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# Rapidly progressive glomerulonephritis: diagnosis and therapy

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8 February 2016

ESIM Winter School 2016, Riga

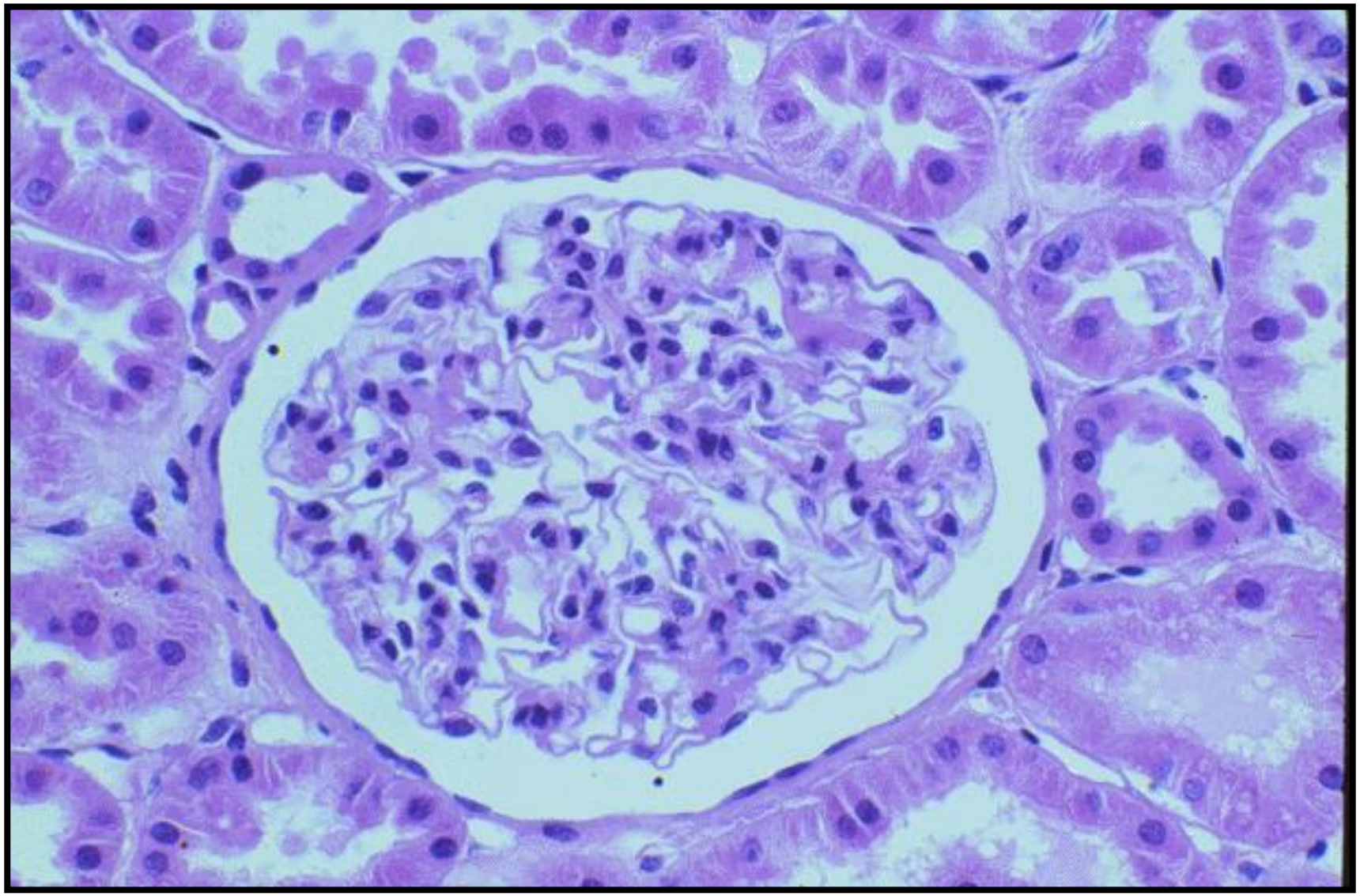
# Disclosures

Nothing to disclose

# Overview

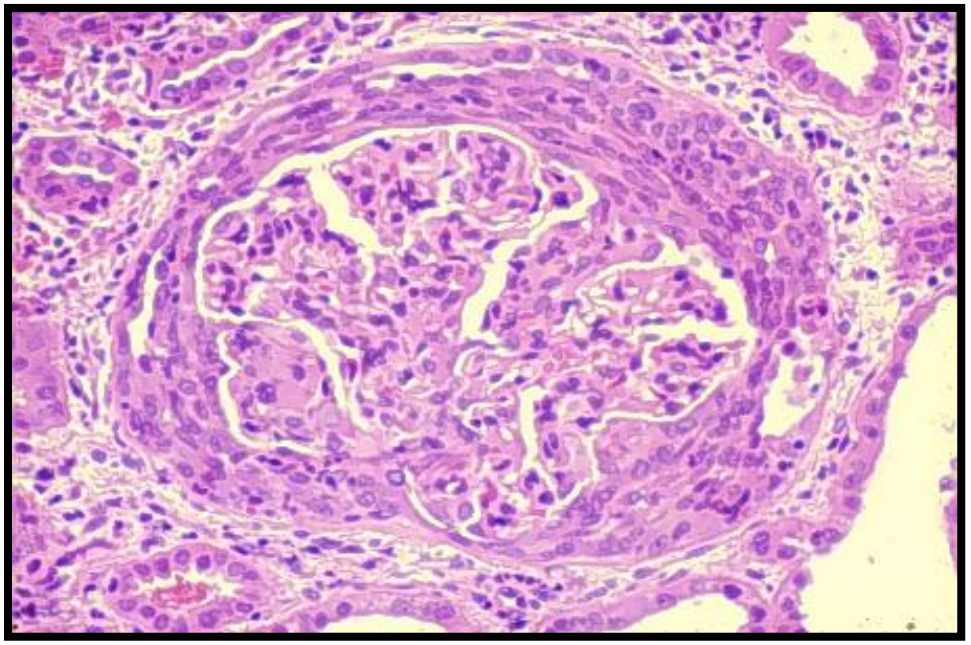
- Clinical presentation of RPGN
- Diagnostic evaluation of RPGN
- Treatment of RPGN
- Management of ANCA-associated GN
- Management of anti-GBM nephritis

# Normal glomerulus

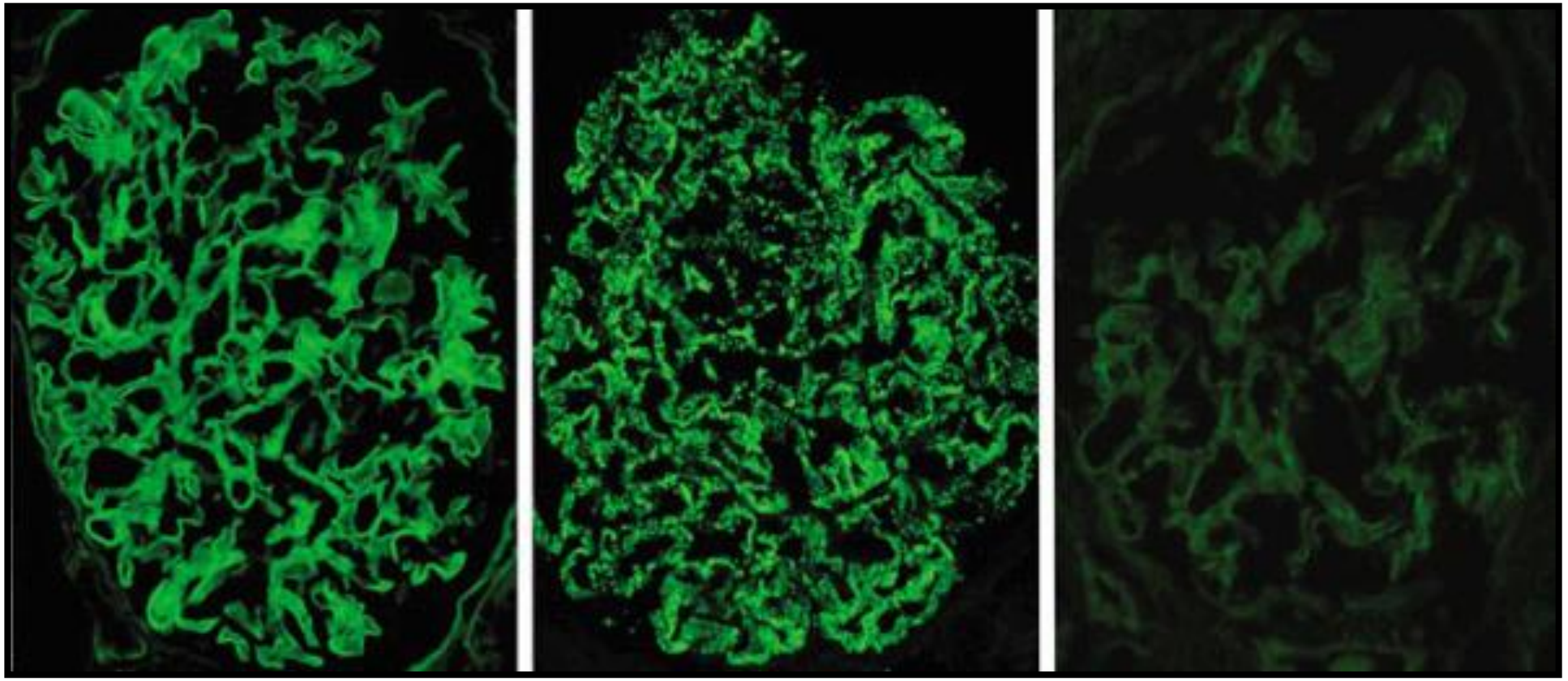


# Rapidly progressive glomerulonephritis

- Clinical syndrome
- Rapid deterioration of kidney function, over days, weeks or months
- Urine microscopy shows signs of glomerulonephritis
- Kidney biopsy usually reveals diffuse crescents (>50% of glomeruli)



# Patterns of immunostaining in crescentic glomerulonephritis



Linear Granular Absent

Jennette JC & Nickeleit V, Hepinstall's Pathology of the Kidney, 6th Ed., 2007

# Immunopathologic classification of RPGN

**1. Linear deposits of IgG**

Anti-GBM nephritis

Goodpasture disease

**2. Granular deposits (immune complex)**

Postinfectious GN

IgA nephropathy/Henoch-Schönlein purpura

Lupus nephritis

Cryoglobulinemic glomerulonephritis

Membranoproliferative glomerulonephritis

**3. Few or no deposits (pauci-immune)**

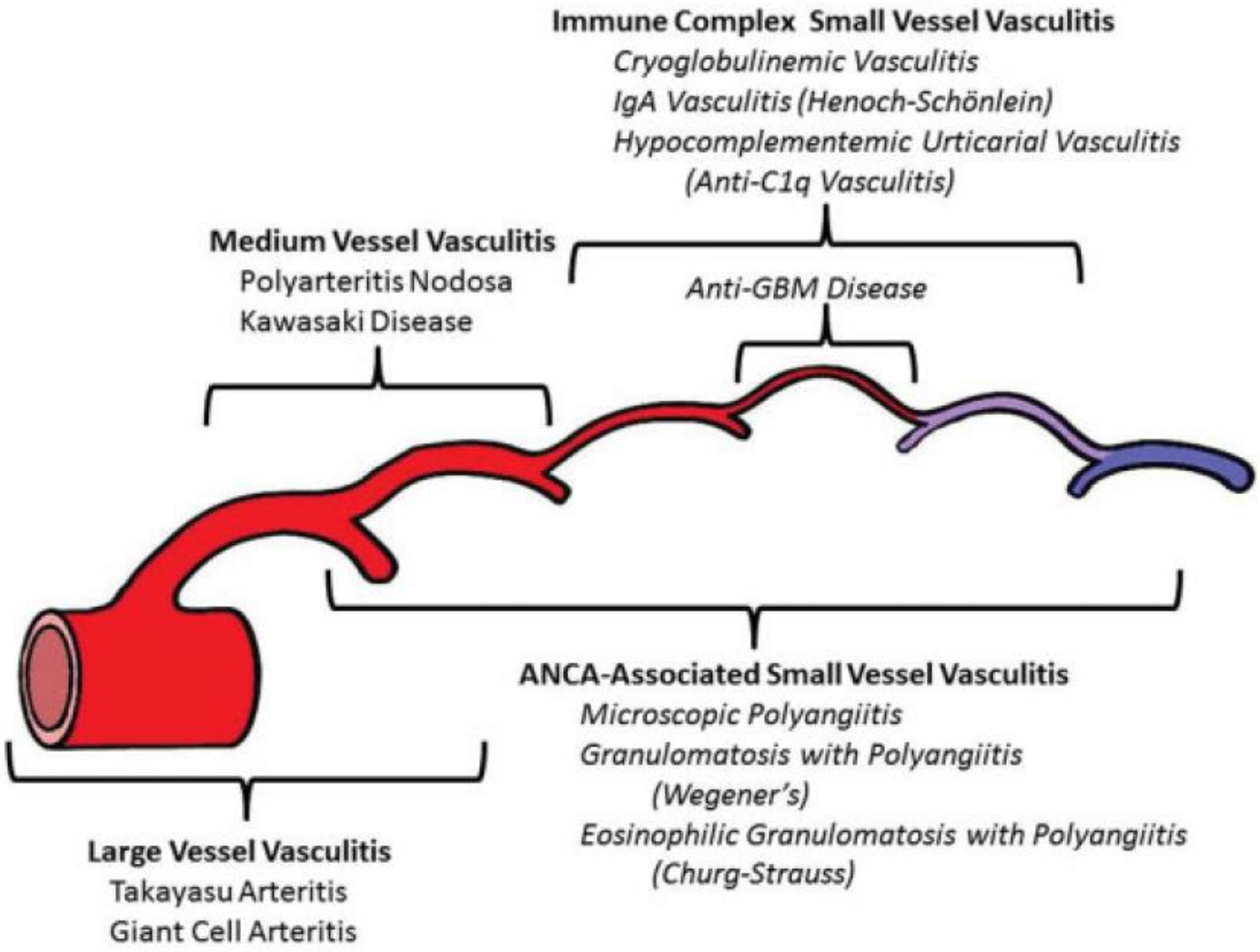
Granulomatosis with polyangiitis (Wegener's granulomatosis)

Microscopic polyangiitis

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Renal-limited vasculitis

# Classification of vasculitis



# Frequency of different types of crescentic glomerulonephritis in renal biopsy specimens evaluated at the University of North Carolina

| Age (yr) | N | Anti-GBM crescentic GN (%) | Pauci-immune crescentic GN (%) | Immune complex crescentic GN(%) | Other crescentic GN (%) |
|---|---|---|---|---|---|
| All | 632 | 15 | 60 | 24 | 1 |
| 1-20 | 73 | 12 | 42 | 45 | 0 |
| 21-60 | 303 | 15 | 48 | 35 | 3 |
| 61-100 | 256 | 15 | 79 | 6 | 0 |

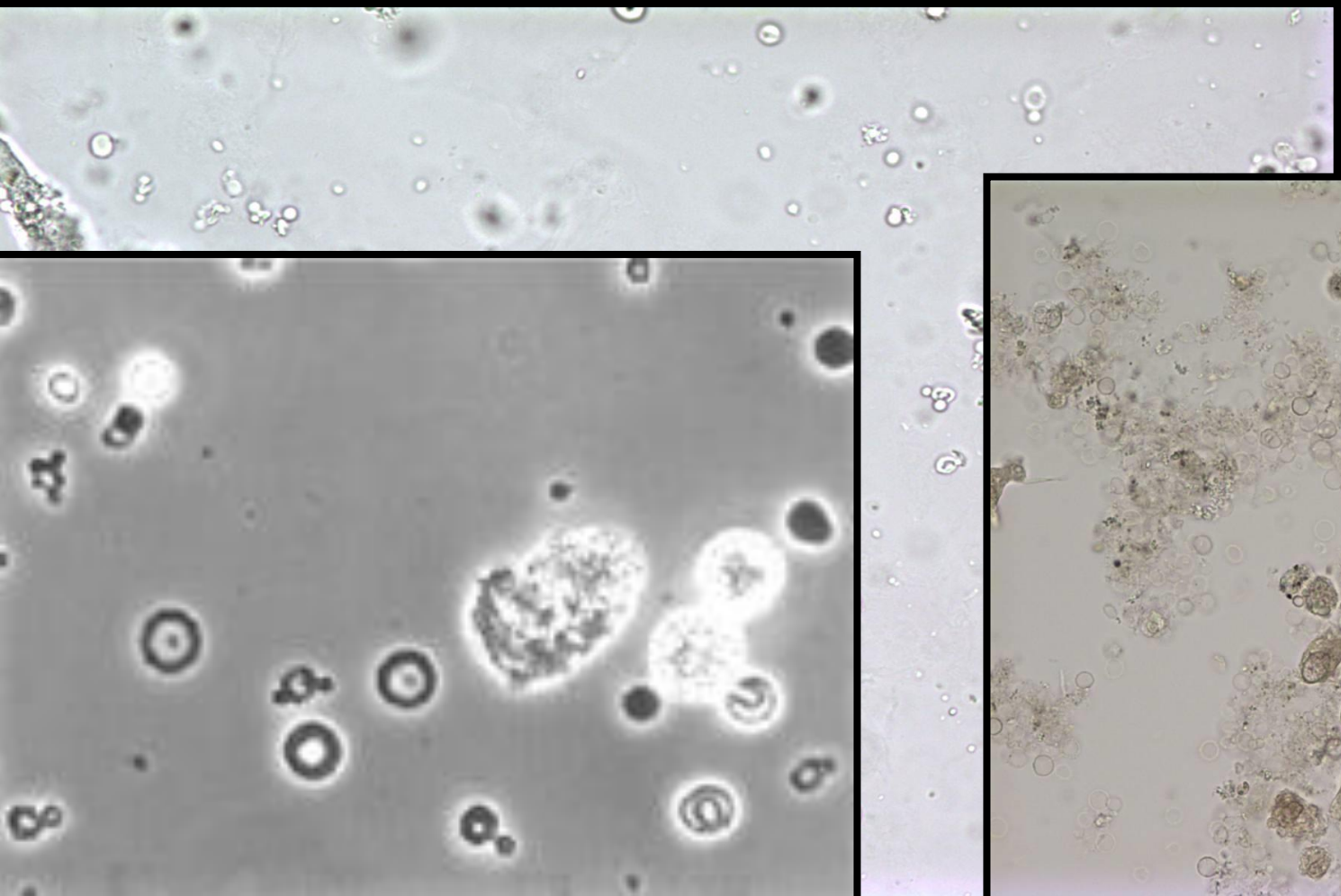
Modified from Jennette JC, Kidney Int 2003;63:1164-77

# Clinical presentation of RPGN

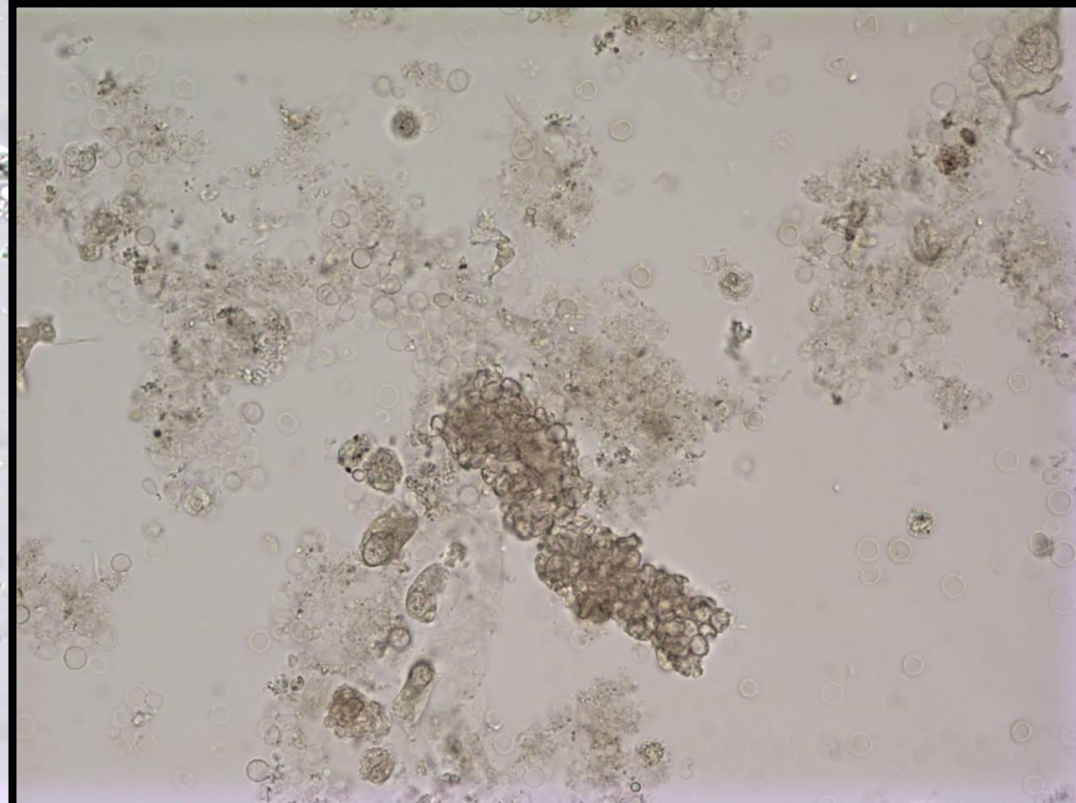
- Characterized by insidious onset and predominantly constitutional symptoms
  - Fever, fatigue, malaise, myalgias and anorexia
- Edema
- Decreased urine output
- Elevated serum creatinine
- Nephritic urinary sediment
- Extrarenal features in patients with systemic diseases

# Glomerular hematuria

Dysmorphic red blood cells

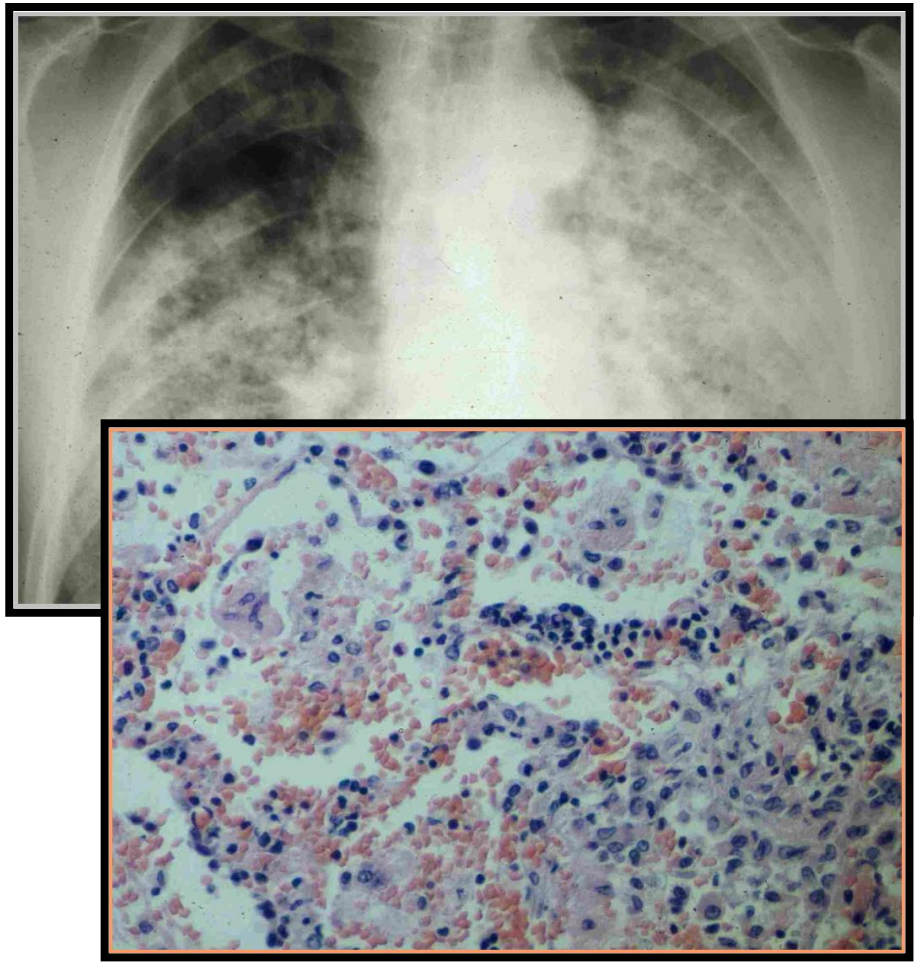


Red blood cell cast



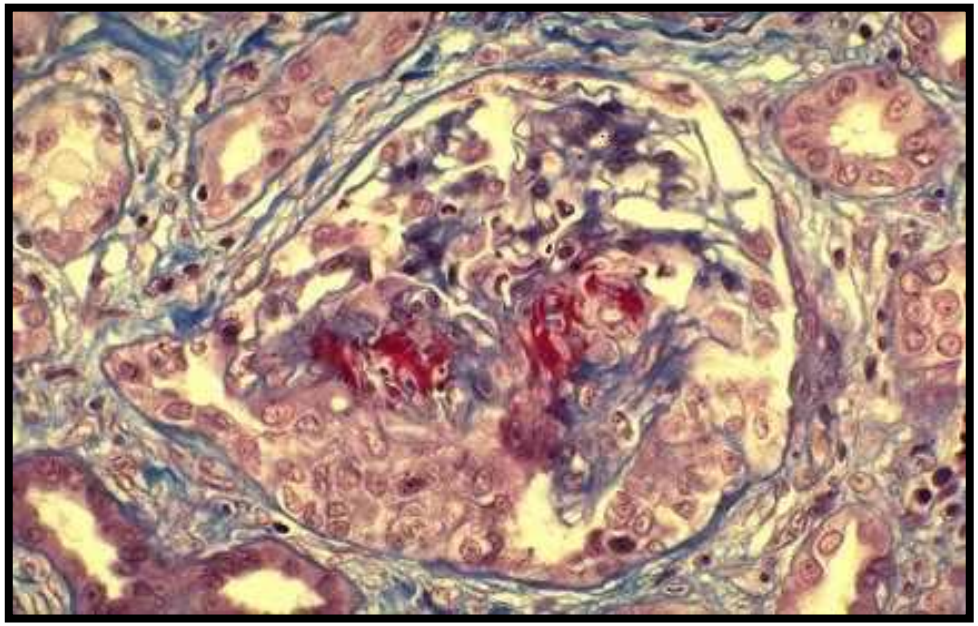
# Pulmonary-renal syndrome

Diffuse pulmonary opacities



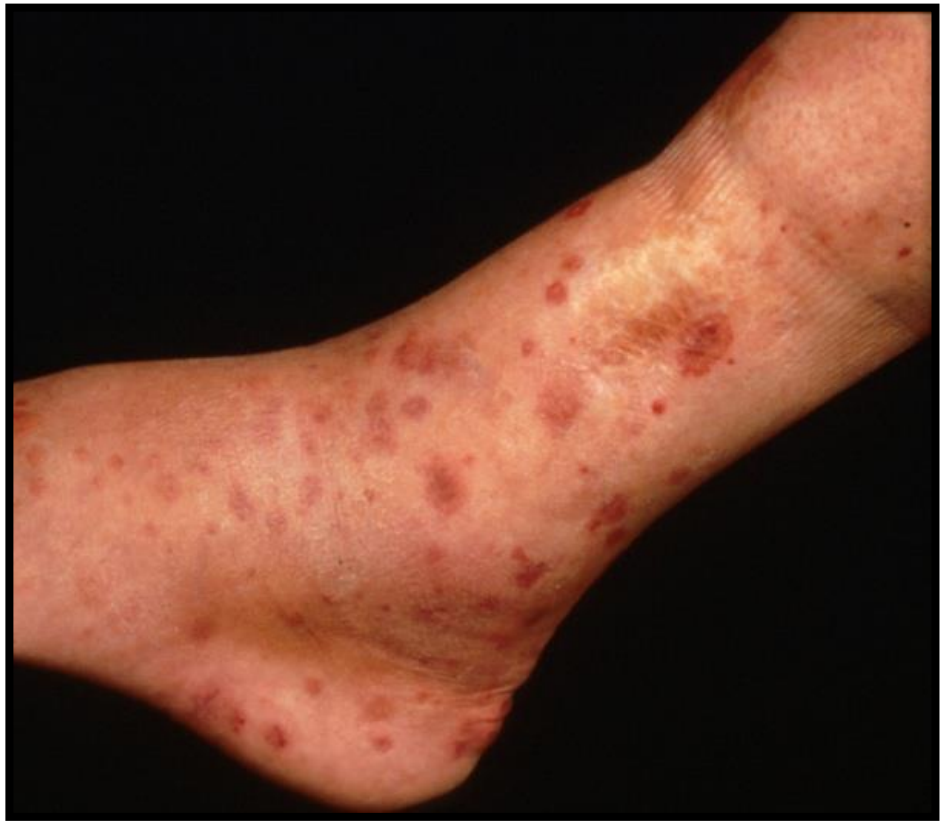
Alveolar capillaritis and hemorrhage

Necrotizing and crescentic glomerulonephritis



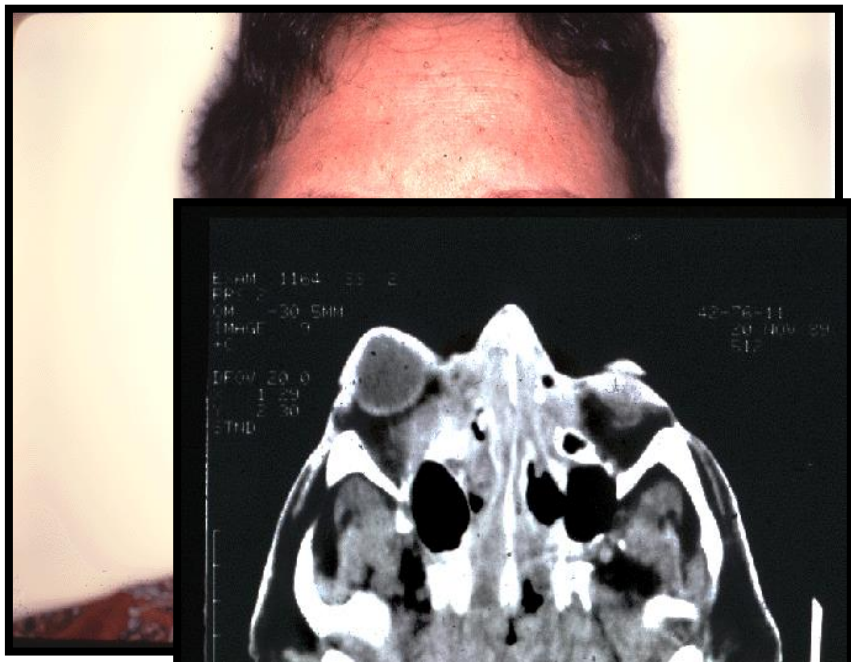
~60% ANCA-associated vasculitis
~20% Goodpasture´s syndrome

# RPGN and purpura



- ANCA-associated vasculitis
- Henoch-Schönlein purpura
- Cryoglobulinemic vasculitis

# Granulomatosis with polyangiitis



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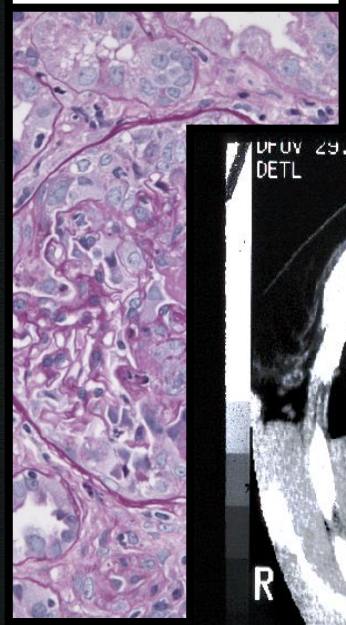
Orbital mass



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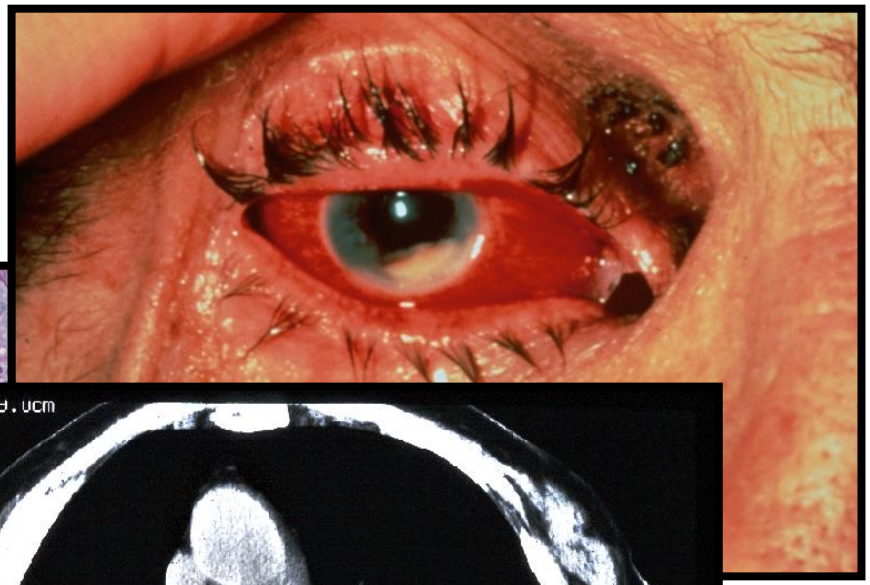
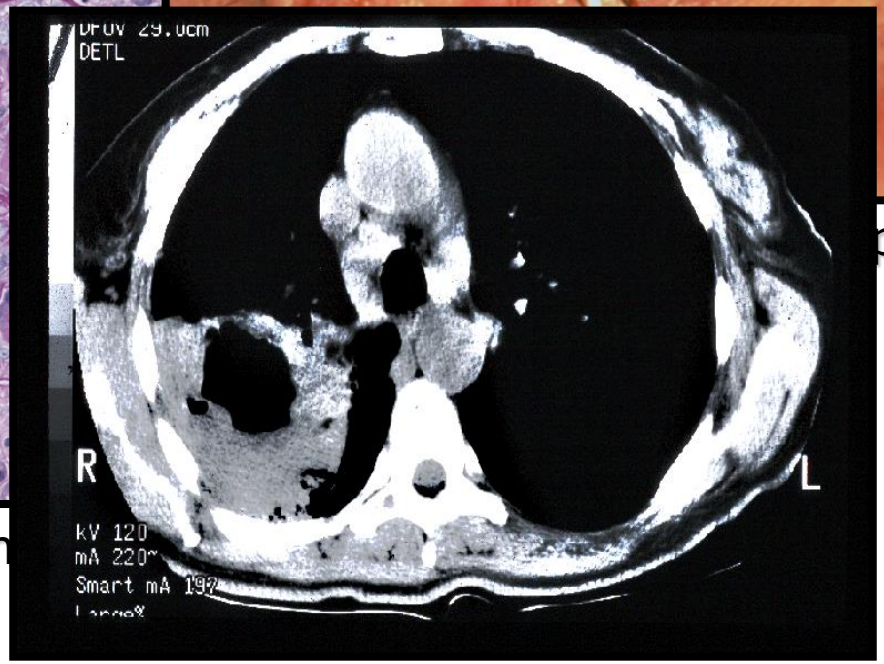


pyon




Cavitary lung lesion

# Urgent and accurate diagnosis is key to successful outcome of RPGN

Early diagnosis is dependent on:

- Recognition of clinical features
- Appropriate use of serologic testing
- Kidney biopsy
  - Confirm the diagnosis
  - Assess disease activity and chronic (irreversible) damage
  - Evaluate likelihood of response to therapy

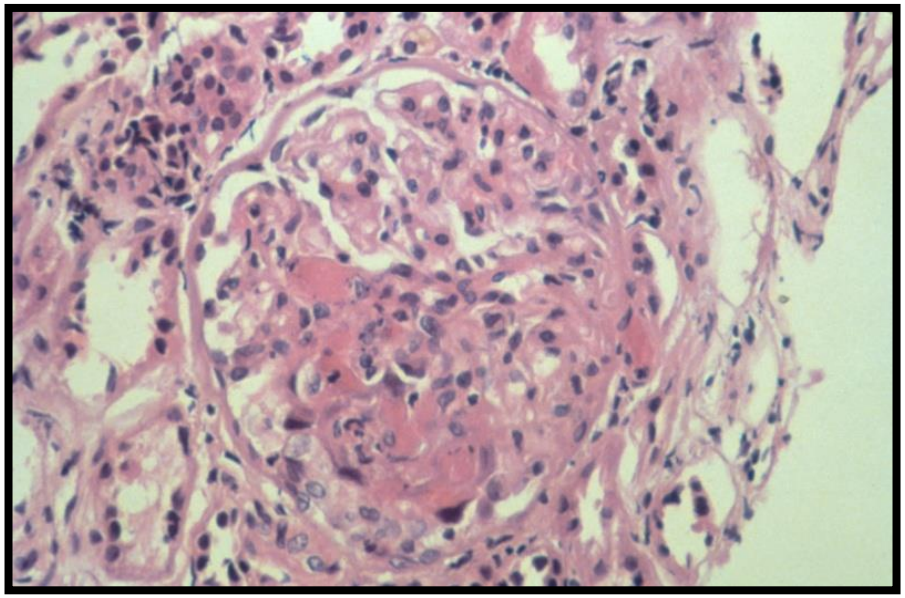
# Serologic tests

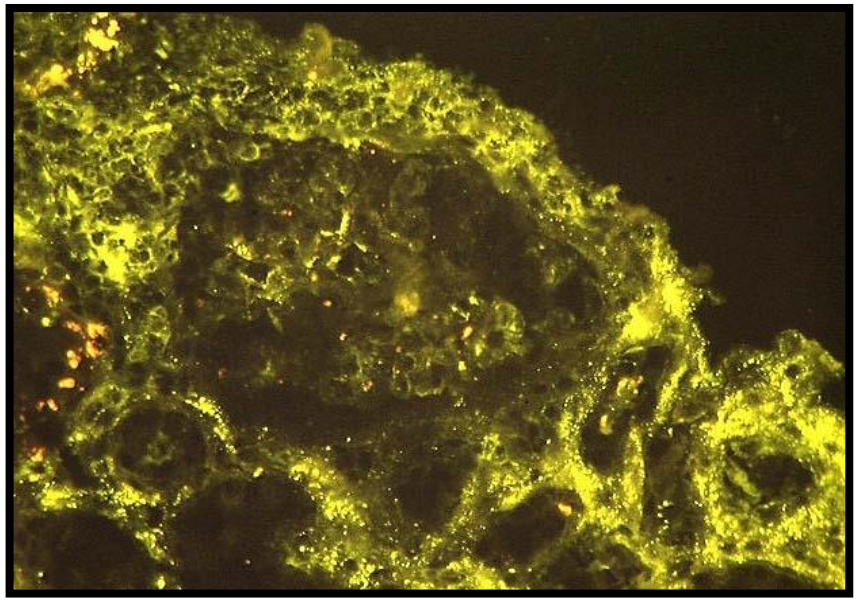
- Anti-GBM
- ANCA
- Anti-streptolysin O, anti-DNAse B
- ANA, anti-DNA
- Complement components
  - C3 and C4
- Cryoglobulin
- Anti-HCV
- C3 nephritic factor

# Treatment of RPGN: principal issues

- Timely initiation of aggressive immunosuppressive therapy is vital to minimize irreversible renal injury
  - Methylprednisolone IV pulse daily for 3 days
  - Cyclophosphamide is used in most cases
  - Plasma exchange is added for anti-GBM disease, severe cases of ANCA-associated renal vasculitis or pulmonary hemorrhage
- More specific treatment is determined once the diagnosis has been established
- Close monitoring for adverse effects is essential
- Avoid prolonged use of high dose steroids
- Reduction or disappearance of hematuria and proteinuria may take a long time, despite successful treatment

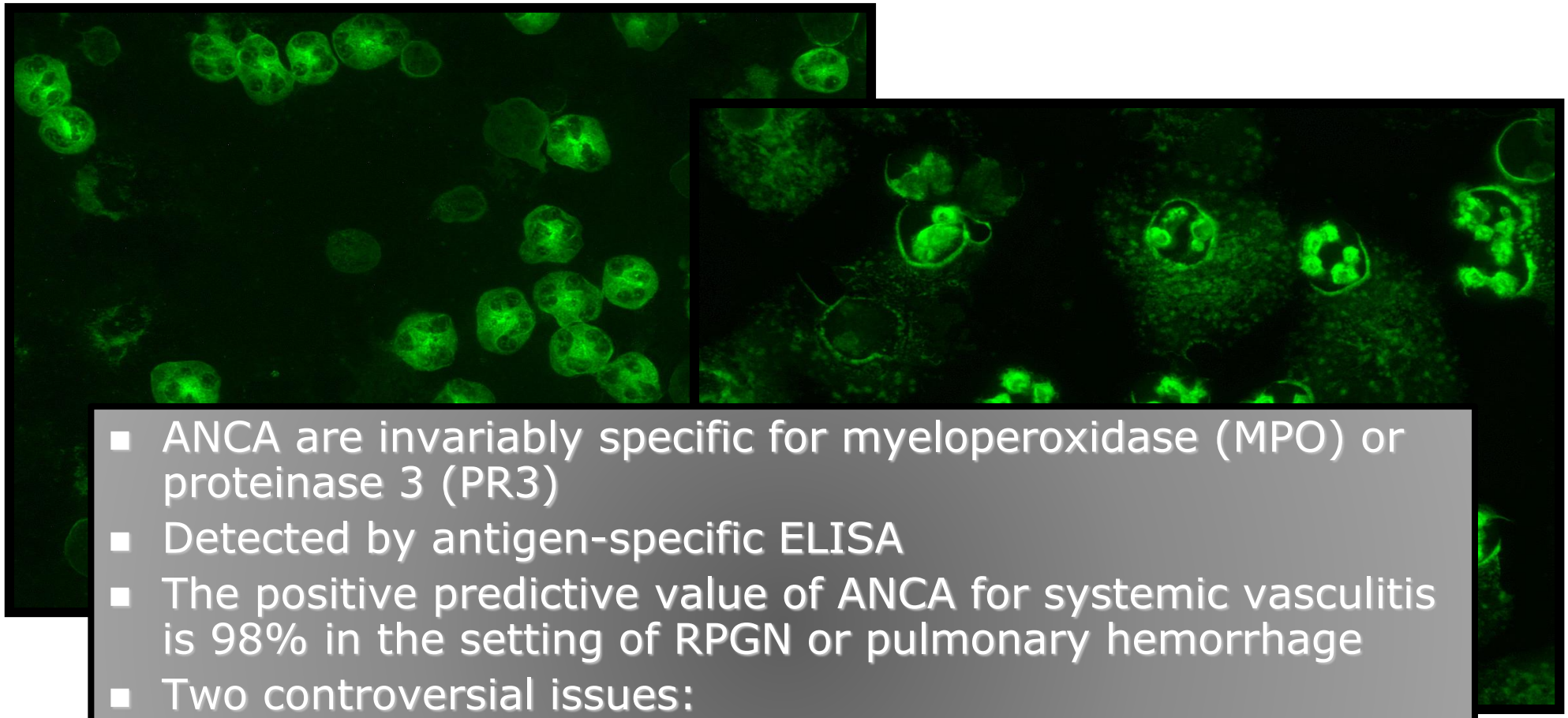
# Pauci-immune necrotizing and crescentic GN





- Close to 90% are ANCA positive
- ANCA is a highly specific marker of systemic small-vessel vasculitides associated with pauci-immune necrotizing and crescentic GN
- ANCA-negative cases share the same features

# Anti-neutrophil cytoplasmic antibodies (ANCA)



- ANCA are invariably specific for myeloperoxidase (MPO) or proteinase 3 (PR3)
- Detected by antigen-specific ELISA
- The positive predictive value of ANCA for systemic vasculitis is 98% in the setting of RPGN or pulmonary hemorrhage
- Two controversial issues:
  - Is positive ANCA test sufficient for diagnosis?
  - Is serial ANCA testing useful for monitoring disease activity?

The Journal of Rheumatology

The Journal of Rheumatology Volume 28, no. 7

# Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies.

H K Choi, S Liu, P A Merkel, G A Colditz and J L Niles

J Rheumatol 2001;28;1584-1590
http://www.jrheum.org/content/28/7/1584

| ANCA Testing System | No. of Studies | Sensitivity, % (95% CI) | Specificity, % (95% CI) Disease Controls | All Controls |
|---|---|---|---|---|
| Anti-MPO | 7 | 37.1 (26.6, 47.6) | 96.3 (94.1, 98.5) | 96.9 (95.2, 98.7) |
| Anti-MPO plus p-ANCA | 6 | 31.1 (21.0, 42.1) | 99.4 (99.0, 99.9)* | 99.3 (98.8, 99.8) |
| Anti-MPO plus p-ANCA or anti-PR3 plus c-ANCA | 5 | 84.7 (70.7, 98.7) | 98.6 (97.9, 99.3)* | 99.2 (99.0, 99.6)* |

*A fixed-effect model for calculating summary estimates was used because chi-square testing suggested that there is no heterogeneity across studies. Other summary estimates were calculated with a random-effects model due to the suggested presence of heterogeneity across the studies.

# Induction therapy of ANCA-associated vasculitis presenting as RPGN

- Methylprednisolone 0.5-1 g IV pulse daily for 3 days, followed by prednisone 1 mg/kg PO daily (maximum 60-80 mg/day)
- Cyclophosphamide 0.5-1 g/$m^2$ (15 mg/kg) IV pulse every 2-3 weeks or 1.5-2 mg/kg/day PO
  - Mercaptoethane sulfonate (MESNA) should be administered with IV pulses to prevent bladder toxicity
  - Adjust the cyclophosphamide dose according to age, kidney function and WBC count
  - WBC count should remain >3.5 x $10^9$/L and ANC >1.5 x $10^9$/L
- Rituximab provides an alternative to cyclophosphamide
- Plasma exchange should be considered for patients with severe renal dysfunction
  - 7 sessions over 2 weeks, 60 mL/kg per session

# Preventive measures during induction therapy

- Low-dose trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis jiroveci*
- Mycostatin or ketoconazole for prevention of mucocutaneous candidiasis
- Gastric protection with PPI
- Osteoporosis prevention using vitamin D and calcium supplementation; consider bisphosphonate in high-risk patients

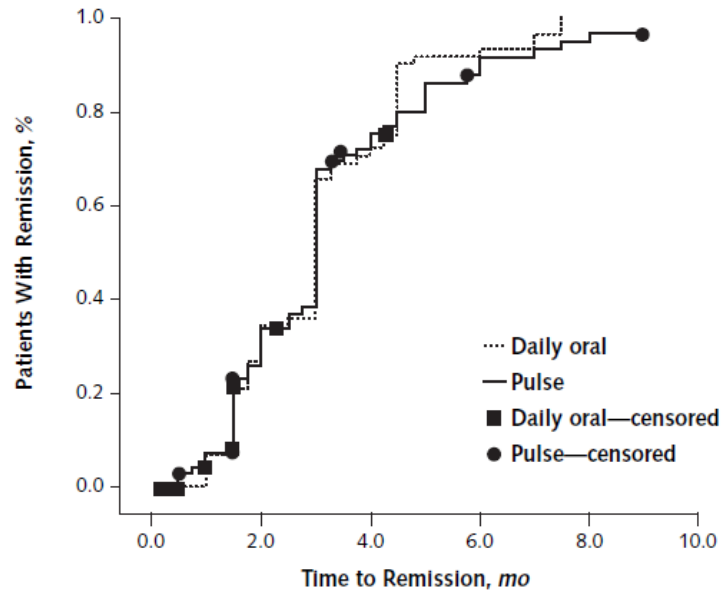
ARTICLE | Annals of Internal Medicine

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

## A Randomized Trial

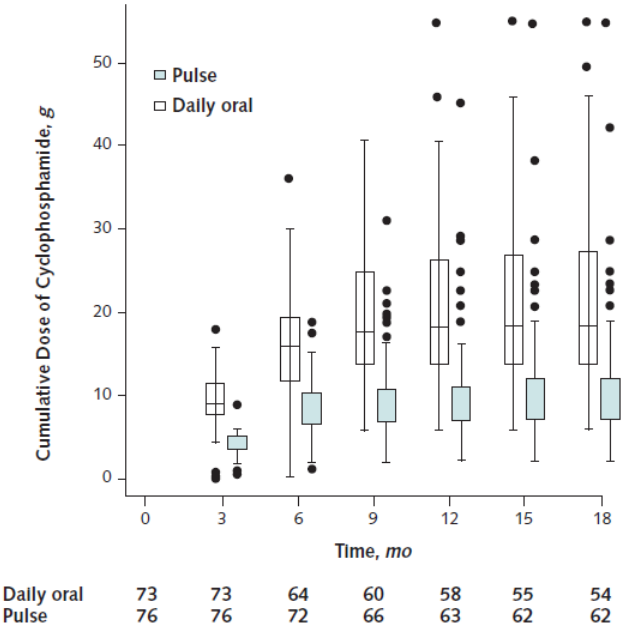
Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.W. Jayne, MD, PhD; Luis Felipe Flores Suarez, MD, PhD; Gina Gregorini, MD; Wolfgang L. Gross, MD; Rashid Luqmani, MD; Charles D. Pusey, MD, PhD; Niels Rasmussen, MD; Renato A. Sinico, MD; Vladimir Tesar, MD, PhD; Philippe Vanhille, MD; Kerstin Westman, MD, PhD; and Caroline O.S. Savage, MD, PhD, for the EUVAS (European Vasculitis Study Group)

Ann Intern Med. 2009;150:670-680.




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

Sample sizes are listed for each group; missing data are from patients who were withdrawn or died.




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Daily oral | 73 | 73 | 64 | 60 | 58 | 55 | 54 |
| Pulse | 76 | 76 | 72 | 66 | 63 | 62 | 62 |

We used a box-and-whiskers plot to describe the median dose per patient and the interquartile range of sequential cumulative cyclophosphamide dose in each treatment group. Extremes and outliers are represented as circles. Sample sizes are listed for each group; missing data are from patients who were withdrawn or died.

Annals of the
RHEUMATIC DISEASES
The EULAR Journal

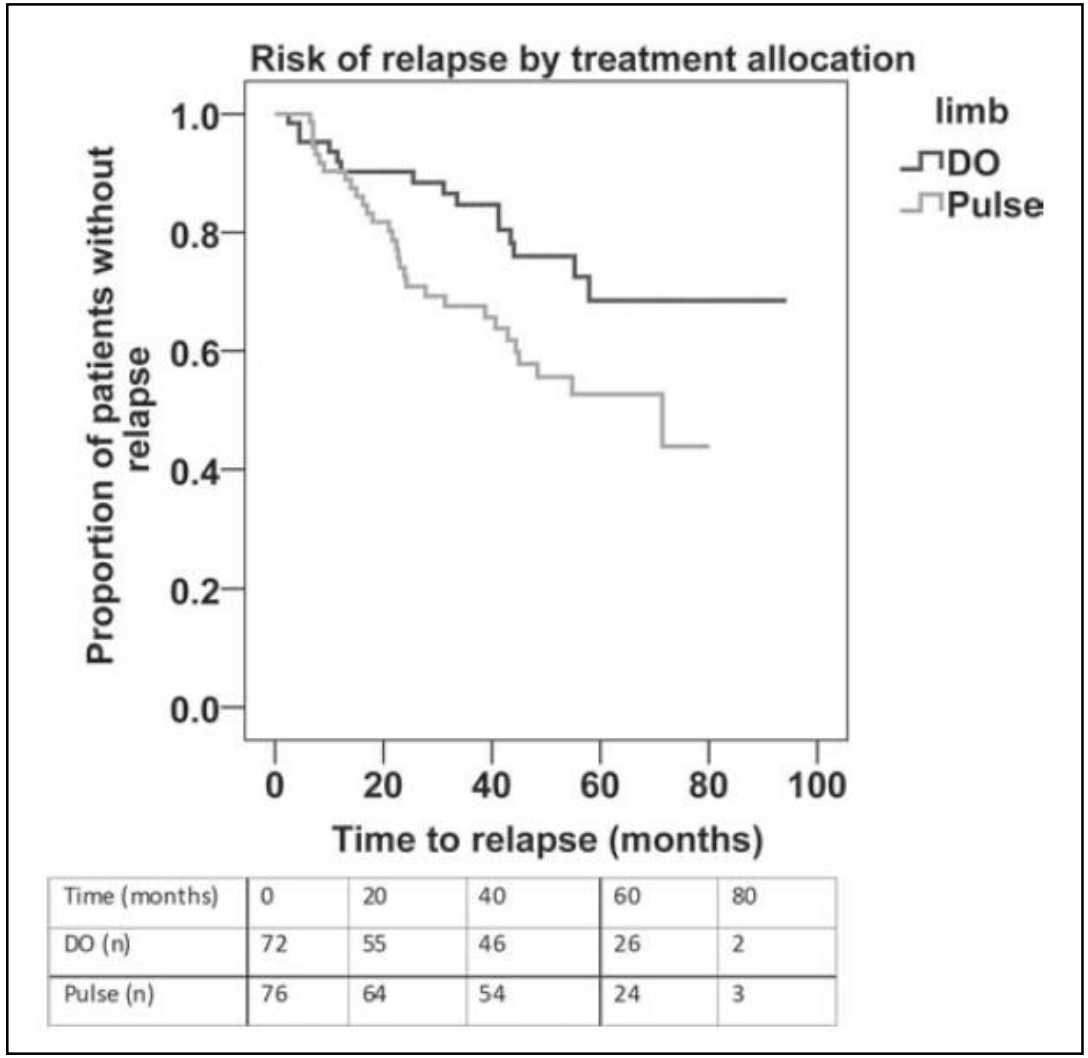
Clinical and epidemiological research

EXTENDED REPORT

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

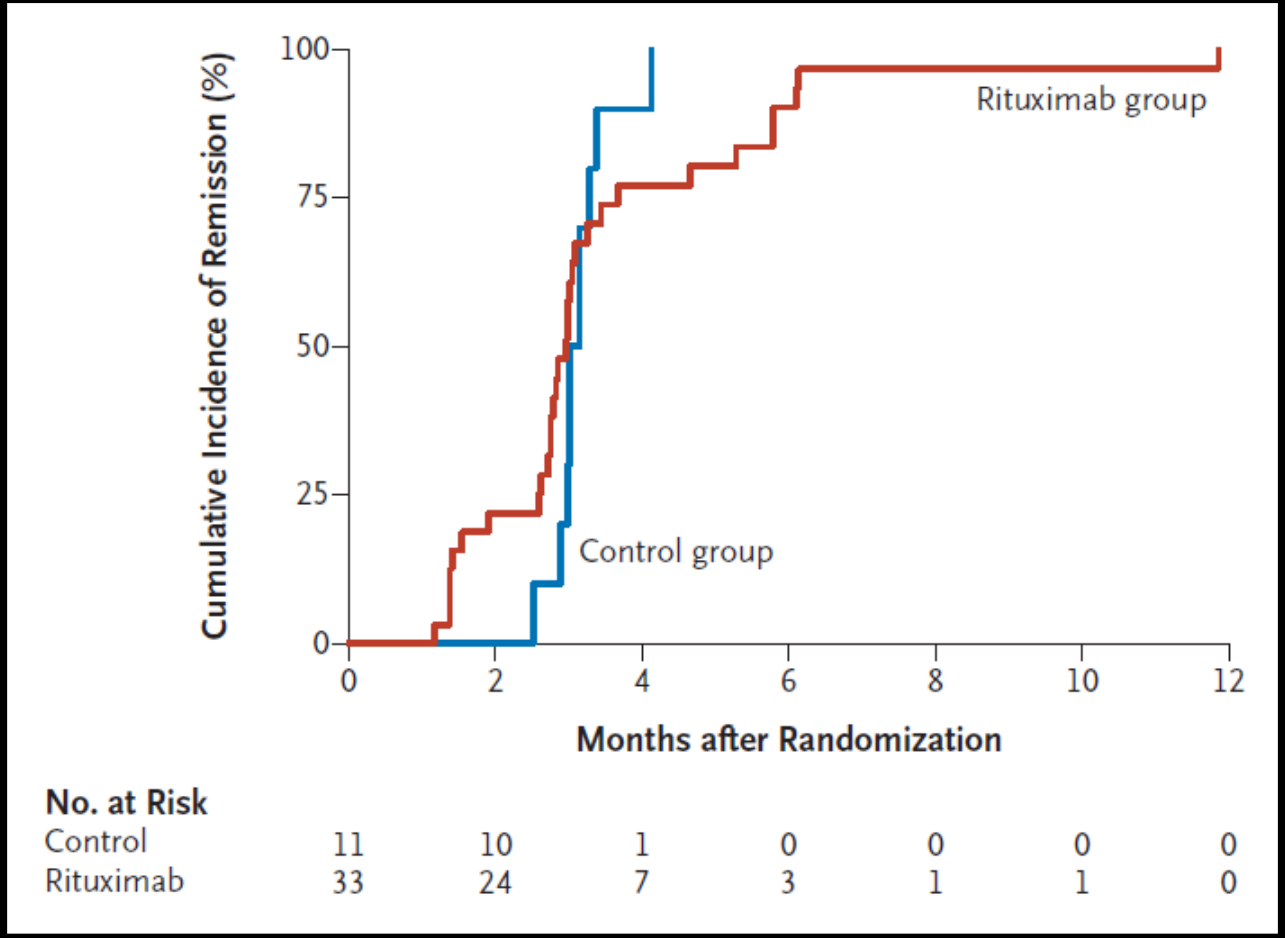
Lorraine Harper,[1] Matthew D Morgan,[1] Michael Walsh,[2] Peter Hoglund,[3] Kerstin Westman,[4] Oliver Flossmann,[5] Vladimir Tesar,[6] Phillipe Vanhille,[7] Kirsten de Groot,[8] Raashid Luqmani,[9] Luis Felipe Flores-Suarez,[10] Richard Watts,[11] Charles Pusey,[12] Annette Bruchfeld,[13] Niels Rasmussen,[14] Daniel Blockmans,[15] Caroline O Savage,[1] David Jayne[1] on behalf of EUVAS investigators

Ann Rheum Dis 2012:71:955–960.




| Time (months) | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| DO (n) | 72 | 55 | 46 | 26 | 2 |
| Pulse (n) | 76 | 64 | 54 | 24 | 3 |

# Rituximab vs. cyclophosphamide in ANCA-associated renal vasculitis: cumulative incidence of remission




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 11 | 10 | 1 | 0 | 0 | 0 | 0 |
| Rituximab | 33 | 24 | 7 | 3 | 1 | 1 | 0 |

The NEW ENGLAND JOURNAL of MEDICINE

Jones RB et al, N Engl J Med 2010;348:2543-56

JASN® Journal of the American Society of Nephrology

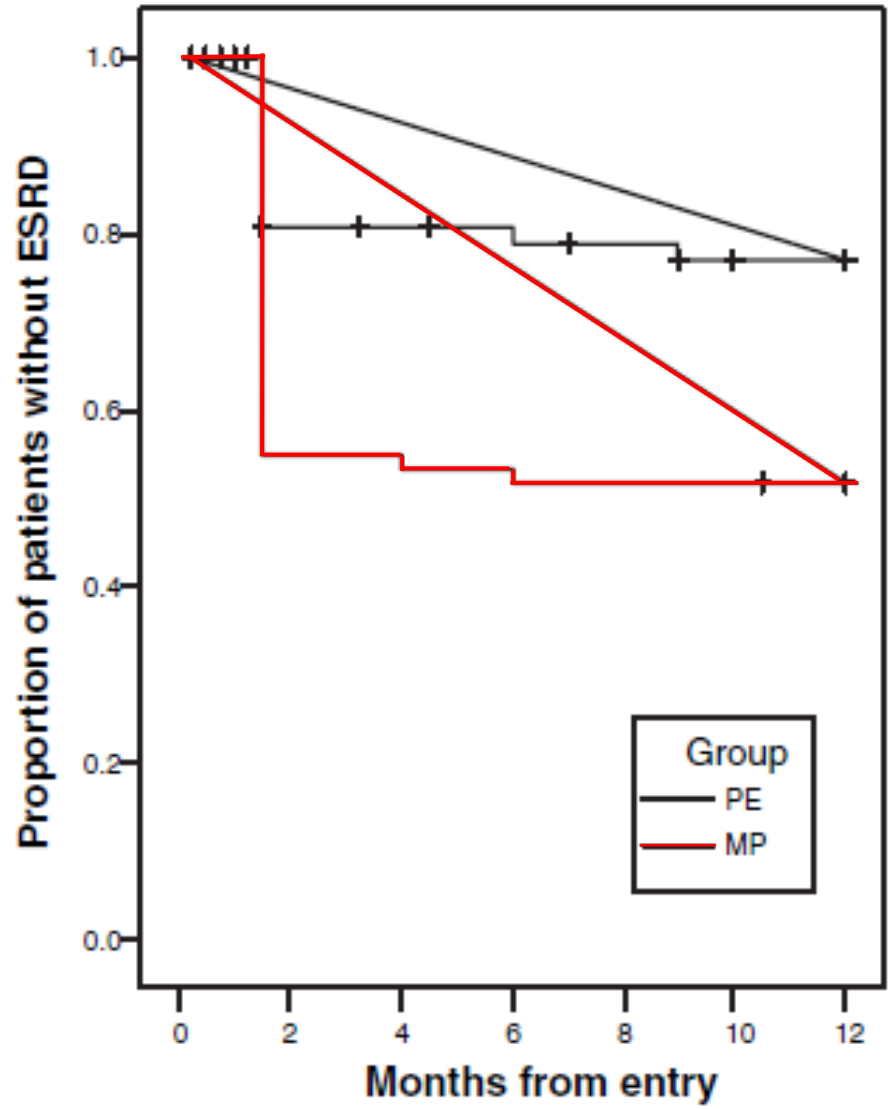
CLINICAL RESEARCH www.jasn.org

# 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,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

J Am Soc Nephrol 18: 2180–2188, 2007. doi: 10.1681/ASN.2007010090

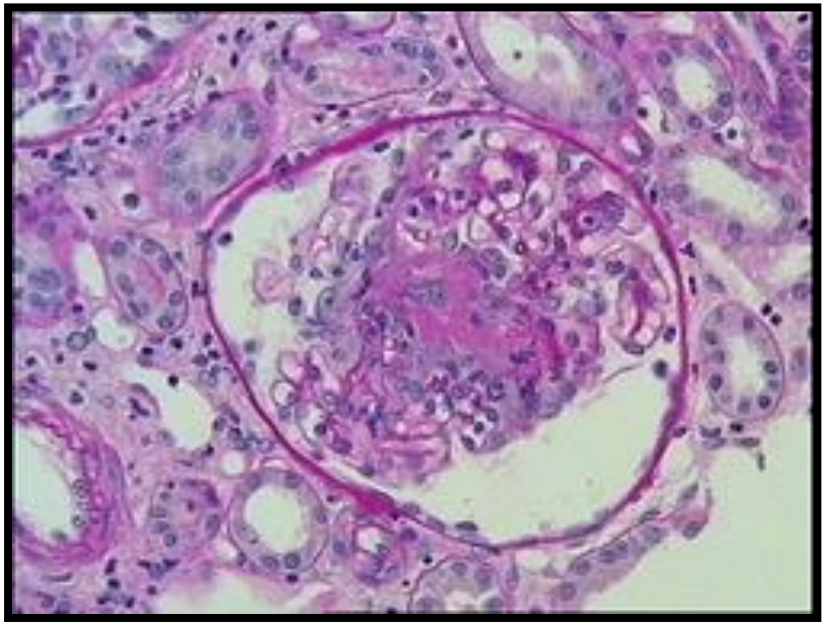
- N=137
- SCr >500 µmol/L
- 69% required dialysis
- Plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% CI, 6.1 to 41)

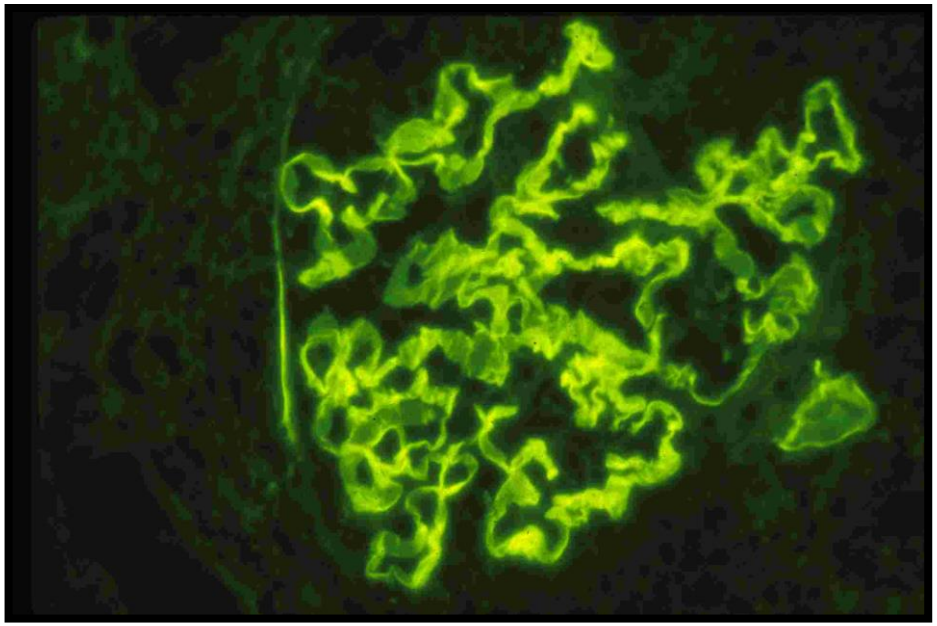


# Maintenance therapy of ANCA-associated vasculitis

- Cyclophosphamide is continued until stable remission has been achieved, usually within 3-6 months
- Conversion to azathioprine 2 mg/kg/day
- Methotrexate, mycophenolate mofetil and leflunamide are alternative options
- Taper prednisolone, aiming for 10 mg qd after 2-3 months
- The optimal duration of treatment is unknown; generally at least 12-18 months
- 80-90% achieve remission, while 50% suffer a relapse within 5 years
- Patients requiring dialysis at presentation may recover kidney function

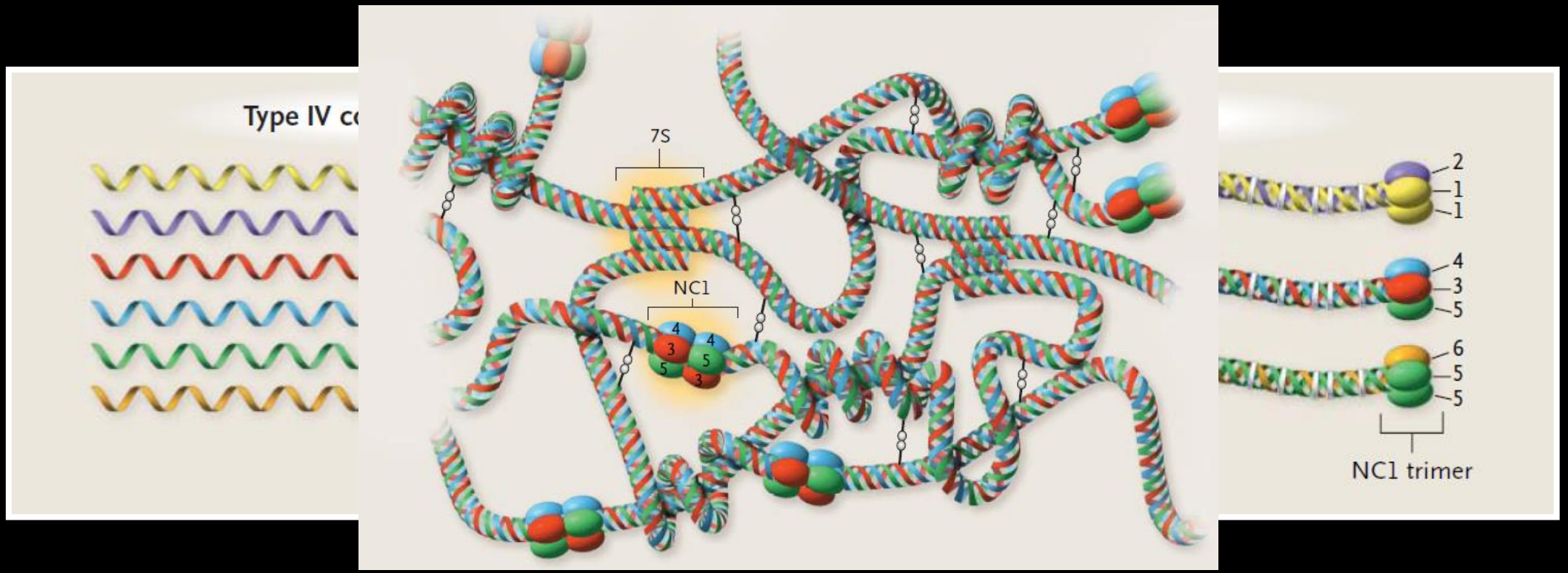
# Anti-GBM glomerulonephritis





- Anti-GBM antibodies detected in the serum of nearly all patients
- Directly pathogenic
- Anti-GBM nephritis (60%)
- Goodpasture´s syndrome (40%)

# Triple helical organization of the type IV collagen family

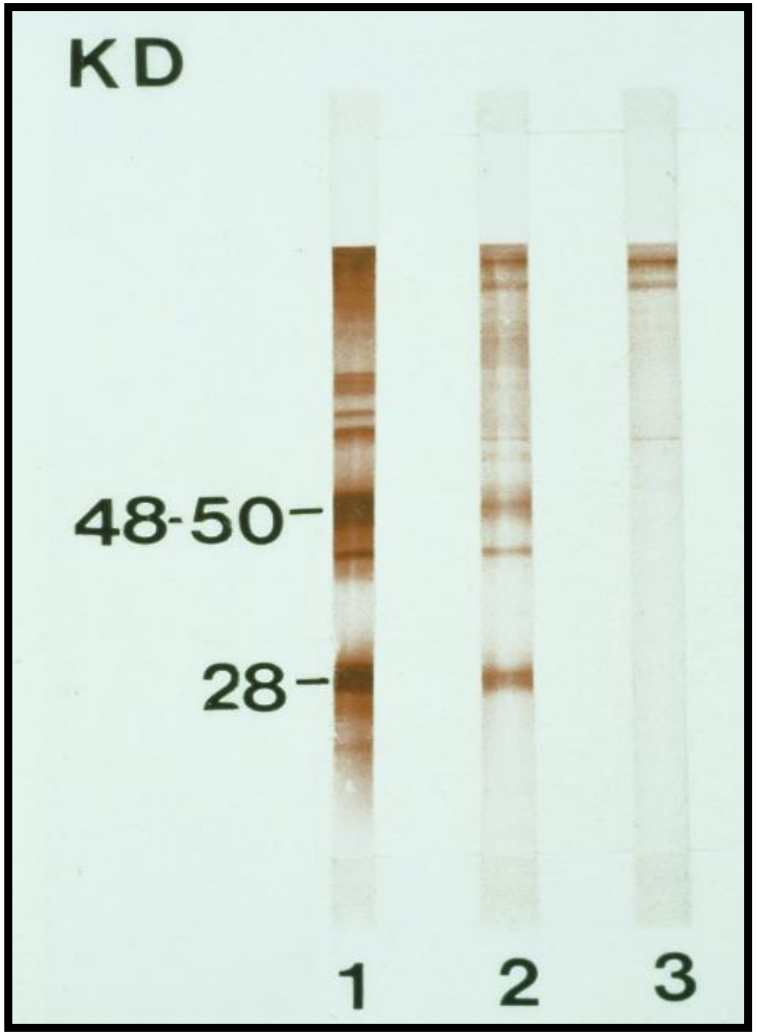



The NEW ENGLAND JOURNAL of MEDICINE

Hudson BG et al., N Engl J Med 2003;348:2543-2556

# Diagnosis of anti-GBM nephritis

- Tests for serum anti-GBM antibodies
  - ELISA
    - GBM from humans, sheep or cattle digested by collagenase
    - Recombinant $\alpha$3(IV)NC1
  - Western blotting
    - GBM treated with collagenase
  - Sensitivity >95% and specificity 97%
- Kidney biopsy



# Anti-GBM and ANCA

- 10-40% of patients with anti-GBM nephritis are also ANCA positive (mostly MPO-ANCA)
- 5-10% of patients with ANCA-associated vasculitis also have anti-GBM antibodies
- The course of the kidney disease resembles anti-GBM nephritis
- Extrarenal manifestations of vasculitis are frequently present

# Treatment of anti-GBM nephritis

- Induction therapy with steroids and cyclophosphamide
  - Methylprednisolone 0.5-1 g IV pulse daily for 3 days, followed by prednisone 1 mg/kg PO daily
  - Cyclophosphamide 2 mg/kg/d
- Plasma exchange
  - Daily (or alternate-day) 4 L exchanges for 2-3 weeks or until anti-GBM antibodies are no longer detectable
  - Benefit not proven
- Duration of therapy
  - Cyclophosphamide is continued for 2-3 months
  - Prednisone is discontinued after 6 months
- Relapses are very rare

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ARTICLE

Ann Intern Med. 2001;134(11):1033-1042. doi:10.7326/0003-4819-134-11-200106050-00009

# Long-Term Outcome of Anti–Glomerular Basement Membrane Antibody Disease Treated with Plasma Exchange and Immunosuppression

Jeremy B. Levy, MA, PhD, MRCP; A. Neil Turner, PhD, FRCP; Andrew J. Rees, MSc, FRCP, FMedSci; and Charles D. Pusey, MSc, FRCP, FRCPath

- 71 patients, media age 40 years (17-76), 40 males
- Diagnosis made by detection of serum anti-GBM antibodies and direct IF on renal biopsy
- 55% of patients required dialysis
- 18% with serum creatinine >500 µmol/L
- Pulmonary hemorrhage in 62%
- All treated with plasma exhange, cyclophosphamide and prednisone

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Ann Intern Med. 2001;134(11):1033-1042. doi:10.7326/0003-4819-134-11-200106050-00009

Article

# Long-Term Outcome of Anti–Glomerular Basement Membrane Antibody Disease Treated with Plasma Exchange and Immunosuppression

Jeremy B. Levy, MA, PhD, MRCP; A. Neil Turner, PhD, FRCP; Andrew J. Rees, MSc, FRCP, FMedSci; and Charles D. Pusey, MSc, FRCP, FRCPath

| | N | One-year patient survival (%) | One-year renal survival (%) |
|---|---|---|---|
| Serum creatinine <500 µmol/L | 19 | 100 | 95 |
| Serum creatinine >500 µmol/L | 13 | 83 | 82 |
| Dialysis | 39 | 65 | 8 |
| Total | 71 | 77 | 53 |

# Take home messages

- ANCA-associated vasculitis is the most common cause of RPGN
- Anti-GBM disease is the most aggressive form, causing rapid loss of kidney function if untreated
- Urgent diagnosis is facilitated by serologic testing and kidney biopsy is essential for successful outcome of RPGN
- Immunosuppressive therapy using glucocorticoids and cyclophosphamide has markedly improved patient and renal survival
- Plasma exchange appears beneficial in anti-GBM nephritis and severe ANCA-associated renal vasculitis

Thank you!

runolfur@landspitali.is