UNIVERSITÀ
CATTOLICA
del Sacro Cuore

Patologie da attivazione del complemento

G.F.Ferraccioli

Istituto di Reumatologia e Scienze Affini
Facolta' di Medicina
Universita' Cattolica del sacro Cuore
Roma

Roma 19.02.2016

TMA: complement disorders associated

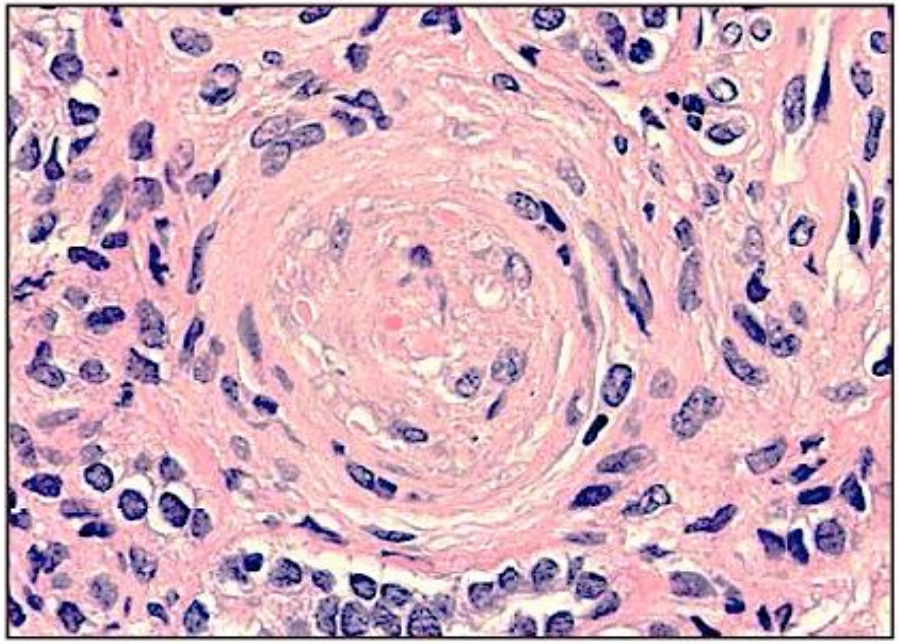
Hereditary TTP

Acquired TTP

Coagulation-mediated TMA

Hereditary complement-mediated TMA

Acquired complement-mediated TMA



Drug-mediated TMA (immune reaction)

Drug-mediated TMA (toxic dose–related reaction)

Metabolism-mediated TMA (cobalamin deficiency)

Shiga toxin-mediated TMA (ST-HUS)

N Engl J Med 2014;371:654-66.

Complement related illnesses

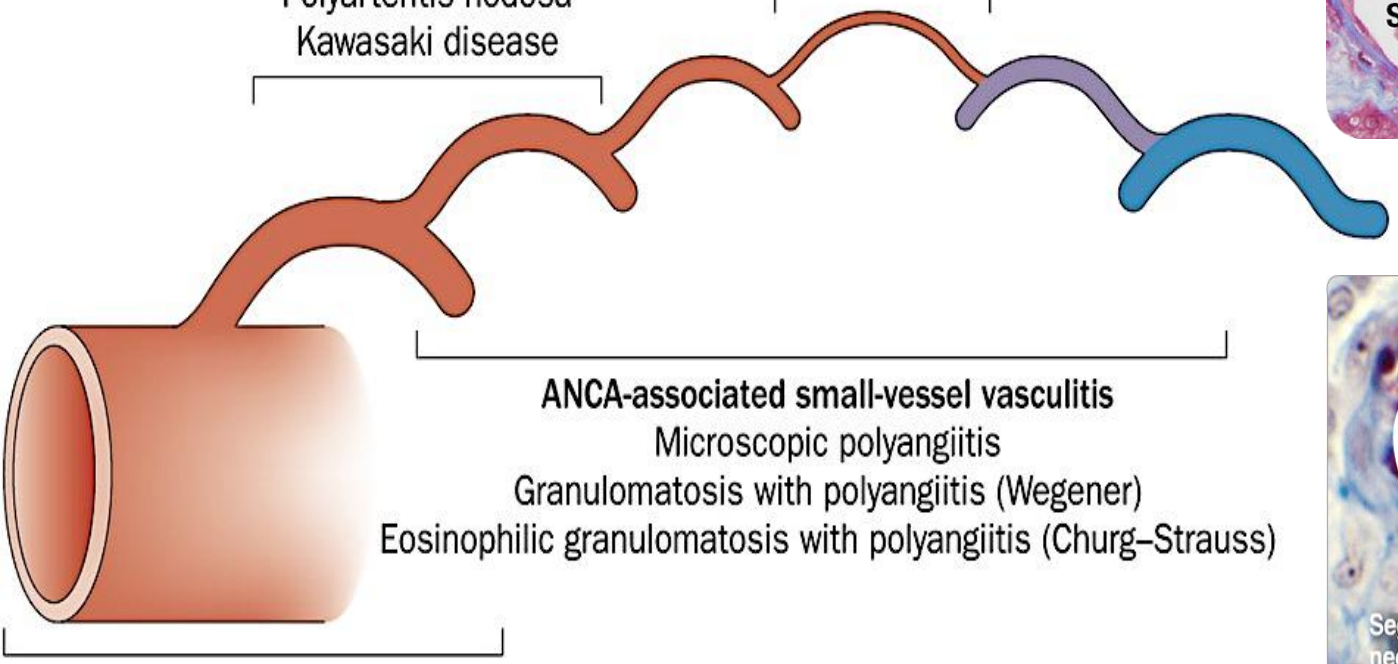
- **Mixed cryoglobulinemia**
- **Schönlein-Henoch**
- **ANCA associated vasculitides**
- **Systemic Lupus Erythematosus**
- **Anti-phospholipid syndrome**
  - CAPS (catastrophic antiphospholipid syndrome)
- **Scleroderma**

ANCA associated vasculitis

Immune complex small-vessel vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch–Schönlein)
Hypocomplementemic urticarial vasculitis
(Anti-C1q vasculitis)

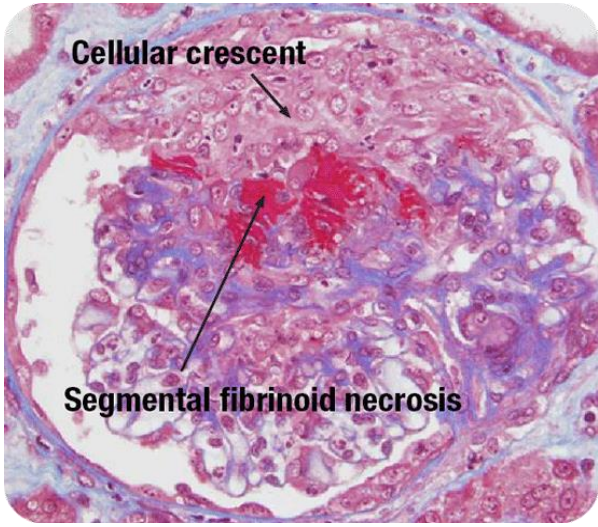
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease

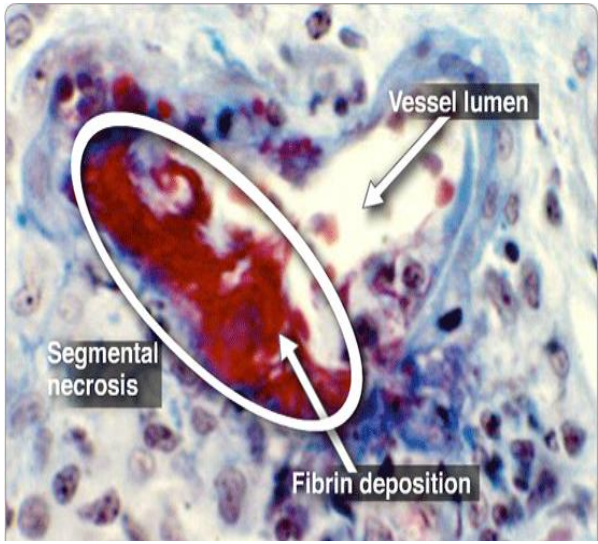
Anti-GBM disease



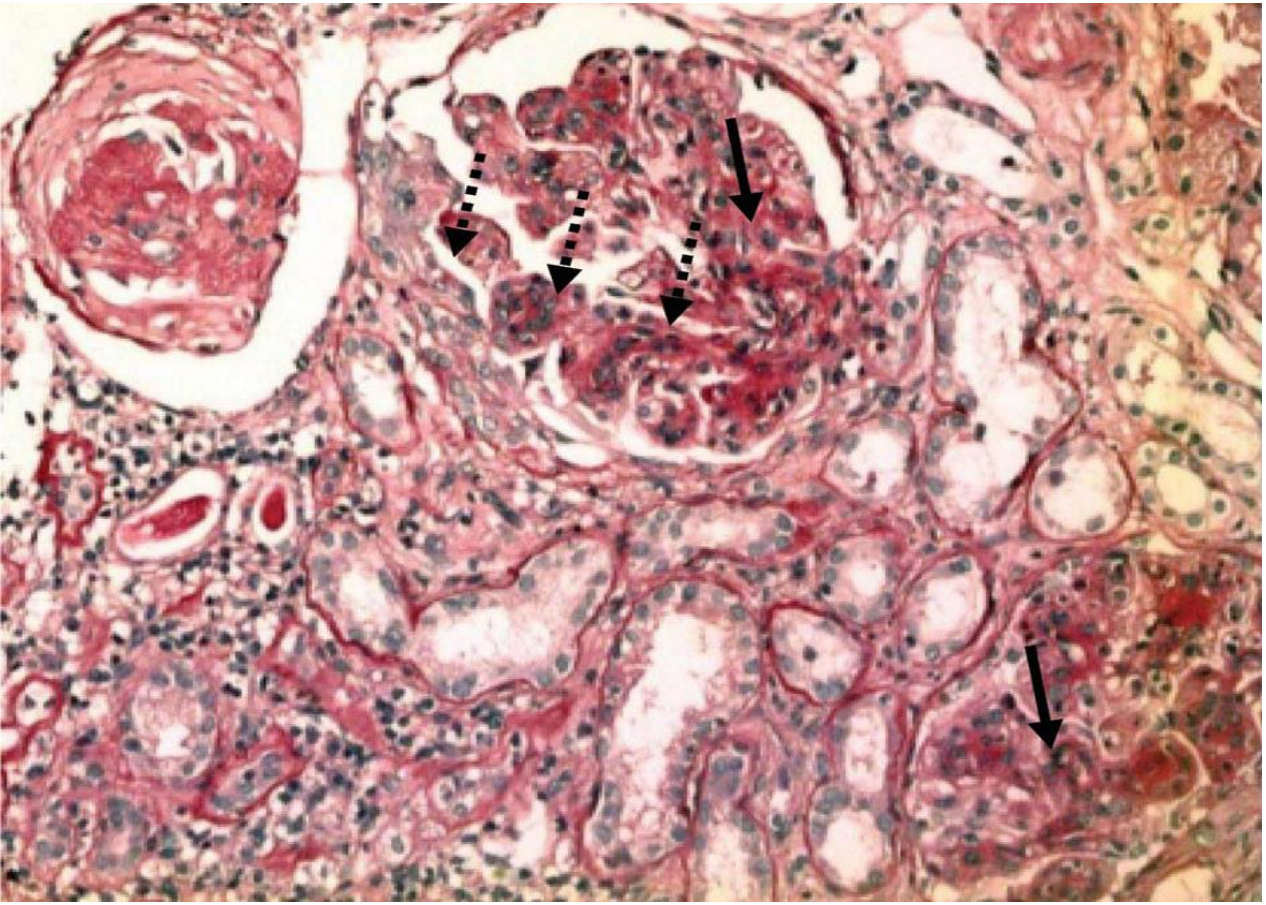
ANCA-associated small-vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis





Hepatitis C Virus-related Heat-insoluble Cryoglobulinemia and Thrombotic Microangiopathy



Anemia, thrombocytopenia, elevated reticulocyte and l-lactate dehydrogenase levels, negative Coombs test and, more importantly, schistocytosis, all support the TMA diagnosis.

Am.J. Medical Sciences 2013, 346, 345-8

Mixed Cryo and complement

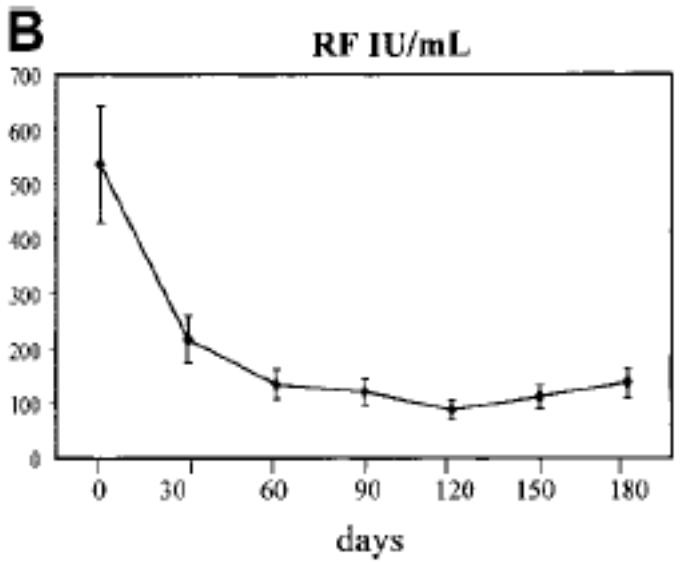
Patient	Age/sex	Disease duration (mo)	HCV genotype	Previous therapies	Main clinical features at baseline	Serum laboratory features at baseline			
						Cryo mg/dL	RF IU/mL	IgM g/L	C4 mg/dL
1	58/M	49	1b	IFN/Cy/CS/PF	Purpura, fever, arthralgias, nephritis	90	868	1.7	8
2	67/F	240	ND	CS/PF	Purpura, urticaria	<50	42	1.0	2
3	68/F	20	HCV neg	CS/PF/IVIG	Purpura, skin ulcers, neuropathy	1500	79	14.0	2
4	68/F	72	ND	CS	NHL, immune anemia, and neutropenia	446	101	8.0	6
5	70/F	132	2c	CS/AZA	Purpura, NHL, neuropathy, arteriopathy	595	552	4.5	2
6	63/F	36	1b	CS/IFN/IVIG/PF	Purpura, neuropathy	2280	206	4.3	2
7	43/F	168	1b	IFN/CS/Cy	Purpura, skin ulcers	1305	197	1.6	2
8	62/M	144	1b	CS/CVP/PF/IFN-R	NHL, hyperviscosity, astenia	+(NA)	216 000	84.0	NA
9	66/F	108	HCV neg	AZA/Cy/CS/CSA/IFN	Purpura, neuropathy, arthralgias	258	414	1.2	2
10	79/M	84	2a2c	CS	Purpura, skin ulcers, neuropathy	770	1920	1.1	6
11	63/F	144	1b	IFN/PF/CS/IVIG	Neuropathy, nephritis	2993	3700	4.4	12
12	73/F	144	ND	PF/IFN/CS/ 2-CdA	Purpura, skin ulcers	60	26	1.7	3
13	69/F	96	3a	IFN/CS/PF/IVIG	Purpura, skin ulcers, neuropathy	1858	3080	3.8	8
14	64/M	8	HCV neg	CS	Purpura, neuropathy, arthralgias	156	526	2.2	2
15	53/F	192	2c	IFN/CS	Purpura, arthralgias	2605	545	1.3	7

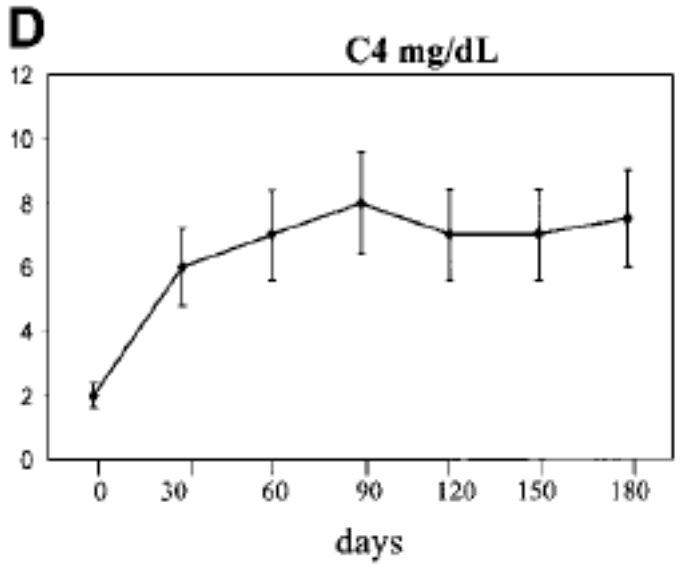
Efficacy and safety of rituximab in type II mixed cryoglobulinemia

F Zaja, S De Vita, C Mazzaro, S Sacco, D Damiani, G De Marchi, A Michelutti, M Baccarani, R Fanin, and **G Ferraccioli.**

Blood. 2003;101:3827-3834

Mixed Cryo and complement





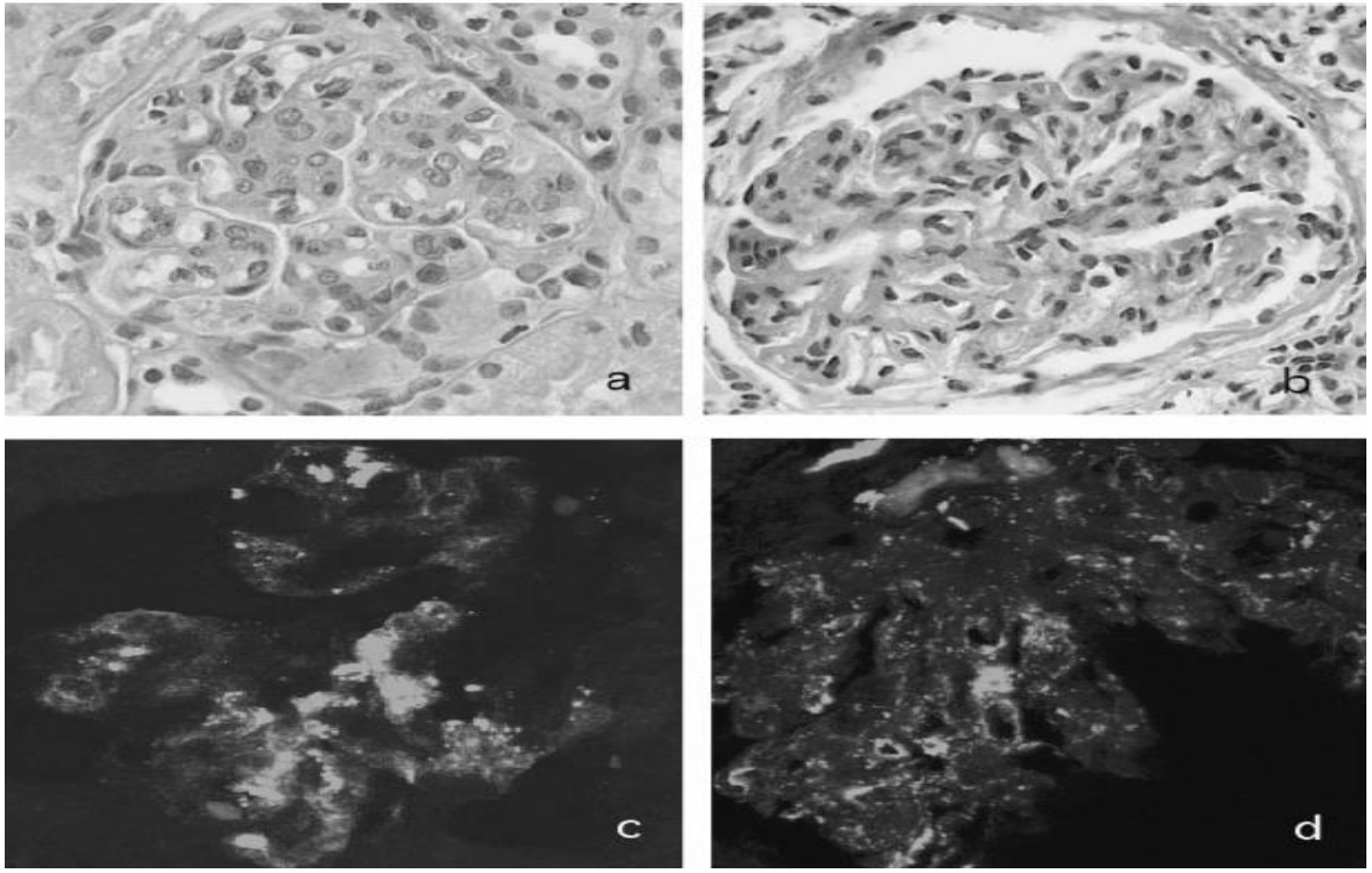
Efficacy and safety of rituximab in type II mixed cryoglobulinemia
F Zaja, S De Vita, C Mazzaro, S Sacco, D Damiani, G De Marchi, A Michelutti, M Baccarani, R Fanin, and **G Ferraccioli.**
Blood. 2003;101:3827-3834

Mixed cryo MPG-nephritis

Gender	F	F	F	M	F
Age (yr)	58	45	62	56	65
HCV genotype	1b	1b	1b	2a/2c	2a/2c
Hepatitis diagnosis (year)	1992	1993	1990	1994	1993
Liver biopsy	Chronic hepatitis	Cirrhosis	Cirrhosis	Chronic hepatitis	Chronic hepatitis
Bone marrow biopsy	LPD	LPD	Not involved	Not involved	Not involved
Serum cryoglobulins (mg/dl)	3550	2434	2993	3283	45
RF (IU/ml)	418	3910	3710	731	146
IgM (mg/dl)	433	400	437	194	472
C4 (mg/dl)	2	4	12	10	3
FcγRIIIa genotype	VV	VF	VF	VF	VF
Previous therapy for nephritis	PEG-interferon, PE, CYC	Interferon, PEG-interferon	None	None	None
Other clinical features	Neuropathy, purpura, fever	Purpura, arthralgias	Neuropathy	Purpura	Purpura

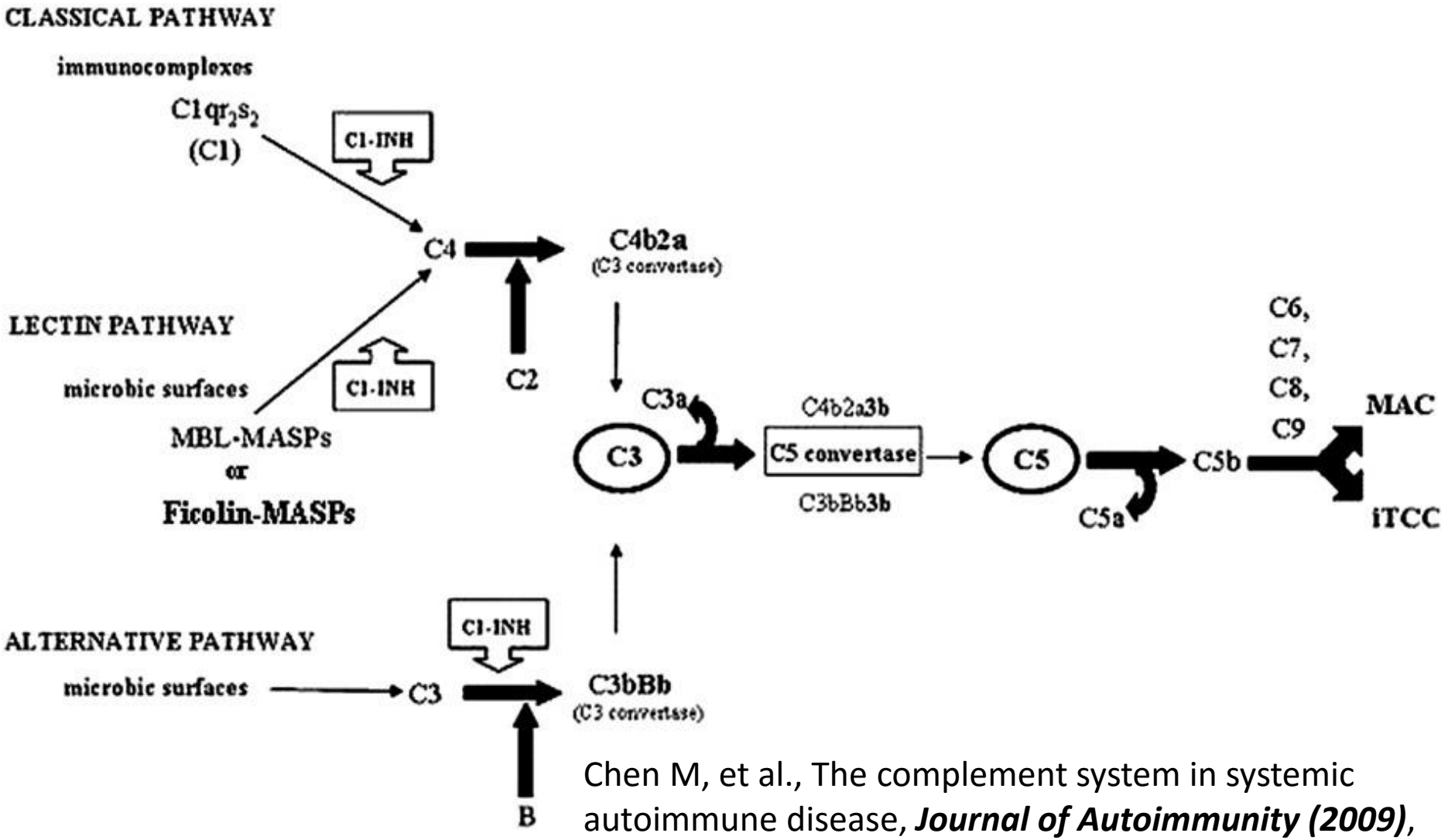
L. Quartuccio, G. Soardo, G. Romano, F. Zaja, C. A. Scott, G. De Marchi, M. Fabris, **G. Ferraccioli,** De Vita S. Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids
Rheumatology 2006;45:842–846

Mixed cryo MPG-nephritis



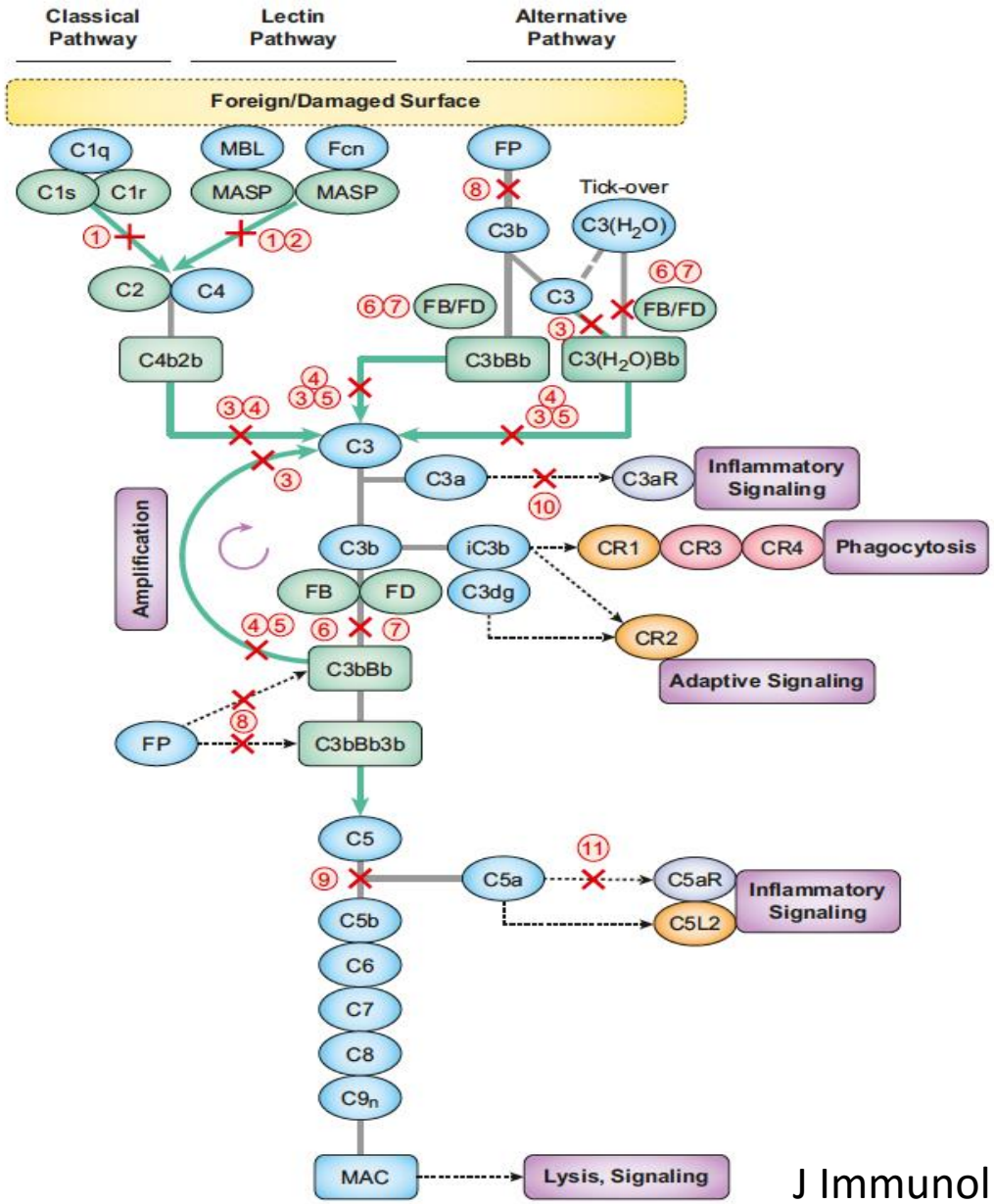
L. Quartuccio, G. Soardo1, G. Romano, F. Zaja, C. A. Scott, G. De Marchi, M. Fabris, **G. Ferraccioli,** De Vita S. Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids
Rheumatology 2006;45:842–846

Complement activation



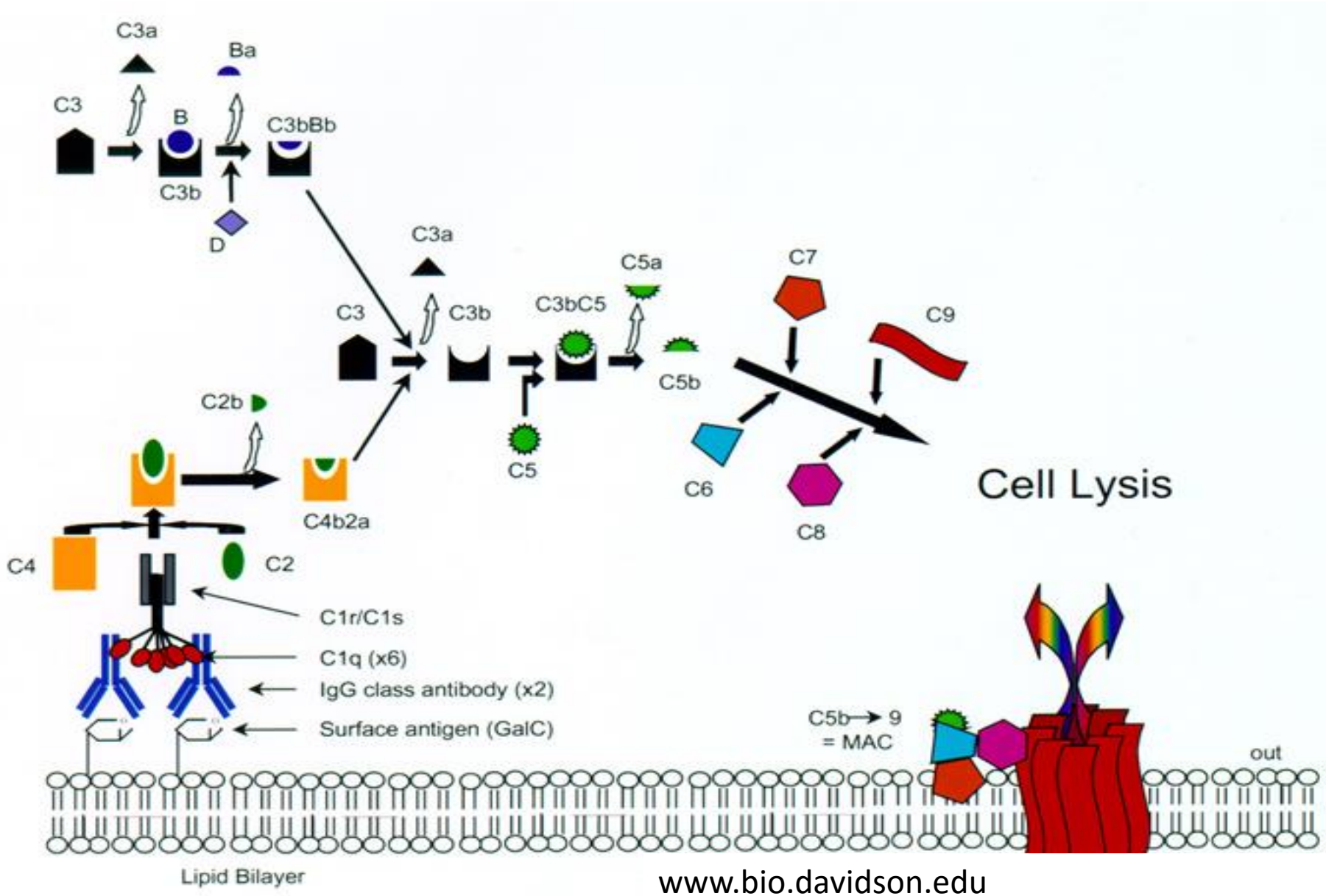
Chen M, et al., The complement system in systemic autoimmune disease, ***Journal of Autoimmunity (2009)***,

Complement cascade



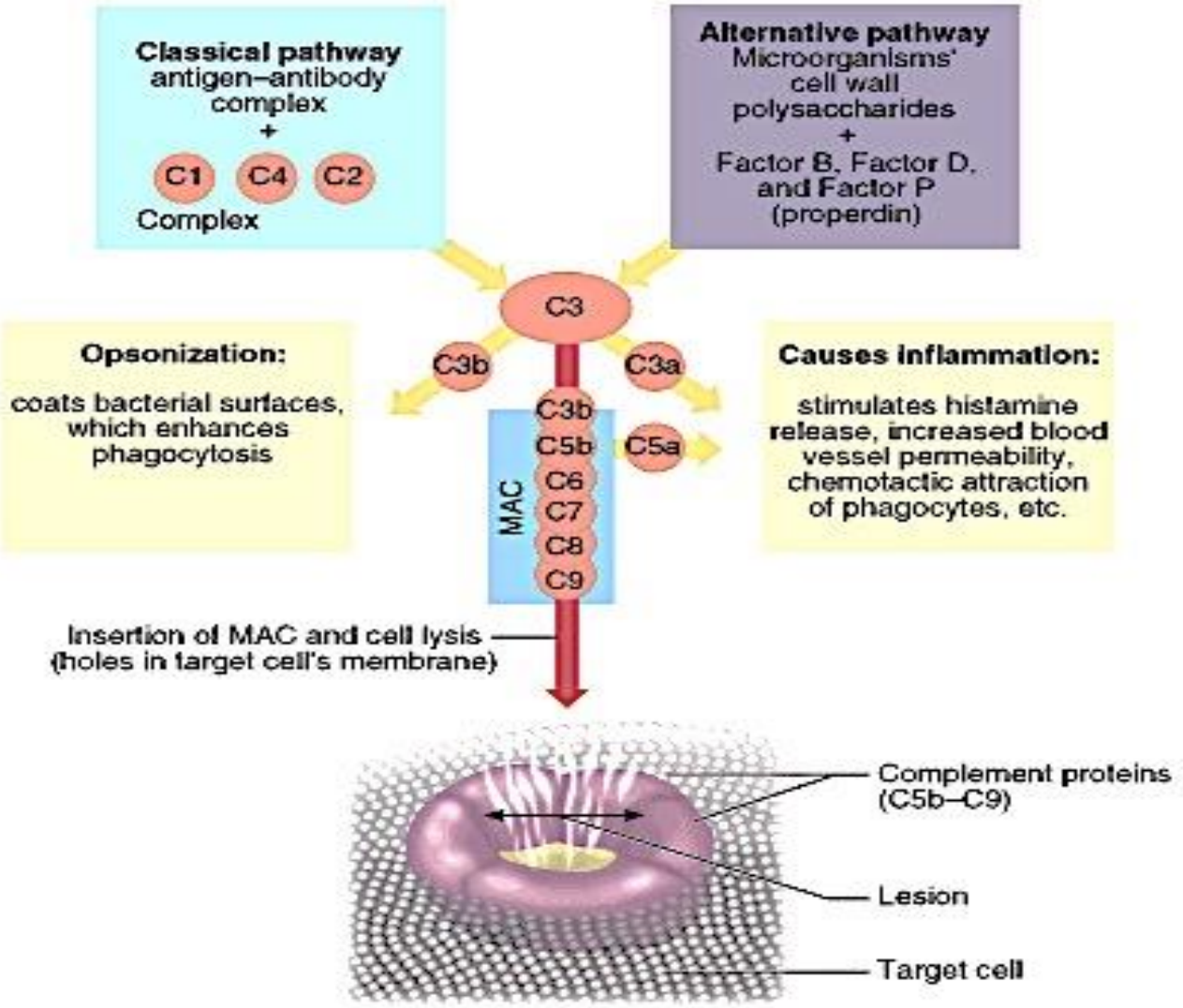
J Immunol 2013; 190:3839-3847

Classical and alternative pathway



www.bio.davidson.edu

Complement : damage



Henoch-Schönlein purpura presenting as terminal ileitis and complicated by thrombotic microangiopathy

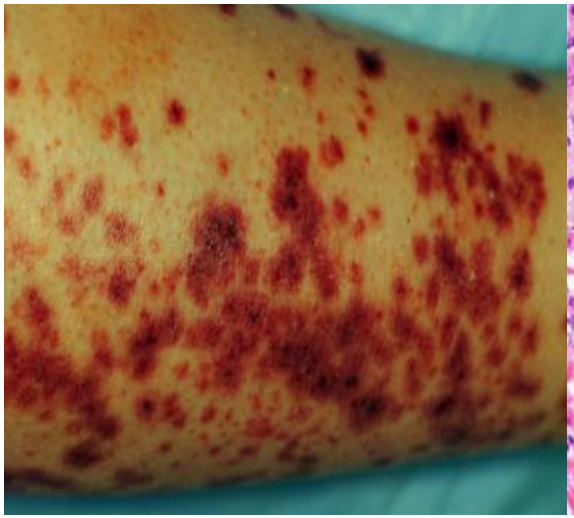
Skin biopsy : leukocytoclastic vasculitis, and immunofluorescence show granular deposits of IgA and C3c (but not IgM, IgG, or C1q) in the subepidermal blood vessels.

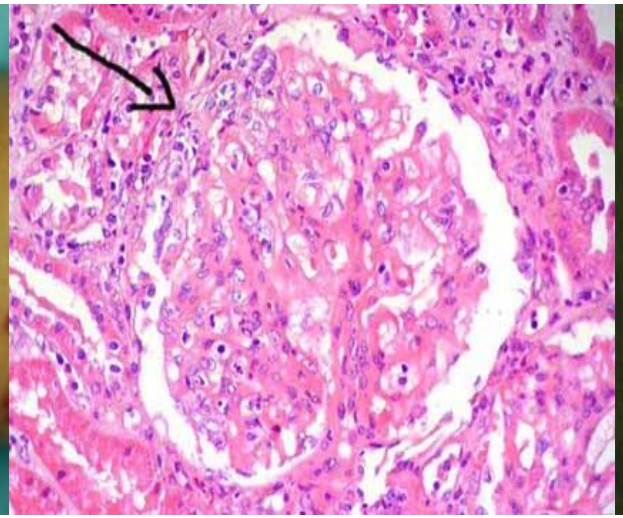
The occurrence of a superimposed TMA characterized by thrombocytopenia, rapidly worsening renal function, and MAHA with fragmented red blood cells can occur in patients with HSP.

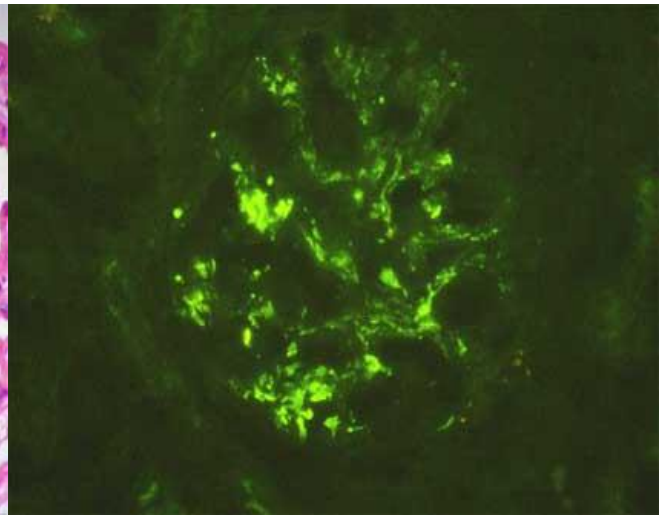
Eur J Intern Med. 2005 Nov;16(7):510-2.

Schonlein-Henoch

Complement activation through both the alternative and lectin pathways is found in patients with HSPN and IgAN. In a study of Hisano et al. , in patients with IgAN, mesangial deposition of C3c, C4, MBL, and MASP-1 has been detected by immunohistology along with IgA1 and A2.

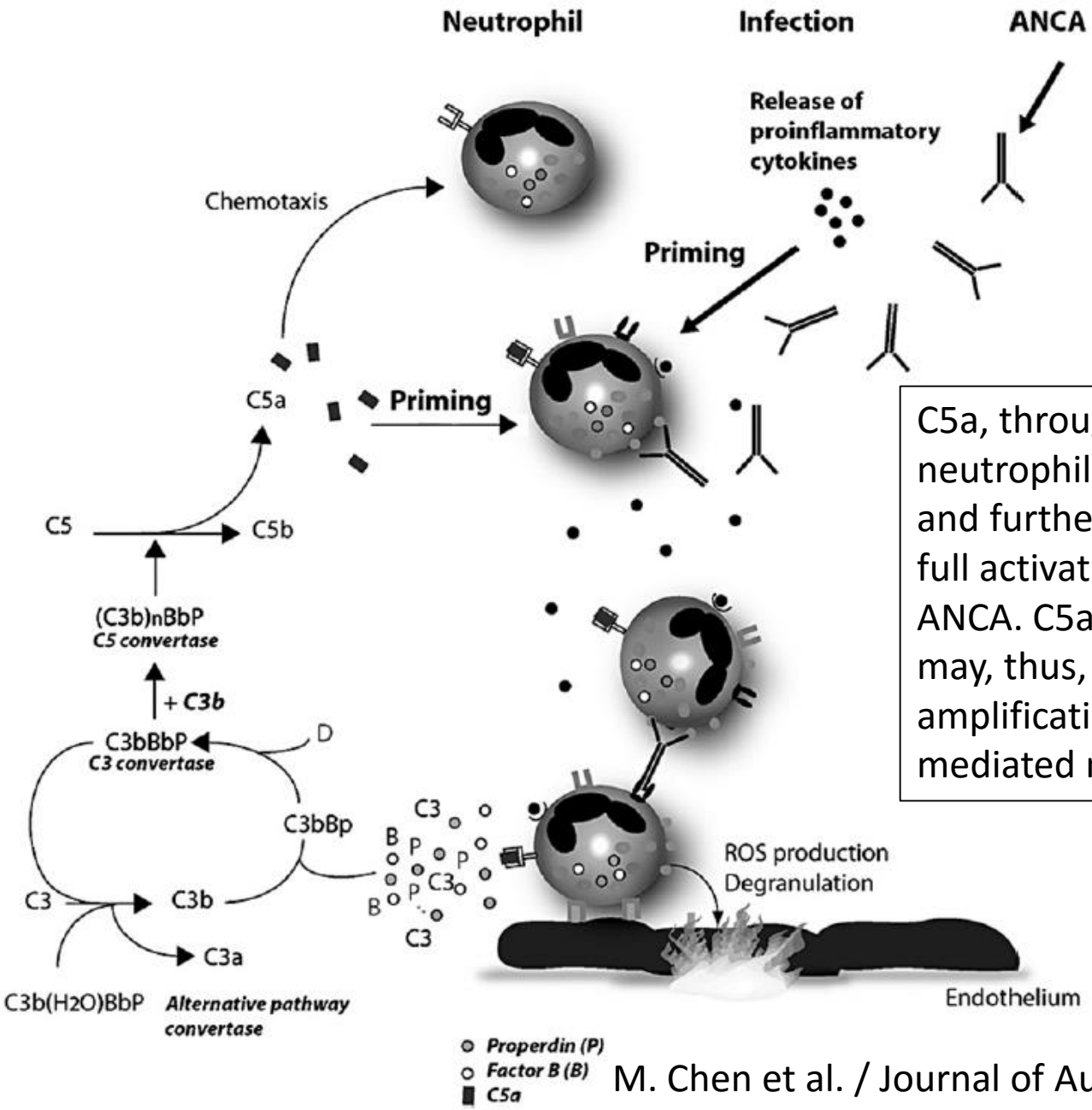






Am J Kidney Dis 2005;45:295e302

ANCA associated vasculitides



C5a, through interaction with neutrophil C5aR, may attract and further prime neutrophils for full activation in response to ANCA. C5a and the neutrophil C5aR may, thus, compose an amplification loop for ANCA-mediated neutrophil activation

M. Chen et al. / Journal of Autoimmunity (2009)

Association of Serum C3 Concentration and Histologic Signs of Thrombotic Microangiopathy with Outcomes among Patients with ANCA-Associated Renal Vasculitis

46 patients with AAV diagnose

sC3 was below the lower limit of normal in 35% of the patients, whereas C4 was low in only 2%. Patients with low sC3 tended to be older (P=0.04) and to have lower eGFR at diagnosis (P=0.06).

Eight of the 30 patients who had undergone biopsy (27%) had histologic signs of TMA; these signs were more frequent in patients with low sC3 (5 of 10 versus 3 of 20; P=0.04)

Low sC3 levels and histologic signs of TMA are associated with a poor renal prognosis in patients with AAV.

Clin J Am Soc Nephrol 10: 2143–2151, 2015

Clinicopathologic characteristics and outcomes of renal thrombotic microangiopathy in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis.

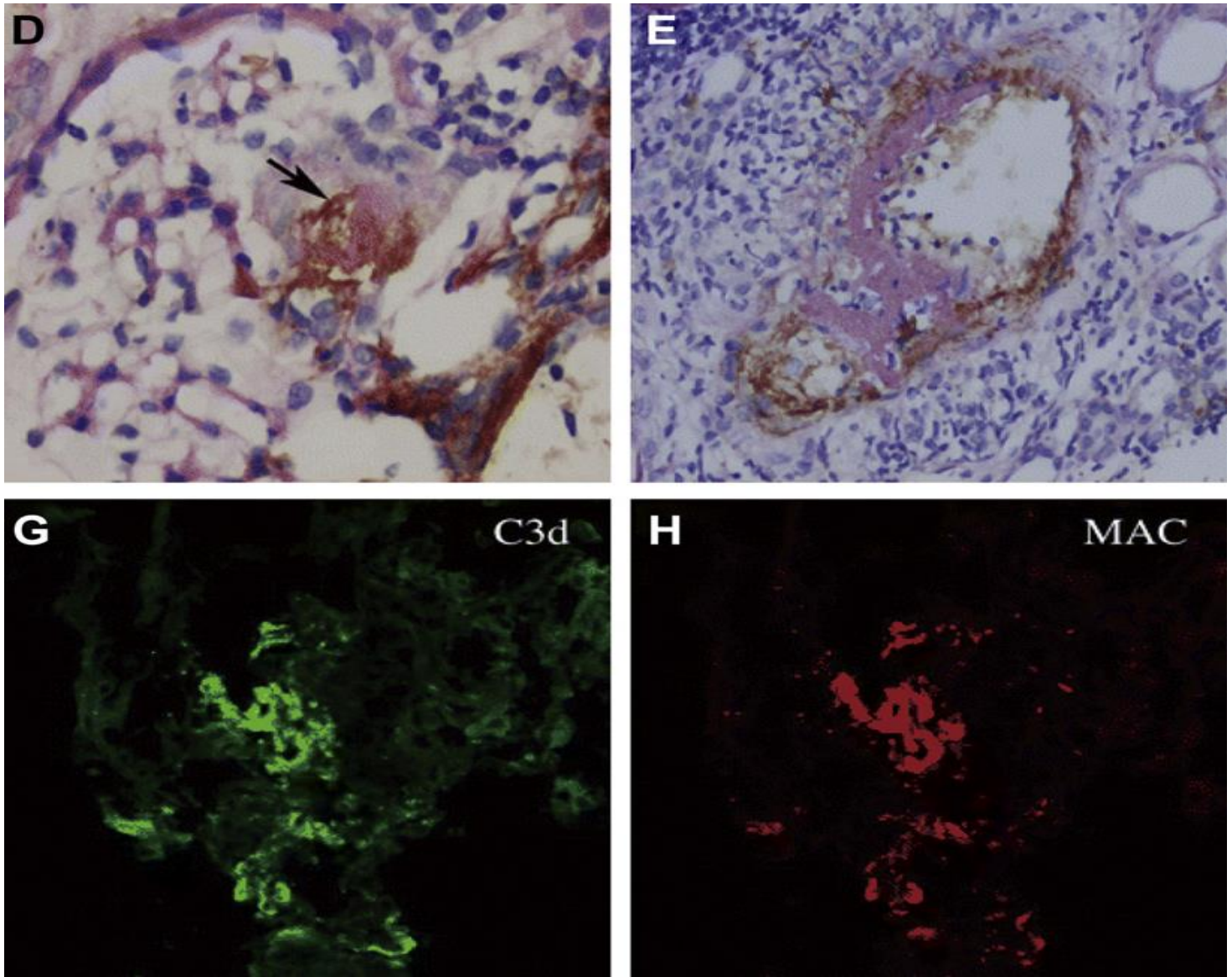
Among the 220 patients with ANCA-associated GN, 30 were identified having concomitant renal TMA by pathologic evaluation. Compared with the non-TMA group, patients with renal TMA presented with more severe renal injury, as evidenced clinically by a higher level of serum creatinine at diagnosis (5.0 [IQR, 3.5-9.0] versus 3.2 [IQR, 1.7-6.8] mg/dl; P=0.02) and pathologically by a higher percentage of cellular crescents (15.0% [IQR, 6.9%-34.9%] versus 6.9% [IQR, 0%-21.1%]; P=0.04) and more severe interstitial infiltration (2 [IQR, 2-2] versus 2 [IQR, 1-2]; P=0.03) in renal biopsies.

Renal TMA was independently associated with mortality of patients with AAV Initial serum creatinine, tubular atrophy, and interstitial fibrosis (hazard ratio, 1.92; 95% confidence interval, 1.08 to 3.41; P=0.03) or for age, sex, tubular atrophy, and interstitial fibrosis

Clin J Am Soc Nephrol 10: 750–758, 2015

ANCA associated nephritis

M. Chen et al. / Journal of Autoimmunity (2009)



ANCA associated nephritis

M. Chen et al. / Journal of Autoimmunity (2009)

C3d was widely deposited in the mesangium and along the capillary wall of diseased glomeruli, both in active and chronic lesions. C3d and MAC co-localized in diseased glomeruli of patients with NCGN. Factor B was detected in glomeruli and also co-localized with MAC. In contrast, C4d was not detected on either renal paraffin or frozen sections. These results suggest that the alternative pathway of the complement system is involved in renal damage of human pauci-immune AAV

Ann Rheum Dis. 1986 Apr; 45(4): 319–322.
Thrombotic thrombocytopenic purpura and systemic lupus erythematosus.
D A Fox, J D Faix, J Coblyn, P Fraser, B Smith,M E Weinblatt

Nephrol Dial Transplant. 2010 Jan;25(1):145-52.
Lupus nephritis combined with renal injury due to thrombotic thrombocytopaenic purpura-haemolytic uraemic syndrome. Yu F, Tan Y, Zhao MH.

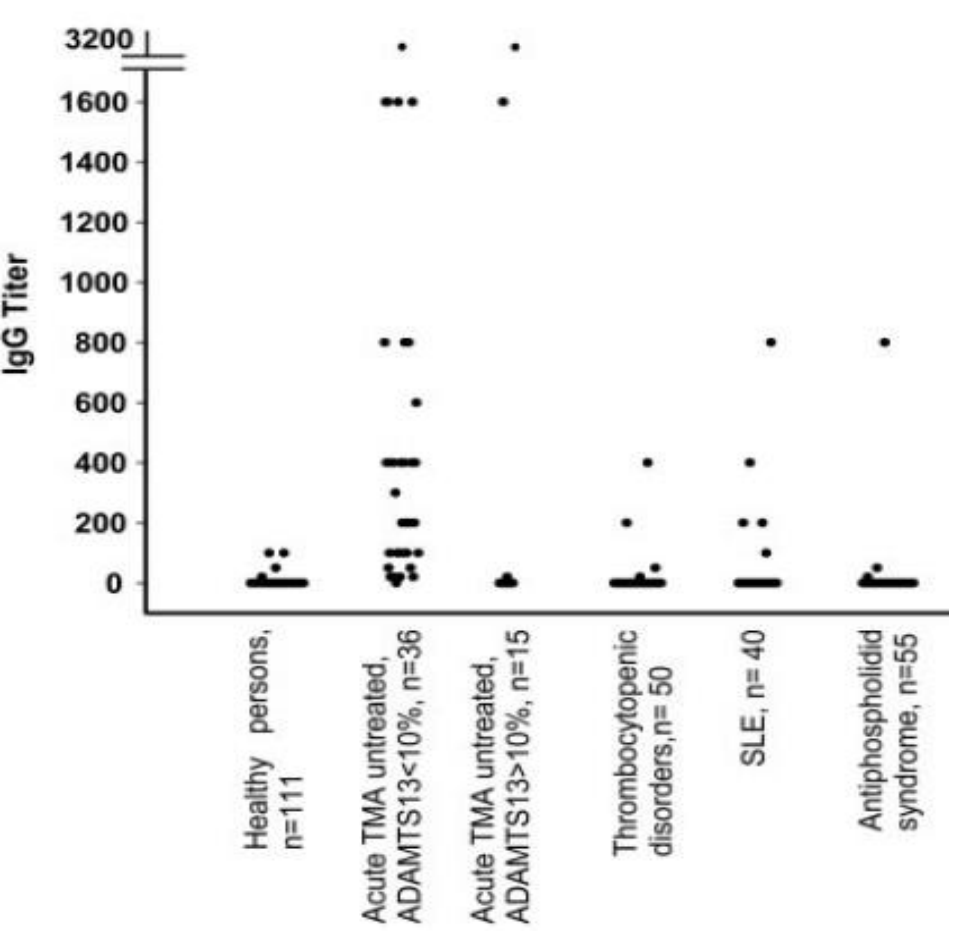
Intern Med J. 2012 Jan;42(1):95-8.
Haemolytic-uraemic syndrome during severe lupus nephritis: efficacy of plasma exchange.
Samson M, Audia S, Leguy V, Berthier S, Janikashvili N, Martin L, Bonnotte B, Lorcerie B.

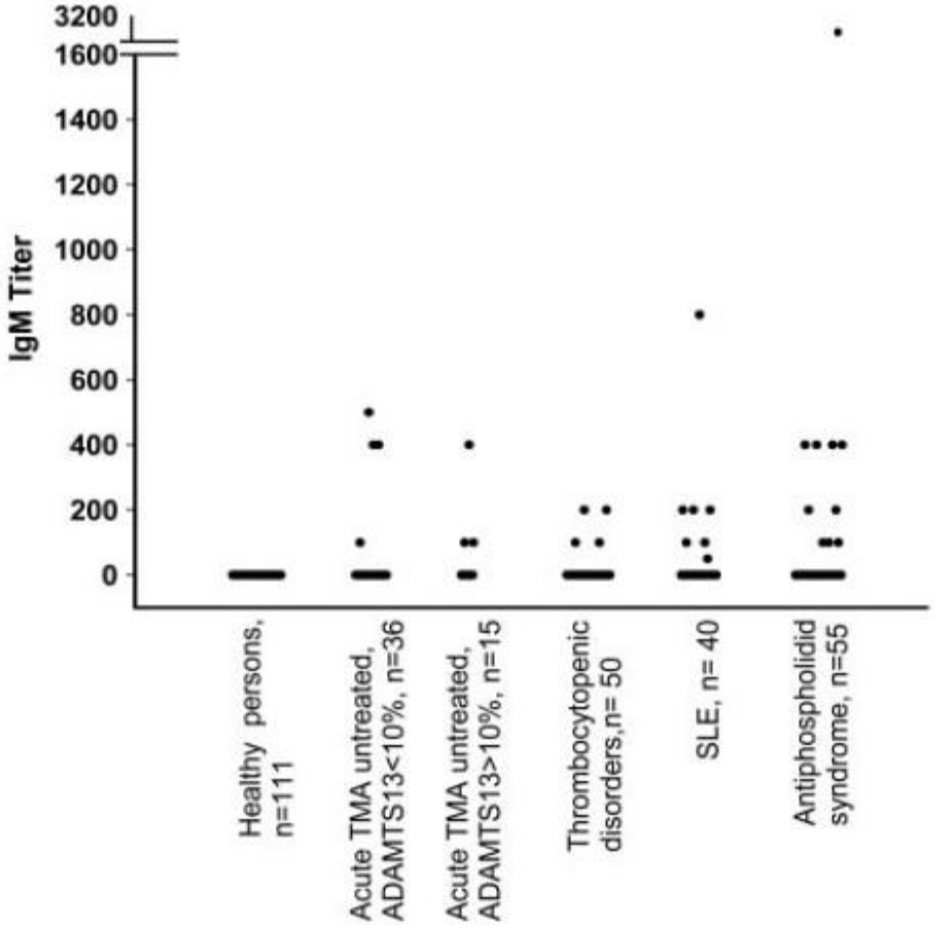
ADAMTS 13 autoantibodies in patients with TMAs in immune mediated diseases

Diagnosis	Patients, n	ADAMTS13 activity, range, %	Presence of anti-ADAMTS13†		
			Inhibitor*	IgG, n (%)	IgM, n (%)
Patients with acute acquired TMA					
Untreated TMA, ADAMTS13 < 10%	36	< 3-10	30/36 (83%)	35 (97)	4 (11)
Untreated TMA, ADAMTS13 > 10%	15	11-100	2/5	3 (20)	3 (20)
Patients with thrombocytopenia, of various causes other than acute TMA or immunologic disorders					
Thrombocytopenia	50	20-100	0/0	4 (8)	4 (8)
Systemic lupus erythematosus	40	22-172	0/5	5 (13)	7 (18)
Antiphospholipid antibody syndrome with thromboembolic complications	55	32-114	0/10	3 (5)	10 (18)
Hemophilia A with anti–factor FVIII alloantibodies	15	10-91	0/0	0	5 (33)

Blood. 2005;106:1262-1267

ADAMTS 13 autoantibodies in patients with TMAs in immune mediated diseases





Blood. 2005;106:1262-1267

Features of patients with CTD-TMAs and ai-TTP

	CTD-TMAs (n=127)				ai-TTP (n=64)	Overall *P* *
	SLE (n=64)	SSc (n=42)	PM/DM (n=11)	RA (n=10)		
Clinical features						
Median age at onset of TMAs, years (25, 75 percentile)	44 (30, 54)	59 (54, 70)	57 (49, 63)	62 (56, 73)	54 (40, 69)	<0.01[a]
Female (%)	84	95	82	90	64	<0.01[b]
Renal involvement (%)	91	95	100	100	83	NS
CNS involvement (%)	69	48	64	80	70	NS
Laboratory findings at TMA diagnosis						
Median platelet count, 10^9/l (25, 75 percentile)	29 (9, 40)	50 (31, 74)	32 (9, 46)	23 (14, 28)	9 (9, 20)	NS
Median haemoglobin, g/dl (25, 75 percentile)	7.5 (6.1, 8.8)	8.3 (7.3, 9.3)	7.4 (6.6, 9.0)	7.2 (6.9, 8.1)	8.1 (6.4, 9.2)	NS
Median serum creatinine, mg/dl (25, 75 percentile)	1.6 (0.7, 2.6)	2.8 (1.9, 3.3)	1.5 (1.2, 2.3)	3.1 (1.1, 4.4)	2.1 (0.7, 2.1)	<0.01[c]
Median VWF:Ag , % (25, 75 percentile)	207 (147, 325)	256 (191, 370)	339 (225, 461)	302 (245, 454)	147 (114, 202)	<0.01[d]

Thromb Haemost 2009; 102: 371–378

Lupus nephritis : outcome

	Cyclosporine	Azathioprine
No. of patients	36	33
Age (yr)	31.7 (±9.1)	31.2 (±11.7)
Female gender	33 (91.7%)	29 (87.9%)
Years since first diagnosis	5.4 (±8.0; median 0.4; range 0 to 24.5)	2.3 (±3.6; median 0.1; range 0 to 9)
Serum creatinine (mg/dl)	0.9 (±0.23)	0.9 (±0.29)
Creatinine clearance (ml/min)	92.5 (±21.5)	104.1 (±46.5)
Proteinuria (g)	2.8 (±3.57)	2.2 (±1.94)
Hemoglobin (mg/dl)	12.2 (±1.4)	12.4 (±1.6)
BP (mmHg)		
SBP	125 (±16.4)	129 (±14.2)
DBP	81 (±9.1)	81 (±9.8)
SLAM total score	13.1 (±5.5)	14.2 (±6.1)
Biopsy WHO category (%)		
IV	84	91
Vc or Vd	16	9
Chronicity index	2.5 (±2.6)	2.8 (±3.7)
Activity index (median/interquartile range)	7 (2 to 24)	7 (2 to 20)

Low C3 in 44 %

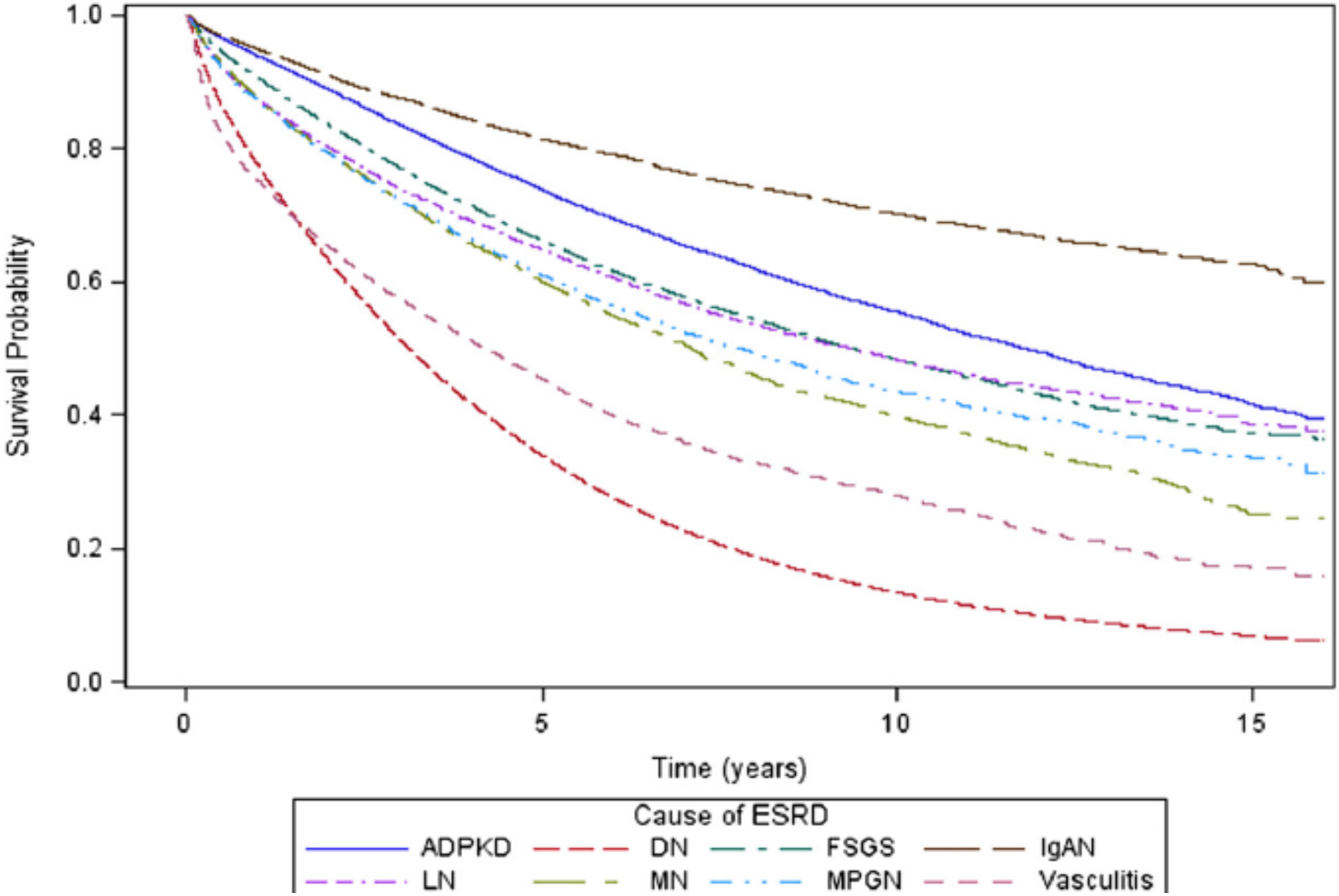
CJASN 2006, 1: 925-32

A Randomized Pilot Trial Comparing Cyclosporine and Azathioprine for Maintenance Therapy in Diffuse Lupus Nephritis over Four Years

G.Moroni, A.Doria, M.Mosca, O.Deklla Casa Alberighi, **G.Ferraccioli,** S.Todesco, C.Marino, P.Alberti, R.Ferrara, S.Greco, C.Ponticelli

CJASN

Systemic lupus erythematosus



Clin J Am Soc Nephrol 10: 1170–1178, 2015

Systemic lupus erythematosus

GN Subtype	No. of Patients (%)	Person Time at Risk, y	No. of Deaths (%)	Mortality Rate per 100 Person Years (95% Confidence Interval)
IgAN	13,012 (15.4)	76,901	2839 (21.8)	3.69 (3.56 to 3.83)
FSGS	34,330 (40.7)	179,364	13,721 (40.0)	7.65 (7.52 to 7.78)
LN	16,463 (19.5)	84,585	6741 (41.0)	7.97 (7.78 to 8.16)
MPGN	5193 (6.2)	26,869	2405 (46.3)	8.95 (8.59 to 9.31)
MN	7177 (8.5)	34,482	3382 (47.1)	9.81 (9.48 to 10.14)
Vasculitis	8126 (9.6)	29,456	4686 (57.7)	15.91 (15.45 to 16.36)

IgAN, IgA nephropathy; LN, lupus nephritis; MPGN, membranoproliferative GN; MN, membranous nephropathy.

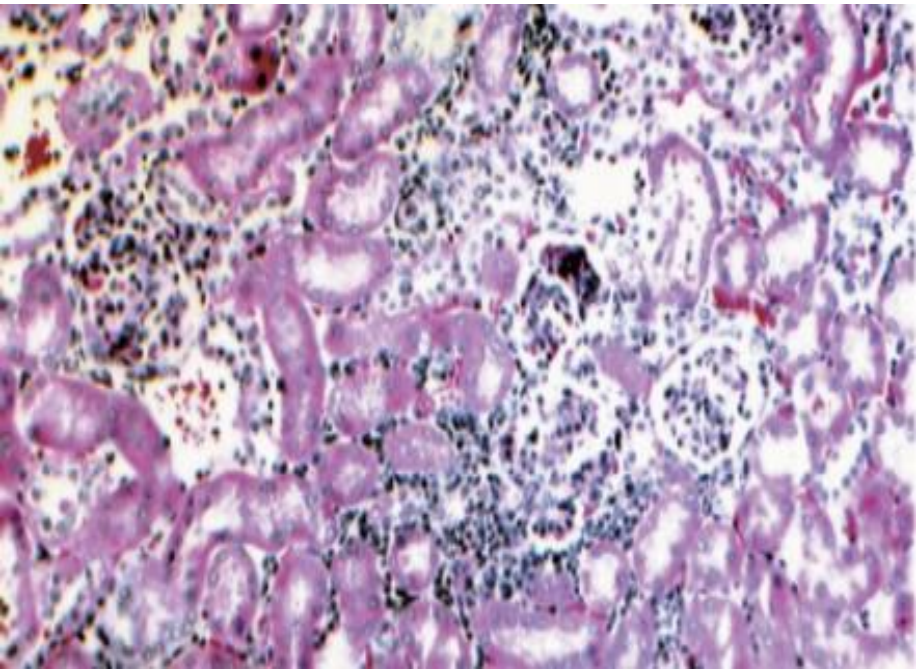
Clin J Am Soc Nephrol 10: 1170–1178, 2015

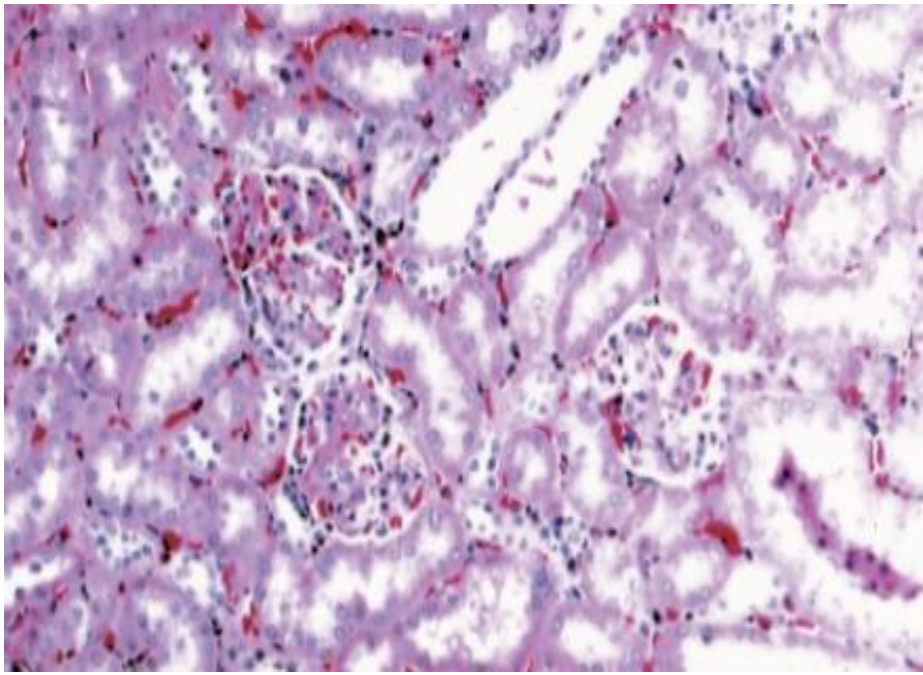
Complement and Lupus Nephritis

Variable	Responders (n = 18)	Nonresponders (n = 7)	*P*
Age at first biopsy, years	38.3 ± 12.6 (16–67)	24.9 ± 3.2 (20–29)	0.003
Disease duration, years	3.2 ± 3.7 (0–13)	2.4 ± 1.9 (0–5)	NS
Steroid dosage at time of biopsy, mg/day in prednisone equivalents	15.6 ± 15.0 (0–40)†	23.8 ± 11.6 (15–50)†	NS
Activity index	6.9 ± 4.0 (2–16)	6.7 ± 5.6 (0–13)	NS
Chronicity index	2.6 ± 1.9 (0–6)	4.6 ± 3.5 (1–9)	NS
HGF extension score	3.3 ± 0.6 (2–4)	1.6 ± 0.5 (1–2)	0.0003
HGF intensity score	2.6 ± 0.6 (1–3)	1.3 ± 0.9 (0.5–3)	0.006
TGFβ1 extension score	1.3 ± 0.6 (1–3)	3.3 ± 0.75 (0.5–3)	0.0004
TGFβ1 intensity score	1.0 ± 0.4 (0.5–2)	2.1 ± 0.9 (1–3)	0.008
HGF:TGFβ1 intensity ratio	2.9 ± 1.3 (0.5–3)	0.8 ± 0.9 (0.5–3)	0.003
HGF:TGFβ1 extension ratio	3.1 ± 1.1 (1–4)	0.5 ± 0.3 (0–1)	0.0004
Proteinuria, gm/24 hours	2.4 ± 1.5 (0.1–7.4)	2.7 ± 1.5 (0.4–4.5)	NS
Serum creatinine, mg/dl	1.1 ± 0.6 (0.5–2.9)	1.0 ± 0.5 (0.5–2.1)	NS
Creatinine clearance, ml/minute	60.7 ± 8.6 (16–173)	71.2 ± 38.8 (53–80)	NS
C3, mg/dl	61.3 ± 25.5 (15–101)	63.2 ± 26.8 (53–90)	NS
C4, mg/dl	9.3 ± 3.1 (4–29)	11.4 ± 6.6 (6–10)	NS
Anti-dsDNA, no. (%) positive	14 (77.7)	6 (85.7)	NS

Hepatocyte Growth Factor and Transforming Growth Factor 1 Ratio at Baseline Can Predict Early Response to Cyclophosphamide in Systemic Lupus Erythematosus Nephritis
A.Capuano,S. Costanzi, G.Peluso, G.Zannoni, V.G.Vellone, E.Gremese, A. Zoli,C.Scott, CA.Beltrami, G.Romano,and **G. Ferraccioli**. ***Arthritis & Rheum 2006, 54, 3633–3639***

Complement and interstitial damage





Cleavage of C5 by the classical or alternative pathway C5 convertases is the first step in generating a MAC. This cleavage generates a small peptide fragment, C5a, which has a variety of independent effects mediated by its occupation of a widely distributed receptor . C5a is a potent chemoattractant, mediating the ingress of inflammatory mediators of both neutrophilic and lymphocytic lineages

C5a is important in the tubulointerstitial component of experimental immune complex glomerulonephritis..***Clin Exp Immunol 2002; 130:1–3***

Complement and Lupus Nephritis

Decreased C3 and C4 levels have been found in about 75% of SLE patients with focal proliferative glomerulonephritis and in 90% of patients with diffuse proliferative glomerulonephritis.

Moreover, complement split products such as C3d and C5b-9 also can be detected in the urine of patients with SLE nephritis.

LUPUS

MAHA, ↓platelets, AKI, proteinuria, hematuria, ↓complement

No immune-complex glomerular disease. Positive serum antiphospholipid antibodies (aPL)

Renal Thrombotic Microangiopathy in Patients With Systemic Lupus Erythematosus and the Antiphospholipid Syndrome . M.D. Hughson et al.Am.J.K.Dis.1992, 20:150-8

MEMBRANE ATTACK COMPLEX IN SYSTEMIC LUPUS ERYTHEMATOSUS

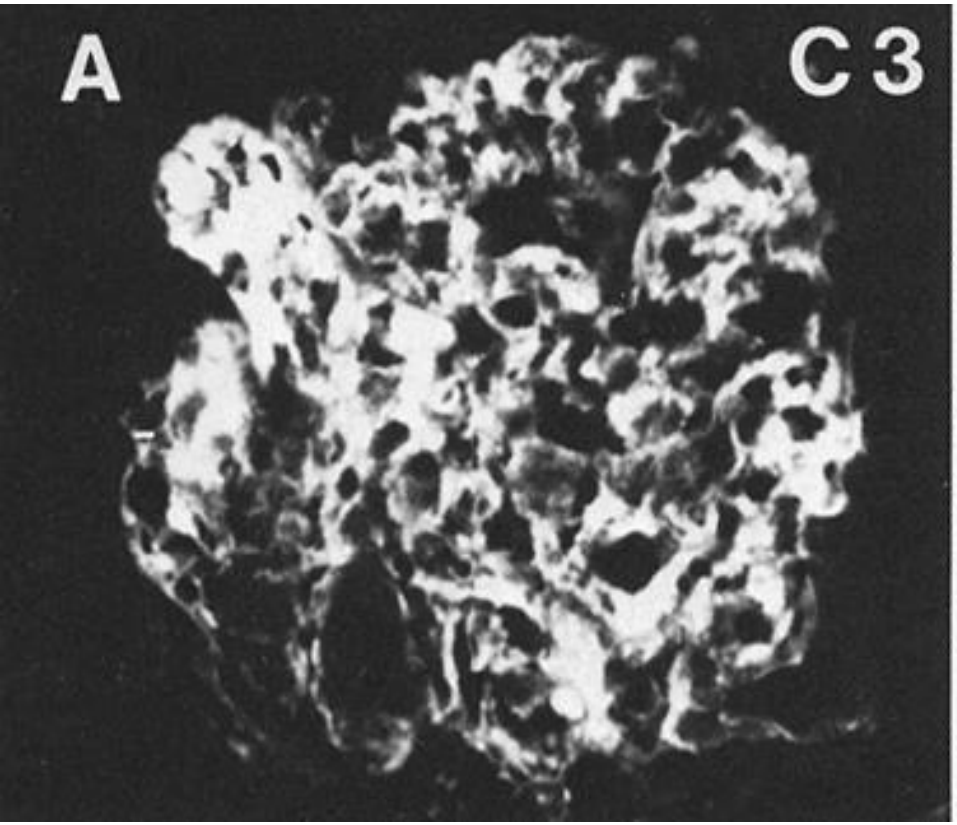
Renal tissue was obtained at autopsy (15 cases) and biopsy (7 cases) from patients with clinical and laboratory findings that fulfilled the American Rheumatism Association criteria for SLE (20). SLE renal disease was classified as mesangial nephropathy (2 cases), focal proliferative glomerulonephritis (7 eases), diffuse proliferative glomerulonephritis (10 cases), and membranous nephropathy (3 cases).

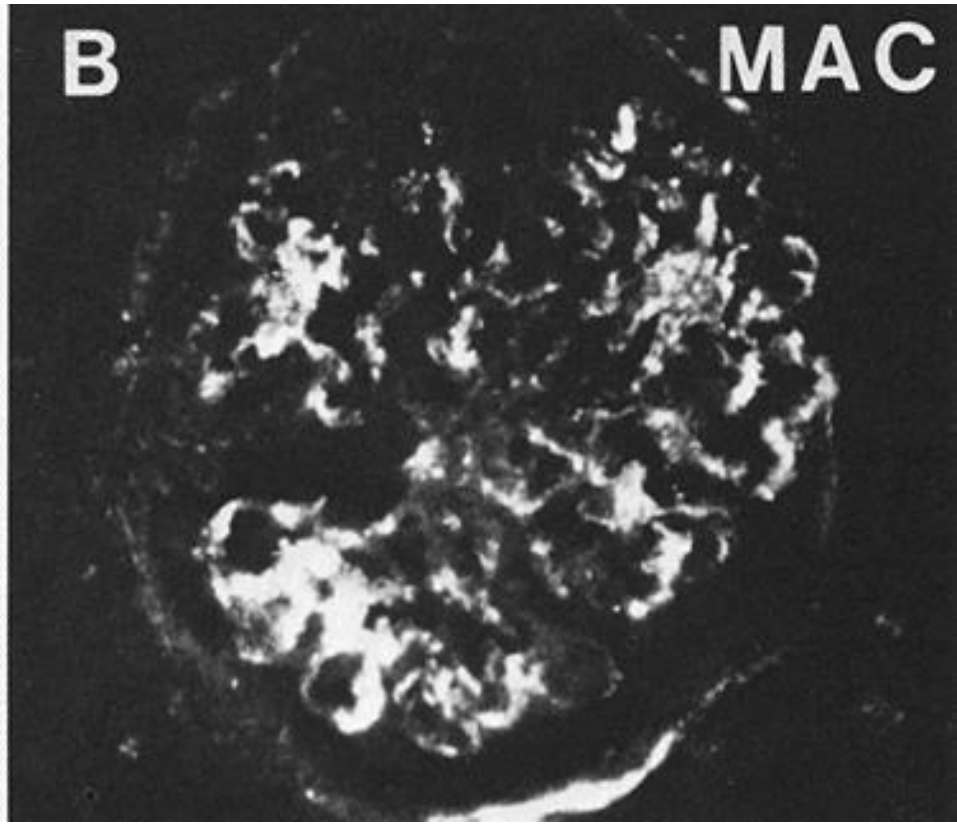
Classification of glomerulonephritis		Relative intensity of fluorescence	Immunofluorescence demonstration of:				
			IgG	IgM	C1q	C3	MAC
Focal proliferative	(7)*	Strong	7‡	1	2	7	1
		Moderate	0	1	5	0	5
		Weak or absent	0	5	0	0	1
Diffuse proliferative	(10)	Strong	9	0	6	8	8
		Moderate	1	5	4	2	2
		Weak or absent	0	5	0	0	0
Membranous nephropathy	(3)	Strong	3	0	2	3	1
		Moderate	0	2	1	0	1
		Weak or absent	0	1	0	0	1

J. Exp. MED. 1981, 154 : 1779 t794

MEMBRANE ATTACK COMPLEX IN SYSTEMIC LUPUS ERYTHEMATOSUS

Renal tissue was obtained at autopsy (15 cases) and biopsy (7 cases) from patients with clinical and laboratory findings that fulfilled the American Rheumatism Association criteria for SLE (20). SLE renal disease was classified as mesangial nephropathy (2 cases), focal proliferative glomerulonephritis (7 eases), diffuse proliferative glomerulonephritis (10 cases), and membranous nephropathy (3 cases).





J. Exp. MED. 1981, 154 : 1779 t794

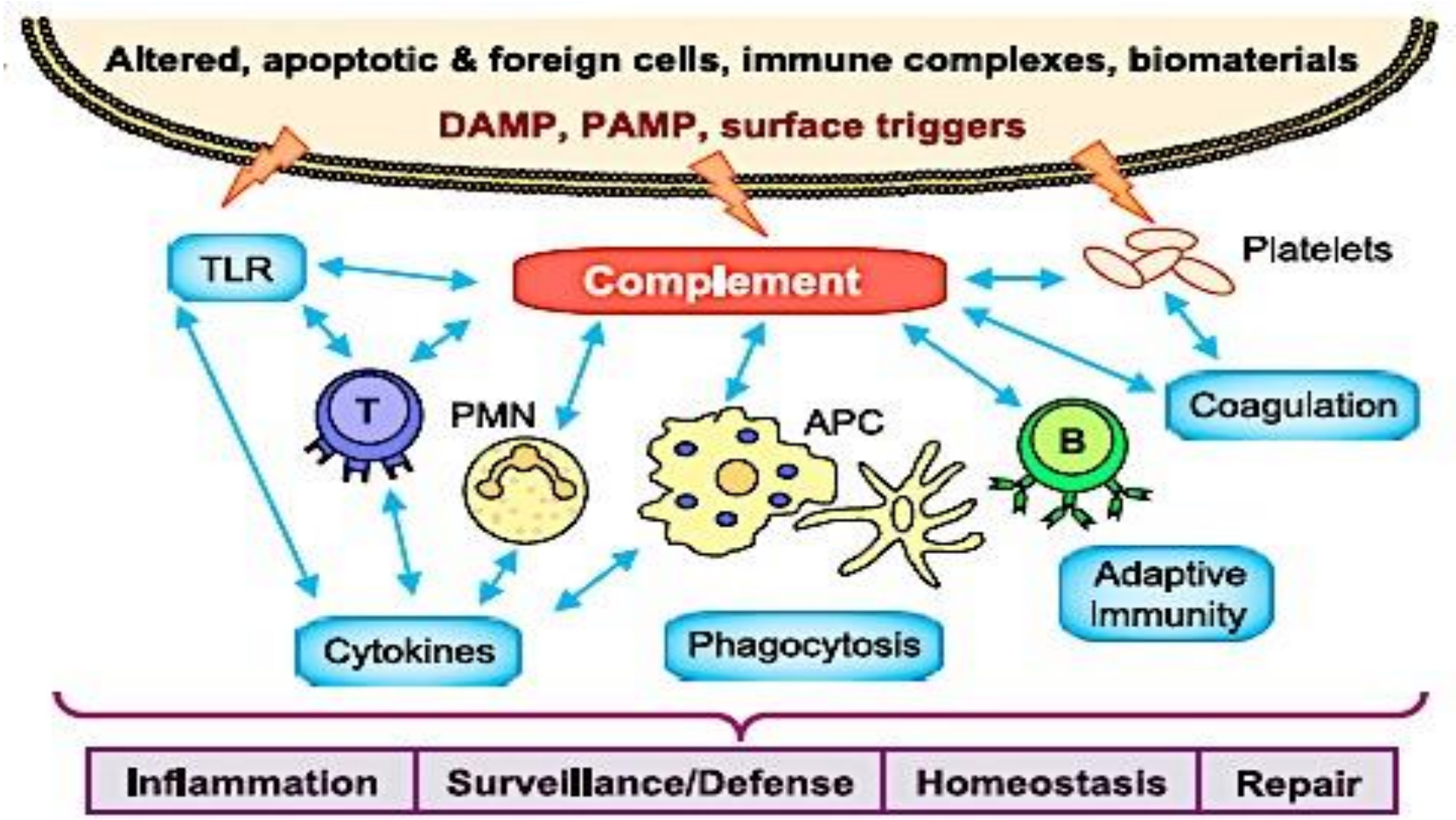
B cell depletion may lead to normalization of anti platelet, anti-erythrocyte and antiphospholipid antibodies in systemic lupus erythematosus.

Haemoglobin (gm/dl) (nv 12-16)	8.7	9.7	9.8	10.2	9	9	10.6	9.9	9.5	10.5
Erythrocytes (nv 4-5.5 x10^6/µl)	2.76	3.1	3.02	3.26	2.96	2.99	3.7	3.49	3.55	3.34
Platelets (PLT) (nv 150-400 x10^3/µl)	2	62	74.9	89	116	93	119	74	49	110
C3 (nv 90-180 mg/dl)	67	81	62	82	70	70	87	89	83	90
C4 (nv10-40 mg/dl)	5	4	4	8	8	10	6	14	10	17

Some coagulation enzymes directly cleave and activate C3 or C5 , thereby bypassing traditional initiation pathways, the products of such activation may themselves influence coagulation, as shown for the stimulation of tissue factor expression by C5a. The LP may also play a linking role, as MASP-2 can activate prothrombin and induce clot formation, whereas MBL and ficolins were described to bind fibrinogen and fibrin

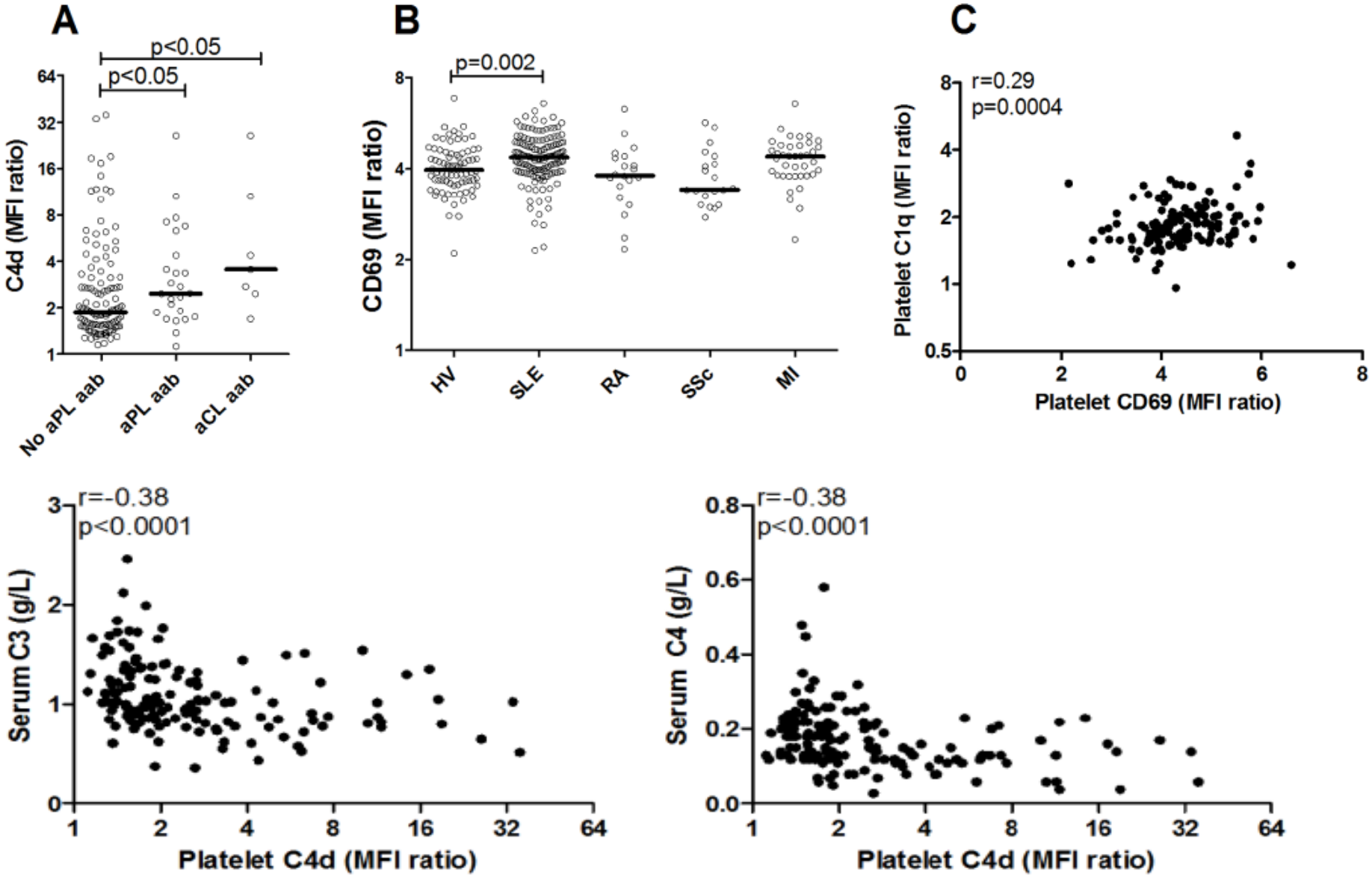
P.Tomietto, E.Gremese, B.Tolusso1, P.Venturini, S.De Vita, G.Ferraccioli
Thrombus Haemost 2004; 92: 1150–3

The role of complement in the stimulation and maturation of B cells via CD21 is well described and critically contributes to autoimmune and other diseases.



J. Immunol 2013; 190:3831-3838;

Complement Activation on Platelets

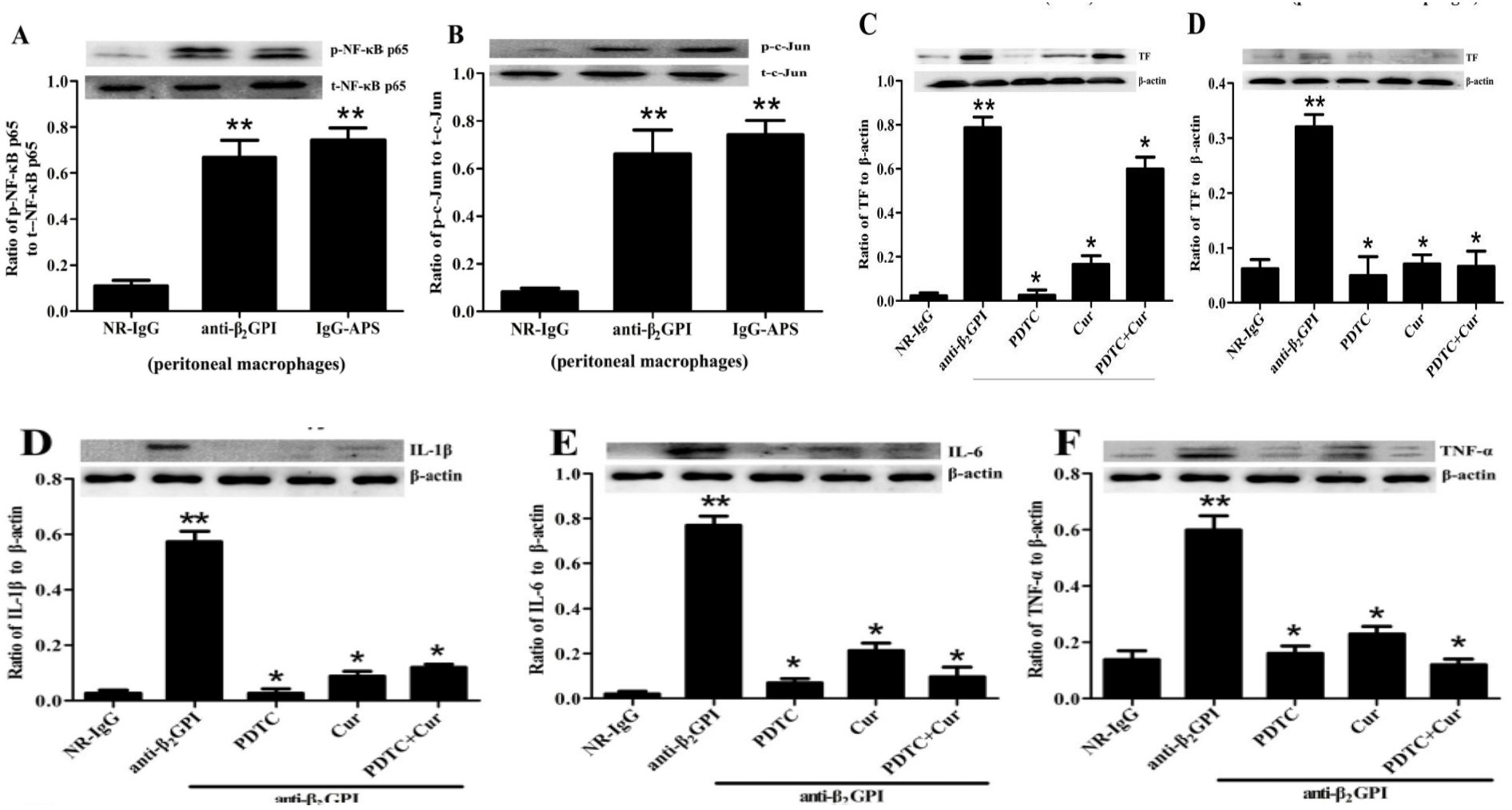


PLoS ONE 9(6): e99386

Pathogenesis of antiphospholipid antibody syndrome (APLS): vasculopathy or vasculitis or both ?

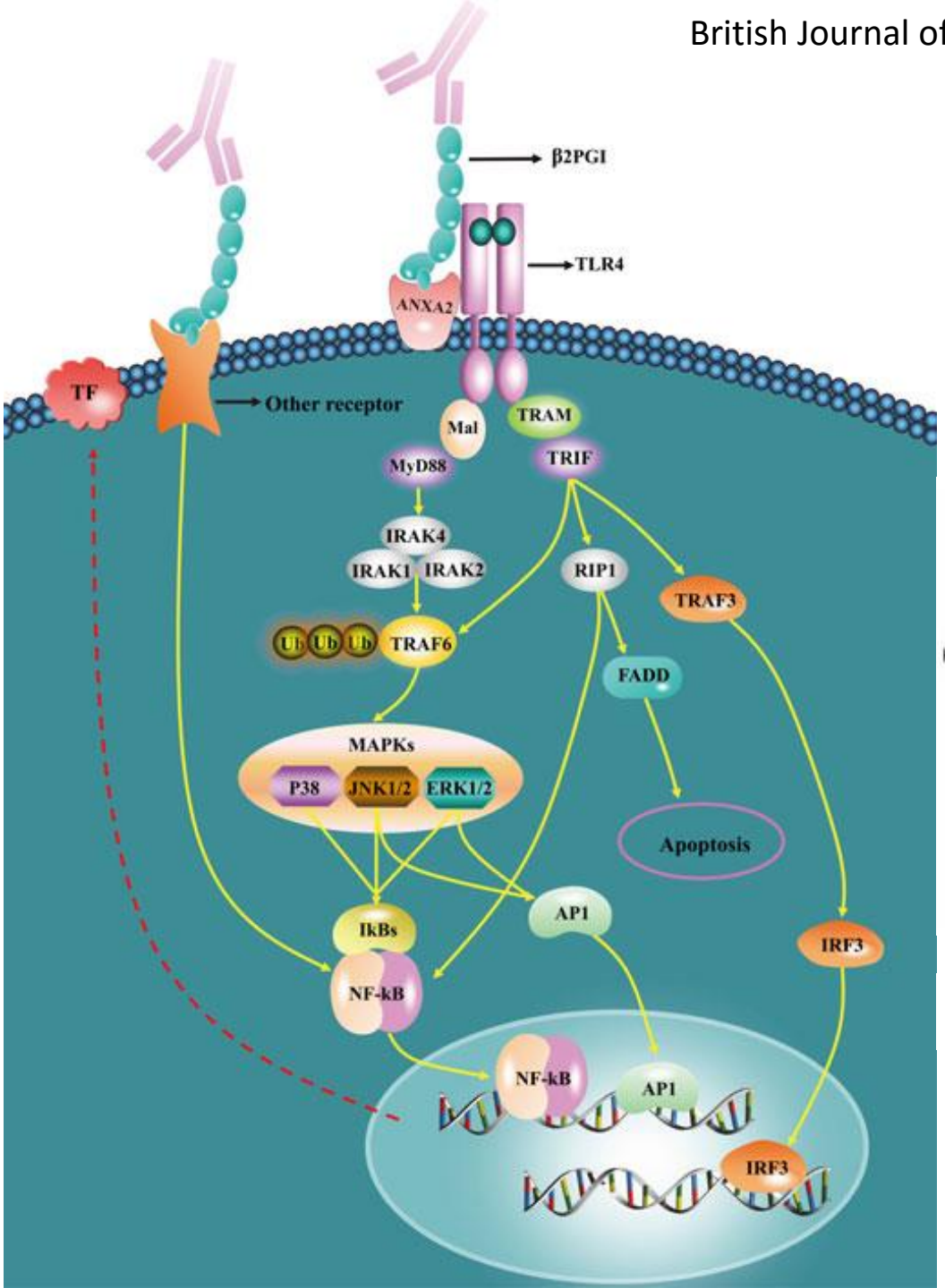
- Activation of the complement cascade has been shown to play an important role in pregnancy loss,fetal growth restriction and thrombosis in mouse models.
- Heparin inhibits complement activation, and its utility in pregnancy may be due to its anticomplement, as opposed to its anticoagulant, effects.
- Treatment aimed at inhibiting specific aspects of the complement cascade may be a novel treatment option for patients with antiphospholipid antibody syndrome (APS).

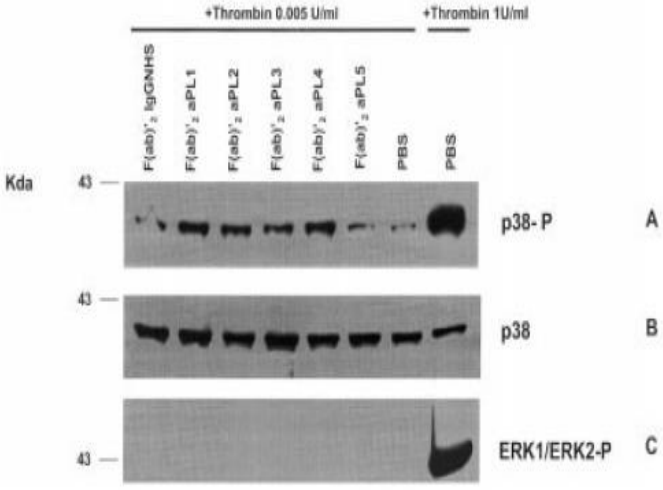
Pathogenesis of antiphospholipid antibody syndrome (APLS)



Plos one 2016, 11(2): e0147958

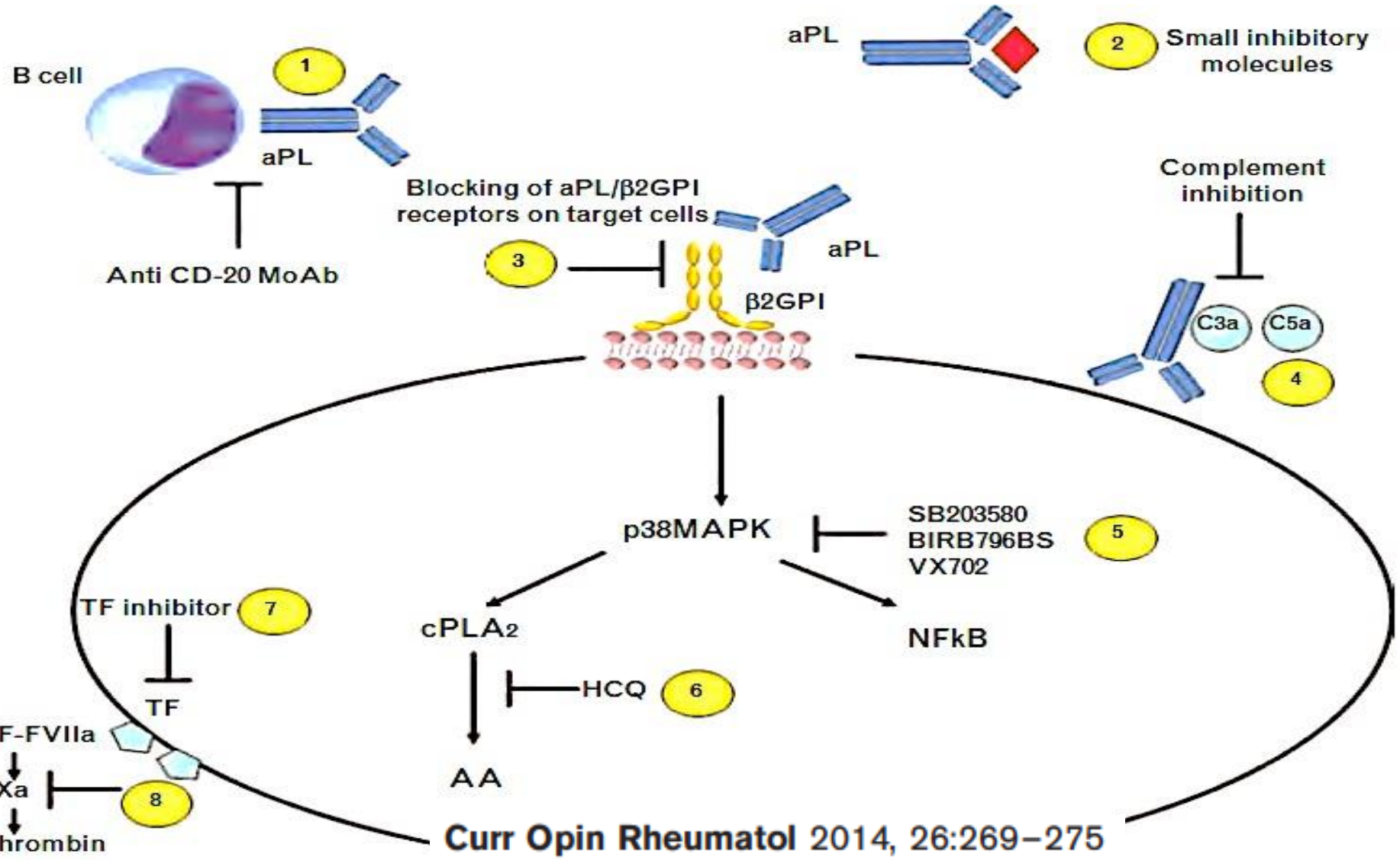
British Journal of Haematology, 2014, 164, 165–176



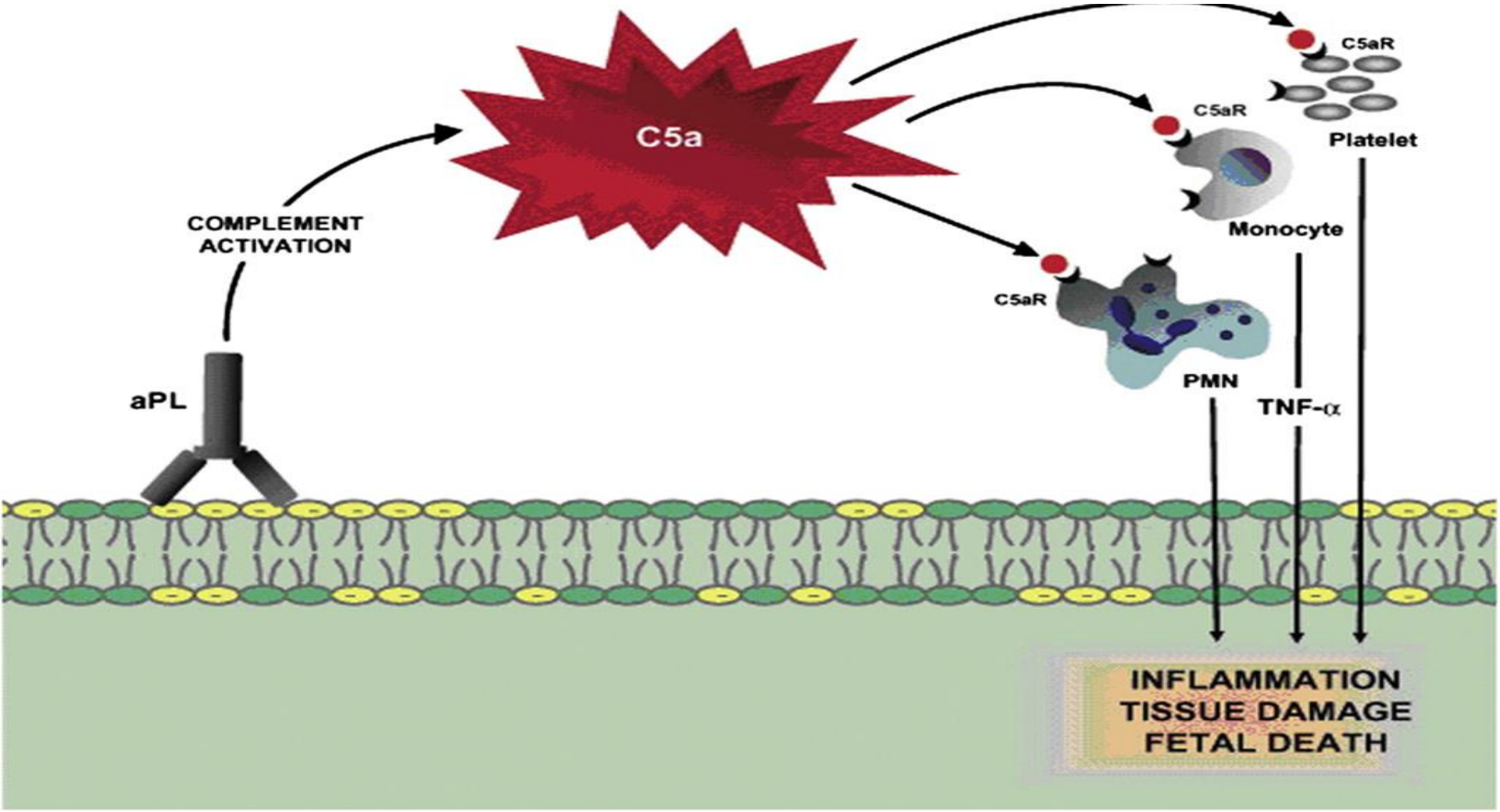


ARTHRITIS & RHEUMATISM
Vol. 50, No. 9, September 2004, pp 2911–2919

Complement and APL



Proposed mechanism for the pathogenic effects of aPL antibodies on tissue injury.



Chen M, et al., The complement system in systemic autoimmune disease, Journal of Autoimmunity (2009),

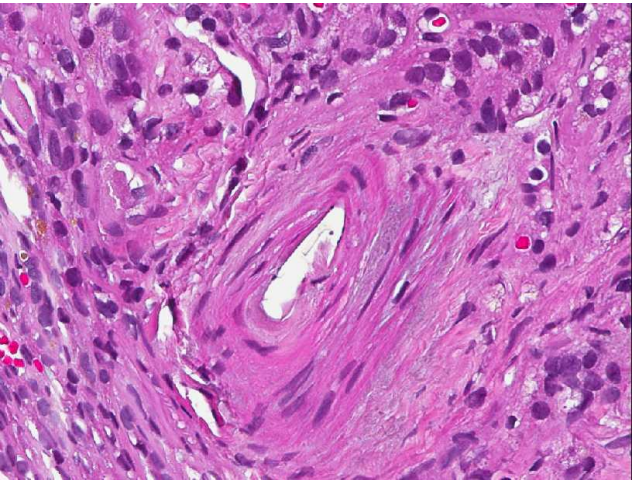
Proposed mechanism for the pathogenic effects of aPL antibodies on tissue injury.

Holers et al. found that a C3 convertase inhibitor can prevent fetal loss and growth restriction, and that mice deficient in complement C3 are resistant to fetal injury induced by antiphospholipid antibodies . C5, and particularly its cleavage product C5a, are key mediators of fetal injury.

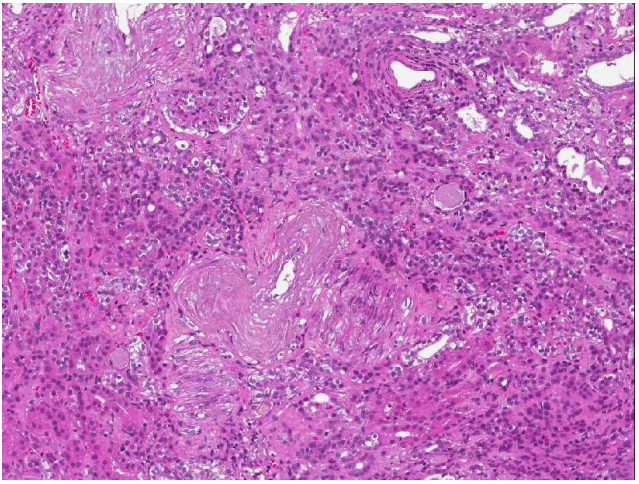
Holers et al. J Exp Med 2002;195:211e20

Chen M, et al., The complement system in systemic autoimmune disease, Journal of Autoimmunity (2009),

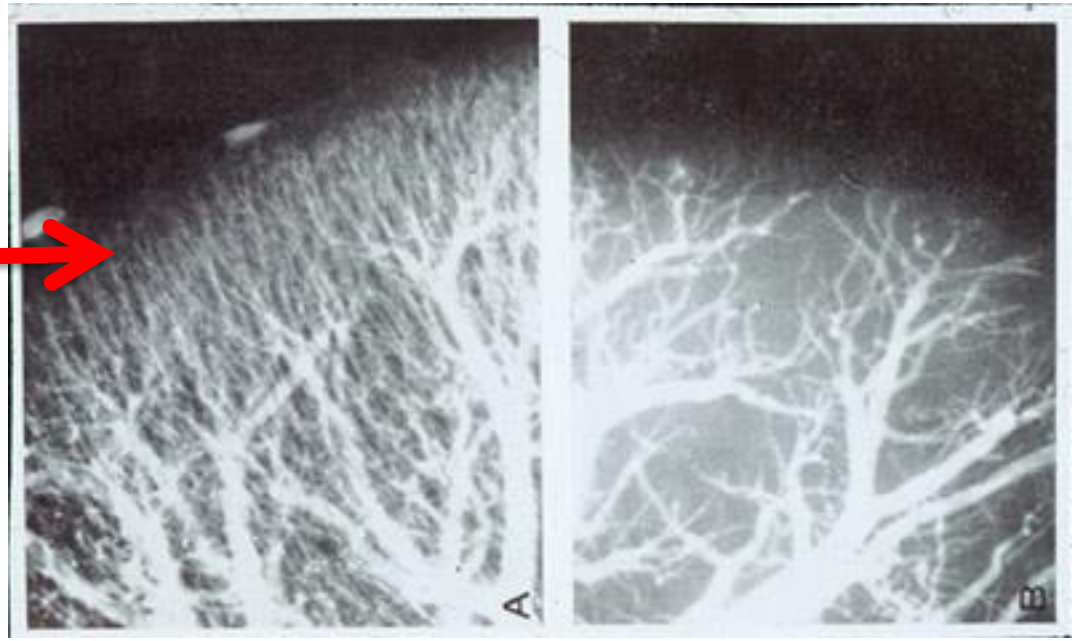
Scleroderma kidney



Onion skinning concentric narrowing of arterioles with ischemia of glomeruli



Normal kidney

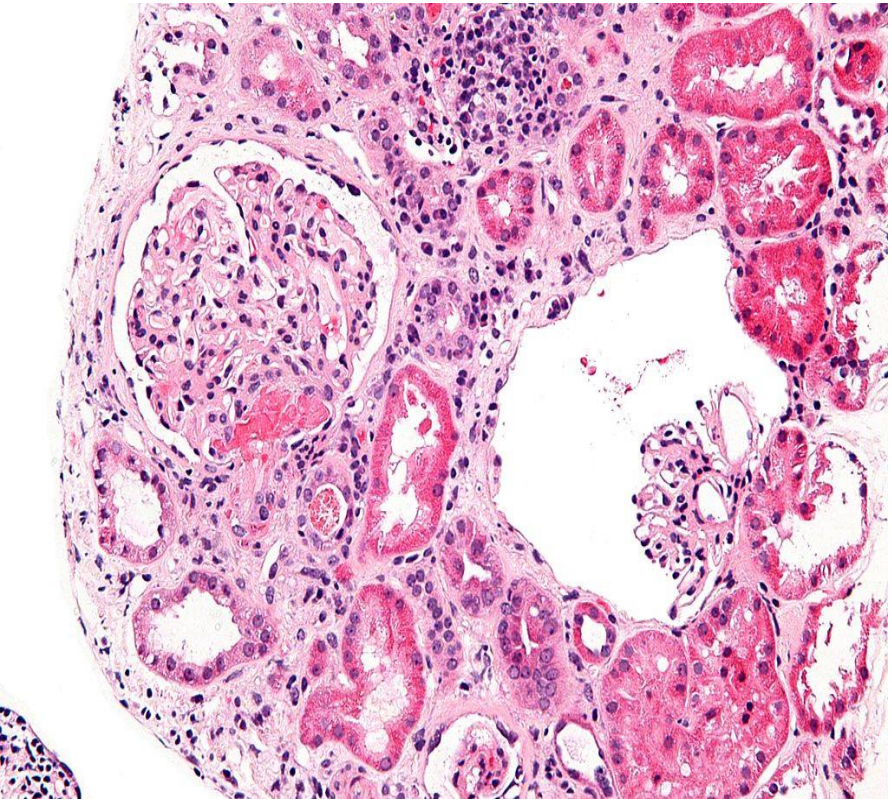


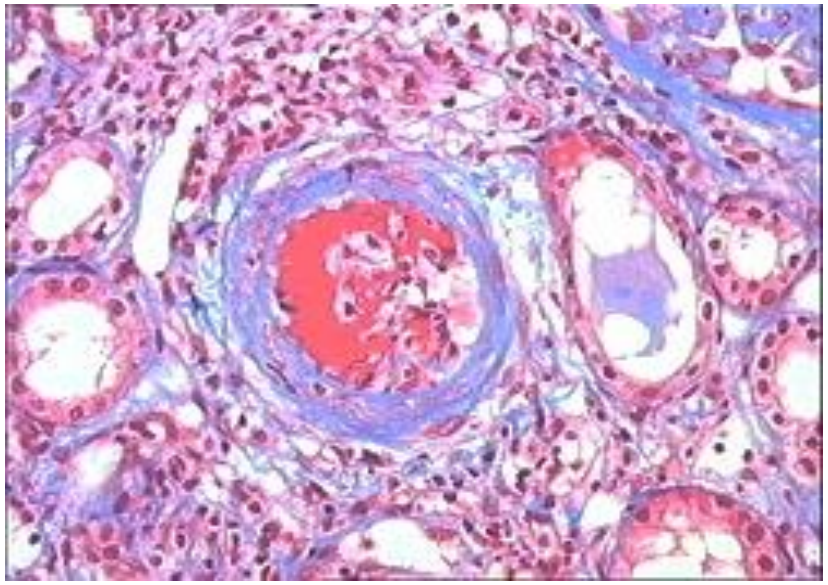
Inflammatory infiltrate in the interstitium
Fibrotic response

Autopsy studies, reveal occult renal pathology in 60% to 80% of patients with systemic sclerosis. Others have found that up to 50% of asymptomatic patients have clinical markers suggesting renal disease such as proteinuria, elevation of creatinine, or hypertension.

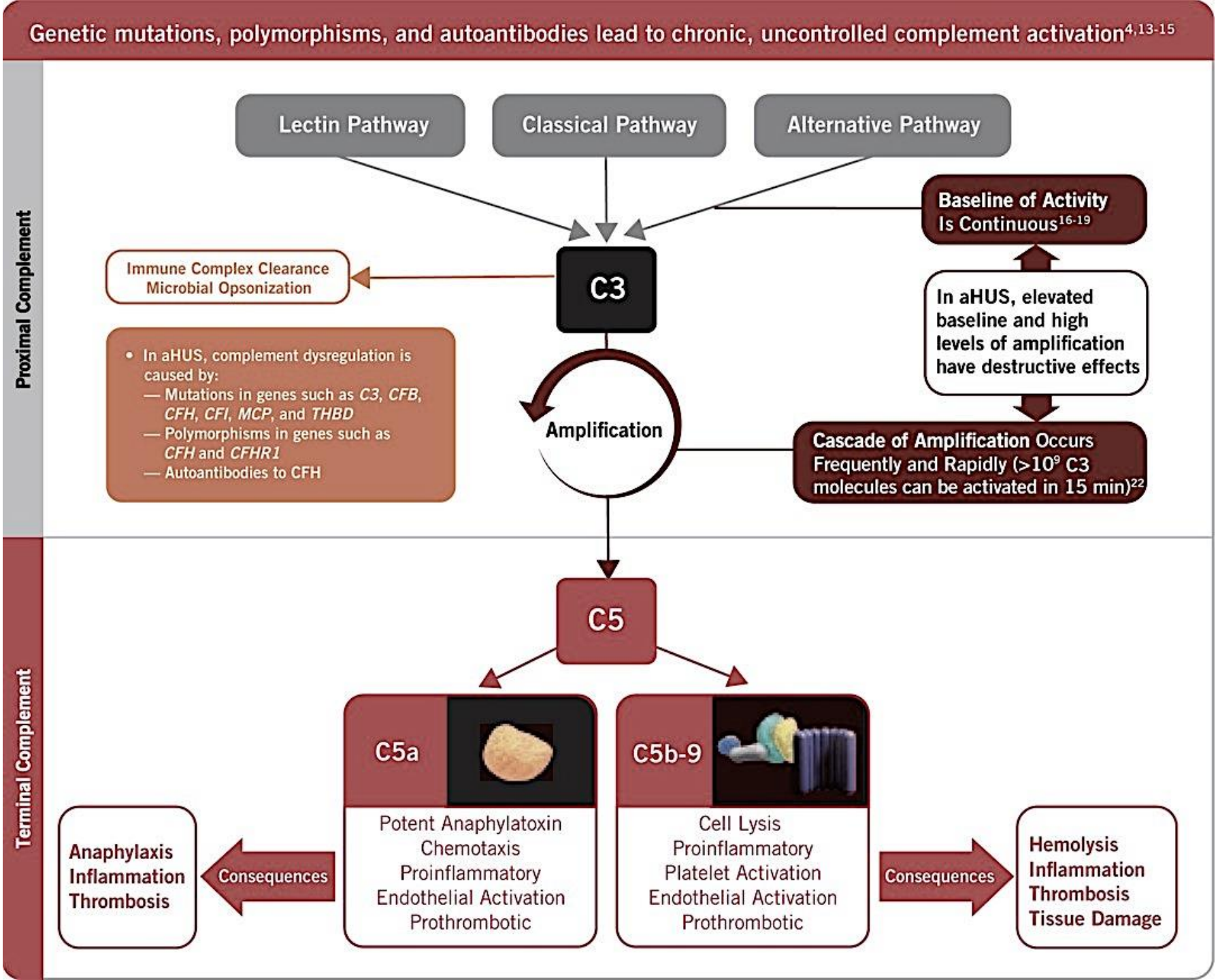
Thrombotic Microangiopathic Nephropathy in Scleroderma and Lupus Anticoagulant.

Positive circulating lupus anticoagulant developed scleroderma nephropathy, characterized by rapidly progressive renal failure caused by thrombotic microangiopathy with widespread thrombi in small arteries and glomeruli.

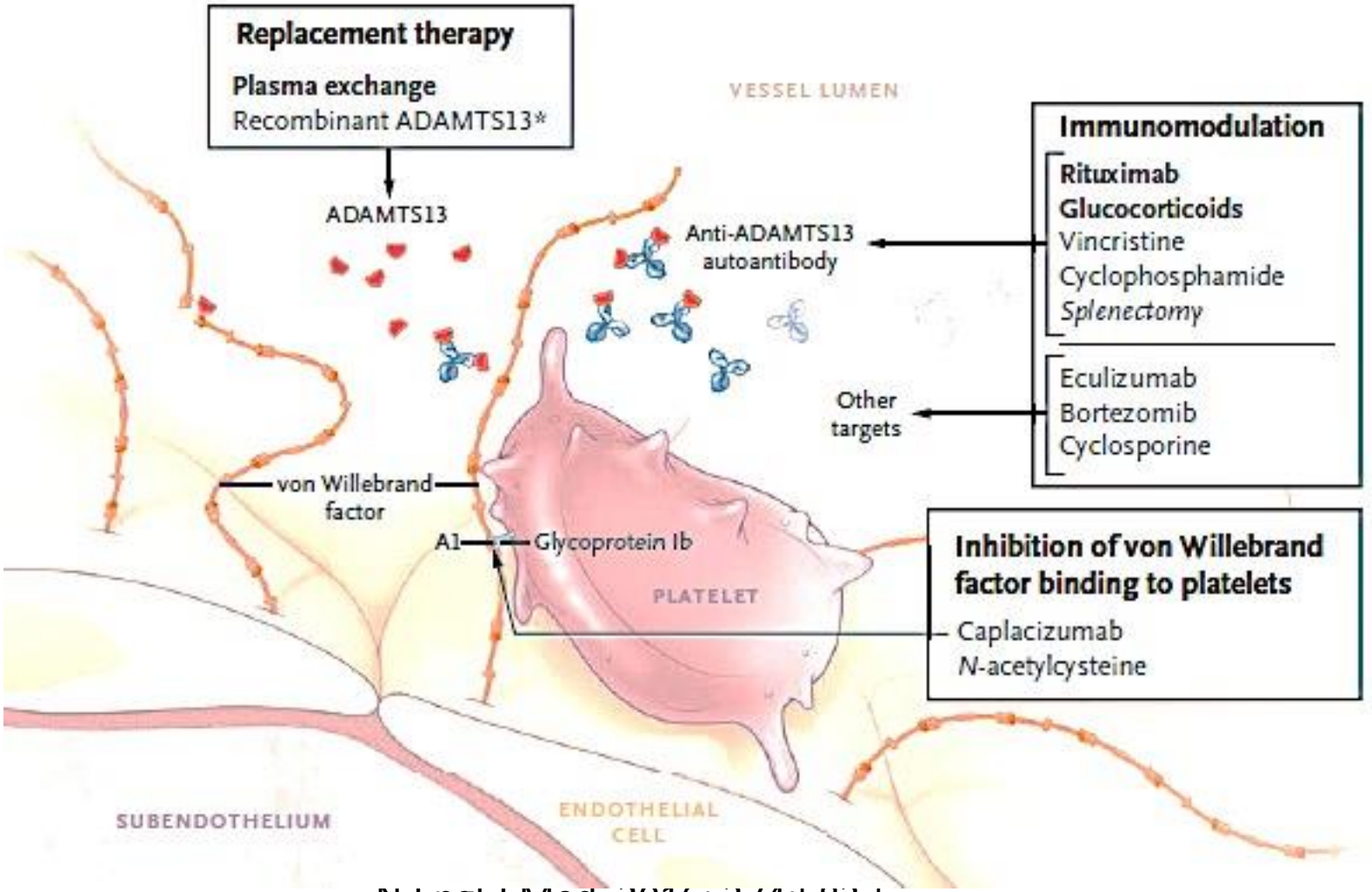




Thrombotic Thrombocytopenic Purpura in the Setting of Systemic Sclerosis. Manadan AM et al. ***Sem.Arthr.Rheum. 2005, 34:683-8***


Genetic mutations, polymorphisms, and autoantibodies lead to chronic, uncontrolled complement activation[4,13-15]
Proximal Complement
Lectin Pathway
Classical Pathway
Alternative Pathway
Baseline of Activity Is Continuous[16-19]
Immune Complex Clearance
Microbial Opsonization
C3
In aHUS, elevated baseline and high levels of amplification have destructive effects
• In aHUS, complement dysregulation is caused by:
— Mutations in genes such as C3, CFB, CFH, CFI, MCP, and THBD
— Polymorphisms in genes such as CFH and CFHR1
— Autoantibodies to CFH
Amplification
Cascade of Amplification Occurs Frequently and Rapidly (>10⁹ C3 molecules can be activated in 15 min)[22]
Terminal Complement
C5
C5a
C5b-9
Potent Anaphylatoxin
Chemotaxis
Proinflammatory
Endothelial Activation
Prothrombotic
Cell Lysis
Proinflammatory
Platelet Activation
Endothelial Activation
Prothrombotic
Consequences
Anaphylaxis
Inflammation
Thrombosis
Consequences
Hemolysis
Inflammation
Thrombosis
Tissue Damage

TMA: acquired



N.Engl.J.Med. 2016: 374:583-5

Take home messages

1. Complement is a major driver of organ damage in autoimmune diseases
2. Thrombocytopenia , MAHA and C3 low levels are red flags to raise the suspicion of a possible atypical thrombotic microangiopathy (TMA) in CTDs
3. Antiphoslipid syndrome is a major feature of atypical TMA in CTDs
4. TMA is a medical emergency in any CTD