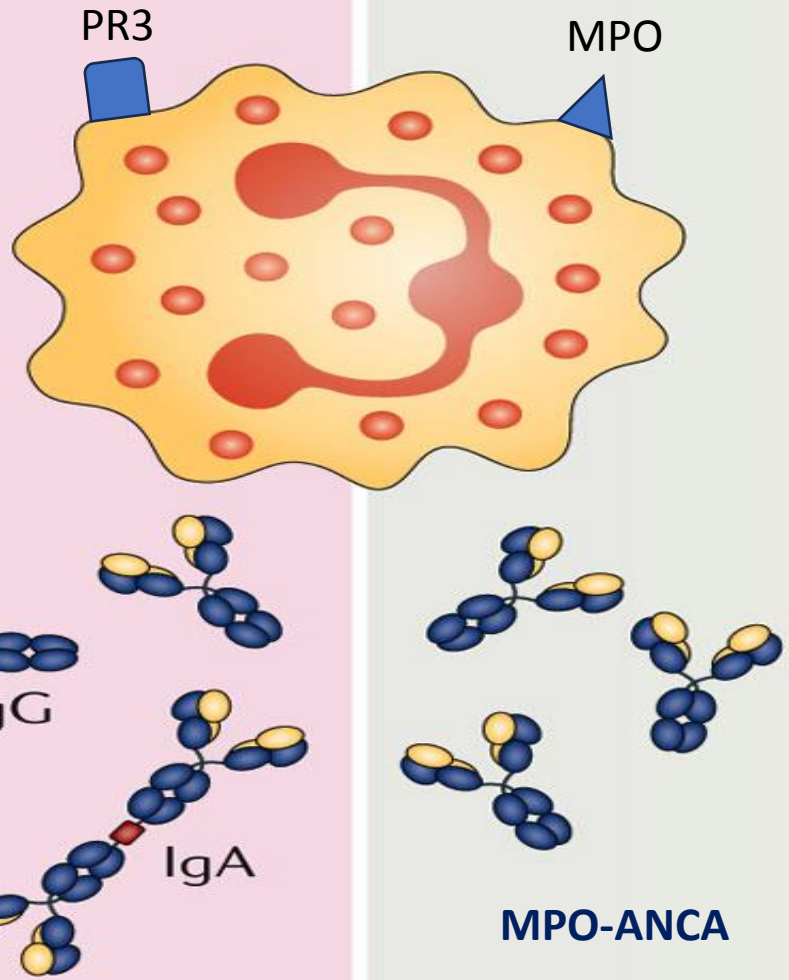

Clinicopathologic Variants of ANCA Vasculitis
renal limited vasculitis (RLV)
vasculitis with no asthma or granulomas
granulomas and no asthma
eosinophilia, asthma and granulomas
Pauci-immune Crescentic GN
Microscopic Polyangiitis
Granulomatosis with Polyangiitis
Eosinophilic GPA
RLV
MPA
GPA
EGPA
Crescentic GN
Purpura, pulmonary capillaritis, and/or arteritis
Necrotizing granulomatous inflammation
Eosinophilia and asthma
PR3-ANCA
MPO-ANCA

PR3

- Chromosome 19p13.3
- Glycoprotein 29–32 kDa
- Stored in primary, secretory and specific granules of neutrophils
- Variable membrane expression on resting neutrophils
- High membrane expression during neutrophil apoptosis

MPO

- Chromosome 17q23.1
- Glycoprotein (homodimer) 146 kDa
- Stored exclusively in primary granules of neutrophils
- No membrane expression on resting neutrophils
- Neutrophil membrane binding of extracellular MPO released during neutrophil degranulation

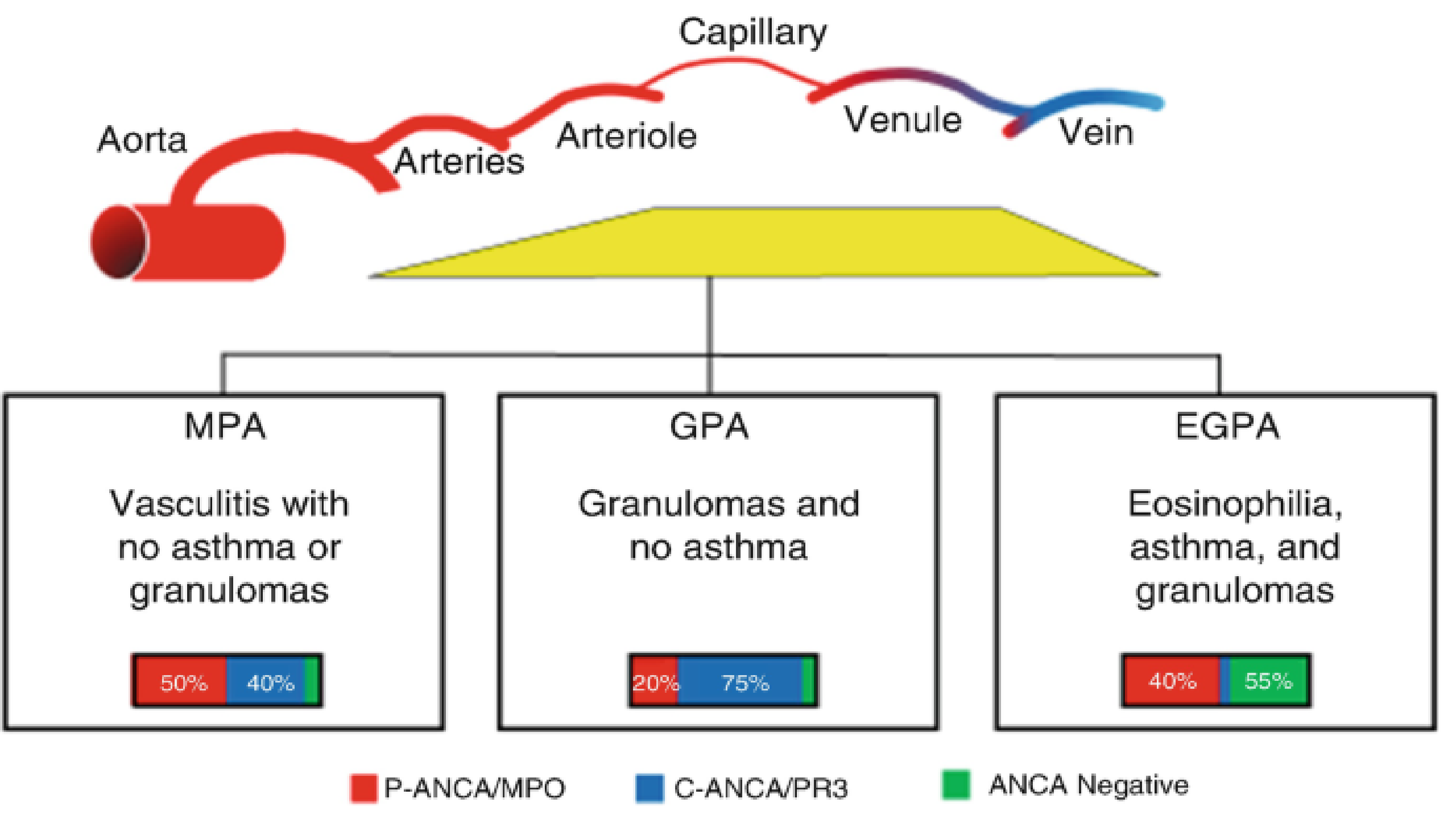


PR3-ANCA

- Mostly IgG (IgA in ≤30% of patients)
- No clearly defined pathogenic epitope
- Induces weak activation of primed neutrophils *in vitro*
- No spontaneous mouse model

MPO-ANCA

- Only IgG
- A well-described linear pathogenic epitope
- Induces strong activation of primed neutrophils *in vitro*
- Pathogenicity proved in several animal models


Capillary
Aorta
Arteries
Arteriole
Venule
Vein
MPA
Vasculitis with no asthma or granulomas
50%
40%
GPA
Granulomas and no asthma
20%
75%
EGPA
Eosinophilia, asthma, and granulomas
40%
55%
P-ANCA/MPO
C-ANCA/PR3
ANCA Negative

AUTOIMMUNITY

IBD

- Chron Disease
- Ulcerative colitis

AAV

- GPA
- EGPA
- MPA

LIVER DISEASES

- Autoimmune hepatitis
- Primary sclerosing cholangitis

OVERLAP SYNDROMES

- Systemic Lupus Erythematosus
- Systemic Sclerosis
- Sjogren Syndrome
- IgG4 related disease
- Rheumatoid arthritis

ANCA

INFECTIONS

Viruses

Bacteria

MALIGNANCY

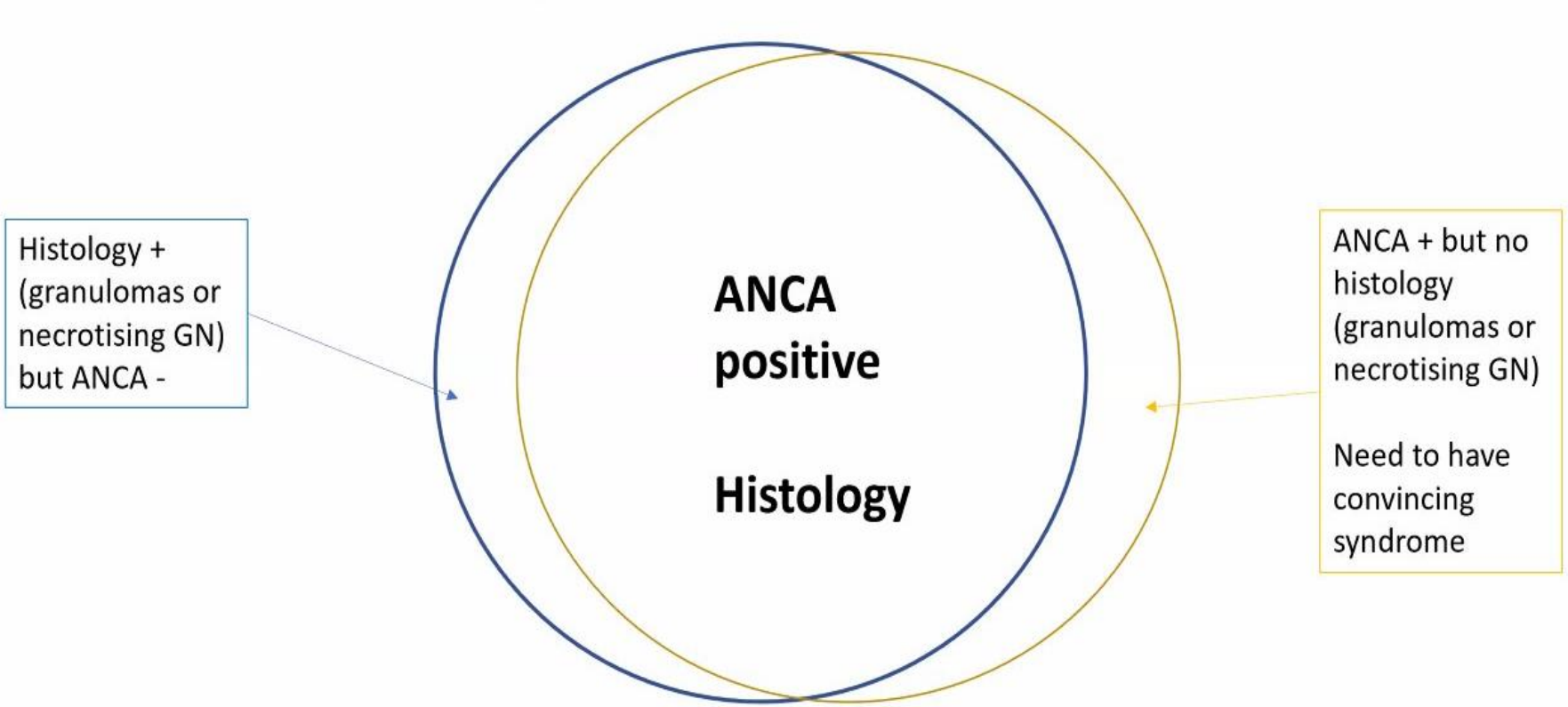
Leukaemia

Solid

DRUGS

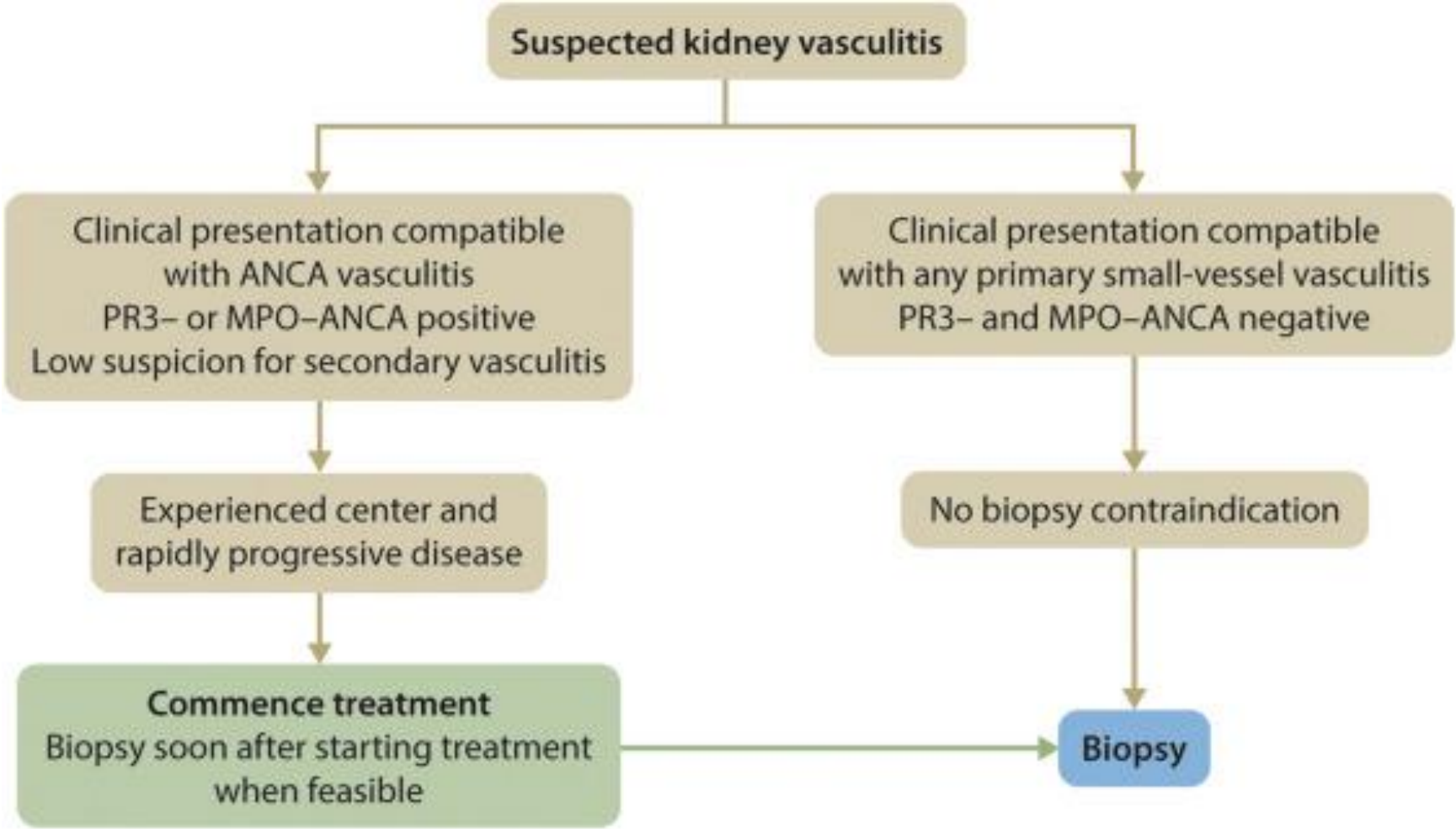
ISOLATED POSITIVITY

Making the Diagnosis in AVV



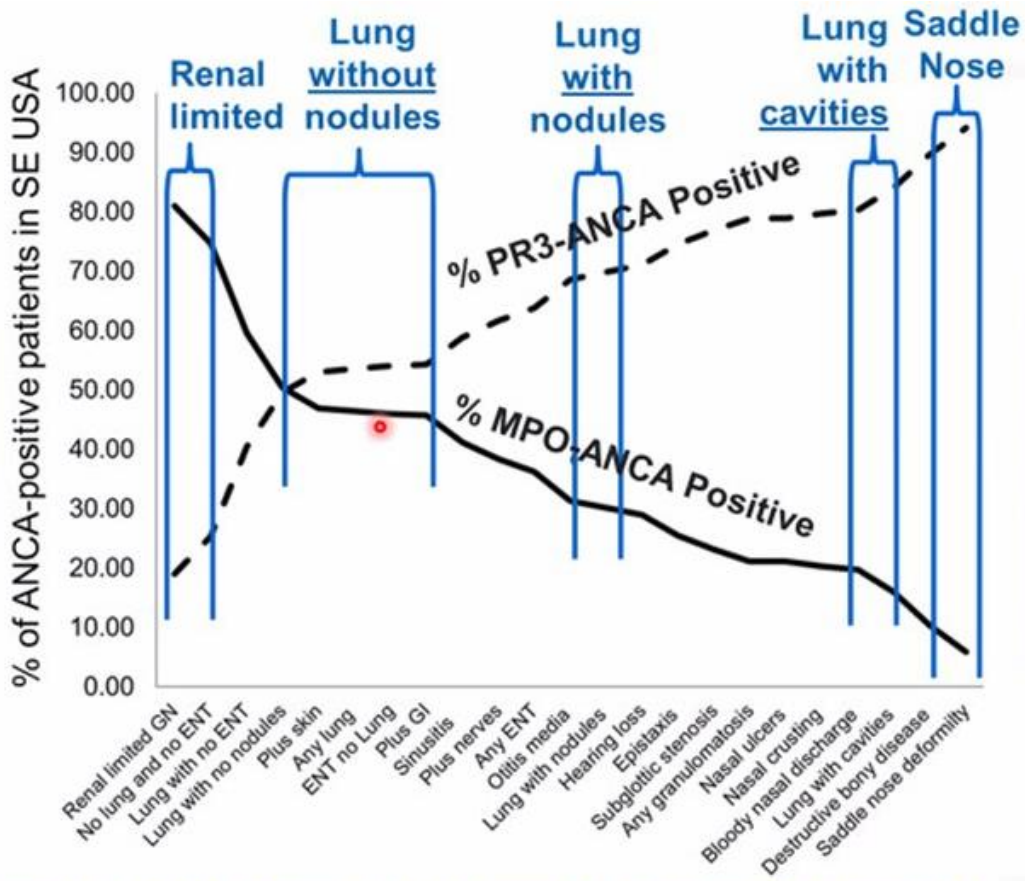
Easy if typical syndrome, ANCA +, and typical histology.
Also important to clarify each of these aspects in order to assess disease activity markers down track

KDIGO Recommendation Bx



Serology Defines Phenotypes

The serotype influences the clinicopathologic phenotype of ANCA disease.



The serotype difference is driven by differences in the genetically determined HLA-dependent antigen binding that initiated the T cell help for the antibody response, and thus is different for PR3-ANCA and MPO-ANCA.

Lionaki S, Blyth E, Hogan S, Hu Y, Senior J, Jennette CE, Nachman P, Jennette JC, Falk RJ. Arthritis Rheum 2012;64:3452-62

Recognize that…

- **ANCA has poor PPV in low prevalence setting**
- Predictive value of ANCA depends upon the likelihood of disease:
- Pts who presents w/ sinus, lung, renal disease >>> PV of ANCA is 90% similar to Bx

- **In an individual pt, ANCA level can vary over time**

- **“predict” relapse & “guide” treatment ?**

- **Serial ANCA measurement to assess disease activity ?**

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

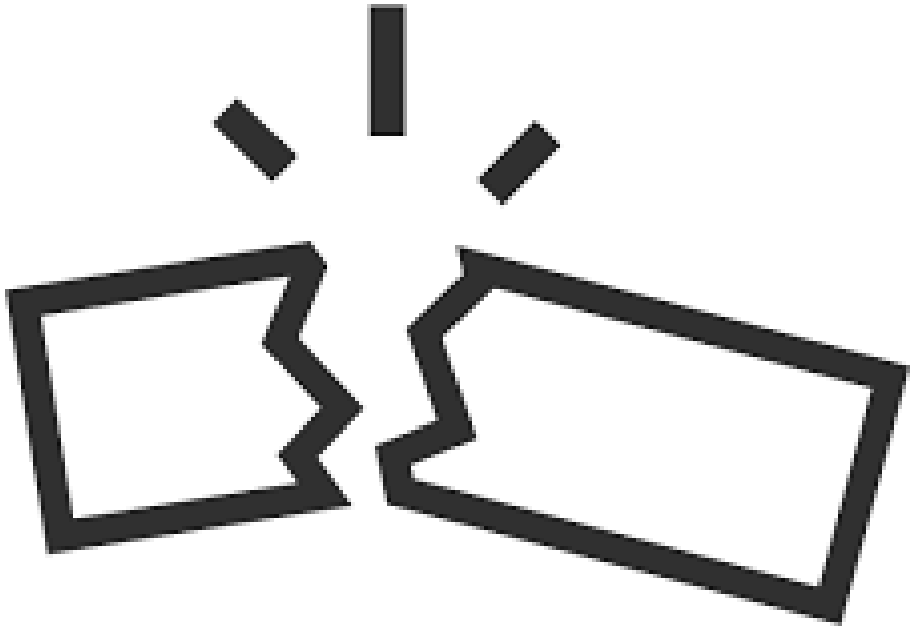
Figure 82 | Factors that increase relapse risk for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

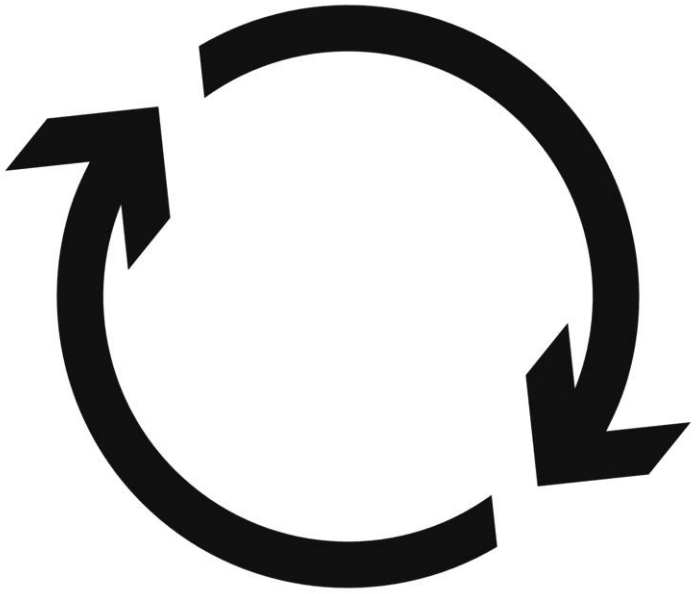
Clinical Indications for ANCA Testing

In order to assure appropriate anti-neutrophil cytoplasmic antibody (ANCA)-test usage to support the diagnosis of ANCA-associated vasculitis (AAV), ANCA should be requested for patients with the following clinical indications.

- Glomerulonephritis, especially rapidly progressive glomerulonephritis
- Pulmonary haemorrhage, especially pulmonary renal syndrome
- Cutaneous vasculitis with systemic features
- Multiple lung nodules
- Chronic destructive disease of the upper airways
- Long-standing sinusitis or otitis
- Subglottic tracheal stenoses
- Mononeuritis multiplex or other peripheral neuropathy
- Retro-orbital mass
- Scleritis

Damage *vs* Recurrence





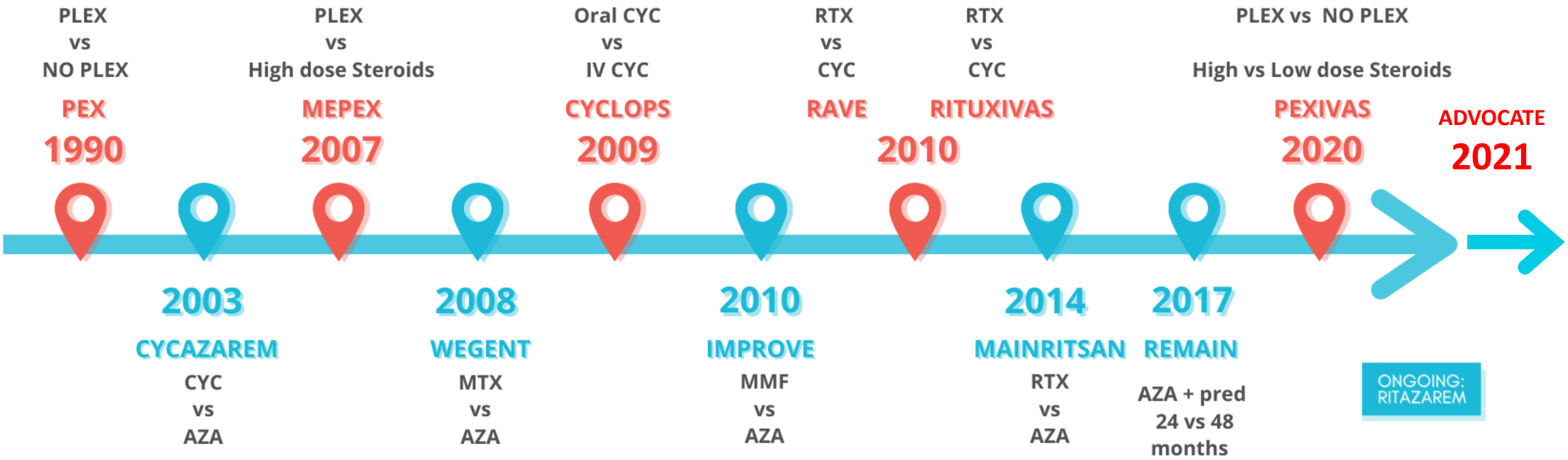
Some organs may be affected for the first time during a relapse

Figure 2. Major organ systems affected by Wegener granulomatosis. ENT = ear, nose, and throat involvement.

LANDMARK TRIALS IN

ANCA GLOMERULONEPHRITIS

INDUCTION



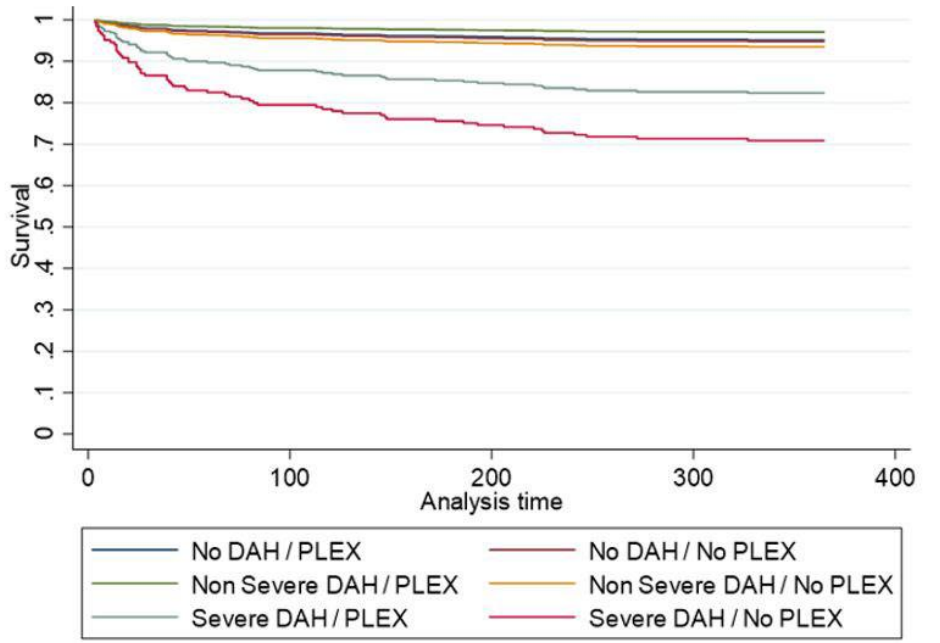
MAINTENANCE

What kind of pts in the PEXIVAS ?

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Plasma Exchange (N=352)	No Plasma Exchange (N=352)	Reduced-Dose Glucocorticoid Regimen (N=353)	Standard-Dose Glucocorticoid Regimen (N=351)
Age — yr	62.8±14.4	63.5±13.7	63.3±14.2	63.1±13.9
Female sex — no. (%)	149 (42.3)	158 (44.9)	156 (44.2)	151 (43.0)
History of vasculitis — no. (%)	35 (9.9)	28 (8.0)	34 (9.6)	29 (8.3)
ANCA subtype — no. (%)				
Proteinase 3	143 (40.6)	143 (40.6)	143 (40.5)	143 (40.7)
Myeloperoxidase	209 (59.4)	209 (59.4)	210 (59.5)	208 (59.3)
Median C-reactive protein level (IQR) — mg/liter	50.9 (13.8–122.8)	42.1 (14.0–97.2)	44.6 (13.0–117.0)	45.5 (14.0–98.0)
Median hemoglobin level (IQR) — g/liter	94 (83–105)	95 (85–105)	95 (84–105)	95 (84.5–105)
Kidney function				
Median serum creatinine level (IQR) — μmol/liter	327 (206–491)	336 (209–495)	320 (190–480)	335 (219–502)
Serum creatinine level ≥500 μmol/liter or undergoing dialysis — no. (%)	101 (28.7)	104 (29.5)	102 (28.9)	103 (29.3)
Undergoing dialysis — no. (%)	66 (18.8)	74 (21)	67 (19.0)	73 (20.8)
Severity of pulmonary hemorrhage — no. (%)				
No hemorrhage	257 (73.0)	256 (72.7)	257 (72.8)	256 (72.9)
Not severe	64 (18.2)	66 (18.8)	65 (18.4)	65 (18.5)
Severe†	31 (8.8)	30 (8.5)	31 (8.8)	30 (8.5)
Organ involvement — no. (%)				
Cutaneous	37 (10.5)	39 (11.1)	34 (9.6)	42 (12.0)
Mucous membranes or eyes	30 (8.5)	36 (10.2)	30 (8.5)	36 (10.3)
Ear, nose, and throat	95 (27.0)	103 (29.3)	98 (27.8)	100 (28.5)
Cardiovascular	6 (1.7)	4 (1.1)	5 (1.4)	5 (1.4)
Gastrointestinal	2 (0.6)	2 (0.6)	1 (0.3)	3 (0.9)
Pulmonary	145 (41.2)	149 (42.3)	147 (41.6)	147 (41.9)
Kidney	342 (97.2)	349 (99.1)	346 (98.0)	345 (98.3)
Nervous system	37 (10.5)	25 (7.1)	33 (9.3)	29 (8.3)
Other	61 (17.3)	59 (16.8)	59 (16.7)	61 (17.4)
Median BVAS/GPA (IQR)‡	9 (7–11)	9 (7–11)	9 (7–11)	9 (7–11)
Planned immunosuppressive treatment — no. (%)				
Intravenous cyclophosphamide	177 (50.3)	177 (50.3)	179 (50.7)	175 (49.9)
Oral cyclophosphamide	120 (34.1)	121 (34.4)	120 (34.0)	121 (34.5)
Rituximab	55 (15.6)	54 (15.3)	54 (15.3)	55 (15.7)

Figure 1: One year survival in PEXIVAS by plasma exchange (PLEX) and severity of diffuse alveolar hemorrhage (DAH), adjusted for age, sex, ANCA type, kidney function, and initial treatments



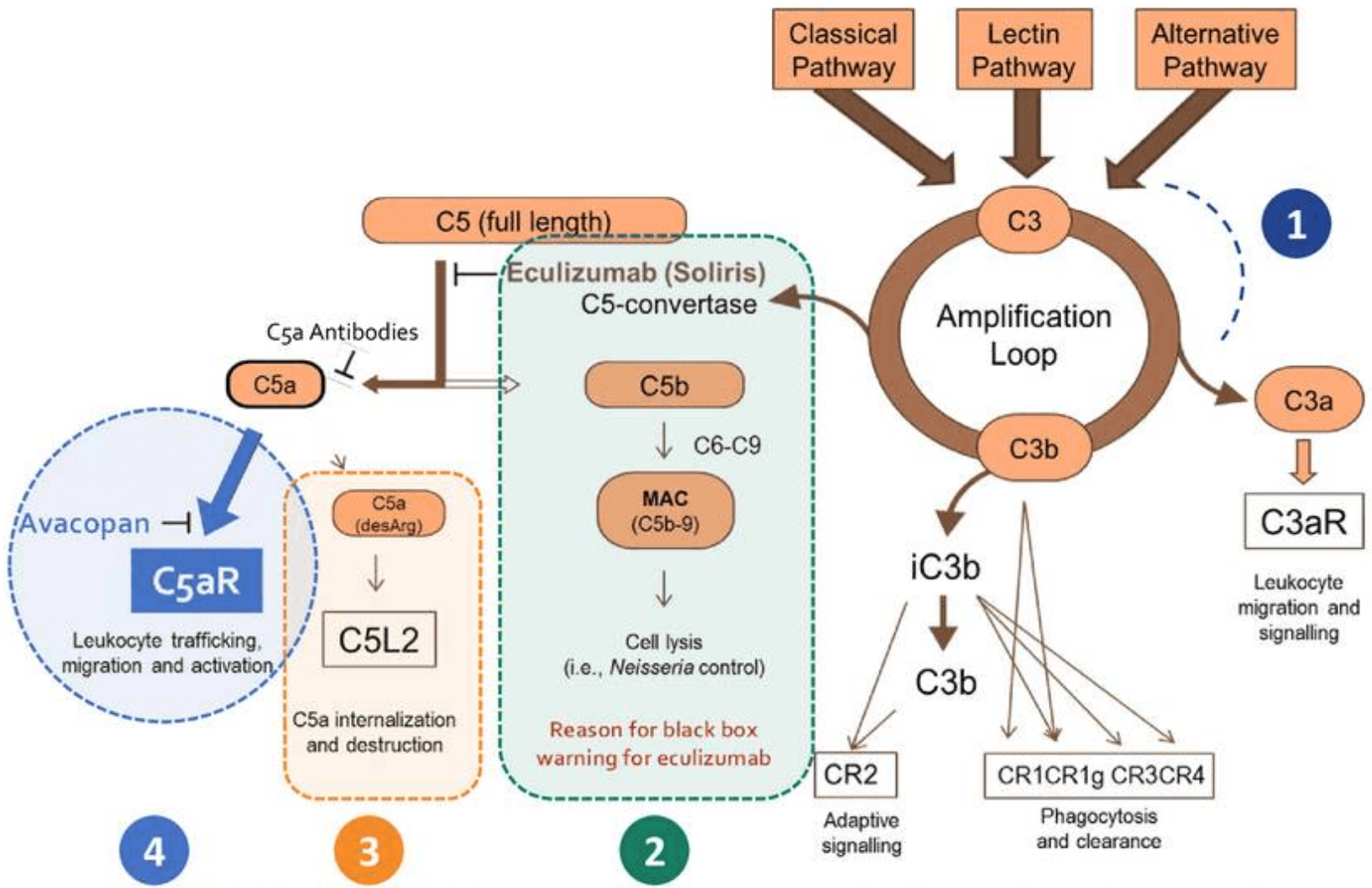
Group	Died 3 months		Died 1 year		Effect of PLEX	
	PLEX	No PLEX	PLEX	No PLEX	HR (95% CI)	Interaction p value
Overall	18 (5.1)	21 (6.0)	25 (7.1)	32 (9.1)	0.74 (0.44 to 1.26)	
No DAH	12 (4.7)	9 (3.5)	17 (6.6)	17 (6.6)	0.86 (0.43 to 1.71)	
Any DAH	6 (6.3)	12 (12.5)	8 (8.4)	15 (15.6)	0.52 (0.21 to 1.24)	0.37
Non-severe DAH	1 (1.6)	3 (4.6)	2 (3.1)	5 (7.6)	0.43 (0.08 to 2.31)	0.42
Severe DAH	5 (16.1)	9 (30.0)	6 (19.4)	10 (33.3)	0.45 (0.14 to 1.40)	0.44

TPE/PLEX

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

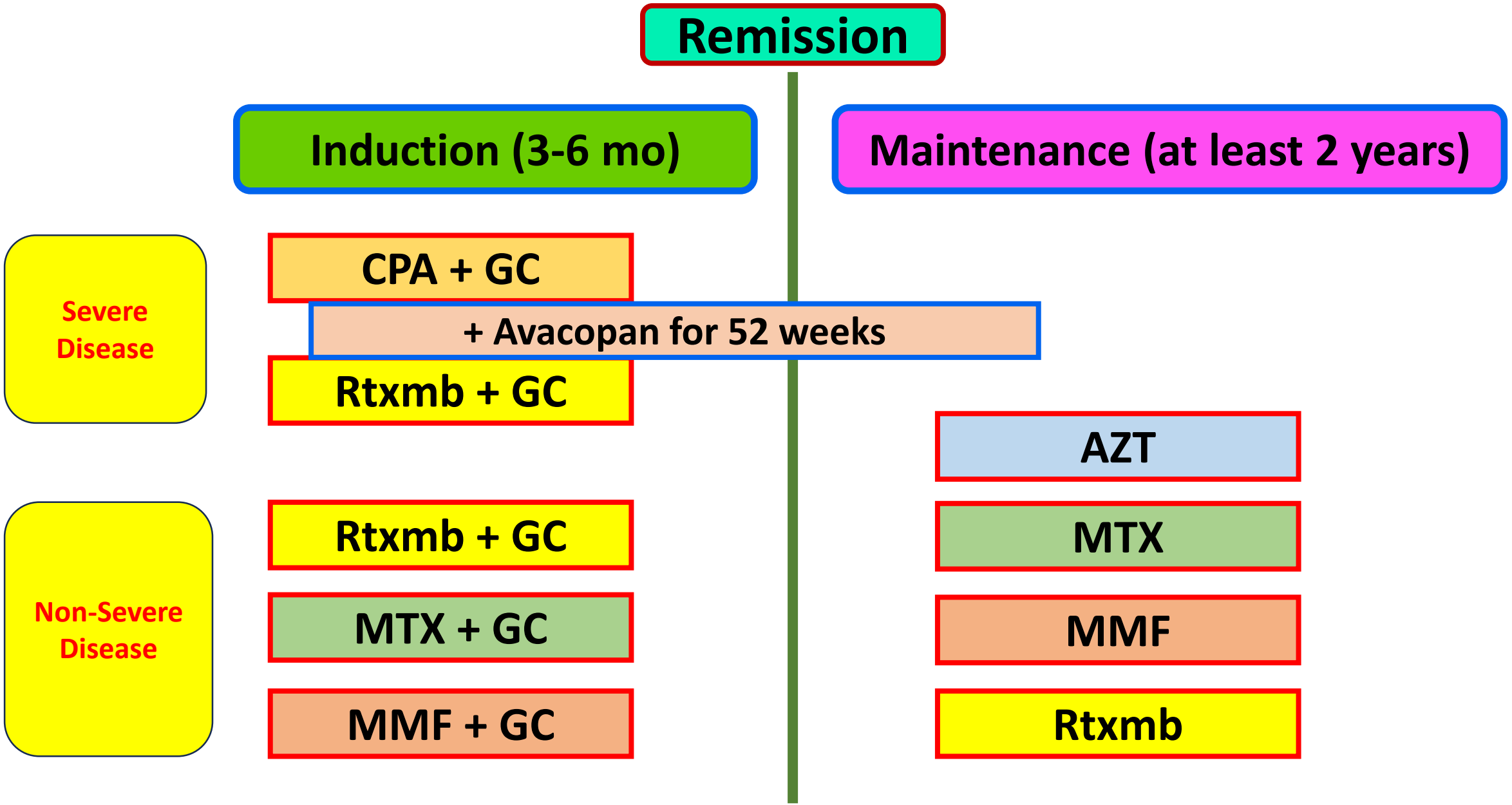
Figure 81 | Plasma exchange dosing and frequency for AAV. If a patient is at risk of bleeding, volume replacement should be with fresh, frozen plasma. ANCA, antineutrophil cytoplasmic antibody.

Avacopan: Unique Orally Administered C5aR Inhibitor



1. We believe avacopan avoids long-term biological consequences of 'upstream' complement inhibition
2. Avacopan does not block C5b-9 production; leaving host defense mechanism (MAC) in place
3. Avacopan preserves beneficial functions of C5L2 pathway
4. Avacopan approach targeting 'downstream' complement pathway we believe is best

ChemoCentryx


Remission
Induction (3-6 mo)
Maintenance (at least 2 years)
Severe Disease
CPA + GC
+ Avacopan for 52 weeks
Rtxmb + GC
Non-Severe Disease
Rtxmb + GC
MTX + GC
MMF + GC
AZT
MTX
MMF
Rtxmb

☞ ***who*** needs ***what***,
and ***when*** and
for ***how long*** ?

MERCI