Update of Pulmonary Vasculitis

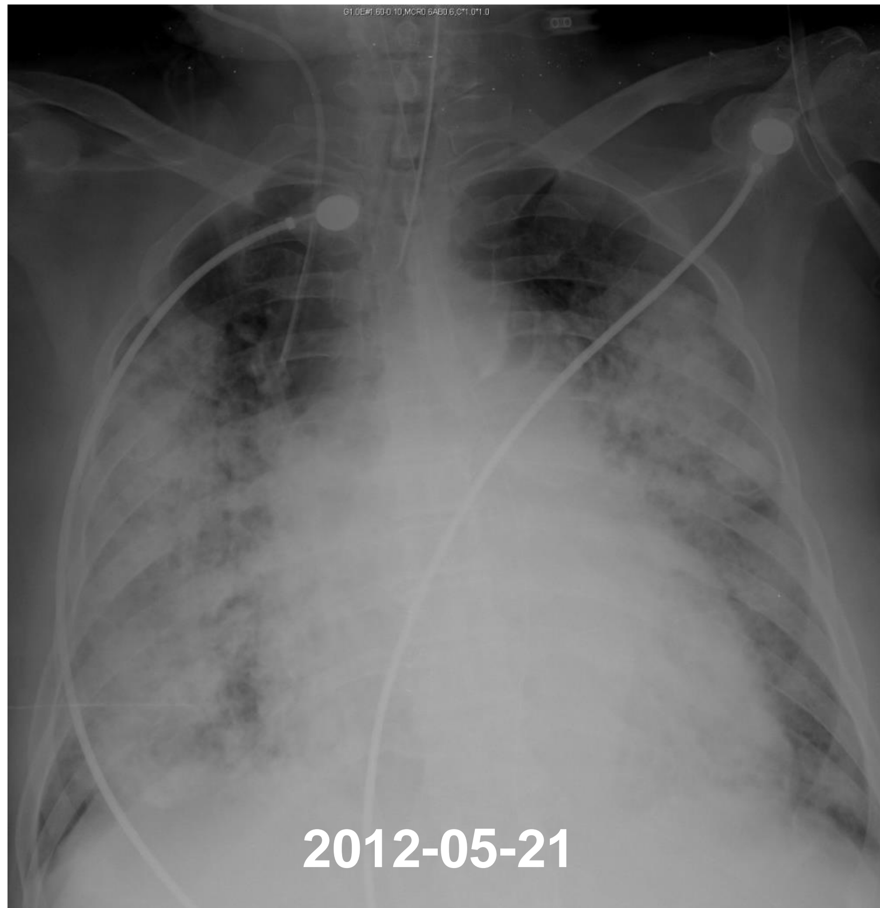
MOO SUK PARK M.D.

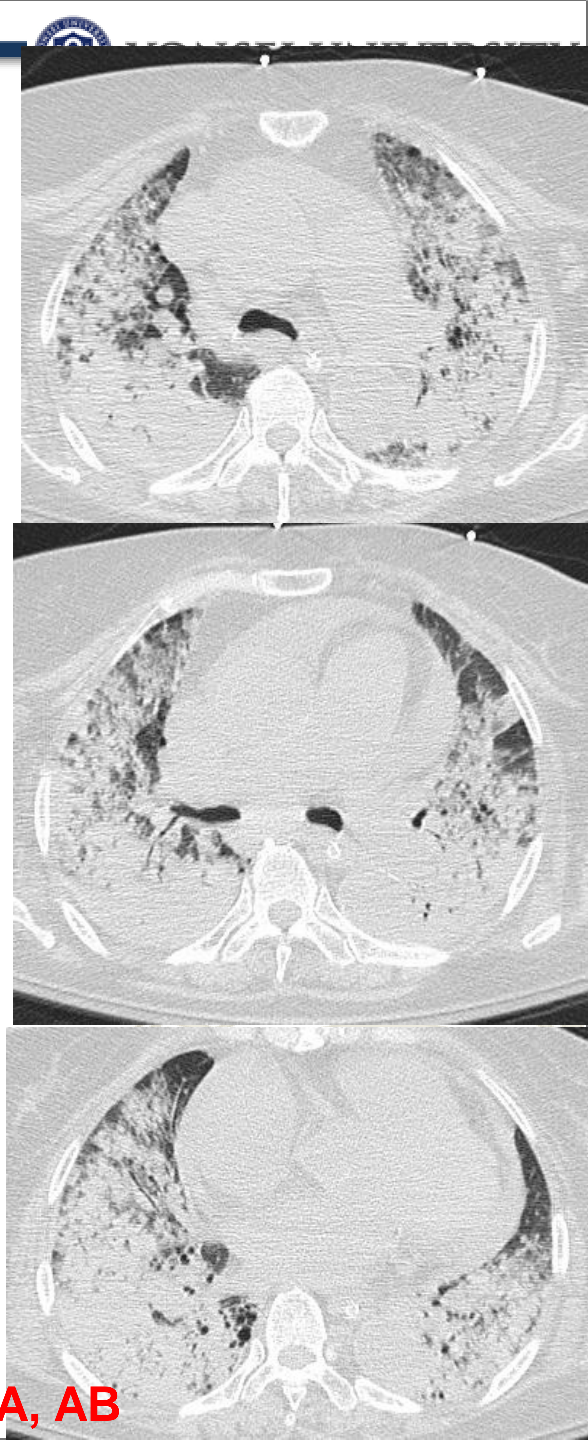
Division of Pulmonary and Critical Care Medicine

Department of Internal Medicine

Yonsei University College of Medicine

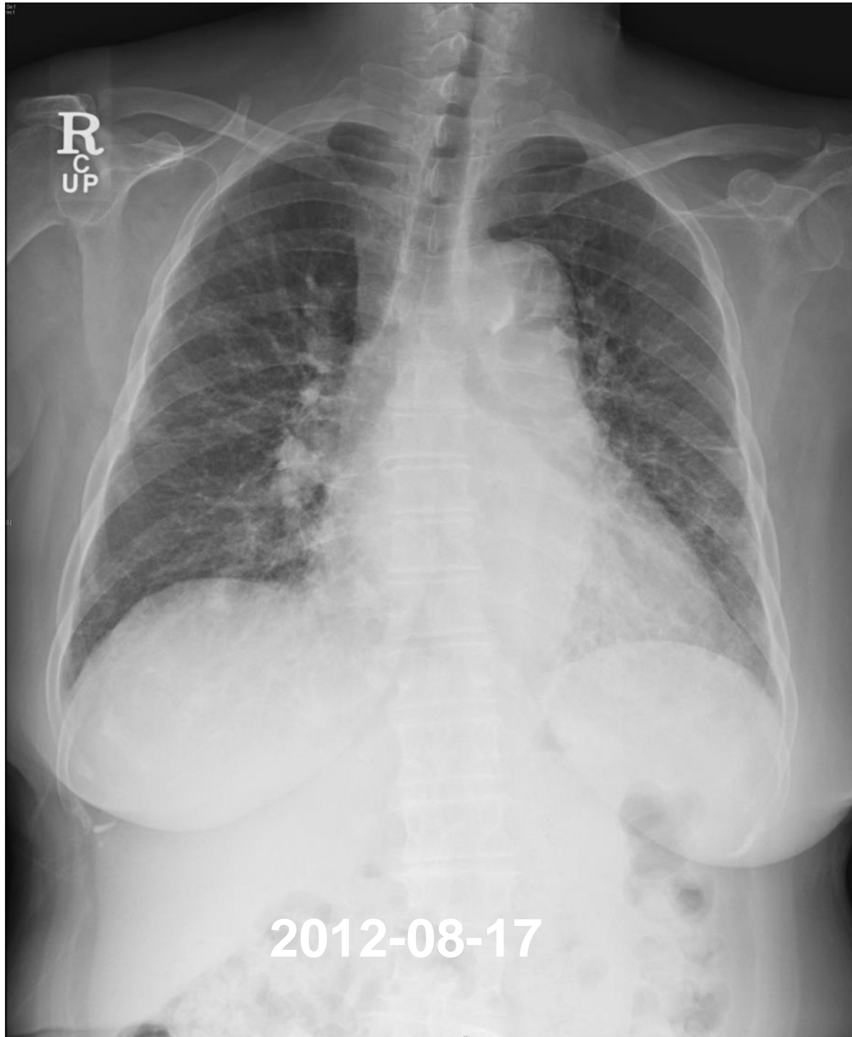
F/71 HTN, CAOD 1VD, CKD
Dyspnea, cough, blood tinged sp





Aspirin+, Hgb 8.0, ANA 1:160+, dsDNA-, SS-A+, RNP w+
P-ANCA+, C-ANCA-, MPO-, PR3-, BUN/cr 37/3.2
BAL – bloody, RBC 15400, WBC 540, poly 92%, Cx-MDR PA, AB

ARDS 치료 후 호전 다시 악화



2012-09-05

Vasculitis: Definition

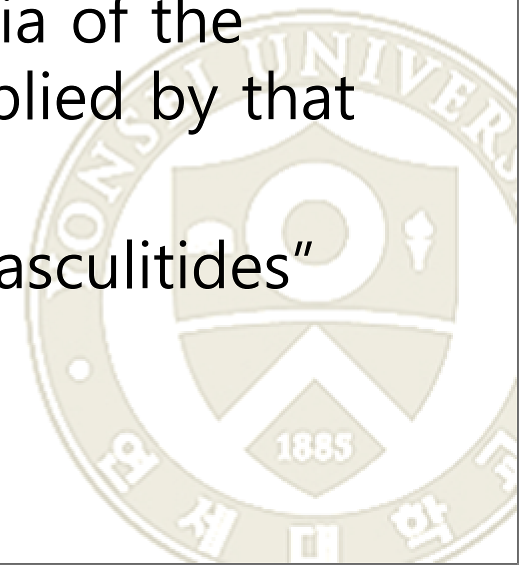
Pathologist

Inflammatory destruction of blood vessels

- **Infiltration** of vessel wall with inflammatory cells
  - Leukocytoclasis
  - Elastic membrane disruption
- **Fibrinoid necrosis** of the vessel wall
- **Ischemia**, occlusion, thrombosis
- **Aneurysm** formation
- Rupture, hemorrhage

Rheumatologist

- A clinicopathologic process characterized by inflammatory destruction of blood vessels that results in occlusion or destruction of the vessel and ischemia of the tissues supplied by that vessel.
- "Systemic vasculitides"



Systemic Vasculitis

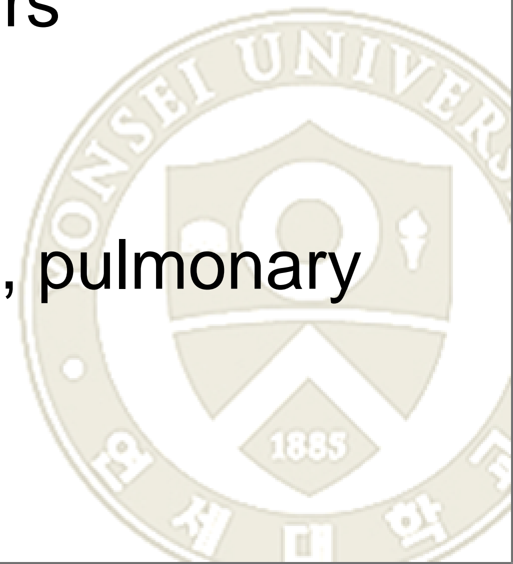
- Incidence 20-100 cases/million/year
- Prevalence 150-450 cases/million/year
- Clinical features : site, size and type of vessel involved
- Nonspecific, overlap with infections, CTDs, and malignancies
- Delay in diagnosis

Classification of Vasculitis

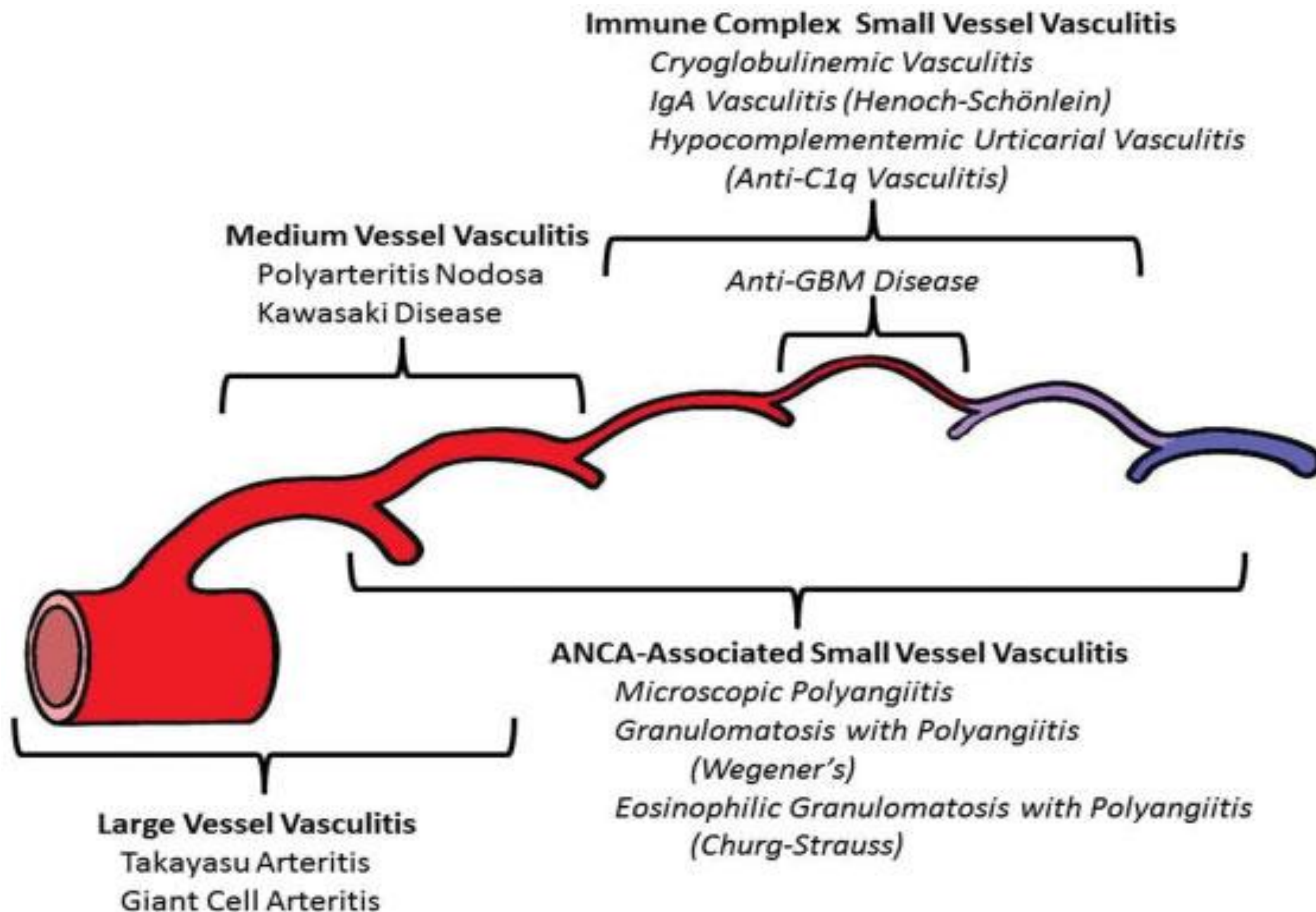
- Anaphylactoid purpura, in 1837 by Schonlein
- Polyarteritis nodosa, in 1866 by Kussmaul & Maier
- Diagnostic criteria for various vasculitis, in 1990 by American College of Rheumatology
- International Consensus Conference in Chapel Hill, in 1992 (1992 CHCC)
- Travis & Koss (1994), Brown (2006)
- 2012 CHCC; update definition
- Final classification; not yet

Vasculitis: Classification

- Large-vessel vasculitis
  - Aorta and the great vessels (subclavian, carotid)
  - Claudication, blindness, stroke
- Medium-vessel vasculitis
  - Arteries with muscular wall
  - Mononeuritis multiplex (wrist/foot drop), mesenteric ischemia, cutaneous ulcers
- Small-vessel vasculitis
  - Capillaries, arterioles, venules
  - Palpable purpura, glomerulonephritis, pulmonary hemorrhage



2012 Update of CHCC classification of vasculitis



ARTHRITIS & RHEUMATISM 2013;65(1):1-11

Large vessel vasculitis (LVV)
- Takayasu arteritis (TAK)
- Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)
- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small vessel vasculitis (SVV)
- Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (Wegener's) (GPA)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Immune complex SVV
  - Anti–glomerular basement membrane (anti-GBM) disease
  - Cryoglobulinemic vasculitis (CV)
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Variable vessel vasculitis (VVV)
- Behçet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology
- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

ARTHRITIS & RHEUMATISM 2013;65(1):1-11

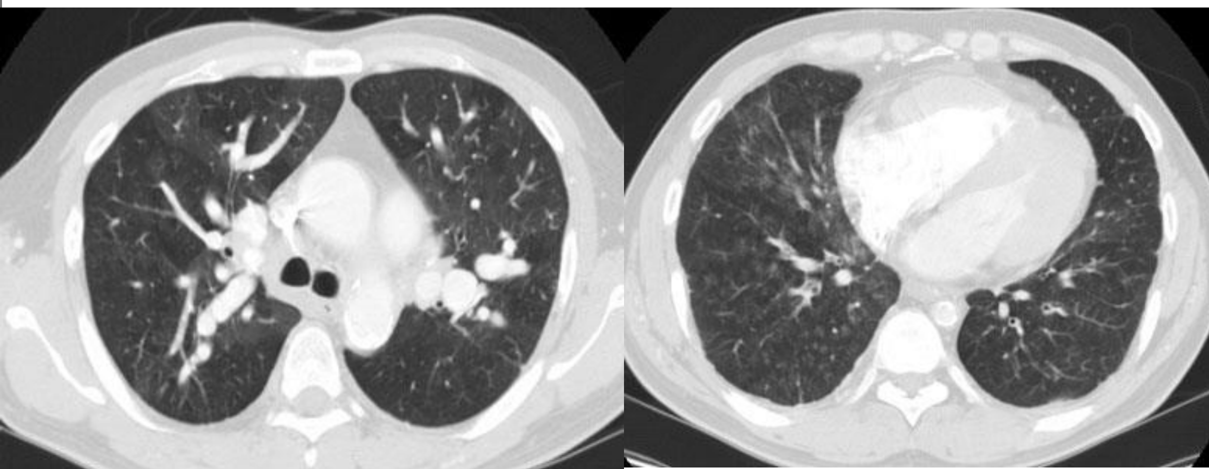
Hemoptysis 5 cups in pts with TAK

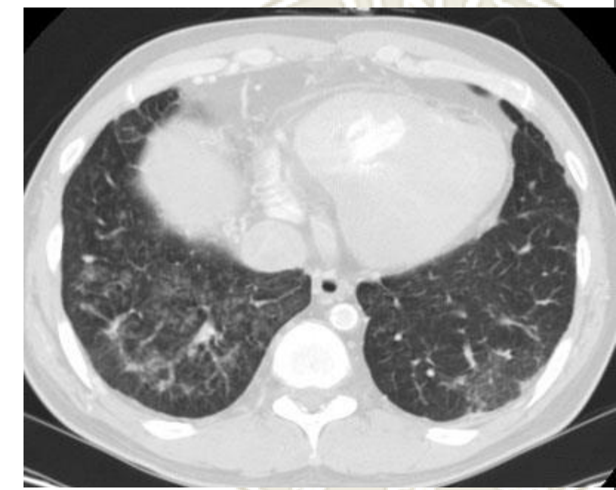
R

TAK, RVSP 100

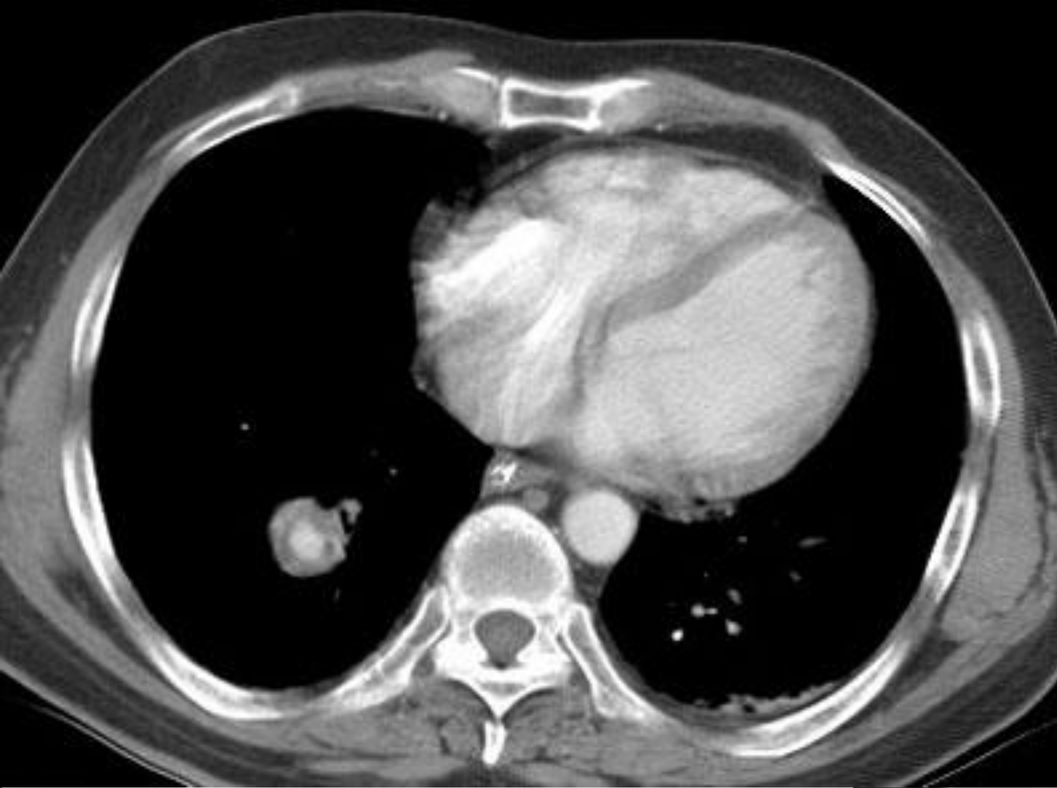
PL 20 + Bosantan

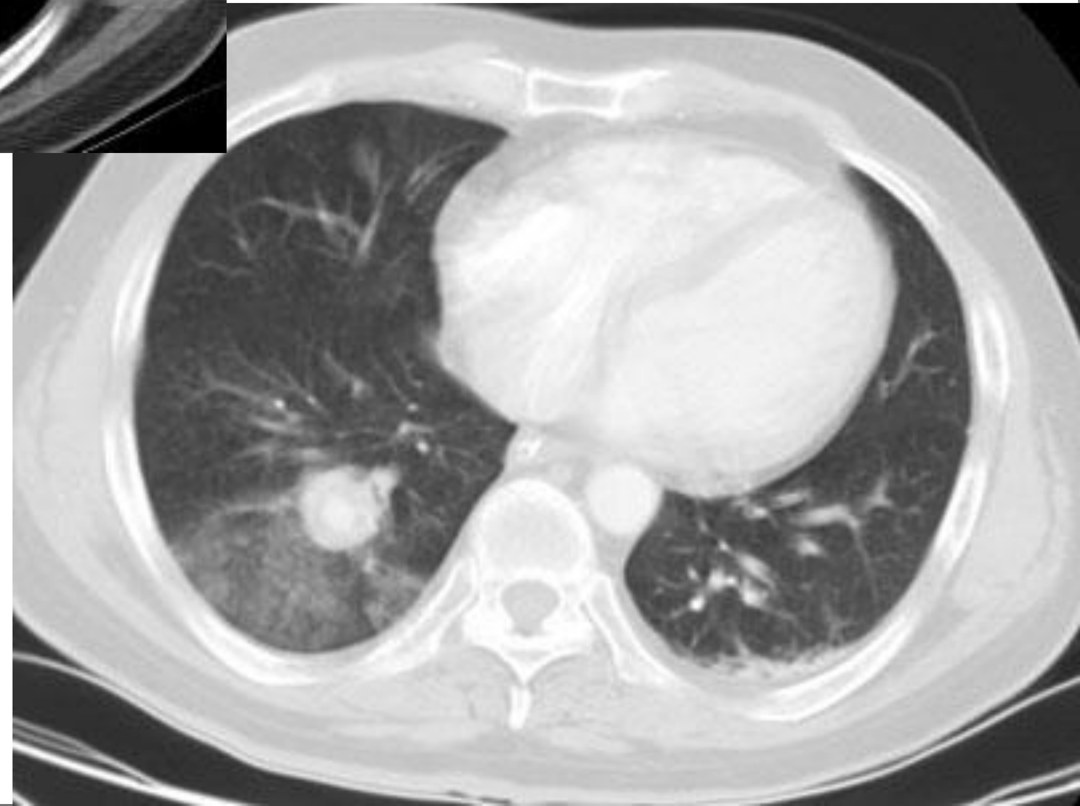
PL 60 + AZA 50 +
Sildenafil + Iloprost





Hemoptysis in Behcet's dis.





Clinical Features Suggesting Vasculitis

- Multisystem inflammatory disease
- Rapidly progressive major organ dysfunction
- Constitutional symptoms (fever, weight loss)
- High ESR, severe anemia, thrombocytosis
- Evidence of small-vessel inflammation:
    - In the kidneys = active urinary sediment
    - In the lungs = hemoptysis, dyspnea
    - In the skin = palpable purpura/hemorrhage
- Acute neurologic changes
    - Footdrop
    - Altered mental status

Clinical scenarios suggestive of vasculitis

1. Diffuse alveolar hemorrhage (DAH)
2. Acute glomerulonephritis (Acute GN) : RPGN
3. Pulmonary-renal syndrome
4. Destructive upper airway lesions
5. Chest imaging of cavitary or nodular disease
6. Palpable purpura
7. Mononeutitis multiplex
8. Multisystem disease

A. Idiopathic vasculitis with common pul. involvement

- Wegener's granulomatosis
- Churg-Strauss vasculitis
- Necrotizing sarcoid granulomatosis
- Vasculitis overap syndrome
- Cryoglobulinemic vasculitis
- Takayasu's arteritis
- Behcet's disease

B. Idiopathic vasculitis with rare pul. involvement

- Polyarteritis nodosa
- Henoch-Shonlein purpura
- Small vessel vasculitis
- Hypocomplementemic vasculitis
- Temporal arteritis

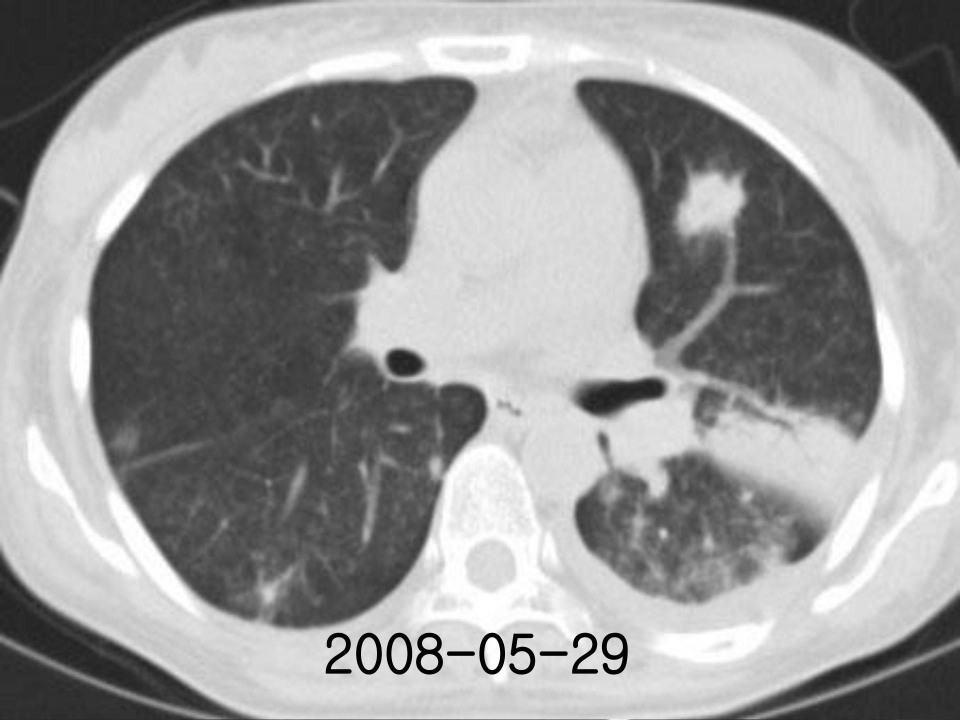
Travis & Koss, 1994

SLE with DAH

R

2008-05-31 오전

2008-05-31 오후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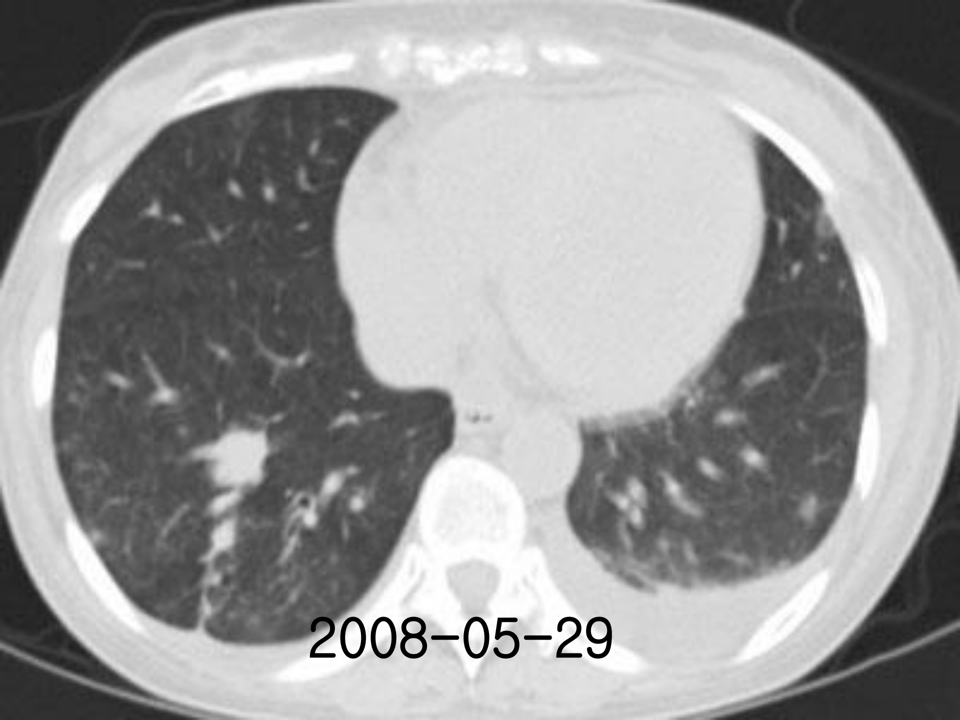
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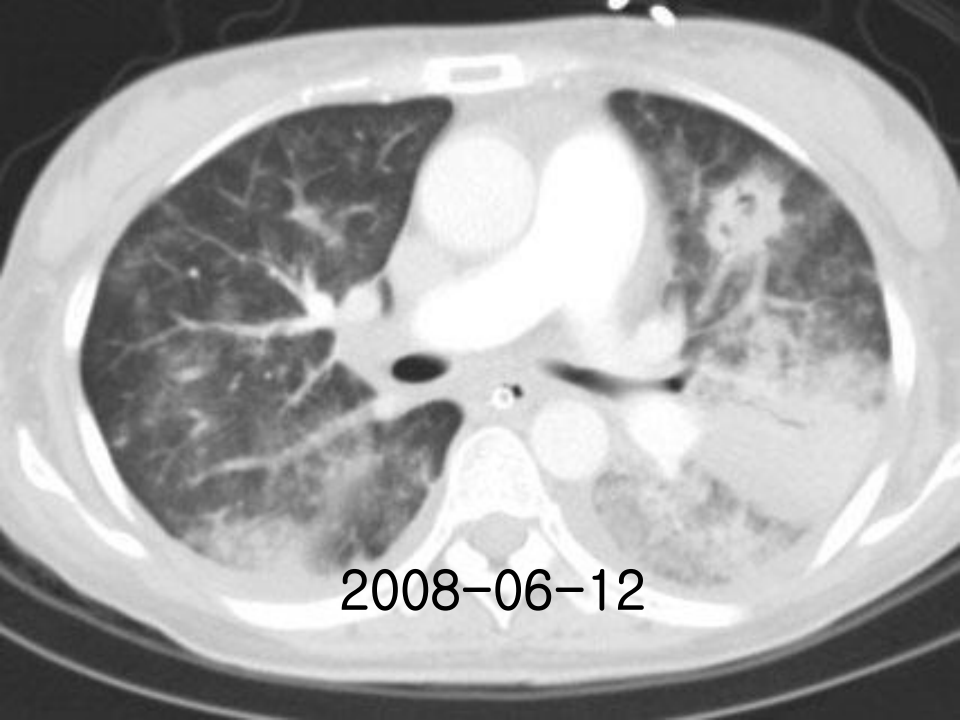
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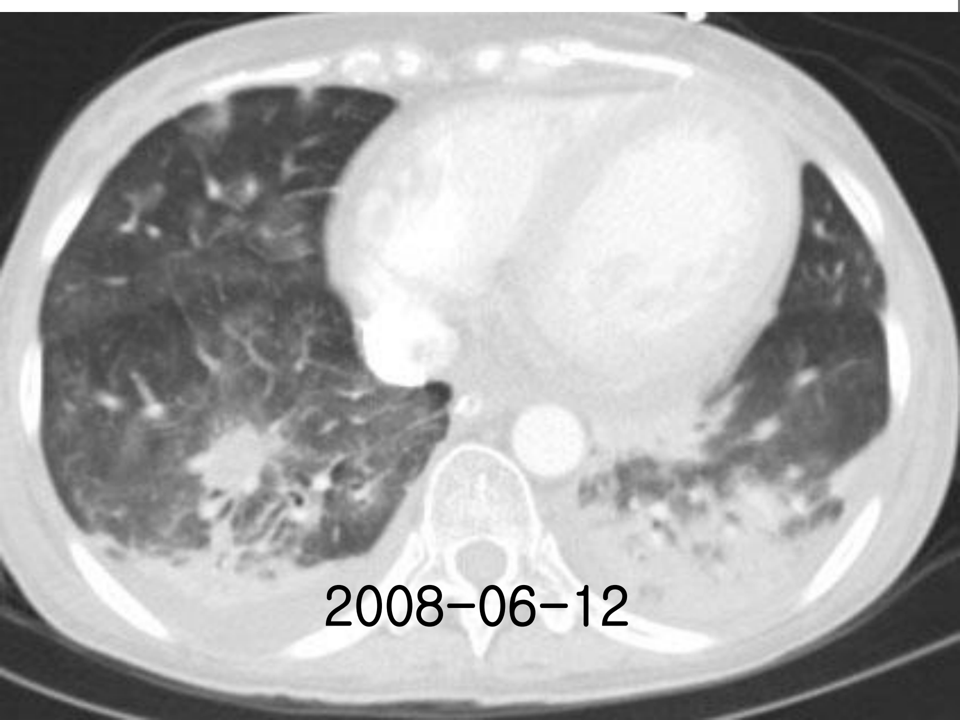
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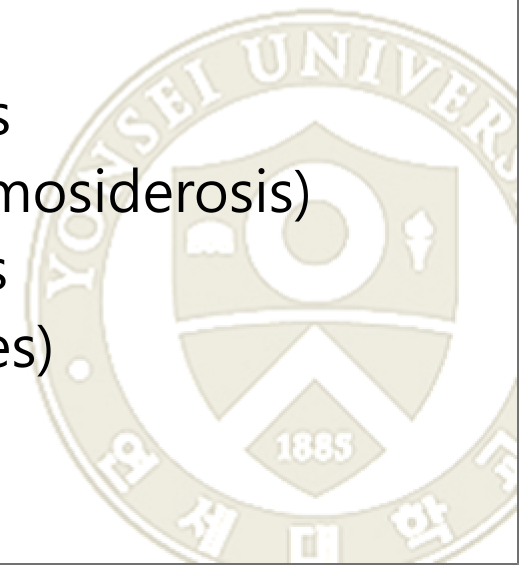
After steroid pulse & plasma exchange

2008-06-12

Vasculitis: Diagnosis

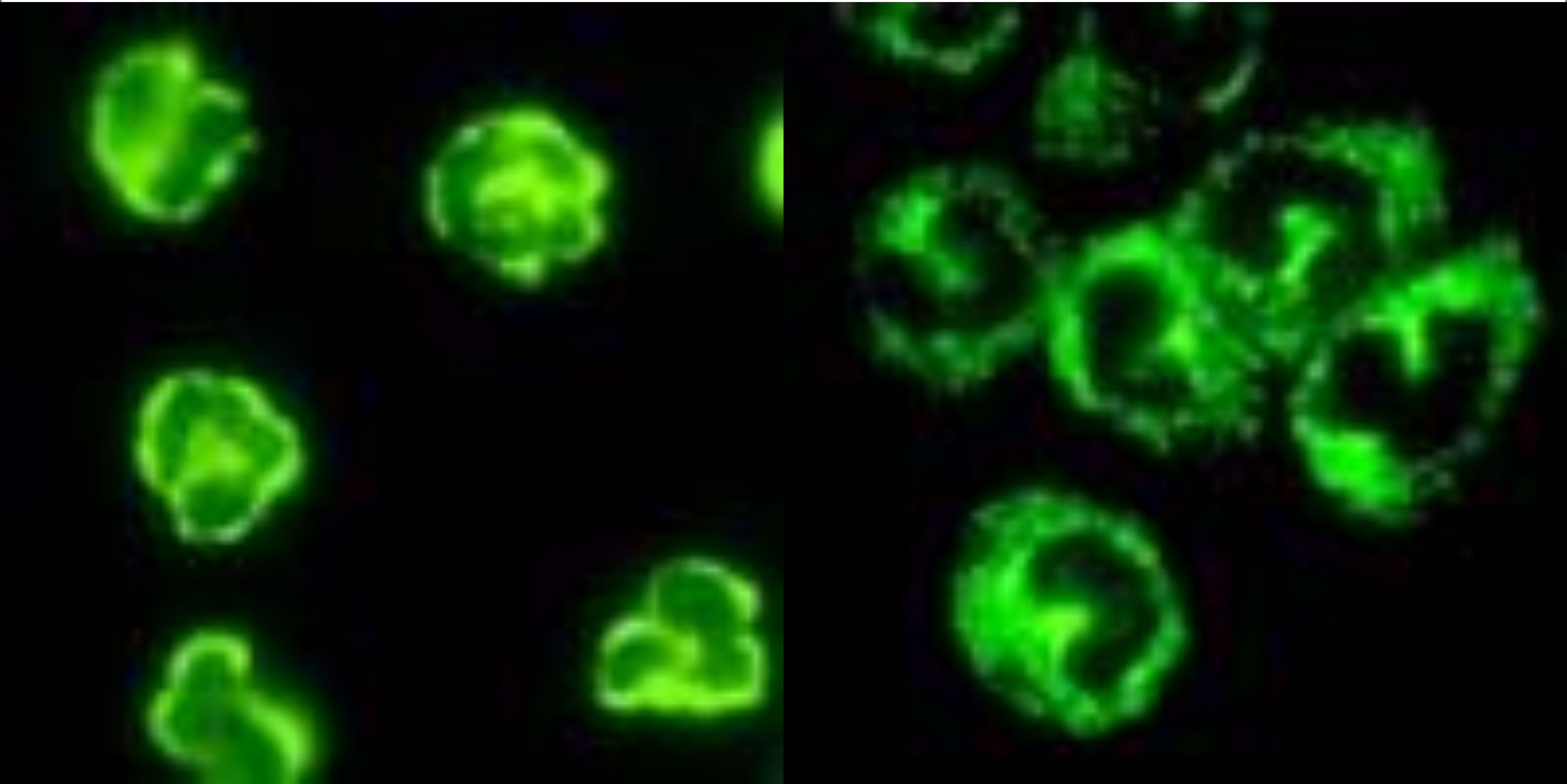
- **Diagnosis of exclusion, based on recognition of the clinical syndrome**
  - e.g. Churg-Strauss: adult onset asthma x 2 years, followed by atypical pneumonias, followed by peripheral nerve involvement
- **Biopsy of involved organ**
  - Biopsy may be helpful to exclude infection/malignancy
- **Other tests may be suggestive, but not diagnostic**
  - ESR, CRP
  - CT: pulmonary hemorrhage, cavitary lesions
  - Bronchoscopy: pulmonary hemorrhage (hemosiderosis)
  - Urinalysis: for patients with kidney vasculitis
  - ANCA (antineutrophil cytoplasmic antibodies)
  - Angiogram (including MRA, CT-angiogram)



Diagnostic Approach to Patients With Suspected Vasculitis (1)

- Consider tissue biopsy of affected organ to determine
  - Vessel size
  - Histologic features of vessel inflammation
    - Vessel wall necrosis
    - Granulomas/giant cells
    - Immune complex and/or C_3 deposition
- Consider angiography of mesenteric or cerebral vessels as clinically indicated

p - ANCA c - ANCA

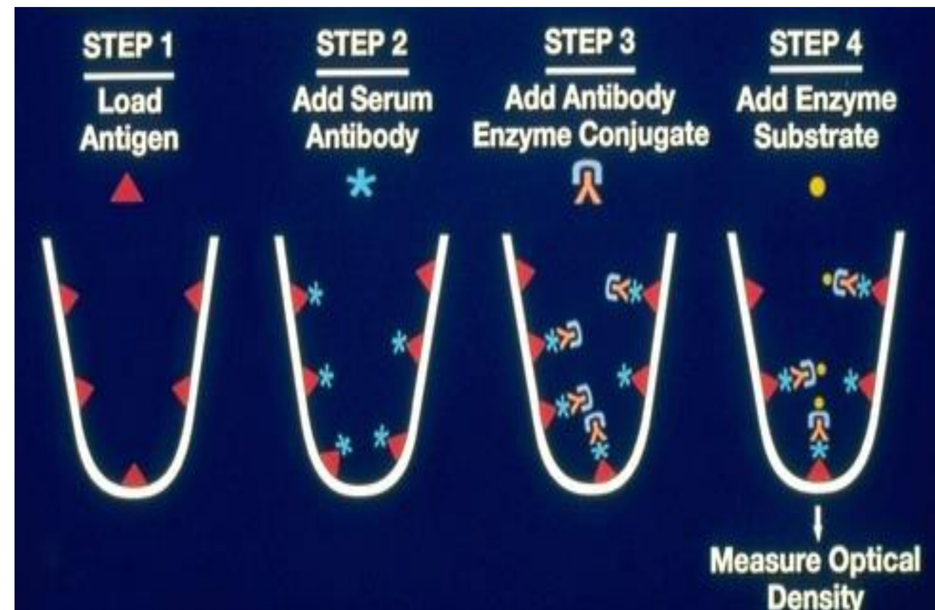


- ANCA by immunofluorescence methods

1885 연세대학

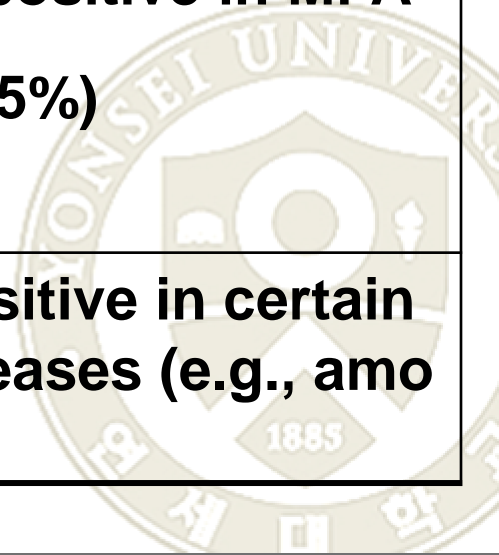
Antineutrophil Cytoplasmic Antibodies

- ANCA by ELISA methods
  - Proteinase 3 (PR3) = Wegener's disease
  - Myeloperoxidase (MPO) = MPA



1. Antineutrophil cytoplasmic antibodies (ANCA)

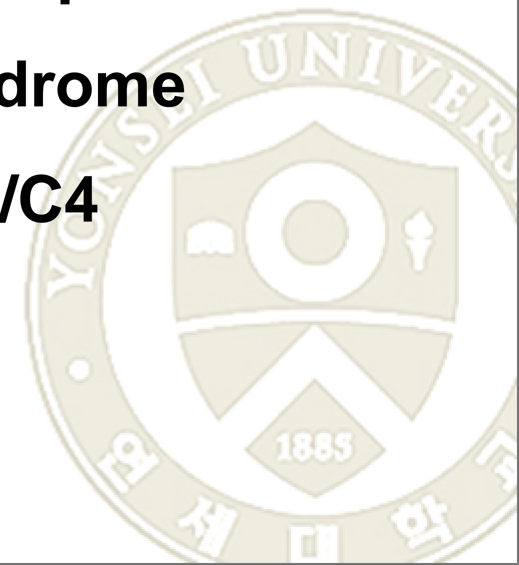
p - ANCA	c - ANCA
Target antigen is usually myeloperoxidase but nonspecific interactions	Target antigen is proteinase3
Most often positive in patients with MPA, CSS, or pauci-immune, RPGN	Highly specific (90-95%) in active, systemic WG, 40% in remission (overall 60~90%)
Positive in 50-75% MPA Positive in 35-75% CSS Positive in 5-30% WG	Occasionally positive in MPA and CSS (10-15%)
May be positive in RA, SLE, Goodpasture's syndrome, IBD, SBE, or other infections	Very rarely positive in certain infectious diseases (e.g., amoebiasia)



Clinical assessment (2)

2. Other laboratories

1) Exclude infection – culture of blood & others
2) Routine CBC, chemistries, BUN/Cr, LFT
3) ESR & CRP –elevated, but non-specific
4) Microscopic urinalysis – hematuria & proteinuria
5) Anti-GBM ab for Goodpasture's syndrome
6) ANA & RF, other specific autoab, C3/C4
7) IgE for CSS



Clinical assessment (3)

3. Radiographic imaging

- CT chest : cavity, nodule, diffuse GGO, rare LNE
- Other site CT, angiography, Echo, brain MRI

4. Bronchoscopy

- assess for infection / alveolar hemorrhage
- rarely positive pathologic diagnosis by TBB

5. Diagnostic biopsy

- skin, sinus or upper airway lesions
- renal biopsy for acute GN
- surgical lung biopsy

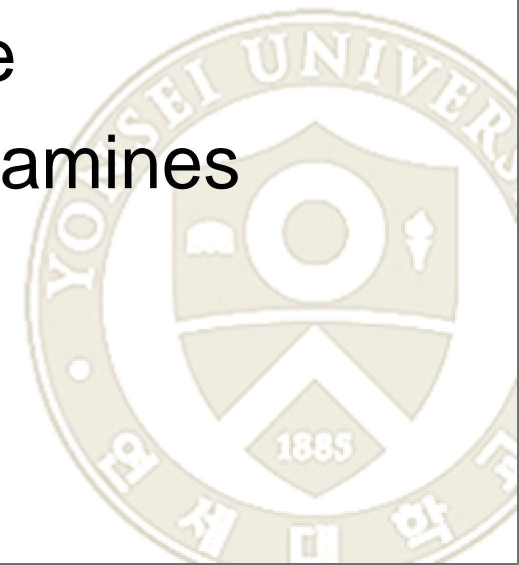
Diseases That Can Present as Vasculitic Syndromes

Vasculitis

- Infectious diseases
  - Bacterial endocarditis
  - HIV infections
  - Viral hepatitis
- Paraneoplastic syndromes
- Atrial myxoma

Vasculopathy

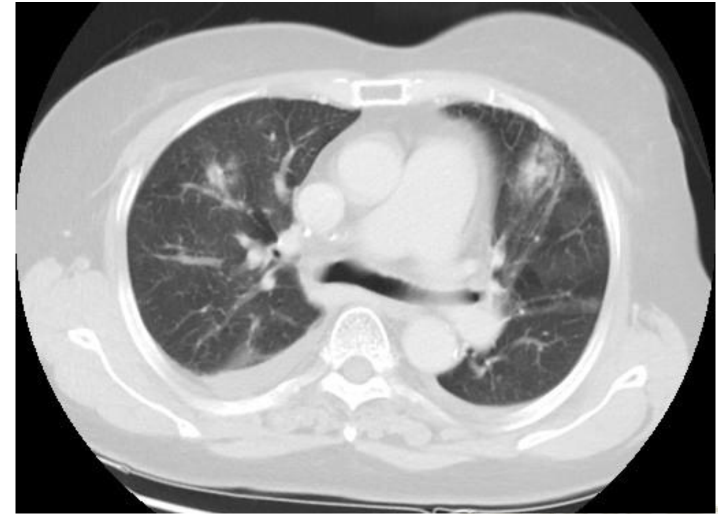
- Cholesterol emboli syndrome
- Toxic drug effects
  - Ergots
  - Cocaine
  - Amphetamines

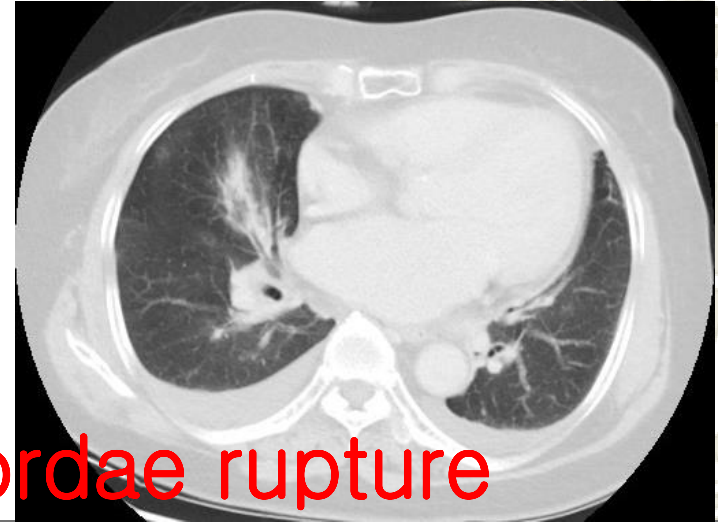


F/74, DOE/cough/hemoptysis

2005 breast ca, HTN, 2016-05 EF=60%

PA-RT





Severe MR with chordae rupture

ANCA associated vasculitis (AAV)

Necrotizing vasculitis

- Sinusitis
- Subglottic stenosis
- Pulmonary nodules
- Orbital pseudotumor

Wegener's

Necrotizing Granuloma

MPA

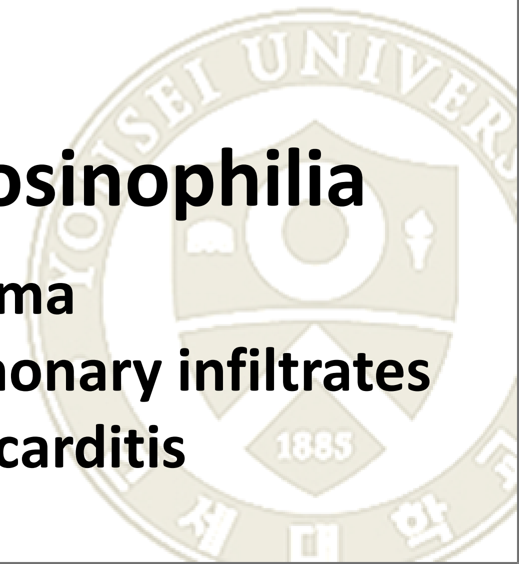
Churg-Strauss

No granuloma

- Pulmonary capillaritis
- Glomerulonephritis
- Sensory neuropathy
- Mononeuritis multiplex

Hypereosinophilia

- Asthma
- Pulmonary infiltrates
- Myocarditis



PR3-ANCAs and MPO-ANCAs in clinical studies

Differences between PR3-ANCA vasculitis and MPO-ANCA vasculitis

Table 1 | **Differences between PR3-ANCA vasculitis and MPO-ANCA vasculitis**

Feature	PR3-ANCA vasculitis	MPO-ANCA vasculitis
Epidemiology[9,91,145,156]	• Frequent in Northern European and American countries and Australia	• Frequent in Southern Europe and Asia
Usual age at diagnosis[153]	• 45–55 years	• 60–65 years
Genetic associations[87,88]	• *HLA-DP* • *SERPINA1* (encoding α1-antitrypsin) • *PRTN3* (encoding PR3)	• *HLA-DQ*
Pathology[153–155]	• Granuloma and vasculitis	• Vasculitis and fibrosis
Organ involvement[23,92–97]	• Frequent upper airway involvement and lung nodules • High number of organs involved	• Frequent renal involvement and pulmonary fibrosis
Prognosis[14,87,109,115–117,137–139]	• Increased risk of relapse	• Increased rate of initial treatment failure • Increased long-term risk of end-stage renal disease[145,146,149,150]
Response to therapy[97,135]	• Rituximab superior to cyclophosphamide for remission induction • PR3-ANCA titre might guide therapy after rituximab	• Similar response to rituximab and cyclophosphamide

ANCA, Anti-neutrophil cytoplasmic antibody; PR3, leukocyte proteinase 3; MPO, myeloperoxidase.

Nat Rev Rheumatol 2016

Vasculitis: Treatment

- Induction of remission : 12 months
- Maintenance : 12-18 months

  24-48 mon (REMAIN trial ongoing)

  - Cyclophosphamide (CYC)→ azathioprine (AZA)

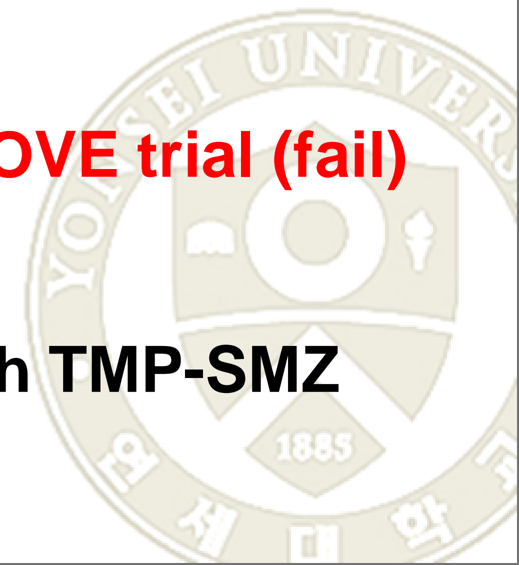
    or methotrexate (MTX)

  - Additional agents

    mycophenolate mofetil (MMF) : IMPROVE trial (fail)

    leflunomide : target T cells

  - Pneumocystis carinii prophylaxis with TMP-SMZ



Vasculitis: Treatment

- **Remission induction**:
  - Cyclophosphamide 2 mg/kg po qd x 3-6 months
    [or 15 mg/kg IV q 2 wk x3 then q 3 weeks x 6-12 months]
  - Prednisone 1 mg/kg po qd x 1 month, then taper
  - [Bactrim, Calcium, Vitamin D]
- **Remission maintenance** (minimum 2 years)
  - Methotrexate 20-25 mg po q week + folate
  - Azathioprine 2 mg/kg po qd
  - Mycophenolate mofetil 1.5 g po BID
  - Leflunomide 20-30 mg po BID

Treatment strategies for remission induction and maintenance of AAV

Nat Rev Nephrol 2014;10:25–36

Standard treatment of vasculitis

CLINICAL REVIEW

Wegener's Granulomatosis: Prospective Clinical and Therapeutic Experience With 85 Patients for 21 Years

ANTHONY S. FAUCI, M.D.; BARTON F. HAYNES, M.D.; PAUL KATZ, M.D.; and SHELDON M. WOLFF, M.D.; Bethesda, Maryland

- CYC (2 mg/kg/d) + CS (1 mg/kg/d)
- Gradually tapering CS
- Complete remission 79/85 (93%)

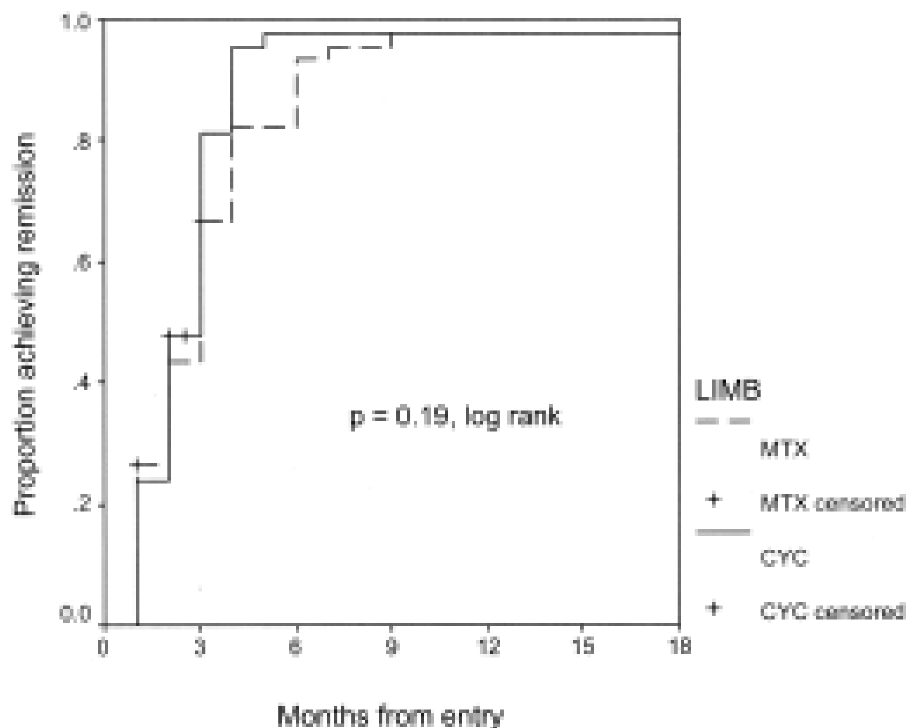
Ann Int Med, 1983

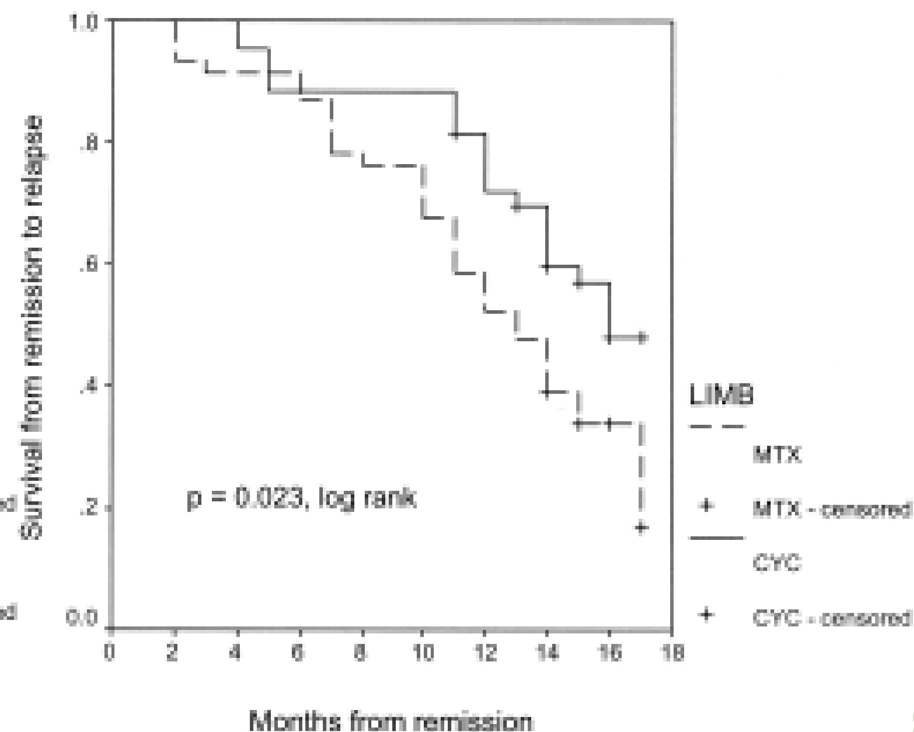
YONSEI UNIVERSITY

EUVAS grading of disease severity

Clinical class	Constitutional symptoms	Renal fx	Threatened vital organ fx	Options for Induction Tx
Limited	No	Cr<120 μmol/l (1.4 mg/dl)	No	CS or MTX or AZA
Early generalized	Yes	Cr<120 μmol/l (1.4 mg/dl)	No	CYC+CS or MTX+CS
Active generalized	Yes	Cr<500 μmol/l (5.7 mg/dl)	Yes	CYC+CS
Severe	Yes	Cr>500 μmol/l (5.7 mg/dl)	Yes	CYC+CS plasma exchange
Refractory	Yes	Any	Yes	Consider investigational agents

MTX vs CYC in early AAV (NORAM)



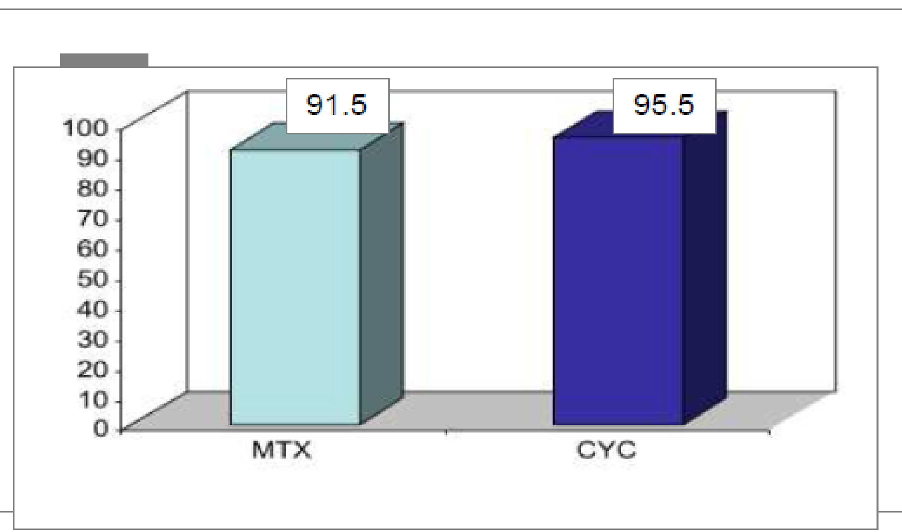


- MTX can replace CYC for initial treatment
- The MTX regimen was less effective in patients with extensive disease and pulmonary involvement than the CYC regimen
- The high relapse rates in both treatment →continuation of treatment beyond 12 months

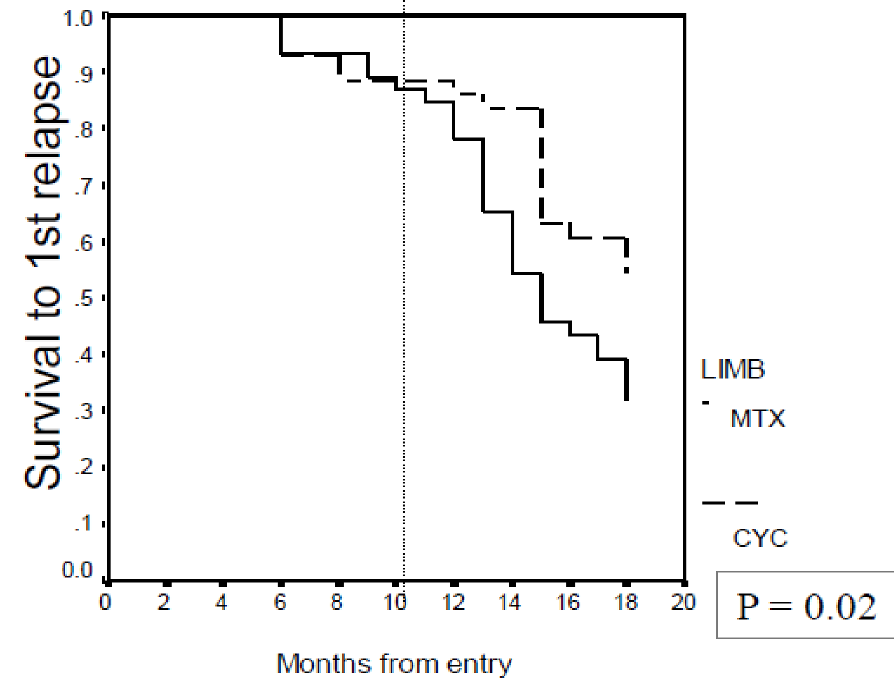
Arthritis & Rheum, 2005

MTX for non-severe disease (NORAM) f/u

Remission



Relapse



- MTX group at 5 years
  - More steroid before and after the trial (p=0.006)
  - More cyclophosphamide after the trial (p=0.047)

de Groot et al, *Arthritis Rheum* 2005; Faurschou et al, Arthritis Rheum 2012

Pulse vs oral CYC for remission induction in AAV (CYCLOPS)

Patients With Remission, %

1.0
0.8
0.6
0.4
0.2
0.0

0.0 2.0 4.0 6.0 8.0 10.0

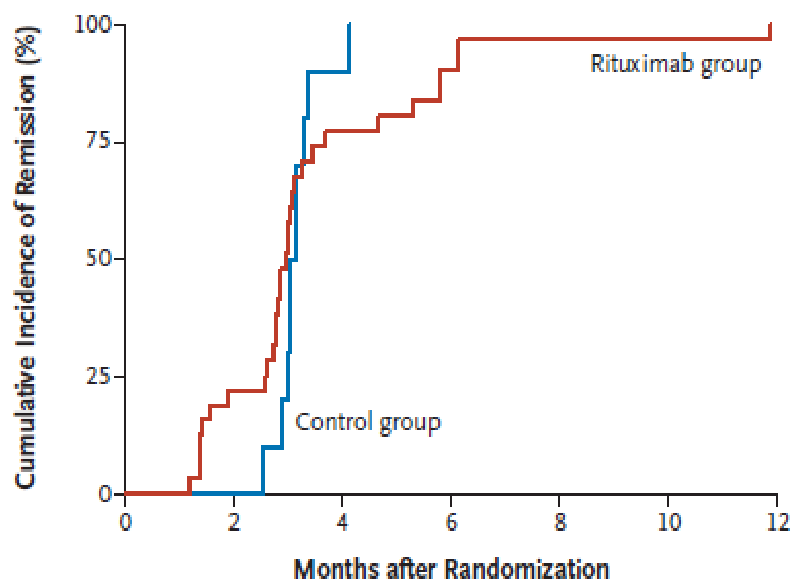
Time to Remission, *mo*

- ···· Daily oral CYC, 2 mg/kg/d (N=73)
- — Pulse CYC, 15 mg/kg/2~3 wks (N=76)
- ■ Daily oral—censored
- ● Pulse—censored

Daily oral	73	43	18	4	0
Pulse	76	46	15	4	2

Ann Intern Med , 2009;150:670-680

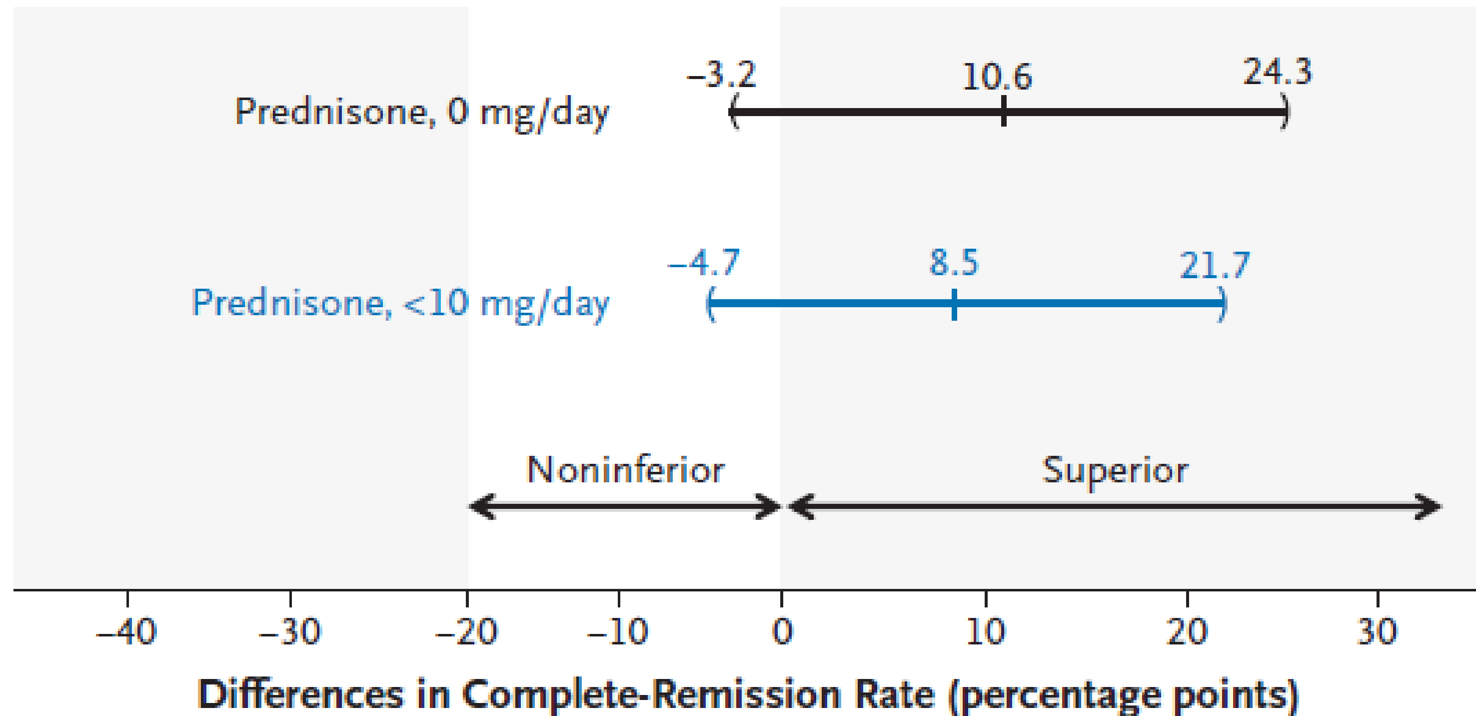
Rituximab vs IV CYC for remission induction in severe AAV (RITUXAVAS)



Results	RTX N=33	CYC N=11
Sustained remission at M12 (BVAS0x2 at 6m)	76%	82%
Deaths	6 (18%)	2 (18%)
Remission	82%	91%
eGFR at M 12 (recovery from dialysis)	51 (5/8)	33 (1/1)
ANCA neg by 6 months	89%	81%

NEJM, 2010;363:211-220

Rituximab vs oral CYC for induction of remission in AAV (RAVE)

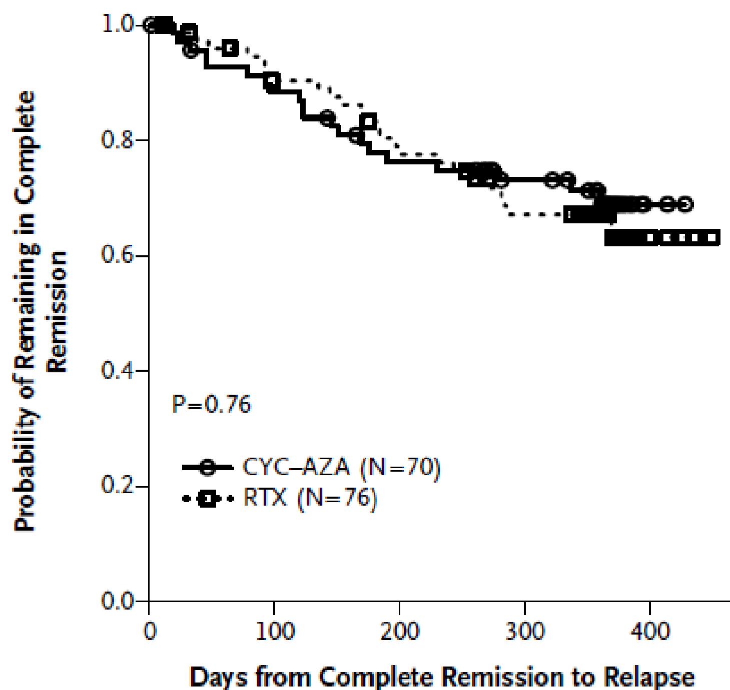


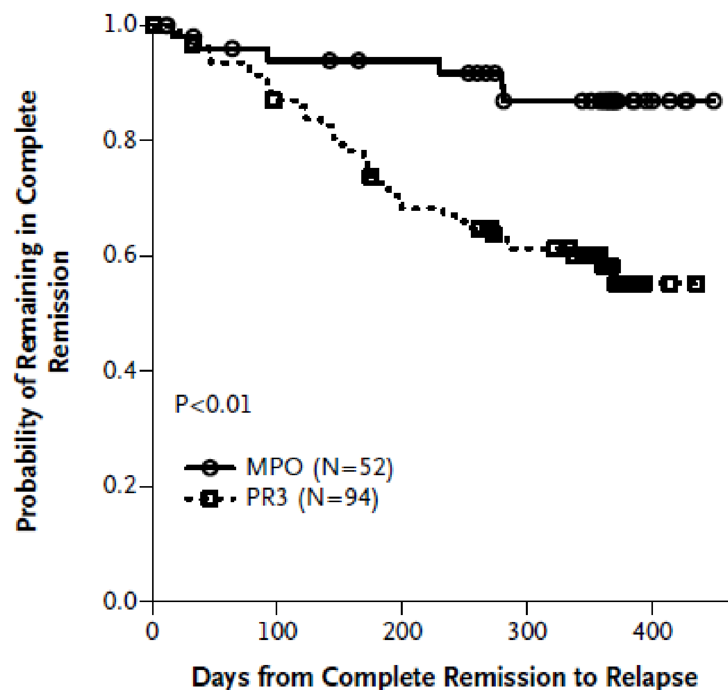
- Remission induction
  - Rituximab - 63/99 (64%)
  - Control - 52/98 (53%)

- Remission induction after relapse
  - Rituximab – 34/51 (67%)
  - Control - 21/50 (42%) p=0.01

NEJM, 2010;363:221-232

Rituximab vs oral CYC for induction of remission in AAV (RAVE), F/U 6, 12, 18 mo





NEJM, 2013;369:417-427

Substitution of CYC to AZA after remission (CYCAZAREM)

P=0.65

Cyclophosphamide group

Azathioprine group

Proportion Surviving without Relapse

1.0
0.9
0.8
0.7
0.6
0.0

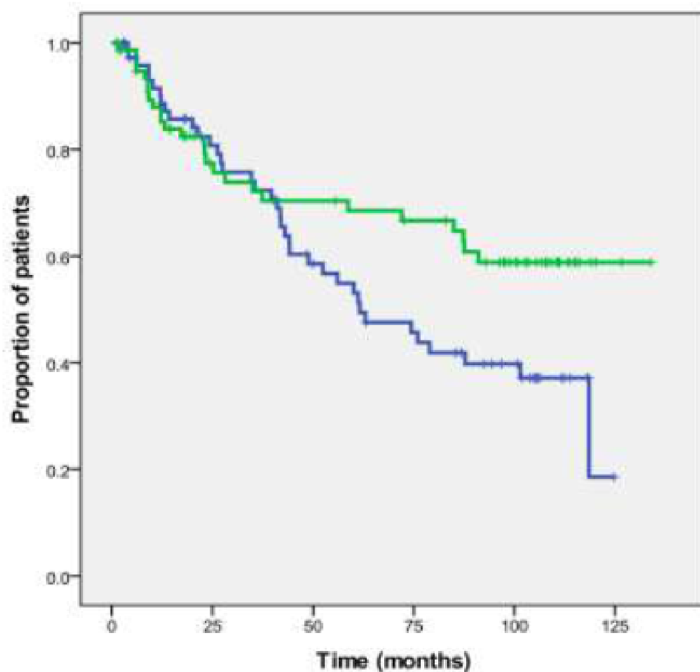
3
6
9
12
15
18

Months after Study Entry

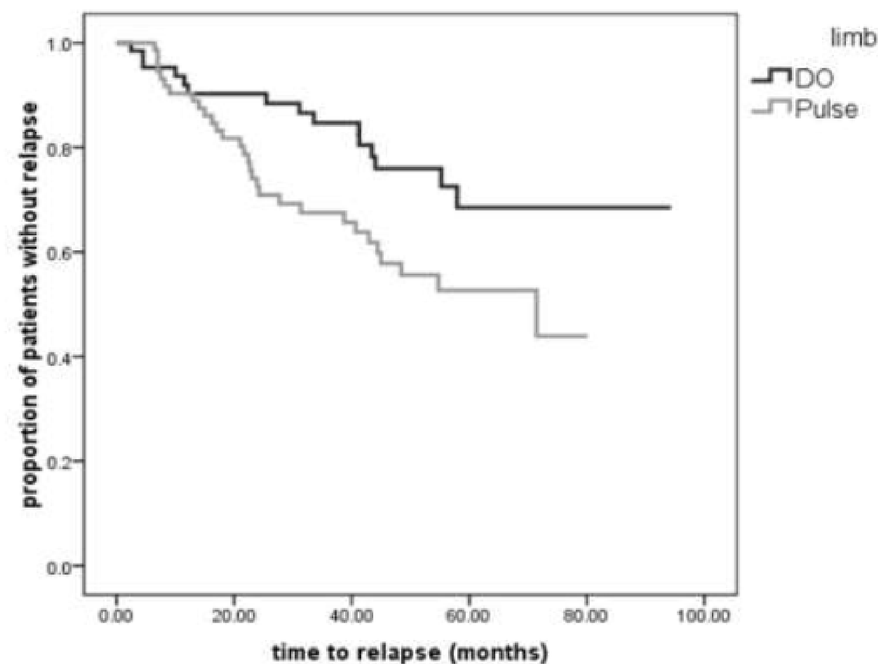
NEJM, 2003

Less cyclophosphamide increases relapse risk

CYCAZAREM

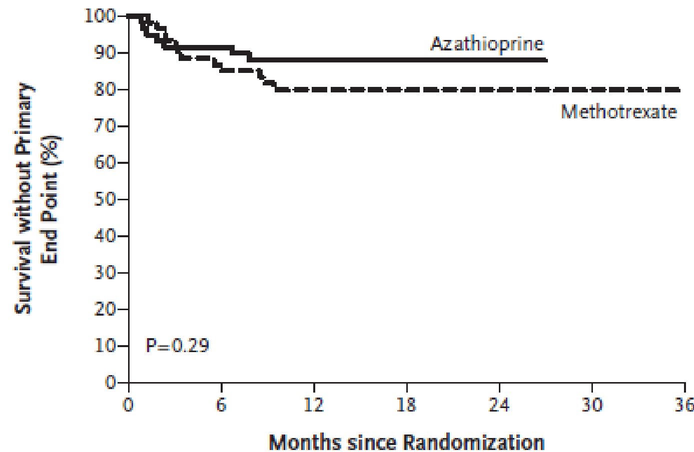


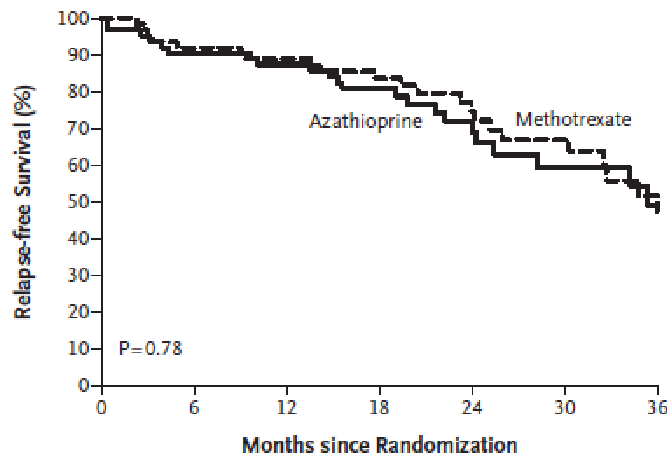
CYCLOPS



Harper et al, *Arthritis Rheum* 2011

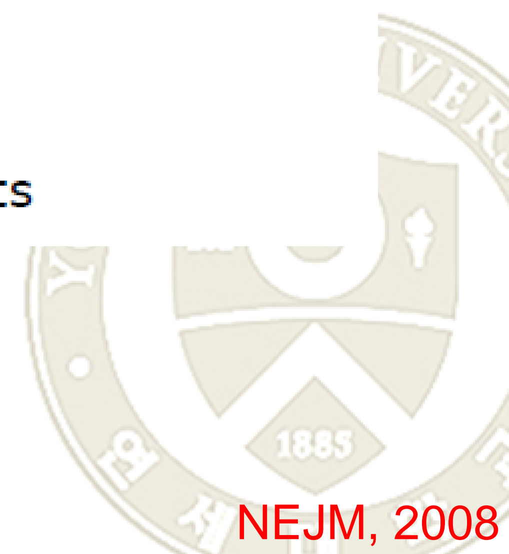
AZA vs MTX Maintenance for AAV





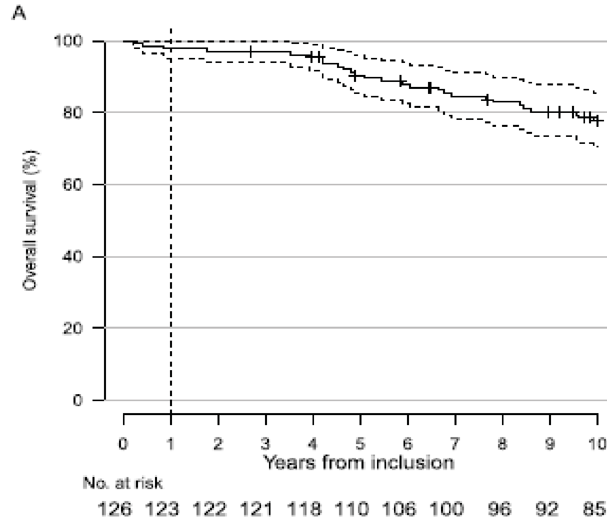
WEGENT

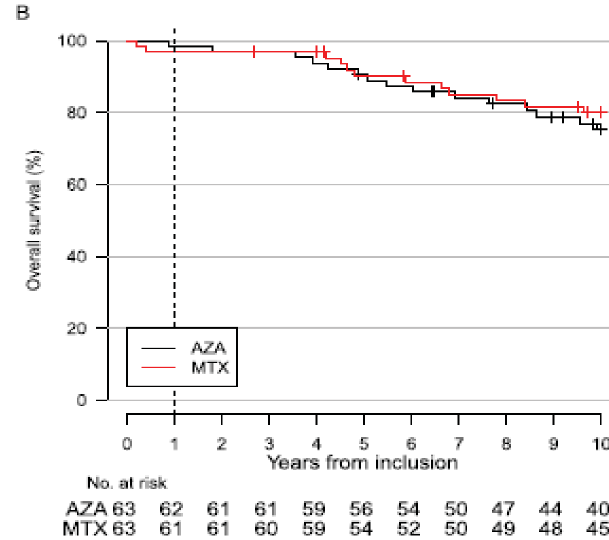
- 159/126 pts
- Relapses (%) at 18m/36m:
  - Aza: 17.8/50.1
  - Mtx: 13.7/46.7
- Drug discontinuation or death
  - Aza: 7 pts
  - Mtx: 12 pts
- SAE:
  - Aza: 5 pts
  - Mtx: 11 pts

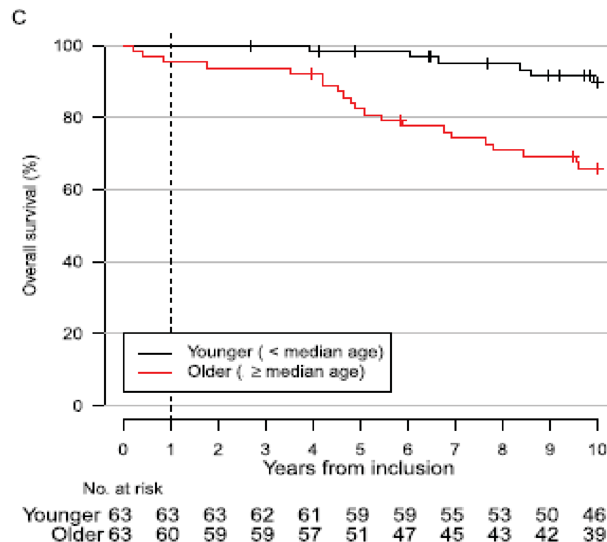


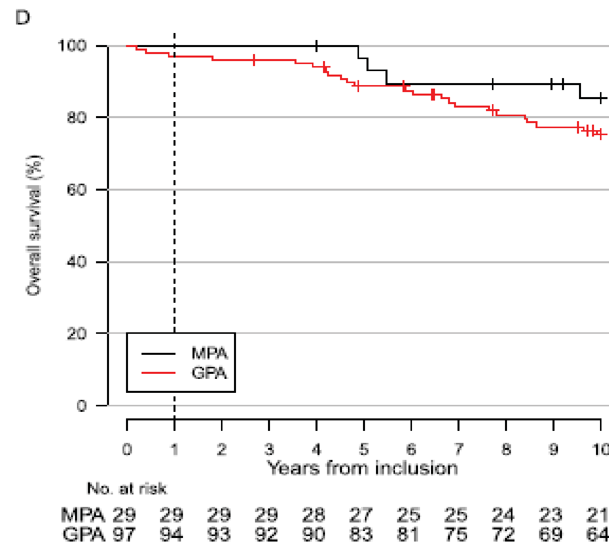
NEJM, 2008

WEGENT long-term F/U



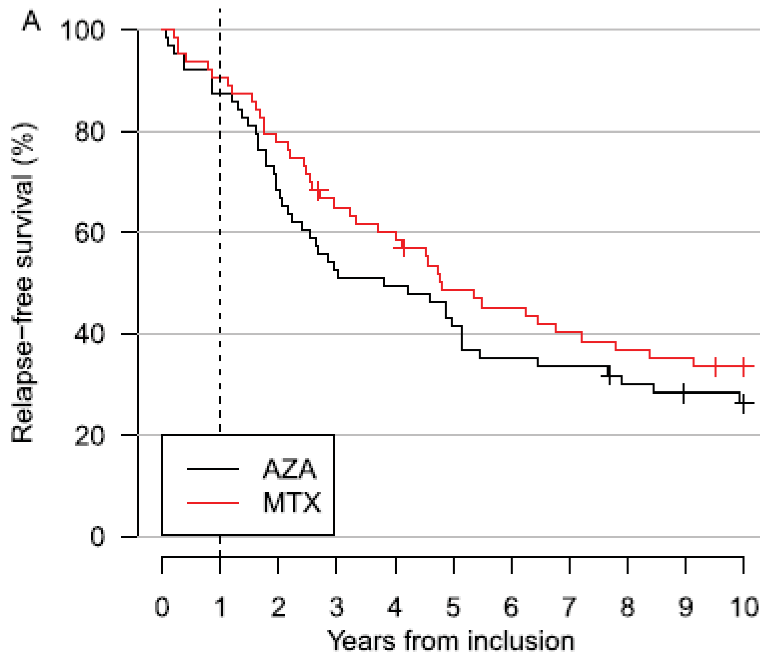


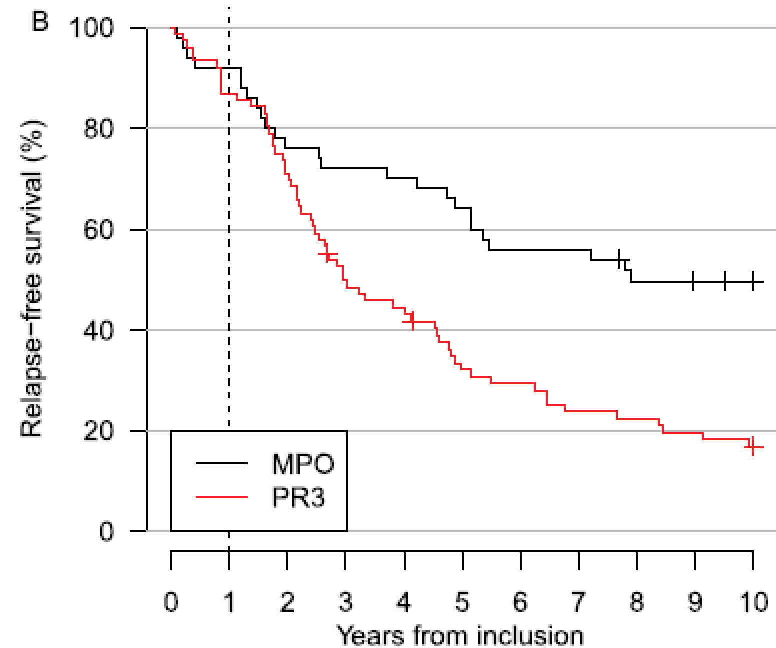




Arthritis Rheumatol. 2016 Mar;68(3):690-701

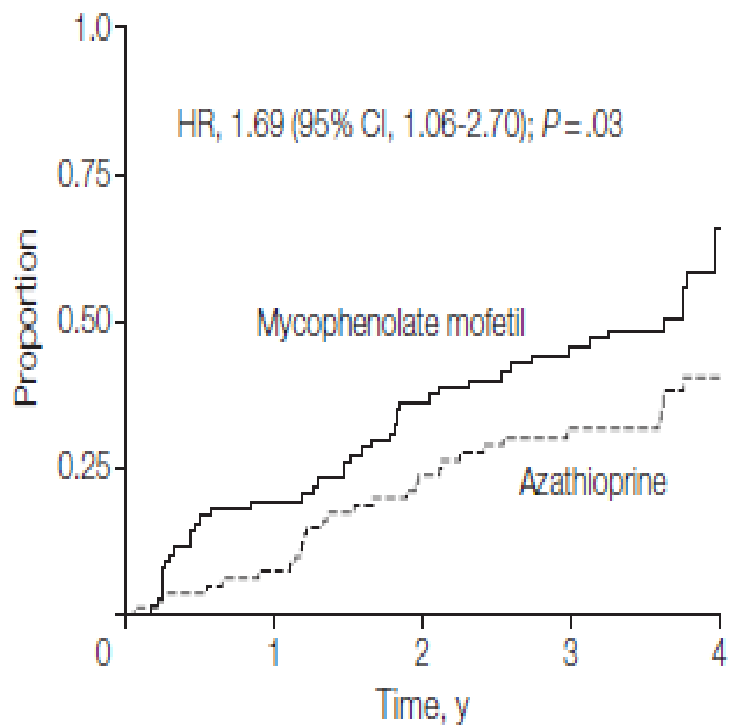
WEGENT long-term F/U

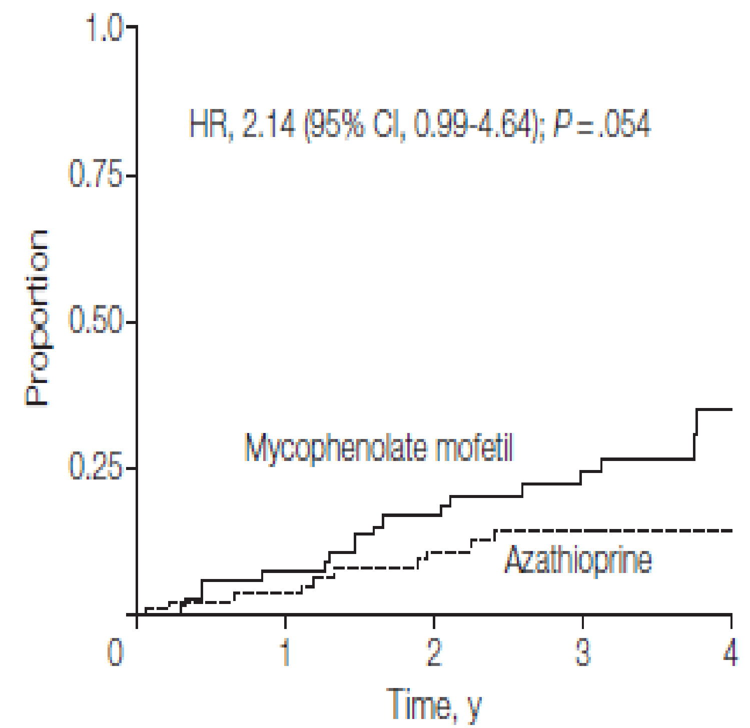




Arthritis Rheumatol. 2016 Mar;68(3):690-701

IMPROVE: AZA vs MMF Maintenance for AAV



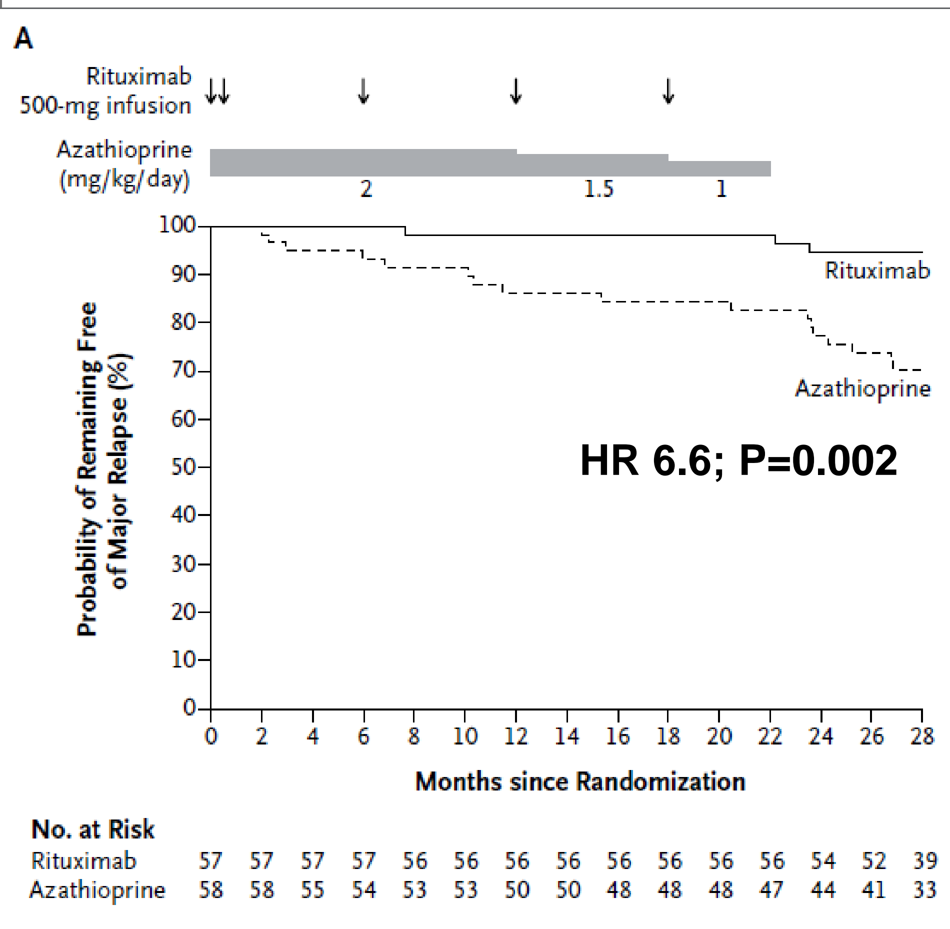


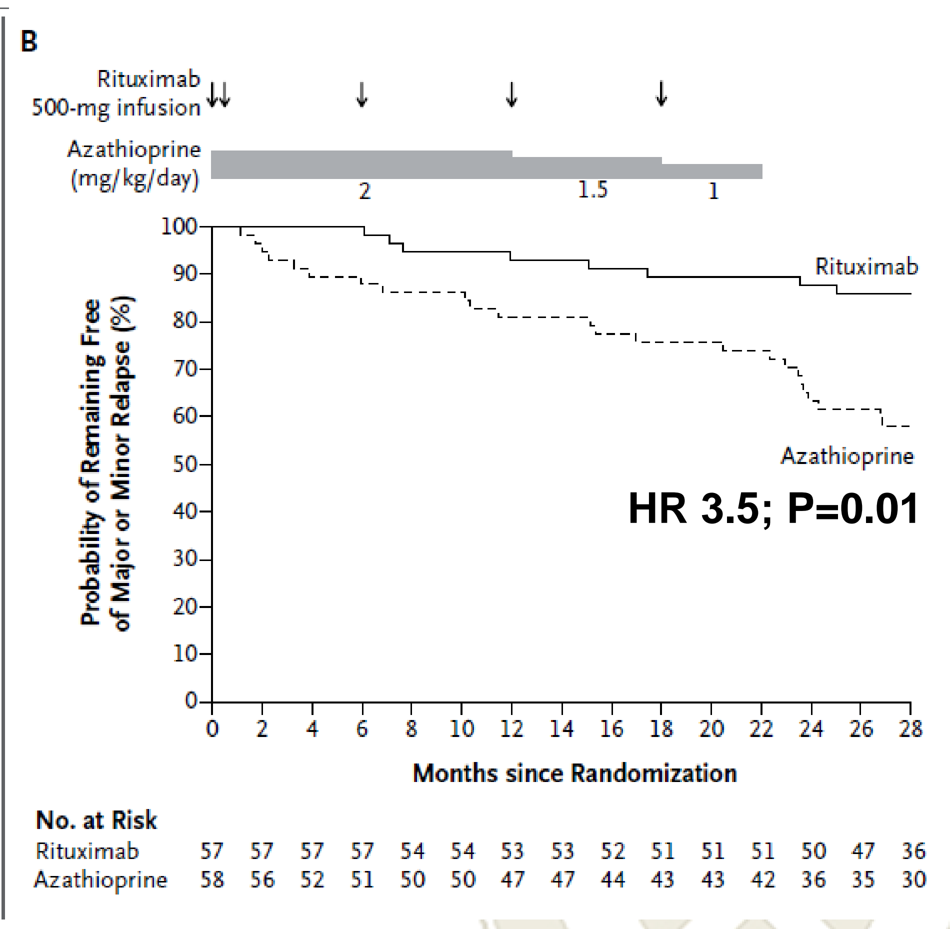
No. at risk

	0	1	2	3	4	0	1	2	3	4
Azathioprine	80	72	57	46	6	80	72	57	46	6
Mycophenolate mofetil	76	60	47	37	4	76	60	47	37	4

JAMA 2010;304(21):2381-2388

MAINRITSAN: Rituximab vs AZA for Maintenance in AAV F/U 28 mo





Major relapse rate: AZA – 17/58 (29%), RTX – 3/57 (5%)

NEJM, 2014;371:1771-1780

YONSEI UNIVERSITY

Protocol target prednisolone dosages in the key induction trials of AAV

Glucocorticoid Dose

0 10 20 30 40 50 60

Mean and 95% CI

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

Weeks post diagnosis

Ann Rheum Dis 2016

Refractory disease in remission

- Not responded to active treatment
- Consider novel or experimental treatment
- Anti-TNF-α therapy (infliximab)
- Anti-thymoglobulin (ATG)
- IV IG (single 2 g/kg or 0.5 g/kg/d X 4 days)
- Anti-CD20 Ab (rituximab)
- Plasma Exchange (PEX)

Etanercept plus standard Tx for WG after remission (WGET)

Cumulative Probability of Sustained Remission

1.00
0.75
0.50
0.25
0.00

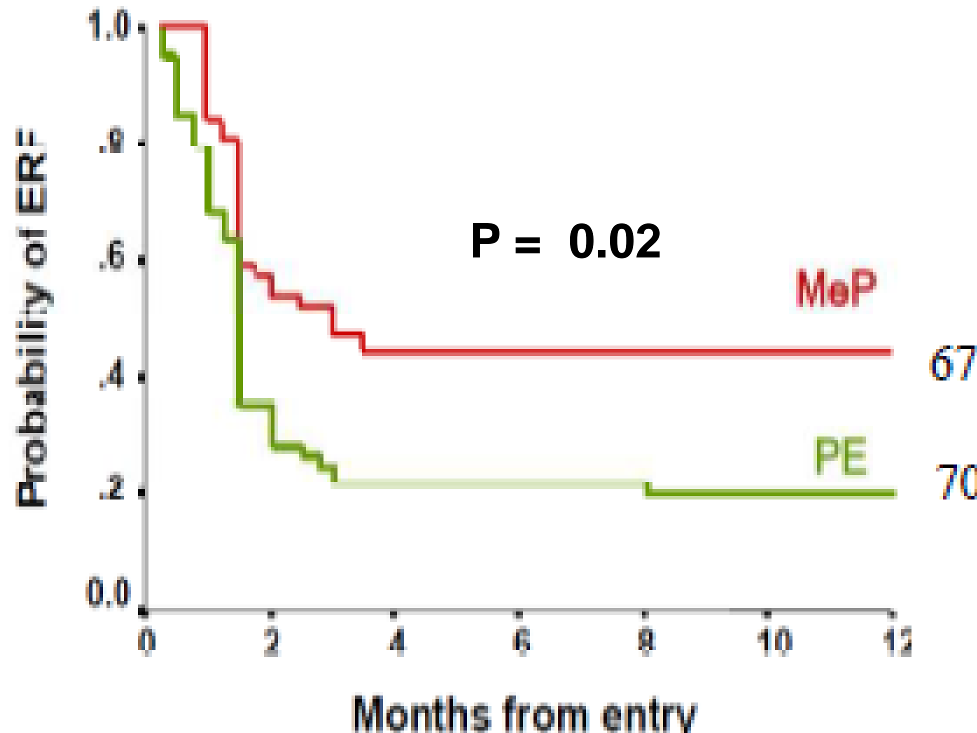
Control
Etanercept
P=0.39

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40

Months

NEJM, 2005

Plasma EXchange vs HD-MEP for severe AAV with RPGN (MEPEX)



1 yr alive & free dialysis rate

33/67 (49%)

48/70 (69%)

151 pts

High mortality in both arms: 25%: infection 19, pulm. hemorrhage 6, CVD 4.

J Am Soc Nephrol 2007;18: 2180–2188

TX recommendation; EULAR 2016

- Remission-induction of new-onset AAV
  - organ-threatening or life-threatening: CS + CYC or RTX
  - non-organ-threatening : CS + MTX or MMF
- Relapse of organ-threatening or life-threatening AAV
  - CS + CYC or RTX
  - PEX in AAV with RPGN (Cr 5.7 mg/dL) or DAH
- Remission-maintenance of AAV
  - Low dose CS + AZA, RTX, MTX, MMF
  - Continued for at least 24 months
- Refractory to remission-induction therapy
  - switching from CYC→RTX or RTX→CYC, or clinical trial

Ann Rheum Dis 2016

Vasculitis: Monitoring

- To minimize morbidity & mortality of the vasculitides and their therapy
- Differential diagnosis in pts with clinical deterioration
  - infection : major contributor, 10% in CTX Tx
  - drug toxicity : 12% cystitis, 8% MDS, 5% solid malignancy in CTX Tx
  - disease relapse :40-65% in WG, 15-25% in CSS
  - a new unrelated problem

Conclusions

- Pulmonary vasculitis is one component of a variety of systemic vasculitis
- Early diagnosis using common clinical scenarios and appropriate investigations
- Aggressive early treatment to minimize disease related mortality & irreversible damage
- Regular monitoring for disease activity and medication toxicity