Περί Θεραπευτικής Αφαίρεσης

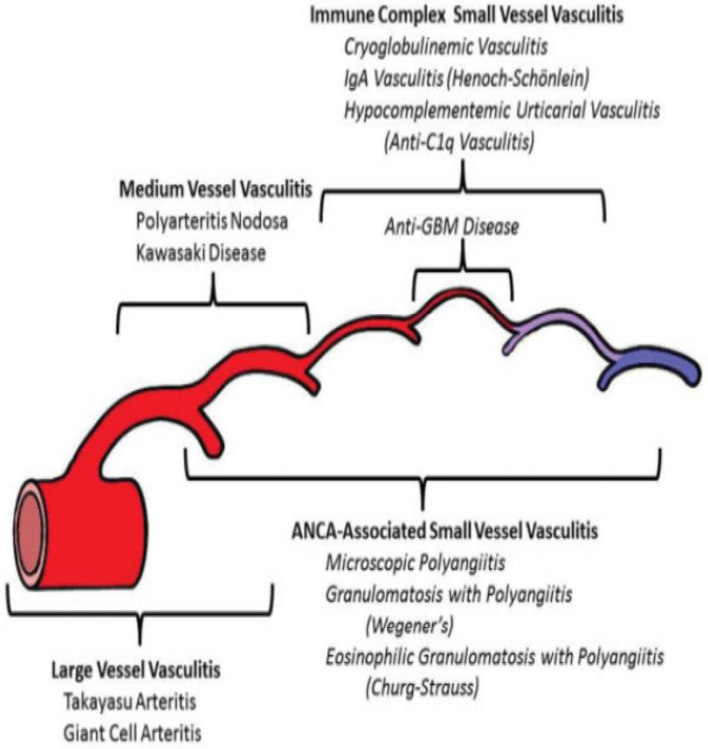
Η ΕΦΑΡΜΟΓΗ ΤΗΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΑΦΑΙΡΕΣΗΣ ΣΤΙΣ ΣΠΕΙΡΑΜΑΤΙΚΕΣ ΠΑΘΗΣΕΙΣ **ΣΥΝΔΡΟΜΟ GOODPASTURE**

4η ΕΤΗΣΙΑ ΕΠΙΣΤΗΜΟΝΙΚΗ ΕΚΔΗΛΩΣΗ
Γ.Ν. «ΠΑΠΑΓΕΩΡΓΙΟΥ» ΘΕΣ/ΝΙΚΗ 14-16/12/2018

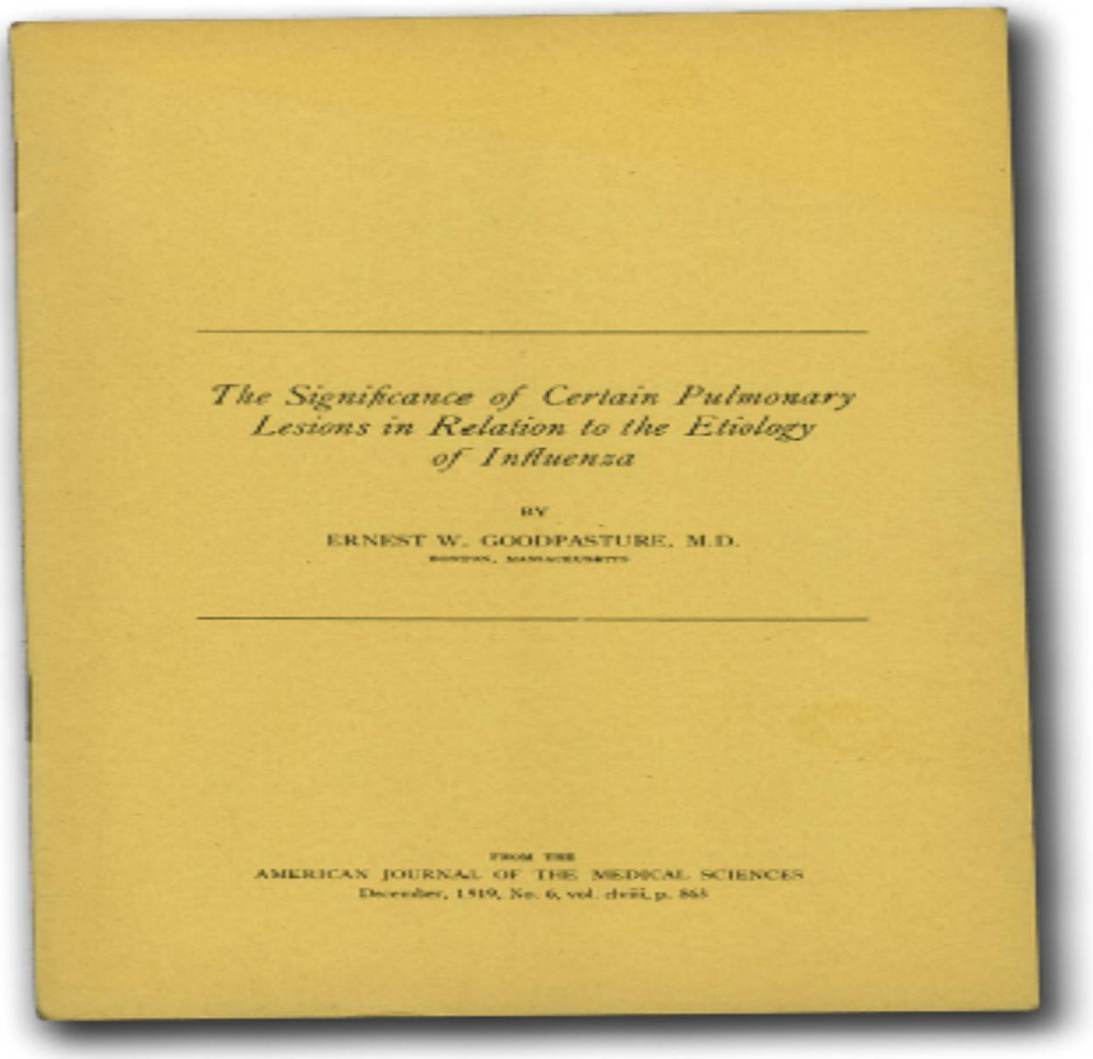
Ευαγγελία Ντουνούση Επίκουρη Καθ. Νεφρολογίας Πανεπιστημίου Ιωαννίνων

2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

tion	CHCC2012 name	CHCC2012 definition
eries more es. Large its major may be	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and
us, e aor usual ears. us, us its ma on fo d vert e temporal tients older sociated with	Anti–glomerular basement membrane (anti-GBM) disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.
ecting medium in visceral s. Any size	Anti–glomerular basement membrane (anti-GBM) disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.



1919: A fatal case of GN and lung hemorrhage attributed to an atypic influenza infection.



The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza

BY

ERNEST W. GOODPASTURE, M.D.

BOSTON, MASSACHUSETTS

FROM THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

December, 1919, No. 6, vol. clviii, p. 863

Dr Ernest Goodpasture

"I was not aware of such a connection between lung and kidney disease"

HISTORY OF GOODPASTURE SYNDROME – ANTI-GBM Abs

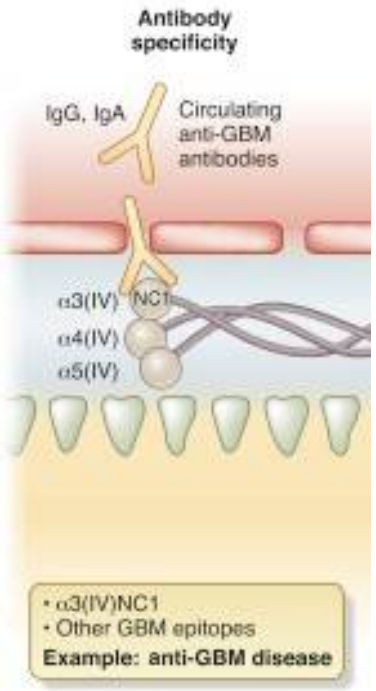
1958
"Goodpasture disease" was first used by *Australians Stanton and Tange*, in their report describing 9 cases of GN associated with lung hemorrhage.

1964
Development of immuno-fluorescence techniques making possible to detect anti-GBM Abs in kidney tissue.

1967
The pathogenic potential of anti-GBM antibodies in kidney tissue was demonstrated upon elution and transfer to nonhuman primates.

1969
Detection of circulating anti-GBM Abs in patients.

1973
The first comprehensive clinical description of "anti-GBM antibody–induced GN" by *Wilson and Dixon in Kidney International*.



IMMUNOSUPPRESSION AND PLASMA-EXCHANGE IN THE TREATMENT OF GOODPASTURE'S SYNDROME

C. M. LOCKWOOD
A. J. REES
T. A. PEARSON
D. J. EVANS
D. K. PETERS

Department of Medicine, Hammersmith Hospital, Royal Postgraduate Medical School, London W12 0HS

C. B. WILSON

Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California, U.S.A.

THE LANCET, APRIL 3, 1976

Summary Seven patients with Goodpasture's syndrome induced by anti-glomerular-basement-membrane (anti-G.B.M.) antibody were treated by a regimen of intensive plasma-exchange, cytotoxic drugs, and steroids. In the three patients retaining some renal function at presentation, this regimen led to suppression and eventual termination of antibody synthesis with improvement in renal function. In four patients, all anuric at presentation, antibody to G.B.M. persisted with variable reduction in the circulating levels. No return of renal function occurred in this group, all of whom had extensive changes on renal biopsy. Pulmonary hæmorrhage, life-threatening in one patient, was rapidly controlled in all five patients in whom it was a presenting feature. In addition to its effect on antibody levels, plasma-exchange, using volume-replacement with plasma-protein fraction (P.P.F.), resulted in substantial depletion of complement and fibrinogen, mediators possibly contributing to the antibody-induced injury.

EPIDEMIOLOGY

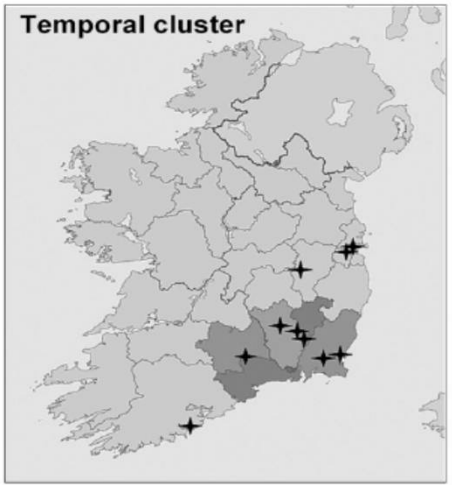
- Incidence of **1 pmp/year** in **European** populations, **rarer in African** populations
- **10%–15% of all cases of crescentic GN** in Bx series
- **Male predominance** (>50%)
- **Bimodal age distribution**:
  - I peak ***3rd decade*** (male predominance, kidney + lung disease)
  - II peak ***6th-7th decades***, (more common isolated kidney disease)
- **Genetic susceptibility:** HLA-DR15, DR4 = increased risk, DR1,DR7 = lesser risk

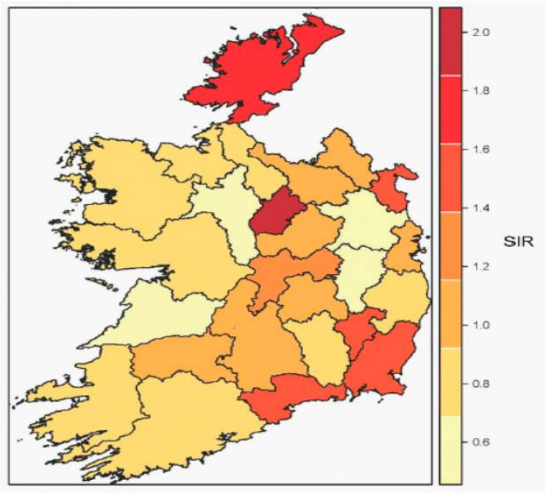
McAdoo & Pusey. CJASN 11:1392-1399,2016

"Outbreaks" and seasonal variation - *spatial and temporal clustering* of disease

ENVIRONMENTAL FACTORS MAY BE IMPORTANT TRIGGERS FOR DISEASE ONSET

- infections
- cigarette smoking
- inhalation of hydrocarbons
- treatment with the anti-CD52 monoclonal Ab alemtuzumab





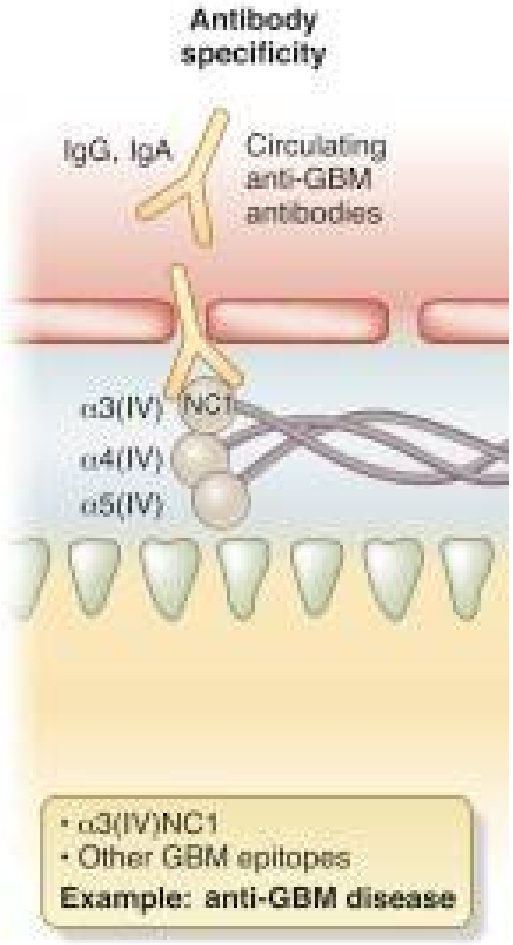
Spatial and temporal clustering of anti-GBM disease

✓ A significant cluster of cases was identified beginning on **December 2012-March 2013**

✓ Western counties had relatively lower incidence

McAdoo & Pusey. CJASN 11:1392-1399,2016

Immunopathogenesis – “Goodpasture AutoAg” - a3(IV)NC1



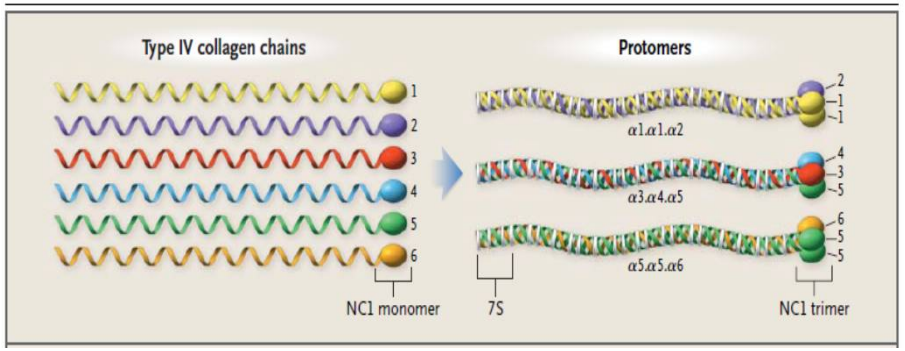
Anti-GBM Abs (IgG>>IgA, IgM)

Principal target

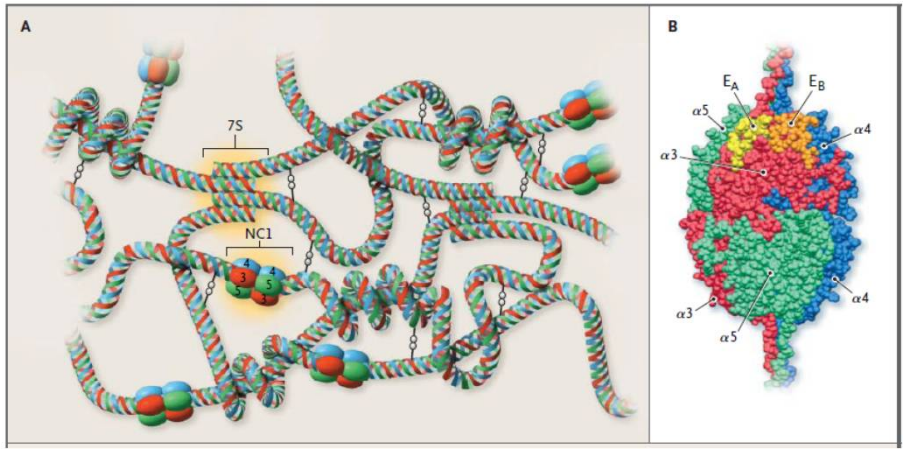
“Goodpasture autoantigen”

NC1 domain of the alpha-3 chain of type IV collagen

(Restricted expression of BM of glomerular and alveolar capillaries)



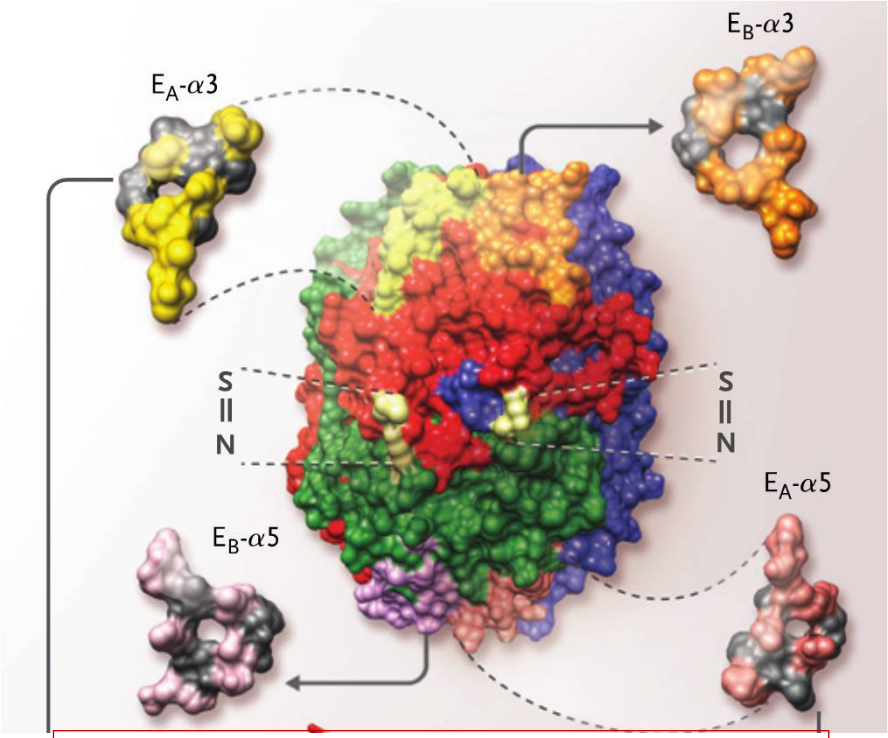
Triple Helical Organization of the Type IV Collagen Family



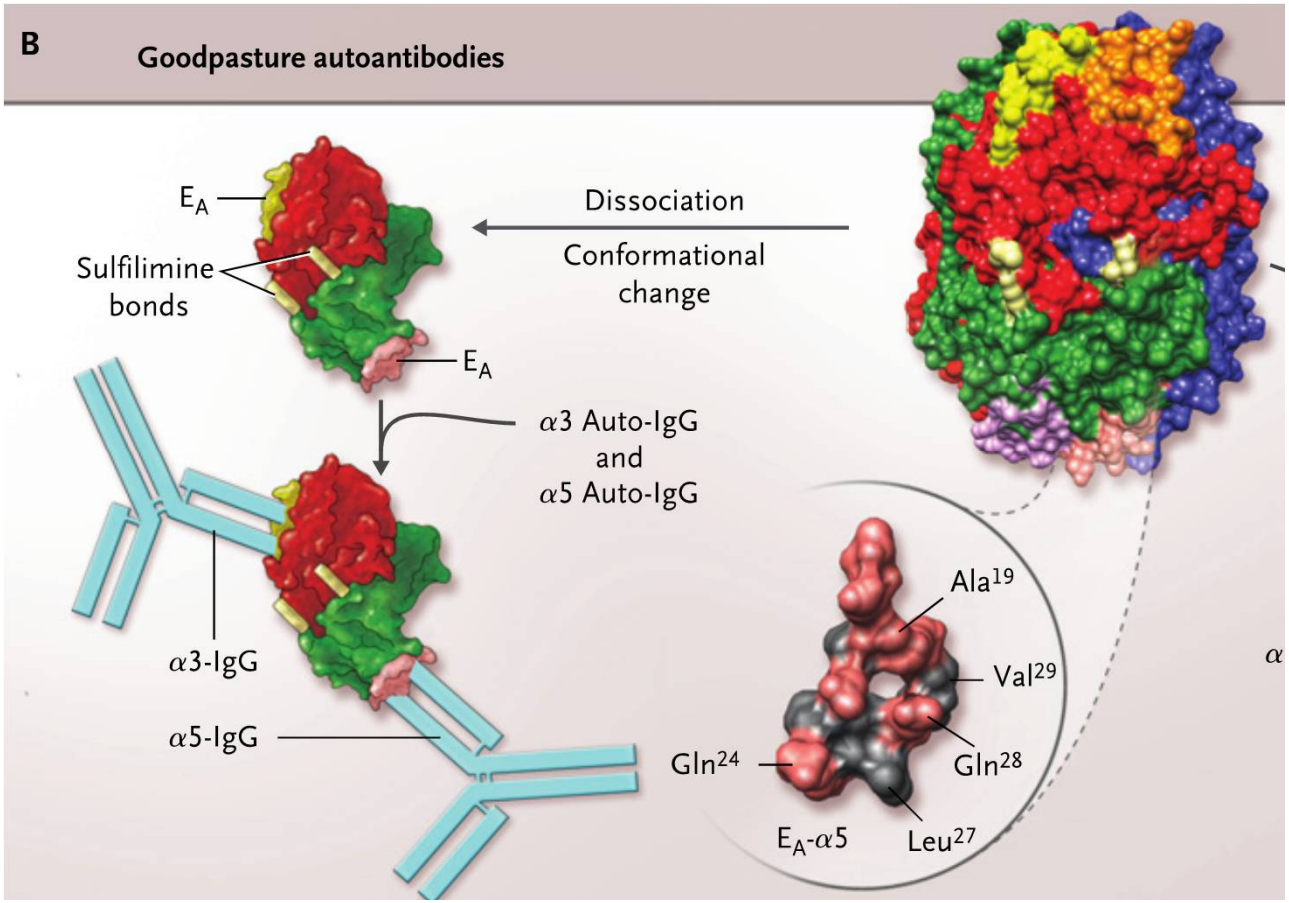
Assembly and Network Organization of Collagen IV

Hudson et al, N Engl J Med 2003

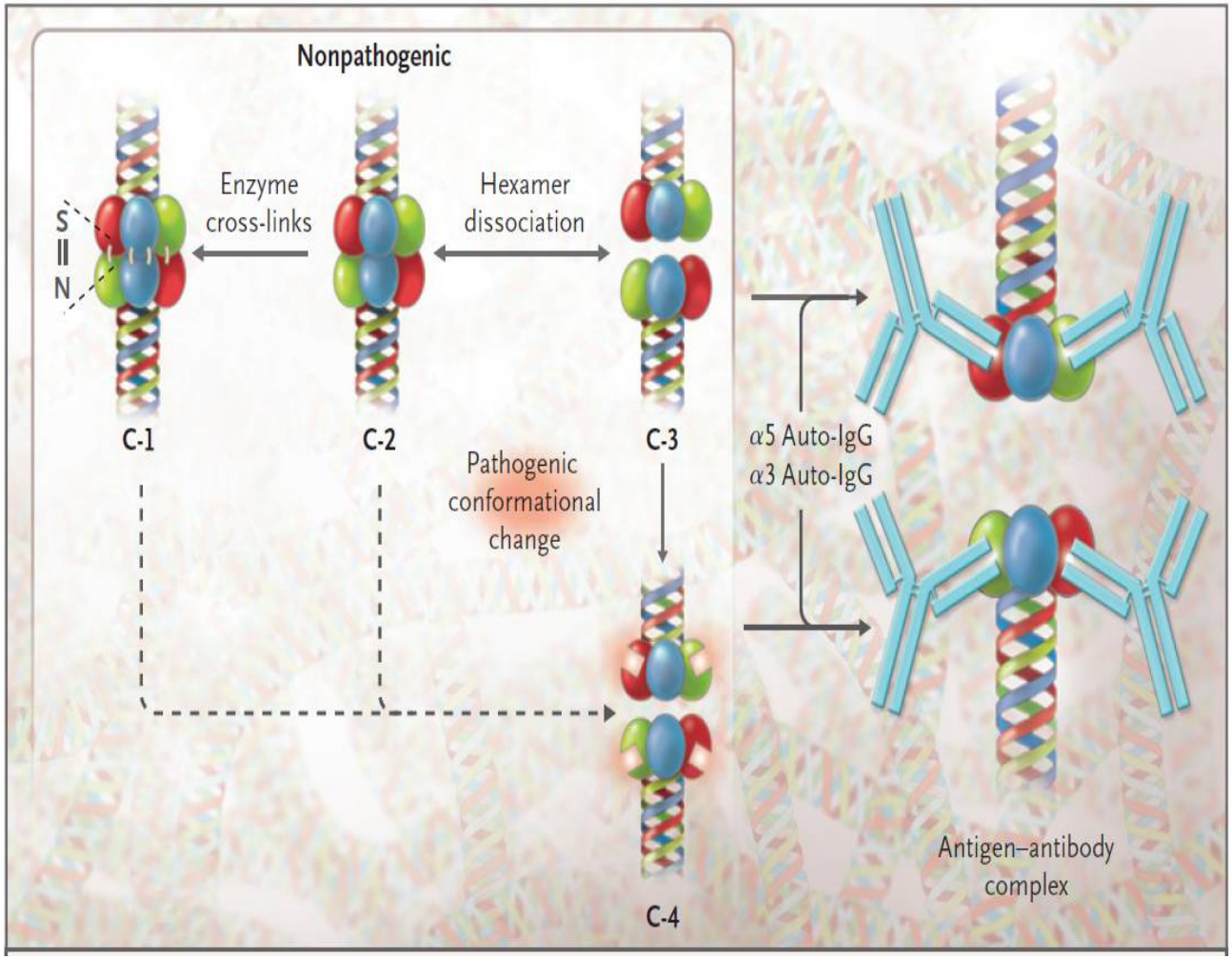
Conformational transitions in subunits of non–cross-linked hexamers or trimers forming pathogenic neoepitopes that elicit Ab production and binding



*Two principle **autoantibody EPITOPES** within the **autoantigen EA and EB, sequestered in native GBM within the quaternary structure** of the noncollagenous domains of the triple helix of a3, 4, and 5 chains.*



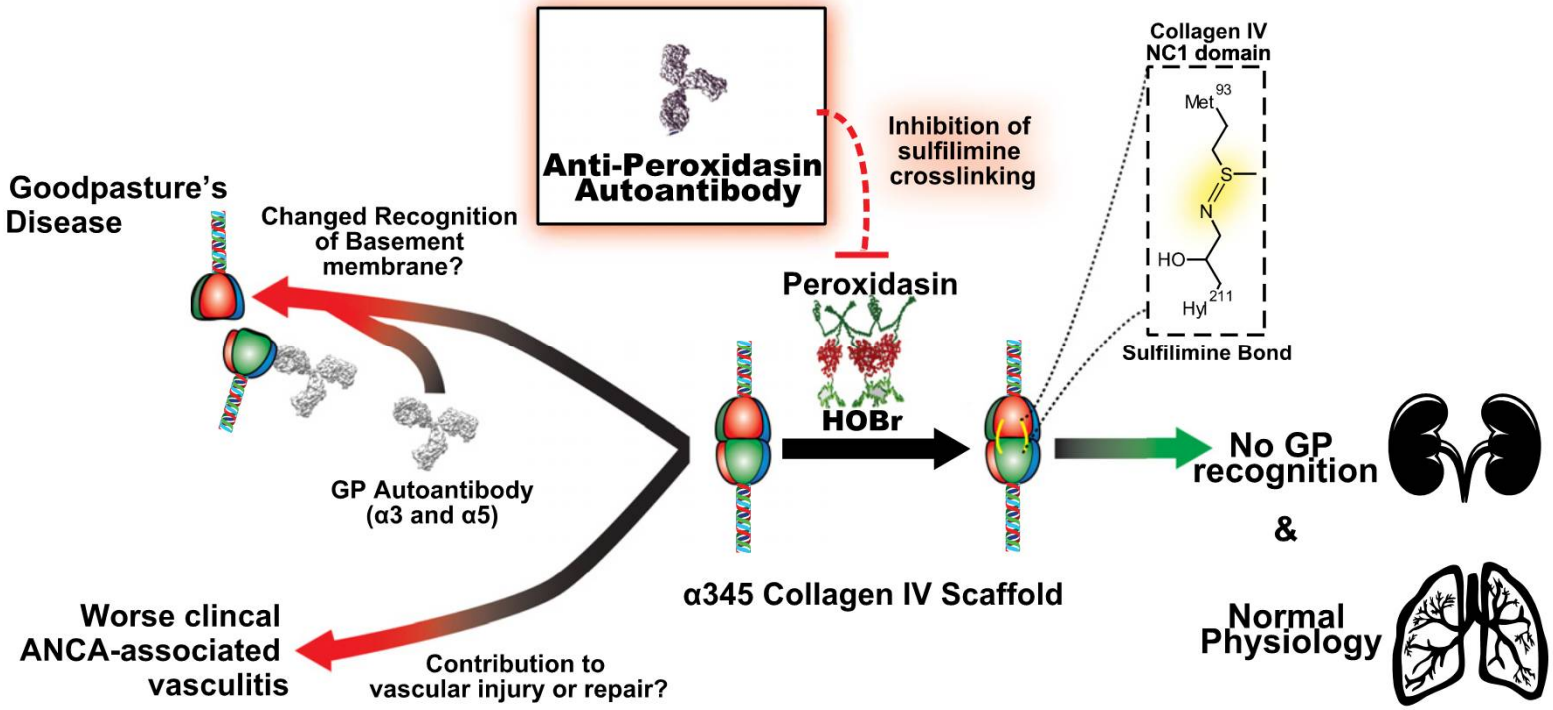
Pedchenko V et al. NEJM 2010



- ❖ The triggering event may be an individual factor or a combination of factors that perturbs the quaternary structure of the hexamer.
  - enzymatic or nonenzymatic post-translational modifications
  - a rise in body temperature
  - proteolytic cleavage
- ❖ Anti-GBM Ab with high affinity could themselves induce the necessary conformational change and bind to the antigen without denaturation

Pedchenko V et al. NEJM 2010

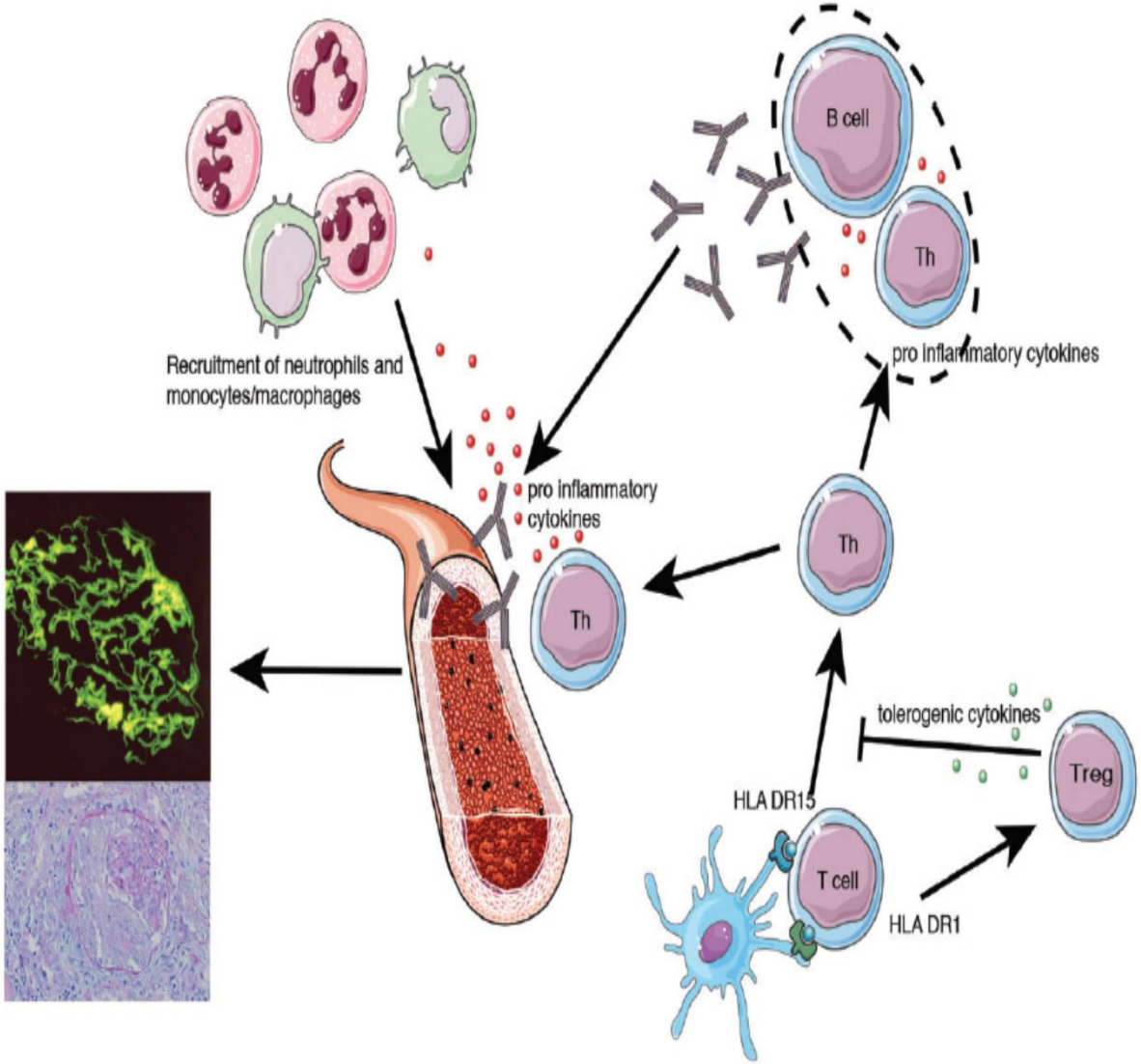
Conclusions Anti-peroxidasin antibodies, which would previously have been mis-characterized, are associated with pulmonary-renal syndromes, both before and during active disease, and may be involved in disease activity and pathogenesis in some patients.



Exposure of the cryptic epitope is thought to occur via disruption of sulfilimine crosslinks in the NC1 domain that are formed by **peroxidasin-dependent production of hypobromous acid**

McCall S et al. JASN Nov 2018

Immune mediated tissue destruction



- T cells stimulated with a3(IV) peptides on HLA-DR15 proliferate into pro-inflammatory CD4+ T cells.
- The same peptides loaded on HLR-DR1 induce Tregs inhibit the pro-inflammatory response.
- The presence of DR15/absence of DR1 cause T-cell influx into the tissue + promote affinity maturation of anti-GBM antibodies from the existing pool of B cells.
- Cytokines produced by the T cells + bound Ab recruit and activate neutrophils + monocytes/macrophages.

Segelmark et al, Nephrol Dial Transplant 2018

Central to the diagnosis of anti-GBM disease is:

- ✓ the identification of anti-GBM Ab either in serum or deposited in tissue
- ✓ along with pathologic features of crescentic GN (80-90& RPGN)
- ✓ with (40-60%) or without evidence of alveolar hemorrhage

Serologic testing for anti-GBM antibodies is by definition, an urgent laboratory test!

- **Results should be available within 24 hours for patients presenting with RPGN**

➢ **ELISA or luminex-based** technologies

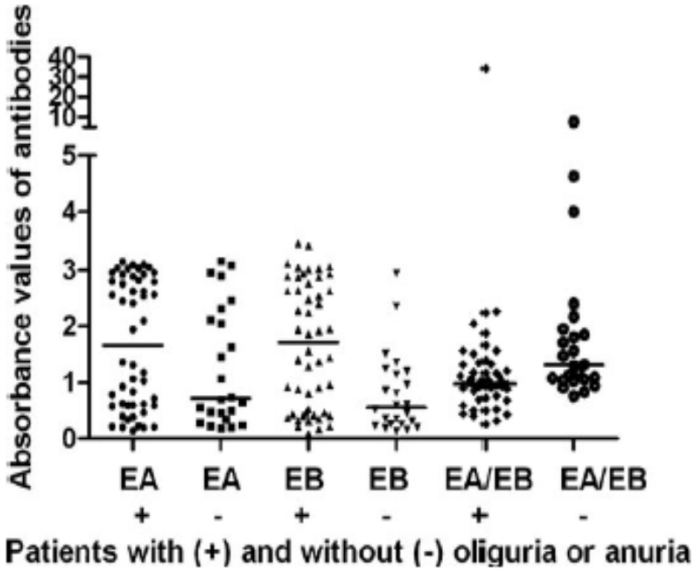
Specificity and sensitivity of assays range **90%-100%** and **95%-100%,** respectively

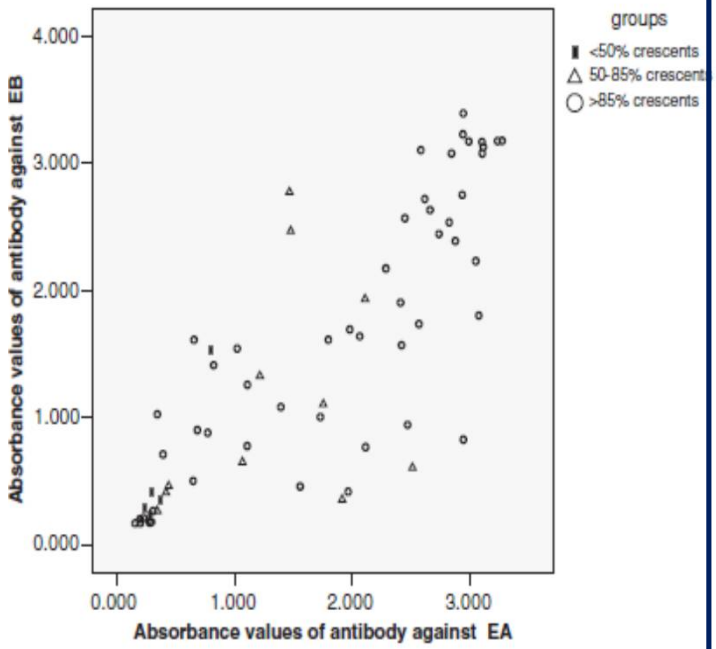
10% of patients do not have identifiable circulating Ab *with conventional assays*

➢ **Western blotting**: more sensitive method, not widely available

➢ **Indirect immunofluorescence using normal kidney tissue:** alternative method, requires input from a kidney pathologist, more false (-) results

High levels of circulating Ab against the specific epitopes EA & EB - more severe renal disease at diagnosis as well as a worse prognosis



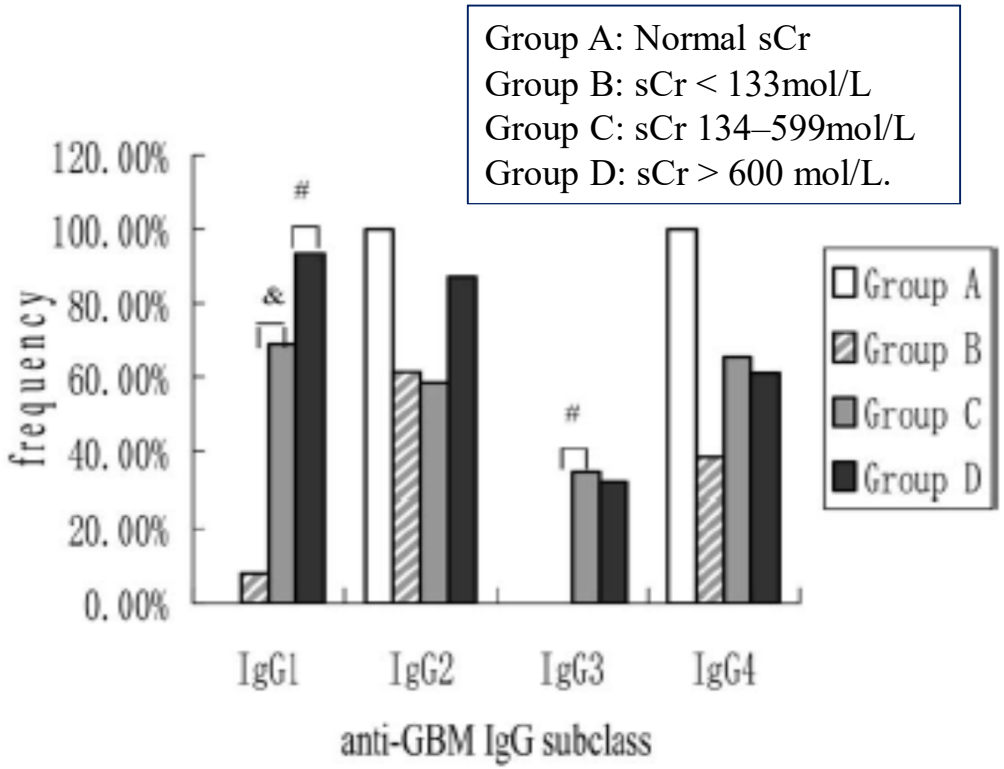


- Pts with oliguria or anuria had higher levels of autoAb against EA and EB at onset.
- Pts with a large amount of crescents had higher levels of anti-GBM Ab vs pts with better preservation of the renal architecture.

Yang et al, Nephrol Dial Transplant 2009

Anti-GBM autoAb-IgG subclass distribution is associated with disease severity

IgG1 and IgG3 may play a major role in the initiation and progression of the disease.



The IgG subclass distribution of natural autoantibodies and anti-GBM autoantibodies in patients with different renal function on diagnosis.

- ✓ In anti-GBM patients, from normal to severely damaged renal function, IgG subclasses change from the restricted subclasses of IgG2 and IgG4 to the four subclasses at the gene level.
- ✓ Different subclasses of IgG have distinct epitope spectra.
- ✓ The increasing types of anti- GBM Ab subclasses reflected possible B-cell epitope spreading in the pathogenesis of anti-GBM disease.

Zhao et al, Human Immunology 2009

A rising titer of anti-GBM antibodies has been shown to predate the onset of clinical disease by several months

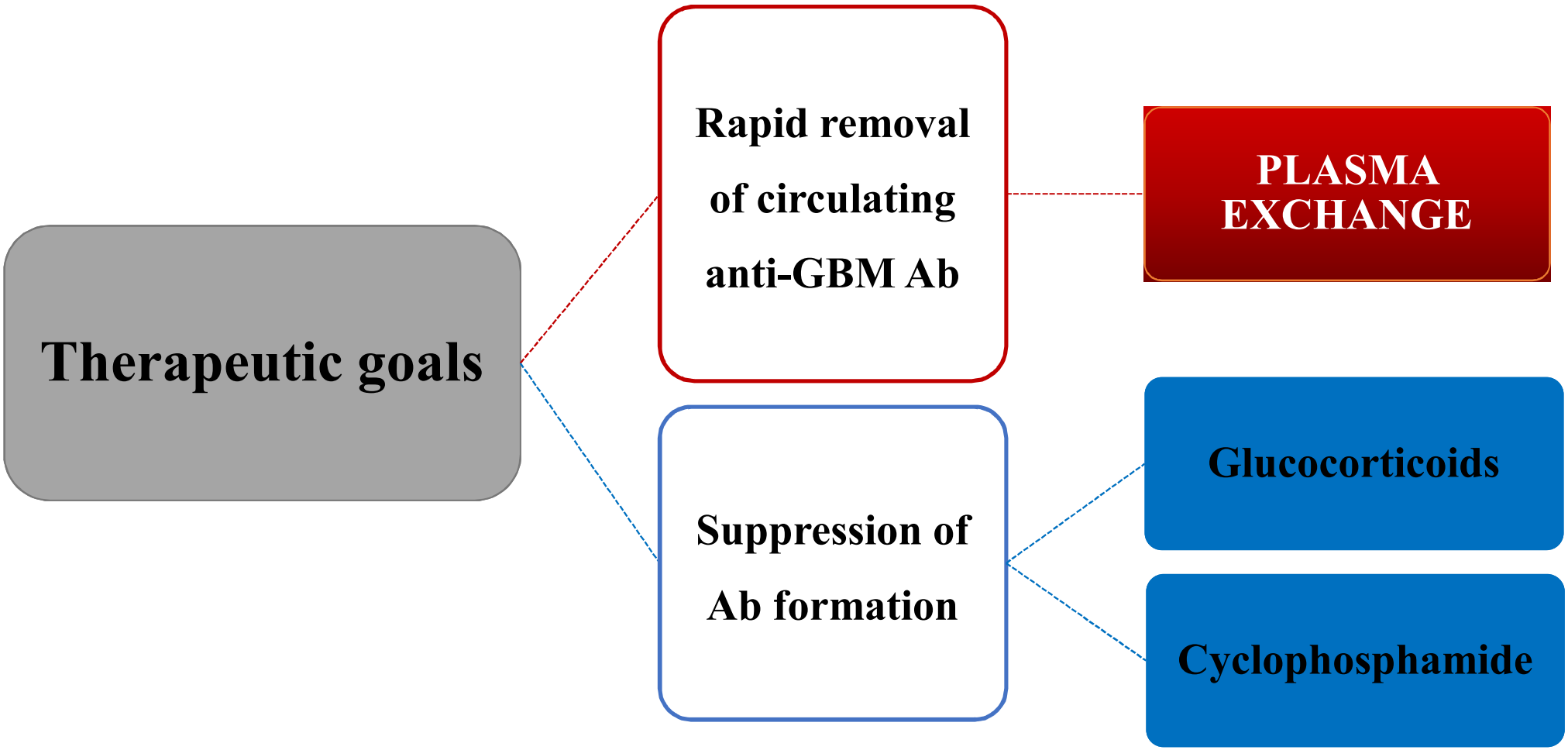
- ✓ A greater % of patients with disease had a single detectable anti-GBM level compared with matching controls at any time point before diagnosis
- ✓ Only patients with disease had multiple detectable anti-GBM levels over time.

Table 2. A comparison of the percentage of study patients with detectable anti-GBM antibody (≥1 U/ml), detectable anti-PR3 antibody (≥1 U/ml), and detectable anti-MPO antibody (>1 U/ml) compared with matched healthy controls

	Patients (%)	Controls (%)	OR	CI	*P* (Fisher's Exact)
GBM	70 (21/30)	17 (5/30)	12	3.3 to 40	<0.001
<1 years	60 (12/20)	9 (2/22)	15	2.7 to 83	<0.001
>1 years	67 (16/24)	13 (3/24)	14	3.2 to 61	<0.001
>3 years	54 (7/13)	13 (2/15)	7.5	1.2 to 48	0.04
>5 years	50 (4/8)	11 (1/8)	7	0.57 to 86	0.28
PR3	80 (24/30)	44 (13/30)	5.1	1.6 to 17	0.007
<1 years	85 (17/20)	36 (8/22)	10	2.2 to 45	0.002
>1 years	83 (20/24)	30 (7/23)	12	3.0 to 49	<0.001
>3 years	92 (12/13)	20 (3/15)	48	4.3 to 529	<0.001
>5 years	100 (8/8)	25 (2/8)	49[a]	2.5 to 949[a]	0.007
MPO	87 (26/30)	60 (18/30)	4.3	1.2 to 16	0.04
<1 years	90 (18/20)	45 (10/22)	11	2.0 to 58	0.003
>1 years	83 (20/24)	54 (13/24)	4.2	1.1 to 16	0.05
>3 years	77 (10/13)	67 (10/15)	1.6	0.3 to 8.9	0.69
>5 years	75 (6/8)	78 (7/9)	0.86	0.09 to 8.1	1.00

Olson et al, J Am Soc Nephrol 2011

TREATMENT OF GOODPASTURE SYNDROME



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*)

14.1.2: Start treatment for anti-GBM GN without delay once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis (Table 31) while waiting for confirmation. (*Not Graded*)

14.1.3: We recommend no maintenance immunosuppressive therapy for anti-GBM GN. (*1D*)

14.1.4: Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months. (*Not Graded*)

Κατευθυντήριες οδηγίες της Αμερικανικής Εταιρείας Αφαίρεσης για θεραπευτικούς σκοπούς –American Society for Apheresis (ASFA) 2016

Journal of Clinical Apheresis 31:149–338 (2016)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

Joseph Schwartz,[1] Anand Padmanabhan,[2] Nicole Aqui,[3] Rasheed A. Balogun,[4] Laura Connelly-Smith,[5] Meghan Delaney,[6] Nancy M. Dunbar,[7] Volker Witt,[8] Yanyun Wu,[9] and Beth H. Shaz[1,10,11]*

Κατηγορία Ι-πλασμαφαίρεση

- **Σύνδρομο Goodpasture με διάχυτη κυψελιδική αιμορραγία (1 C) ή όταν δεν απαιτείται αιμοκάθαρση (1 B)**

Incidence: 1/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Dialysis-dependence[a], no DAH	TPE	Grade 2B	III
	DAH	TPE	Grade 1C	I
	Dialysis-independence[a]	TPE	Grade 1B	I
No. of reported patients: > 300	**RCT**	**CT**	**CS**	**CR**
	1(17)	0	19(468)	21

[a]At presentation, defined as Cr > 6 mg/dL. DAH = diffuse alveolar hemorrhage.

- Combination of PLEX + CS +CTX
- DO NOT PERFOM PLEX UNLESS DAH IS PRESENT in pts with an initial creatinine>6.6 mg/dL or who are dialysis-dependent at the time of initiation

Plasmapheresis=PLEX, Cyclophosphamide=CTX

Schwartz et al J Clin Apheresis 2016; 31: 149-338

Who should we treat?

PLEX + Prednisone + CTX should be administered:

- In **pulmonary hemorrhage**, independent of the presence and/or severity of renal involvement
- In **renal involvement with sCreatinine >5 - 7 mg/dL** not requiring immediate renal replacement therapy
- In **less severe renal disease** (<30 – 50% crescents on renal Bx) ?

Plasmapheresis=PLEX, Cyclophosphamide=CTX

Who should we treat?

- **Very low likelihood of renal response** in pts presenting with **dialysis-dependent renal failure** ***BUT…***
- **Inability to accurately identify the dialysis-dependent patient who may recover renal function Rx should be considered**:
  - In very **acute disease**
  - **Younger pts** able to tolerate aggressive immunosuppression
  - Pts with **anti-GBM Ab + ANCA**

Table 1. Initial Treatment of Anti-GBM Disease

Agent	Details and Duration	Cautions
Plasma exchange	Daily 4 L exchange for 5% human albumin solution. Add fresh human plasma (300–600 ml) within 3 d of invasive procedure (*e.g.*, kidney biopsy) or in patients with alveolar hemorrhage. Continue for 14 d or until antibody levels are fully suppressed. Monitor antibody levels regularly after cessation of treatment because plasma exchange may require reinstatement if antibody levels rebound	Monitor and correct as required: platelet count, aim $>70 \times 10^9$/L; fibrinogen, aim >1 g/L (may require cryoprecipitate supplementation to support PEX); hemoglobin, aim for >90 g/L; corrected calcium, aim to keep in normal range
	fluconazole) while on high-dose steroids. Peptic ulcer prophylaxis (*e.g.*, with PPI) while on high-dose steroid treatment. Prophylaxis against PCP (*e.g.*, cotrimoxazole) while receiving high-dose corticosteroids and cyclophosphamide. Consider acyclovir for CMV prophylaxis. Consider prophylaxis against HBV reactivation (*e.g.*, lamivudine) in patients who have evidence of previous infection (HBV cAb positive).	contribute to leukopenia; monitor leukocyte count. Alternatives include nebulized pentamidine.

PLEX

Daily 4L exchange for 5% human albumin solution

+ FFP (300–600 ml) within 3 d of invasive procedure (e.g., kidney biopsy) or alveolar hemorrhage

Duration: 14d or until Ab levels are fully suppressed

Monitor Ab levels regularly after cessation of Rx because PLEX may require reinstatement if Ab rebound

McAdoo & Pusey. CJASN 11:1392-1399,2016

IMMUNOSUPPRESSION AND PLASMA-EXCHANGE IN THE TREATMENT OF GOODPASTURE'S SYNDROME

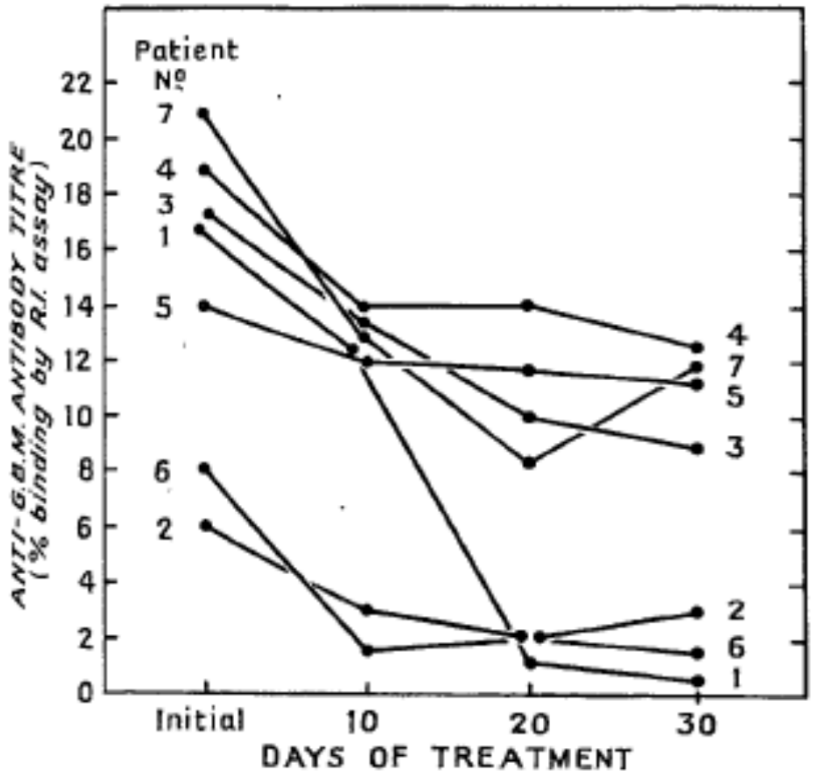
C. M. LOCKWOOD
A. J. REES
T. A. PEARSON
D. J. EVANS
D. K. PETERS

Department of Medicine, Hammersmith Hospital, Royal Postgraduate Medical School, London W12 0HS

C. B. WILSON

Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California, U.S.A.

Summary Seven patients with Goodpasture's syndrome induced by anti-glomerular-basement-membrane (anti-G.B.M.) antibody were treated by a regimen of intensive plasma-exchange, cytotoxic drugs, and steroids. In the three patients retaining some renal function at presentation, this regimen led to suppression and eventual termination of antibody synthesis with improvement in renal function. In four patients, all anuric at presentation, antibody to G.B.M. persisted with variable reduction in the circulating levels. No return of renal function occurred in this group, all of whom had extensive changes on renal biopsy. Pulmonary hæmorrhage, life-threatening in one patient, was rapidly controlled in all five patients in whom it was a presenting feature. In addition to its effect on antibody levels, plasma-exchange, using volume-replacement with plasma-protein fraction (P.P.F.), resulted in substantial depletion of complement and fibrinogen, mediators possibly contributing to the antibody-induced injury.

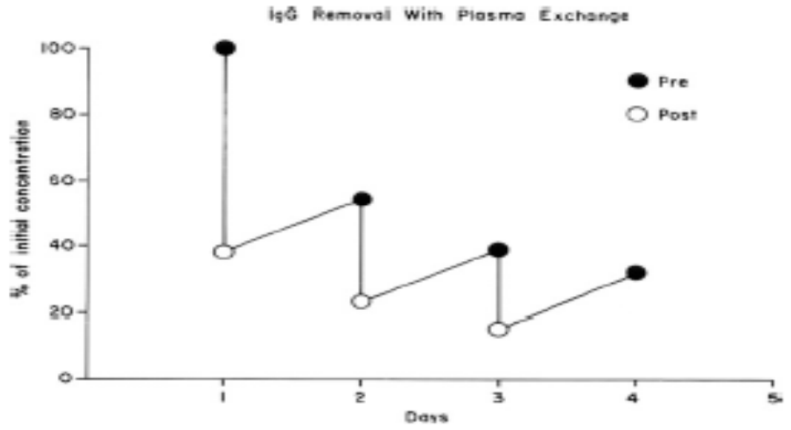


A single four-litre plasma-exchange using P.P.F. reduced the plasma IgG by 70%, and daily exchanges lowered C3 to approximately 30% and fibrinogen to around 75 mg/100ml.

ONLY 1 RANDOMIZED PROSPECTIVE STUDY

PLEX is generally recommended for the treatment of anti-GBM disease

- ✓ Improved morbidity and mortality in the era of plasmapheresis compared to historic rates
- ✓ Greater amelioration of disease consequences with rapid removal of anti-GBM antibody



0025-7974/85/6404-0219$02.00/0
MEDICINE

Vol. 64, No. 4

1 RANDOMIZED TRIAL (1985)

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

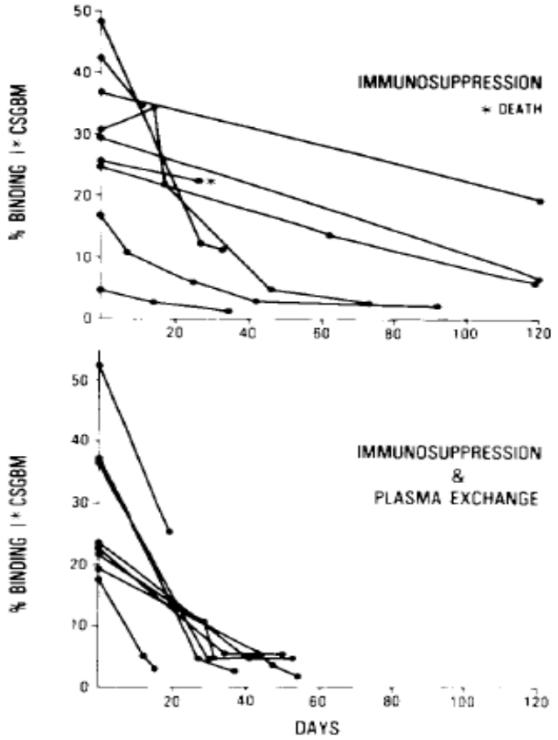
JOHN P. JOHNSON, M.D., JACK MOORE, JR., M.D., HOWARD A. AUSTIN, III, M.D., JAMES E. BALOW, M.D., TATIANA T. ANTONOVYCH, M.D., AND CURTIS B. WILSON, M.D.[1]

- **17 pts – 2 Groups**

→ 9 pts PREDNISONE + CTX → 6/9 dialysis dependent

→ 8 pts PLEX (every 3d) + DRUG REGIMEN → 2/8 dialysis dependent

- **PLEX group**: rate of disappearance of anti-GBM Ab x2
  mean sCreat end of Rx = ½ Group PS+CTX
- Two groups similar in terms of entry clinical characteristics, pulmonary manifestations and complications associated with therapy



Johnson JP et al. Medicine(Baltimore) 1985

0025-7974/85/6404-0219$02.00/0
MEDICINE

Vol. 64, No. 4
Printed in U.S.A.

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.[1]

CONCLUSIONS

- **% of crescents on initial renal Bx + entry sCreat** correlated better with **outcome** vs therapeutic modality
- Pts with **<30% crescents + sCreat < 3 mg/dL good outcome**
  Pts with **>75% crescents + sCreat > 4 mg/dL poor outcome**
- **Limitations** : inconclusive results due to the lack of adequate power and more severe baseline disease in the patients treated with plasmapheresis.

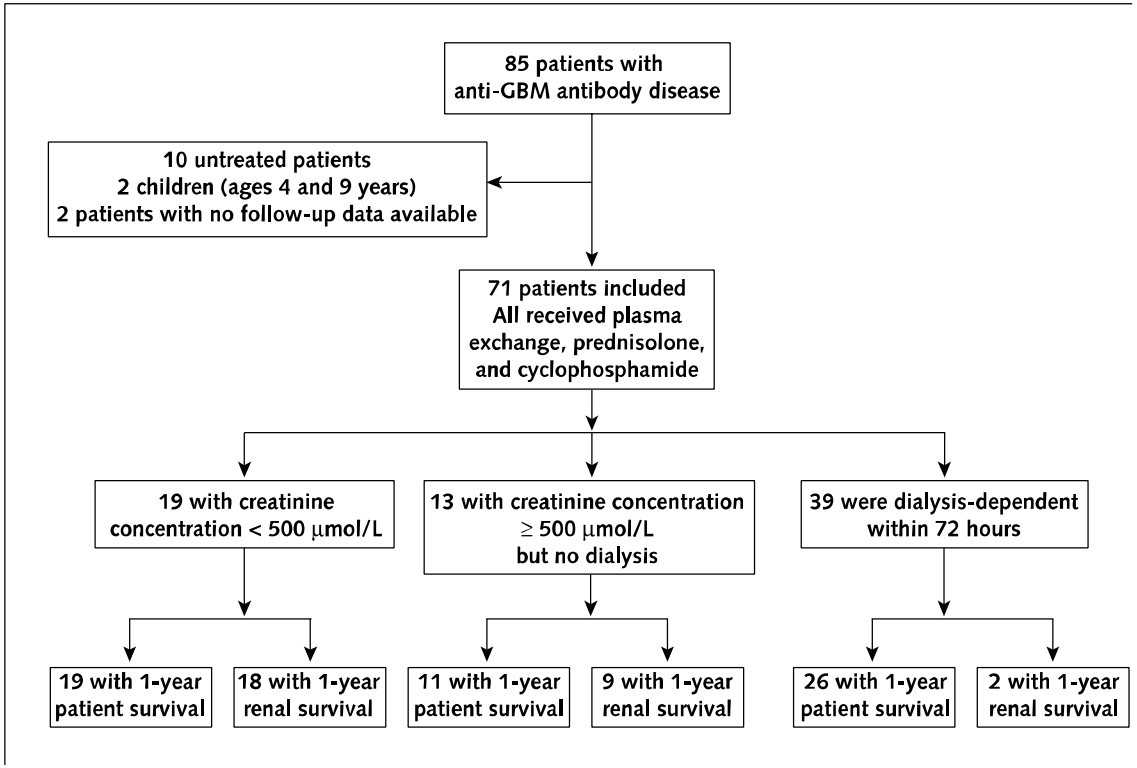
Johnson JP et al. Medicine(Baltimore) 1985

RETROSPECTIVE STUDY

Long-Term Outcome of Anti–Glomerular Basement Membrane Antibody Disease Treated with Plasma Exchange and Immunosuppression

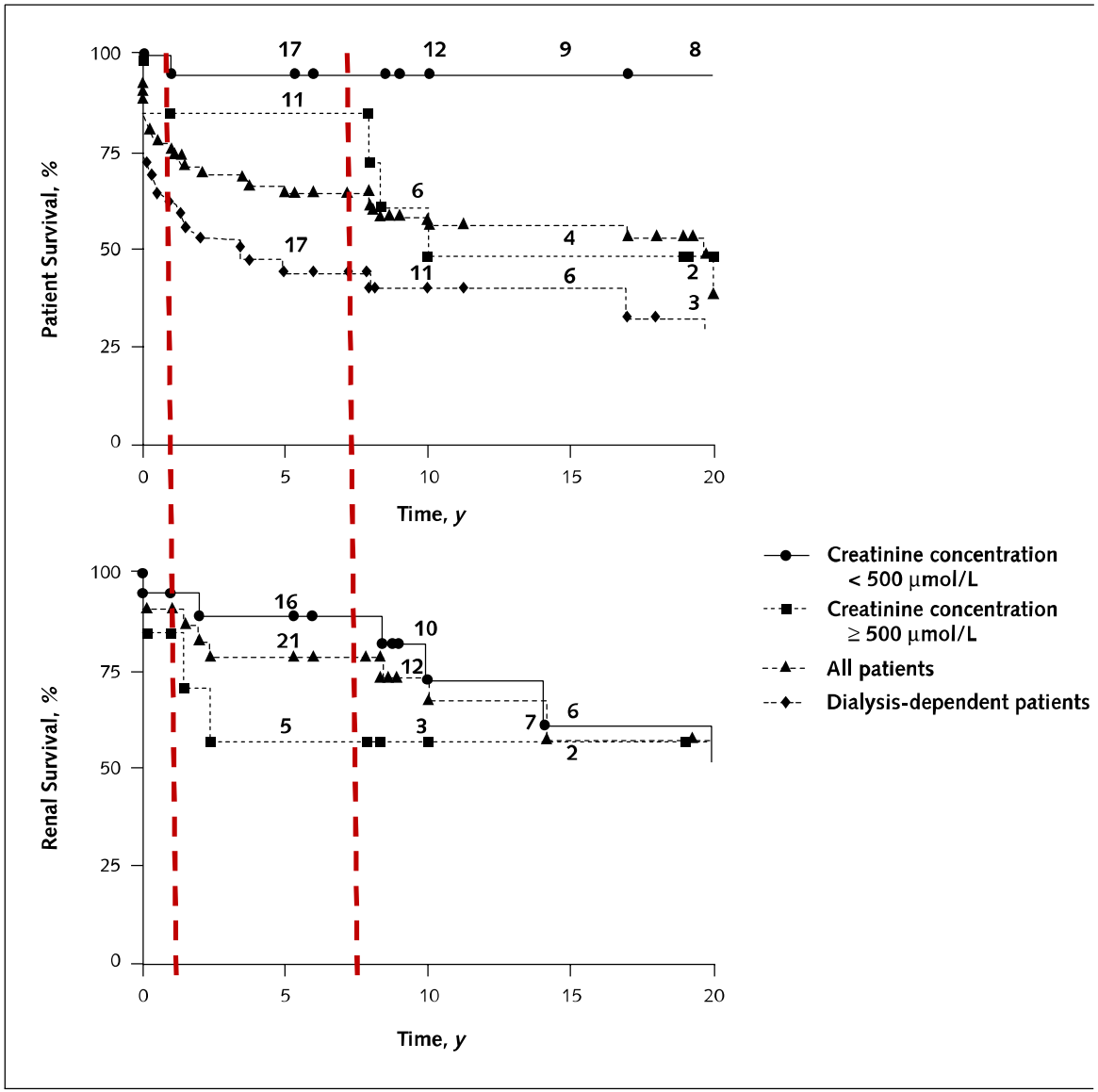
- **Design:** Retrospective, max FU25 years
- **Setting:** UK / 71 treated patients with anti-GBM Ab disease
- **Intervention:** All patients received PLEX+PS+CTX
- **Patients:** 3 Groups – according to initial renal function level
- **Measurements:** Patient and renal survival

Figure 1. **Flow chart showing patients in the study and outcomes at 1 year.**



Levy JB et al. *Ann Intern Med.* 2001;134:1033-1042

- **Results: SURVIVAL at 1 YEAR & MEDIAN FU 7Y**
- **19 pts sCreat <5.7 mg/dL**
  patient survival 100% & 84%
  renal survival 95% & 74%
- **13 pts sCreat >5.7 mg/dL but did not require immediate dialysis**
  patient survival 83% & 62%
  renal survival 82% & 69%
- **39 patients dialysis-dependent**
  patient survival 65% & 36%
  renal survival 8% & 5%
- *All patients who required immediate dialysis + 100% crescents on renal Rx remained dialysis dependent*



Levy JB et al. *Ann Intern Med.* 2001;134:1033-1042

RETROSPECTIVE STUDY

Medicine (Baltimore). 2011 Sep;90(5):303-11. doi: 10.1097/MD.0b013e31822f6f68.

Anti-glomerular basement membrane disease: outcomes of different therapeutic regimens in a large single-center Chinese cohort study.

Cui Z[1], Zhao J, Jia XY, Zhu SN, Jin QZ, Cheng XY, Zhao MH.

- **221 pts** anti-GBM disease - 1998-2008 in Peking University 1st Hospital
- **Treatment Protocol**:
  PLEX (2-4L,) daily or every other day → 14 sessions or until anti-GBM Ab (-)
  (HA 5% + FFP in pulmonary hemorrhage)
  MPS pulses 3 days (7-15mg/kg/d,<1g/d) → PS (1mg/kg/d,<60 mg/d) → tapering in 6-12m
  Oral CTX (2-3 mg/kg/d) for 2-3 months
- **3 different therapeutic regimens**:
  1) 76pts PLEX+CS+CTX
  2) 59pts CS+CTX
  3) 41pts CS alone

TABLE 1. Demographic, Clinical, and Pathologic Characteristics of 176 Patients With Anti-GBM Disease Treated With 3 Different Therapeutic Regimens

	PE+C+CTX (n = 76) No. (%)	PE+C (n = 59) No. (%)	C Alone (n = 41) No. (%)	P
Male/female	54/22	38/21	30/11	0.59
Age, yr	39.0 ± 18.0	46.7 ± 18.2	41.2 ± 20.7	0.061
Exposure to hydrocarbons	9 (11.8)	5 (8.5)	6 (14.6)	0.76
Smoking	38 (50.0)	16 (27.1)	17 (41.5)	0.085
Prodromal infection	38 (50.0)	17 (28.8)	22 (53.7)	0.021
Hemoptysis	39 (51.3)	24 (40.7)	17 (41.5)	0.40
Renal involvement	76 (100.0)	59 (100.0)	40 (97.6)	0.23
Initial involvement (kidney/lung/both)	20/16/3	12/12/0	7/9/0	0.59
Oliguria/anuria	36 (47.4)	28 (47.5)	25 (61.0)	0.31
Gross hematuria	24 (31.6)	12 (20.3)	8 (19.5)	0.21
Urinary protein in patients without oliguria/anuria, g/24 h*	3.3 (0–14.6)	3.5 (0.3–13.9)	0.9 (0.7–3.9)	0.071
Nephrotic syndrome	24 (31.6)	7 (11.9)	5 (12.2)	**0.011**
Serum albumin, g/dL	2.9 ± 0.4	2.9 ± 0.4	3.0 ± 0.7	0.46
Hemoglobin, g/dL	8.3 ± 2.1	7.8 ± 2.5	7.9 ± 1.8	0.42
Scr at presentation, mg/dL*	8.7 (1.3–18.3)	9.4 (0.8–11.3)	6.4 (2.7–12.4)	0.12
Percentage of crescents in glomeruli	78.1 ± 27.3	77.9 ± 31.7	83.9 ± 27.9	0.78
ANCA positive	14 (18.4)	19 (32.2)	6 (14.6)	0.067
MPO-ANCA/PR3-ANCA/both	13/0/1	18/1/0	4/2/0	0.11
Level of MPO-ANCA, U/mL	73.8 ± 35.6	91.2 ± 36.5	74.5 ± 51.0	0.41
Level of anti-GBM antibodies, U/mL	84.9 ± 43.2	60.9 ± 39.7	73.5 ± 47.1	**0.012**
Interval from onset to diagnosis, d*	32.5 (4–1110)	70 (6–300)	28 (24–45)	0.091
Duration of positive anti-GBM antibodies, d*	29 (5–328)	71 (6–451)	59 (26–61)	0.058
Follow-up period, mo, mean (range)	18.0 (0.3–120)	18.8 (0.3–110)	8.7 (0.3–120)	0.13

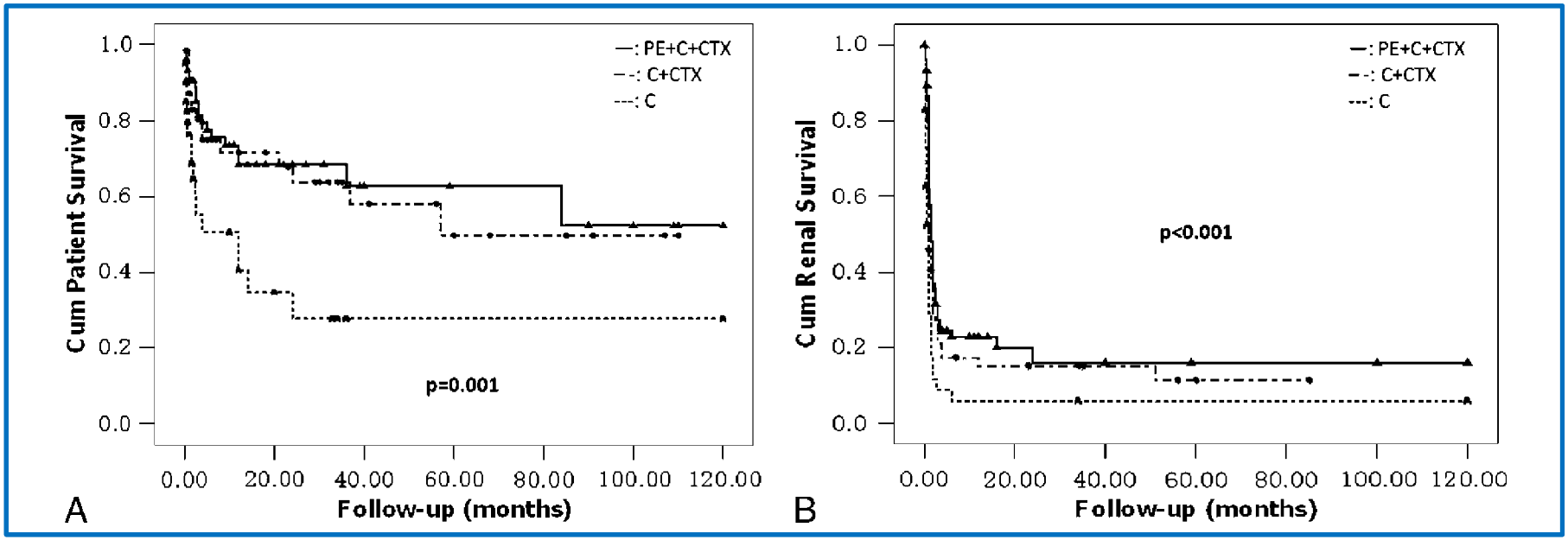
TABLE 2. Prognostic Significance of Patient Characteristics and Treatment for Patient and Renal Outcome of Anti-GBM Disease, by Univariate and Multivariate Survival Analysis

	Patient Mortality, HR (95% CI)				Renal Failure, HR (95% CI)			
Variable	**Univariate**	**P**	**Multivariate**	**P**	**Univariate**	**P**	**Multivariate**	**P**
Clinical features								
Age (increased by 10 yr)	1.18 (1.03–1.35)	**0.016**	1.08 (0.91–1.28)	0.40	0.98 (0.90–1.07)	0.64	1.00 (0.90–1.12)	0.96
Sex (female)	0.99 (0.57–1.72)	0.97	1.09 (0.60–1.99)	0.77	0.94 (0.66–1.34)	0.74	0.97 (0.65–1.43)	0.86
Hemoptysis	1.46 (0.86–2.47)	0.16	1.54 (0.88–2.71)	0.13	1.22 (0.87–1.69)	0.25	1.18 (0.83–1.69)	0.35
Oliguria/anuria	2.05 (1.19–3.54)	**0.010**	1.34 (0.68–2.64)	0.40	2.58 (1.81–3.67)	**<0.001**	1.20 (0.78–1.84)	0.40
Gross hematuria*	2.20 (1.24–3.91)	**0.007**	-	-	1.36 (0.93-1.98)	0.11	-	-
Nephrotic syndrome*	0.60 (0.23–1.56)	0.30	-	-	1.26 (0.74–2.15)	0.39	-	-
Scr at presentation (doubling from 1.5 mg/dL)	1.56 (1.19–2.05)	**0.002**	1.28 (0.89–1.83)	0.18	2.17 (1.78–2.66)	**<0.001**	2.07 (1.61–2.65)	**<0.001**
Crescent percentage (increased by 20%)*	1.20 (0.88–1.63)	0.26	-	-	1.75 (1.39–2.21)	**<0.001**	-	-
Cellular crescents	0.92 (0.73–1.18)	0.52	-	-	0.98 (0.86–1.11)	0.74	-	-
Fibrocellular crescents	1.02 (0.76–1.38)	0.88	-	-	1.04 (0.89–1.22)	0.60	-	-
Fibrous crescents	1.23 (0.83–1.82)	0.30	-	-	0.83 (0.61–1.14)	0.24	-	-
Anti-GBM antibody levels (increased by 20 U/mL)	1.15 (1.04–1.28)	**0.008**	1.16 (1.04–1.30)	**0.009**	1.07 (0.99–1.15)	0.082	1.02 (0.95–1.11)	0.56
Positive ANCA	2.36 (1.38–4.03)	**0.002**	2.18 (1.09–4.38)	**0.028**	1.00 (0.68–1.48)	0.99	1.02 (0.64–1.63)	0.95
Treatments								
PE+C+CTX	0.35 (0.19–0.66)	**0.001**	0.31 (0.15–0.63)	**0.001**	0.46 (0.30–0.70)	**<0.001**	0.60 (0.37–0.96)	**0.032**
C+CTX	0.40 (0.21–0.77)	**0.006**	0.43 (0.21–0.90)	**0.024**	0.57 (0.37–0.88)	**0.010**	0.92 (0.56–1.49)	0.73
C alone (reference)	1.00	-	1.00	-	1.00	-	1.00	-

Medicine (Baltimore). 2011 Sep;90(5):303-11. doi: 10.1097/MD.0b013e31822f6f68.

Anti-glomerular basement membrane disease: outcomes of different therapeutic regimens in a large single-center Chinese cohort study.

Cui Z[1], Zhao J, Jia XY, Zhu SN, Jin QZ, Cheng XY, Zhao MH.



- The patient and renal survival rates at **1y were 72.7% and 25.0%**
- **PLEX+PS+CTX > PS+CTX > PS**

MONITORING OF Anti-GBM Levels

- ✓ **Anti-GBM Ab titers should be regularly monitored**

  every 1-2 weeks until they are **negative on two occasions**

  periodical monitoring for **up to 6 months**

  at any time if there are **clinical signs** suggestive of **recurrence**

- ✓ Anti-GBM Ab will **disappear** naturally over **2 years on average**

Atypical Variants And Subgroups of anti-GBM disease

- **Double-Positive Anti-GBM and ANCA-Associated GN**
- Post-Transplant Anti-GBM Disease in Alport Syndrome
- Anti-GBM Disease Associated with Membranous Nephropathy
- “Atypical” Anti-GBM Disease
- Anti-GBM disease following immunotherapy

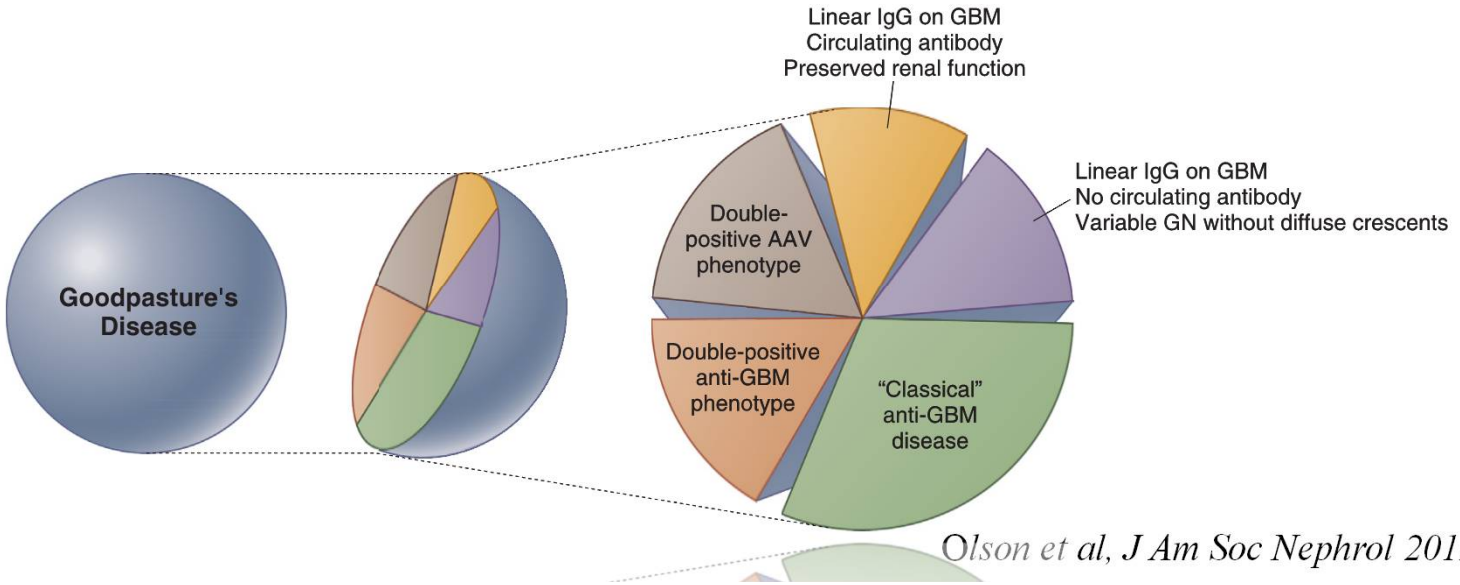
Case series of anti-GBM disease published after 2000

Double-Positive Anti-GBM and ANCA: 20-47%

Reference	Country	Period	*n*	Age (years)	ANCA-positive (%)	Lung disease (%)	Patient survival[a] (%)	Renal survival[a] (%)
Levy *et al.* [15]	UK	1975–1999	81	40	Exclusion criterion	54	79	36
Li *et al.* [16]	China	1992–2003	10	59	20	40	80	20
Segelmark *et al.* [6]	Sweden	1987–1995	75	59	39	21	64	21
Cui *et al.* [14]	China	1997–2002	97	38	26	57	NA	15
Rutgers *et al.* [8]	Netherlands	1978–2003	24	57	46	NA	91	13
Kitagawa *et al.* [17]	Japan	1990–2005	16	61	25	25	88	31
Taylor *et al.* [10]	New Zealand	1998–2008	23	45	Exclusion criterion	39	89	48
Dammacco *et al.* [18]	Italy	2003–2012	10	49	33	60	80	60
Canney *et al.* [9]	Ireland	2003–2014	79	63	33	23	74	na
Alchi *et al.* [19]	UK	1991–2011	43	53	21	40	88	23
McAdoo *et al.* [13]	Czech Republic, UK, Sweden	2000–2013	78	61	47	38	86	42
van Daalen *et al.* [7]	Netherlands, UK, USA, New Zealand	1986–2015	123	51	40	35	NA	37

Segelmar et al, Nephrol Dial Transplant 2018

- ANCA may be detected before the onset of anti-GBM disease
- ANCA-induced glomerular inflammation may be a trigger for the development of an anti-GBM response
- MPO-ANCA predominate in double- positive patients, frequencies of 66–81%
- Clinical course: more like anti-GBM associated RPGN in the short-term but more like ANCA-associated RPGN in the long-term



Olson et al, J Am Soc Nephrol 2011, McAdoo et al, KI 2017

Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients

	AAV	Anti-GBM	Double positive	AAV versus DP versus GBM	AAV versus DP	GBM versus DP	AAV versus GBM
Cases, *n*	568	41	37	–	–	–	–
• United Kingdom	171	19	20				
• Sweden	100	13	8				
• Czech Republic	297	9	9				
Cases, %	87.9%	6.3%	5.7%				
Demographics							
Age, yr (range)	62.3 (11–95)	58.3 (13–91)	63.6 (17–88)	0.17	0.99	0.31	0.21
Gender							
• Male	54%	46%	38%	0.11	0.06	0.49	0.34
• Female	46%	54%	62%				
Clinical Features							
Duration of symptoms,[a] wk (range)	12 (0–56)	2 (0–20)	10 (1–26)	**<0.01**	0.99	**<0.01**	**<0.01**
Lung	131/568	16/41	14/37	**0.01**	**0.04**	0.85	**0.02**
hemorrhage	23%	40%	38%				
Required RRT at	132/568	26/41	21/37	**<0.01**	**<0.01**	0.55	**<0.01**
presentation	23%	63%	57%				
eGFR,[b] ml/min (range)	29 (5–90)	20 (5–90)	19 (6–76)	0.06	0.11	0.99	0.67
Serum creatinine,[b] µmol/l (range)	186 (39–693)	275 (62–667)	309 (71–606)	0.06	0.18	0.99	0.37
Serology							
Anti-GBM level, xULN (range)	–	5.4 (1–29.1)	14.2 (1–50.4)		–	0.06	–
Proportion seronegative for anti-GBM, %	–	4/41	4/37		–	1.00	–
		11%	11%				
ANCA serology, %					**<0.01**	–	–
• Anti-MPO	48%		70%				
• Anti-PR3	51%		27%				
• Anti-MPO & PR3	<1% (*n* = 2)		3%				

McAdoo et al, KI 2017

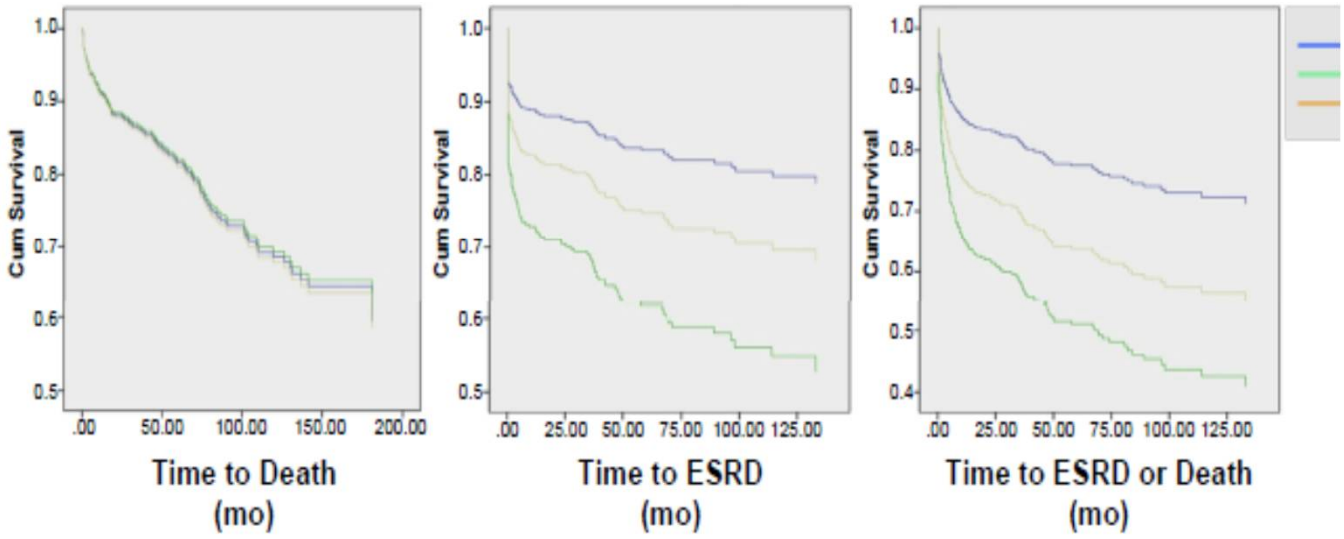
www.kidney-international.org clinical investigation

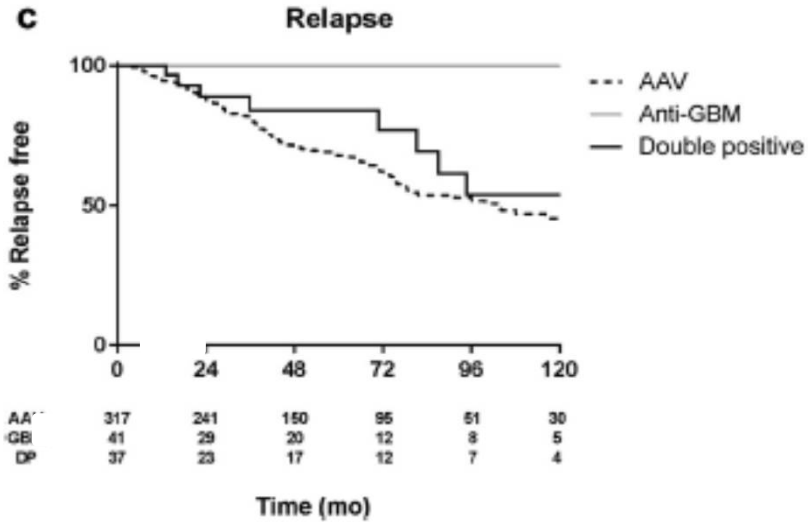
Kidney International (2017) 92, 693–702

Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients

see commentary on page 544

OPEN



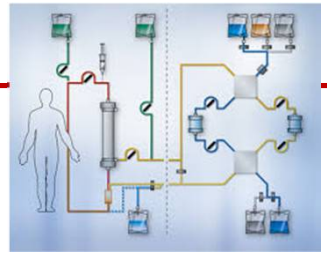


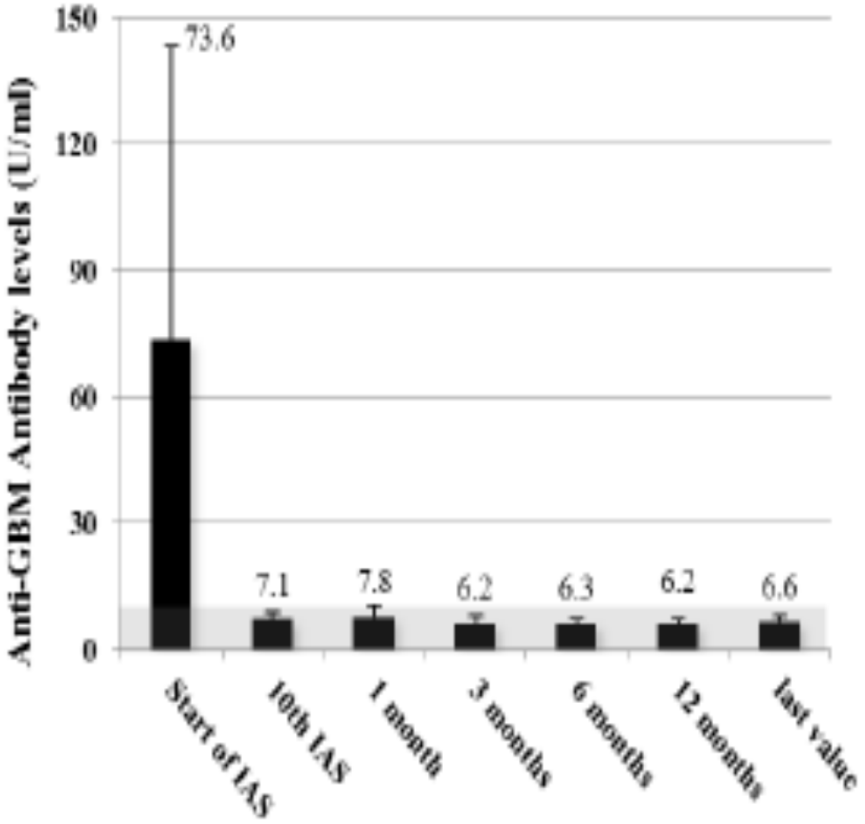
Double-positive patients have a greater tendency to recover from being dialysis dependent after treatment and intermediate long term renal survival compared to single-positive patients.

Double-positive patients have a greater risk of relapse compared with patients who are positive for anti-GBM only.

McAdoo et al, KI 2017

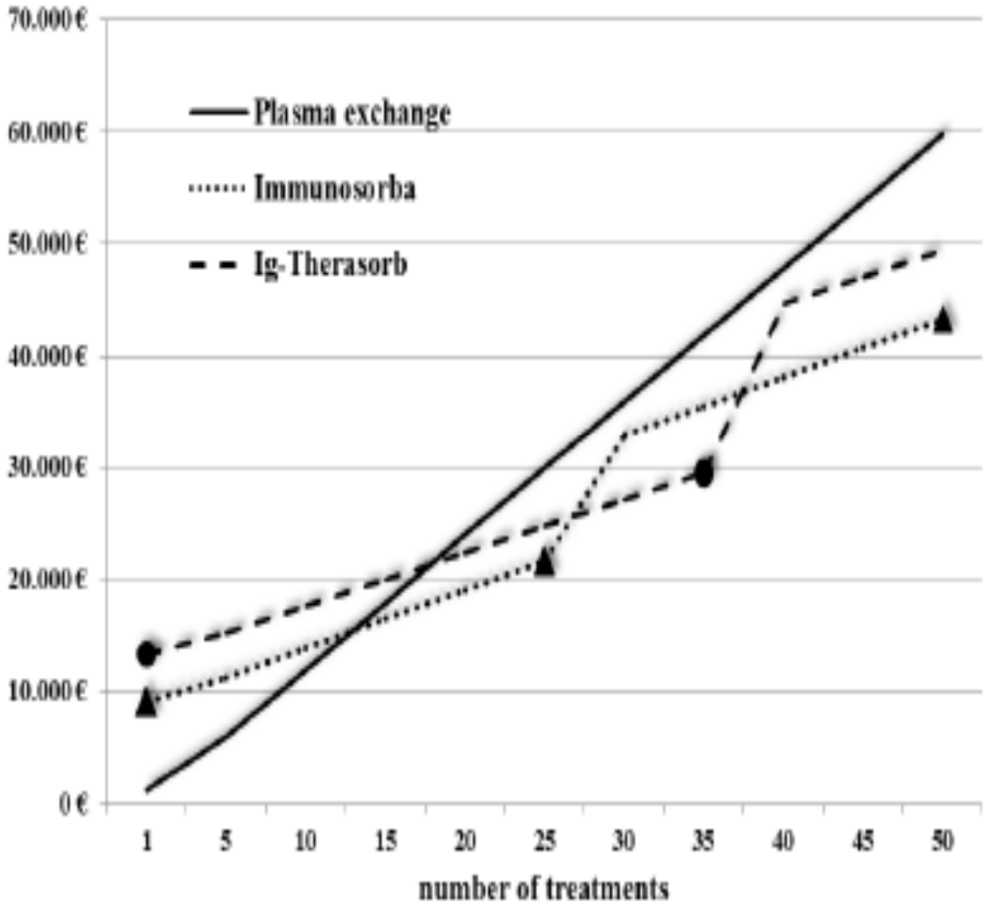
Immunoadsorption offers an effective therapy for direct removal of circulating anti-GBM Ab and is non-inferior to PLEX





- ✓ 10 patients with anti-GBM-disease treated with IAS / retrospective
- ✓ IAS was highly effective at removing anti-GBM-Ab with a **reduction** of **71 - 86%** / treatment
- ✓ Combined with immunosuppression, anti-GBM-antibodies became undetectable (<10 U/ml) in all patients within 2 to 9 IAS treatments.

Biesenbach et al, Plos One 2014

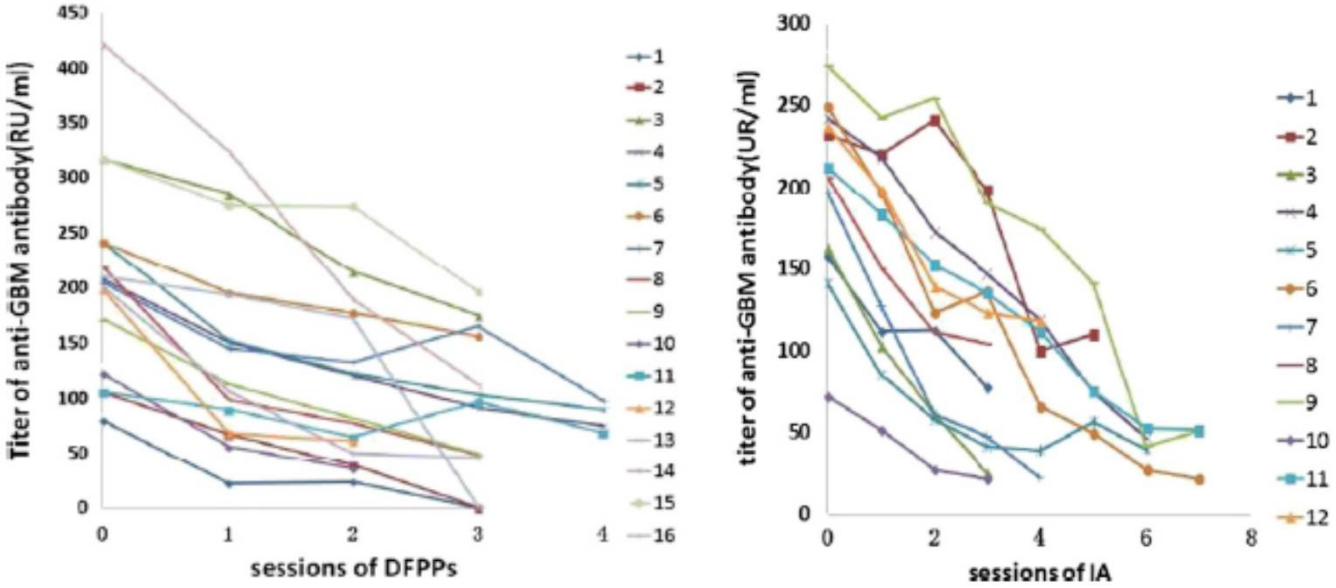


- The per-treatment cost of IAS varies and depends on the type of adsorber and on the number of treatments performed as the absorber can be reused.
- The mean number of IAS per patient was 23.
- **The costs for 23 Therasorb treatments were 1035 € per treatment, compared to PE with 4 liters of human albumin including personnel and disposables costs of 1194 €.**

Biesenbach et al, Plos One 2014

Double filtration plasmapheresis

Fewer plasma-associated side effects and reduced loss of IgG



Comparative effects of IA and DFPP on changes in anti-GBM antibody and IgG concentrations

	IA	DFPP	P
anti-GBM (RU/ml)	141	124	0.452
IgG (g/L)	10.6	8.1	0.049

28 pts (16 DFPP, 12 IAS) + All Immunosuppression

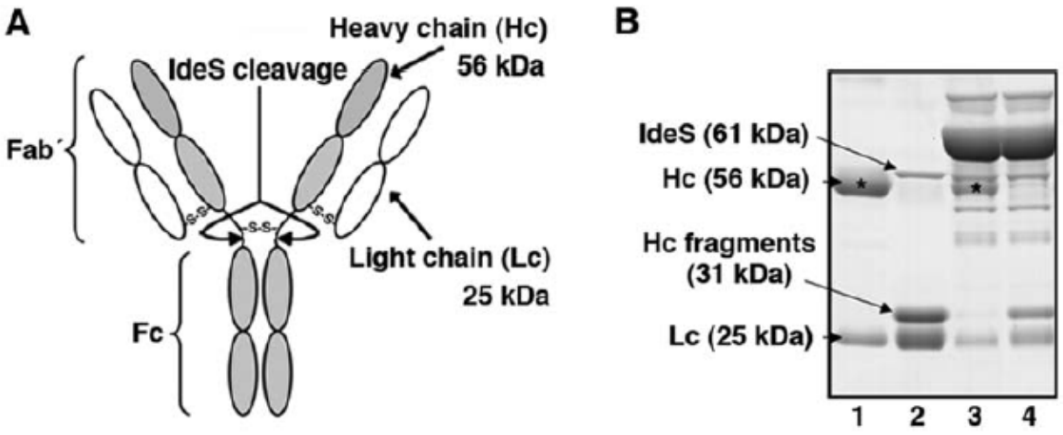
Effects of IAS and DFPP on concentrations of anti-GBM antibodies in individual patients:

- In DFPP group, the average reduction of anti-GBM-antibody was 123.7 RU/ml (61.9%).
- In the IA group the average reduction of anti-GBM-antibody was 142 RU/ml (70.8%).

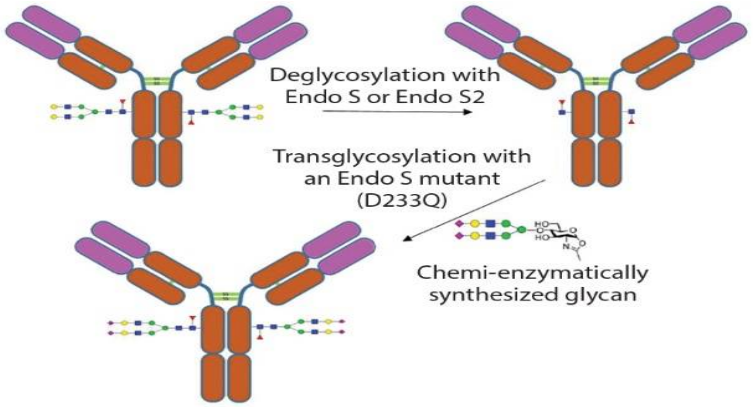
Zhang et al. BMC Nephrology 2014

Removal of tissue-bound anti-GBM Ab IgG can be targeted by virtue of the properties of bacterial proteins secreted by Streptococcus pyogenes

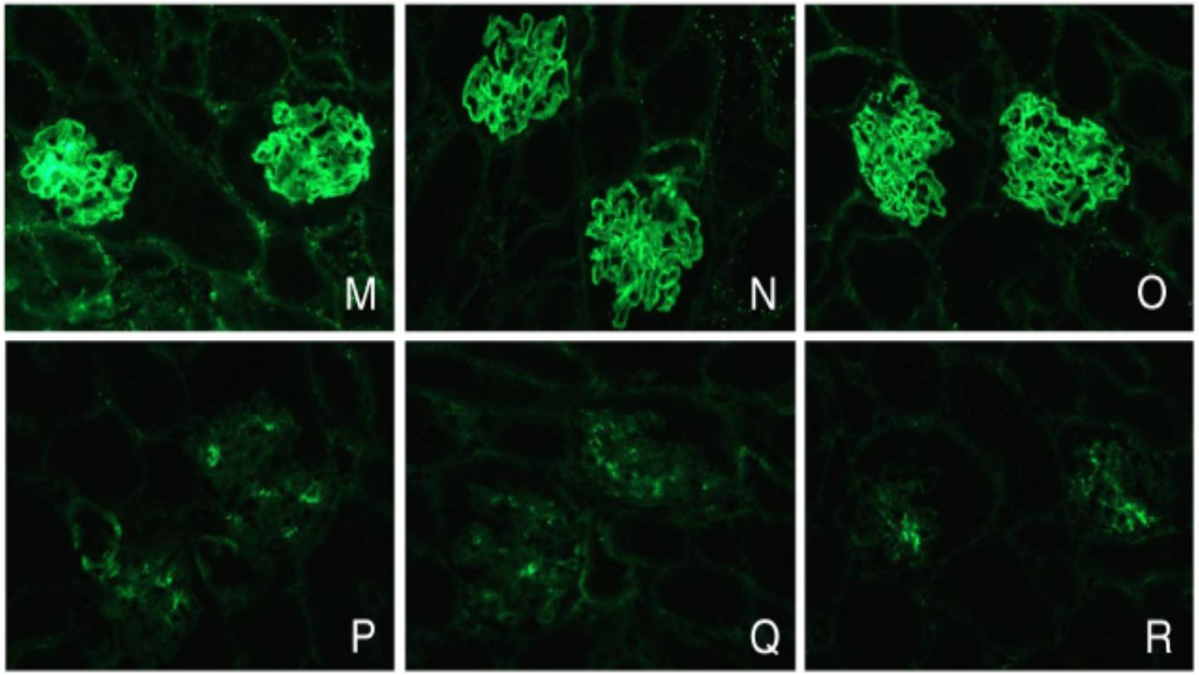
- **IgG-degrading enzyme of S. pyogenes (IdeS)** cleaves the heavy chain of IgG resulting in one F(ab')2 and 2 monomeric Fc fragments, directly affecting IgG effector functions.



Endoglycosidase (EndoS) hydrolysis of all IgG subclass glycans diminishes C1q binding and complement activation as well as IgG-mediated opsonization by impairing IgG FccR binding.



Successful treatment of experimental glomerulonephritis with IdeS and EndoS, IgG-degrading streptococcal enzymes



In an experimental model of anti-GBM disease, a massive deposition of mouse IgG could be detected in kidneys from placebo-treated animals while there was only small amounts of mouse IgG in the kidneys from the IdeS-treated animals.

Yang R et al. NDT 2010

FUTURE DIRECTIONS

- **EudraCT 2016–004082–39** - Clinical study of **IdeS** in severe **anti-GBM disease**, where it may promote rapid clearance of pathogenic IgG

- **GOODIdeS NCT03157037 –** Clinical study for the efficacy of **IdeS** in removing pathogenic tissue-bound **anti-GBM Ab**


ΕΥΧΑΡΙΣΤΩ
ΚΑΛΑ ΧΡΙΣΤΟΥΓΕΝΝΑ

ΟΝΟΜΑΤΟΛΟΓΙΑ

- “Goodpasture disease” for patients with anti-GBM Abs
- “Goodpasture syndrome” copresentation with GN and pulmonary hemorrhage of any cause
- “anti-GBM GN” specifically to the kidney involvement
- “anti-GBM disease” broader spectrum of kidney and lung disease

Anti-GBM is associated with a specific allele HLA-DRB1*1501

Strength of association	DRB1*	Amino acid position β13	β26	β28	β70	β71	β74
+++	1501	R	F	D	Q	A	A
	1502	—	—	—	—	—	—
	1503	—	—	—	—	—	—
+	0401	H	—	—	—	K	—
	0403	H	—	—	—	R	E
	0404	H	—	—	—	R	—
	0405	H	—	—	—	R	—
	0406	H	—	—	—	R	E
	0407	H	—	—	—	R	E
	0410	H	—	—	—	R	—
Neutral	0301	S	Y	—	—	K	R
	1601/2	—	—	—	D	R	—
	0101	F	L	E	—	R	—
	0102	F	L	E	—	R	—
	0103	F	L	E	D	E	—
—	07	Y	—	E	D	R	Q
	DRB5* 0101	Y	—	H	D	R	—

Fisher et al, Kidney Int 1997

Polymorphisms and copy number variation in non-HLA genes have also been implicated in disease susceptibility, such as the genes encoding Fcg-receptors.

- As main role of DR molecules is to bind and present antigenic peptides to CD4+ T cells, the association of DR alleles with anti-GBM disease is explained by presence of polymorphic residues enabling DRB1*15 alleles to bind peptides.
- *Dominant-negative protective effect of DRB1*07* .
- DRB1*15 and DRBI*04 alleles share a glutamine (Q) at position β/70 on the α helix, while the protective DRBI*07 alleles contain charged residues, aspartic acid (D) at β/70 and arginine (R) at β71, altering both size and charge of the pocket.
- Residues at β/70 and β/71 might also contact the T cell receptor, directly affecting T cell responses.

- The immune response is polyclonal, and autoantibodies are mainly found against the a3(IV)NC1.
- Most patients also have Ab against other epitopes on the a3(IV)NC1 and other a(IV) chains.
- Of the 2 major epitopes - EA and EB, only autoantibodies against the EA epitope reflect toxicity.
- Such antibodies are present at low levels and with low affinity in healthy persons.
- The epitope is a cryptotope and conformational changes are necessary for the anti- GBM Ab to bind.
- Anti-GBM Ab with high affinity could themselves induce the necessary conformational change and bind to the antigen without denaturation.
- T cells contribute directly to cell-mediated glomerular injury but the pathogenic T cell epitopes have not been defined.

- Positive anti-GBM serology may be occasionally associated with pathology that is pauci immune
- False (+) anti-GBM Ab tests may be found in states of polyclonal activation such as in hepatitis C or HIV infection and with diverse renal pathologies
- 10% of patients do not have identifiable circulating Ab with conventional assays which may result in diagnostic delay, until a renal biopsy is performed.

- **Early diagnosis and initiation of PLEX** are important for response to therapy and long-term prognosis
- The proportion of **preserved glomeruli** and the **presence of oligoanuria** may be the best prognostic factors
- Pts requiring dialysis within 72 hours of presentation, usually need maintenance dialysis

Table 3. **Renal Recovery in Treated Patients with Anti–Glomerular Basement Membrane Antibody Disease from Published Series***

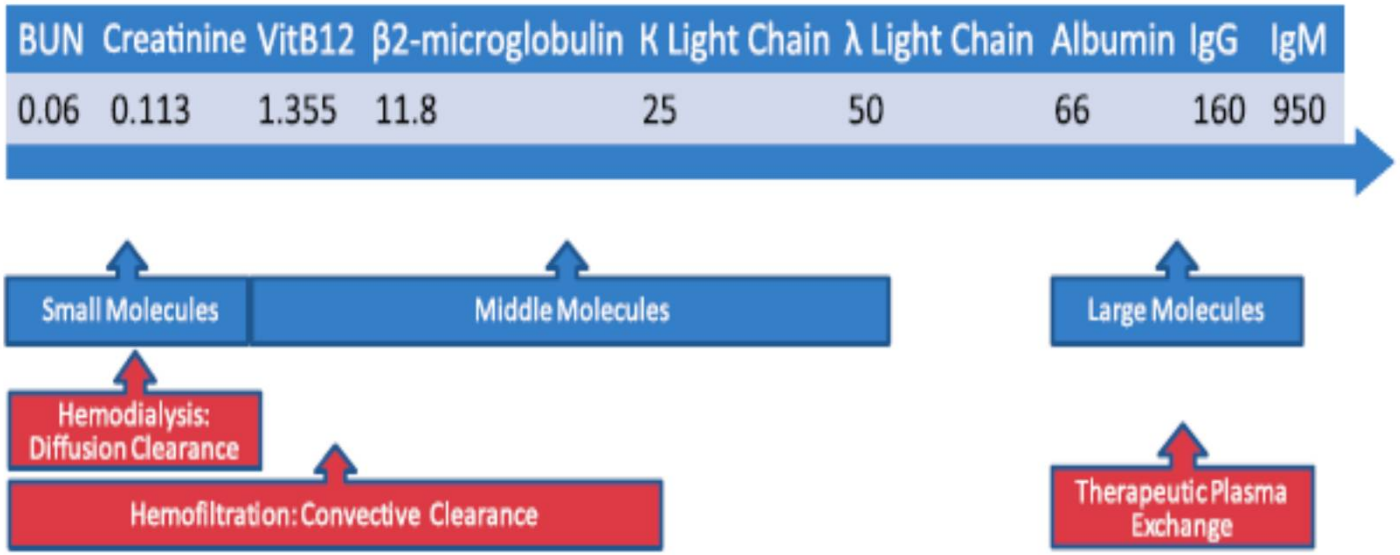
Study, Year (Reference)	Patients	Patients with Independent Renal Function at 1 Year		Treatment
		Initial Serum Creatinine Concentration < 600 μmol/L (<6.8 mg/dL)	Initial Serum Creatinine Concentration ≥ 600 μmol/L (≥6.8 mg/dL)	
	n	%		
Briggs et al., 1979 (21)	15	36	0	Half of the patients were treated; few received plasma exchange
Simpson et al., 1982 (22)	12	70	0	Patients with pulmonary hemorrhage were excluded
Johnson et al., 1985 (19)	17	69	0	Half of the patients received plasma exchange
Walker et al., 1985 (20)	22	82	18	All patients received plasma exchange
Bolton and Sturgill, 1989 (24)	17	100	0	Only 2 patients presented with no need for dialysis; both received methylprednisolone and improved
Bouget et al., 1990 (18)	13	50	0	Most patients received plasma exchange
Herody et al., 1993 (9)	29	93	0	Most patients received plasma exchange
Merkel et al., 1994 (10)	32	64	3	25 patients received plasma exchange (moderate intensity)
Andrews et al., 1995 (23)	15	–	7	All patients had creatinine concentration >600 μmol/L; only 8 patients treated
Daly et al., 1996 (12)	40	20	0	23 patients received plasma exchange

Levy JB et al. *Ann Intern Med.* 2001;134:1033-1042

IgG resides 30%–45% in the extravascular space.

With such a large plasma volume, under otherwise identical circumstances, several plasma exchanges will be required to remove the Ig from the circulation and the interstitial space and to achieve meaningful clearance.

For IgG-mediated processes, for example, six TPEs would be expected to decrease circulating IgG levels to one-fifth or one-sixth of the baseline levels.



ASFA category I renal indications for therapeutic plasma exchange

Kidney Disease	Indication	Reported RCTs
ANCA-associated rapidly progressive GN	Dialysis dependence or diffuse alveolar hemorrhage	8
Anti-GBM disease	Diffuse alveolar hemorrhage or dialysis independence	1
Cryoglobulinemia	Symptomatic, severe[a]	0
FSGS		0
Atypical hemolytic uremic syndrome	Factor H antibodies	0
Kidney transplant	ABO compatible; antibody-mediated rejection	3
	Desensitization; living donor with positive cross-match	0
	ABO incompatible; desensitization; live donor	0
Thrombotic thrombocytopenic purpura		7
Drug-associated thrombotic microangiopathy	Ticlopidine	0

The combination therapy of had an overall beneficial effect on both patient survival and renal survival!

✓ *particularly renal survival for those with anti-GBM nephritis with initial sCreatinine> 6.8 mg/dL*

Patients with anti-GBM nephritis (n = 96)				
Clinical features				
Age (increased by 10 yr)	1.16 (0.95–1.42)	0.15	0.97 (0.86–1.09)	0.61
Sex (female)	1.02 (0.47–2.22)	0.96	0.87 (0.55–1.38)	0.55
Oliguria/anuria	1.69 (0.77–3.72)	0.19	3.34 (2.03–5.50)	**<0.001**
Gross hematuria*	2.27 (0.97–5.29)	0.059	1.45 (0.86–2.45)	0.16
Nephrotic syndrome*	0.89 (0.26–3.05)	0.85	1.00 (0.45–2.20)	0.99
Scr at presentation (doubling from 1.5 mg/dL)	1.47 (1.02–2.13)	**0.038**	2.13 (1.65–2.76)	**<0.001**
Crescent percentage (increased by 20%)*	1.13 (0.78–1.64)	0.53	1.83 (1.34–2.48)	**<0.001**
Cellular crescents	0.83 (0.60–1.13)	0.23	0.94 (0.79–1.11)	0.44
Fibrocellular crescents	1.11 (0.73–1.68)	0.64	1.08 (0.85–1.37)	0.53
Fibrous crescents	1.52 (1.02–2.27)	**0.038**	0.93 (0.67–1.28)	0.66
Anti-GBM antibody levels (increased by 20 U/mL)	1.10 (0.91–1.34)	0.34	1.06 (0.94–1.18)	0.34
Positive ANCA	2.57 (1.18–5.61)	**0.018**	1.10 (0.65–1.86)	0.72
Treatments				
PE+C+CTX	0.43 (0.16–1.12)	0.085	0.41 (0.23–0.73)	**0.002**
C+CTX	0.44 (0.17–1.17)	0.10	0.57 (0.32–1.01)	0.055
C alone (reference)	1.00	-	1.00	-

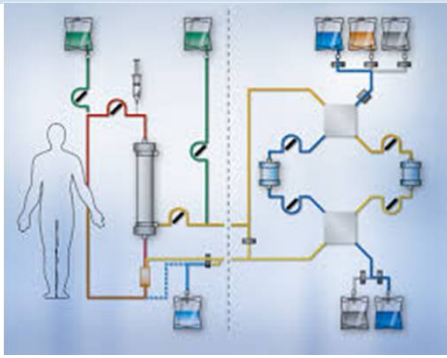
Cui et al, Medicine 2011

- Double-positive patients have broader antigenic specificity with preferential binding of anti-GBM antibodies to a5 chains of type IV.
- ANCA directed against myeloperoxidase (MPO) predominates in double- positive patients, with reported frequencies of 66–81%.
- Double-positive patients are affected later in and there appears to be a male preponderance.
- Clinical presentation is almost indistinguishable from patients with only anti-GBM antibody positivity but clinical course often differs.

TABLE 3. Clinical and Pathologic Characteristics of Patients With and Without Pulmonary Hemorrhage

	Patients With Goodpasture Syndrome (n = 80) No. (%)	Patients With Anti-GBM Nephritis (n = 96) No. (%)	P
Male/female	66/14	56/40	**0.001**
Age, yr	39.2 ± 18.2	44.5 ± 19.3	0.067
Exposure to hydrocarbons	12 (15.0)	8 (8.3)	0.13
Smoking	43 (53.8)	28 (29.2)	**0.001**
Prodromal infection	27 (33.8)	50 (52.1)	**0.030**
Renal involvement	79 (98.8)	96 (100)	0.46
Systemic involvement	16 (20.0)	22 (22.9)	0.98
Oliguria/anuria	40 (50.0)	49 (51.0)	0.89
Gross hematuria	22 (27.5)	22 (22.9)	0.48
Urinary protein in patients without oliguria/anuria, g/24 h, median (range)	3.4 (0.0–14.6)	2.5 (0.26–13.0)	0.14
Nephrotic syndrome	18/40 (45.0)	18/47 (38.3)	0.51
Serum albumin, g/dL	2.9 ± 0.5	2.9 ± 0.5	0.57
Hemoglobin, g/dL	7.6 ± 2.2	8.5 ± 2.1	**0.009**
Scr at presentation, mg/dL	9.7 ± 4.3	9.4 ± 5.8	0.69
ANCA positive	16 (20.0)	23 (24.0)	0.53
MPO-ANCA/PR3-ANCA/both	13/2/1	22/1/0	0.29
Level of anti-GBM antibodies, U/mL	78.9 ± 45.5	69.3 ± 42.4	0.17
Percentage of crescents in glomeruli	81.3 ± 28.4	77.6 ± 28.7	0.56
Interval from onset to diagnosis, d, median (range)	44.5 (6–1825)	37 (4–1110)	0.26

Immunoadsorption (IAS)



- IAS is an alternative method removing antibody from the circulation used in the treatment of autoimmune diseases.
- In renal disease, IAS is mainly used in ABO incompatible and highly sensitized renal transplant recipients, in antibody mediated rejection and in SLE
- Advocates have proposed IAS as a therapy in FSGS, AAV and anti-GBM disease.
- IAS has additional benefits to PLEX
  - selective high-affinity binding of IgG subclasses 1, 2 and 4
  - requires no FFP or albumin
  - allows a greater plasma volume to be processed.

Processing of 2.5 plasma volumes has the capacity to remove up to 87% of IgG, with multiple sessions increasing IgG clearance to>98%.