Rapidly Progressive Glomerulonephritis

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Disclosure information

- **Prof. Bancha Satirapoj, M.D.**
- **Scientific Advisor/Honoraria:**
  - **Astra Zeneca, Boehringer Ingelheim, LG Life Sciences, Janssen-Cilag, MSD, Novo Nordisk, Osotspa Taisho, Sanofi Aventis and Abbott Laboratories**
- **DISCLAIMER**
  - **This presentation is intended for educational purpose for HCPs only. It may contain new science data which is currently not in approved package insert information and is not intended for off-label promotion.**

Asymptomatic
Isolated proteinuria 150 mg to 3 g/day
Hematuria > 2 red blood cells (RBC)/high-power field in spun urine (RBC usually dysmorphic)

Nephrotic syndrome
- Proteinuria
  - Adult >3.5 g/day
  - Child > 40 mg/h per m^2
- Edema
- Hypoalbuminemia <3.5 g/dl
- Hypercholesterolemia
- Lipiduria

Nephritic syndrome
- An abrupt onset of glomerular hematuria (RBC cast or dysmorphic RBCs)
- Proteinuria <3 g/day
- Azotemia
- Edema
- Oliguria
- Recent onset hypertension

Rapidly progressive glomerulonephritis
- Glomerular disease characterized by extensive crescents (usually >50%)
- A rapid loss of renal function (usually a 50% decline in GFR within 3 months)

Chronic glomerulonephritis
- Slowing developing renal insufficiency
- Proteinuria > 3 g/day and hematuria
- Hypertension
- Shrunken smooth kidneys

Satirapoj B. Common Problems in Internal Medicine. Bangkok 2010. p. 498-513.
Satirapoj B. Essential Glomerular Disease 2018

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Manifestation of glomerular diseases

Diseases	Nephrotic syndrome	Nephritic syndrome
Minimal change glomerulopathy or IgM nephropathy	++++	-
Membranous glomerulopathy	++++	+
Focal segmental glomerulosclerosis	+++	++
Mesangial proliferative glomerulonephritis (IgA nephropathy, Lupus nephritis)	++	++
Membranoproliferative glomerulonephritis (MPGN)	++	+++
Severe proliferative glomerulonephritis (IgA nephropathy, Lupus nephritis)	++	+++
Acute diffuse proliferative glomerulonephritis	+	++++
Crescentic glomerulonephritis	+	++++

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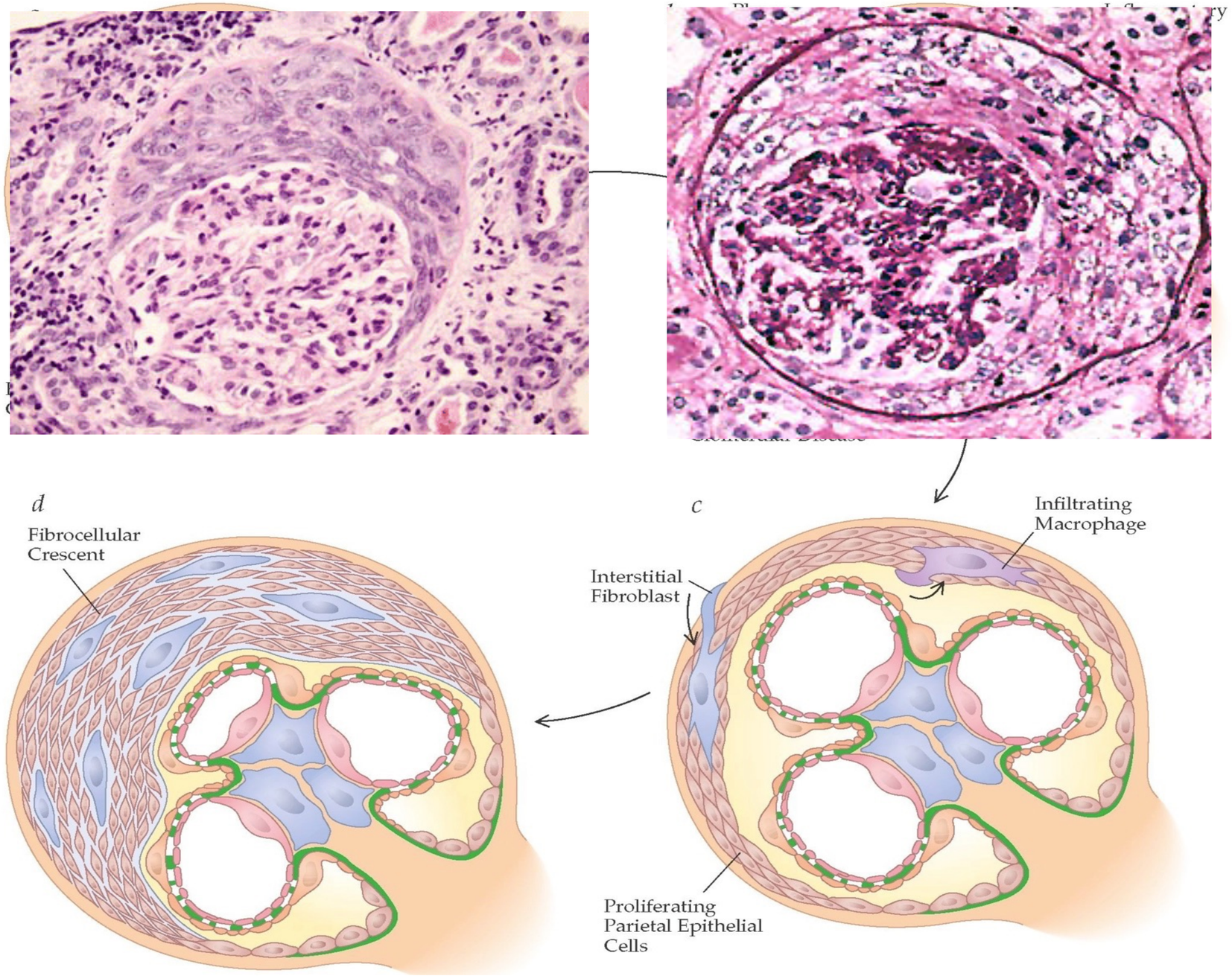
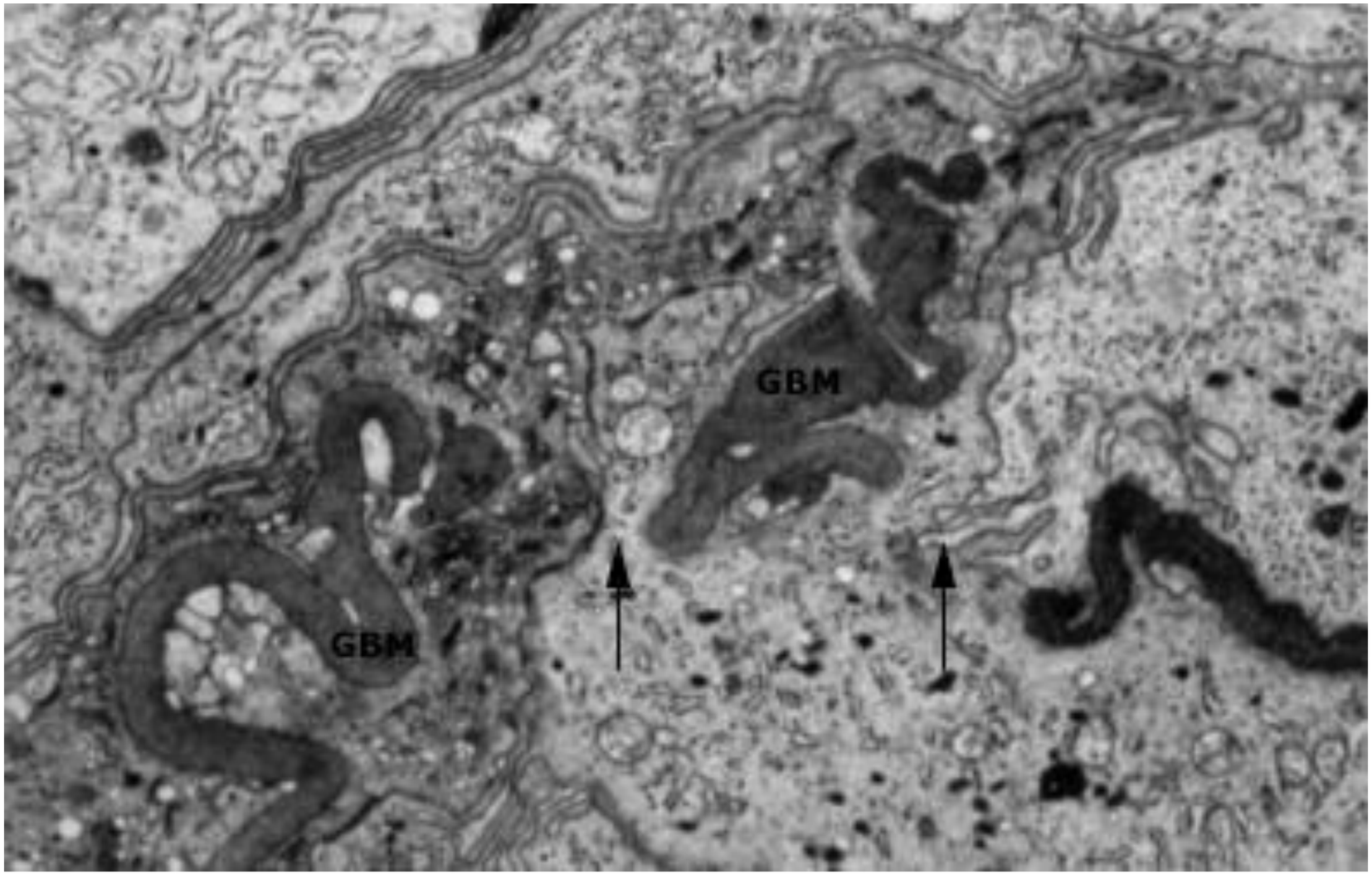
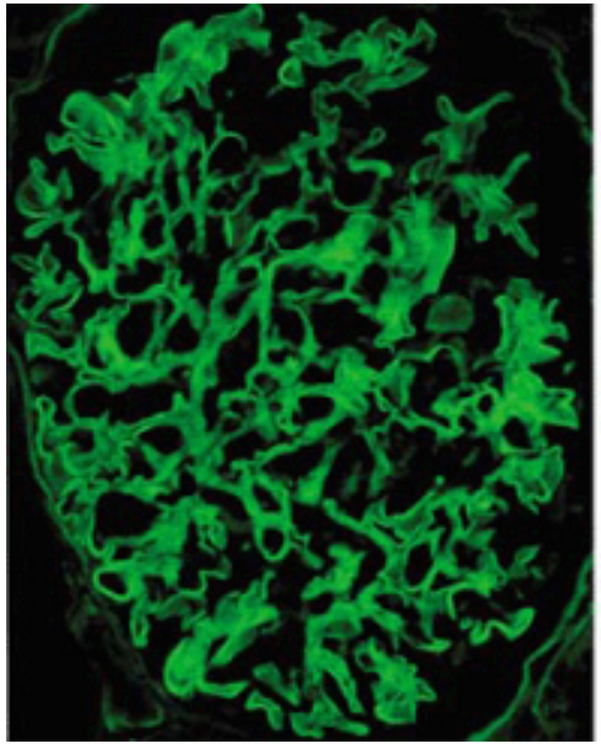

d
Fibrocellular
Crescent
c
Infiltrating
Macrophage
Interstitial
Fibroblast
Proliferating
Parietal Epithelial
Cells

Breaks in the glomerular basement membrane

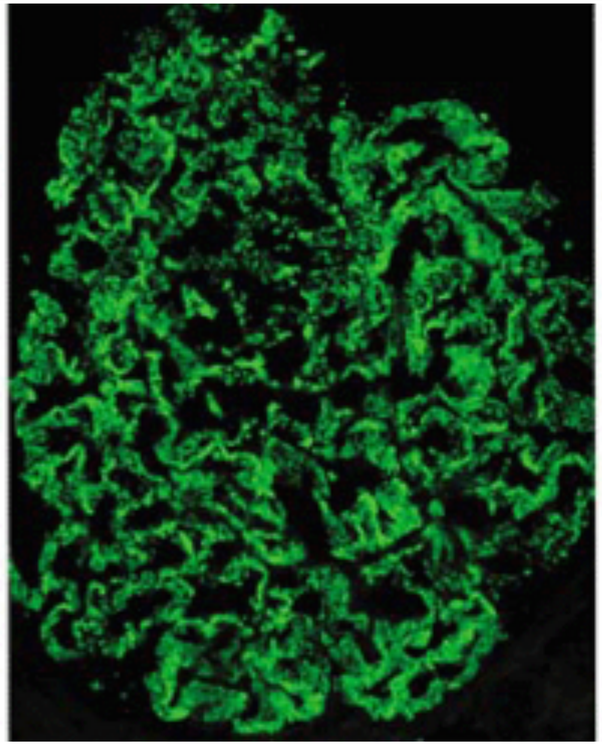


Type of RPGN



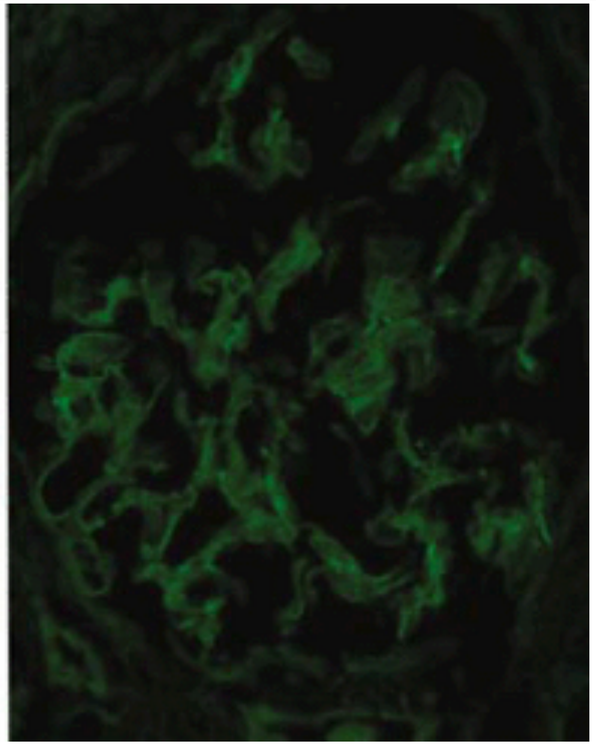
Linear staining for IgG

Anti-GBM GN



Granular staining

Immune complex GN



Pauci immune staining

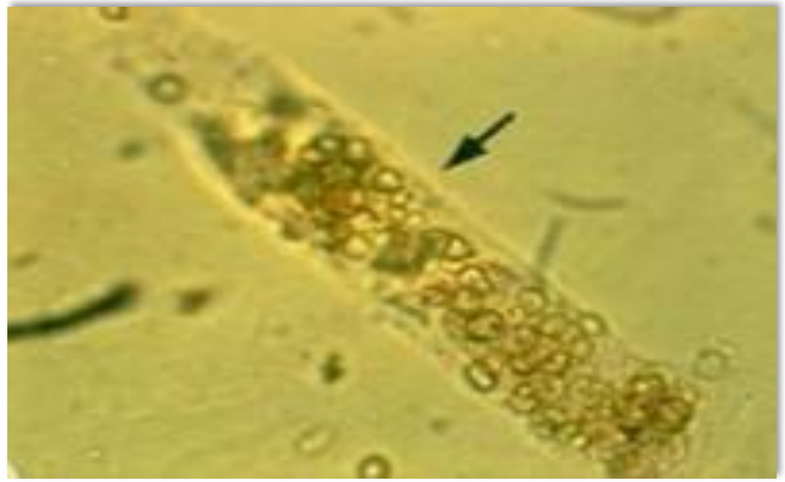
ANCA GN

Immunopathologic categories

- **Type I: Anti- GBM crescentic glomerulonephritis**
- **Type 2: Immune-complex crescentic GN**
- **Type 3: Pauci-immune crescentic glomerulonephritis**
- **Type 4: Double-antibody positive disease: types 1+3**
- **Type 5: Pauci-immune crescentic glomerulonephritis with ANCA negative**

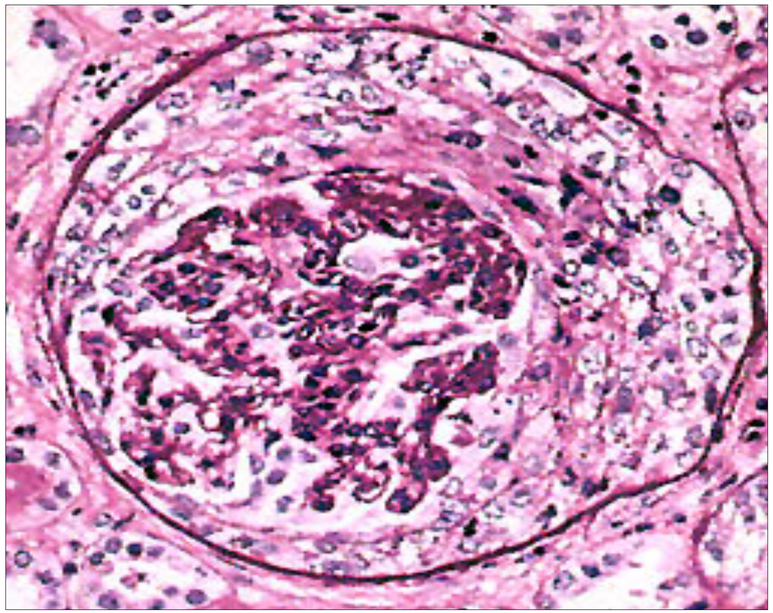
RPGN: Clinical features

- Acute nephritic picture
- Dysmorphic hematuria, red cell and other casts, and a variable degree of proteinuria
- Hypertension
- Hypervolemia, and edema
- Oliguria



RPGN: Clinical features

- Insidious onset with the initial symptoms being fatigue
- Almost all cases with serum Cr > 3 mg/dL
- Nephrotic syndrome is unusual



Different types of crescentic glomerulonephritis

Categories of RPGN	Age			
	10-19 (n=20)	20-39 (n=42)	40-64 (n=61)	>65 (n=66)
Anti-GBM mediated glomerulonephritis	15%	24%	2%	11%
Immune complex mediated glomerulonephritis	50%	48%	30%	8%
Pauci-immune glomerulonephritis	35%	28%	69%	82%

Jennette JC. Kidney Int 2003;63:1164-77.

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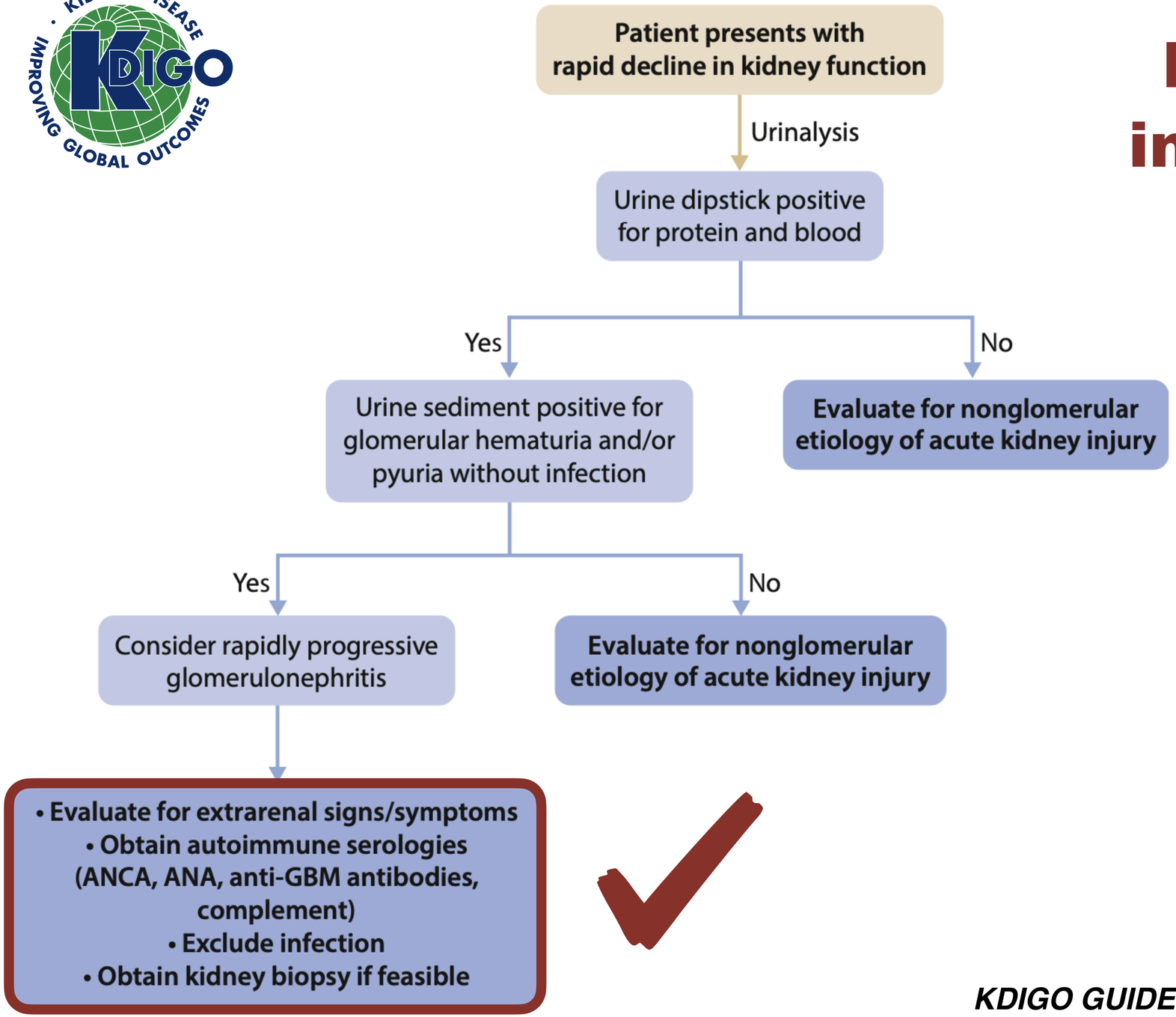
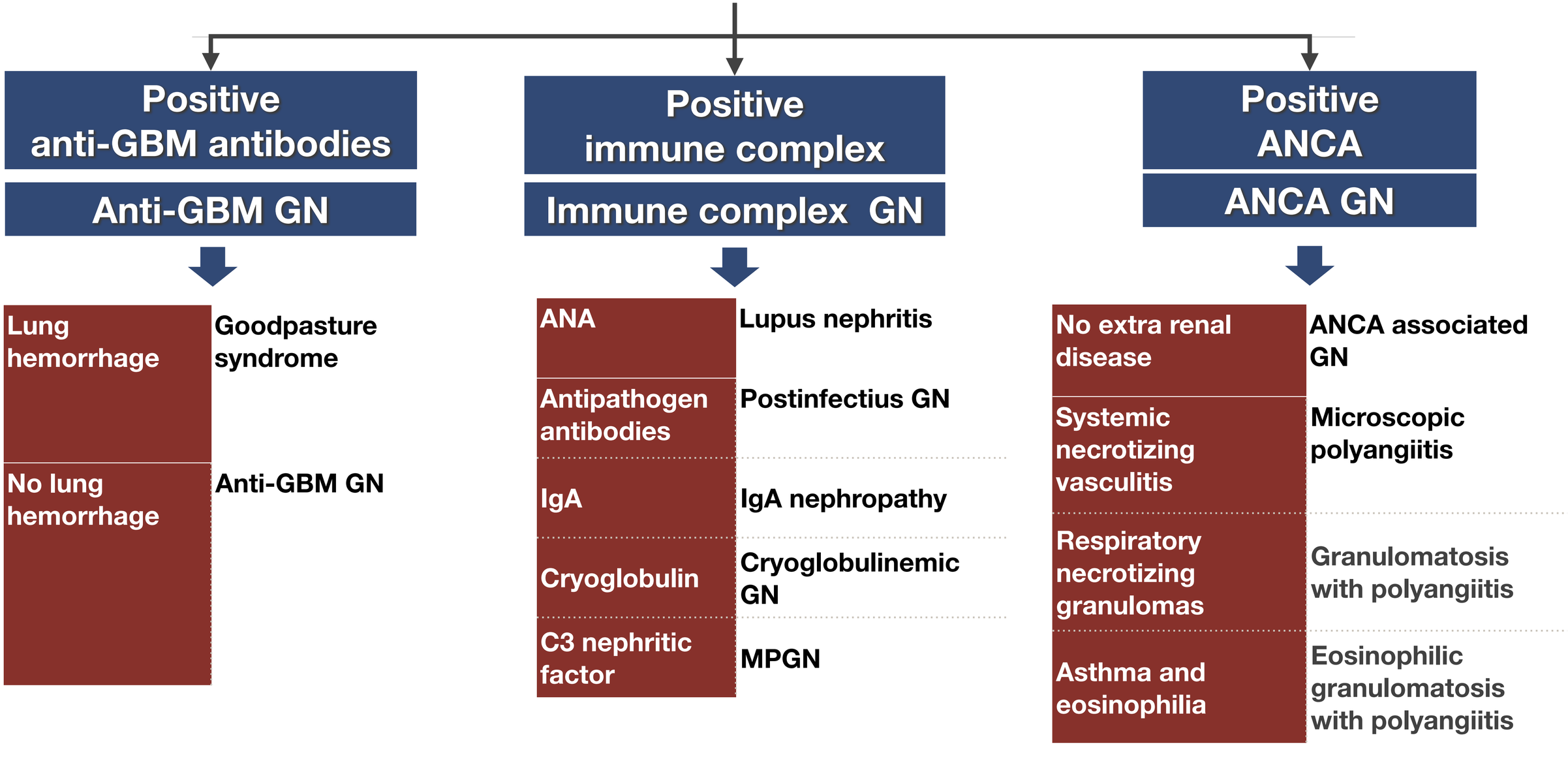
Diagnostic strategy in rapidly progressive glomerulonephritis



KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Serologic analysis of patients with RPGN



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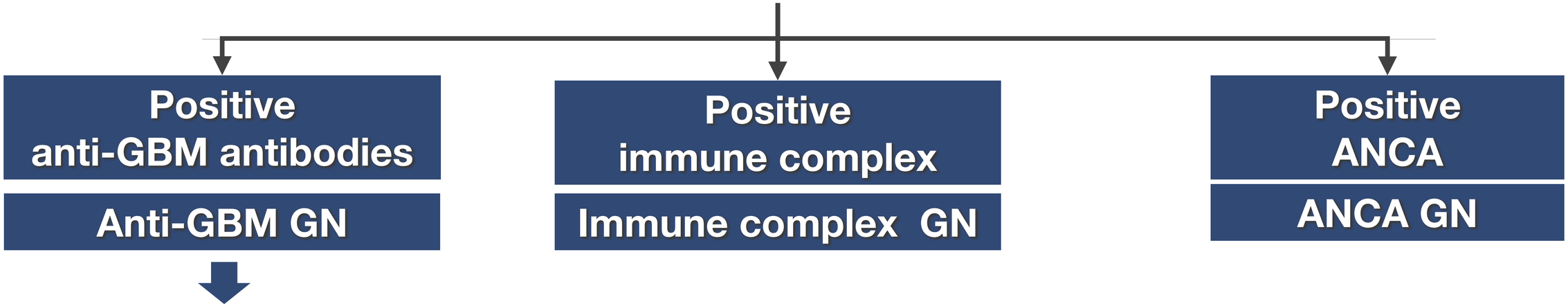
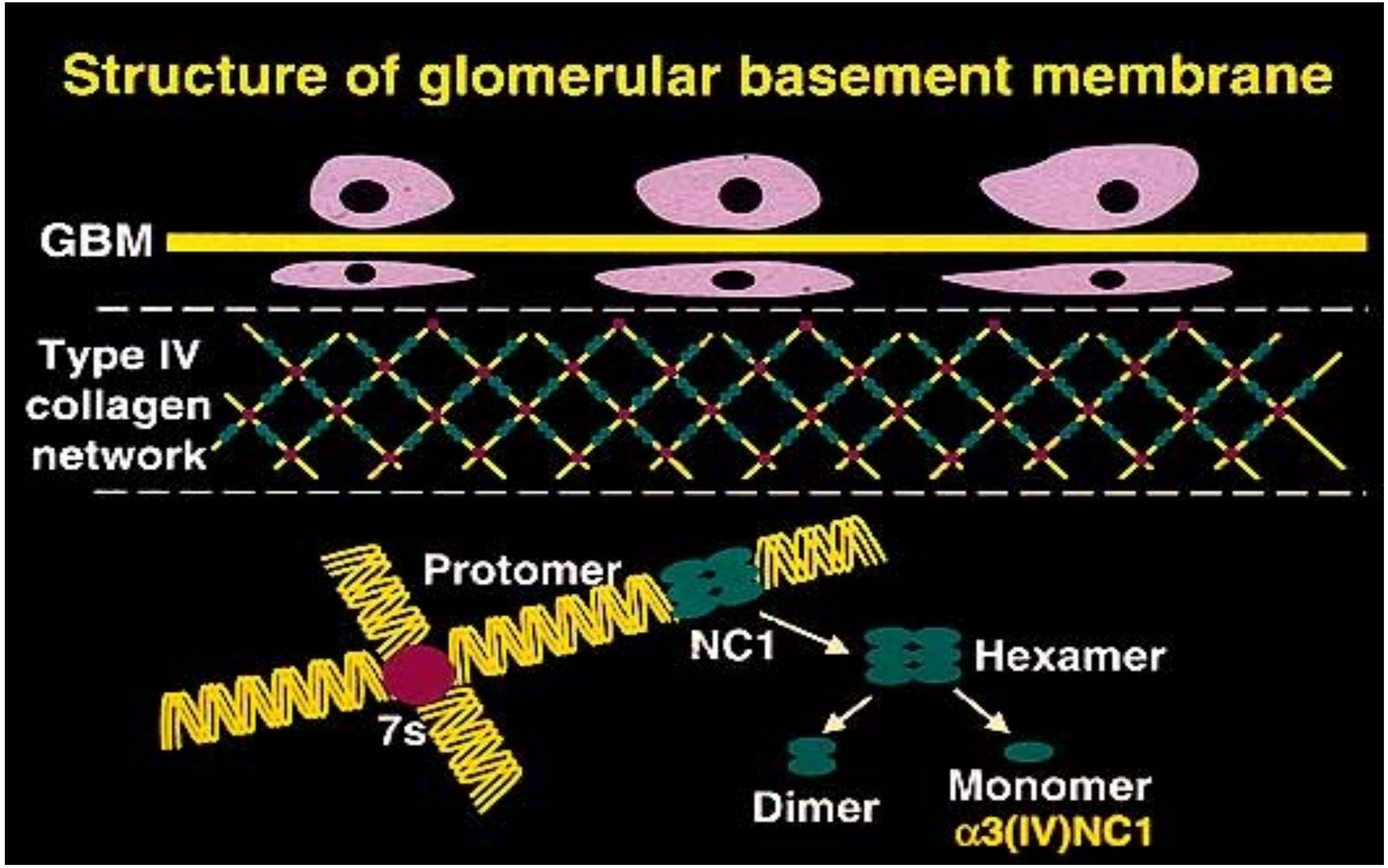


Lung hemorrhage	Goodpasture syndrome
No lung hemorrhage	Anti-GBM GN

Anti-GBM GN: Clinical features

- Peak incidence in the third and sixth decades
- Malaise, fatigue, and weight loss, and anemia from pulmonary hemorrhage or to the effects of uremia
- Pulmonary hemorrhage and hemoptysis in anti-GBM disease
- Renal disease progresses rapidly and rarely resolves spontaneously

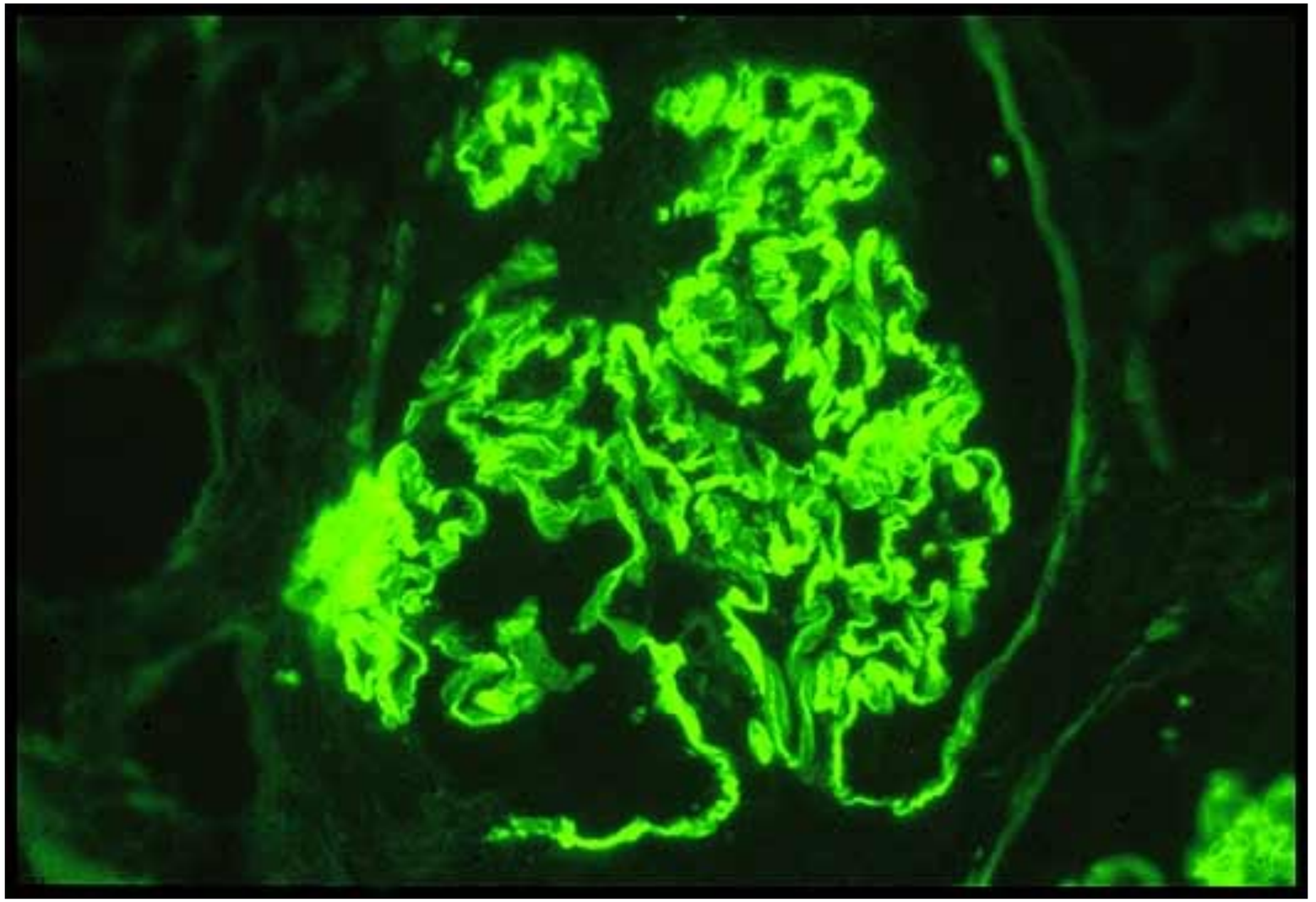
McAdoo SP, et al. Clin J Am Soc Nephrol 2017: 12: 1162–1172.
Segelmark M, et al. Nephrol Dial Transplant 2019: 34: 1826–1832.
McAdoo SP, et al. Semin Respir Crit Care Med 2018;39:494–503.



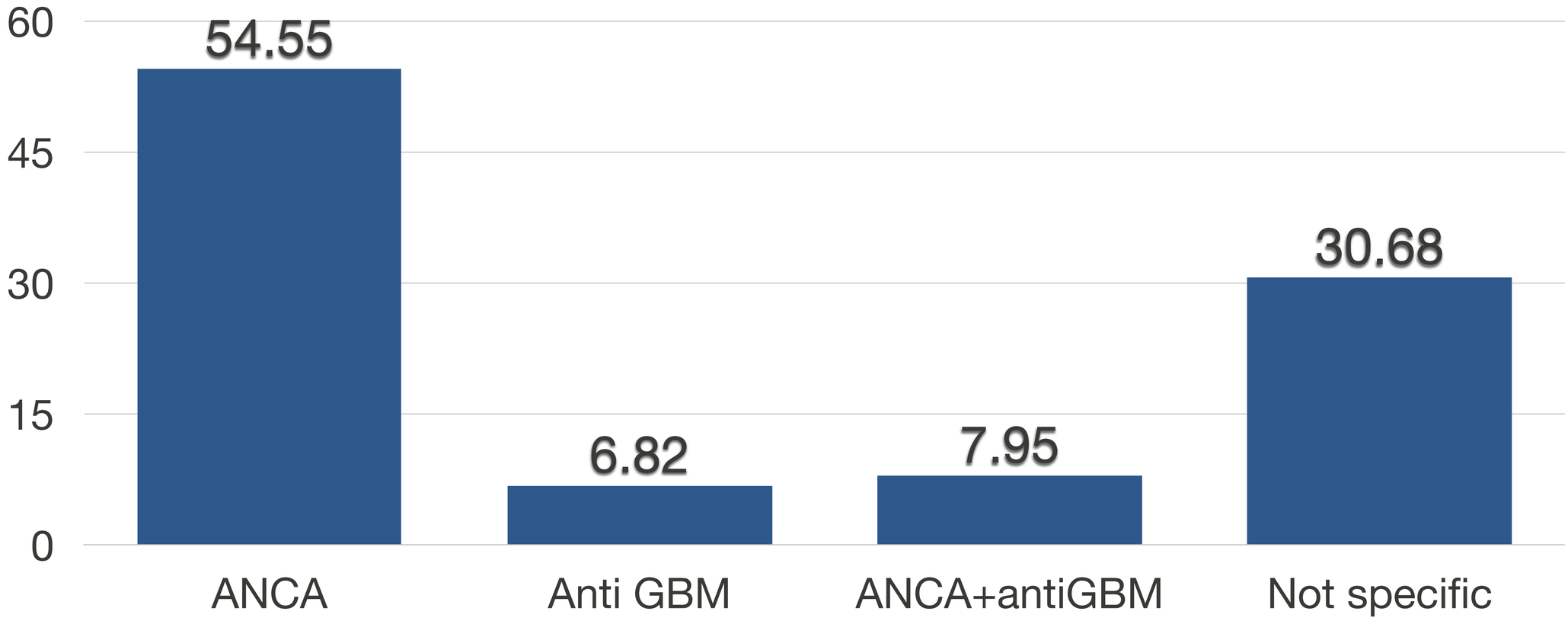
Main target of the autoantibodies is the noncollagenous domain (NC1) of the α 3 chain of type IV collagen.

Hellmark T, et al. Kidney Int . 1999: 55:936–44.

Linear deposition of IgG/C3 along glomerular basement membrane



Pulmonary hemorrhage and nephritis



Niles JL, et al. Arch Intern Med 1996; 26;156(4):440-5.

Initial treatment of RPGN

- Aggressive immunosuppressive agents
  - Intravenous methylprednisolone (IVMP) 500-1000 mg/day x 3 days
  - Cyclophosphamide (IVCY/Oral CY)

- Need to be confirm definite diagnosis for further Rx
  - Serology + kidney biopsy

Treatment of anti-GBM GN

- IV methylprednisolone 500-1000 mg/day x 3 days and then prednisoone 1 mg/kg/day for first week then reduce at weekly intervals to 45, 30, 25, 20, 15, 10 and 5 mg/day
- Cyclophosphamide: 2 mg/kg/day for 3 months
- Plasma exchange: 4 L exchanges daily with albumin as replacement solution x 14 days or no detection of anti-GBM ab

McAdoo SP, et al. Semin Respir Crit Care Med 2018;39:494–503.

Outcome of patients with Goodpasture's disease

	Number of patients	1-year patient survival %	1-year renal survival %	Renal recovery if initial creatinine >600 µmol/L (6.6 mg/dL) % *treated patients*
Johnson et al [85]	17	94	45	0
Walker et al [86]	22	59	45	18
Savage et al [68]	59	75	8.5	NA[a]
	49	84	35	11
Bouget et al [87]	14	79	29	0
Herody et al [88]	29	93	41	0
Merkel et al [89]	35	89	40	6
Daly et al [90]	40	—	20	0

Pusey CD, et al. Kidney Int, 2003: 64: 1535–50.

Treatment of anti-GBM disease

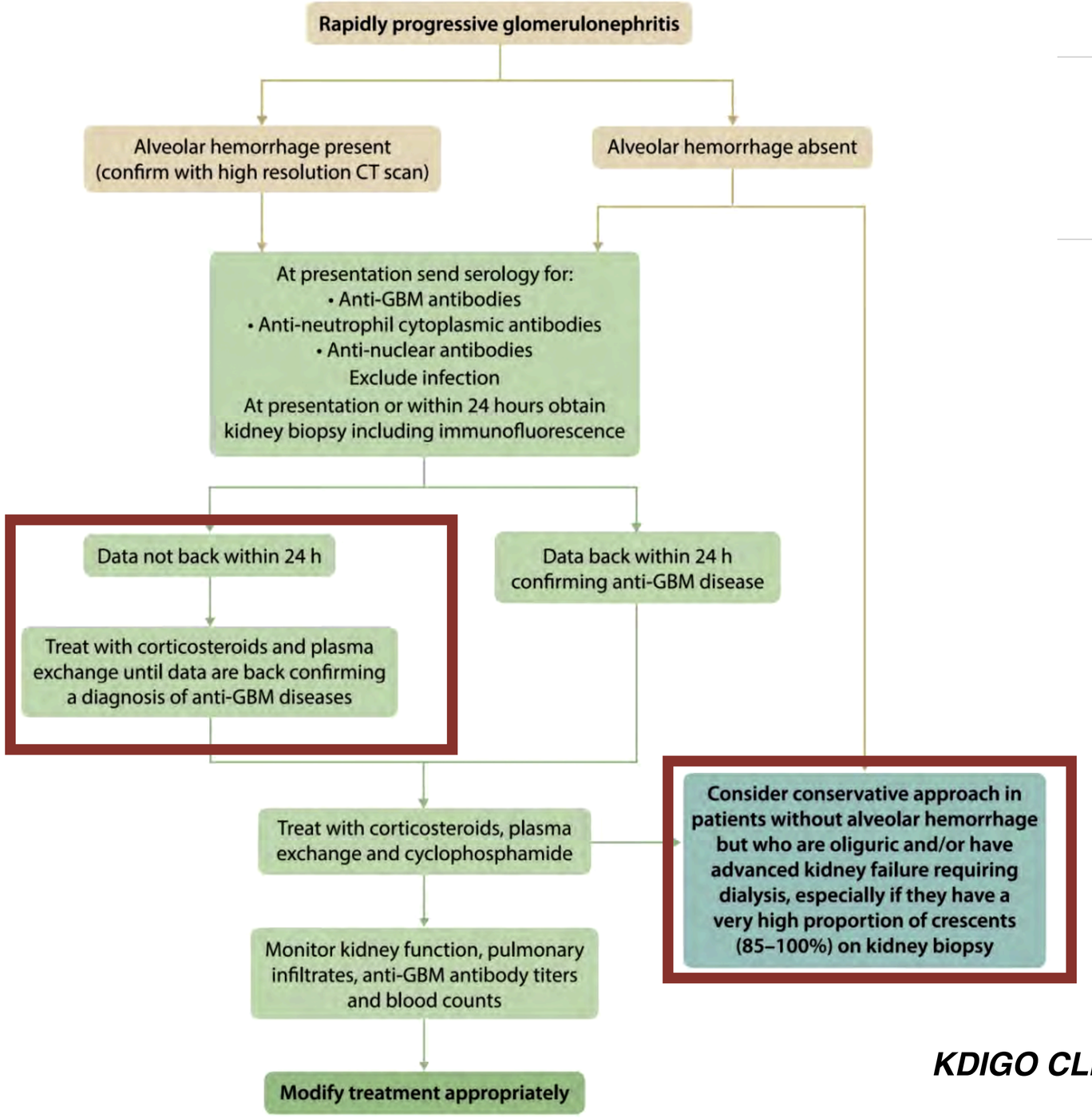
- We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis in all patients with anti-GBM GN
- Except those who are dialysis-dependent at presentation, have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage (1C).

Practice Point

- Plasma exchange should be performed until anti-GBM titers are no longer detectable.

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES. Kidney Int. 2021: 100, S1–S276.

Treatment of anti-GBM disease



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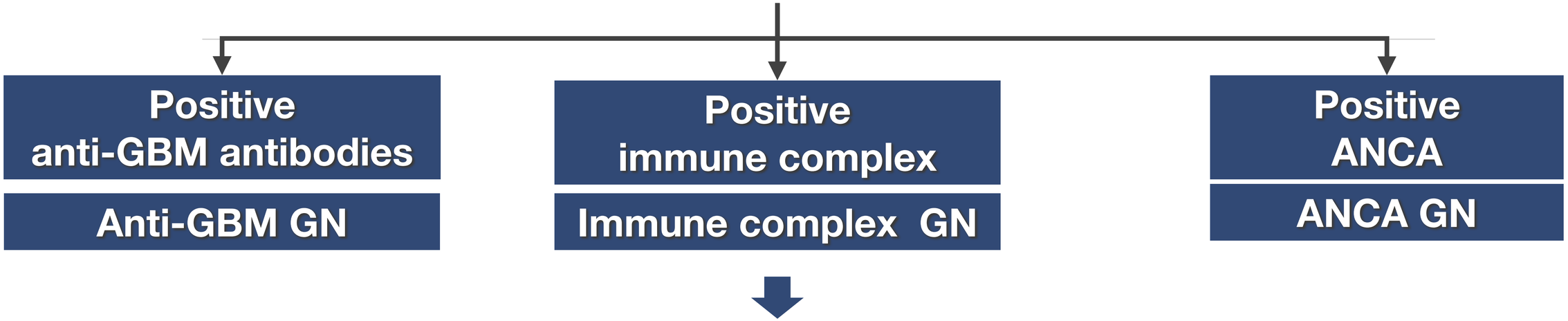

ANA	Lupus nephritis
Antipathogen antibodies	Postinfectius GN
IgA	IgA nephropathy
Cryoglobulin	Cryoglobulinemic GN
C3 nephritic factor	MPGN

Treatment of IgAN with RPGN

Practice Point

- A kidney biopsy demonstrate mesangial and endocapillary hypercellularity and a high proportion of glomeruli affected by crescents with areas of focal necrosis.
- The presence of crescents in a kidney biopsy in the absence of a concomitant change in SCr does not constitute rapidly progressive IgAN.
- We suggest patients with rapidly progressive IgAN are treated with cyclophosphamide and corticosteroids in accordance with the guidelines for ANCA-associated vasculitis

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES. Kidney Int. 2021: 100, S1–S276.

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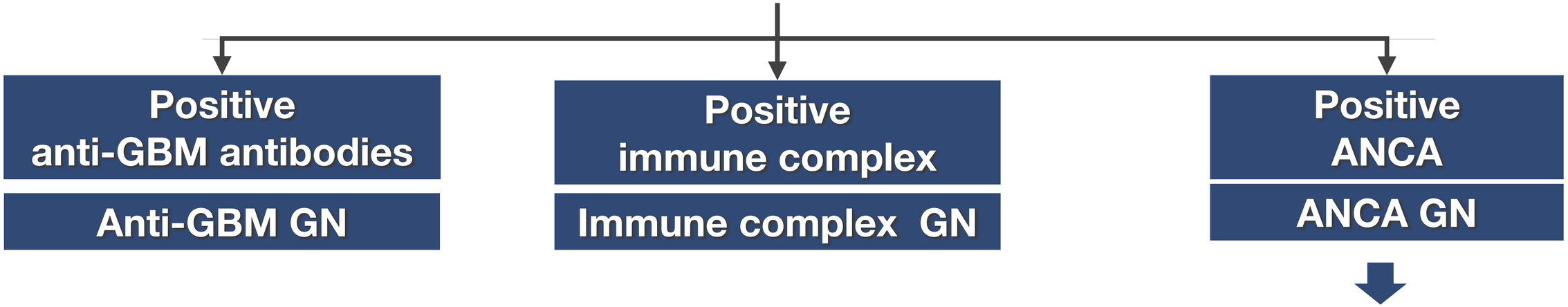


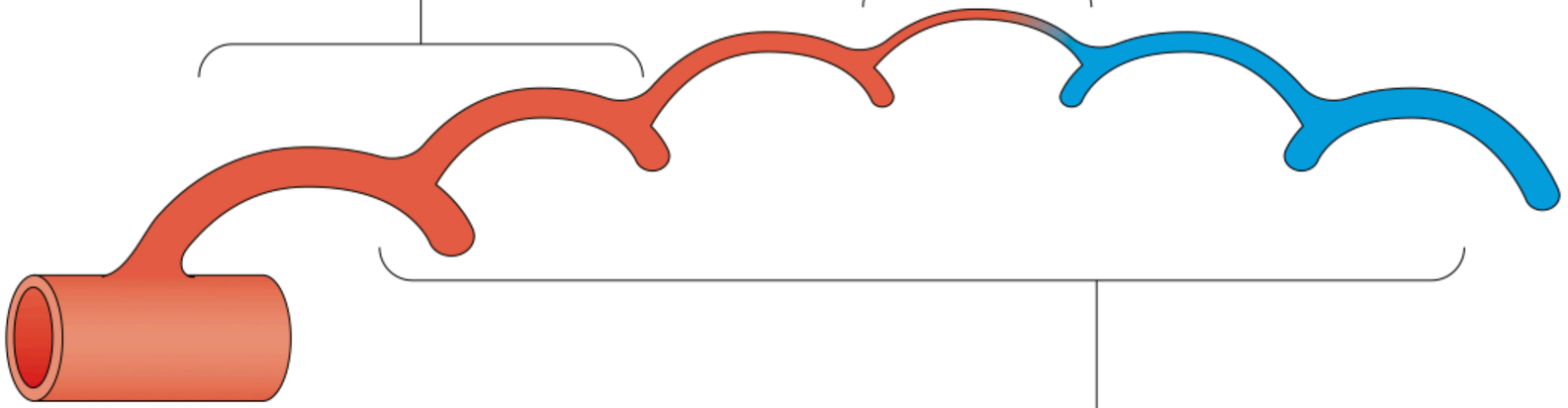
No extra renal disease	ANCA associated GN
Systemic necrotizing vasculitis	Microscopic polyangiitis
Respiratory necrotizing granulomas	Granulomatosis with polyangiitis
Asthma and eosinophilia	Eosinophilic granulomatosis with polyangiitis

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)

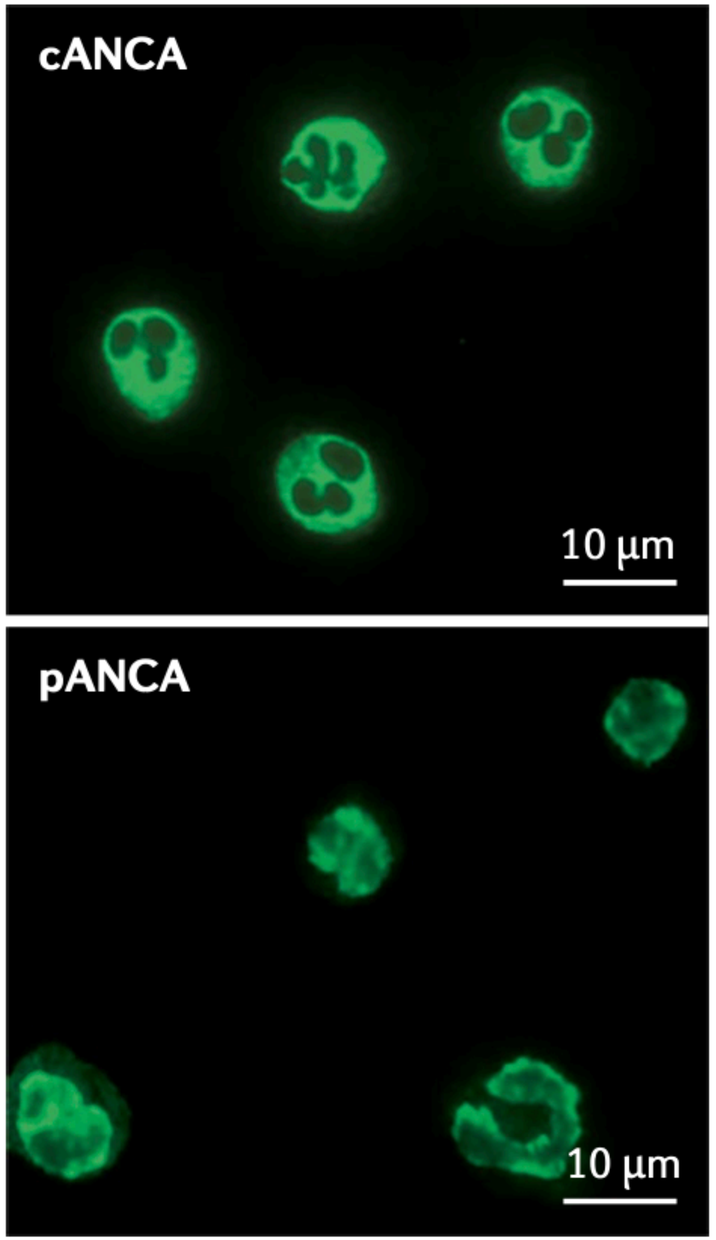
Anti-GBM disease



Large vessel vasculitis
- Takayasu arteritis
- Giant cell arteritis

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

b



Kitching AR, et al. Nat Rev Dis Primers. 2020; 6(1):71.

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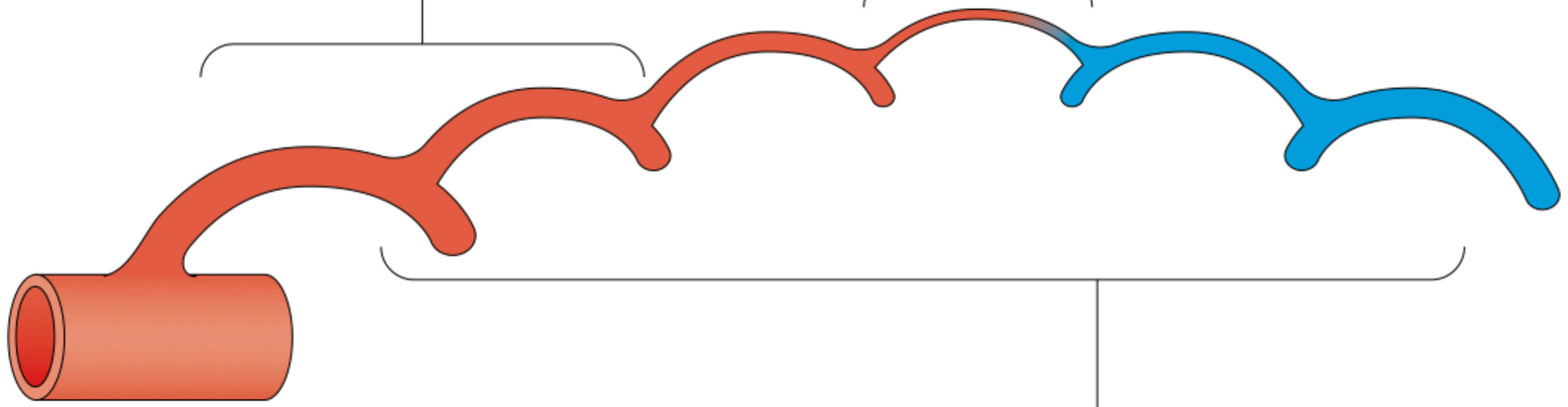

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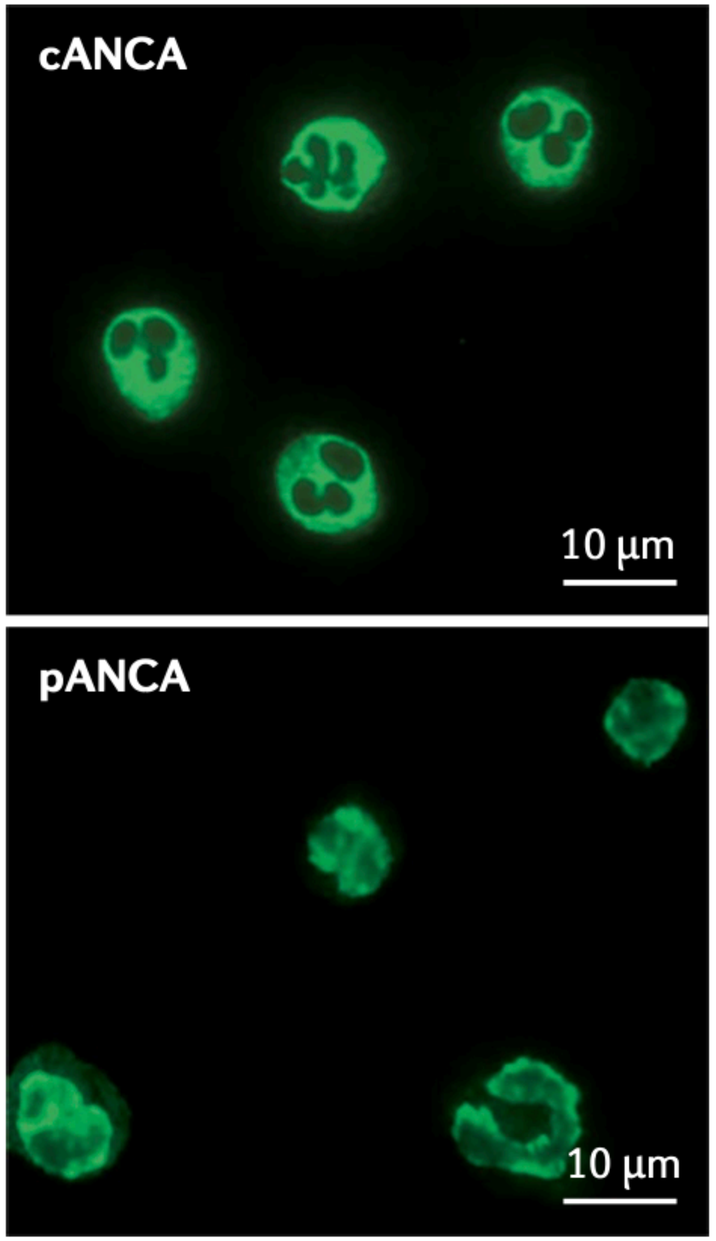

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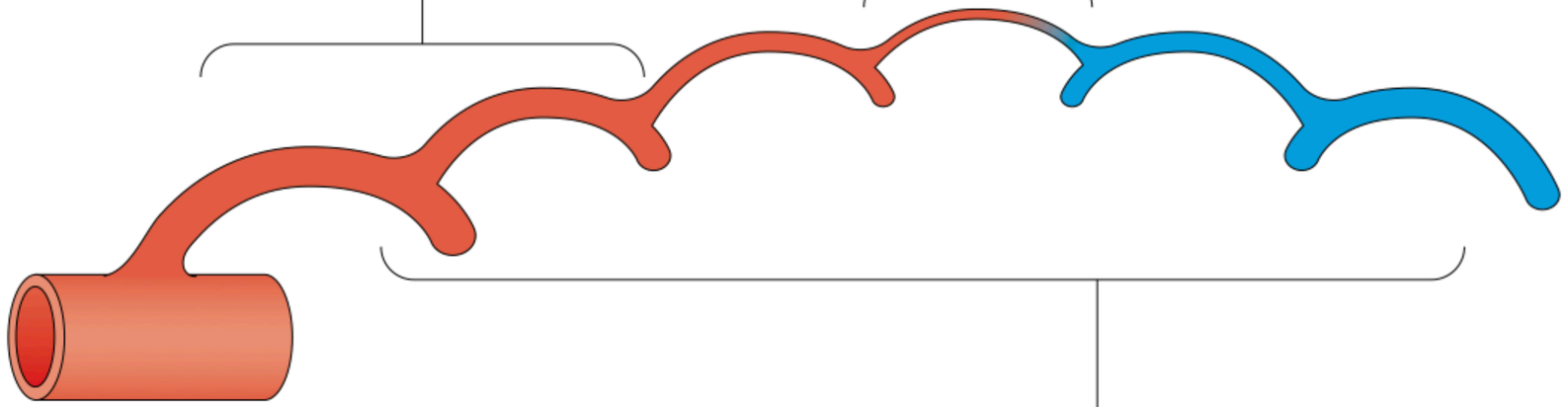

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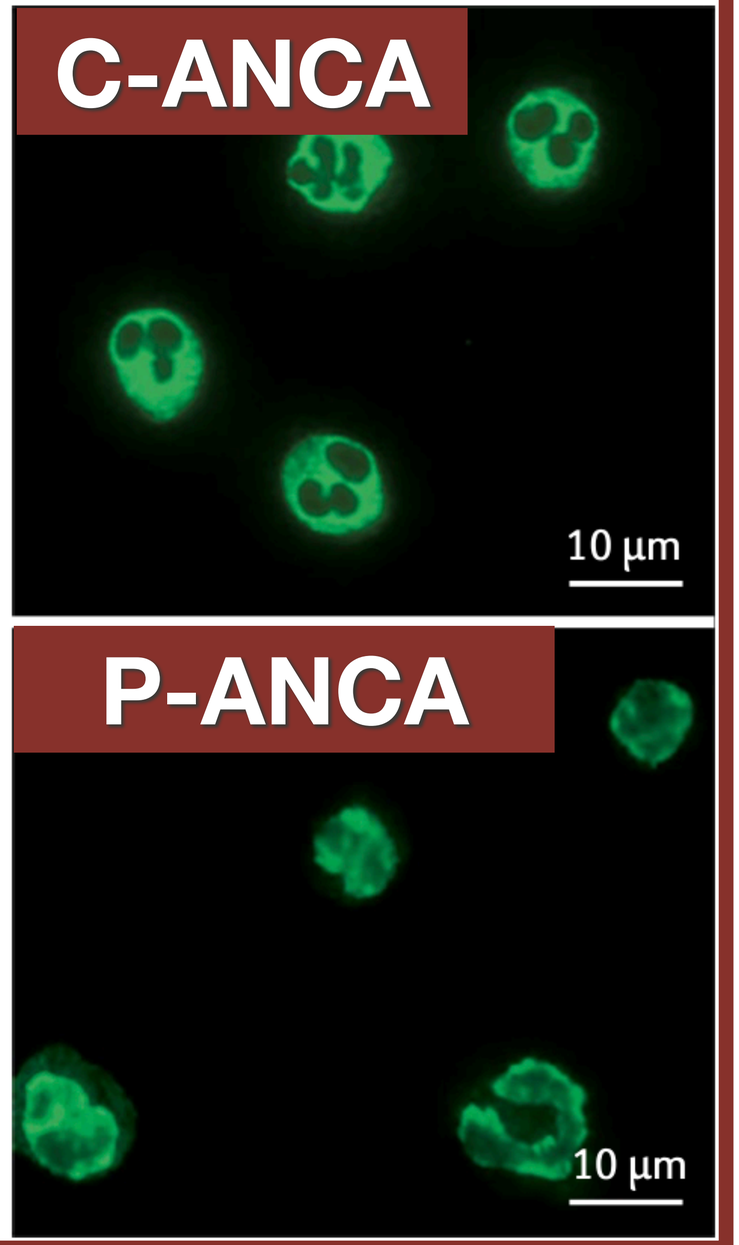

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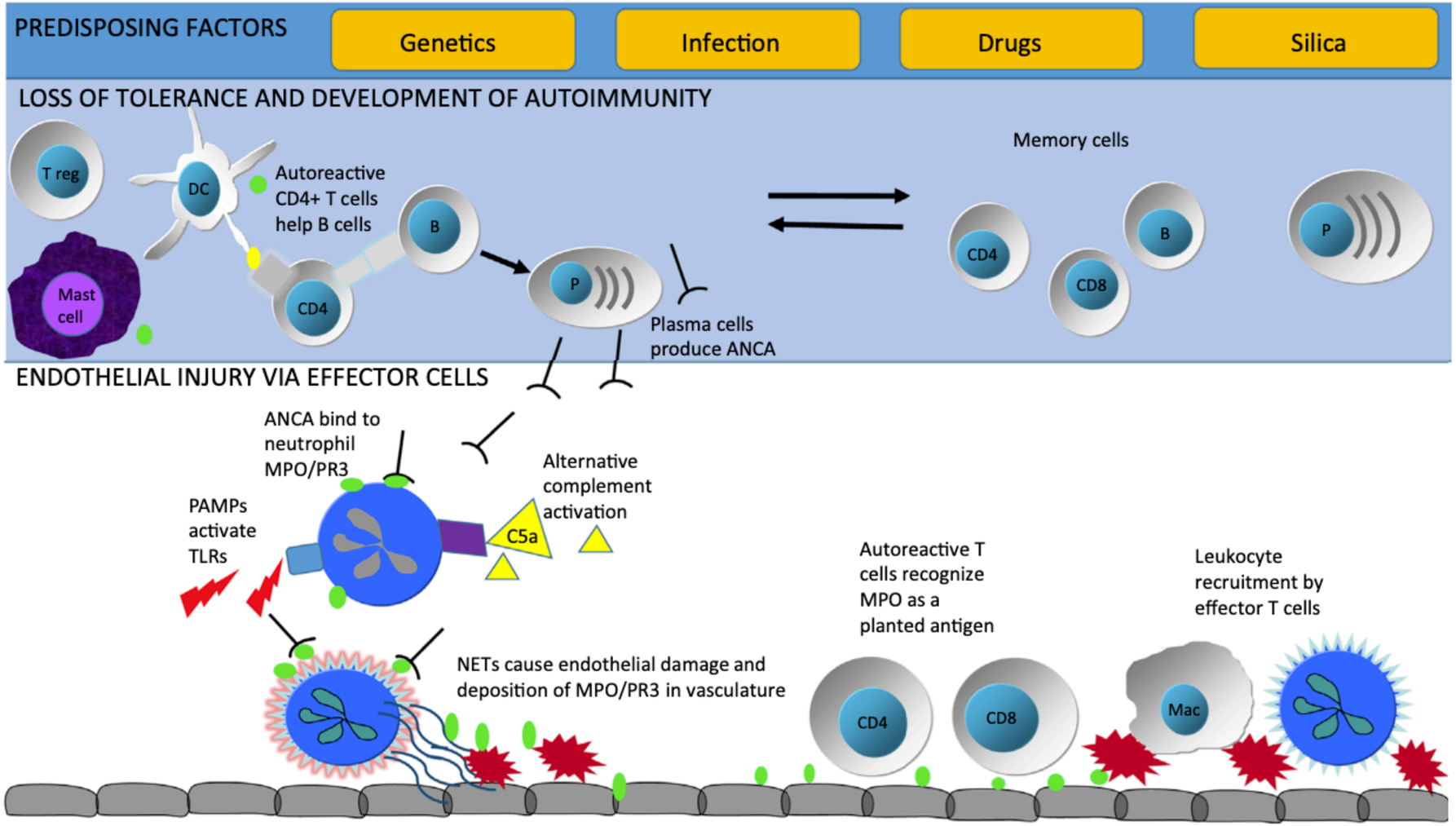
Pathogenesis of ANCA-associated vasculitis

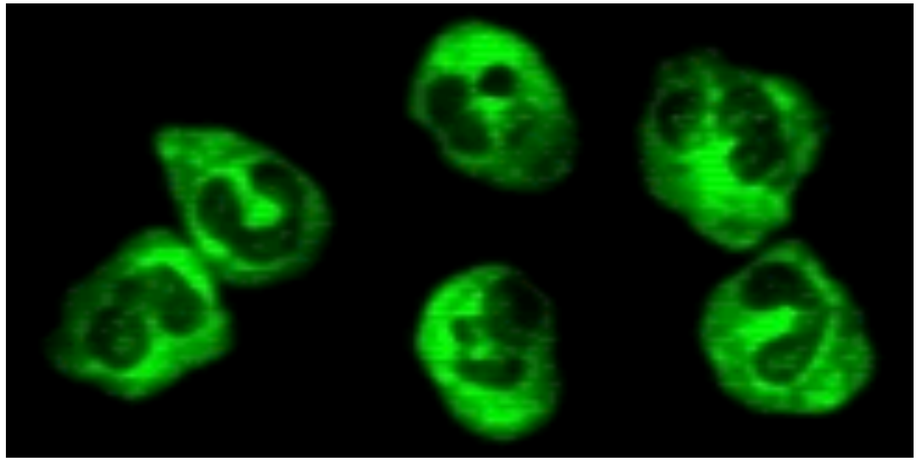


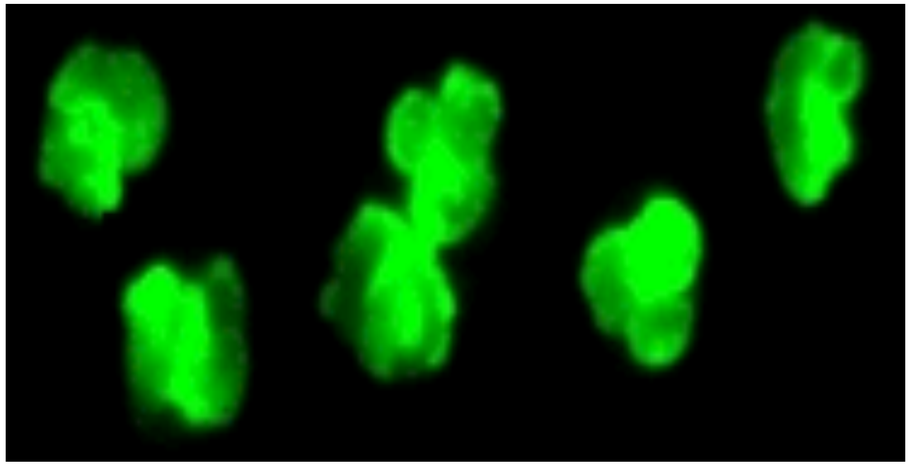
Hutton HL, et al. Semin Nephrol. 2017; 37(5):418-435.

Indirect immunofluorescence

Antibodies directed against PR3	
PGA	80-90%

Antibodies directed against MPO	
Renal limited vasculitis	80%
MPA	70%
APA	70%





C-ANCA

P-ANCA

Indirect immunofluorescence assay : more sensitive
Enzyme-linked immunosorbent assay (ELISA): more specific

Frequency of ANCA Positivity in Different Conditions

	PR3-ANCA (mostly cANCA)	MPO-ANCA (mostly pANCA)
ANCA-Associated Vasculitis		
GPA	75%	20%
MPA	30%	60%
EGPA	5%	45%
Renal-limited vasculitis	10%	80%
Drug-induced vasculitis	10%	90%

Geetha D, et al. Am J Kidney Dis. 2020; 75(1):124-137.

Frequency of ANCA Positivity in Different Conditions

	PR3-ANCA (mostly cANCA)	MPO-ANCA (mostly pANCA)
Nonvasculitis Conditic		
Systemic lupus	10% atypical ANCA	
Endocarditis		
Inflammatory bowel disease	Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%)	
Primary sclerosing cholangitis	Atypical ANCA, various antigens: 60%-80%	
Cystic fibrosis	Atypical ANCA pattern, directed against BPI (90%)	

Geetha D, et al. Am J Kidney Dis. 2020; 75(1):124-137.

ANCA negative

- Up to 40 % of patients with limited PGA
- 30 % of all MPA patients
- 50 % of all APA patients
- 10 percent of patients with severe disease (RPGN)

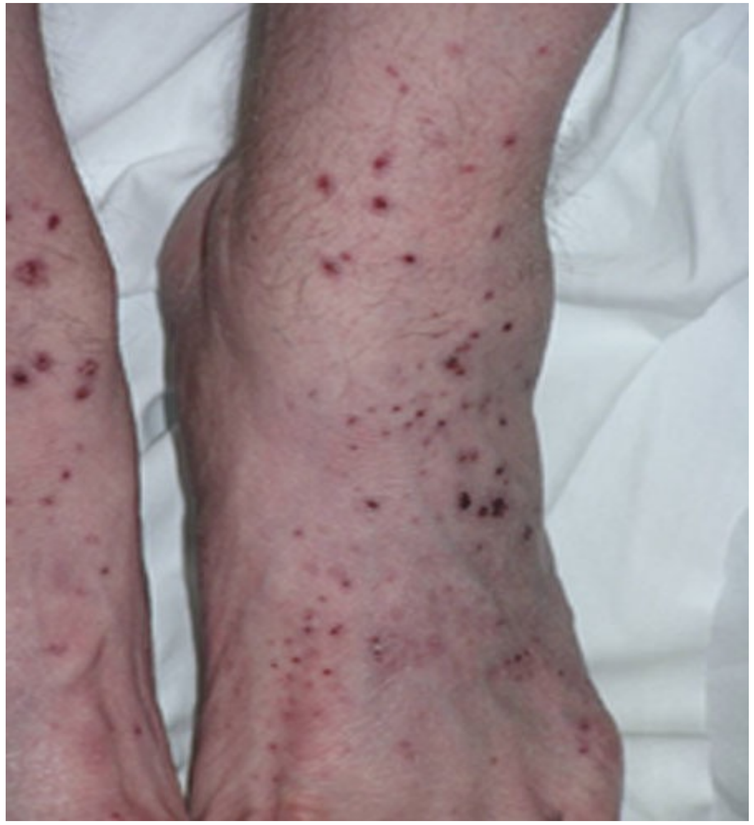
Pauci-immune RPGN

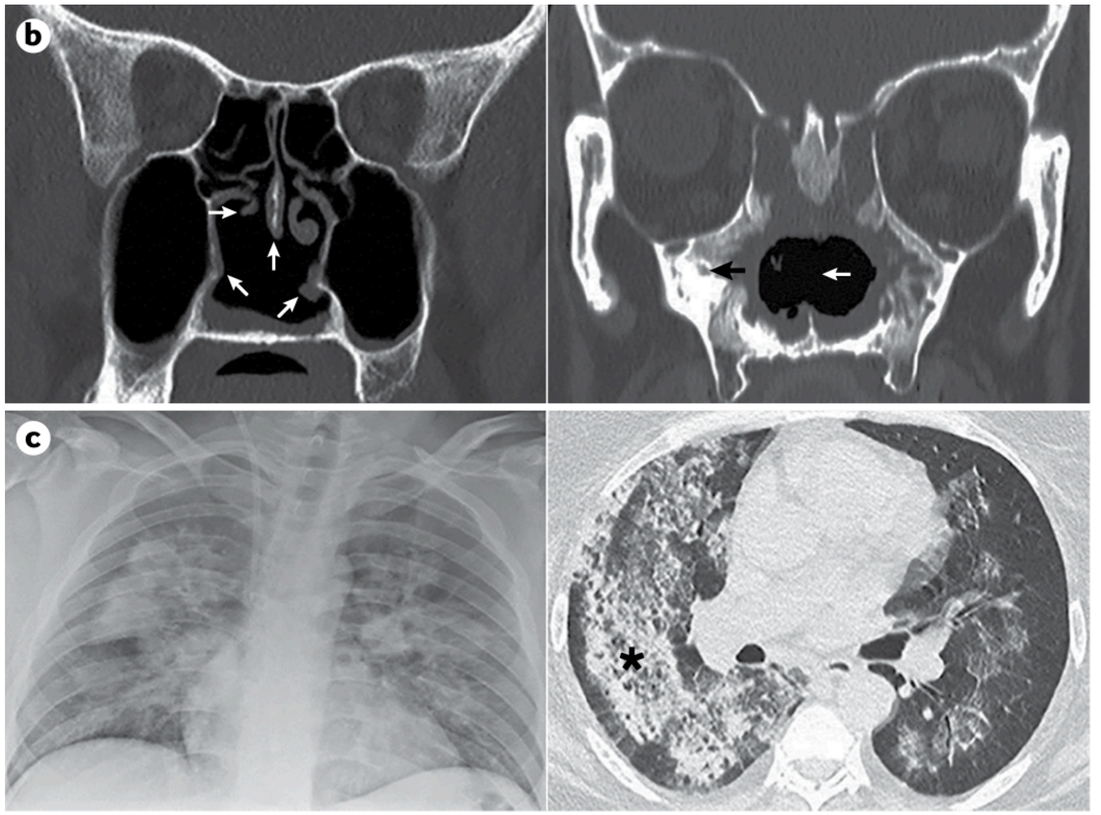
- Systemic vasculitis
  - Systemic complaints
  - Constitutional symptoms, such as fever, myalgia, anorexia, weight loss, malaise, and night sweats

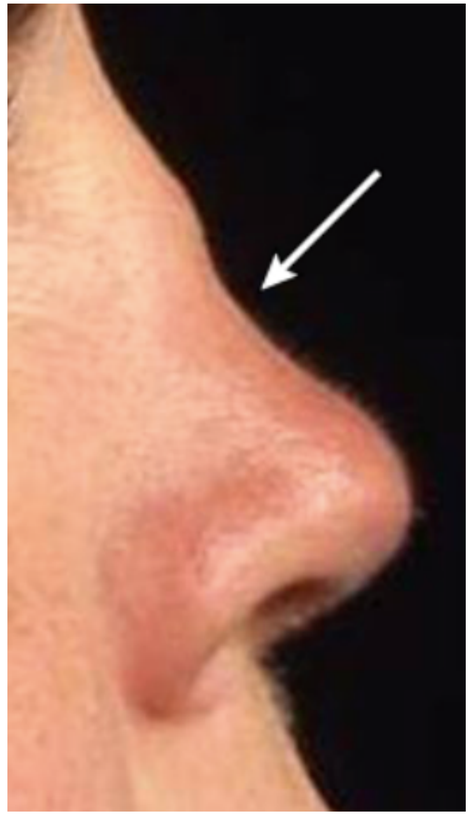
- Renal-limited vasculitis

Kain R; et al. Nat Med. 2008; 14:1088-96.
Salama AD. Kidney Int. 2009;76(1):15-7.

Systemic vasculitis







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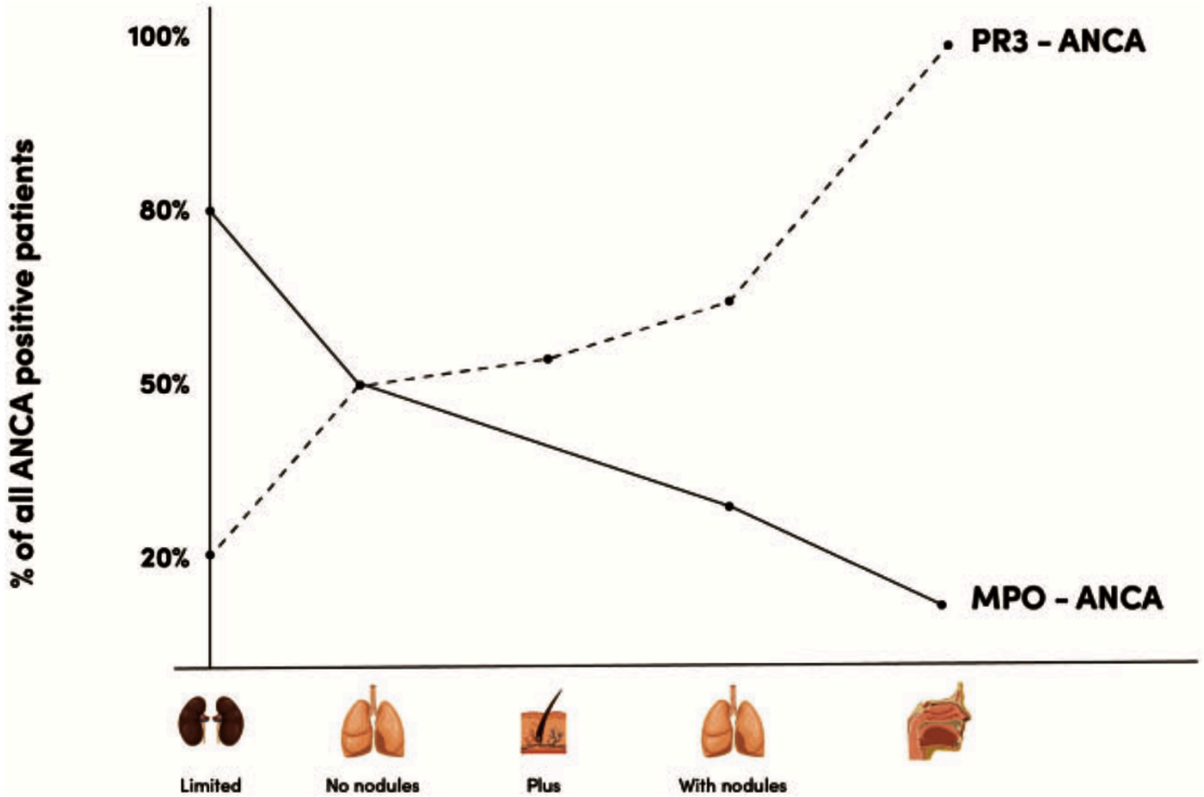
Frequency of organ involvement in AAV

Organ system	Microscopic polyangiitis (MPA) (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (EGPA) (%)
Cutaneous	40	40	60
Kidney	90	80	45
Pulmonary	50	90	70
Ear, nose, and throat	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Proposal for a more practical classification of antineutrophil cytoplasmic antibody-associated vasculitis



Antibody + Affected Organ	Classification
MPO - ANCA	**MPO-ANCA** vasculitis with Kidney involvement
MPO - ANCA	**MPO - ANCA** necrotizing vasculitis with multiorgan involvement.
PR3 - ANCA	**PR3-ANCA** granulomatous vasculitis with kidney, ENT and lung involvement

Oliva-Damaso N, et al. Clin Kidney J. 2020; 14(5):1327-1334.

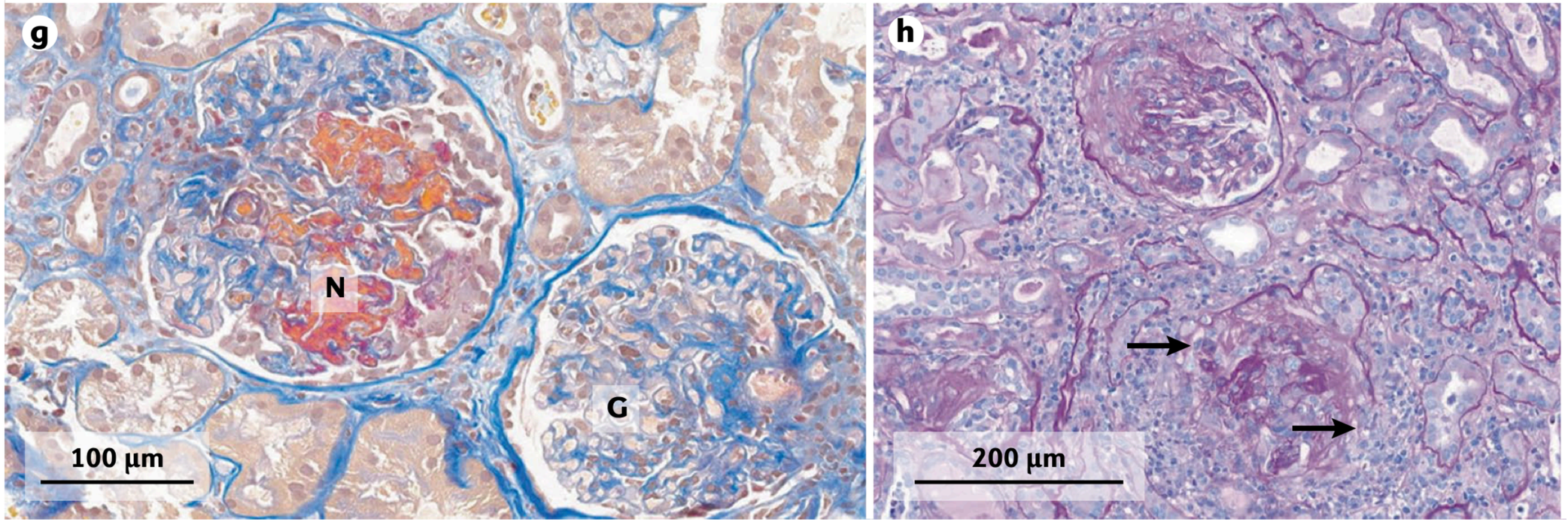
ANCA-associated glomerulonephritis

- Ages of 40 and 55 years > 70% of cases
- Microscopic hematuria with dysmorphic red blood cells and red cell casts
- Proteinuria usually moderate (1–3 g/day)
- Rapidly declining GFR over days or weeks
  - Pauci-immune focal and segmental necrotizing and crescentic GN
- Few subjects: asymptomatic microscopic hematuria and minimal proteinria

Seo P, Stone JH. Am J Med. 2004;117(1):39.
Bacon PA. N Engl J Med 2005; 27;352(4):330e2.
Jara LJ, et al. Curr Rheu- matol Rep 2003; 5(2):107e15.

Renal histopathology of AAV

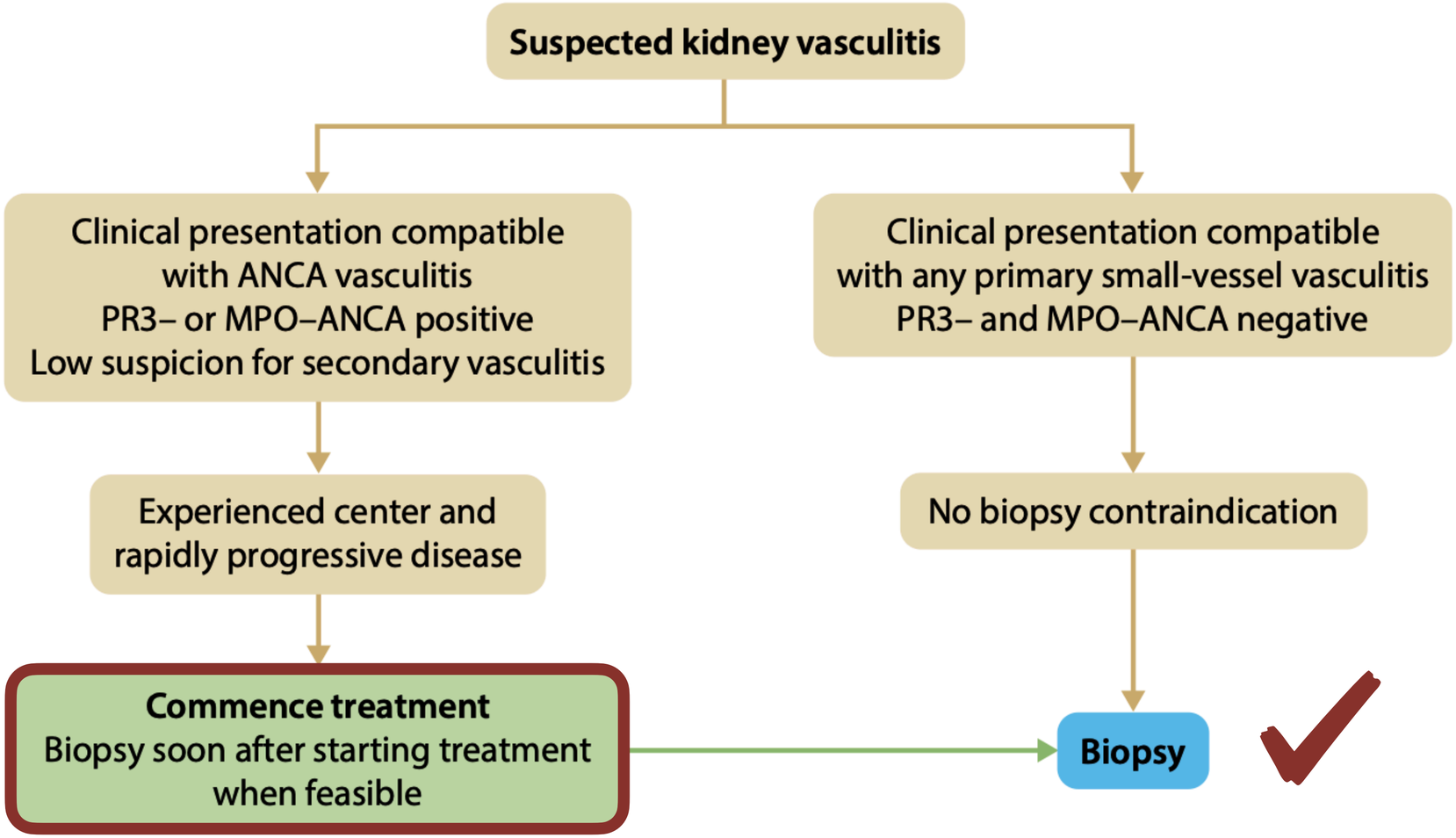
Necrosis of glomerular capillaries is seen adjacent to an unaffected glomerulus in MPA



Lesions of different age are seen with partial or circumferential crescents and variable destruction of the Bowman capsule in MPA

Kitching AR, et al. Nat Rev Dis Primers. 2020; 6(1):71.

Biopsy strategy in suspected kidney vasculitis



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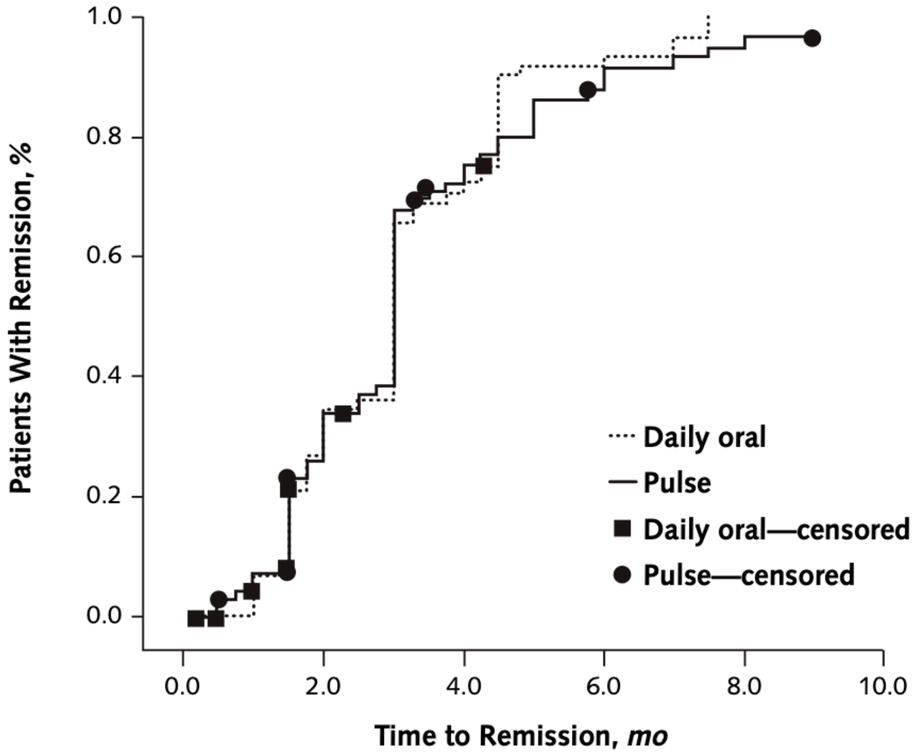
ARTICLE | Annals of Internal Medicine

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Trial

Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.W. Jayne, MD, PhD; Luis Felipe Flores Suarez, MD, PhD; Gina Gregorini, MD;



Daily oral	73	43	18	4	0
Pulse	76	46	15	4	2

42 centers in 12 European countries: 149 patients, Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in ANCA associated vasculitis

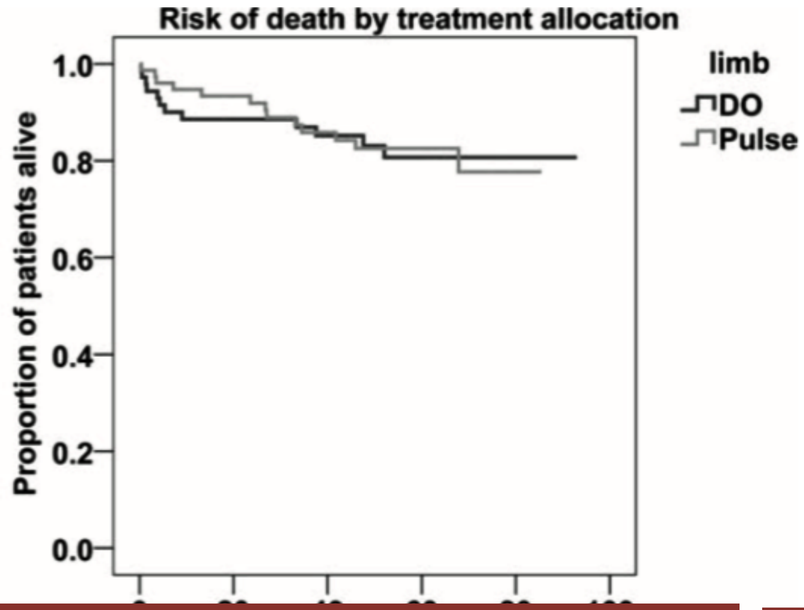
- **Infectious side effects**
- **Oral CYC (69.6%)**
- **IV CYC (40.7%) (P < 0.05)**

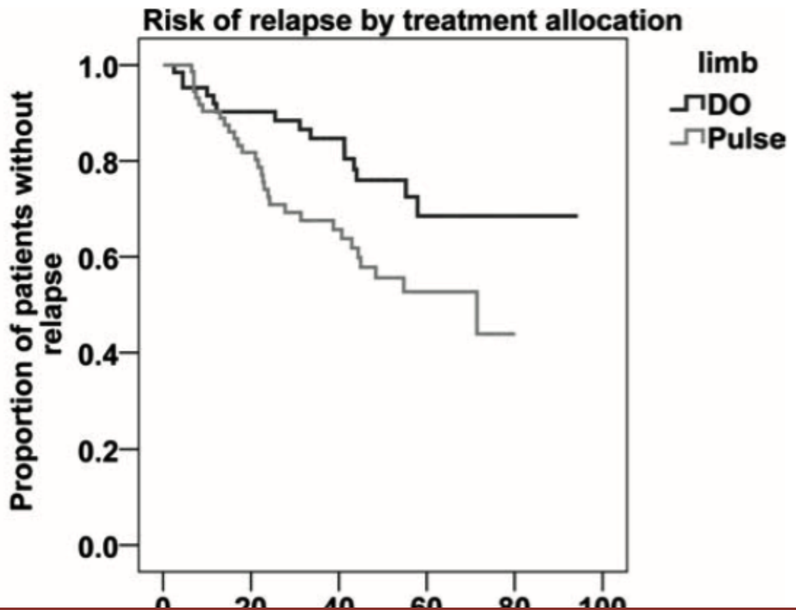
de Groot K; et al. Ann Intern Med. 2009;150(10):670-80.

Clinical and epidemiological research
Extended report

Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up

- **Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up: 4.3 years**





No difference in survival, renal function and adverse events

Lower relapse in the oral cyclophosphamide (HR=0.50, 95% CI 0.26 to 0.93; p=0.029)

Harber L, et al. Ann Rheum Dis 2012;71:955-960

Rituximab

RAVE–trial and RITUXVAS trial

ORIGINAL ARTICLE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

Jones RB, et al. N Engl J Med 2010;363:211-20.

Stone JH, et al. N Engl J Med 2010;363:221-32.

ORIGINAL ARTICLE

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Barri J. Fessler, M.D., Linna Ding, M.D., Ph.D., Lisa Viviano, R.N., Nadia K. Tchao, M.D., Deborah J. Phippard, Ph.D., Adam L. Asare, Ph.D., Noha Lim, Ph.D., David Ikle, Ph.D., Brett Jepson, M.S., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina Keogh, M.B., B.Ch., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., Mark Mueller, B.S., C.C.R.P., Lourdes P. Sejismundo, R.N., Kathleen Mieras, C.C.R.P., and John H. Stone, M.D., M.P.H., for the RAVE-ITN Research Group*

101 patients who had relapsing disease at baseline, rituximab was superior to conventional immunosuppression at 6 months (P=0.01) and at 12 months (P=0.009) but not at 18 months (P=0.06).

Specks U, et al. N Engl J Med 2013; 369: 417-427.

CONCISE REPORT

Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type

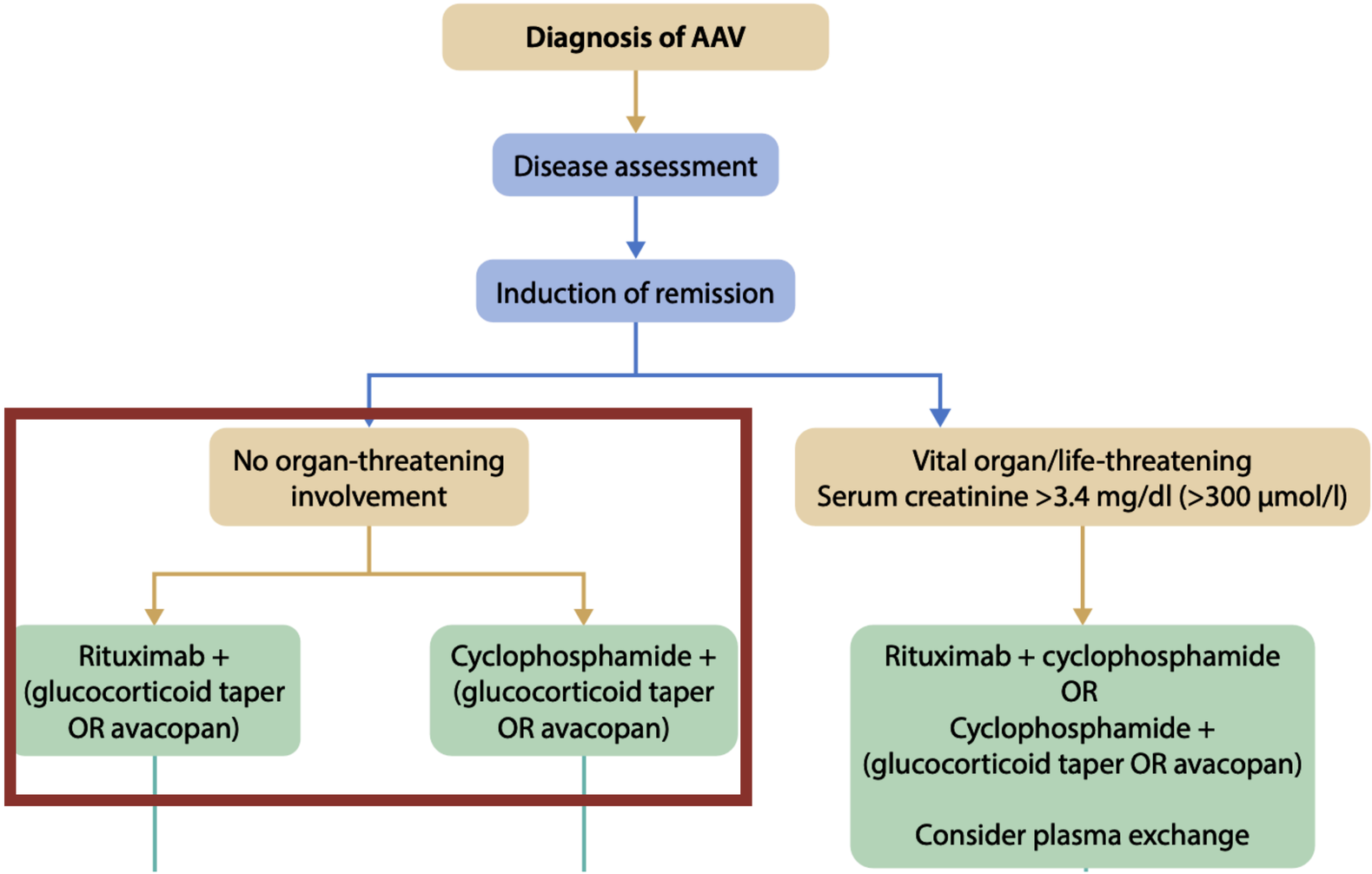
Table 3 Treatment response among patients with PR3-AAV who received RTX versus patients with PR3-AAV who received CYC/AZA

	OR*	95% CI	p Value
All patients with PR3-AAV (n=131)†			
CR at 6 months	2.11	1.04 to 4.30	0.04
CR at 12 months	1.96	0.95 to 4.05	0.07
CR at 18 months	1.44	0.68 to 3.05	0.34
Patients with PR3-AAV with relapsing disease at baseline (n=81)‡			
CR at 6 months	3.57	1.43 to 8.93	<0.01
CR at 12 months	4.32	1.53 to 12.15	<0.01
CR at 18 months	3.06	1.05 to 8.97	0.04

Patients with PR3-AAV respond better to RTX than to CYC/AZA

Unizony S, et al. C. Ann Rheum Dis 2016; 75: 1166-1169.

Treatment algorithm for AAV with kidney involvement



KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Treatment of ANCA associated vasculitis (RPGN)

- We recommend that glucocorticoids in combination with rituximab or cyclophos- phamide be used as initial treatment of new-onset AAV (1B).

Practice Point

- In patients presenting with markedly reduced or rapidly declining glomerular filtration rate (GFR) (serum creatinine [SCr] >4 mg/dl), there are limited data to support rituximab and glucocorticoids.
- Both cyclophosphamide and glucocorticoids, and the combination of rituximab and cyclophosphamide can be considered in this setting.
- Consider discontinuation of immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Considerations for choosing the route of administration of cyclophosphamide

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Immunosuppressive drug dosing for AAV

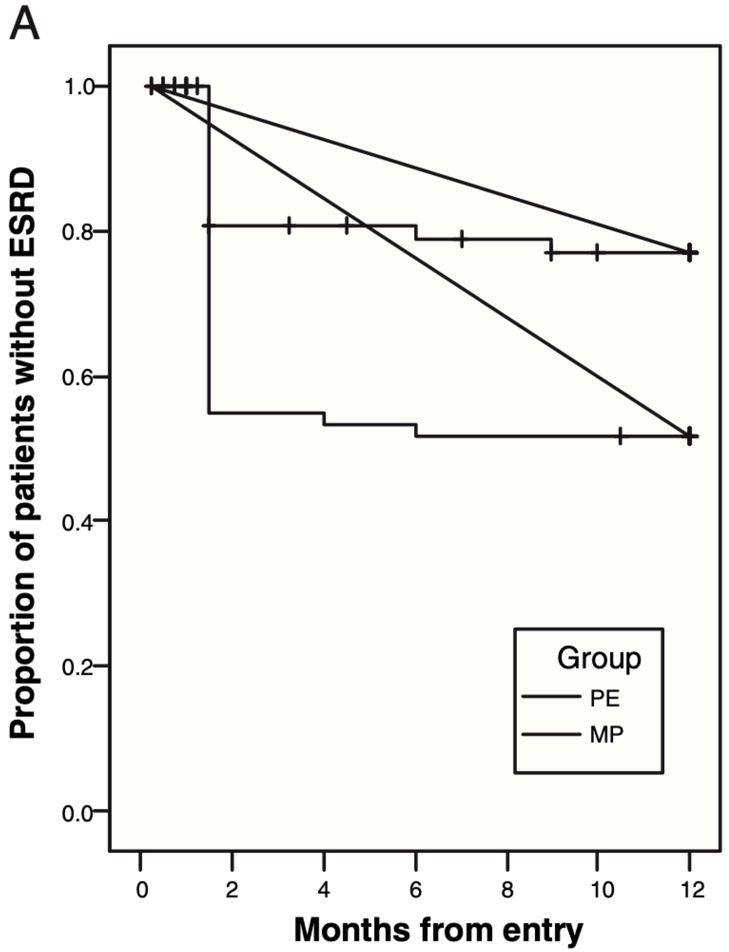
Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF	Avacopan
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with i.v. cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response	30 mg twice daily as alternative to glucocorticoids, in combination with rituximab or cyclophosphamide induction
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2				

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Plasma exchange

Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖



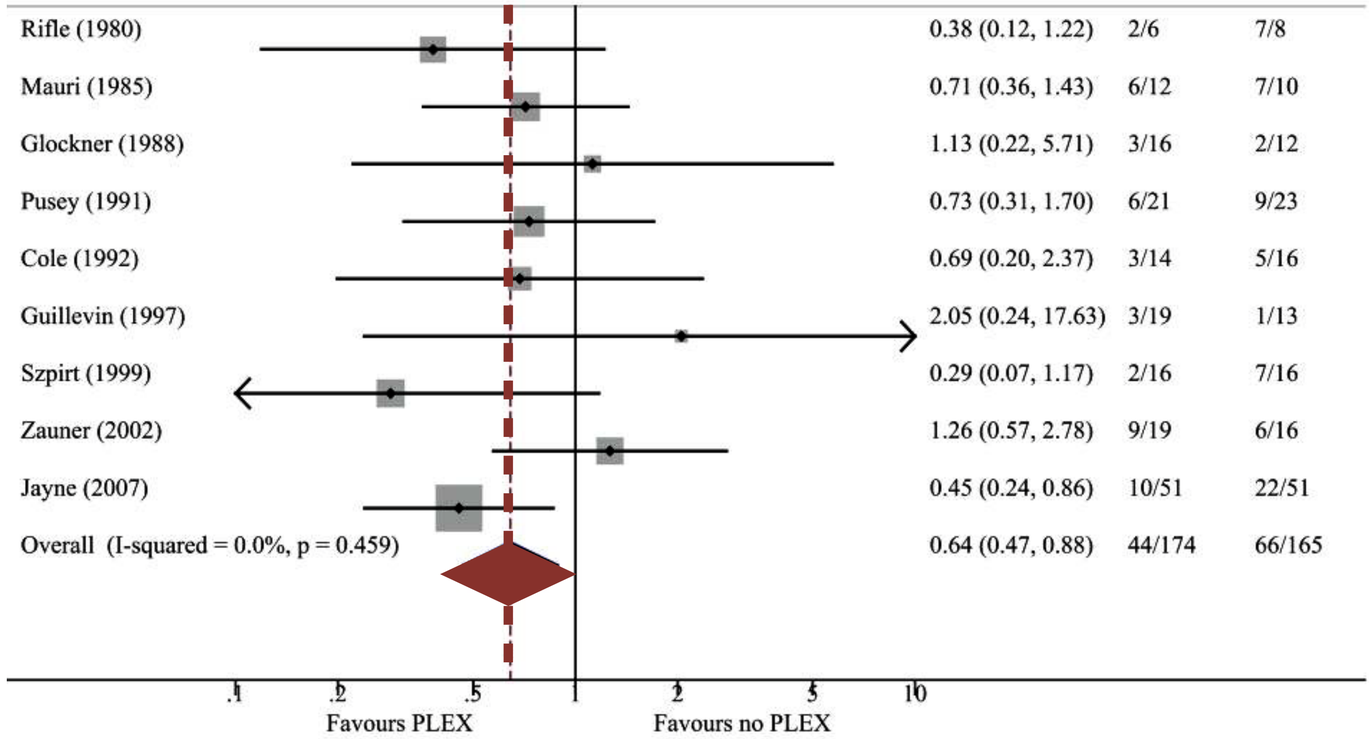
137 patients with pauci-immune glomerulonephritis, and serum creatinine >5.7 mg/dL.
Serum creatinine was 8.3 mg/dL and 69 percent required dialysis,

Plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% CI 6.1 to 41%), from 43 to 19%, at 12 months

Jayne DR, et al. J Am Soc Nephrol. 2007;18(7):2180-8

Plasma exchange for renal vasculitis: a meta-analysis

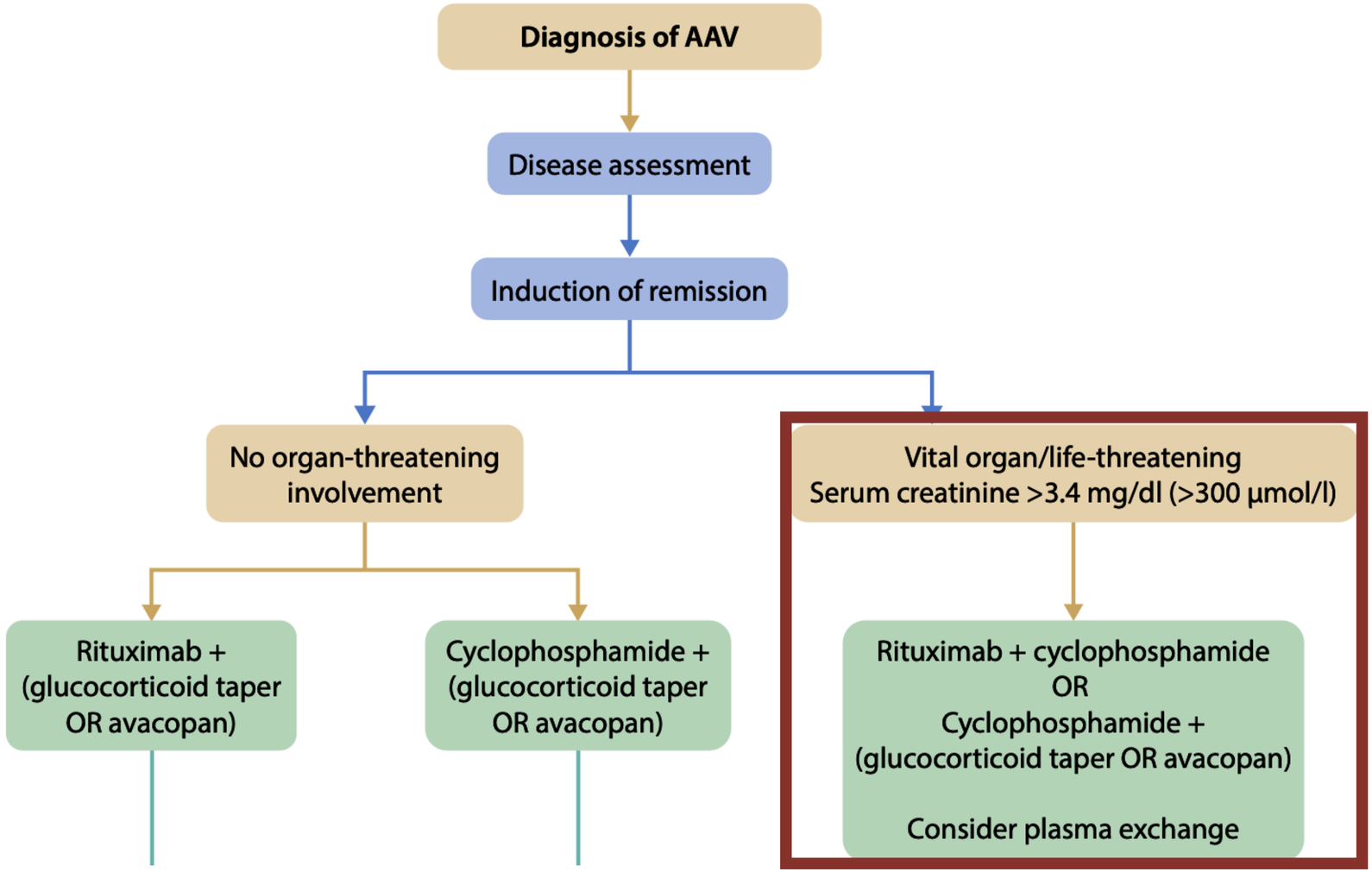
The RR for ESRD was 0.64 (95% CI, 0.47-0.88; P = 0.006),
The RR for death was 1.01 (95% CI, 0.71-1.4; P = 0.9).



Forest plot of the effects of adjunctive plasma exchange on the endpoint of ESRD in patients with ANCA associated vasculitis.

Walsh M, et al. Am J Kidney Dis. 2011;57(4):566.

Treatment algorithm for AAV with kidney involvement



KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Plasma exchange

- **Consider plasma exchange for patients with SCr >3.4 mg/dl, patients requiring dialysis or with rapidly increasing SCr, and patients with diffuse alveolar hemorrhage who have hypoxemia.**
- **Add plasma exchange for patients with an overlap syndrome of ANCA-associated vasculitis and anti- glomerular basement membrane (GBM)**

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

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

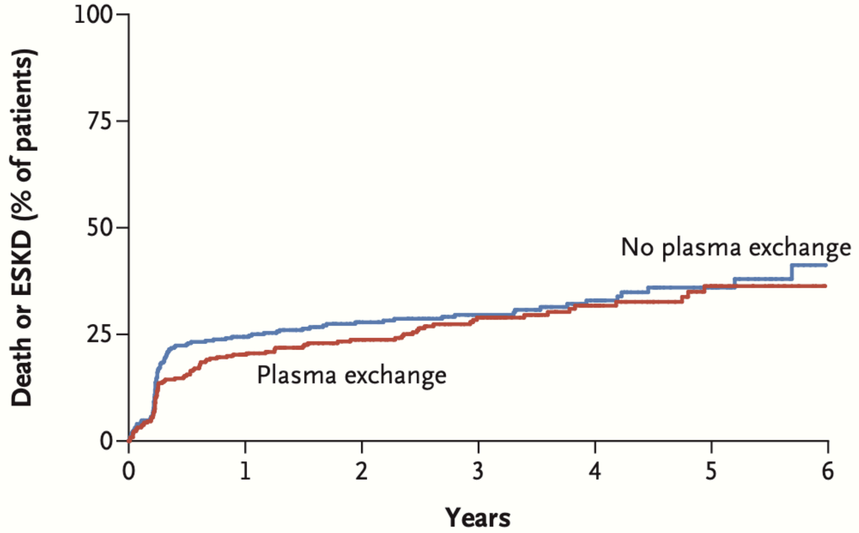
M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne, for the PEXIVAS Investigators*

Walsh M, et al. N Engl J Med. 2020 Feb 13;382(7):622-631.

Plasma exchange in ANCA-associated renal vasculitis

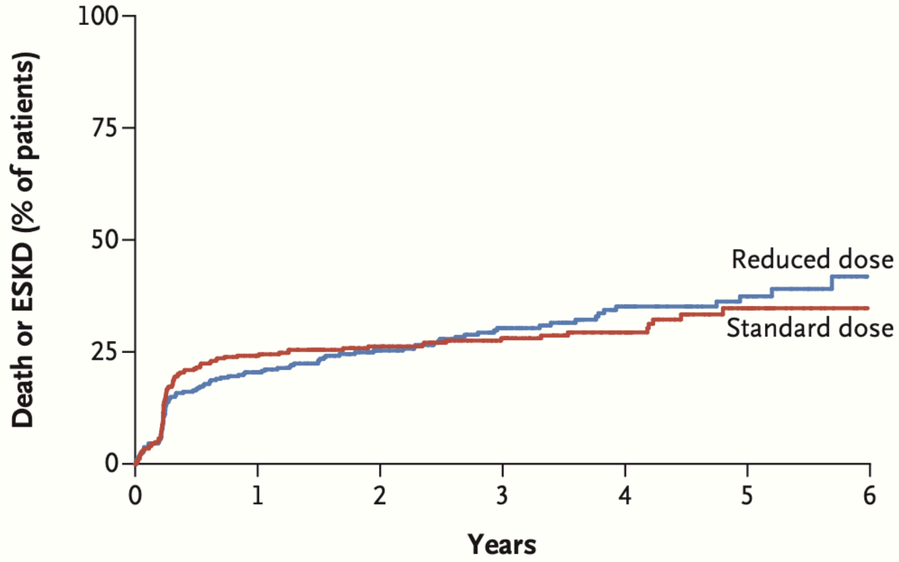
Death from any cause or ESKD occurred in 28.4% in the plasma-exchange group and in 31.0% in the control group (hazard ratio, 0.86; 95% CI 0.65 to 1.13; P=0.27).

A Primary Outcome According to Plasma Exchange



No. at Risk							
No plasma exchange	352	244	183	136	82	44	10
Plasma exchange	352	252	186	135	82	43	10

B Primary Outcome According to Glucocorticoid Regimen



No. at Risk							
Reduced dose	353	256	185	133	80	48	9
Standard dose	351	240	184	138	84	39	11

Walsh M, et al. N Engl J Med. 2020 Feb 13;382(7):622-631.

Maintenance immunosuppressive therapy

- Long-term cyclophosphamide has significant treatment-related toxicity
- Almost all patients with WG or MPA are switched to a less toxic non-cyclophosphamide maintenance regimen
- Azathioprine, MMF or methotrexate, to reduce the risk of relapse.

Azathioprine

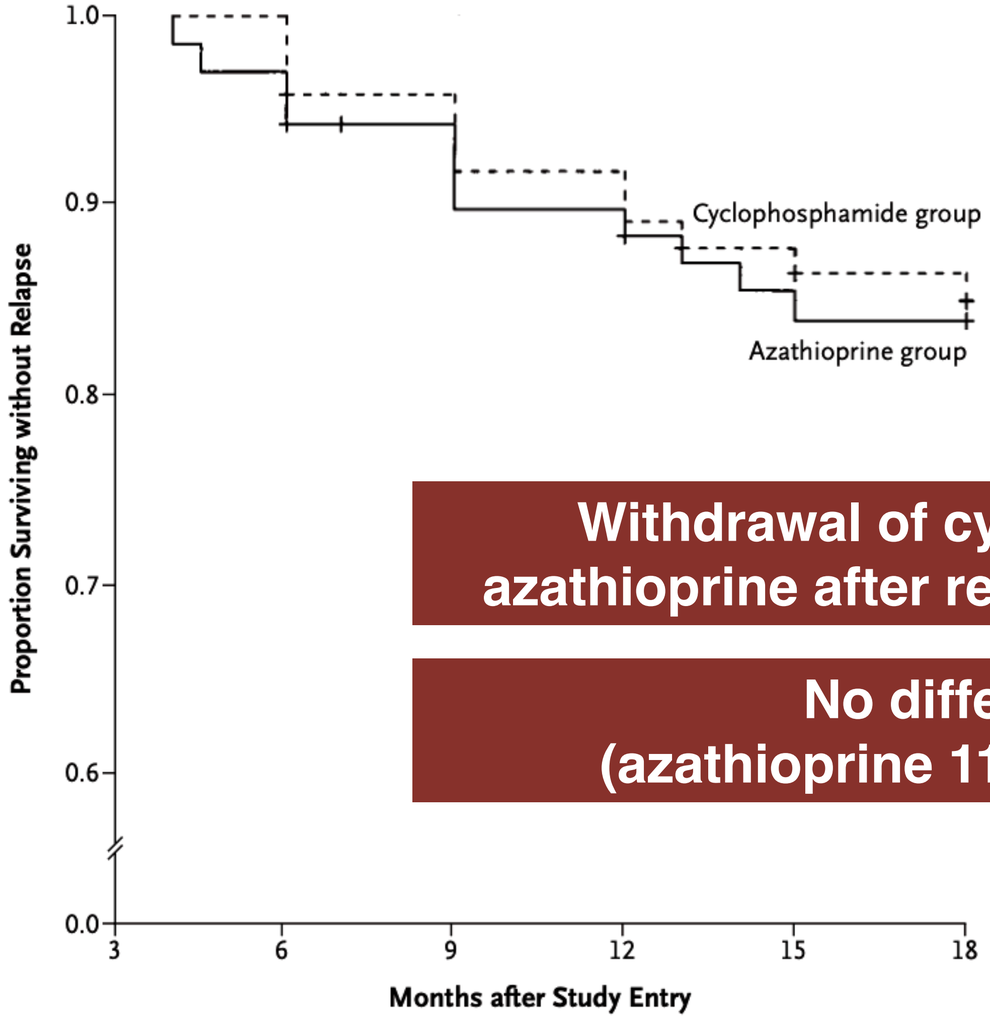
ORIGINAL ARTICLE

A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies

David Jayne, F.R.C.P., Niels Rasmussen, M.D., Konrad Andrassy, M.D., Paul Bacon, F.R.C.P., Jan Willem Cohen Tervaert, Ph.D., Jolanta Dadoniené, Ph.D., Agneta Ekstrand, M.D., Gill Gaskin, Ph.D., Gina Gregorini, M.D., Kirsten de Groot, M.D., Wolfgang Gross, M.D., E. Christiaan Hagen, M.D., Eduardo Mirapeix, M.D., Erna Pettersson, Ph.D., Carl Siegert, M.D., Alberto Sinico, Ph.D., Vladimir Tesar, Ph.D., Kerstin Westman, Ph.D., and Charles Pusey, F.R.C.P., for the European Vasculitis Study Group*

Jayne D, et al. N Engl J Med 2003;349:36-44.

CYCAZAREM trial



Cyclophosphamide group 86.3%

Azathioprine group 84.5%

Withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse.

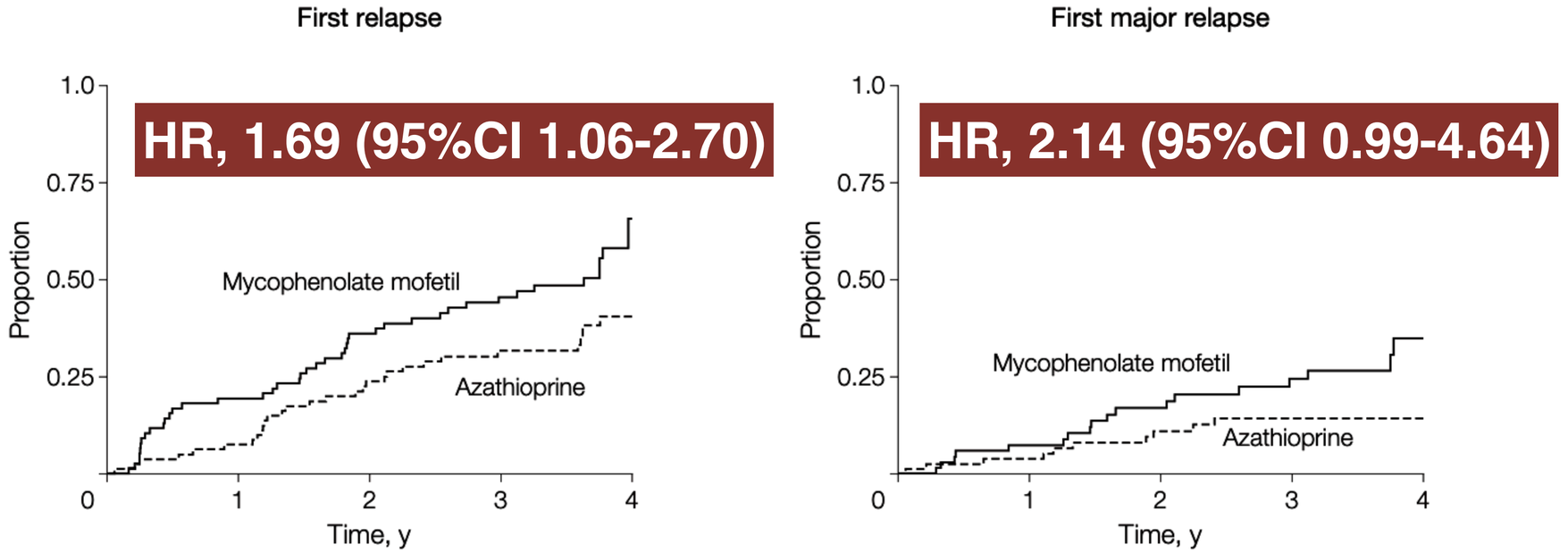
No difference in severe adverse events (azathioprine 11% vs. cyclophosphamide 10 %, P=0.94)

Jayne D, et al. N Engl J Med 2003;349:36-44.

MMF

Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Controlled Trial

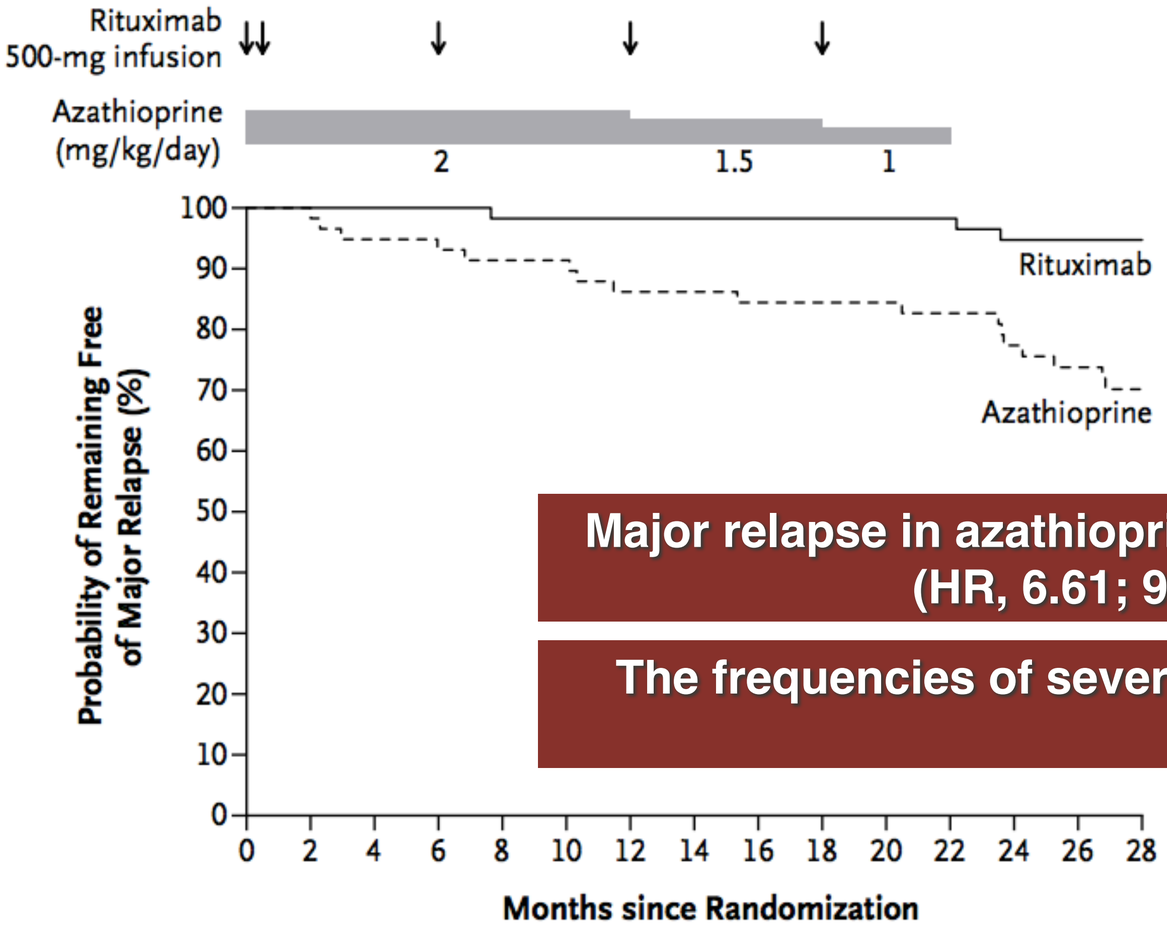


No. at risk
Azathioprine
Mycophenolate mofetil

Severe adverse events did not differ significantly between groups

Hiemstra TF, et al. JAMA. 2010; 304(21): 2381-2388.

Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis

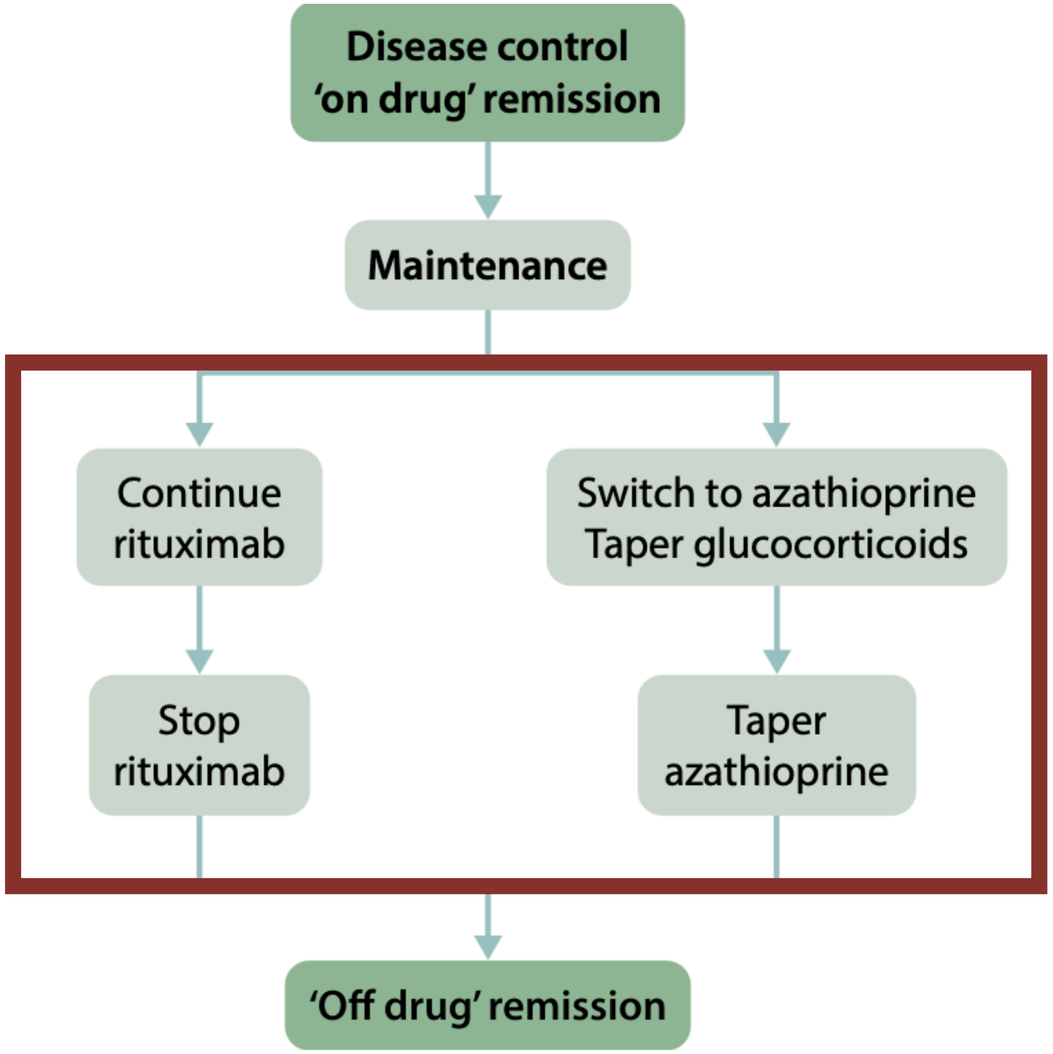


Major relapse in azathioprine group (29%) and rituximab group (5%) (HR, 6.61; 95% CI, 1.56-27.96; P=0.002)

The frequencies of severe adverse events were similar in the two groups.

Guillevin L, et al. N Engl J Med 2014;371:1771-80.

Maintenance immunosuppressive therapy



KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Maintenance therapy of ANCA associated vasculitis

- **We recommend maintenance therapy with either rituximab, or azathioprine and low- dose glucocorticoids after induction of remission (1C).**
- **The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.**
- **Consider mycophenolate mofetil (MMF) or methotrexate as alternatives to azathioprine for maintenance therapy in patients intolerant of azathioprine. Methotrexate should not be used for patients with a GFR <60 ml/min per 1.73 m2.**

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until 1 yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yr

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Considerations for using rituximab or azathioprine for AAV maintenance therapy

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Limited availability of rituximab

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Factors that increase relapse risk for AAV

- **When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur**

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher 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

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Relapses:

Treatment of ANCA associated vasculitis

Practice Point

- **The persistence of ANCA positivity, an increase in ANCA levels, or a change in ANCA from negative to positive may be predictive of future disease relapse and should be considered when making treatment decisions.**
- **Patients with relapsing disease (life- or organ-threatening) should be reinduced, preferably with rituximab.**

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis

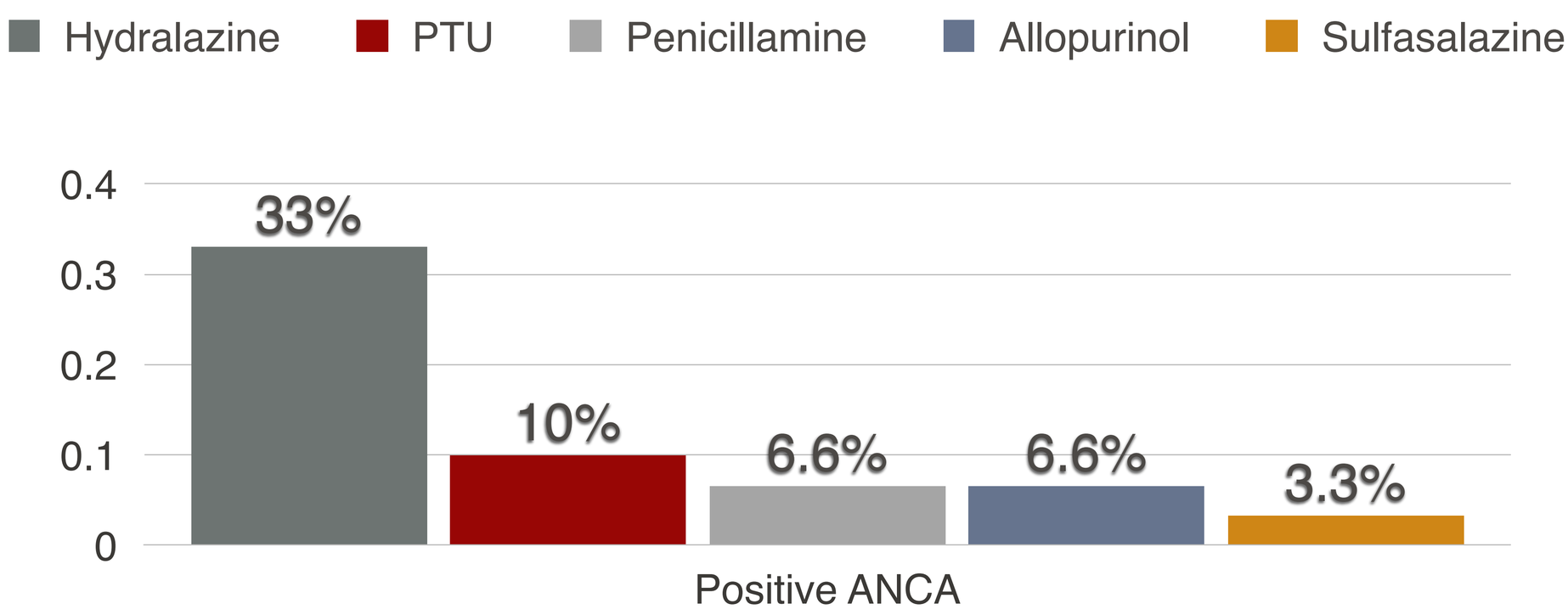
- 524 patients with newly diagnosed AAV
- 1-year mortality probability was 11.1%
  - 59% therapy-associated adverse events
  - 14% active vasculitis

Severe infection

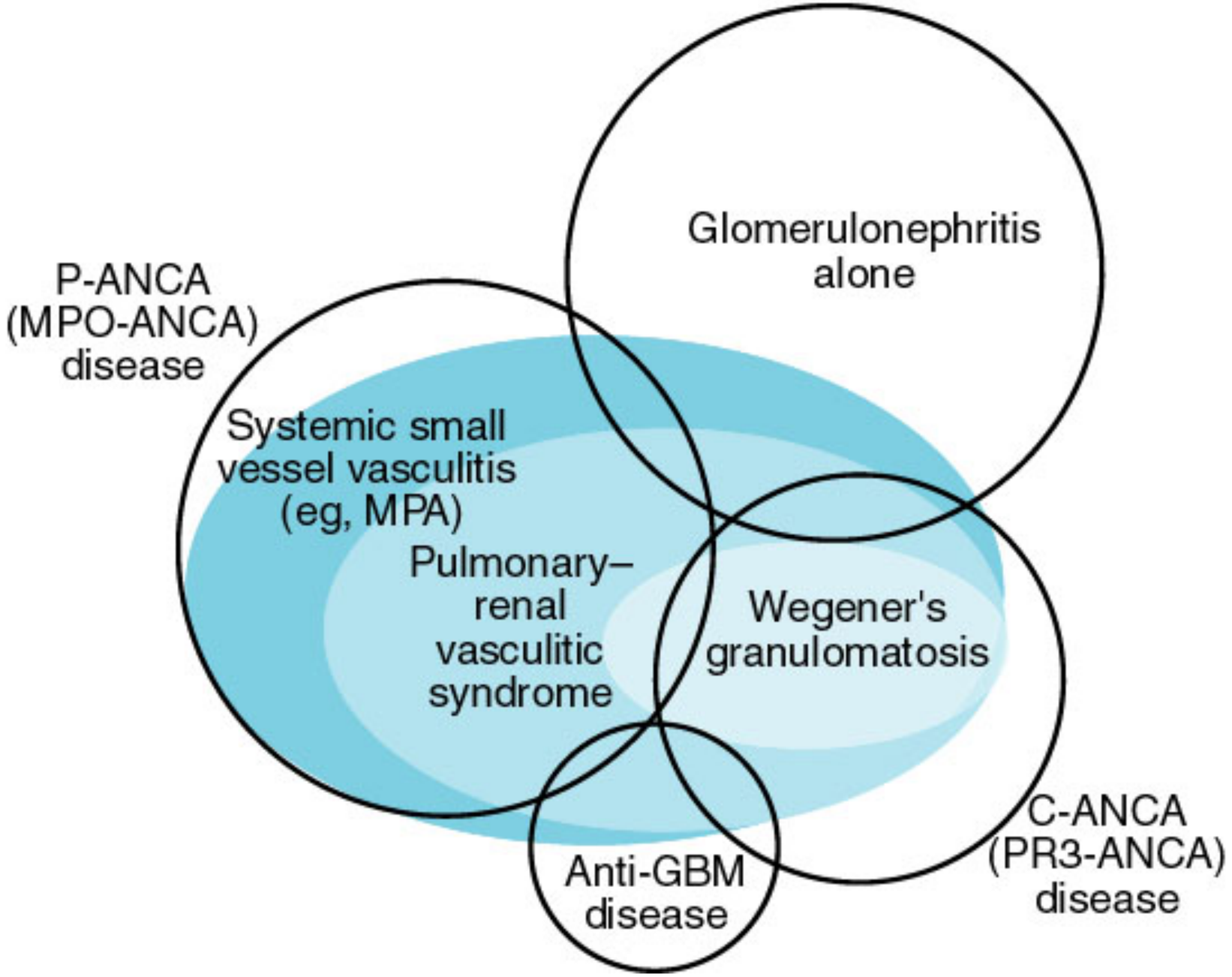
Mark A Little, et al. Ann Rheum Dis 2010;69:1036-1043

Drug-associated ANCA-positive vasculitis

- **High titers of anti-MPO antibodies are drug-associated hydralazine and PTU**



Choi HK, et al. Arthritis Rheum. 2000;43(2):405.


Glomerulonephritis alone
P-ANCA (MPO-ANCA) disease
Systemic small vessel vasculitis (eg, MPA)
Pulmonary–renal vasculitic syndrome
Wegener's granulomatosis
Anti-GBM disease
C-ANCA (PR3-ANCA) disease

PTU induced ANCA vasculitis

- Most common offending agent in drug-induced ANCA seropositivity
- Take the medication for months or even years
- A relatively high percentage of patients administered PTU develop ANCA
- Vasculitis syndrome usually resolves with discontinuation of PTU, but severe cases may require treatment with corticosteroids and other immunosuppression.
- ANCA titers usually persist in low titers, even after active vasculitis has abated.

Refractory disease:

Treatment of ANCA associated vasculitis

Practice Point

- **Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.**
- **In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange can be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.**

KDIGO GUIDELINE. Kidney Int. 2024: 105 (Suppl 3S), S71–S116.

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