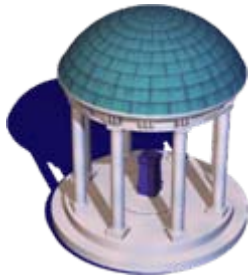

ANCA-Small Vessel Vasculitis



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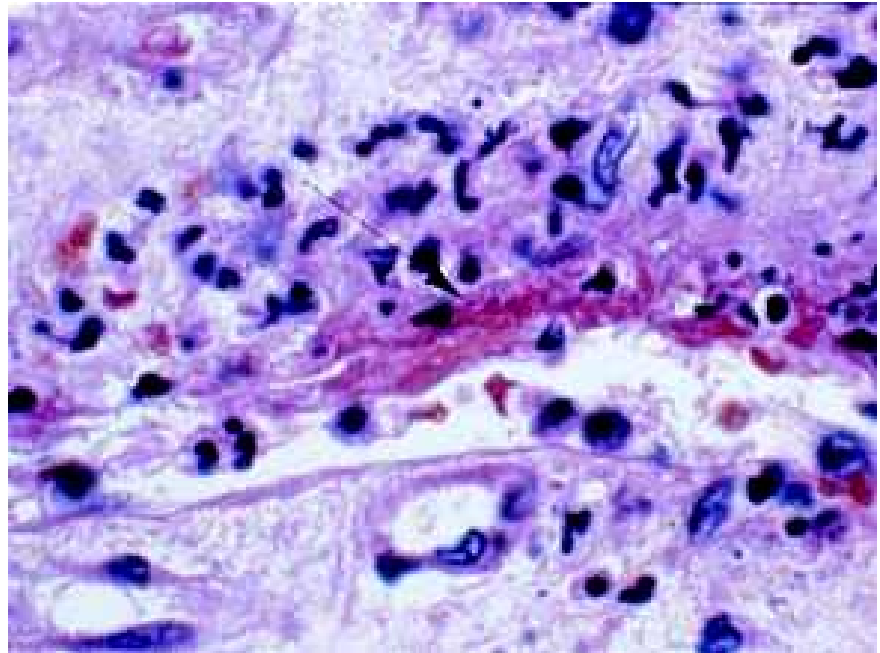
Microscopic Polyangiitis

Necrotizing vasculitis with few or no immune deposits affecting small vessels, i.e. capillaries, venules and arterioles.

Necrotizing arteritis involving small and medium-sized arteries may be present.

Necrotizing glomerulonephritis is very common.

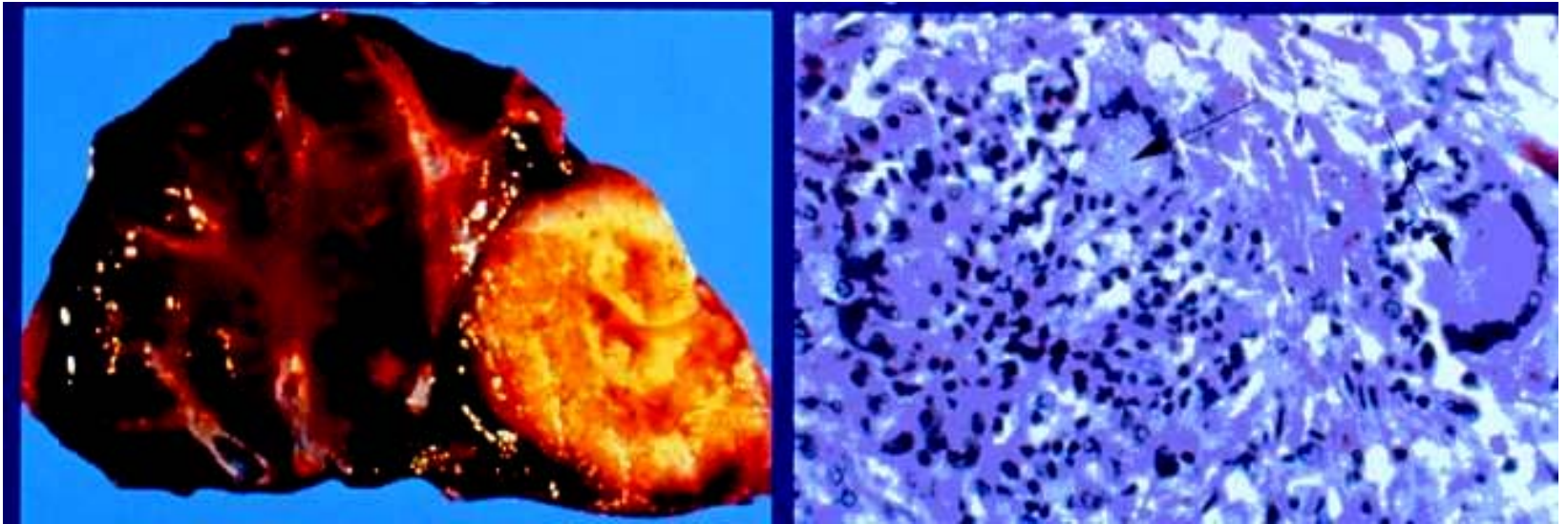
Pulmonary capillaritis often occurs.



Wegener's Granulomatosis

Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, e.g. capillaries, venules, arterioles, and arteries.

Necrotizing glomerulonephritis is common.

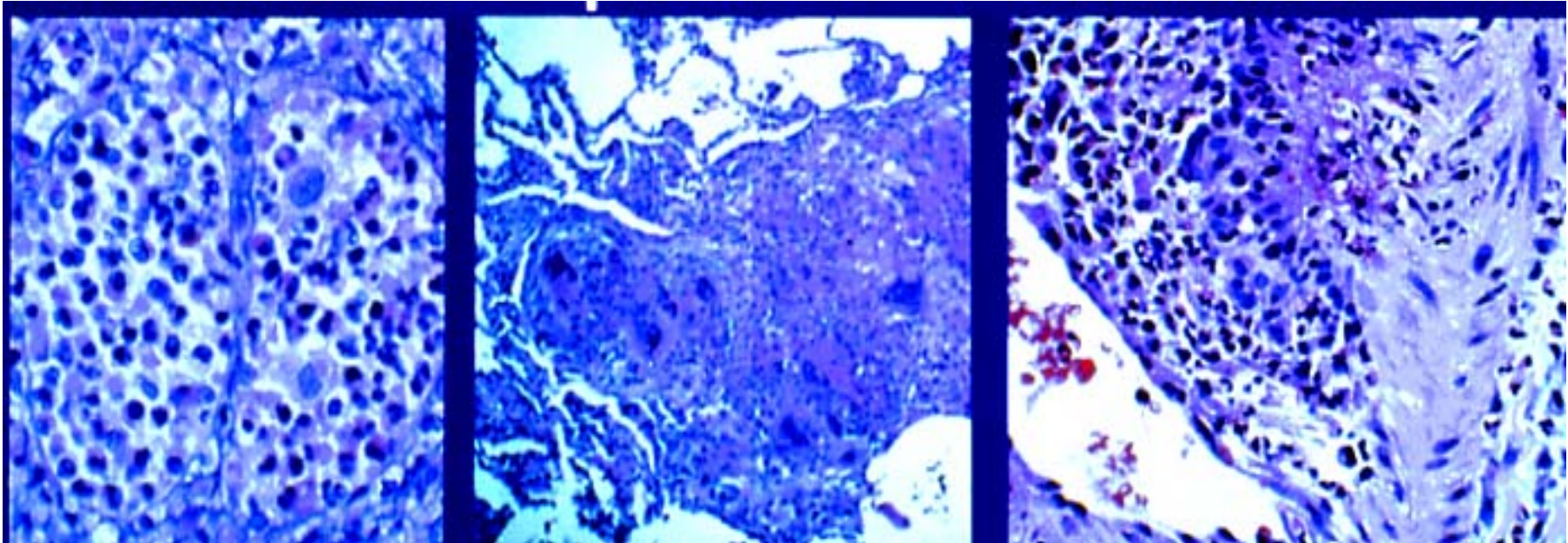


Churg-Strauss Syndrome

Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and blood eosinophilia.

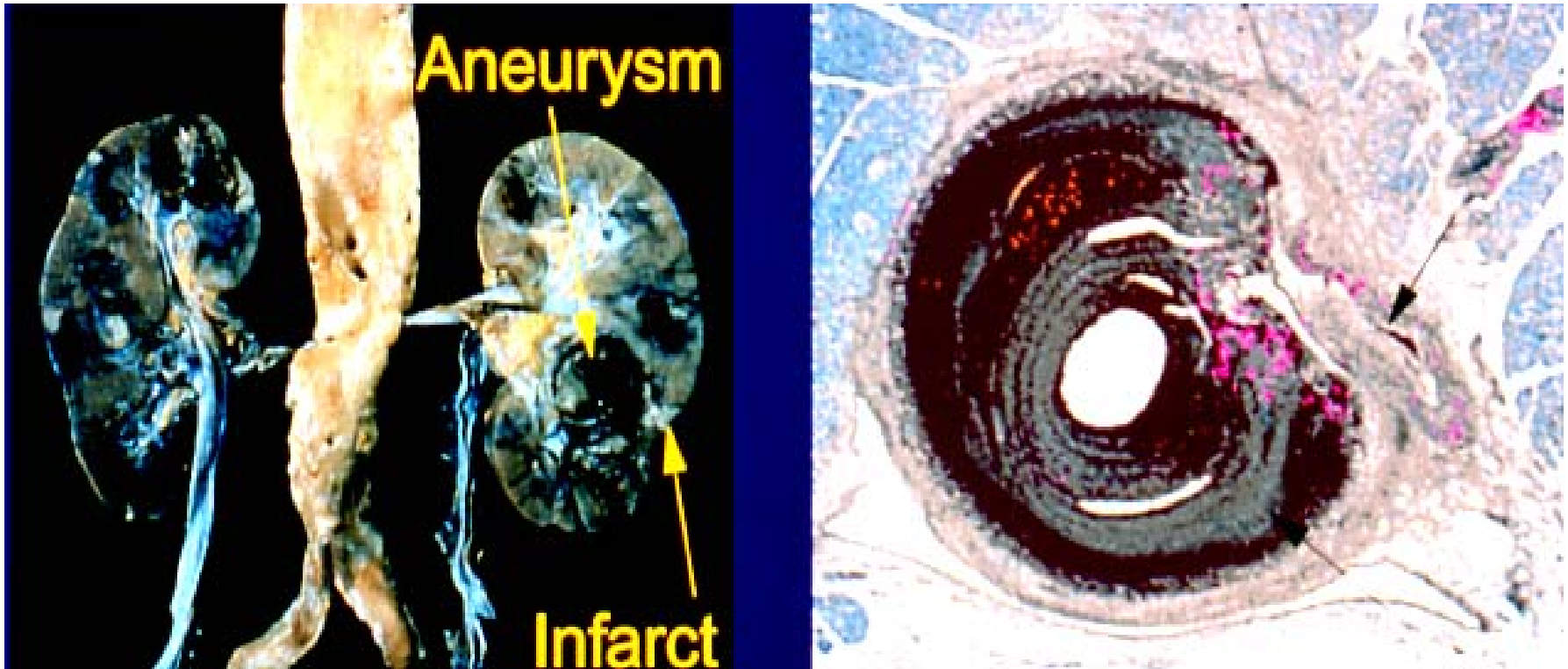
ANCA is present in ~40% of patients (anti-MPO).

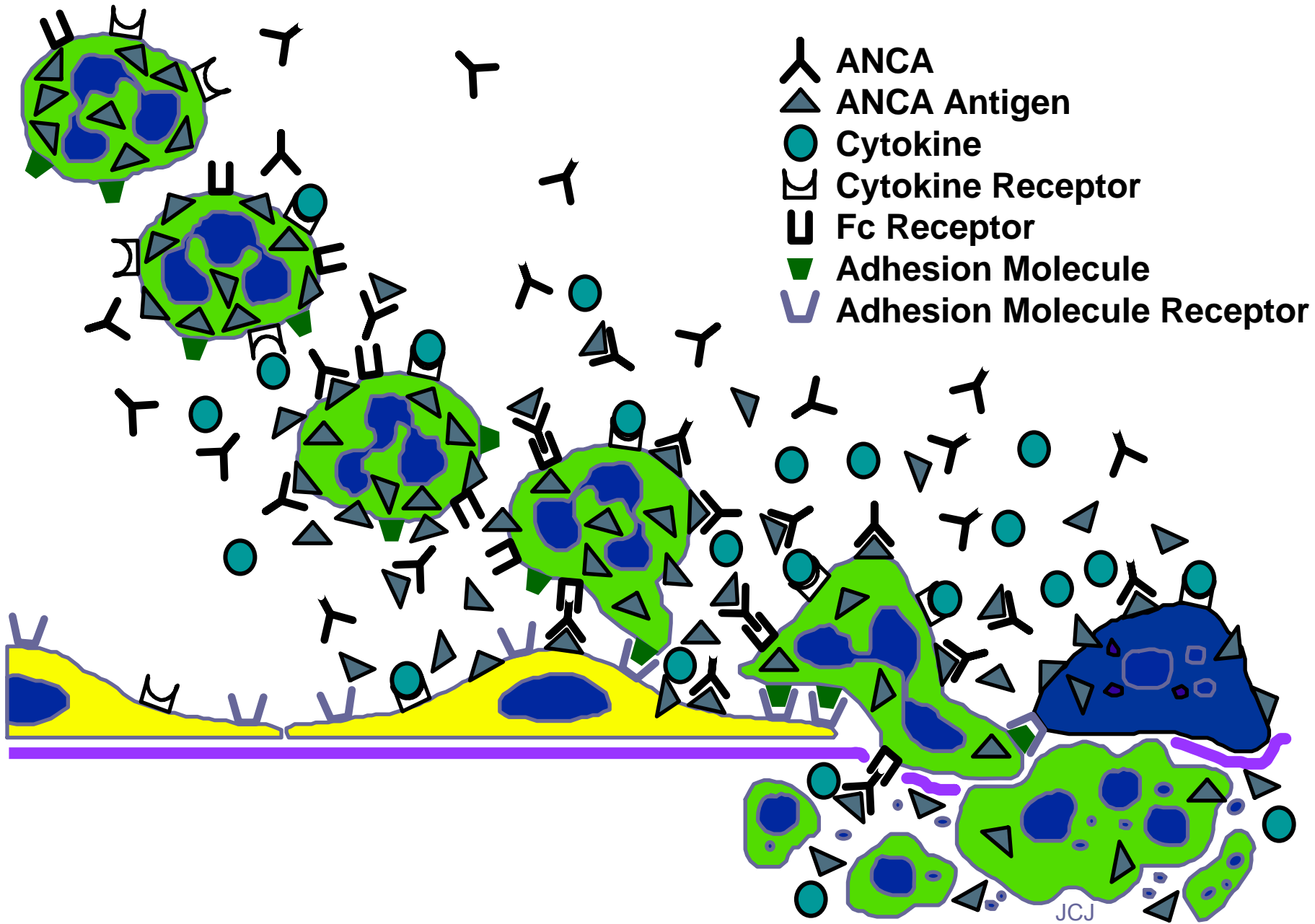
ANCA +ve associated with renal involvement, neuropathy, and biopsy-proven vasculitis. ANCA –ve associated with heart disease and fever.



Polyarteritis Nodosa (Classic Polyarteritis Nodosa)

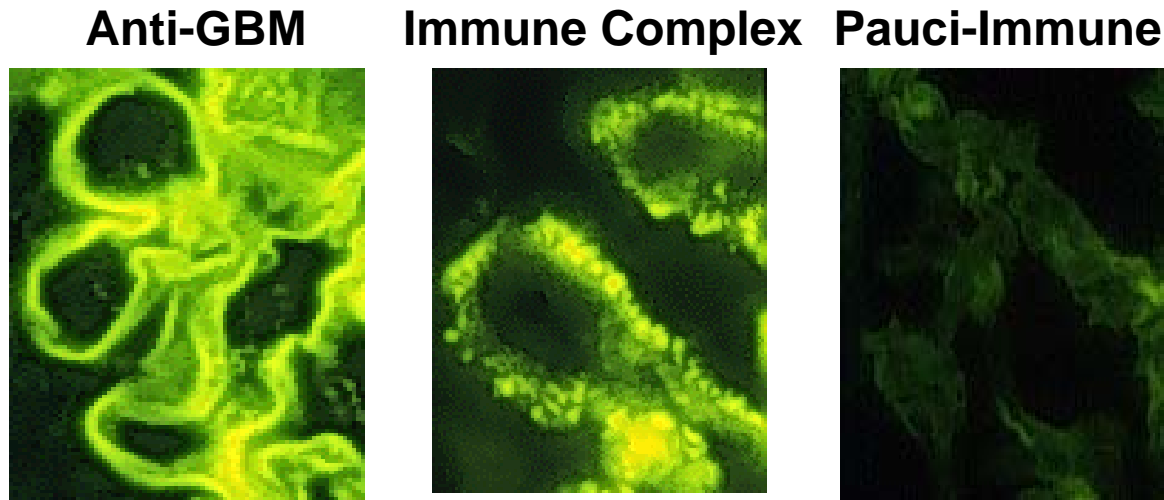
Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules. ANCA is negative.



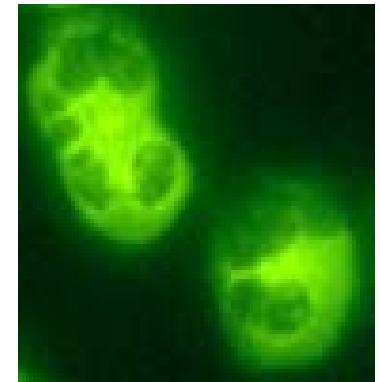


Antineutrophil Cytoplasmic Autoantibodies (ANCA)

Most crescentic glomerulonephritis and systemic small vessel vasculitis in adults is “pauci-immune” and associated with ANCA.

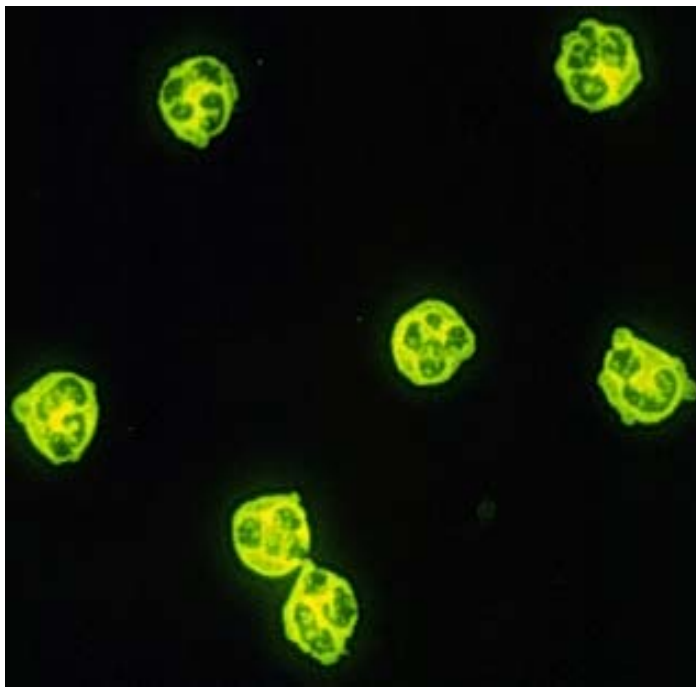


ANCA are specific for proteins in the cytoplasmic primary granules of neutrophils and the peroxidase-positive lysosomes of monocytes (myeloperoxidase and proteinase 3)

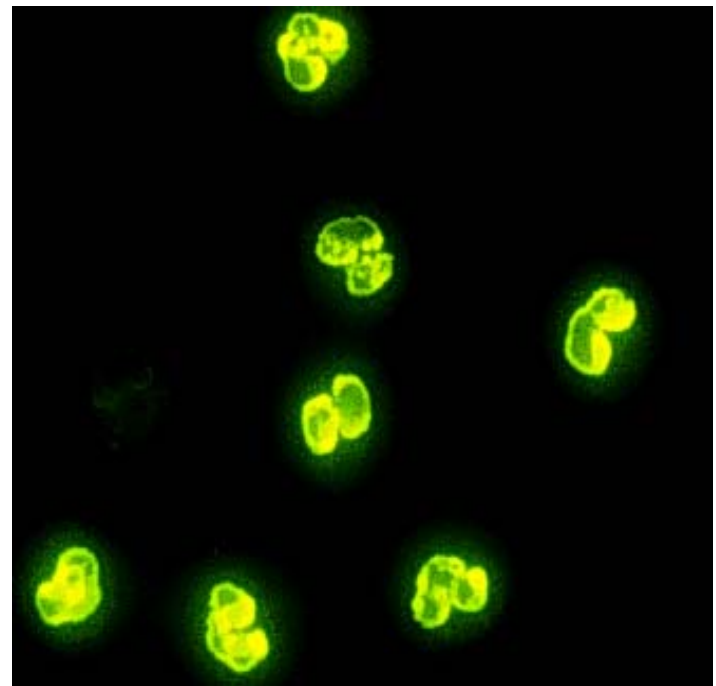


Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA)

C-ANCA Cytoplasmic Pattern
Anti-Proteinase 3
PR3-ANCA

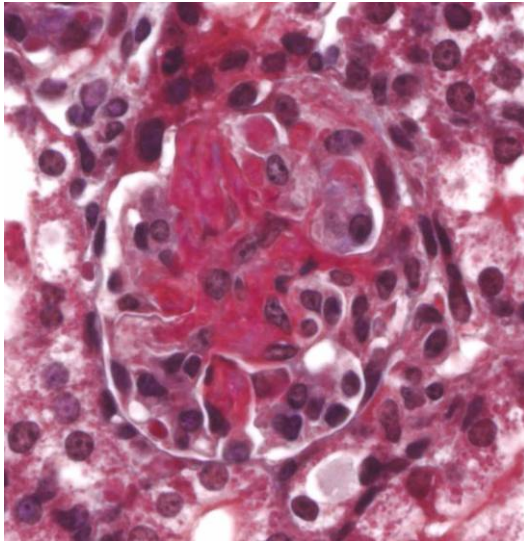


P-ANCA Perinuclear Pattern
Anti-myeloperoxidase
MPO-ANCA

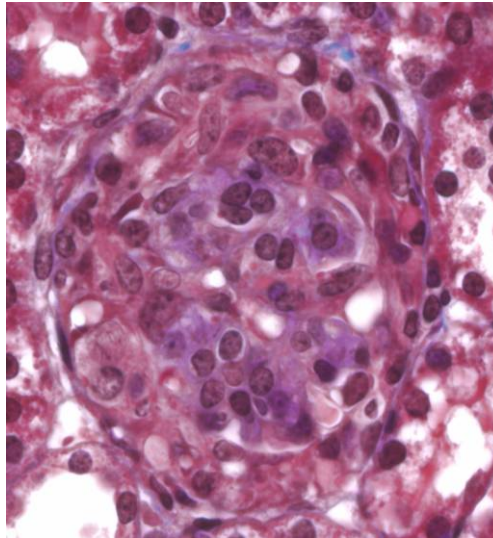


Anti-MPO antibodies are Pathogenic

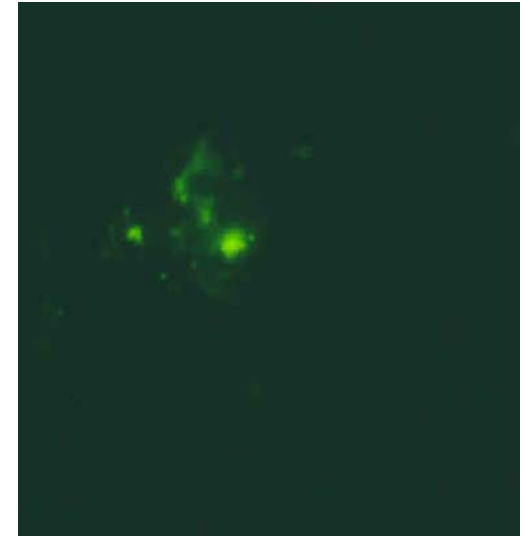
1. Transfer of anti-MPO IgG into Rag2^{-/-} mice causes glomerulonephritis with glomerular necrosis and crescent formation that is identical to human ANCA-associated glomerulonephritis by light microscopy and immunofluorescence microscopy.



necrosis



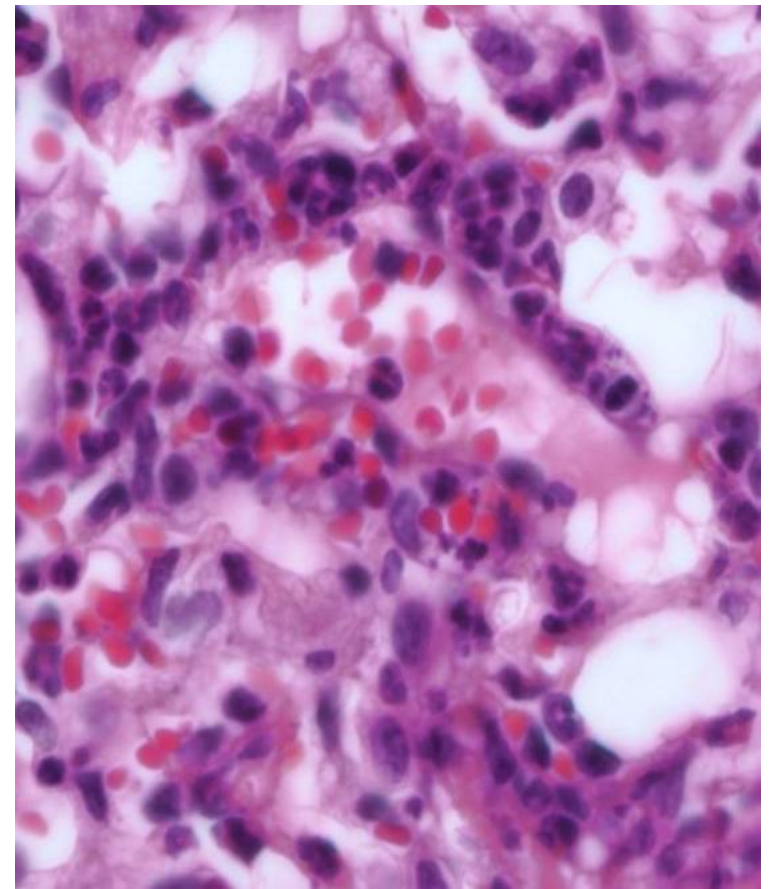
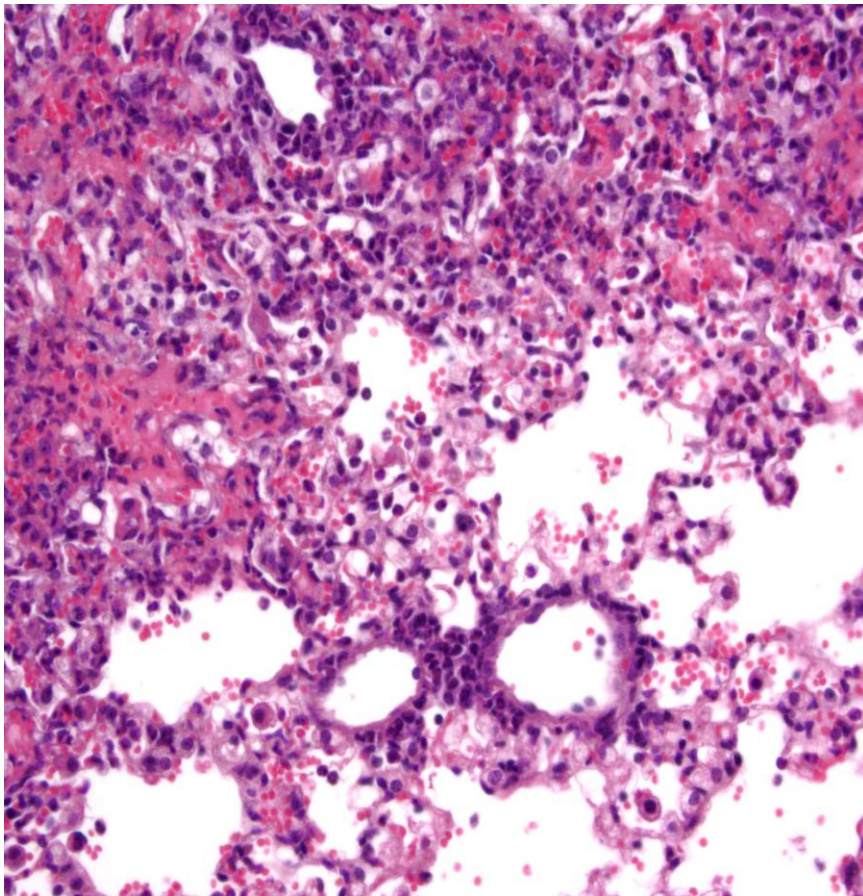
crescent



“pauci-immune”

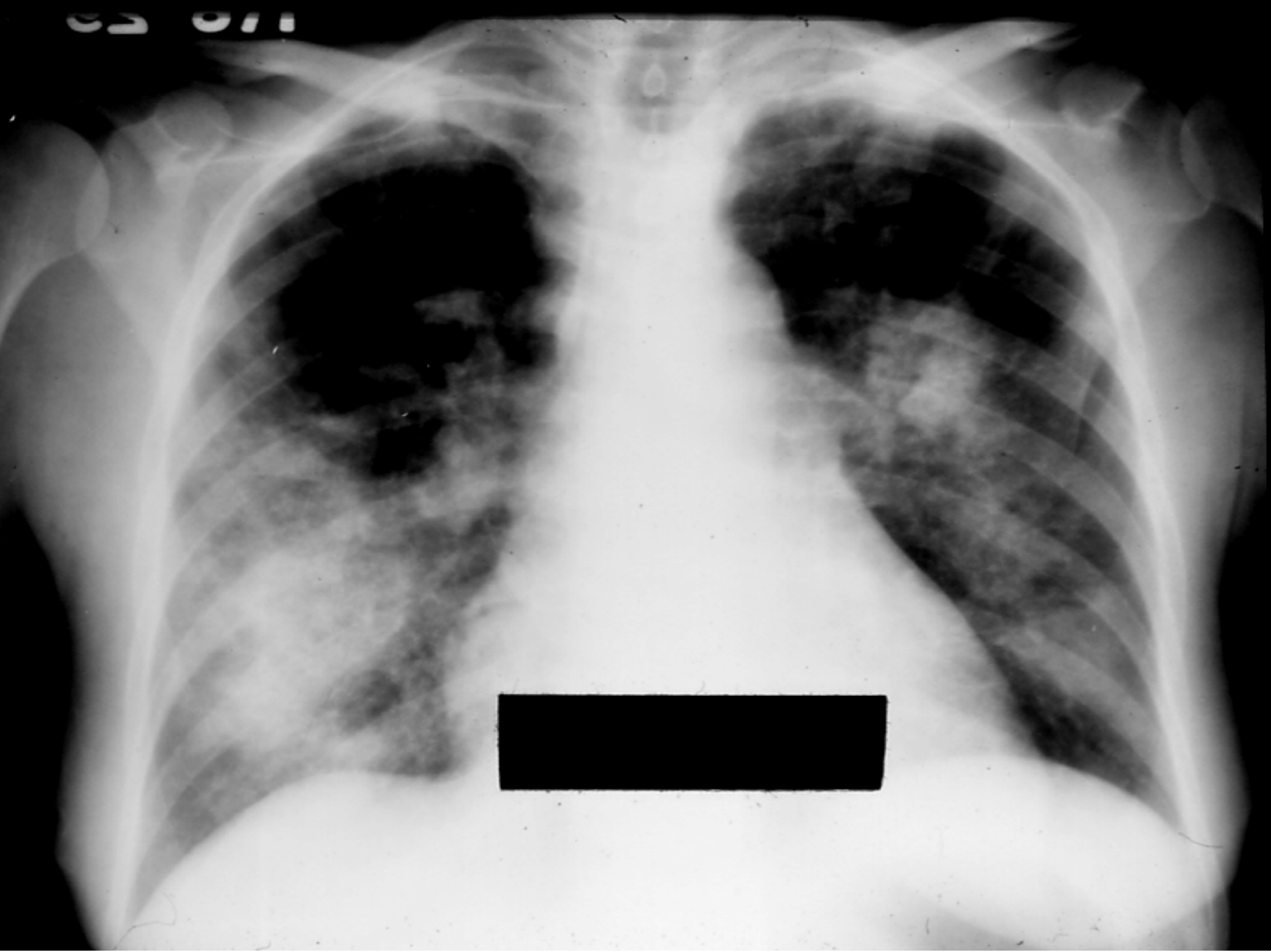
2. This type of glomerulonephritis can be caused by anti-MPO IgG in the absence of antigen-specific T-lymphocytes.

MPO-ANCA Mediated Pulmonary Capillaritis in RAG-2 Mice





02 071



Signs and Symptoms of Necrotizing Small Vessel Vasculitis

- Cutaneous purpura, nodules and ulcerations
 - Peripheral neuropathy (mononeuritis multiplex)
 - Abdominal pain and blood in stool
 - Hematuria, proteinuria and renal insufficiency
 - Hemoptysis and pulmonary infiltrates or nodules
 - Necrotizing (hemorrhagic) sinusitis
 - Subglottic stenosis
 - Myalgias and arthralgias
-

Risk Factors for Death and ESRD in Patients with ANCA-NCGN and MPA

Feature	Risk of Death	Risk of ESRD
Hemoptysis	8.6 (p = 0.0002)	
Lung disease	2.4 (p = 0.61)	1.0 (p = 0.97)
MPA vs GN	1.7 (p = 0.61)	1.0 (p = 0.93)
Creatinine		2.9 (p = 0.0002)
GN activity		1.1 (p = 0.16)
GN chronicity		1.1 (p = 0.24)

Therapy:

What is the most
effective induction
therapy?

Corticosteroids Alone Are Not Sufficient

- Remission rate

- cyclophosphamide 85%
- corticosteroids 56% ($p = 0.003$)

- Risk of relapse increased 3-fold in corticosteroids alone group

- (RP = 3.2, 95% CI, = 1.2, 8.3*)
 - *controlling for age, serum creatinine, duration of treatment, and presence of arteriosclerosis on biopsy
-

Treatment of ANCA-GN With or Without MPA or WG

IV pulse methylprednisolone 7 mg/kg x 3 days

Prednisone 1 mg/kg X 4 weeks then tapered
with either

IV cyclophosphamide 0.5-1 g/m²* X 6 months

or

Oral cyclophosphamide 2 mg/kg* X 6 to 12 months

*adjusted based on leukocyte count

Plasmapheresis for Diffuse Alveolar Hemorrhage

- 20 patients between 1995-2001 with massive pulmonary hemorrhage
- Treatment with Medrol, IV Cytoxan, and plasmapheresis
- 20/20 patients had resolution of lung symptoms with 4-9 exchanges

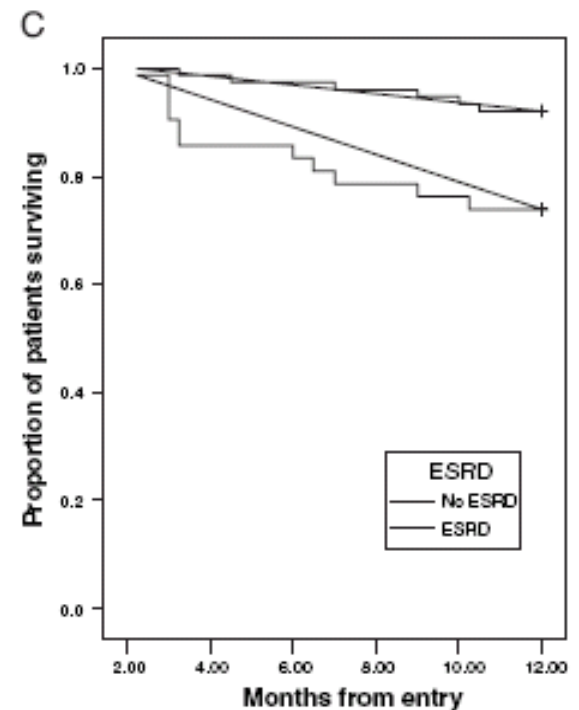
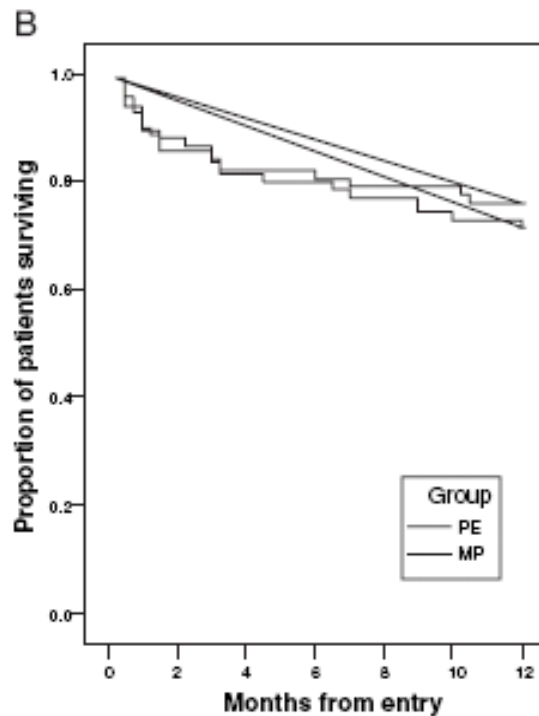
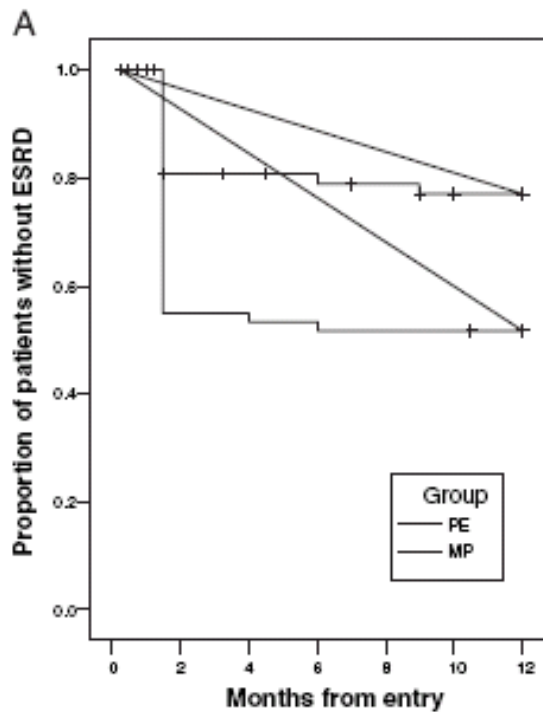
Treatment of patients with severe renal disease: MEPEX Trial

- Plasma exchange (PE) versus pulse methylprednisolone (MeP) as adjunctive therapy with initial creatinine > 5.8mg/dl
- 137 patients with new dx of ANCA vasculitis given either:
 - 7 PE treatments of 60 ml/kg each within 14 days, vs iv MeP 1000 mg iv daily x 3
 - All patients received:
 - oral cyclophosphamide: 2.5 mg/kg/day x 3 months then 1.5 mg/kg/day x 3 months; then azathioprine 2 mg/kg/day.
 - prednisolone started at 1 mg/kg/day down to 0.25 mg/kg/d by week 10 then tapered to 10 mg/day from month 5 to 12.
- The primary end point was dialysis independence at 3 mo.
- Secondary end points included renal and patient survival at 1 yr and severe adverse event rates.

MEPEX: Outcomes

- At 3 mo, 49% of patients treated with iv MeP vs 69% of those who received PE were alive and independent of dialysis (95% CI for the difference 18 - 35%; $P=0.02$).
- As compared with MeP, plasma exchange was associated with a reduction in risk for progression to ESRD of 24% (95% CI 6.1 - 41%), from 43 to 19%, at 12 mo.
- Patient survival and severe adverse event rates at 1 yr were 76% and 48% in the iv methylprednisolone group vs. 73% and 50% in the plasma exchange group, respectively.
- Overall mortality: 25% over 12 months. Major cause of death is infectious complication of therapy

MEPEX: Outcomes



Major cause of death: infection (n=19); pulmonary hemorrhage (n=6); CVD (n=4)

Strategies for minimizing exposure to Cyclophosphamide

- Decrease exposure to cyclophosphamide.
 - Use of monthly IV pulse vs. daily oral regime
 - Shorter course of cyclophosphamide and switch to a less toxic drug
 - Prevention of relapse
 - Avoidance of cyclophosphamide:
 - Methotrexate (MTX)?
 - Mycophenolate mofetil (MMF)?
 - Rituximab?
-

Is IV pulse as effective as daily oral cyclophosphamide?

- Meta-analysis of 3 randomized-controlled studies comprising 143 patients (101 with WG + 42 MPA)
- Pulse Cyc compared with po Cyc was significantly less likely to fail to induce remission (OR 0.29; 95% CI 0.12-0.73); with significantly lower risk of infection (OR 0.45; 95% CI 0.23-0.89) or leucopenia (OR 0.36; 95%CI 0.17-0.76)
- Relapses occurred more often under pulse Cyc treatment, although not statistically significant (OR 1.79; 95% CI 0.85-3.75)

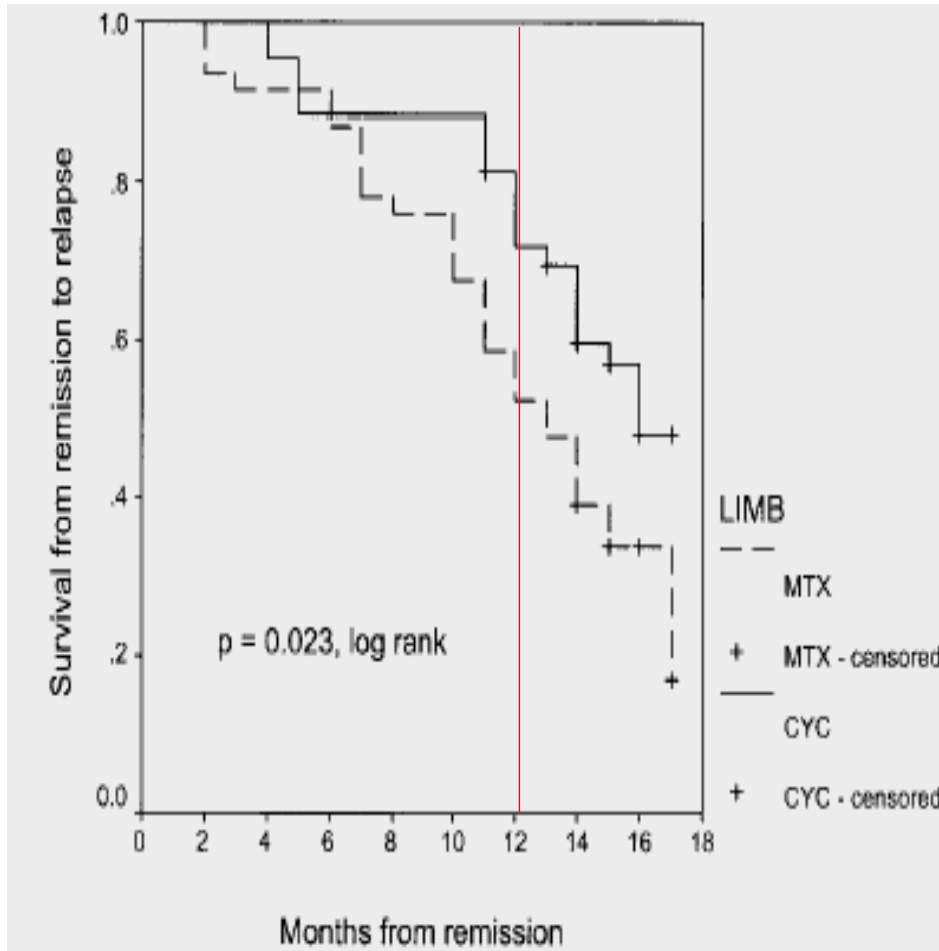
Sequential treatment with Cyclophosphamide and Azathioprine

- CYCAZAREM trial:
 - 144 patients who attained a remission with p.o. Cyclophos. and prednisolone were randomized to continued Cyclophos. or switched to Aza. to complete 12 months of therapy, at which time all patients were switched to Aza.
 - The rates of relapses were not significantly different between the two groups (13.7 % vs 15.5%, $P=0.65$).
 - No significant difference in the rate of severe adverse events (11 vs 10%, $P=0.94$)
 - Substituting Cyclophos. with Aza. after remission does not increase the rate of relapse.

Positive C-ANCA at switch to azathioprine is associated with relapse.

- 33 patients with PR3-ANCA were switched from cyclophosphamide to azathioprine following at least 3 months of complete remission.
- 19 of these (58%) relapsed, (10 while still on aza).
- 13 of the 33 patients (39%) who switched to aza had a positive C-ANCA titer in IIF at the time of switch.
- 10 of 13 patients who were C-ANCA–positive at treatment switch relapsed.
- Relative risk of relapse associated with a positive C-ANCA at treatment switch was 2.6 (95% CI 1.1–8.0, $P < 0.04$).

Methotrexate in lieu of Cyclophos. (NORAM trial)



- Randomized controlled trial of induction therapy with cyclophos. vs MTX.
- 100 patients with “early” ANCA vasculitis (no organ- or life-threatening disease, Cr < 150 $\mu\text{mol/l}$).
- Similar remission rates at 6 months.
- Delayed response in MTX-treated patients with extensive or lung disease.
- Relapse rate:
 - MTX group: 69,5%
 - Cyclophos group: 46,5%

Maintenance Therapy:

How can one prevent relapses?

Current Status: Relapse

- Reported rates of relapse are very variable
 - Definition of relapse and time-to-relapse
 - Study population
 - The risk of relapse is not uniform among all patients with ANCA-vasculitis.
 - The presence of certain clinical and serologic characteristics is associated with an increased risk of relapse.
-

Risk Factors of Relapse

Consistent Predictors of Relapse	Hazard Ratio (95% CI)
PR3-ANCA	1.87 (1.1, 3.1)
Lung involvement	1.71 (1.04, 2.8)
Upper respiratory involvement	1.73 (1.04, 2.9)
With all of the above	3.7 (1.4, 9.7)

Maintenance therapy for the prevention of relapse.

- If the risk of relapse is determined (at least in part) by the presence of risk factors: Can we tailor long term maintenance therapy to patients at risk?
 - In order to demonstrate that an immunosuppressive drug is effective at preventing relapse; the study of maintenance therapy should:
 - Include enough patients at high risk for relapse
 - Be of sufficient duration
 - Have a control group.
-

S. aureus and Wegener's granulomatosis

- 71 patients with Wegener's
 - 63% nasal carriage of *S. aureus*
 - 22/33 patients with Staph relapsed
 - 1/21 patients without Staph relapsed

Trimethoprim Sulfamethoxazole for Prevention of Relapse of Wegener's Granulomatosis

- 48 patients received cotrimoxazole
- 40 patients received placebo
- 20% of patients stopped cotrimoxazole because of side effects
- 82% of patients in cotrimoxazole group were in remission at 24 months compared with 60% in placebo group
- Fewer respiratory tract infections in cotrimoxazole group

Clinical Features of Wegener's Granulomatosis at the Time of Relapse in Patients Treated with Co-Trimoxazole or Placebo

Characteristic	Co-Trimoxazole (n = 7)	Placebo (n = 16)
Group	Number of patients	
1	3	10
2	1	3
3	3	3
Clinical feature		
Progressive GN	4	7
Pulmonary lesions	3	2
Nasal or upper airway lesions	1	11
Miscellaneous scleritis	1	4
Mononeuritis multiplex	2	0
Dermal granulomatous vasculitis	2	4

Prevention of Relapse: which agent?

- Longer course of cyclophosphamide?
 - Methotrexate?
 - Azathioprine?
 - Mycophenolate mofetil?
 - Etanercept?
 - Leflunomide?
-

Relapse rate among 143 patients in remission with cyclophos. + steroids and followed without maintenance therapy.

Category	Patients treated \leq 6 months	Patients treated > 6 Months	Hazard Ratio [†] (CI 95%)	P
All patients	34%	35%	1.41 (0.80–2.50)	0.145
High risk patients*	41%	40%	1.50 (0.82–2.78)	0.186
Low risk patients [#]	11%	19%	2.17 (0.19–24.72)	0.53

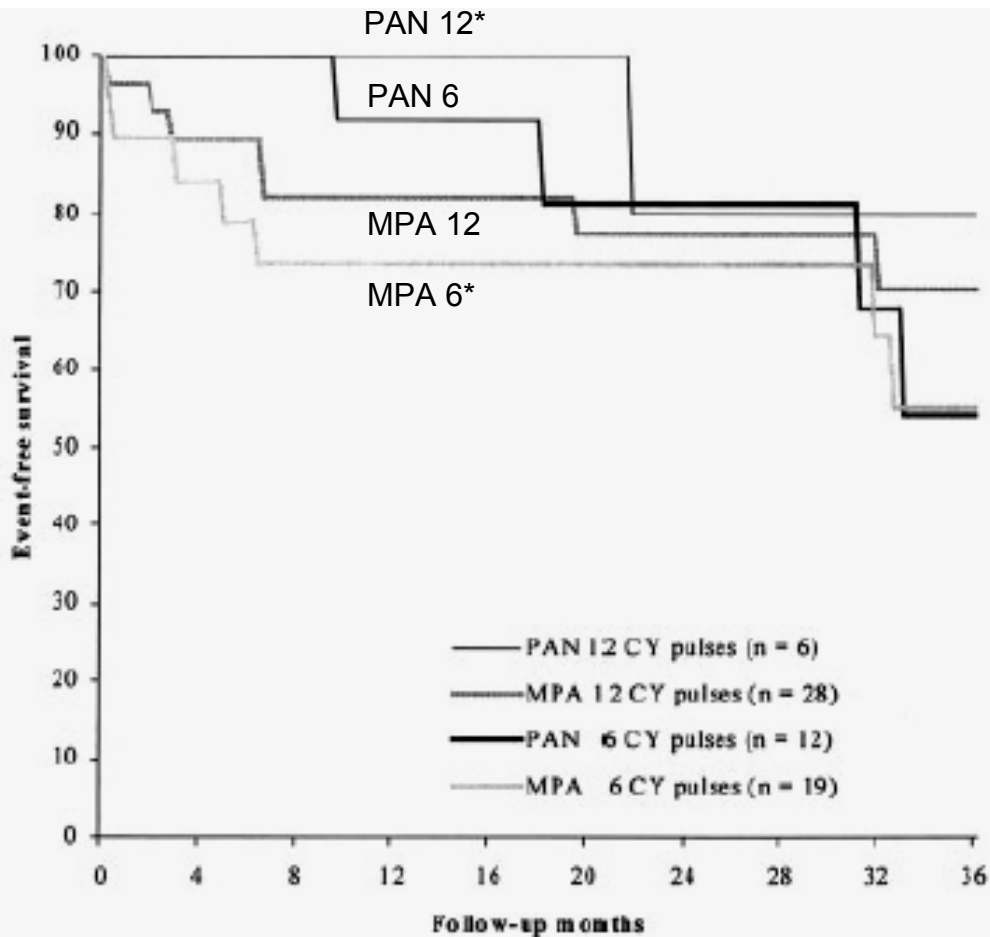
* High-risk: patients presenting with at least 1 of the 3 risk factors for relapse.

Low-risk: patients presenting with none of the risk factors.

† Hazard ratio compared to patients treated > 6 months.

Adapted from Hogan SL et al. *Ann Intern Med.* 2005;143:621-631.

Cyclophosphamide: 6 vs. 12 months.



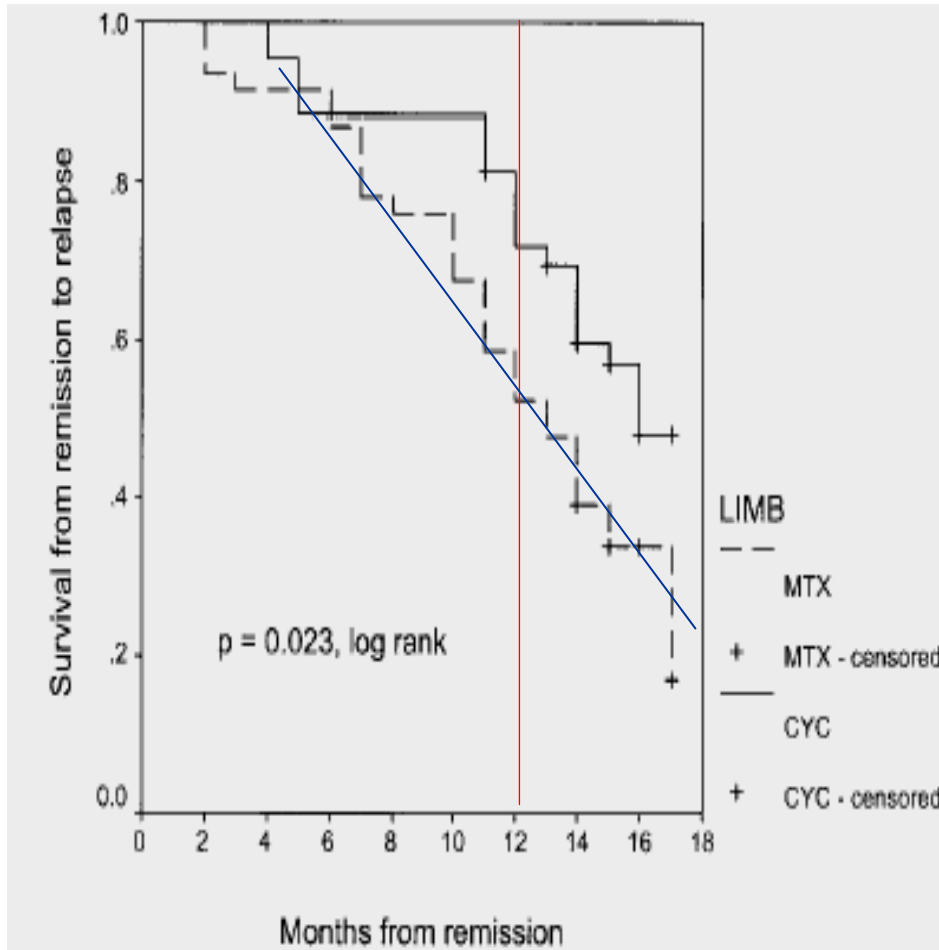
- Randomized, controlled trial.
- 65 patients (18 PAN + 47 MPA).
- Deaths: 12 MPA + 2 PAN. 8/12 MPA deaths during treatment.
- Difference in the rate of relapse among patients with MPA was not significant.

Methotrexate for maintenance therapy

- **Langford C. et al. , *Arthritis Rheum* 1999;42: 2666-2673.**
 - 42 patients in remission with cyclophosphamide and steroids
 - MTX: initial weekly dose 0.3 mg/kg (max. 15 mg/week) and increased gradually to a maximum of 25 mg/kg per week.
 - Median follow-up: 32 months (5–71 months).
 - **Relapse rate: 52%. 72% of relapsers with glomerulonephritis.**

- **Reinhold-Keller,E., et al. *Arthritis Rheum.* 2002;47: 326-332.**
 - 71 patients in remission with oral cyclophos. and steroids.
 - MTX at 0.3 mg/kg IV once weekly (+ low-dose steroids in 77.5% of patients).
 - Mean follow-up of 25.2 months
 - **Relapse rate: 36.6% (mean of 19.4 months).**
 - Relapses occurred most commonly in upper respiratory (69%) and the **kidney (61%).**

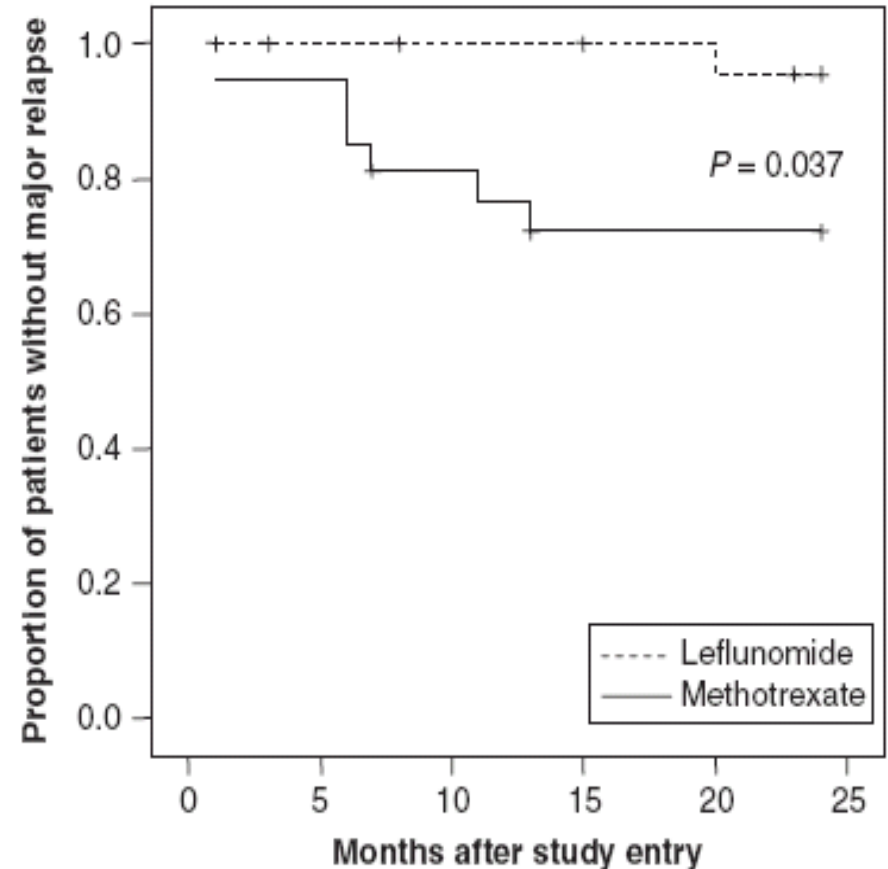
MTX: NORAM trial



- Relapse rate:
 - MTX group: 69.5%
 - Cyclophos group: 46.5%
- ~ 50 % of relapses in MTX group occurred during MTX treatment.

Maintenance therapy in Wegener's granulomatosis: Leflunomide vs. MTX

- Randomized controlled trial.
- 54 patients.
- induction Rx with cyclophos.
- LEF 30 mg/day (n= 26) vs oral MTX (starting with 7.5 mg/week reaching 20 mg/week after 8 weeks) (n=28)
- maintenance Rx for 2 yrs.
- Primary endpoint: incidence of relapses.
- LEF-group: 6 patients relapsed (median time 7 months), with 1 major relapse: new pulmonary manifestation.
- MTX-group: 13 relapses (median time 6 months), of which 7 were major: RPGN (n=4), pulmonary haemorrhage (n=2) and cerebral granuloma (n=1).



Maintenance therapy in Wegener's granulomatosis: Leflunomide vs. MTX

TABLE 2. Adverse events, withdrawals, infections and major relapses during treatment with methotrexate or leflunomide for Wegener's granulomatosis

(n=)	Leflunomide group	Methotrexate group
Adverse events total	34	17
Severe side effects/ withdrawals	2 (hypertension) 1 (peripheral neuropathy) 1 (leucopenia) 1 (lack of compliance)	0
Infections	13	12
Major relapses	Pulmonary granuloma <i>n</i> = 1	Renal involvement <i>n</i> = 4 (3/4 with decrease of renal function) Pulmonary haemorrhage <i>n</i> = 2 CNS-granuloma <i>n</i> = 1

TABLE 4. Comparison of relapse-ratios (*n*/100 patient-yrs) for maintenance of remission treatments in Wegener's granulomatosis

Medication	Author	Observation time (months)	Total Relapses	Major Relapses	Minor Relapses
Azathioprine	Jayne [2003] ^a	18	10.32	4.68	5.64
Methotrexate	De Groot [1996]	22	26.44	n.a.	n.a.
Methotrexate	Reinhold-Keller [2002]	24	17.6	12.67	10.68
Methotrexate	Langford [2003]	32	19.64	5.36	14.28
Leflunomide	Metzler [2004]	21	25.71	2.85	22.86
Leflunomide	This study	21	13.1	2.05	10.9
Methotrexate	This study	21	26.5	14.3	12.3

^aincluding patients with Wegener's granulomatosis and microscopic polyangiitis.

Wegener's Granulomatosis Etanercept Trial (WGET)

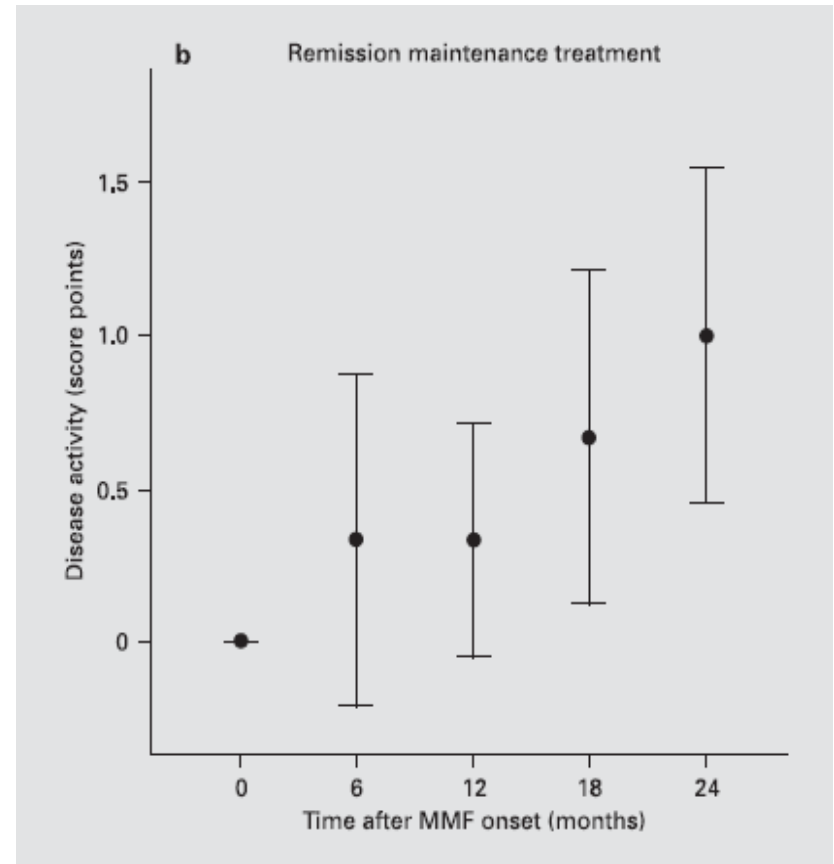
- Randomized, placebo-controlled trial
- Evaluate etanercept for the maintenance of remission in 180 patients with WG.
- Primary outcome: sustained remission, defined as a BVAS/WG of 0 for at least 6 months.
- In addition to etanercept or placebo, patients received standard therapy (glucocorticoids plus cyclophos. or methotrexate).
- After remission, standard medications were tapered according to the protocol.

Wegener's Granulomatosis Etanercept Trial (WGET)

- Mean follow-up 27 months.
- Of 174 patients evaluated, 126 (72.4%) had a sustained remission
- Only 86 (49.4%) remained in remission.
- No significant differences between the etanercept and control groups in the rates of sustained remission (69.7% vs. 75.3%, $P=0.39$), sustained periods of low-level disease activity (86.5% vs. 90.6%, $P=0.32$).
- Disease flares were common in both groups, (118 flares in the etanercept group and 134 in the control group).
- There was no significant difference between the etanercept and control groups in the relative risk of disease flares.

Maintenance therapy with MMF

- Retrospective study in 51 sequential patients with ANCA vasculitis.
- 29 patients treated for **maintenance of remission**.
- Prednisolone decreased from 14.1 ± 12.4 mg/day to 8.3 ± 9.4 and 5.1 ± 1.8 mg/day by 6 and 12 months, respectively.
- 14 patients (48.3%) eventually relapsed.
- Mean time to relapse: 14.1 ± 13.9 months.



Treatment of Resistant Disease

Rituximab: Uncontrolled Case Series

Author/Reference	N
Keogh KA. Arthritis Rheum. 2005 Jan;52(1):262-8.	11
Erickson P. J Intern Med. 2005 Jun;257(6):540-8.	9
Omdal R. Scand J Rheumatol. 2005;34(3):229-32.*	3
Keogh KA. Am J Respir Crit Care Med. 2006;173(2):180-7.	10
Aries PM. Ann Rheum Dis. 2006;65(7):853-8.*	8
Stasi R. Rheumatology (Oxford). 2006;45(11):1432-6	10
Brihaye B. Clin Exp Rheumatol. 2007;25(1 Suppl 44):S23-7	8
Henes JC. Clin Rheumatol. 2007 (EPub)	7

*Not efficacious in patients with WG with refractory granulomatous manifestations.

Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis

- This study is currently recruiting patients.
 - Sponsors and Collaborators: National Institute of Allergy and Infectious Diseases (NIAID) & Immune Tolerance Network
-

Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis

1: Experimental Drug:

Rituximab 375 mg/m² once weekly x 4 + Azathioprine 2 mg/kg/day for months 4-6

2: Active Comparator Drug:

Rituximab 375 mg/m² once weekly x 4 +
Cyclophosphamide 2 mg/kg/day for months 1-3 then
Azathioprine 2 mg/kg/day for months 4-6

All patients receive Methylprednisolone 1 g/day IV for up to 3 days within 14 days prior to receiving rituximab followed by Prednisone 1 mg/kg/day, (<80 mg/day) with taper to be completed by the Month 6 study visit.

Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis

- goal to enroll 200 patients.
 - Total enrolled to date : ~183.
 - Anticipate last patient be enrolled by June 08.
 - Primary outcome is remission at 6 months.
 - Therefore, primary outcome data will be available after Jan 2009
-

TNF- α blockade: Infliximab

Patients	n	Disease	Other Rx	Outcome	Reference
resistant	6	WG	CyP+Cs	remission	Lamprecht, P. Rheumatology 2002;41:1303–1307
resistant	7	WG	Cs + IS*	remission	Bartolucci, P. Rheumatology 2002;41:1126–1132
resistant	6	3WG + 3MPA	Cs	remission	Booth, AD. Ann Rheum Dis 2002;61:559
acute	16	7WG + 9MPA	CyP+Cs	88% remission	Booth A. J Am Soc Nephrol 15: 717–721, 2004
resistant	18	12WG + 4MPA	Cs + IS**	18% relapse	Booth A. J Am Soc Nephrol 15: 717–721, 2004

Summary 1:

- Standard therapy with cyclophosphamide and corticosteroids is effective for the majority of patients.
 - Once remission is achieved, prolonged treatment with cyclophosphamide is likely not necessary. Switch to azathioprine is an option.
 - Alternatives to cyclophosphamide are not yet established (except for mild/limited disease?). Rituximab and MMF are under investigation.
 - Several new immunomodulatory agents potentially useful for patients with resistant disease.
-

Summary 2:

- Prevention of relapse:
 - Prolonged course of cyclophosphamide does not appear to lead to better relapse prevention.
 - Etanercept NOT effective.
 - Methotrexate does not appear to be effective.
 - No good data for other agents, as studies are underpowered and uncontrolled.
-