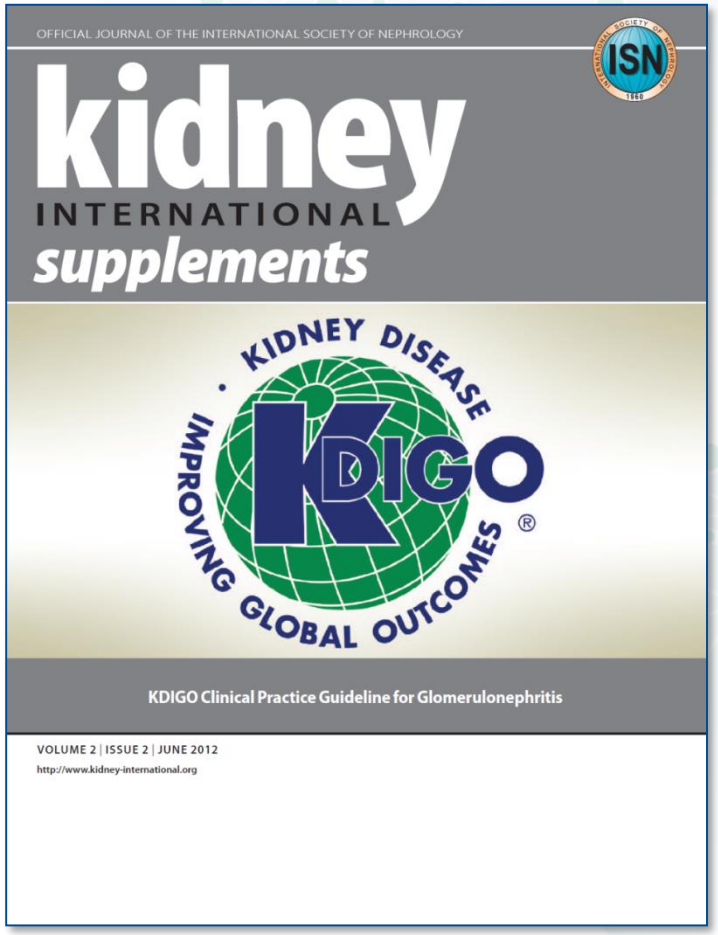
# SUMMARY OF KDIGO CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF ANCA-ASSOCIATED VASCULITIS

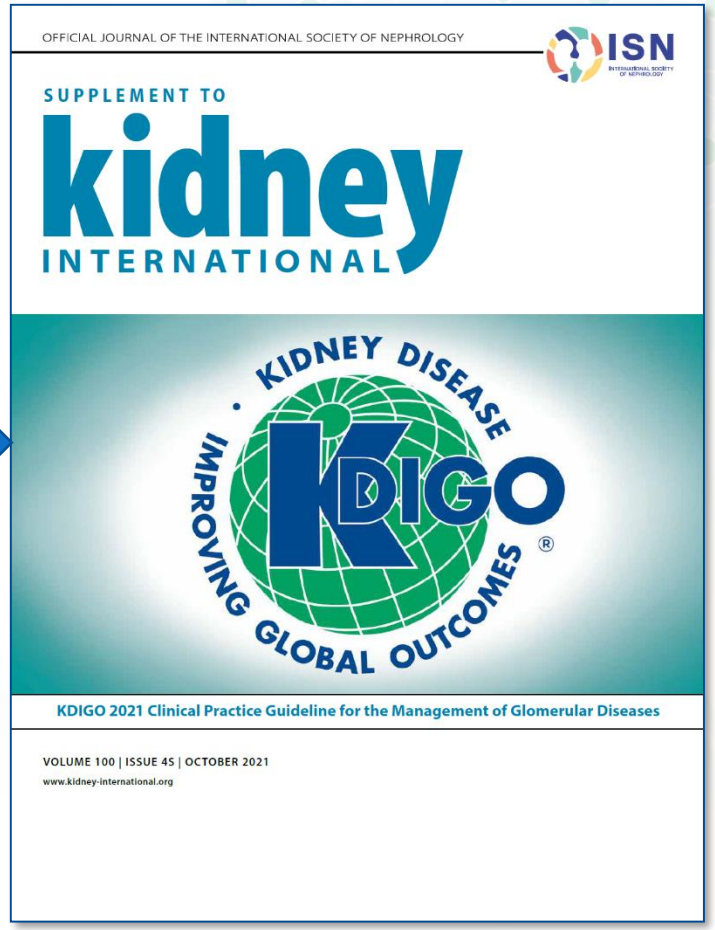
KDIGO Guideline Co-Chairs: Jürgen Floege, MD, Brad H. Rovin, MD, FACP, FASN

**Shahrzad Ossareh- M.D.**
**Hasheminejad Kidney Center- Iran University of Medical Sciences**
**President of the Iranian Society of Nephrology**
**Previous Chair of the Middle East Board of International Society of Nephrology**

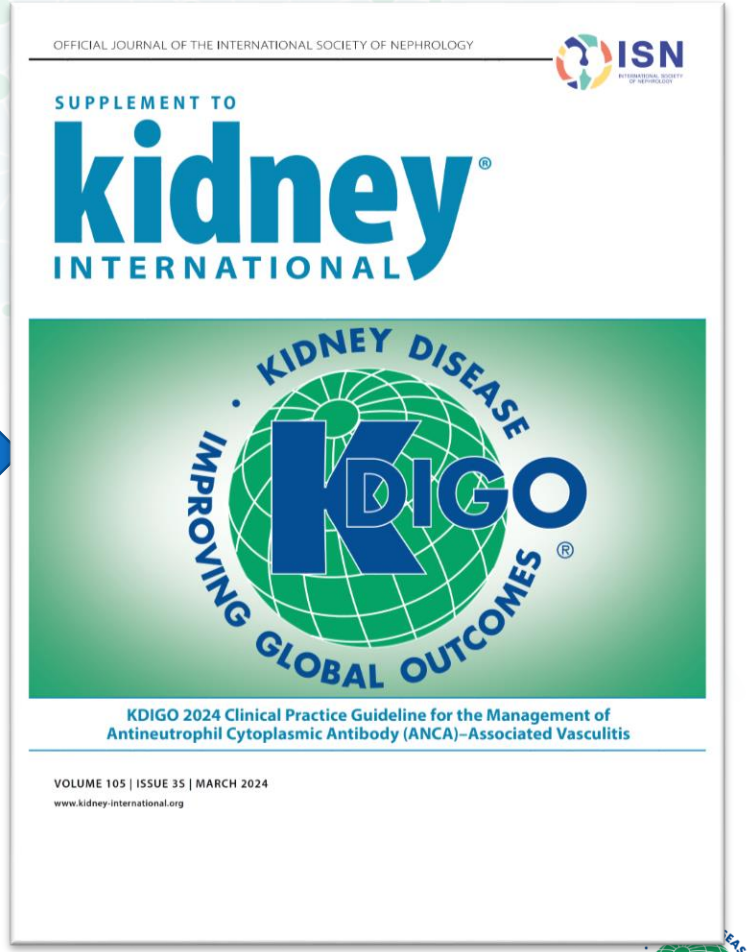
## KDIGO 2012 Guideline: The Beginning




## KDIGO 2021 Guideline: The Update




## KDIGO 2024 Guideline: The ANCA Update



# What Is New Since the 2021 KDIGO Guideline

- The **C5a receptor inhibitor, avacopan**, has been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as add-on therapy to standard-of-care for the treatment of ANCA-associated vasculitis (AAV).

- This development directly relates to the second major emerging novel approach to the treatment of AAV, namely, **a reduction of systemic glucocorticoid exposure**.

- Identifying the profile of an AAV patient who needs avacopan in order to allow for lower glucocorticoid dosages is less clear.

- Additionally, this new therapy adds significant cost to treatment, and long-term safety data are currently lacking.

# Evidence Review

- ERT – 2021 Guideline: Cochrane Kidney Transplant; 2024 Update: Brown University
  - Existing **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **S**tudy design (**PICOS**) questions
  - Clinical and important outcomes identified
    - The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (**1–9 Likert scale**). **Critical** outcomes were rated 7–9, and **important outcomes** were rated 4–6 on the 9-point scale.

| Critical outcomes | Important outcomes |
|---|---|
| • All-cause mortality<br>• Kidney failure<br>• ≥50% loss of GFR<br>• Infection<br>• Glucocorticoid-related adverse events<br>• Malignancy | • Complete remission or relapse<br>• Annual GFR loss (minimum 3 years follow-up) |

GFR, glomerular filtration rate

# Grading Recommendations

- GRADE methodology
  - The certainty of the evidence – Level A, B, C, D
    - Study limitations
    - Inconsistency
    - Indirectness
    - Imprecision
    - Publication bias
  - Strength of the recommendation – Level 1, “We recommend” or Level 2, “We suggest”
    - Key Information
      - Balance of benefits and harms
      - Certainty of the evidence
      - Patient values and preferences
      - Resources and costs
      - Considerations for implementation
    - Rationale

# Nomenclature

- Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are a group of disorders that include:
  1. Granulomatosis with polyangiitis (GPA),
  2. Microscopic polyangiitis (MPA),
  3. Renal-limited vasculitis,
  4. Eosinophilic granulomatosis with polyangiitis (EGPA)

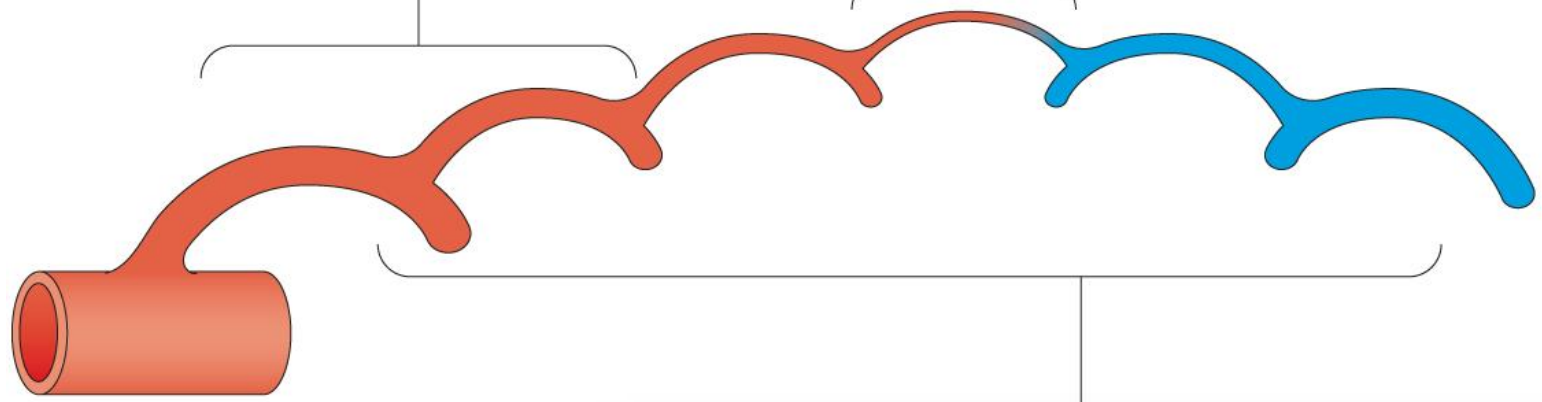
Arthritis Rheum. 2013;65(1):1

a

**Medium vessel vasculitis**
- Polyarteritis nodosa
- Kawasaki disease

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

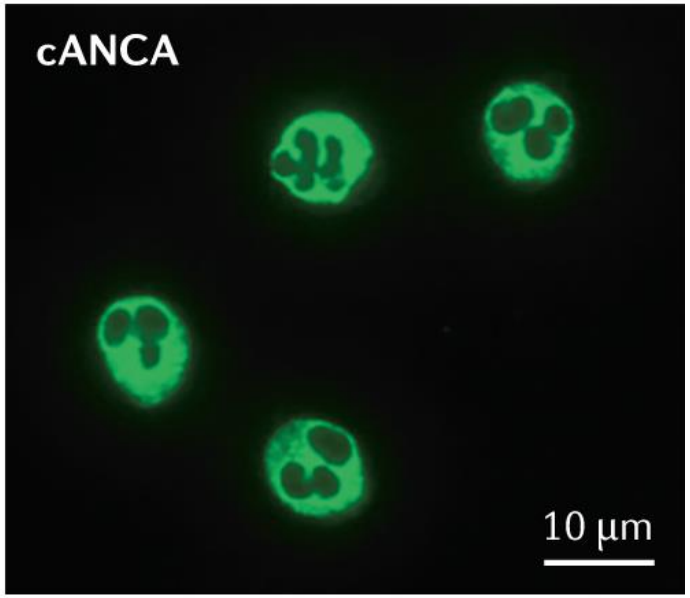
Anti-GBM disease

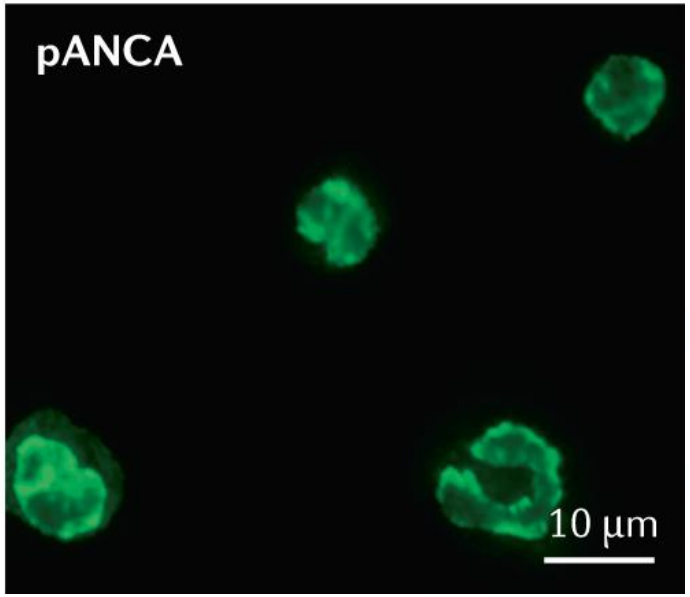


**Large vessel vasculitis**
- Takayasu arteritis
- Giant cell arteritis

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

b

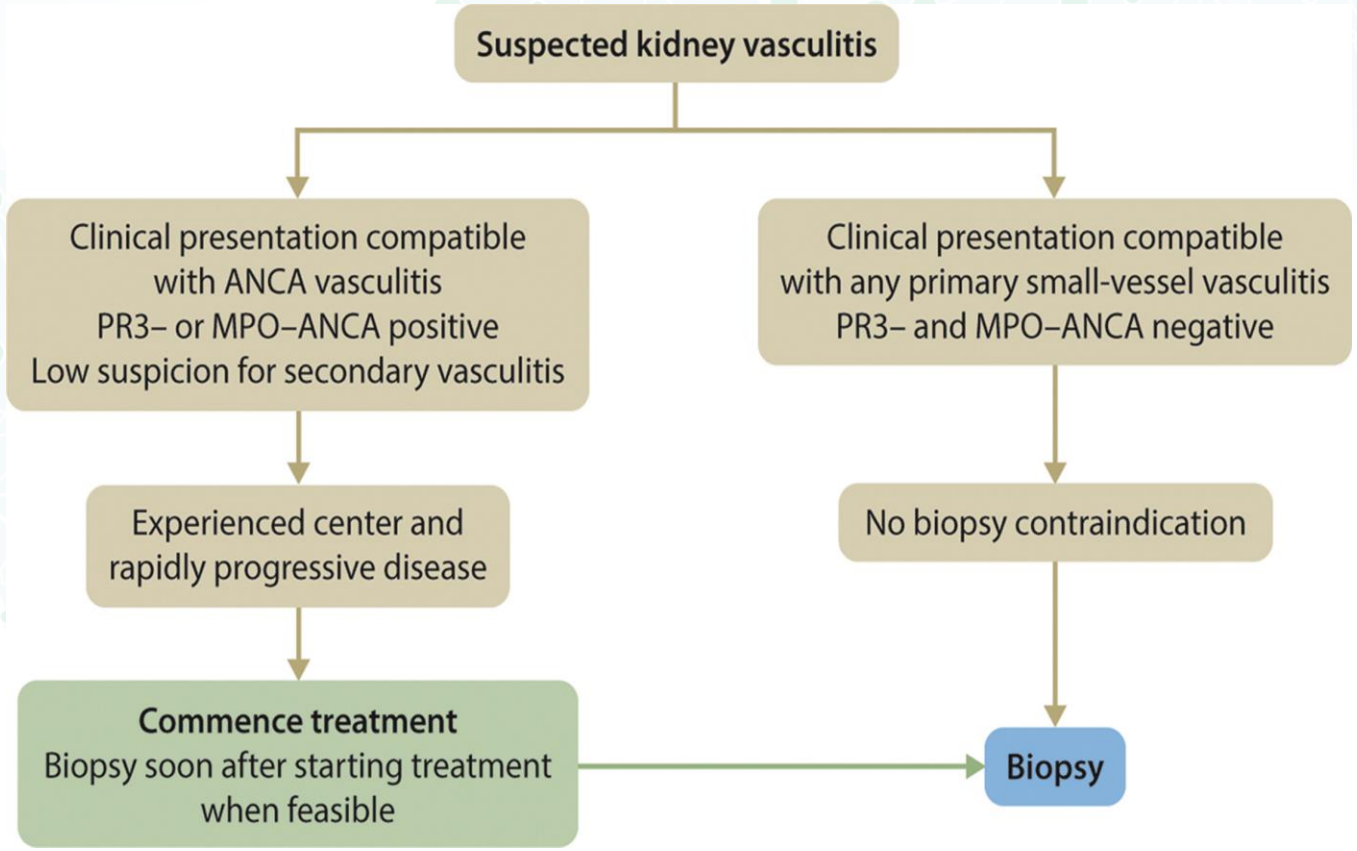


# Guideline Statements and Rationale

# ANCA-ASSOCIATED VASCULITIS - DIAGNOSIS

Practice Point 9.1.1: In the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (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.



# ANCA-ASSOCIATED VASCULITIS - DIAGNOSIS

## Practice Point 9.1.2: Patients with ANCA-associated vasculitis (AAV) should be treated at centers **with experience in AAV management**

**Disease activity** of ANCA-associated vasculitis represents signs or symptoms attributable to active di… any organ system

**Remission** is defined as the absence of manifestations of vasculitis and GN. For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinu… f active disease and can resolve completely, their persistence does not necessarily im…

**Relapse** is defined as the occurrence of increased disease activity after a period of partial or complete rem… A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided … major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse incl… diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis threatening vision

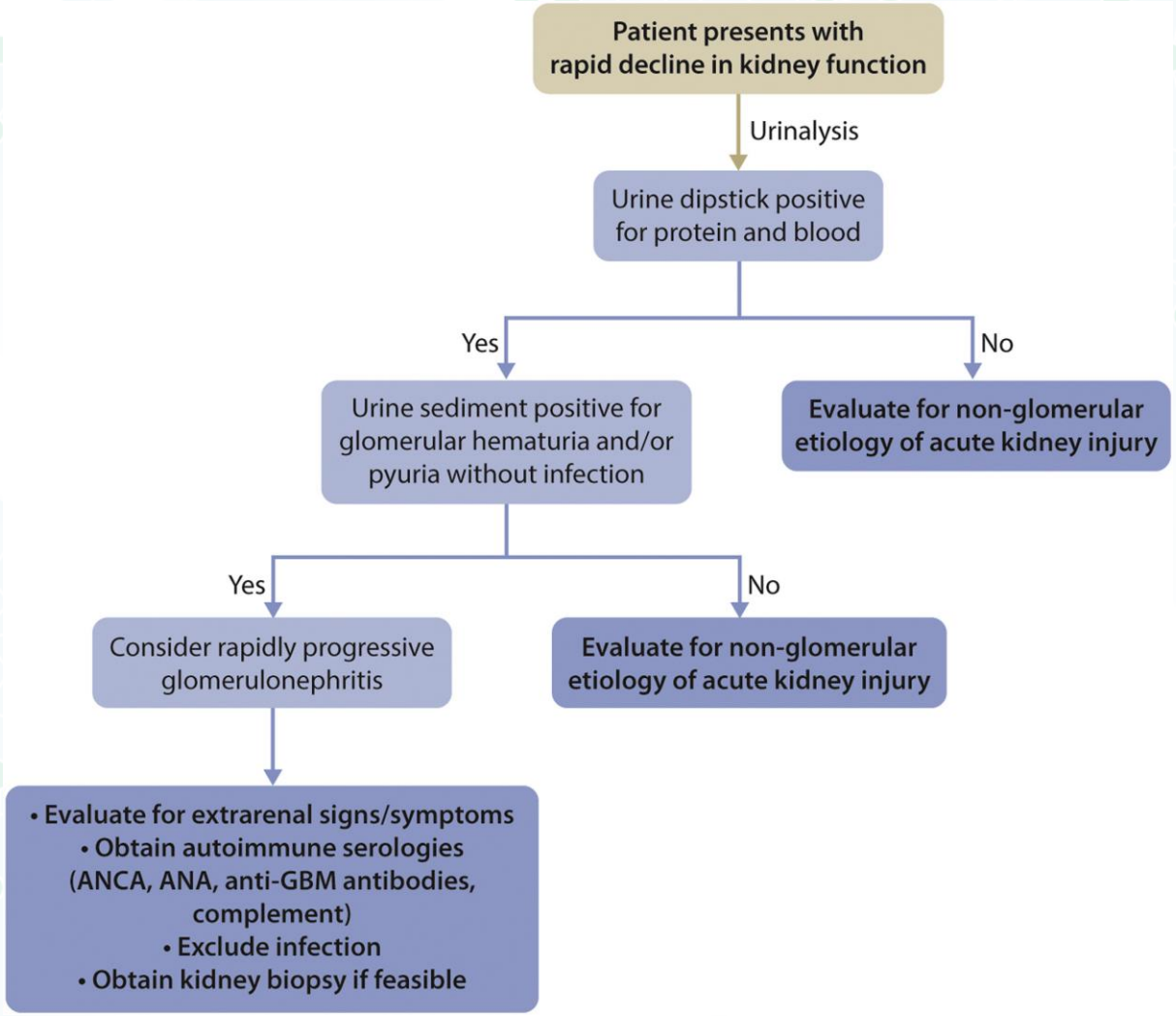
**Treatment-resistant disease** is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy

Stable or improved GFR

Increased disease activity

Persistence of kidney or other manifestations

# ANCA-ASSOCIATED VASCULITIS - DIAGNOSIS



# ANCA-ASSOCIATED VASCULITIS - DIAGNOSIS

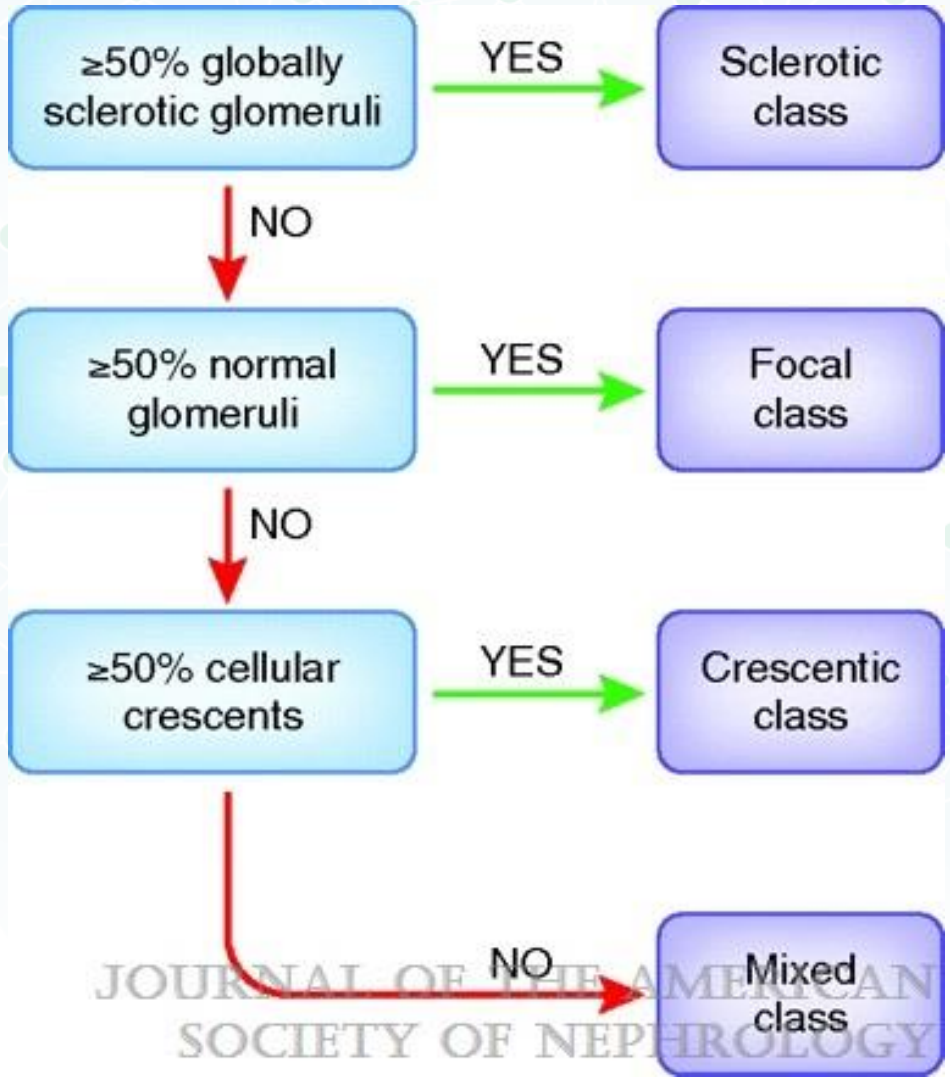
| Organ system | Microscopic polyangiitis (MPA) (%) | Granulomatosis with polyangiitis (GPA) (%) | Eosinophilic granulomatosis with polyangiitis (EGPA) (%) |
|---|---|---|---|
| Cutaneous | 40 | 40 | 60 |
| Kidney | 90 | 80 | 45 |
| Pulmonary | 50 | 90 | 70 |
| Ear, nose, and throat | 35 | 90 | 50 |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

# ANCA-associated Vasculitis – Prognosis: Kidney Prognosis and Treatment Response

Biopsies should be scored for glomerular lesions in the following order:

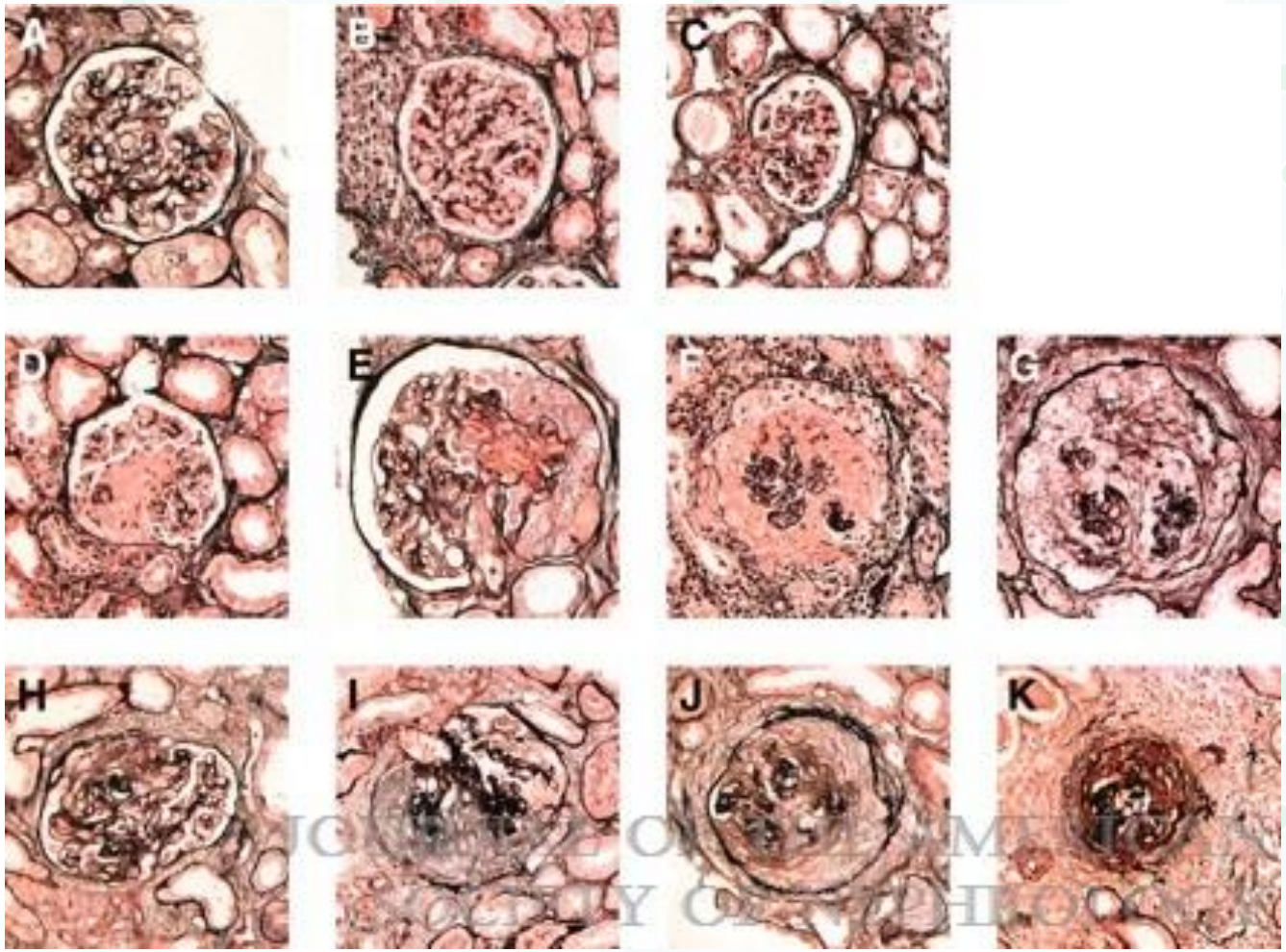
1. Globally sclerotic glomeruli,
2. Normal glomeruli,
3. Cellular crescentic glomeruli.

Any biopsies that do not fit into one of the categories on the basis of a predominant glomerular phenotype will automatically be included in the mixed category






Berden AE.JASN,1636-1628:(10)21




**Typical examples of glomerular lesions in each of the four categories.**

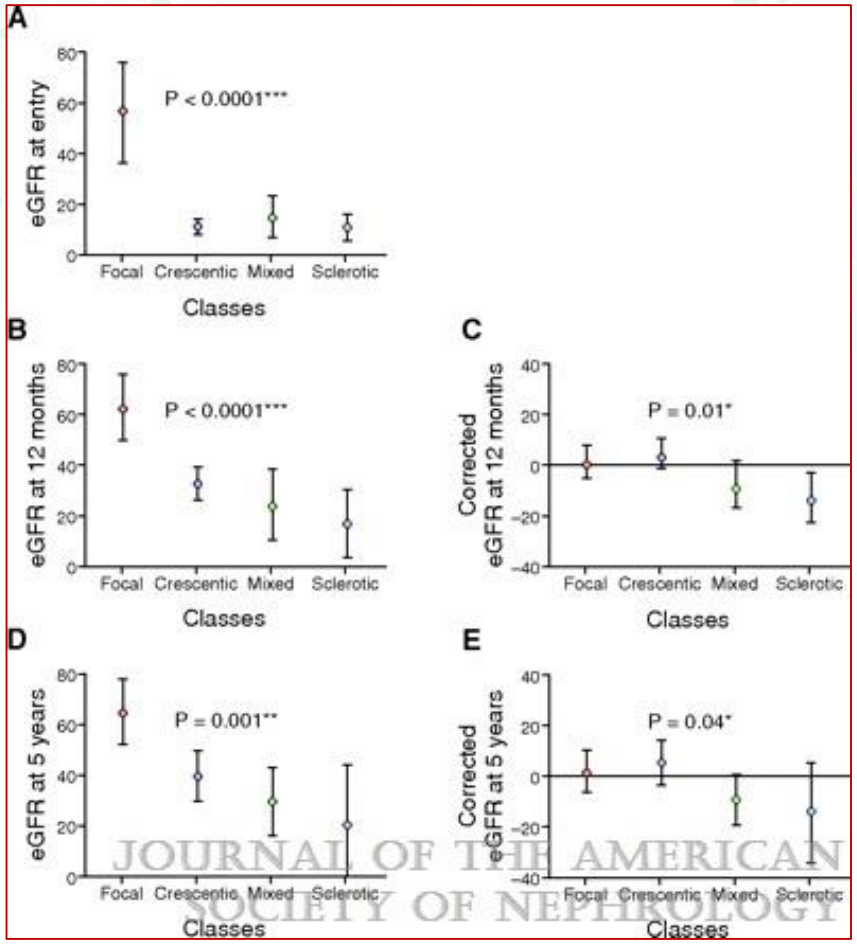
- (A through C) Normal glomeruli, allowing for fewer than four leukocytes in the capillary tuft (B) or mild ischemic changes such as wrinkling of the GBM (C).
- (D through G) Examples of cellular crescents. Cellular crescents contain >10% of cellular components. Whether crescents are segmental or circumferential is irrelevant for the classification schema.
- (H through J) The amount of fibrinoid necrosis is irrelevant.
- (K) If >90% of a crescent consists of extracellular matrix, then the term fibrous crescent is used.
- Global glomerulosclerosis refers to sclerotic changes in the glomerulus composing >80% of the tuft.
- Global glomerulosclerosis excludes the designation of any other glomerular lesion.

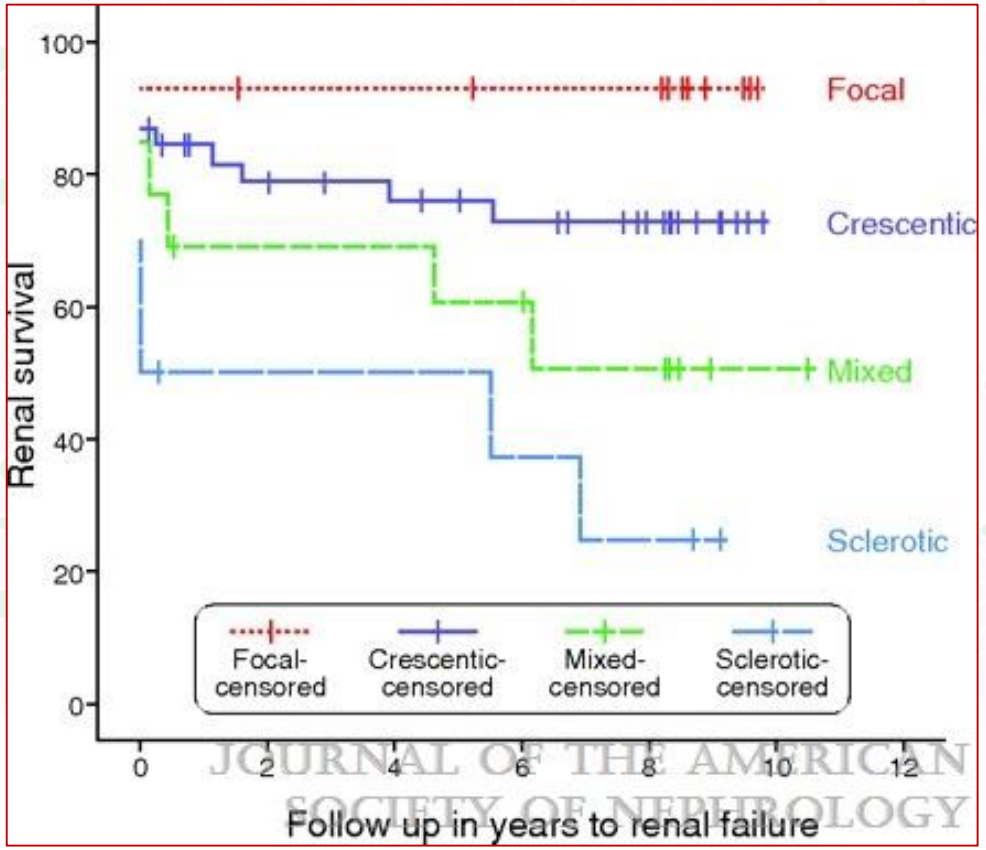
Berden AE.JASN,1636-1628:(10)21

## Table 3. Renal outcome according to class

| Class | eGFR Entry | | eGFR 12 Months | | eGFR 12 Months[a] | | eGFR 60 Months | | eGFR 60 Months[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | *n* | Mean ± SD | *n* | Mean ± SD | *n* | Mean ± SD | *n* | Mean ± SD | *n* |
| Focal | 56.4 ± 36.8 | 16 | 63.3 ± 23.7 | 15 | 1.2 ± 10.6 | 15 | 65.6 ± 20.3 | 11 | 1.4 ± 11.8 | 11 |
| Crescentic | 11.2 ± 10.9 | 55 | 32.8 ± 20.8 | 40 | 4.3 ± 17.8 | 40 | 39.5 ± 22.5 | 23 | 5.2 ± 21.1 | 23 |
| Mixed | 15.4 ± 16.2 | 16 | 24.5 ± 21.4 | 12 | −7.3 ± 15.2 | 12 | 29.9 ± 16.7 | 8 | −9.5 ± 11.6 | 8 |
| Sclerotic | 10.8 ± 9.5 | 13 | 16.6 ± 15.9 | 8 | −12.8 ± 12.4 | 8 | 20.4 ± 15.1 | 4 | −14.6 ± 12.1 | 4 |

[a]Corrected for entry eGFR.



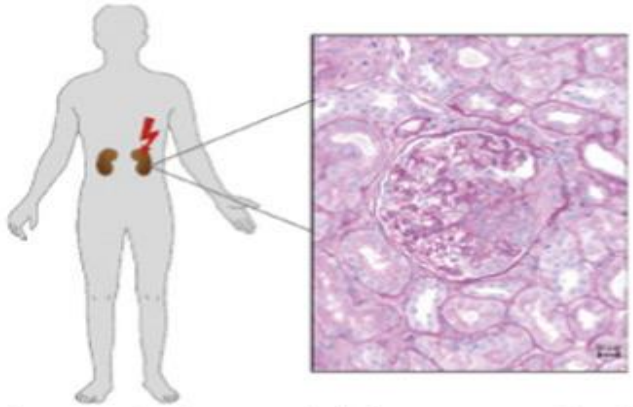





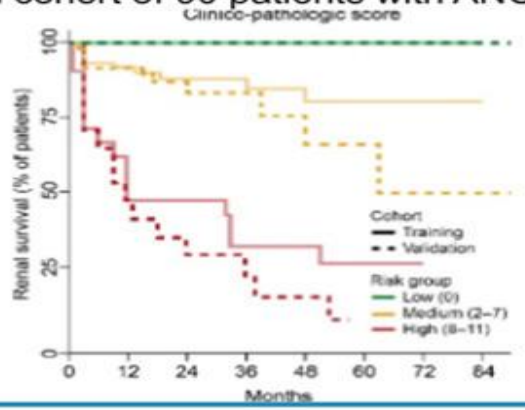

Berden AE.JASN,1636-1628:(10)21

# Development and validation of a renal risk score in ANCA-associated glomerulonephritis

Prospective training cohort of 115 patients with a new ANCA-associated glomerulonephritis.



Development of a renal risk score and validation in a second cohort of 90 patients with ANCA GN.




Detailed histopathologic and clinical analyses identifying risk factors for ESRD.

| Risk factor | | HR | P Value | Points |
|---|---|---|---|---|
| Normal glomeruli (N) | | | | |
| N0 | > 25 % | | | 0 |
| N1 | 10 – 25 % | 4.42 | 0.027 | 4 |
| N2 | < 10 % | 10.9 | < 0.001 | 6 |
| Tubular atrophy (T) | | | | |
| T0 | ≤ 25 % | | | 0 |
| T1 | > 25 % | 2.22 | 0.117 | 2 |
| Renal function (GFR) | | | | |
| G0 | > 15 ml/min | | | 0 |
| G1 | ≤ 15 ml/min | 2.89 | 0.019 | 3 |

Implementation of the 'ANCA Renal Risk Score' into an application for mobile devices.

ELSEVIER

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Brix SR, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis, KI 2018

KIDNEY DISEASES IJKD

# The Outcome of Pauci-immune Crescentic Glomerulonephritis and Its Prognostic Factors; A single Center Case Series

Neda Najafi,[1] Shahrzad Ossareh,[1] Mitra Mehrazma,[2,3] Mohsen Vahedi[4]

[1]Nephrology Section, Department of Medicine, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Pathology, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[3]Oncopathology Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Biostatistics and Epidemiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

**Keywords.** crescentic glomerulonephritis, pauci-immune glomerulonephritis, CKD, kidney survival, cyclophosphamide

Original Paper

**Introduction.** Pauci-immune crescentic glomerulonephritis (GN) is the most common cause of rapidly progressive GN in adults. The aim of this study was to determine the outcome of patients with pauci-immune crescentic GN and risk factors of the development of end-stage kidney disease (ESKD) in these patients.
**Methods.** This case series study was carried on 120 patients with pauci-immune crescentic GN biopsied in our center betwen 1998 and 2016. Inclusion criteria were age > 16 years, at least one crescentic glomerulus, maximally 1+ deposition of immunoglobulins and complement components at fluorescent microscopy, and at least 6 months follow-up. The main outcomes were ESKD and death.
**Results.** The study population included 120 patients with pauci-immune crescentic GN (mean age was 47 ± 17 years and 49.1% male). There was no significant difference in outcome between patients with diffuse or focal crescentic GN. Seventy-two patients (60%) developed ESKD and 31 patients (25.8%) died. The need for dialysis at admission, lower baseline hemoglobin and GFR and GFR at four months and high percentage of glomerulosclerosis and interstitial fibrosis had a significant relationship with low kidney survival ($P < .05$). The rate of ESKD was higher in patients who did not receive cyclophosphamide therapy, due to focal crescentic GN or high chronicity, compared to patients who received it (70.7 vs. 28.5%, $P < .001$).
**Conclusion.** In our study, a high percentage of patients with pauci-immune crescentic GN developed ESKD. Low first GFR and high chronicity in biopsy were associated with lower kidney survival. Failure to administer cyclophosphamide in seemingly limited or advanced cases, together with late referral may have led to poor prognosis.

# Results

120 patients:

59 ♂

61 ♀

Age: 47 ± 17 years

FU: 44 ± 45.7 months

Baseline Proteinuria: 3.69 ± 3.552 g/d

Median Baseline GFR:10.09 (15.02) mL/min

ESKD:

72 patients (60%)

(46 or 38% at onset)

**Table 2.** Effect of Age, Laboratory and Pathologic Characteristics on ESKD in Pauci-immune Crescentic GN

| | ESKD | NO ESKD | *P* |
|---|---|---|---|
| Number (%) | 72 (60) | 48 (40) | |
| Age (year)* | 47 ± 19 | 47.1 ± 15 | .969 |
| Initial GFR (mL/min)** | 8 (7.1) | 18.9 (25.61) | < .001 |
| GFR at 4 months (mL/min)* | 22.5 ± 9.077 | 47.8 ± 25.703 | < .001 |
| Hemoglubin (g/dL)* | 9.2 ± 1.7 | 10.4 ± 2 | .001 |
| Need for dialysis at admission (%) | 69.4 | 27 | < .001 |
| Proteinuria (mg/24h)* | 3597 ± 2639 | 3832 ± 4550 | .131 |
| Total crescent percentage (%)* | 49.3 ± 29.8 | 40.5 ± 30.5 | .075 |
| Active crescent percentage (%)* | 49.8 ± 31.4 | 41.4 ± 29.6 | .076 |
| Percentage of glomerulosclerosis (%)* | 32.3 ± 27.2 | 14.4 ± 18.3 | < .001 |
| Percentage of IF/TA* | 43.3 ± 22.9 | 23.6 ± 18.3 | < .001 |
| ANCA positive (%) | 37 (51.3) | 25 (52.2) | .424 |

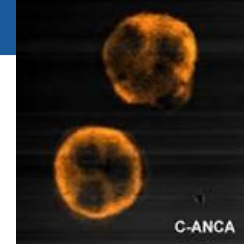
*mean ± standard deviation
**median (interquartile rang)
Abbreviations: GN, glomerulonephritis; ESKD, end stage kidney disease; GFR, glomerular filtration rate; IF/TA, interstitial fibrosis/tubular atrophy; ANCA, anti neutrophil cytoplasmic antibody.

**Table 5.** Outcome of Kidney in Pauci-immune Crescentic GN According to Berden Classification

| | Number | ESKD Cases (%) | *P* |
|---|---|---|---|
| Focal | 37 | 13 (35.1) | |
| Crescentic | 38 | 23 (60.5) | |
| Mixed | 20 | 15 (75) | .001 |
| Sclerotic | 25 | 21 (84) | |
| Total | 120 | 72 (60) | |

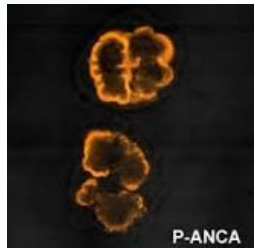
Abbreviations: GN, glomerulonephritis; ESKD, end stage kidney disease.

# ANCA-ASSOCIATED VASCULITIS – PROGNOSIS: RELAPSE




- PR3- and MPO-AAV are characterized by the occurrence of relapses.
- Patients who are PR3-ANCA-positive experience more relapses than those who are MPO-ANCA positive.
- The achievement of ANCA-negativity after induction treatment is associated with a lower risk of relapse.
- Both a rise or persistence of ANCA are only modestly predictive of future disease relapse.
- Also, a change in ANCA status from negative to positive has been associated with a higher incidence of relapse, and more frequent clinical assessments should be considered.
- However, regarding the relapsing phenotype of AAV, ANCA measurements should not guide treatment decisions in individual patients.

- **Practice Point 9.2.3.1: 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.**



# ANCA-associated Vasculitis – Treatment: Induction

**Recommendation 9.3.1.1:**

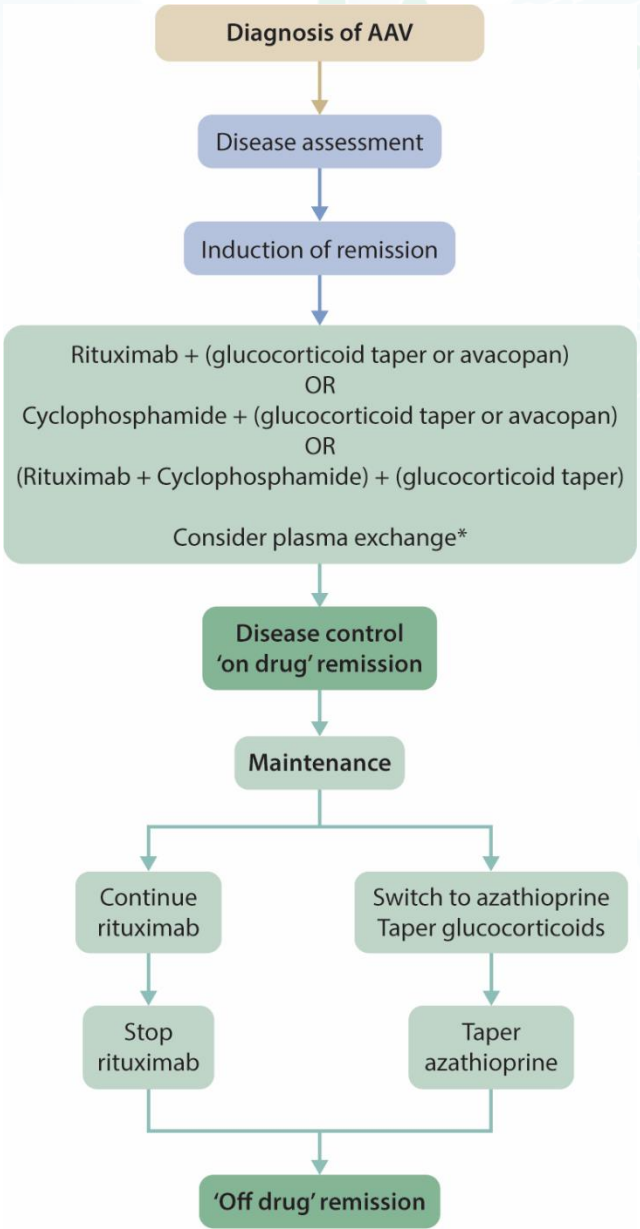
**We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV (*1B*).**

The initial therapy of new-onset AAV has been updated to include induction with cyclophosphamide or rituximab combined with glucocorticoids.

The best evidence is available for patients with new-onset AAV. In patients with severe (SCr >4 mg/dl [>354 mmol/l]) kidney disease, limited data for induction therapy with rituximab are available.

# ANCA-ASSOCIATED VASCULITIS – TREATMENT: INDUCTION

Practice Point 9.3.1.1:
A practical treatment algorithm for AAV with kidney involvement is given in the figure.



# ANCA-ASSOCIATED VASCULITIS – TREATMENT: INDUCTION

- Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining glomerular filtration rate (GFR) (serum creatinine [SCr] >4 mg/dl [>354 mmol/l]), there are limited data to support rituximab and glucocorticoids. Both cyclophosphamide and glucocorticoids, and the combination of rituximab and cyclophosphamide can be considered in this setting.

- Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in the figure below.

| Rituximab preferred | Cyclophosphamide preferred |
|---|---|
| • Children and adolescents<br>• Pre-menopausal women and men concerned about their fertility<br>• Frail older adults<br>• Glucocorticoid-sparing especially important<br>• Relapsing disease<br>• PR3–ANCA disease | • Rituximab difficult to access<br>• Severe GN (SCr >4 mg/dl [354 µmol/l])* |

***A combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered.**

# ANCA-associated Vasculitis – Treatment: Induction

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in the figure.

| Intravenous cyclophosphamide | Oral cyclophosphamide |
|---|---|
| • Patients who already have a moderate cumulative dose of cyclophosphamide<br>• Patients with lower white blood cell counts<br>• Patients with ready access to an infusion center<br>• Patients who may have trouble adhering to an oral regimen | • Patients for whom cost is an important factor<br>• Patients who do not have easy access to an infusion center<br>• Patients for whom a self-administered oral regimen will not be difficult |

Practice Point 9.3.1.5: Consider discontinuation of immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.

# ANCA-associated Vasculitis – Treatment: Induction

Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in the figure.

| Week | 'Reduced-corticosteroid dose' in PEXIVAS trial | | |
|---|---|---|---|
| | <50 kg | 50–75 kg | >75 kg |
| 1 | 50 | 60 | 75 |
| 2 | 25 | 30 | 40 |
| 3–4 | 20 | 25 | 30 |
| 5–6 | 15 | 20 | 25 |
| 7–8 | 12.5 | 15 | 20 |
| 9–10 | 10 | 12.5 | 15 |
| 11–12 | 7.5 | 10 | 12.5 |
| 13–14 | 6 | 7.5 | 10 |
| 15–16 | 5 | 5 | 7.5 |
| 17–18 | 5 | 5 | 7.5 |
| 19–20 | 5 | 5 | 5 |
| 21–22 | 5 | 5 | 5 |
| 23–52 | 5 | 5 | 5 |
| >52 | Investigators' local practice | | |

# ANCA-associated Vasculitis – Treatment: Induction

Practice Point 9.3.1.7:

- **Avacopan** may be used as an alternative to glucocorticoids.
- Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan.
- Patients with lower GFR may benefit from greater GFR recovery.

# ANCA-associated Vasculitis – Treatment: Induction

## Practice Point 9.3.1.8: Recommendations for immunosuppressive dosing

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

# ANCA-associated Vasculitis – Treatment: Induction

**Practice Point 9.3.1.9:** Consider plasma exchange for patients with

- **SCr >3.4 mg/dl** (>300 mmol/l),
- patients **requiring dialysis** or **with rapidly increasing SCr**,
- patients with **diffuse alveolar hemorrhage who have hypoxemia.**

**Practice Point 9.3.1.10**: Add plasma exchange for patients with an

- **overlap syndrome of ANCA-associated** vasculitis and anti-glomerular basement membrane (**anti-GBM**)

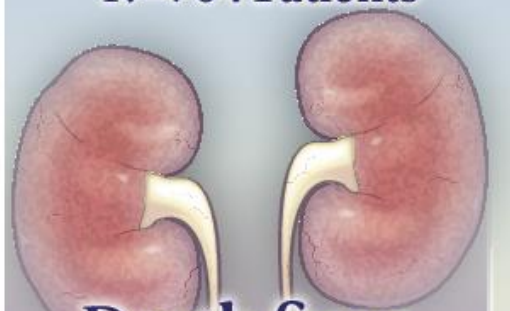
| ANCA vasculitis with severe kidney disease | Vasculitis with diffuse pulmonary hemorrhage | Vasculitis in association with anti-GBM antibodies |
|---|---|---|
| Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution | Daily until bleeding stops, replace albumin with fresh, frozen plasma | Daily for 14 days or until anti-GBM antibodies are undetectable |

The NEW ENGLAND JOURNAL of MEDICINE

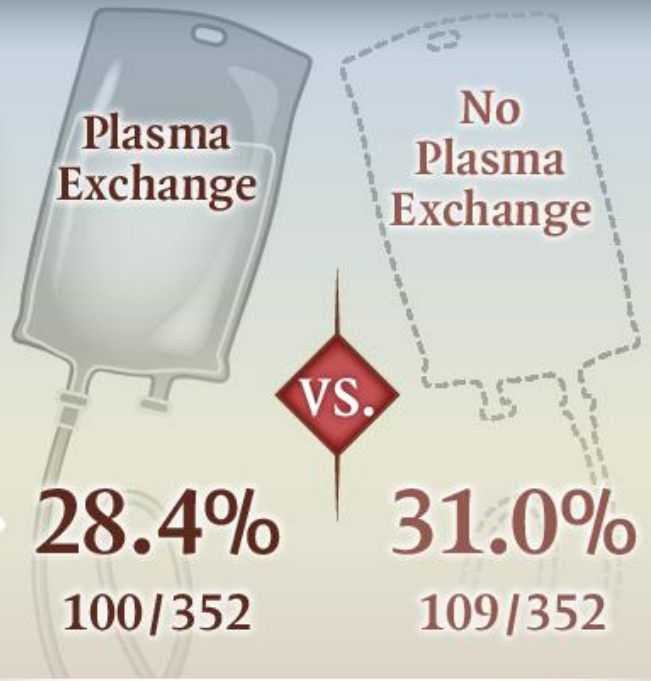
# Plasma Exchange and Glucocorticoids for ANCA-Associated Vasculitis

## PEXIVAS, A MULTICENTER, RANDOMIZED, 2X2 FACTORIAL TRIAL

N=704 Patients



Death from any cause or end-stage kidney disease




28.4% (100/352) vs. 31.0% (109/352)

P=0.27


25.5% (83/325) vs. 27.9% (92/330)

Noninferiority margin, 11 percentage points

No significant differences in serious adverse events

Serious infections at 1 yr less common with reduced-dose glucocorticoids

M. Walsh et al. 10.1056/NEJMoa1803537



N Engl J Med 2020;382:622-631

# Conclusion

- Among patients with severe ANCA-associated vasculitis, the use of plasma exchange did not reduce the incidence of death or ESKD.
- A reduced-dose regimen of glucocorticoids was non-inferior to a standard-dose regimen with respect to death or ESKD.
- (Funded by the U.K. National Institute for Health Research and others; PEXIVAS Current Controlled Trials number, ISRCTN07757494; ClinicalTrials.gov number, NCT00987389.)

# ANCA-associated Vasculitis – Treatment: Maintenance Therapy

**Recommendation 9.3.2.1: We recommend maintenance therapy, after induction of remission with either**

- **rituximab, or**
- **azathioprine and low-dose glucocorticoids (*1C*).**

Practice Point 9.3.2.1: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

Practice Point 9.3.2.2: The optimal duration of remission therapy is between **18 months and 4 years after induction of remission.**

# ANCA-associated Vasculitis – Treatment: Maintenance Therapy

Practice Point 9.3.2.3: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur.

| Baseline factors | Factors after diagnosis | Treatment factors |
|---|---|---|
| • Diagnosis of granulomatosis with polyangiitis<br>• PR3–ANCA subgroup<br>• Higher serum creatinine<br>• More extensive disease<br>• Ear, nose, and throat disease | • History of relapse<br>• ANCA positive at the end of induction<br>• Rise in ANCA | • Lower cyclophosphamide exposure<br>• Immunosuppressive withdrawal<br>• Glucocorticoid withdrawal |

Practice Point 9.3.2.4: Consider mycophenolate mofetil (MMF) or methotrexate as alternatives to azathioprine for maintenance therapy in patients intolerant of azathioprine. Methotrexate should not be used for patients with a GFR <60 ml/min per 1.73 $m^2$.

# ANCA-associated Vasculitis – Treatment: Maintenance Therapy

Practice Point 9.3.2.5: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in the figure.

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

# ANCA-associated Vasculitis – Treatment: Maintenance Therapy

Practice Point 9.3.2.6: Recommendations for dosing and duration of maintenance therapy are given in the figure.

| Rituximab | Azathioprine | MMF |
|---|---|---|
| Scheduled dosing protocol:<br>**1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme)<br>OR<br>**2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme) | 1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo | 2000 mg/d (divided doses) at complete remission for 2 yrs |
| | Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo | |

# ANCA-associated Vasculitis – Treatment: Relapsing Disease

Practice Point 9.3.3.1: Patients with relapsing disease should be reinduced (Recommendation 9.3.1.1), preferably with rituximab.

- Relapses respond to immunosuppression with a similar response rate as the initial presentation, and severe relapses should be treated by reintroducing induction therapy.
- When deciding whether to use cyclophosphamide again, the cumulative dose of cyclophosphamide already given should be taken into account. Cumulative dosages above **36 g** have been associated with the occurrence of malignancies.
- In a *post hoc* analysis of the RAVE trial, higher remission rates were seen in relapsing patients treated with rituximab compared to cyclophosphamide, especially for patients with PR3-AAV.

# ANCA-associated Vasculitis – Treatment: Relapsing Disease

Practice Point 9.3.3.1: Patients with relapsing disease should be reinduced (Recommendation 9.3.1.1), preferably with rituximab.

- In patients with non-severe relapses, immunosuppression should be increased while avoiding cyclophosphamide.
- Apart from MMF, which has been tested in combination with glucocorticoids in RCTs for induction therapy in relapsing patients, there is no strong evidence to support other regimens.
- However, if non-severe relapses are treated with MMF, there is an increased rate of future relapse, and glucocorticoid exposure will be increased accordingly.
- Rituximab is therefore preferred for relapsing AAV.

# ANCA-associated Vasculitis – Special Situations: Refractory Disease

Practice Point 9.4.1.1: Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.

Practice Point 9.4.1.2: In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange can be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.

# ANCA-associated Vasculitis – Special Situations: Transplantation

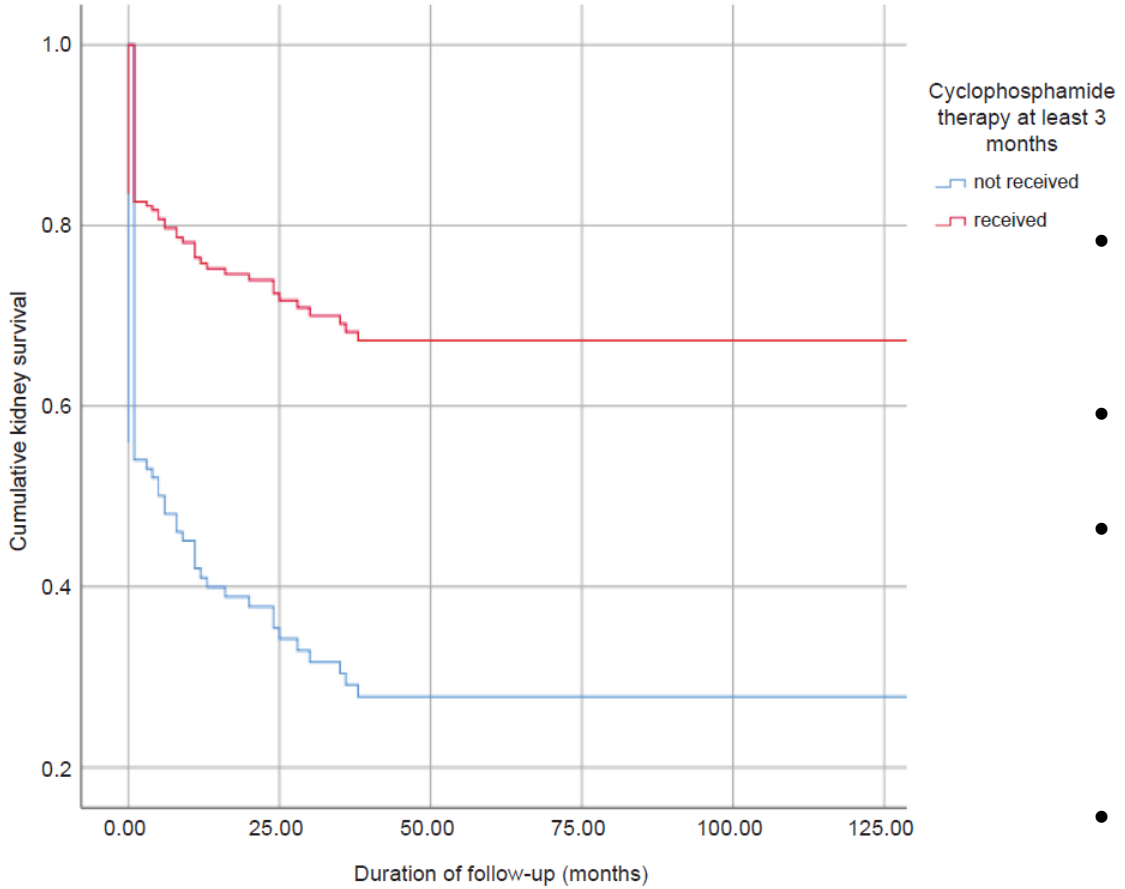
Practice Point 9.4.2.1: Delay transplantation until patients are in complete clinical remission for ≥6 months. The persistence of ANCA should not delay transplantation.

70.7% of patients who did not receive any or the minimum required cyclophosphamide dose developed ESKD compared to 28.5% of patients who had received the minimum required cyclophosphamide dose ($P < .001$)

**Table 6.** Comparison of Characteristics and Outcome of Pauci-immune Crescentic GN Patients With or Without Cyclophosphamide Administration

| | With Cyclophosphamide | Without Cyclophosphamide | *P* |
|---|---|---|---|
| Number (%) | 28 (23.3) | 92 (76.7) | - |
| ESKD (%) | 8 (28.5) | 65 (70.7) | < .001 |
| Baseline Creatinin, mg/dL* | 3.8 (4.07) | 5.7 (5.5) | .187 |
| Baseline GFR, mL/min* | 14.63 (14.47) | 9.6 (15.15) | .462 |
| Percentage of Glomerolosclerosis* | 13.5 (33.2) | 26.7 (45.5) | .02 |
| Percentage of IF/TA* | 20 (36.25) | 40 (40) | .037 |
| Active Crescent Percentage* | 57.7 (46) | 40 (42) | .137 |
| Total Crescent Percentage* | 64.5 (45) | 34 (44.75) | .015 |

*median (interquartile range)
Abbreviations: ESKD, end stage kidney disease; IF/TA, interstitial fibrosis/tubular atrophy; SD, standard deviation.




Kidney Survival in Patients With and Without Cyclophosphamide Therapy

- By plotting the ROC Curve, we noticed that patients with IF/TA ≥ 25% and total crescent percentage < 55% had been more likely not to receive cyclophosphamide (C-statistics: 0.635 and 0.652, respectively).
- In patients with IF/TA ≥ 25%, the development of ESKD was more likely in patients who did not receive cyclophosphamide compared to those who received it
- (*P* = .002, OR = 9.33, 95% CI: 2.25 to 38.6).
- Also, in patients with total crescent percentage < 55%, ESKD was more likely to develop in patients who did not receive cyclophosphamide (*P* = .065, OR = 3.88, 95% CI: 0.918 to 16.4).
- From 28 patients who received at least 3 doses of cyclophosphamide, 10 patients had IF/TA 25 to 60% and 7 patients didn't develop ESKD.

In binary logistic analysis, cyclophosphamide administration was associated with reduced risk of development of ESKD in patients with:

- baseline GFR ≤ 15.22 mL/min (OR = 6.3, 95% CI: 1.82 to 21.83, *P* = .004),
- serum creatinine ≥ 3.8 mg/dL (OR = 7.06, 95% CI: 2.01 to 24.8, *P* = .002),
- GS ≥ 17% (OR = 8.2, 95% CI: 1.89 to 35.4, *P* = .005).

We believe that the unfavorable prognosis of our patients has been mainly due to late referral and advanced chronicity in a number of patients, in addition to unwillingness of the physicians to deliver standard cyclophosphamide regimen to patients with low number of crescents, and believing that adverse effects may overcome the benefits.

# Research Recommendations

- RCTs are needed to incorporate patient-reported outcomes, to assess long-term outcomes, to define the use of rituximab in severe AAV, and to assess therapies in ethnically diverse populations.
- Biomarker studies to identify early markers of disease relapse, markers to guide the choice of therapy, including plasma exchange, markers to predict optimal dosing and dosing interval for rituximab, and surrogate markers of remission

# Questions?