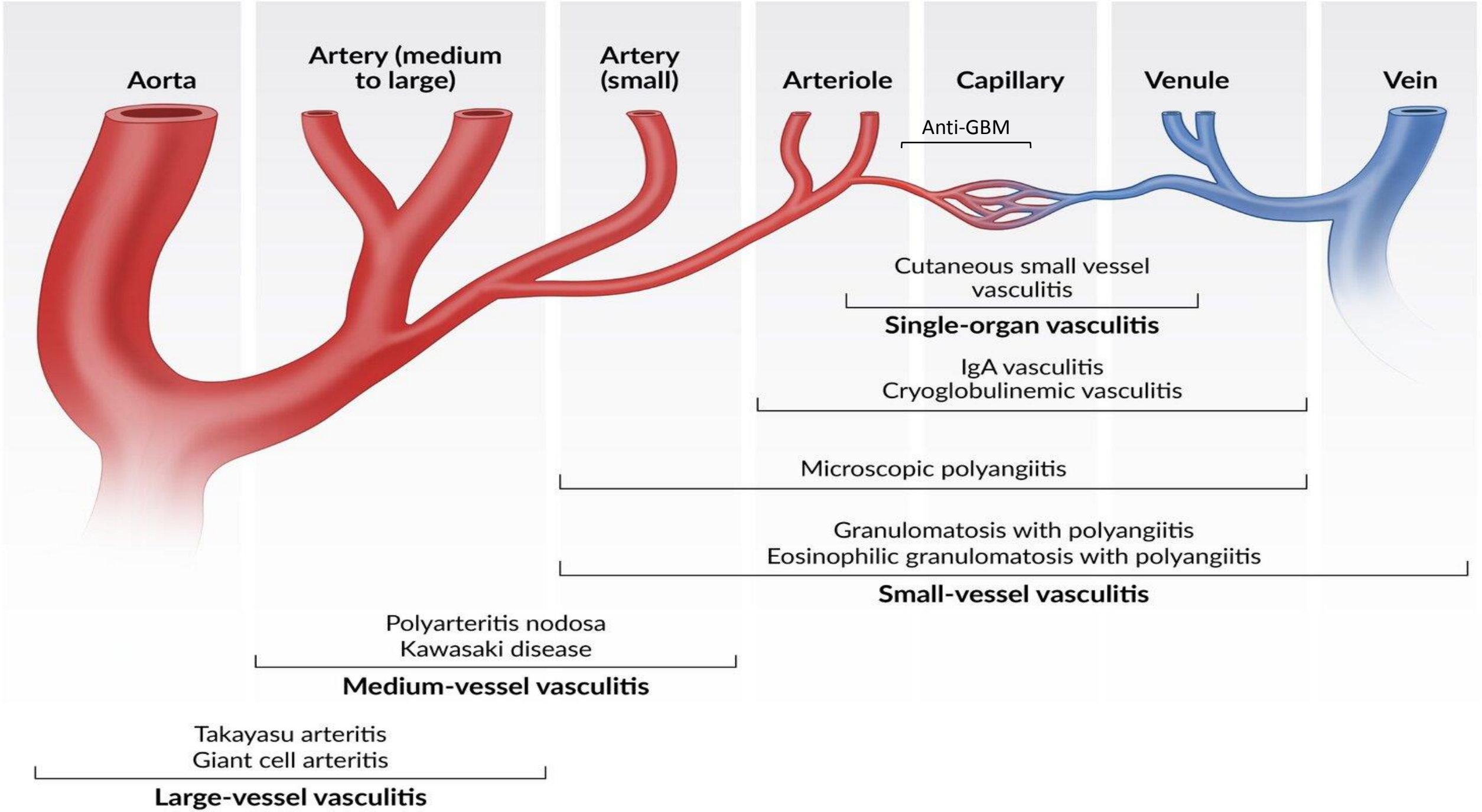
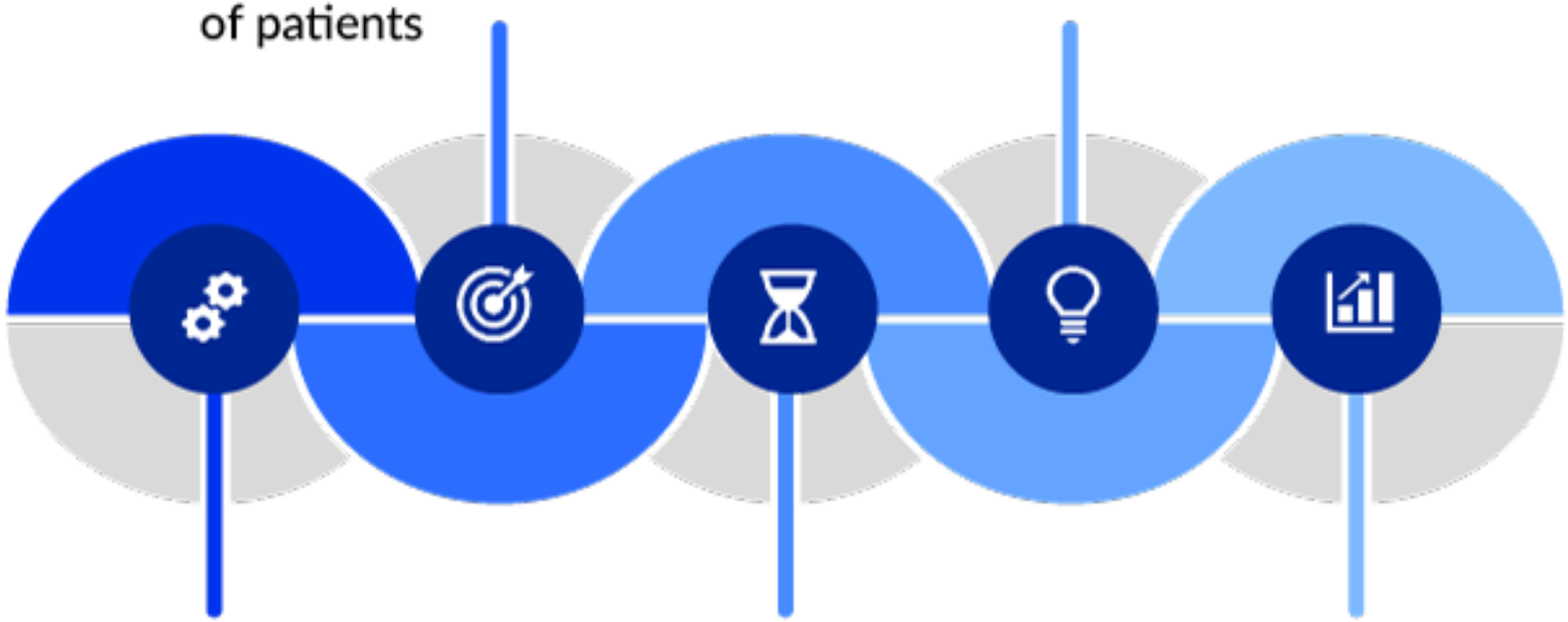
Final Thoughts


Aorta
Artery (medium to large)
Artery (small)
Arteriole
Capillary
Venule
Vein
Anti-GBM
Cutaneous small vessel vasculitis
Single-organ vasculitis
IgA vasculitis
Cryoglobulinemic vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Small-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Medium-vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Large-vessel vasculitis

Heterogeneity of ANCA-Associated Vasculitis



Initial presentation is varied; many specialist and health issues involved

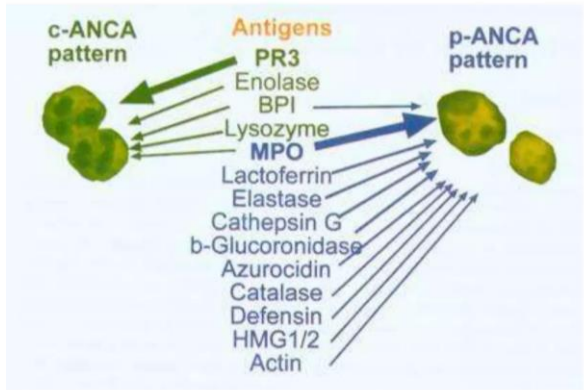
>6 months diagnostic delay is experienced by one-third of patients

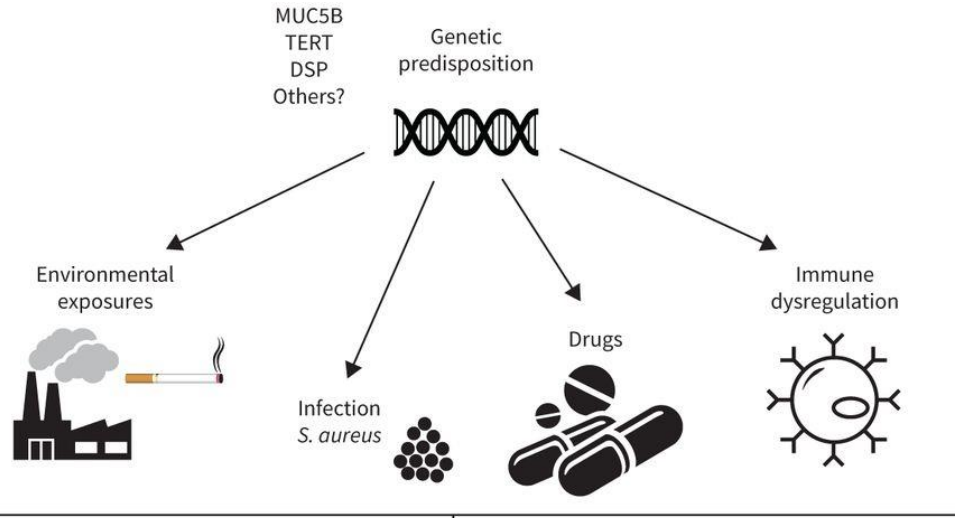
2.6x higher mortality risk in AAV patients There is no biomarker that can be used to predict the development of AAV or disease flares

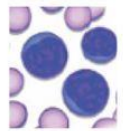
1 in 3 patients fail to achieve remission at 6 months. GC-related AEs linked to mortality and substantial comorbidities

Disease relapse is more frequent in PR3-ANCA 1 in 2 patients unable to sustain remission at 12 months without GC

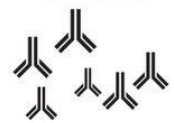
Small vessels and medium arteries	Bacterial	Streptococcus
	Viral	HBV, HCV, HIV, CMV
	Bacterial	Staphylococcus, Salmonella, mycobacteria, Streptococcus, Yersinia, Neisseria, Rickettsiae



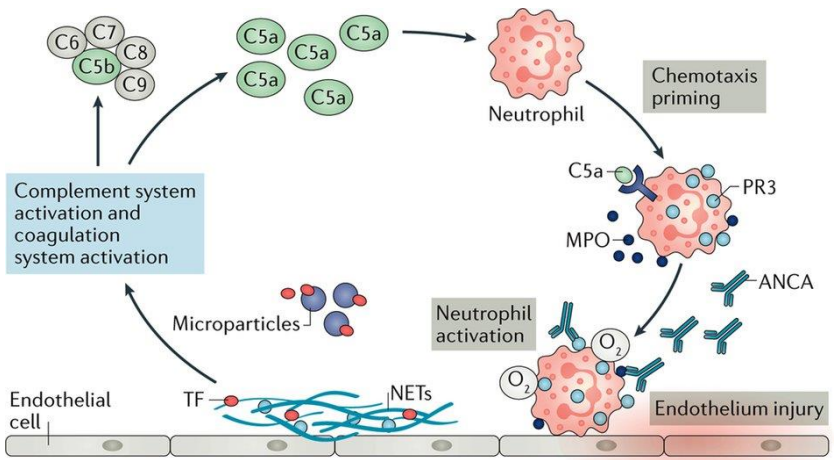


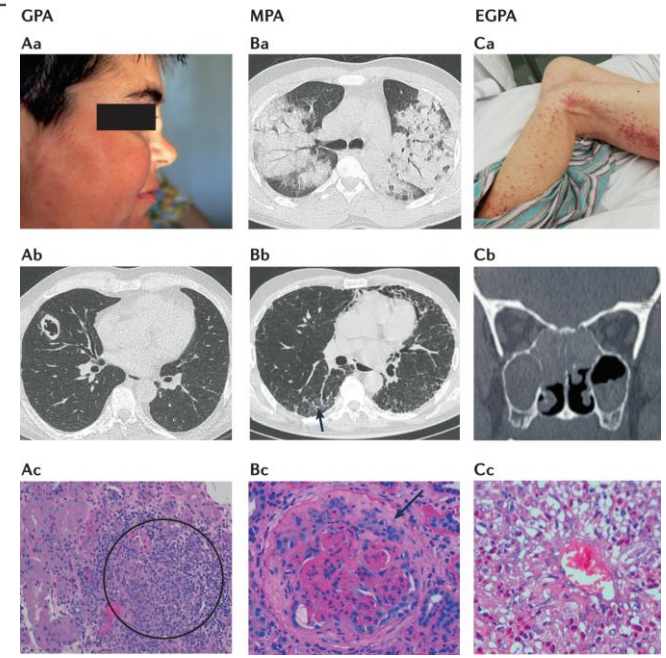


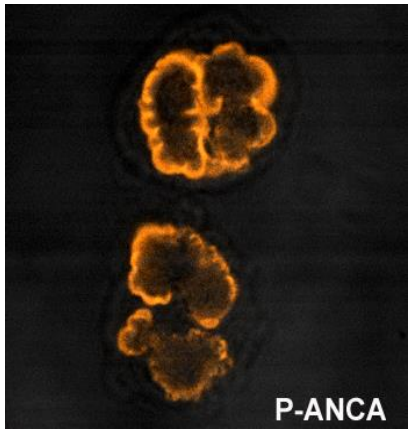
B and T cell loss of tolerance to MPO or PR3 proteins

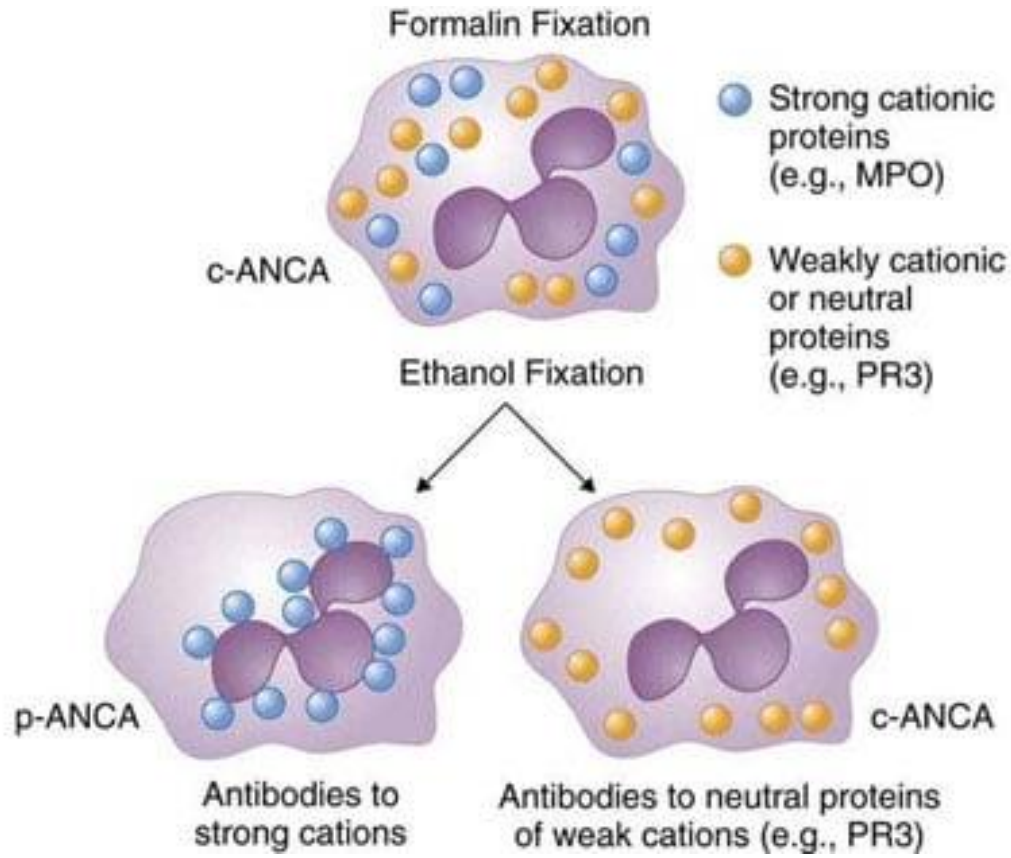


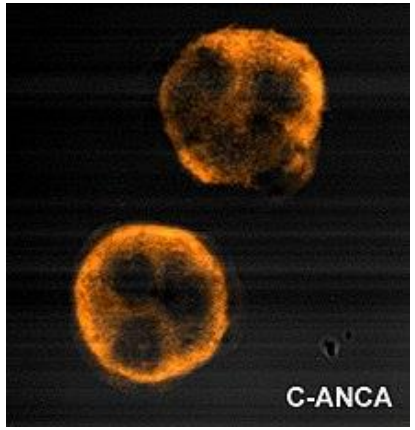
ANCA production





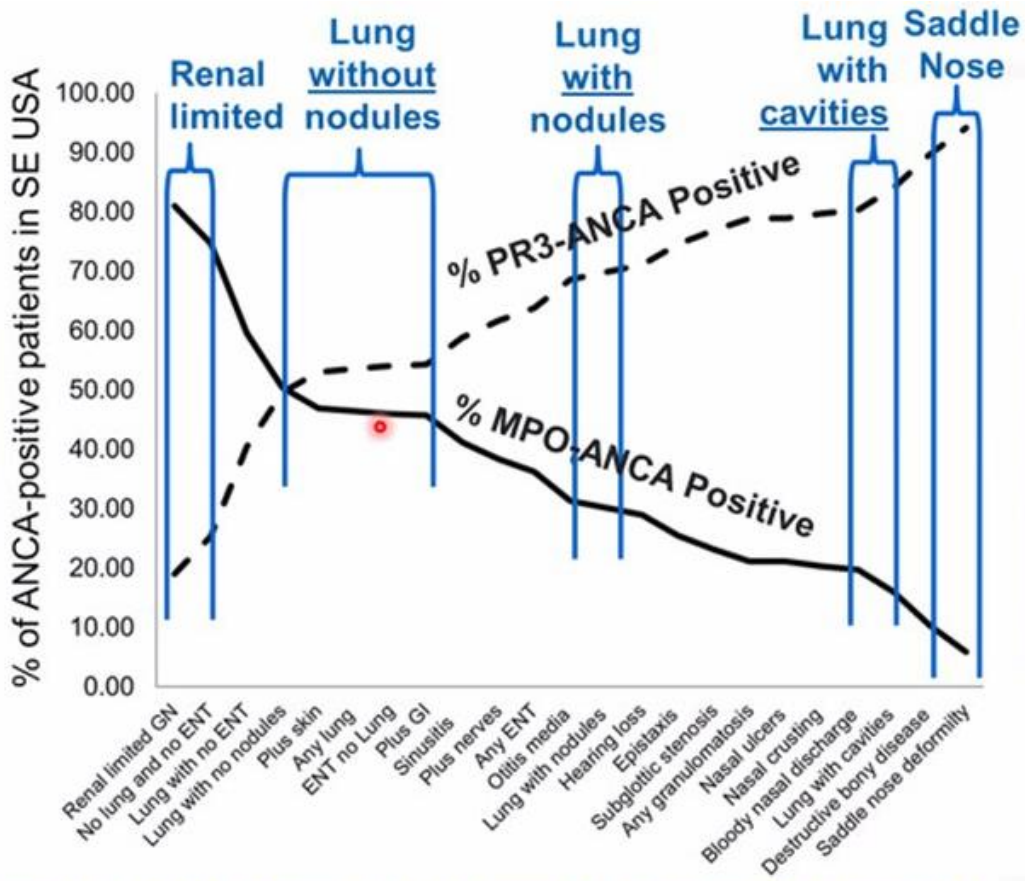

P-ANCA


Formalin Fixation
c-ANCA
Strong cationic proteins (e.g., MPO)
Weakly cationic or neutral proteins (e.g., PR3)
Ethanol Fixation
p-ANCA
c-ANCA
Antibodies to strong cations
Antibodies to neutral proteins of weak cations (e.g., PR3)


C-ANCA

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.

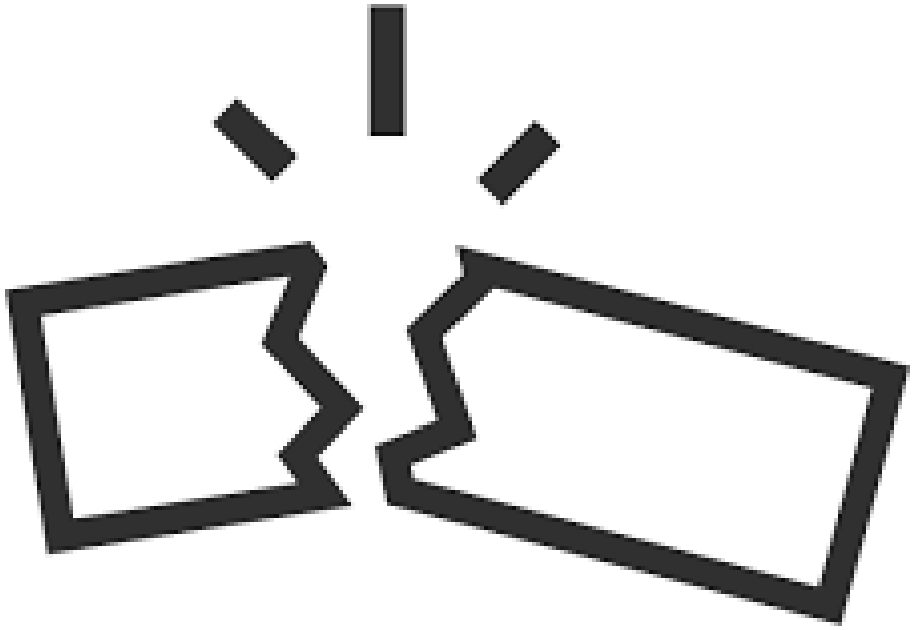
Lionaki S, Blyth E, Hogan S, Hu Y, Senior J, Jennette CE, Nachman P, Jennette JC, Falk RJ. Arthritis Rheum 2012;64:3452-62

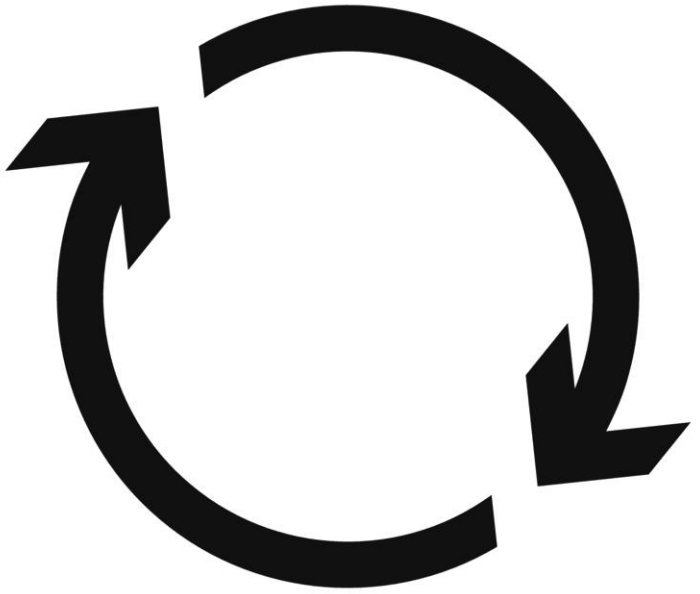
Clinical Indications for ANCA Testing

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



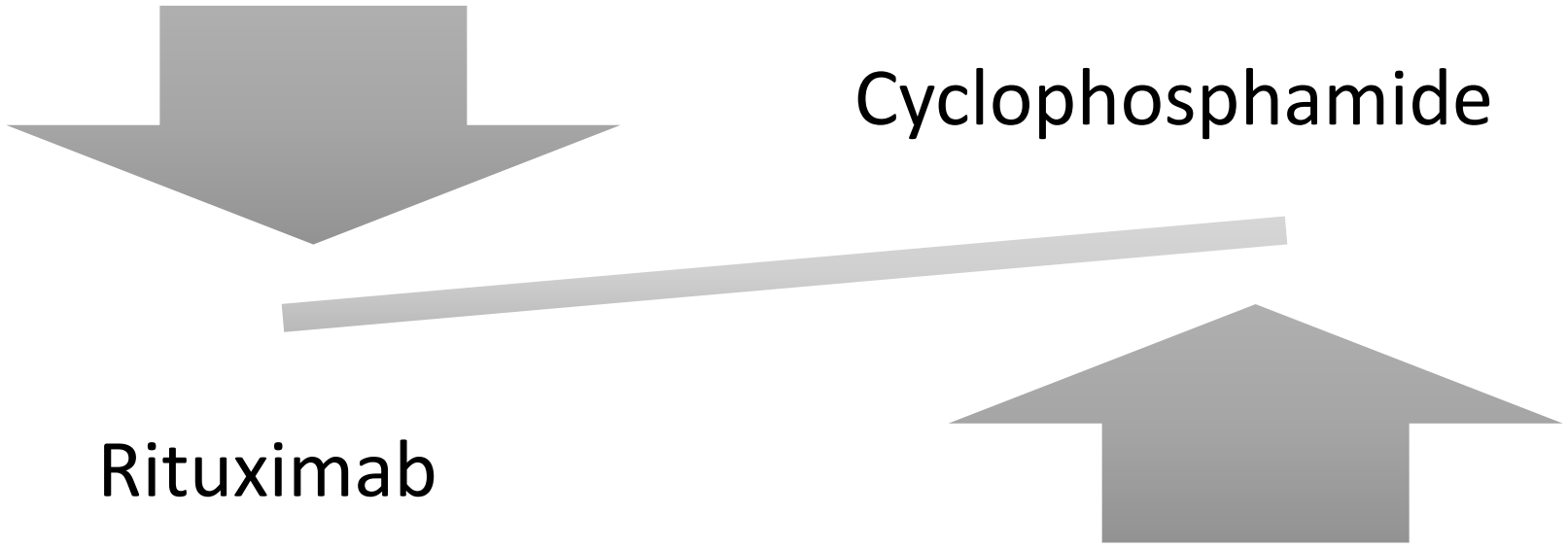


Some organs may be affected for the first time during a relapse

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

GN can occur later down the course which is why U/A is a very important test.

Which One Is Better?!

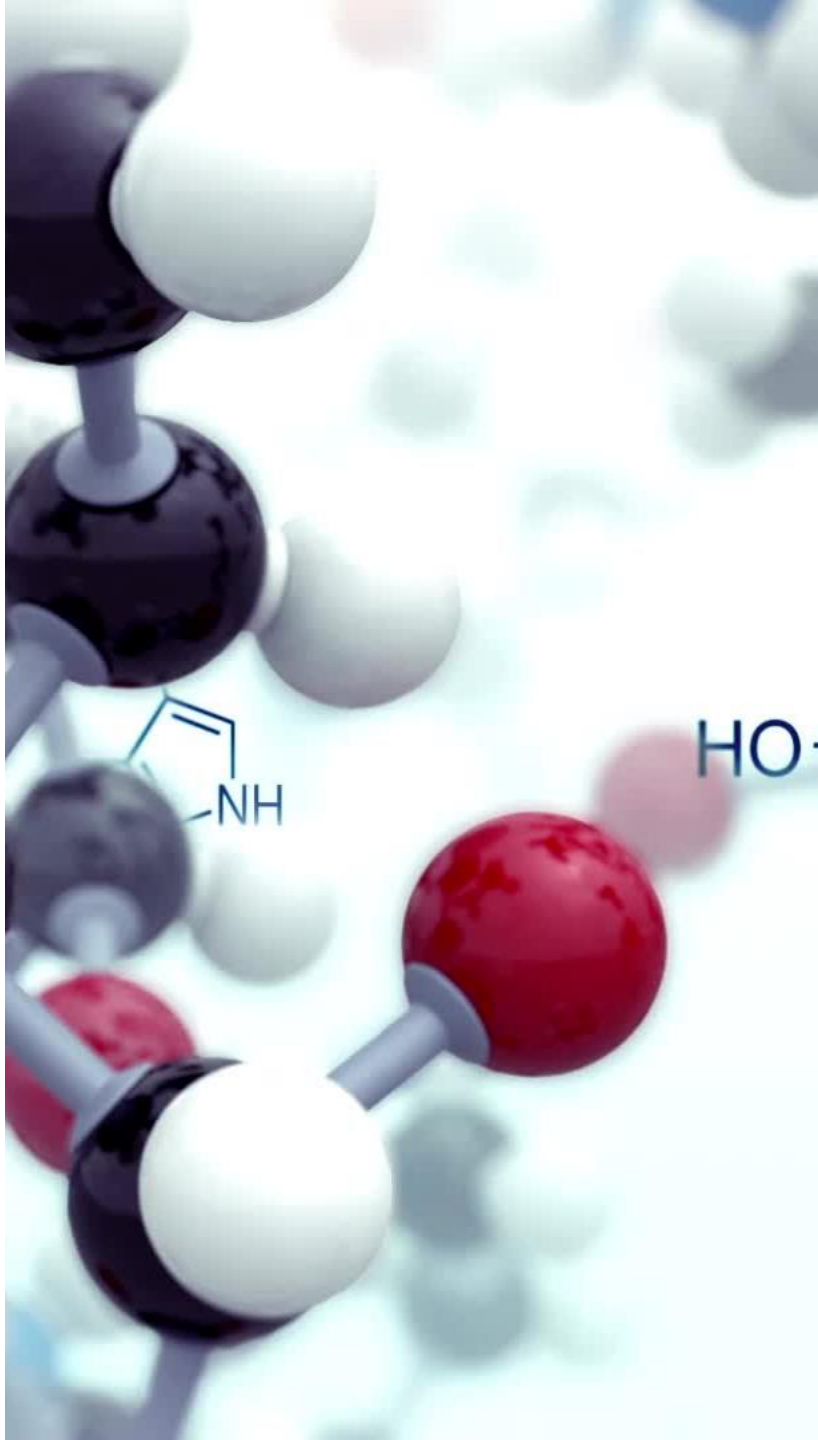


Low Dose vs High Dose Glucocorticoid

WHICH ONE IS BETTER?!

Avacopan

- Some clinicians use the complement C5a receptor inhibitor avacopan as an adjunctive agent with standard induction therapy to limit the use of glucocorticoids.



What factors contribute to damage?

Are there ways to minimize damage ?

Why is damage different for individual tissues ?

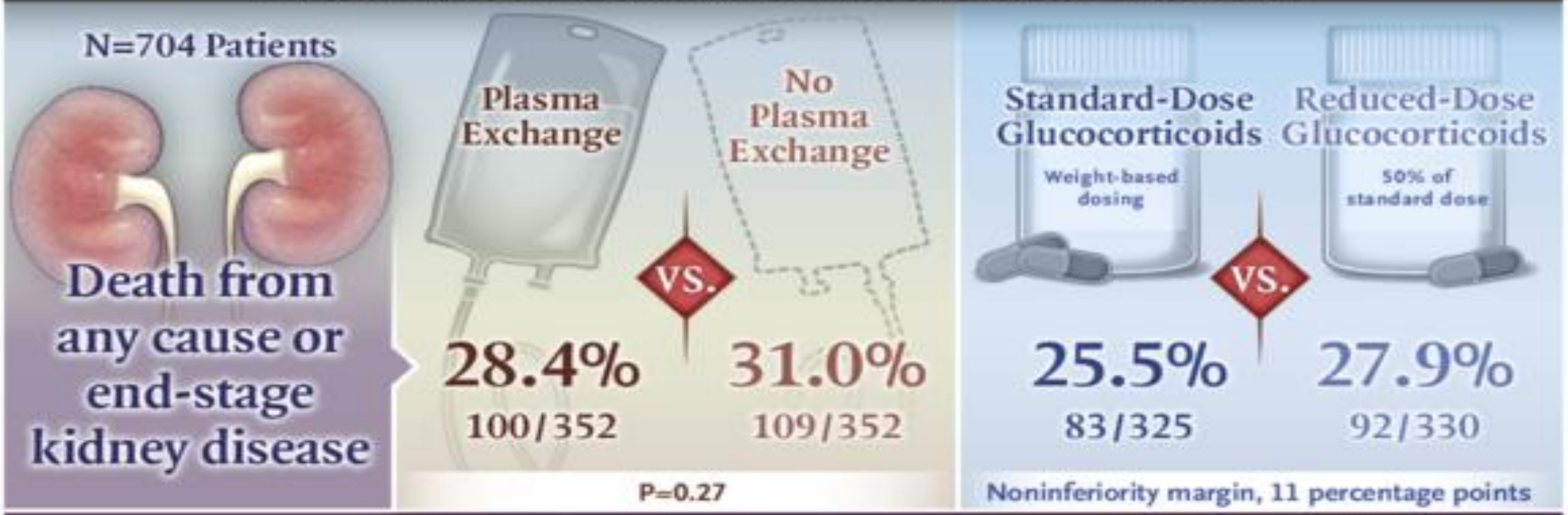
Can individual treatments impact damage ?

Can we clearly differentiate damage form active inflammation ?

The NEW ENGLAND JOURNAL of MEDICINE

Plasma Exchange and Glucocorticoids for ANCA-Associated Vasculitis

PEXIVAS, A MULTICENTER, RANDOMIZED, 2X2 FACTORIAL TRIAL



No significant differences in serious adverse events
Serious infections at 1 yr less common with reduced-dose glucocorticoids

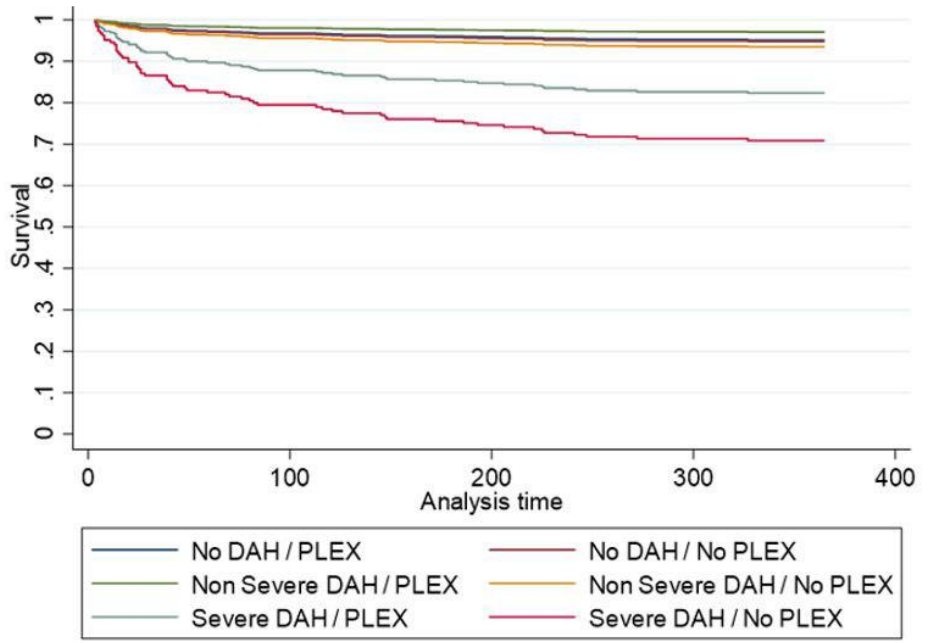
M. Walsh et al. 10.1056/NEJMoa1803537

What kind of pts in the PEXIVAS ?

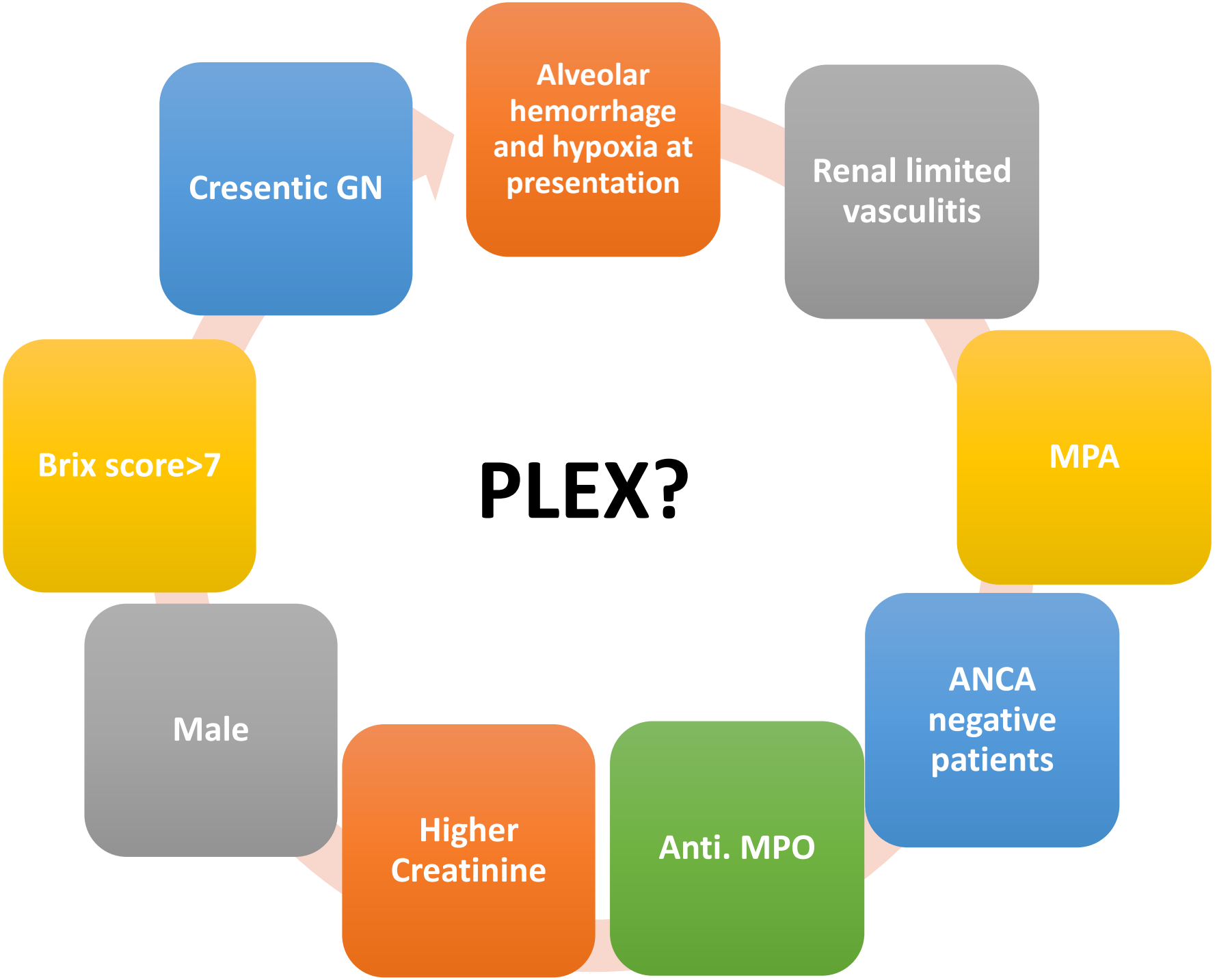
Table 1. Characteristics of the Patients at Baseline.*

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)

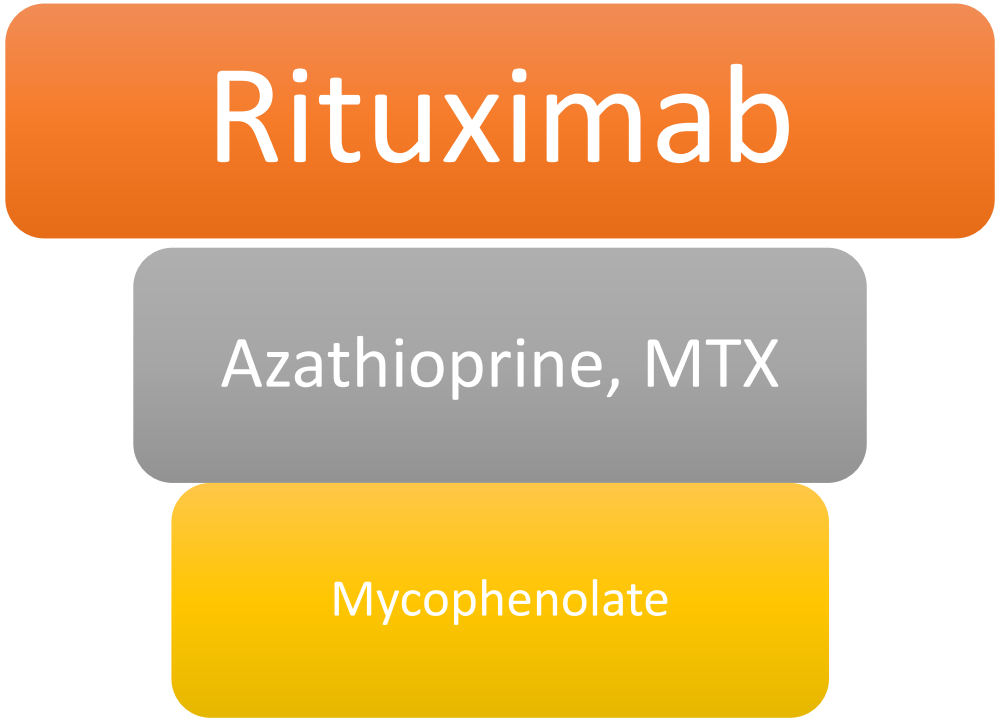
Figure 1: One year survival in PEXIVAS by plasma exchange (PLEX) and severity of diffuse alveolar hemorrhage (DAH), adjusted for age, sex, ANCA type, kidney function, and initial treatments

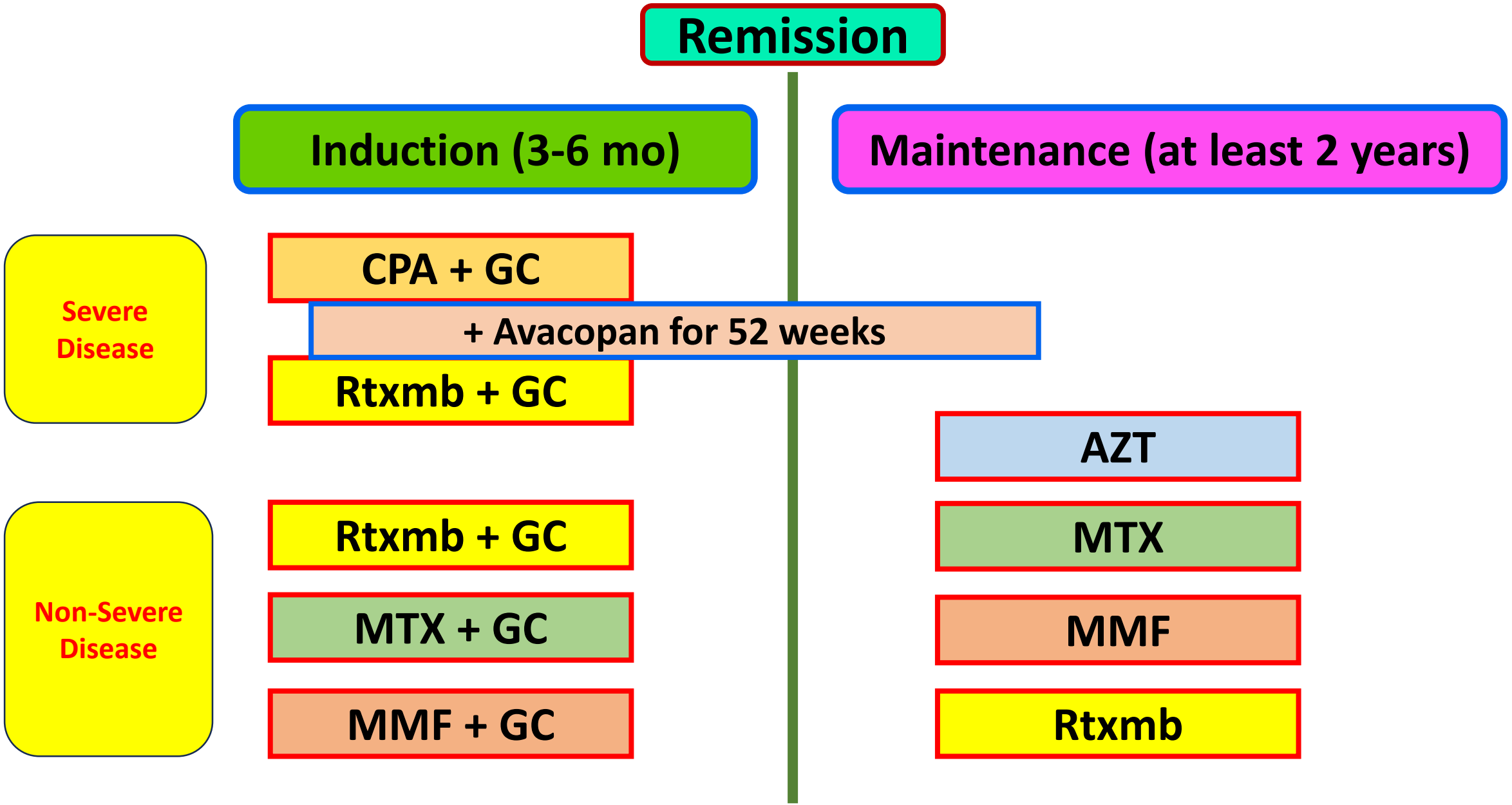


Group	Died 3 months		Died 1 year		Effect of PLEX	
	PLEX	No PLEX	PLEX	No PLEX	HR (95% CI)	Interaction p value
Overall	18 (5.1)	21 (6.0)	25 (7.1)	32 (9.1)	0.74 (0.44 to 1.26)	
No DAH	12 (4.7)	9 (3.5)	17 (6.6)	17 (6.6)	0.86 (0.43 to 1.71)	
Any DAH	6 (6.3)	12 (12.5)	8 (8.4)	15 (15.6)	0.52 (0.21 to 1.24)	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


Alveolar hemorrhage and hypoxia at presentation
Renal limited vasculitis
MPA
ANCA negative patients
Anti. MPO
Higher Creatinine
Male
Brix score>7
Cresentic GN
PLEX?

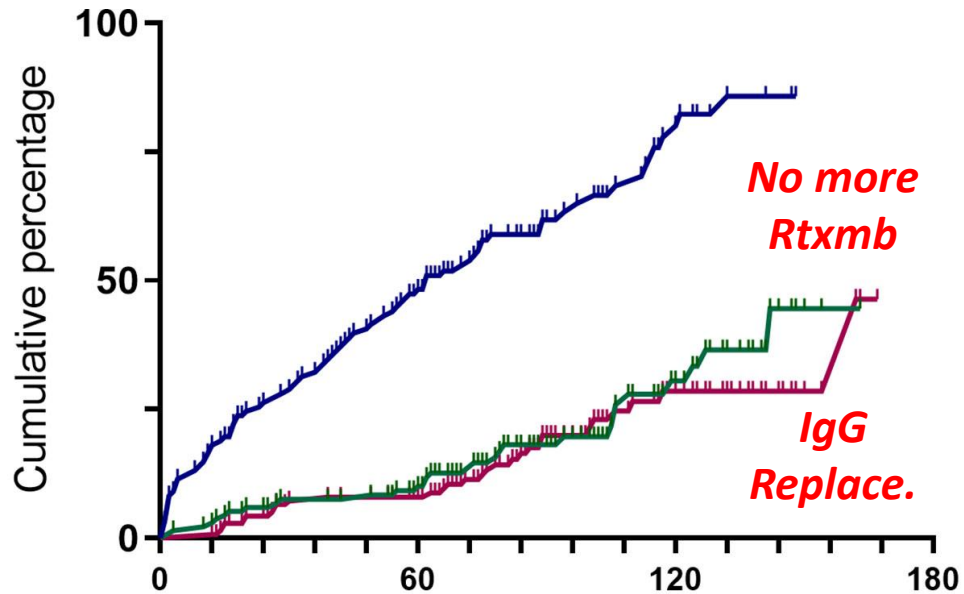
Choice of maintenance therapy




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

Around 70 % with AAV will *relapse*

Monitor IgG if using Rtxmb ?



number at risk						Duration of follow-up (m)
moderate < 5 g/L	122	86	61	27	10	2
severe < 3 g/L	135	118	107	57	27	3
IgG rep	142	126	117	66	32	6

If the pt has failed to deplete B cells, that is a clear evidence of a “failure” of Rtxmb, this is when we measure B cells


You've got a long way to go!
You've come a long way

Concluding Thoughts…

- In 2024, AAV is “not a life-threatening” and can be associated with long-term survival, *however…*
- Relapse, organ damage, and treatment –related toxicity
- Biomarkers

Top 10 Takeaways for Clinicians from the KDIGO 2021 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis (AAV)

GLOMCON HAWAII 2024

1 Diagnosis of AAV

- Early diagnosis to prevent permanent loss of kidney function
- If there are clinical findings and positive serologies, don't delay immunosuppressive (IS) therapy waiting for a kidney biopsy

2 Initial therapy

- Glucocorticoids + cyclophosphamide or rituximab
- If markedly reduced or rapid decline in kidney function consider:
  - glucocorticoids + cyclophosphamide
  - cyclophosphamide + rituximab

3 Avacopan

- Can be used as an alternative to glucocorticoids
- Patients with lower GFR may benefit from greater GFR recovery

4 Plasma exchange

- Should be considered for patients:
  - serum creatinine >3.4mg/dL
  - requiring dialysis
  - diffuse alveolar hemorrhage
- Add to initial treatment if overlap with ANCA vasculitis and anti-GBM

5 Glucocorticoid use

- Low doses may be equally effective as high doses
- Low doses with fewer short- and long-term toxicities

6 Maintenance treatment

- Rituximab or azathioprine + low dose glucocorticoids.
- Optimal duration is not known, but should be 18 months to 4 years

7 Preferred maintenance treatment

- Rituximab is preferred in patients with:
  - relapsing disease
  - PR3-ANCA
  - frail older adults
  - azathioprine allergy
  - when glucocorticoid sparing is important

8 Withdrawal of maintenance therapy

- Factor in the risk of relapse
- Inform patients of the need of prompt attention if symptoms recur

9 Relapsing disease

- Re-induction, preferably with rituximab

10 Refractory disease

- Treatment options:
  - increase in glucocorticoids
  - add rituximab if previously treated with cyclophosphamide, or vice versa
  - consider plasma exchange

Infographic by: Stephanie Torres, MD @stephanietr612