Rapidly Progressive Glomerulonephritis

Assoc. Prof. Bancha Satirapoj, MD
Division of Nephrology
Department of Medicine
Phramongkutklao Hospital and College of Medicine

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

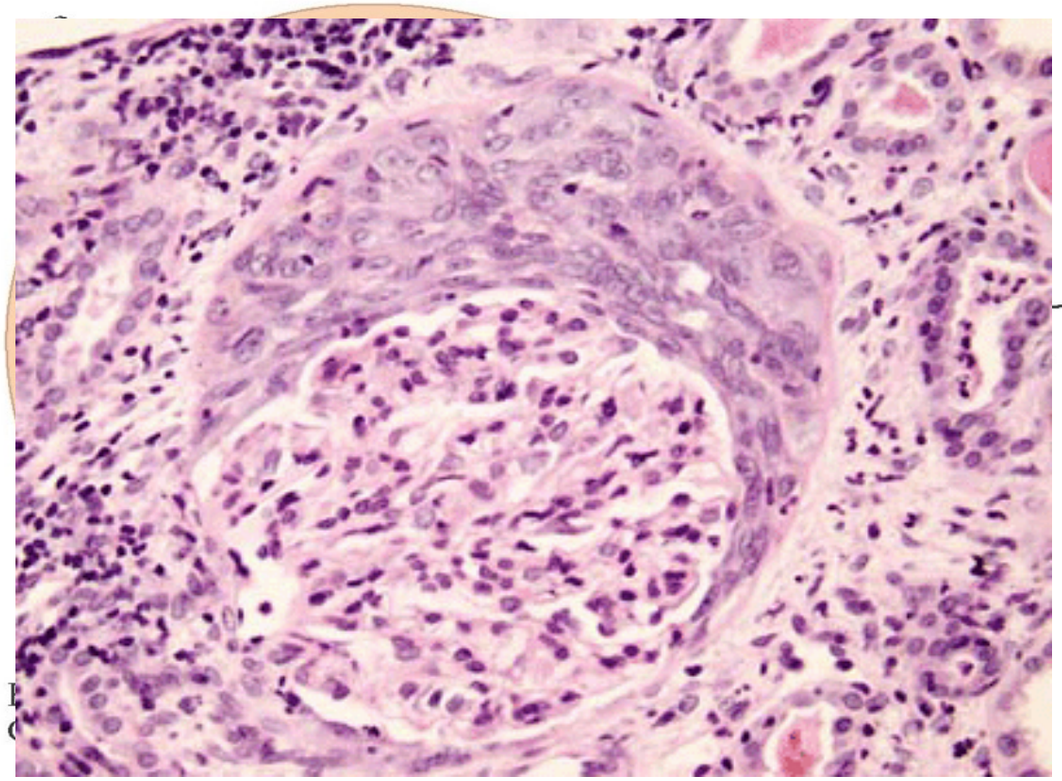
- Slowing developing renal insufficiency
- Proteinuria > 3 g/day and hematuria
- Hypertension
- Shrunken smooth kidneys

Satirapoj B. Common Problems in Internal Medicine. Bangkok 2010. p. 498-513.

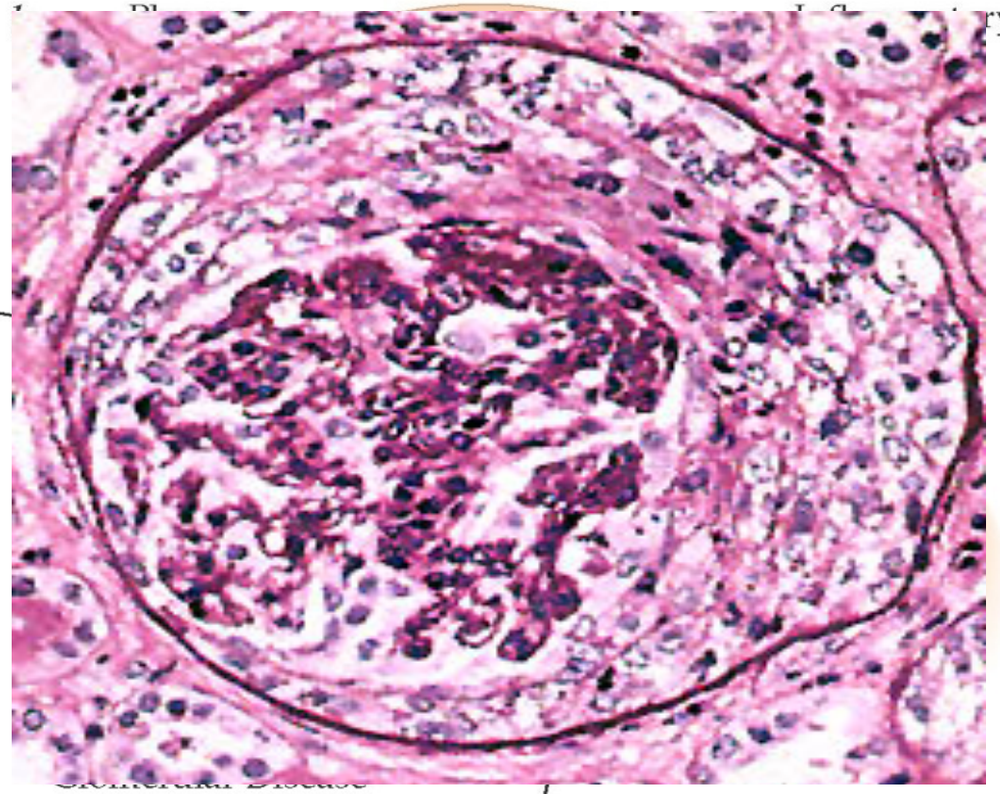
Manifestation of glomerular diseases

Disease	Nephrotic features	Nephritic features
Minimal change glomerulopathy	++++	-
Membranous glomerulopathy	++++	+
Focal segmental glomerulosclerosis	+++	++
Fibrillary glomerulonephritis	+++	++
Mesangioproliferative glomerulopathy (IgAN, LN)	++	++
Membranoproliferative glomerulonephritis (MPGN)	++	+++
Proliferative glomerulonephritis (IgAN, LN)	++	+++
Acute diffuse proliferative glomerulonephritis (PSGN)	+	++++
Crescentic glomerulonephritis	+	++++

Adapted from Brenner & Rector's the kidney 10th edition, 2016



d



c

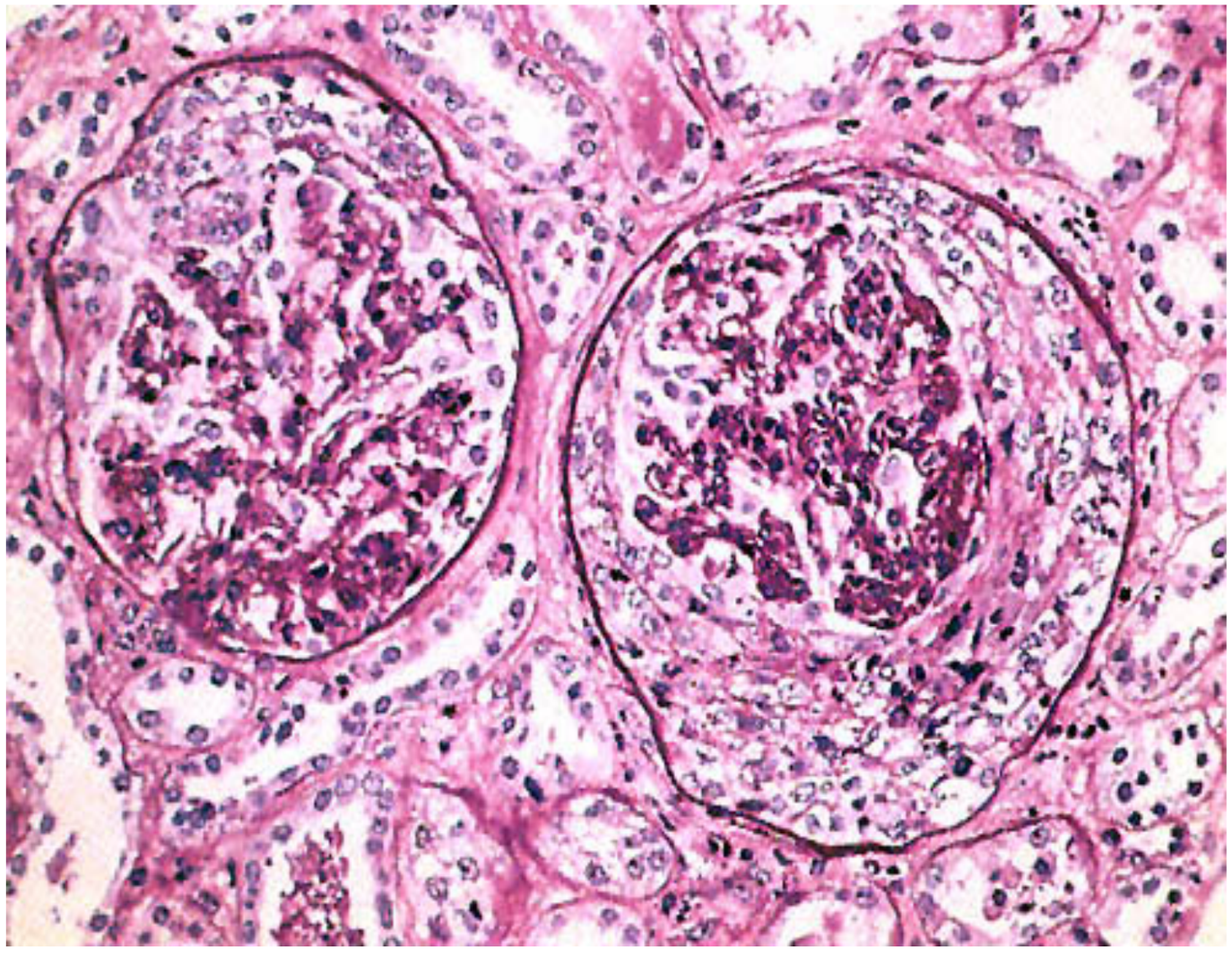
Infiltrating Macrophage

Interstitial Fibroblast

Fibrocellular Crescent

Proliferating Parietal Epithelial Cells

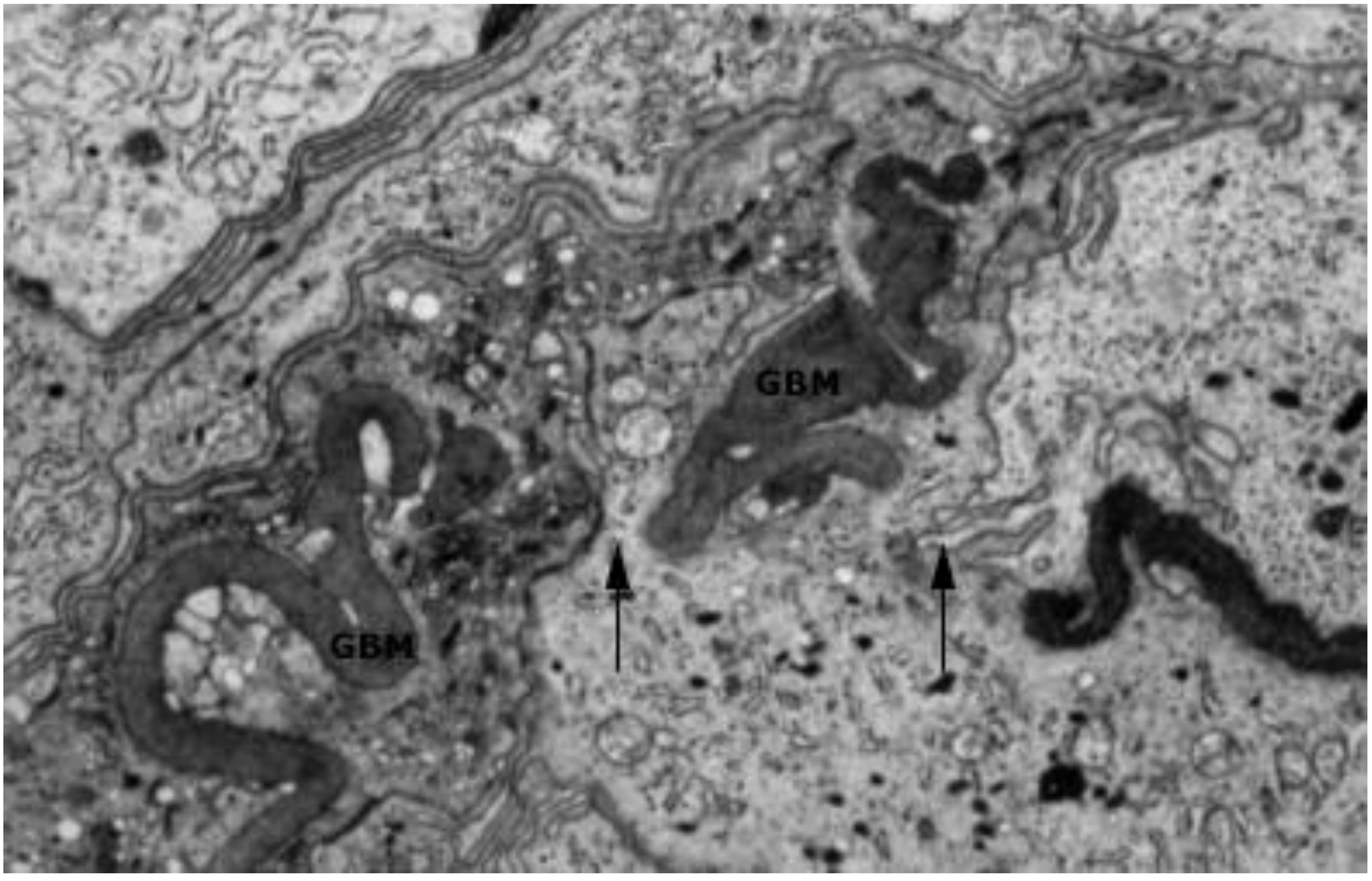
RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS



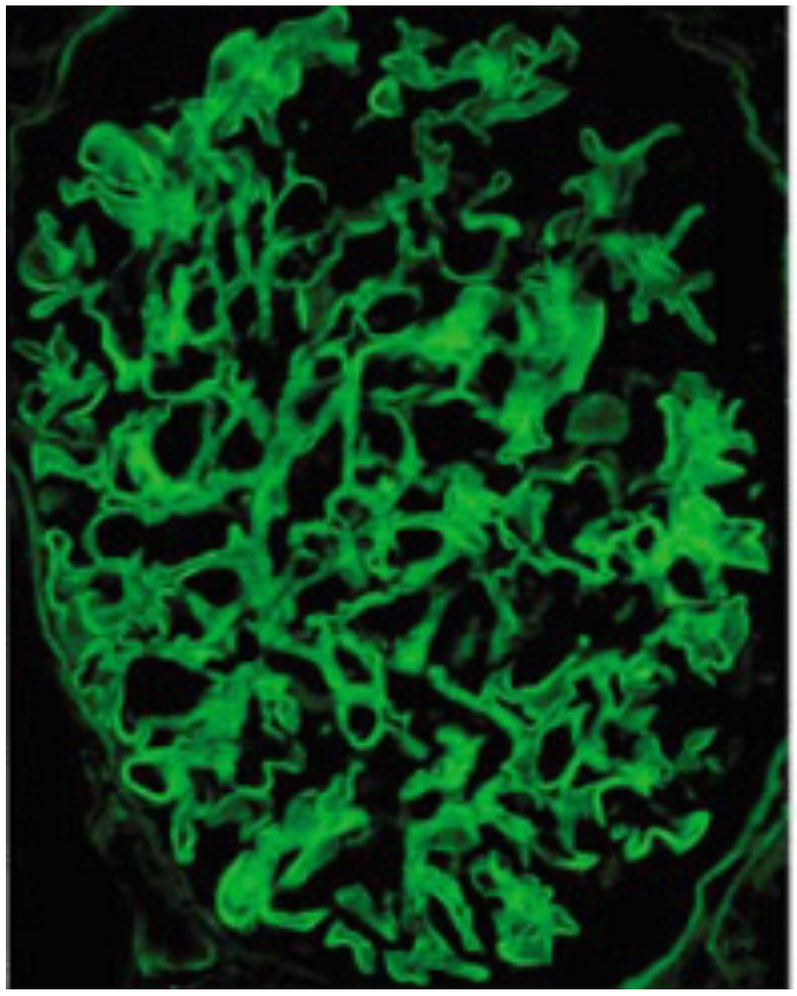
Crescentric glomerulonephritis

Collapsed glomerular tuft and crescent-shaped mass of proliferating parietal epithelial cells

Breaks in the glomerular basement membrane

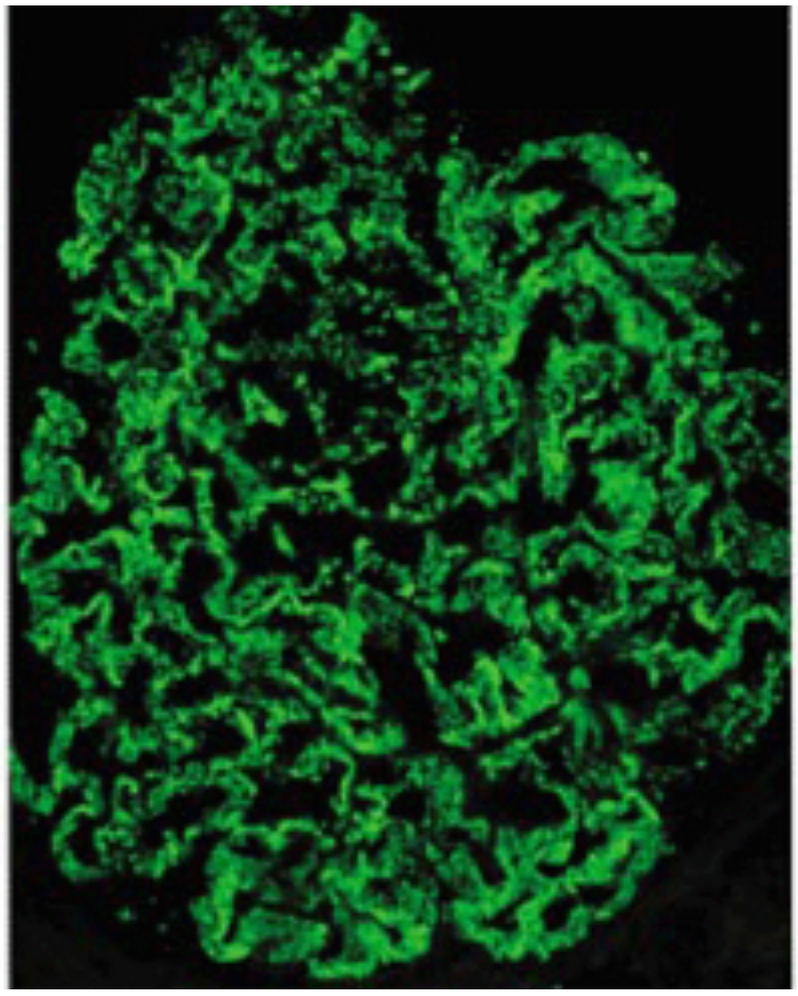


Type of RPGN



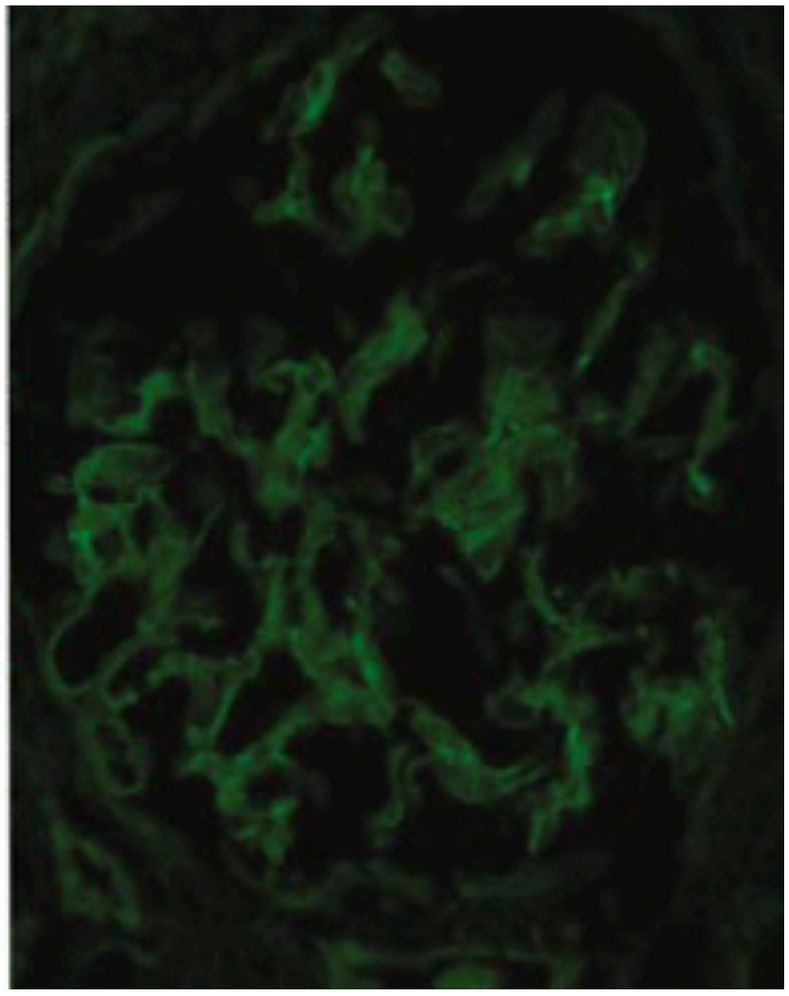
Linear staining for IgG

Anti-GBM GN



Granular staining

Immune complex GN



Pauci immune staining

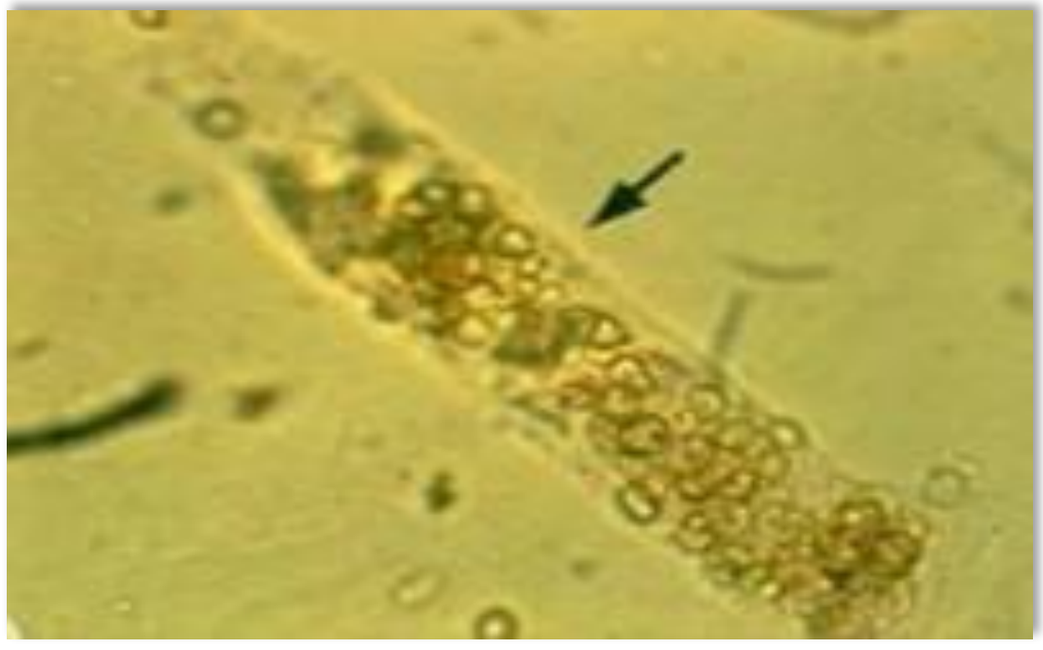
ANCA GN

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

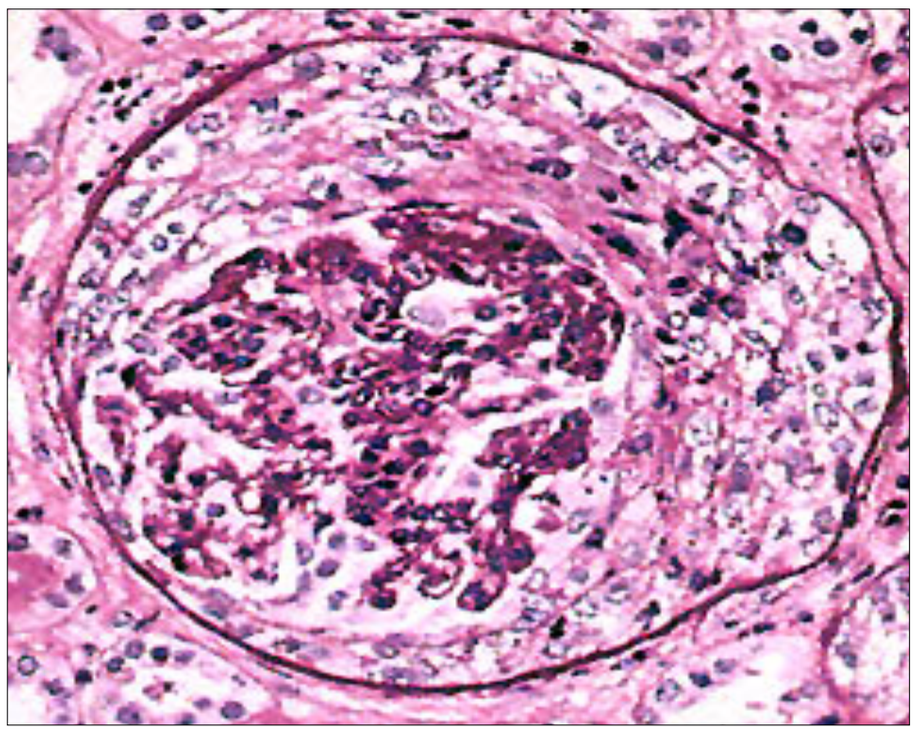
RPGN: Clinical features

- 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



Frequency of 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

Positive anti-GBM antibodies	Positive immune complex	Positive ANCA
Anti-GBM GN	Immune complex GN	ANCA GN

Lung hemorrhage	Goodpasture syndrome
No lung hemorrhage	Anti-GBM GN

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

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

Serologic analysis of patients with RPGN

Positive anti-GBM antibodies

Positive immune complex

Positive ANCA

Anti-GBM GN

Immune complex GN

ANCA GN

Lung hemorrhage

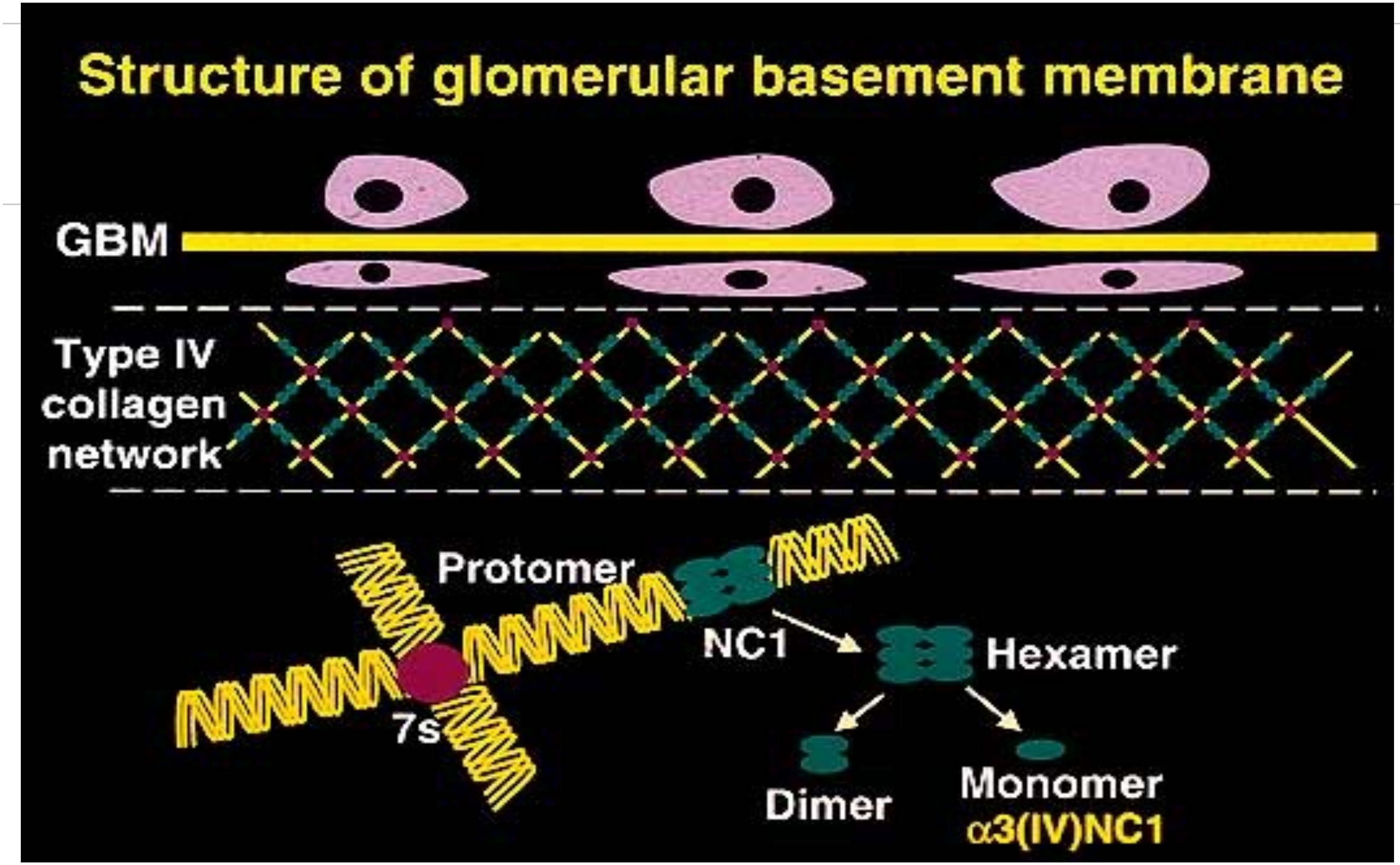
No lung hemorrhage

Goodpasture syndrome

Anti-GBM GN

Anti-GBM GN: Clinical features

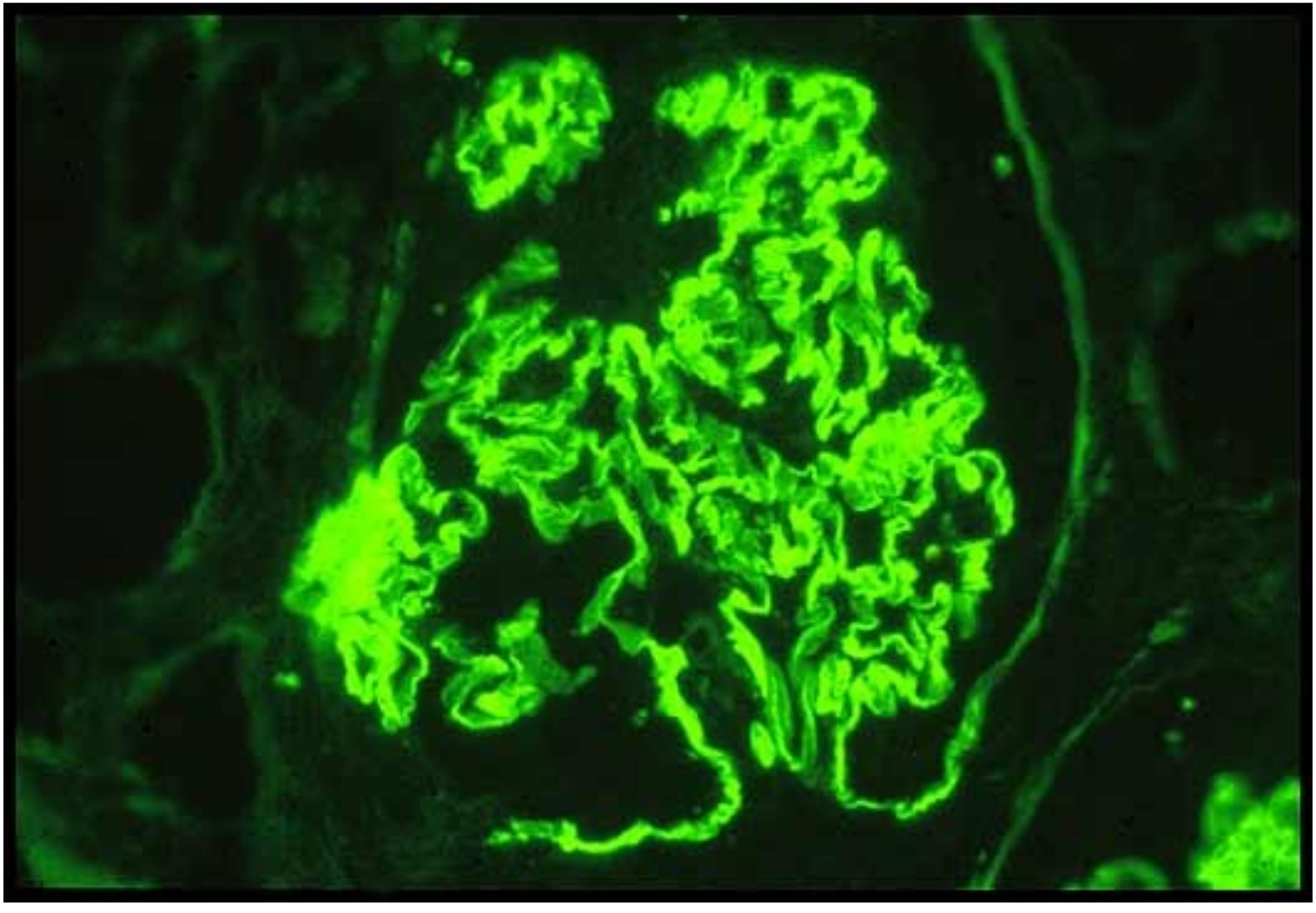
- Peak incidence in the third and sixth decades
- Malaise, fatigue, and weight loss, and anemia from pulmonary hemorrhage or to the effects of uremia
- Pulmonary hemorrhage and hemoptysis in anti-GBM disease
- Renal disease progresses rapidly and rarely resolves spontaneously



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

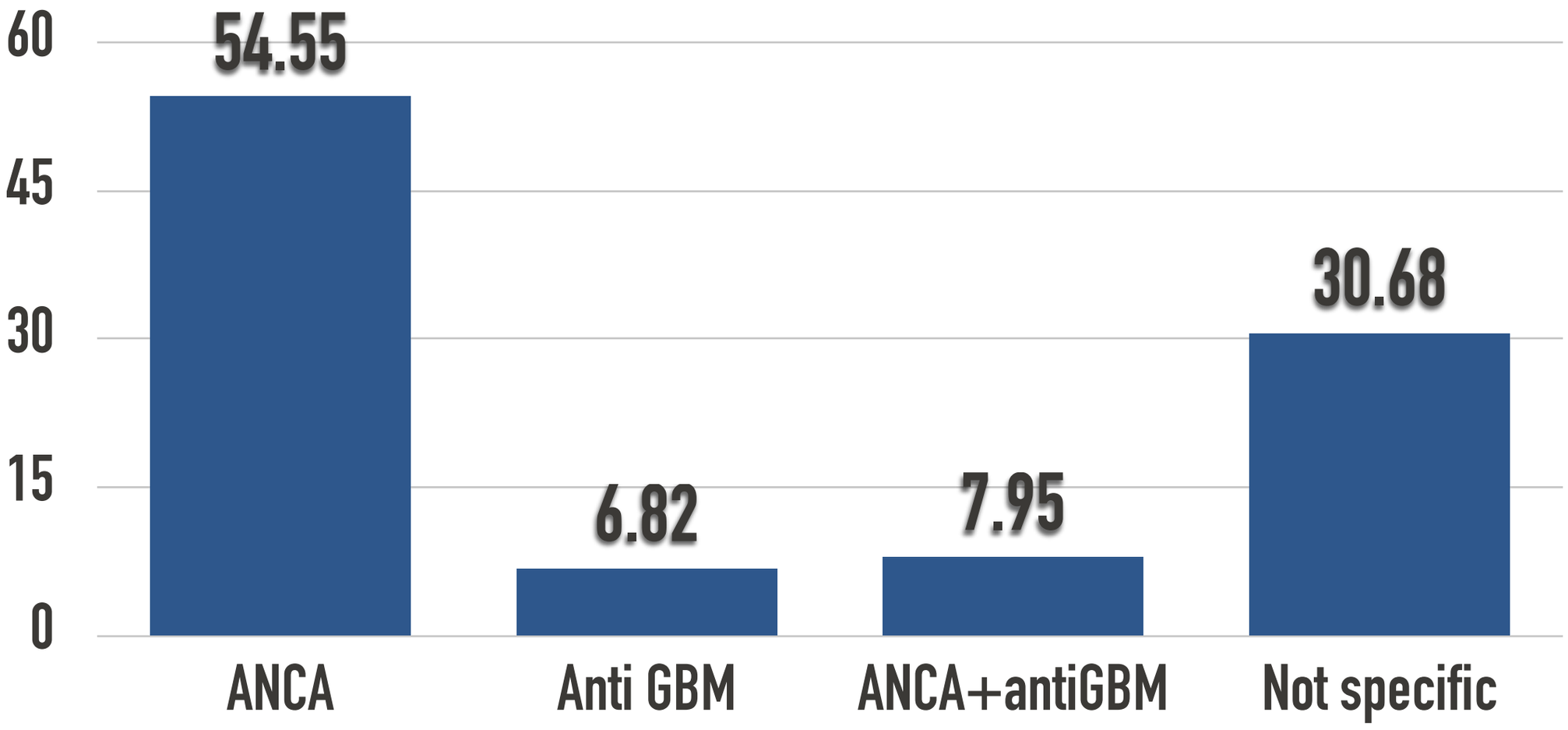
Hellmark T, et al. Kidney Int . 1999: 55:936–44.

Linear deposition of IgG/C3 along glomerular basement membrane



Pulmonary hemorrhage and nephritis

Pulmonary renal syndrome



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

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

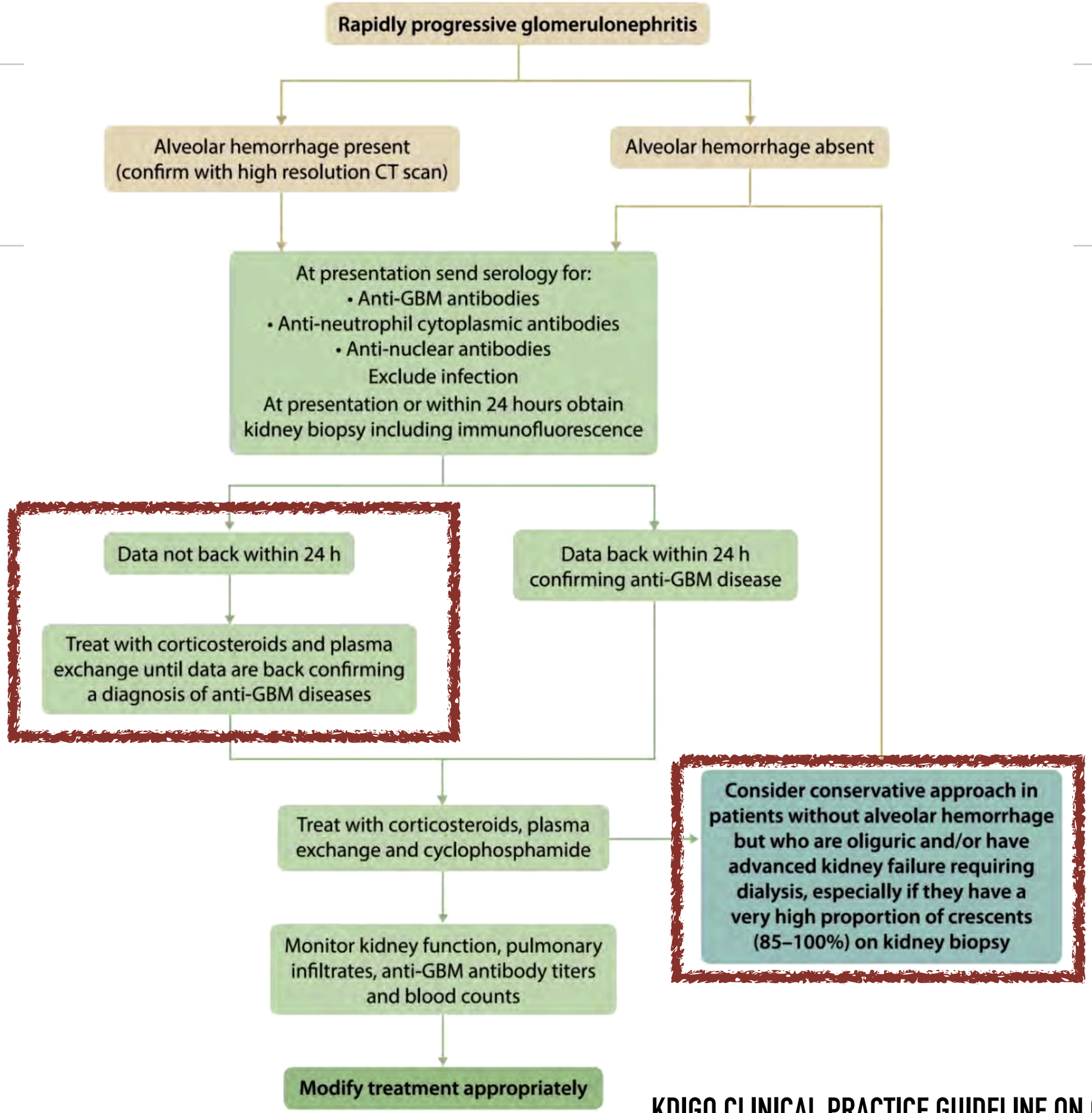
- We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis in all patients with anti-GBM GN
- Except those who are dialysis-dependent at presentation, have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage (1C).

Practice Point

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

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

Treatment of anti-GBM disease



Serologic analysis of patients with RPGN

Positive anti-GBM antibodies	Positive immune complex	Positive ANCA
Anti-GBM GN	Immune complex GN	ANCA GN

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

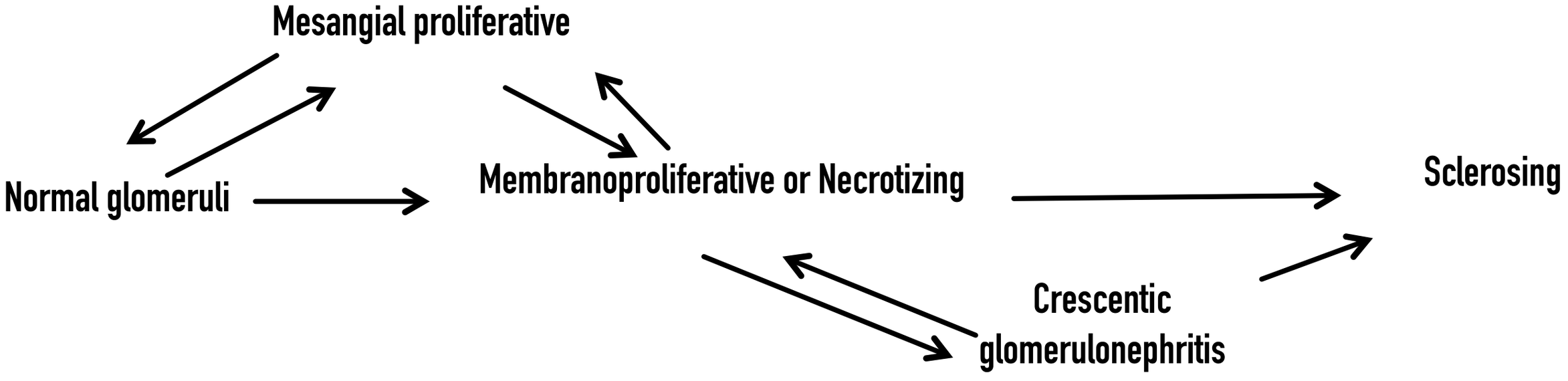
IgA nephropathy

Lupus nephritis

Clinical presentation

Asymptomatic hematuria/proteinuria	Acute nephritic/ Nephrotic syndrome	Rapidly progressive Glomerulonephritis	Chronic Glomerulonephritis

Renal pathology



IgA nephropathy: Clinical feature

- Wide spectrum of clinical presentations
- Recurrent macroscopic hematuria provoke by mucosal infection (synpharyngitis) (40–50%)
- Microscopic hematuria with or without proteinuria (30–40%)
- Nephrotic syndrome (5%)
- RPGN (<10%)

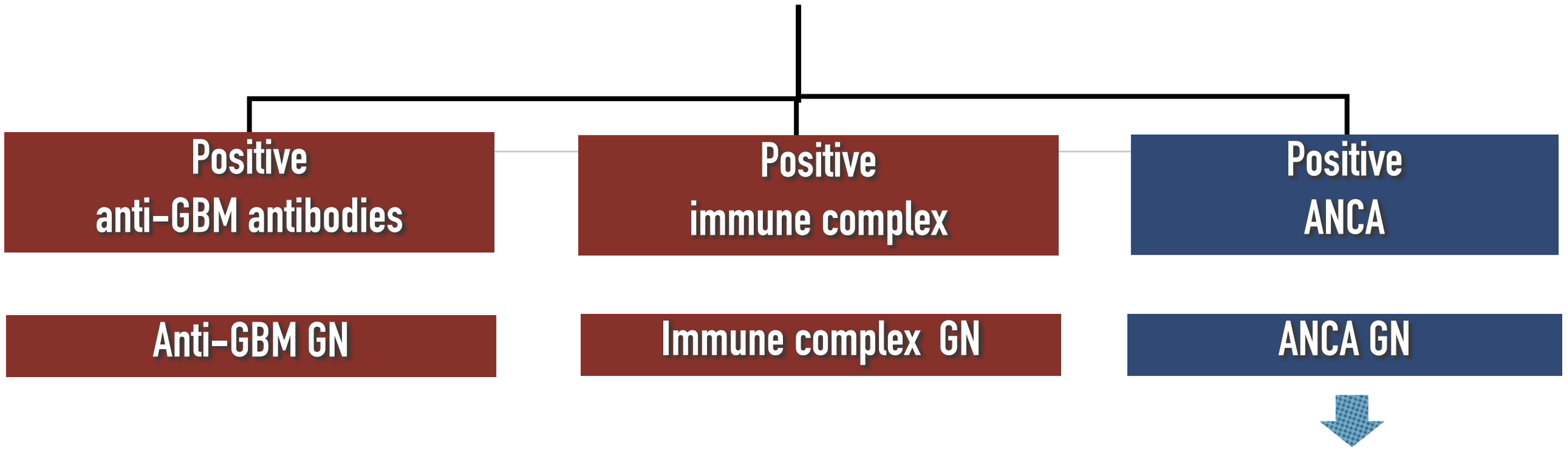
Treatment of IgAN with RPGN

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 2020

Serologic analysis of patients with RPGN

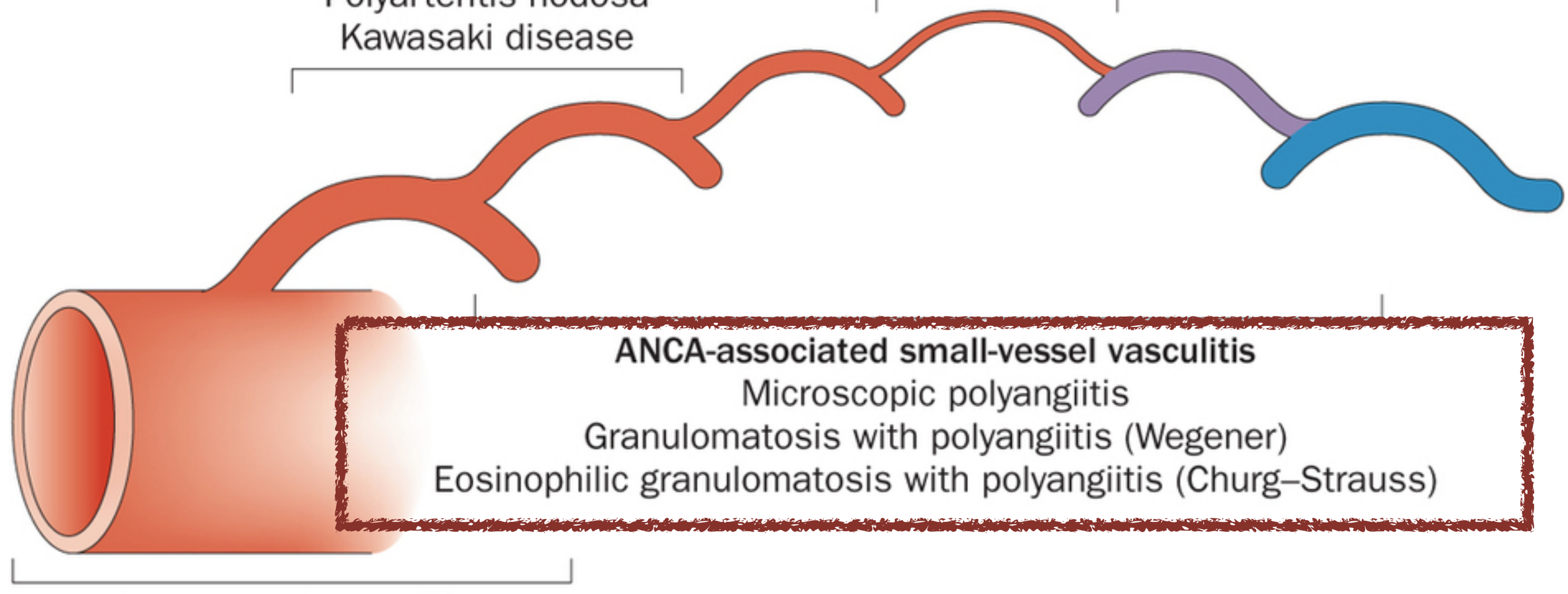


No extra renal disease	ANCA associated GN
Systemic necrotizing vasculitis	Microscopic polyangiitis
Respiratory necrotizing granulomas	Granulomatosis with polyangiitis
Asthma and eosinophilia	Eosinophilic granulomatosis with polyangiitis

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

Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease

Anti-GBM disease



ANCA-associated small-vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis

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

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.

American College of Rheumatology: 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 %

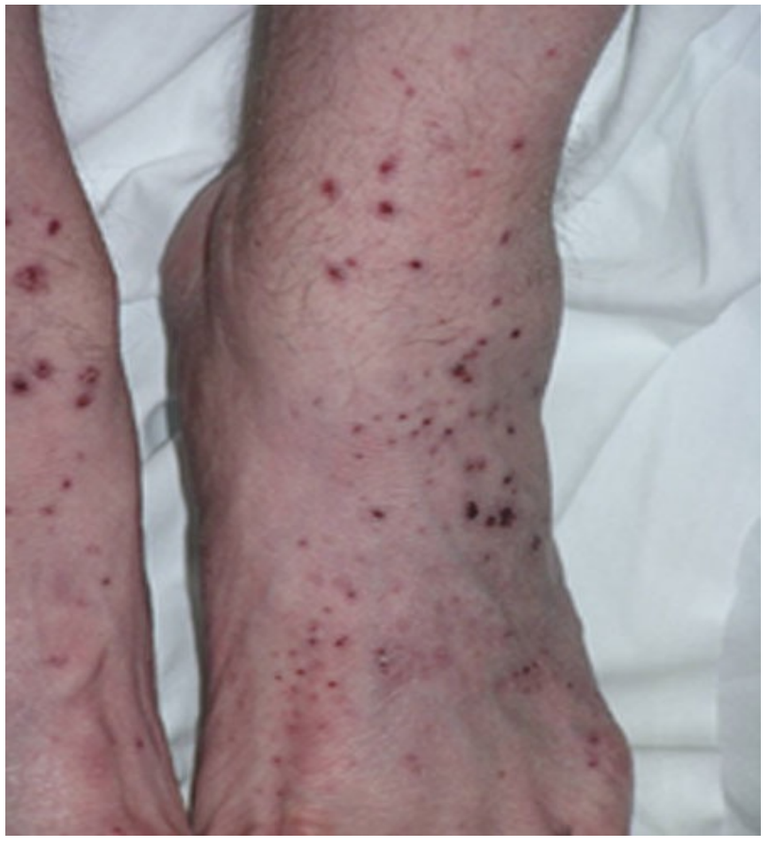
Leavitt RY, et al. Arthritis Rheum 1990;33(8):1101–7.

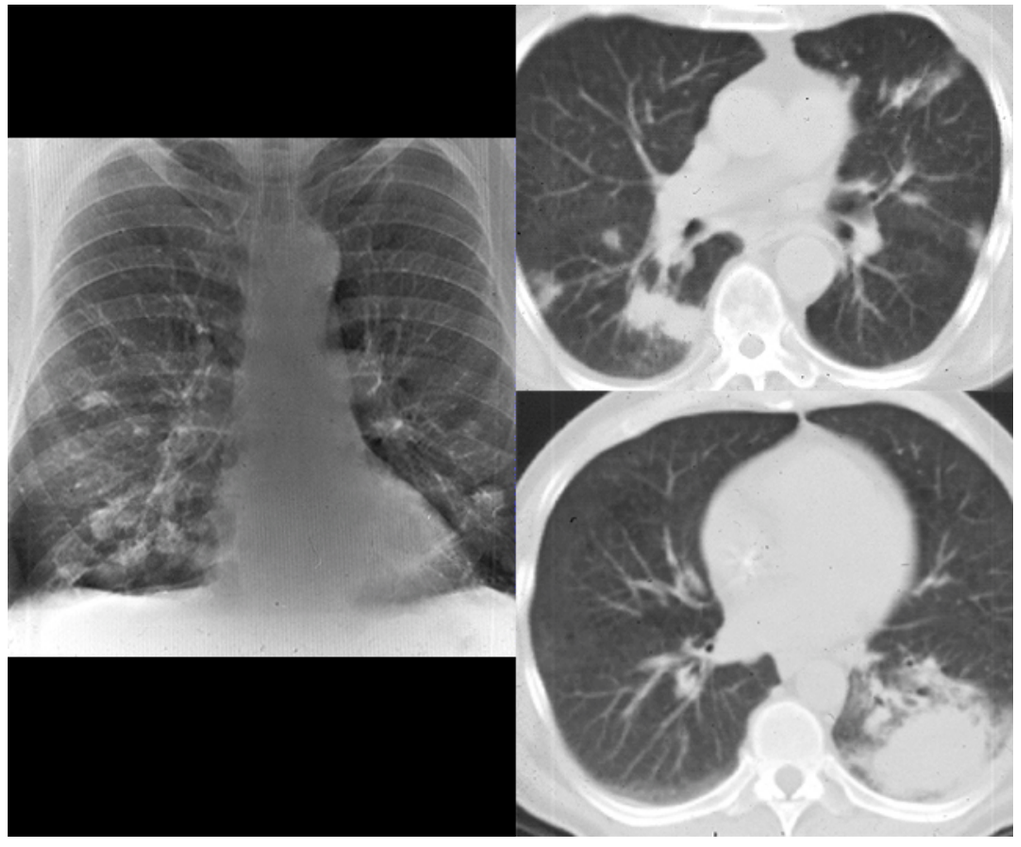
ACR 1990 criteria of Churg-Strauss syndrome

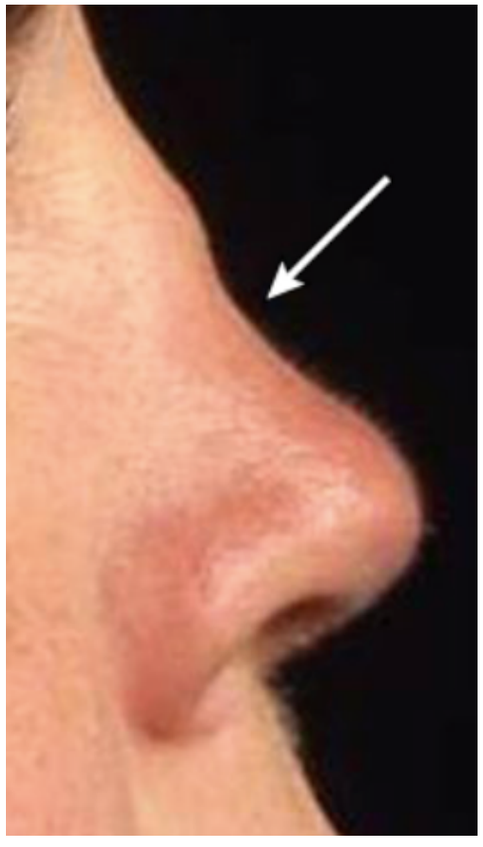
Criteria	Remarks
1.Asthma	History of expiratory rales
2.Eosinophilia	More than 10 %
3.Mononeuropathy or polyneuropathy	Caused by systemic vasculitis
4.Pulmonary infiltrate, non-fixed	Migratory/ transitory infiltrate
5.Paranasal sinus abnormality	Clinical evidence of acute or chronic paranasal sinusitis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

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

Systemic vasculitis







ANCA associated Glomerulonephritis

- Pauci- immune focal and segmental necrotizing and crescentic GN
- Microscopic hematuria with dysmorphic red blood cells and red cell casts
- Proteinuria usually moderate (1–3 g/d)
- Rapidly declining GFR over days or weeks
- Few subjects: asymptomatic microscopic hematuria and minimal proteinria

Pauciimmune GN

Systemic vasculitis

Yes

No

No asthma
Or granulomas

Granulomas
and no asthma

Eosinophilia
asthma and
granulomas

Allergic granulomatous angiitis (AGA)

Granulomatosis with polyangiitis (GPA)

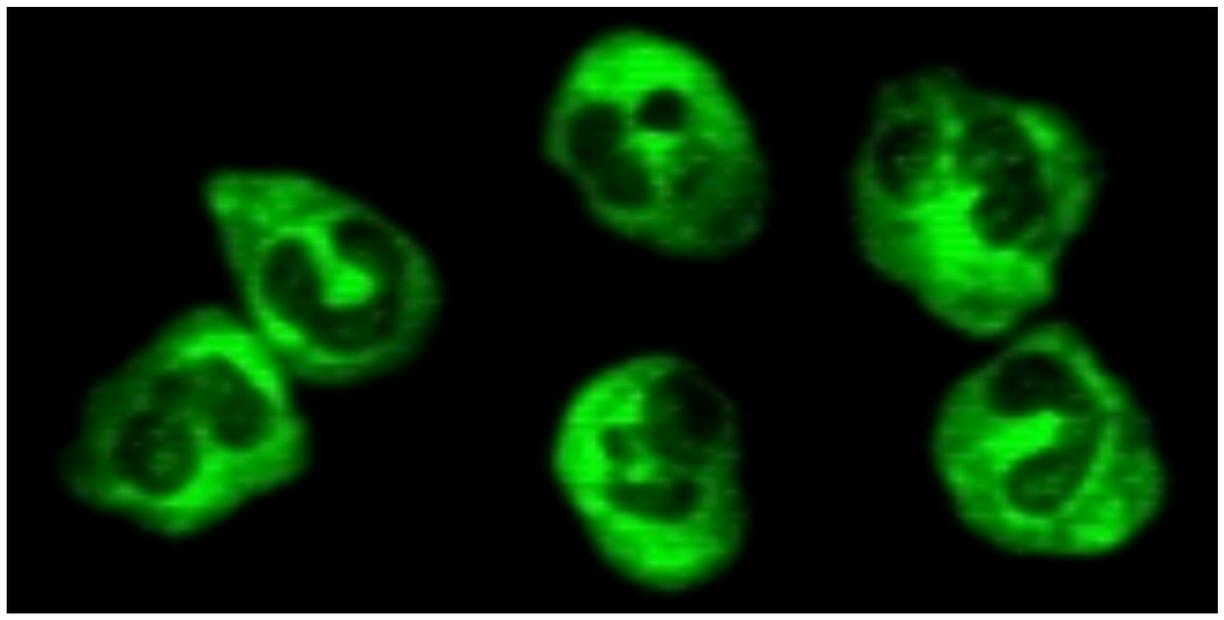
Microscopic polyangiitis

PI-CGN

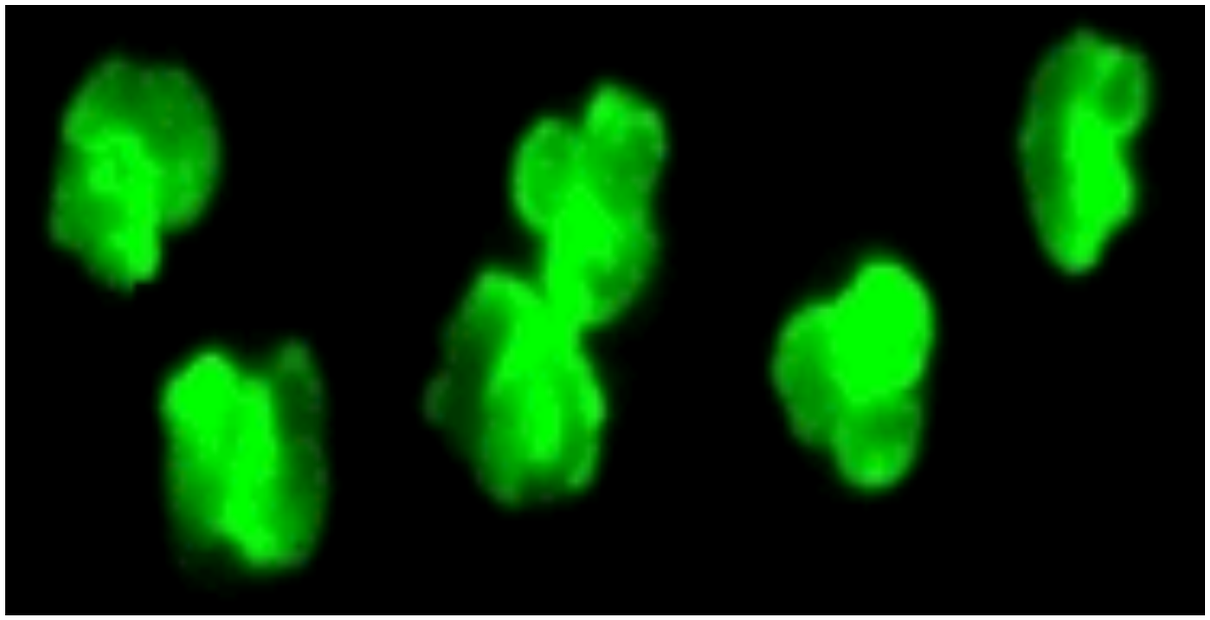
Indirect immunofluorescence

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

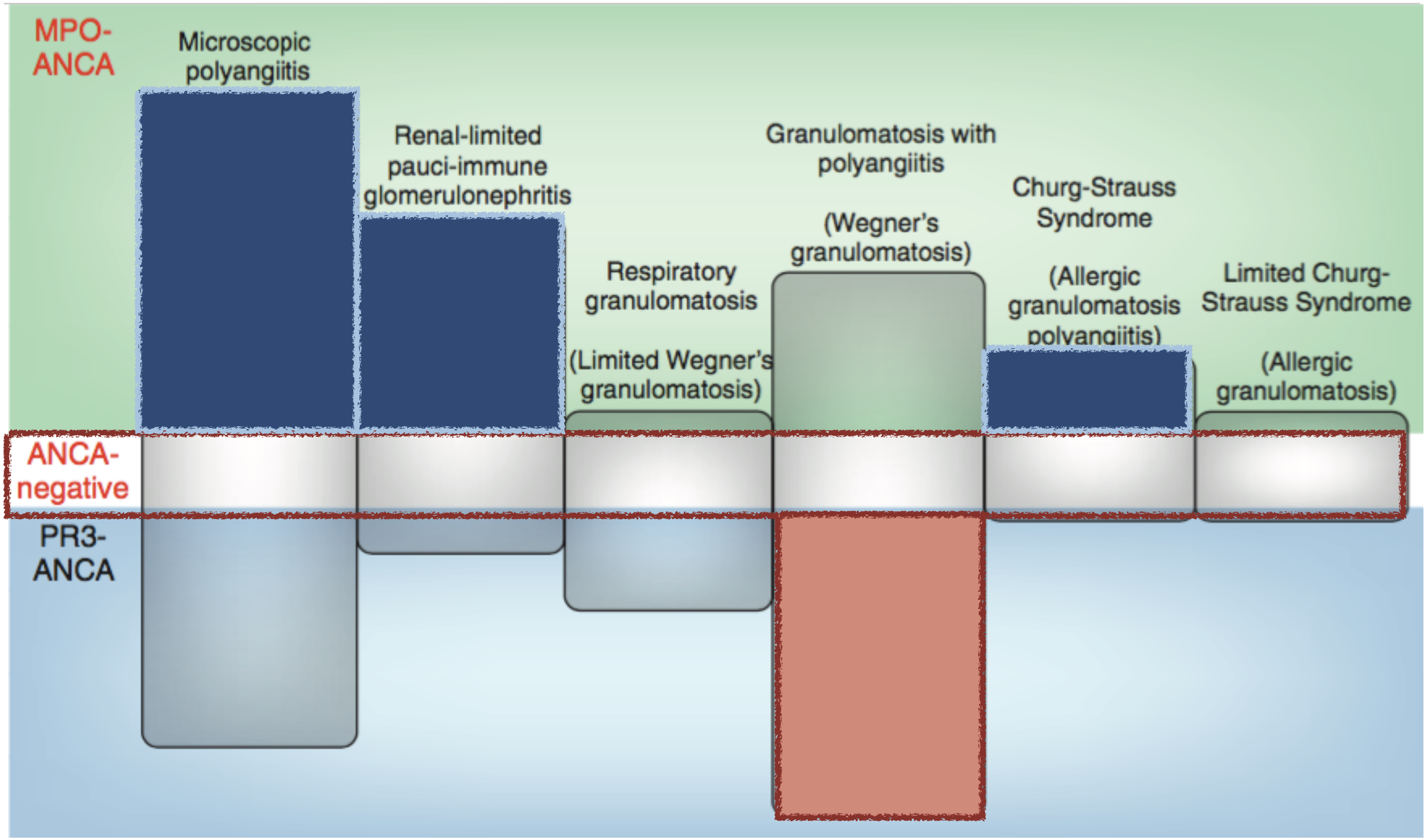
Indirect immunofluorescence

- 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

A proposed nomenclature for ANCA disease



Falk RJ, et al. J Am Soc Nephrol; 2010: 21: 745–752.

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)

Positive ANCA serology

Clinical presentation	Prevalence of pauci-immune GN (%)	Positive predictive value	Negative predictive value
Rapidly progressive glomerulonephritis	47	98	80
Hematuria, proteinuria, and creatinine >3 mg/dL	21	92	93
Hematuria, proteinuria, and creatinine 1.5–3 mg/dL	7	77	98
Hematuria, proteinuria, and creatinine <1.5 mg/dL	2	47	99

Jennette, JC, et al. . Kidney Int 1998; 53:796.

Positive ANCA serology

Clinical presentation	Prevalence of pauci-immune GN (%)	Positive predictive value	Negative predictive value
Rapidly progressive glomerulonephritis	47	98	80
Hematuria, proteinuria, and creatinine >3 mg/dL	21	92	93
Hematuria, proteinuria, and creatinine 1.5–3 mg/dL	7	77	98
Hematuria, proteinuria, and creatinine <1.5 mg/dL	2	47	99

Clinical presentation of RPGN: PPV at least 98 %.
Adults with hematuria, proteinuria, and a serum creatinine of less than 1.5 mg/dL: PPV only 47 %

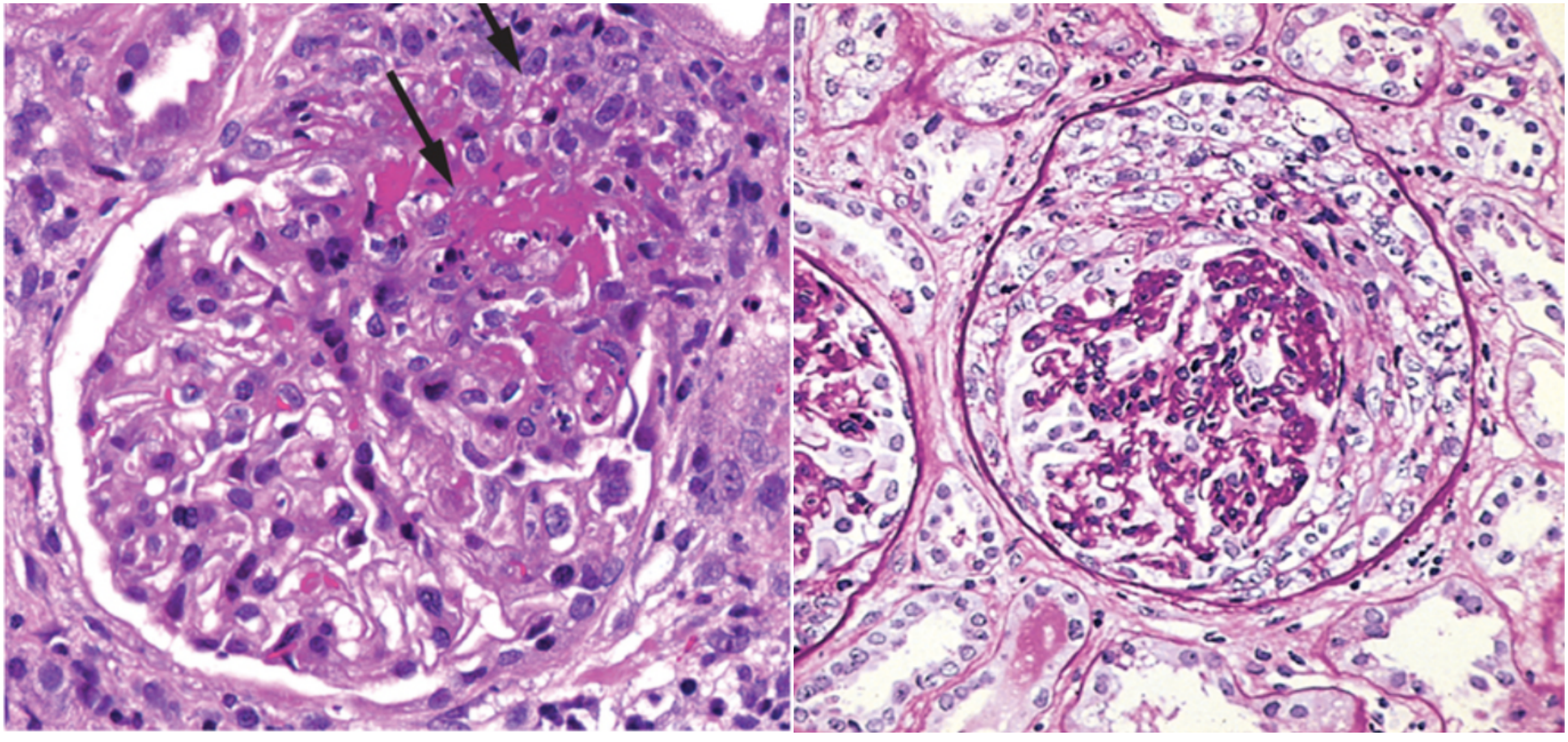
Jennette, JC, et al. . Kidney Int 1998; 53:796.

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.

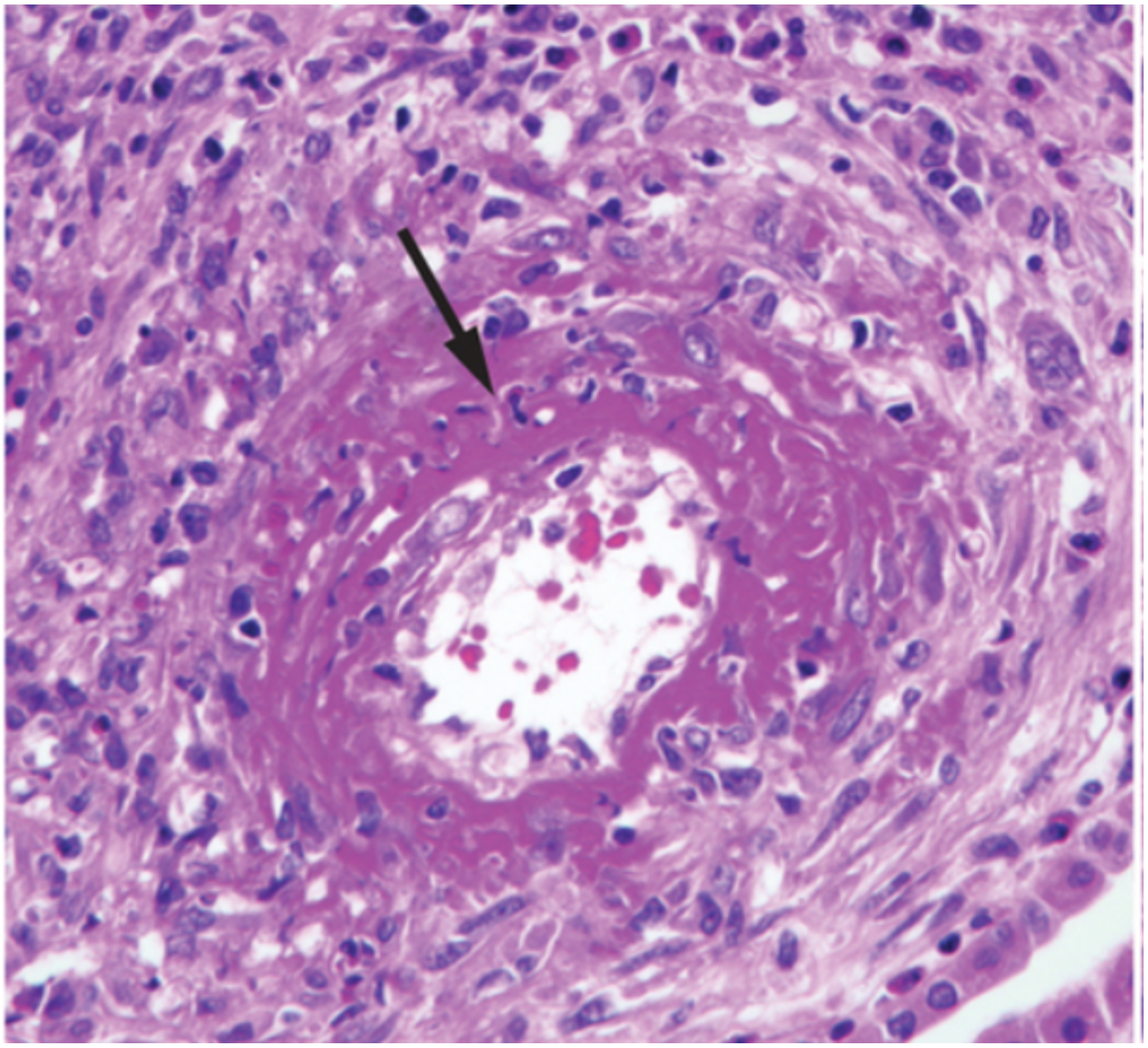
Cellular crescent composed of mononuclear leukocytes and epithelial cells



Segmental fibrinoid necrosis and cellular crescent

Jennette JC, et al. Nature Reviews Rheumatology: 2014: 10, 463–473.

Necrotizing arteritis of a small artery in the kidney



A circumferential zone of fibrinoid necrosis (arrow) and perivascular leukocytes that, at this phase, contain predominantly mononuclear leukocytes

Jennette JC, et al. Nature Reviews Rheumatology: 2014: 10, 463–473.

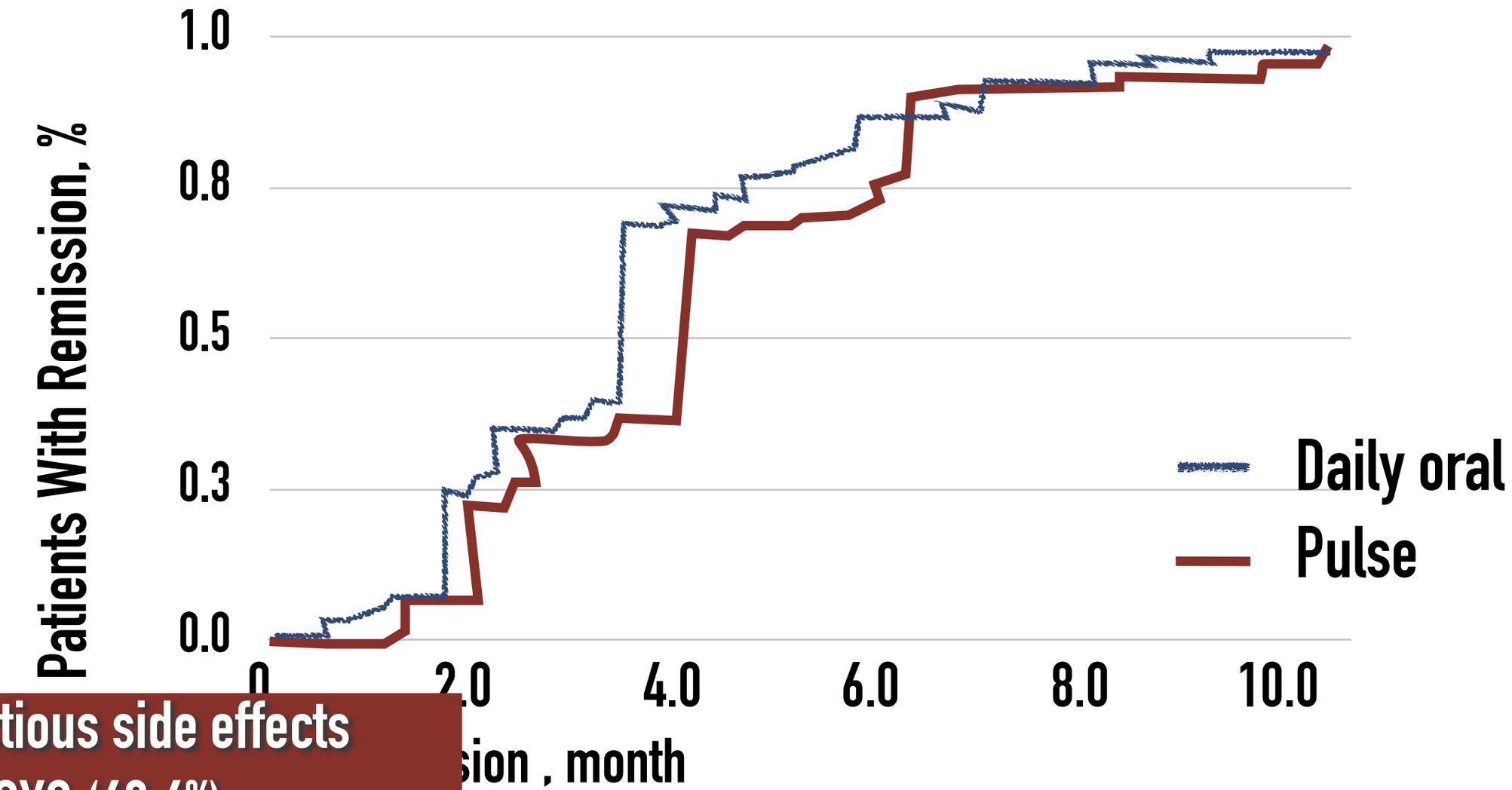
Initial treatment of RPGN

- 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

CYCLOPS study

42 centers in 12 European countries: 149 patients

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in ANCA associated vasculitis

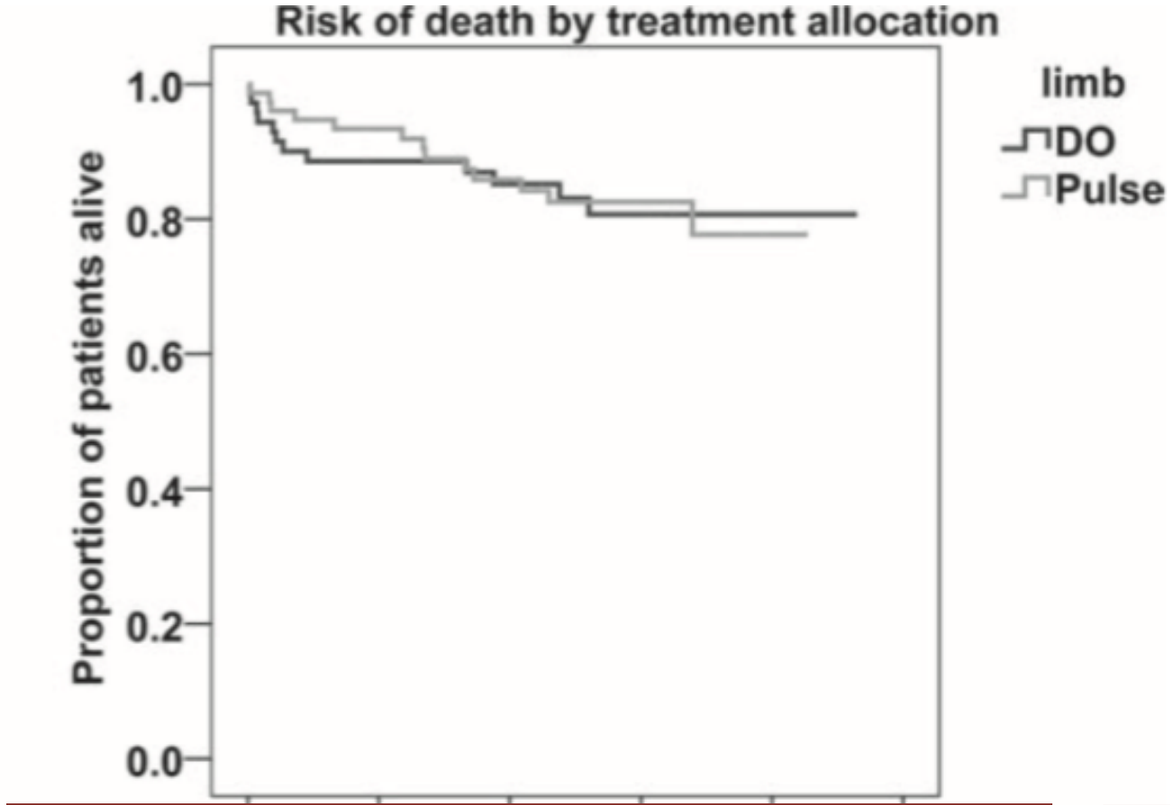


- Infectious side effects
- Oral CYC (69.6%)
- IV CYC (40.7%) ($P < 0.05$)

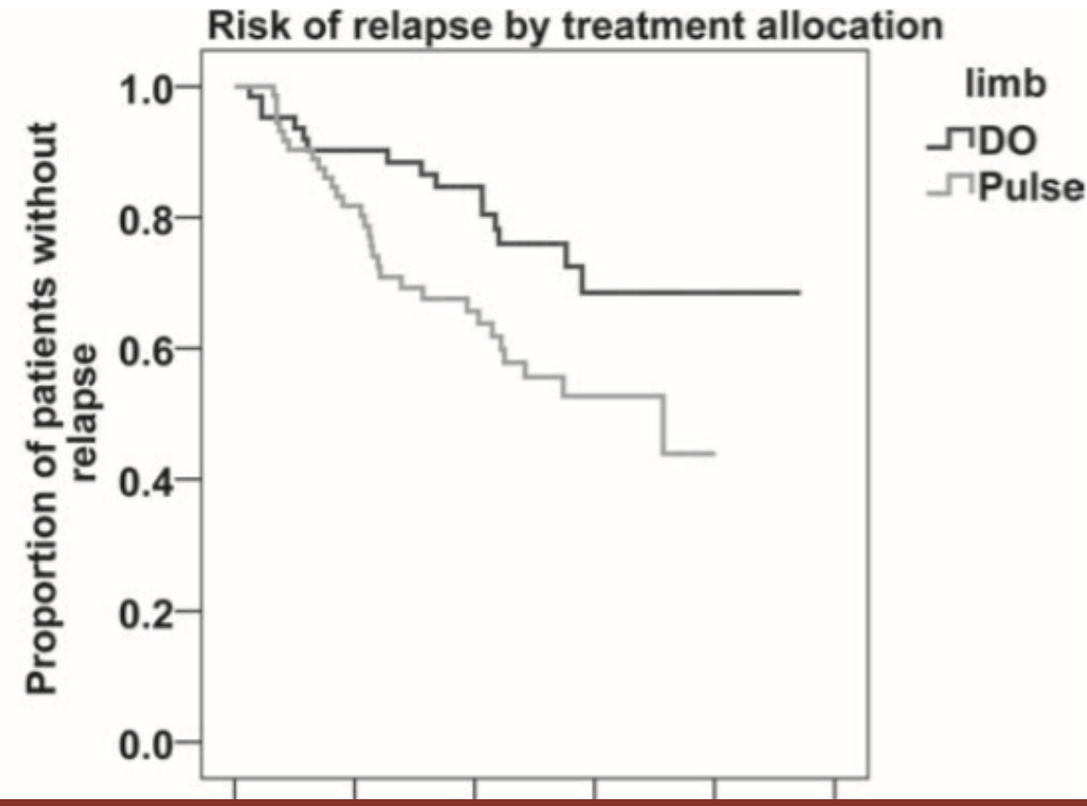
de Groot K; et al. Ann Intern Med. 2009;150(10):670–80.

Long-term outcomes in CYCLOPS study

- 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



Significantly 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

Treatment of ANCA associated vasculitis (RPGN)

- **Considerations for choosing the route of administration of cyclophosphamide**

Practice Point

IVCY	Oral CY
Patients who already have a moderate cumulative dose of cyclophosphamide	Cost is an important factor
Patients with lower WBC counts	
Ready access to an infusion centre	Access to an infusion centre difficult
Adherence may be an issue	Adherence is not an issue

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

Rituximab

- RAVE–trial
- RITUXVAS trial

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

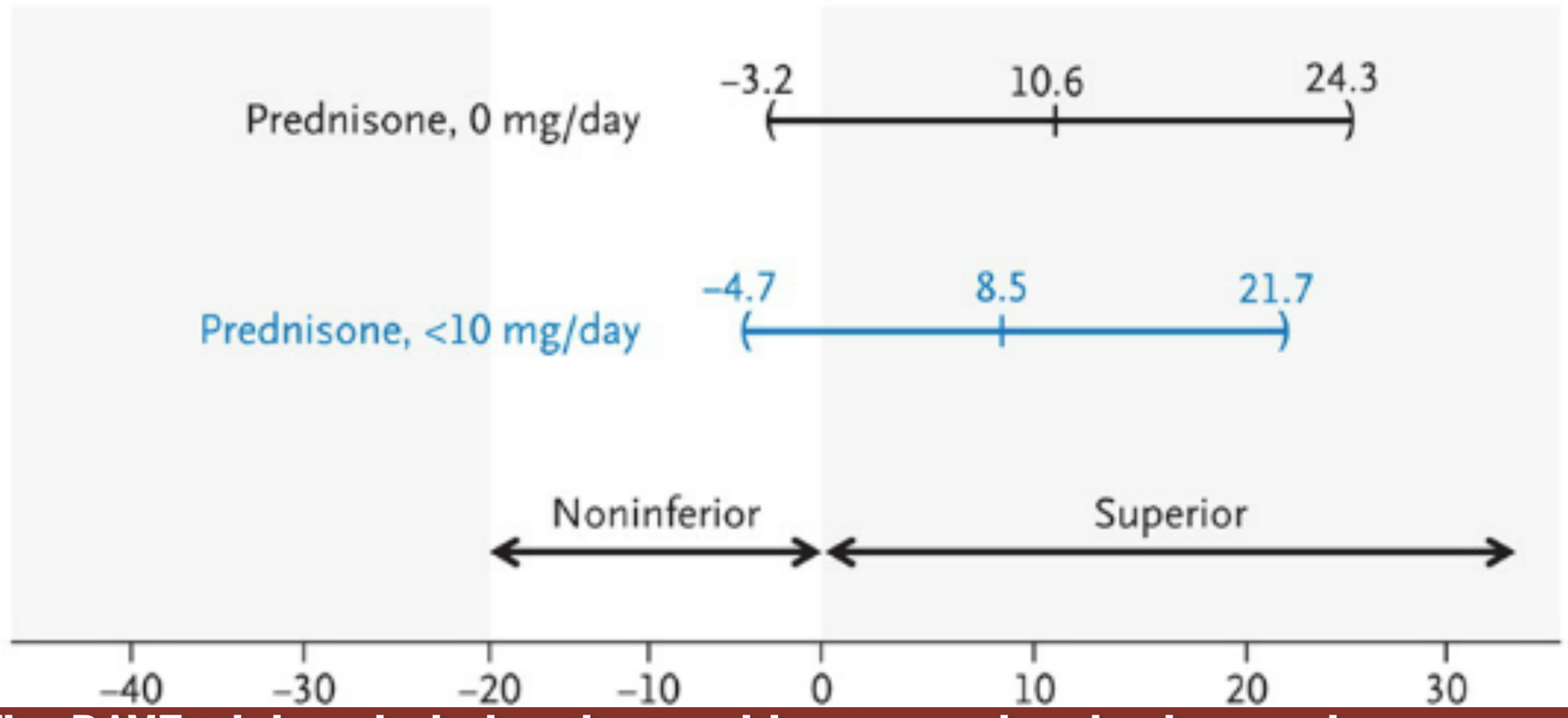
Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

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*

- **Rituximab 375 mg per m^2 per week for 4 weeks vs. Cyclophosphamide 2 MKD**

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

RAVE trial: Rituximab vs. Cyclophosphamide in ANCA-Associated Renal Vasculitis



- 64% in the rituximab group
- 53% in the control group

The RAVE trial excluded patients with severe alveolar hemorrhage or severe kidney dysfunction (SCr >4 mg/dl, so the role of rituximab for such patients remains unknown.

Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease

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

The NEW ENGLAND JOURNAL of MEDICINE

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

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

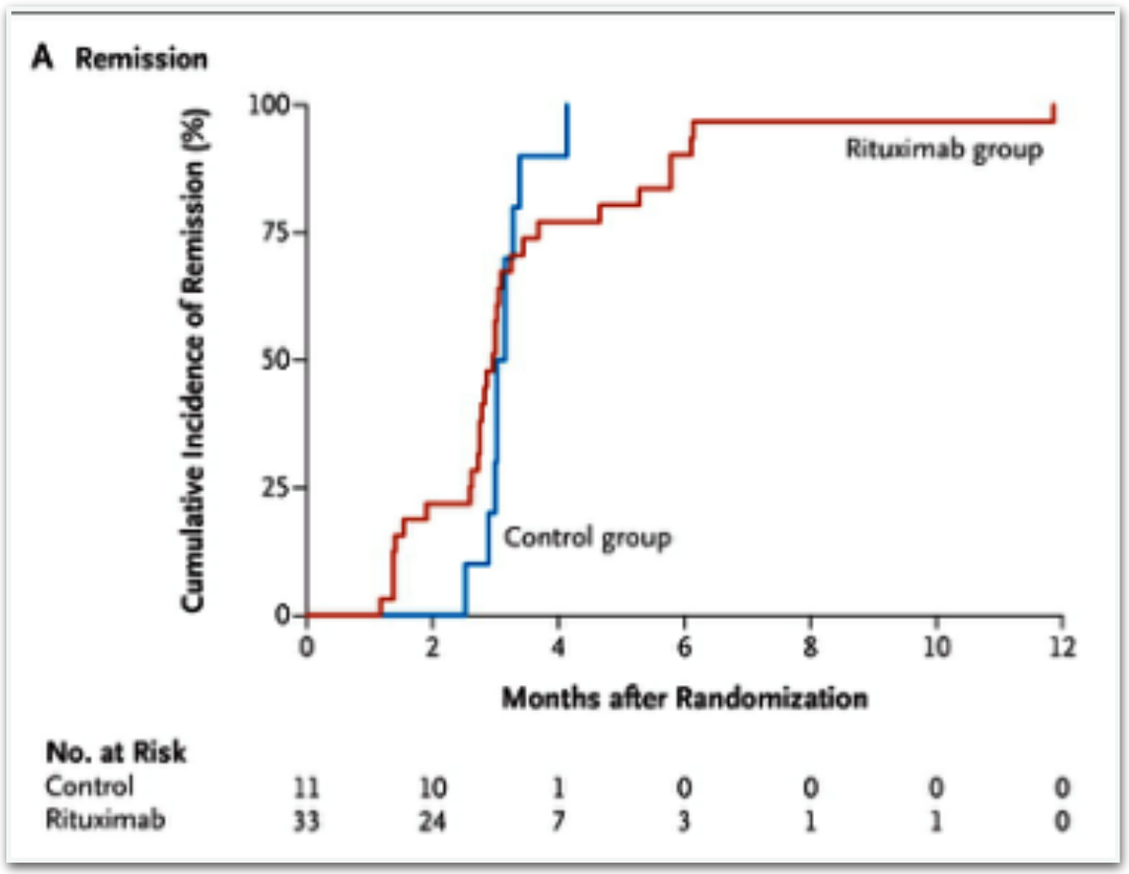
Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, 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

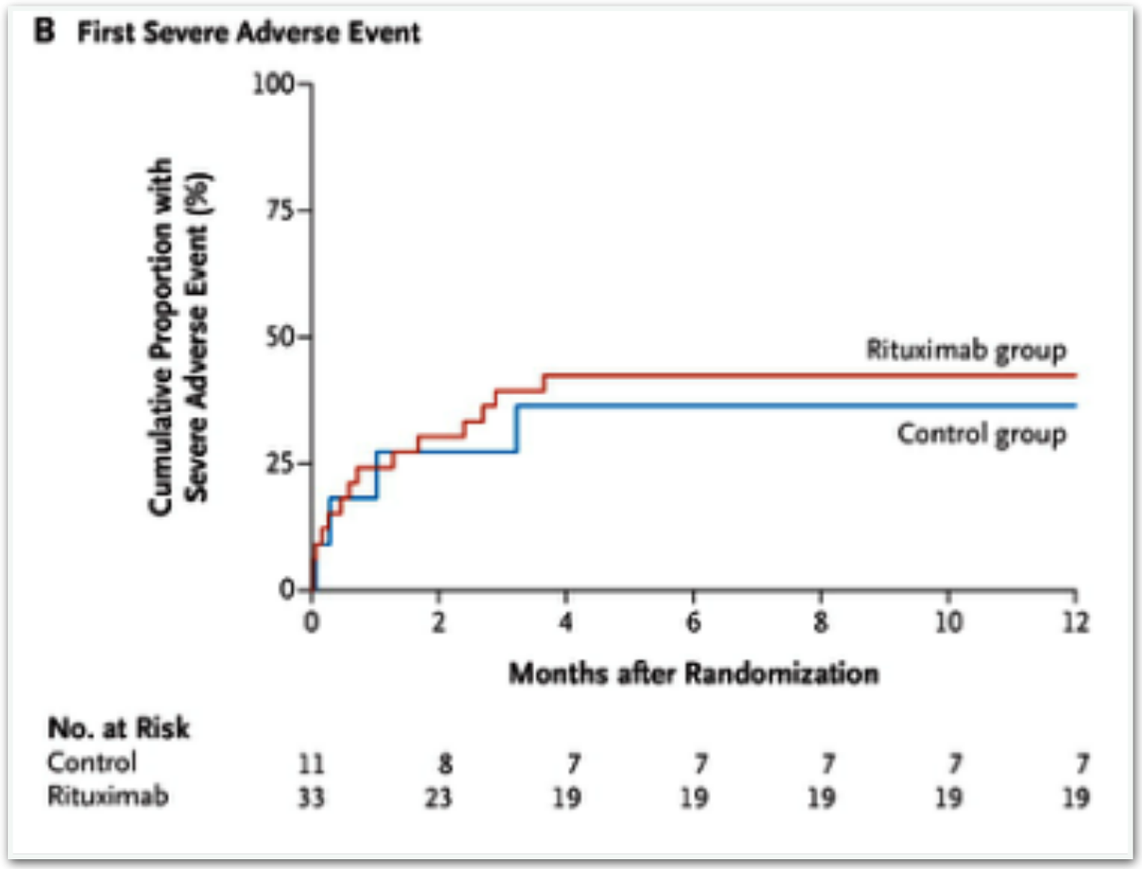
- **RITUXVAS: 44 patients with newly diagnosed ANCA-associated renal vasculitis**

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

RITUXVAS: Rituximab versus cyclophosphamide in ANCA–associated renal vasculitis

- 44 patients with newly diagnosed antineutrophil cytoplasmic antibody (ANCA)–associated renal vasculitis





At 12 months, there was no difference in the rate of sustained remission between the rituximab– and cyclophosphamide–only groups (76 versus 82 percent).

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.

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

Patients with PR3–AAV respond better to RTX than to 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

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**

Practice Point

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 important	
Relapsing disease	
PR-3 ANCA disease	

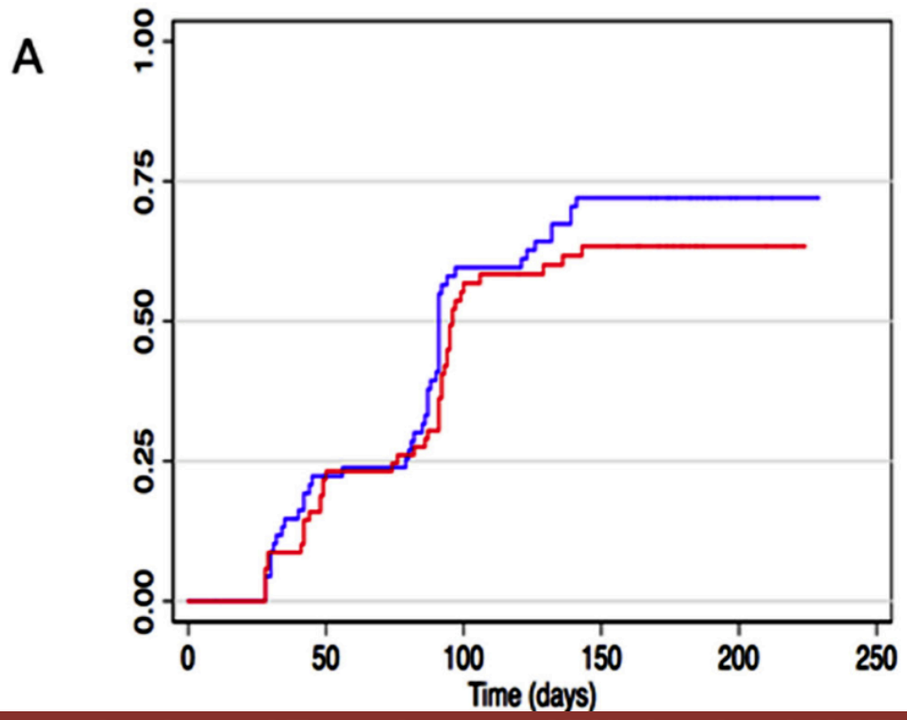
KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

MMF

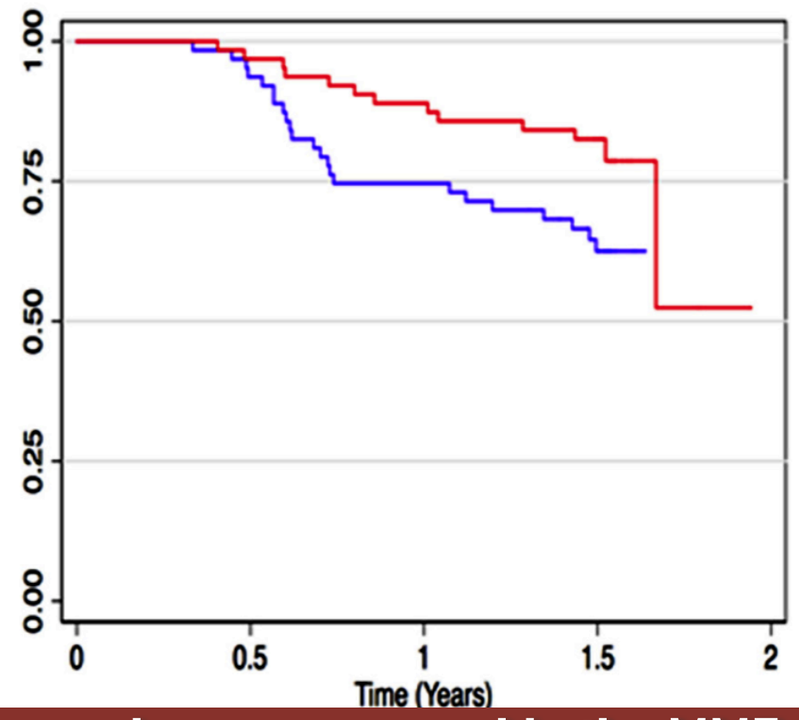
CLINICAL SCIENCE

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]



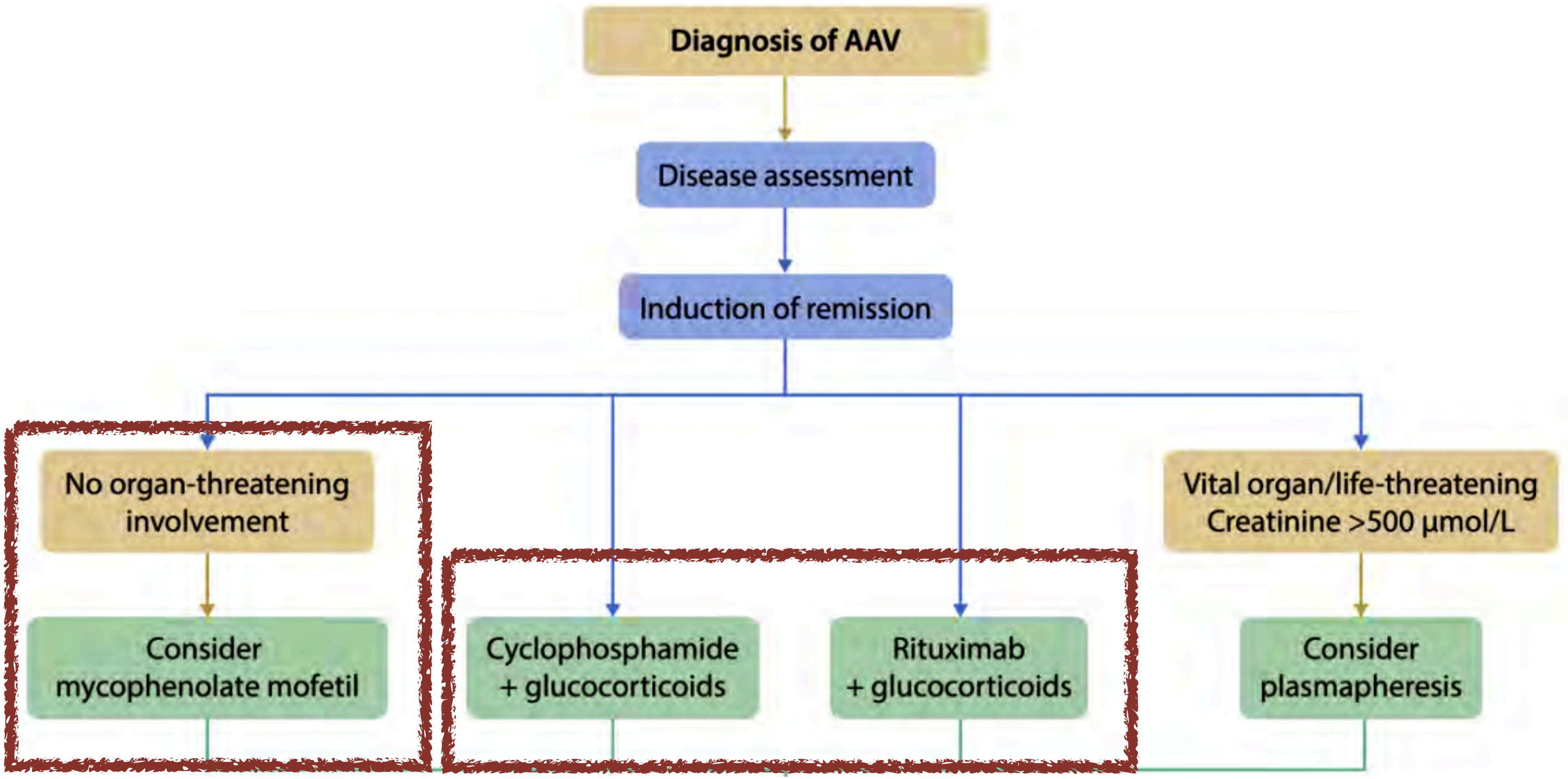
Primary remission: 47 patients (67%) in the MMF group and 43 patients (61%) in the CY group (risk difference 5.7%, 90% CI −7.5% to 19%)



More relapses occurred in the MMF group (33%) compared with the CY group (19%) (incidence ratio 1.97, 95% Ci 0.96 to 4.23)

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

Treatment of ANCA associated vasculitis (RPGN)



KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

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

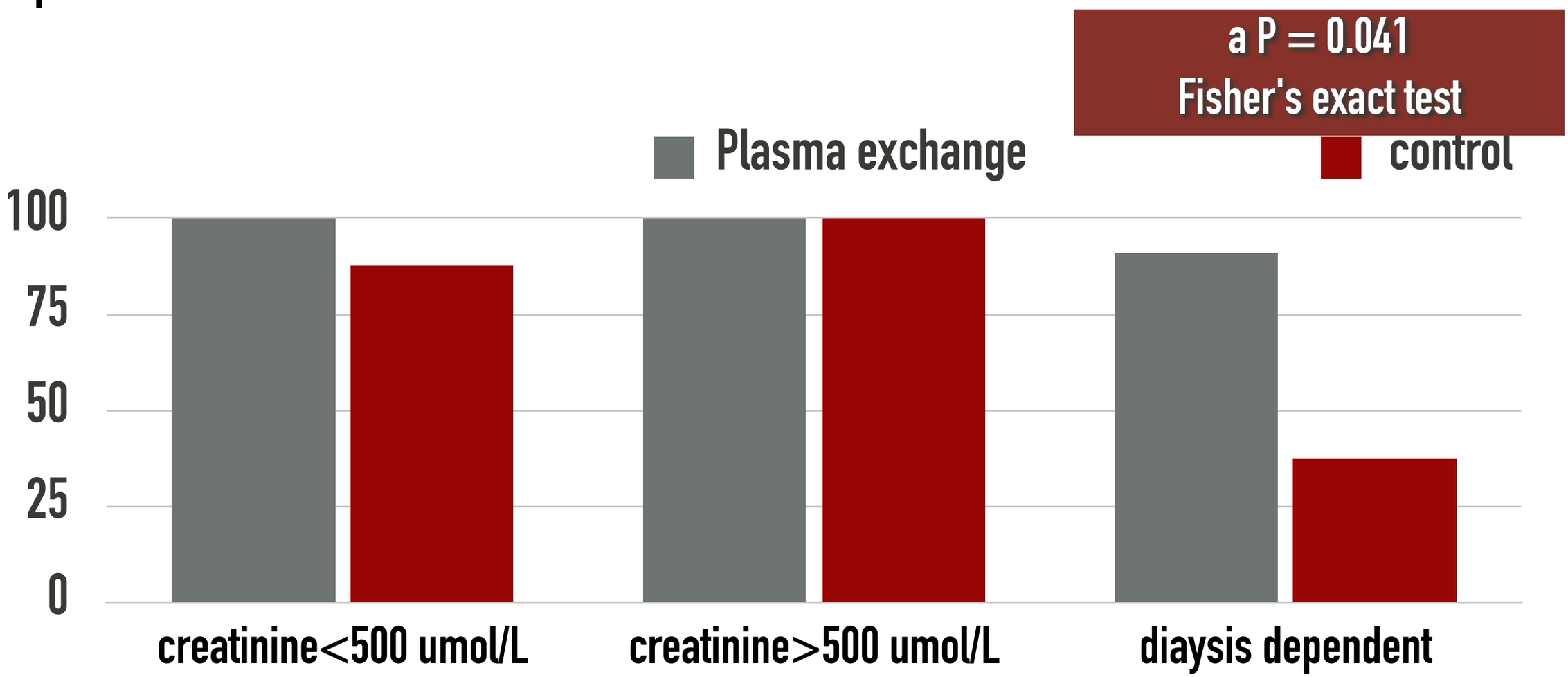
Oral CY	IVCY	Rituximab	Rituximab and IVCY	MMF
2 MKD for 3 months , continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0,2,4,7,10,13 (16,19,21,24 if required)	375 mg/m2/wk x 4 wk or 1 g at wk 0 and 2	375 mg/m2/wk x 4 wk with IVCY 15 mg/kg at wk 0 and 2 or rituximab 1 g at 0 and 2 wk with IVCY 500 mg/ 2 wk x 6	2000 mg/d may be increased to 3000 mg/d for poor treatment response

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

Plasma exchange

Plasma exchange in focal necrotizing glomerulonephritis

Improvement in renal function at one month

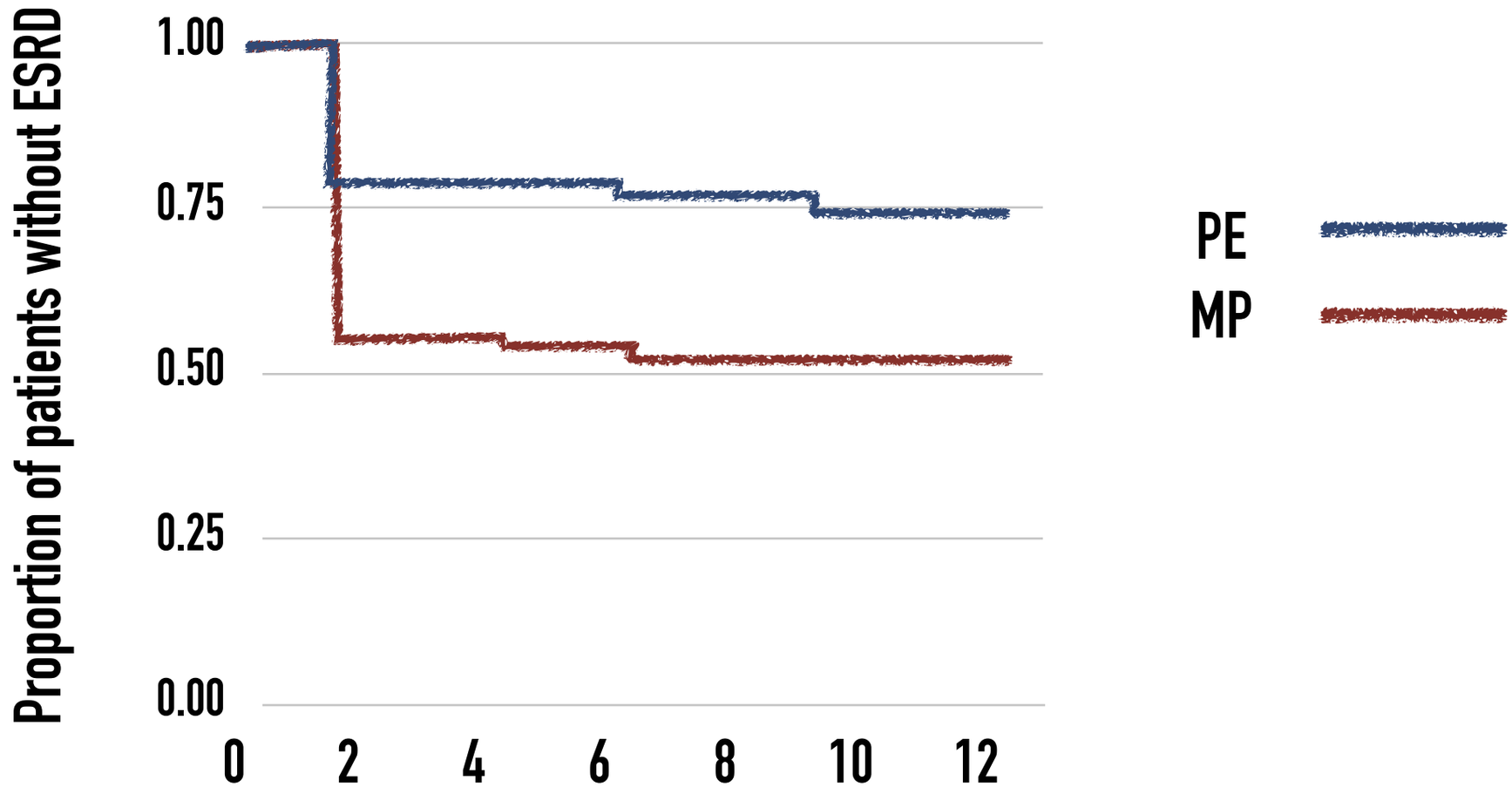


Treatment: plasma exchange, prednisolone, cyclophosphamide and azathioprine
Control: drug alone

Pusey CD, et al. Kidney Int 1991;40(4):757–63.

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

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

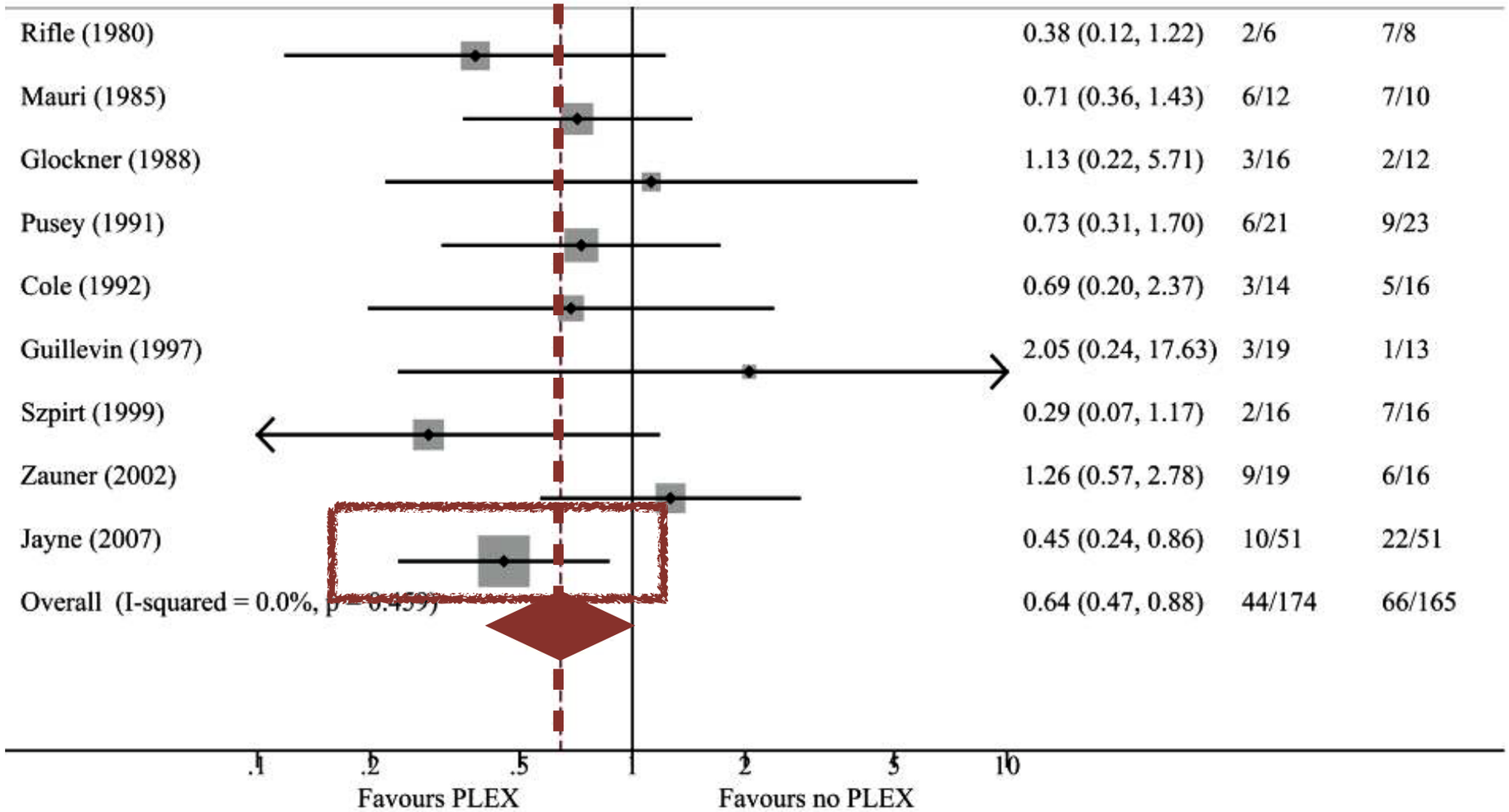


Plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% CI 6.1 to 41%), from 43 to 19%, at 12 mo.

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 2020

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*

- **704 patients at 95 centers in 16 countries; 352 were assigned to undergo plasma exchange and 352 to undergo no plasma exchange**

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

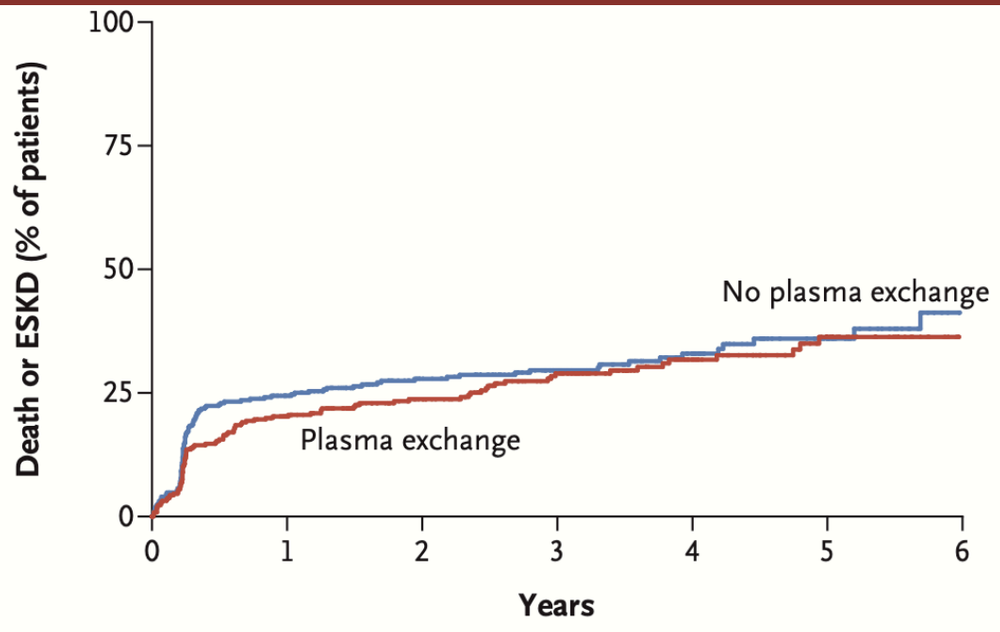
Characteristic	Plasma Exchange (N=352)	No Plasma Exchange (N=352)
Age — yr	62.8±14.4	63.5±13.7
Female sex — no. (%)	149 (42.3)	158 (44.9)
History of vasculitis — no. (%)	35 (9.9)	28 (8.0)
ANCA subtype — no. (%)		
Proteinase 3	143 (40.6)	143 (40.6)
Myeloperoxidase	209 (59.4)	209 (59.4)
Median C-reactive protein level (IQR) — mg/liter	50.9 (13.8–122.8)	42.1 (14.0–97.2)
Median hemoglobin level (IQR) — g/liter	94 (83–105)	95 (85–105)
Kidney function		
Median serum creatinine level (IQR) — μmol/liter	327 (206–491)	336 (209–495)
Serum creatinine level ≥500 μmol/liter or undergoing dialysis — no. (%)	101 (28.7)	104 (29.5)
Undergoing dialysis — no. (%)	66 (18.8)	74 (21)
Severity of pulmonary hemorrhage — no. (%)		
No hemorrhage	257 (73.0)	256 (72.7)
Not severe	64 (18.2)	66 (18.8)
Severe†	31 (8.8)	30 (8.5)

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

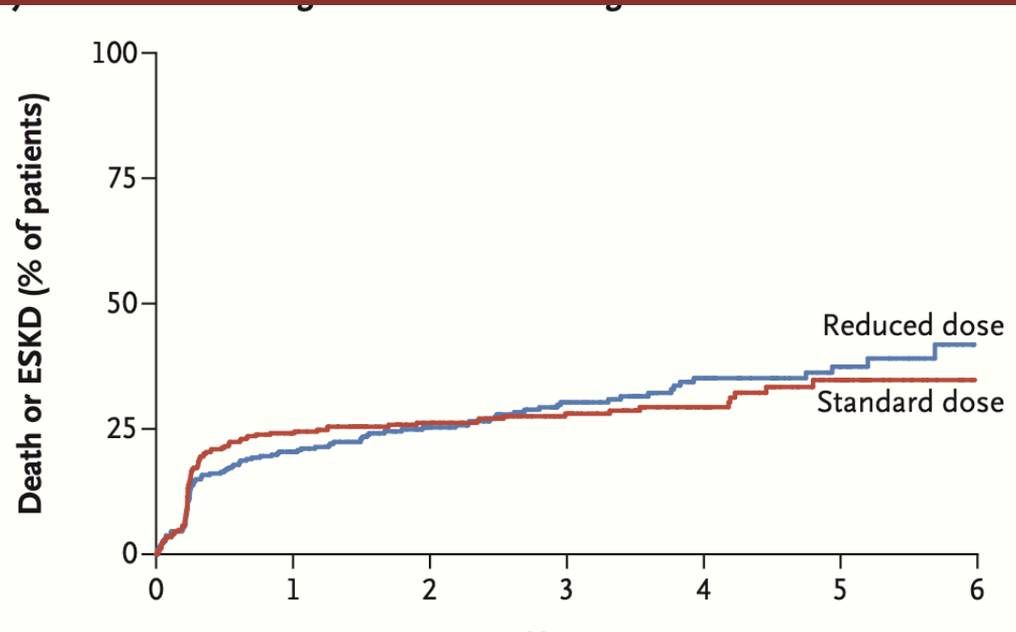
ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

Death from any cause or ESKD occurred in 100 of 352 patients (28.4%) in the plasma-exchange group and in 109 of 352 patients (31.0%) in the control group (hazard ratio, 0.86; 95% CI 0.65 to 1.13; P=0.27).



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



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.

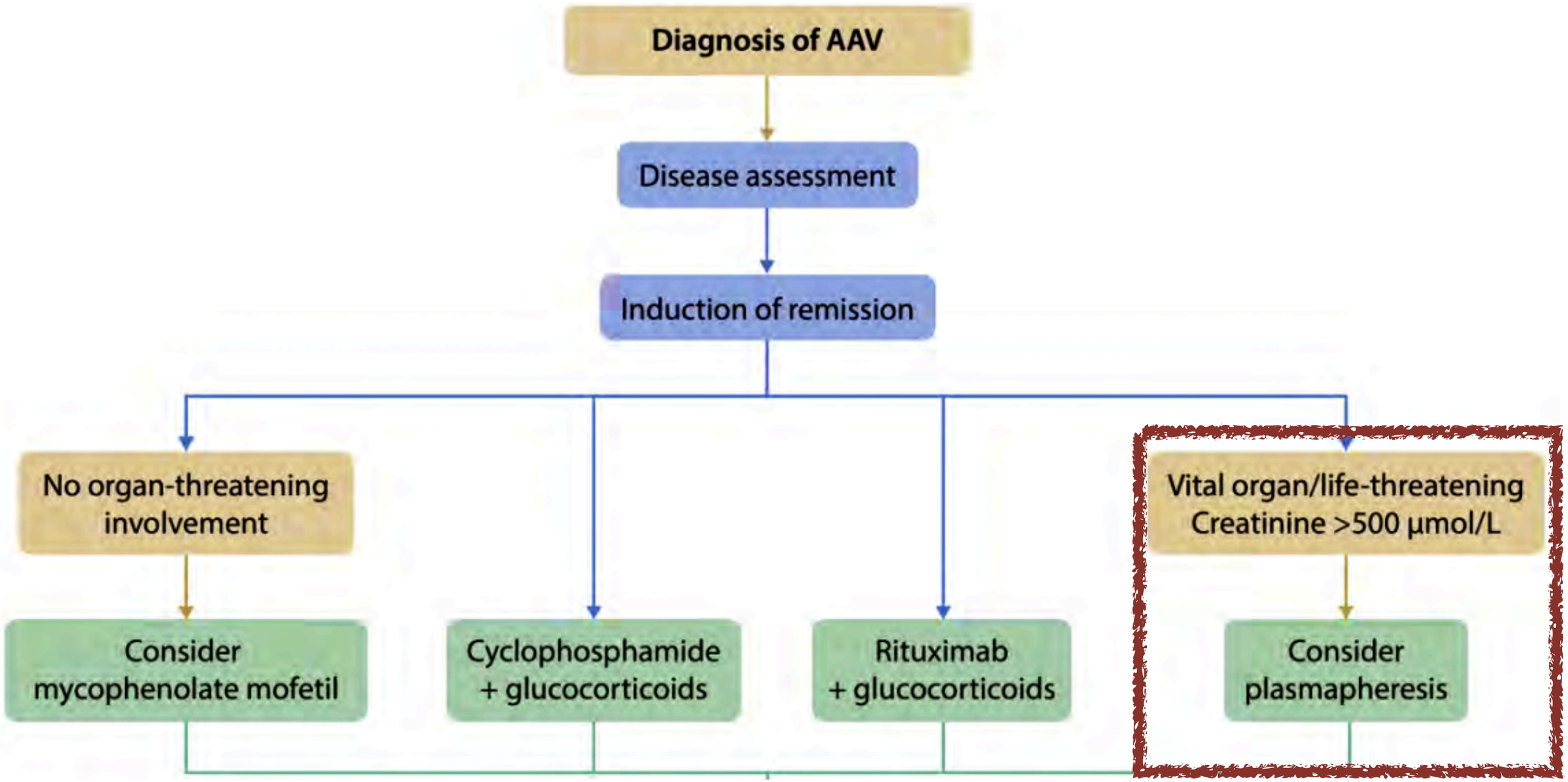
Plasma exchange

- 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 2020

Treatment of ANCA associated vasculitis (RPGN)



KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

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

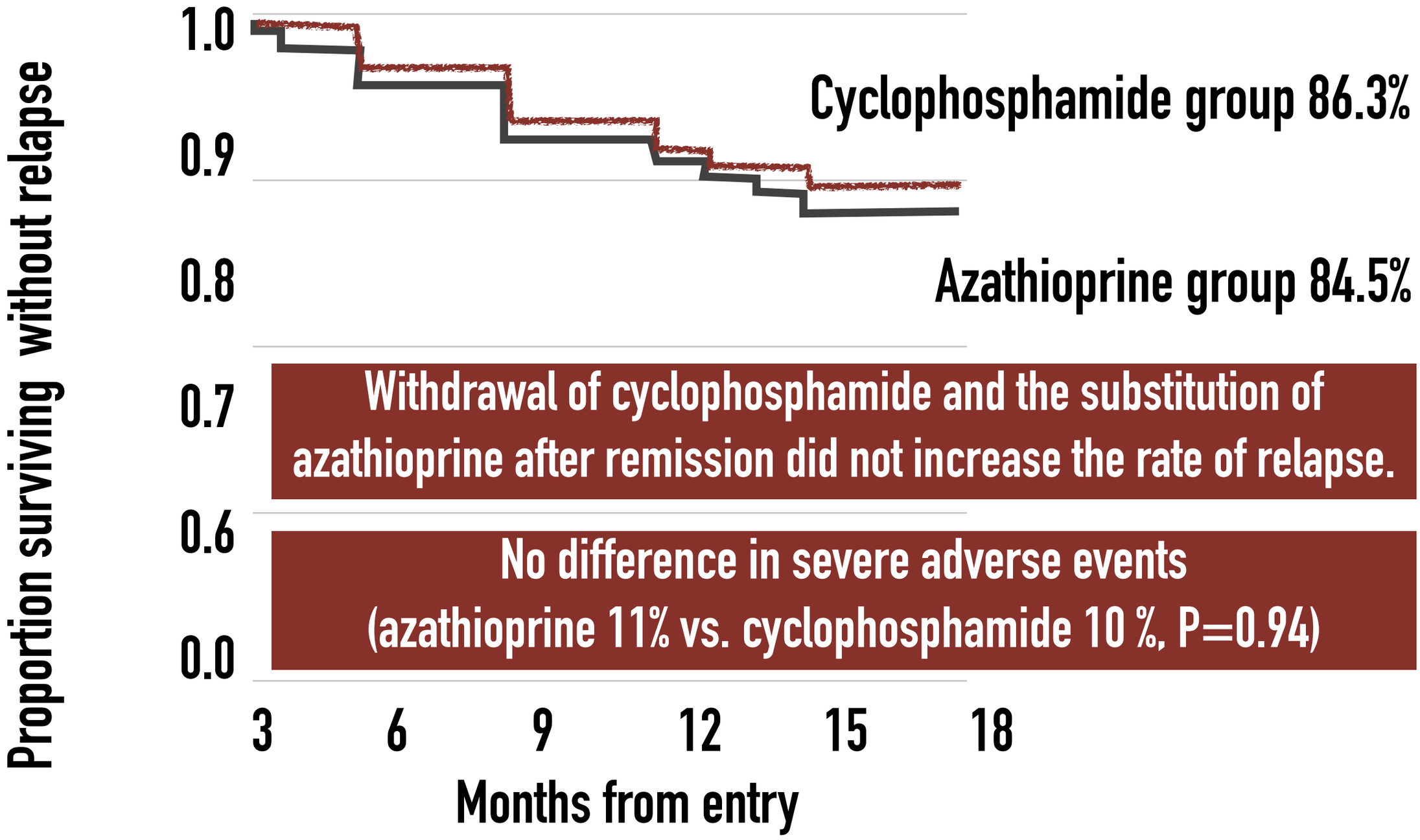
The NEW ENGLAND JOURNAL of MEDICINE

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*

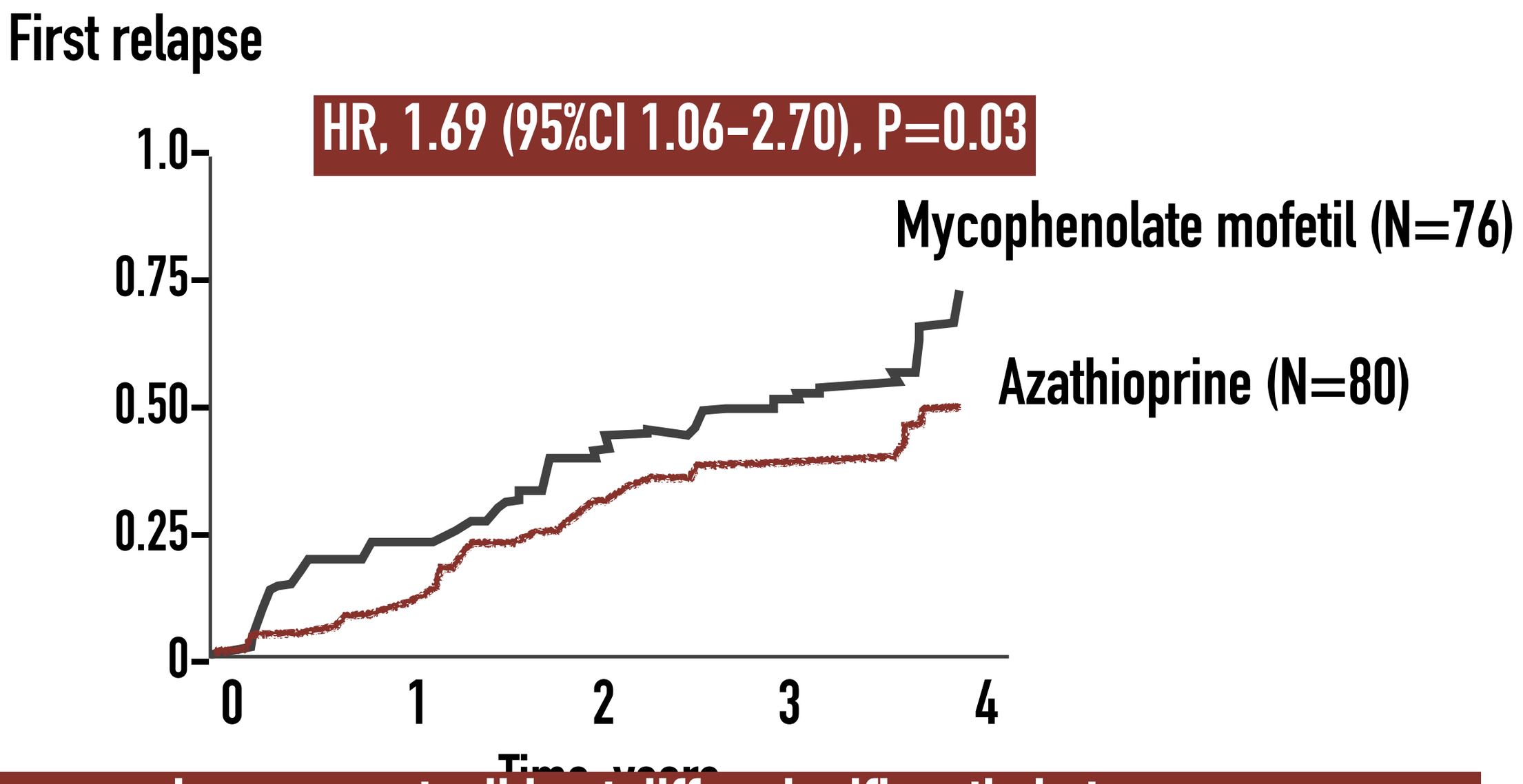
CYCAZAREM trial



N ENGL J MED 349;1 www.NEJM.ORG JULY 3, 2003

MMF

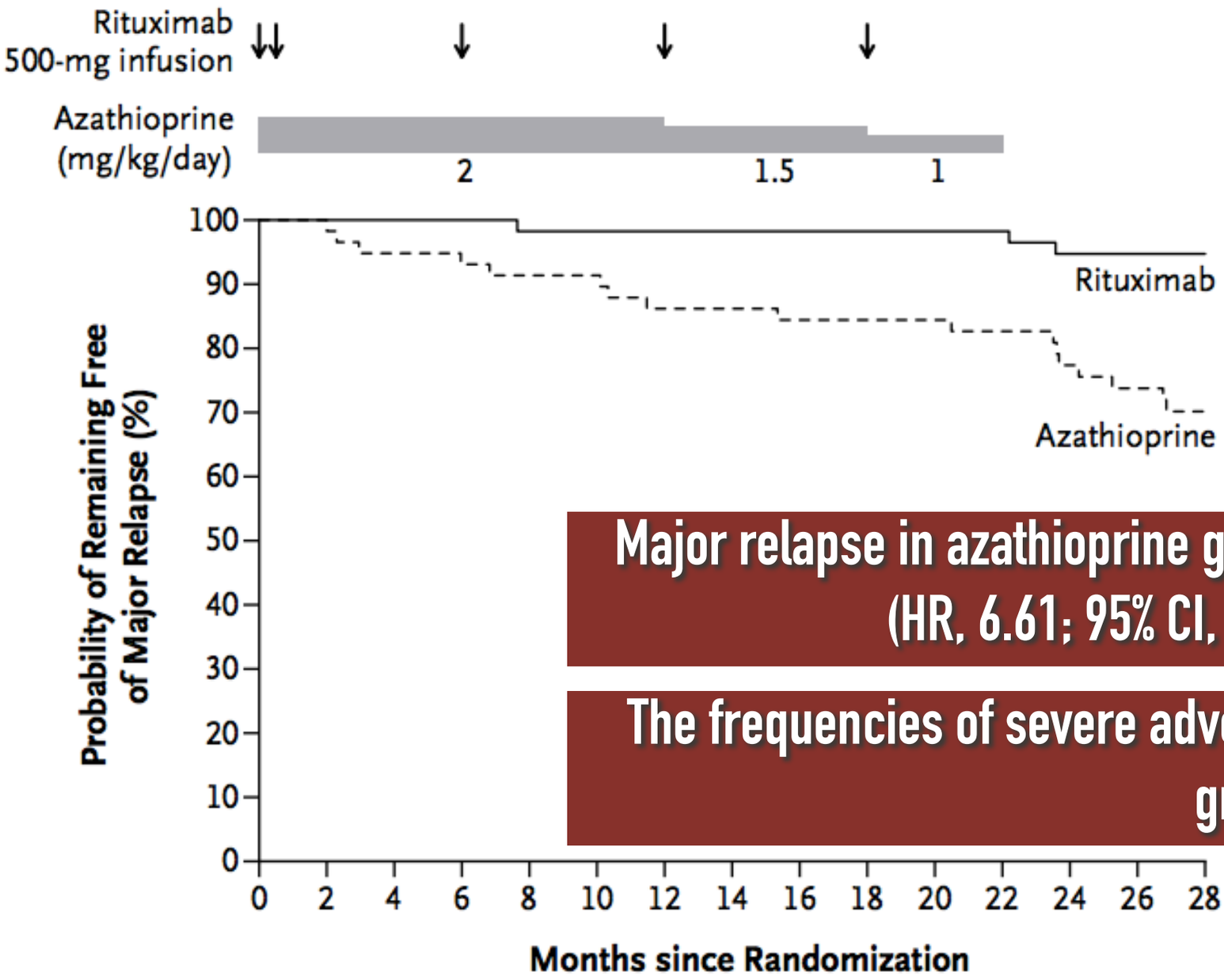
MMF vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Controlled Trial



Severe adverse events did not differ significantly between groups

Hiemstra TF, et al. JAMA 2010;304:2381–8.

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)

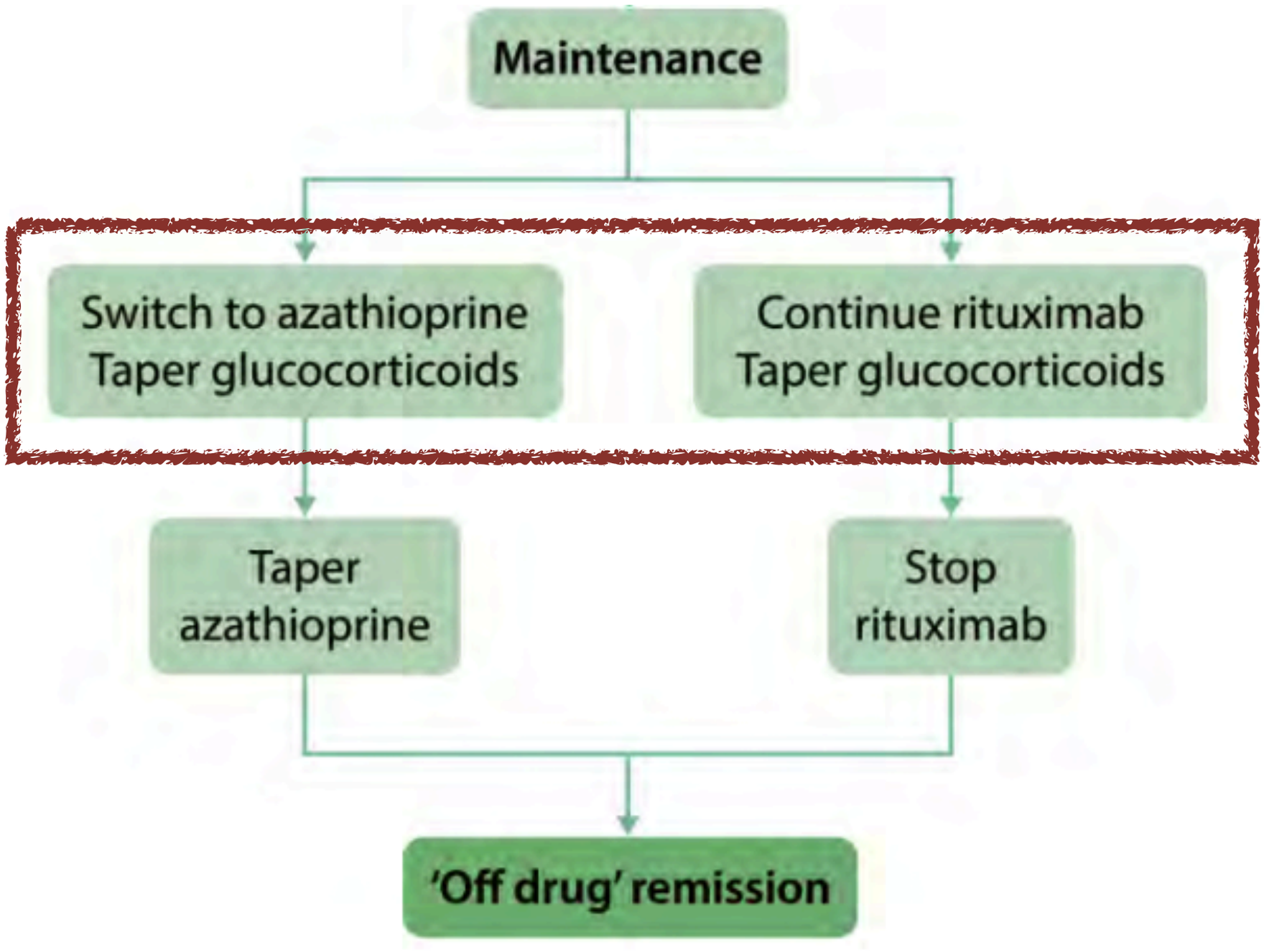
The frequencies of severe adverse events were similar in the two groups.

No. at Risk

Rituximab	57	57	57	57	56	56	56	56	56	56	56	56	54	52	39
Azathioprine	58	58	55	54	53	53	50	50	48	48	48	47	44	41	33

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

Treatment of ANCA associated vasculitis (RPGN)



KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

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 2020

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

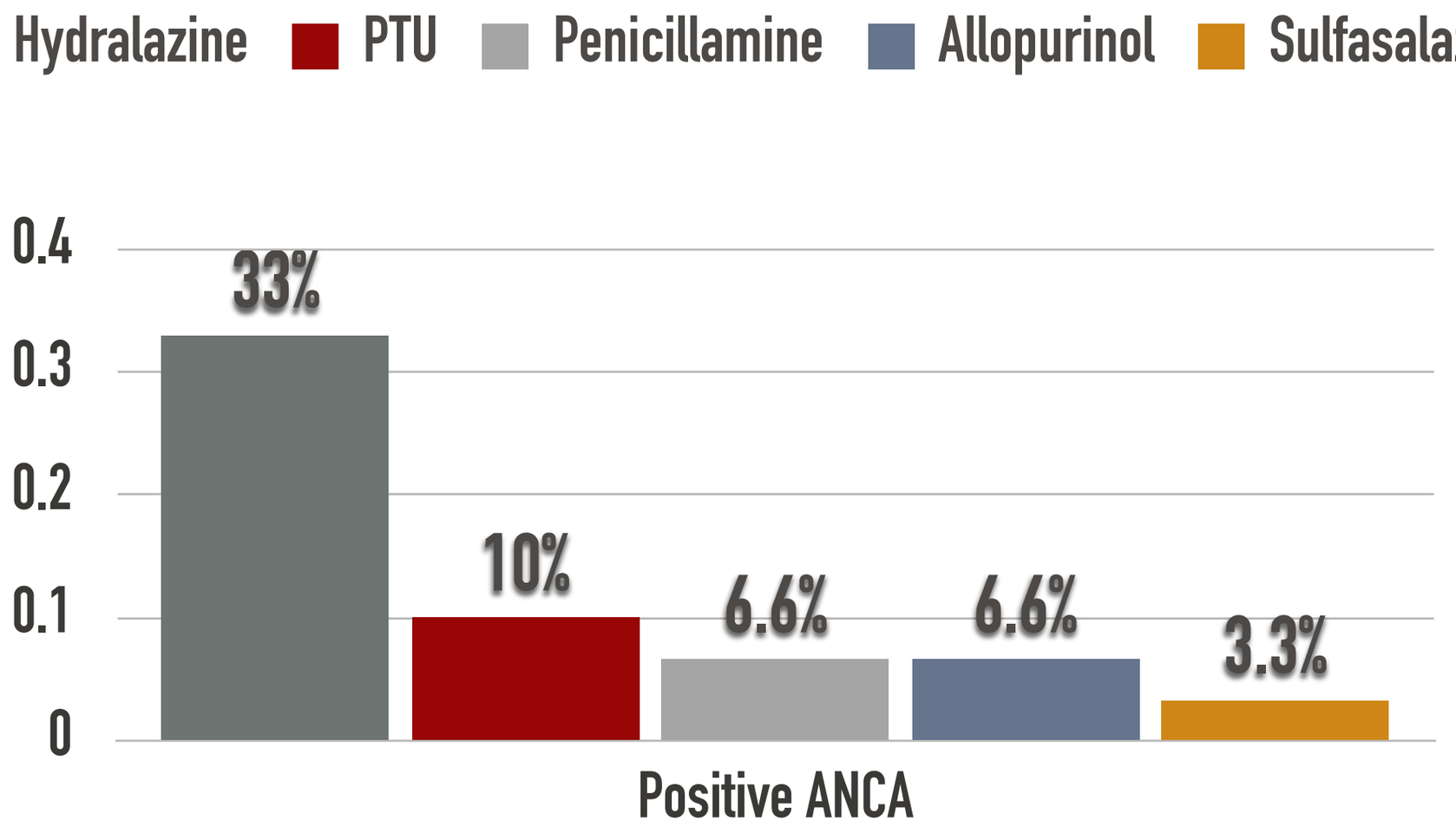
Mark A Little, et al. Ann Rheum Dis 2010;69:1036-1043

RPGN: Prognosis

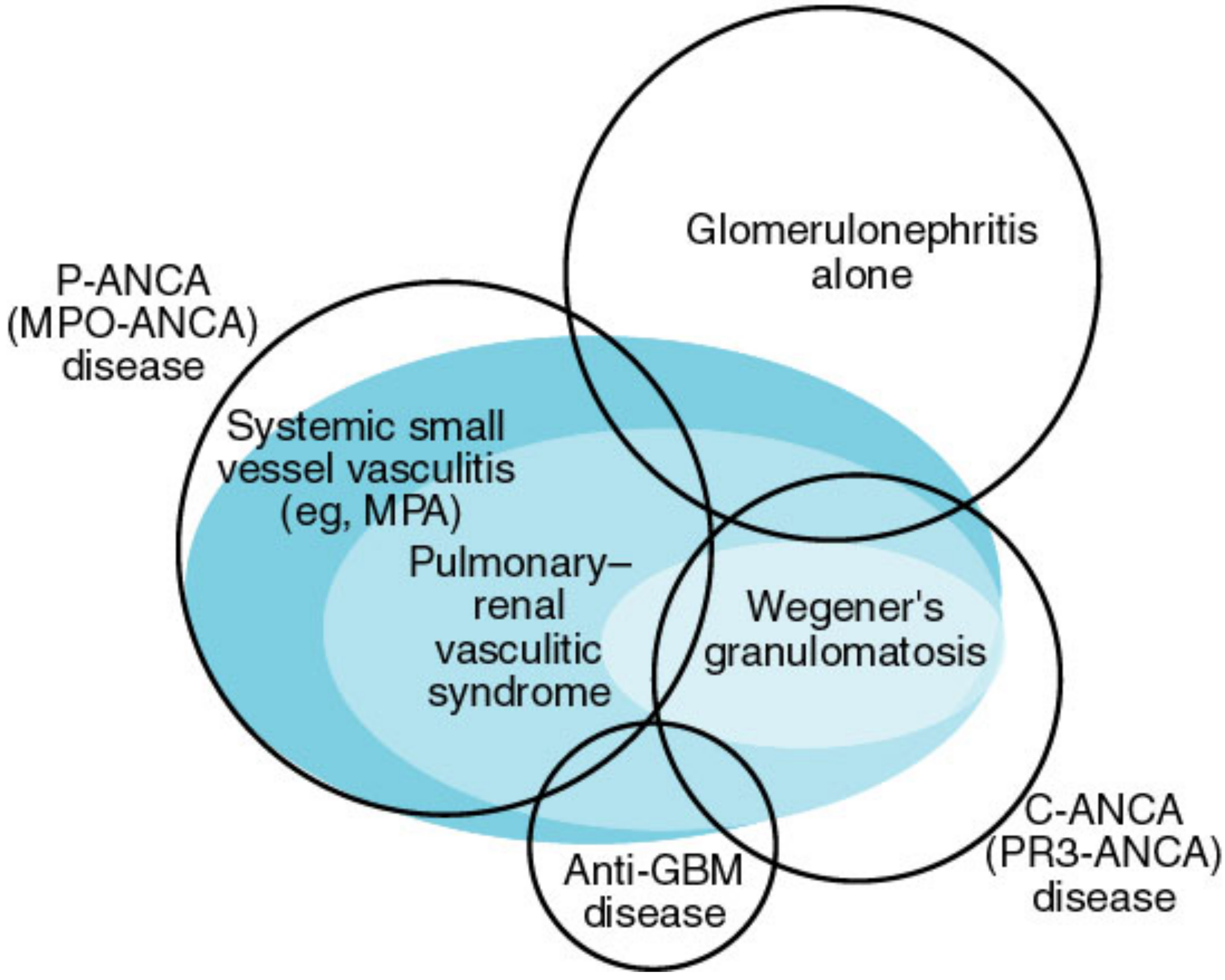
Factors	Poorer prognosis	Better prognosis
Urine output at presentation	Oliguric	Non-oliguric
Extent of crescent formation	>80%	50-80%
Glomerulus	Fibrinoid necrosis	Endocapillary cell proliferation
Glomerular immune deposits	Linear deposition (anti-GBM)	Granular deposition (immune complex) or no immune reactants
Interstitium	Interstitial fibrosis and tubular atrophy	

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
PHRAMONGKUTKLAO HOSPITAL

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL

Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine