Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis

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Disclosures C.A. Stegeman

- More than 30 years in UMC Groningen (“departmental furniture”)
- Born and raised in Groningen (“stadjer”)
- Involved in 2 industrial sponsored trials (no fee)
- Fee for moderating NephSAP and Expert meeting sessions (Vifor, Astra Zeneca)
- Grant’s from Nierstichting Nederland, Reumafonds, Dutch Research Council (NWO)
- Evidence level C = Coen

Program / Content

- Role of histology in the diagnosis of active AAV
- Syndrome diagnosis / classification in AAV: is it important and how should it be done?
  - syndrome, phenotype, serotype
- Is it time to change the nomenclature of AAV?

Recommendation

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

Bernhard Hellmich ,[1] Beatriz Sanchez-Alamo,[2] Jan H Schirmer,[3] Alvise Berti ,[4,5] Daniel Blockmans,[6] Maria C Cid ,[7] Julia U Holle,[8] Nicole Hollinger,[1] Omer Karadag,[9] Andreas Kronbichler,[10,11] Mark A Little,[12] Raashid A Luqmani,[13] Alfred Mahr,[14] Peter A Merkel ,[15] Aladdin J Mohammad ,[11,16] Sara Monti ,[17,18] Chetan B Mukhtyar ,[19] Jacek Musial,[20] Fiona Price-Kuehne,[11] Mårten Segelmark,[21] Y K Onno Teng ,[22] Benjamin Terrier ,[23] Gunnar Tomasson ,[24,25] Augusto Vaglio ,[26] Dimitrios Vassilopoulos ,[27] Peter Verhoeven,[28] David Jayne [11]

Ann Rheum Dis 2024;83(1):30-47

General principles deemed fundamental for the management

Table 3 EULAR recommendations for the management of AAV—2022 update

	Overarching principles
A	Patients with AAV should be offered best care which must be based on shared decision-making between the patient and the physician considering efficacy, safety and costs.
B	Patients with AAV should have access to education focusing on the impact of AAV and its prognosis, key warning symptoms and treatment (including treatment-related complications).
C	Patients with AAV should be periodically screened for treatment-related adverse effects and comorbidities. We recommend prophylaxis and lifestyle advice to reduce treatment-related complications and other comorbidities.
D	AAV are rare, heterogeneous, and potentially life-threatening and organ-threatening diseases and thus require multidisciplinary management by centres with, or with ready access to, expertise in vasculitis.

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Recommendations (total 17)

	Recommendations	LoE	SoR	FV (%)	LoA (0–10)
1	A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis of AAV and for further evaluation of patients suspected of having relapsing vasculitis.	3b	C	90	8.7±1.9
2	In patients with signs and/or symptoms raising suspicion of a diagnosis of AAV, we recommend testing for both PR3-ANCA and MPO-ANCA using a high-quality antigen-specific assay as the primary method of testing.	1a	A	100	10.0±0
3	For induction of remission in patients with new-onset or relapsing GPA or MPA with organ-threatening or life-threatening disease, we recommend treatment with a combination of glucocorticoids and either rituximab or cyclophosphamide.* Rituximab is preferred in relapsing disease.†	1a* 2b†	A* B†	100	9.6±0.8
4	For induction of remission of non-organ-threatening or non-life-threatening GPA or MPA, treatment with a combination of glucocorticoids and rituximab is recommended. Methotrexate or mycophenolate mofetil can be considered as alternatives to rituximab.	1b	B	90	9.2±0.8
5	As part of regimens for induction of remission in GPA or MPA, we recommend treatment with oral glucocorticoids at a starting dose of 50–75 mg prednisolone equivalent/day, depending on body weight. We recommend stepwise reduction in glucocorticoids according to table 4 and achieving a dose of 5 mg prednisolone equivalent per day by 4–5 months.	1b	A	100	9.4±0.8
6	Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to glucocorticoids.	1b	B	100	9.0±0.9
7	Plasma exchange may be considered as part of therapy to induce remission in GPA or MPA for those with a serum creatinine >300 µmol/L due to active glomerulonephritis.*	1a*	B*	95*	8.0±1.7
	Routine use of plasma exchange to treat alveolar haemorrhage in GPA and MPA is not recommended.†	1b†	B†	90†	8.8±1.3
8	For patients with GPA or MPA with disease refractory to therapy to induce remission, we recommend a thorough reassessment of disease status and comorbidities and consideration of options for additional or different treatment. These patients should be managed in close	5	D	100	9.9±0.5

Recommendations 11 – 14: specific for eGPA

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Recommendation 1

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Diagnosis and classification of vasculitis requires histology

Ann Rheum Dis 2024;83(1):30-47

ACR 1990 classification criteria for vasculitis

- Polyarteritis nodosa (n=118 / 52)
- Churg-Strauss syndrome (n=20 / 6)
- Wegener's granulomatosis (n=85 / 26)
- Hypersensitivity vasculitis (n=93 / 43)
- Henoch-Schönlein purpura (n=85 / 12)
- Giant cell (temporal) arteritis (n=214 / 47)
- Takayashu arteritis (n=63 / 3)

Clinical and/or histological criteria

No serologic data included

Hunder GG, et al. Arthritis Rheum 1990;33:1065-7

Sensitivity / specificity of histology in AAV

GPA/MPA (AAV)	sensitivity	specificity
Skin biopsy	20-60%	~50%
Muscle biopsy	10-30%	~50%
Lung biopsy (transbronchial)	20-25%	~90%
VATS / thoracotomy	40-70%	~90%
ENT biopsy	≤50%	~100%*
Kidney biopsy	~90%	~90%

* If inflammation with necrosis. granulomatous inflammation and/or vasculitis

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What is the contribution of histology in the individual case?

- Diagnosis correct?
- Realistic differential diagnosis (infection, malignancy)
- Is disease active or not?
- Prognosis?
- An invasive procedure must have impact on management

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NO INDICATION FOR BIOPSY, UNLESS……

- Doubt about the diagnosis
- Realistic differential diagnosis (infection, malignancy)
- Doubt about disease activy
- The outcome of the invasive procedure has impact on the management of the disease

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ANCA-specificity and classification/sensitivity

788 patients with ANCA-associated vasculitis/necrotizing glomerulonephritis 1990-2022 in Groningen

Diagnosis	PR3	MPO	none	positive (%)
GPA (n=460)	404	32	26*,a	94%
MPA (n=169)	37	123	12**	93%
NCGN (n=86)	8	67	11***	87%
EGPA (n=77)	1	30	46****	40%

anti-elastase antibodies positive * 5, ** 8, *** 1, **** 1

[a] 18 of 26 ENT limited WG

Eosinophilic Granulomatous Polyangiitis

- eosinophilia ($\geq 1.5 \times 10^9$/l)
- late-onset asthma
- nasal polyposis

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Eosinophilic infiltration
- pulmonary infiltrates
- cellulitis
- tubulointerstitial nephritis
- myocarditis
- gastroenteritis

Vasculitis
- alveolar hemorrhage
- leukocytoclastic vasculitis
- glomerulonephritis
- mononeuritis multiplex
- gastro-intestinal vasculitis

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ANCA negative

ANCA (MPO) positive

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Vasculitis
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ANCA negative
Anti-eosinophil therapy

ANCA (MPO) positive
AAV immunosuppression

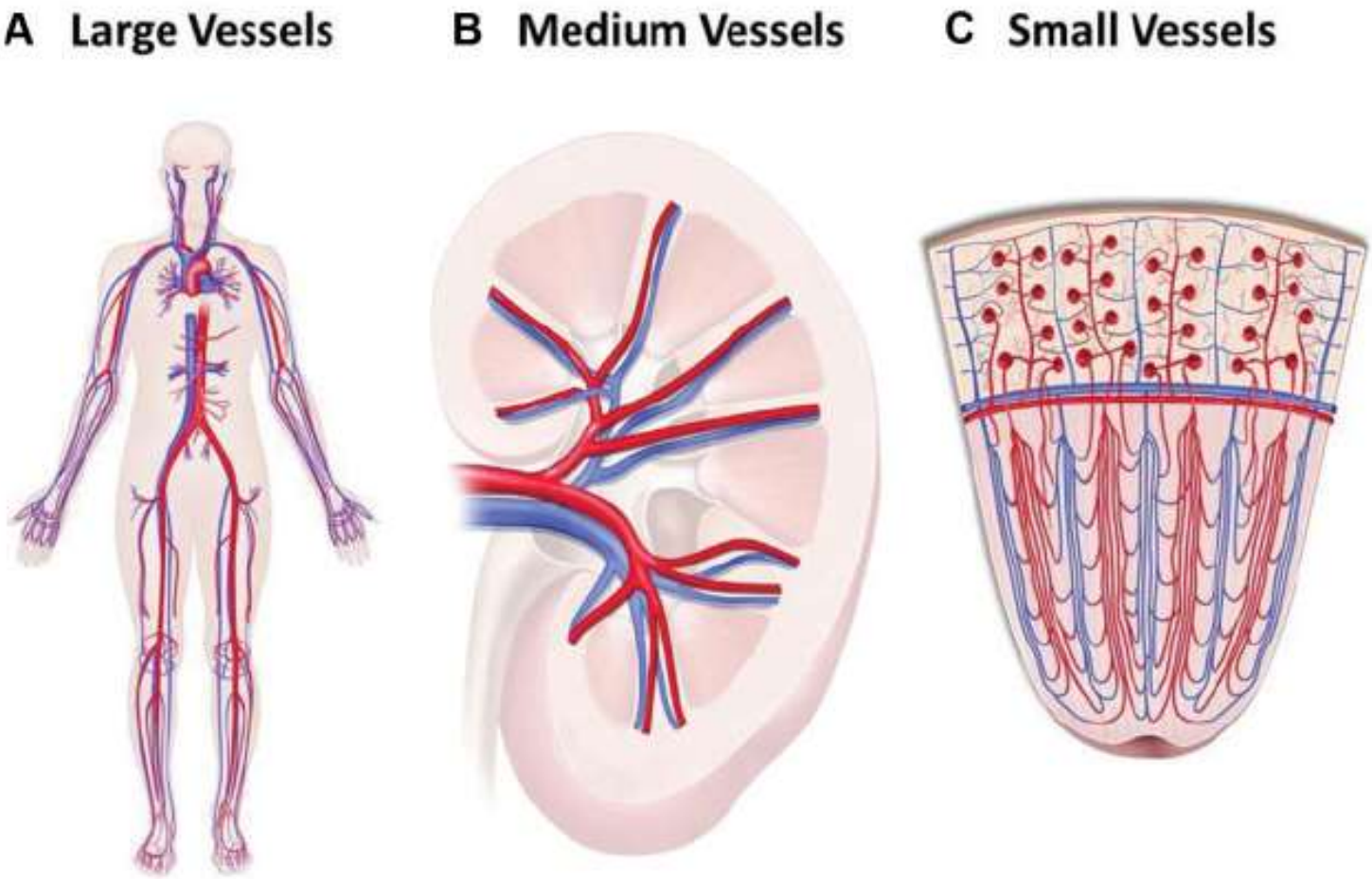

Figure 1. Types of vessels that are defined as large vessels (A), medium vessels (B), and small vessels (C) in the Chapel Hill Consensus Conference nomenclature system. The kidney is used to exemplify medium and small vessels. Large vessels are the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches. Small vessels are intraparenchymal arteries, arterioles, capillaries, venules, and veins.

Jennette JC et al. Arthritis Rheum 2013;65:1-11

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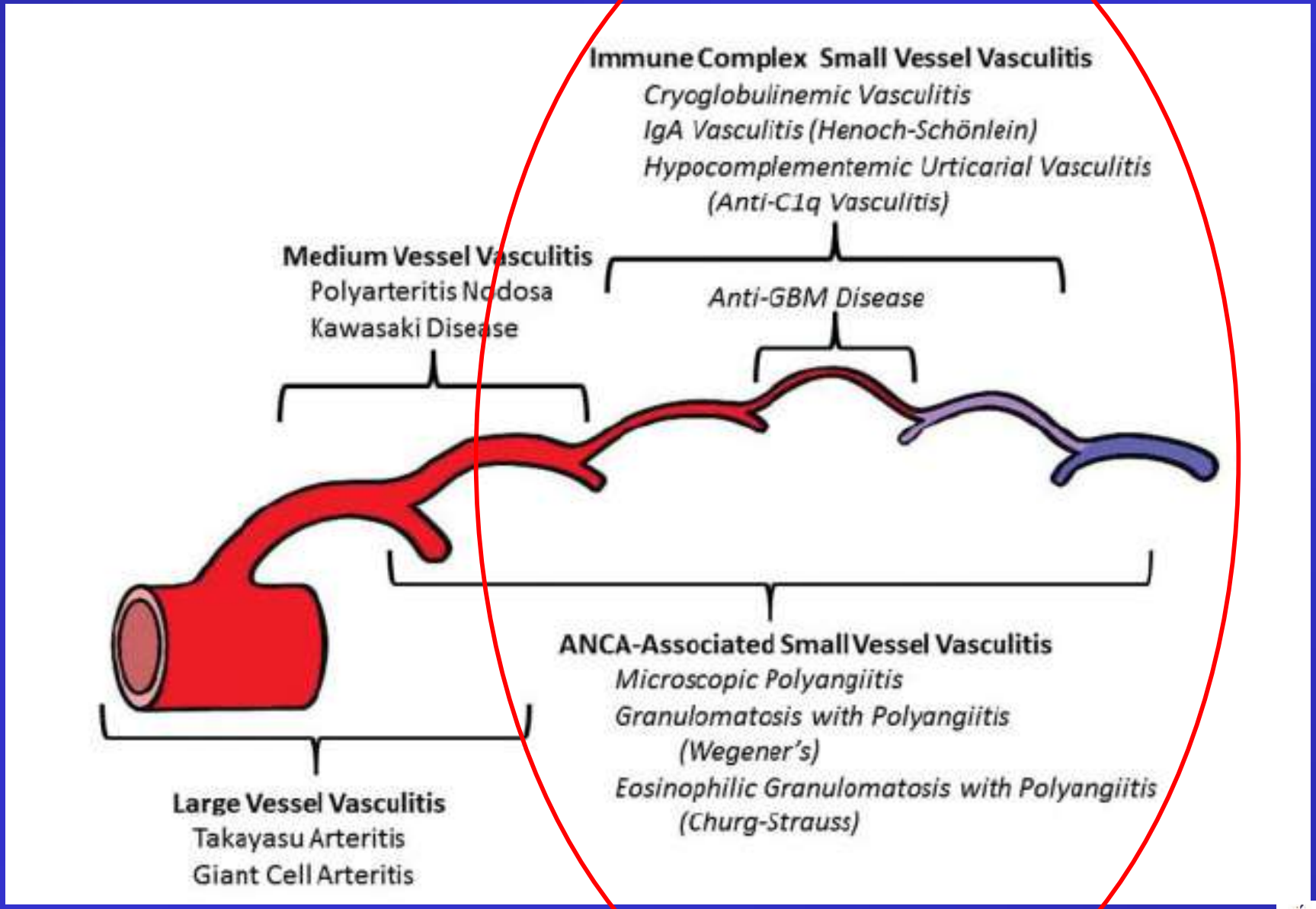


Jennette JC et al. Arthritis Rheum 2013;65:1-11

UMCG

Chapel Hill Consensus Conference (1993/2012)

Table 1
Nomenclature of the Systemic Vasculitides defined during the 2012 International Chapel Hill Consensus Conference [1].

Systemic Vasculitides
Small-vessel vasculitis (SVV)
Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (Wegener's) (GPA)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA)
Immune complex SVV
Anti-glomerular basement membrane (anti-GBM) disease
Cryoglobulinaemic vasculitis (CV)
IgA vasculitis (Henoch–Schonlein) (IgAV)
Hypocomplementaemic 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's disease (BD)
Cogan's syndrome (CS)

Watts RA, et al. Best Pract Res Clin Rheumatol 2018;32:3-20

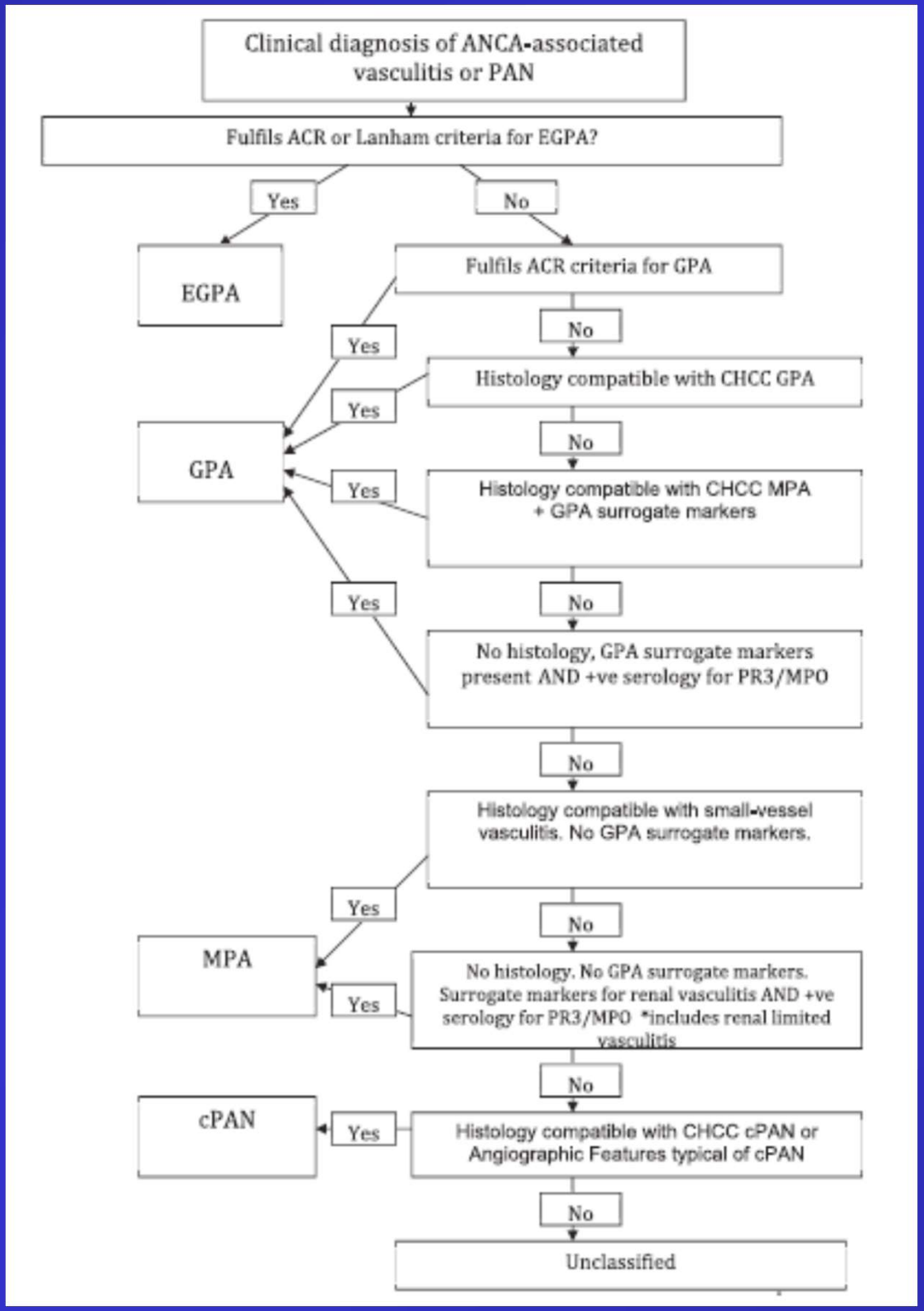
Classification of small vessel vasculitis based on clinical manifesttations

TABLE 4. APPROXIMATE FREQUENCY OF ORGAN-SYSTEM MANIFESTATIONS IN SEVERAL FORMS OF SMALL-VESSEL VASCULITIS.*

ORGAN SYSTEM	HENOCH–SCHÖNLEIN PURPURA	CRYOGLOBULINEMIC VASCULITIS	MICROSCOPIC POLYANGIITIS	WEGENER'S GRANULOMATOSIS	CHURG–STRAUSS SYNDROME
			percent		
Cutaneous	90	90	40	40	60
Renal	50	55	90	80	45
Pulmonary	<5	<5	50	90	70
Ear, nose, and throat	<5	<5	35	90	50
Musculoskeletal	75	70	60	60	50
Neurologic	10	40	30	50	70
Gastrointestinal	60	30	50	50	50

*Approximate frequencies are estimated from data in previous reports.[49-65]

Jennette JC et al. N Engl J Med 1997;337:1512-1522



Watts RA, et al.
Ann Rheum Dis 2007;66:222-7.

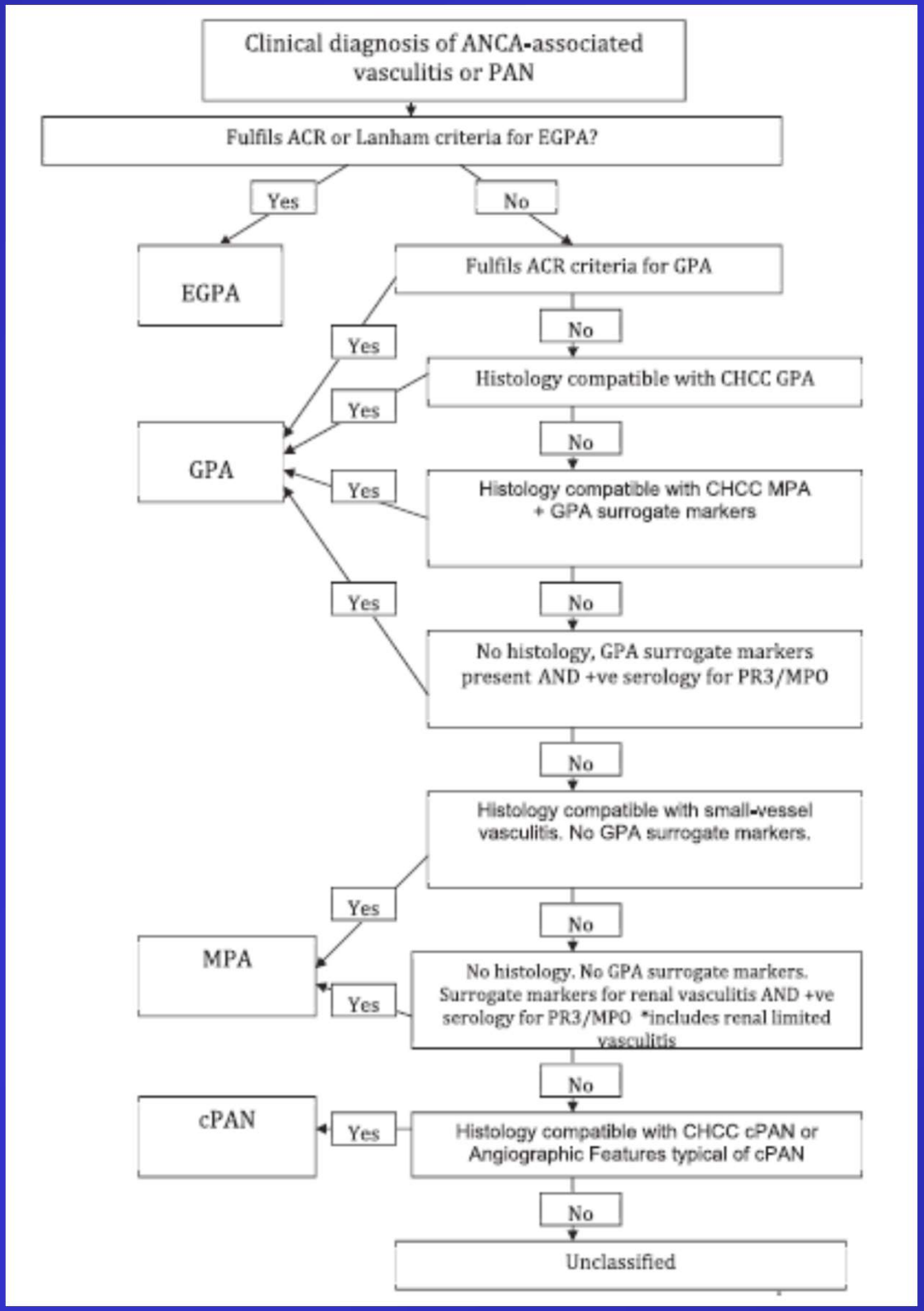
ACR 1990 classification criteria for GPA

Classified as GPA ≥ 2 of criteria present

- Nasal or oral inflammation
- Abnormal chest radiograph
- Microhematuria / red cell casts in urinary sediment
- Granulomatous inflammation on biopsy
- Hemoptysis*

* used as surrogate if biopsy data are unavailable

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



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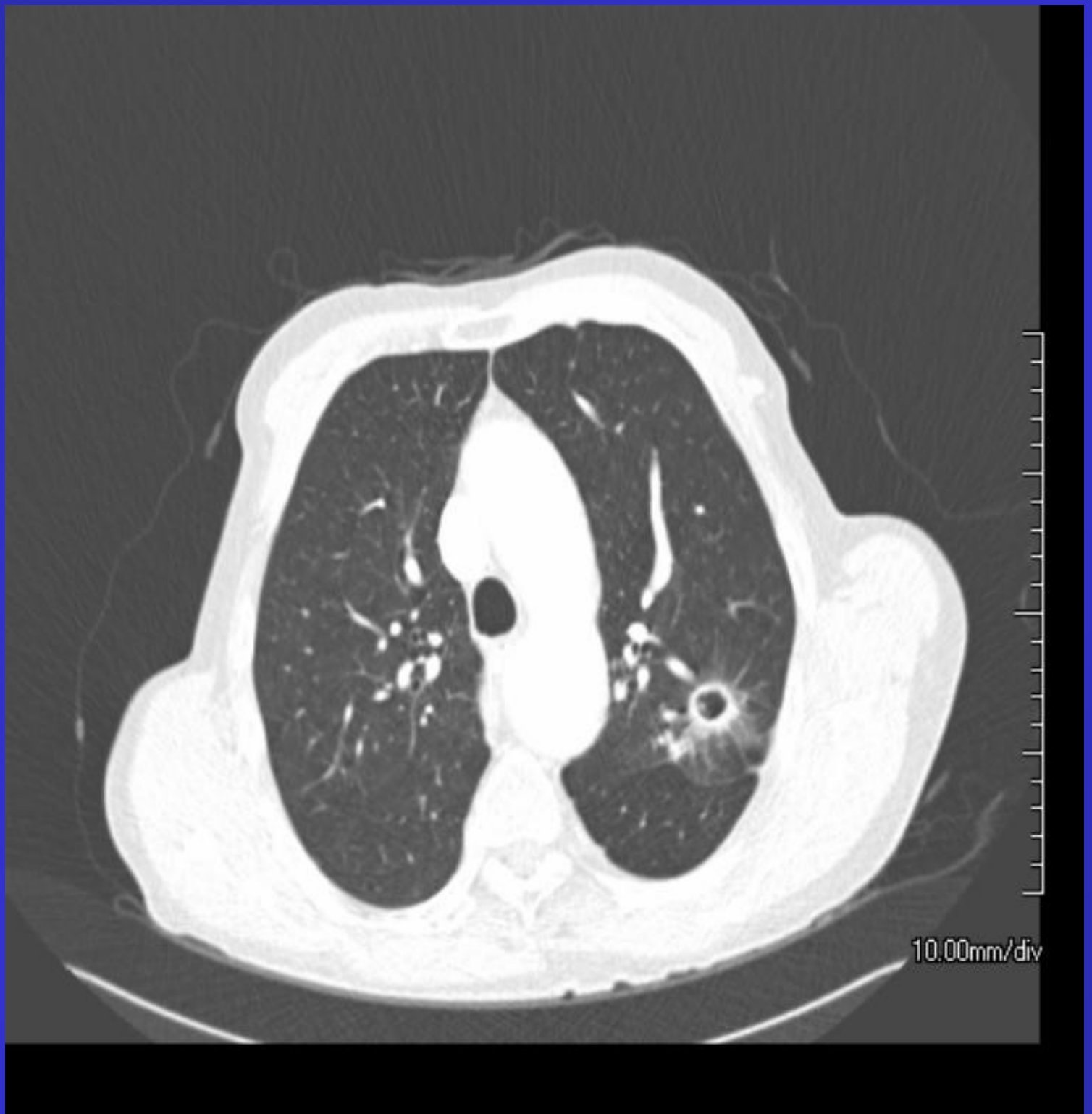
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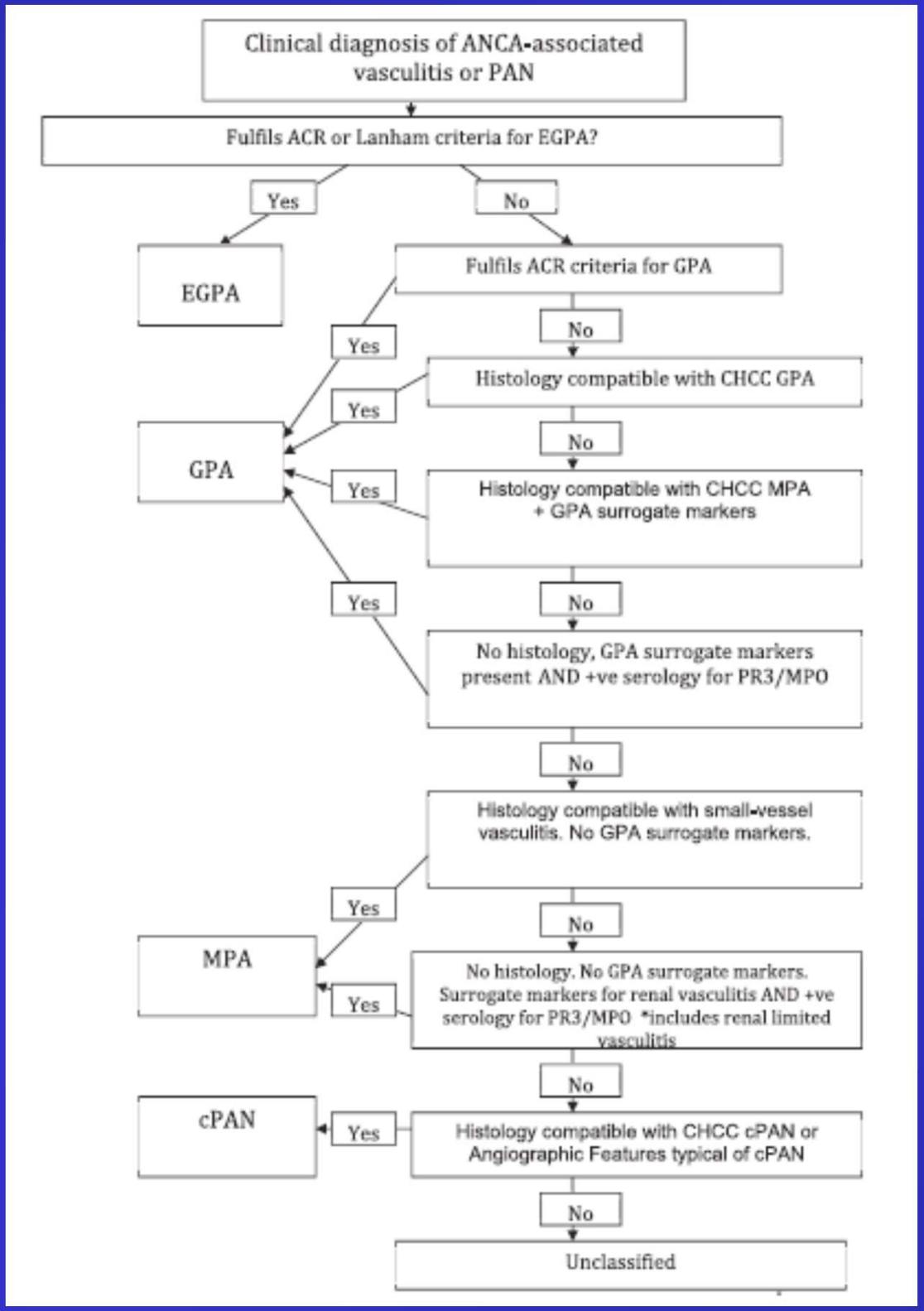

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Does distinction between GPA and MPA matter?

- Guidelines: diagnosis discussed, but treatment and follow up is not different

- Induction treatment intensity based on disease extent/severity

- Is outcome different?
  - recovery of organ function
  - relapse risk

Table 1. Clinical characteristics at baseline of 273 patients with ANCA-associated vasculitis: Differences between patients without and with renal involvement

Characteristic	Patients without Renal Involvement	Patients with Renal Involvement	*P* Value
Number	61	212	
Age (yr)	52±14	58±16	0.01[a]
Sex	32	126	0.94
Diagnosis			
Granulomatosis with polyangiitis	55	132	<0.001[a]
Microscopic polyangiitis	6	52	0.01[a]
Renal limited vasculitis	0	28	
Comorbidity			
Hypertension	1	4	0.90
Diabetes mellitus	1	15	0.11
Cardiovascular disease	6	20	0.34
Autoimmune diseases[b]	1	9	0.34
Malignancy	4	15	0.89
Ear, nose, and throat	52	124	<0.001[a]
Pulmonary	26	40	<0.001[a]
Birmingham Vasculitis Activity Score	13 (7–27)	23 (7–48)	<0.001[a]
Creatinine (mg/dl)	0.94±0.20	3.63±3.42	<0.001[a]
C-reactive protein	7.6±8.3	10.8±9.0	0.001[a]
Proteinuria (g/24 h)	0.09	1.7	<0.001[a]
Renal replacement therapy	0	49[c]	
Plasmapheresis	0	48	

Data are presented as the number, mean ± SD, or median (range).

a Statistically significant.

b Concomitant autoimmune diseases included Crohn's disease (n=1) in patients without renal involvement, and Sjögren's syndrome (n=1), sarcoidosis (n=1), psoriasis (n=1), hypothyroidism (n=4), and hyperthyroidism (n=2) in patients with renal involvement.

c There were 48 PR3-ANCA–positive and MPO-ANCA–positive patients, and 1 PR3-ANCA–negative and MPO-ANCA–negative patient.

de Joode AAE, et al. Clin J Am Soc Nephrol 2013;8(10):1709-17.

Table 2. Clinical characteristics at baseline of 212 AAV patients with renal involvement: differences between PR3-ANCA–positive patients, MPO-ANCA–positive patients, and PR3-ANCA–negative and MPO-ANCA–negative patients (statistical analysis for PR3 versus MPO)

Characteristic	PR3	MPO	*P* Value	ANCA Negative
Number	138	65		9
Age (mean)	56±16	61±15	0.02[a]	60±15
Sex	91	31	0.01[a]	4
Comorbidity				
Hypertension	3	0	0.23	1
Diabetes mellitus	8	7	0.21	0
Cardiovascular disease	10	8	0.24	2
Autoimmune diseases[b]	3	5	0.06	1
Malignancy	12	2	0.14	1
Diagnosis				
Granulomatosis with polyangiitis	122	7		3
Microscopic polyangiitis	13	38		1
Renal limited vasculitis	3	20		5
Ear, nose, and throat	106	15	<0.001[a]	3
Pulmonary	31	8	0.08	1
Birmingham Vasculitis Activity Score	26 (7–48)	18 (10–32)	<0.001[a]	18 (12–25)
Creatinine (mg/dl)	(3.04±2.84)	4.82±4.22	<0.001[a]	3.54±2.75
C-reactive protein	13±9.5	7.2±6.5	<0.001[a]	4.3± 4.2
Proteinuria (g/24 h)	1.6	2.4	0.004[a]	1.4
Renal replacement therapy	28	20	0.10	1
Plasmapheresis	33	15	0.90	0

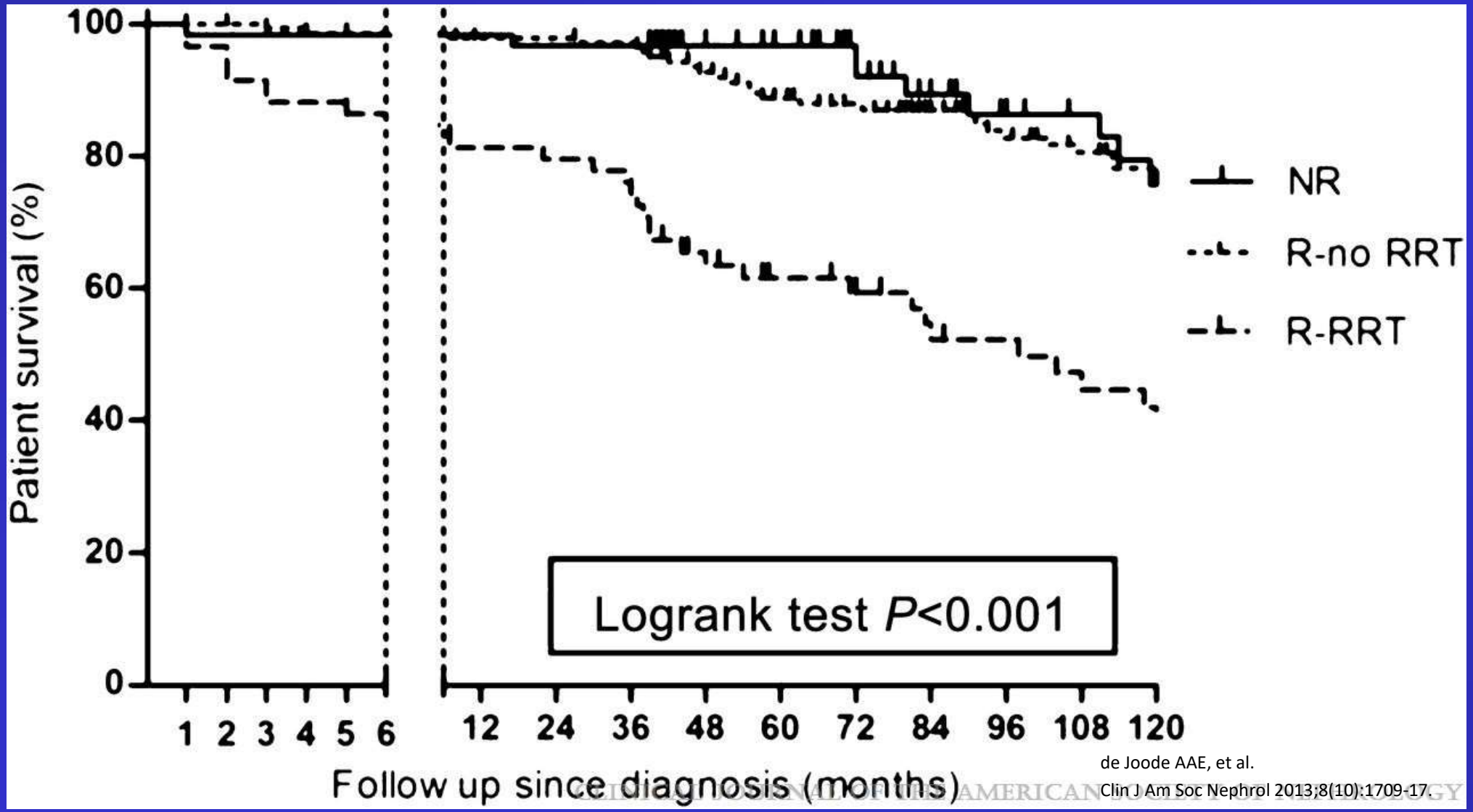
Data are presented as the number, mean ± SD, or median (range). PR3, proteinase 3; MPO, myeloperoxidase; AAV, ANCA-associated vasculitis.

a Statistically significant.

b Concomitant autoimmune diseases included hypothyroidism (n=2) and psoriasis (n=1) in PR3-ANCA–positive patients; hypothyroidism (n=2), hyperthyroidism (n=1), sarcoidosis (n=1), and Sjögren's syndrome (n=1) in MPO-ANCA–positive patients; and hyperthyroidism (n=1) in ANCA–negative patients.

de Joode AAE, et al. Clin J Am Soc Nephrol 2013;8(10):1709-17.

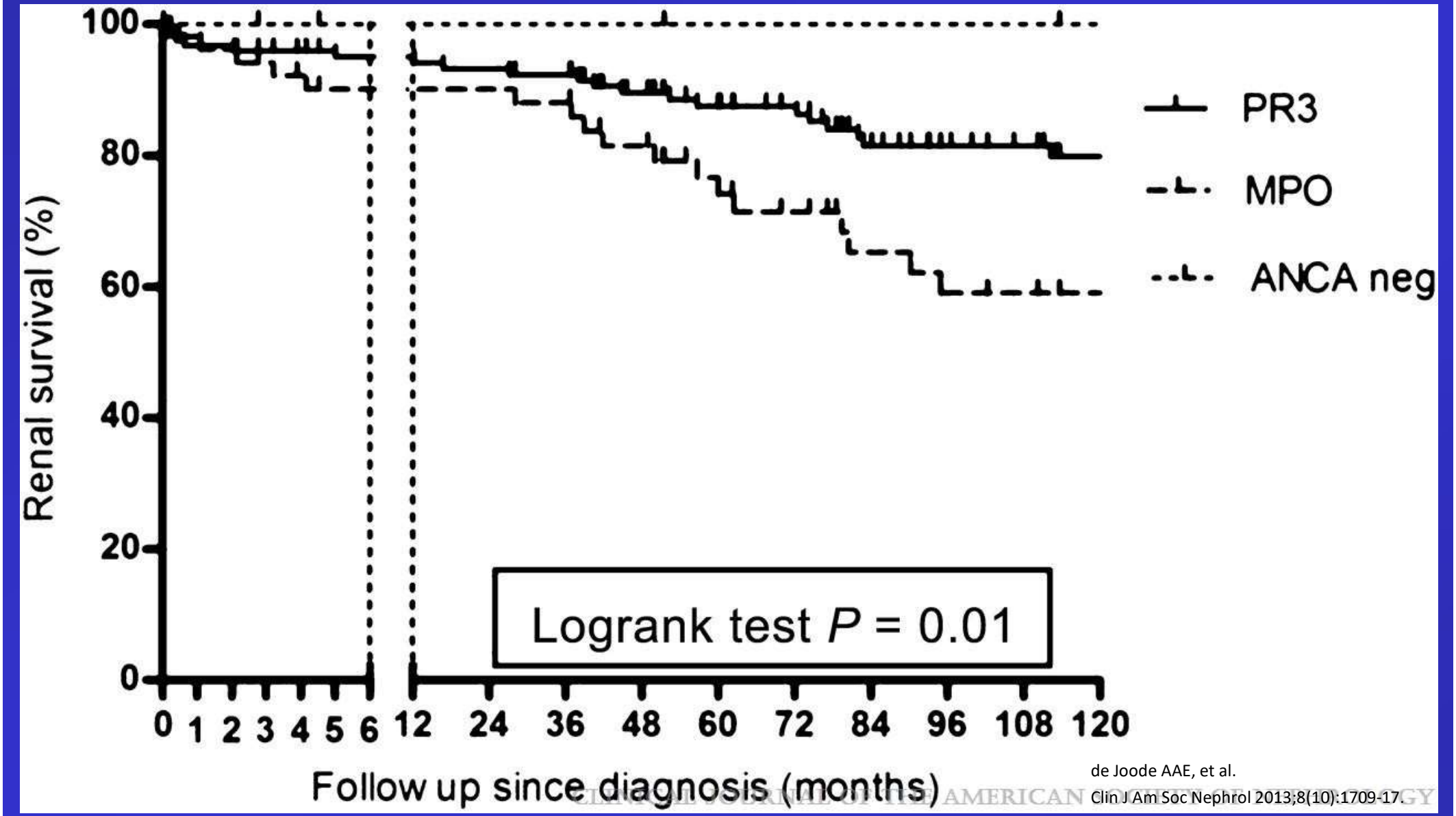
AAV Cohort 1990 -2007 (n = 273)



de Joode AAE, et al.
Clin J Am Soc Nephrol 2013;8(10):1709-17.

Patient survival in ANCA-associated vasculitis without renal involvement compared with patients with renal involvement and renal replacement therapy and patients with renal involvement without renal replacement therapy. NR, nonrenal; R-RRT, renal involvement and renal replacement therapy; R-no RRT, renal involvement without renal replacement therapy.

AAV Cohort 1990 -2007 (n = 273)



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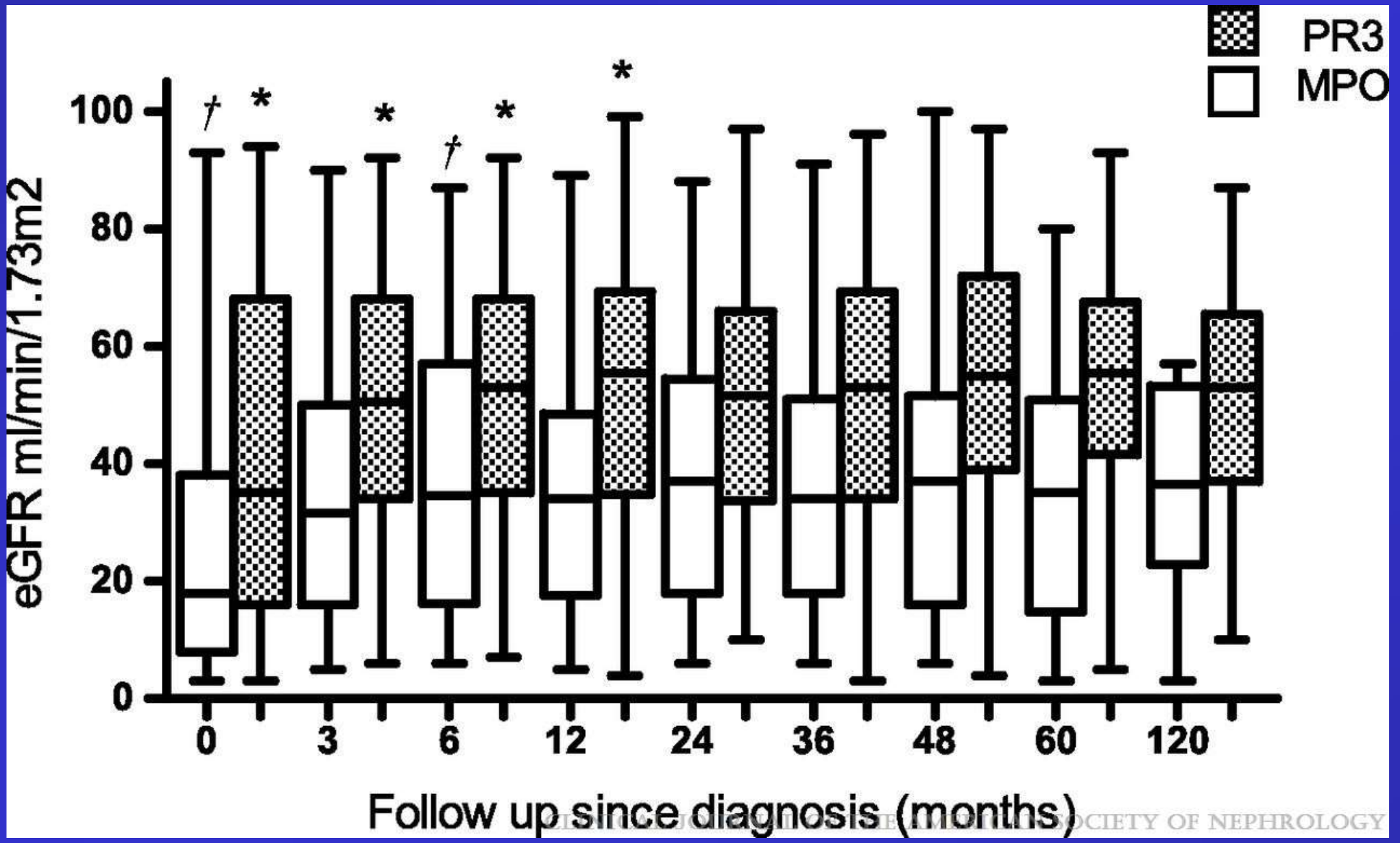
Differences in patient survival in PR3-ANCA–positive patients, MPO-ANCA–positive patients, and ANCA-negative patients (statistical analysis for PR3 versus MPO). PR3, proteinase 3; MPO, myeloperoxidase; neg, negative.

AAV Cohort 1990 -2007 (renal involvement n = 212



Differences in patient survival in PR3-ANCA–positive patients, MPO-ANCA–positive patients, and ANCA-negative patients (statistical analysis for PR3 versus MPO). PR3, proteinase 3; MPO, myeloperoxidase; neg, negative.

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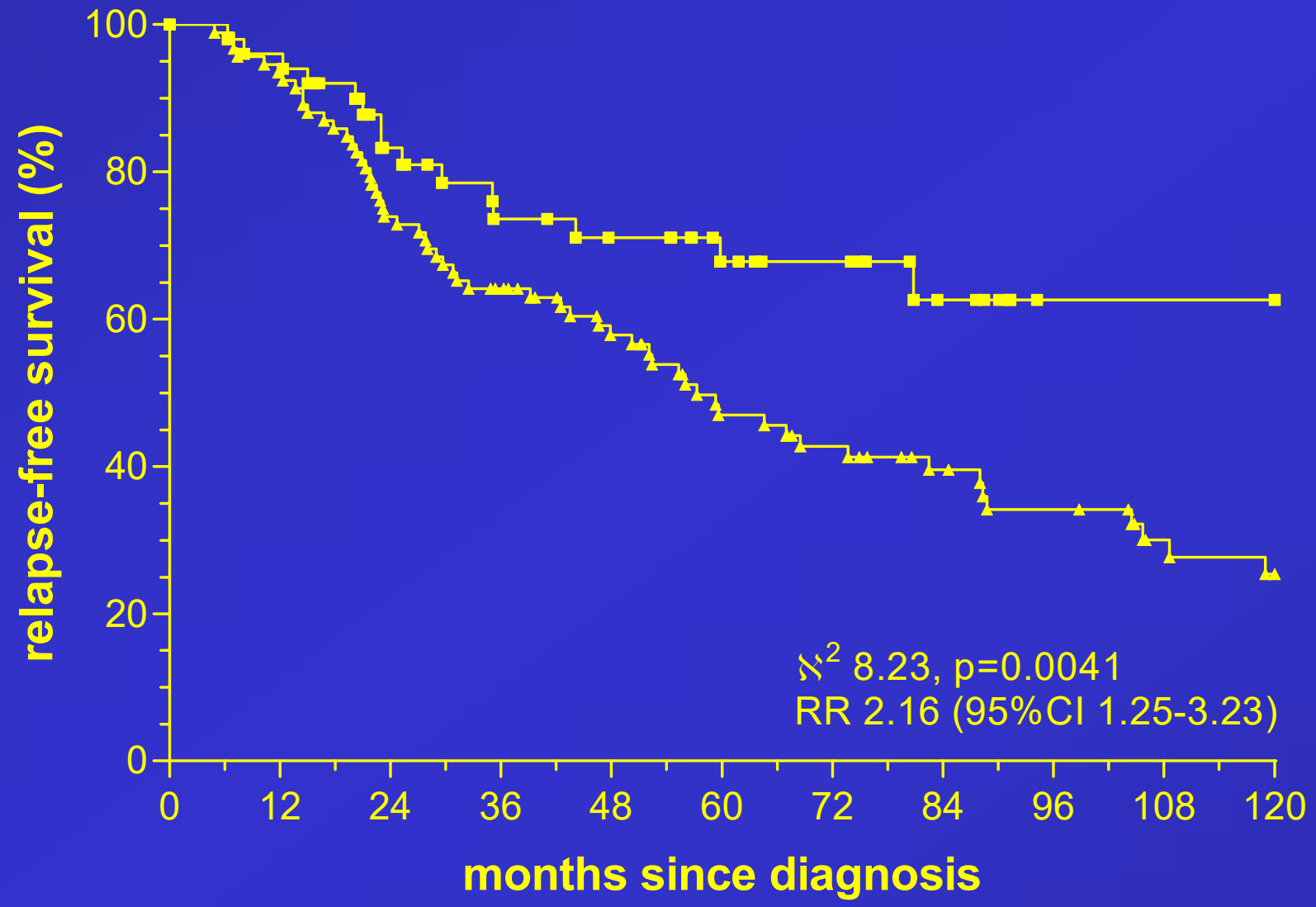
Figure 1


relapse-free survival (%)
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
108
120
months since diagnosis
χ^2 8.23, p=0.0041
RR 2.16 (95%CI 1.25-3.23)
MPO-ANCA positive patients (n=65)
PR3-ANCA positive patients (n=138)

Relapse risk according to ANCA specificity

	Relapse-free survival at month		
	24	60	120
PR3-ANCA (138)	76%	43%	27%
MPO-ANCA (65)	91%	81%	65%

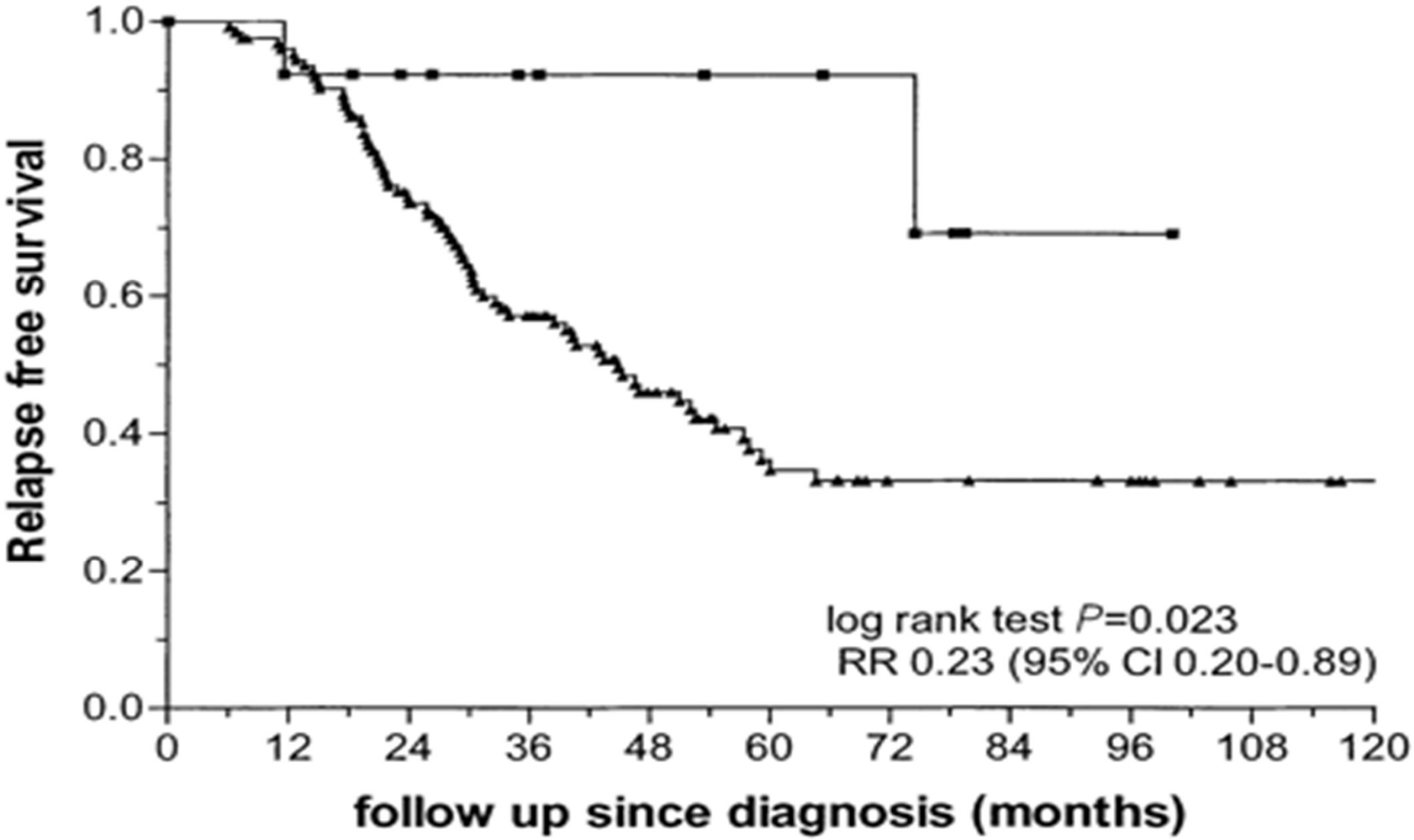


Fig. 1. Relapse-free survival during follow up according to ANCA antigenic specificity for PR3 (PR3-ANCA) and MPO (MPOANCA),respectively, in patients diagnosed with WG at the University Hospital Groningen between 1990 and 2000 (ns137).
Squares, WG MPO-ANCA (ns13); triangles, WG PR3-ANCA (ns124).

Nephrol Dial Transplant, Volume 17, Issue 12, December 2002, Pages 2077–2080, https://doi.org/10.1093/ndt/17.12.2077

PR3-ANCA and MPO-ANCA AAV differ in:

- number of organ(systems) involved
- severity of organ involvement
- response to therapy
- relapse during follow up
- genetic background / associations

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- number of organ(systems) involved
- severity of organ involvement
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- relapse during follow up
- genetic background / associations

None of these differences is influenced / mitigated by

inclusion of the clinical syndrome

Formulation of the AAV diagnosis in an individual patient

- do not use GPA or MPA, but instead …

- describe ANCA-type, organ involvement and response to therapy

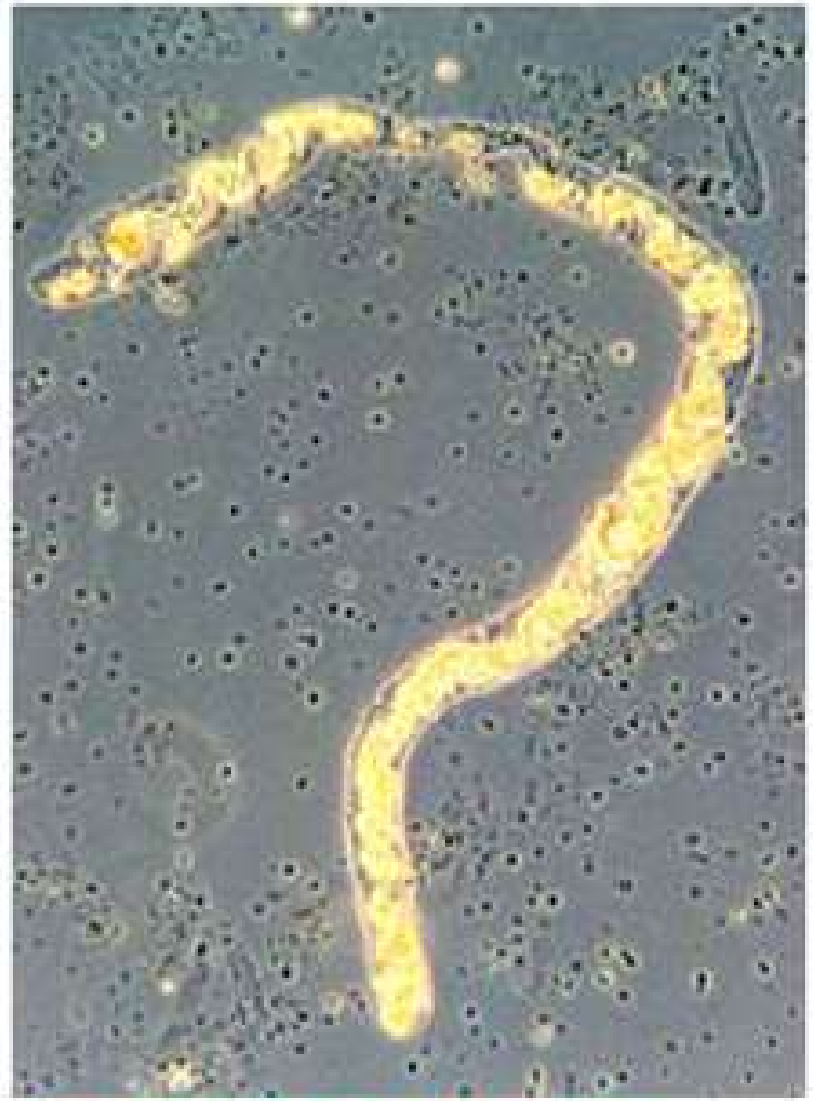
"A 49-year old male with PR3-ANCA associated vasculitis with ENT involvement (sinusitis, ulceration), pulmonary nodules and glomerulonephritis with moderate renal failure (creatinine max. 212 µmol/L).
Good response to therapy with cyclophosphamide and prednisolon with full remission and improvement of renal function (current creatinine 107 µmol/L)"

Take to work messages:

- Serotype is superior to phenotype/syndrome in AAV
    - aspects of the phenotype follow the serotype
    - gives better information
    - improves prediction(s)
    - EGPA is the exception to this rule
- Importance of histology is overrated (dangerously)
    - role in seronegative AAV

Future goals:

- Improve the diagnositic description of an individual patient
- We have to improve our individualisation of disease management
    - therapy (esp. maintenance)
    - follow up



QUESTION MARKS....