



# Secondary Glomerular Disease, Vasculitis – Plasmapheresis Therapy

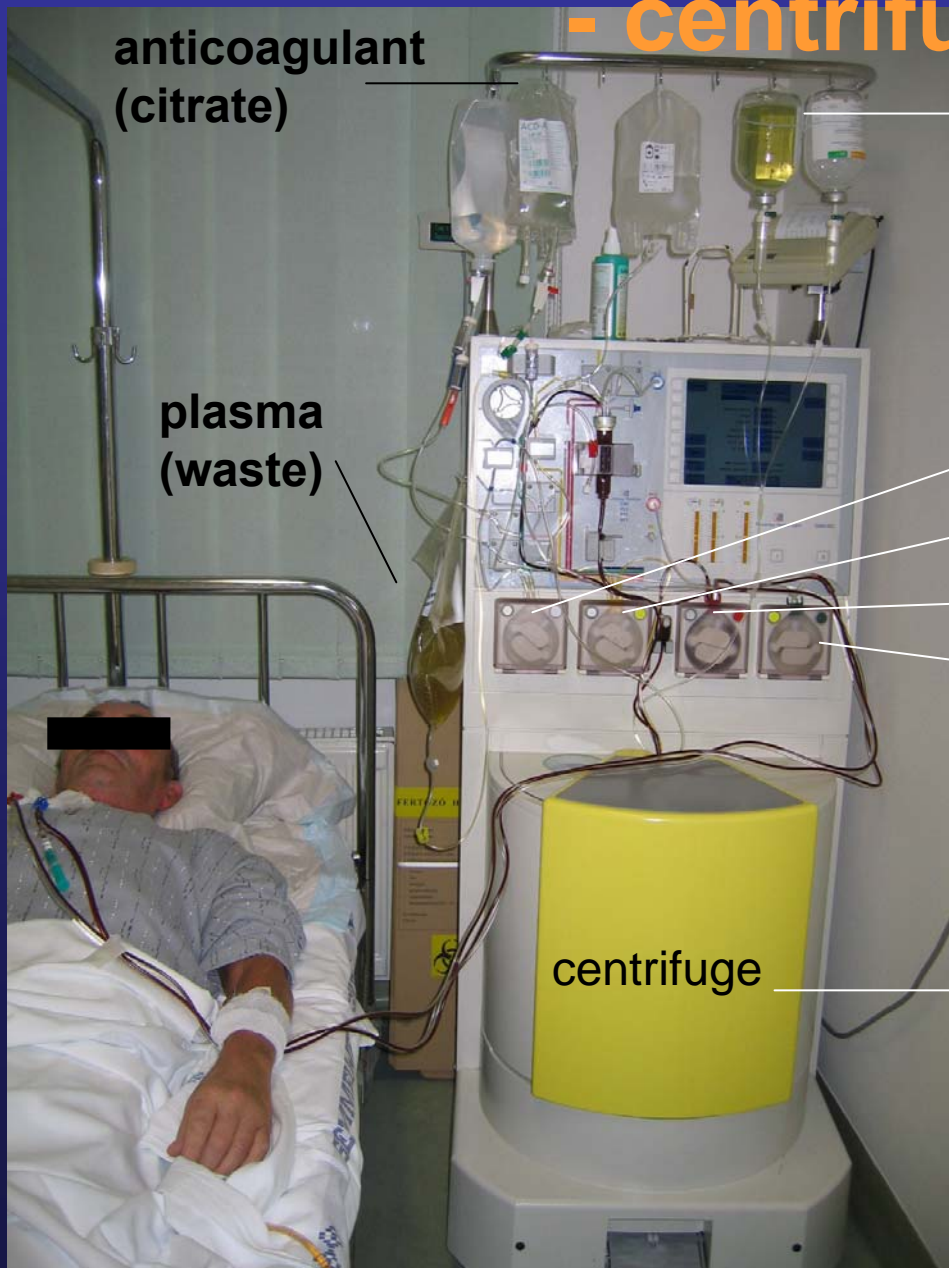
György Deák

Semmelweis University, Budapest

# Clinical approach to glomerulonephritis

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

# Therapeutic plasma exchange (TPE) - centrifugation -



anticoagulant  
(citrate)

plasma  
(waste)

centrifuge

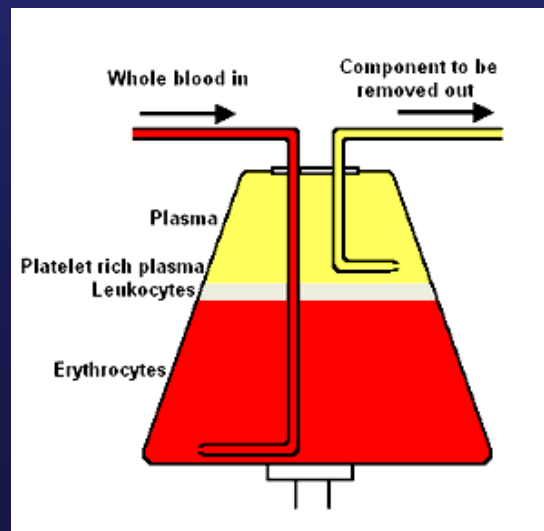
replacement fluid  
crystalloid  
albumin  
fresh frozen plasma

replacement fluid pump

plasma pump

blood pump

anticoagulant pump



Whole blood in

Component to be removed out

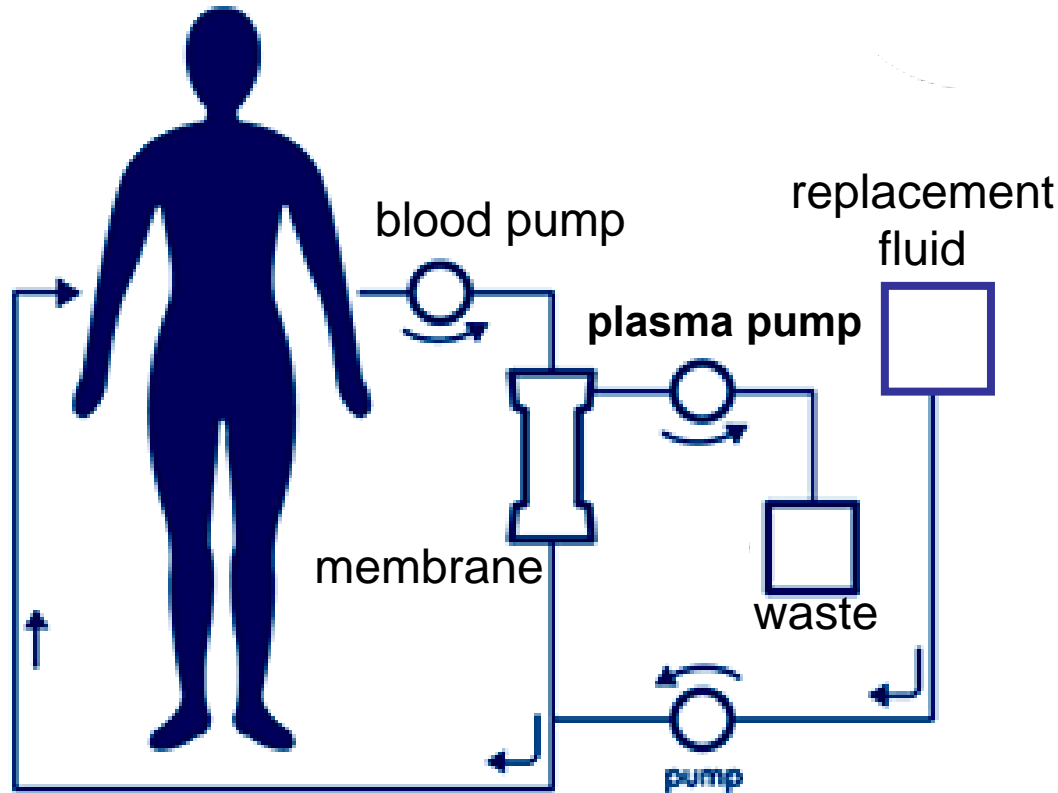
Plasma

Platelet rich plasma  
Leukocytes

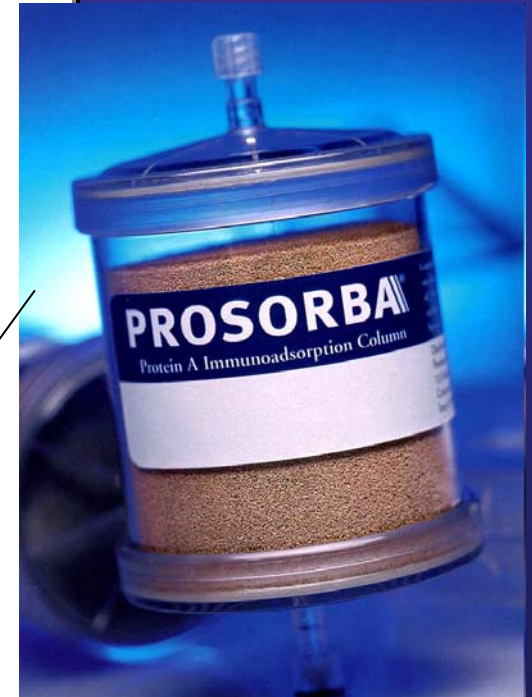
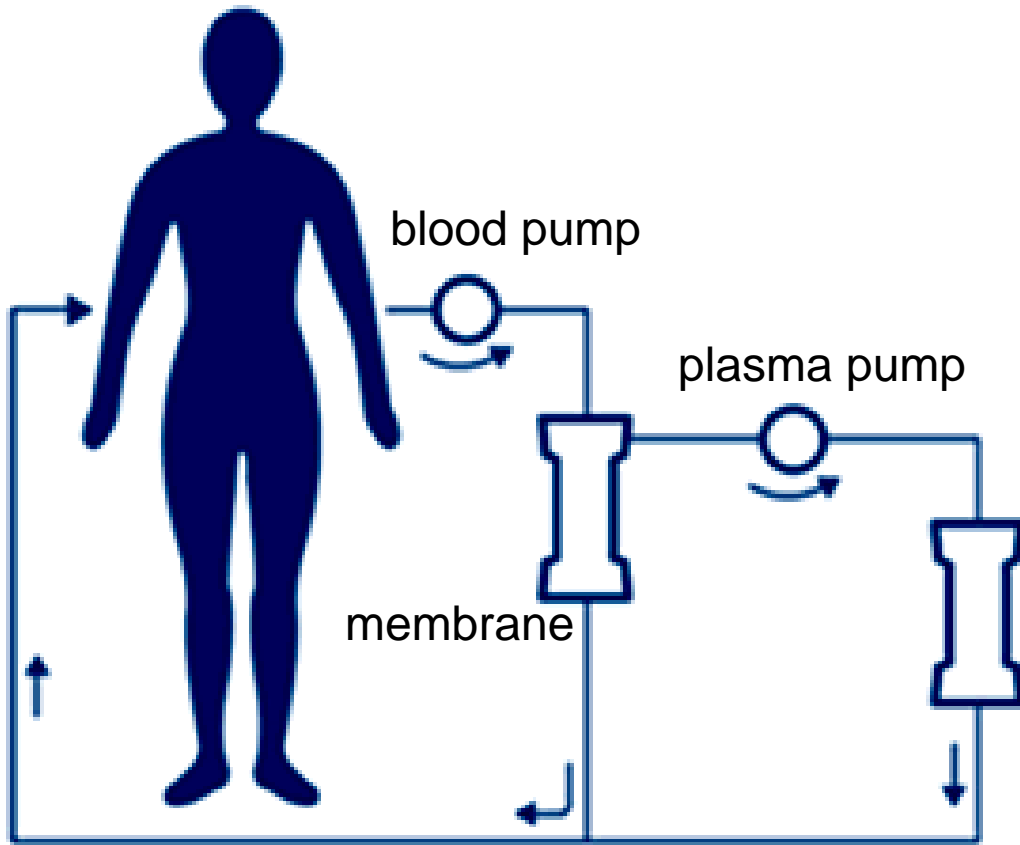
Erythrocytes

# 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

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

# Grading of recommendations

**1: Strong recommendation**

**2: Weak recommendation**

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

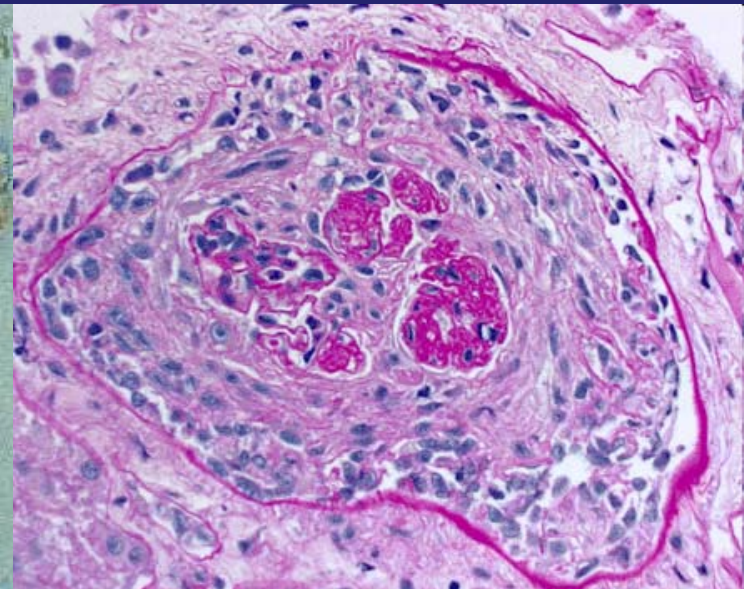
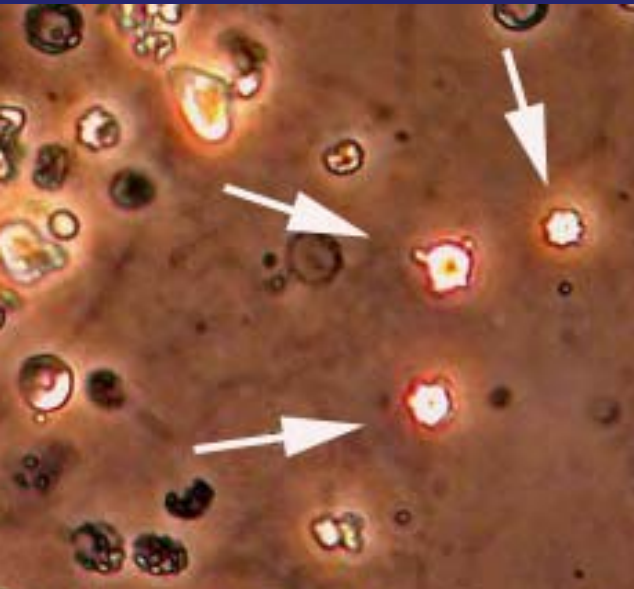
**B: Moderate quality evidence - RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.**

**C: Low quality evidence - Observational studies or case series**

# Rapidly progressive glomerulonephritis

## Clinical features

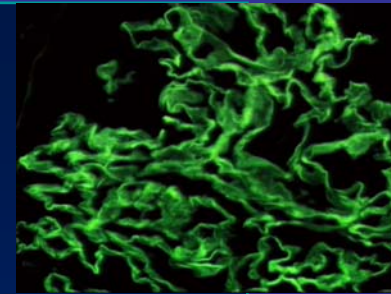
- **Dysmorphic hematuria, active urinary sediment**
- **Proteinuria - nephrotic in 1/3 of patients**
- **Hypertension**
- **Progressive loss of renal function - GFR halves over 3 months**
- **Histology: extracapillary proliferation - crescentic GN**



# Crescentic GN (RPGN)

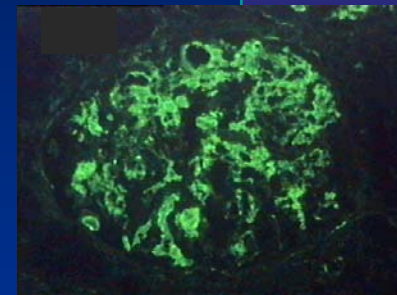
## I. Anti GBM antibodies (linear IF)

- Goodpasture's sy.,
- Renal localized form



## II. Immunecomplex-mediated GN (granular IF)

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



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

- Wegener's granulomatosis
- Microscopic polyangiitis (MPA)
- Churg Strauss sy



# Goodpasture's syndrome

## Pathogenesis

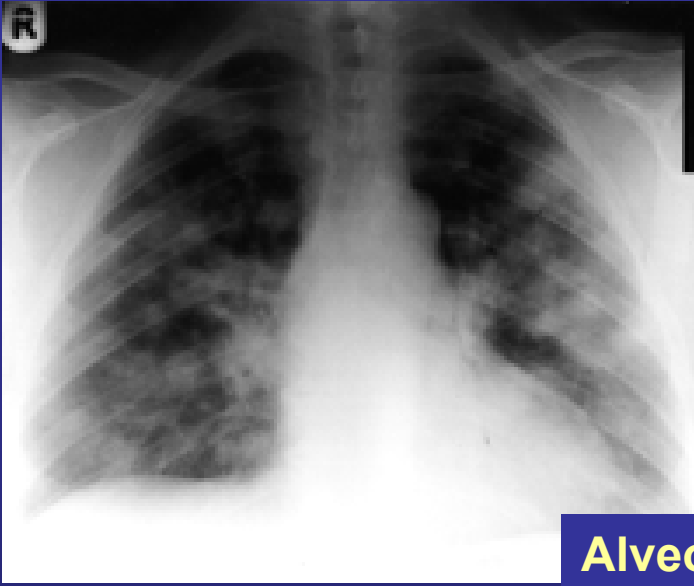
Anti- GBM antibody (Antigene: IV. collagene  $\alpha$ -3 chain NC1 domaine)

Binding to basal membrane - complement activation - inflammation

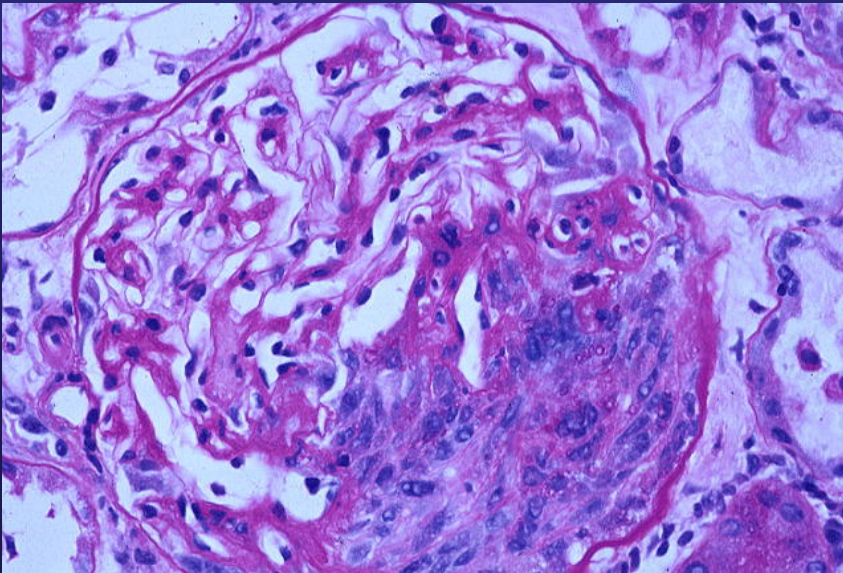
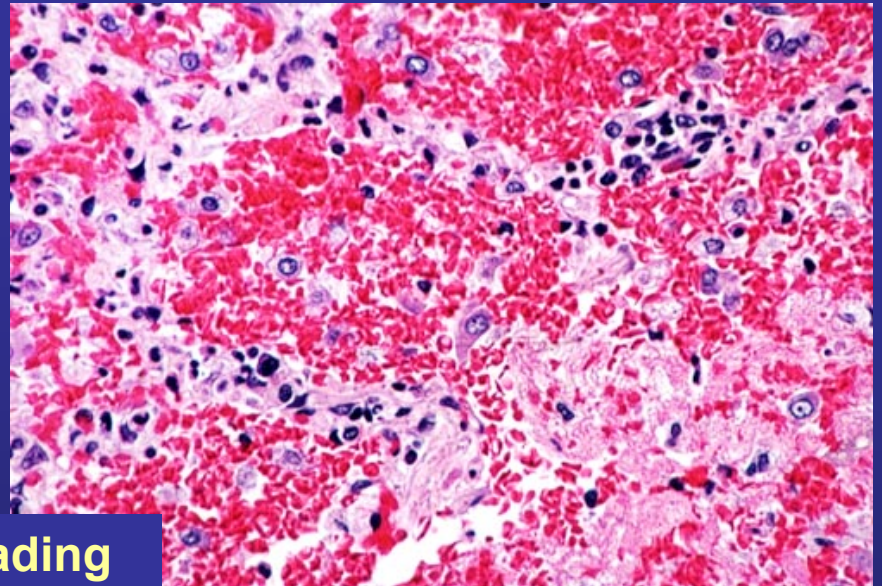
## Clinical features

- 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 does not relapse

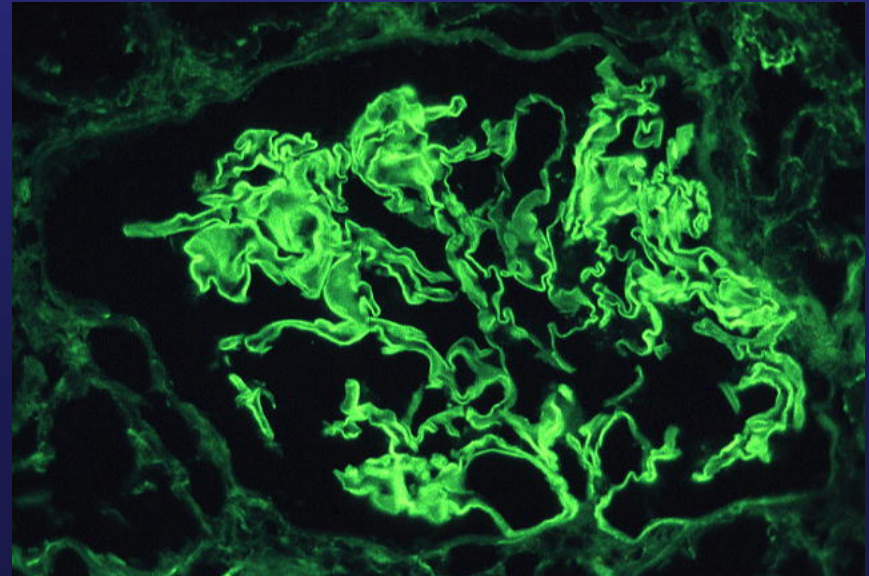
# Goodpasture's syndrome



**Alveolar bleeding**



**Extracapillary proliferative GN**



**Linear IgG immunofluorescence**

# Therapy of Goodpasture's syndrome

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

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

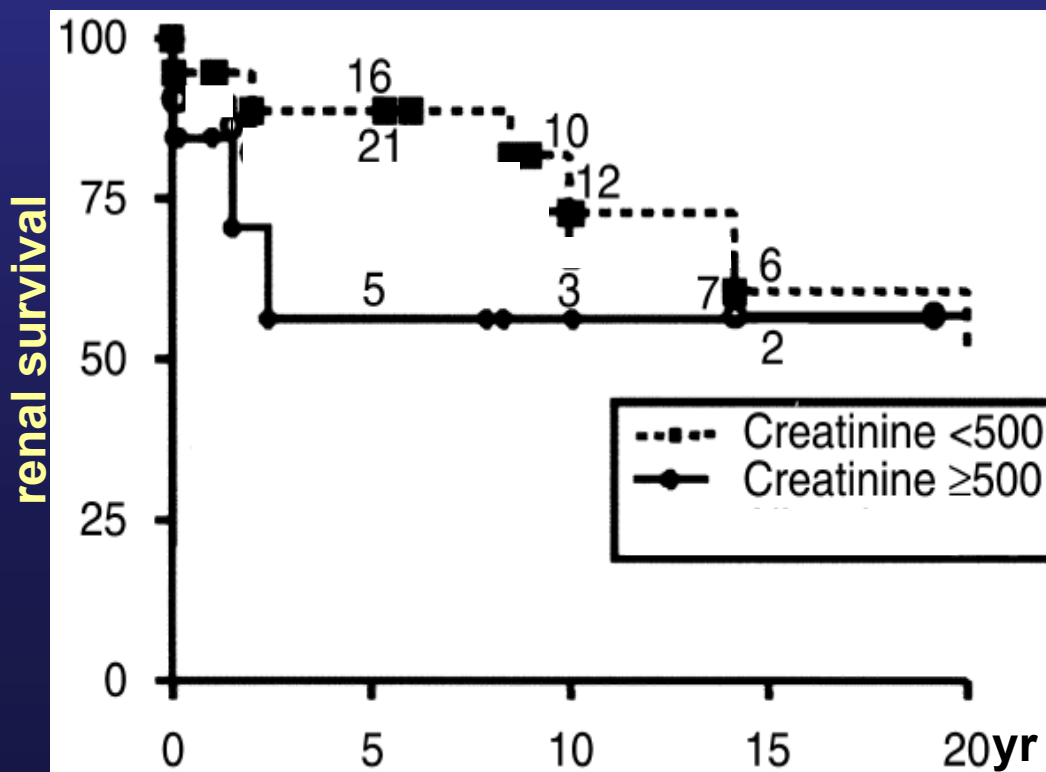
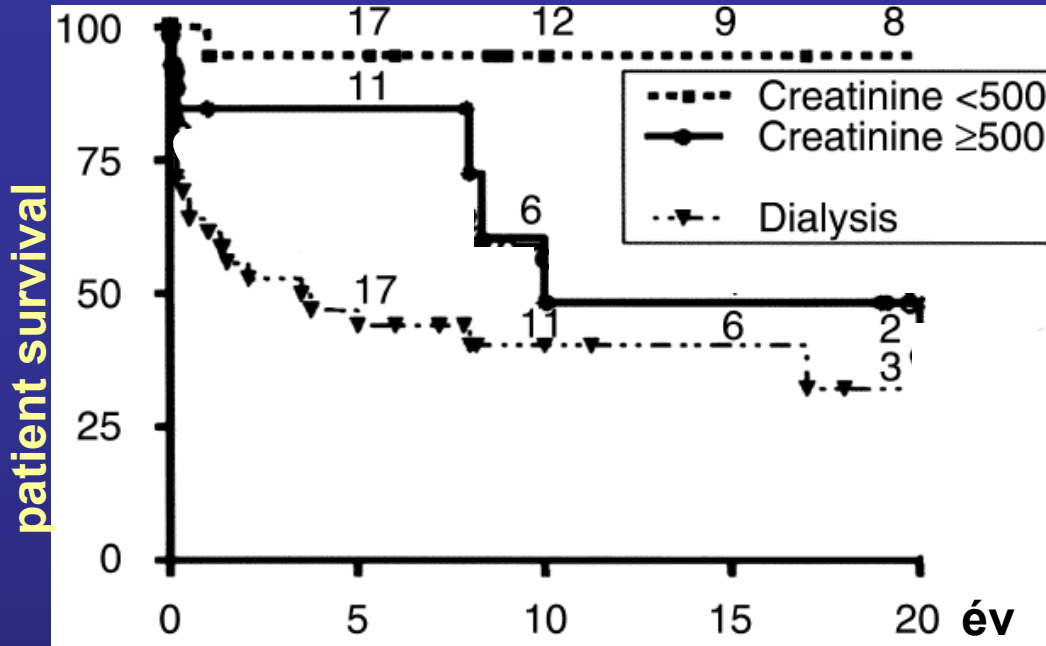
- **Methylprednisone pulse x3, Prednisone 1 mg/kg x 6 months**
- **Cyclophosphamide 2-3 mg/kg x 2-3 months**

Levy JB. Ann Intern Med 2001;134:1033.

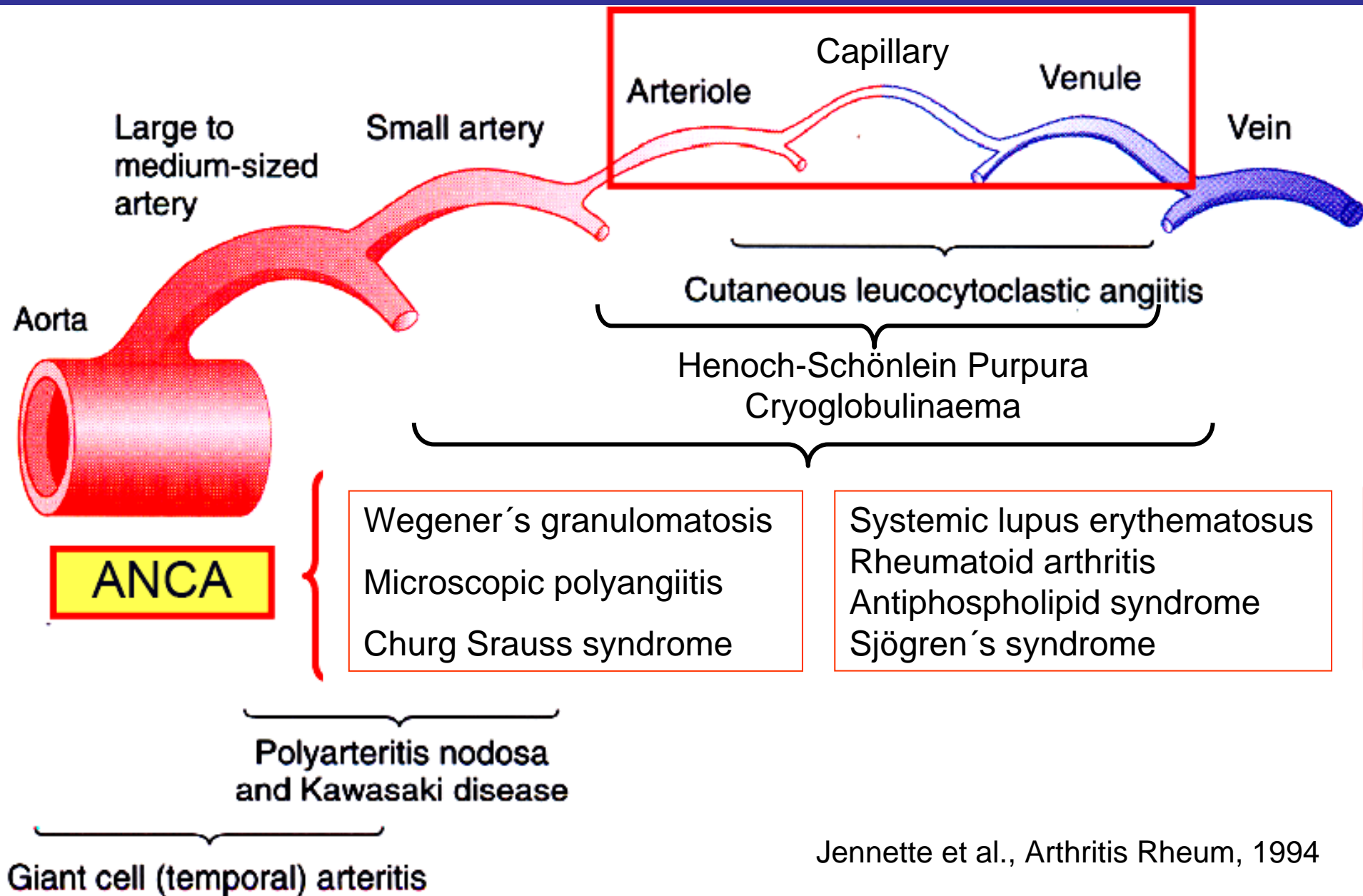
Lazor R. Medicine 2007;86:181.

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

# Prognosis depends on initial renal function in Goodpasture's syndrome

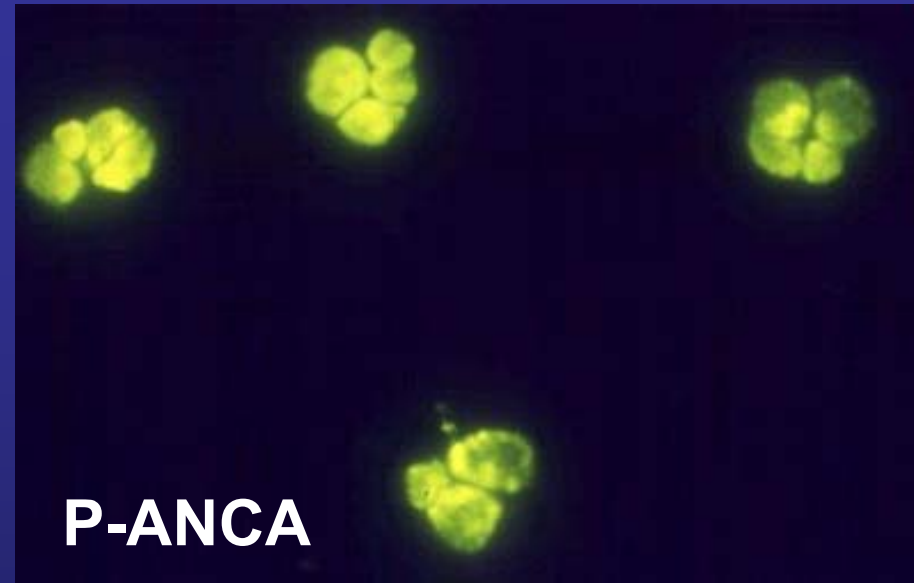
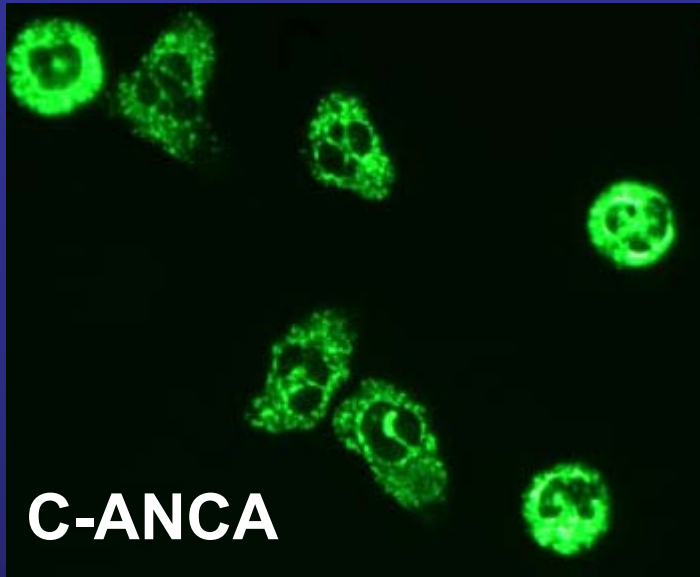


# Systemic vasculitis



# Anti-neutrophyl cytoplasmic antibodies

I I F



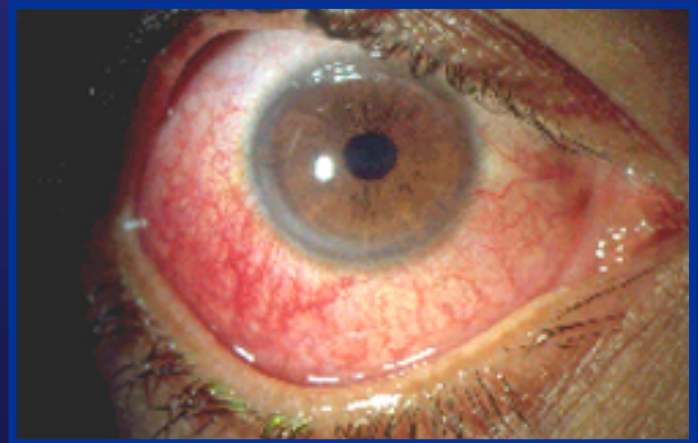
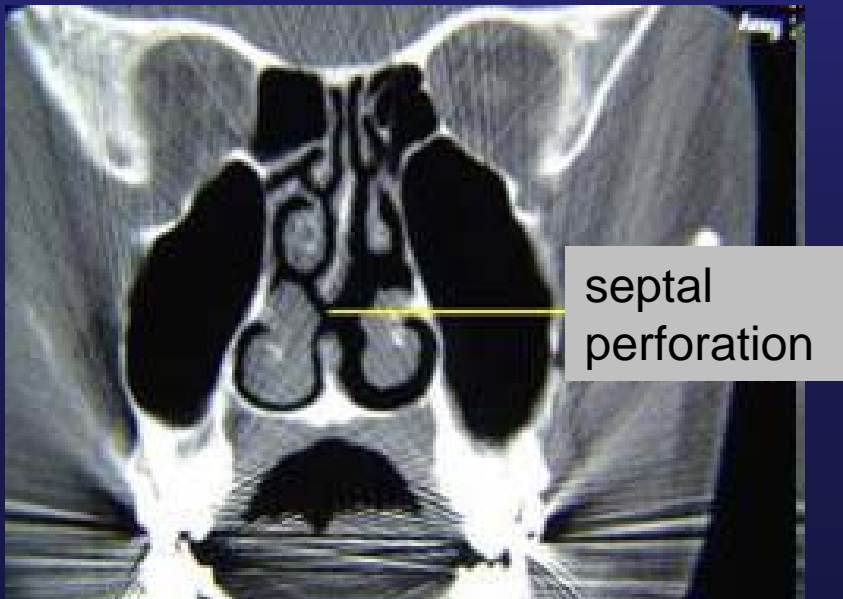
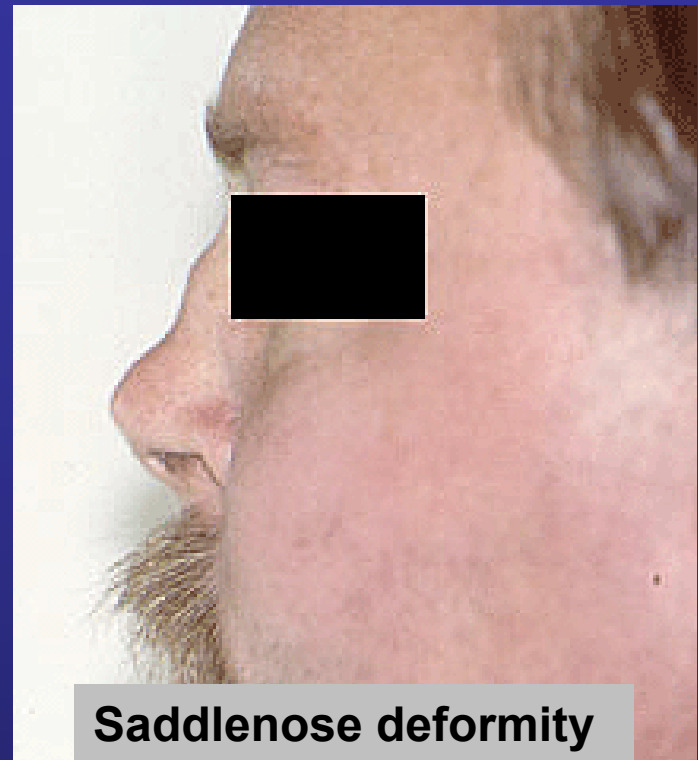
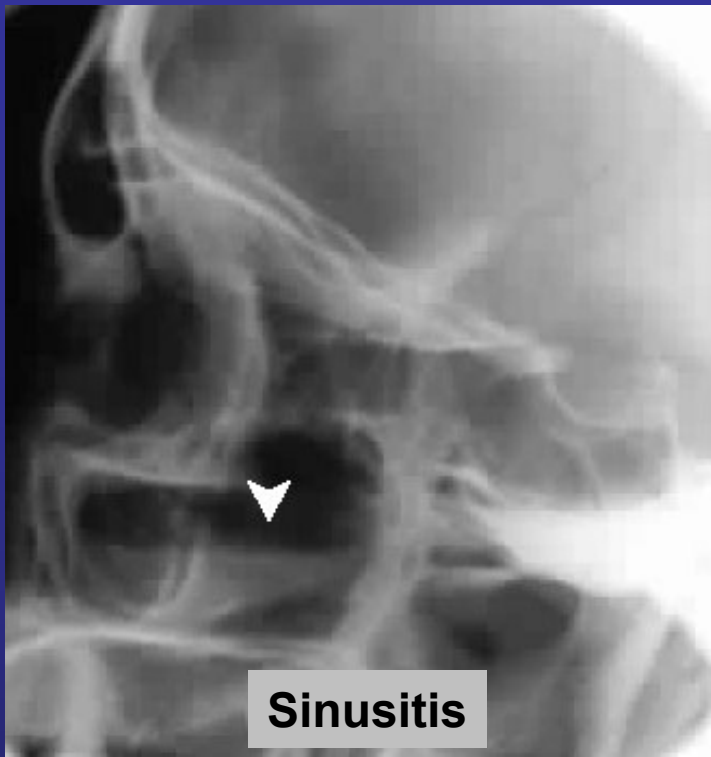
ELISA: anti-Proteinase-3 (PR3)  
antibodies

anti-Myeloperoxidase (MPO)  
antibodies

# Wegener's granulomatosis

## Clinical 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**

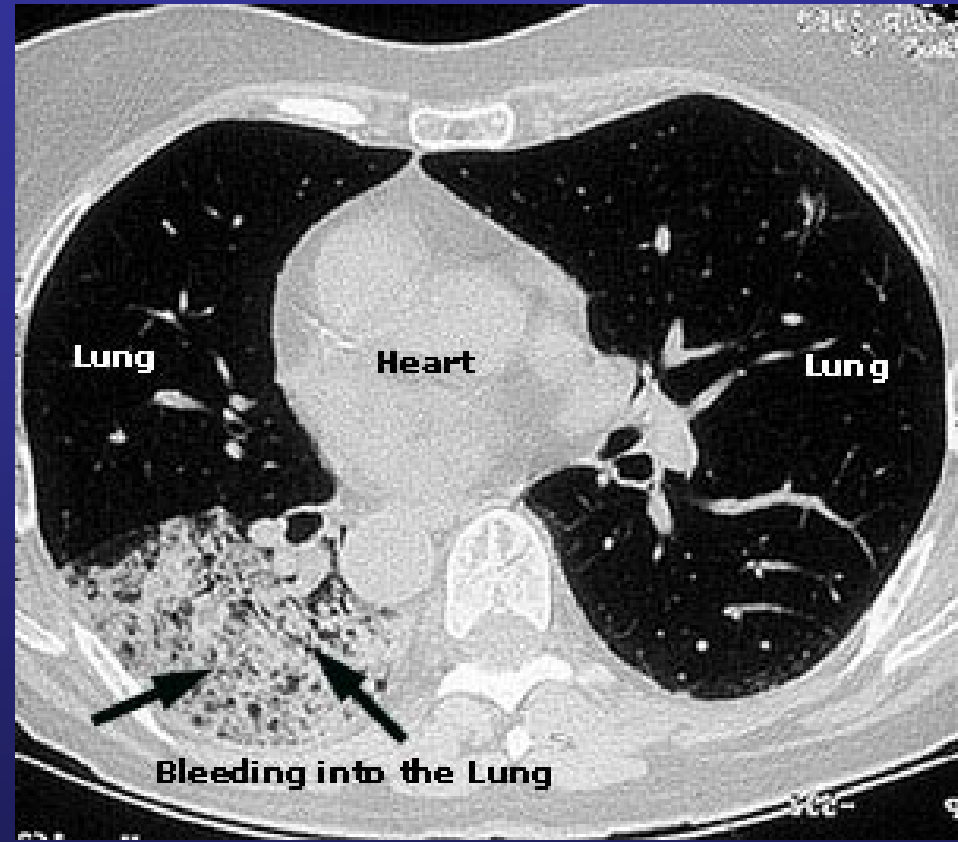
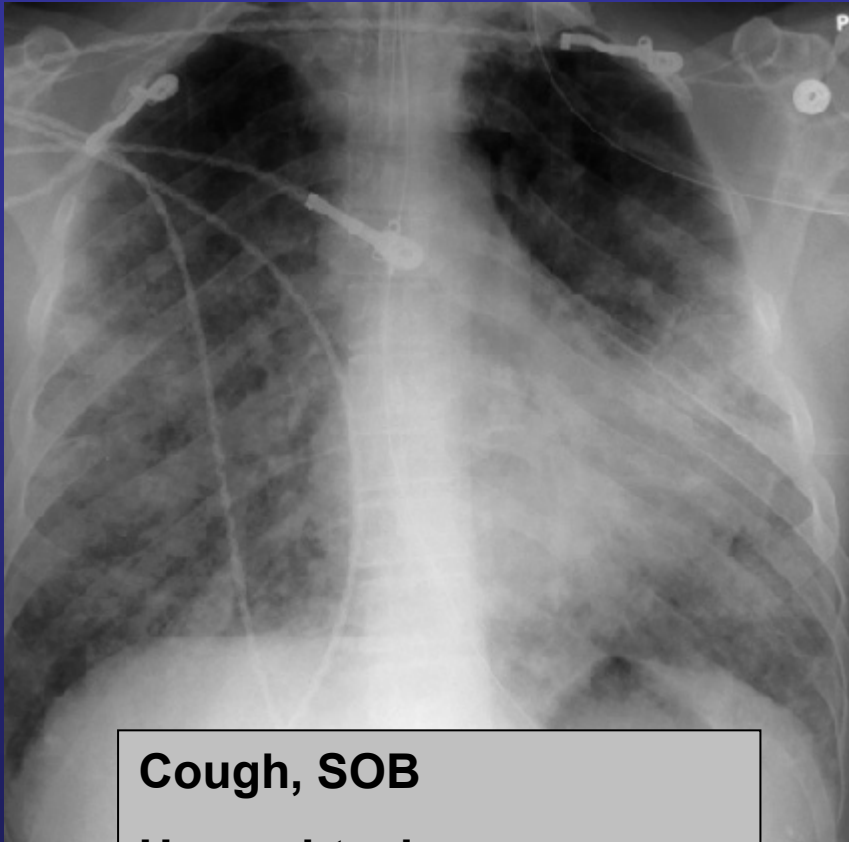


# Palpable purpura: Microscopic (leukocytoclastic) vasculitis



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

# Lower respiratory tract inflammation



**Cough, SOB**

**Hemoptysis**

**Alveolar capillaritis**

**Intraalveolar bleeding**

**Migrating infiltrates**

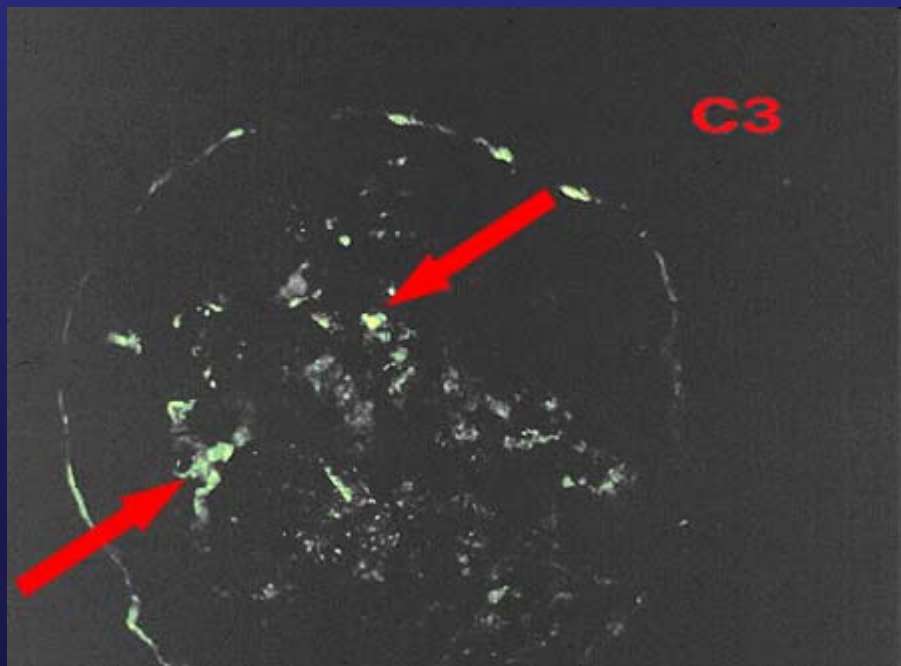
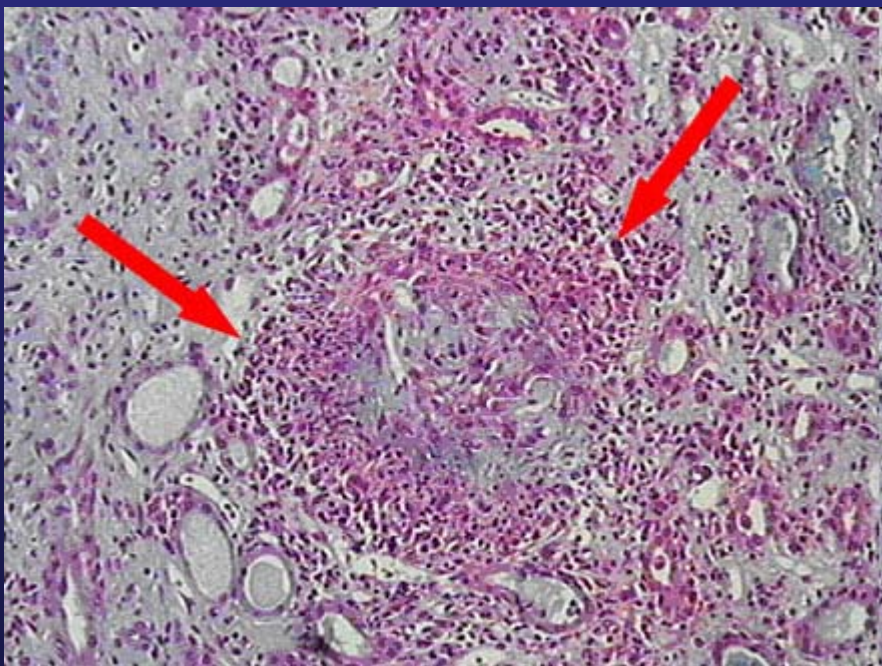
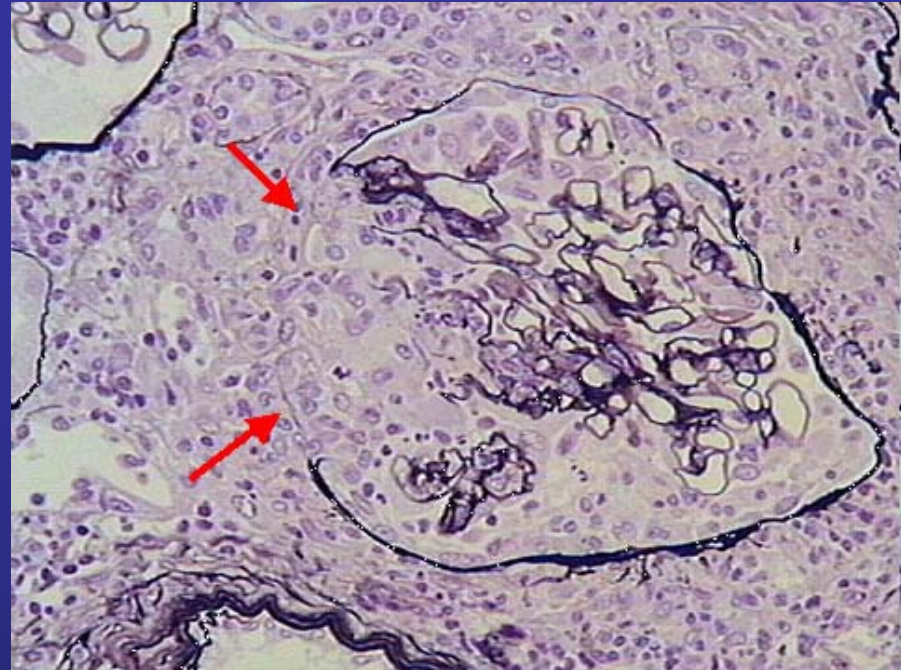
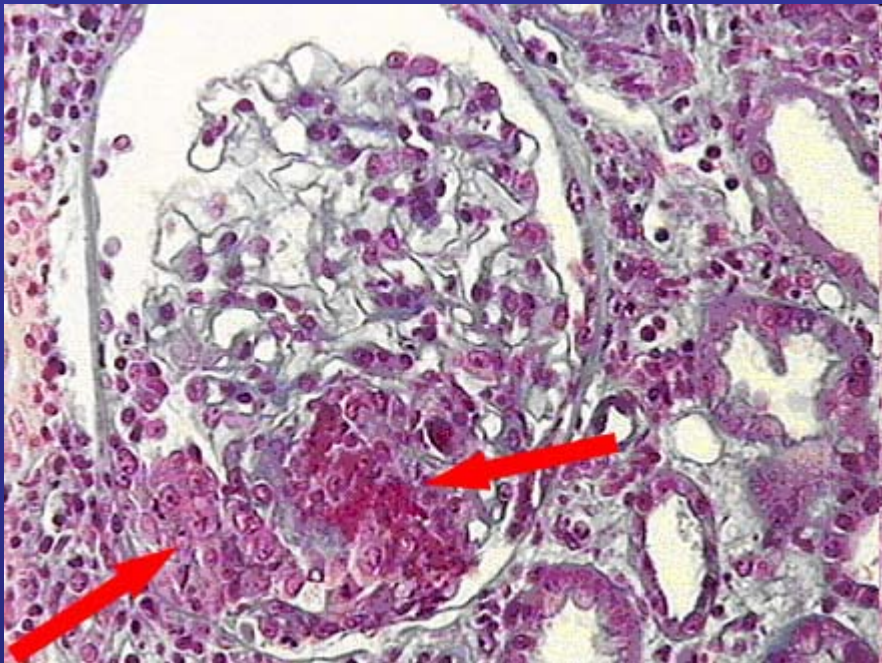
**May resemble pneumonia**

# Microscopic polyangiitis

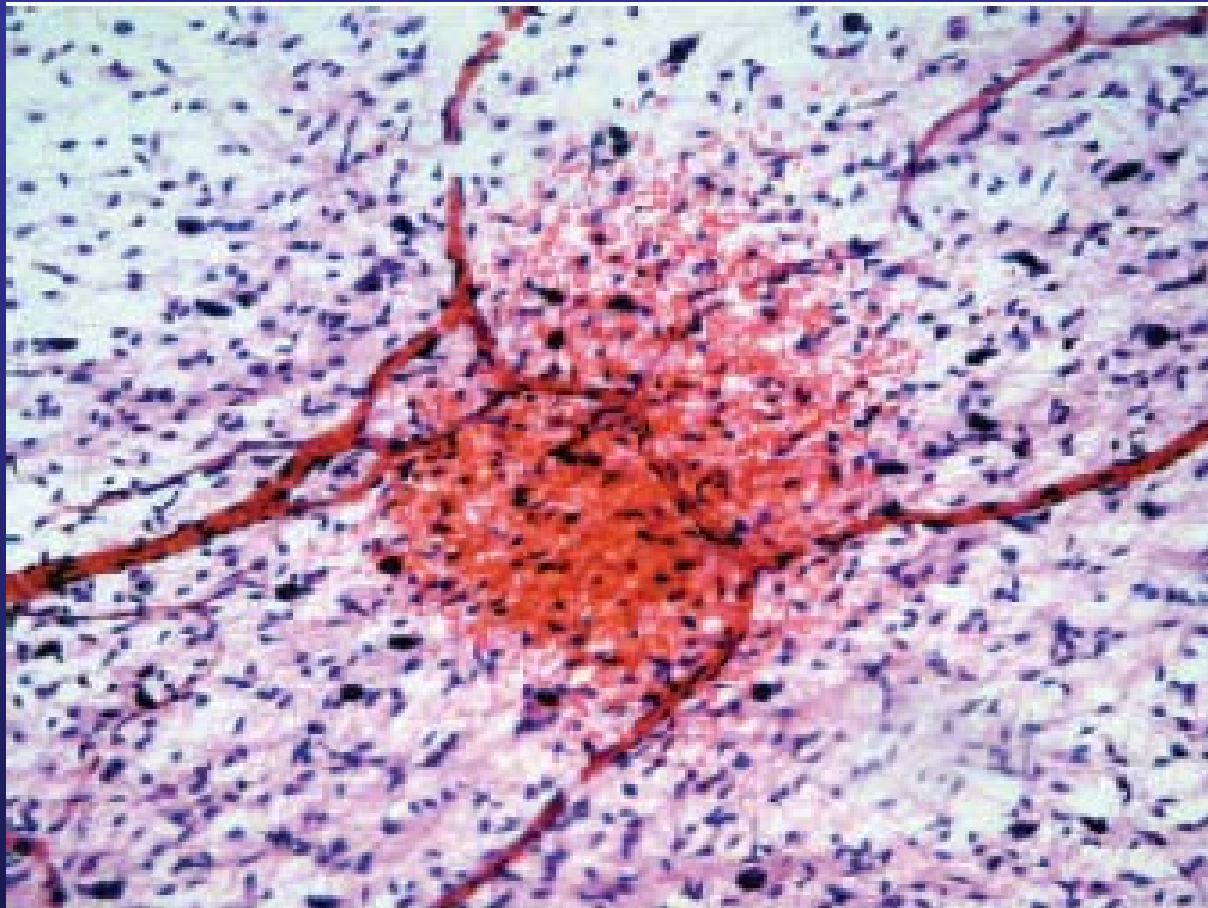
- Less frequent upper respiratory tract inflammation
- No granuloma
- Serology: P-ANCA - anti myeloperoxidase antibody

# Churg-Strauss syndrome

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

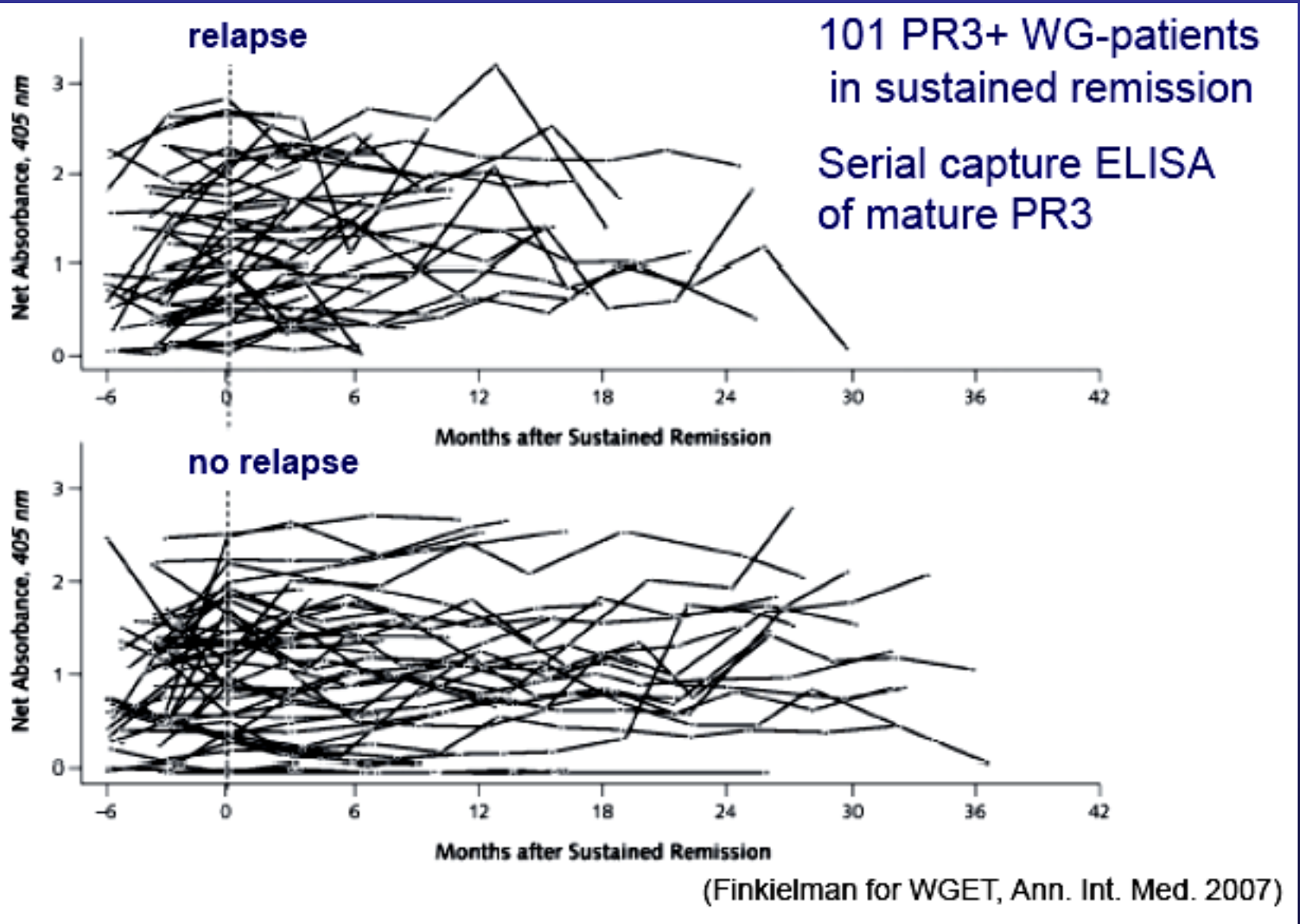


# ANCA plays a role in the pathogenesis of microscopic vasculitis



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

# ANCA titer and relapse rate



# 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 <i>Staphylococcus aureus</i> *	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 $\geq$ 20 mg/day for <2.75 months	RH 2.41
Co-trimoxazole as adjuvant to remission maintenance therapy	RR 0.32

# Clinical trials in ANCA associated vasculitis

**Induction**



3 - 6 mo.



**Maintenance**



NORAM: MTX vs CYC

MEPEX: PE vs MP

CYCLOPS: CYC iv vs oral

WEGET: Etanercept vs placebo

SOLUTION: ATG

MYCYC: MMF Vs CYC

RITUXIVAS

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

# 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 **3**
- Sumetrolim (PCP prophylaxis) (?)
- Plasma exchange: 

	Indication category	
Dialysis dependence (recent)	I	<b>1A</b>
Diffuse alveolar hemorrhage (DAH)	I	<b>1C</b>
Dialysis independence, no DAH	III	<b>2C</b>

### 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

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

# Methylprednisolone *versus* Plasma Exchange (MEPEX) trial

- N=100, randomized design
- ANCA-associated vasculitis
- Necrotizing, crescentic GN
- creatinine > 500  $\mu\text{mol/l}$ , 2/3: on dialysis, 1/3: predialysis
- Therapy:

Methylprednisolon 1000 mg/day x3

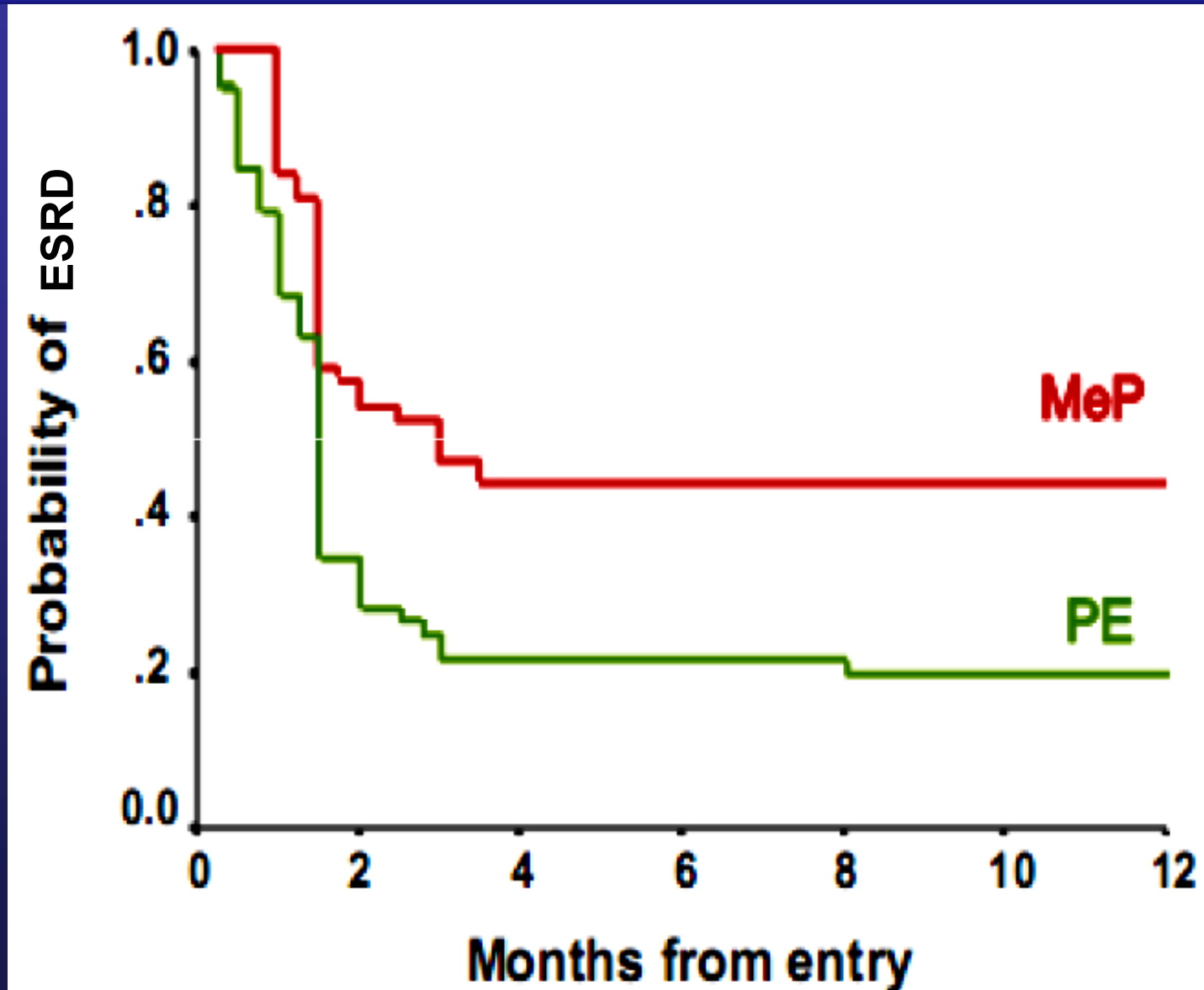
vs

Plazma exchange 60 ml/kg x 7

Methylprednisolon 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



# Immune-complex-mediated RPGN

- **IgA nephropathy**
- **Henoch Schönlein purpura**
- **Primary membranoproliferative GN**  
C4NeF, C3NeF: antibodies that stabilize classic or alternative C3 convertases
- **Lupus nephritis**

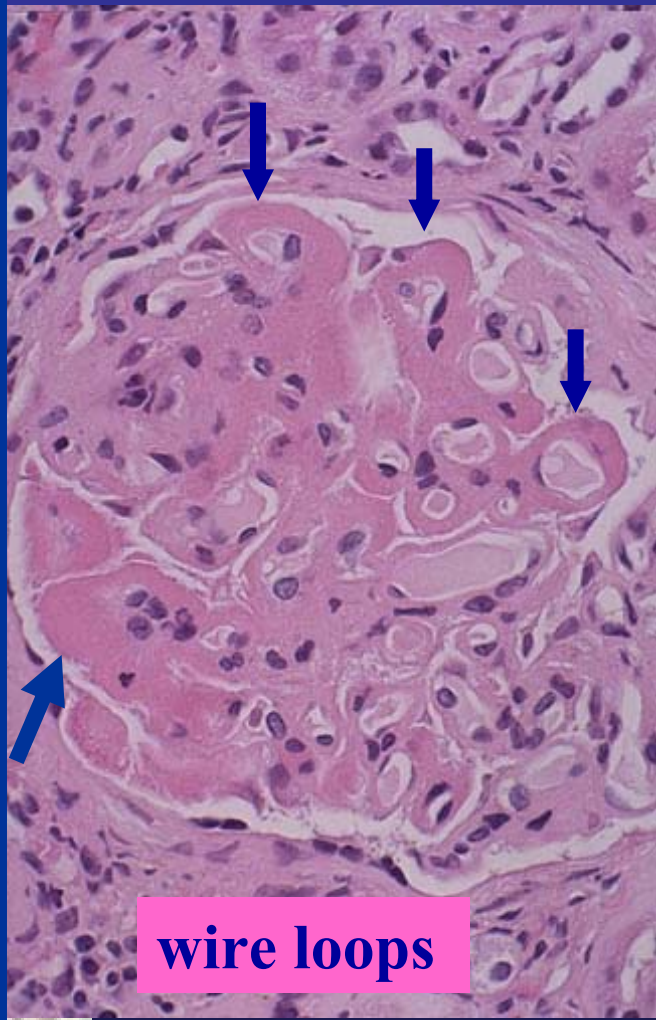
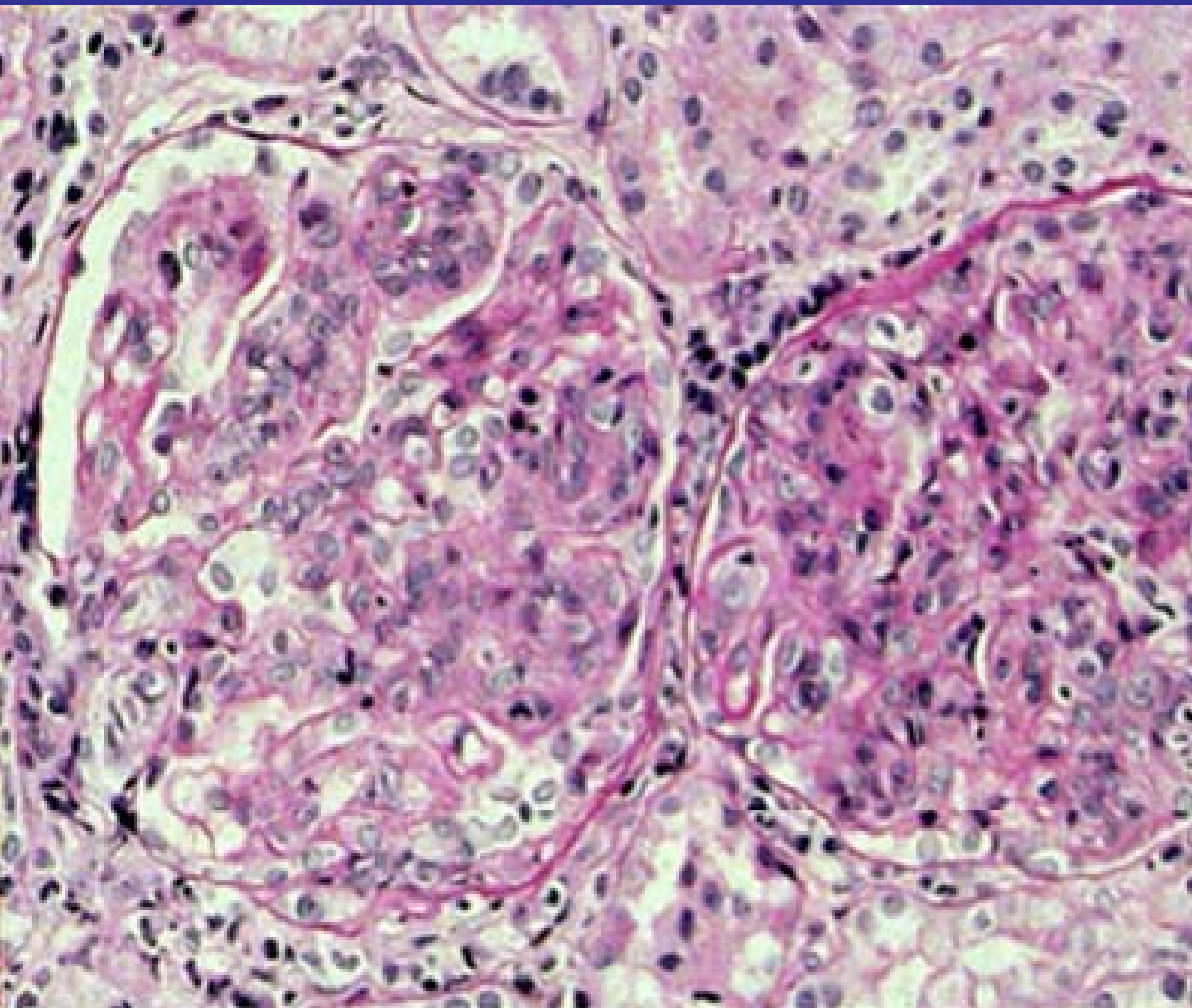
## WHO Class

## Renal histology

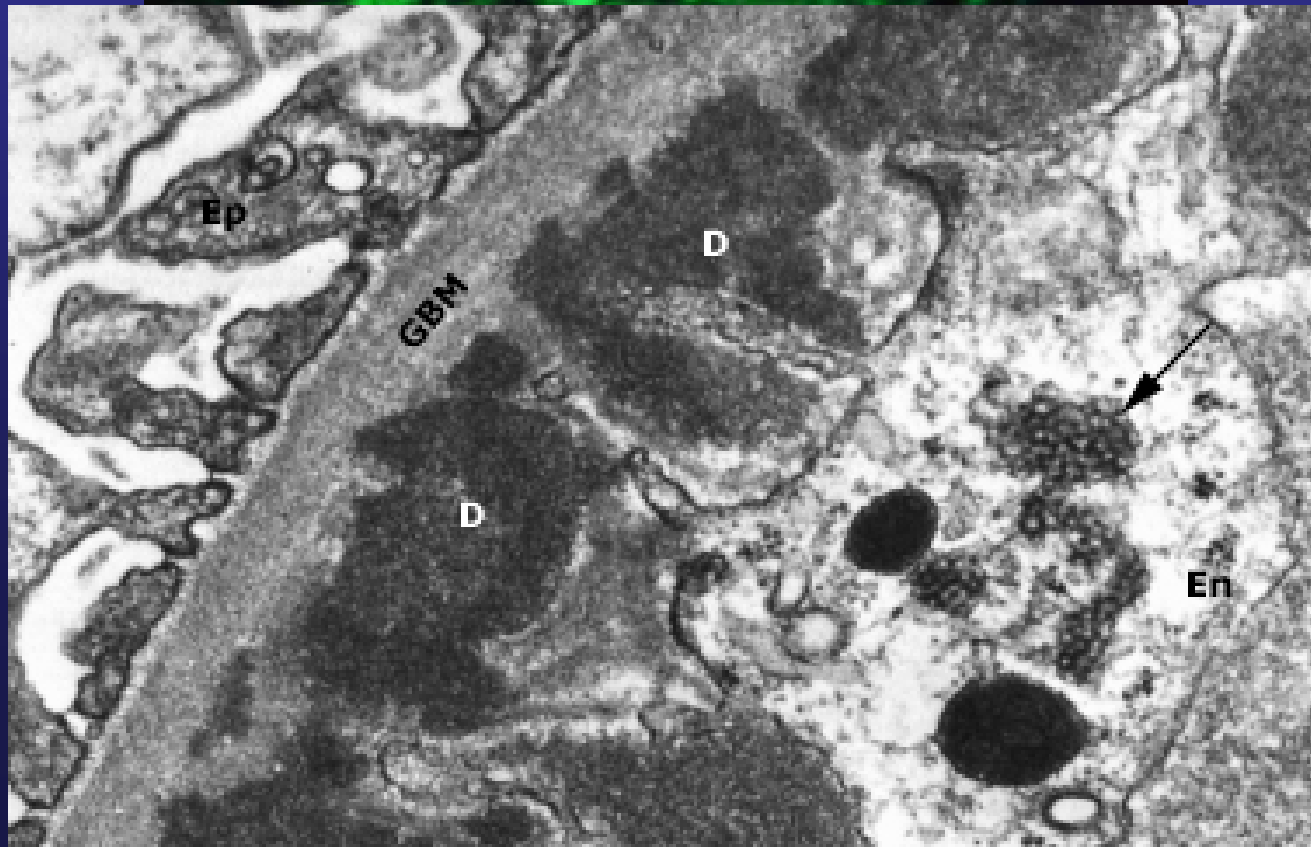
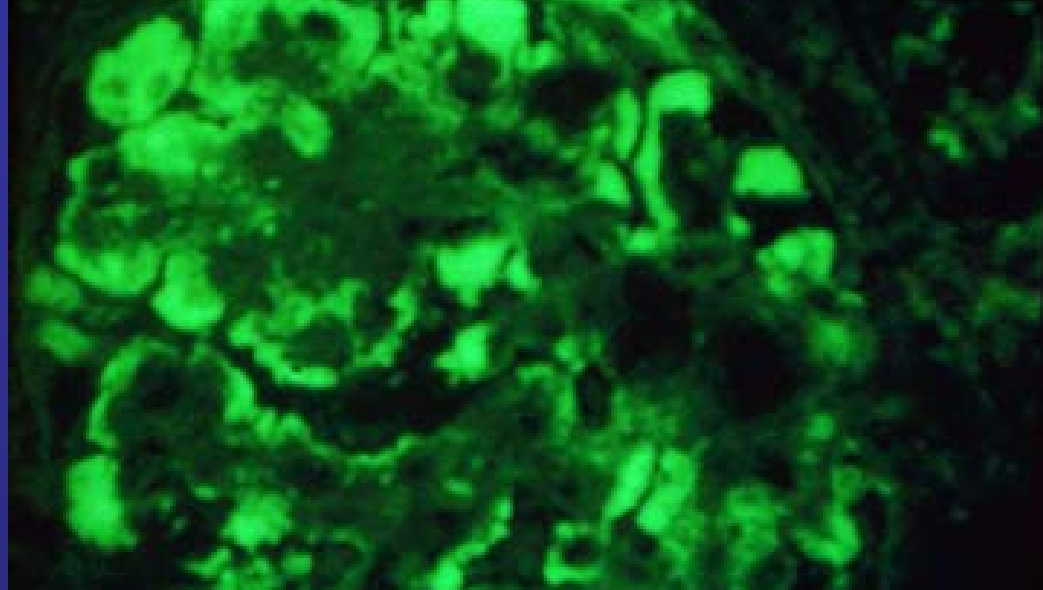
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I.	Minimal mesangial
II.	Mesangial proliferative
III.	Focal proliferative
IV.	Diffuse proliferative
V.	Membranous
VI.	Advanced sclerosing

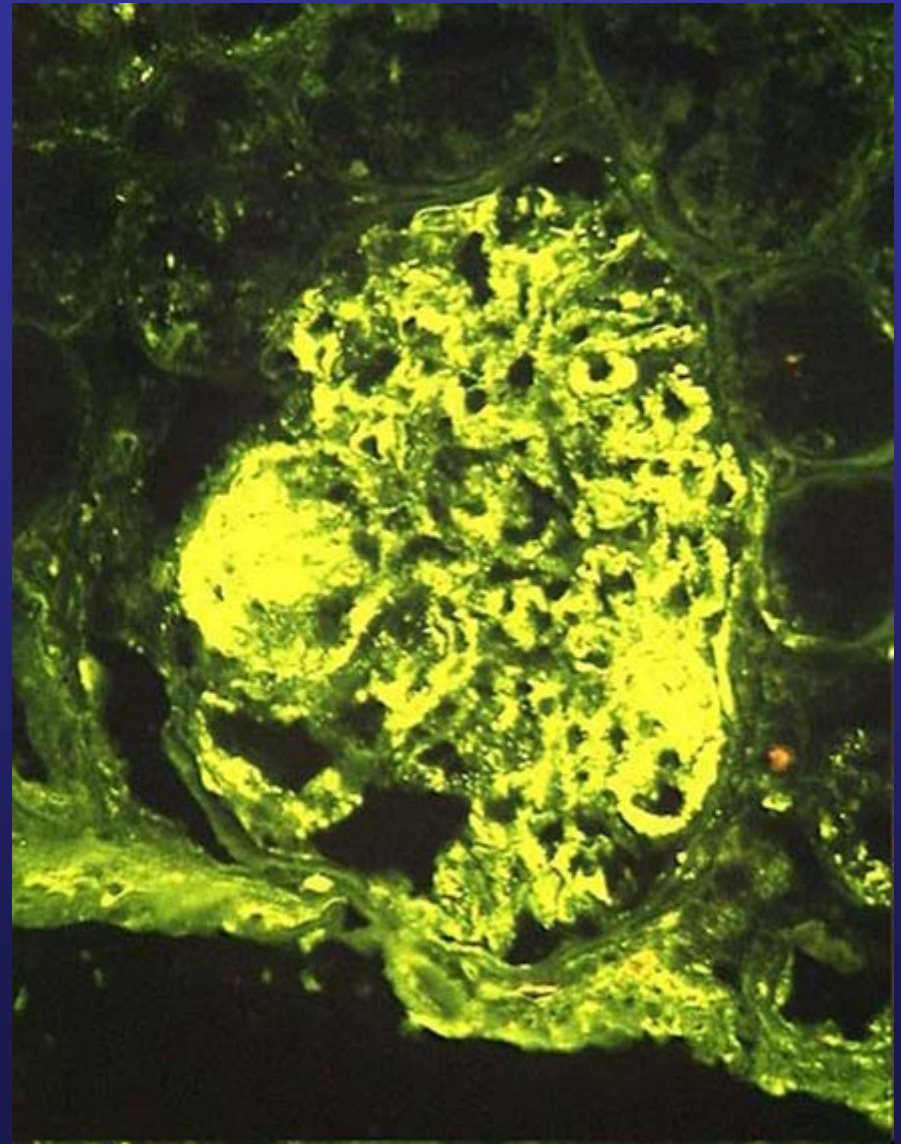
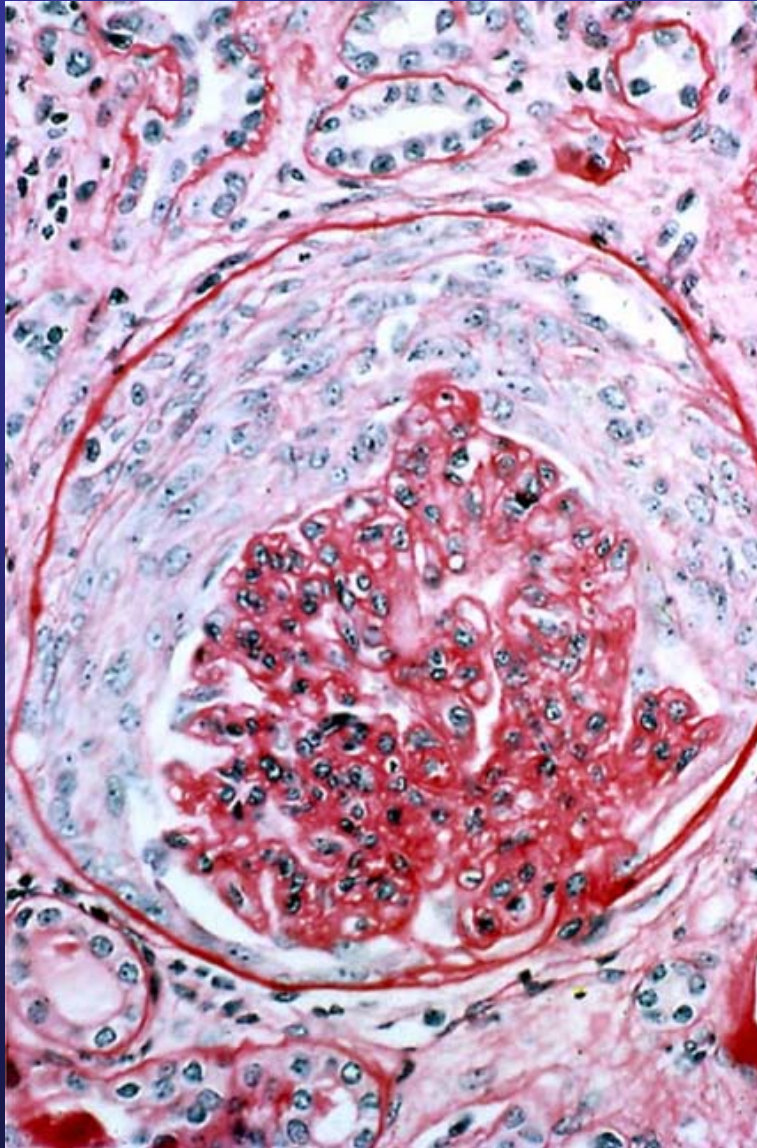
# IV. Diffuse proliferative lupus nephritis



wire loops



# Crescentic glomerulonephritis



**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**

<b>Plasma exchange + cytotoxics v cytotoxics</b>	<b>No. of studies</b>	<b>NN</b>	<b>RR</b>	<b>95% CI</b>
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

# PEX in immunecomplex RPGN and SLE

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

# Therapy of severe focal proliferative and diffuse proliferative lupus nephritis

## Remission induction

### NIH protocol

- Solu-Medrol 1 g/m<sup>2</sup> iv, monthly x at least 1yr
  - Prednisone (metyl-prednisone) 0,5 mg/kg/d → 0,25 mg/kg qOD
  - Cyclophosphamide  
0,5-1 g/ m<sup>2</sup> monthly x 6 mo., then 3 monthly x 24 mo.
- 
- 25-35%: major infection
  - 50% of women : amenorrhoea

# Therapy of severe focal proliferative and diffuse proliferative lupus nephritis

## Euro-lupus trial

- Solu-Medrol 750 mg iv for 3 days
- Metyl-prednisone 0,5 mg/kg/day → 0,25 mg/kg qOD
- Cyclophosphamide
  - 500 mg iv 2 weekly x 6
  - vs
  - 0,5 g/m<sup>2</sup>/mo x 6 ( ↑ by 250 mg), then 3 monthly x 2
- Maintenance: Azathioprin 2 mg/kg/day x 30 months + low dose MP

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

## Cumulative CYC dose

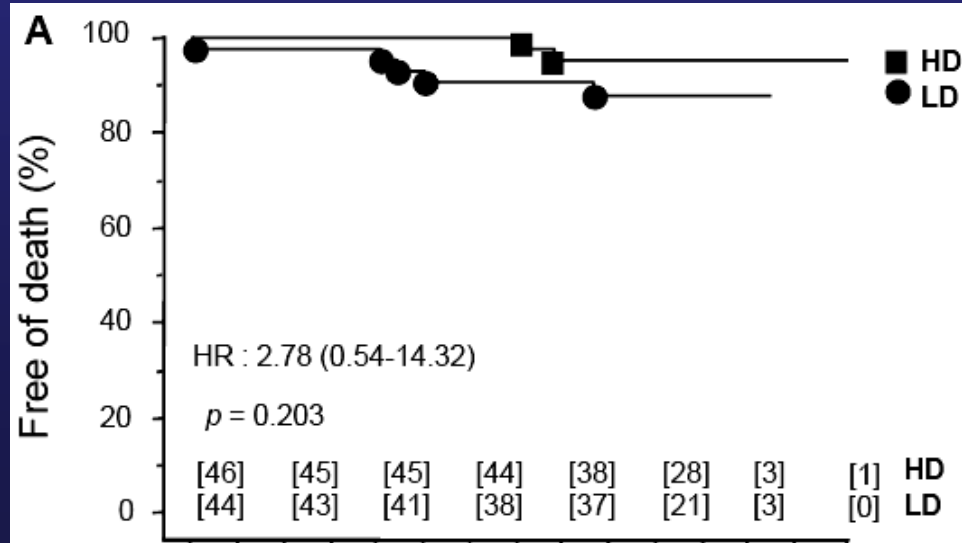
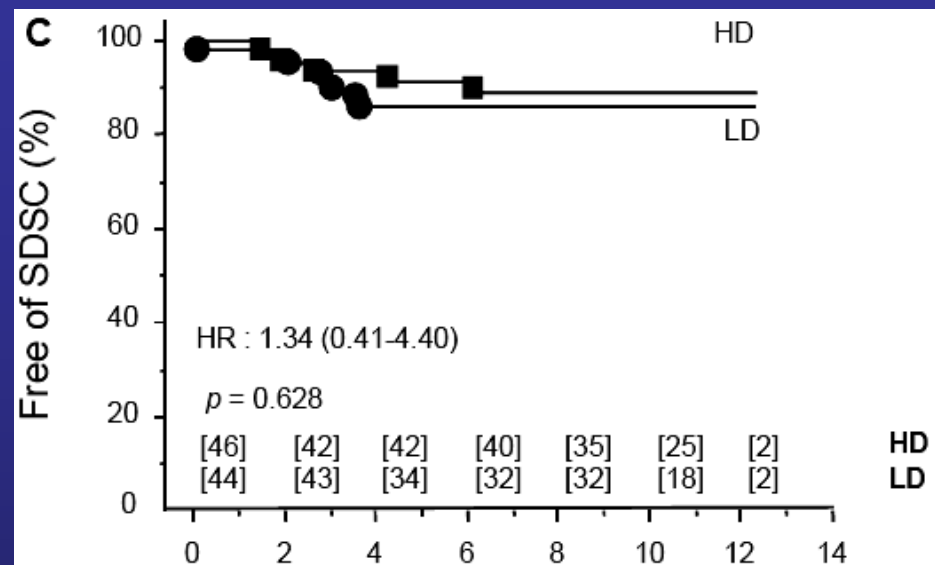
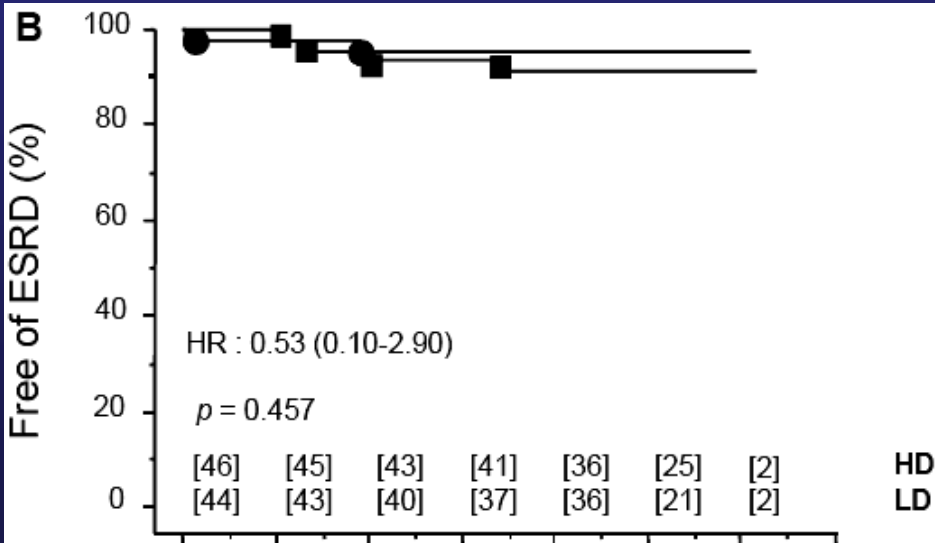
**HD**

**LD**

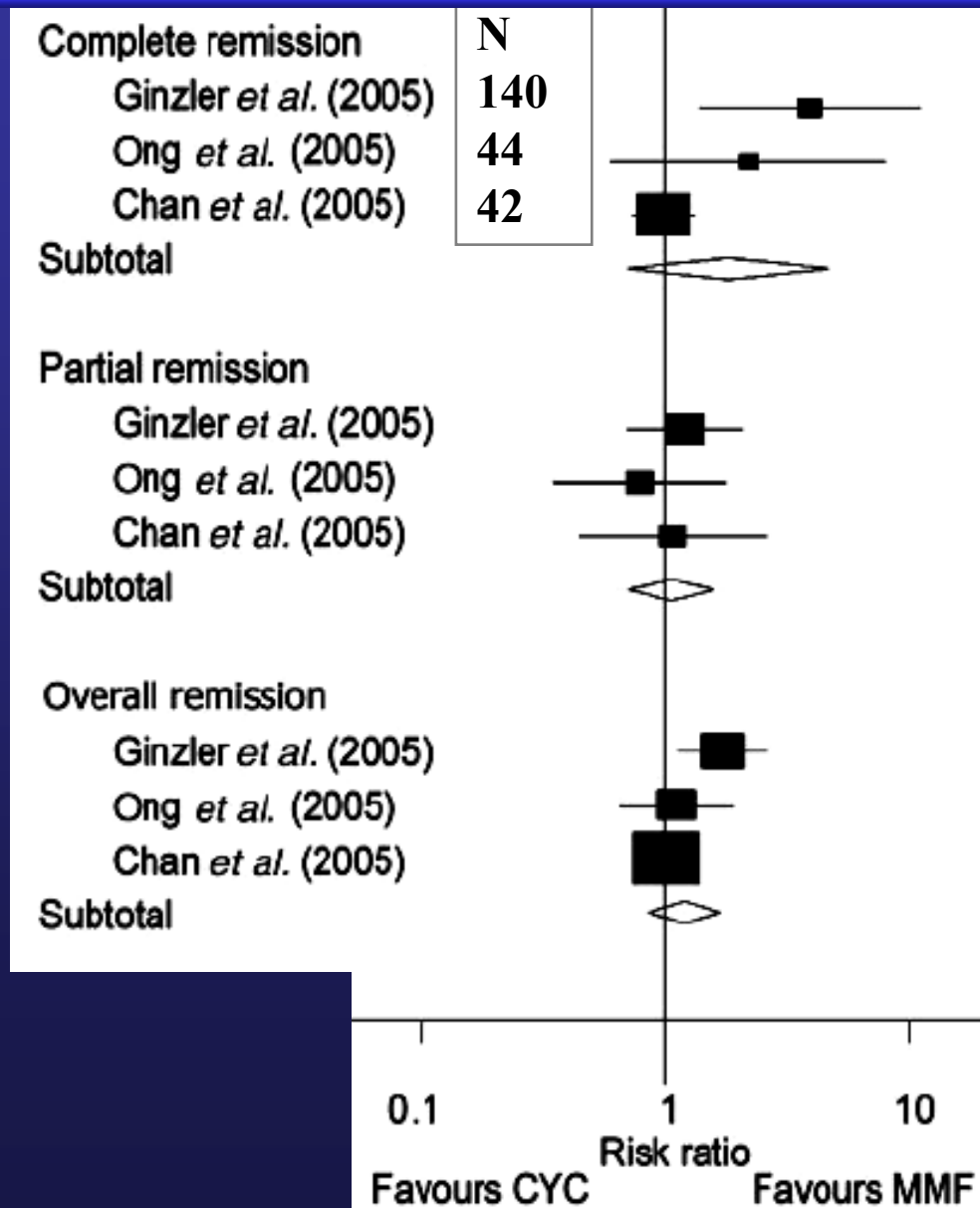
**9,5 g**

**5,5 g**

**2/3: 3g**



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



**MMF**

**2-3 g/day x 6-12 mo**

**CYC**

**Iv pulse CYC**

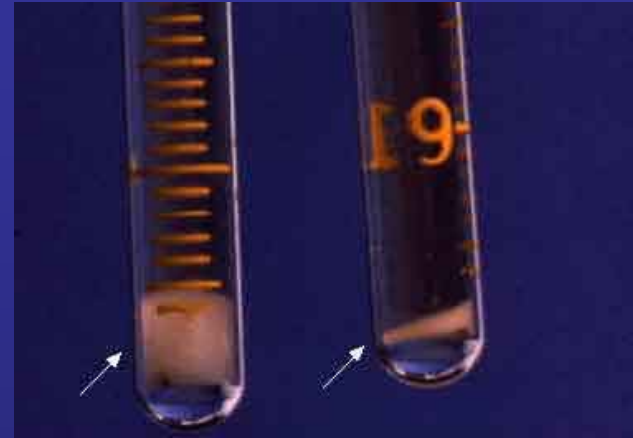
**(Ginzler, Ong)**

**Oral CYC (Chan)**

# Cryoglobulinemia



Cryoglobulin, 4 °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

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

Type I.

Type II.-III.

## Diagnosis

Low complement levels (type II, III)

Screening: separate serum at 37 °C - keep serum at 4 °C x 5 days

Type II-III: Rheumatoid factor

Quantitative measurement: no close relationship with symptoms

Characterization: immunofixation

# Hyperviscosity

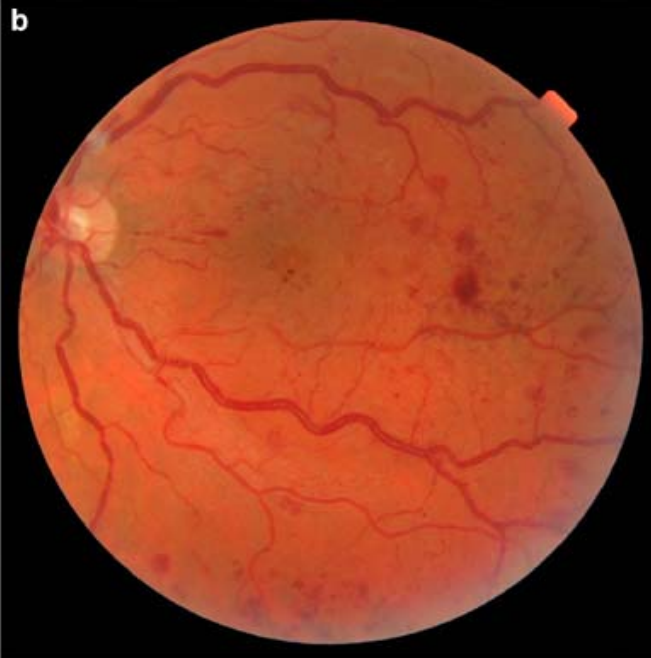
- Mucous membrane bleeding
- Visual disturbances, retinopathy
- Tinnitus, hearing loss
- Headache, vertigo, nystagmus,
- Somnolency
- Muscle cramps
- Heart failure, respiratory failure
- Coma



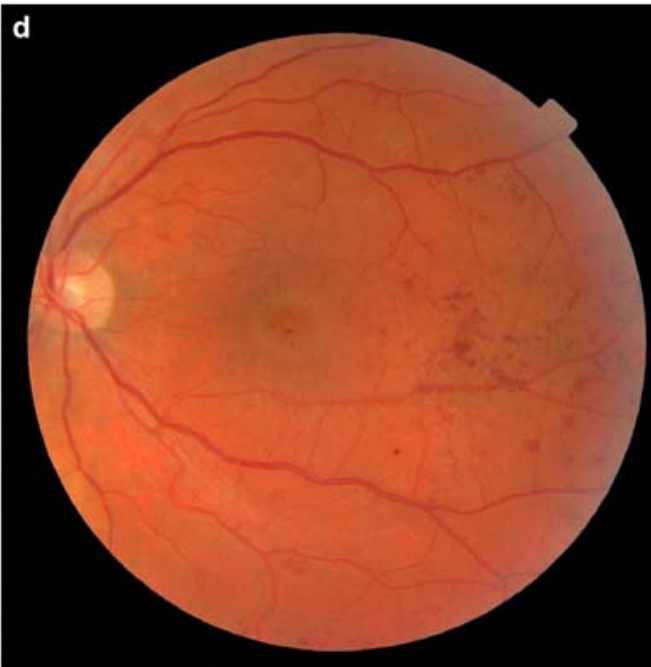
Ostwald  
viscometer

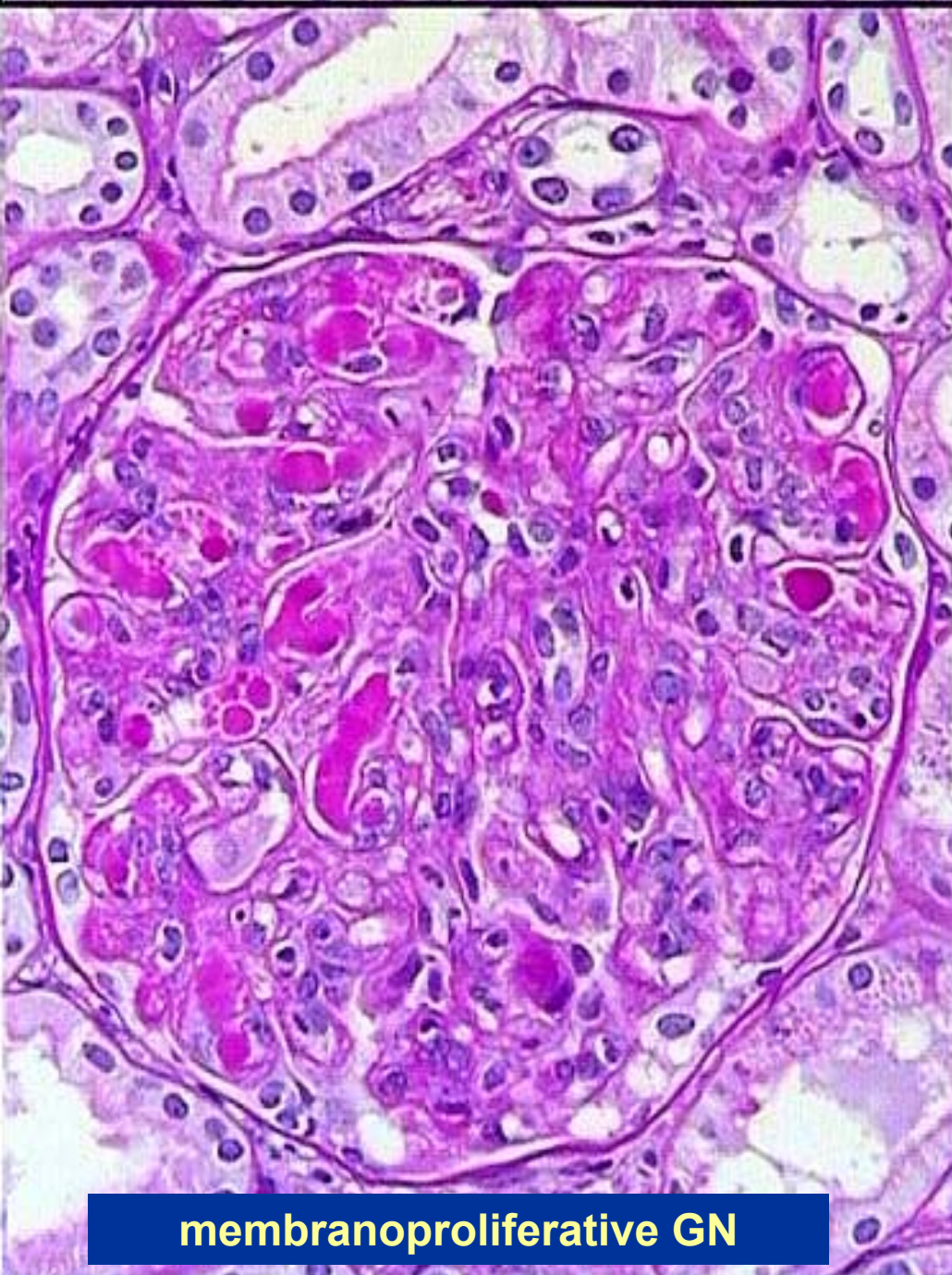
**Waldenstöm's  
macroglobulinemia**

**Pre - PEX**

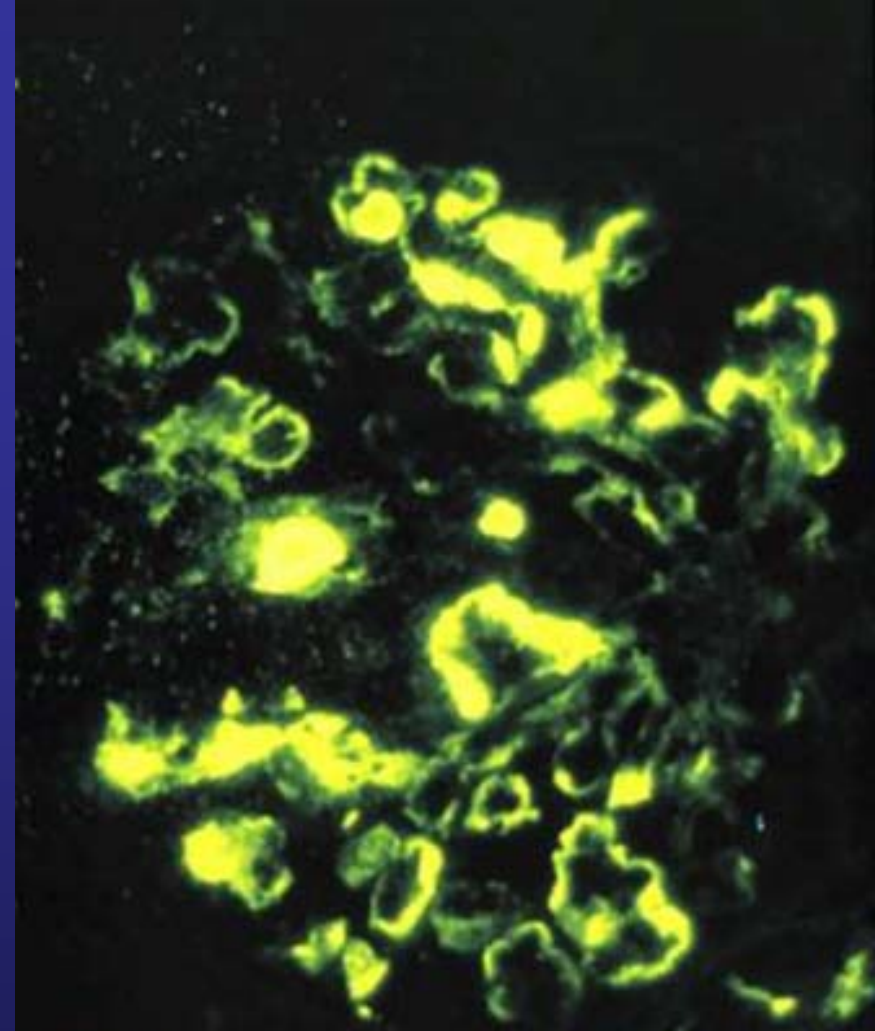


**Post - PEX**

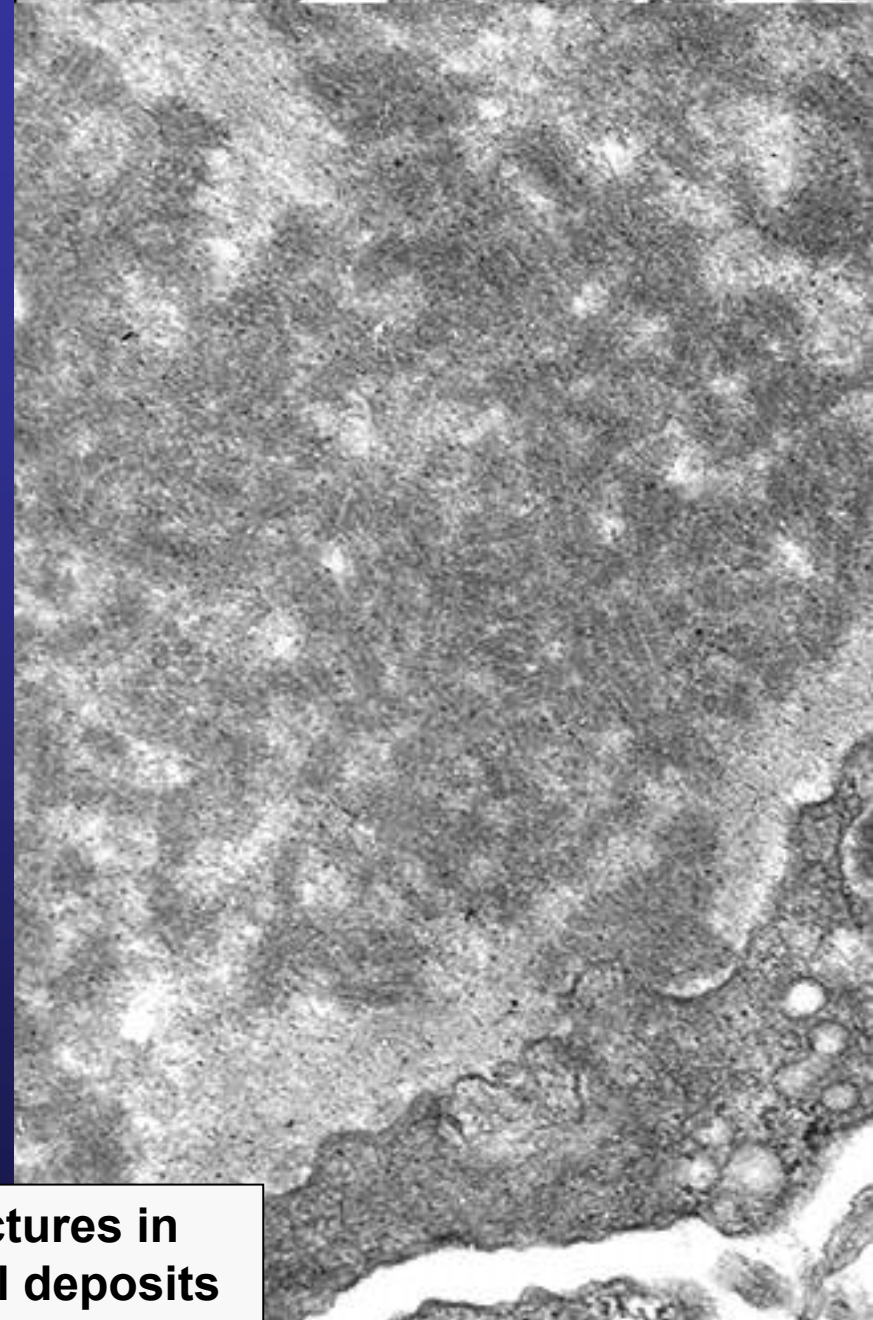
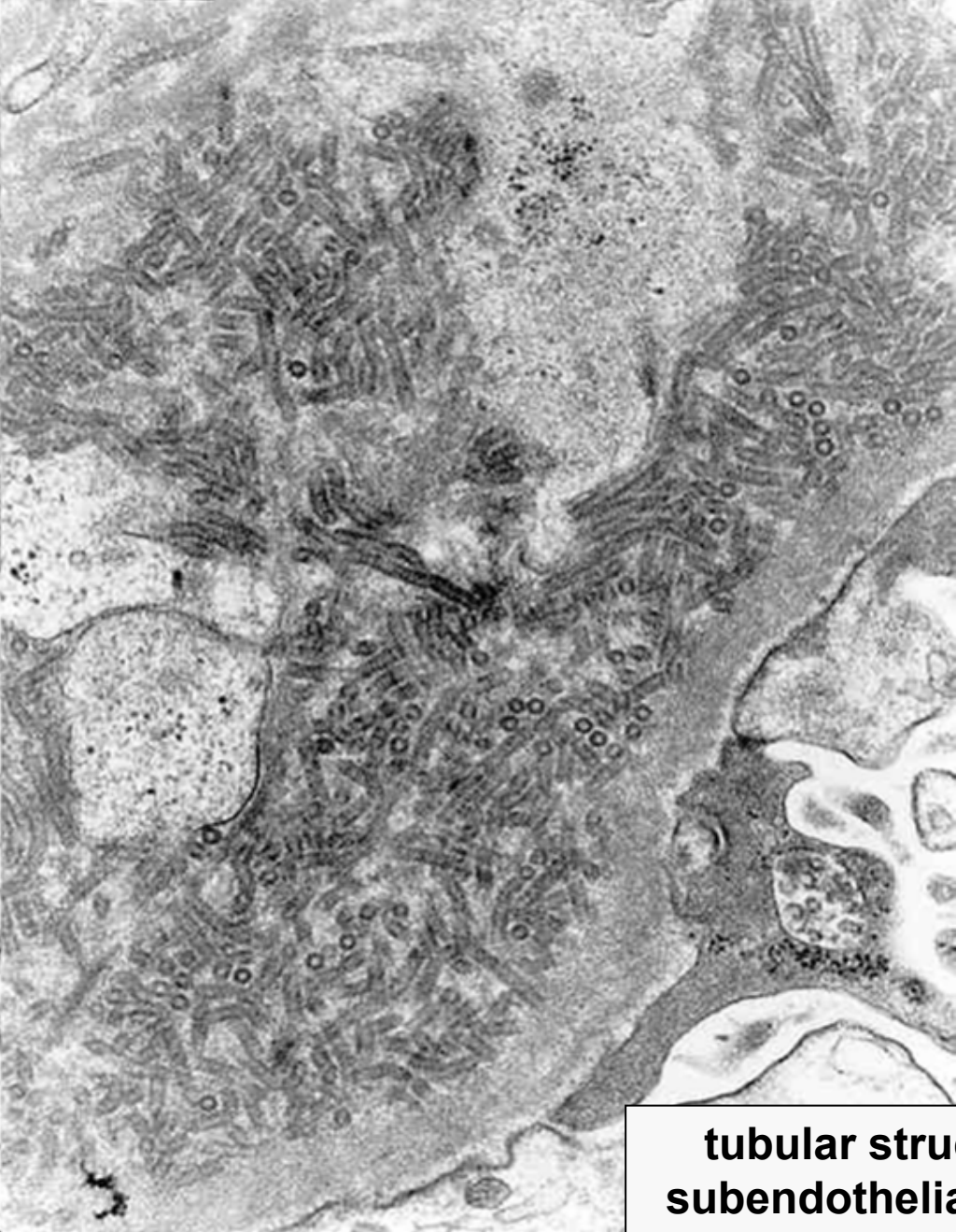




**membranoproliferative GN**



**globular accumulations of  
cryoglobulin in the  
capillary lumens**



**tubular structures in subendothelial deposits**



**palpable purpura, necrosis**



**Raynaud**



**livedo reticularis**

# Plasma exchange in cryoglobulinemia

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

# Cryofiltration



Immunoglobulins, IFN, albumin, and fibrinogen are preserved.

# Therapy of HCV-related cryoglobulinemia

- **No severe symptoms**

Antiviral therapy:  $\alpha$  - 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

- Methylprednisolon pulse 0,5-1 g x3

- Immune adsorption or cryofiltration, (PEX)

- Cyclophosphamide or Rituximab

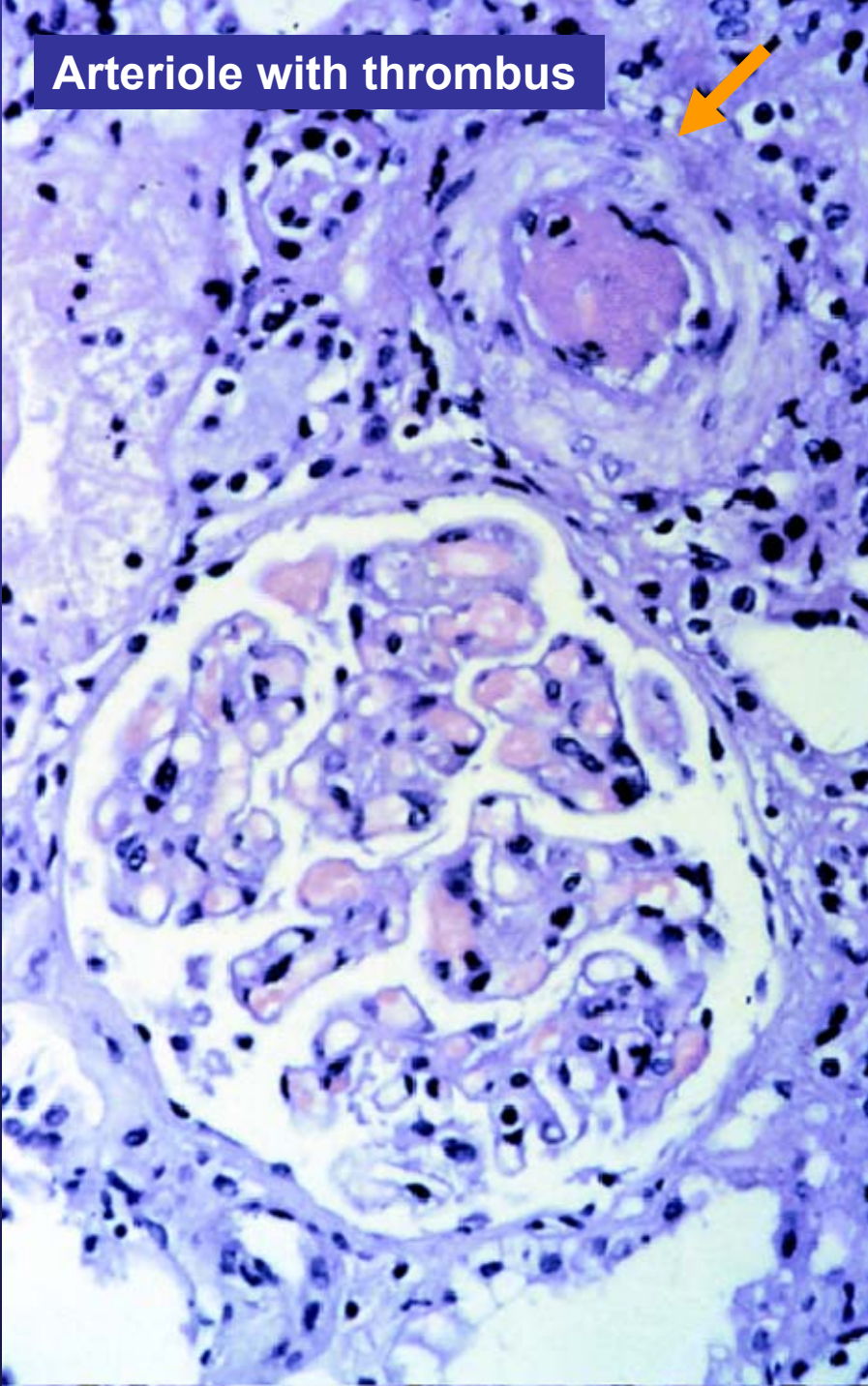
# Antiphospholipid syndrome

## Clinical features

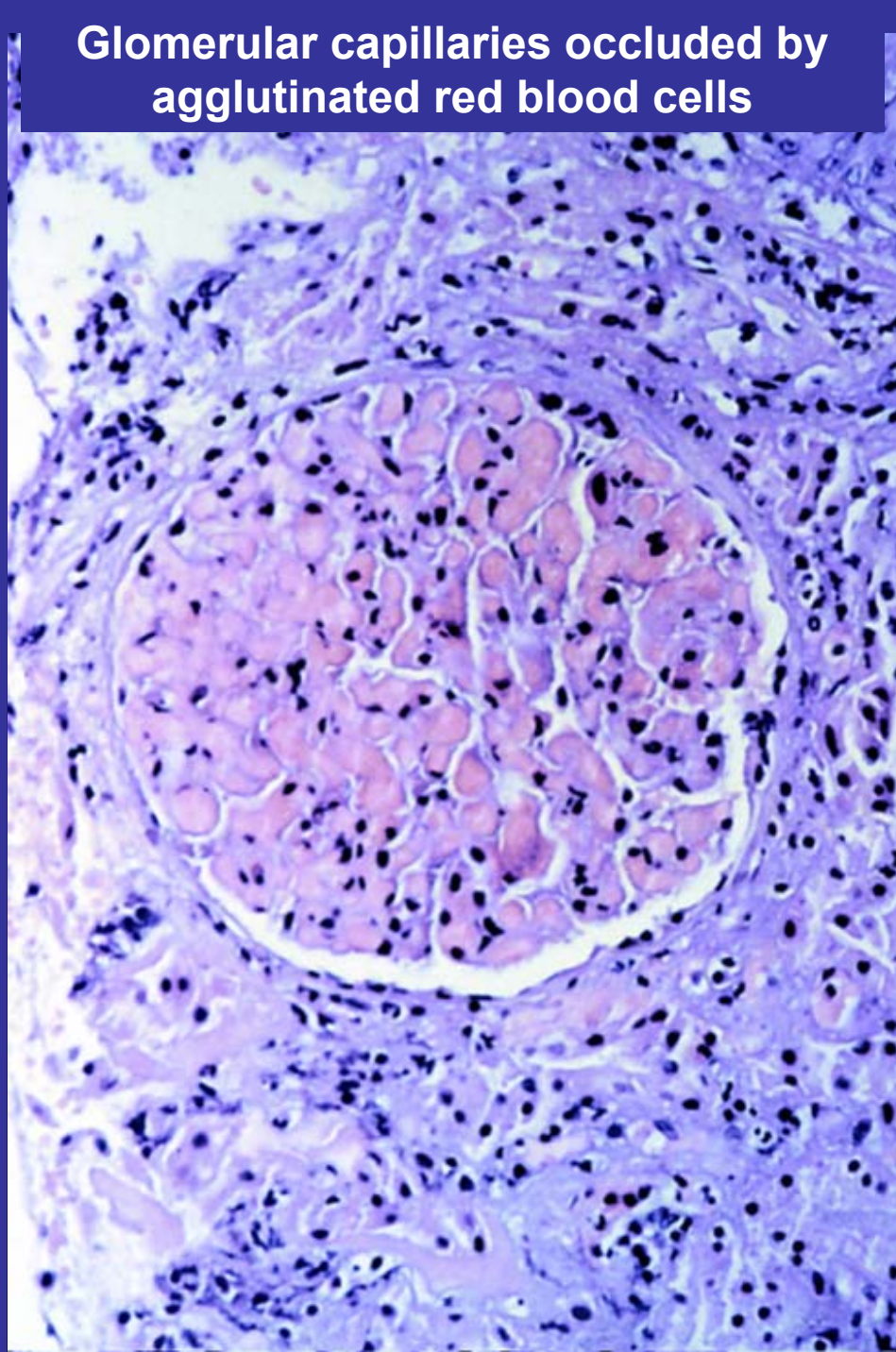
- **Antiphospholipid antibodies**
  - anti-cardiolipin antibody (ELISA)
  - anti  $\beta$ 2-glycoprotein ( ELISA)
  - lupus anticoagulant - prolonged APTT
- **Venous thrombosis: deep veins, renal-, hepatic-, retinal veins, vena cava and/or**
- **Arterial thrombosis: cerebral-, renal-, mesenteric arteries, 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**



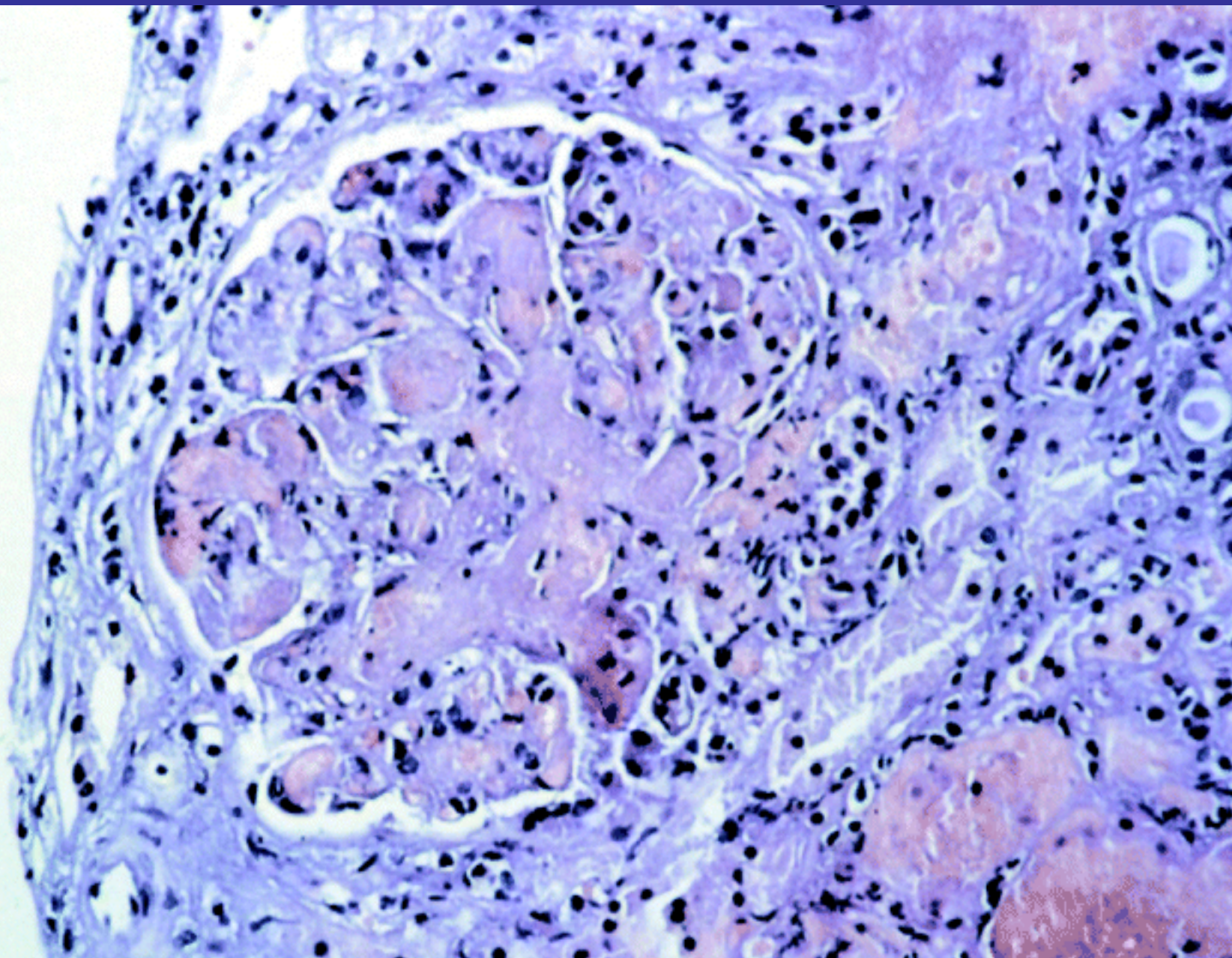
**Arteriole with thrombus**

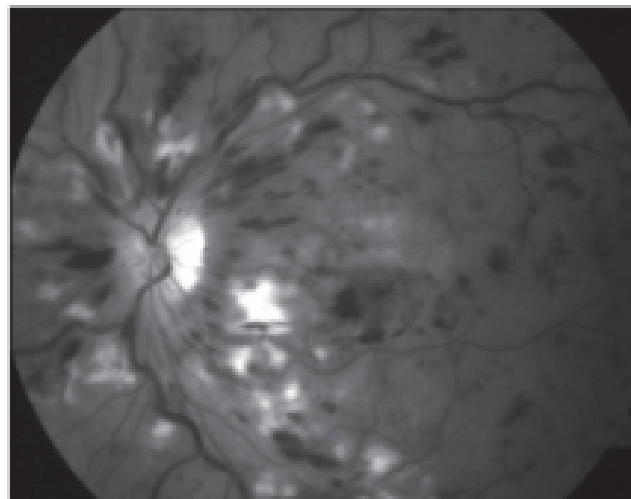
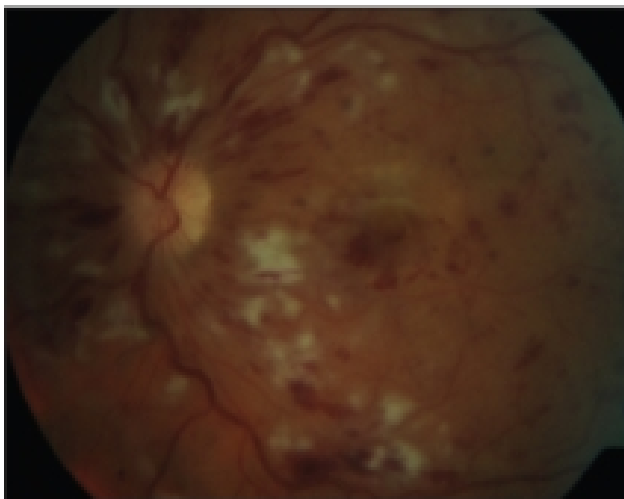
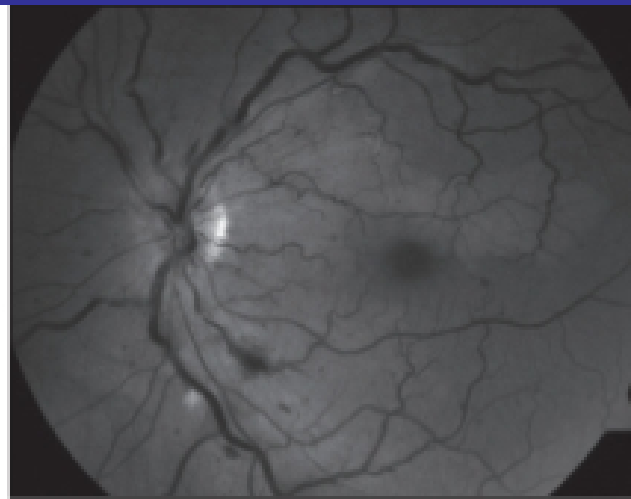
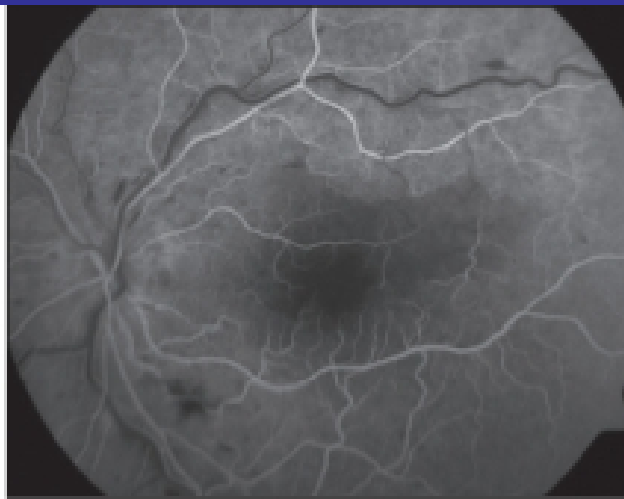


**Glomerular capillaries occluded by agglutinated red blood cells**



# 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 immunoglobulin**

  - **Plasma exchange**

**indication category**

**grade**

**II.**

**2C**

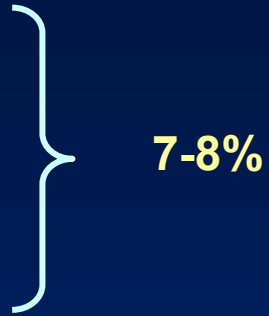
  - **rituximab**

  - **autologous bone marrow transplantation**



**experimental**

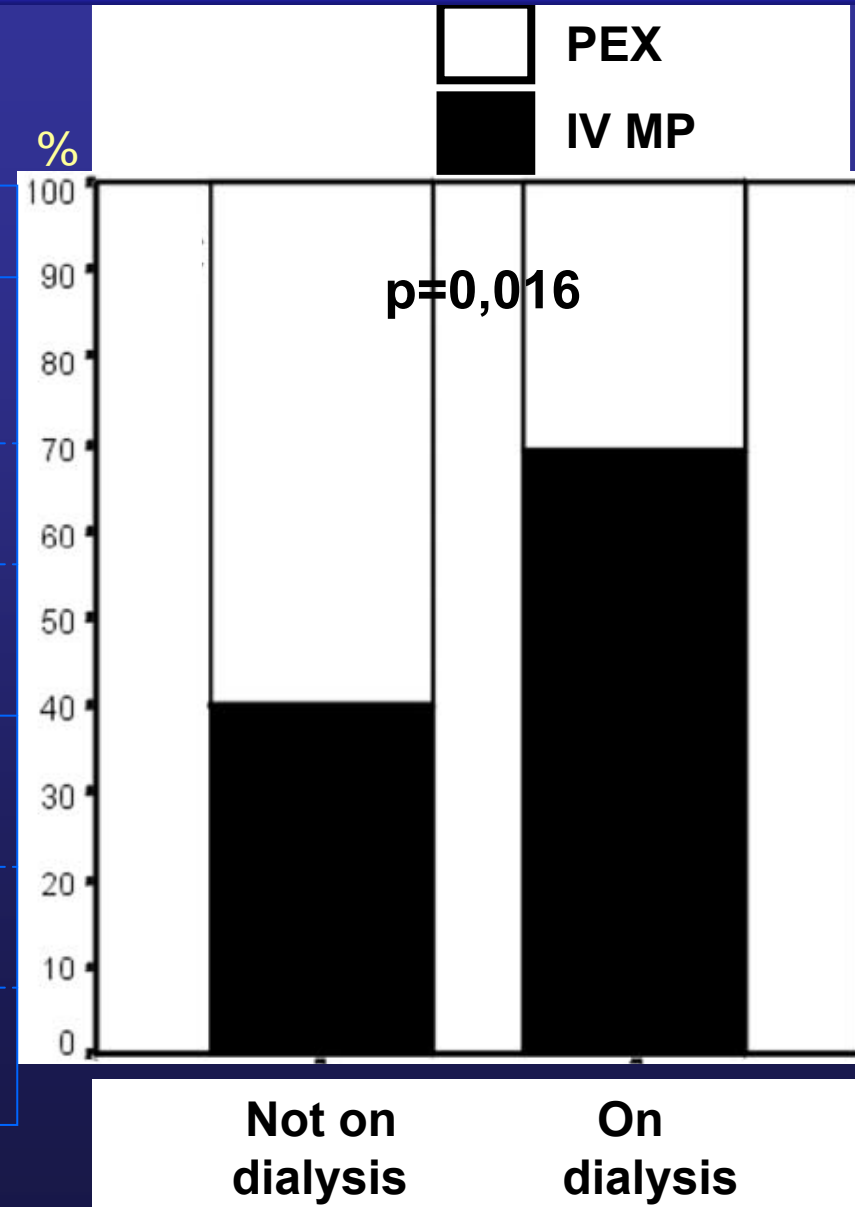
# PEX - complications

- Fever
  - Urticaria
  - Hypocalcemia
  - Hypotension
  - Bleeding diathesis
  - Hypogammaglobulinemia - immunosuppression
  - 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
- 



# MEPEX: outcome at one year

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



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

**N = 149, creatinine 150-500  $\mu\text{mol/l}$**

**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**

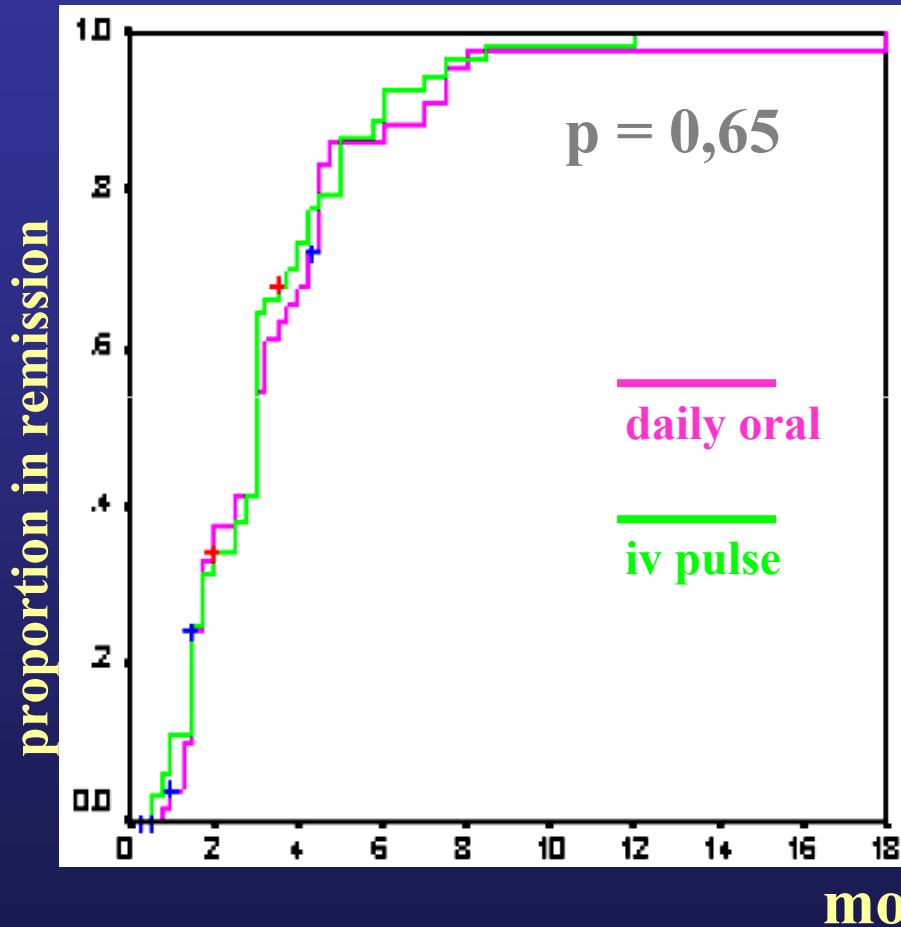
**followed by AZA**

**f/u: 18 mo**

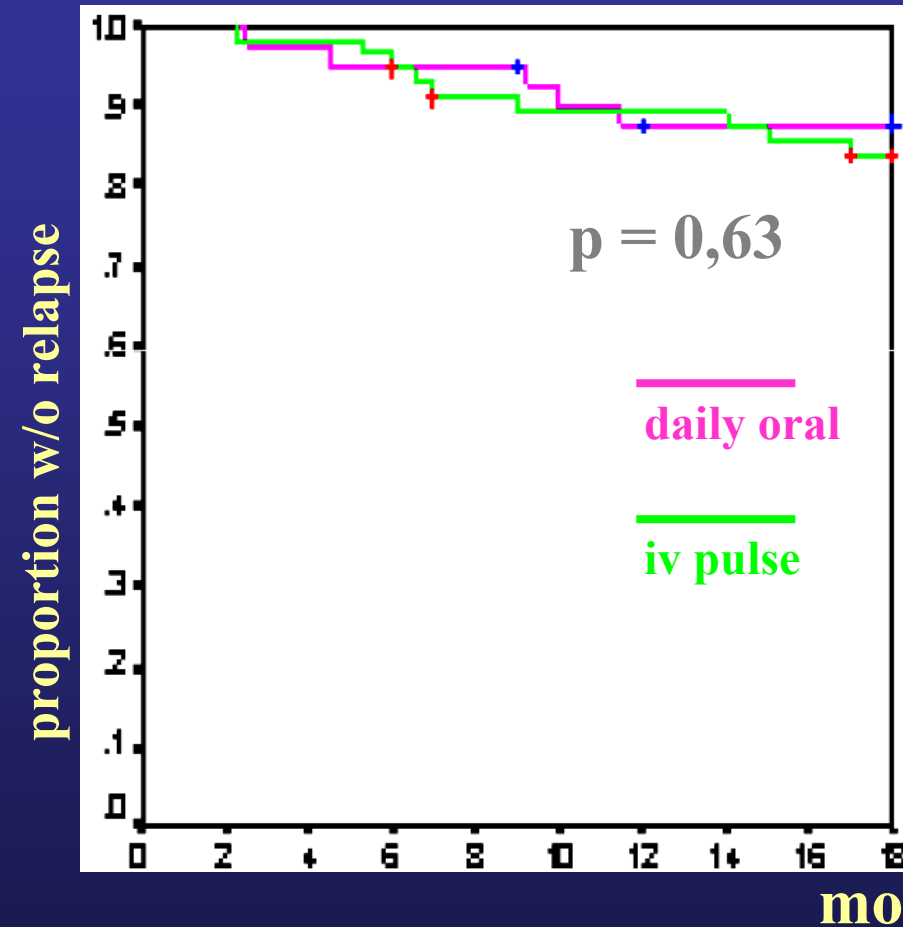
**Primary endpoint: disease free survival at 9 mo**

# 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%,  $p < 0,02$

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

<b>Disease</b>	<b>Indication category</b>	<b>Grading</b>
• 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

