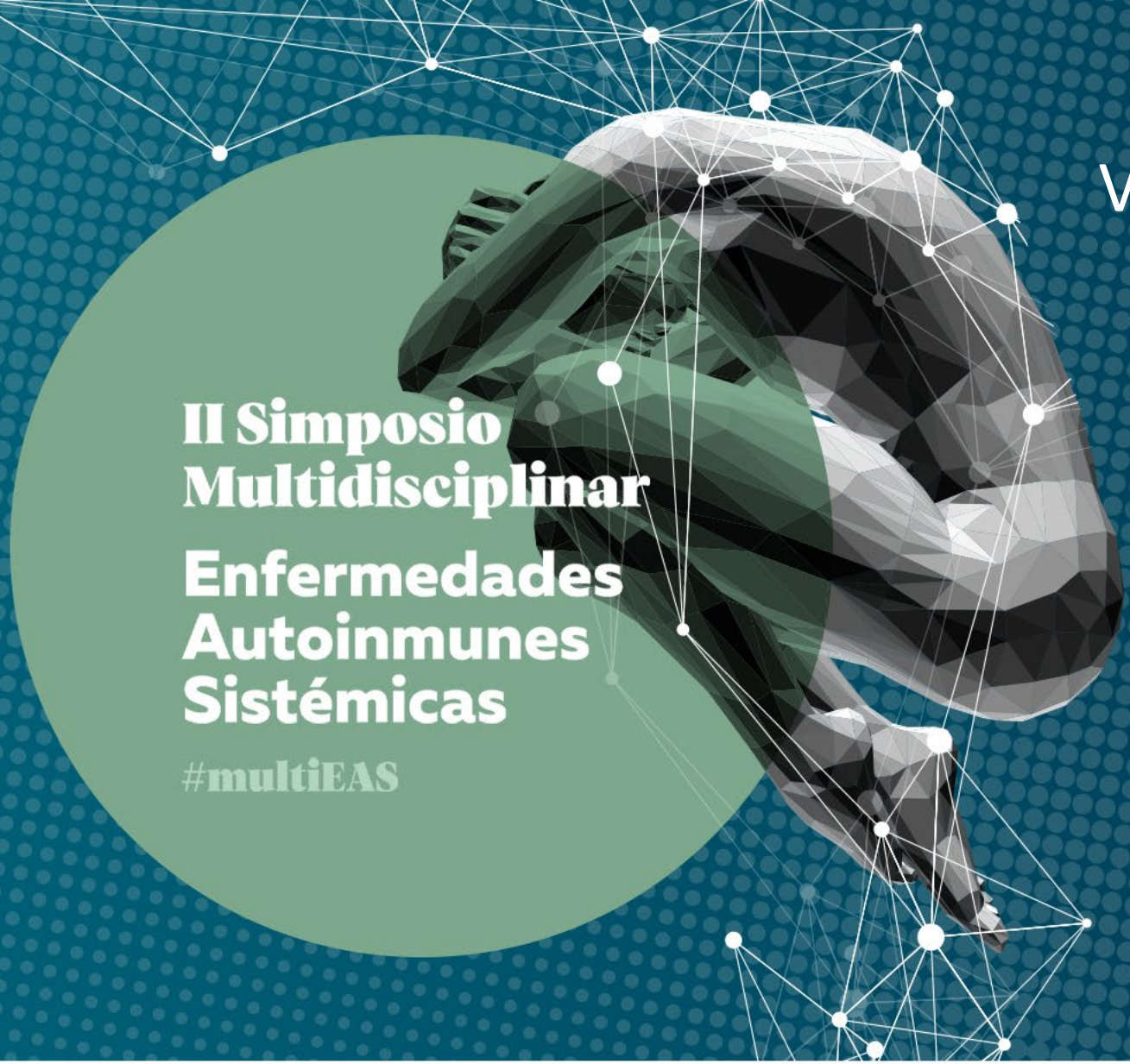
Vasculitis ANCA negativo.



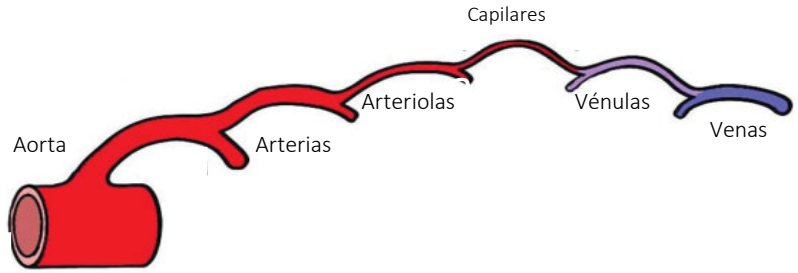
Madrid
20-21 enero 2023
NH COLLECTION EUROBUILDING

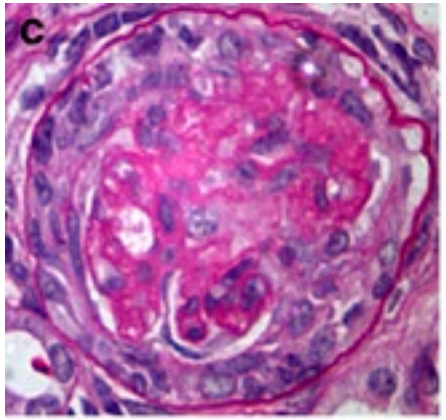
Javier Villacorta
Nefrología.
Hospital Ramón y Cajal.

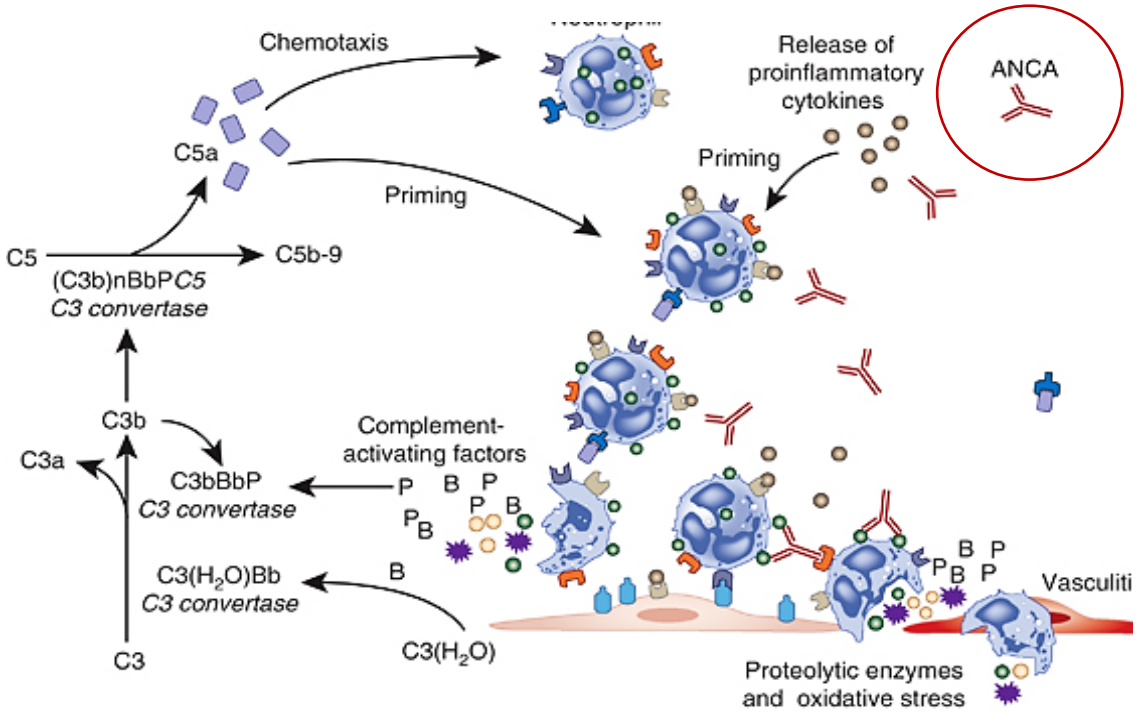
AEDV Academia Española de Dermatología y Venereología
SEMI Sociedad Española de Medicina Interna
SEI Sociedad Española de Inmunología
Sociedad Española de Nefrología
Sociedad Española de Neumología y Cirugía Torácica SEPAR
Sociedad Española de Reumatología
SEPD Sociedad Española de Patología Digestiva

VASCULITIS ANCA-NEGATIVO

- Patogenia.
- Características clínicas e histológicas.
- Diagnóstico y Tratamiento.

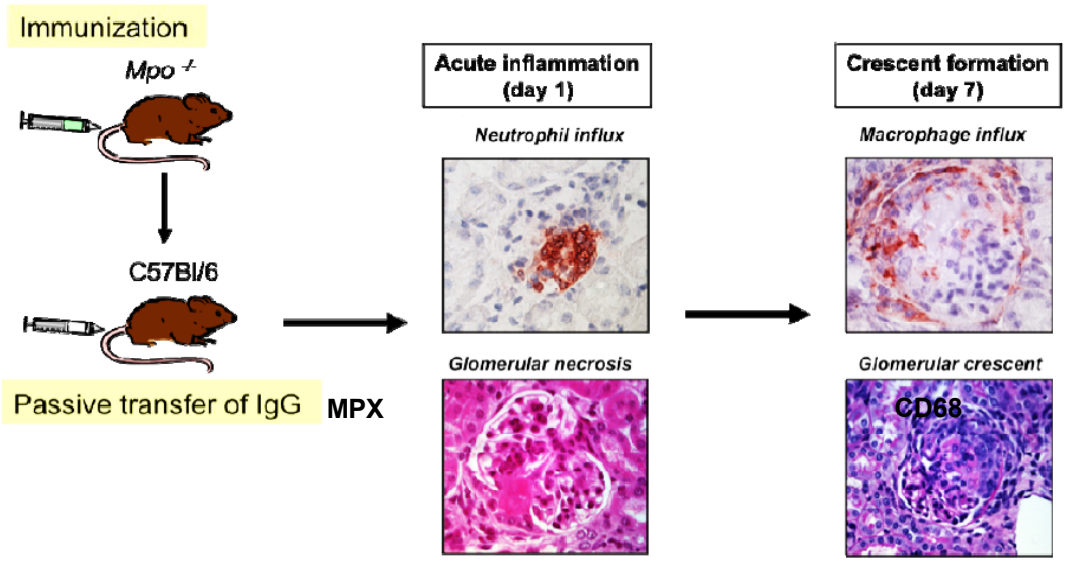




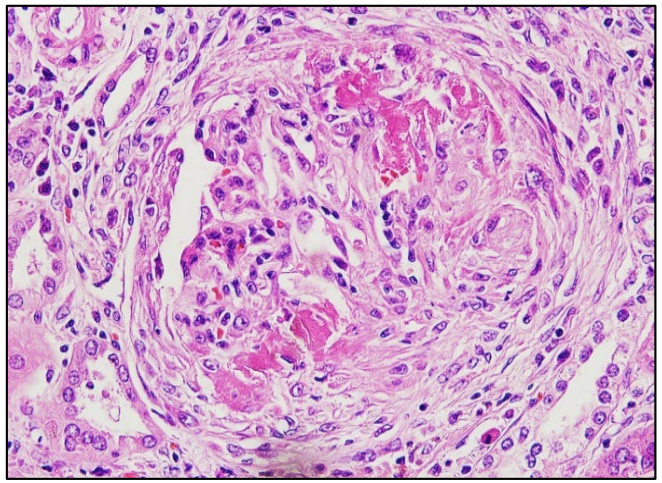


Pathogenesis of ANCA-associated vasculitis.. Cllin Experimen Inmunol 2011;164 1:23-6

Modelo animal de Vasculitis asociada a ANCAs



Xiao H et al. J Clin Invest. 2002 .



Afectación renal: 60-80%

Glomerulonefritis necrotizante con proliferación extracapilar y ausencia de depósito inmunes (pauciinmune)

Vasculitis renal ANCA-negativo.

- **Hipótesis patogénicos:**

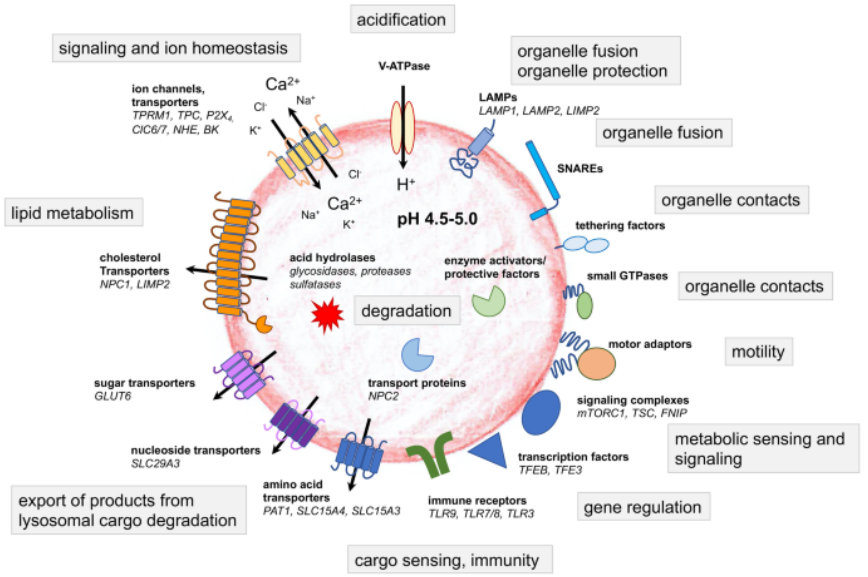
1) Presencia de otros autoanticuerpos:

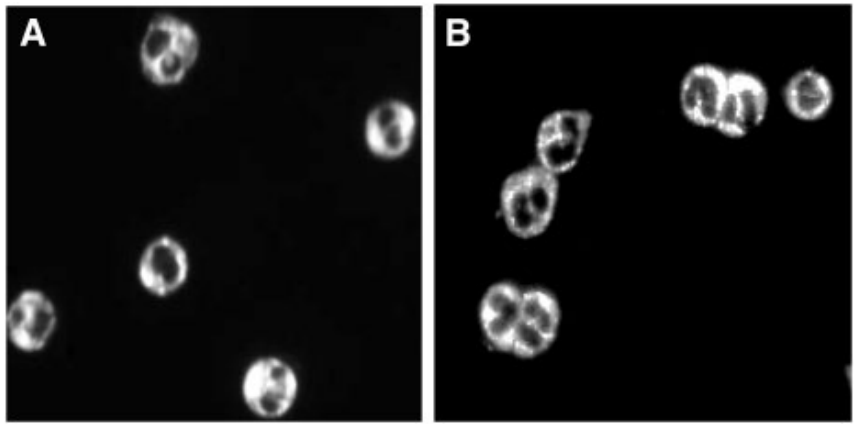
   - Ac frente a la Proteina 2 de membrana lisosomal (h- AcLamp-2**).**
   - Ac anti-plasminógeno.

2) Existen ANCAs en estos sujetos, pero existe una problemática en su detección por la metodología convencional (ELISA/IFI).

Autoantibodies to hLAMP-2 in ANCA-Negative Pauci-Immune Focal Necrotizing

- Presentes en los lisosomas, pero también en la superficie celular de monocitos, neutrófilos y cels endoteliales.
- Se identifican también en las vesículas de MPO/PR3 en el interior de los netrófilos.
- 100% Homologia con adhesina presente en en pared de E Coli.

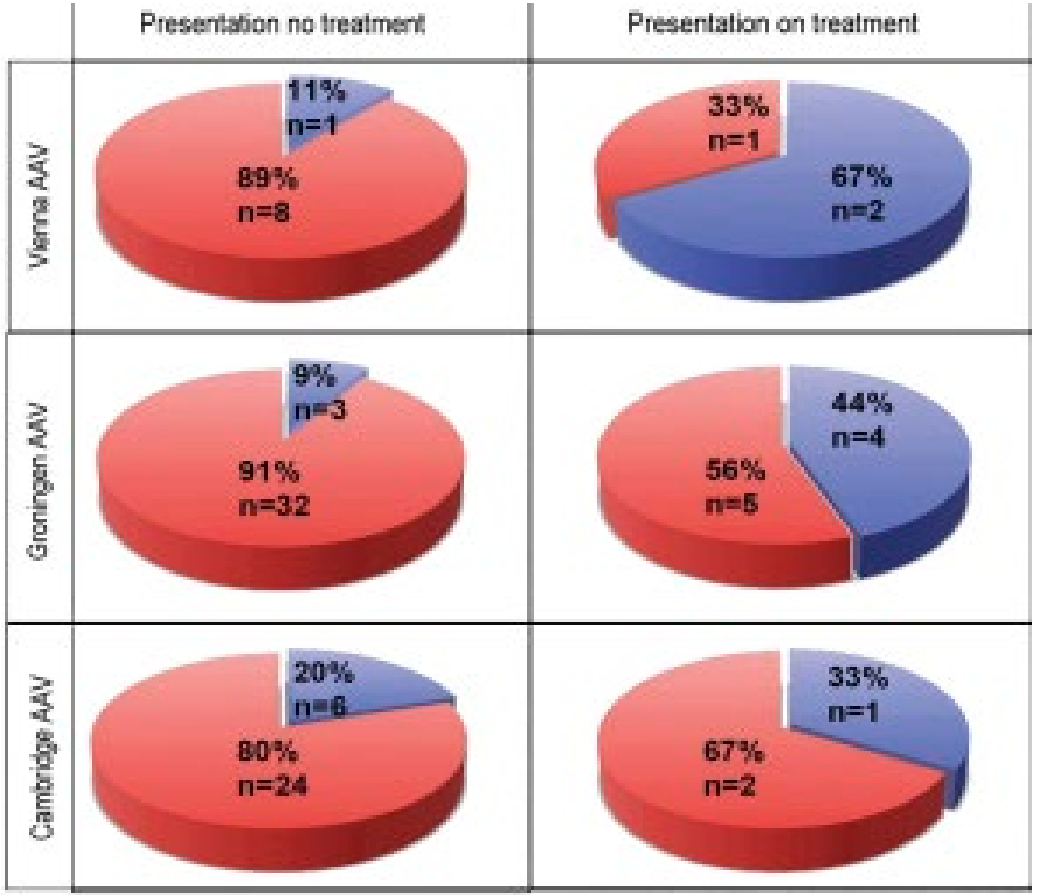




Patrón de Inmunofluorecencia indirecta de Ac AntiLamp2

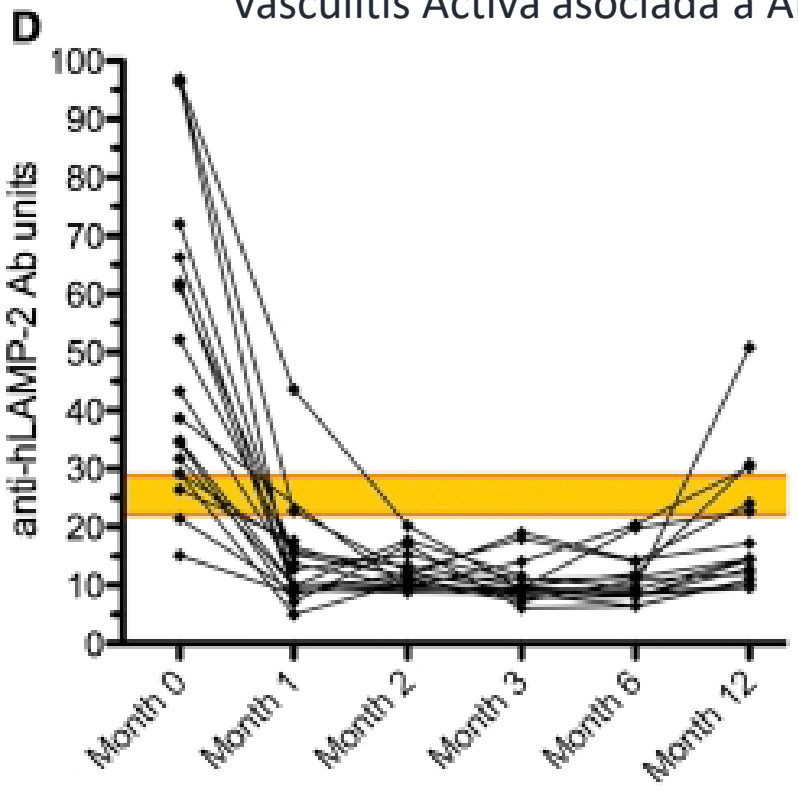
Kain R. J. Exp. Med. 181, 585-597 (1995).

High prevalence of autoantibodies to hlamp-2 in anti-neutrophil cytoplasmic antibody-associated vasculitis



Prevalencia antiLamP2 en Vasculitis Activa asociada a ANCAs

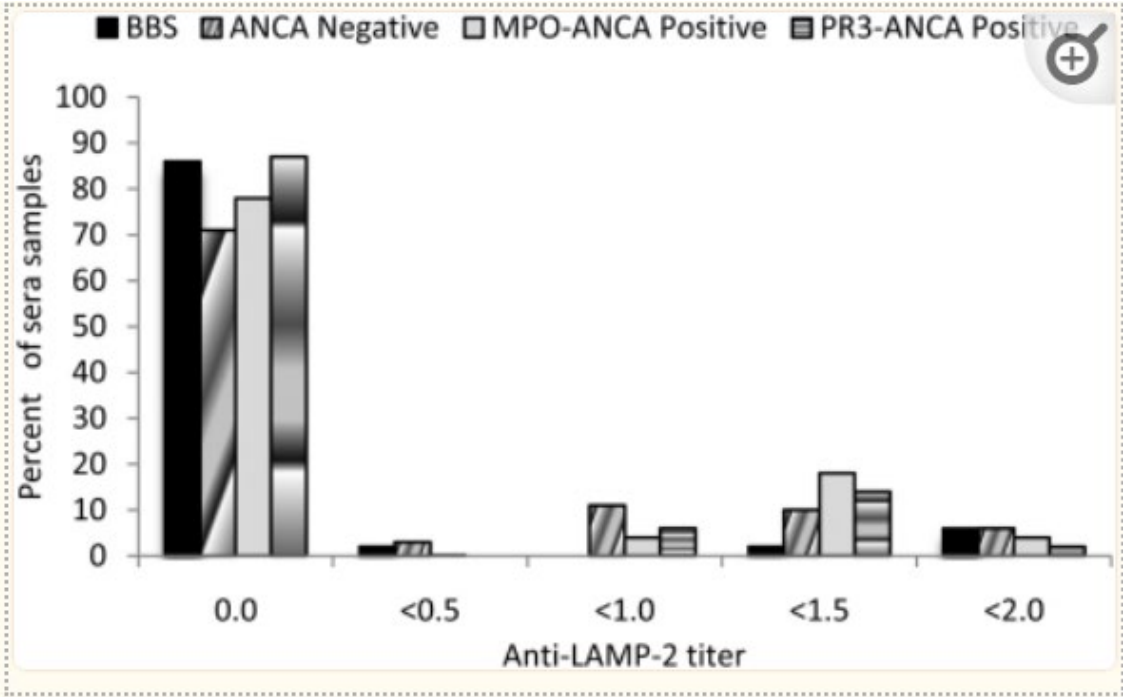
Evolución antiLamp2 en el curso Vasculitis Activa asociada a ANCAs



Kain R. J Am Soc Nephrol 2012;23:556-66

Anti-LAMP-2 antibodies are **not prevalent** in patients with antineutrophil cytoplasmic autoantibody glomerulonephrit

ANCA GN	R-LAMP-2 (glycosylated)	22/103 (21.3)	
	R-LAMP-2 (non-glycosylated)		48/226 (21)
	LAMP-2-peptide	4/101 (3.8%)[e]	
			75/329 (22.8)[d]

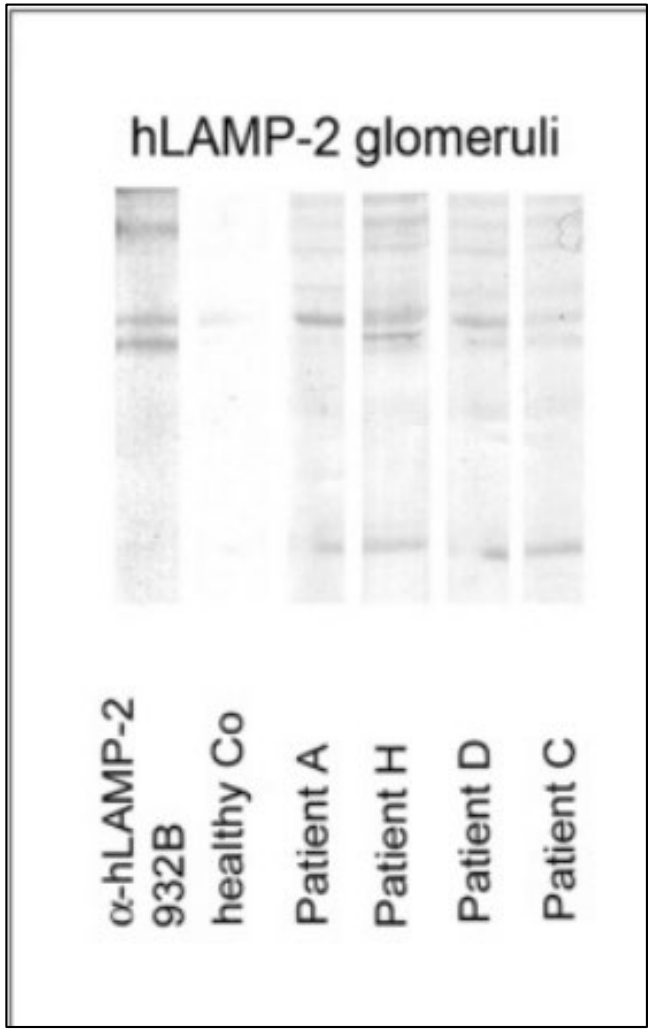


Diferencias atribuidas a; Metodología: Test Diferente
Poblaciones incluidas distintas

J Am Soc Nephrol 2012 Mar; 23(3): 545–555.

Autoantibodies to hLAMP-2 in ANCA-Negative Pauci-Immune Focal Necrotizing

						Anti-hLAMP-2 assay results			Overall
No	Sex/Age	Diagnosis	Organ	ANCA	MPO/PR3	ELISA	Western	IIF IdID/hL-2	Summary
ANCA negative/hLAMP-2 autoantibody positive									
A	F 60	FNGN	K	Neg	Neg	52.54	Pos	Low pos	Pos
B	F 65	FNGN	K/L/S/J	Neg	Neg	34.83	Pos	Pos	Pos
C	F 33	FNGN	K	Neg	Neg	28.55	Pos	Pos	Pos
D	M 33	FNGN	K	Neg	Neg	68.21	Pos	Pos	Pos
E	F 22	FNGN	K/L	Neg	Neg	50.35	Low pos	NA	Pos
F	F 85	FNGN	K	Neg/atyp C	Neg	64.16	Pos	Pos	Pos
G	F 70	FNGN	K	Neg/atyp C	Neg	44.49	NA	Pos	Pos
H	F 17	FNGN	K	Neg/atyp C	Neg	53.76	Pos	Pos	Pos
ANCA/hLAMP-2 negative									
I	M 29	FNGN	K	Neg	Neg	13.11	Neg	Neg	Neg
J	F 73	FNGN	K	Neg	Neg	6.88	Neg	NA	Neg
K	M 59	FNGN	K	Neg	Neg	193.18	Neg	Neg	Neg



J Am Sol Nephrol 2014 Mar; 25(3): 455–463

Vasculitis renal ANCA-negativo.

- **Hipótesis patogénicos:**

1) Presencia de otros autoanticuerpos:

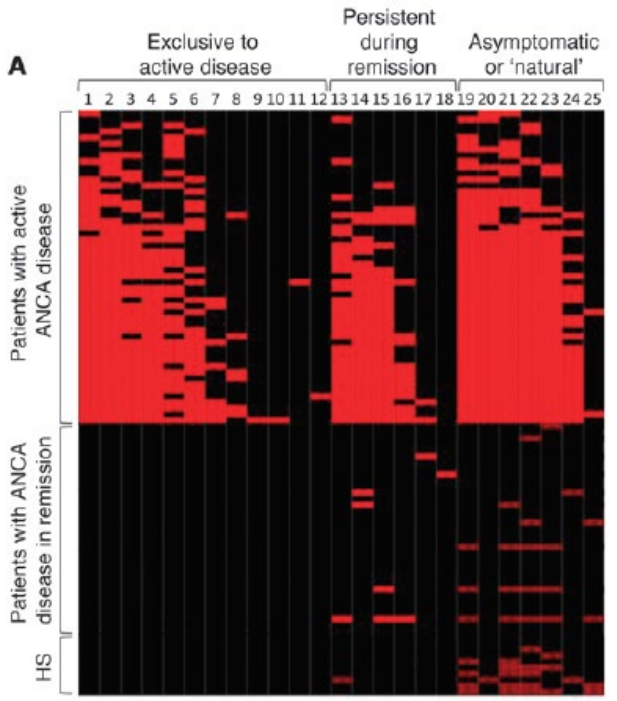
- Ac frente a la Proteina 2 de membrana lisosomal (h- AcLamp-2**).**
- Ac antiplasminógeno.

2) Existen ANCAs en estos sujetos, pero existe una problemática en su detección por la metodología convencional (ELISA/IFI).

Epitope specificity determines pathogenicity and Detectability in ANCA-associated vasculitis

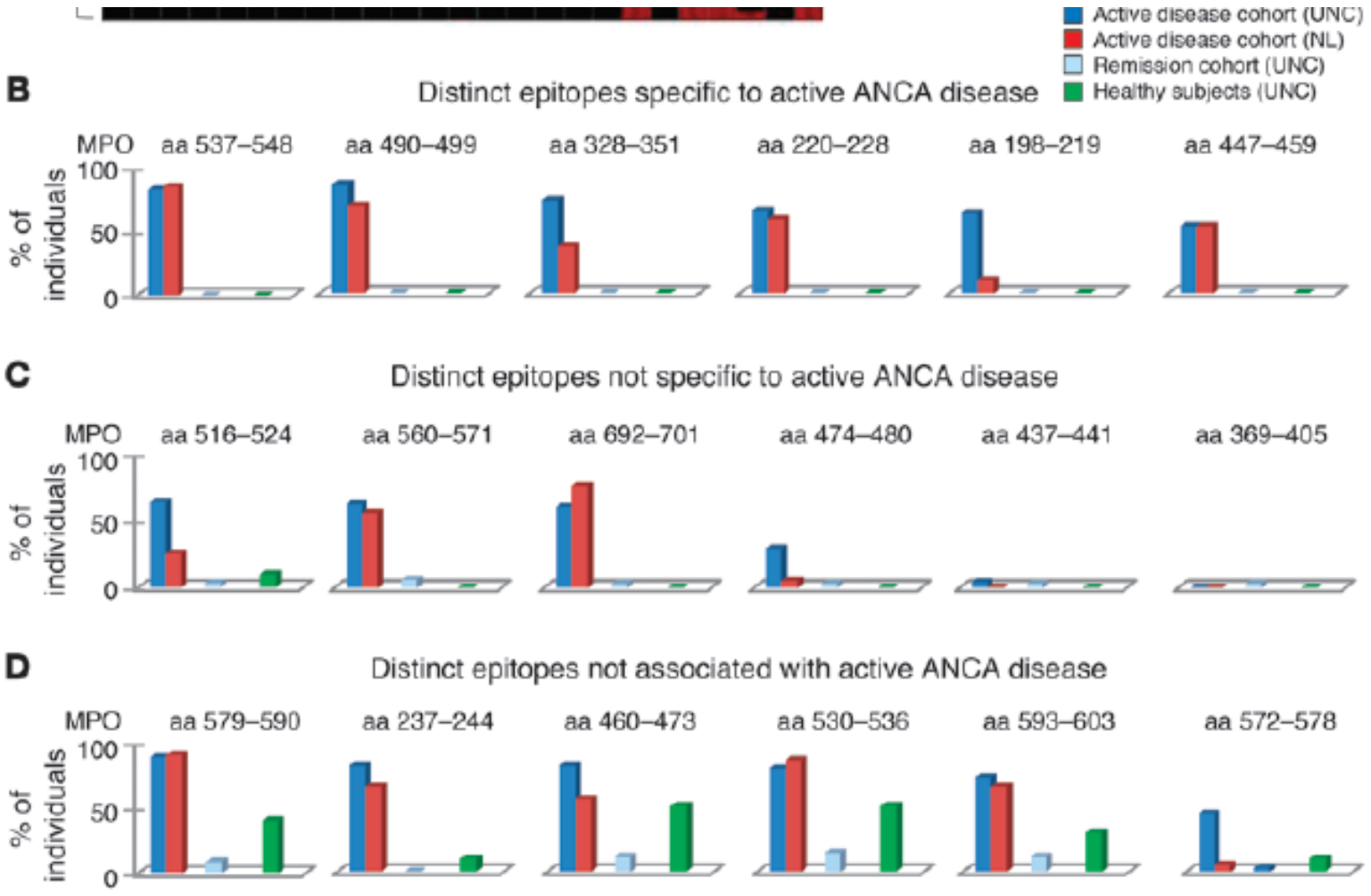
Cohorte de pacientes a estudio

	MPO-ANCA cohort (CH)	MPO-ANCA cohort (NL)	ANCA-negative cohort (CH)	ANCA-negative cohort (NL)	Healthy volunteers (CH)	Healthy volunteers (NL)
Median age (range)	59.0 (19–83)	66.0 (41–78)	44.0 (12–72)	60.7 (17–69)	27.5 (20–53)	35.0 (25–59)
Sex						
Male	48.9% (22/45)	50.0% (10/20)	20.0% (2/10)	38.5% (5/13)	40.0% (4/10)	55.6% (5/9)
Female	51.1% (23/45)	50.0% (10/20)	80.0% (8/10)	61.5% (8/13)	60.0% (6/10)	44.4% (4/9)
Race						
Asian	0.0% (0/45)	0/0% (0/20)	0.0% (0/10)	0.0% (0/13)	0.0% (0/10)	0.0% (0/9)
African American	13.3% (6/45)	0.0% (0/20)	10.0% (1/10)	0.0% (0/13)	10.0% (1/10)	0.0% (0/9)
Hispanic	4.4% (2/45)	0.0% (0/20)	0% (0/10)	0.0% (0/13)	0.0% (0/10)	0.0% (0/9)
Mixed European	80.3% (36/45)	95.0% (19/20)	80.0% (8/10)	100.0% (13/13)	70.0% (7/10)	100% (9/9)
Other	1.5% (1/45)	5.0% (1/20)	10.0% (1/10)	0.0% (0/13)	20.0% (2/10)	0.0% (0/9)
Diagnosis						
MPA	37.8% (17/45)	45.0% (9/20)	30.0% (3/10)	0.0% (0/13)	–	–
Renal limited	31.1% (14/45)	40.0% (8/20)	0.0% (0/10)	38.5% (5/13)	–	–
GPA	22.2% (10/45)	15.0% (3/20)	60.0% (6/10)	61.5% (8/13)	–	–
Churg-Strauss	6.7% (3/45)	0.0% (0/20)	0.0% (0/10)	0.0% (0/13)	–	–
Autoimmune overlap	2.2% (1/45)	0.0% (0/20)	0.0% (0/10)	0.0% (0/13)	–	–
Unknown	0.0% (0/45)	0.0% (0/20)	10.0% (1/10)	0.0% (0/13)	–	–



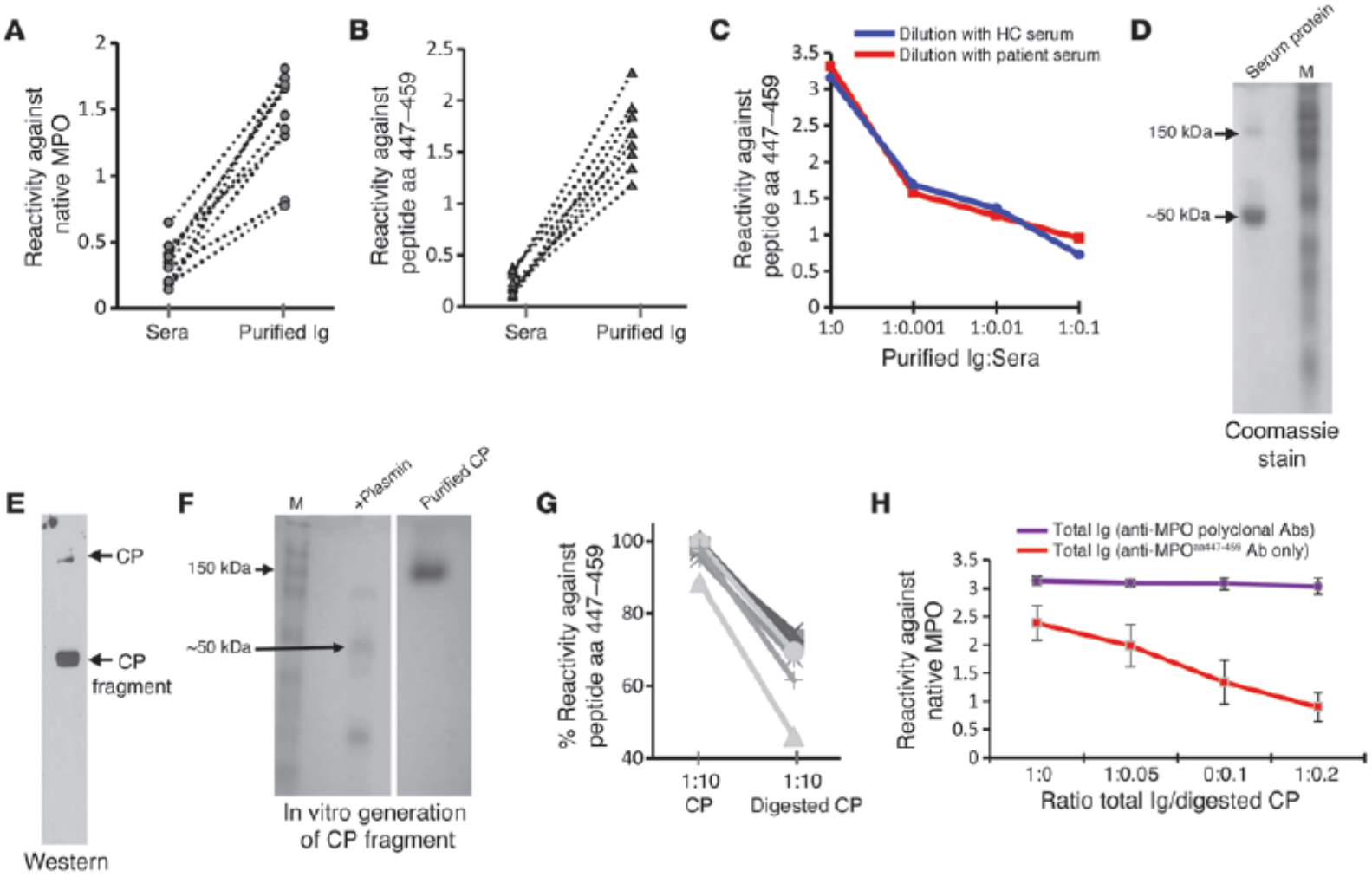
Estudio de especificidad epitopica en ANCA-MPO . Mapa de calor demostrando afininidad/union epitopica (alta color rojo rojo)

Roth et cols. J Clin Invest. 2013;123(4):1773–1783.



Epitope specificity determines pathogenicity and Detectability in ANCA-associated vasculitis

Estudios en casos ANCA negativos.



Epitope specificity determines pathogenicity and Detectability in ANCA-associated vasculitis

Vasculitis Anti-PR3 y anti-MPO: EPIDEMIOLOGIA

Mexico

España

USA

China

Europa

Korea

Lituania

USA

Japón

Taiwan

UK

Polonia

Inidia

Study		Year of Publication	Selection (Up to 4)	Comparability (Up to 2)	Outcome (Up to 3)	Total
1	Córdova-Sánchez *et al.* (8)	2016	3	1	2	6
2	Villacorta *et al.* (20)	2016	4	2	3	9
3	Shah *et al.* (17)	2015	4	1	3	8
4	Chen *et al.* (5)	2007	3	1	3	7
5	Eisenberger *et al.*(18)	2005	2	2	2	6
6	Lee *et al.*(7)	2015	4	2	3	9
7	Kantauskaite *et al.*(33)	2018	4	2	3	9
8	Shah *et al.*(19)	2015	3	1	2	6
9	Iwakiri *et al.* (34)	2013	4	1	3	8
10	Hung et al. (6)	2006	4	2	3	9
11	Hedger *et al.* (4)	2000	4	2	3	9
12	Sokolowska *et al.* (35)	2014	4	1	3	8
13	Sharma *et al.* (36)	2016	3	1	2	6

Porcentaje ANCA negativo en series: **15-25%**

Antineutrophil cytoplasmic antibody negative pauci-immune extracapillary glomerulonephritis

JAVIER VILLACORTA,[1*] FRANCISCO DIAZ-CRESPO,[3*] MERCEDES ACEVEDO,[4] CARMEN GUERRERO,[2] MANUELA MOLLEJO[3] and GEMA FERNANDEZ-JUAREZ[1]

Características clínicas de pacientes ANCA negativo

Feature	ANCA (–) (*n* = 29)	ANCA (+) (*n* = 85)	*P*-value
Male / Female	20 / 9	48 / 37	ns
Age at onset	54.8 ± 17.2	62 ± 14.6	0.03
Constitutional symptoms	6 (20.6%)	24 (28.2%)	ns
Pulmonary	5 (17.2%)	21 (24.7%)	ns
Skin lesions	10 (34.4%)	13 (15.2%)	0.02
Articular	5 (17.2%)	18 (21.1%)	ns
Nervous system	4 (13.7%)	2 (2.3%)	ns
Gastrointestinal	1 (3.4%)	2 (2.3%)	ns
Otic, nose and throat	0 (0%)	7 (8.2 %)	ns
Ophthalmic	0 (0%)	4 (4.7%)	ns
BVAS score	15.6 ± 4.9	15 ± 3.9	ns
Median follow-up period (months)	24.1 (3.9 - 100.8)	42.8 (9–120.8)	ns
Evolution to ESRD in the follow-up	8 (27.5%)	25 (29.4%)	ns

Estudio Español (H Toledo, H Alcorcon, H.12Octubre)

Vasculitis con afectación renal entre 1995 y 2015.

Características renales de pacientes ANCA negativo

Feature	ANCA (–) (*n* = 29)	ANCA (+) (*n* = 85)	*P*-value
Median initial SCr (mmol/L)	256.3 (159–389)	300.5 (185–565)	ns
Median eGFR (mL/min)	23.3 (12–39.6)	15.8 (8.1 - 25.6)	0.06
Nephrotic syndrome	1 (3.4%)	5 (5.8%)	ns
Macroscopic haematuria	1 (3.4%)	7 (8.2%)	ns
Need for dialysis	10 (34.4%)	36 (42.3%)	ns

Nephrology 2016: 2: 301-7

Características histológicas pacientes con vasculitis renal ANCA negativo.

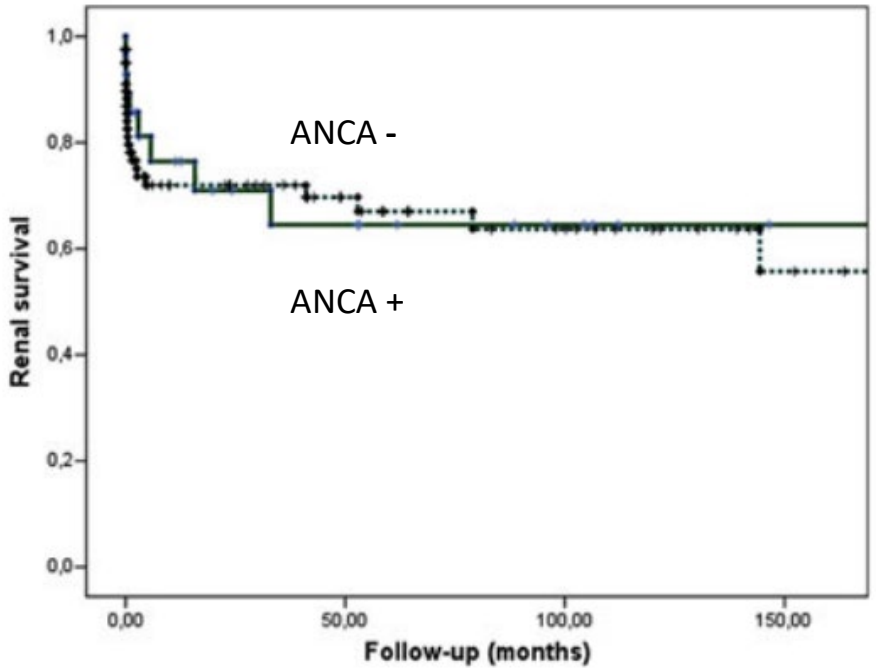
Feature	ANCA (–) (*n* = 29)	ANCA (+) (*n* = 85)	*P*-value
Number glomeruli	18.3 ± 11.9	18.8 ± 12.5	ns
Crescents %	40.5 ± 23	49.8 ± 23	ns
Cellular crescents %	70.8 ± 36	72.8 ± 33	ns
Fibrous crescents %	5 ± 11	6.3 ± 17	ns
Glomerular sclerosis %	14 (0–28)	11 (1–26.5)	ns
Mesangial proliferation	15 (51.7%)	24 (28.2%)	0.02
Endocapillary proliferation	13 (44.8%)	26 (30.5%)	ns
Fibrinoid necrosis	18 (62%)	57 (67%)	ns
Medium arterioles vasculitis	2 (6.8%)	14 (16.4%)	ns
Tubulitis	5 (17.2%)	34 (40%)	0.02

Suptipos histológicos de la clasificación de Berden:

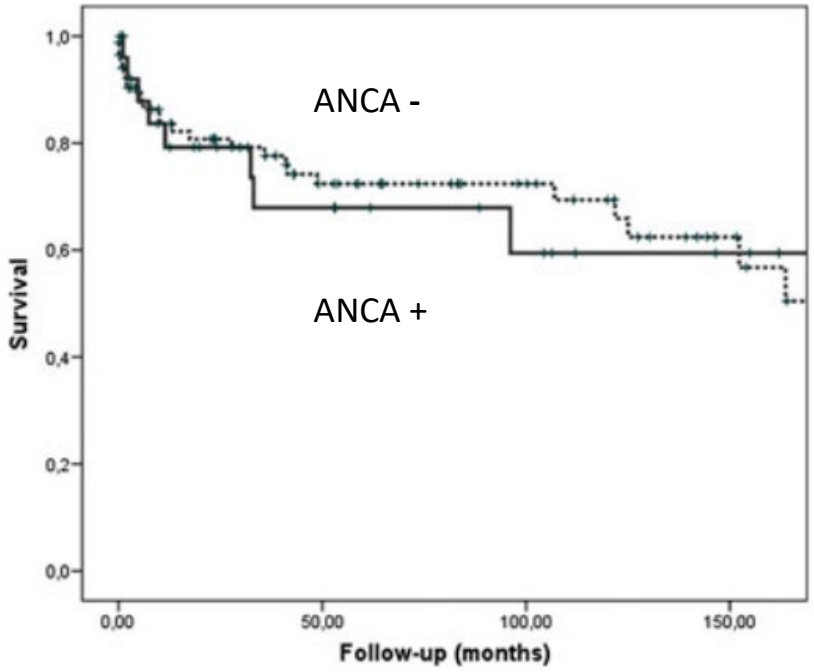
- Esclerótica : 8.8%
- Focal: 23.7%
- Crescética : 46.5%
- Mixta: 21.1%.

Nephrology 2016: 2: 301-7

Supervivencia renal pacientes ANCA negativo vs positivo.



Supervivencia global pacientes ANCA negativo vs positivo.

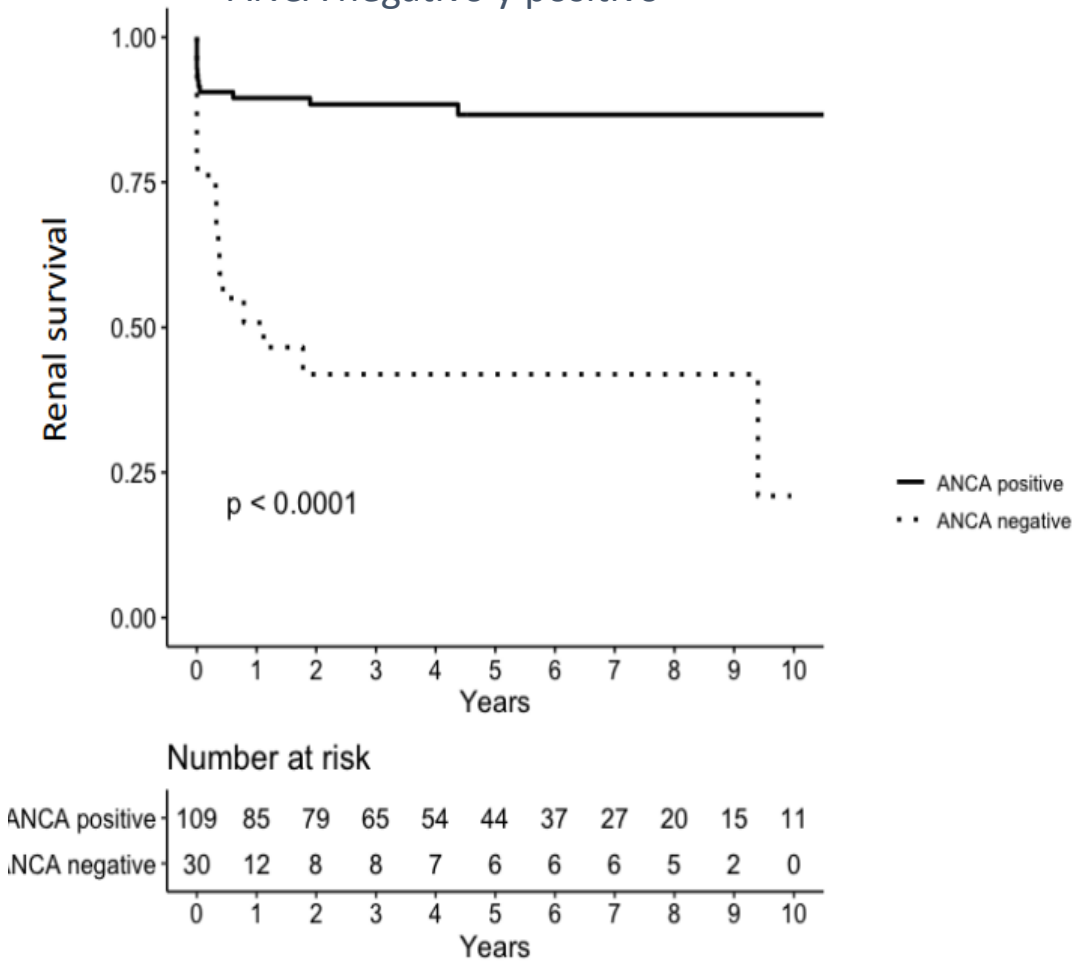


Nephrology 2016: 2: 301-7

Meta-analysis and cohort study of histopathological and clinical outcomes in ANCA negative versus positive vasculitis

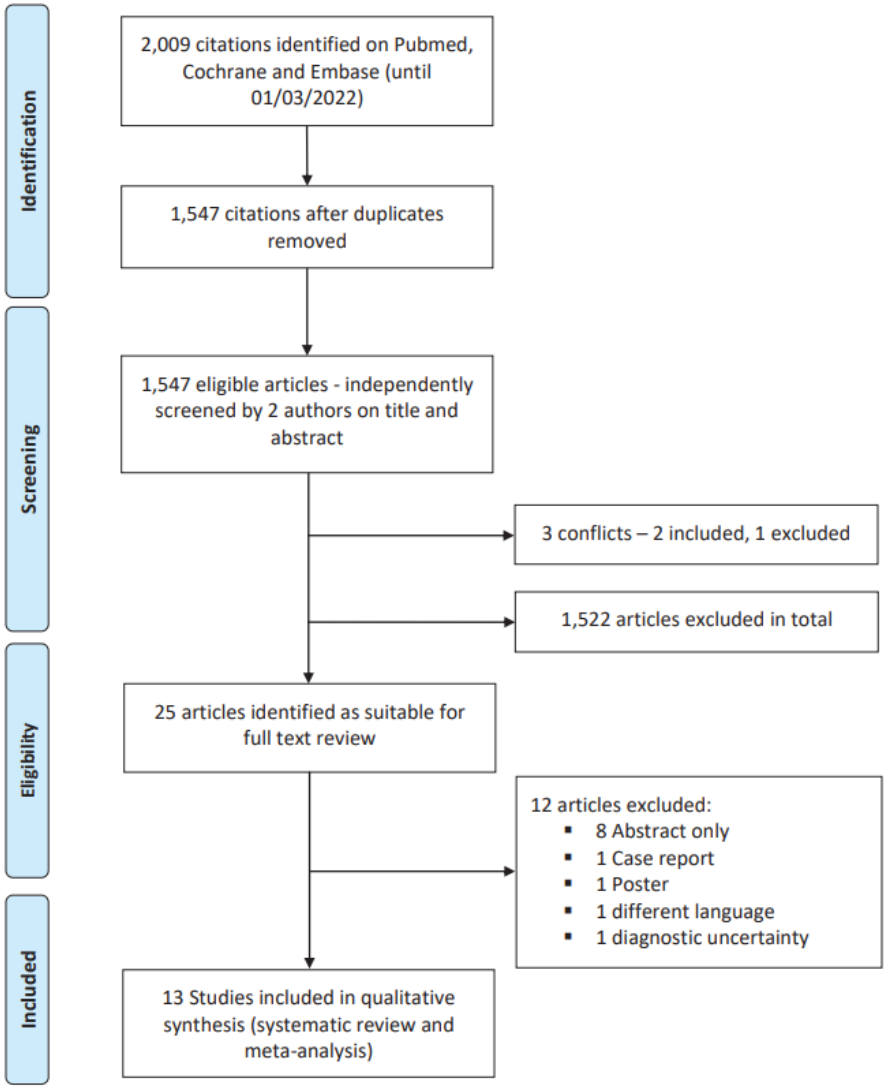
	ANCA positive *n=114, (%)*	ANCA negative *n=32, (%)*	*P* Value
Patient demographics			
Age, years (mean ± SD)	65.6 ± 12.10	51.44 ± 19.57	<0.001
Gender (M:F)	59:55	21:11	0.23
eGFR at presentation, median (IQR)	18.0 (11.0 -39.3)	14.0 (7.0 – 26.0)	0.10
Clinical features and systems involvement (%)			
Constitutional symptoms	32 (28.1)	0	<0.001
Renal	113 (99.1)	31 (96.9)	0.39
Pulmonary	28 (24.6)	4 (12.5)	0.22
ENT	27 (23.7)	0	<0.001
CNS	14 (12.3)	1 (3.1)	0.19
Cutaneous	16 (14.0)	8 (25.0)	0.18
Ophthalmic	6 (5.3)	0	0.34
Gastrointestinal	4 (3.5)	1 (3.1)	1.00
Histopathological findings (%)			
Normal Glomeruli (N0 >25%)	73 (64.0)	16 (50.0)	0.01
IFTA 0	21 (18.42)	8 (25.0)	0.42
Extra-glomeruli arteritis	15 (13.2)	7 (21.9)	0.26

Supervivencia renal entre pacientes ANCA negativo y positivo



Kidney360 ():10.34067; 2022

Meta-analysis and cohort study of histopathological and clinical outcomes in ANCA negative versus positive vasculitis



Supplementary Table S1: Risk of bias of included studies on the Newcastle-Ottawa scale

Study		Year of Publication	Selection (Up to 4)	Comparability (Up to 2)	Outcome (Up to 3)	Total
1	Córdova-Sánchez *et al.* (8)	2016	3	1	2	6
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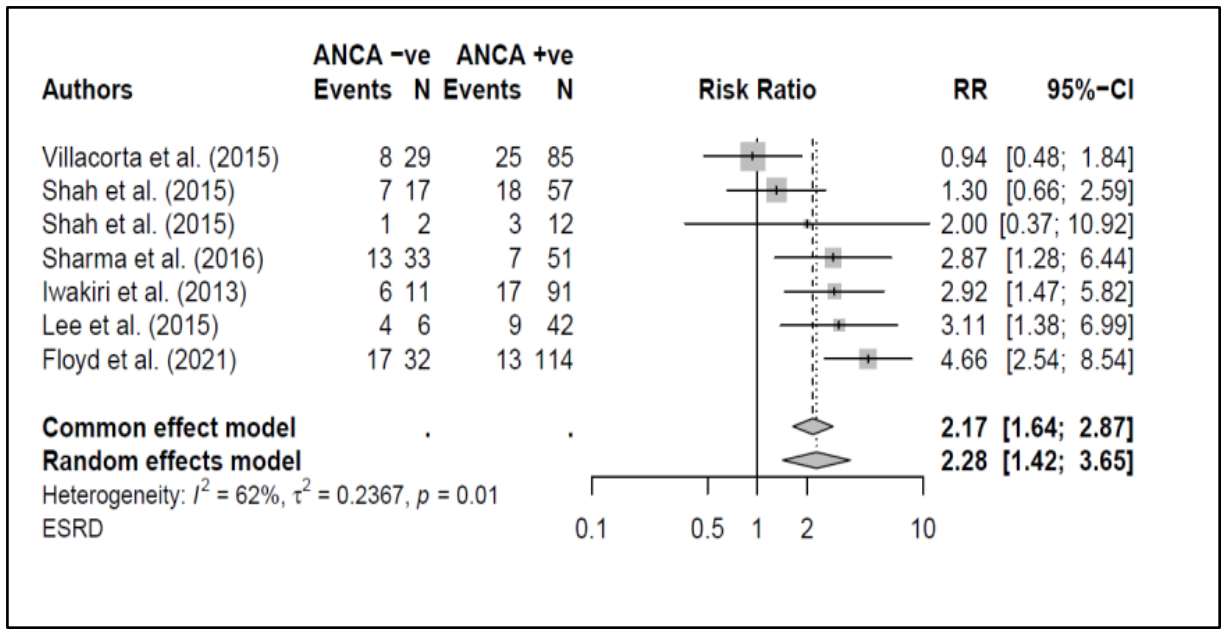
Kidney360 ():10.34067; 2022

Metanálisis analizando desarrollo de Enfermedad renal crónica terminal en ANCA negativo vs positivo



Análisis mulitvariable sobre el desarrollo de Enfermedad renal crónica terminal.

ESKD at 1 year follow up

Variable	HR (95% CI)	P value
ANCA status	5.18 (2.00, 13.43)	<0.001
Gender	0.91 (0.40, 2.09)	0.83
eGFR at diagnosis	0.98 (0.95, 1.00)	0.09
Age	0.98 (0.96, 1.00)	0.11
Induction Therapy	0.84 (0.26, 2.74)	0.77

Kidney360 ():10.34067; 2022

Características de los pacientes ANCA negativo en series más extensas.

Series que reportan peor pronóstico renal

	N	TFG al diagnóstico ANCA - vs ANCA +	% glom normales
Sharma et cols.	33	**16.1** vs **20** ml/min.	32%
Floyd et cols	32	**14.5** vs **18** ml/min	50%
Villacorta et cols.	29	**23** vs **16** ml/min	53%

Diagnóstico tardío
Tratamiento tardío

Características de los pacientes ANCA negativo en series más extensas

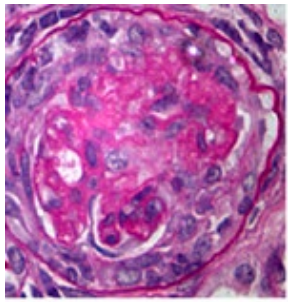
Series que reportan peor pronóstico renal

	N	TFG al diagnóstico ANCA - vs ANCA +	% glom normales	Tratamiento inducción ANCA - vs ANCA +
Sharma et cols.	33	**16.1** vs **20** ml/min ml/min.	32%	Esteroides + CF **77%**
Floyd et cols	32	**14.5** vs **18** ml/min	50%	Esteroides y CF **68% vs 91%**
Villacorta et cols.	29	**23** vs **16** ml/min	53%	Est + CF : **87%** Est +RTX : **7%**

Diagnóstico tardío
Tratamiento tardío

Tratamiento insuficiente

Vasculitis ANCA negativo: Importancia **Diagnóstico temprano.**
Tratamiento adecuado.



Estrategias para el diagnóstico:

Paciente con púrpura cutánea y/o hemorragia alveolar y/o sdme constitucional/anemia.

- Estudio autoinmunidad negativo.

ANCAs: IFI y ELISa

- Búsqueda de afectación renal (proteinuria, microhematuria, deterioro función real)

Sedimento.

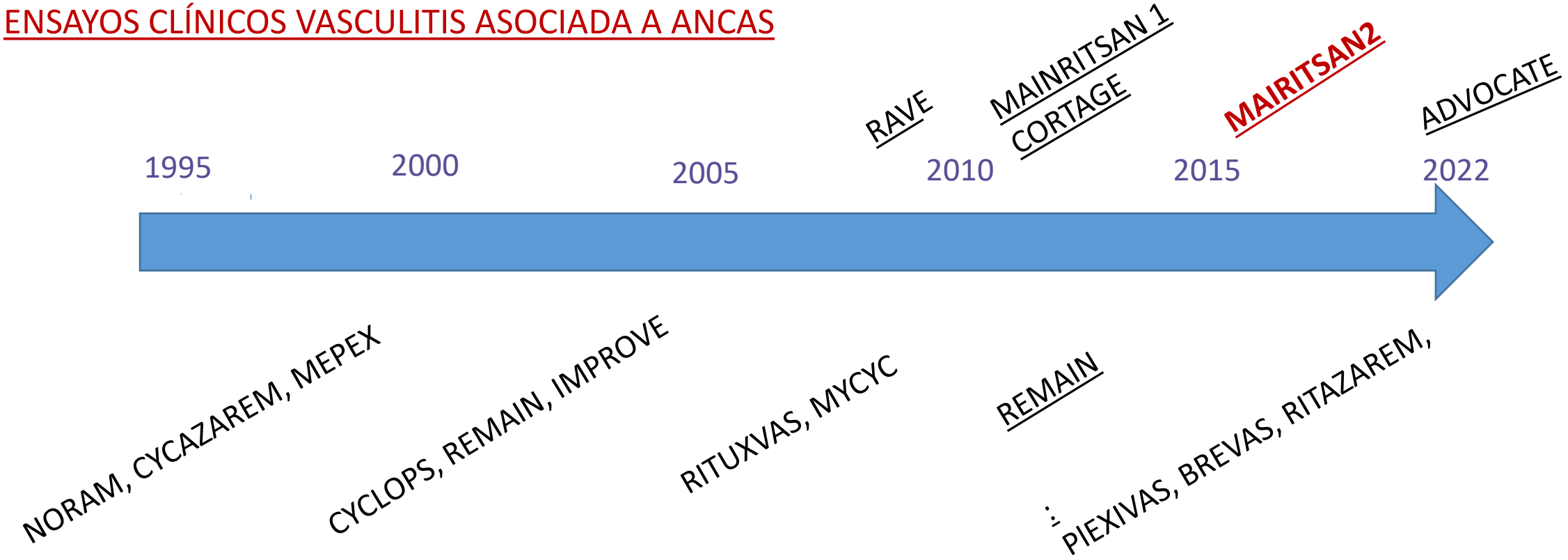
- Bx cutánea con Estudio de inmunofluorescencia.

Vasculitis leucocitoclástica con IF neg.

- Biopsia renal precoz en caso de alteraciones urinarias/ Deterioro fx renal.

Glomerulonefritis extracapilar pauciinmune

ENSAYOS CLÍNICOS VASCULITIS ASOCIADA A ANCAS



The European Vasculitis Study Group (EUVAS) therapeutic trials in ANCA associated vasculitis.

Comparison of individually tailored versus fixed schedule rituximab regimen to maintain ANCAassociated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

Table 1 General characteristics at inclusion

Characteristic	Rituximab infusions: Individually tailored (n=81)	Rituximab infusions: Fixed-schedule (n=81)
Age, means±SD, years	62±14	59±13
Female sex, n (%)	31 (38.3)	37 (45.7)
Vasculitis type, n (%)		
GPA	56 (69.1)	61 (75.3)
MPA	25 (30.9)	20 (24.7)
ANCA-positive at diagnosis, n (%)*	74/77 (96.1)	72/79 (91.1)
Indirect immunofluorescence	68/77 (88.3)	6579 (82.3)
ELISA	64/77 (83.1)	61/79 (77.2)
Anti-PR3	38/77 (49.4)	38/79 (48.1)
Anti-MPO	26/77 (33.8)	24/79 (30.4)
ANCA-positive at inclusion, n (%)†	45/80 (56.3)	58/80 (72.5)
Indirect immunofluorescence	40/80 (50)	54/80 (67.5)
ELISA	28 (35)	43 (53.7)

Table 2 ANCA evolution and B-cell detection patterns throughout follow-up for patients with ≥1 relapses or none

Parameter profile	Patients with: ≥1 relapse(s) (n=22)*	Patients with: No relapse (n=139)
ANCA evolution (%)		
Always negative	7 (31.8)	33 (23.7)
Negative at inclusion and became positive	3 (13.6)	14 (10.1)
Positive at inclusion and became negative	2 (9.1)	51 (36.7)
Positive at inclusion and titres rose	1 (4.5)	10 (7.2)
Positive at inclusion and remained stable	9 (40.9)	29 (20.9)
Circulating CD19+ B cell evolution (%)		
Always negative	11 (50)	8 (5.8)
Detected at least once	11 (50)	131 (94.2)
ANCA and circulating CD19+ B cell evolutions (%)		
ANCA-negative and no circulating B cells detected	4 (18.2)	5 (3.6)
Other	18 (81.8)	134 (96.4)

TRATAMIENTO DE MANTENIMIENTO VASCULITIS

Vasculitis ANCA-negativo

Tratamiento vasculitis renal ANCA negativo. → Similar a vasculitis ANCA-MPO

Inducción:

- Esteroides + Rituximab
- Esteroides + Ciclofosfamida

Mantenimiento:

- Rituximab cada 4-6 meses.
- Azatioprina

Remisión tras Inducción: **60-80%**

71% (Cohorte española)

TRATAMIENTO DE MANTENIMIENTO VASCULITIS

Vasculitis ANCA-negativo

Factores de riesgo para presenta recaída

- PR3 ✖
- Recaedores previos
- Microhematuria persitente
- ANCAs + persistentes ✖
- Positivizacion de ANCAs ✖

Duración de de tratamiento de mantenimiento; → Similar a ANCA-MPO

Tasa de Recaída → **13%** **(Cohorte española)**

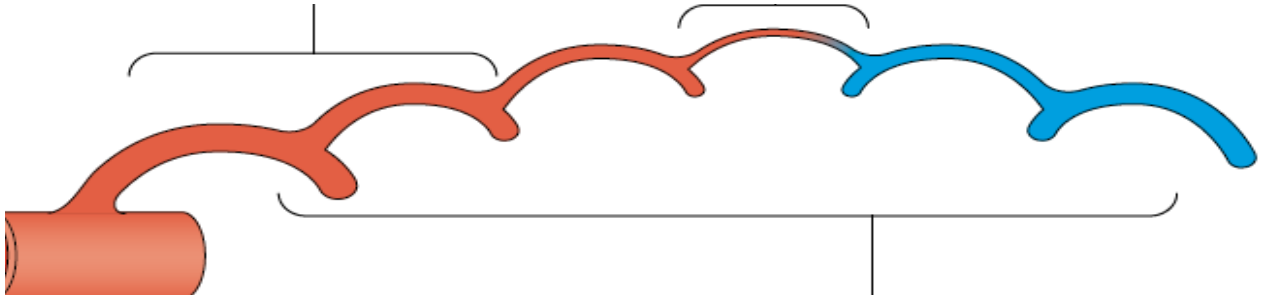
MENSAJES

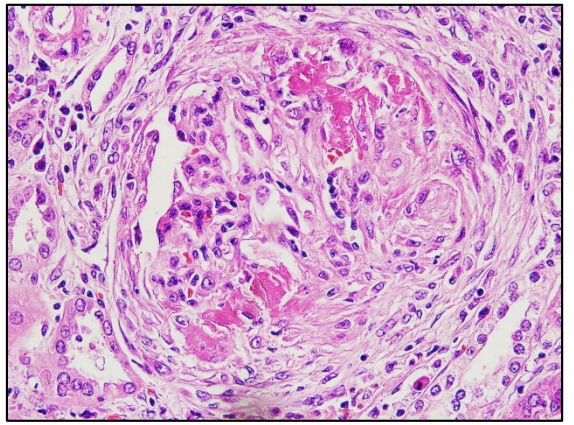
- La Vasculitis renal ANCA negativo aparece en sujetos más **jóvenes** y La **afectación sistémica/extrarrenal** es comparable a la observada en pacientes ANCA-MPO.

- Algunos estudios muestran **peor función renal** al debut y mayor presencia de **lesiones crónicas**, lo cual al podría traducir un diagnóstico más tardío en estos casos.

- Si bien existen **diferencias en el pronóstico renal** reportado en la literatura; la peor supervivencia renal en algunas series podría estar condicionada por mayor cronicidad al diagnóstico y una menor tasa de tratamiento.

- Sería deseable la mayor inclusión de pacientes ANCA negativo en los estudios y ensayos clínicos.





GRACIAS POR LA ATENCIÓN