ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

13η ΗΜΕΡΙΔΑ
ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΑΙΜΑΦΑΙΡΕΣΗΣ
Σάββατο, 10 Οκτωβρίου 2020

Εργαστηριακές Εξετάσεις στις μεθόδους Αιμαφαίρεσης

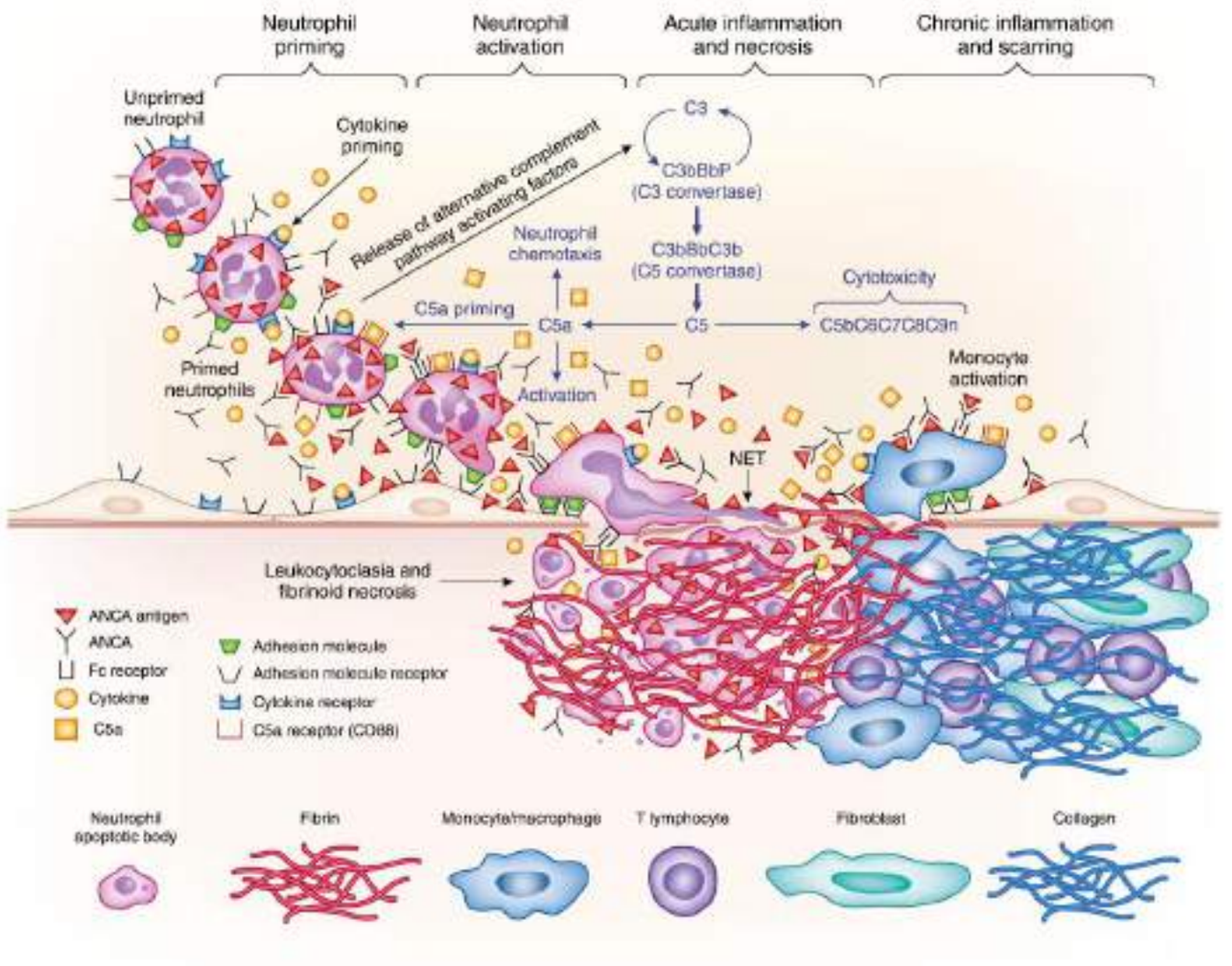
Π.Πατεινάκης
Νεφρολόγος, Επ.Α'
ΓΝΘ Παπαγεωργίου

Εργαστηριακές τιμές και ΠΑ

- Ένδειξη εφαρμογής
- Ένδειξη διακοπής
- Ένδειξη τροποποίησης συνταγογράφησης

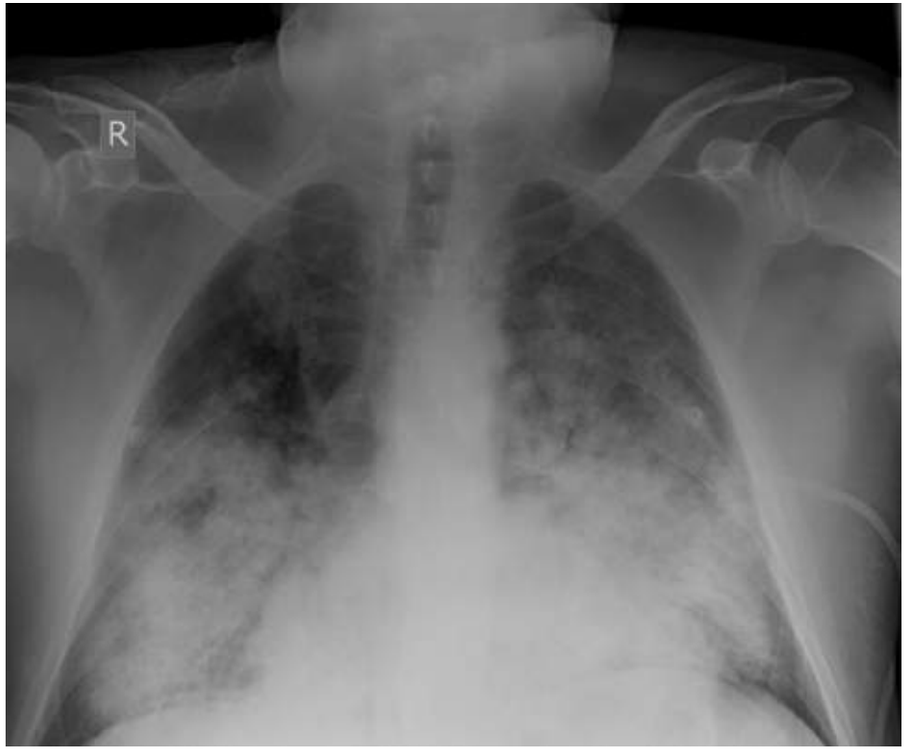
ANCA ΑΓΓΕΙΪΤΙΣ
ANCA Associated Vasculitis (AAV)

ANCA ΑΓΓΕΙΪΤΙΣ



Clin J Am Soc Nephrol 12: 1680–1691

ANCA ΑΓΓΕΙΪΤΙΣ



Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

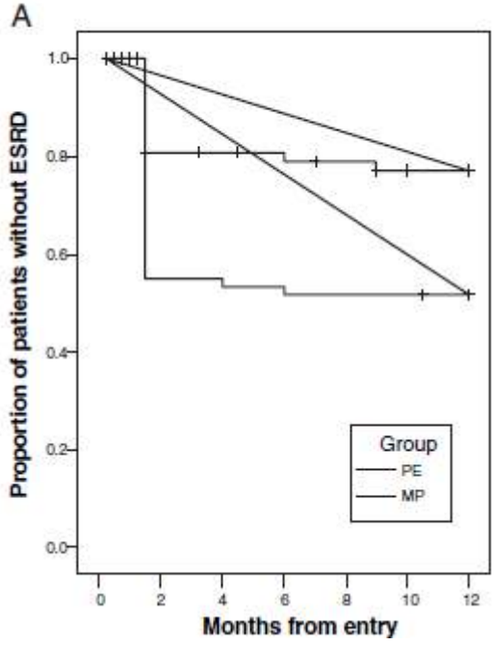
Κρεατινίνη: **500 mol/L = 5.66 mg/dl.**

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

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

ABSTRACT

Systemic vasculitis associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA) is the most frequent cause of rapidly progressive glomerulonephritis. Renal failure at presentation carries an increased risk for ESRD and death despite immunosuppressive therapy. This study investigated whether the addition of plasma exchange was more effective than intravenous methylprednisolone in the achievement of renal recovery in those who presented with a serum creatinine >500 μmol/L (5.8 mg/dl). A total of 137 patients with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine >500 μmol/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. The primary end point was dialysis independence at 3 mo. Secondary end points included renal and patient survival at 1 yr and severe adverse event rates. At 3 mo, 33 (49%) of 67 after intravenous methylprednisolone compared with 48 (69%) or 70 after plasma exchange were alive and independent of dialysis (95% confidence interval for the difference 18 to 35%; $P = 0.02$). As compared with intravenous methylprednisolone, plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% confidence interval 6.1 to 41%), from 43 to 19%, at 12 mo. Patient survival and severe adverse event rates at 1 yr were 51 (76%) of 67 and 32 of 67 (48%) in the intravenous methylprednisolone group and 51 (73%) of 70 and 35 of (50%) 70 in the plasma exchange group, respectively. Plasma exchange increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both groups.

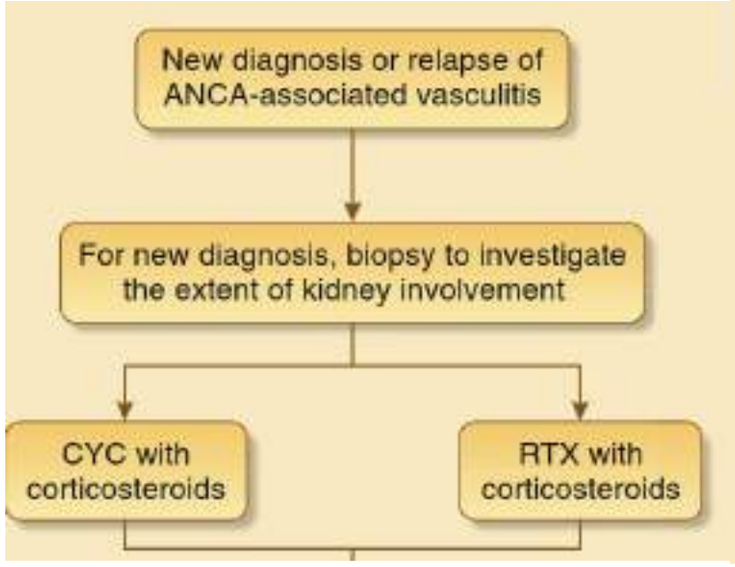


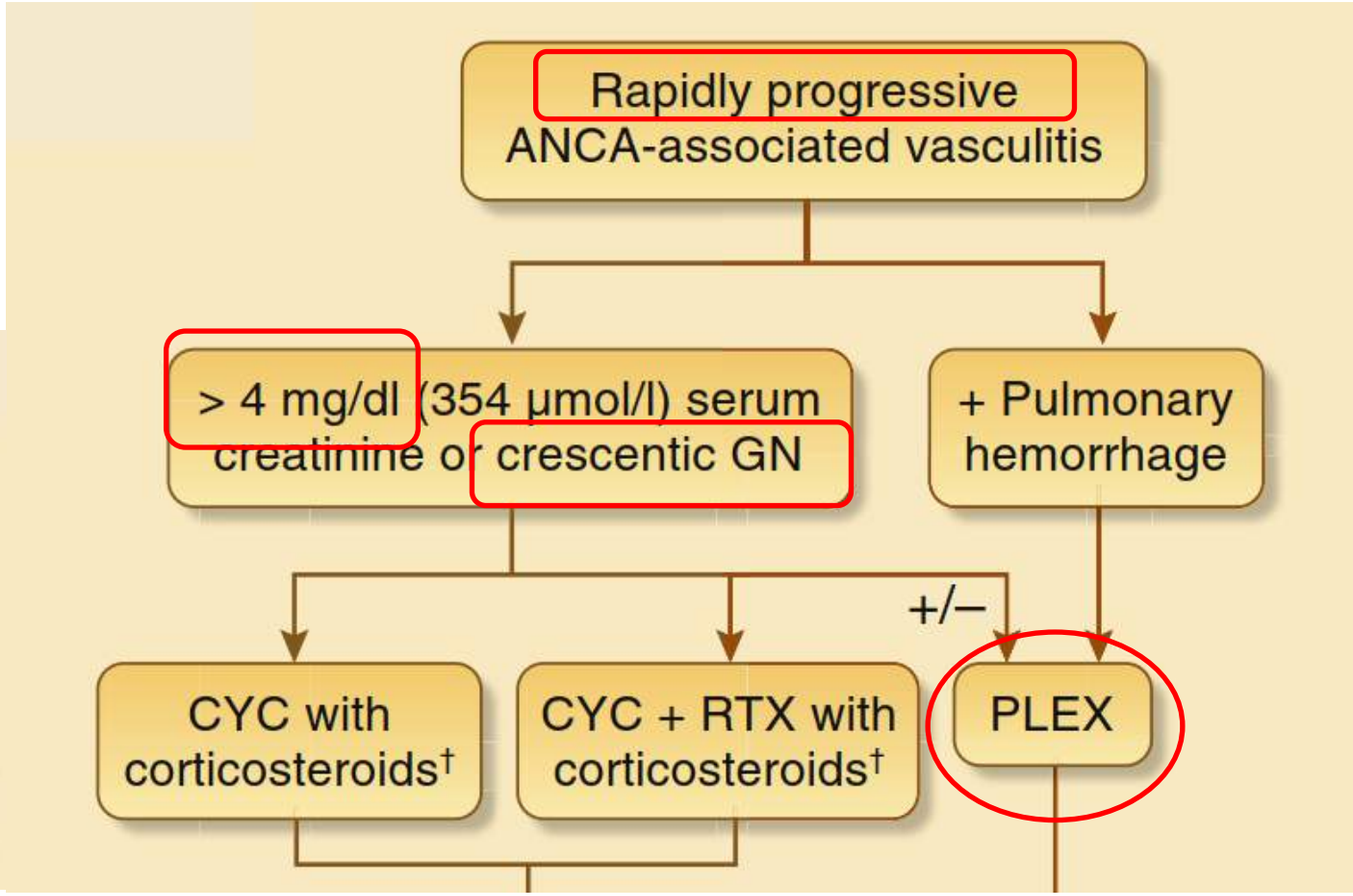
Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

Brad H. Rovin[1], Dawn J. Caster[2], Daniel C. Cattran[3], Keisha L. Gibson[4], Jonathan J. Hogan[5], Marcus J. Moeller[6], Dario Roccatello[7], Michael Cheung[8], David C. Wheeler[9], Wolfgang C. Winkelmayer[10] and Jürgen Floege[11]; for Conference Participants[12]

Kidney International (2019) **95,** 281–295; https://doi.org/10.1016/j.kint.2018.11.008





The NEW ENGLAND JOURNAL of MEDICINE

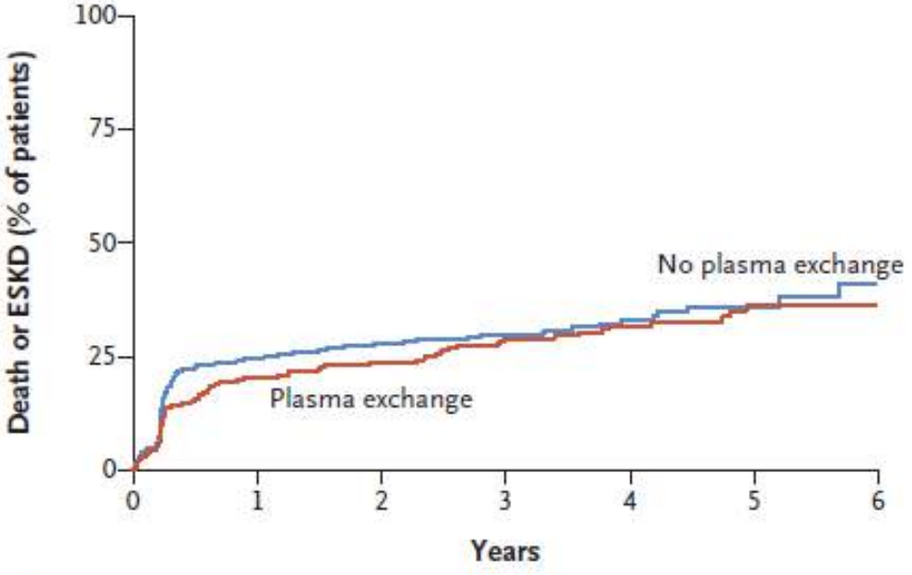
Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne, for the PEXIVAS Investigators*

N Engl J Med 2020;382:622-31.
DOI: 10.1056/NEJMoa1803537

We conducted a randomized trial with a 2-by-2 factorial design to evaluate the use of plasma exchange and two regimens of oral glucocorticoids in patients with severe ANCA-associated vasculitis (defined by an estimated glomerular filtration rate of <50 ml per minute per 1.73 m^2 of body-surface area or diffuse pulmonary hemorrhage). Patients were randomly assigned to undergo plasma exchange (seven plasma exchanges within 14 days after randomization) or no plasma exchange (control group). Patients were also randomly assigned to follow either a standard-dose regimen or a reduced-dose regimen of oral glucocorticoids. Patients were followed for up to 7 years for the primary composite outcome of death from any cause or end-stage kidney disease (ESKD).

A Primary Outcome According to Plasma Exchange



No. at Risk							
No plasma exchange	352	244	183	136	82	44	10
Plasma exchange	352	252	186	135	82	43	10

ANCA ΑΓΓΕΙΪΤΙΣ – ΚΡΕΑΤΙΝΙΝΗ - ΠΑ

VASCULITIS, ANCA-ASSOCIATED (AAV)

Incidence: 1-3/100,000/yr (geographical and ethnic differences; MPA: 48-65%, GPA: 25-40%, EGPA: 10-12%)	**Indication**	**Procedure**	**Recommendation**	**Category**
	MPA/GPA/RLV			
	RPGN, Cr ≥5.7 mg/dl*	TPE	Grade 1A	I
	RPGN, Cr <5.7 mg/dl*	TPE	Grade 2C	III
	DAH	TPE	Grade 1C	I
	EGPA	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	10(1091)	5(345)	NA	NA

MPA = microscopic polyangiitis; GPA = granulomatosis with polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis; RLV = renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis; DAH = diffuse alveolar hemorrhage;
*Cr thresholds for renal function at presentation adopted from Yates, 2016; Cr ≥5.7 mg/dl includes "on dialysis".

ANCA ΑΓΓΕΙΪΤΙΣ – ΚΡΕΑΤΙΝΙΝΗ - ΠΑ

Recommendation

EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T Hauser,[7] B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R A Luqmani,[12] A Mahr,[13] P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelmark,[16,17] V Tesar,[18] K Westman,[19] A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22] C Mukhtyar[1]

PLEX use is usually reserved for patients with either severe renal impairment or those with diffuse alveolar haemorrhage.[87–89] The largest trial published to date is MEPEX which recruited those individuals with either a serum creatine >500 μmol/L (5.7 mg/dL) or those requiring dialysis.[68]

Yates M, et al. Ann Rheum Dis 2016;75:1583–1594

re	Recommendation	Category
	Grade 1A	I
	Grade 2C	III
	Grade 1C	I
	Grade 2C	III

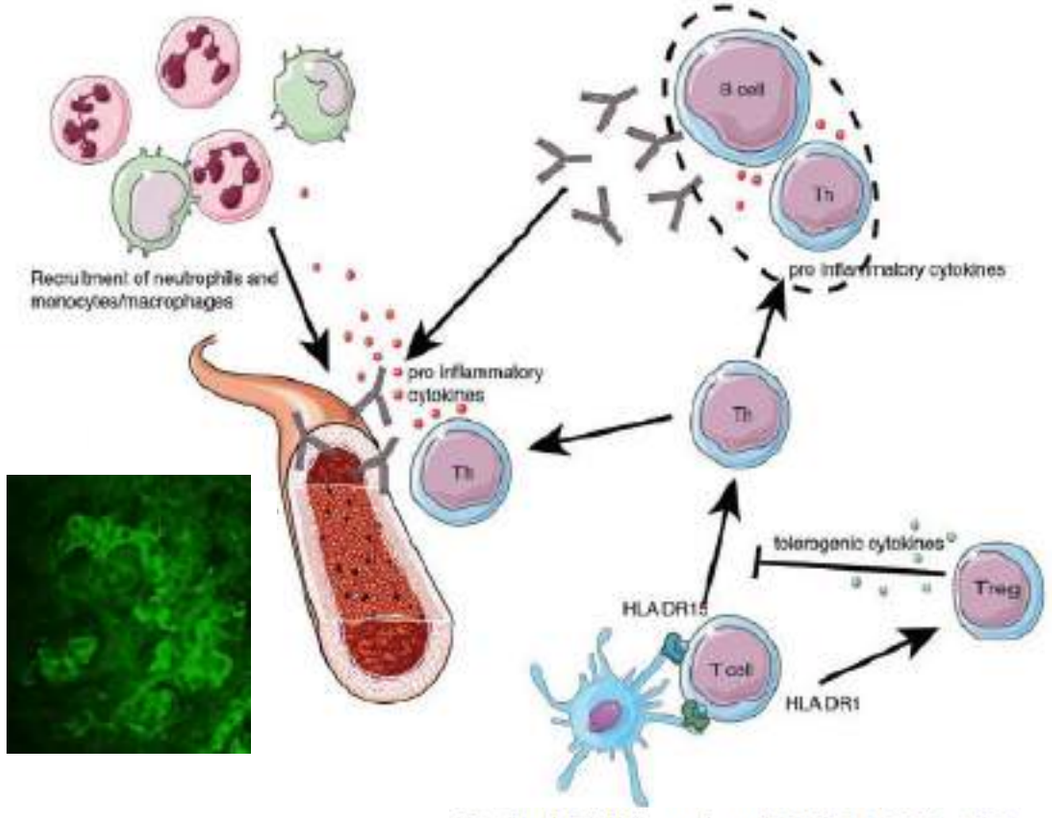
CT	CS	CR
5(345)	NA	NA

ilic granulomatosis with polyangiitis; RLV = renal-
orrhage;
ades "on dialysis".

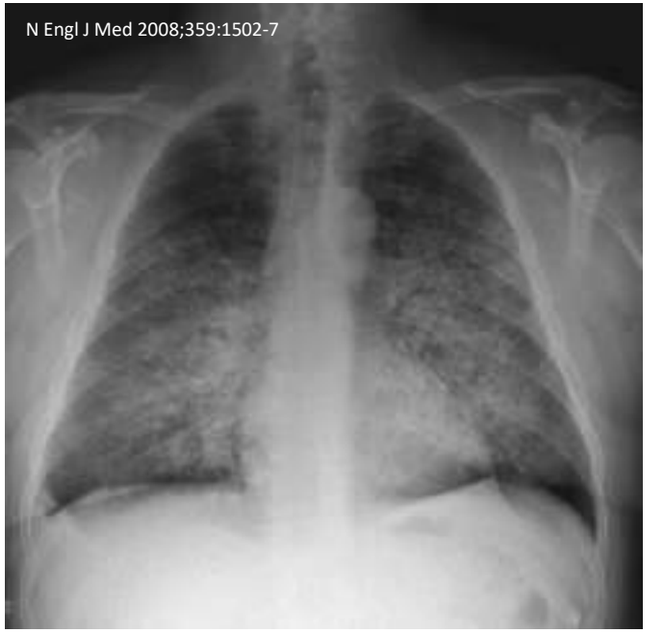
American Society for Apheresis *J Clin Apher.* 2019;34:171–354.

anti-GBM νόσος

anti-GBM νόσος



Nephrol Dial Transplant (2019) 34: 1826–1832



anti-GBM νόσος και πλασμαφαίρεση

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE SYNDROME)

Incidence: <2/1,000,000/yr	Indication	Procedure	Recommendation	Category
	DAH	TPE	Grade 1C	I
	Dialysis-independence	TPE	Grade 1B	I
	Dialysis-dependence*, no DAH	TPE	Grade 2B	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1(17)	0	22(516)	NA

DAH = diffuse alveolar hemorrhage;

*At presentation, Cr ≥5.7 mg/dl indicates "dialysis-dependence"

American Society for Apheresis

J Clin Apher. 2019;34:171–354

Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

JOHN P. JOHNSON, M.D., JACK MOORE, JR., M.D., HOWARD A. AUSTIN, III, M.D., JAMES E. BALOW, M.D., TATIANA T. ANTONOVYCH, M.D., AND CURTIS B. WILSON, M.D.

Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

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Patients randomized to Group I (immunosuppression alone) received oral prednisone 2 mg/kg daily for 1 week, which was reduced to 1 mg/kg daily for the next 3 weeks, then tapered to alternate-day dosage for the next 3 months. Cyclophosphamide was given orally at 2 mg/kg daily for 3 months beginning concomitantly with prednisone, then 1 mg/kg/d for the remainder of treatment. Patients in Group II (plasma exchange) received the identical drug regimen with the addition of 4-liter plasma exchanges every 3 days. Plasma exchange was continued until anti-GBM antibody titer was less than 5% binding or the patient had been stable on maintenance hemodialysis for longer than 30 days. For patients in both groups, cyclophosphamide

Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

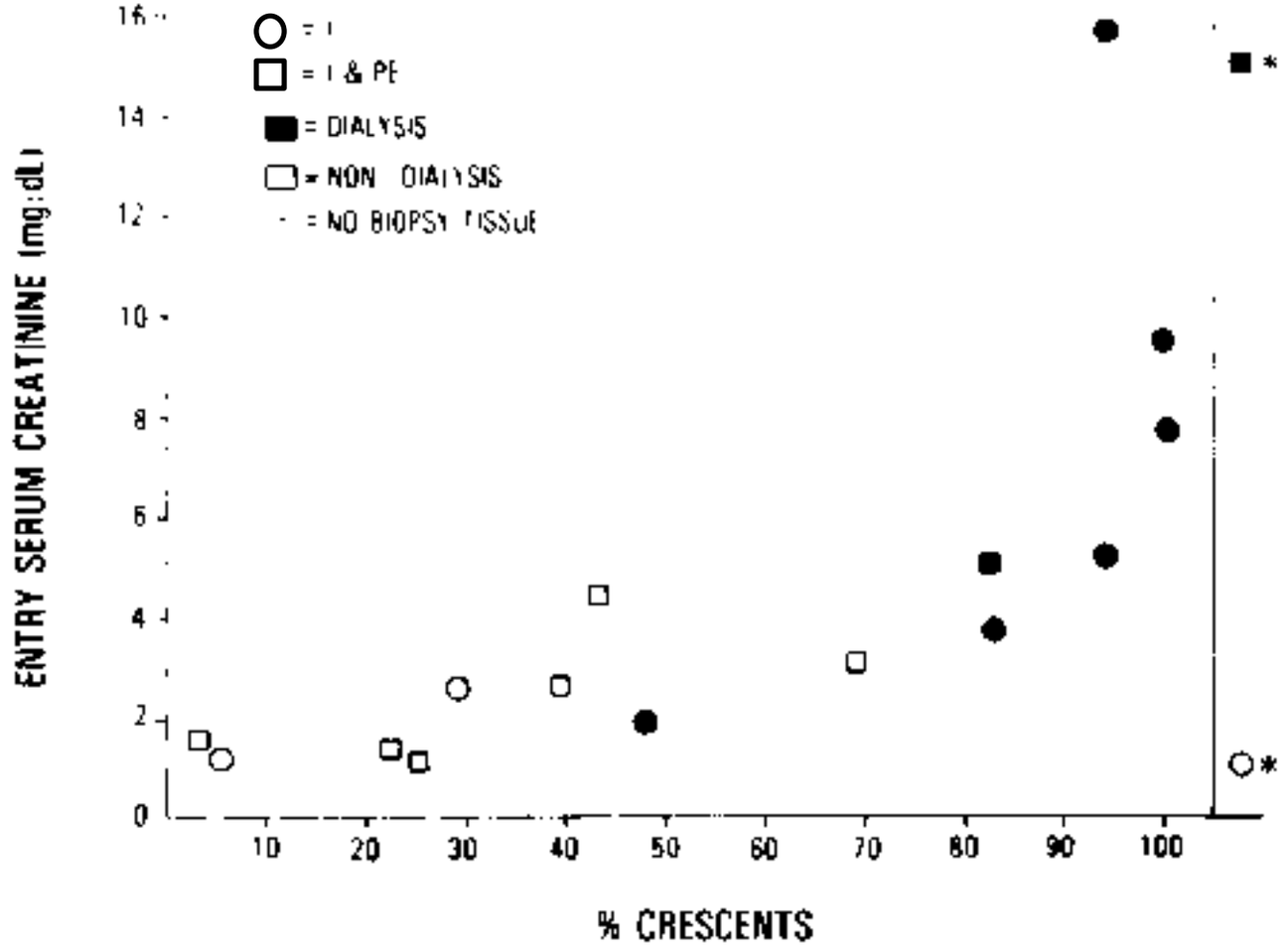


FIG. 2. Distribution of prognostic features in the treatment groups. Entry serum creatinine and % crescents for patients succeeding (alive and not receiving dialysis) or failing (dead or receiving dialysis) in the two treatment groups are depicted. * Indicates either no biopsy (serum creatinine 14.6 mg/dl) or no glomeruli on light microscopy for scoring (serum creatinine 1.0 mg/dl).

Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

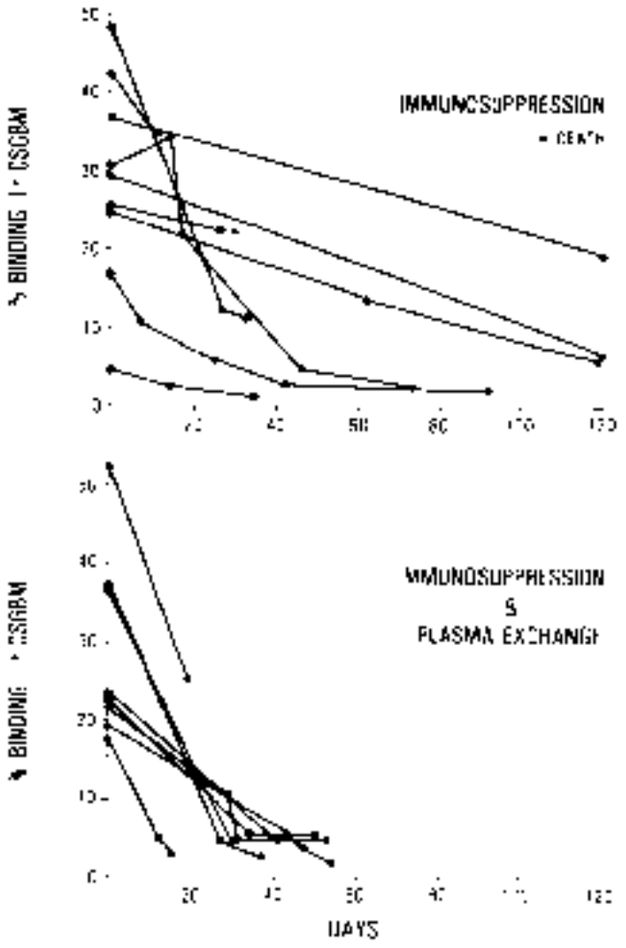


TABLE 3. Clinical outcomes and complications of treatment for the two groups

Patient No.	Duration of Therapy (weeks)	Serum Creatinine at End of Therapy	Serum Creatinine at Discharge	Chronic Dialysis	Change in Renal Function During Therapy	Bolus Steroid (Reason)	Leukopenia (WBC < 3K)	Infections
Group I								
1	10	15.0	11.5	+*	↓	P	−	−
2	6	15.0	10.5	+*	↓	−	+	+
3	12	1.1	1.1	−	→	−	−	−
4	4	15.0	13.0	+**	↓	P	−	+
5	20	1.1	1.2	−	→	−	−	−
6	24	0.8	0.8		↑	−	−	−
7	2	13.0	12.0	+	→	P	+	+
8	36	13.4	12.0	+	↓	P	+	−
9	18	10.8	11.0	+	↓	R	+	−
Mean ± S.E.M.	14.7 ± 3.7	9.5 ± 1.7	9.2 ± 1.7					
Group II								
10	20	10.4	8.9	+	↓	P	+	+
11	24	1.3	1.3	−	→	−	−	−
12	6	12.4	12.0	+	→	P	+	+
13	20	1.3	1.3	−	↓	−	−	−
14	8	2.3	2.3	−	↑	−	−	−*
15	24	1.2	1.2		↑	−	−	−
16	32	1.5	1.5		↑	P	−	−
17	18	4.9	4.2	−***	↑***	P + R	+	−*
Mean ± S.E.M.	18.9 ± 3.1	4.1 ± 0.6	3.1 ± 0.5					

Chronic dialysis (+ = yes, − = no); * = progression to dialysis while on therapy; ** = death during therapy; *** = transient dialysis required.

Change in renal function during therapy: ↑ = improvement, ↓ = decline, → = no change.

Bolus steroid: P = pulmonary hemorrhage, RF = rapid deterioration in renal function.

Infections: Either fever with positive cultures or a febrile episode which responded to reduction in immunosuppressive therapy with or without antibiotics. * = presumed non-A, non-B hepatitis.

+ = $p < 0.05$ compared to Group I by non-paired t test.

Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

TABLE 4. Incidence of renal failure by levels of prognostic factors

Prognostic Factor*	Number†	Failures‡	p Value§
Entry serum creatinine (mg/dl)			<.01
≤3.0	9	1	
>3.0	8	7	
Anti-GBM Antibody Titer (%)			<.1
<24	7	1	
≥24	10	7	
Percent crescents			<.05
<50	8	1	
≥50	7	6	
Treatment			>.2
Drugs alone	9	6	
Drugs + PE	8	2	

therapeutic modality. Thus, though plasma exchange may offer some advantage over immunosuppression alone in the treatment of this disease, degree of pathologic involvement appears to be the major factor affecting outcome. Patients with low cresents (< 30%) and well preserved function did well with either treatment, while patients with severe crescentic involvement and impaired glomerular filtration rate did poorly.

Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

Thus, though plasma exchange may offer some advantage over immunosuppression alone in the treatment of this disease, degree of pathologic involvement appears to be the major factor affecting outcome. Patients with low cresents (< 30%) and well preserved function did well with either treatment, while patients with severe crescentic involvement and impaired glomerular filtration rate did poorly.

Chapter 14: Anti-glomerular basement membrane antibody glomerulonephritis

Kidney International Supplements (2012) **2,** 240–242; doi:10.1038/kisup.2012.27

14.1: Treatment of anti-GBM GN

14.1.1: We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis (see Table 31) in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage. (*1B*)

Cr ≥5.7 mg/dl

AAV

antiGBM

Cr ≥5.7 mg/dl

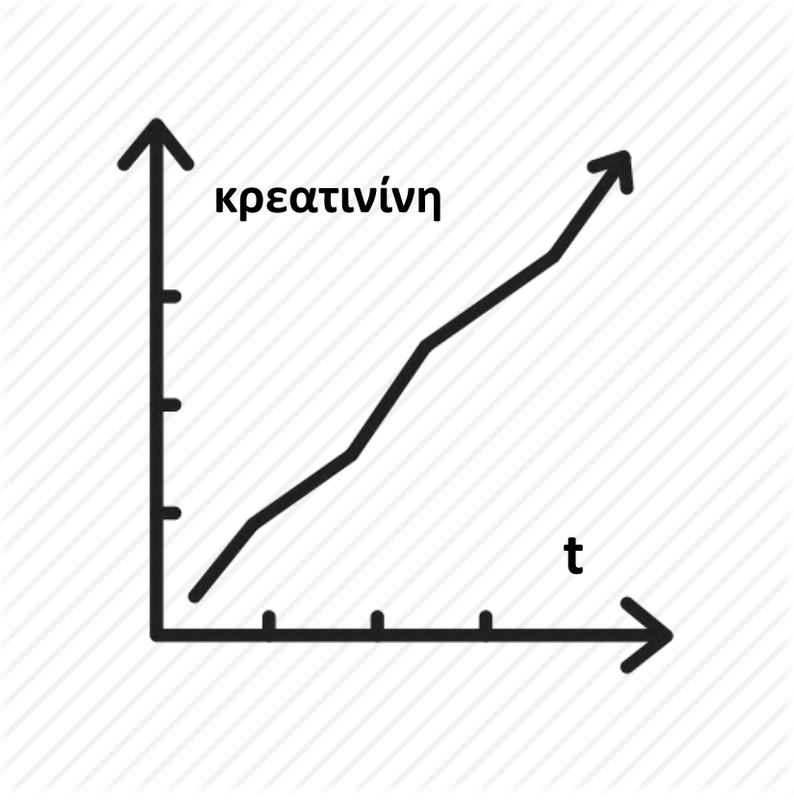
Cr ≥5.7 mg/dl

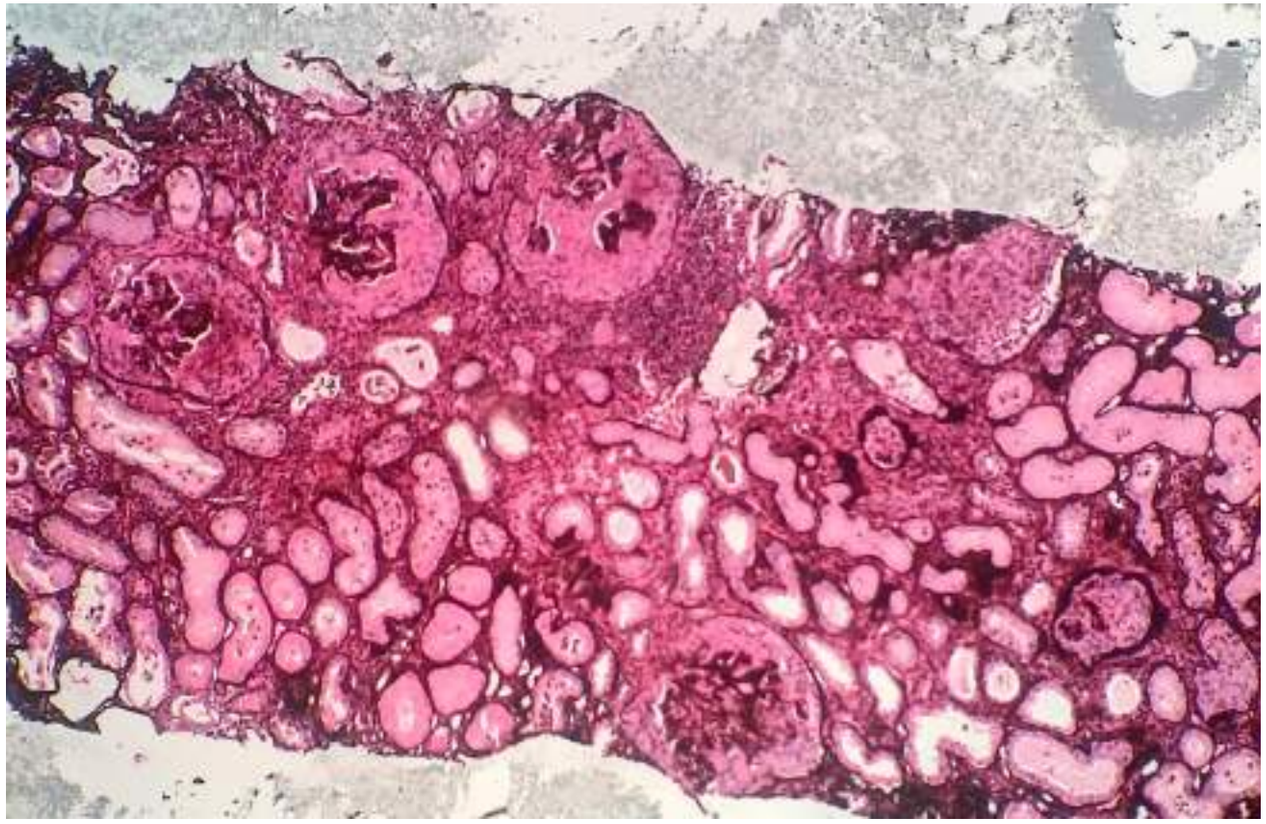
AAV

antiGBM


REALITY
CHECK
AHEAD

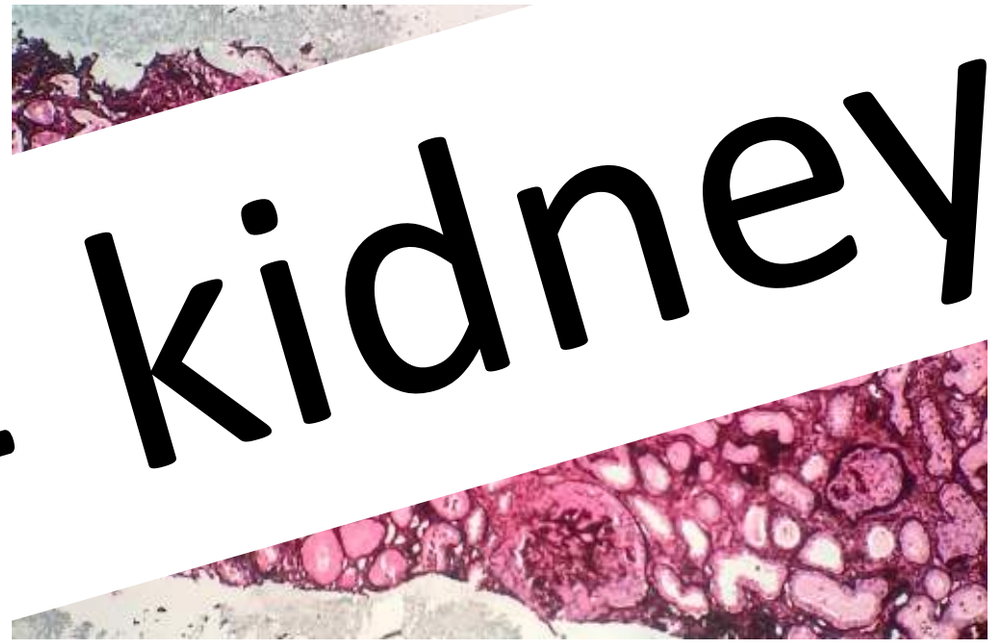
Ταχέως εξελισσόμενη νεφρική βλάβη





Ταχέως εξελισσόμενη νεφρική βλάβη

time = kidney



Διάγνωση AAV vs antiGBM

- **Ανοσολογικός έλεγχος (ANCA, MPO, PR3, antiGBM)**
- **Βιοψία**

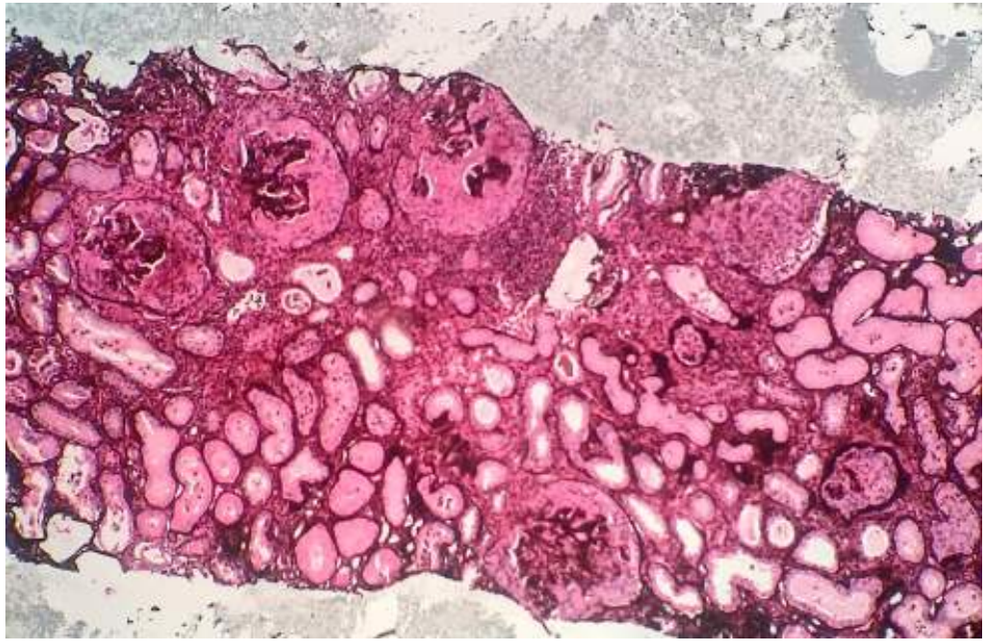
Διάγνωση AAV vs antiGBM

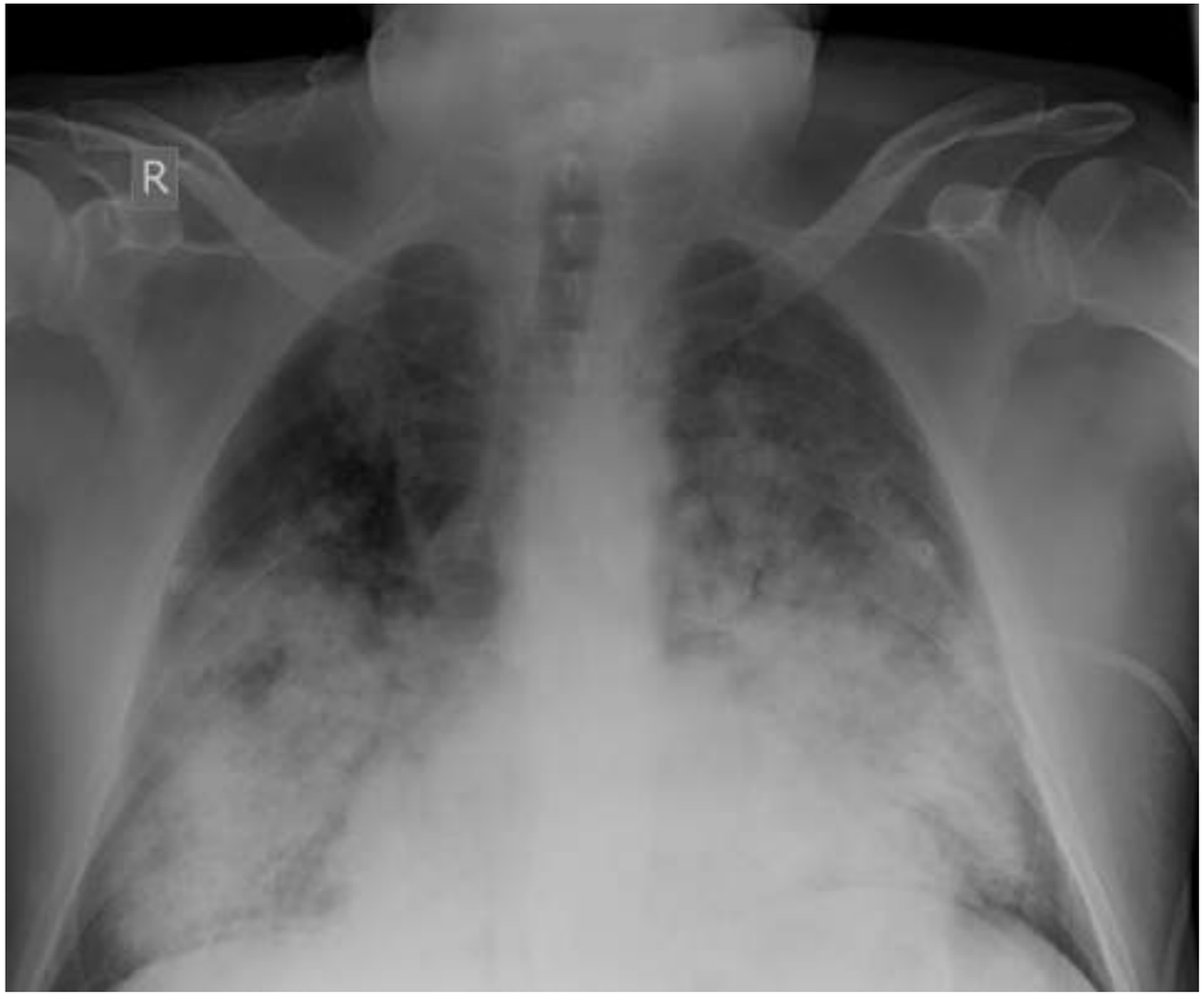
- **Ανοσολογικός έλεγχος (ANCA, MPO, PR3, antiGBM)**
- **Βιοψία**

AAV , antiGBM και ΠΑ

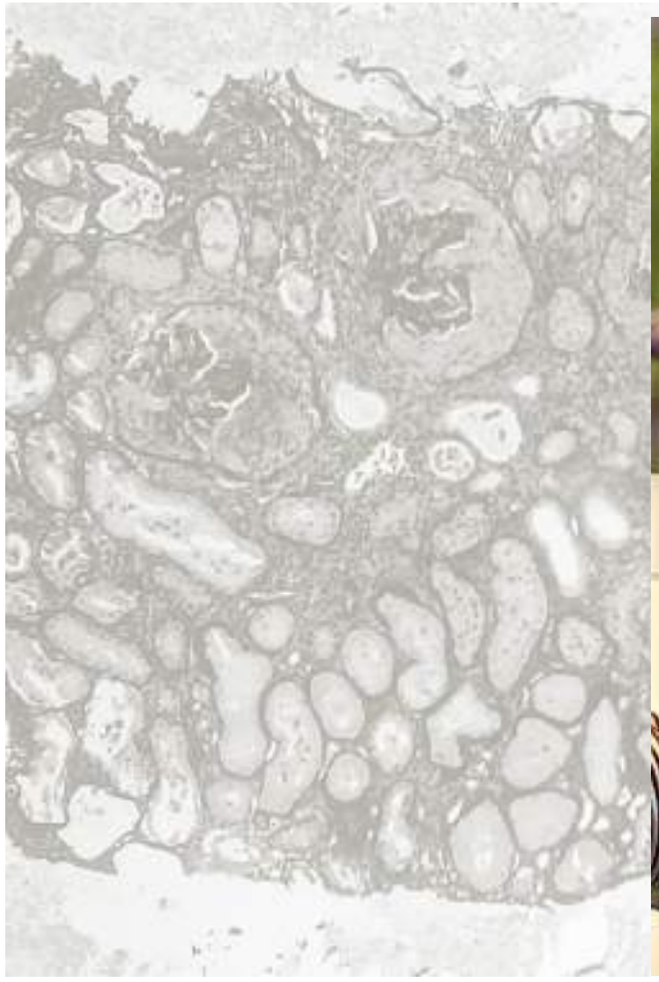
- Ανοσολογικός έλεγχος (ANCA, MPO, PR3, antiGBM)
- Βιοψία

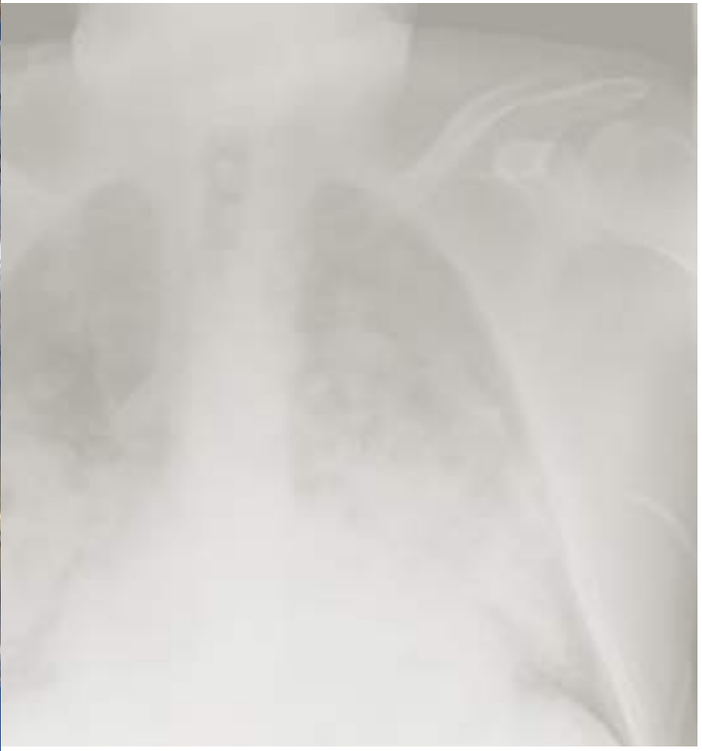
AAV ή antiGBM + πνευμονική αιμορραγία



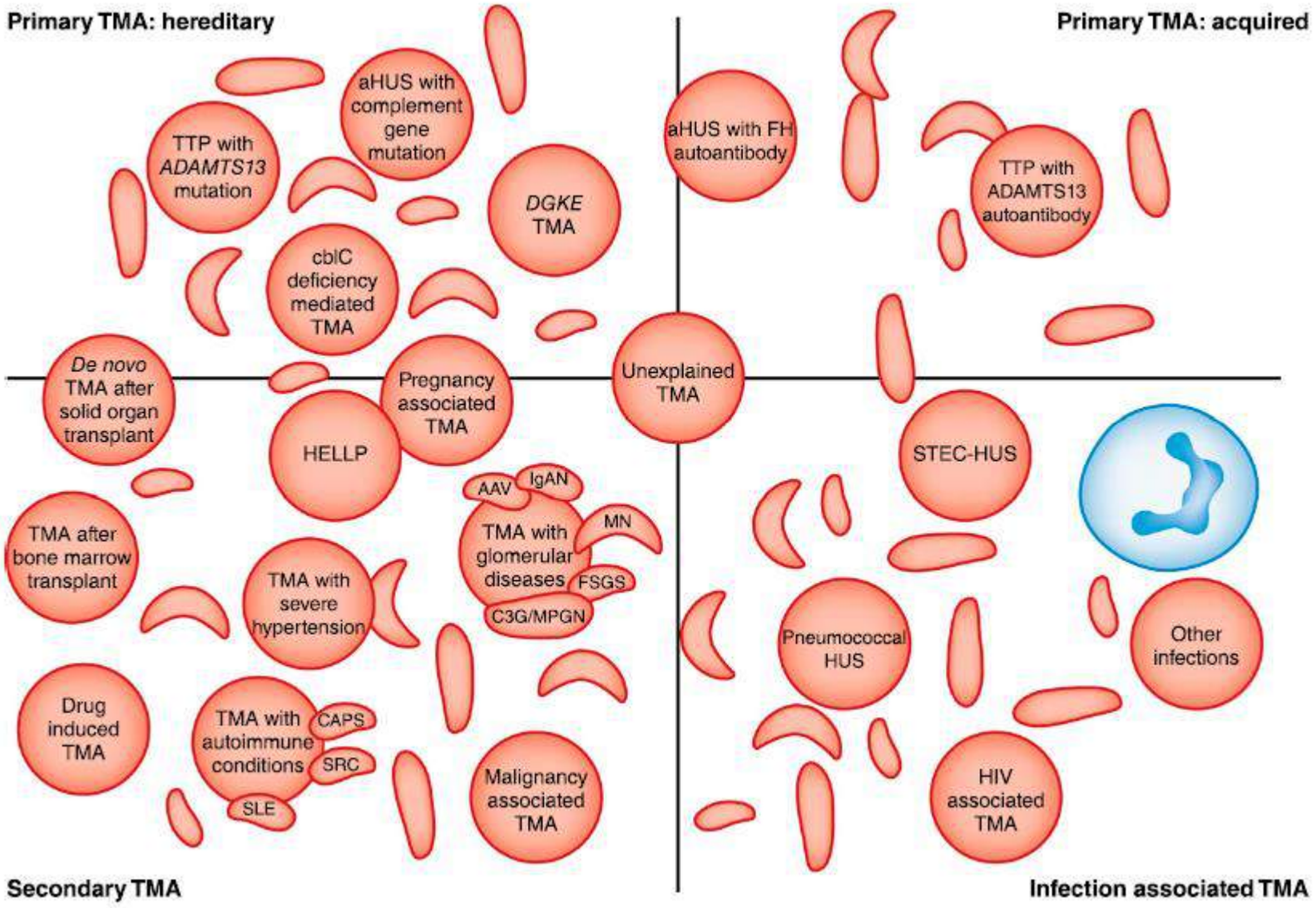


AAV ή antiGBM + πνευμονική αιμορραγία





Θρομβωτική μικροαγγειοπάθεια (ΘΜΑ)



Clin J Am Soc Nephrol 13: 300–317, 2018

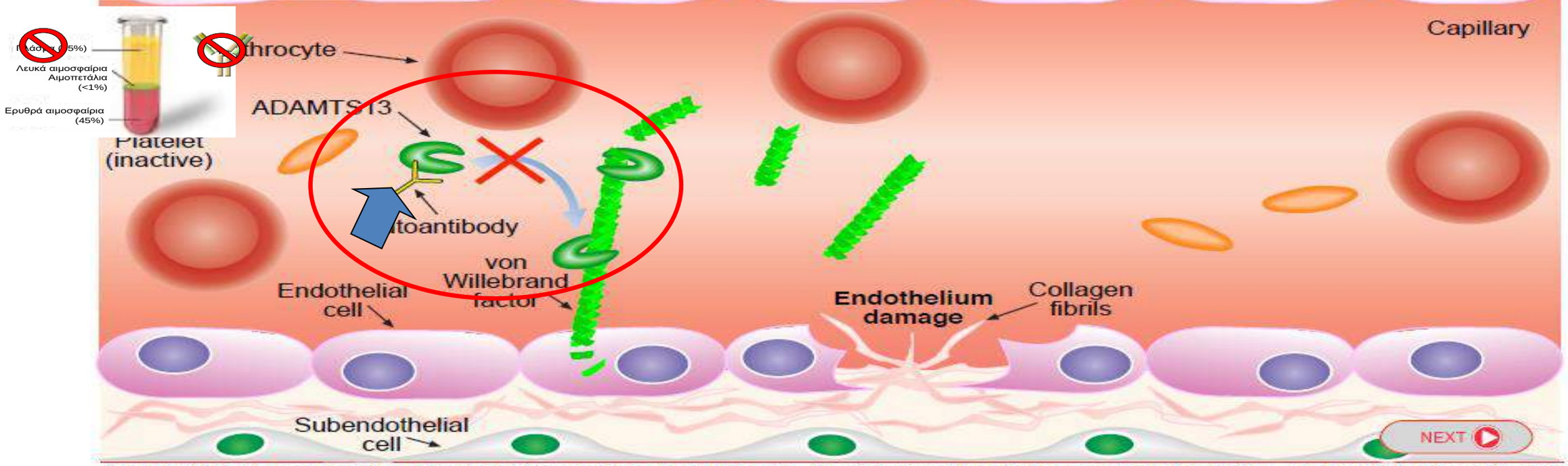
ΘΜΑ και ΠΑ

Thrombotic microangiopathy, coagulation mediated	TPE	*THBD, DGKE*, and *PLG* mutations	III	2C
Thrombotic microangiopathy, complement mediated	TPE	Factor H autoantibody	I	2C
	TPE	Complement factor gene mutations	III	2C
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I	2B
	TPE	Clopidogrel	III	2B
	TPE	Gemcitabine/Quinine	IV	2C
Thrombotic microangiopathy, infection associated	TPE/IA	STEC-HUS, severe	III	2C
	TPE	pHUS	III	2C
Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP)	TPE		I	1A
Thrombotic microangiopathy, transplantation associated	TPE		III	2C

Θρομβωτική Θρομβοπενική Πορφύρα
Thrombotic Thrombocytopenic Purpura (TTP)

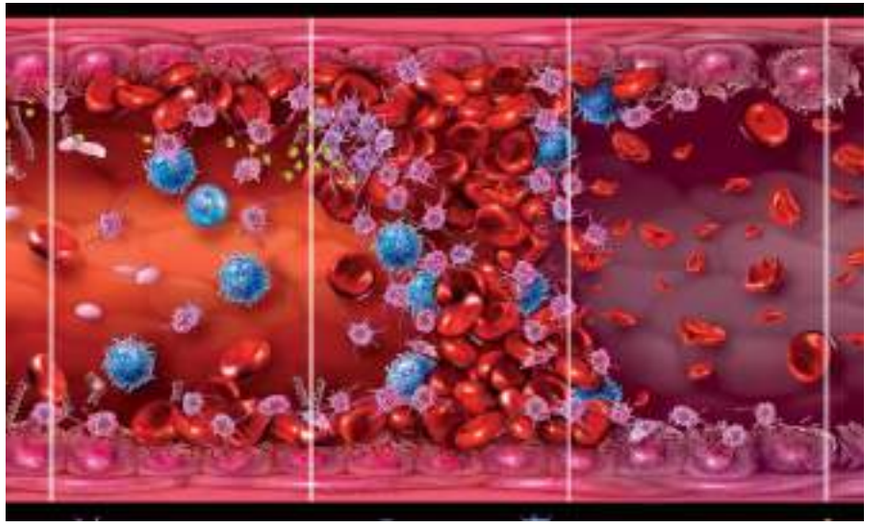
Θεραπεία ΤΤΡ με πλασμαφαίρεση

Αφαίρεση αναστολέα και χορήγηση ADAMTS13



Με την ΠΑ η θνητότητα από 90% έπεσε στα 25%
50% υποτροπή

TTP – Διακοπή αφαίρεσης



- TPE is generally performed daily until the platelet count is **>150 × 109/L, and LDH is near normal for 2-3 consecutive days**.

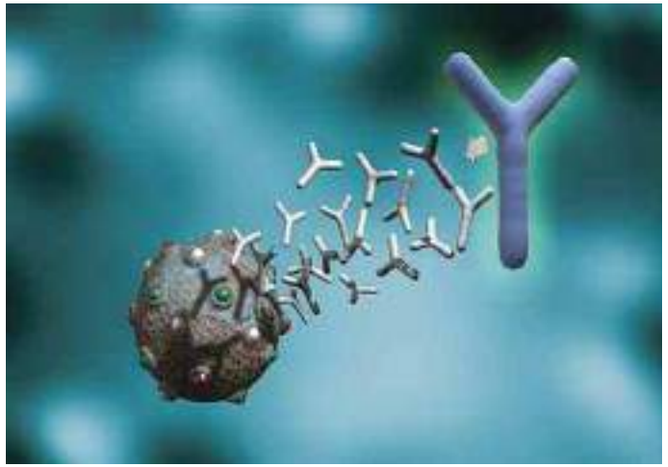
American Society for Apheresis

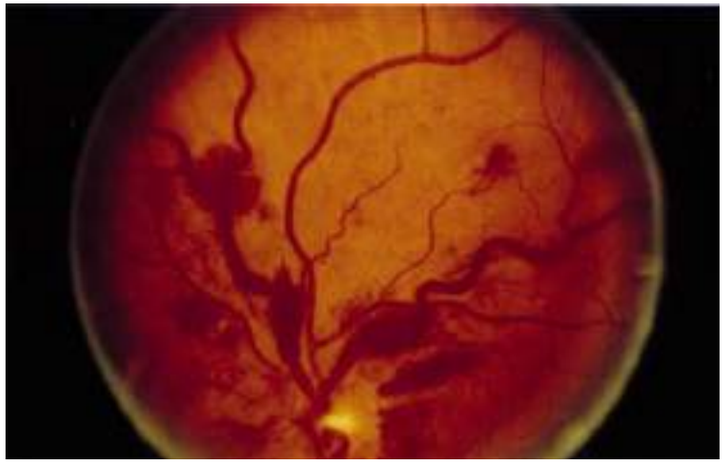
J Clin Apher. 2019;34:171–354

Υπεργλοιότητα - Υπεργαμμασφαιριναιμία

Σύνδρομο υπεργλοιότητας (ΣΥΓ)

- Αύξηση σφαιρινών(αντισωμάτων) λόγω αιματολογικής νόσου (πολλαπλούν μυέλωμα ή νόσος Waldestroem)
- Αύξηση ιξώδους – γλοιότητας πλάσματος
- Κεφαλαλγία, κακουχία, υπνηλία, ακουστικές/οπτικές διαταραχές, σπασμοί, κώμα





ΠΑ και ΣΥΓ

HYPERVISCOSITY IN HYPERGAMMAGLOBULINEMIA

Incidence: 5/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Symptomatic	TPE	Grade 1B	I
	Prophylaxis for rituximab	TPE	Grade 1C	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Symptomatic	0	3(46)	21(279)	NA
Prophylaxis for rituximab	0	0	3(45)	3(3)

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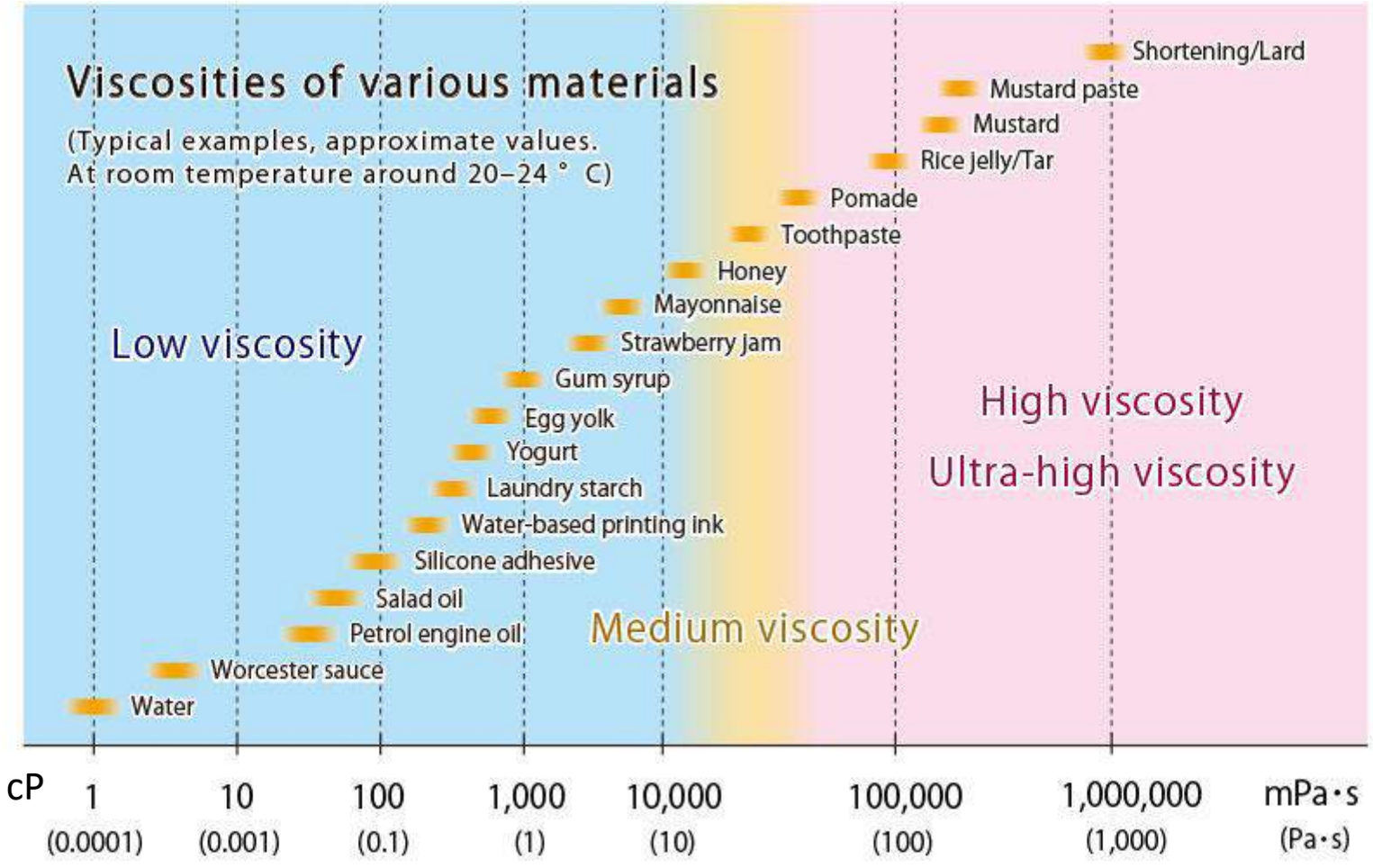
Γλοιότητα - ιξώδες

Measurement units of viscosity

- pascal seconds (Pa·s)
- millipascal second (mPa·s)
- centipoise (cP)

0.001 Pa·s	=	1 mPa·s	=	1 cP
pascal seconds		millipascal seconds		centipoise

https://www.thinkymixer.com/en-us/library/topic/about-viscosity-difference-in-viscosity-seen-with-your-own-eyes/


Viscosities of various materials
(Typical examples, approximate values.
At room temperature around 20–24 ° C)
Shortening/Lard
Mustard paste
Mustard
Rice jelly/Tar
Pomade
Toothpaste
Honey
Mayonnaise
Strawberry jam
Gum syrup
Egg yolk
Yogurt
Laundry starch
Water-based printing ink
Silicone adhesive
Salad oil
Petrol engine oil
Worcester sauce
Water
Low viscosity
Medium viscosity
High viscosity
Ultra-high viscosity
cP
1
(0.0001)
10
(0.001)
100
(0.1)
1,000
(1)
10,000
(10)
100,000
(100)
1,000,000
(1,000)
mPa・s
(Pa・s)

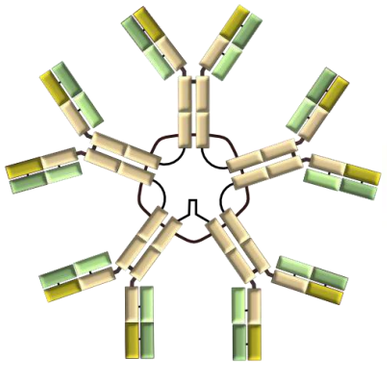
Επίπεδα Ig και ΣΥΓ

Worcester sauce: **6-7 cp**

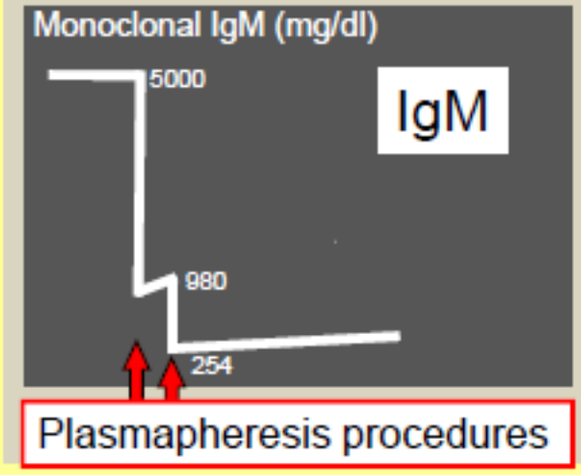
- «Symptoms of hyperviscosity usually appear when the normal serum viscosity of 1.4 to 1.8 cp reaches **4 to 5** cp, corresponding to a serum IgM level of at least 3 g/dL, an IgG level of 4 g/dL, and an IgA level of 6 g/dL»

Semin Thromb Hemost 2003; 29(5): 467-472

Igs, μέγεθος, κατανομή και απομάκρυνση με ΠΑ

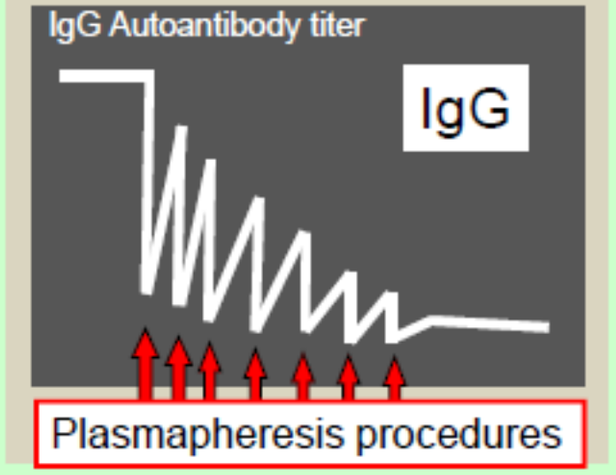


Removal of IgM
(Ward DM, *Updates to Harrison's Principle's of Internal Medicine*, Volume V, 1984)

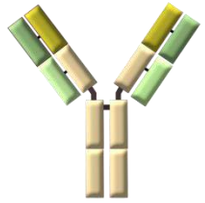


Waldenstrom's macroglobulinemia
- IgM is large (~970,000 Daltons)
- 85% of IgM stays intravascular

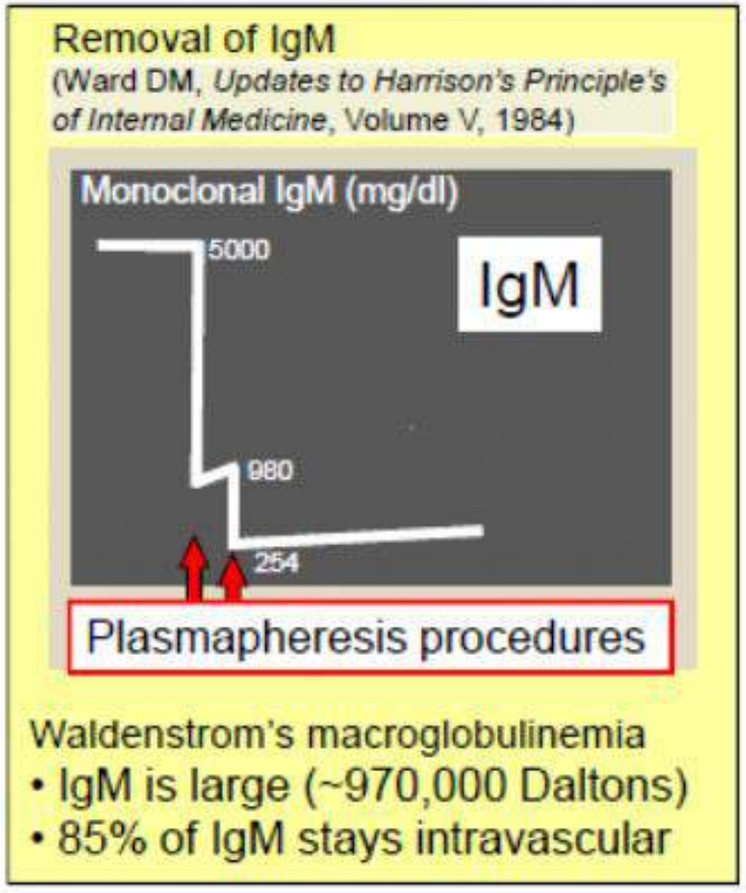
Removal of IgG
(Ward DM, *Updates to Harrison's Principle's of Internal Medicine*, Volume V, 1984)



Most antibody mediated diseases:
- IgG is smaller (~146,000 Daltons)
- Only 30%-40% is intravascular



Αποτελεσματικότητα ΠΑ σε ΣΥΓ από IgM



- "IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels.
- Thus, a relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity.
- TPE reduces viscosity 20-30% per treatment."

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WM, ΣΥΓ, Rituximab, IgM και ΠΑ

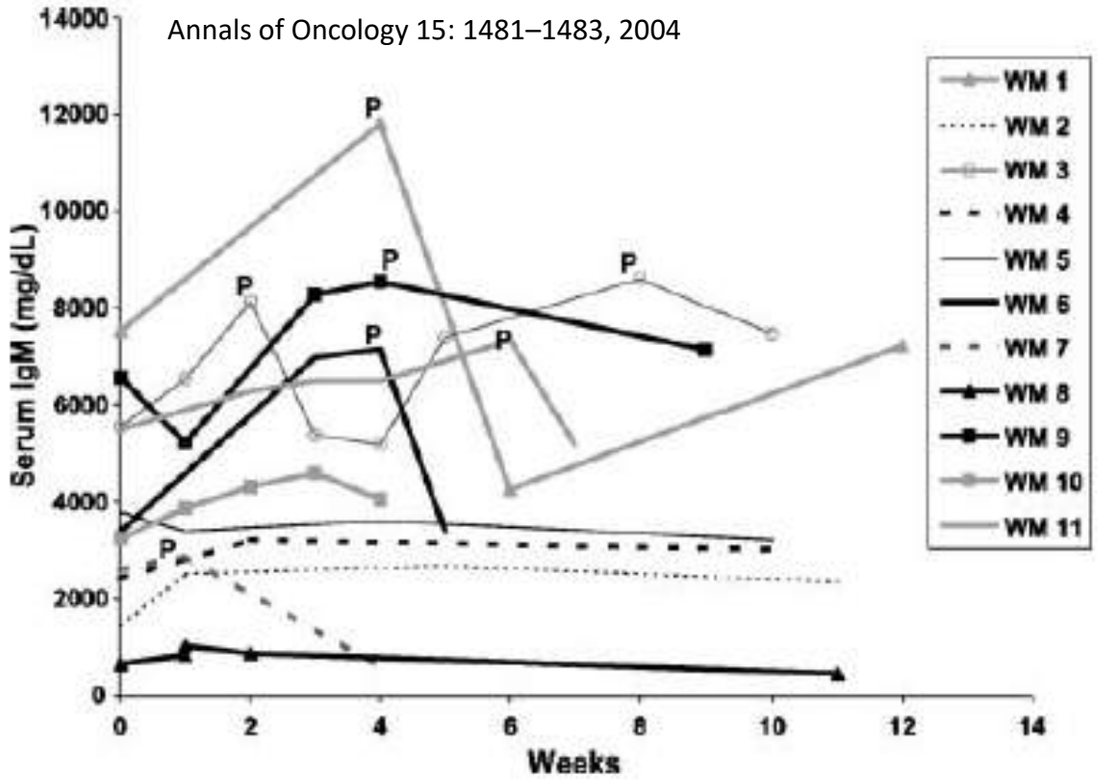

Figure 1. Serial IgM serum levels for 11 patients with Waldenstrom's macroglobulinemia who received treatment with rituximab. P denotes patient required plasmapheresis for hyperviscosity.

- "A transient **increase in IgM** level **after rituximab** therapy (flares), has been reported
- **TPE should be considered before giving rituximab if serum viscosity >3.5 cp or IgM > 4 g/dL.**
- **to lower IgM to <4 g/dL prior to rituximab therapy**."

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ΠΑ και αιμορραγική διάθεση

ΠΑ και ινωδογόνο

- Καθημερινές ΠΑ με αλβουμίνη

- χαμηλό ινωδογόνο

- Αιμορραγική διάθεση

- Παρακολούθηση επιπέδων ινωδογόνου
- Προσθήκη FFP

Έγκυμοσύνη και ινωδογόνο

TABLE I. Recommendations for Conducting Therapeutic Plasma Exchange in a Pregnant Patient

Recommendation	Reasoning
Left Lateral Decubitus Position	Placing the patient in a slight left lateral decubitus position may help minimize inferior vena cava compression and poor vascular return
Adjustment of Plasma Volume	Increase calculated plasma volume by 50% to account for physiologic changes associated with pregnancy at the start of the 2nd trimester
Prevention of hypocalcemia	May consider administration of calcium gluconate (starting dose 1 g) to mitigate calcium citrate toxicity
Fibrinogen levels	Consider the lower limit of normal fibrinogen to be 50% higher than the lower limit for non-pregnant individuals to account for physiologic changes. Postpone procedures or modify replacement fluid to include FFP if clinically indicated
Consultation of Obstetrics	Involvement of Obstetrics and/or Fetal-Maternal Medicine may help with overall management of patient and fetus
Determination of Rh Status and RhIg Administration	Plasma exchange may reduce RhIg levels below recommended levels. Re-administration of RhIg may be considered after cessation of plasma exchange

Fibrinogen levels

Consider the lower limit of normal fibrinogen to be 50% higher than the lower limit for non-pregnant individuals to account for physiologic changes. Postpone procedures or modify replacement fluid to include FFP if clinically indicated

Journal of Clinical Apheresis (2016)DOI: 10.1002/jca.21468

Ευχαριστώ για την προσοχή σας