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)

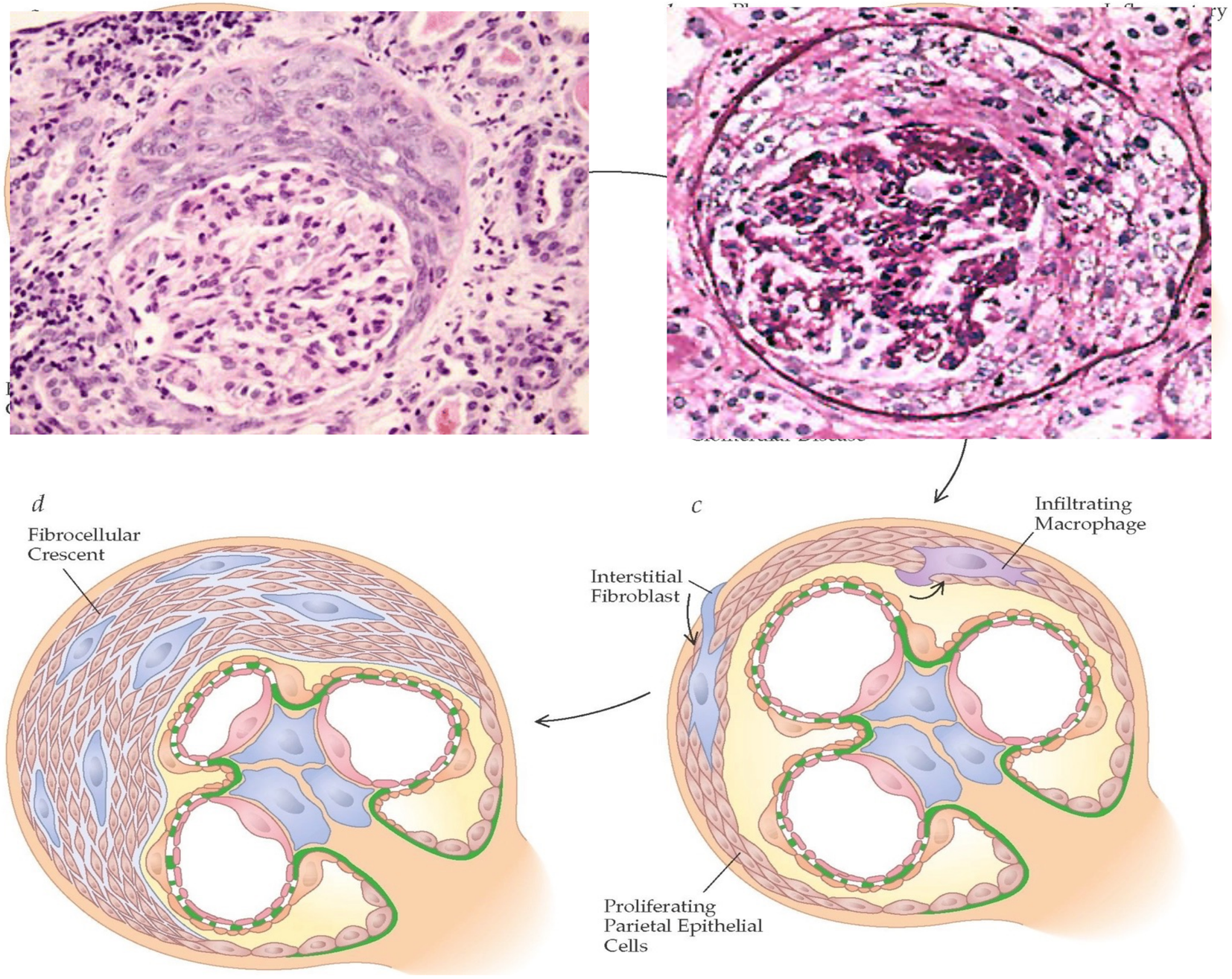
Chronic glomerulonephritis
- Slowing developing renal insufficiency
- Proteinuria > 3 g/day and hematuria
- Hypertension
- Shrunken smooth kidneys

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

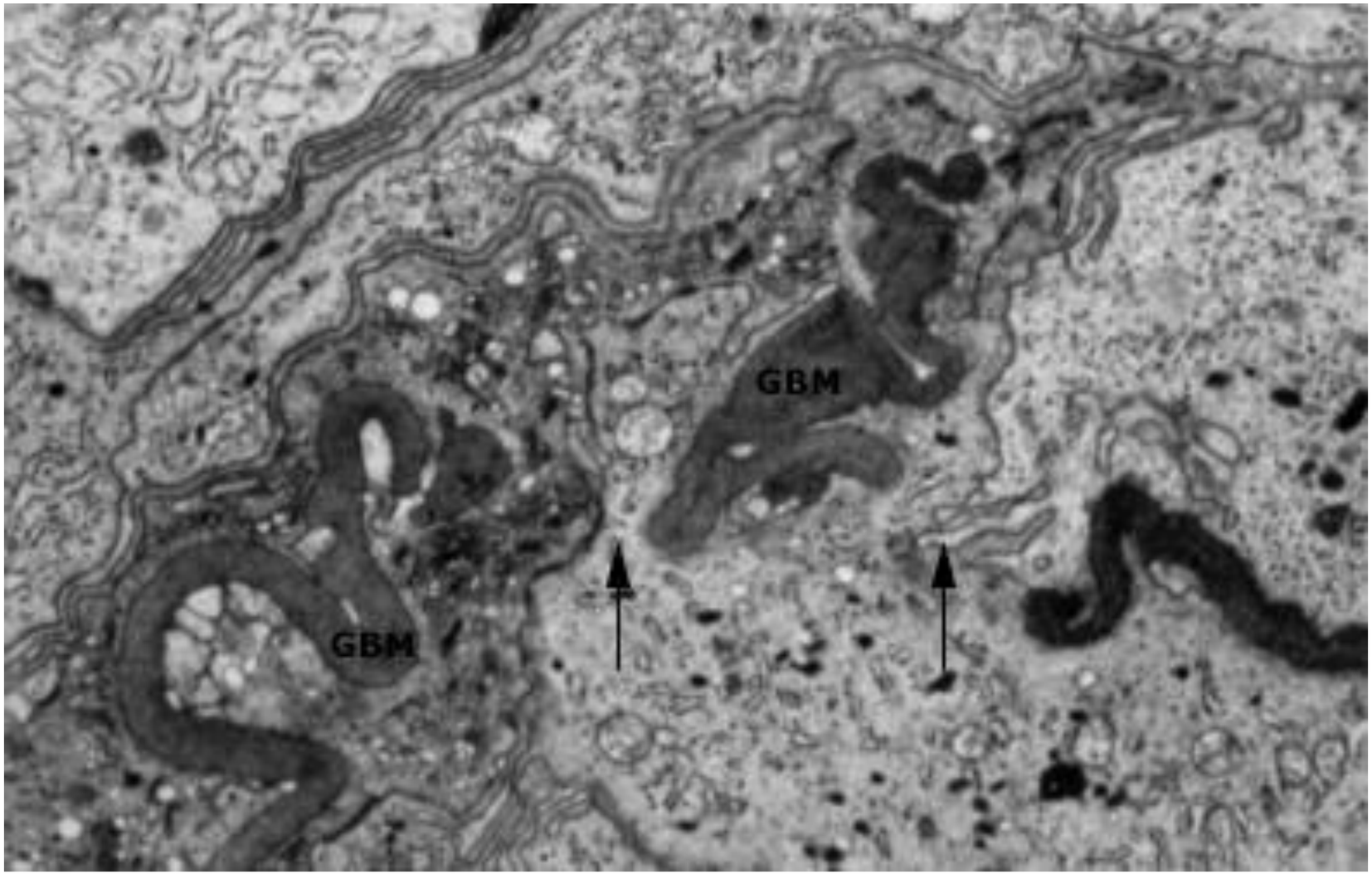
Manifestation of glomerular diseases

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	+	++++

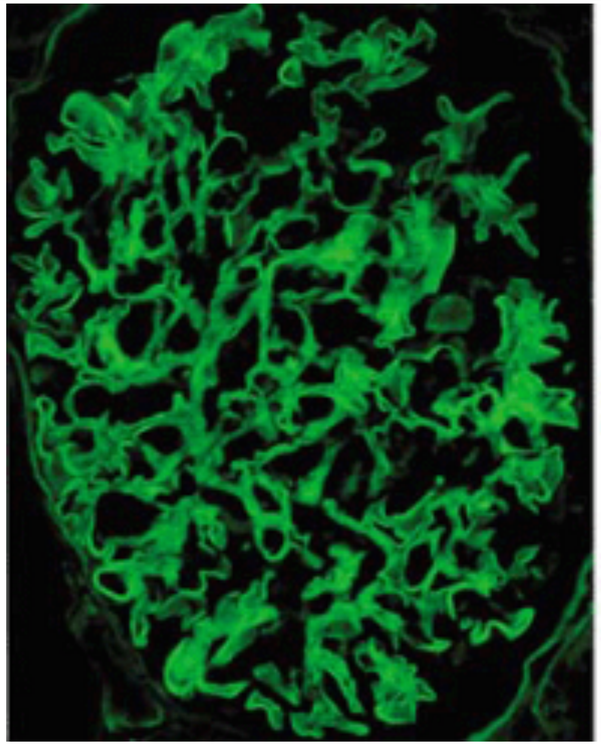
Satirapoj B. Essential Glomerular Disease 2018


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

Breaks in the glomerular basement membrane

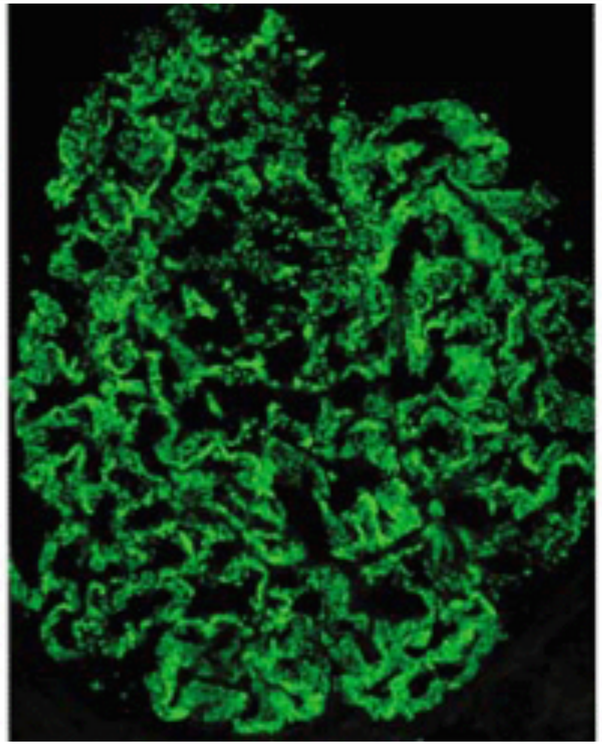


Type of RPGN



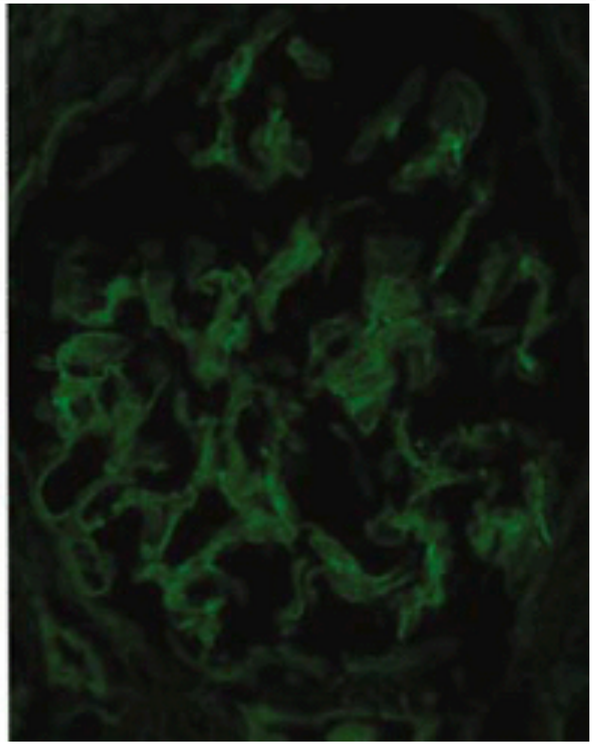
Linear staining for IgG

Anti-GBM GN



Granular staining

Immune complex GN



Pauci immune staining

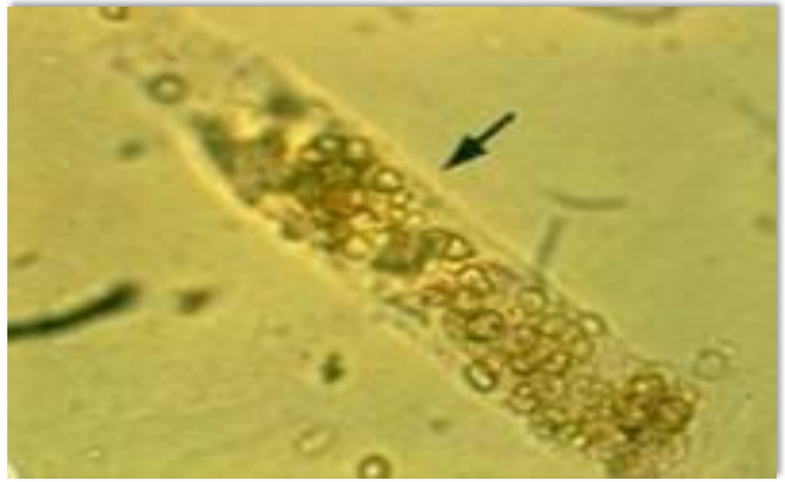
ANCA GN

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**

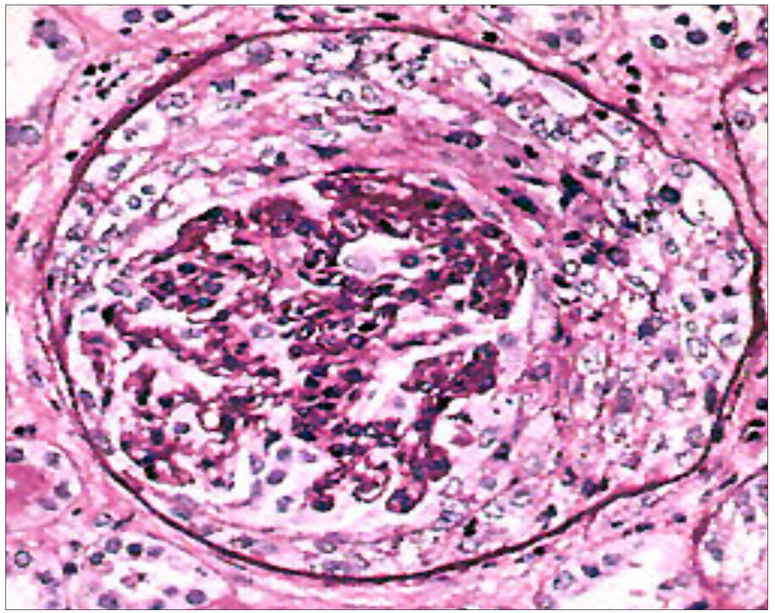
RPGN: Clinical features

- 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

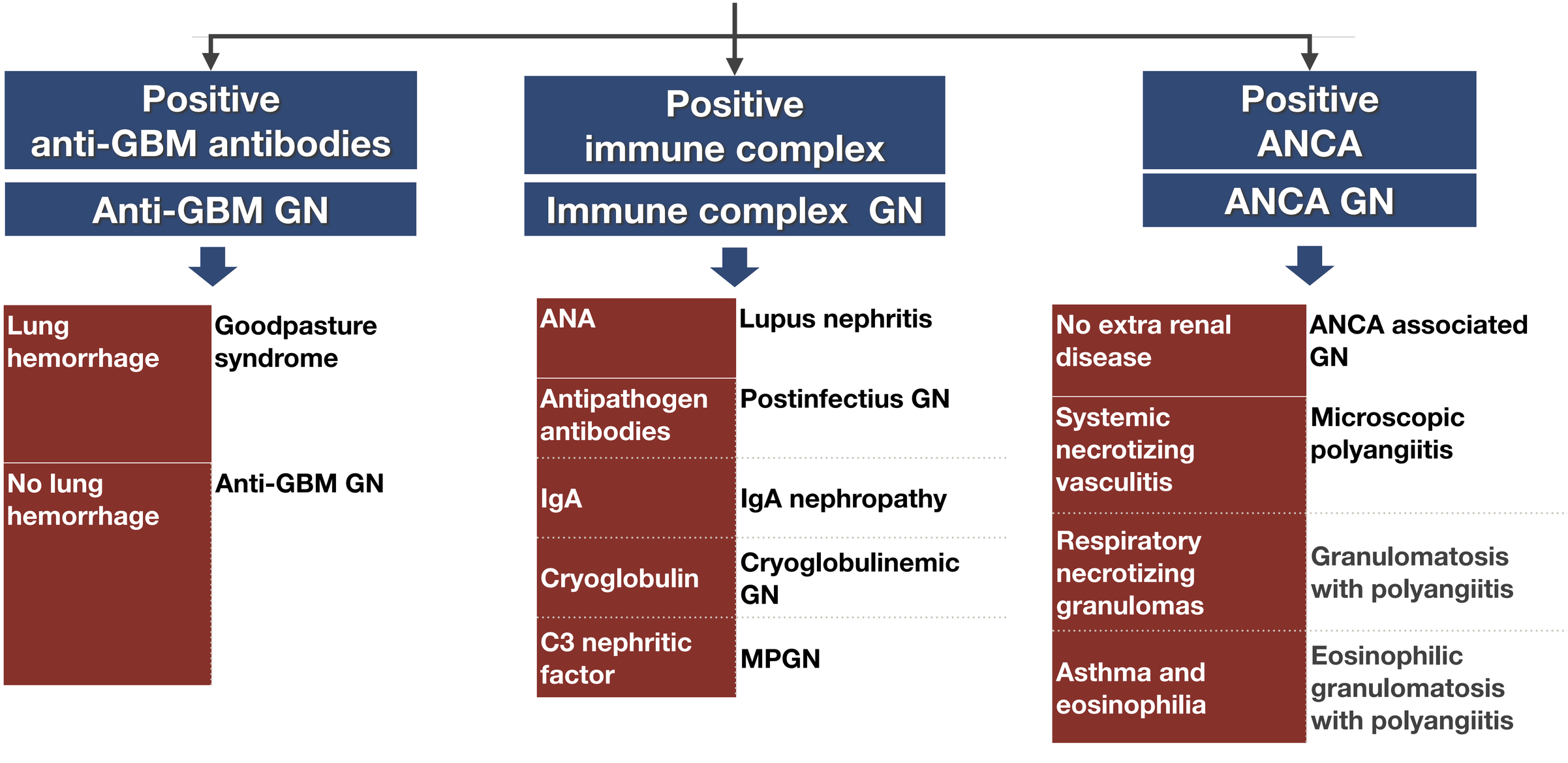
Categories of RPGN	Age			
	10-19 (n=20)	20-39 (n=42)	40-64 (n=61)	>65 (n=66)
Anti-GBM mediated glomerulonephritis	15%	24%	2%	11%
Immune complex mediated glomerulonephritis	50%	48%	30%	8%
Pauci-immune glomerulonephritis	35%	28%	69%	82%

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

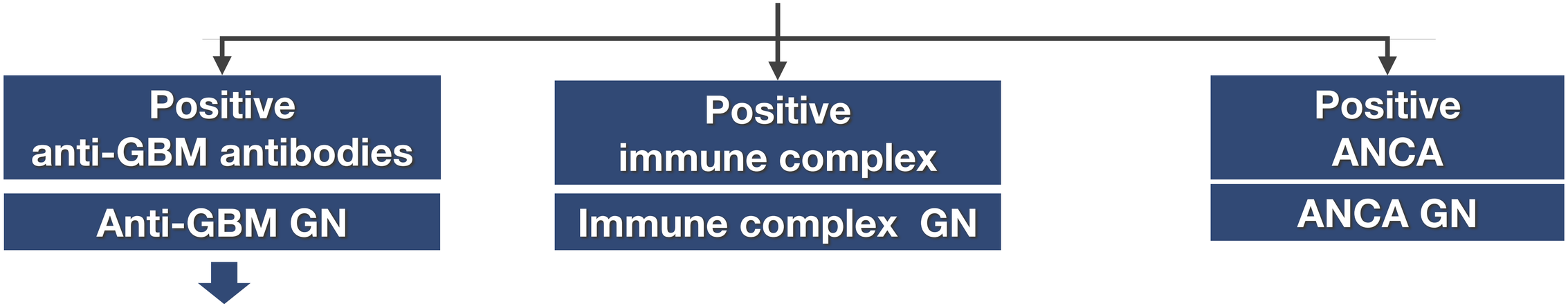
Evaluation

- Serologic tests
- Anti-GBM antibodies
- Immune complex
  - Complement component assays
  - Antinuclear antibodies
  - Cryoglobulinemia
  - ASO titer
- ANCA antibodies

Serologic analysis of patients with RPGN



Serologic analysis of patients with RPGN

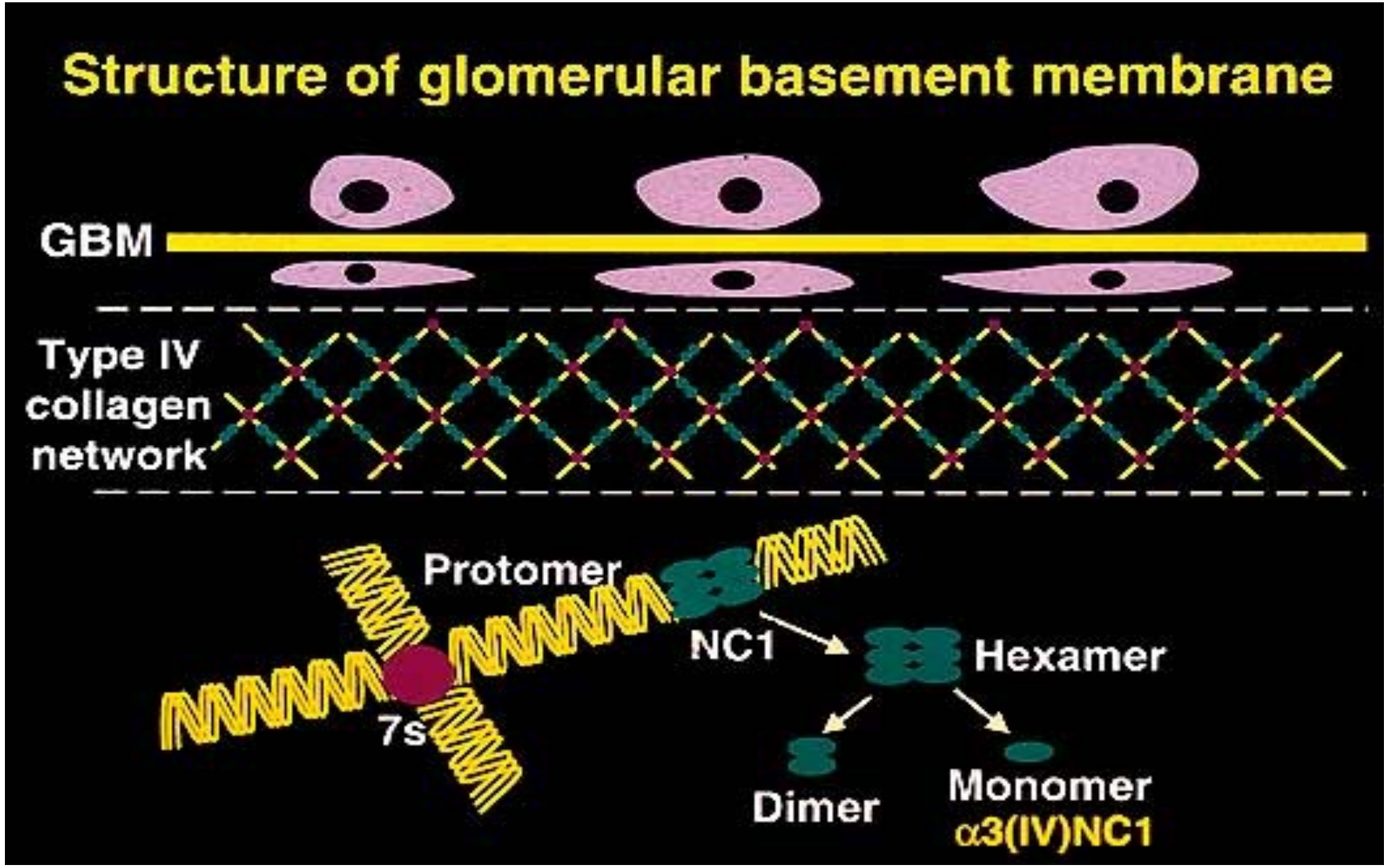


Lung hemorrhage	Goodpasture syndrome
No lung hemorrhage	Anti-GBM GN

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

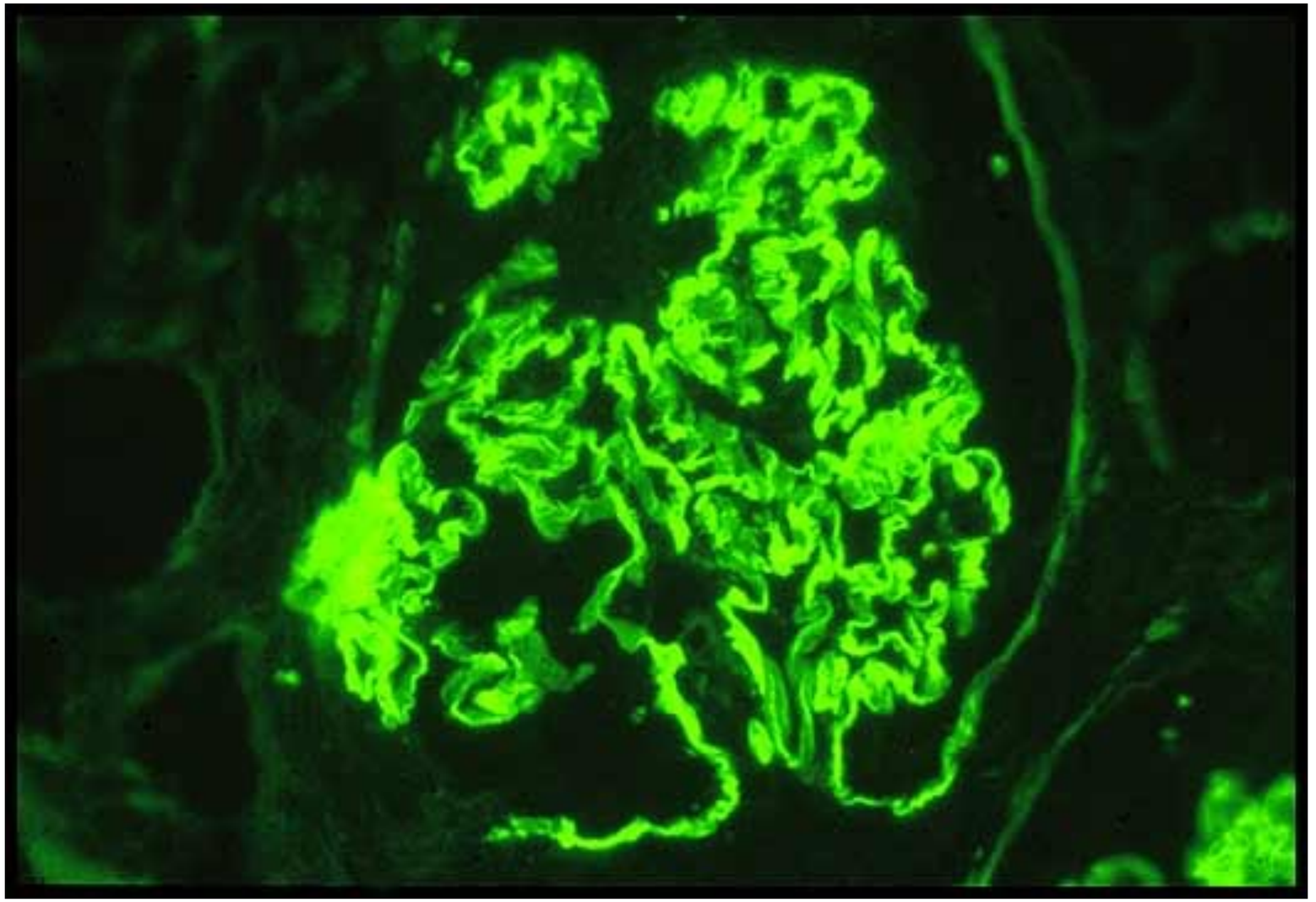
McAdoo SP, et al. Clin J Am Soc Nephrol 2017: 12: 1162–1172.
Segelmark M, et al. Nephrol Dial Transplant 2019: 34: 1826–1832.
McAdoo SP, et al. Semin Respir Crit Care Med 2018;39:494–503.



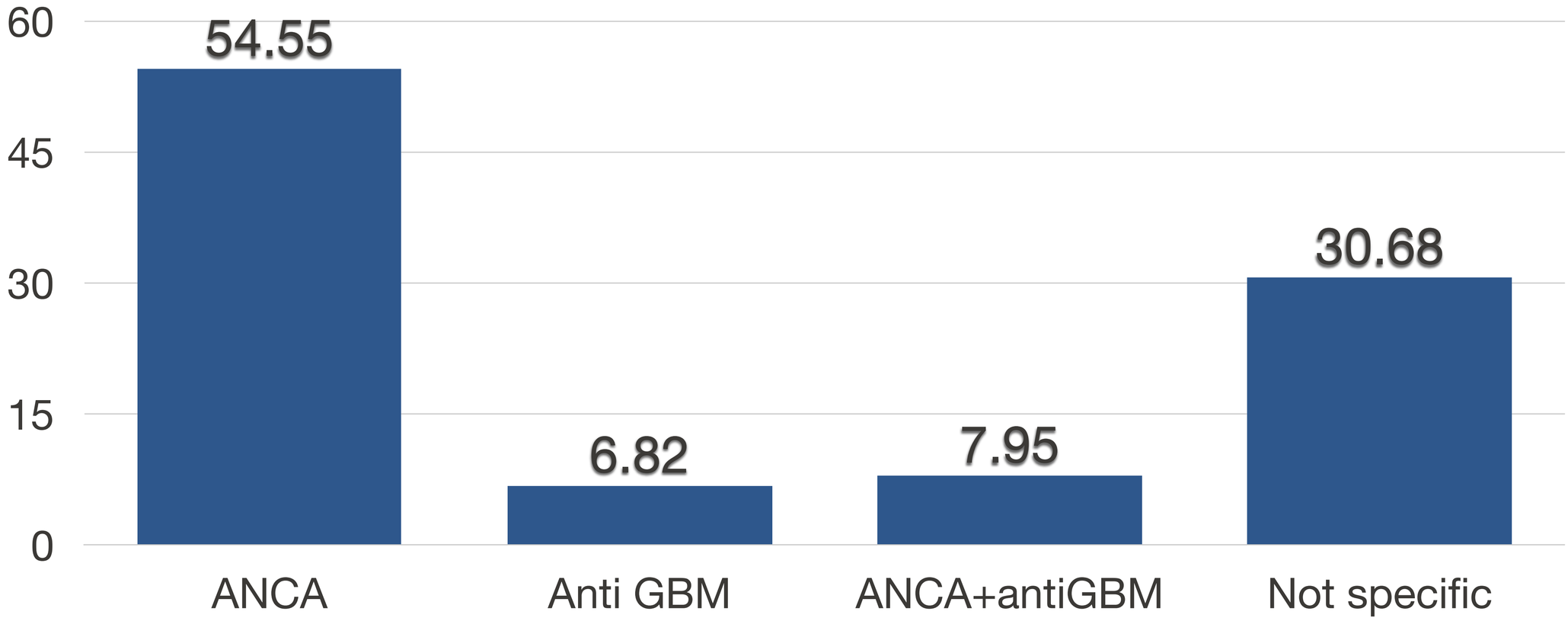
Main target of the autoantibodies is the noncollagenous domain (NC1) of the α 3 chain of type IV collagen.

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

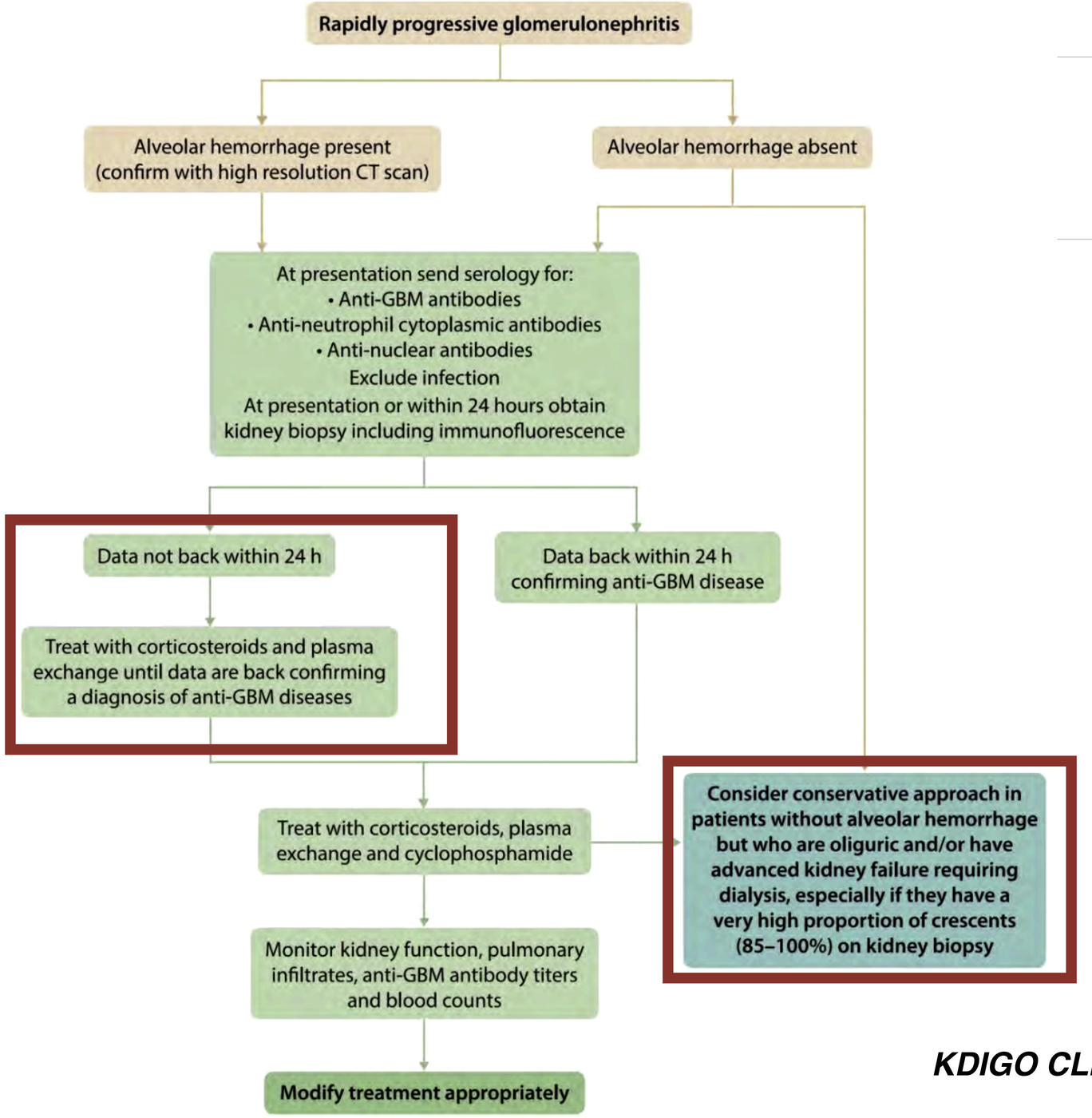
- We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis in all patients with anti-GBM GN
- Except those who are dialysis-dependent at presentation, have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage (1C).

Practice Point

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

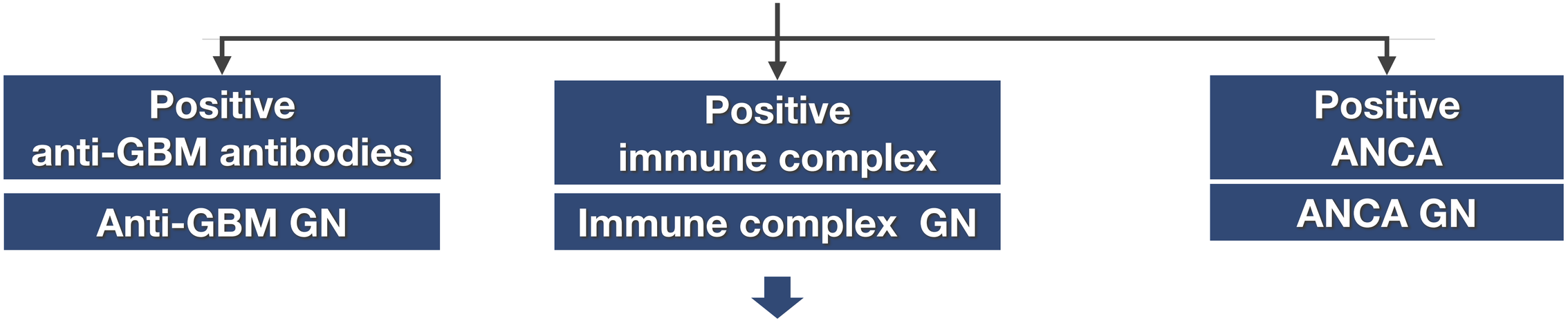
KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES. Kidney Int. 2021: 100, S1–S276.

Treatment of anti-GBM disease



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

Serologic analysis of patients with RPGN



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

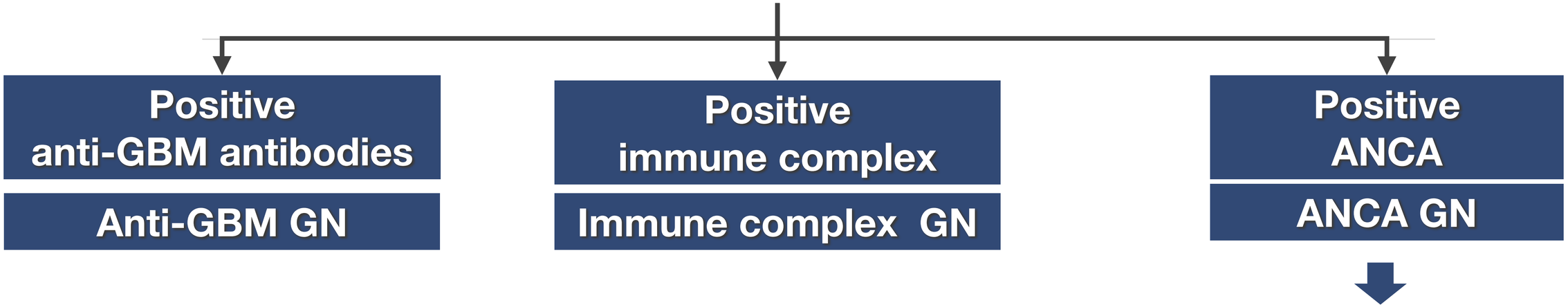
Treatment of IgAN with RPGN

Practice Point

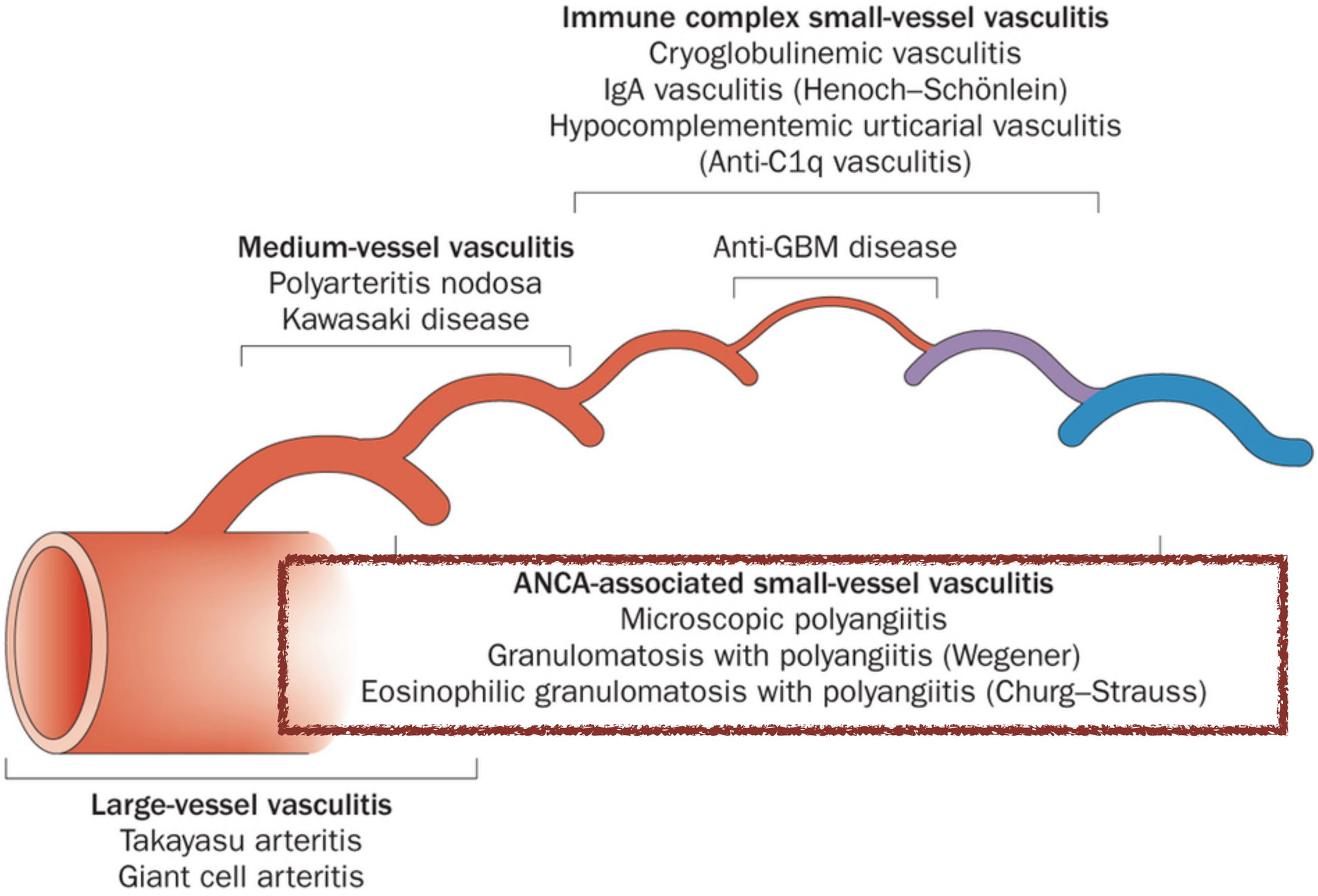
- A kidney biopsy demonstrate mesangial and endocapillary hypercellularity and a high proportion of glomeruli affected by crescents with areas of focal necrosis.
- The presence of crescents in a kidney biopsy in the absence of a concomitant change in SCr does not constitute rapidly progressive IgAN.
- 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.

Serologic analysis of patients with RPGN

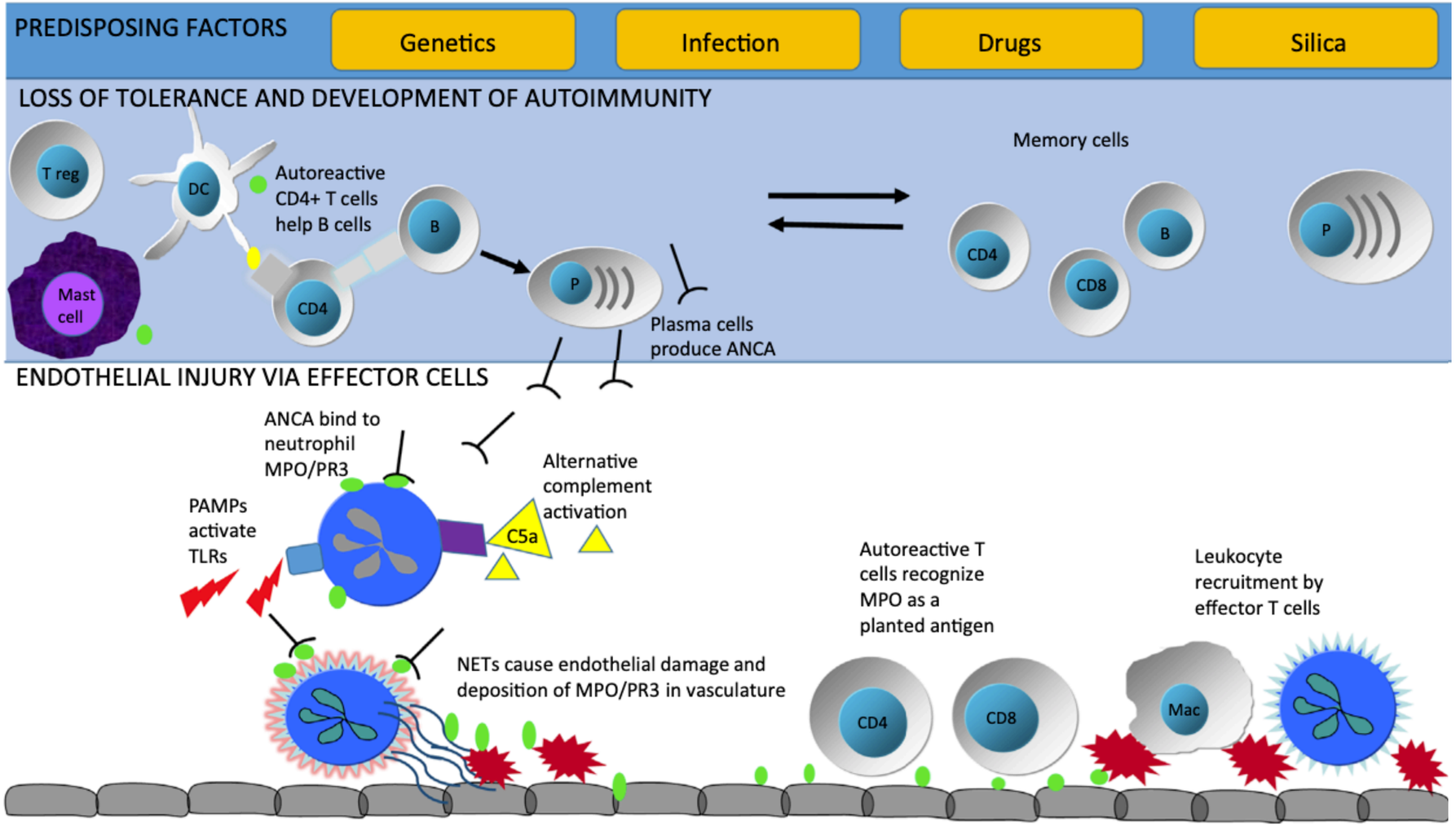


No extra renal disease	ANCA associated GN
Systemic necrotizing vasculitis	Microscopic polyangiitis
Respiratory necrotizing granulomas	Granulomatosis with polyangiitis
Asthma and eosinophilia	Eosinophilic granulomatosis with polyangiitis



Jennette, J. C. et al. Arthritis Rheum. 2013: 65, 1–11.

Pathogenesis of ANCA-associated vasculitis



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

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.

ACR: Wegener's granulomatosis

- Nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge)
- Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment (microscopic hematuria with or without red cell casts)
- Granulomatous inflammation on biopsy of an artery or perivascular area

>2 criteria: a sensitivity of 88 % and a specificity of 92 %

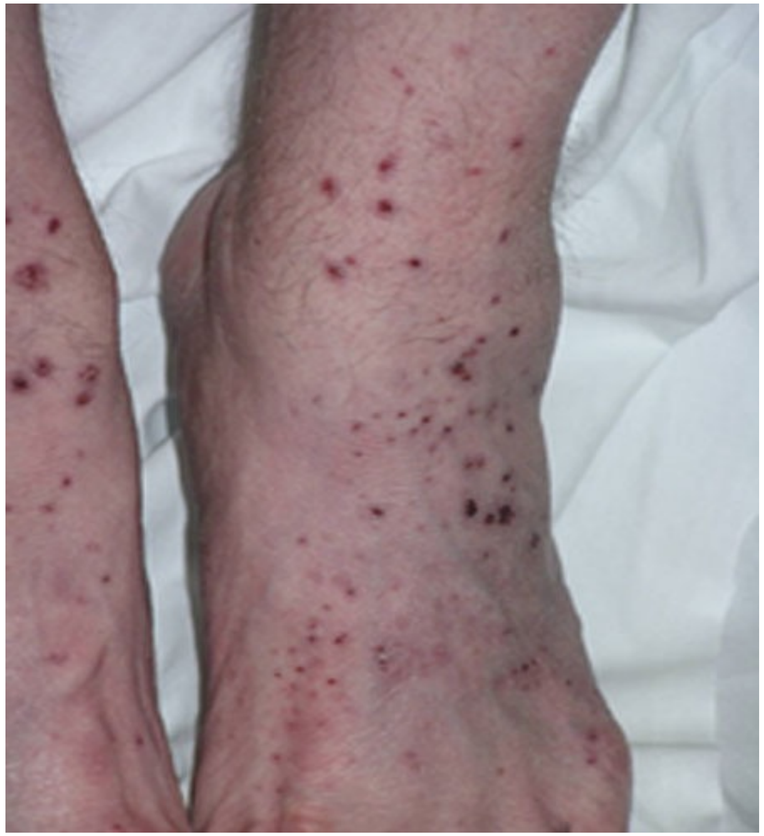
Leavitt RY, et al. Arthritis Rheum 1990;33(8):1101-7.

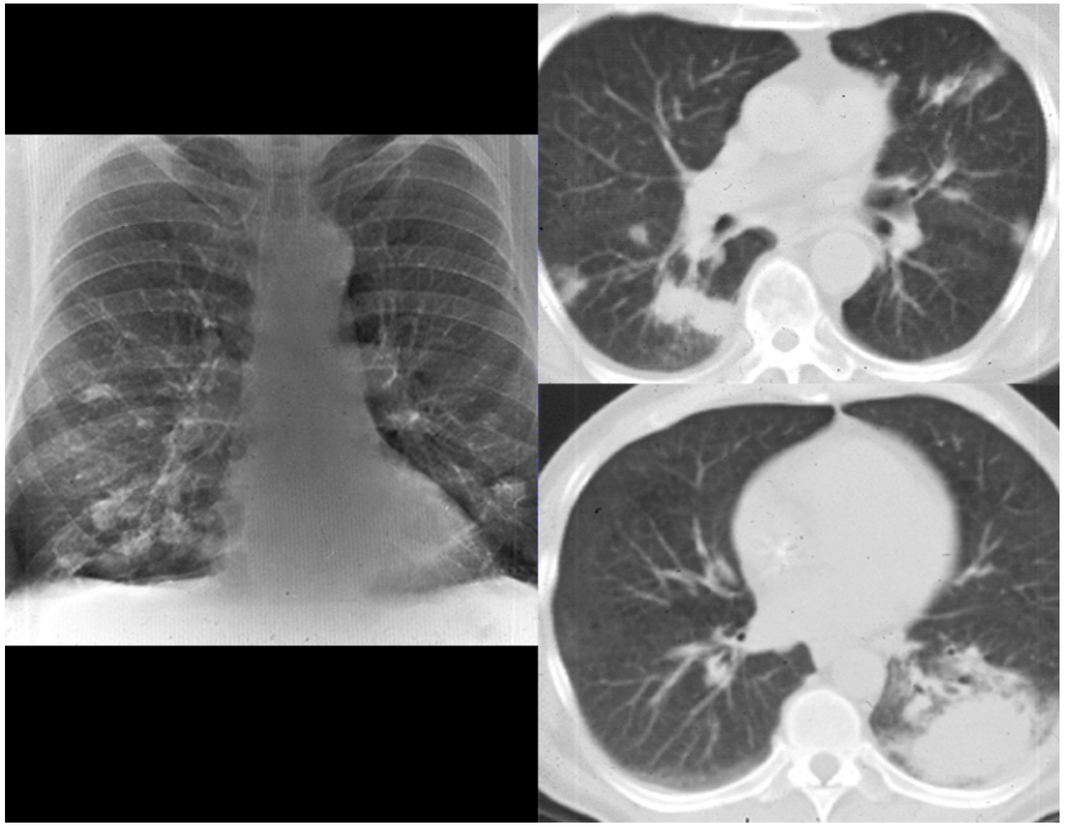
ACR 1990 criteria of Churg-Strauss syndrome

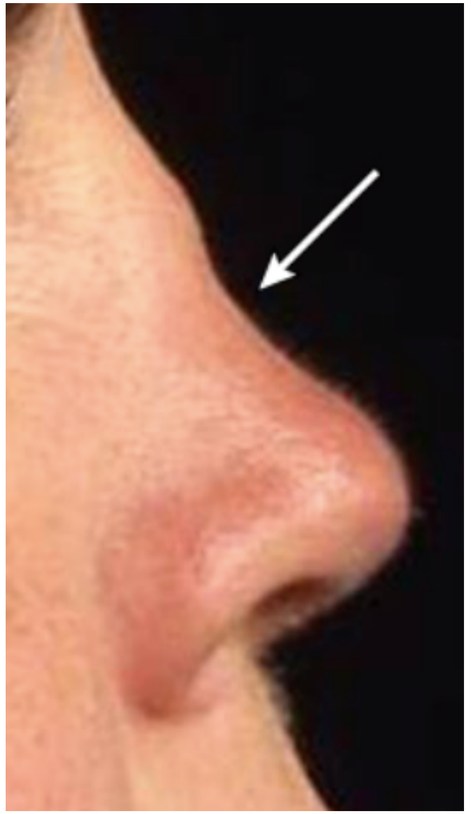
Criteria	Remarks
1.Asthma	History of expiratory rales
2.Eosinophilia	More than 10 %
3.Mononeuropathy or polyneuropathy	Caused by systemic vasculitis
4.Pulmonary infiltrate, non-fixed	Migratory/ transitory infiltrate
5.Paranasal sinus abnormality	Clinical evidence of acute or chronic paranasal sinusitis
6.Extravascular eosinophils accumulation	

>4 criteria: sensitivity of 85 % and specificity of 99.7 %

Systemic vasculitis







ANCA-associated glomerulonephritis

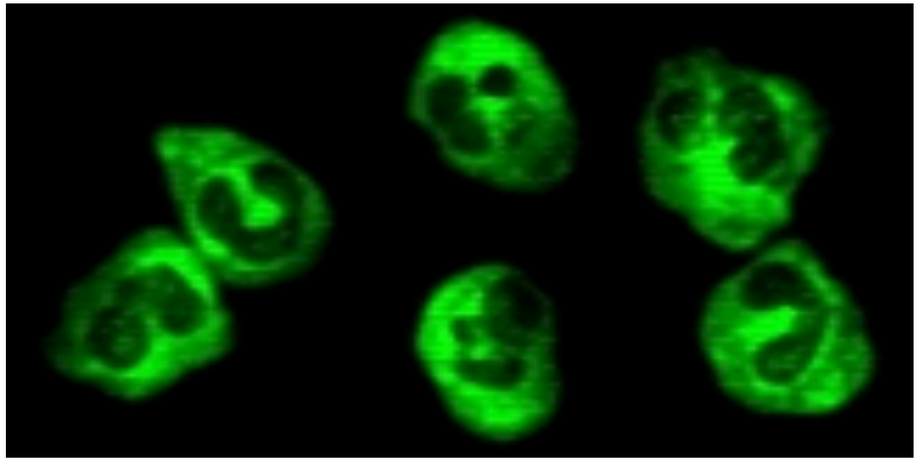
- Ages of 40 and 55 years > 70% of cases
- Microscopic hematuria with dysmorphic red blood cells and red cell casts
- Proteinuria usually moderate (1–3 g/day)
- Rapidly declining GFR over days or weeks
  - Pauci-immune focal and segmental necrotizing and crescentic GN
- Few subjects: asymptomatic microscopic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

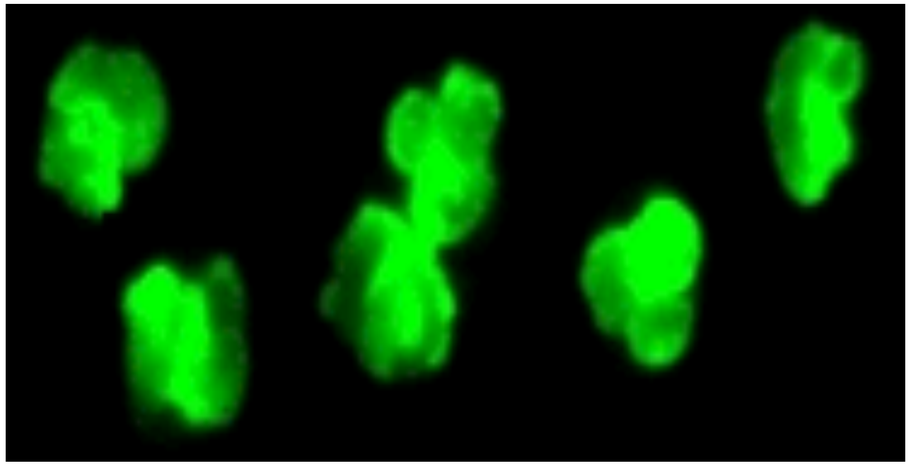
Indirect immunofluorescence

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

Indirect immunofluorescence

- C-ANCA pattern
  - C-ANCA high specificity > P-ANCA pattern for vasculitis
- P-ANCA
  - Variety of inflammatory illnesses, and low specificity for vasculitis.
  - Antibodies directed against lactoferrin, elastase, cathepsin G, bactericidal permeability inhibitor, catalase, lysozyme, beta-glucuronidase, etc……

ANCA in other diseases

- Autoimmune diseases
  - Systemic vasculitis : HSP, Kawasaki’s disease
  - Other rheumatic disease: RA, SLE, Sjögren syndrome
  - Inflammatory bowel disease
- Infections
  - Endocarditis, respiratory tract infection, chromomycosis, HIV, amoebiasis
- Drugs
  - Propylthiouracil, hydralazine, minocycline

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%)	

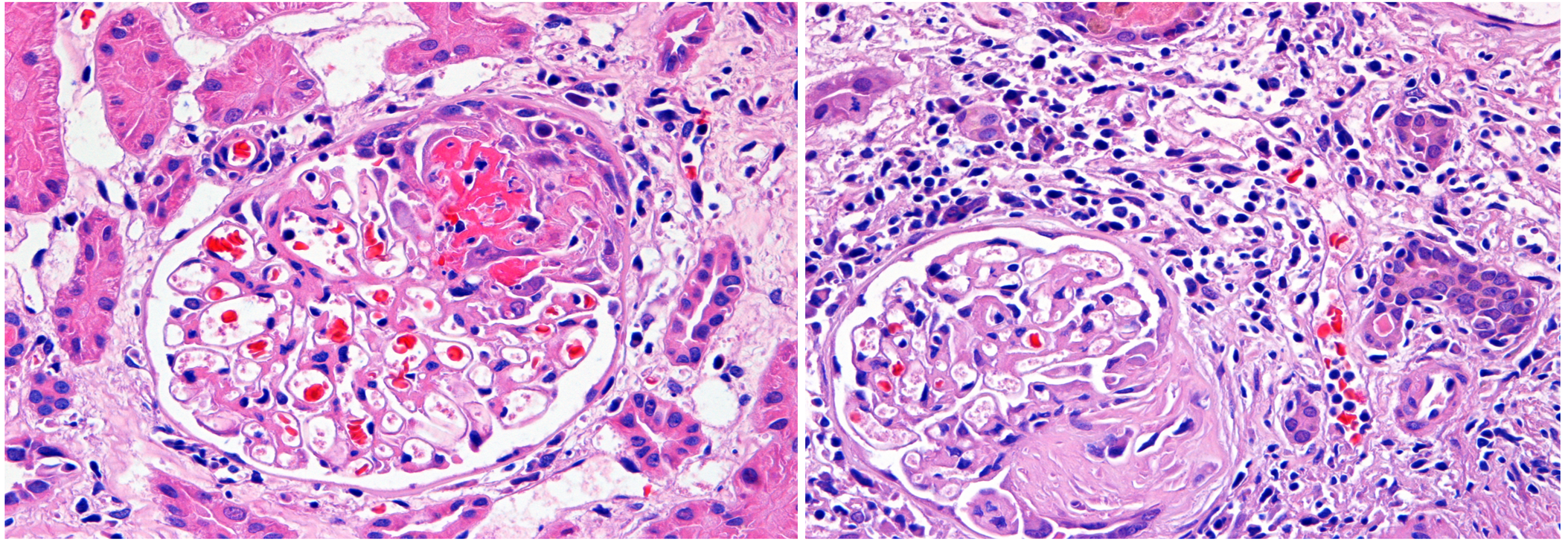
Geetha D, et al. Am J Kidney Dis. 2020; 75(1):124-137.

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)

Kidney Biopsy

Segmental fibrinoid necrosis and cellular crescent composed of mononuclear leukocytes and epithelial cells



Satirapoj B. Essentials of Glomerular Disease 2018.

Diagnosis of ANCA-associated vasculitis

Practice Point

- **In case of a clinical presentation compatible with small-vessel vasculitis in combination with positive MPO- or PR3-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating**

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ANCA test: Relapses

Practice Point

- **The persistence of ANCA positivity, an increase in ANCA levels, and a change in ANCA from negative to positive are only modestly predictive of future disease relapse and should not be used to guide treatment decisions.**

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Initial treatment of RPGN

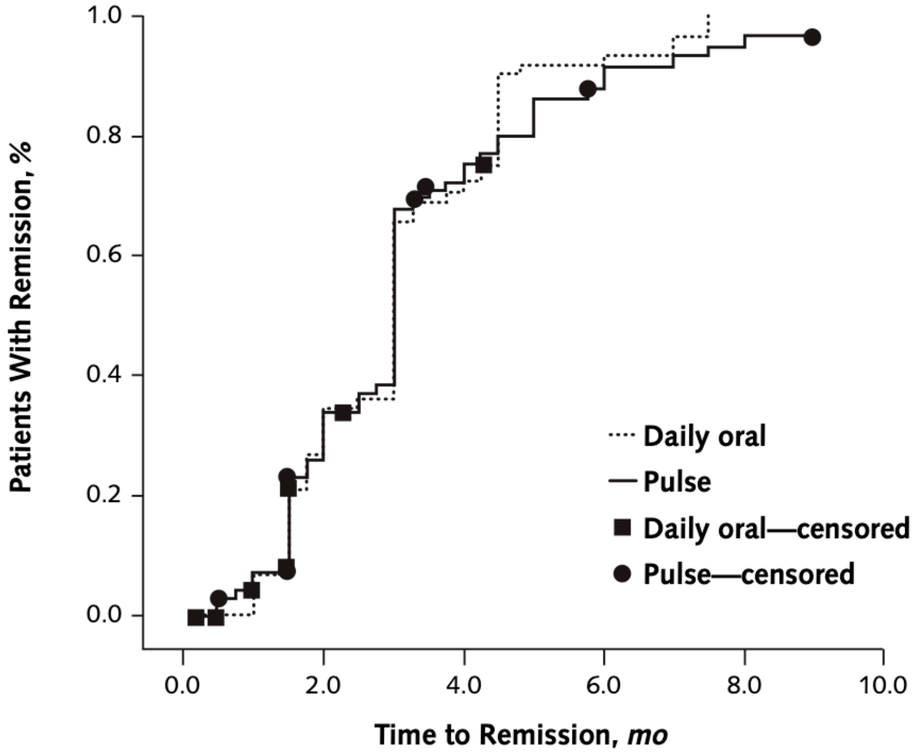
- Aggressive immunosuppressive agents
  - Intravenous methylprednisolone 500-1000 mg/day x 3 days
  - Cyclophosphamide (IVCY/Oral CY)
- Need to be confirm definite diagnosis for further Rx
  - Serology + kidney biopsy

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

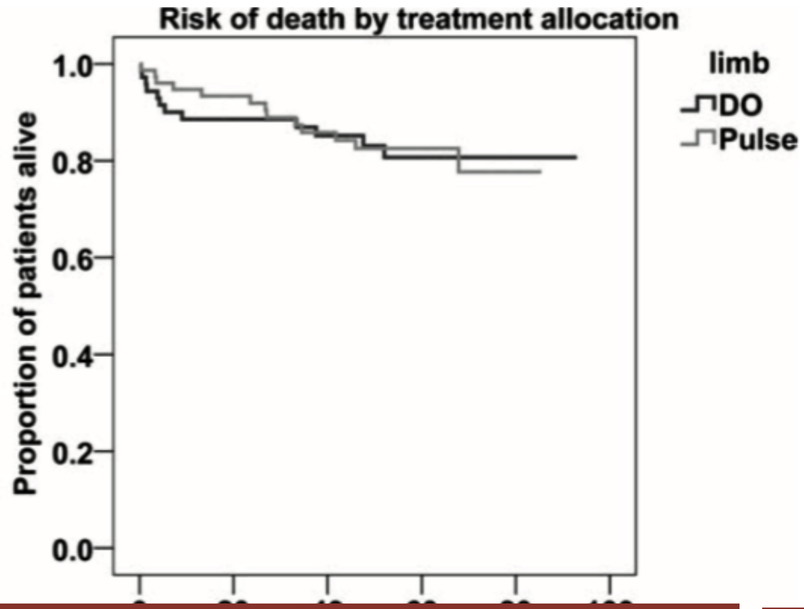
- **Infectious side effects**
- **Oral CYC (69.6%)**
- **IV CYC (40.7%) (P < 0.05)**

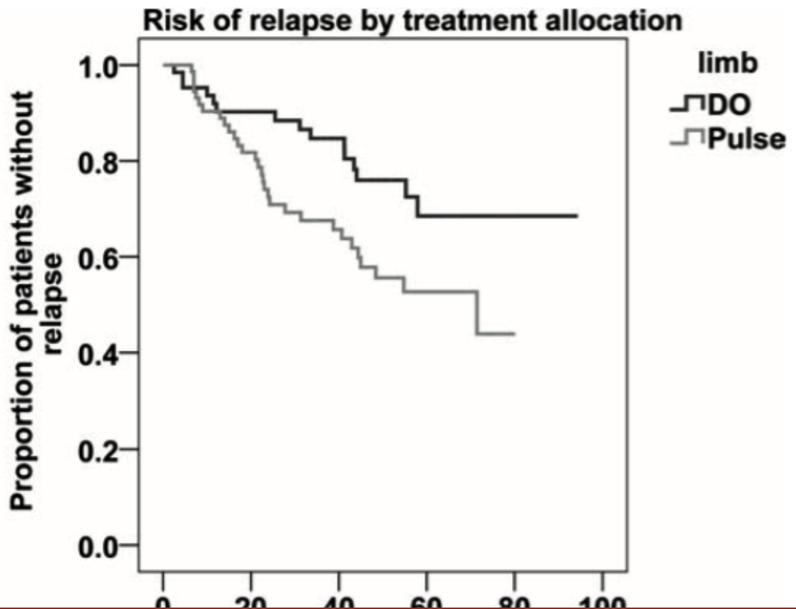
de Groot K; et al. Ann Intern Med. 2009;150(10):670-80.

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*

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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.

Treatment of ANCA associated vasculitis (RPGN)

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

Practice Point

- In patients presenting with markedly reduced or rapidly declining GFR (SCr >4.0 mg/dL), there are limited data to support rituximab and glucocorticoids.
  - Cyclophosphamide and glucocorticoids are preferred for induction therapy.
  - Combination of rituximab and cyclophosphamide can also be considered in this setting.

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

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 of ANCA associated vasculitis (RPGN)

- Considerations for choosing between rituximab and cyclophosphamide for induction therapy

Rituximab preferred	Cyclophoshamide preferred
Children and adolescents	Rituximab difficult to access
Pre-menopausal women and men concerned about their family	Severe GN (Scr > 4 mg/dL at diagnosis) combination of two IVCY with rituximab can be considered.
Frail older adults	
Glucocorticoid sparing especially	
Relapsing disease	
PR-3 ANCA disease	

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

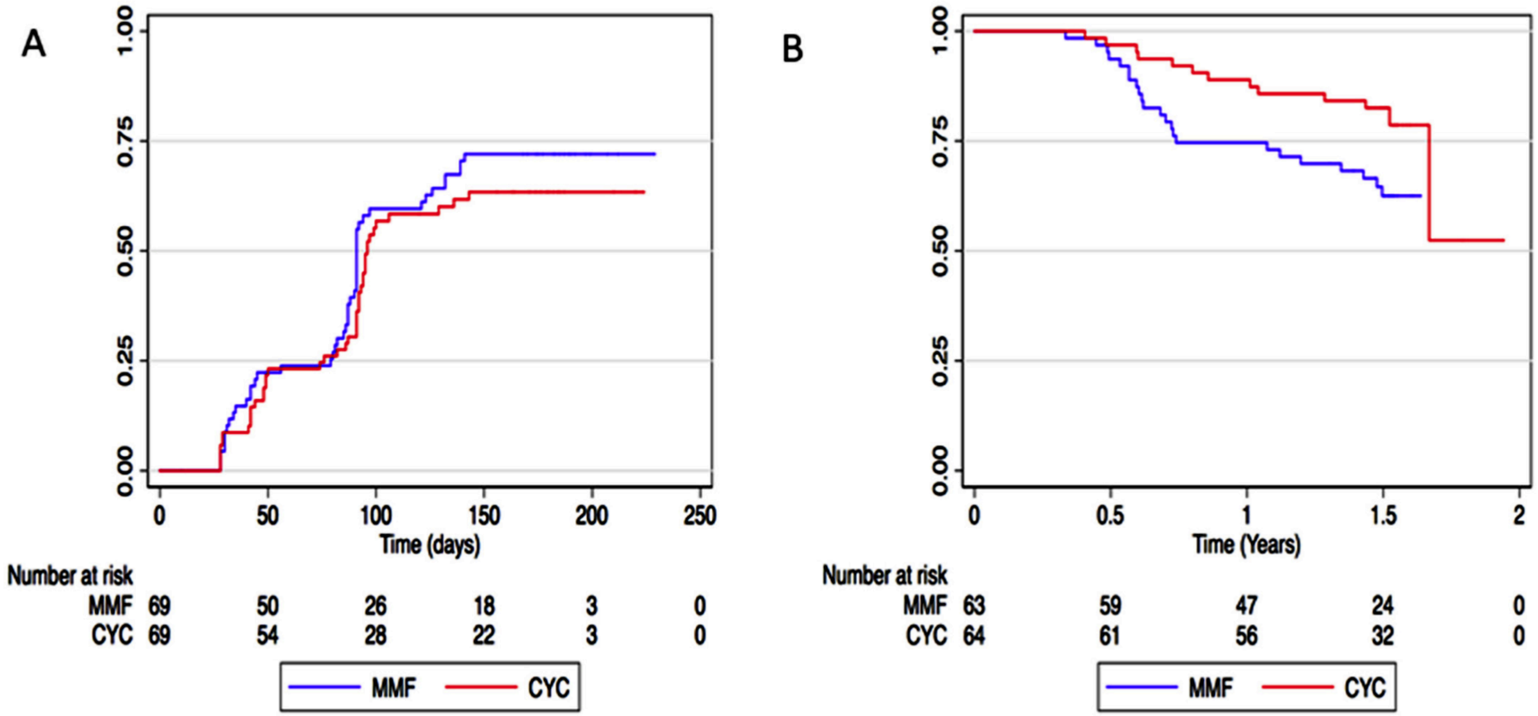
MMF

CLINICAL SCIENCE

Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial

Rachel B Jones,[1] Thomas F Hiemstra,[2,3] Jose Ballarin,[4] Daniel Engelbert Blockmans,[5]

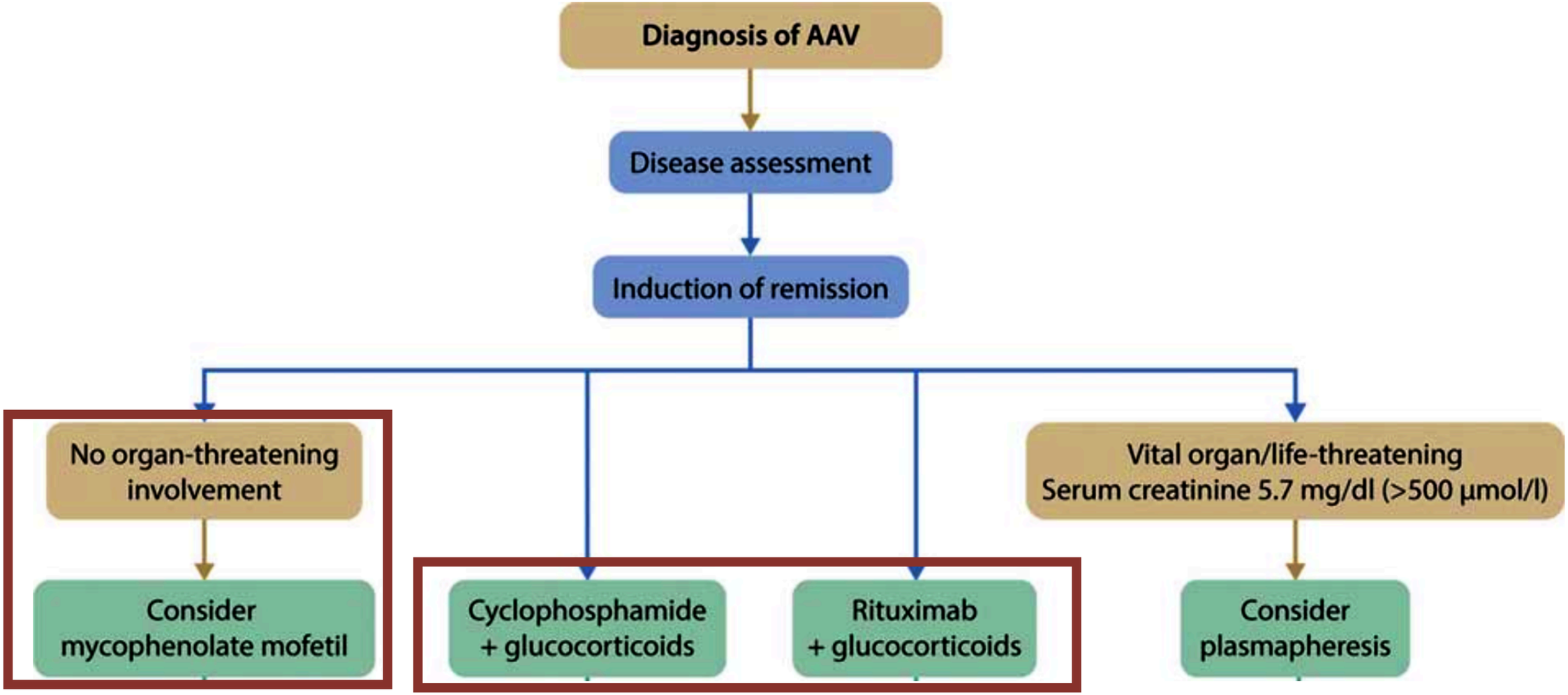
Primary remission: 67% in the MMF group and 61% in the CY group



More relapses occurred in the MMF group (33%) compared with the CY group (19%)

Jones RB, et al. Ann Rheum Dis 2019; 78: 399-405.

Treatment of ANCA associated vasculitis (RPGN)



KDIGO GUIDELINE. Kidney Int. 2021:100: S1–S276.

Treatment of ANCA associated vasculitis (RPGN)

- **Discontinue immunosuppressive therapy after three months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease**

Oral CY	IVCY	Rituximab	Rituximab and IVCY	MMF
2 MKD 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/m2/wk x 4 wk or 1 g at wk 0 and 2	375 mg/m2/wk x 4 wk with IVCY 15 mg/kg at wk 0 and 2 or rituximab 1 g at 0 and 2 wk with IVCY 500 mg/ 2 wk x 6	2000 mg/d may be increased to 3000 mg/d for poor treatment response

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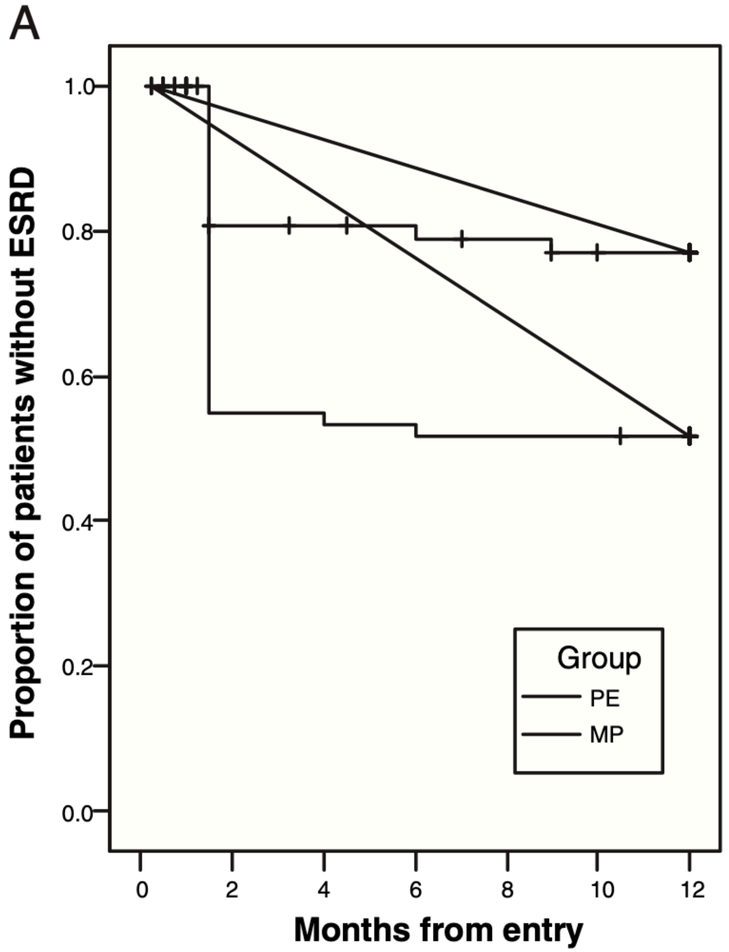
Plasma exchange

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,‖



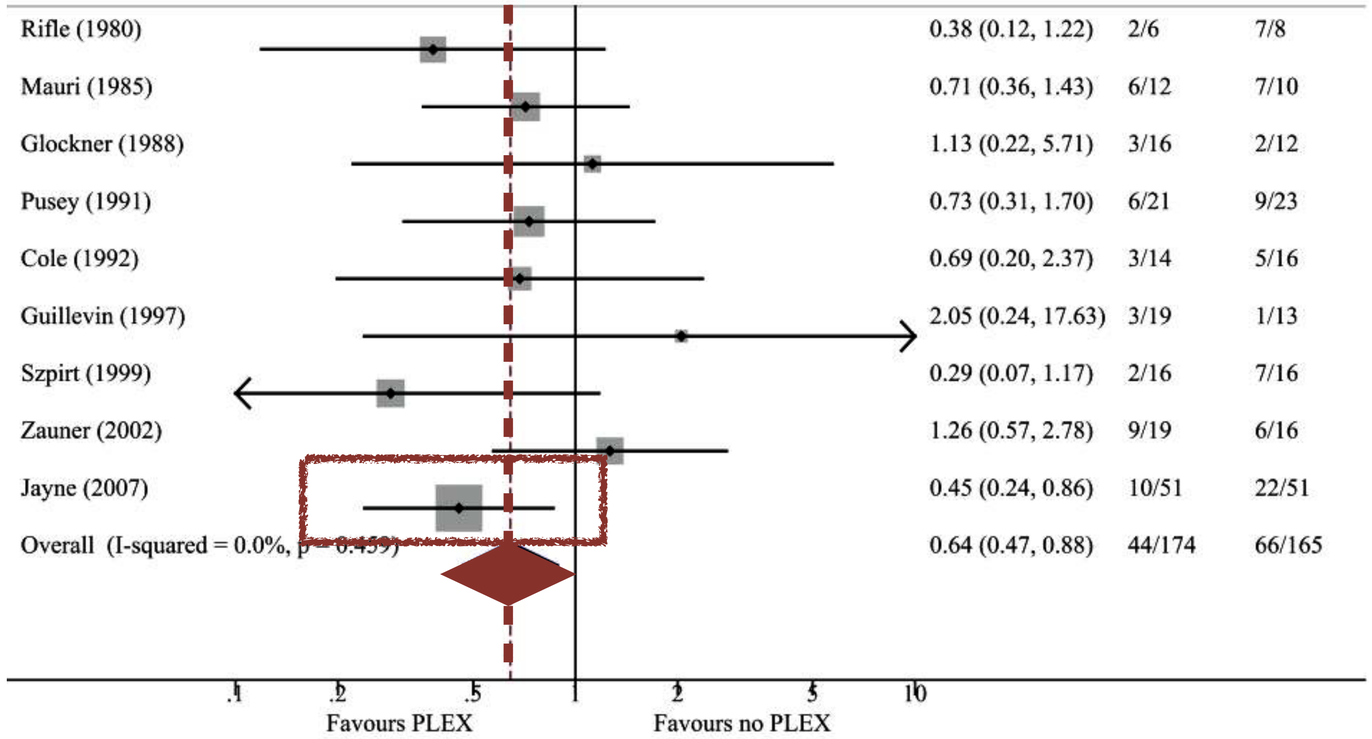
137 patients with pauci-immune glomerulonephritis, and serum creatinine >5.7 mg/dL.
Serum creatinine was 8.3 mg/dL and 69 percent required dialysis,

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.

Plasma exchange

- Patients requiring dialysis or with rapidly increasing serum creatinine
- Patients with diffuse alveolar hemorrhage who have hypoxemia
- Patients with an overlap syndrome of ANCA vasculitis and anti-GBM

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary haemorrhage	Vasculitis in associated with anti-GBM disease
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 fort 14 days or until ant-GBM antibodies are undetectable

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

ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

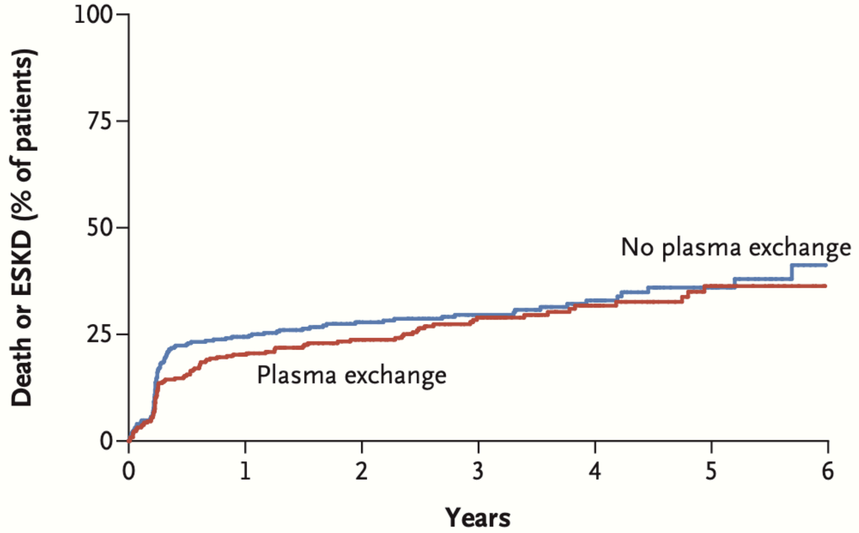
M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, 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

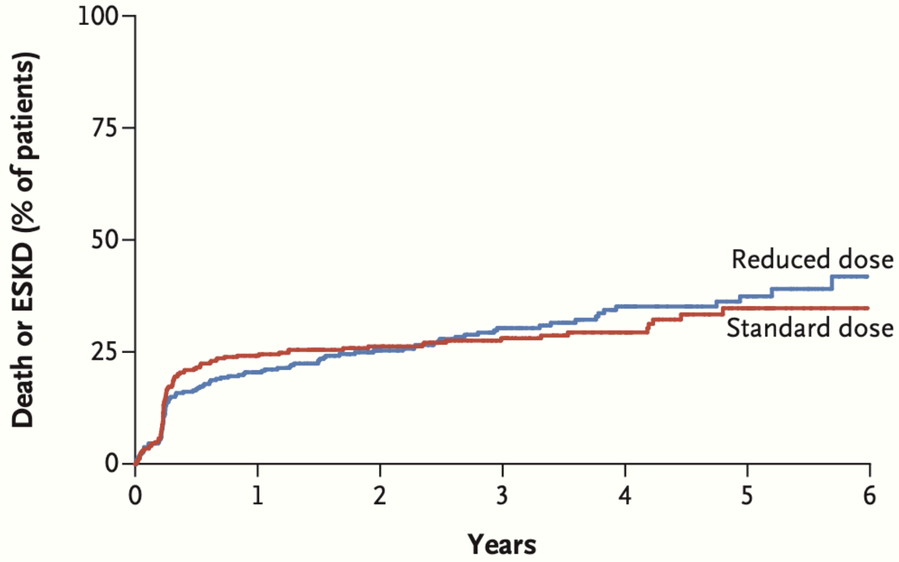
Death from any cause or ESKD occurred in 28.4% in the plasma-exchange group and in 31.0% in the control group (hazard ratio, 0.86; 95% CI 0.65 to 1.13; P=0.27).

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

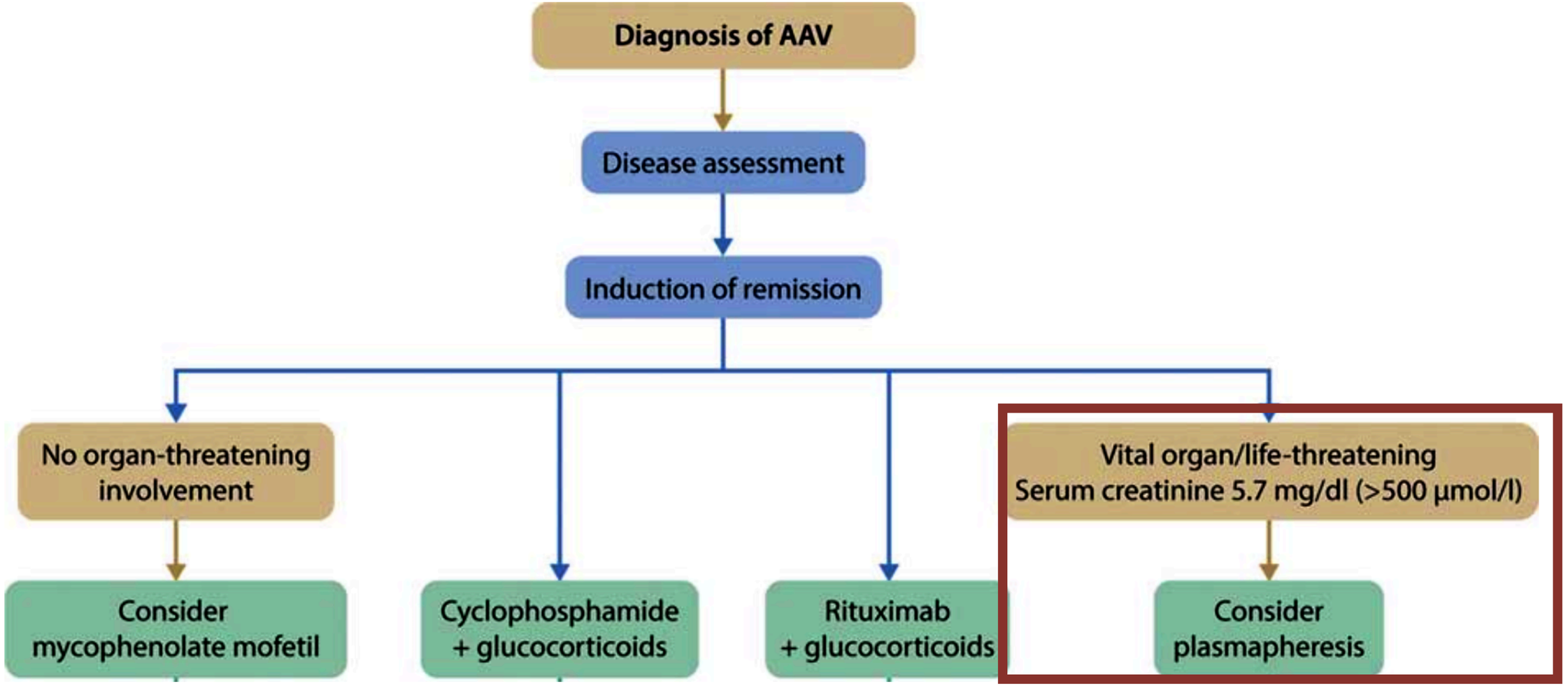
B Primary Outcome According to Glucocorticoid Regimen



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.

Treatment of ANCA associated vasculitis (RPGN)



KDIGO GUIDELINE. Kidney Int. 2021:100: S1–S276.

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

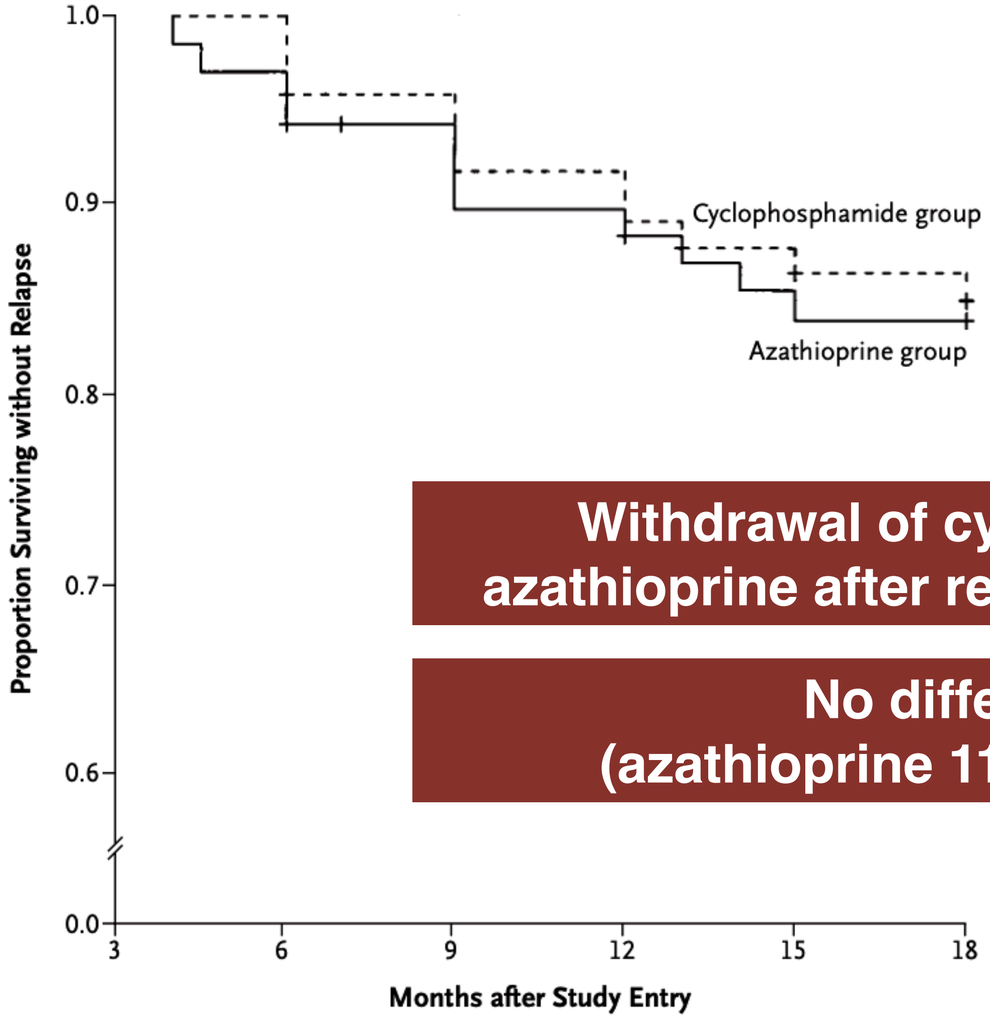
ORIGINAL ARTICLE

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.

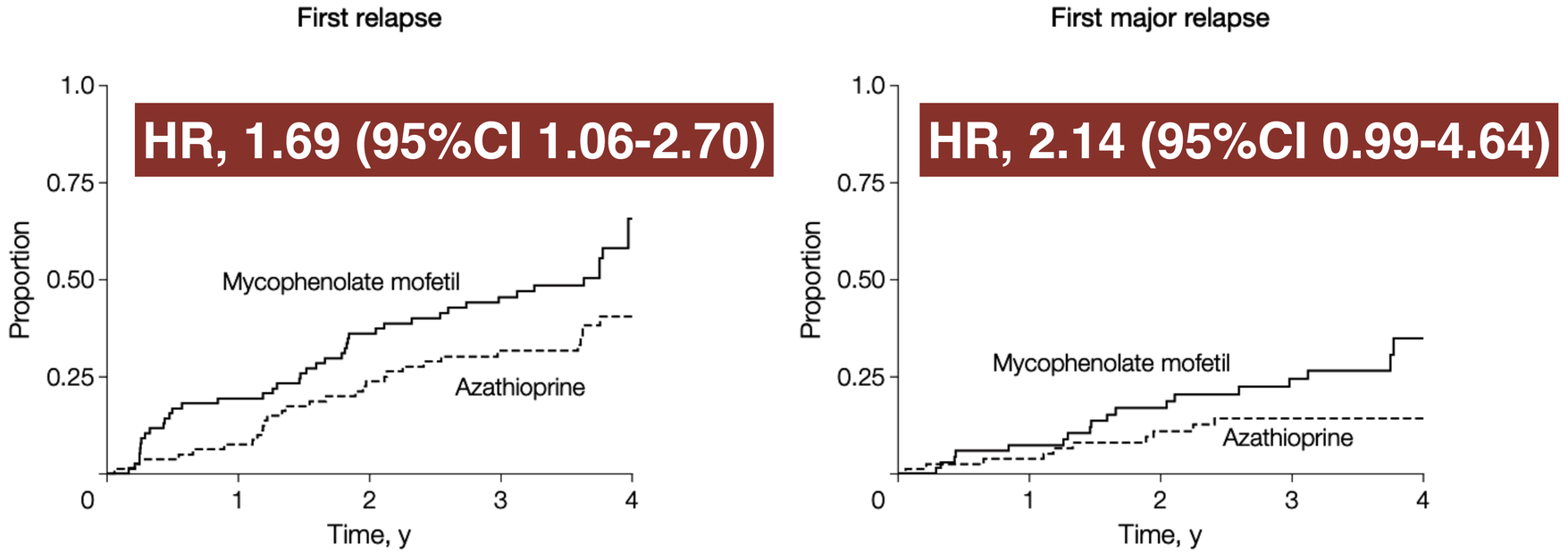
No difference in severe adverse events (azathioprine 11% vs. cyclophosphamide 10 %, P=0.94)

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

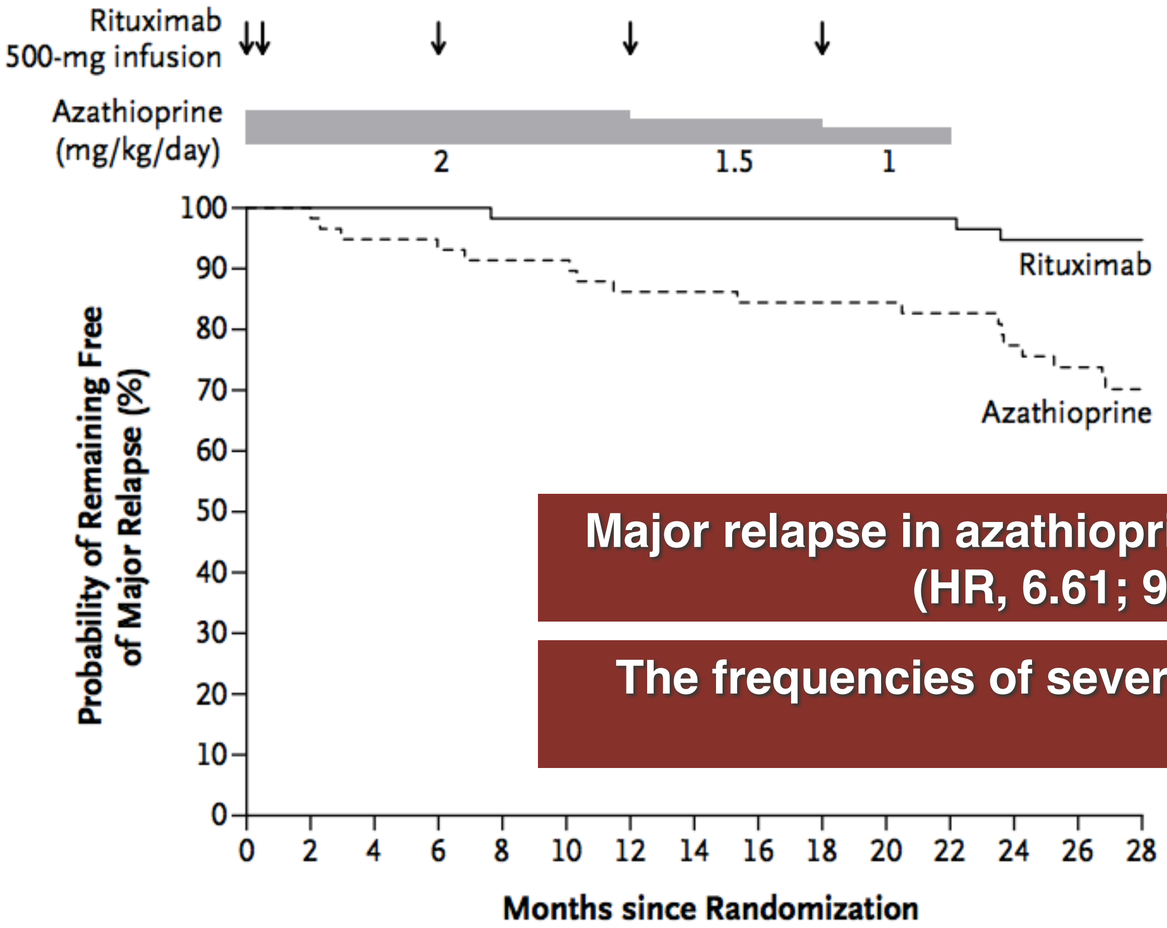


No. at risk
Azathioprine
Mycophenolate mofetil

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

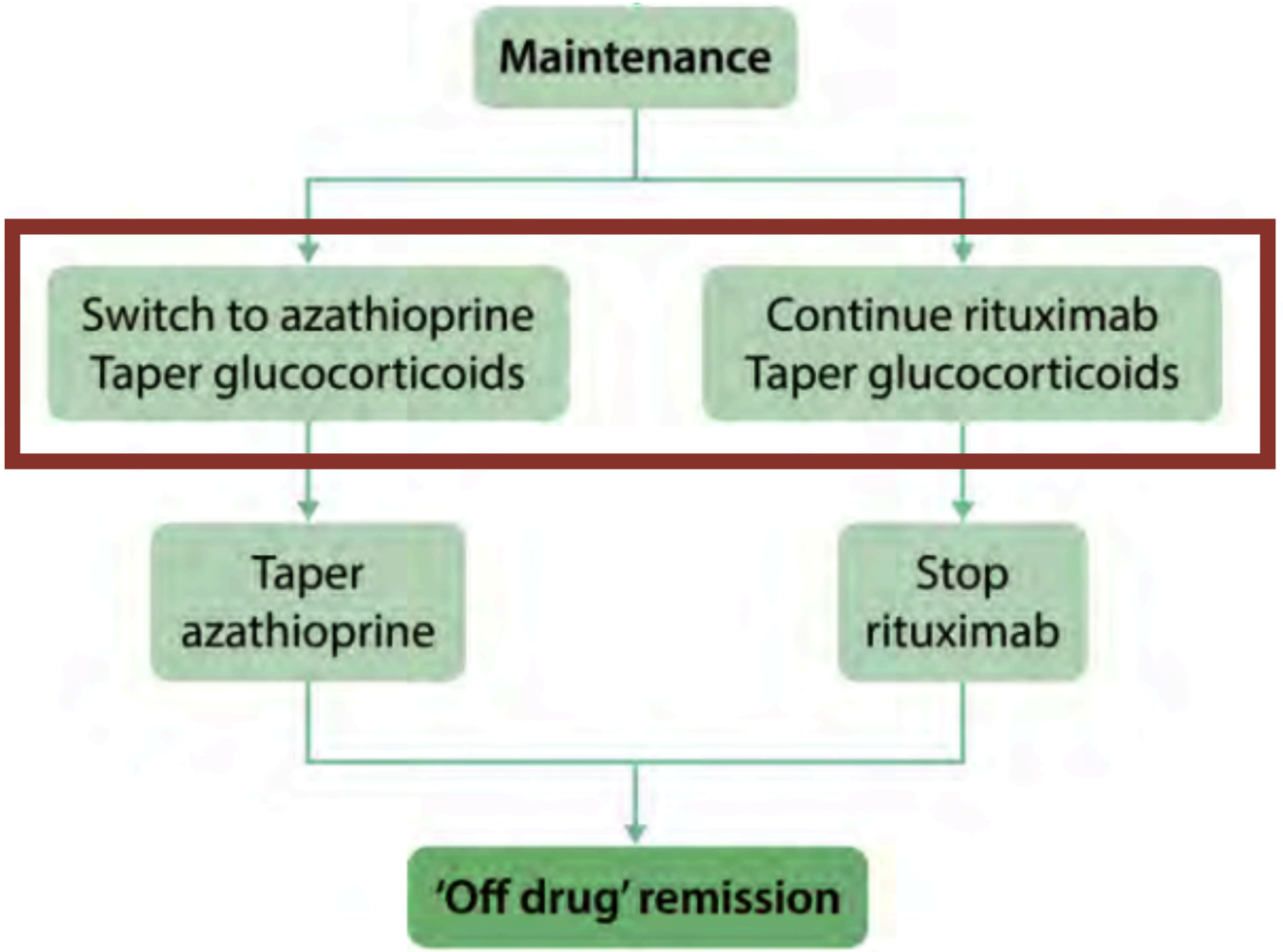


Major relapse in azathioprine group (29%) and rituximab group (5%) (HR, 6.61; 95% CI, 1.56-27.96; P=0.002)

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

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

Treatment of ANCA associated vasculitis (RPGN)



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Treatment of ANCA associated vasculitis (RPGN)

- We recommend maintenance therapy with either rituximab or azathioprine and low-dose glucocorticoids after induction of remission (1C).
- The optimal duration of azathioprine plus low-dose glucocorticoids is not known but should be between 18 months and four years after induction of remission.

Rituximab preferred	Azathioprine preferred
Relasping disease	Low baseline IgG< 300 mg/dL
PR-3-ANCA disease	Hepatitis B exposure (HBsAg positive)
Frail older adults	LImited availability of rituximab
Glucocorticoid sparing especially important	
Azathioprine allergy	

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

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

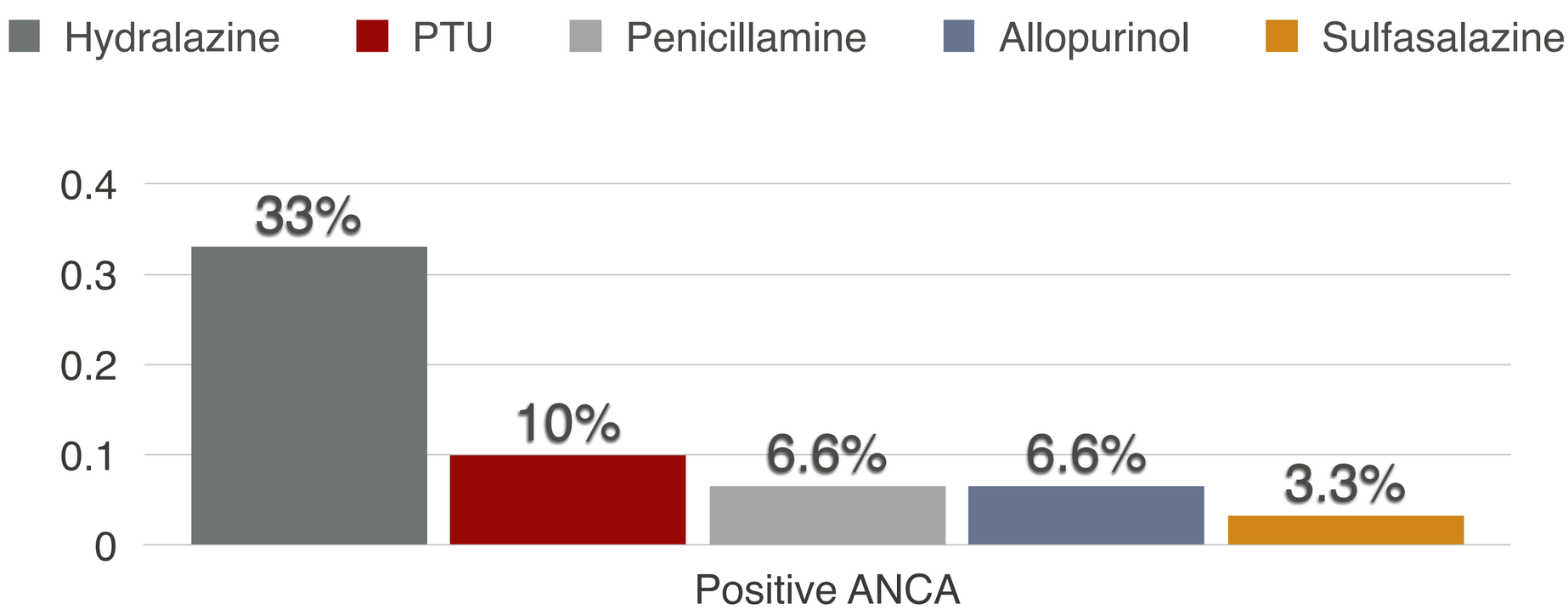
- 524 patients with newly diagnosed AAV
- 1-year mortality probability was 11.1%
  - 59% therapy-associated adverse events
  - 14% active vasculitis

Severe infection

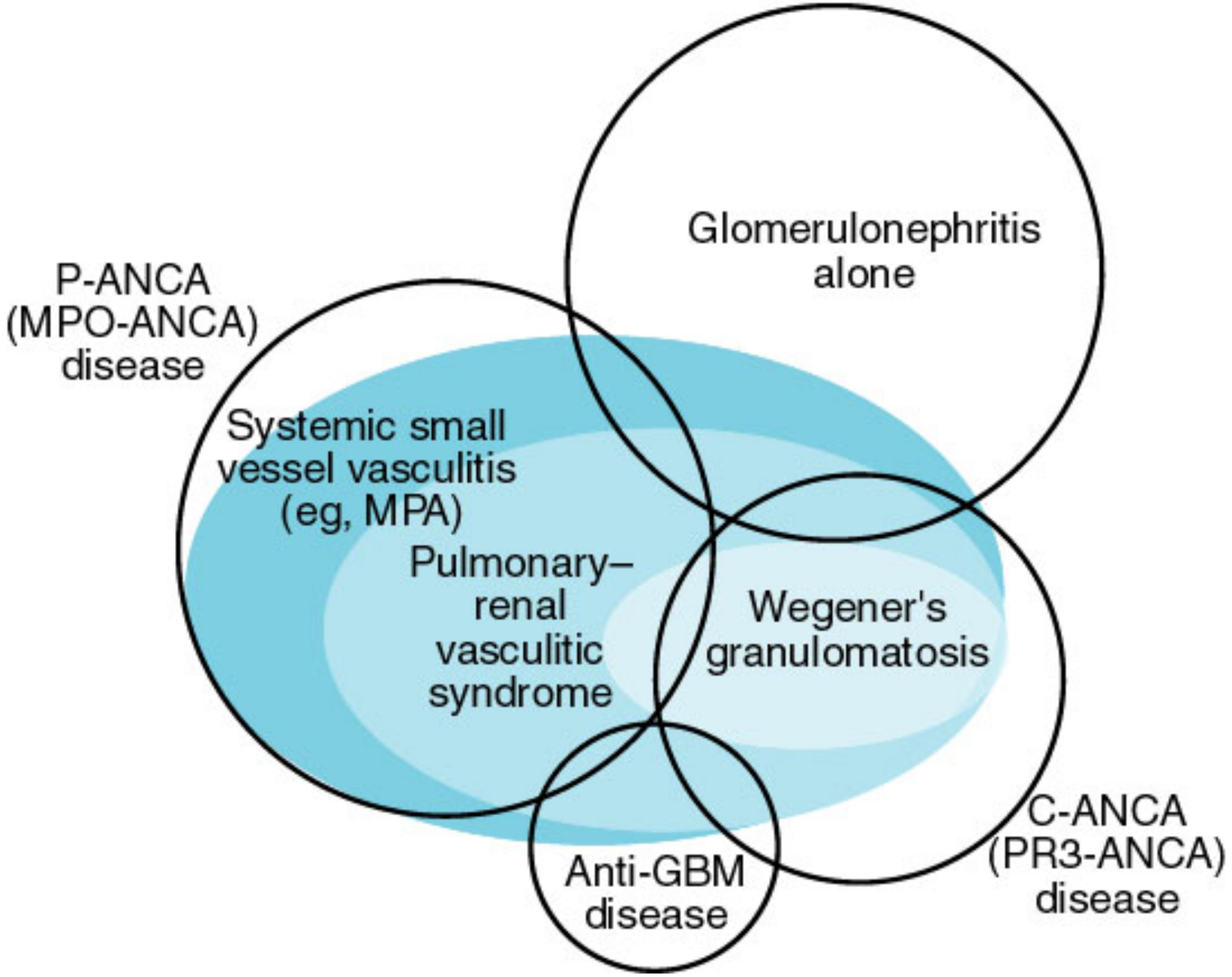
Mark A Little, et al. Ann Rheum Dis 2010;69:1036-1043

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.

DEPARTMENT OF MEDICINE
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