



ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

9<sup>ο</sup>

Περιφερειακό Συνέδριο  
Ελληνικής Εταιρείας  
Αιμαφαίρεσης

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# ANCA Αγγειίτιδες

Ο ρόλος του  
Νεφρολόγου  
στην  
Θεραπευτική  
Αφαίρεση

Αθανασία Καποτά

Επικουρική Επιμελήτρια  
Νεφρολόγος

ΓΝΑ Ιπποκράτειο

# Κατάταξη Συστηματικών Αγγειιτίδων International Chapel Hill Consensus Conference (CHCC 2012)

- Βάσει του μεγέθους των προσβεβλημένων αγγείων
- Η υποομάδα που χαρακτηρίζεται από την προσβολή των μικρών αγγείων και από την παρουσία κυκλοφορούντων αντιουδετεροφιλικών κυτταροπλασματικών αντισωμάτων ( ANCA )

## Box 1. Systemic Vasculitis Nomenclature

### Small-vessel vasculitis (SVV)

- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
  - ◇ Microscopic polyangiitis (MPA)
  - ◇ Granulomatosis with polyangiitis (Wegener) (GPA)
  - ◇ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Immune complex SVV
  - ◇ Anti-glomerular basement membrane (anti-GBM) disease
  - ◇ Cryoglobulinemic vasculitis (CV)
  - ◇ Immunoglobulin A (IgA) vasculitis (Henoch-Schönlein) (IgAV)
  - ◇ Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

### Medium-vessel vasculitis (MVV)

- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

### Large-vessel vasculitis

- Takayasu arteritis (TA)
- Giant cell arteritis (GCA)

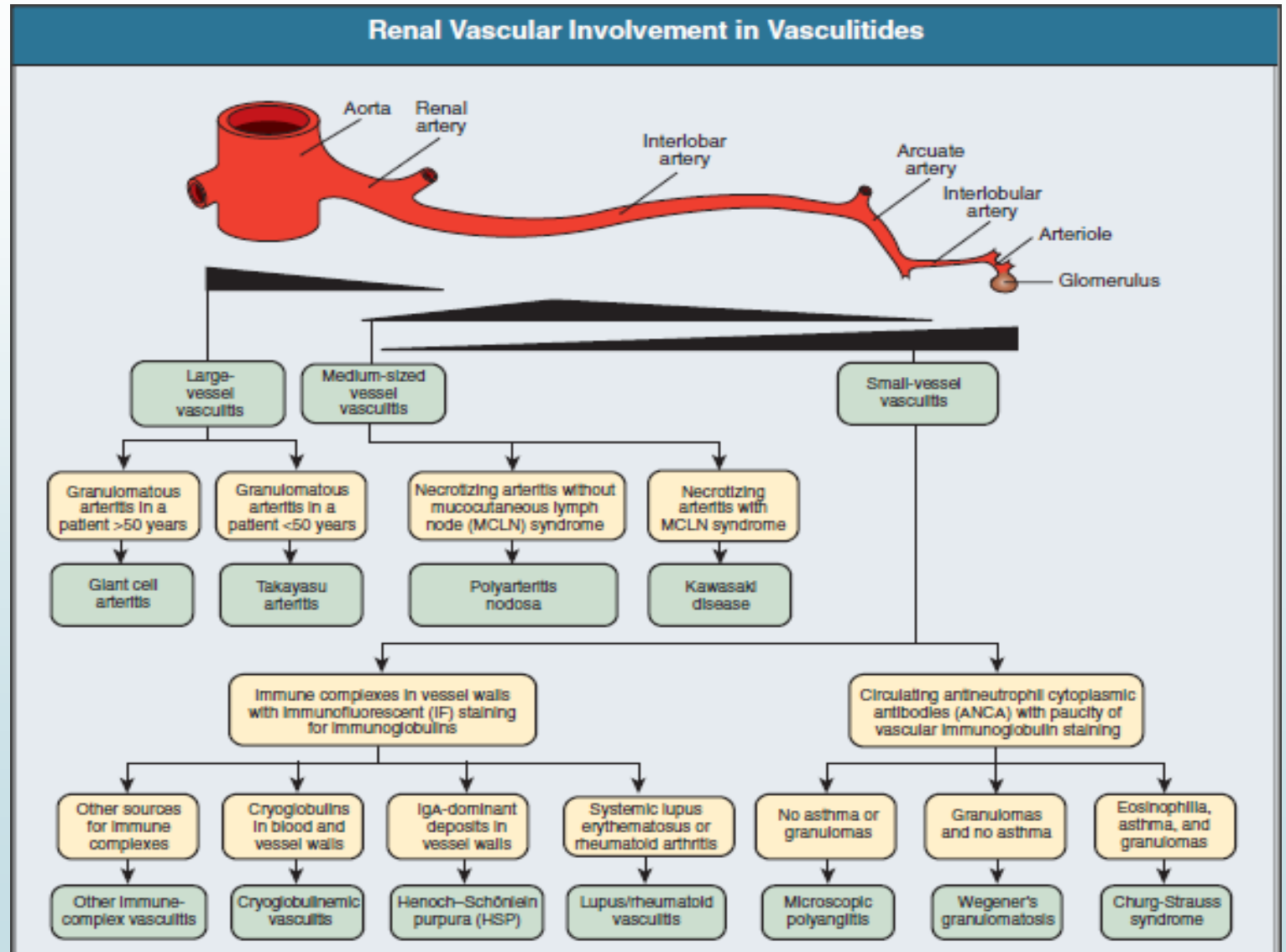
### Variable vessel vasculitis (VVV)

- Behçet disease (BD)
- Cogan syndrome (CS)

Based on 2012 International Chapel Hill Consensus Conference (see Jennette et al in Additional Readings).

# ANCA σχετιζόμενες αγγειίτιδες

- Μικροσκοπική πολυαγγειίτιδα (MPA)
- Κοκκιωμάτωση με πολυαγγειίτιδα (GPA) (Wegener)
- Ηωσινοφιλική κοκκιωμάτωση με πολυαγγειίτιδα (EGPA) (Churg-Strauss)



# Κλινική Αλληλοεπικάλυψη

Table 1. Syndromes of AAV.

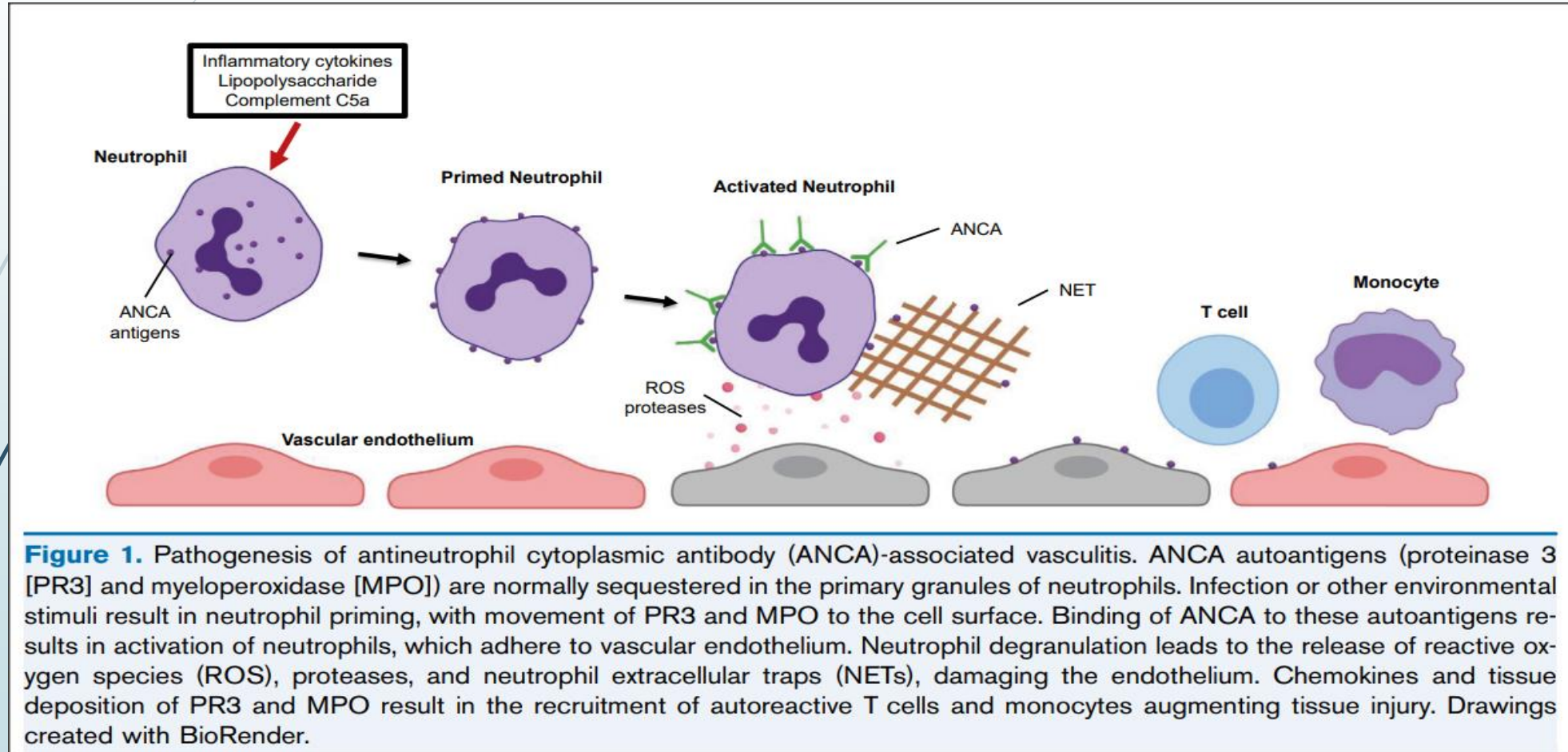
Disease	Incidence * [7]	ANCA-Positivity	PR3-ANCA	MPO-ANCA	Predominant Organ Involvement	Rate of Renal Involvement [77]	RPGN [77]
GPA	1.9-13	~90%	~75%	~20%	Nose and sinuses, lungs, kidneys, joints, eyes	~70%	~50%
EGPA	0.8-4	~40%	<10%	30-40%	Lungs, upper airways, peripheral nerves, heart, skin	~25%	<15%
MPA	1.5-16	~90%	~25%	~60%	Kidneys	>90%	~65%

\* per million person-years. Abbreviations: AAV: ANCA-associated vasculitis. ANCA: Antineutrophil cytoplasmic antibody. PR3: leukocyte proteinase 3. MPO: myeloperoxidase. RPGN: rapidly progressive glomerulonephritis. GPA: granulomatosis with polyangiitis. EGPA: eosinophilic granulomatosis with polyangiitis. MPA: microscopic polyangiitis.

# ANCA : Antineutrophil cytoplasmic antibody

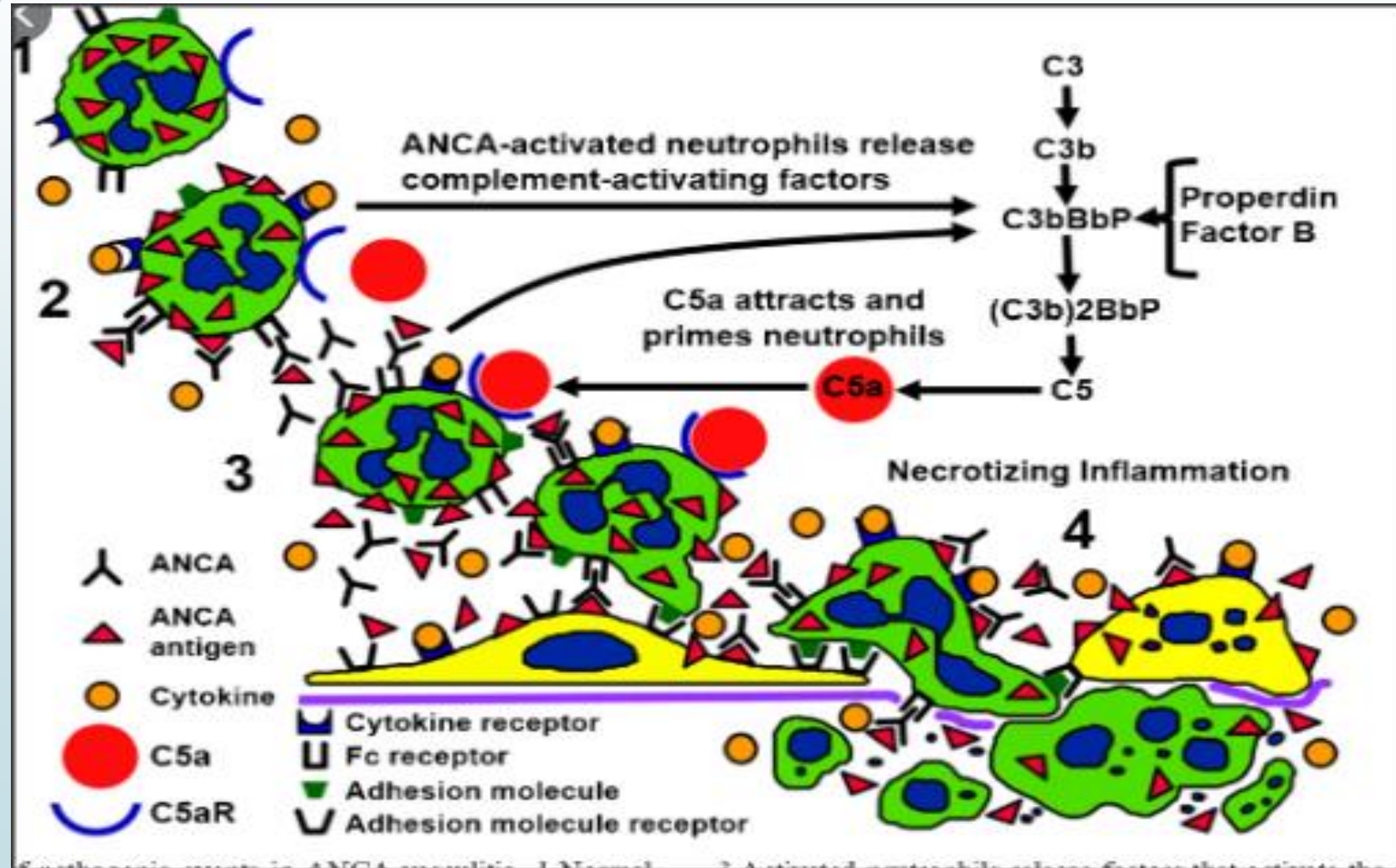
- ▶ Αυτοαντισώματα που στρέφονται έναντι αντιγόνων που βρίσκονται στα πρωτογενή κοκκία του κυτταροπλάσματος των ουδετεροφίλων και στα λυσοσώματα των μονοκυττάρων
- ▶ Τα κοκκία περιέχουν πληθώρα αντιγόνων έναντι των οποίων μπορούν να αναπτυχθούν αυτοαντισώματα. Τα κλινικά σημαντικά είναι αυτά έναντι της Μυελοπεροξειδάσης και της Πρωτεάσης 3
- ▶ Κατά το ενεργό στάδιο της νόσου : τυπικά ανήκουν στην IgG ανοσοσφαιρίνη

# Παθοφυσιολογία



**Figure 1.** Pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA autoantigens (proteinase 3 [PR3] and myeloperoxidase [MPO]) are normally sequestered in the primary granules of neutrophils. Infection or other environmental stimuli result in neutrophil priming, with movement of PR3 and MPO to the cell surface. Binding of ANCA to these autoantigens results in activation of neutrophils, which adhere to vascular endothelium. Neutrophil degranulation leads to the release of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), damaging the endothelium. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes augmenting tissue injury. Drawings created with BioRender.

# Παθοφυσιολογία



# Ορολογική Κατάταξη των ANCA

- ▶ proteinase 3 (PR3) - cANCA
- ▶ myeloperoxidase (MPO)- pANCA

**Table 2.** Comparison of Clinical Features by ANCA Specificity

	PR3-ANCA	MPO-ANCA
Demographics	50-70 y	60-80 y (mean, 10 y older than PR3-ANCA)
Geography	Northern Europe, North America	Southern Europe, Asia
Genetic risk alleles	<i>HLA-DP, PRTN3, SERPINA1</i>	<i>HLA-DQ</i>
Pathology	Necrotizing vasculitis, granulomatous inflammation	Necrotizing vasculitis, no granulomatous inflammation
Renal	More acute presentation	More common, more chronic injury on biopsy, may have a slow indolent course, more likely renal limited, isolated interstitial kidney disease (rare), usually MPO-ANCA
Respiratory involvement	More common; nodules, cavitation, and central airway disease more specific to PR3	Less common; may be chronic lung fibrosis, peripheral reticulation, honeycombing and usual interstitial pneumonia more specific to MPO
Upper airway disease	More common, destructive lesions (nasal perforation, saddle nose)	Rare
Outcomes	More likely to have resistant disease	Worse long-term survival (more chronic injury)
Relapse rate	Higher	Lower
Treatment	May respond better to rituximab than cyclophosphamide	Similar response to rituximab and cyclophosphamide

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

- Όχι απλοί βιοδείκτες
- Καλύτερη ειδικότητα και στενότερη σχέση στις γενετικές μελέτες ο τύπος των ANCA από τον κλινικό φαινότυπο
- CHCC 2012 : να τοποθετείται το πρόθεμα PR3 – ANCA GPA / MPO-ANCA GPA

# Εργαστηριακή Αλληλοεπικάλυψη

**Table 1.** Frequency of ANCA Positivity in Different Conditions

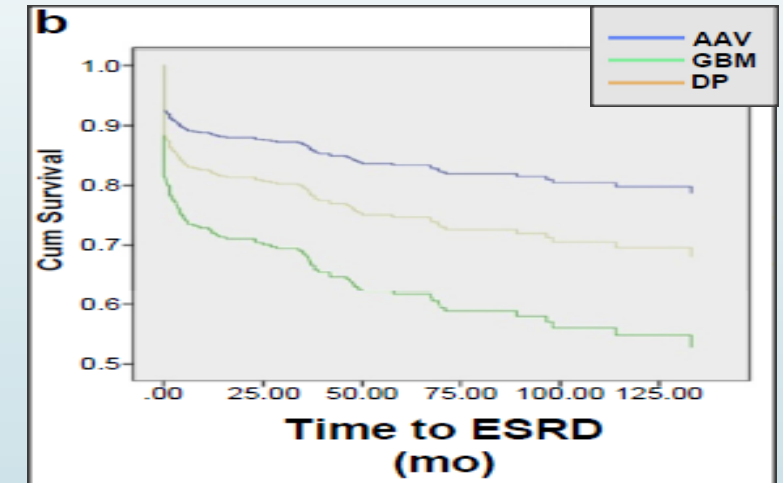
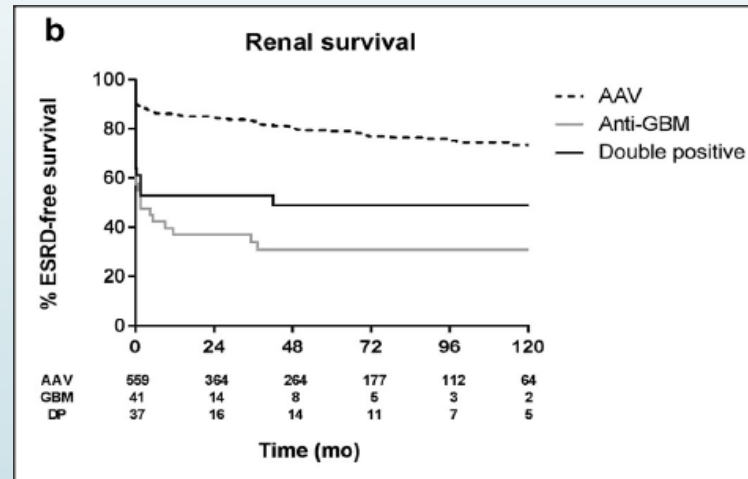
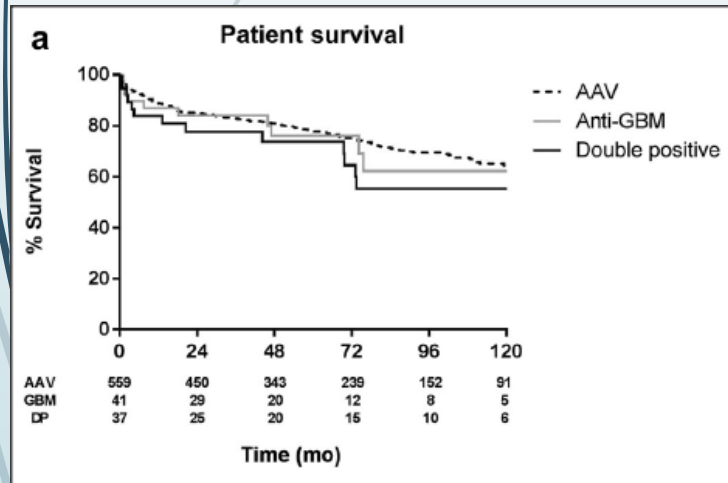
	PR3-ANCA (mostly cANCA)	MPO-ANCA (mostly pANCA)	Other
<b>ANCA-Associated Vasculitis</b>			
GPA	75%	20%	5% ANCA negative
MPA	30%	60%	10% ANCA negative
EGPA	5%	45%	50% ANCA negative
Renal-limited vasculitis	10%	80%	10% ANCA negative
Drug-induced vasculitis	10%	90%	Often high titer, dual positivity for MPO and PR3
<b>Nonvasculitis Conditions</b>			
Systemic lupus	2%	10%	10% atypical ANCA
Endocarditis	15%	5%	
Inflammatory bowel disease	Negative	Negative	Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%)
Primary sclerosing cholangitis	Negative	Negative	Atypical ANCA, various antigens: 60%-80%
Cystic fibrosis	Negative	Negative	Atypical ANCA pattern, directed against BPI (90%)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BPI, bactericidal/permeability-induced protein; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3.

10% - 30% χωρίς ανευρεθέντα ANCA  
Πολύ σπάνια MPO και PR3 - ANCA

# Double – positive AAV

- ▶ Διπλά θετική ανοσοσπενική αγγειίτις -Double positive pauci-immune vasculitis :anti-GBM(+), anti- MPO (+) ή anti-PR3(+)



Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients Stephen P. McAdoo et al Kidney International (2017)



# the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS)

- ▶ 6.991 patients from 136 sites in 32 countries

## 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Microscopic Polyangiitis

Ravi Suppiah,<sup>1</sup> Joanna C. Robson,<sup>2</sup>  Peter C. Grayson,<sup>3</sup>  Cristina Ponte,<sup>4</sup> Anthea Craven,<sup>5</sup> Sara Khalid,<sup>5</sup> Andrew Judge,<sup>6</sup> Andrew Hutchings,<sup>7</sup> Peter A. Merkel,<sup>8</sup>  Raashid A. Luqmani,<sup>5</sup> and Richard A. Watts<sup>9</sup> 

specificity of 92.5% sensitivity of 82.4%.

### 2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

## CLASSIFICATION CRITERIA FOR **MICROSCOPIC POLYANGIITIS**

#### CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having microscopic polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

#### CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect / perforation	-3
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#### LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
Fibrosis or interstitial lung disease on chest imaging	+3
Pauci-immune glomerulonephritis on biopsy	+3
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$ /liter	-4

Sum the scores for 6 items, if present. A score of  $\geq 5$  is needed for classification of **MICROSCOPIC POLYANGIITIS**.

## 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis

Joanna C Robson <sup>1</sup>, Peter C Grayson <sup>2</sup>, Cristina Ponte <sup>3</sup>, Ravi Suppiah,<sup>4</sup>  
Anthea Craven,<sup>5</sup> Andrew Judge <sup>6,7</sup>, Sara Khalid,<sup>5</sup> Andrew Hutchings,<sup>8</sup>  
Richard A Watts <sup>5,9</sup>, Peter A Merkel <sup>10</sup>, Raashid A Luqmani<sup>5</sup>

specificity of 94.6% sensitivity of 83.8%

### 2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY CLASSIFICATION CRITERIA FOR **GRANULOMATOSIS WITH POLYANGIITIS**

#### CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

#### CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1

#### LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$ /liter	-4

Sum the scores for 10 items, if present. A score of  $\geq 5$  is needed for classification of **GRANULOMATOSIS WITH POLYANGIITIS**.

## 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis

Peter C Grayson <sup>1</sup>, Cristina Ponte <sup>2,3</sup>, Ravi Suppiah,<sup>4</sup> Joanna C Robson <sup>5</sup>,  
Anthea Craven,<sup>6</sup> Andrew Judge <sup>6,7</sup>, Sara Khalid,<sup>6</sup> Andrew Hutchings,<sup>8</sup>  
Raashid A Luqmani,<sup>6</sup> Richard A Watts <sup>6,9</sup>, Peter A Merkel <sup>10</sup>

specificity of 99% sensitivity of 75%.

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

### CLASSIFICATION CRITERIA FOR **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**

#### CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

#### CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

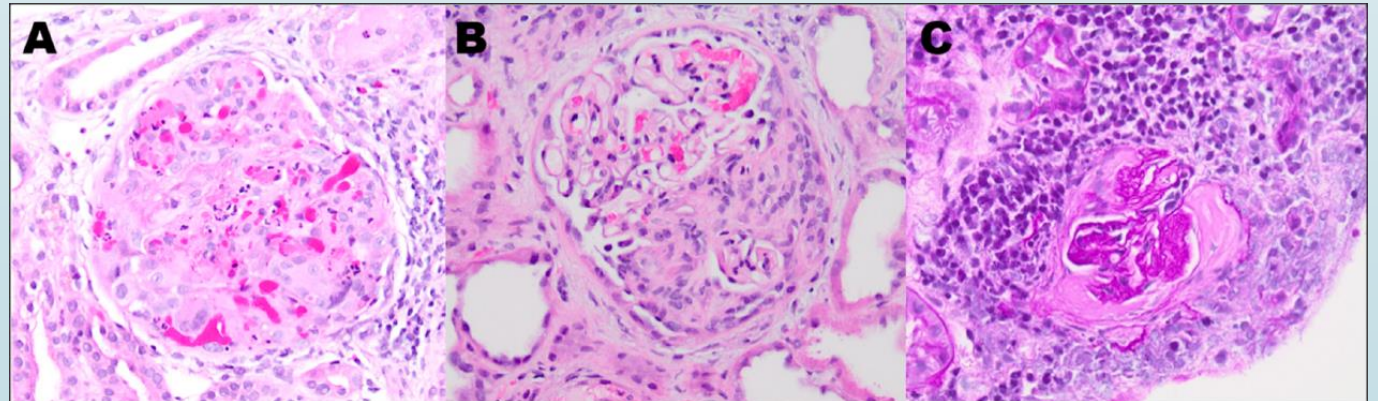
#### LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count $\geq 1 \times 10^9$ /liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Sum the scores for 7 items, if present. A score of  $\geq 6$  is needed for classification of **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**.

# Βιοψία Νεφρού

- ▶ Ανοσοπενική σπειραματονεφρίτιδα : Ο έμμεσος ανοσοφθορισμός αποκαλύπτει ελάχιστη ή καθόλου χρώση για ανοσοσφαιρίνες ή συμπλήρωμα
- ▶ Νεκρωτική μηνοειδής σπειραματονεφρίτιδα : Στο φωτονικό μικροσκόπιο μηνοειδείς σχηματισμοί διαφορετικής ηλικίας και κυτταροβρίθειας
- ▶ Διαμεσοσωληναριακή φλεγμονώδης κυτταρική διήθηση
- ▶ Σπειραματοσκλήρυνση



# Βιοψία Νεφρού

## ► Πρόγνωση

**Table 2.** Classification of ANCA-associated glomerulonephritis \*.

Class	Criteria
Focal	≥50% of glomeruli are normal
Crescentic	≥50% of glomeruli have cellular crescents
Sclerotic	≥50% of glomeruli are globally sclerosed
Mixed	Not fulfilling any of the above criteria

\* Adapted from [78].

# Θεραπεία Επαγωγής

## **13.1: Initial treatment of pauci-immune focal and segmental necrotizing GN**

- 13.1.1:** We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (1A)
- 13.1.2:** We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (1B)

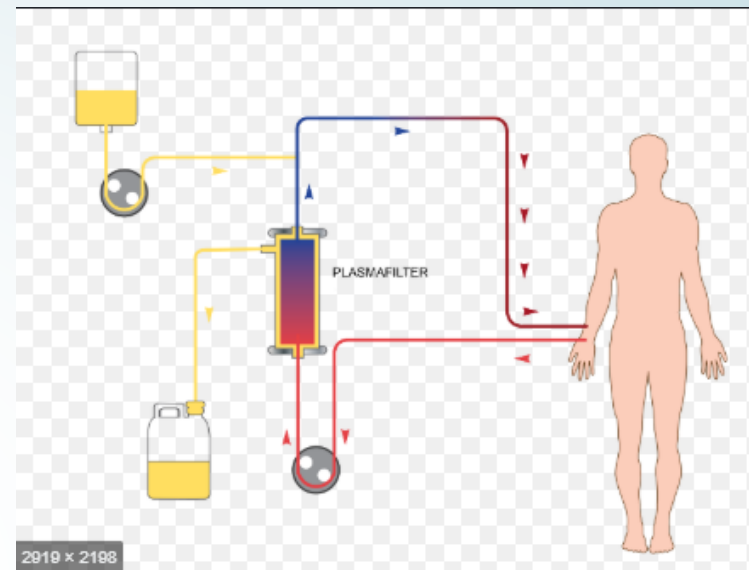
## **13.2: Special patient populations**

- 13.2.1:** We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (1C)
- 13.2.2:** We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (2C)
- 13.2.3:** We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see Chapter 14). (2D)
- 13.2.4:** We suggest discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease. (2C)



# Πλασμαφαίρεση

- Η απομάκρυνση των ANCA αλλά και άλλων φλεγμονωδών διαμεσολαβητών μπορεί να προάγει την πρώιμη αναστροφή της ανοσολογικής απόκρισης και να ελαχιστοποιεί την ιστική βλάβη



**Table 30 | Recommended treatment regimens for ANCA vasculitis with GN**

Agent	Route	Initial dose
Cyclophosphamide <sup>a</sup>	i.v.	0.75 g/m <sup>2</sup> q 3-4 weeks. Decrease initial dose to 0.5 g/m <sup>2</sup> if age > 60 years or GFR < 20 ml/min per 1.73 m <sup>2</sup> . Adjust subsequent doses to achieve a 2-week nadir leukocyte count > 3000/mm <sup>3</sup> .
Cyclophosphamide <sup>b</sup>	p.o.	1.5-2 mg/kg/d, reduce if age > 60 years or GFR < 20 ml/min per 1.73 m <sup>2</sup> . Adjust the daily dose to keep leukocyte count > 3000/mm <sup>3</sup> .
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3-4 months.
Rituximab <sup>c</sup>	i.v.	375 mg/m <sup>2</sup> weekly × 4.
Plasmapheresis <sup>d</sup>		60 ml/kg volume replacement. <i>Vasculitis:</i> Seven treatments over 14 days. If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7-10 treatments. <i>Vasculitis in association with anti-GBM antibodies:</i> Daily for 14 days or until anti-GBM antibodies are undetectable.

# ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ

**Table 4.** Major clinical trials for induction therapy in ANCA-associated vasculitis.

Trial Name	N, Population	Kidney Involvement	Intervention	Control	Primary Endpoint and Conclusion	Other Outcomes
CYCLOPS [99]	149, new AAV	100% (excluded patients with sCr > 5.7 mg/dL)	Pulse CYC (15 mg/kg) every 2–3 weeks	DO CYC (2 mg/kg/d)	No difference in time to remission	Higher risk of relapse in the pulse CYC group on long-term follow up [100]
MEPEX [109]	137, AAGN and sCr > 5.7 mg/dL	100%	PLEX	IV MP	Renal recovery at 3 months. PLEX superior	No difference in long-term outcomes [110]
PEXIVAS [92]	704, new or relapsing	98% (29% with sCr > 5.7 mg/dL)	(1) PLEX * (2) low-dose GC *	(1) no PLEX * (2) standard-dose GC *	(1) Death or ESRD at 12 months. No difference (2) No difference in efficacy	No difference in subgroup analysis for ESRD, death, alveolar hemorrhage
RAVE [101]	197, new or relapsing	52%, (excluded patients with sCr > 4 mg/dL)	RTX (375 mg/m <sup>2</sup> ) for 4 weekly doses	PO CYC (2 mg/kg/d) followed by AZA	Remission (BVAS = 0) and completion of steroid taper at 6 months. No difference	RTX better for relapsing disease
RITUXVAS [104]	44, new AAGN	100%	RTX (375 mg/m <sup>2</sup> ) for 4 weekly doses + IV CYC (15 mg/kg) for 2 doses	IV CYC (15 mg/kg/d) for 6–10 doses followed by AZA	Sustained remission (BVAS = 0 for 6 months). No difference	
ADVOCATE [73]	331, new or relapsing	81%	Avacopan with RTX or CYC	Prednisone with RTX or CYC	(1) Clinical remission (BVAS = 0 and no steroids # at week 26). No difference (2) Sustained remission (BVAS = 0 at weeks 26 and 52 and no steroids # at week 52). Avacopan superior	

\* 2 × 2 factorial design. # no steroids for 4 weeks prior to endpoint. Abbreviations: AAV: ANCA-associated vasculitis. AAGN: ANCA-associated glomerulonephritis. AZA: azathioprine. sCr: serum creatinine. IV: intravenous. DO: daily oral. CYC: cyclophosphamide. ESRD: end-stage renal disease. PLEX: plasma exchange. MP: methylprednisolone. RTX: Rituximab. GC: glucocorticoids. BVAS: Birmingham Vasculitis Activity Score.

# MEPEX

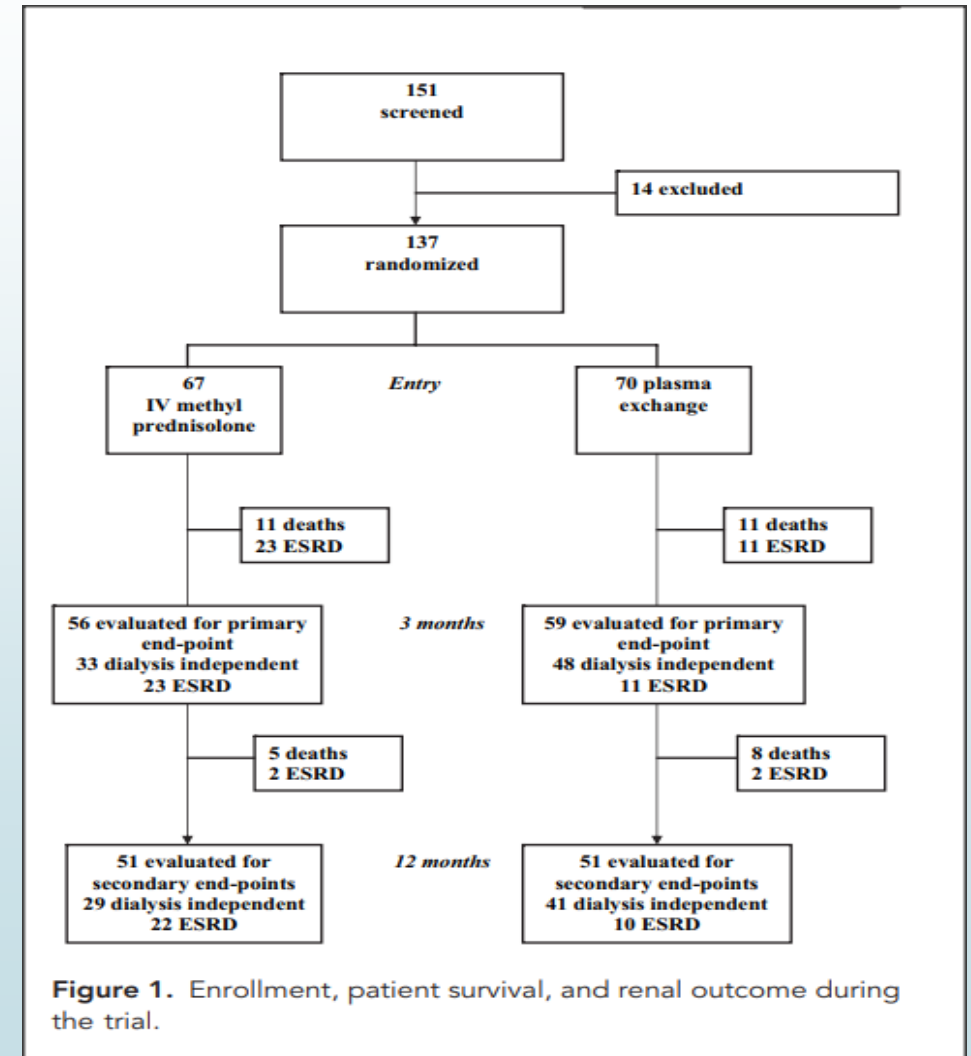
Randomized Controlled Trial > J Am Soc Nephrol. 2007 Jul;18(7):2180-8.

doi: 10.1681/ASN.2007010090. Epub 2007 Jun 20.

## Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis

David R W Jayne <sup>1</sup>, 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, Charles D Pusey; European Vasculitis Study Group

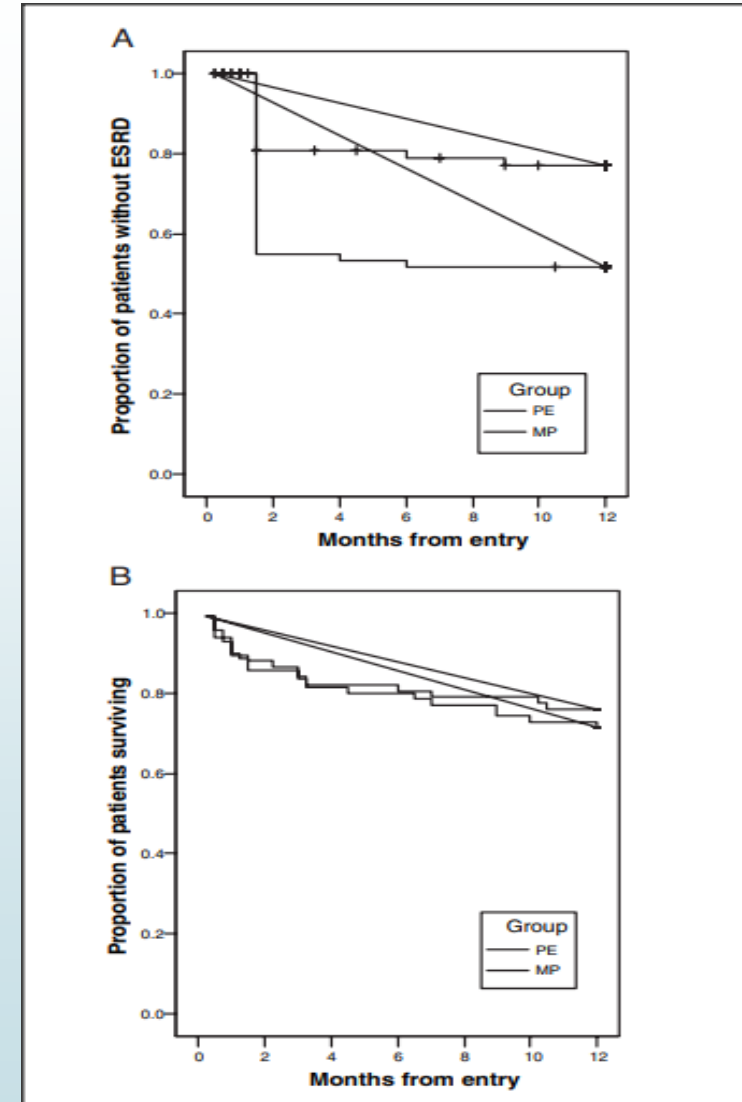
A total of 137 patients with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine 500  $\mu\text{mol/L}$  (5.8 mg/dl) were randomly assigned to receive seven plasma exchanges (n 70) or 3000 mg of intravenous methylprednisolone (n 67). Both groups received oral cyclophosphamide and oral prednisolone



# ΜΕΡΕΧ

- ▶ Η ομάδα που έλαβε Πλασμαφαίρεση εμφάνισε 24% μειωμένο κίνδυνο ανάπτυξης ΧΝΝΤΣ στους 12 μήνες. Αποτέλεσμα αμετάβλητο στην πολυπαραγοντική ανάλυση.
- ▶ Η Πλασμαφαίρεση αύξησε τον ρυθμό νεφρικής αποκατάστασης σε σχέση με την IV μεθυλοπρεδνιζολόνη.
- ▶ Η επιβίωση των ασθενών και τα ποσοστά σοβαρών ανεπιθύμητων ενεργειών ήταν παρόμοια και στις δύο ομάδες.
- ▶ Η μακροχρόνια παρακολούθηση με διάμεσο τα 3,95 έτη δεν έδειξε καμία διαφορά στα ποσοστά ΧΝΝΤΣ ή θανάτου

Walsh, M. et al Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear *Kidney Int.* 2013



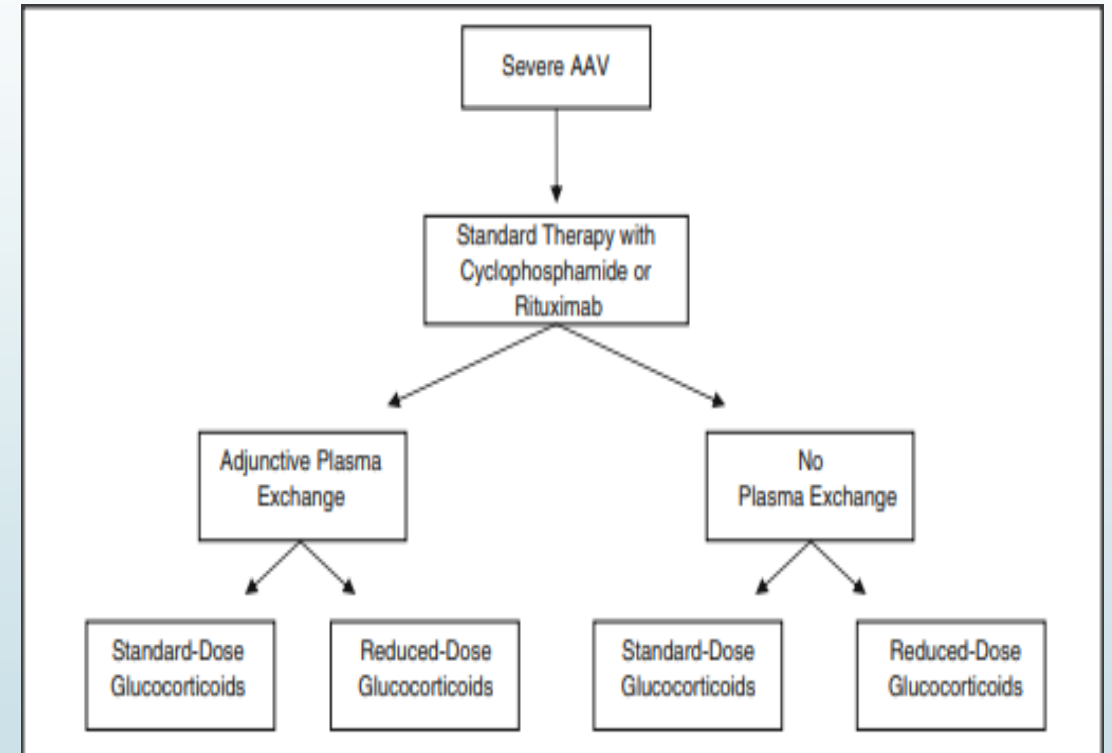
# PEXIVAS

Randomized Controlled Trial > N Engl J Med. 2020 Feb 13;382(7):622-631.

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## Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

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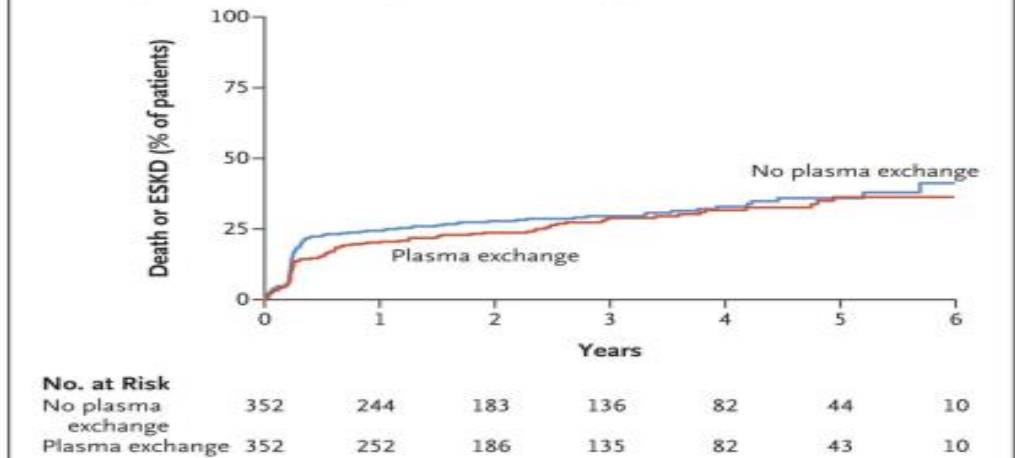


704 ασθενείς με GFR <50ml/min ή πνευμονική αιμορραγία,  
205 με κρεατινίνη ορού > 5.7 mg/dl ή σε HD

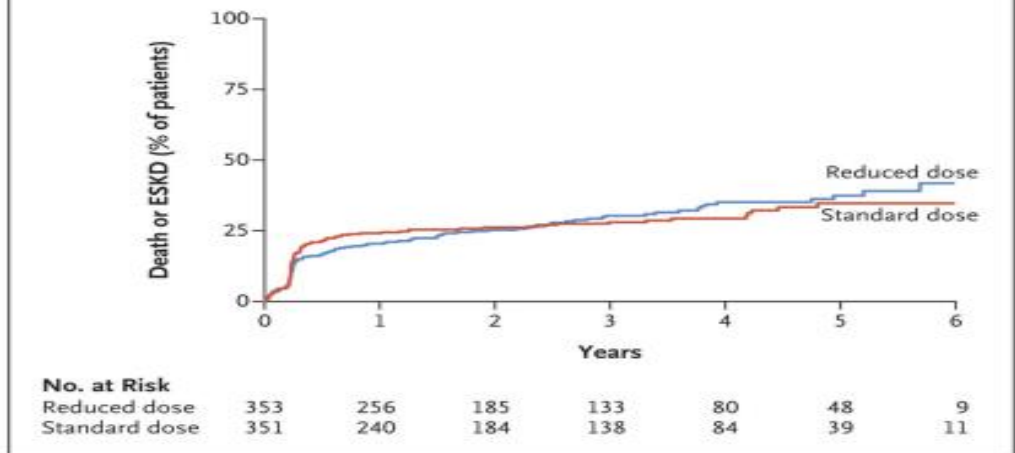
# PEXIVAS

**Conclusion:** Plasma exchange does not reduce the risk of end-stage renal disease or death in patients with ANCA-associated vasculitis. Compared to a standard dose, reduced glucocorticoids did not substantially increase the risk of death or end-stage renal disease and resulted in fewer serious infections. The primary results of PEXIVAS, regarding both the use of plasma exchange and dosing of glucocorticoids, will have immediate and substantial impact on the standard of care for patients with ANCA-associated vasculitis.

**A Primary Outcome According to Plasma Exchange**



**B Primary Outcome According to Glucocorticoid Regimen**



**Figure 1. Kaplan–Meier Curves for the Primary Outcome.** The primary composite outcome was death from any cause or end-stage kidney disease (ESKD). In a trial with a 2-by-2 factorial design, patients with severe antineutrophil cytoplasm antibody–associated vasculitis were assigned to undergo plasma exchange or no plasma exchange (Panel A) and to follow either a reduced-dose regimen or a standard-dose regimen of oral glucocorticoids (Panel B).

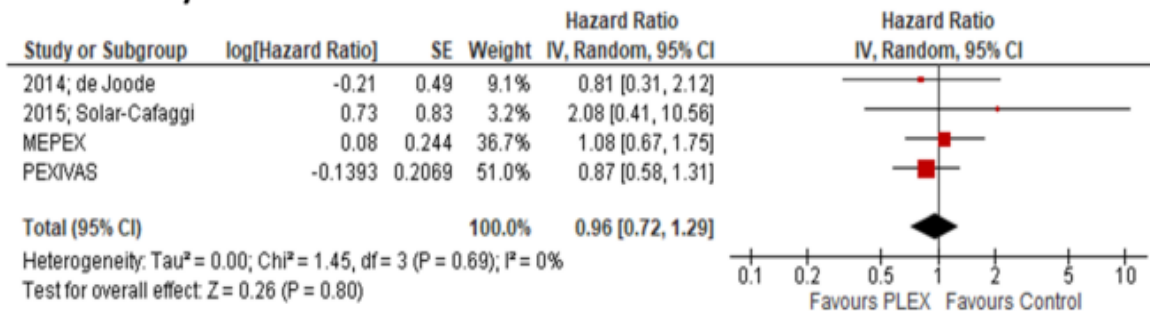
## The role of plasma exchange in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis

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Affiliations + expand

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### a Mortality



### b End-stage renal disease

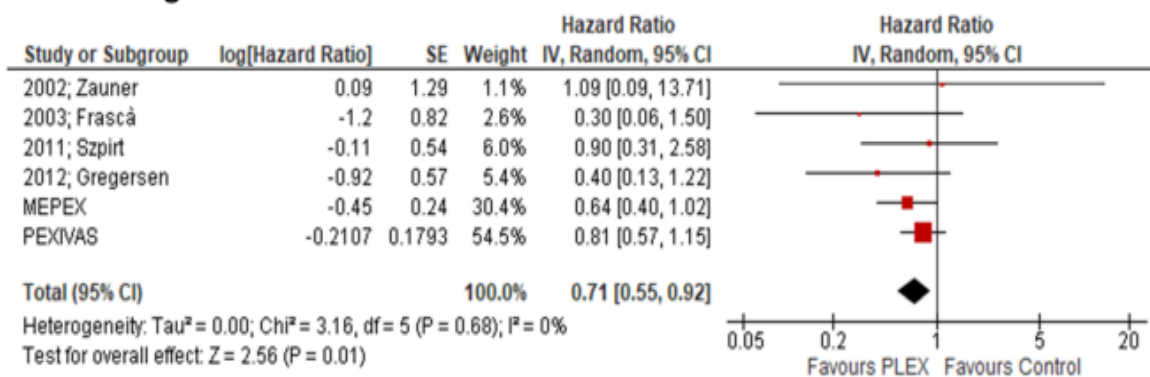


Fig. 3 Forest plot of overall mortality and end-stage renal disease. PLEX, plasma exchange

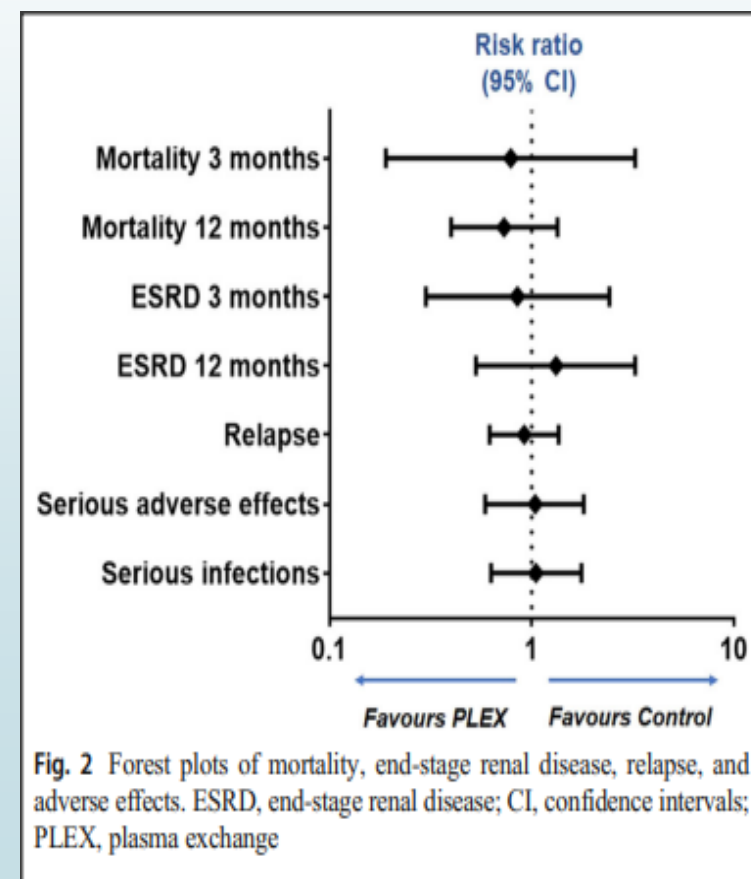


Fig. 2 Forest plots of mortality, end-stage renal disease, relapse, and adverse effects. ESRD, end-stage renal disease; CI, confidence intervals; PLEX, plasma exchange

# Θεραπεία Συντήρησης

- Τα δεδομένα υποδηλώνουν ότι το Rituximab είναι αποτελεσματικό στην διατήρηση της ύφεσης και η μακροχρόνια θεραπεία έως και 46 μήνες σχετίζονται με χαμηλότερο κίνδυνο υποτροπής, ειδικά σε ασθενείς με PR3 ANCA (+)

Table 5. Major clinical trials for maintenance therapy in ANCA-associated vasculitis.

Trial Name	N, Population	Kidney Involvement	Induction Agent	Intervention	Control	Primary Endpoint and Conclusion	Other Outcomes
CYCAZAREM [114]	155, new AAV	94% (excluded those with sCr > 5.7 mg/dL)	DO CYC	AZA (2 mg/kg/d)	DO CYC (1.5 mg/kg/d)	Relapse at 18 months. No difference	MPA relapses less frequently than GPA
MAINRITSAN [118]	115, new or relapsing	70%	Pulse CYC	RIX (500 mg) days 0, 14 then every 6 months	AZA (2 mg/kg/d) for 1 year followed by a taper	Major organ relapse at 28 months. RTX superior.	Most relapses occurred after B-cell return
MAINRITSAN 2 [121]	162, new or relapsing	72%	CYC or RTX or MTX **	Tailored * RTX (500 mg)	Scheduled RTX (500 mg) every 6 months	Relapse at 28 months. No difference	No difference in adverse events. Fewer RTX doses in tailored arm
MAINRITSAN 3 [122]	97 patients from MAINRITSAN 2	63%	CYC or RTX or MTX **	RIX (500 mg) every 6 months for 18 months	Placebo	Relapse-free survival at 28 months. Less relapses with extended treatment	Most relapses occurred in GPA patients
RITAZAREM [120]	170, relapsed AAV	N/A	RTX	RIX (1 g) every 4 months for 20 months	AZA (2 mg/kg/d)	Time to relapse. RTX superior.	
IMPROVE [117]	156, new AAV	N/A	CYC	AZA (2 mg/kg/d) for 1 year followed by a taper	MMF (2 g/d) for 1 year followed by a taper	Relapse-free survival. Relapses more common with MMF	
BREVAS [123]	105, new or relapsing	N/A	CYC or RIX	Belimumab (10 mg/kg) + AZA	Placebo + AZA	Time to protocol-specified event †. No difference.	No relapses in patients induced with RTX and receiving belimumab

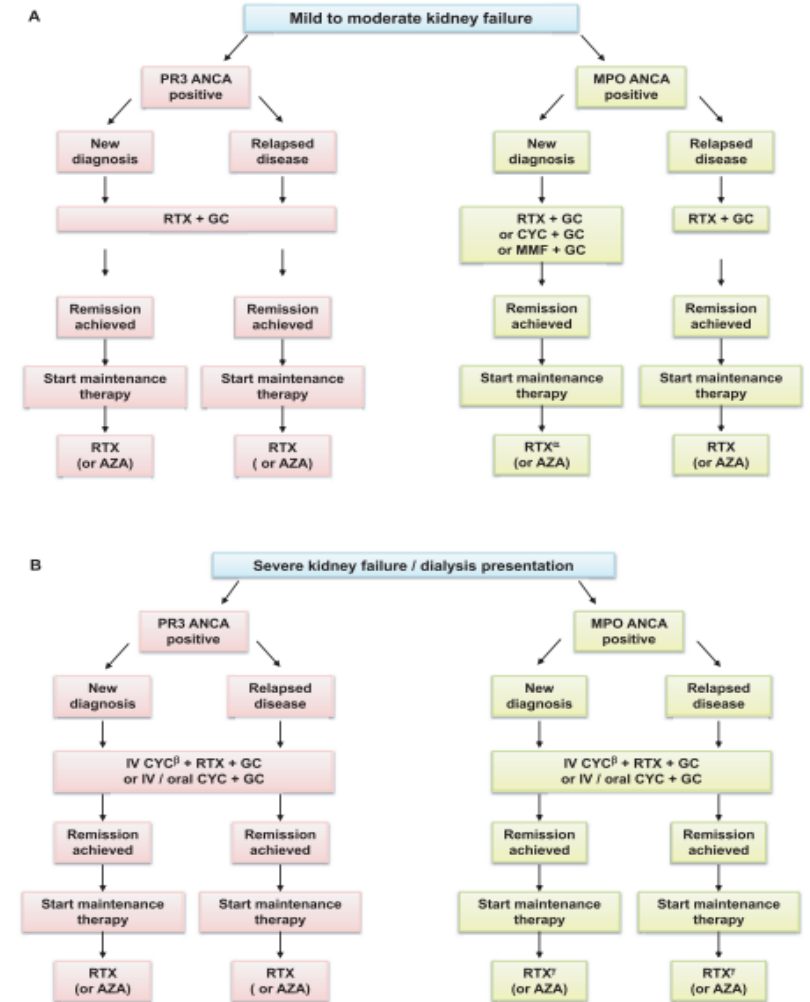
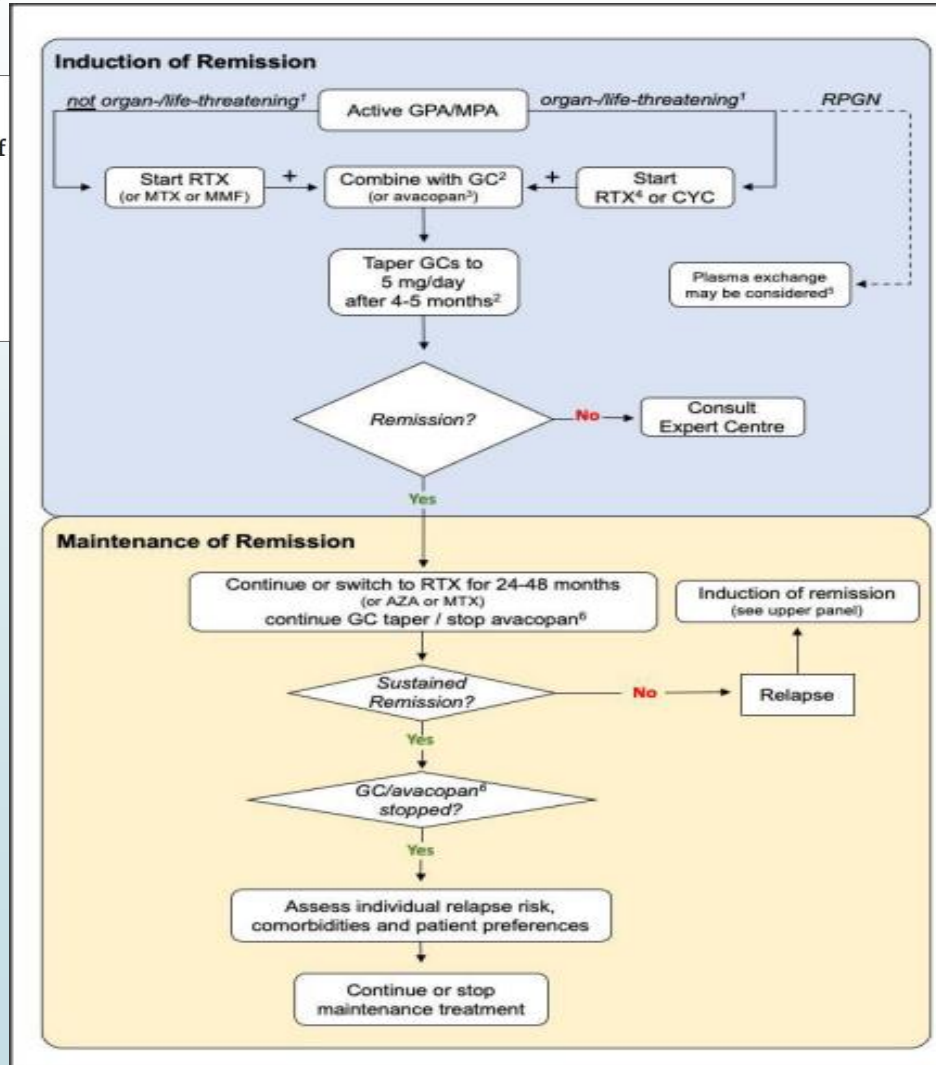
\* RTX re-dosed with B-cell return, or ANCA seroconversion (negative to positive), or increase in ANCA \*\* only one patient induced with MTX † Birmingham Vasculitis Activity Score (BVAS) of  $\geq 6$ , or presence of  $\geq 1$  major BVAS item, or receipt of prohibited medications for any reason, resulting in treatment failure Abbreviations: AAV: ANCA-associated vasculitis. D: day. DO: daily oral. CYC: cyclophosphamide. AZA: Azathioprine. RTX: Rituximab. MTX: Methotrexate. MMF: mycophenolate mofetil. N/A: data unavailable.

# Αλγόριθμοι

> Ann Rheum Dis. 2023 Mar 16;ard-2022-223764. doi: 10.1136/ard-2022-223764. Online ahead of print.

## EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

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B) Proposed treatment algorithm for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. <sup>1</sup>Maintenance therapy should be individualized according to the risk for relapse. Patients with myeloperoxidase (MPO)-ANCA have a lower relapse rate. <sup>2</sup>Maintenance therapy duration (18-24 months) of therapy may be appropriate after initial presentation. <sup>3</sup>Data are limited in patients with severe kidney failure at presentation; the authors prefer a cyclophosphamide (CYC)-based regimen, such as that used in the FOCUS trial in this setting. <sup>4</sup>Patients who have reached end-stage kidney disease and have no extrarenal manifestations may benefit from plasma exchange immunosuppression. Abbreviations: AZA, azathioprine; GC, glucocorticoids; MMF, mycophenolate mofetil; RTX, rituximab.

# Για το τέλος

- ▶ 8% των ασθενών με ANCA σχετιζόμενη αγγειίτιδα θα καταλήξουν με ΧΝΝΤΣ στους 6 μήνες ενώ το ποσοστό ανεβαίνει στο 14% στα 7 έτη.
- ▶ Ασθενείς με MPA είναι πιθανότερο να αναπτύξουν ΧΝΝΤΣ σε σχέση με αυτούς με GPA.
- ▶ Οι ασθενείς με ΧΝΝΤΣ θα πρέπει να εξετάζονται για το ενδεχόμενο της μεταμόσχευσης ανεξάρτητα αν τα ANCA είναι θετικά.
- ▶ Ασθενείς που βρίσκονται σε ύφεση για λιγότερο του έτους από την λήψη μοσχεύματος έχουν μεγαλύτερη θνησιμότητα.
- ▶ Τα ποσοστά υποτροπής είναι χαμηλότερα μετά την μεταμόσχευση ( 2,8 ανά ασθενή-έτος)



**Ευχαριστώ**

