Secondary Glomerular Disease, Vasculitis – Plasmapheresis Therapy

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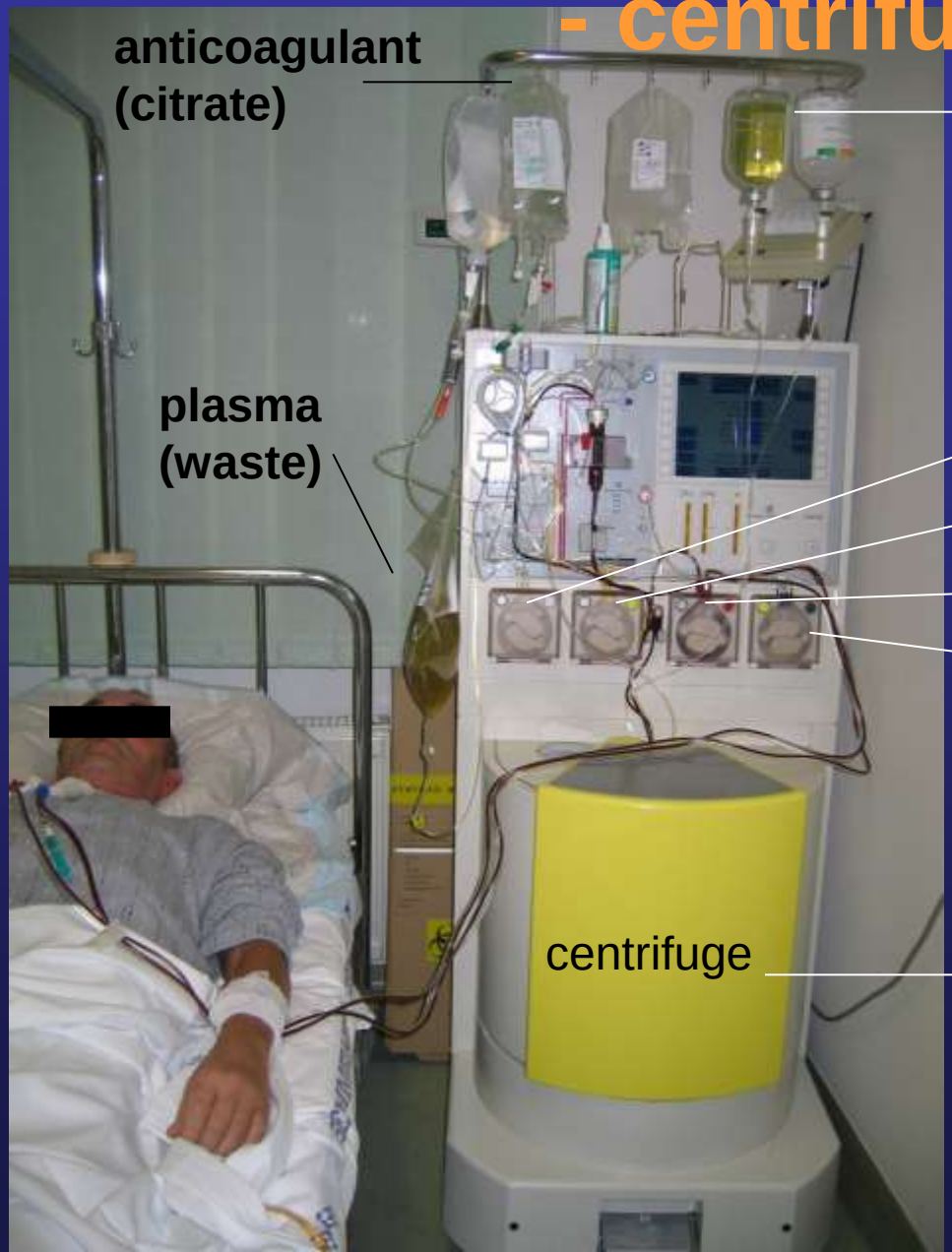
Therapeutic plasma exchange (TPE) - centrifugation-



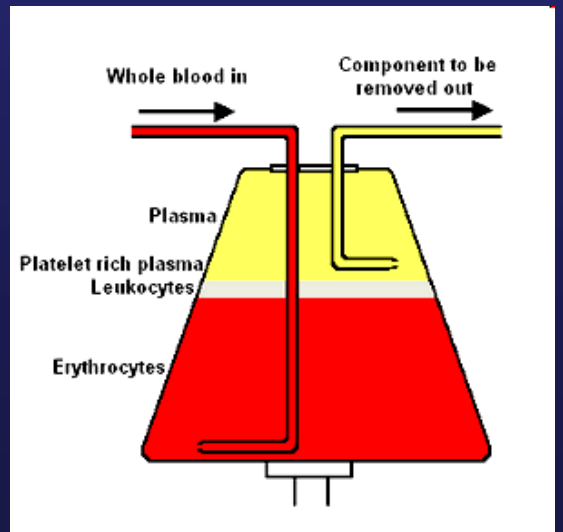
replacement fluid
- cristalloid
- albumin
- fresh frozen plasma

replacement fluid pump

plasma pump

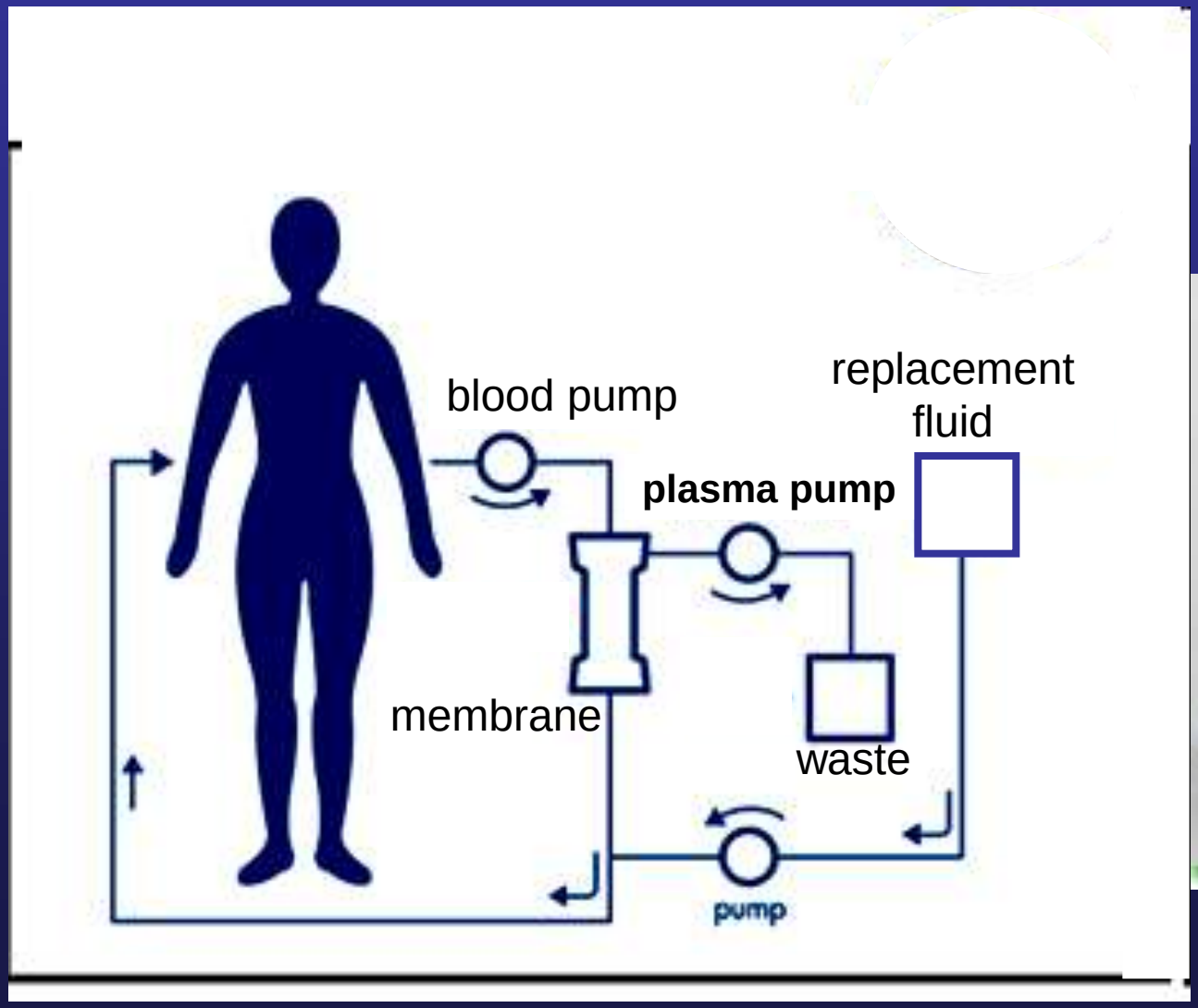
blood pump

anticoagulant pump

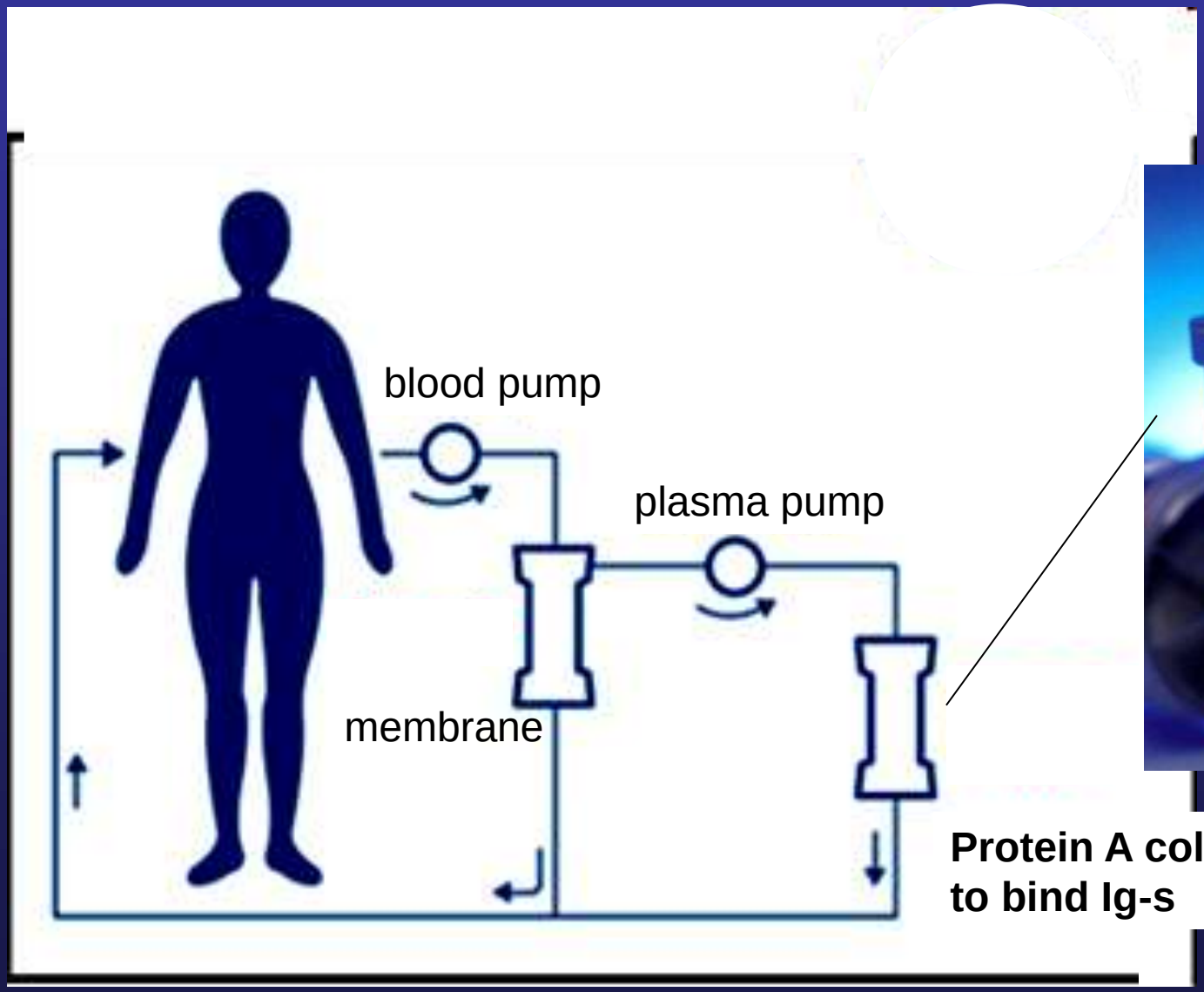


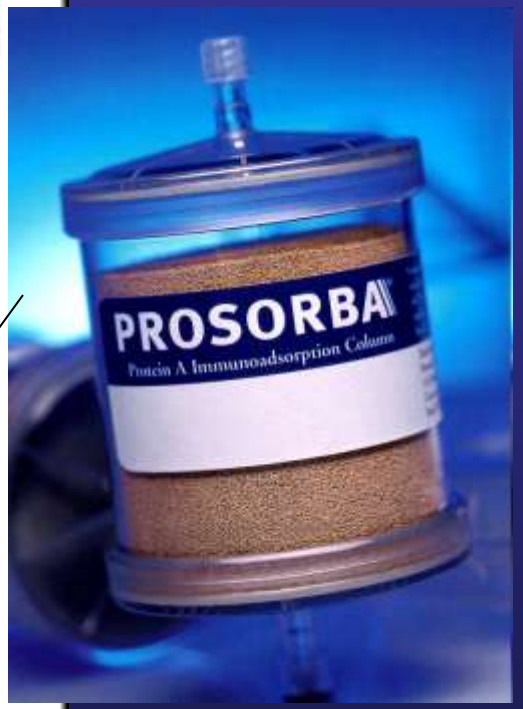
Therapeutic plasma exchange (TPE)

- membrane separation -



Immune adsorption (IA)





Protein A column to bind Ig-s

Evidence based indication categories for PEX

American Society for Apheresis ,
Journal of Clinical Apheresis 25:83–177 (2010)

Category	Description
I.	Disorders for which apheresis is accepted as first-line therapy either as a primary standalone treatment or in conjunction with other modes of treatment.
II.	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III.	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV.	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.

Szczepiorkowski ZM. J Clin Apheresis 2010;25:83.

Grading of recommendations

1: Strong recommendation

2: Weak recommendation

A: High quality evidence - RCTs without important limitations or overwhelming evidence from observational studies.

B: Moderate quality evidence - RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.

C: Low quality evidence - Observational studies or case series

Guyatt G. Chest 2006;129:174

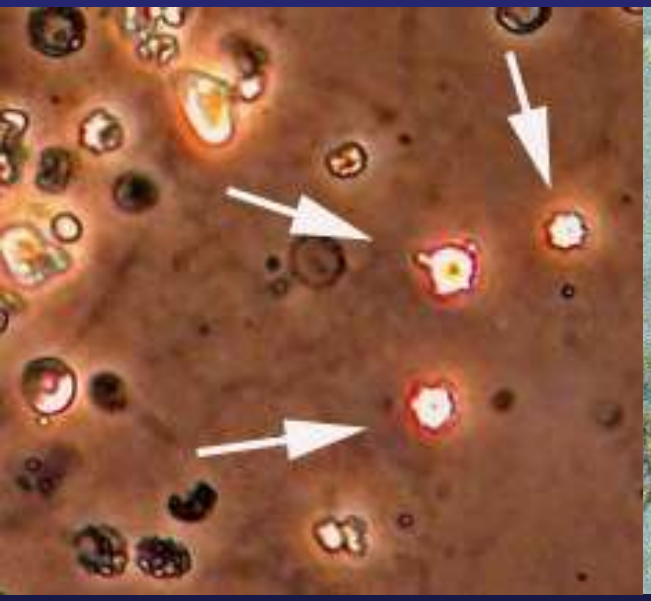
Clinical approach to glomerular disease

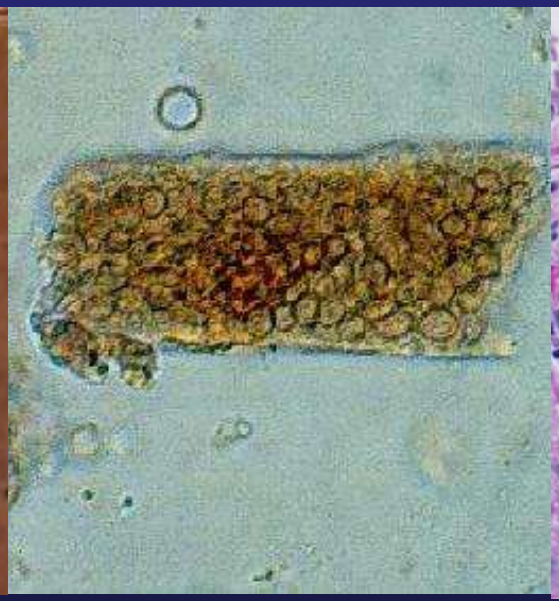
Clinical syndrome	Histology	Etiology
Isolated hematuria	<u>Non-proliferative</u>	Primary
Isolated proteinuria	MCD, FSGS, MGP	Infection
Hematuria-proteinuria	DN, Amyloid, Alport	Tumor
Nephrotic syndrome	<u>Proliferative</u>	Autoimmune
Acute glomerulonephritis	Mesangial-	Vasculitis
Rapidly progressive GN	Focal-	Drugs, metals
	Diffuse-	Metabolic
	Membrano-	Hereditary
	Extracapillary-	

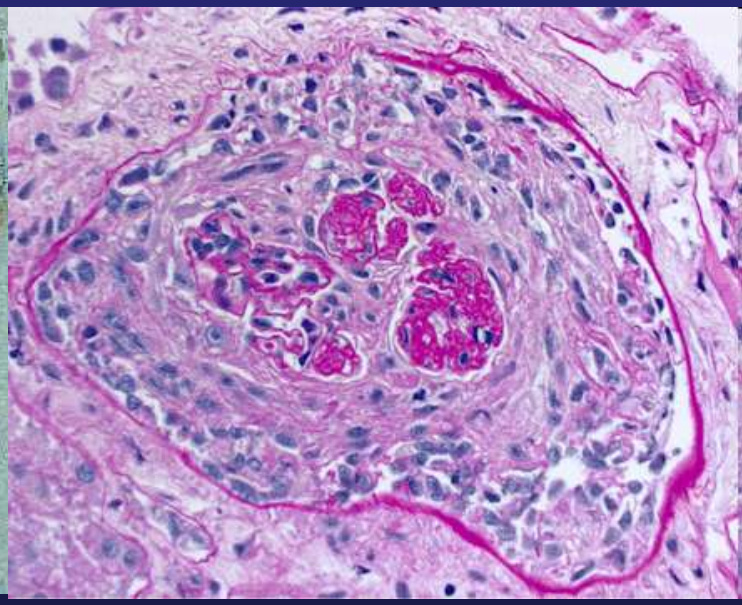
Rapidly progressive glomerulonephritis

Clinical features

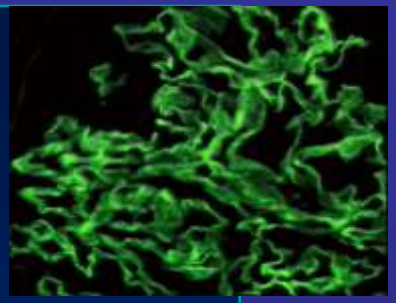
- Dysmorphic hematuria, active urinary sediment
- Proteinuria - nephrotic in 1/3 of patients
- Hypertension
- Progressive loss of renal function - GFR halves over 3 months
- Histology: extracapillary proliferation - crescentic GN







Crescentic GN (RPGN)

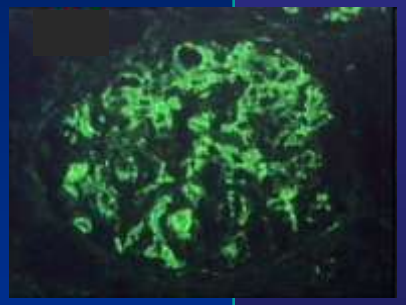


I. Anti GBM antibodies (linear IF)

- Goodpasture´s sy.,
- Renal localized form

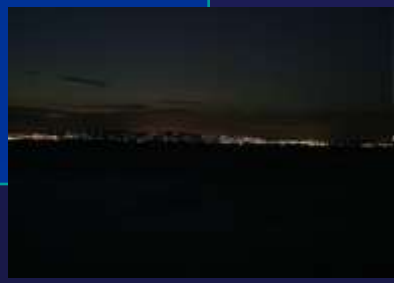
II. Immunecomplex-mediated GN (granular IF)

- Primary GN: IgA GN, Membranoproliferative GN
- Henoch Schönlein purpura
- Autoimmune: SLE
- Postinfectious



III. ANCA associated GN (no IF = pauci immune)

- Wegener`s granulomatosis
- Microscopic polyaangiitis (MPA)
- Churg Strauss sy



Goodpasture´s syndrome

Pathogenesis

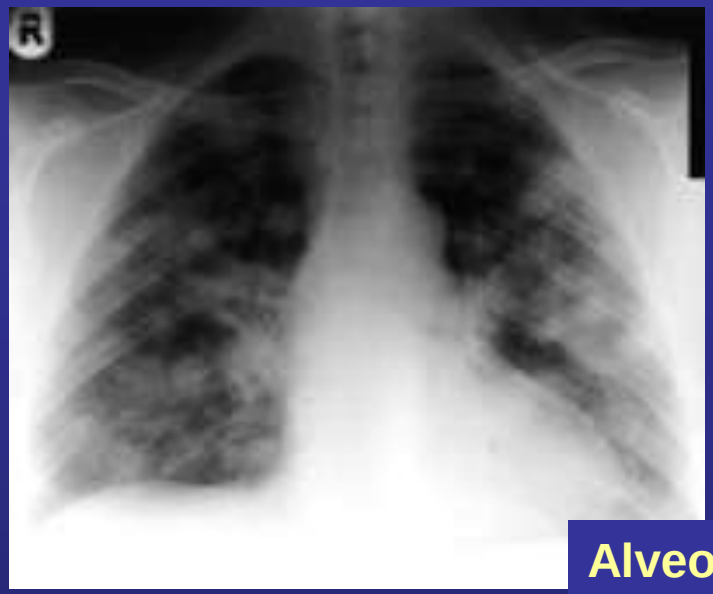
Anti- GBM antibody (Antigene: IV. collagene α-3 chain NC1 domaine)

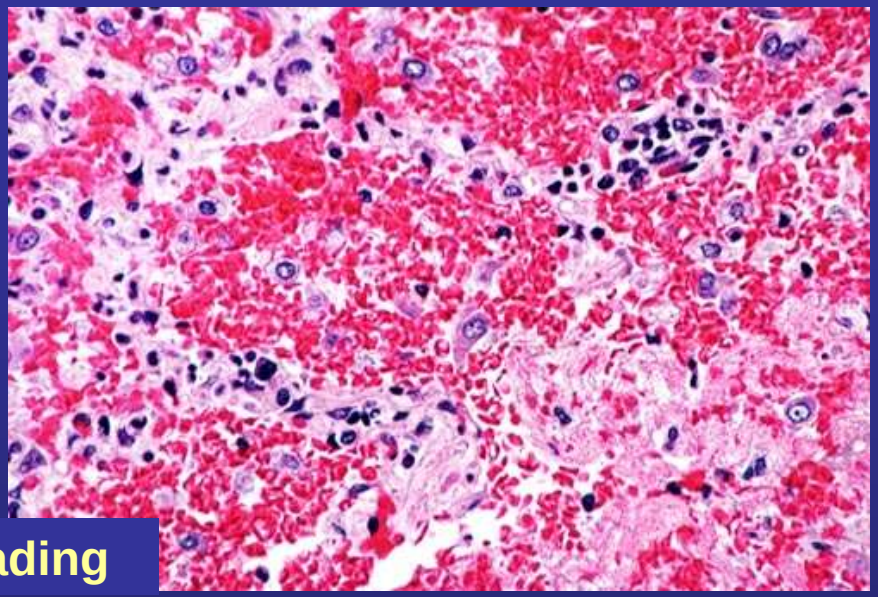
Binding to basal membrane - complement activation - inflammation

Clinical features

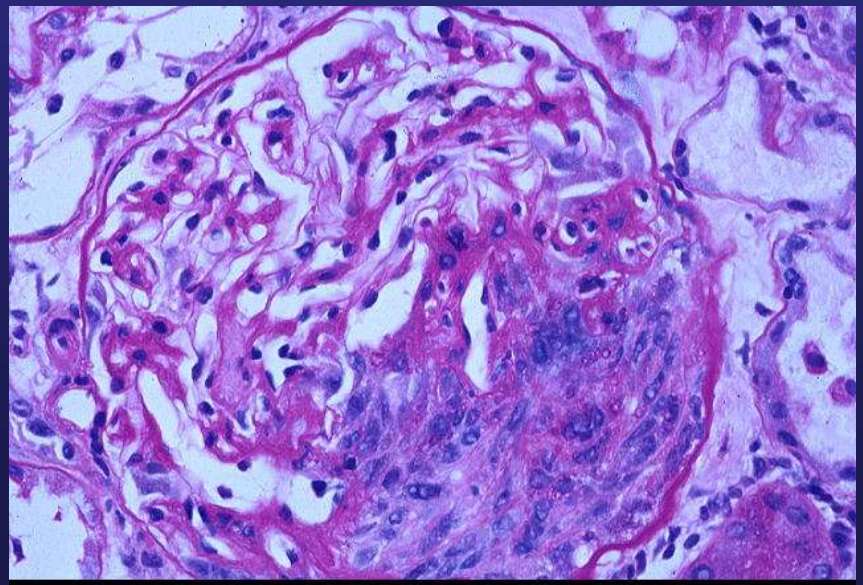
- Renal-pulmonary syndrome
- RPGN
- Shortness of breath, hemoptysis - diffuse alveolar haemorrhage (DAH)
  DAH associated with exposure to hydrocarbons, cocaine, marijuana, hard metal dust, fire smoke, cigarette smoking
- Association with HLA allele DR B1-1501
- Diagnosis: a-GBM antibody, ANCA (positive in 30%), renal biopsy
- The disease seldom relapses

Goodpasture´s syndrome

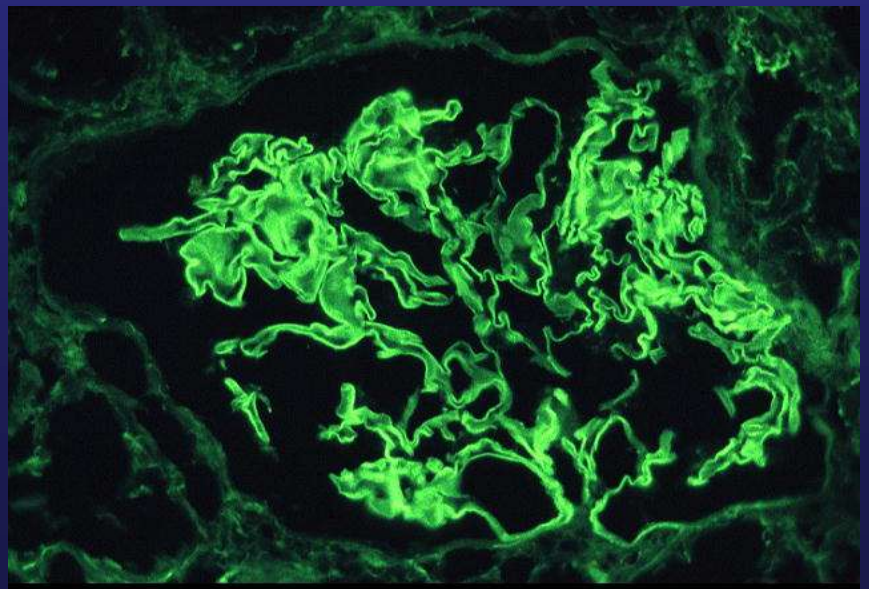




Alveolar bleading



Extracapillary proliferative GN



Linear IgG immunfluorescence

Therapy of Goodpasture´s syndrome

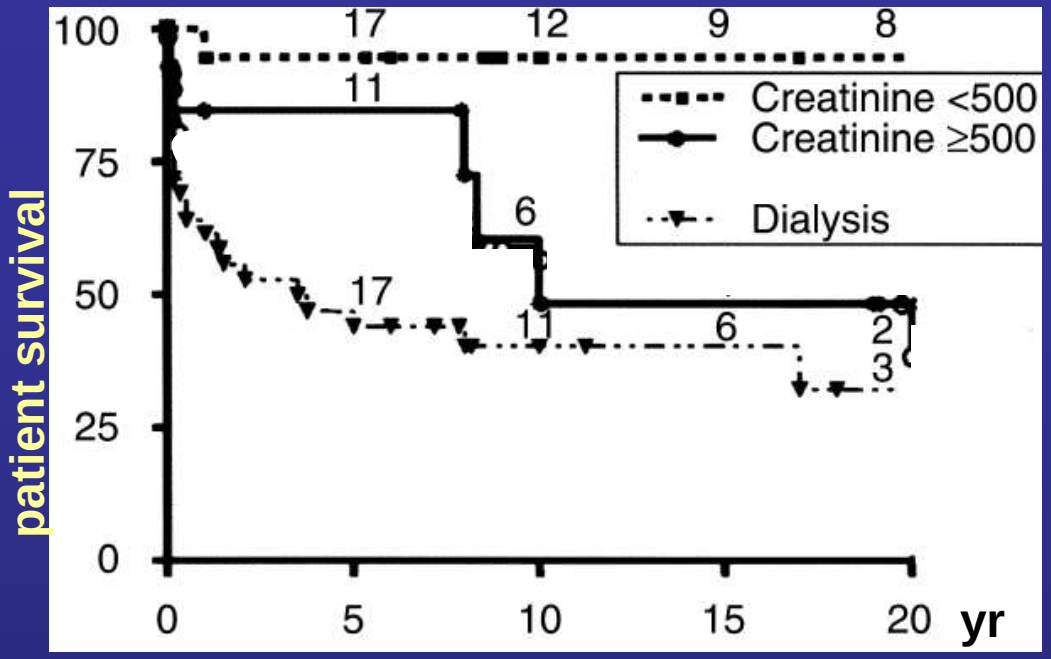
- **Plasma exchange daily, 1-1,5 x PV x 7-14**

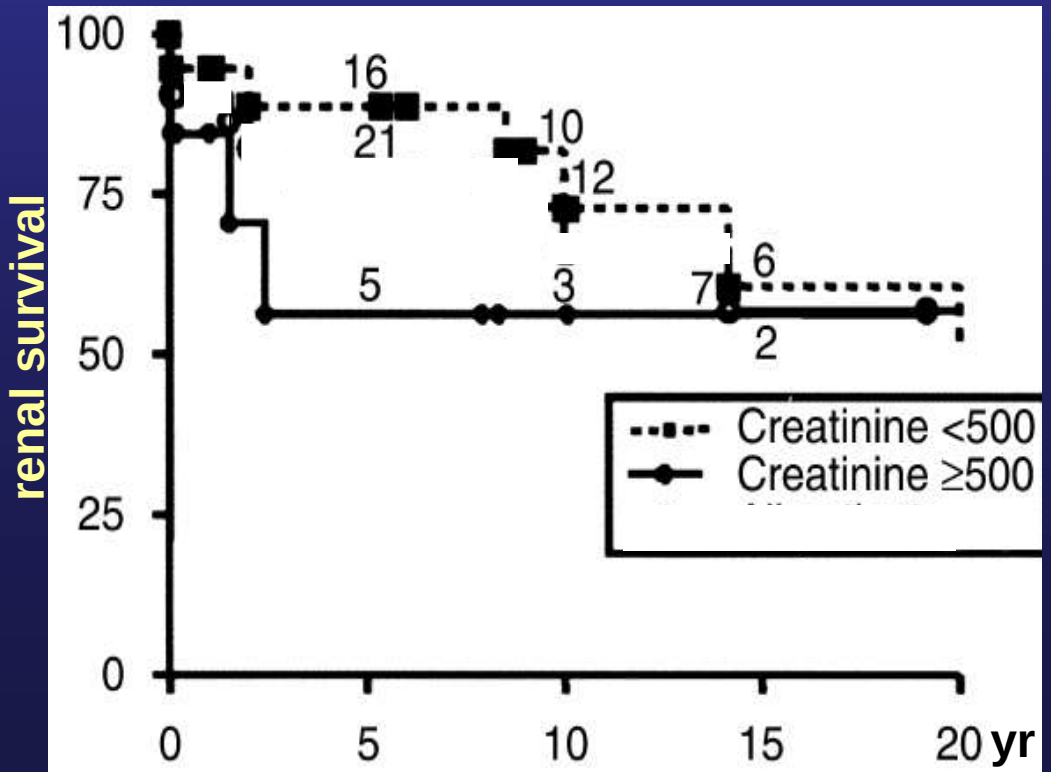
	Indication category	Grading
- Dialysis independence	I	1A
- Diffuse alveolar hemorrhage	I	1B
In case of DAH replace fresh frozen plasma		
- Dialysis dependent, no DAH	IV	1A

- **Metylprednisone pulse x3, Prednisone 1 mg/kg x 6 months**
- **Cyclophosphamide 2-3 mg/kg x 2-3 months**

Levy JB. Ann Intern Med 2001;134:1033.
Lazor R. Medicine 2007;86:181.
Szczepiorkowski ZM. J Clin Apheresis 2010;25:83.

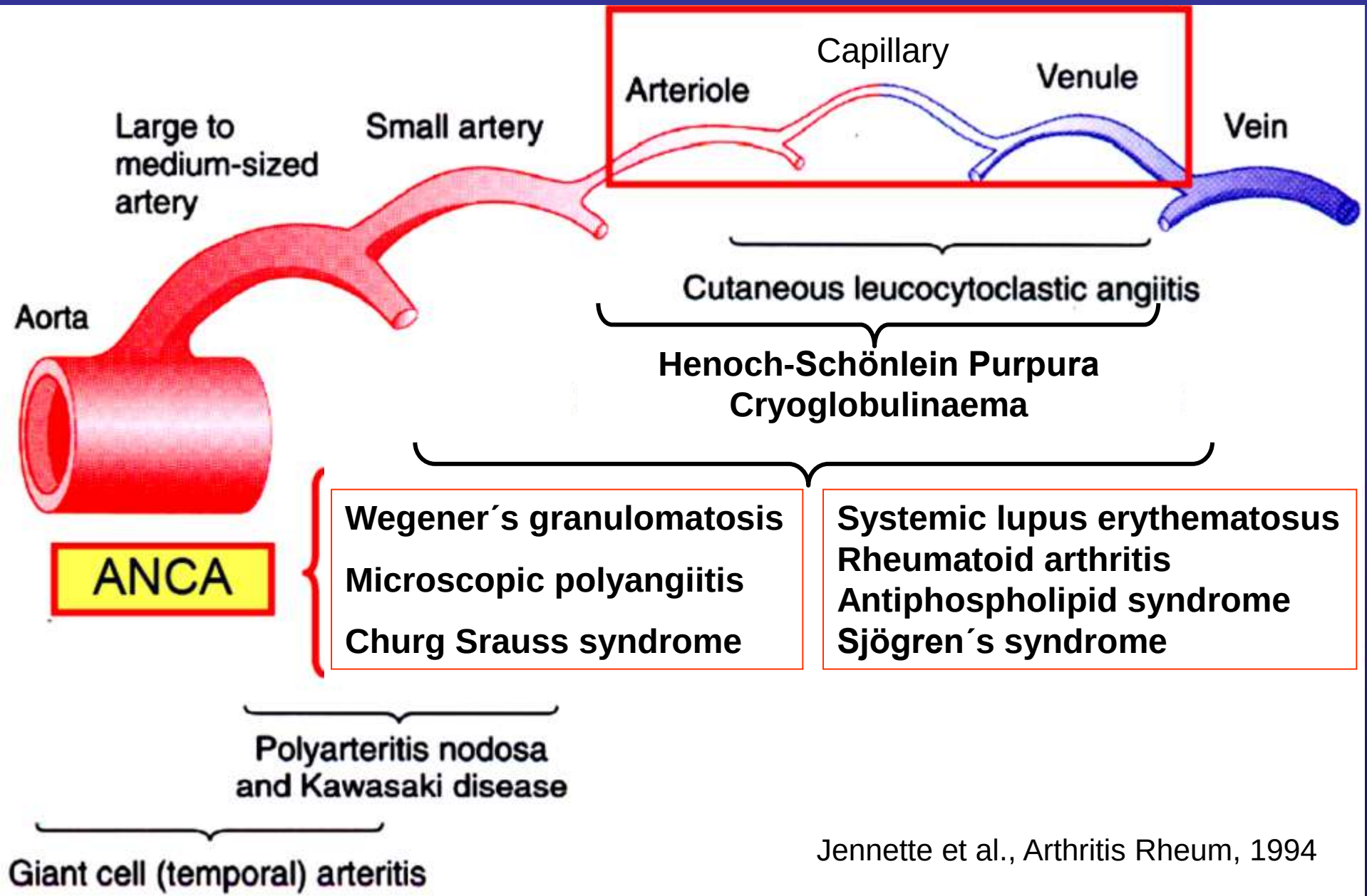
Prognosis depends on initial renal function in Goodpasture´s syndrome





Pusey CD. *Kidney Int 2003,64:1535*

Systemic vasculitis



Jennette et al., Arthritis Rheum, 1994

Anti-neutrophyl cytoplasmic antibodies

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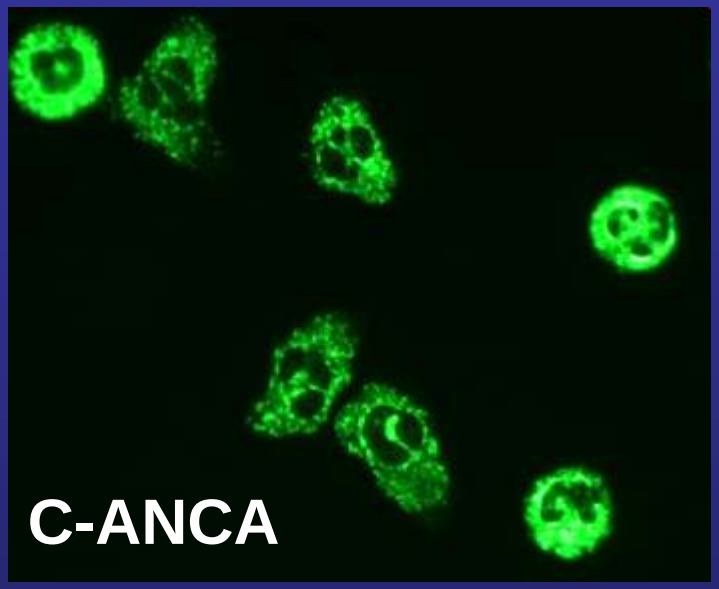
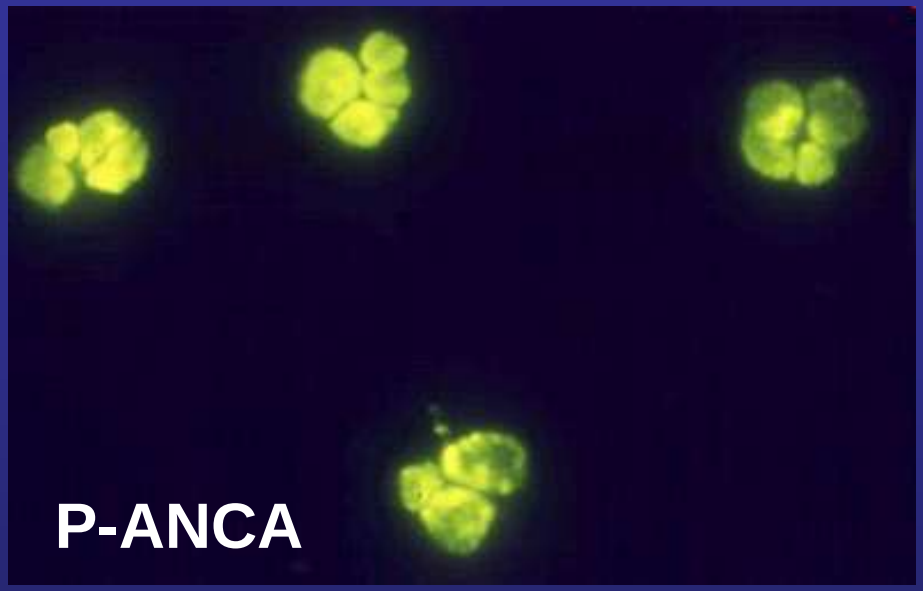




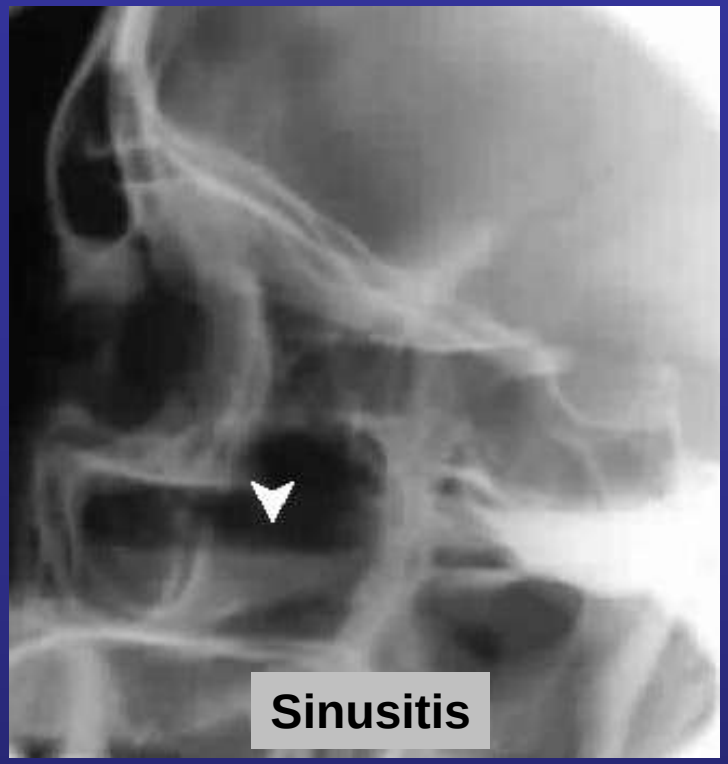
ELISA:

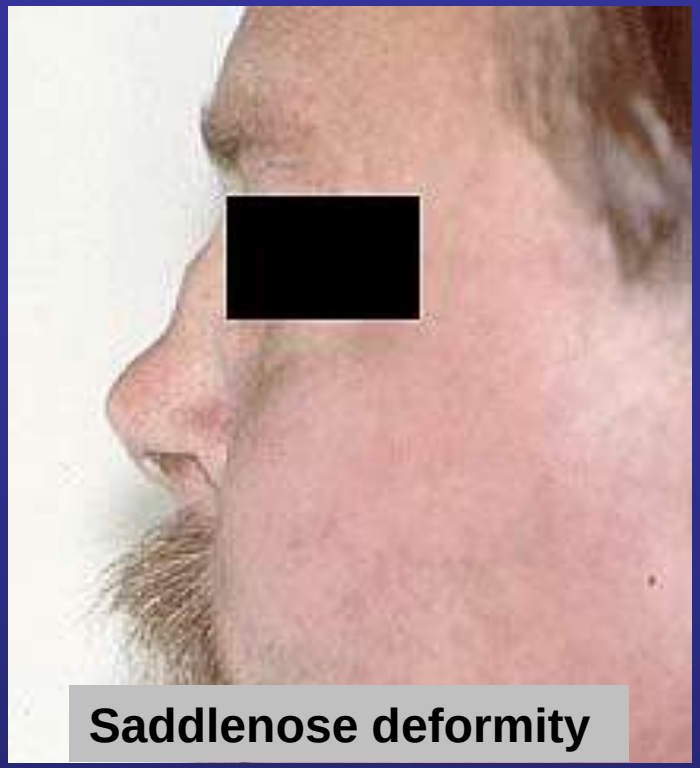
anti-Proteinase-3 (PR3) antibodies	anti-Myeloperoxidase (MPO) antibodies

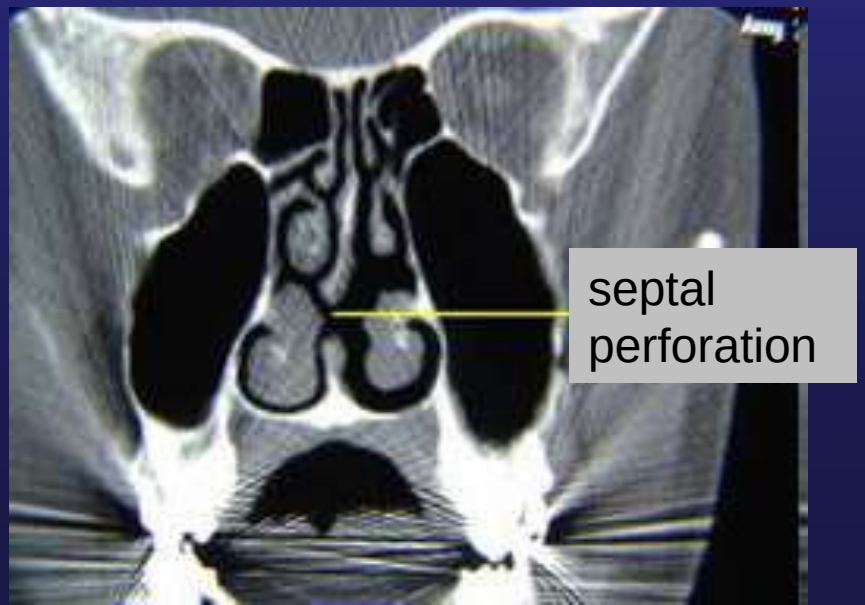
Wegener´s granulomatosis
Clininical features

- General: malaise, weight loss, fever, anemia
- Arthralgia, myalgia
- Palpable purpura, livedo reticularis, necrosis
- Gastrointestinal symptoms - pain, bleeding
- Uveitis, retinitis
- Mononeuritis multiplex, seizures

- Upper respiratory tract inflammation
- Alveolar hemorrhage, capillaritis
- RPGN; focal necrotizing, extracapillary GN
- Granuloma formation
- Serology: C-ANCA - anti proteinase-3 antibody

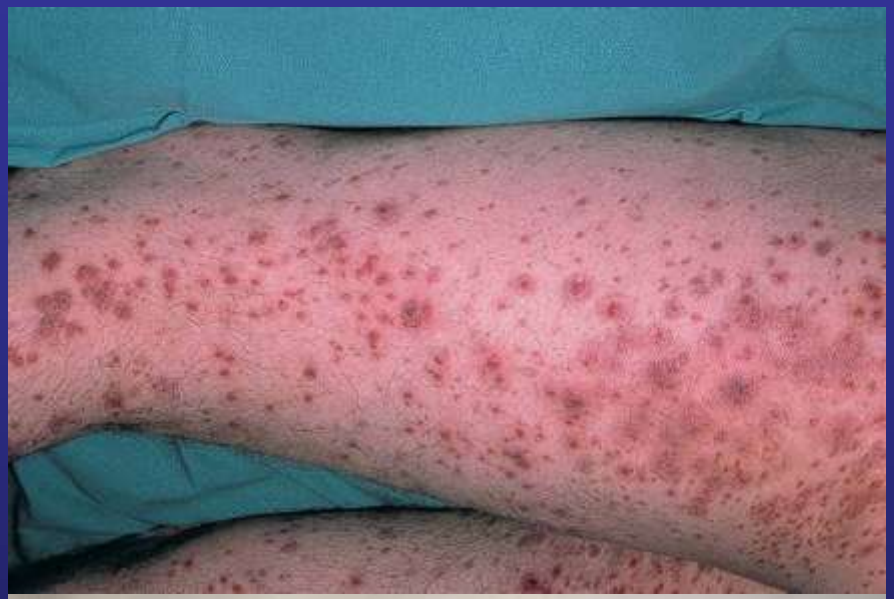


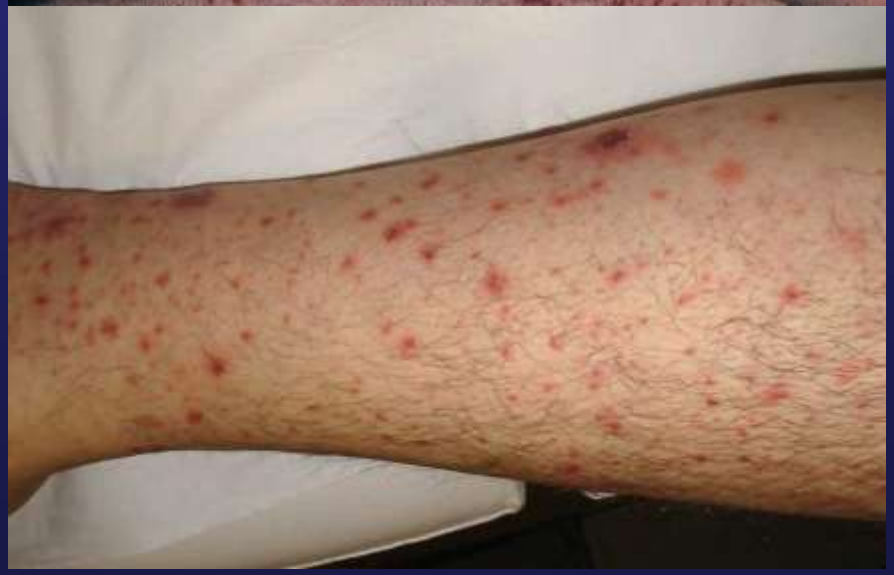




uveitis

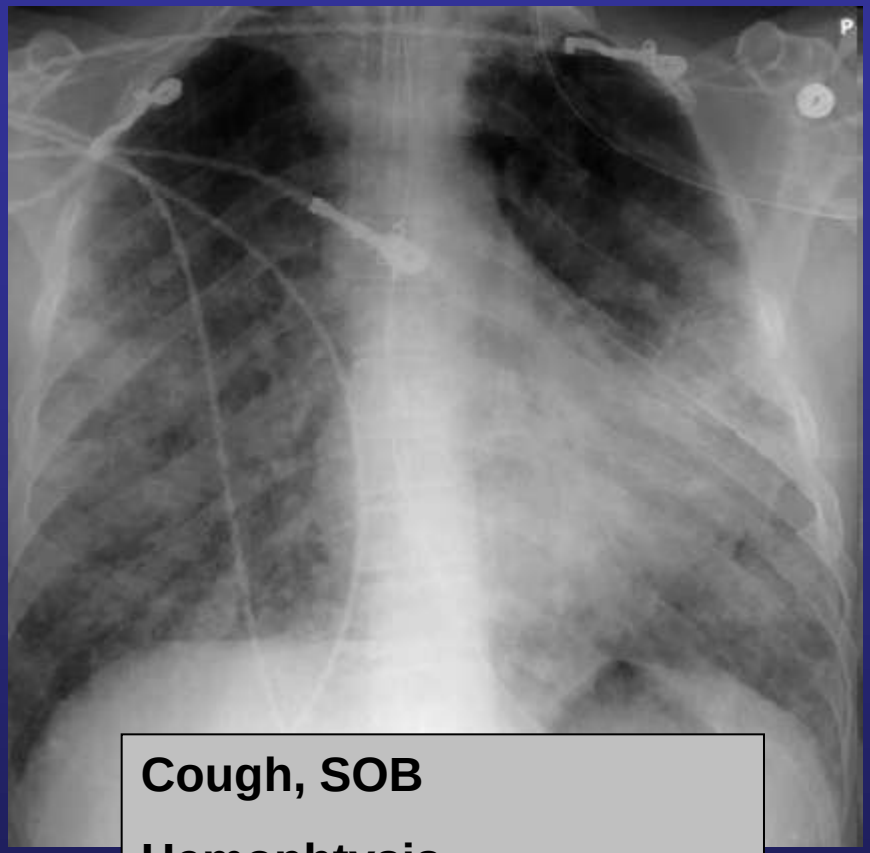
Palpable purpura:
Microscopic (leukocytoclastic) vasculitis

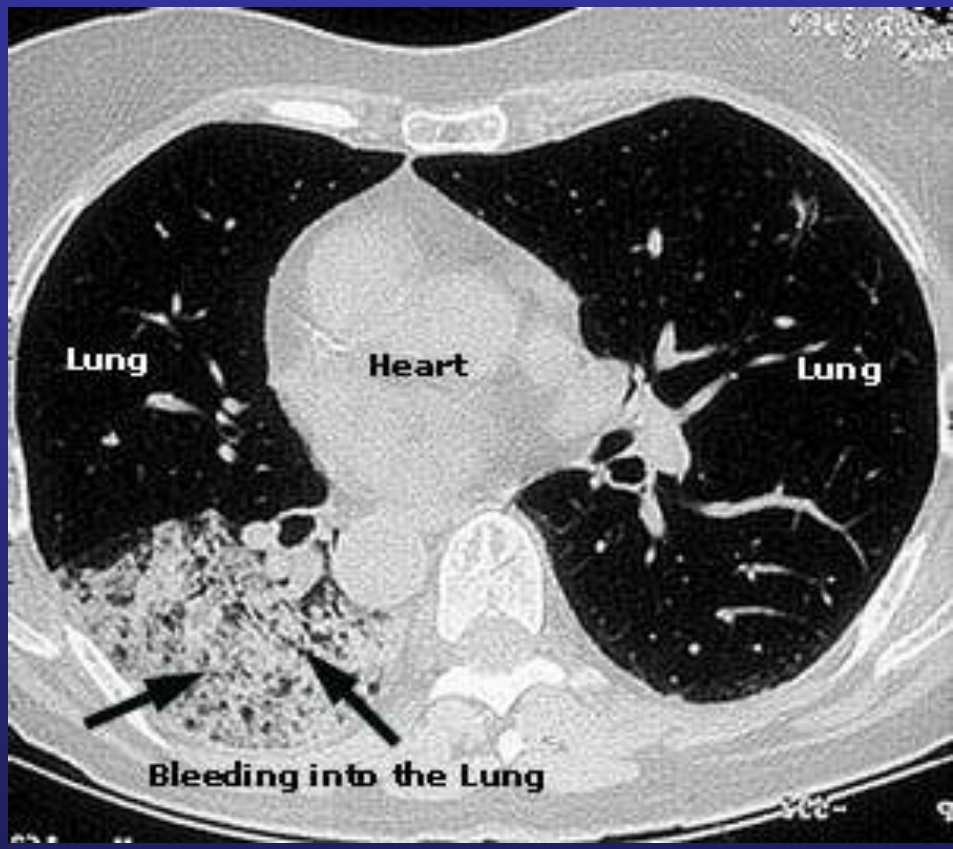




- Wegener´s granulomatosis
- Microscopic polyangiitis
- Cryoglobulinemia
- Henoch-Schönlein purpura
- Anti Phospholipid Sy
- Drug-induced

Lower respiratory tract inflammation





Cough, SOB

Hemophtysis

Alveolar capillaritis

Intraalveolar bleeding

Migrating infiltrates

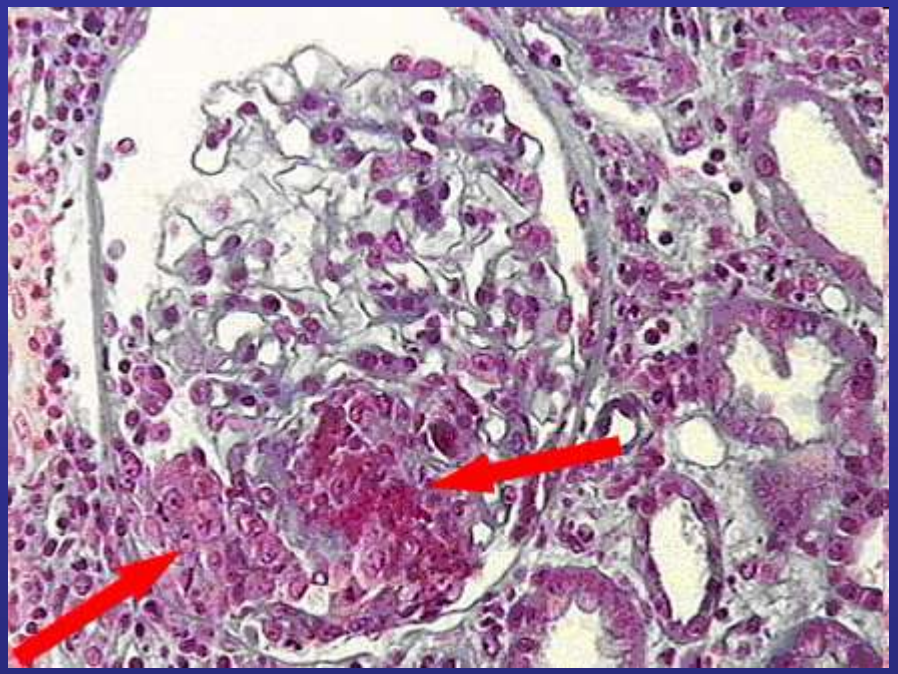
May resemble pneumonia

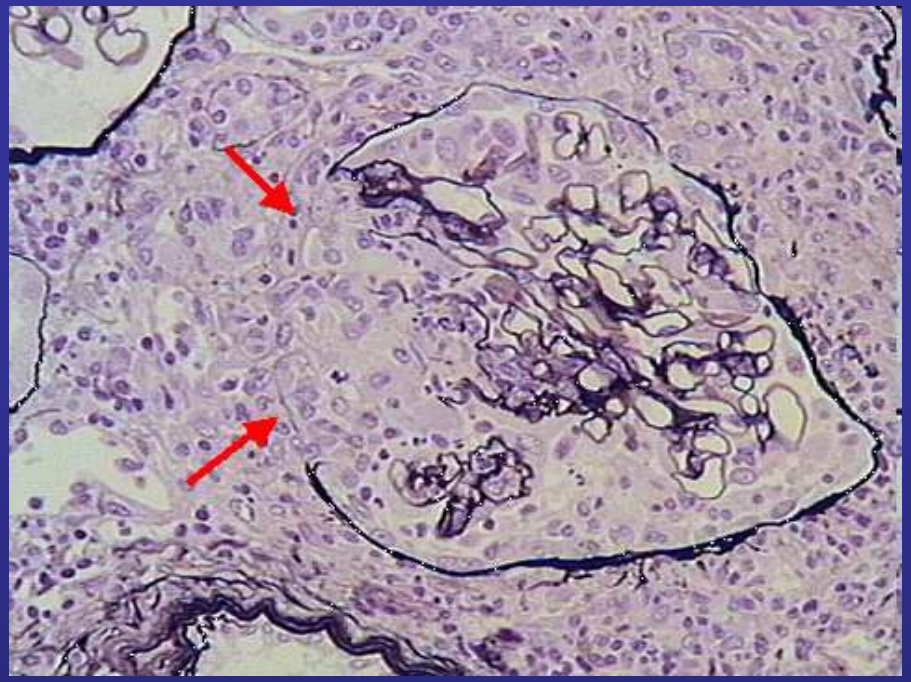
Microscopic polyaangiitis

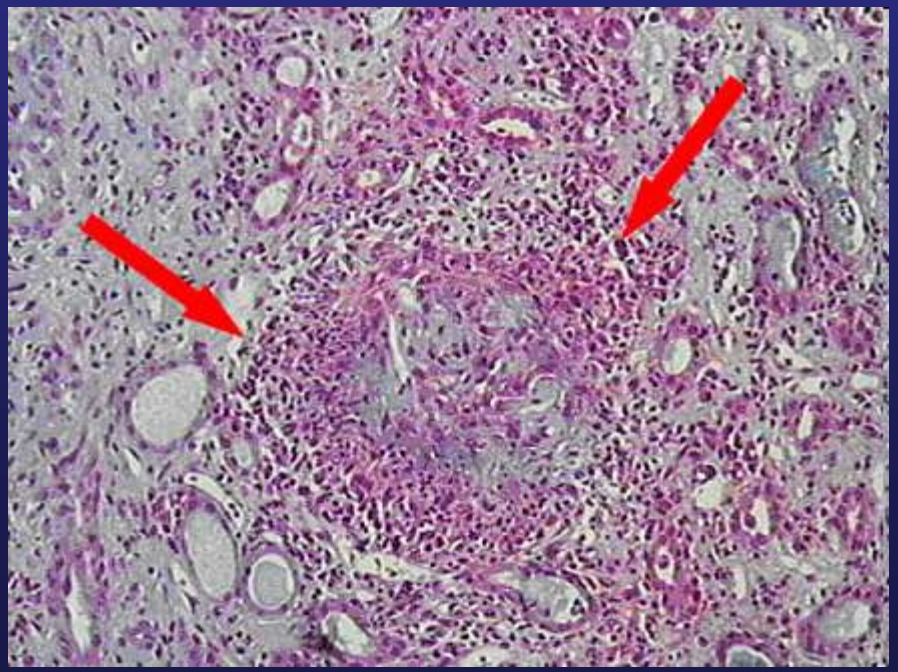
- Less frequent upper respiratory tract inflammation
- No granuloma
- Serology: P-ANCA - anti myeloperoxidase antibody

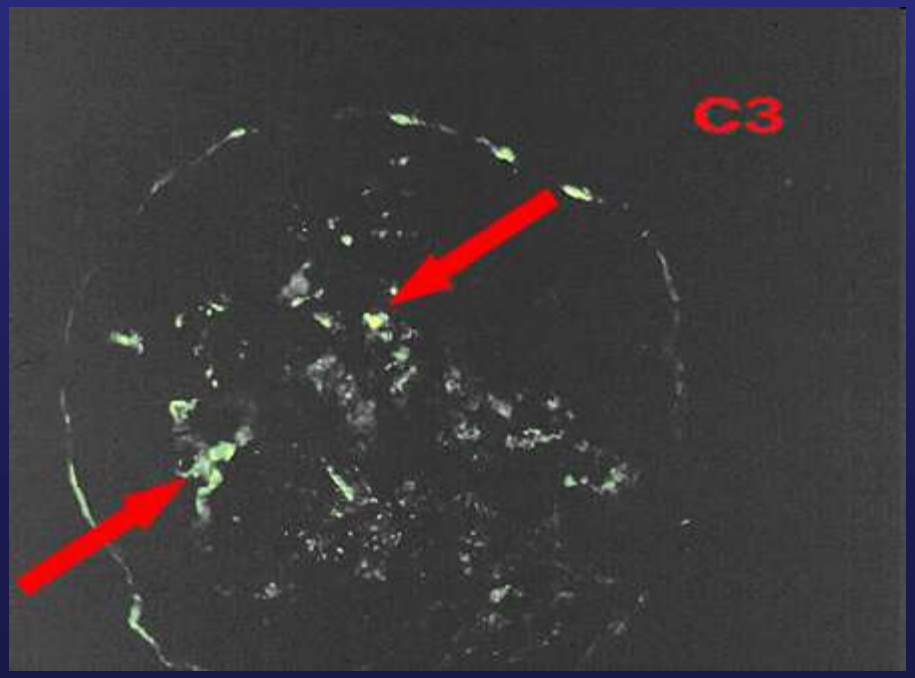
Churg-Strauss syndrome

- Asthma
- Upper and lower respiratory tract inflammation
- Peripheral/tissue eosinophylia
- Granuloma formation
- Serology: P-ANCA

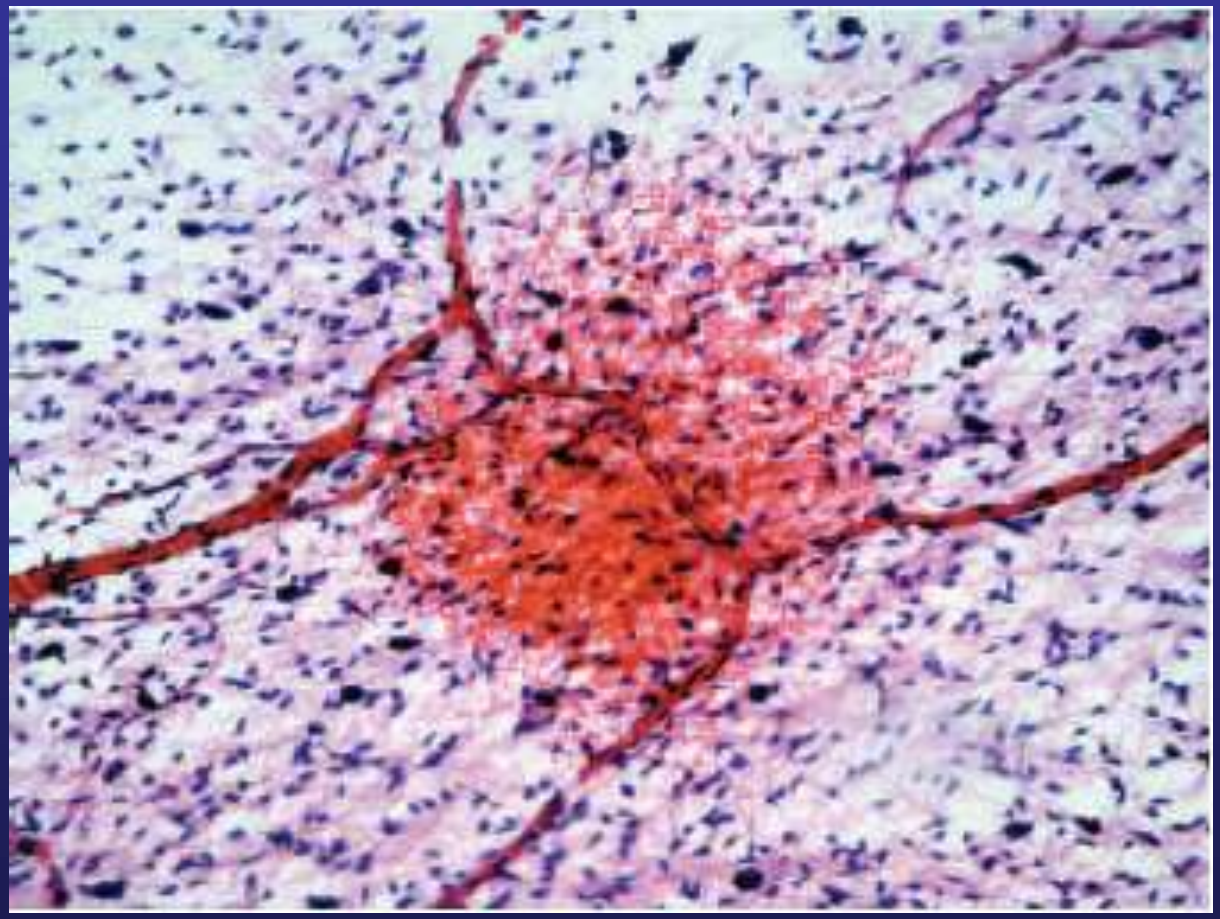







C3

ANCA plays a role in the pathogenesis of microscopic vasculitis



Mesenteric microvascular hemorrhage in a WKY rat after infusion of anti-MPO antibodies and superfusion with Chemokine ligand-1 (CXCL-1)

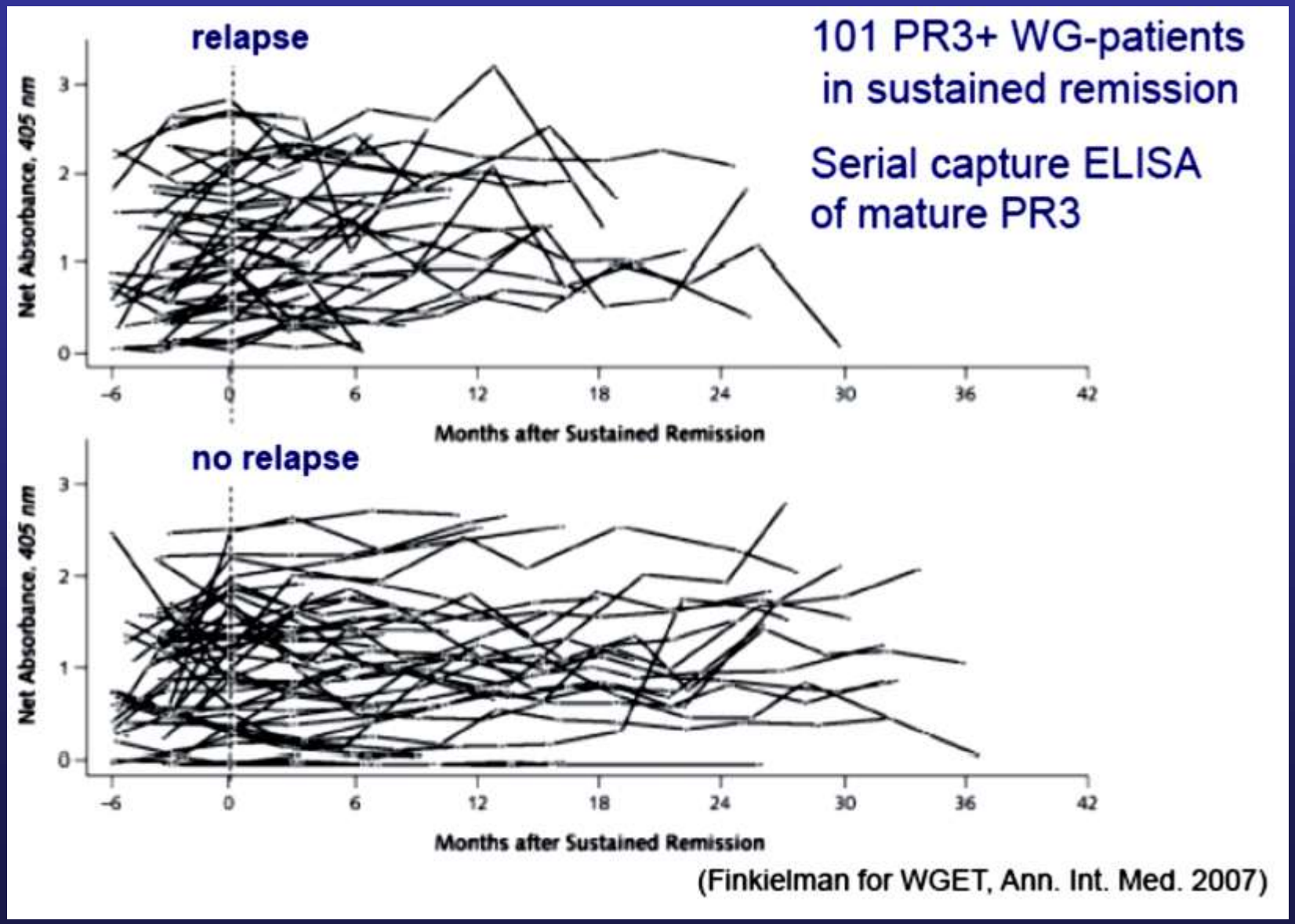
Morgan M, *J Am Soc Nephrol* 17: 1224–1234, 2006.

Factors associated with Wegener granulomatosis relapse

Risk factor	Risk of relapse
A fourfold rise in C ANCA/PR3 ANCA titre	RR 42.5
Chronic nasal carriage of *Staphylococcus aureus**	RR 7.16
Creatinine clearance >60 ml/min	RR 2.94
The presence of ANCA at diagnosis	RR 2.89
Cardiac involvement at diagnosis	RH 2.87
Cumulative cyclophosphamide dose <10 g in the first 6 months	RH 2.83
Prednisolone ⩾20 mg/day for <2.75 months	RH 2.41
Co-trimoxazole as adjuvant to remission maintenance therapy	RR 0.32

Ann Rheum Dis 2008;67:1004–10.

ANCA titer and relapse rate



Clinical trials in ANCA associated vasculitis

Induction

3 - 6 mo.

NORAM: MTX vs CYC
MEPEX: PE vs MP
CYCLOPS: CYC iv vs oral
WEGET: Etanercept vs placebo
SOLUTION: ATG
MYCYC: MMF Vs CYC
RITUXIVAS

Maintenance

LEM: LEF vs MTX
NORAM: MTX vs CYC
CYCAZAREM: AZA vs CYC
IMPROVE: AZA vs MMF
REMAIN: AZA, 24 mo vs 48 mo

Alternative agents

MAINRITSAN - Rituximab
RAVE - Rit vs CYC
ABAVAS - Abatacept
RATTRAP - Rit vs infliximab

Methylprednisolone *versus* Plasma Exchange (MEPEX) trial

- N=100, randomized design
- ANCA-associated vasculitis
- Necrotizing, crescentic GN
- creatinine > 500 µmol/l, 2/3: on dialysis, 1/3: predialysis
- Therapy:

Metylprednisolon 1000 mg/day x3

vs

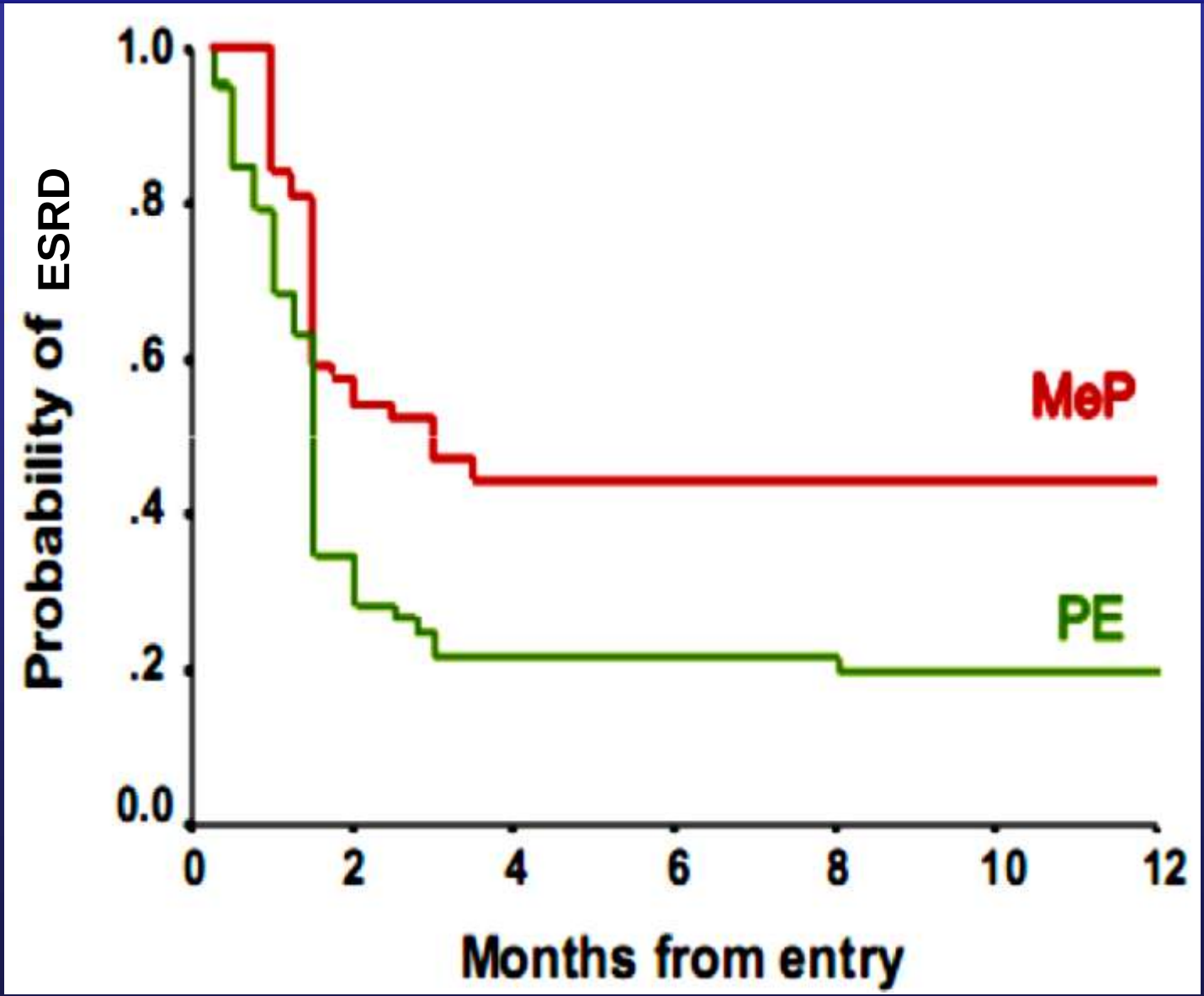
Plazma exchange 60 ml/kg x 7

Metylprednisolon 1 mg/kg/day starting dose with dose decrease

+ cyclophosphamide 2,5 mg/kg/day x 3 mo, followed by azathioprin

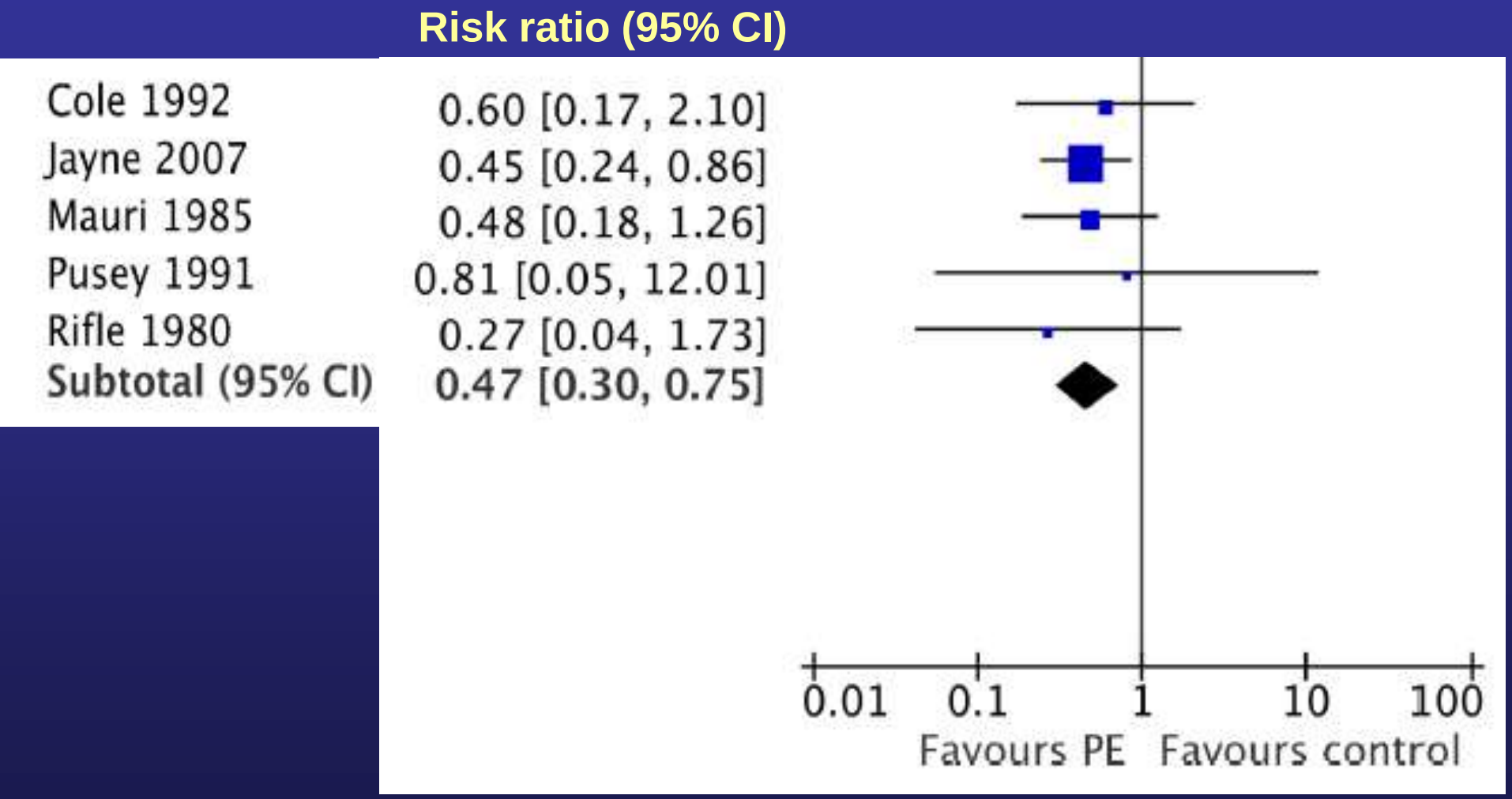
- F/U: 1 yr

MEPEX: probability of end stage renal failure



MEPEX, *J Am Soc Nephrol* 17: 2264–2274, 2006.

Risk of requiring renal replacement therapy at 12 months in patients treated with or without plasma exchange



Walters *et al. BMC Nephrology 2010,* ***11:12***

CYCLOPS (Cyclophosphamide Daily Oral Versus Pulsed) trial in ANCA associated vasculitis

N = 149, creatinine 150-500 µmol/l

Prednisone +

CYC 15 mg/kg iv pulse 2-3 weekly to remission ➡ monthly x3

vs 2 mg/kg /day oral to remission ➡ 1,5 mg/kg/d x 3 mo

followed by AZA

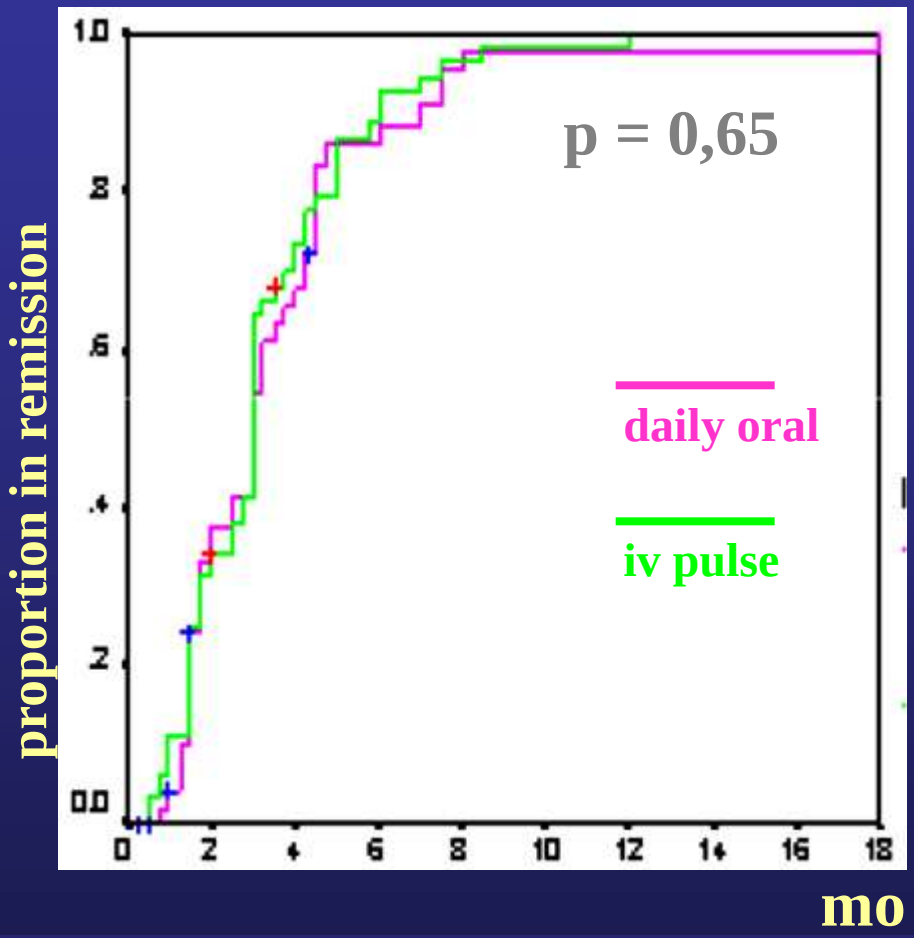
f/u: 18 mo

Primary endpoint: disease free survival at 9 mo

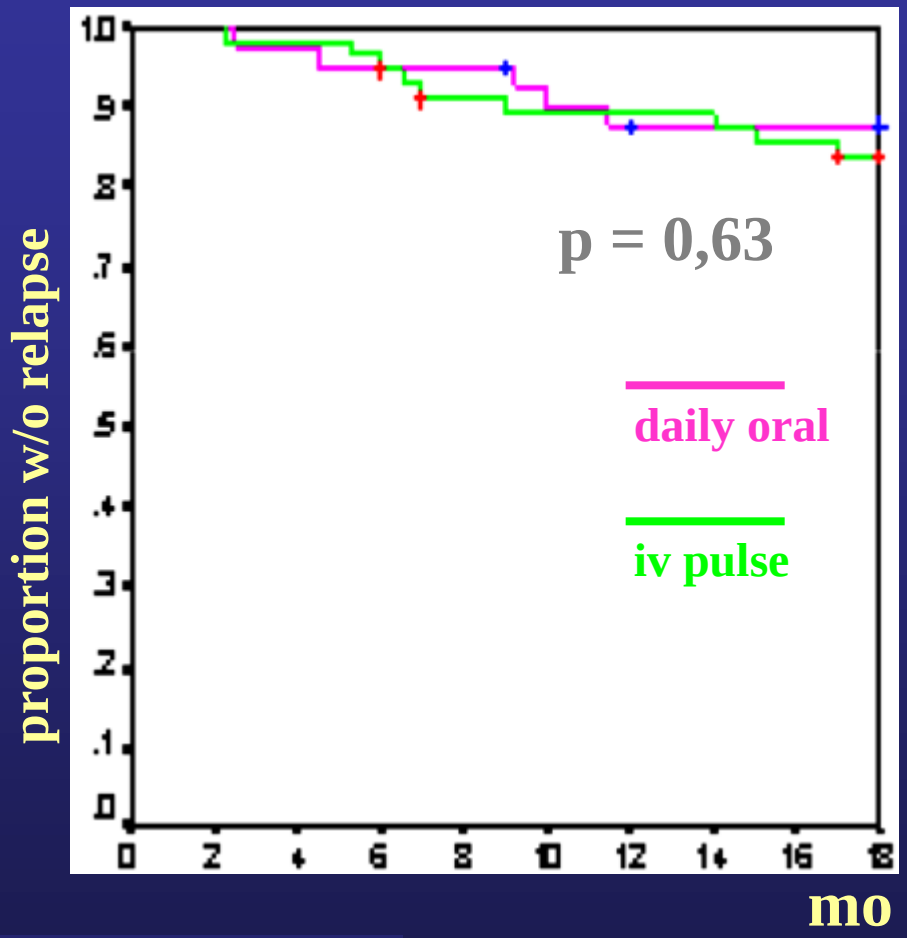
de Groot K. Ann Intern Med 2009;150:670

CYCLOPS: main results

Time to remission



Time to relapse



No difference in any endpoint

Cumulative CYC dose: daily oral - 15,9 g; iv pulse - 8,2 g

Leukopenia: daily oral - 45%; iv pulse - 26%, p<0,02

Ann Intern Med 2009;150:670

Microscopic vasculitis: therapy of severe disease

(EULAR Recommendations: Ann Rheum Dis. 2009;68:310)

Therapy		Grade of recommendation
Remission induction		
• Metyl-prednisone oral, 1 mg/kg/d oral, decrease dose		
• Cyclophosphamide, (iv pulse)		1A, (1B)
• Solu-Medrol iv daily 250-1000 mg x 3 days		2C
• Sumetrolim (PCP prophylaxis) (?)		
• Plasma exchange:	Indication category	
Dialysis dependence (recent)	I	1A
Diffuse alveolar hemorrhage (DAH)	I	1C
Dialysis independence, no DAH	III	2C
Remission maintenace :		
Low dose Metyl-prednisone +		
- Azathioprin 1,5 -2 mg/kg/day		1B
or: - Leflunomide 30 mg/day		1B
or: - Methotrexate 0,3 mg/kg/w: if creat < 180 µmol/l		2B

Alternative therapies for remission induction in relapsing, refractory or persistent disease

Drug	Dose
Mycophenolate mofetil	2 g/day
Rituximab	375 mg/m^2 body surface area weekly for 4 weeks
15-Deoxyspergualin	0.5 mg/kg/day x 21days , 7 days washout x 6 cycles wait until the white cell count returns to > 4000/ml
IVIG	2 g/kg over 5 days
Infliximab	3–5 mg/kg/infusion every 1 to 2 months
Anti-thymocyte globulin	2.5 mg/kg/day for 10 days adjusted according to lymphocyte count: no anti-thymocyte globulin if <150/ml, 1.5 mg/kg/day if 150–300/ml, full dose if >300/ml

EULAR. Ann Rheum Dis 2009;68;310-7

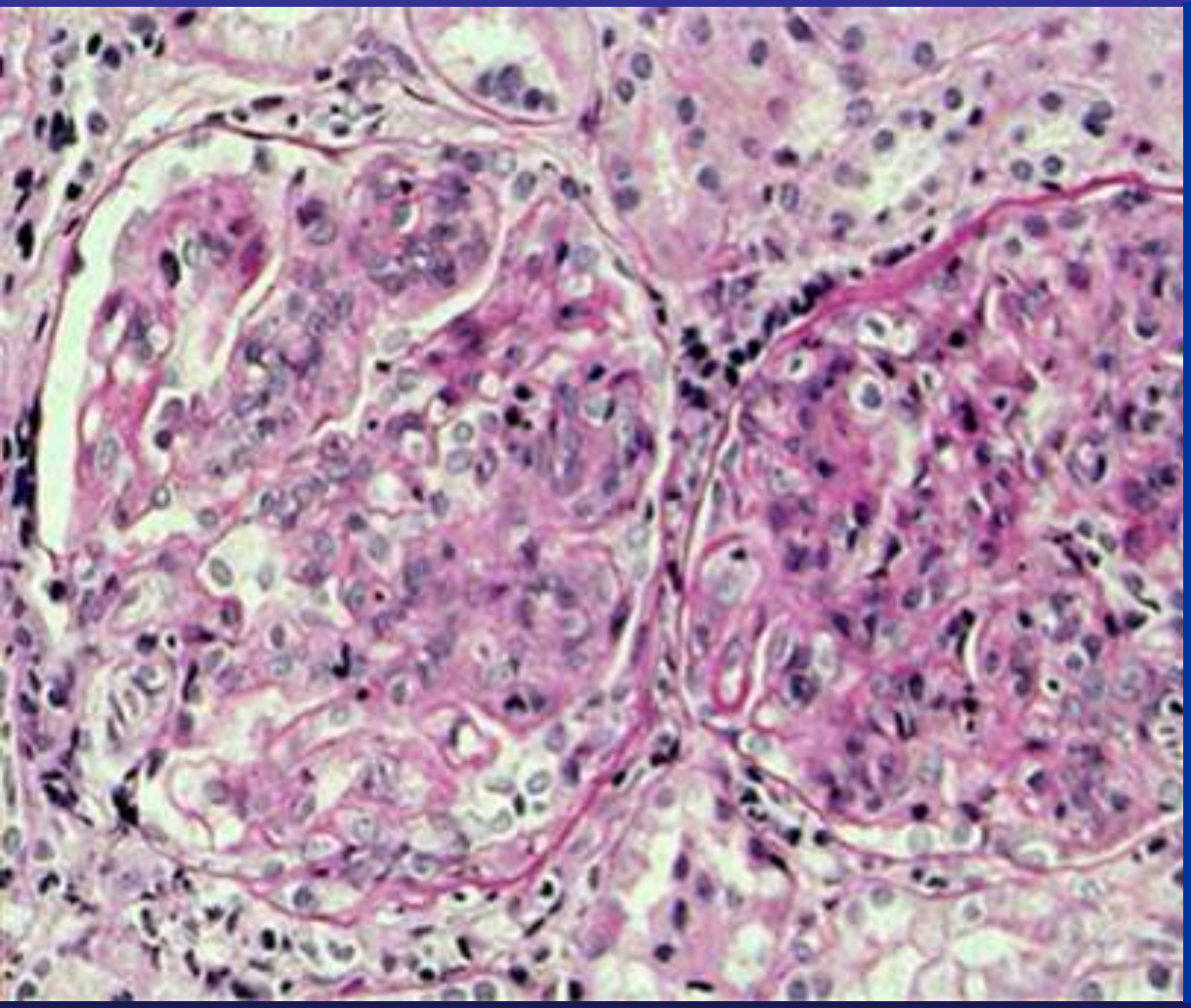
Immunecomplex-mediated RPGN

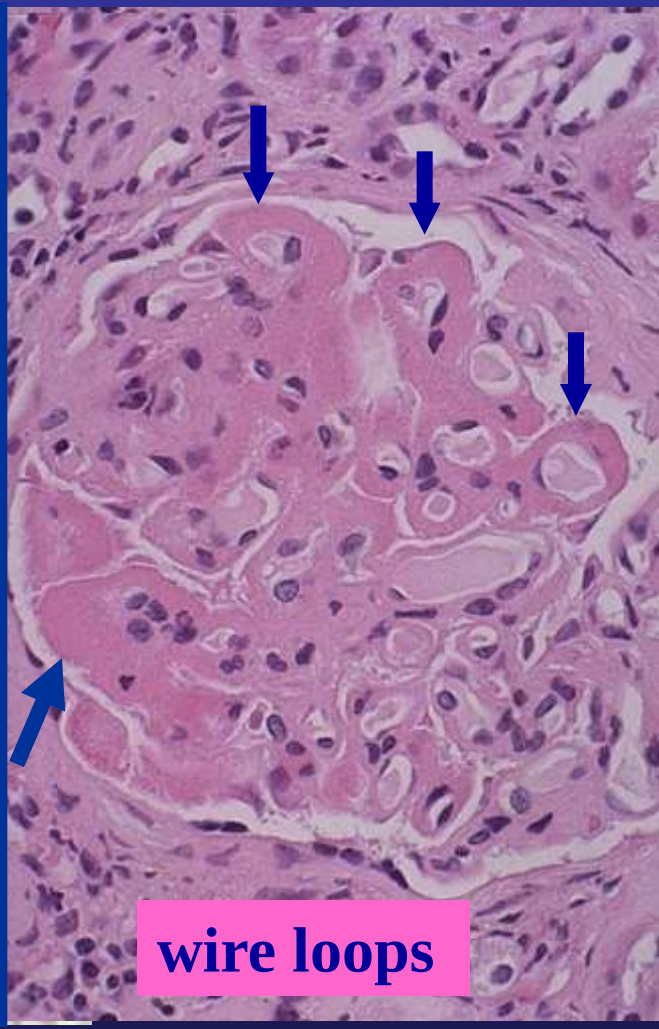
- IgA nephropathy
- Henoch Schönlein purpura
- Primary membranoproliferative GN

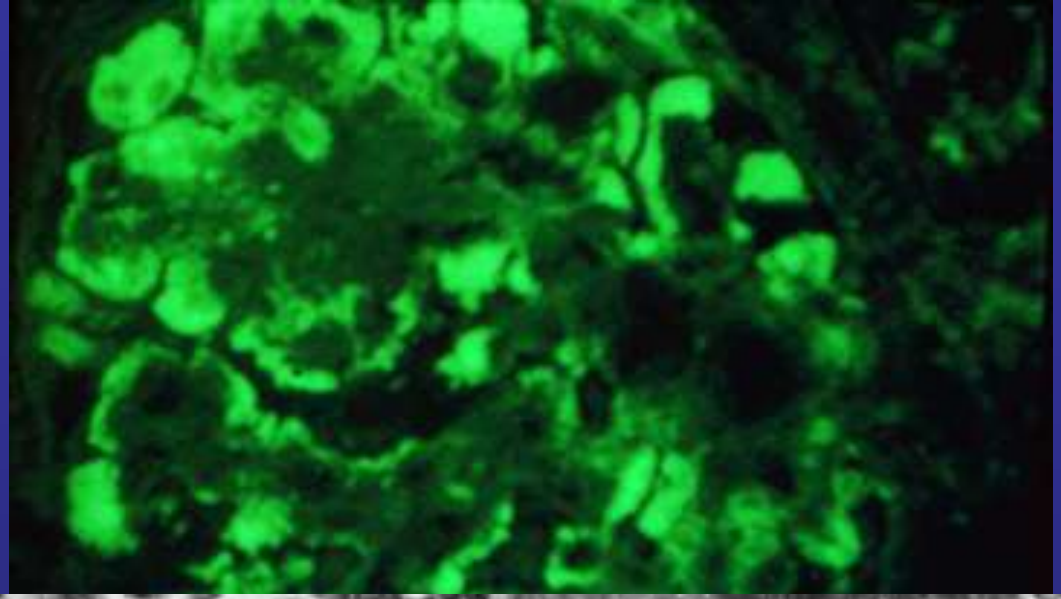
  C4NeF, C3NeF: antibodies that stabilize classic or alternative C3 convertases
- Lupus nephritis

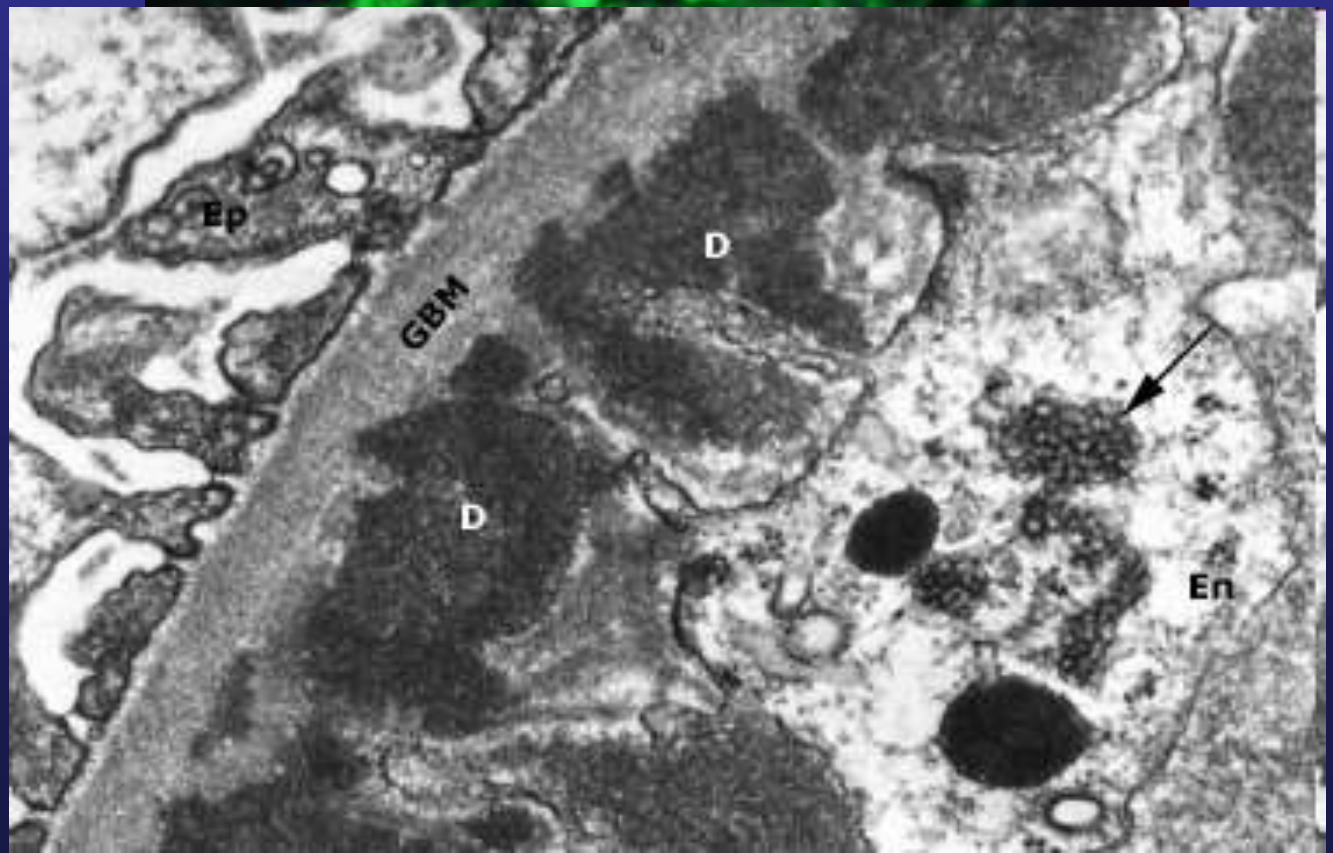
WHO Class	Renal histology
I.	Minimal mesangial
II.	Mesangial proliferative
III.	Focal proliferative
IV.	Diffuse proliferative
V.	Membranous
VI.	Advanced sclerosing

IV. Diffuse proliferative lupus nephritis

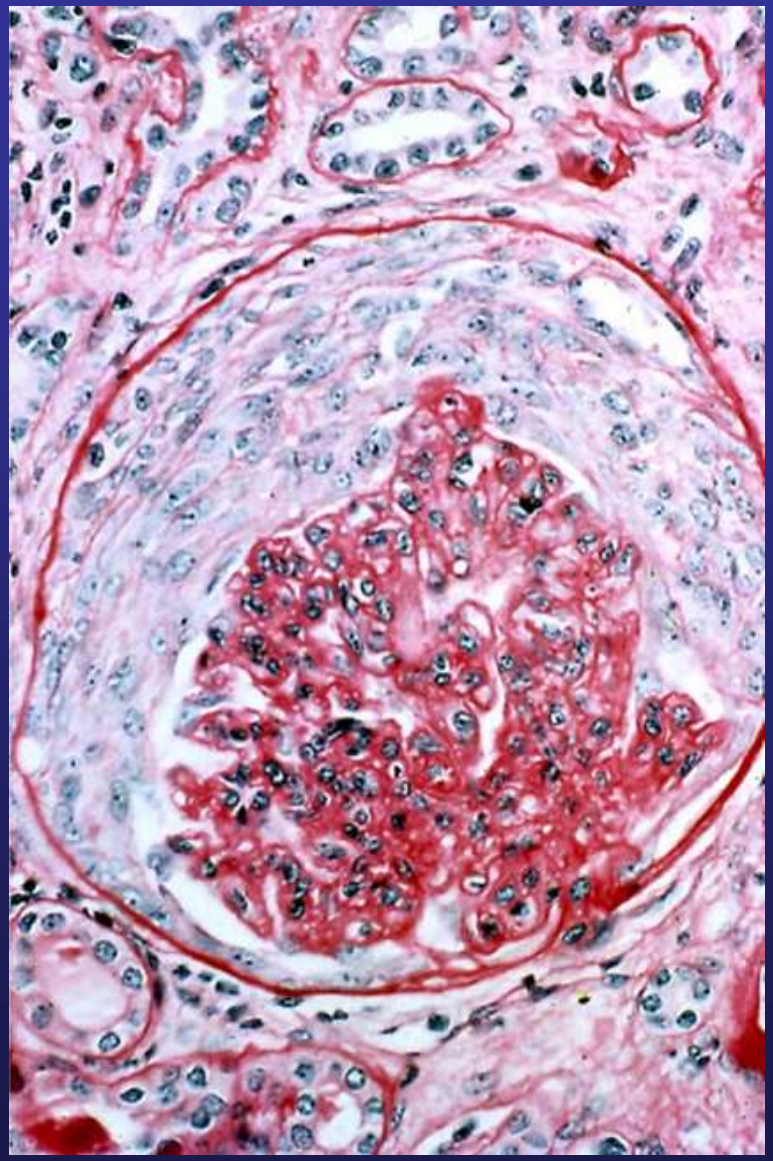


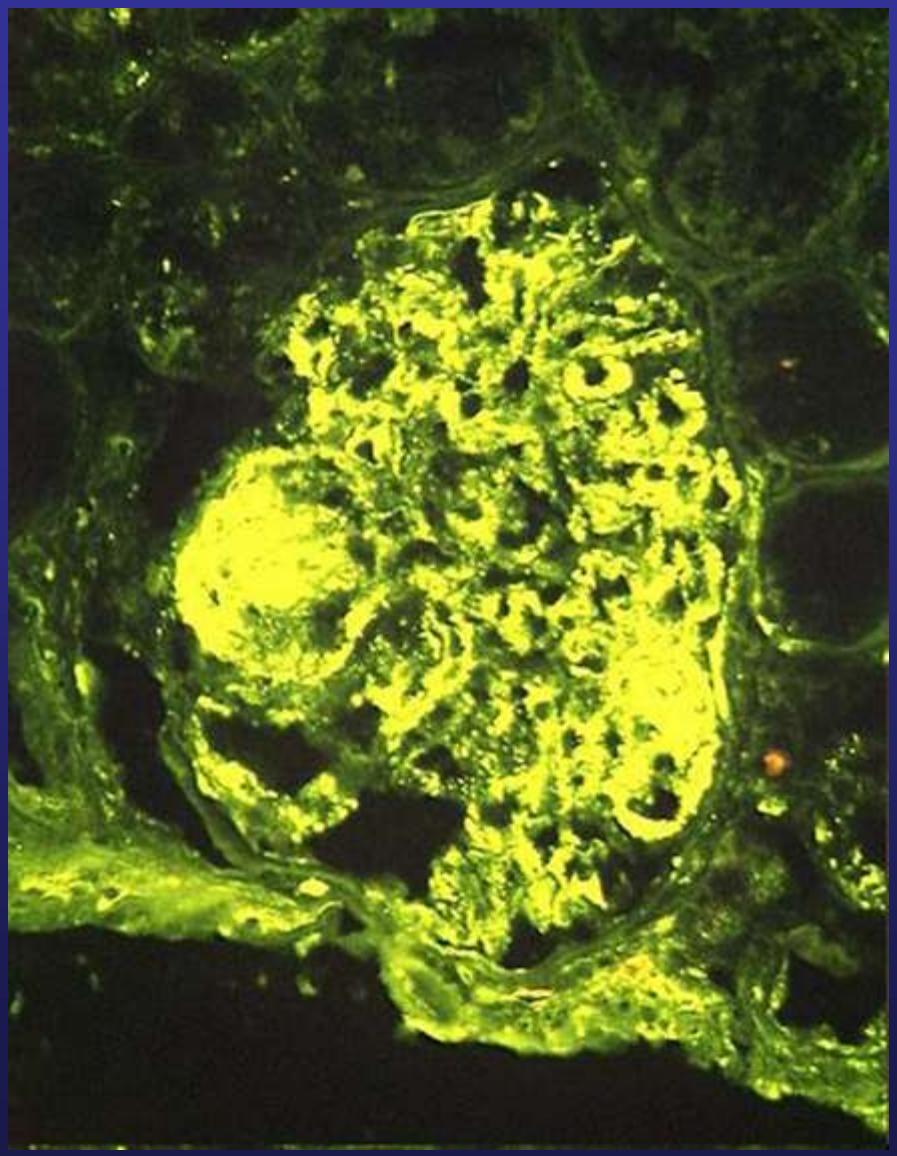





Ep
GBM
D
D
En

Crescentic glomerulonephritis





Therapy of severe focal proliferative and diffuse proliferative lupus nephritis

Remission induction

NIH protocol

- Solu-Medrol 1 g/m^2 iv, monthly x at least 1yr
- Metyl-prednisolone 0,5 mg/kg/d → 0,25 mg/kg qOD
- Cyclophosphamide

  0,5-1 g/ m^2 monthly x 6 mo., then 3 monthly x 24 mo.

- 25-35%: major infection
- 50% of women : amenorrhoea

Ann Intern Med 2001;135:248.

Therapy of severe focal proliferative and diffuse proliferative lupus nephritis

Euro-lupus trial

- **Solu-Medrol 750 mg iv for 3 days**
- **Metyl-prednisolone 0,5 mg/kg/day → 0,25 mg/kg qOD**
- **Cyclophosphamide**
  - **500 mg iv 2 weekly x 6**

  vs

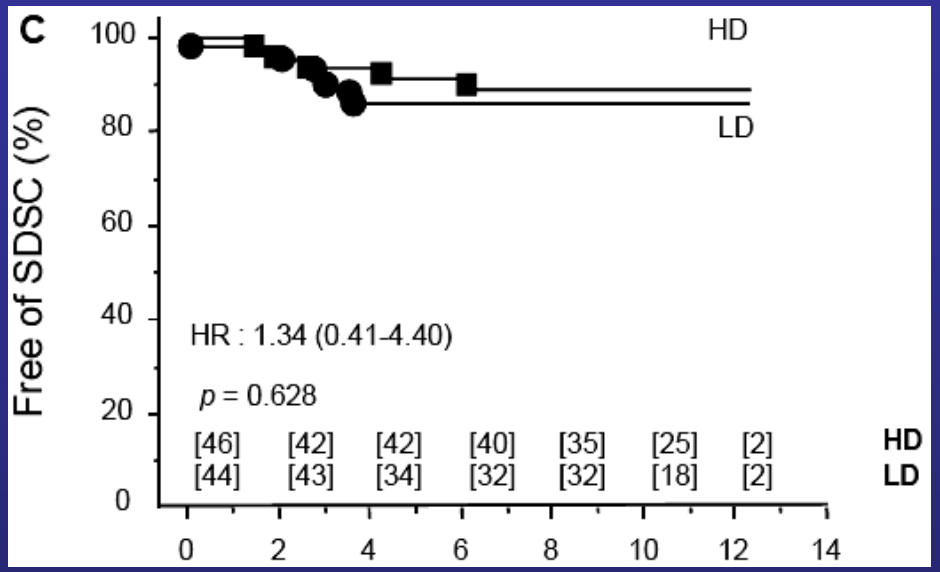
  - **0,5 g/m^2/mo x 6 (↑ by 250 mg), then 3 monthly x 2**

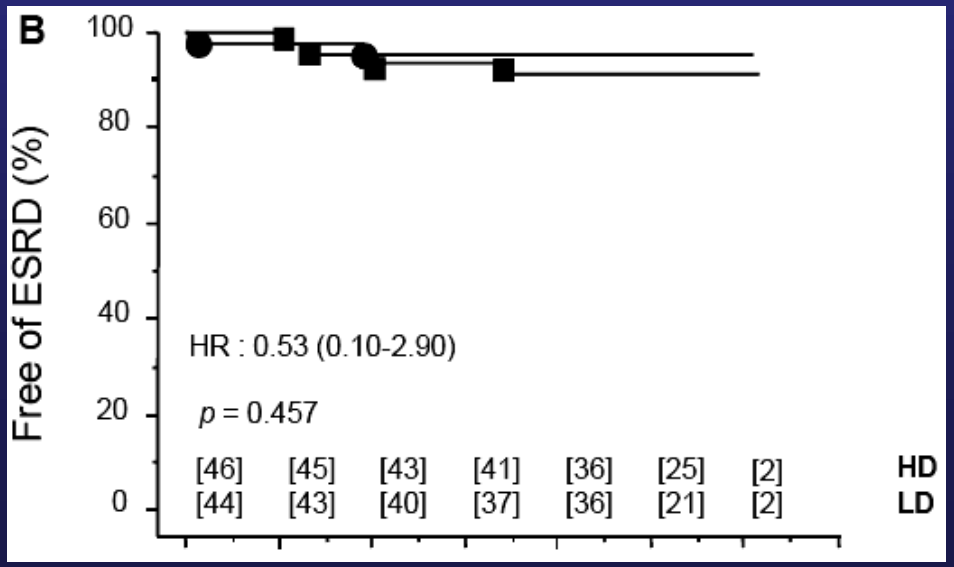
- **Maintenance: Azathioprin 2 mg/kg/day x 30 months + low dose MP**

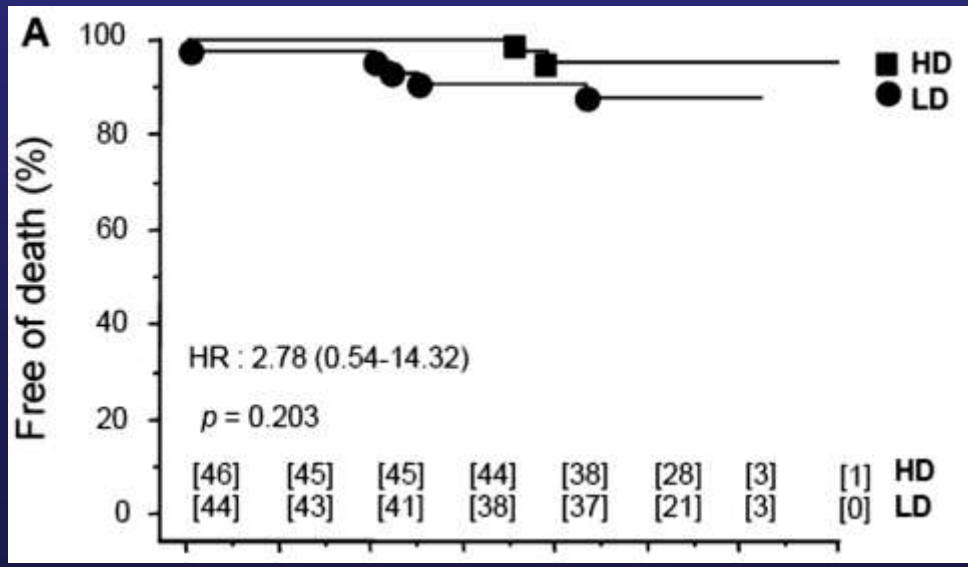
Houssiau F. Arthritis & Rheumatism 2002;46:2121–31

10-year follow-up data of the Euro-Lupus Trial

Cumulative CYC dose	
HD	LD
9,5 g	5,5 g
	2/3: 3g

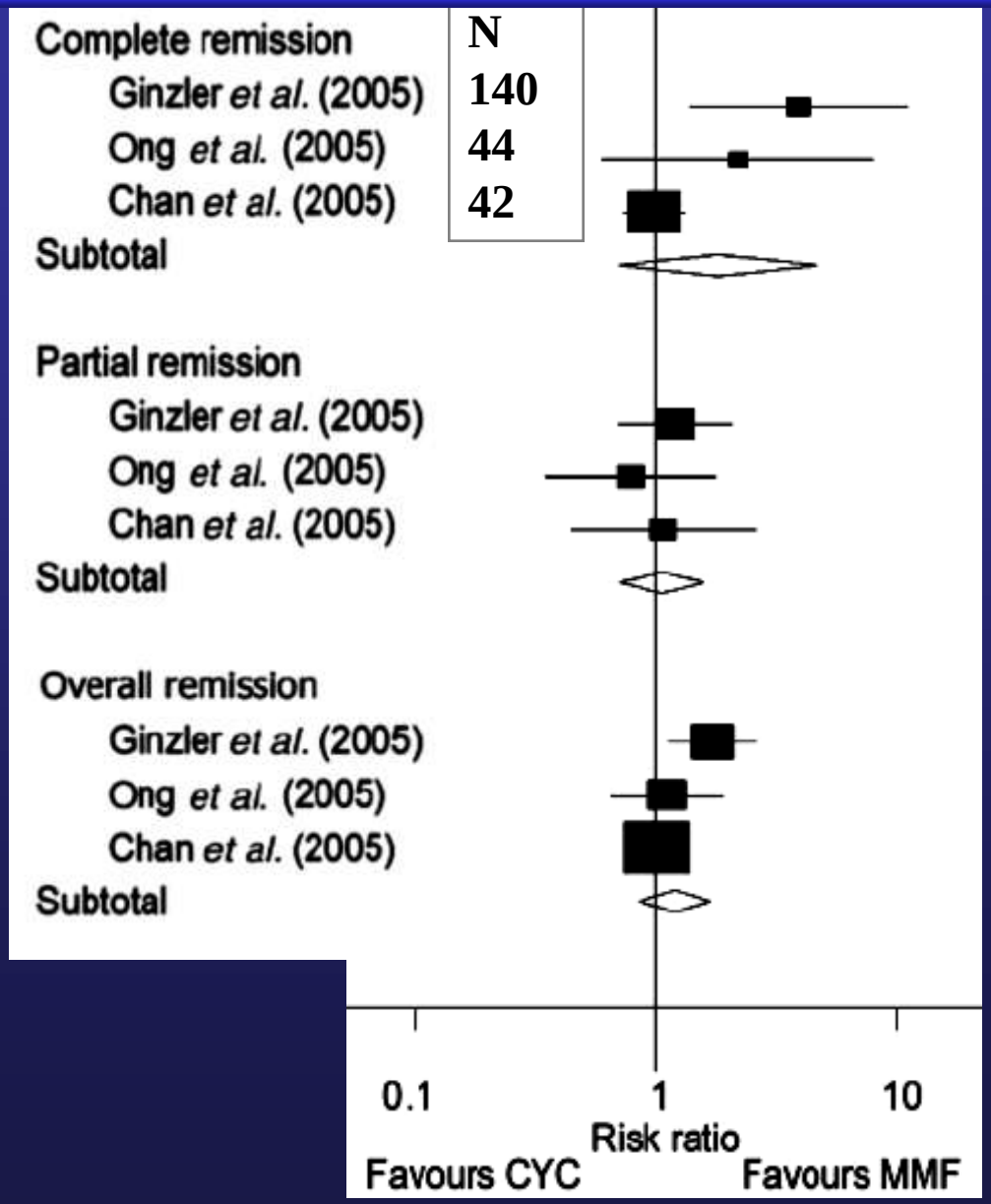






Houssiau F. Ann Rheum Dis 20 Jan 2009

Mycophenolate mofetil for severe lupus nephritis
(classes III, IV, V)



MMF

2-3 g/day x 6-12 mo

CYC

Iv pulse CYC (Ginzler, Ong)

Oral CYC (Chan)

NDT 2007;22: 1933–42.

No studies with homogenous groups of patients with immune complex RPGN were conducted except for diffuse proliferative lupus nephritis

Analysis of PEX studies in diffuse proliferative LN

Plasma exchange + cytotoxics *v* cytotoxics	No. of studies	NN	RR	95% CI
All cause mortality	2	125	1.62	0.64 to 4.09
ESRD	3	143	1.24	0.60 to 2.57
Doubling of serum creatinine	2	51	0.17	0.02 to 1.26
Major infection	2	125	0.69	0.35 to 1.37
Herpes zoster virus	2	104	1.69	0.10 to 29.42

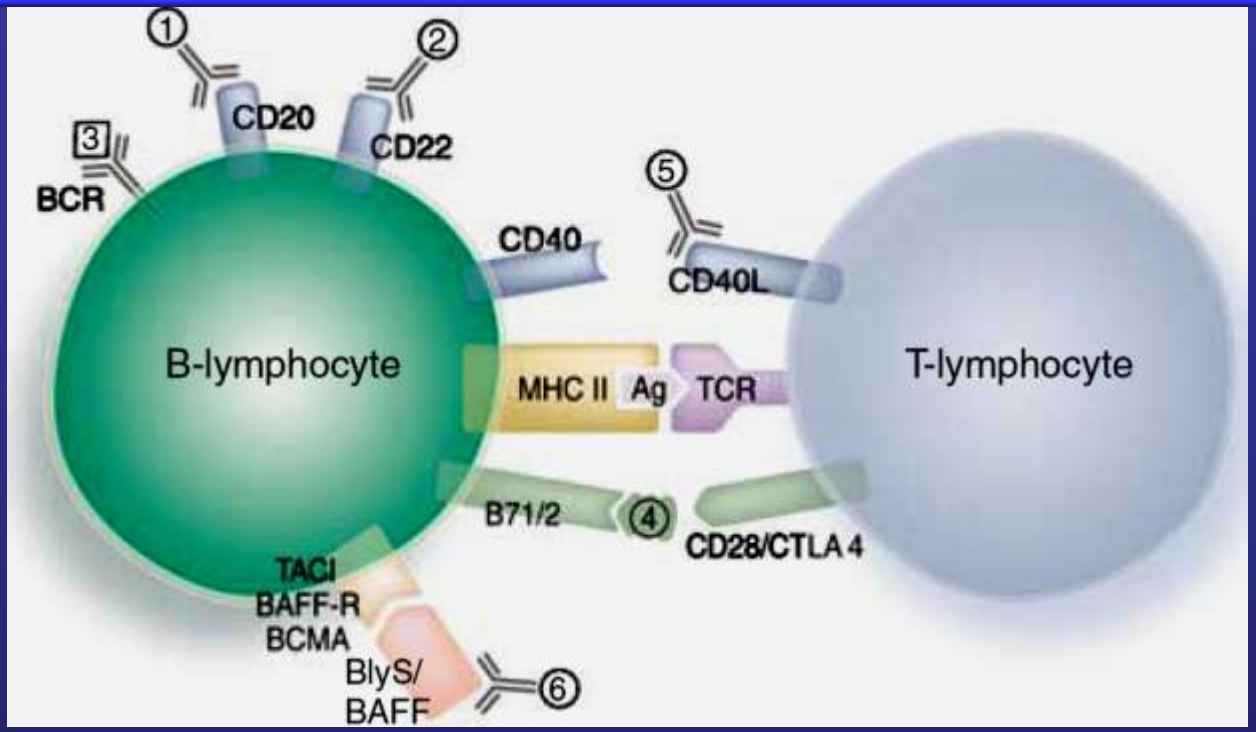
Flanc R. *Am J Kidney Dis* 43:197-208.

PEX in immunecomplex RPGN and SLE

Disease	Indication category	Grading
• Immune complex RPGN	III	2B
• Systemic lupus erythematosus		
Severe *Cerebritis, Alveolar hemorrhage, Catastrophic APS, Cryoglobulinemia, Hyperviscosity Thrombotic Thrombopenic purpura*	II	2C
Nephritis	IV	1B

Szczepiorkowski ZM. J Clin Apheresis 2010;25:83.
Pagnoux C, Transfus Apher Sci. 2007;36:187

New and evolving therapies for lupus nephritis



B cell depletion

- Rituximab: anti CD20 (1)
- Epratuzumab: anti-CD22 (2)

Induction of B cell tolerance

- Abetimus (ds-oligoDNA molecule) (3)
- IVIG

Anti - C5, IL1, IL10, IFN, TNF-α

Blockade of B-T cell costimulation

- Abatacept: CD28-Ig fusion (4)
- IDEC-131: anti CD40L (5)

Blockade of B-cell stimulation

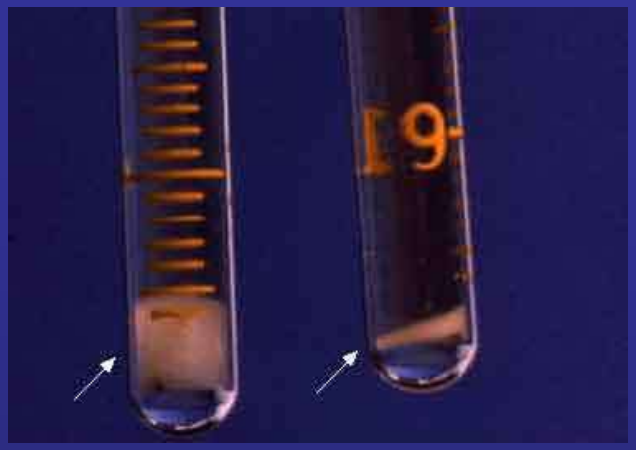
- Belimumab: anti BlyS (6)

Autologous stem cell transplantation

Kidney Int 2008;73:261–8.

Cryoglobulinemia

Cryoglobulin, 4 ^{o}C



cryocrit

Type I. Monoclonal IgM: plasmacell dyscrasia, NonHodgkin Lymphoma

Type II. Monoclonal IgM-polyclonal IgG - Rheumatoid factor: HCV, HBV

Type III. Polyclonal IgM-polyclonal IgG - Rheumatoid factor: SLE, infections

Clinical features

- Hyperviscosity
- Microthrombi, gangrena, Raynaud, livedo reticularis

Type I.

- Microscopic vasculitis
- Membranoproliferative GN (80%)
- Mesangial proliferative GN, Membranous GN
- Peripheral neuropathy
- Arthritis, myalgia
- Sicca sy

Type II.-III.

Diagnosis

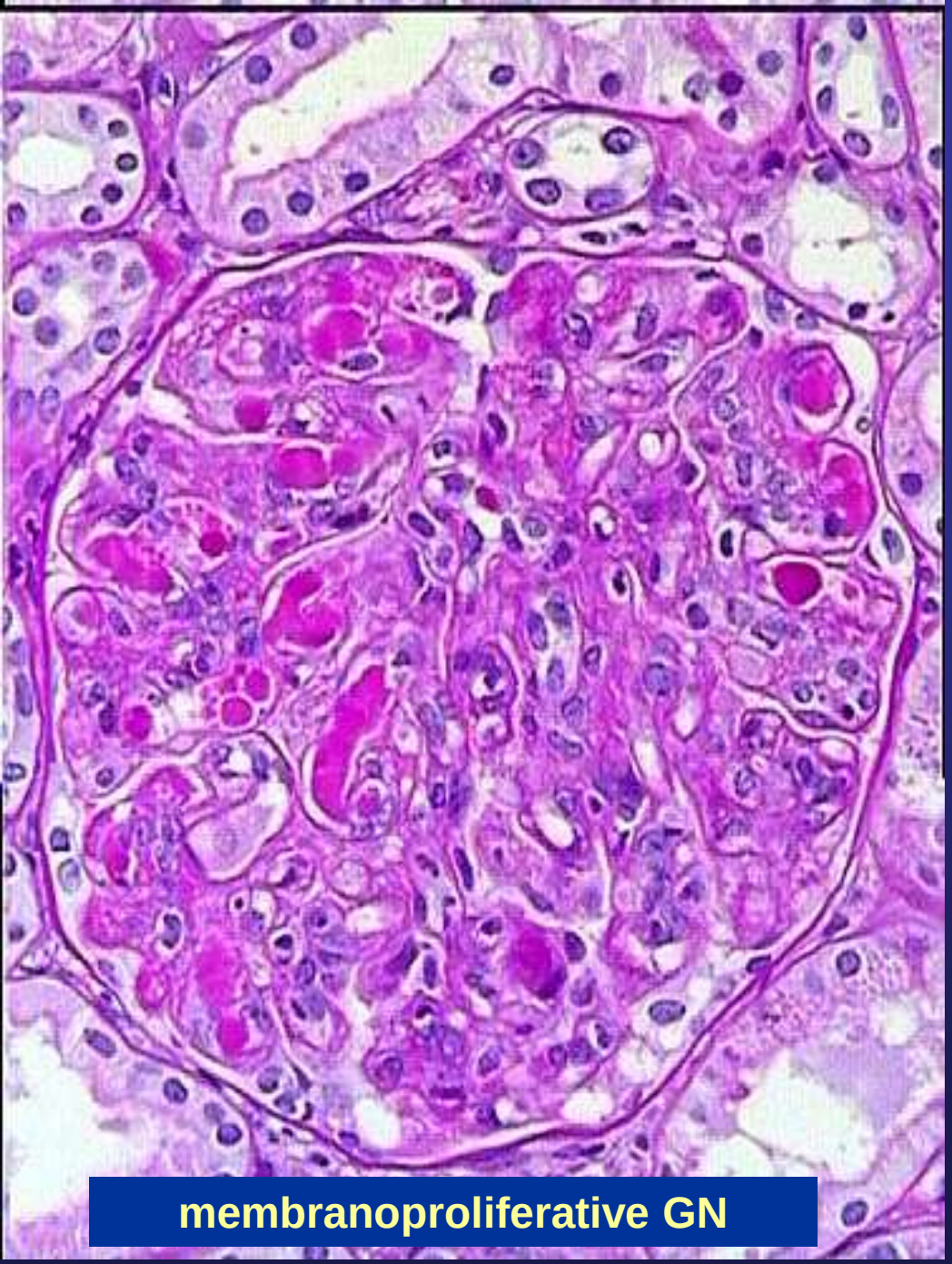
Low complement levels (type II, III)

Screening: separate serum at 37 ^{o}C - keep serum at 4 ^{o}C x 5 days

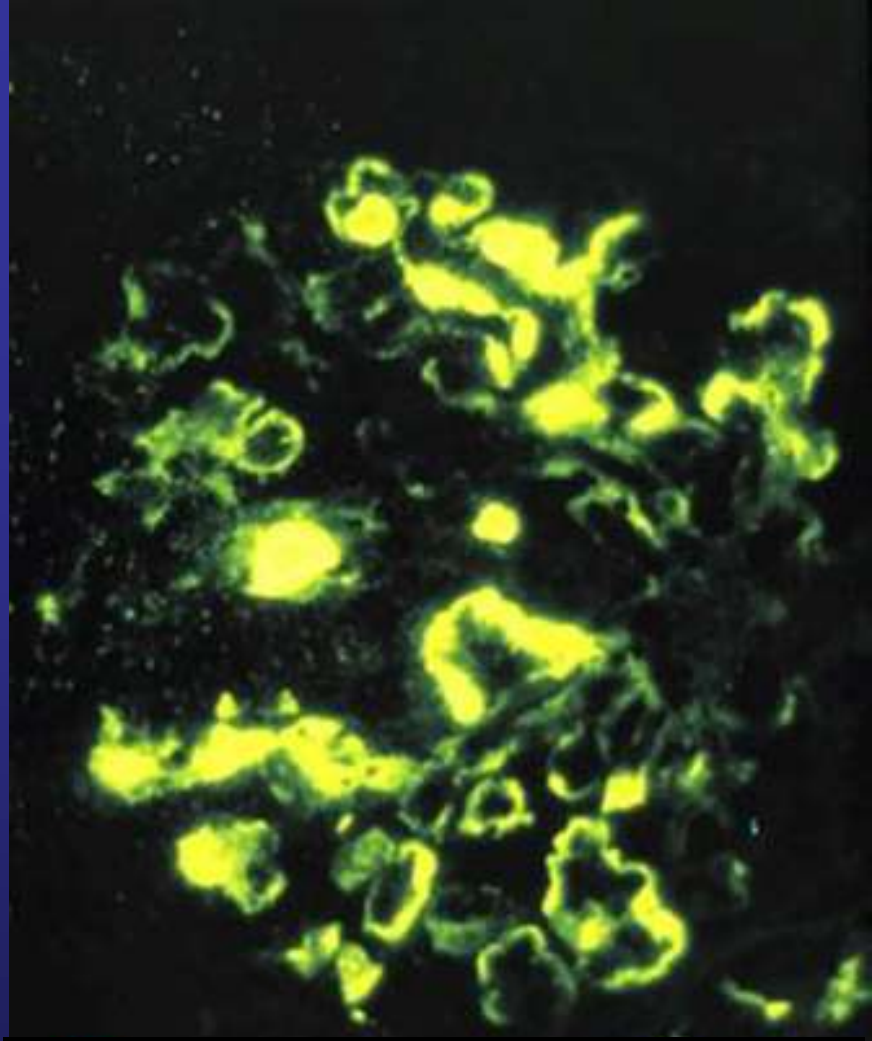
Type II-III: Rheumatoid factor

Quantitative measurement: no close relationship with symptoms

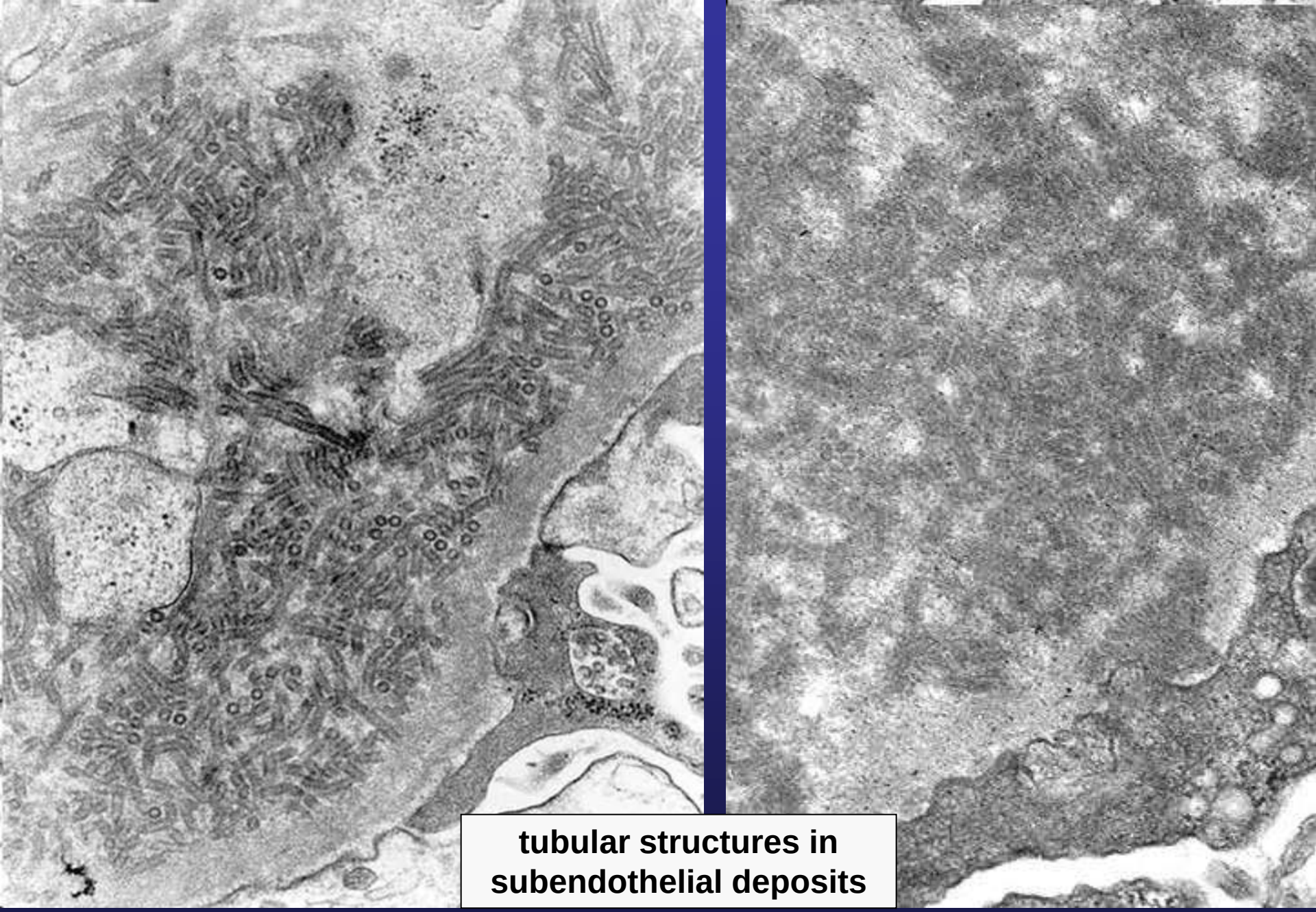
Caracterization: immunofixation



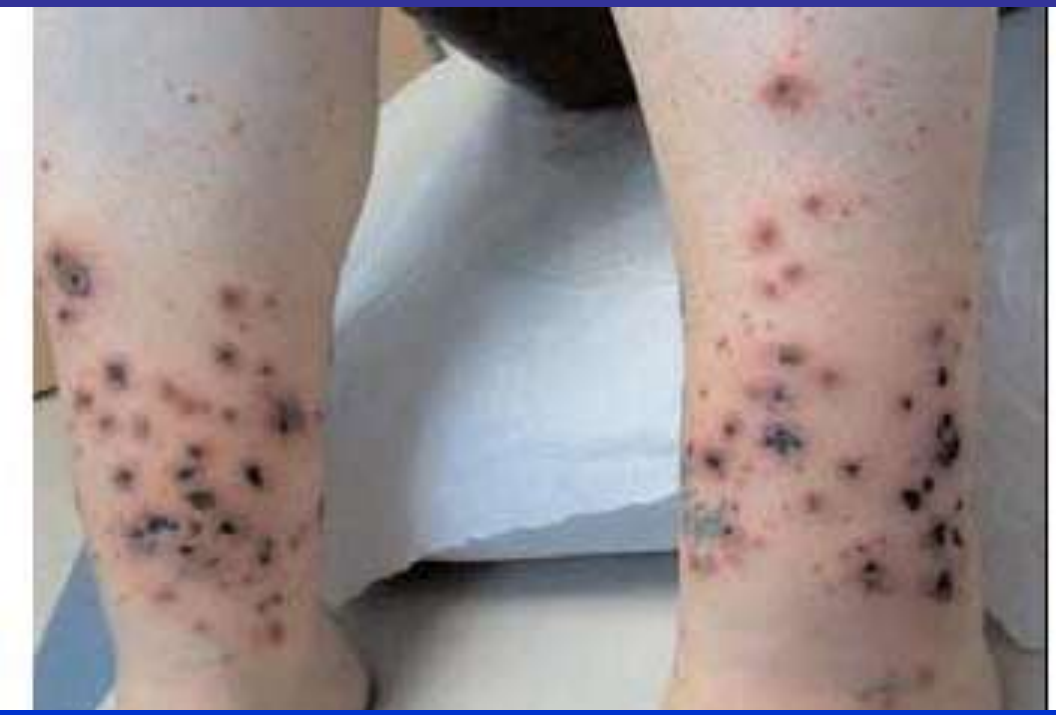
membranoproliferative GN

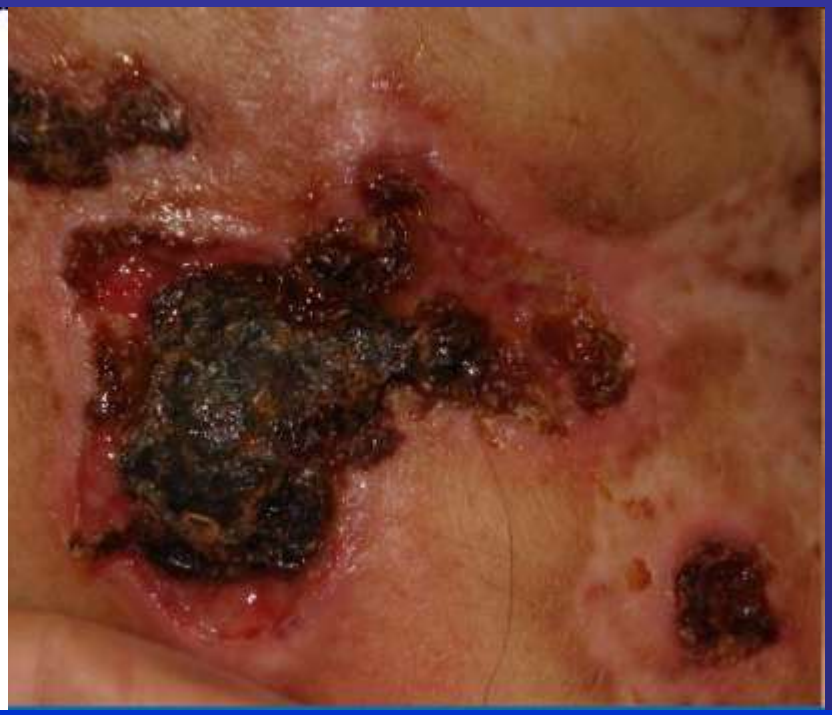


globular accumulations of cryoglobulin in the capillary lumens

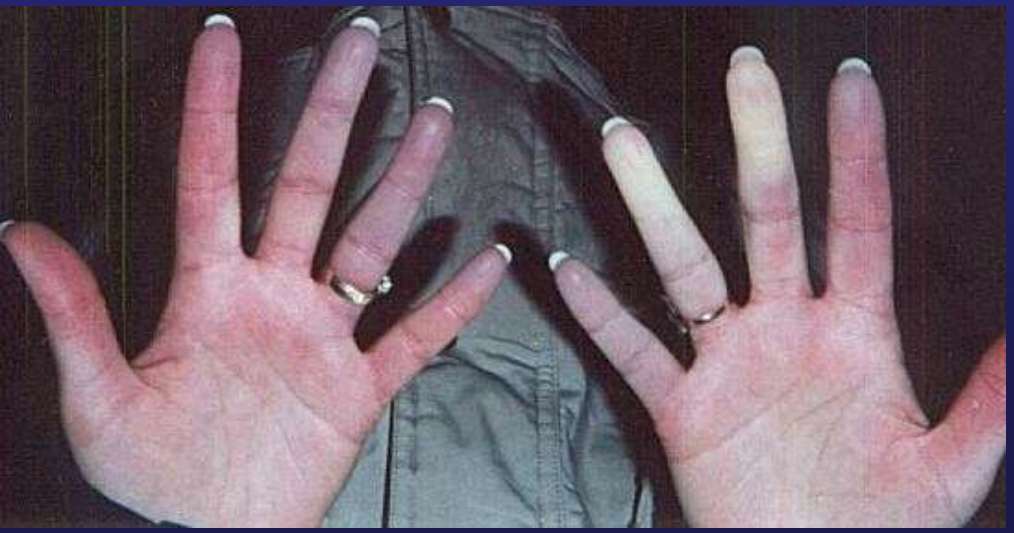


tubular structures in subendothelial deposits

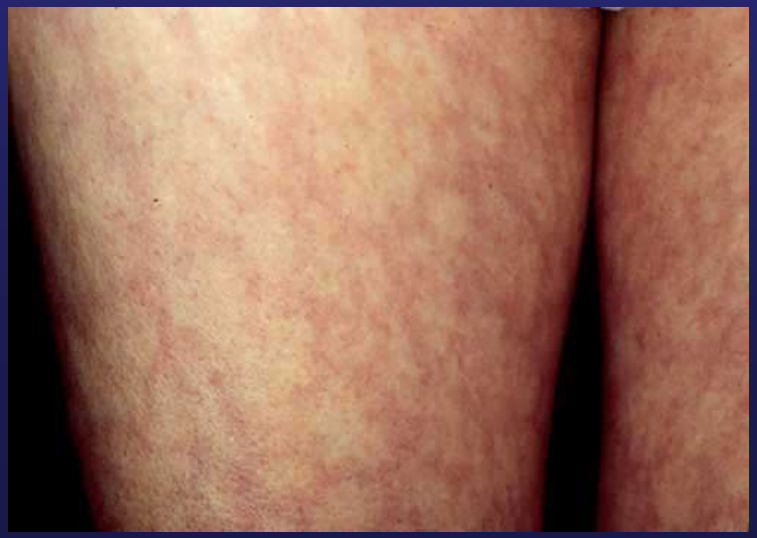




palpable purpura, necrosis



Raynaud



livedo reticularis

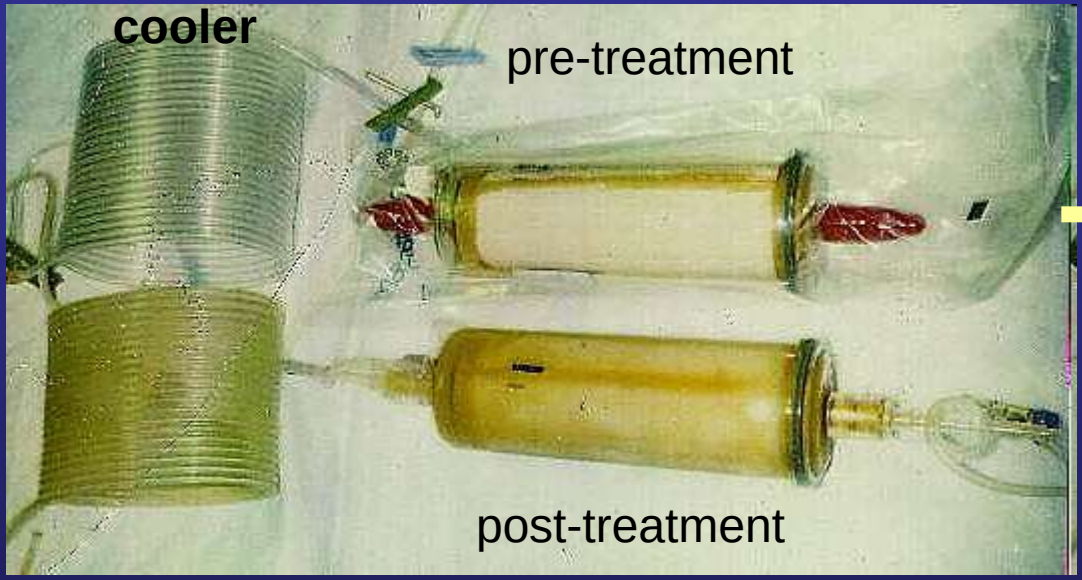
Plasma exhange in cryoglobulinemia

Disease	Indication category	Grading
Cryoglobulinemia		
Severe/symptomatic	**I (TPE)**	**1B**
Systemic vasculitis		
Acute glomerulonephritis sy		
Acute renal failure		
Nephrotic sy		
Neuropathy		
Hyperviscosity		
Secondary to HCV	**II (IA)**	**2B**

Szczepiorkowski ZM. J Clin Apheresis 2010;25:83.

Cryofiltration

Plasma →



→ 36°C → patient

Immunoglobulins, IFN, albumin, and fibrinogen are preserved.

Therapy of HCV-related cryoglobulinemia

- **No severe symptoms**

  Antiviral therapy: α - IFN or PEG - IFN

  Ribavirin

- **Severe symptoms**

  - Antiviral therapy as above

  Ribavirin dose adjusted to GFR

  No Ribavirin and PEG - IFN if GFR < 50 ml/min

  - Metylprednisolon pulse 0,5-1 g x3

  - Immune adsorption or cryofiltration, (PEX)

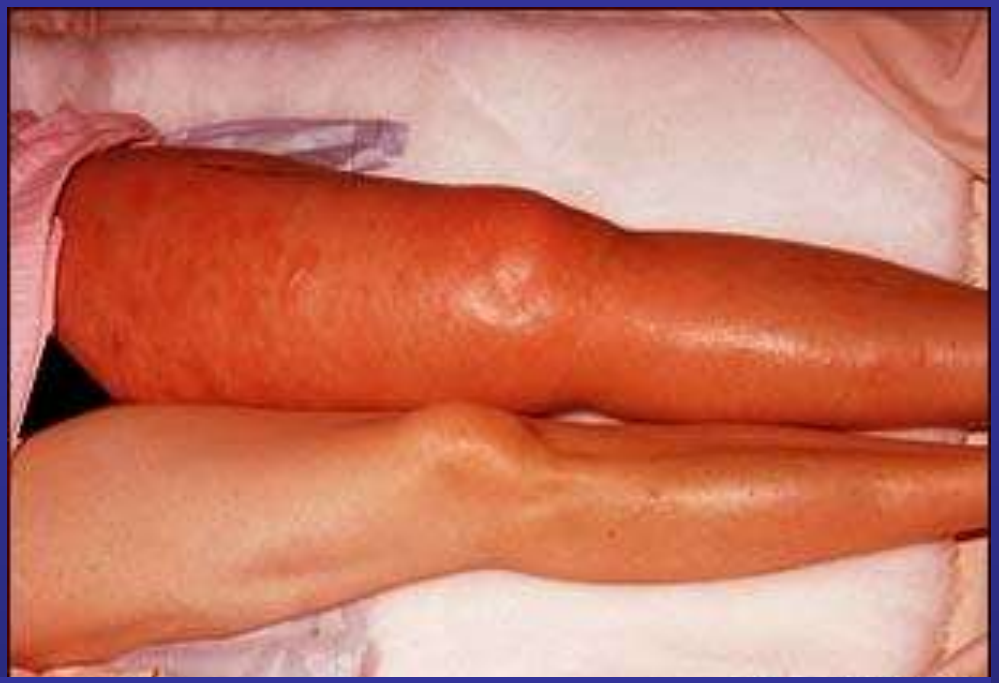
  - Cyclophosphamide or Rituximab

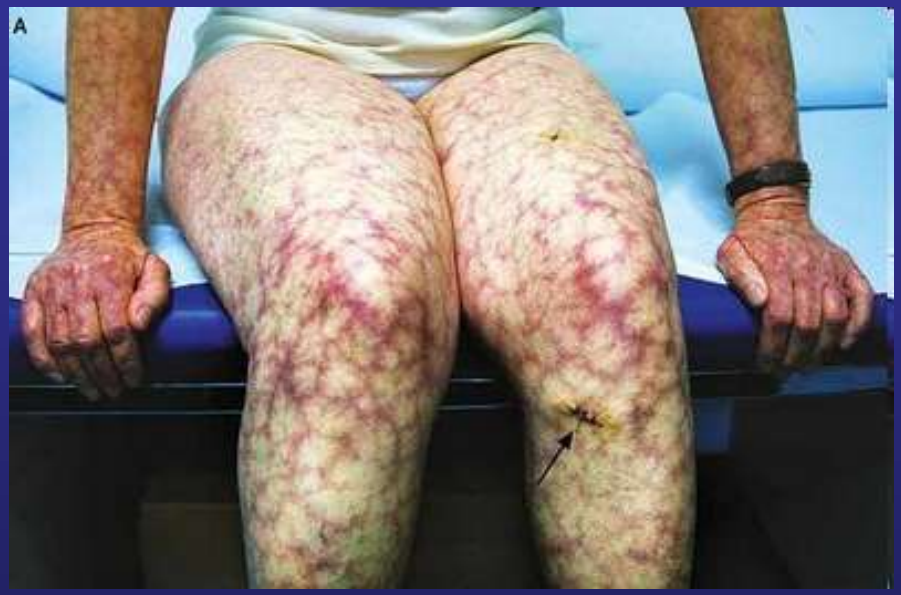
Stefanutti C. J Clin Apher. 2009;24:241

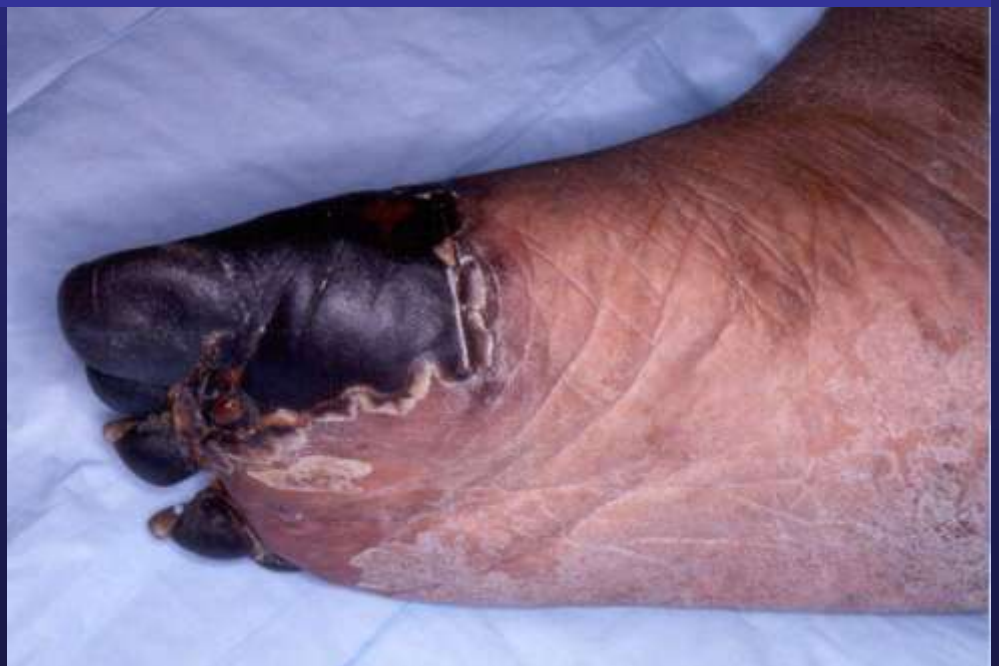
Antiphospholipid syndrome
Clinical features

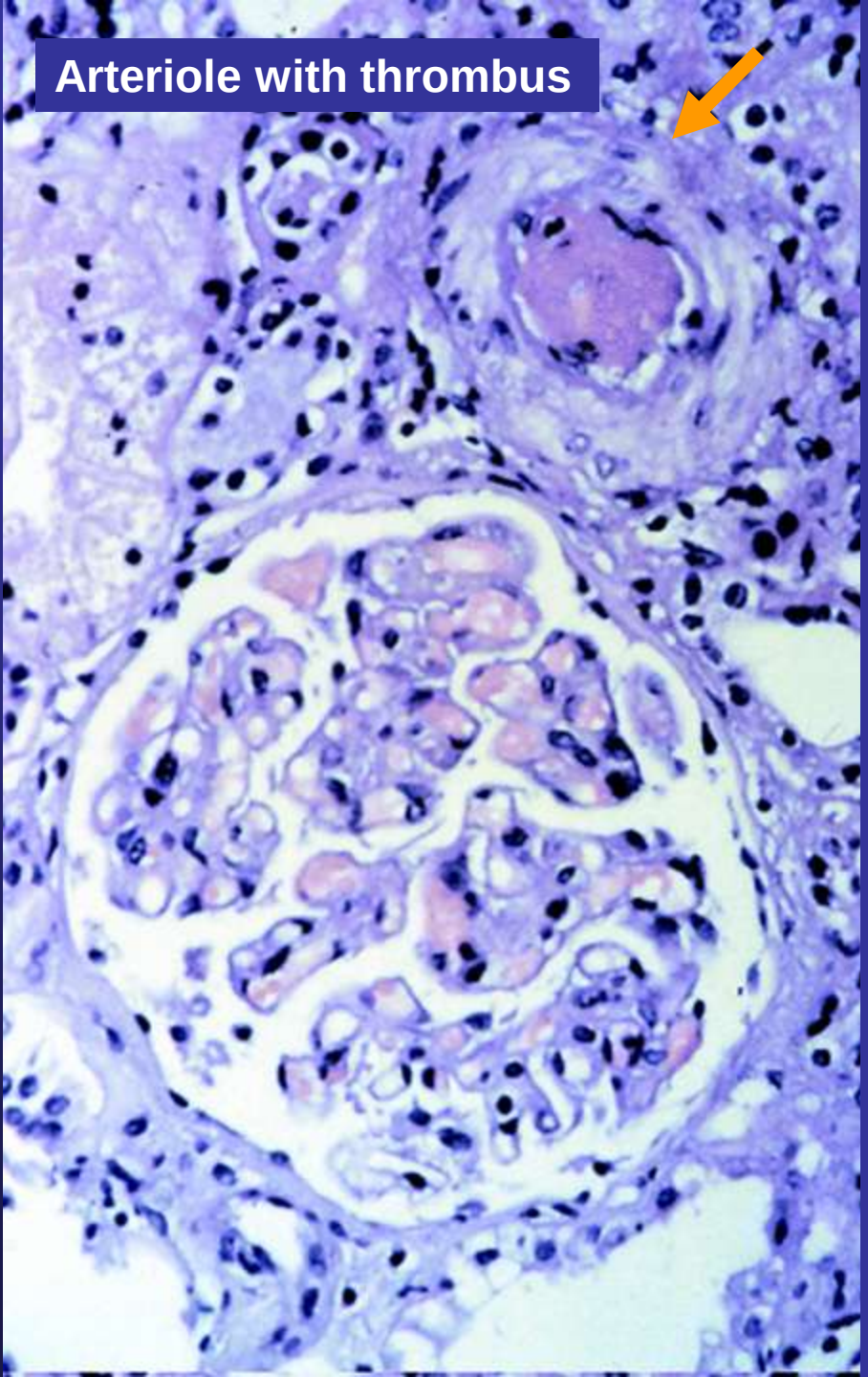
- Antiphospholipid antibodies
  - anti-cardiolipin antibody (ELISA)
  - anti β2-glycoprotein (ELISA)
  - lupus anticoagulant - prolonged APTT
- Venous thrombosis: deep veins, renal-, hepatic-, retinal veins, vena cava

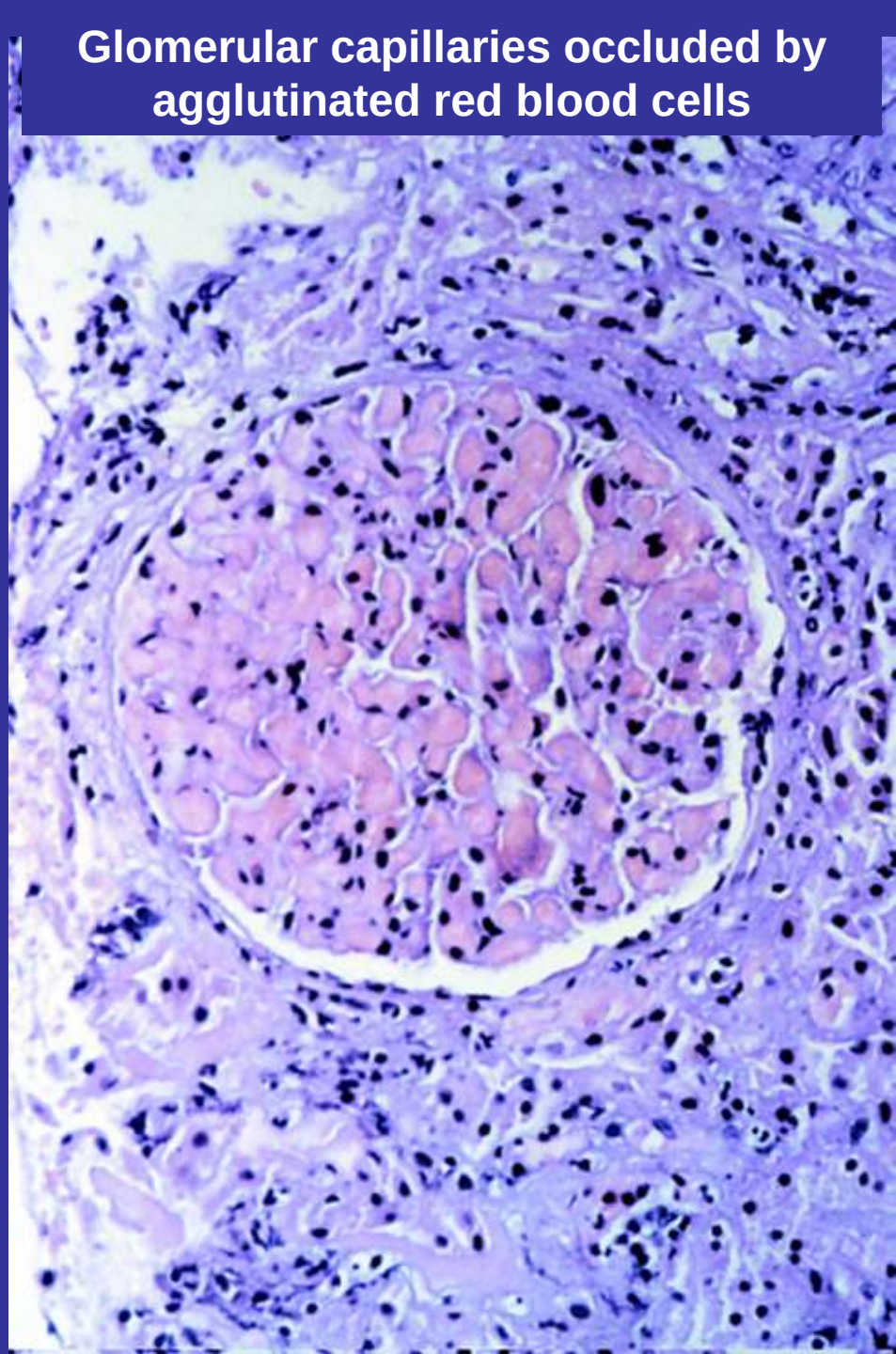
  and/or
- Arterial thrombosis: cerebral-, renal-, mesenteric arteries, coronaries pulmonary hypertension, amaurosis fugax
- Precipitating factors: smoking, anticoncipients, pregnancy, tumors, autoimmunity, immobilization, hyperlipidemia
- Habitual abortion, preeclampsia/eclampsia
- Hematology: Thrombotic microangiopathy - thrombopenia, hemolysis; bleeding
- Renal (25%): Thr. renal artery- glomerular capillary - vein, secondary FSGS
- Mitral-, aortic regurgitation / stenosis



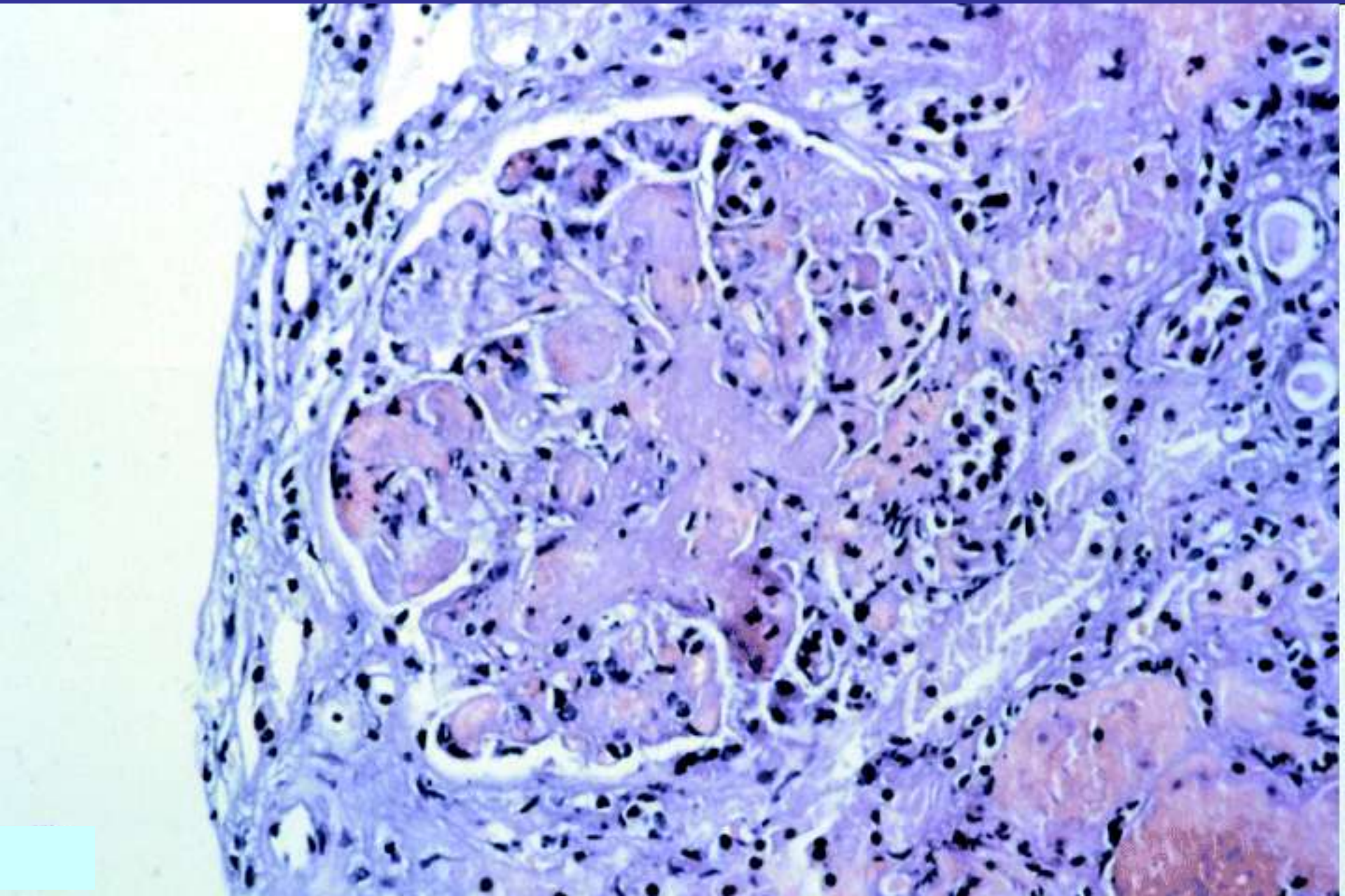

A




Arteriole with thrombus


Glomerular capillaries occluded by agglutinated red blood cells

Glomerular capillaries filled with fibrin thrombi



Catastrophic antiphospholipid syndrome

- Involvement of at least three organs/tissues
- Symptoms develop within one week
- Histological proof of vessel thrombosis
- Presence of antiphospholipid antibodies
- Life threatening condition

Therapy of antiphospholipid syndrome

- Aspirin/clopidogrel (prophylaxis!)
- Heparin/warfarin
  - INR 2.5-3.0
  - life-long
- Catastrophic APS
  - Anticoagulation with heparin
  - Glucocorticoids
  - Intravenous immunglobulin
  - Plasma exchange

	indication category	grade
	II.	2C

  - rituximab
  - autologous bone marrow transplantation

} experimental

PEX - complications

- Fever
- Urticaria
- Hypocalcemia
- Hypotension

} 7-8%

- Bleeding diathesis
- Hypogammaglobulinemia - immunsuppression
- Premature termination of procedure 0,2%
- ICU admission 0,1 %
  - Anaphylaxis
  - Bronchospasm
  - Cardiac failure, respiratory failure
- Viral infection (FFP)
- Catheter-related: Thrombosis, sepsis, bleeding
- Death

Shemin D, J Clin Apher. 2007 Oct;22(5):270-6.

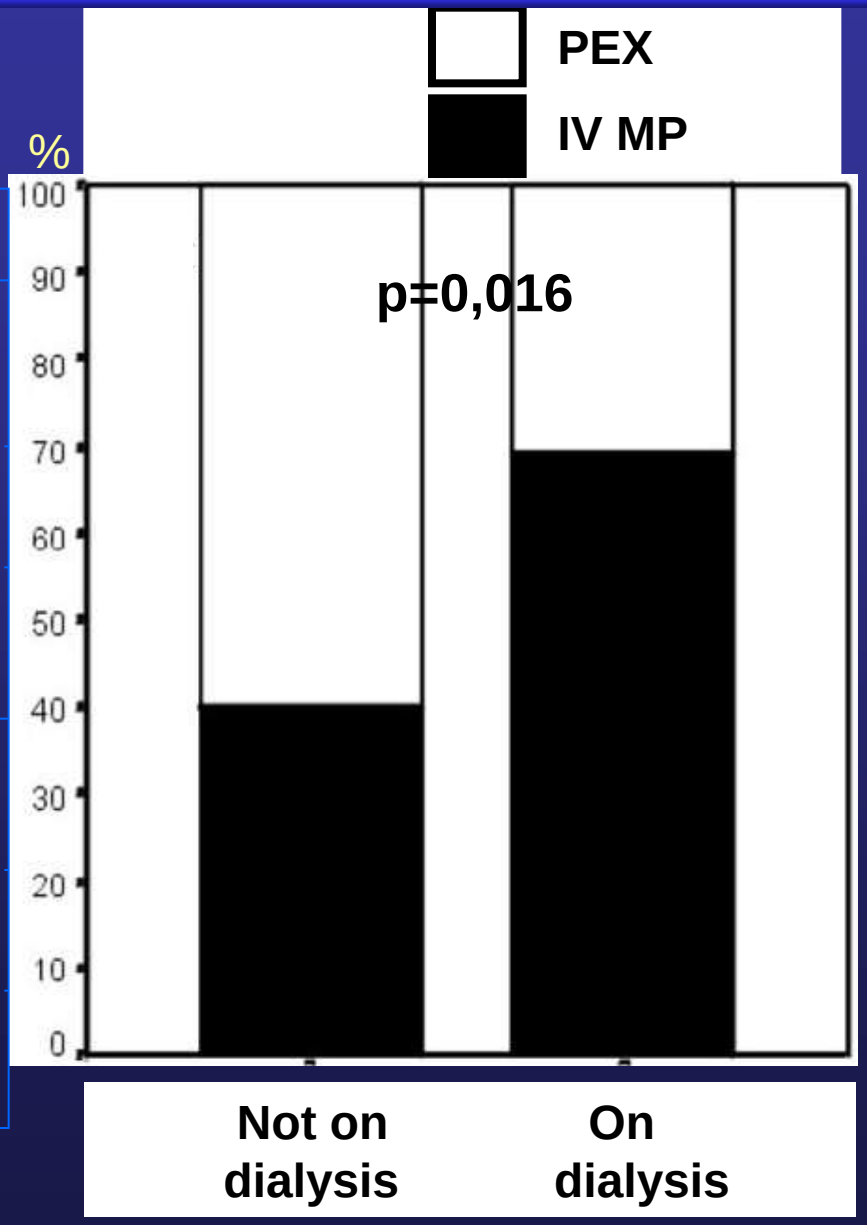
Disease	Indication category	Grading
• Goodpasture's syndrome		
Dialysis independence	I	1A
Diffuse alveolar hemorrhage	I	1B
Dialysis dependent, no DAH	IV	1A
• ANCA- associated RPGN		
Dialysis dependence	I	1A
Diffuse alveolar hemorrhage (DAH)	I	1C
Dialysis independence, no DAH	III	2C
• Catastrophic antiphospholipid syndrome	II	2C
• Cryoglobulinemia		
Severe/symptomatic	I (TPE)	1B
Secondary to HCV	II (IA)	2B
• Immune complex RPGN	III	2B
• Systemic lupus erythematosus		
Severe	II	2C
Cerebritis, Alveolar hemorrhage, Catastrophic APS, Cryoglobulinemia, Hyperviscosity		
Nephritis	IV	1B

Szczepiorkowski ZM. J Clin Apheresis 2010;25:83.

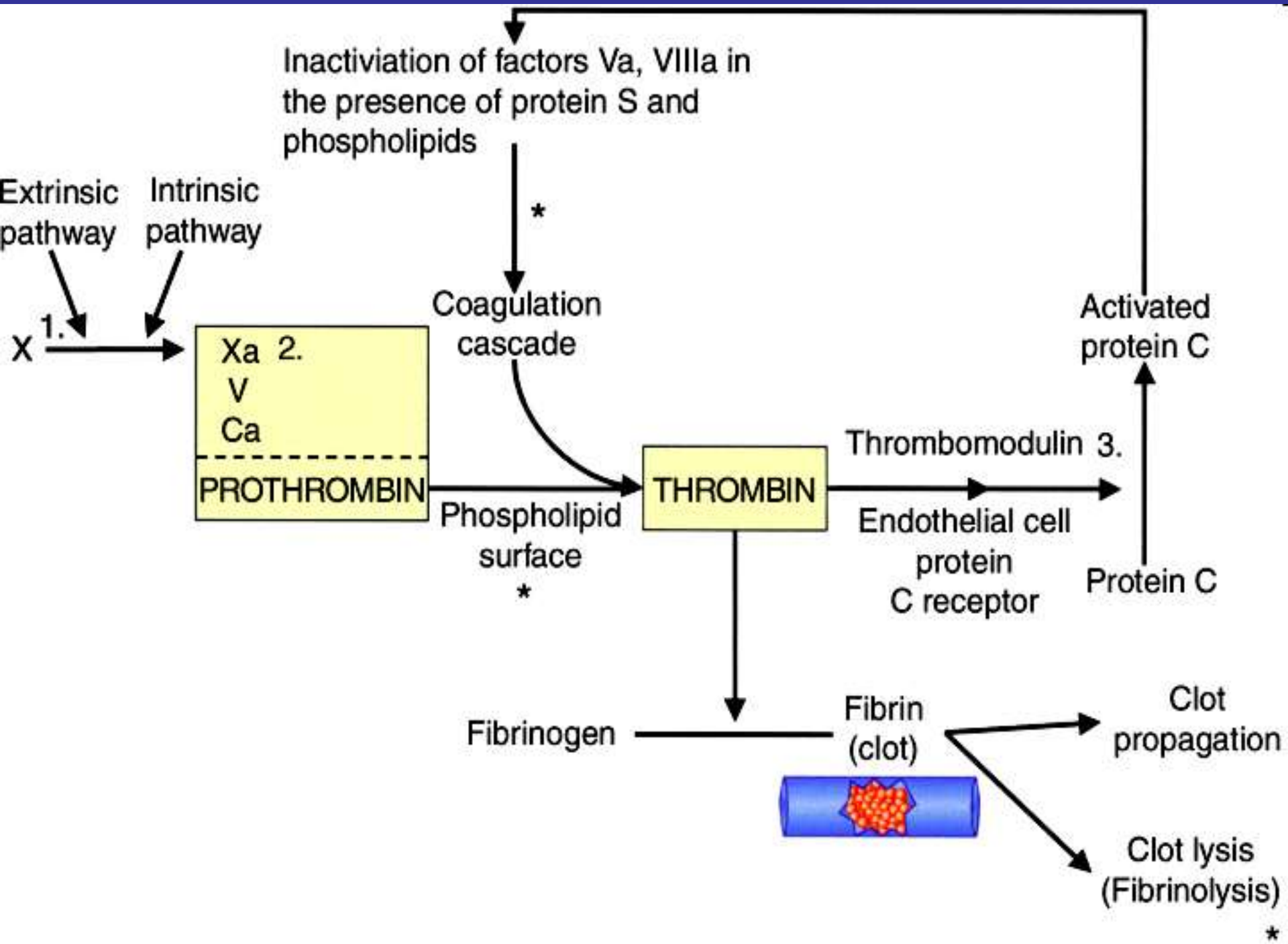
Disease	Indication category	Grading
• Scleroderma	III	2C
• Focal segmental glomerulosclerosis, recurrent	I	1C
• Myeloma cast nephropathy	II	2B
• Renal transplantation		
Antibody mediated rejection	I	1B
Desensitization, donor specific HLA AB	II	1B
High PRA; cadaveric donor	III	2C

MEPEX: outcome at one year

Baseline	1 yr
Not on dialysis N=31 (31%)	Not on dialysis n=20 (64%)
	On dialysis n= 4 (13%)
	Death n=7 (23%)
On dialysis N=69 (69%)	Not on dialysis n=30 (43%)
	On dialysis n=22 (32%)
	Death n=17 (25%)



MEPEX, *J Am Soc Nephrol* 17: 2264–2274, 2006.


Inactiviation of factors Va, VIIIa in the presence of protein S and phospholipids
*
Extrinsic pathway
Intrinsic pathway
X
1.
Xa
2.
V
Ca
PROTHROMBIN
Coagulation cascade
Phospholipid surface
*
THROMBIN
Thrombomodulin
3.
Endothelial cell protein C receptor
Activated protein C
Protein C
Fibrinogen
Fibrin (clot)
Clot propagation
Clot lysis (Fibrinolysis)
*

Hyperviscosity

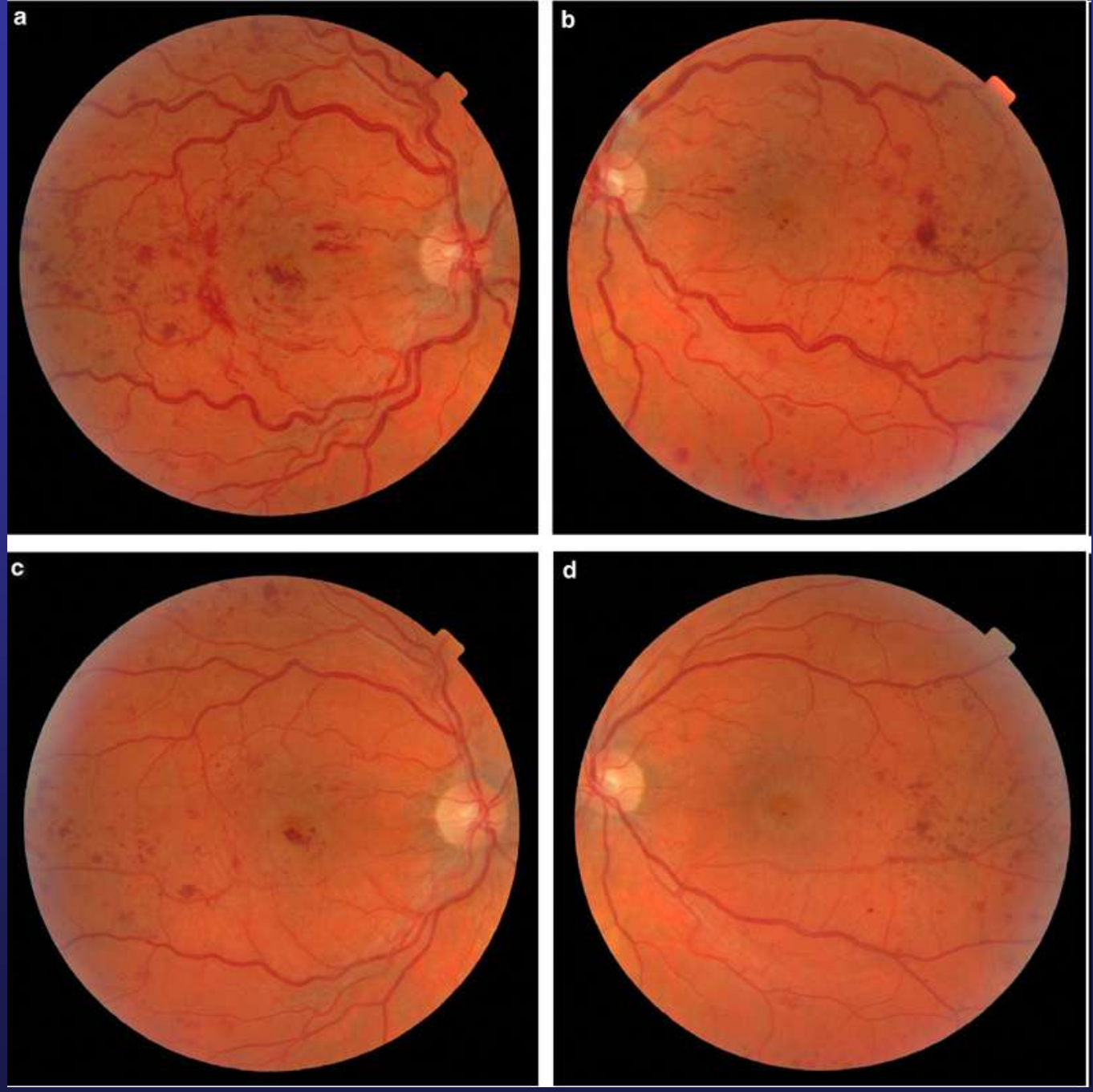
- Mucous membrane bleeding
- Visual disturbancies, retinopathy
- Tinnitus, hearing loss
- Headache, vertigo, nystagmus,
- Somnolency
- Muscle cramps
- Heart failure, respiratory failure
- Coma

Ostwald viscometer

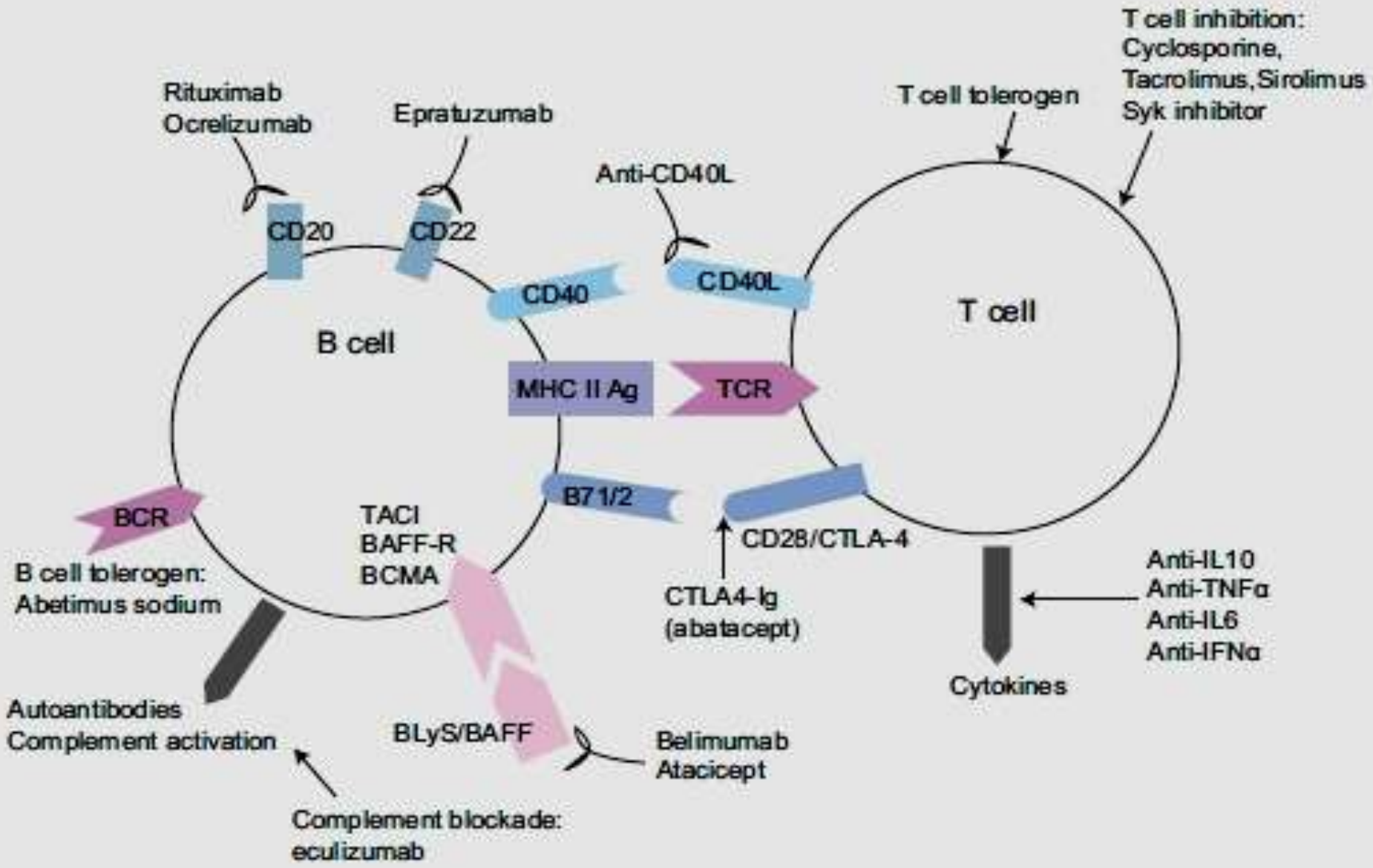
Waldenstöm´s macroglobulinemia

Pre - PEX

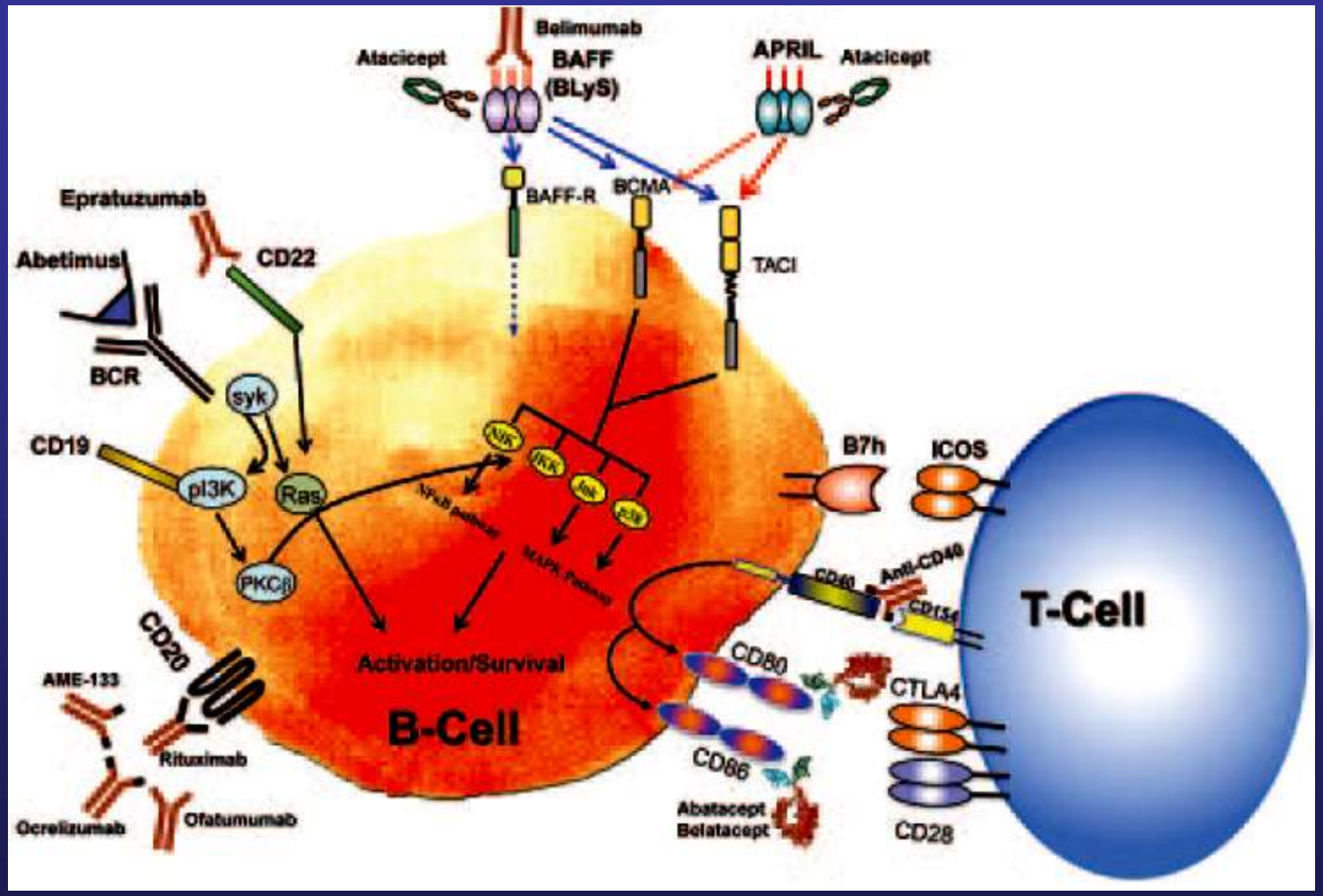
Post - PEX



Targeted therapies for SLE



Novel B Cell Therapeutic Targets in Immune-Mediated Glomerular Diseases



Clin J Am Soc Nephrol 5: 142–151, 2010.

IgG subclass swiching | **Nephritogenic Ig subclasses** | **Final stage**