

Rapidly progressive glomerulonephritis ANCA vasculitis

Intensive Review of Nephrology
Continuing Education

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL**

Disclosures

- Study support
 - Chemocentryx Amgen
 - Classic and ADVOCATE trials
 - Alexion/ AstraZeneca
 - Vera Therapeutics

ANCA Vasculitis

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ANCA Vasculitis 2025

Outline

- Disease
- Diagnosis
- Pathophysiology
- Treatments -- Tools
- Strategies
 - Induction
 - Maintenance
- (Special Scenarios)



ANCA Vasculitis



Disease

Spectrum of Vasculitis Associated with ANCA

Granulomatosis with polyangiitis

- Wegener's granulomatosis

Microscopic polyangiitis

- Including the syndrome of alveolar hemorrhage and nephritis

Renal limited variant

- Pauci-immune necrotizing and crescentic glomerulonephritis

EGPA -- Churg Strauss Syndrome

Spectrum of Vasculitis Associated with ANCA

PR3 ANCA vasculitis

MPO ANCA vasculitis

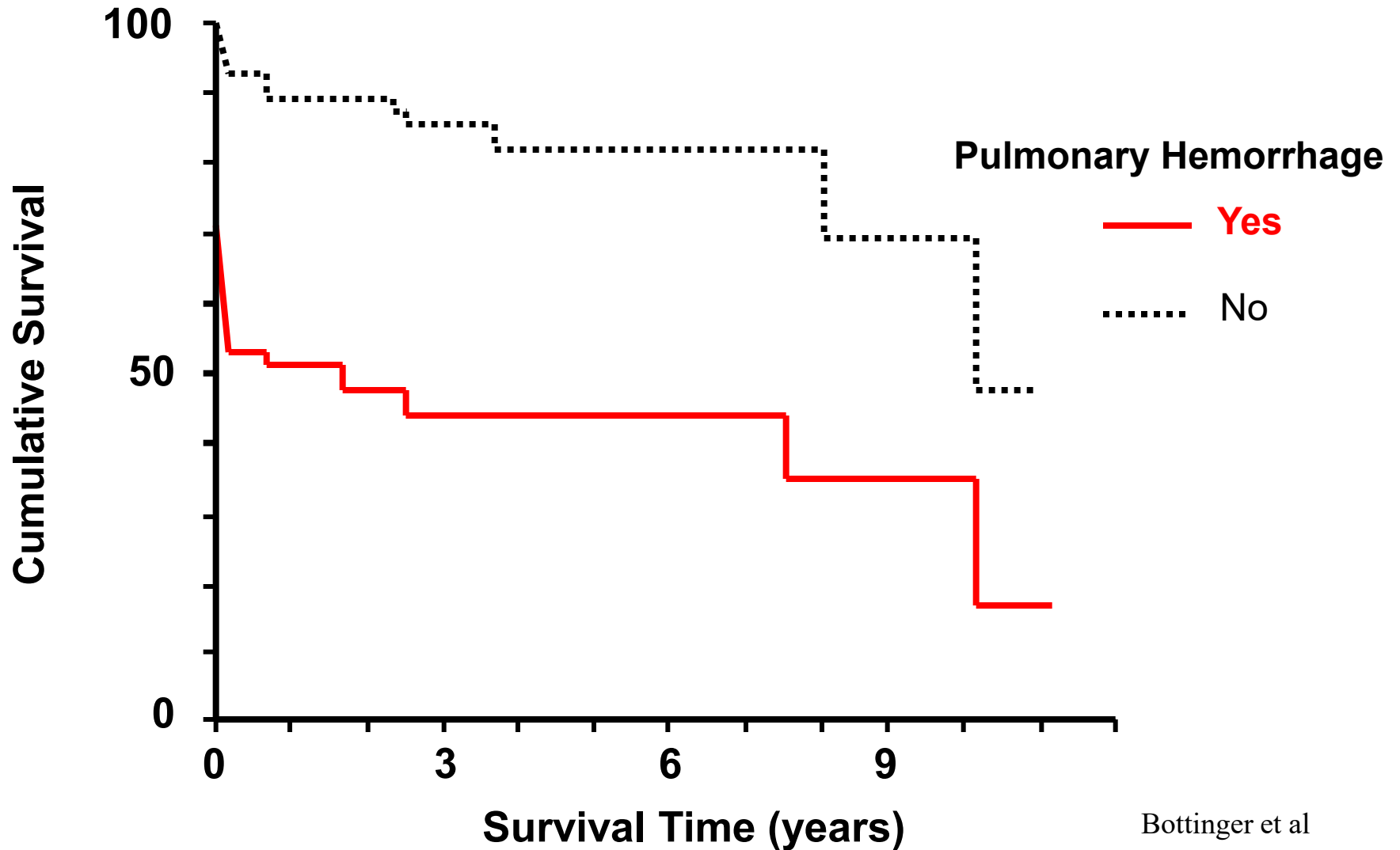
ANCA negative ANCA vasculitis (rare)

~~Other ANCA vasculitis~~

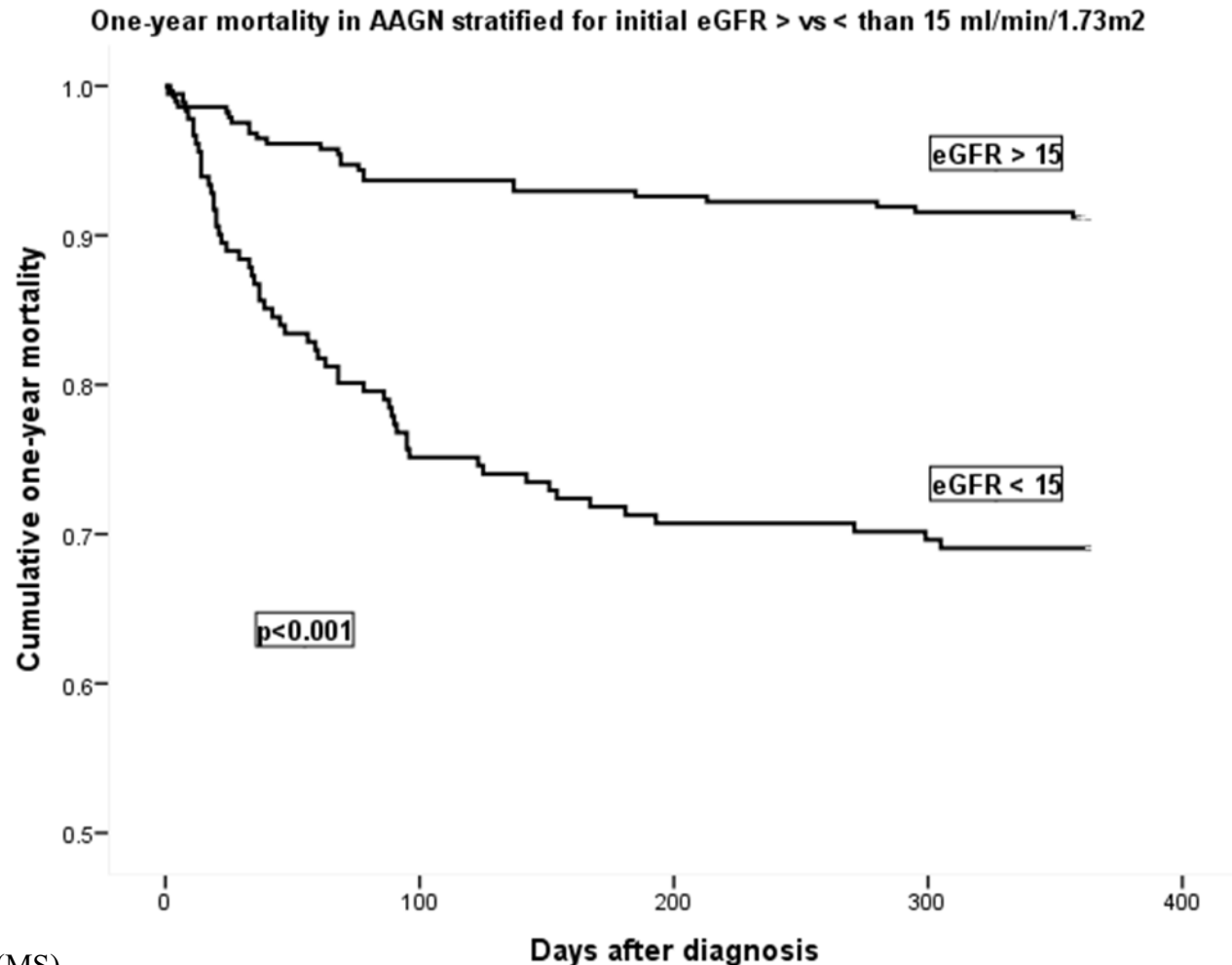
ANCA

Pulmonary Hemorrhage

MGH 1981-1994



Prognostic impact of initial eGFR < 15 ml/min/1.73m²



ANCA-Associated Vasculitis:

Medical Emergency

Features of ANCA associated vasculitis

- **Early** features are often non-specific
 - Malaise, myalgia, arthralgia
 - Anorexia
 - Cough, rhinitis
- Hemoptysis and shortness of breath may be first specific clinical feature
- Microscopic hematuria (often with RBC casts) may be the first available clue
- Broad spectrum of features



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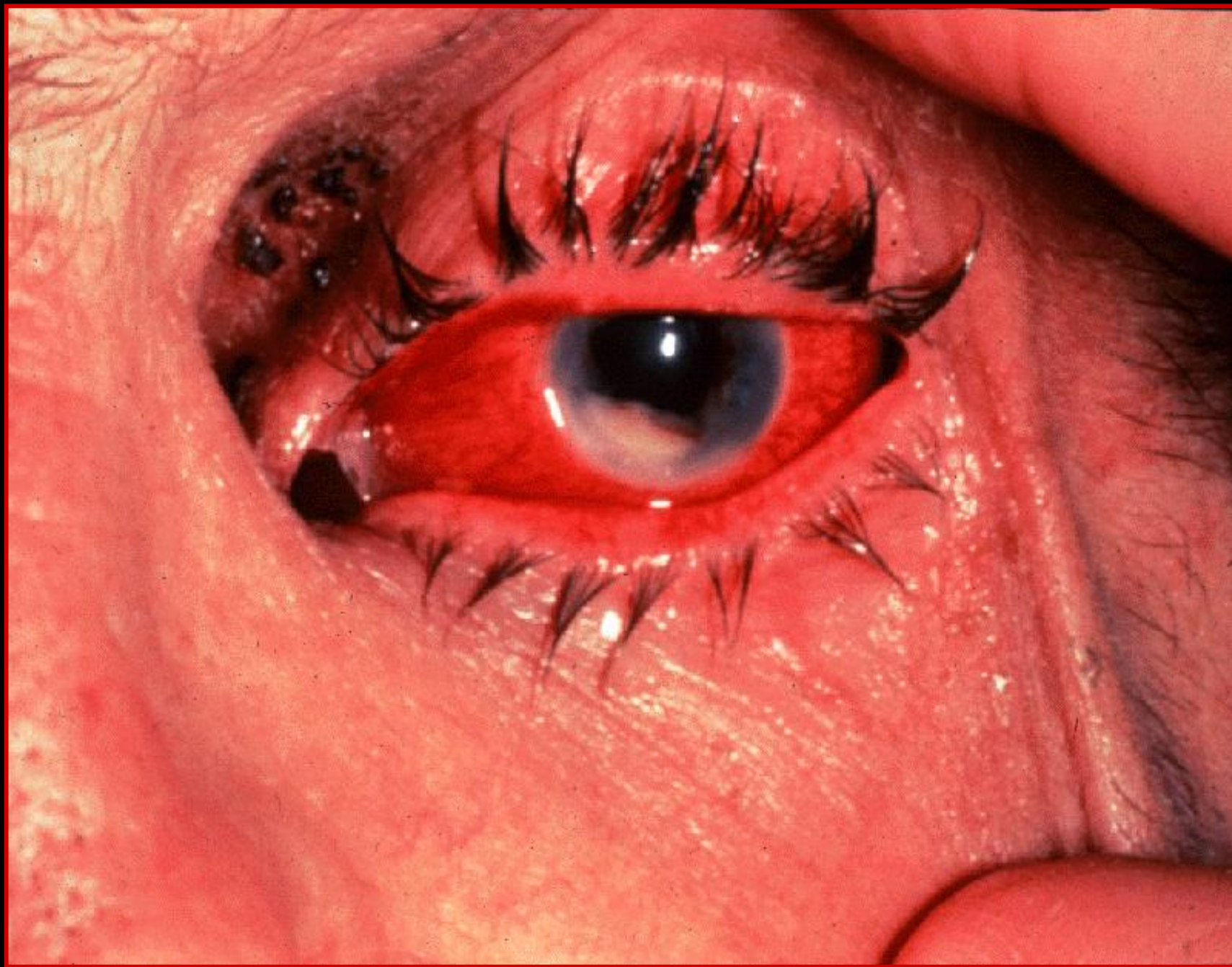


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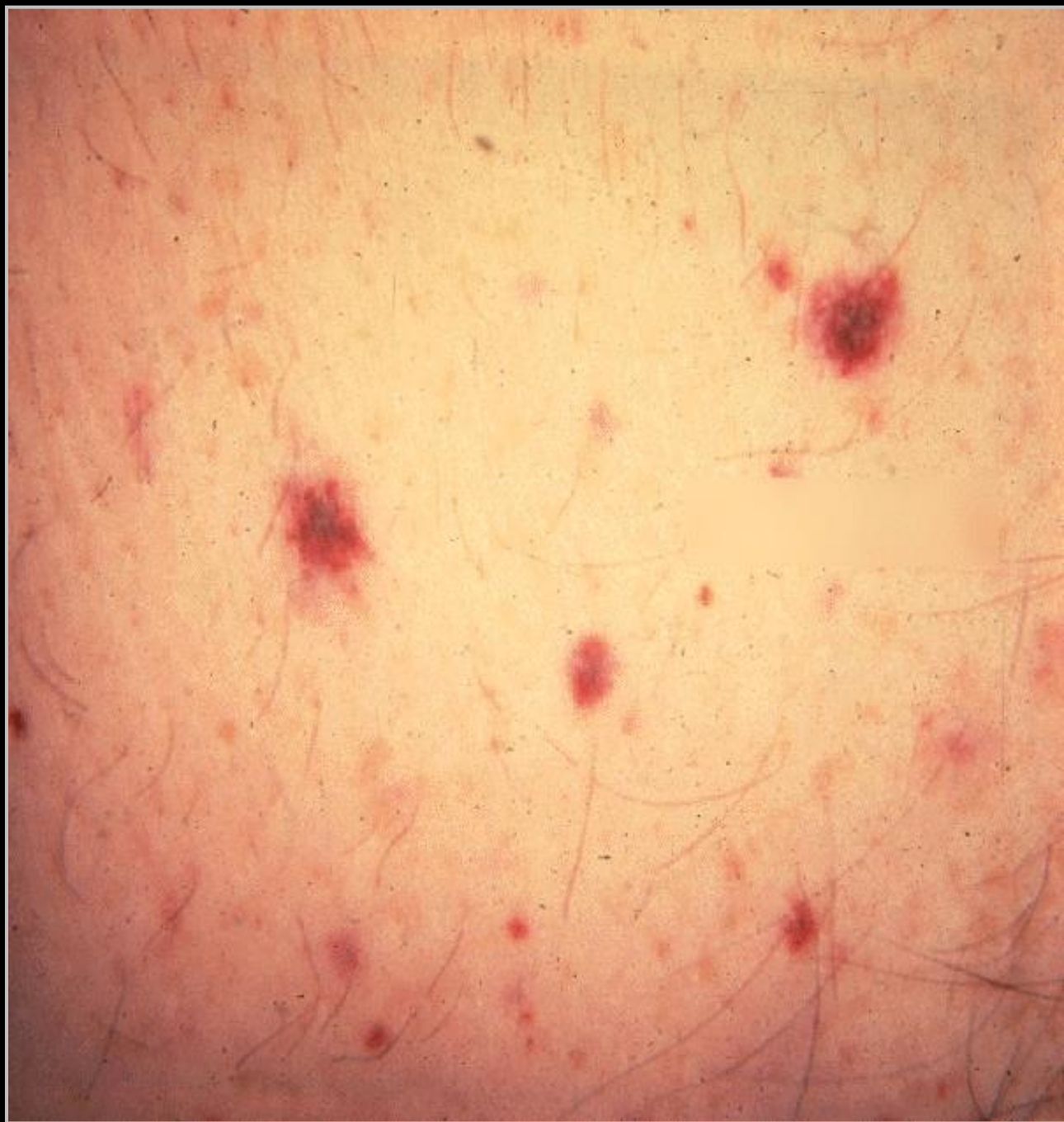
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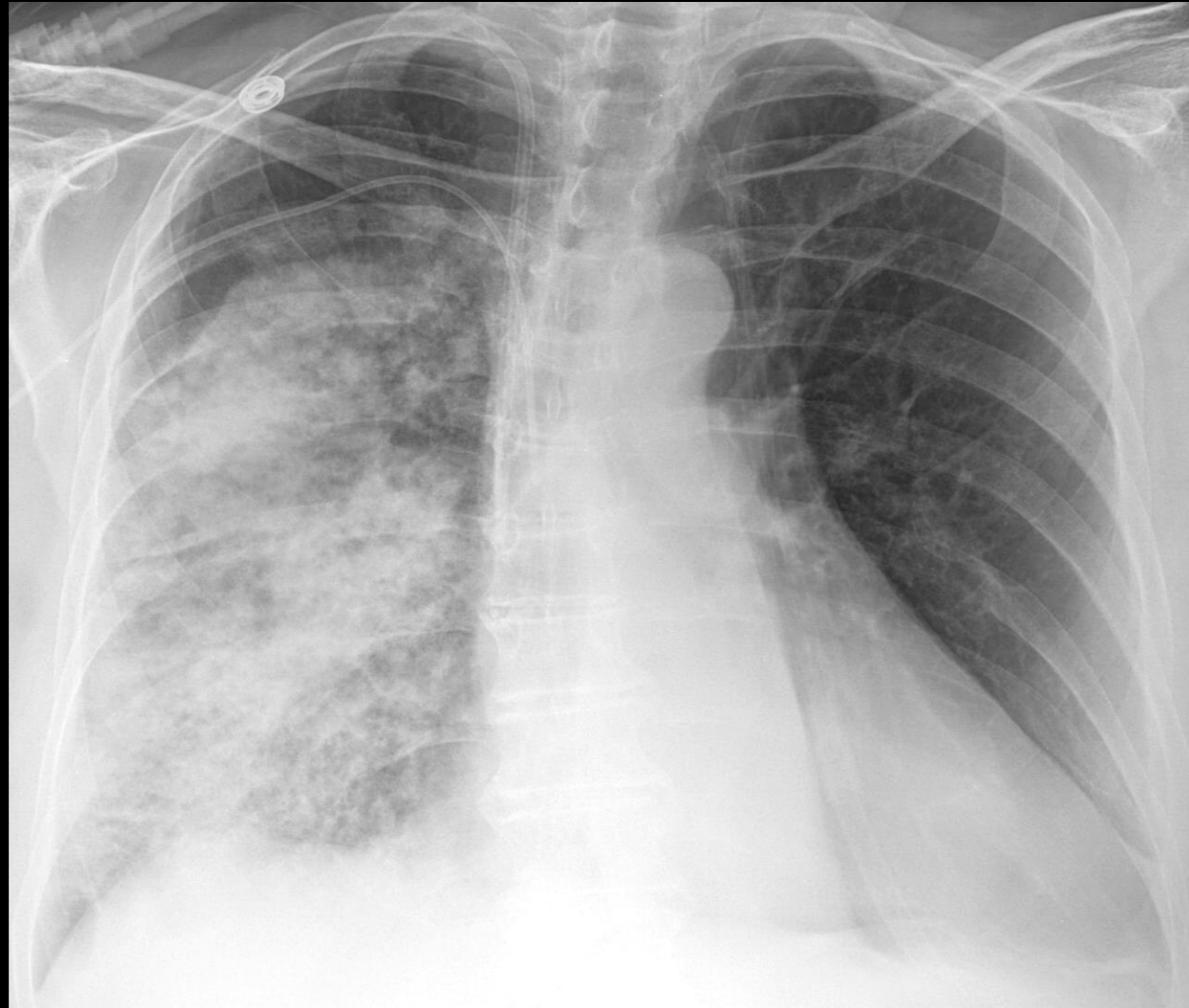




ANCA

Alveolar Hemorrhage

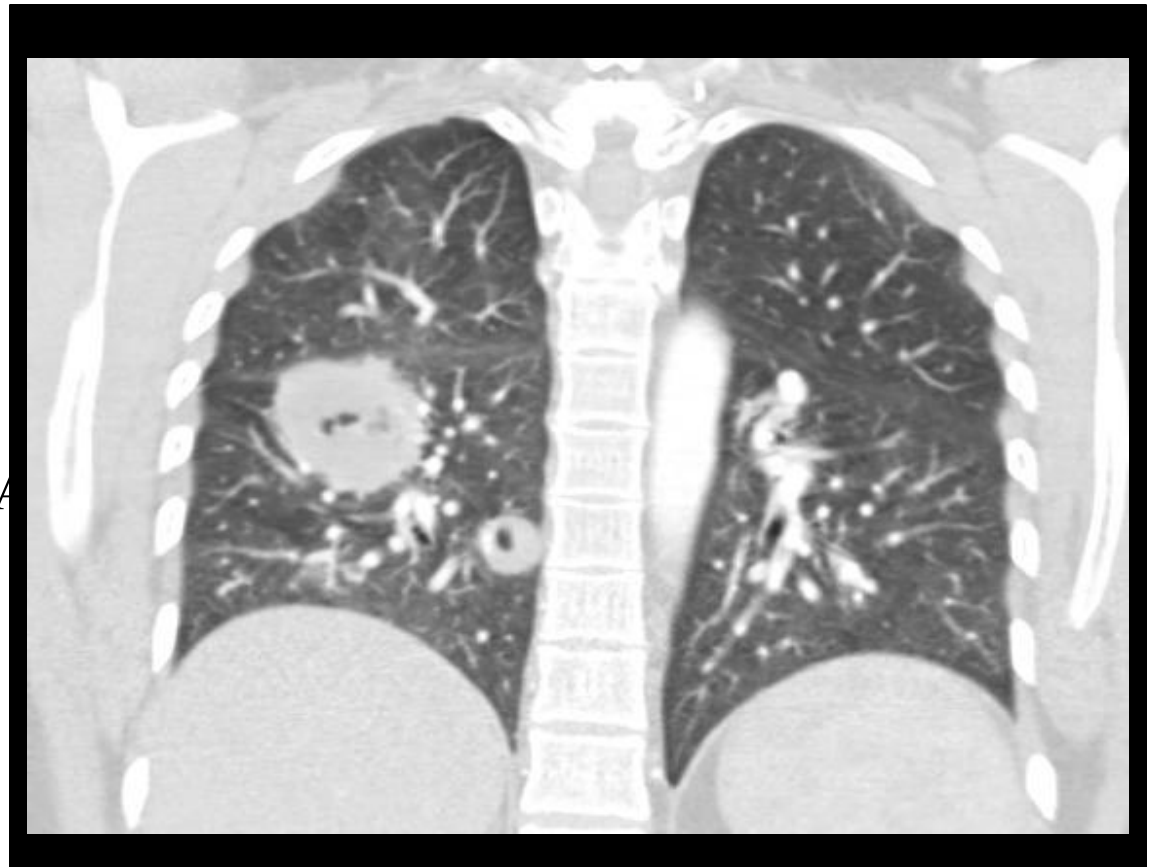
- Alveolar hemorrhage
- Typically
 - High titer MPO
 - or
 - High PR3 ANCA
 - Often very high titer.



ANCA

Cavitary Lung Masses

- Nodules
- Cavitary nodules
- Typically
 - Medium titer PR3 ANCA
 - Rarely MPO ANCA



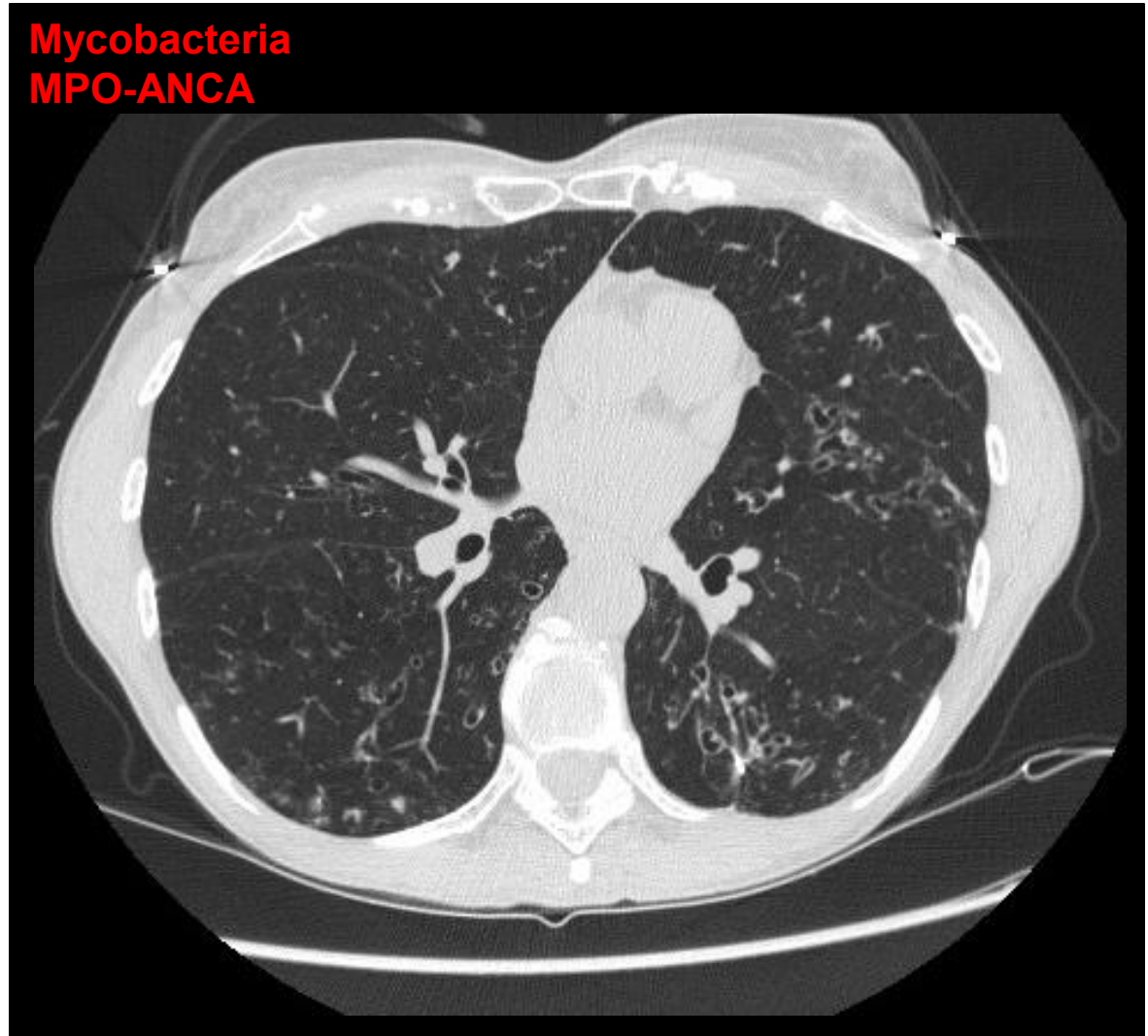
Pulmonary presentations of ANCA associated vasculitis

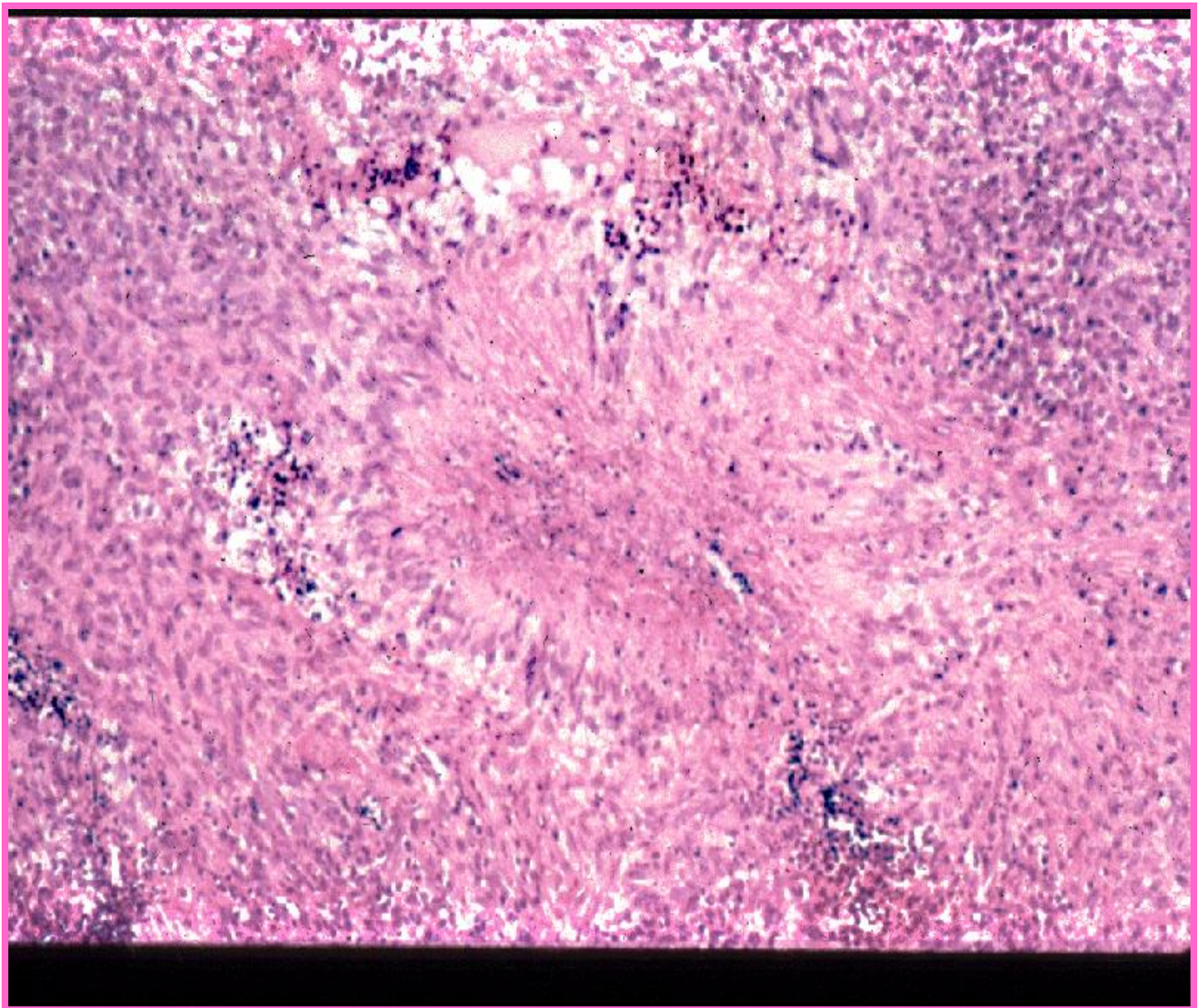
- Interstitial lung disease
 - GGO
 - Fibrosis
 - UIP
 - NSIP
- Typically
 - Almost exclusively MPO

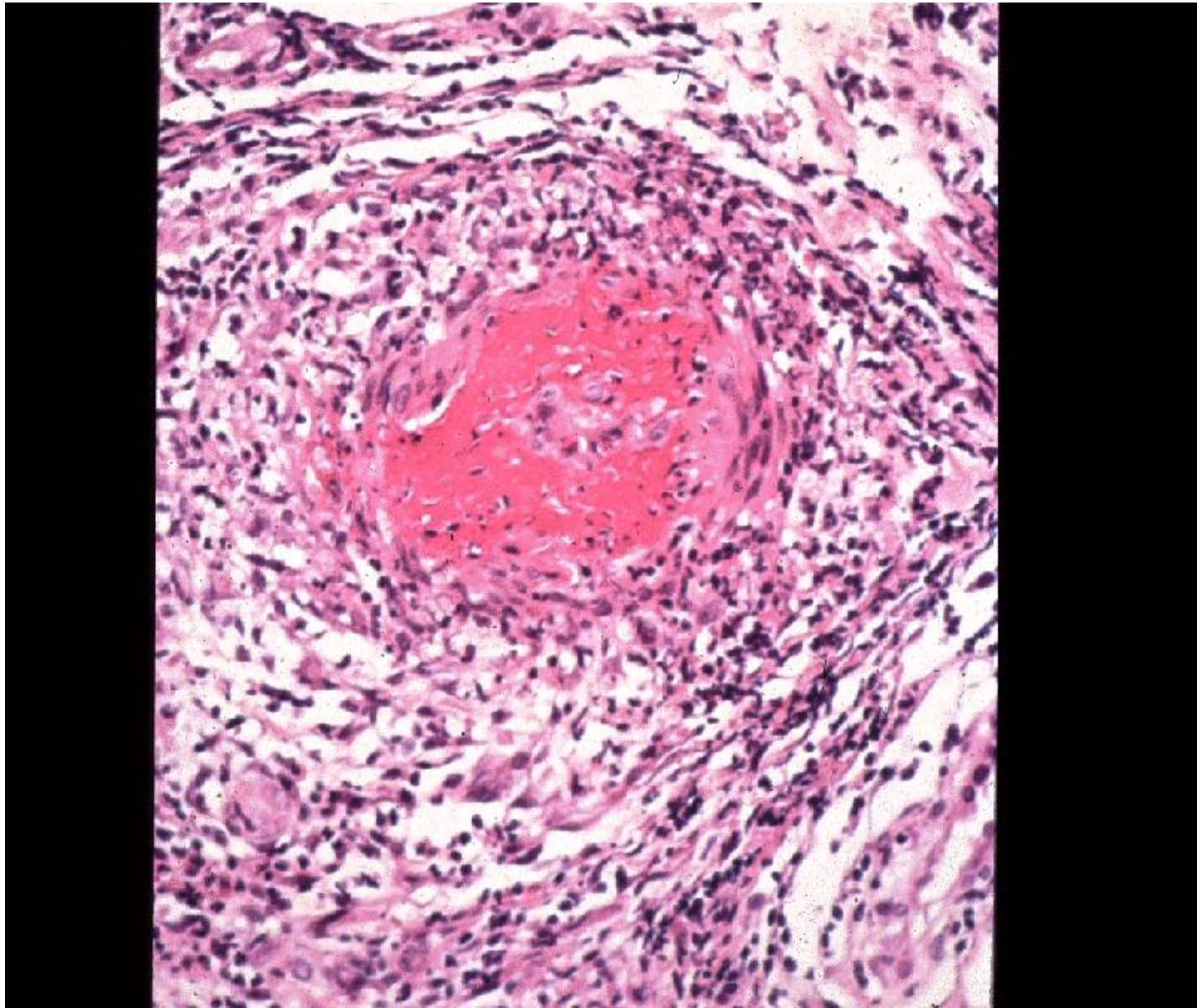


Pulmonary presentations of ANCA associated vasculitis

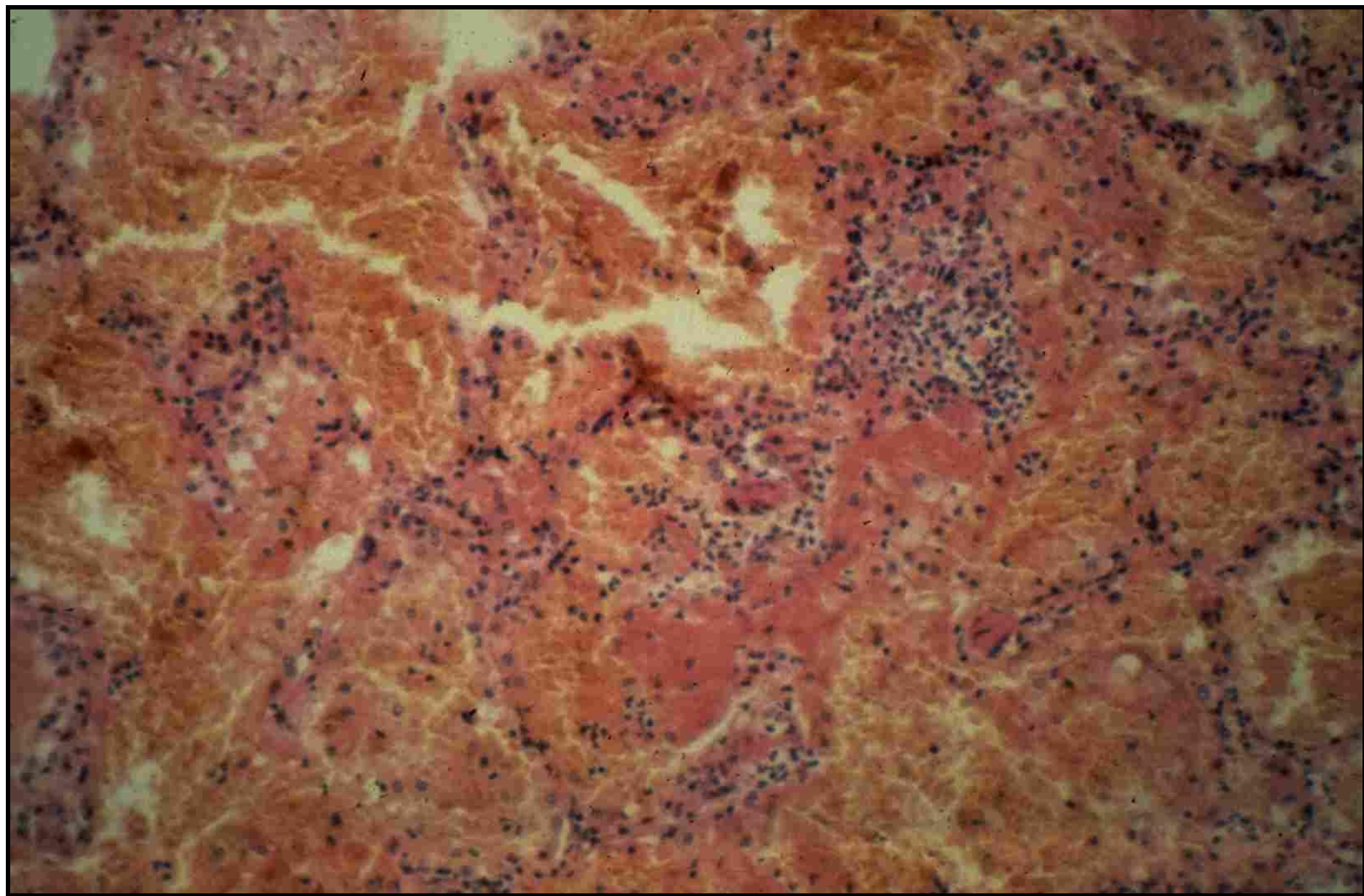
- Bronchiectasis
 - Includes a subset with mycobacterial infection
- Exclusively MPO ANCA
 - Moderate titers.

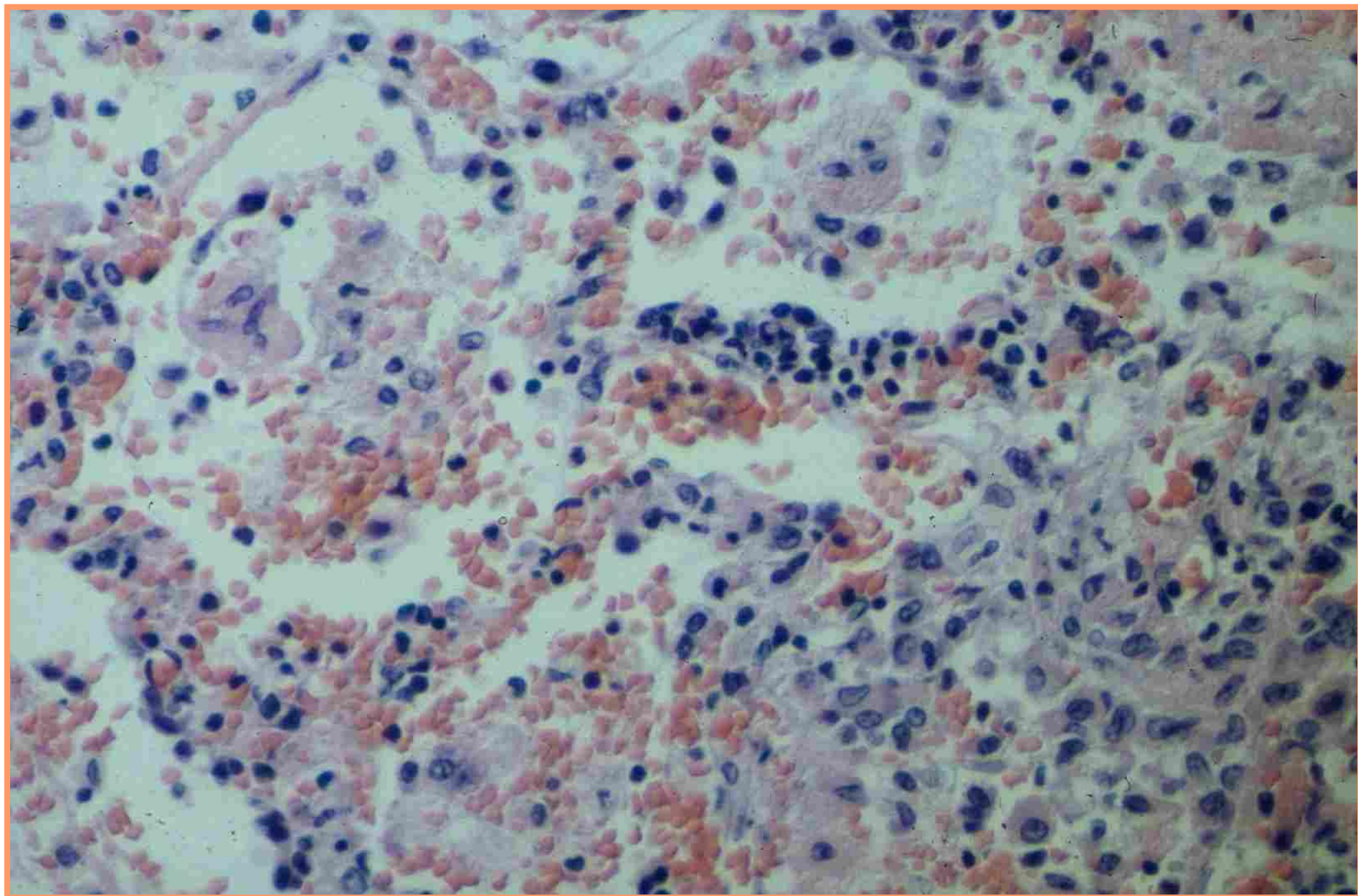


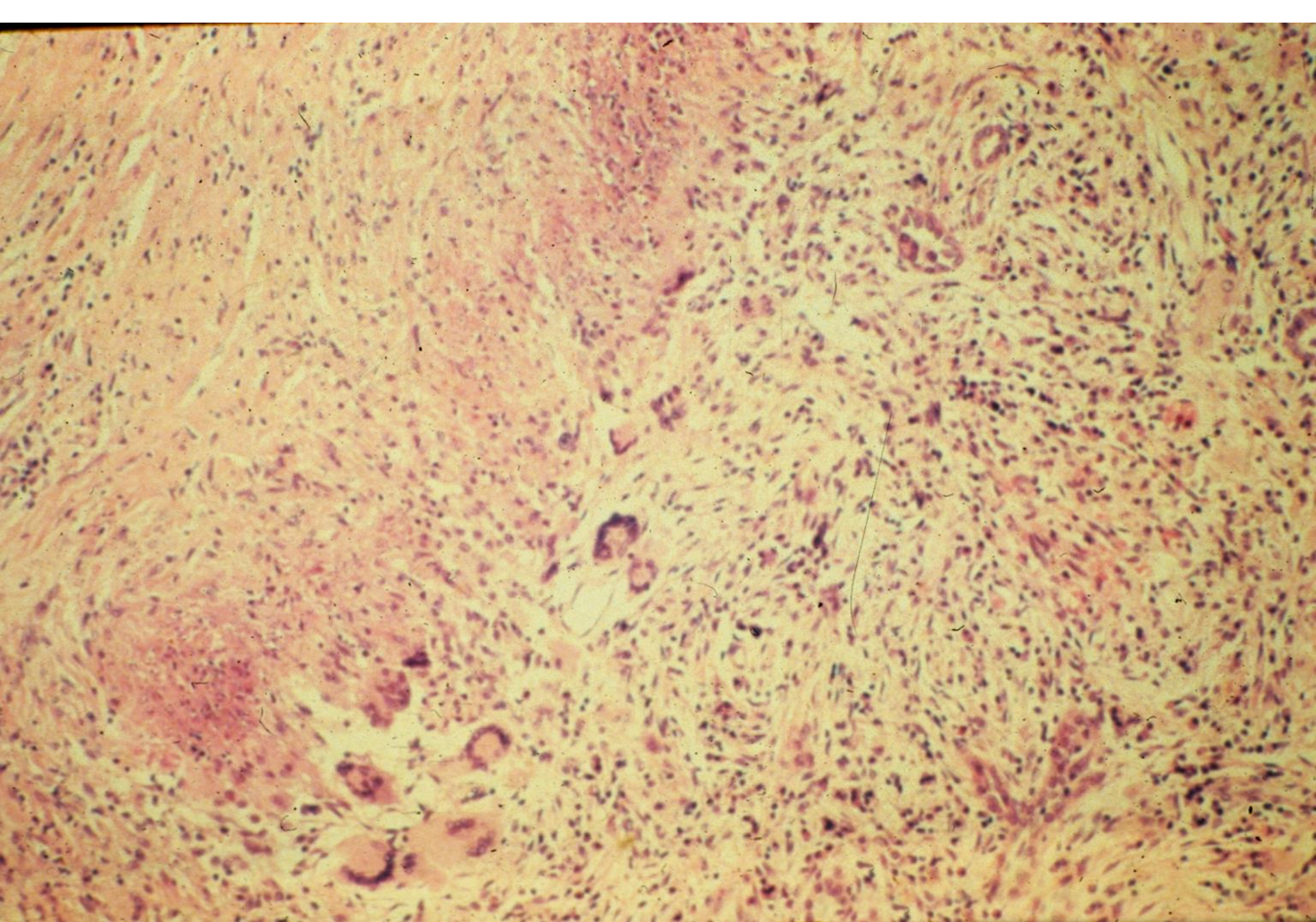


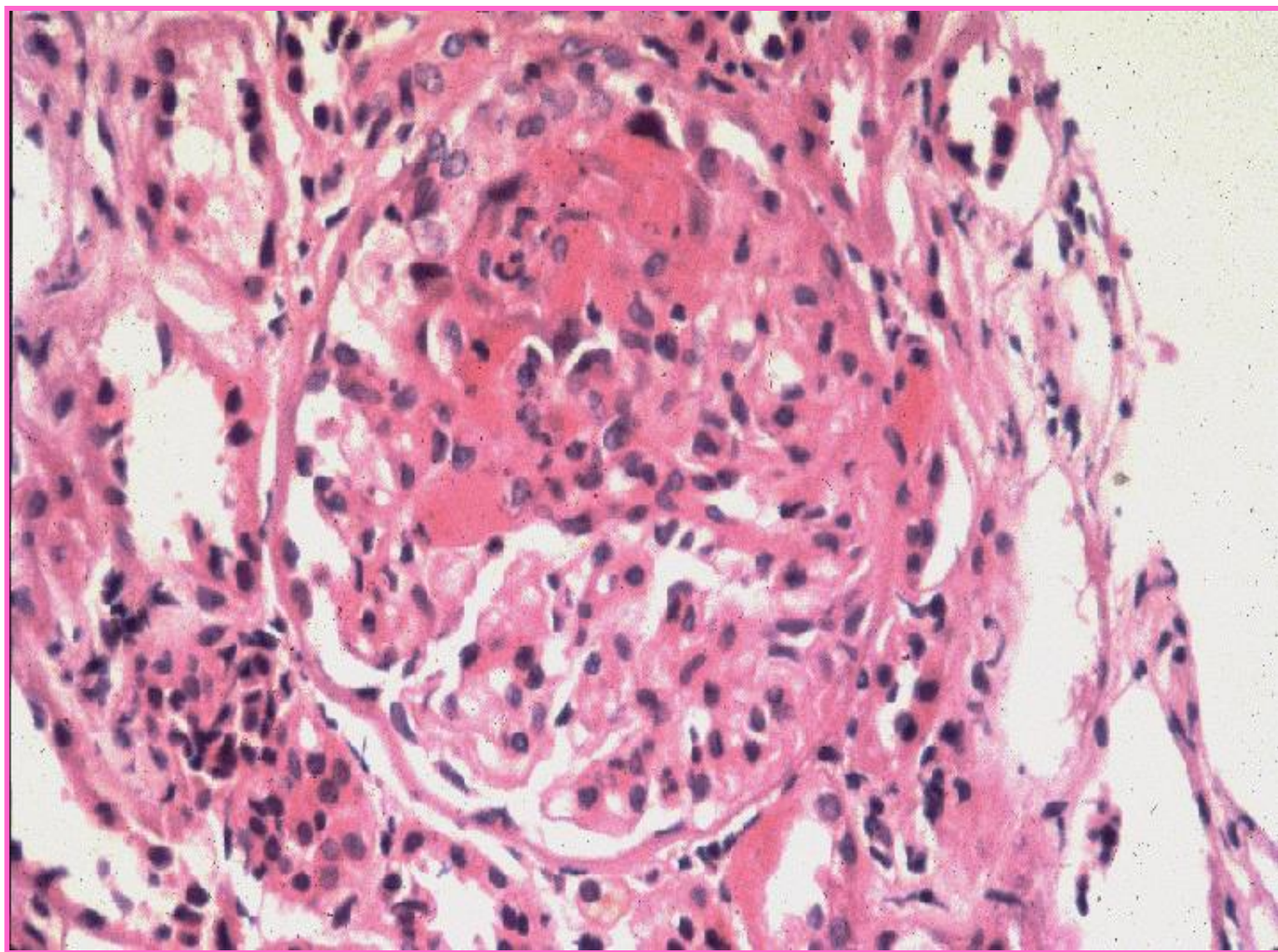


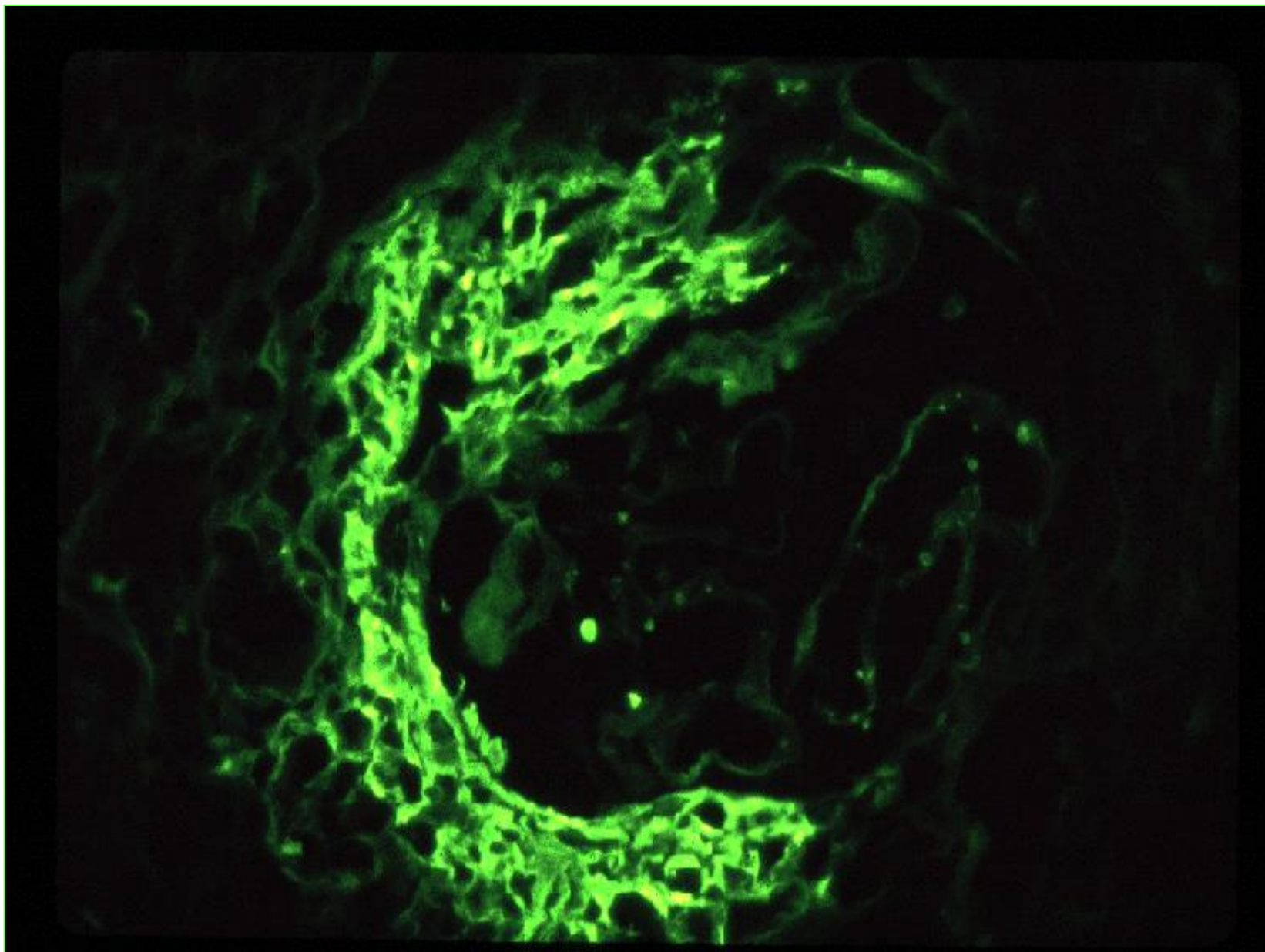












Other non-renal and non - pulmonary features of ANCA VASCULITIS

- **Otitis, conductive hearing loss, sensorineural hearing loss, mastoiditis**
- **Lacrimal gland, salivary gland inflammation**
- **Meningeal masses**
- **Mononeuritis multiplex**
 - **Rapid onset, severe damage, long term consequences**
- **Rare presentations involving**
 - **Breast, gall bladder, pancreas (with pancreatitis), urethra, testicles, prostate, cardiac, pituitary**

ANCA Vasculitis

Diagnosis

Early Treatment is Dependent on Early Diagnosis

Early diagnosis is dependent on:

- Recognition of **early** clinical features
- Appropriate use of ANCA testing
- Tissue histology in selected cases

Only two specific types of ANCA have been shown to be of diagnostic value

**Antigen
recognized**

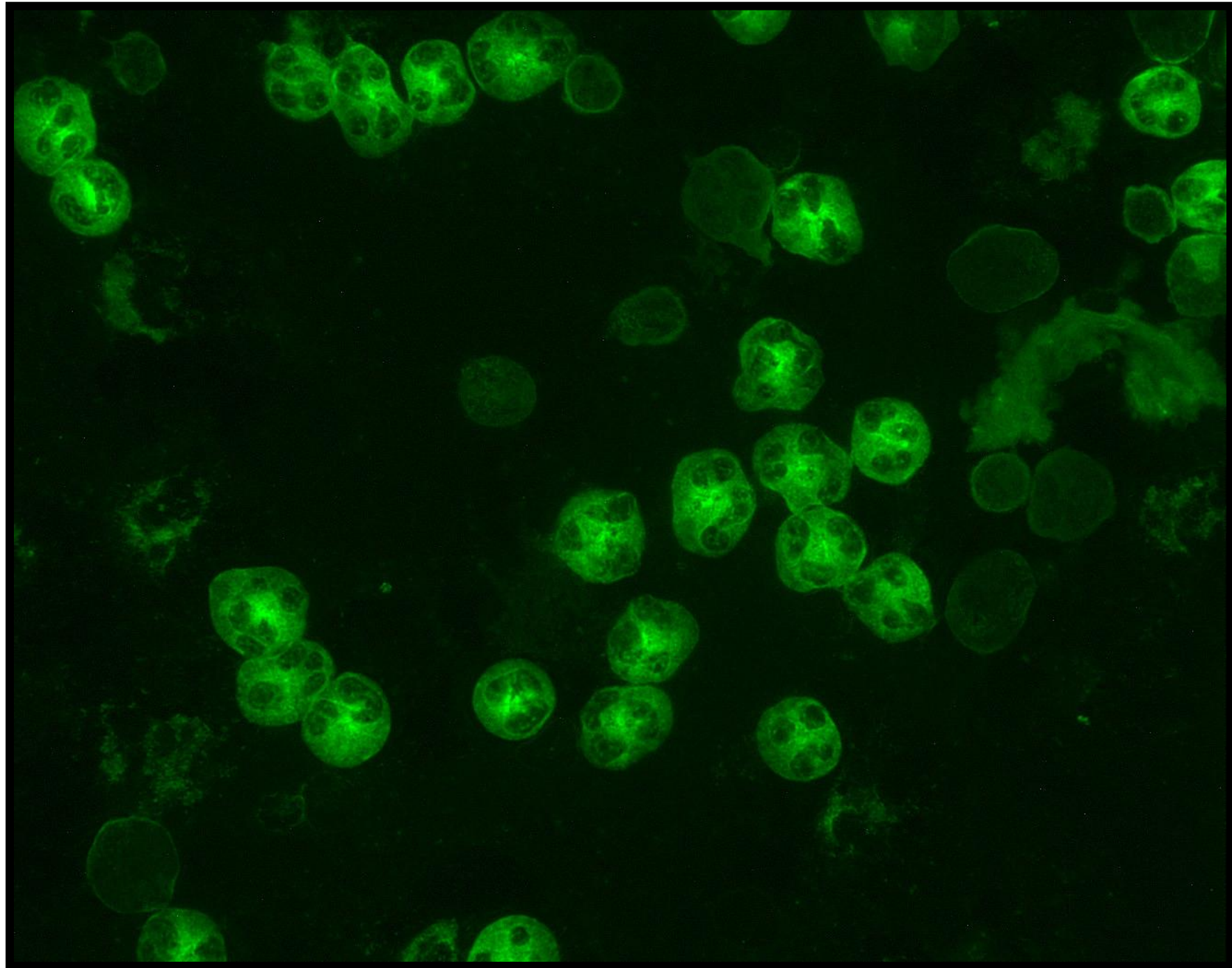
**Pattern of staining by
immunofluorescence**

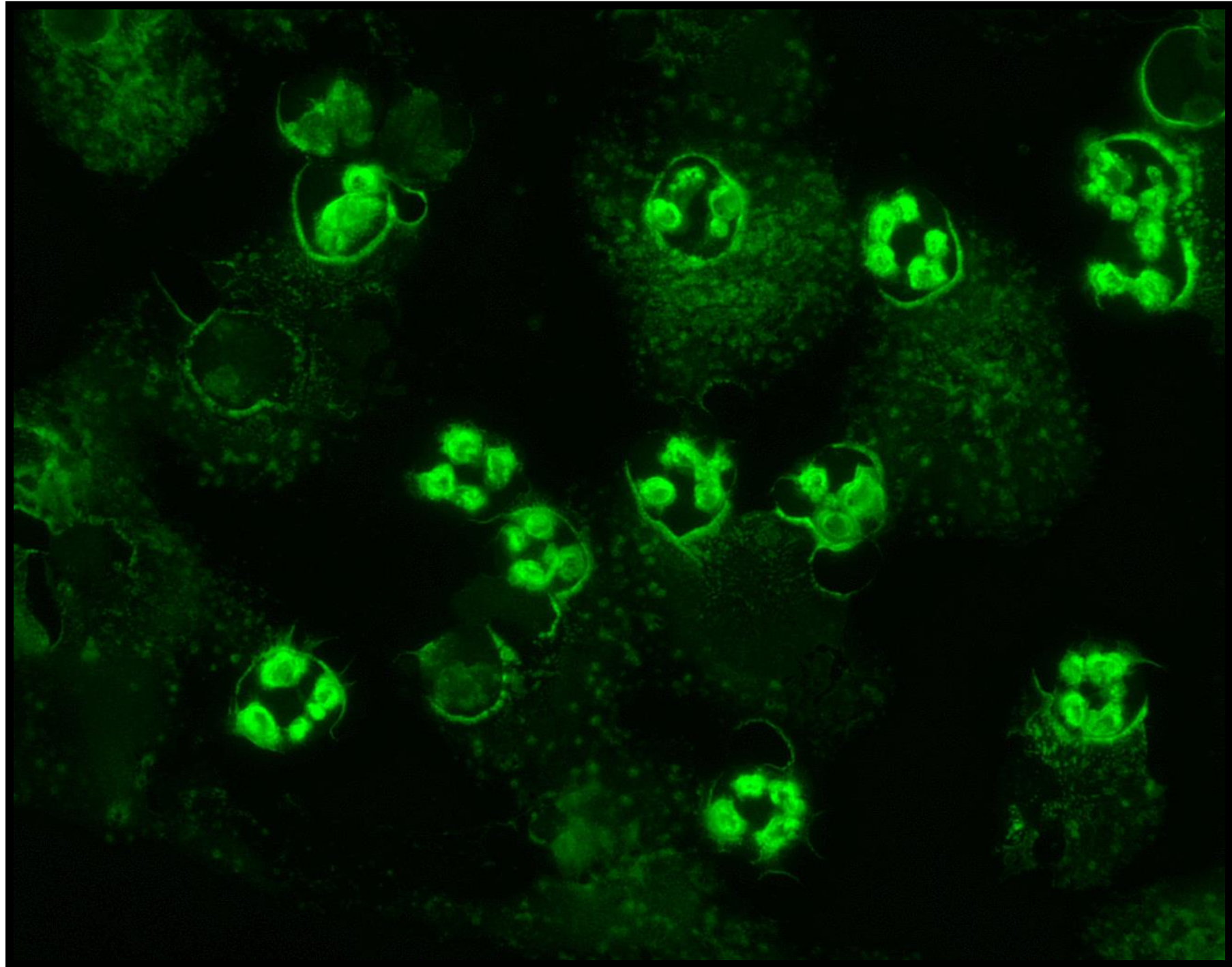
1) Proteinase 3

C-ANCA

2) Myeloperoxidase

P-ANCA





Diagnostic value of ANCA

- Meta-analysis*
 - Sensitivity of MPO/P-ANCA 31 %
 - Sensitivity of PR3/C-ANCA 53 %
 - Combined sensitivity of ANCA 84 %
 - Combined specificity of ANCA 98.6 %
- Predictive value of ANCA very high in the appropriate clinical setting

*Choi et al, J Rheumatol 29:505, 2002

Diagnostic value of ANCA

- Two more nuances:

- Sensitivity of ANCA

- Even higher in the setting of alveolar hemorrhage and glomerulonephritis
 - Lower in the setting of localized forms of vasculitis

- Specificity of ANCA

- Higher with higher cut-off values
 - Lower with lower cut-off values
 - And, on average,
 - Titers run higher with severe disease
 - Titers run lower with localized disease

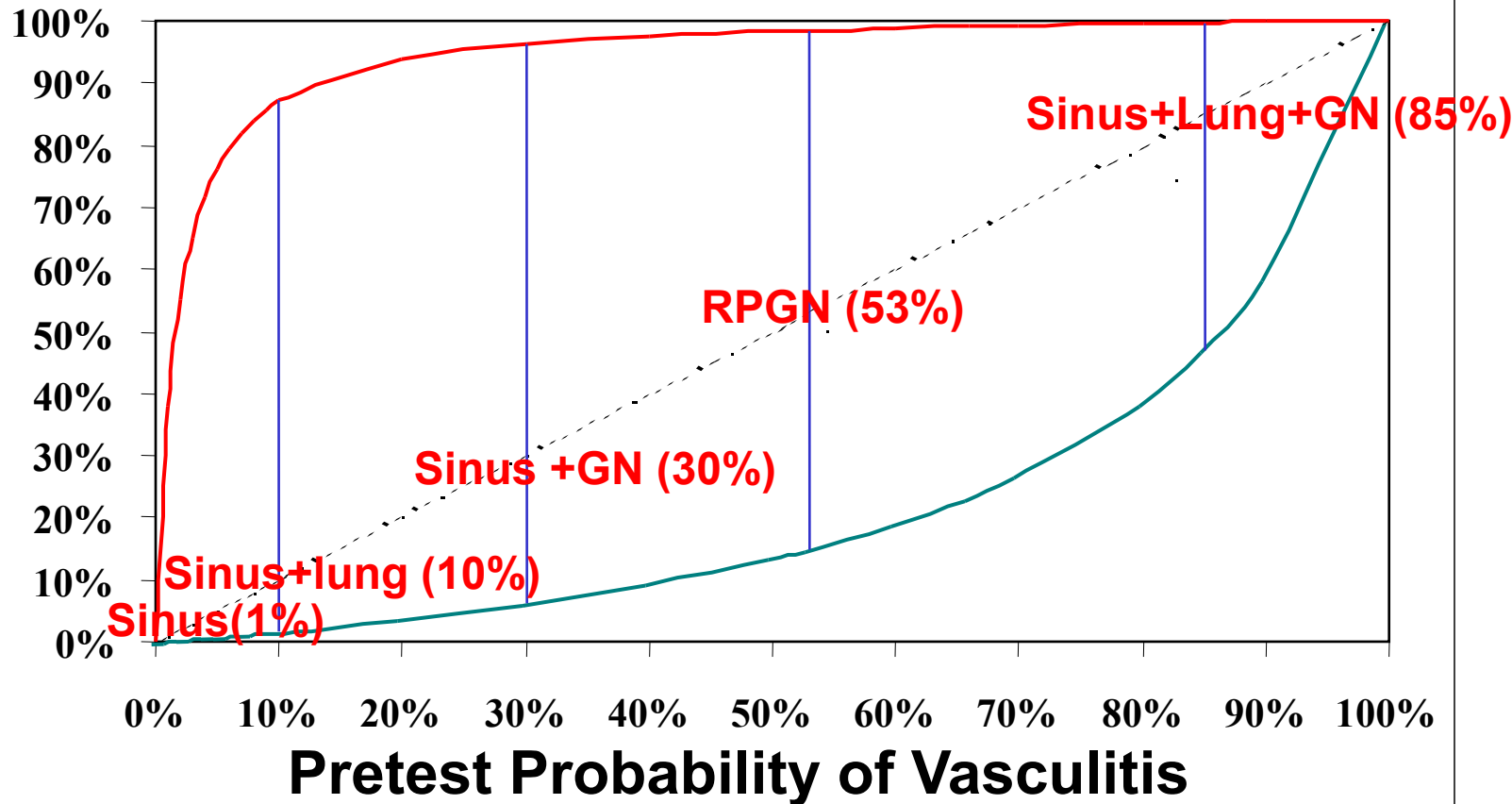
- So,

- what are the appropriate **early** clinical settings?
 - How does this work?

Comments: Application

Diagnostic Probability Revision with ANCA

Posttest Probability of Vasculitis



Diagnosis with ANCA

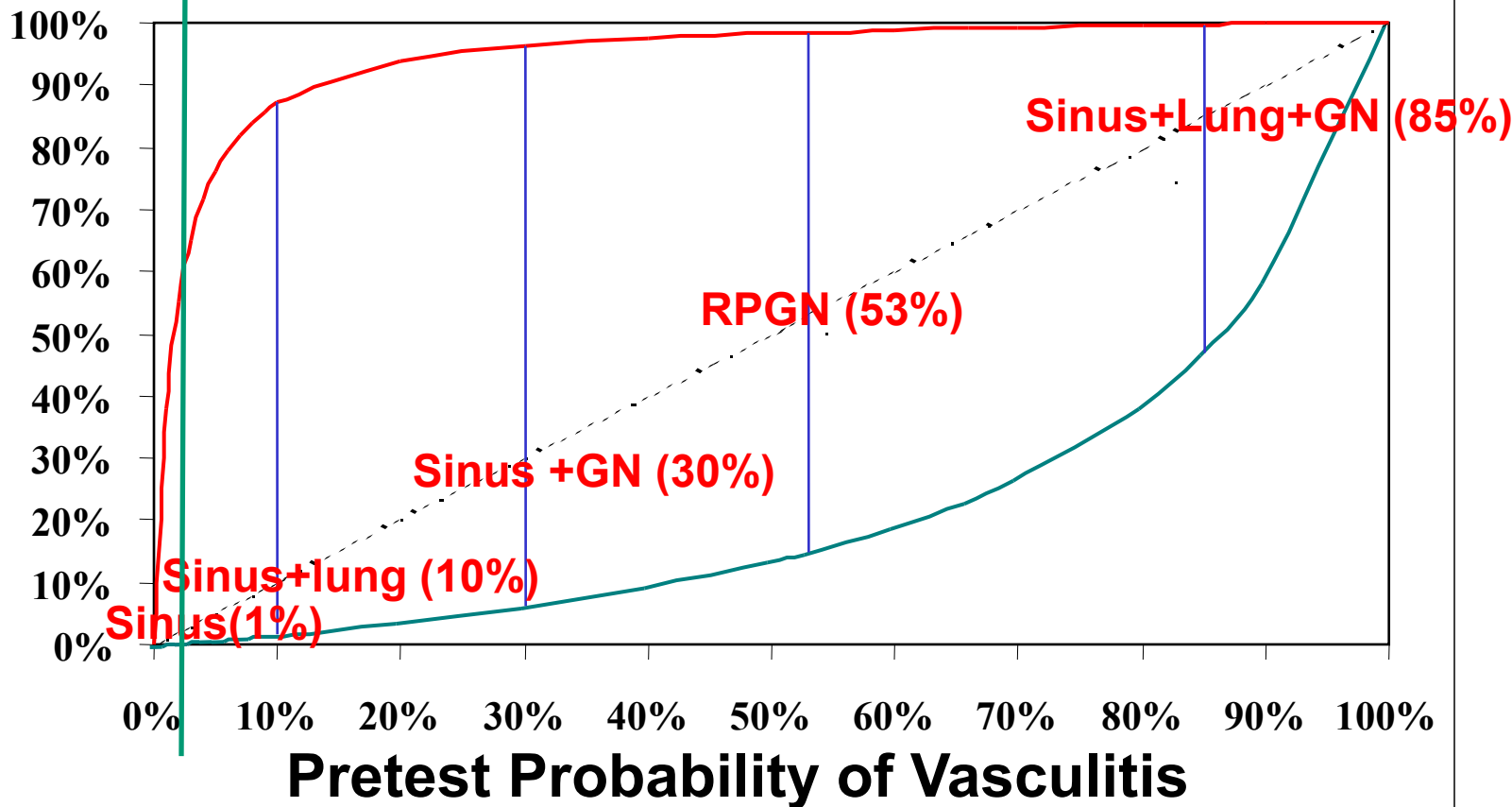
		1990 to 1995	2020 to 2025
MPO	median titer (n)	72 units (222)	28 units (643)
PR3	median titer (n)	181 units (115)	102 units (405)
Positive samples as % of tested samples		8%	2.8%

Trend to more early testing and earlier diagnosis

Comments: Application

Diagnostic Probability Revision with ANCA

Posttest Probability of Vasculitis



Is it ANCA Vasculitis ?

- **With low titer MPO ANCA, should you treat in the setting of:**
 - Tracheal stenosis ?
 - New Hoarseness ?
 - Unilateral optic neuritis with partial vision loss ?
 - Headache, high ESR, negative temporal artery biopsy ?
 - Migratory oligoarthritis ?
 - Migratory oligoarthralgias?
 - ILD with UIP pattern?
 - Cavitary lung lesion with MAC ?
 - Renal transplant for IgA nephropathy with slow ILD ?
 - Anterior uveitis controlled with drops ?

Is it ANCA Vasculitis ?

- **What to do when:**
 - Clinical features of vasculitis are marginal
 - ANCA levels are marginal
 - Especially, in the setting of other confounding diseases
- **Follow with ongoing re-assessments**
 - Serial ANCA testing
 - Confirmation of anti-MPO or anti-PR3 antibodies
 - Trend levels
 - Re-examination of clinical features - Experience counts
 - Are they typical of ANCA?
 - Could they be consistent with ANCA?
 - Are there diagnostic findings of alternative diagnoses that explain the potential ANCA features
 - Understanding the broad spectrum of potential early features
 - Tissue biopsy of available lesions
 - Recognizing that false negative biopsies are common with ANCA disease and do not rule out vasculitis
 - Have they been treated with courses of steroids
 - Did it work?
 - Watch for emergence of other definitive diagnoses
- Be prepared to treat urgently if organ threatening disease emerges

ANCA Vasculitis

Pathophysiology

Are ANCA pathogenic ?

Pathophysiology – simplistic understanding

■ Triggers

■ B cells

■ Plasma cells

- Activated B cell (CD19, CD20)
- Plasma blast (CD19, CD20)
- Long lived plasma cell (no CD19/20)

■ Antibodies

- Good antibodies
- **Pathogenic autoantibodies, ANCA**

■ Inflammation

- Activate neutrophils
- Alternative complement pathway
- C5a release
- Recruitment and priming of more neutrophils

■ Damage

■ Seeds

■ Plants

- Seedlings
- Annuals
- Perennials, trees

■ Fruit

- Good fruit
- **Poison fruit**

■ Disease

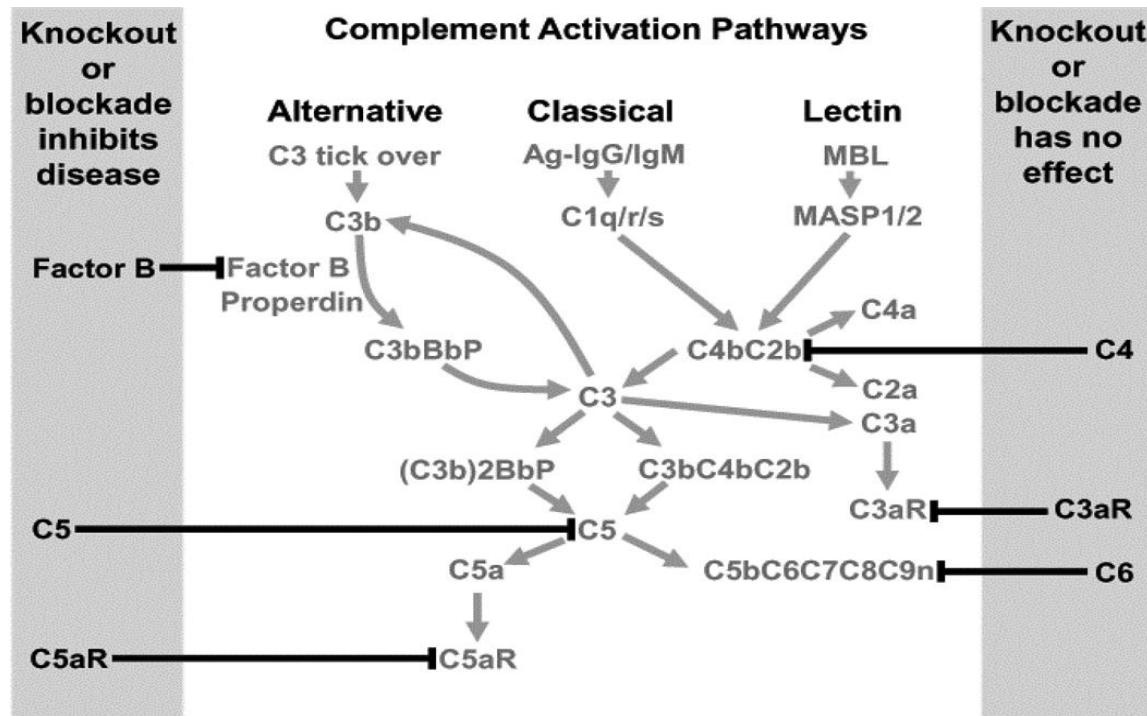
- Functional disruption
- Metabolic destruction
- Spiral out of control

■ Damage

Pathophysiologic role of ANCA

- Animal model
 - Xiao et al, *Journal of Clinical Investigation* 110(7):955-63, 2002
 - **Solidified the central tenant of our theory of a pathophysiologic role of ANCA**

Complement in ANCA



Semin Nephrol. 2013 Nov;33(6):557-64.

ANCA Vasculitis

Treatment

Approaches

Tools

Strategies

Therapeutic approaches to antibody mediated autoimmune disease

- ANCA vasculitis
-
- Membranous nephropathy, lupus nephritis, MPGN, Cryoglobulinemia
- Myasthenia gravis, NMO, multiple sclerosis
- Pemphigus
- Systemic lupus erythematosus, scleroderma, polymyositis , RA
- Anti-synthetase syndrome, polymyositis
- . . .

Therapeutic approaches to antibody mediated autoimmune disease

Block antibody production

and /or

Block antibody effector mechanisms

Therapeutic approaches to antibody mediated autoimmune disease

Block antibody production

and /or

Block antibody effector mechanisms

Therapeutic approaches to antibody mediated autoimmune disease

Block antibody production

and /or

Block antibody effector mechanisms

Pathophysiology – simplistic understanding

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- **ANCA / pathogenic autoantibodies**

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Therapeutic approaches to antibody mediated autoimmune disease

Block antibody production

and /or

Block antibody effector mechanisms

Pathophysiology – simplistic understanding

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■ Damage

Treatments of ANCA vasculitis

- Eliminate triggers
 - Unfortunately, they are mostly unknown
 - Certain drugs implicated occasionally
 - Hydralazine
 - Propylthiouracil
 - Penicillamine
 - Minocycline
 - Cocaine / levamisole
 - Allopurinol
 - Possibly INH, sulfasalazine
 - Silicone exposure
 - Stone workers

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- Eliminate triggers
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Characterization of Drug-induced ANCA vasculitis at MGH

- Apparent drug-induced ANCA cases have:
 - long exposures to culprit drugs
 - higher rates of MPO positivity and lower rates of PR3
 - higher MPO-ANCA titers
 - higher propensity for double-positive ANCA
 - higher rates of other autoantibodies

Pathophysiology – simplistic understanding

■ Triggers

■ Eliminate triggers

■ B cells

■ Clear the seeds

■ Seeds

■ Plasma cells

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■ Damage

■ Damage

Treatments of ANCA vasculitis

- Clear circulating B-cells
 - Pulse steroids
 - Cytotoxic agents
 - Cyclophosphamide
 - Azathioprine, methotrexate
 - Anti-B-cell antibodies
 - Rituximab
 - And other anti-B-cell monoclonals
-

Rituximab

What do we know?

- **Sustained B cell depletions (median 8-9 months)**

- **What about antibodies?**

1. Suppresses **new** antibody responses

(Arthritis Rheum. 2010;62:75-81)

(Sci Transl Med. 2023 Nov 29;15(724))

Blocks response to recall antigens

(Blood. 2002;100:2257-2259), (Arthritis Rheum. 2010;62:64-74)

Specific B-cell responses return as B-cells return

(Arthritis Rheum. 2010;62:75-81)

2. Slow fall of IgM levels

3. **Little immediate effect on IgG levels**

Little effect on established plasma cells

Very slow fall over the long term

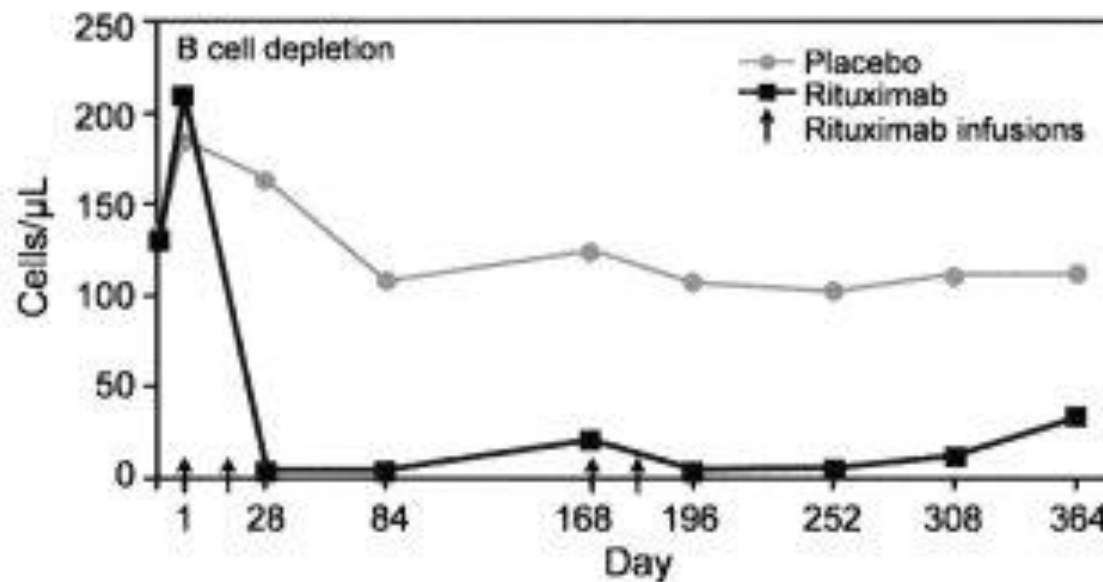
Rituximab

- Rapid clearance of B-cells **does not correlate**
 - with rapid antibody response or
 - rapid clinical response
- Not in SLE or RA* or Membranous
- Not in ANCA vasculitis

•*Rituximab pharmacokinetics in patients with rheumatoid arthritis: b-cell levels do not correlate with clinical response. Breedveld et al. J Clin Pharmacol 2007;47_1119-1128

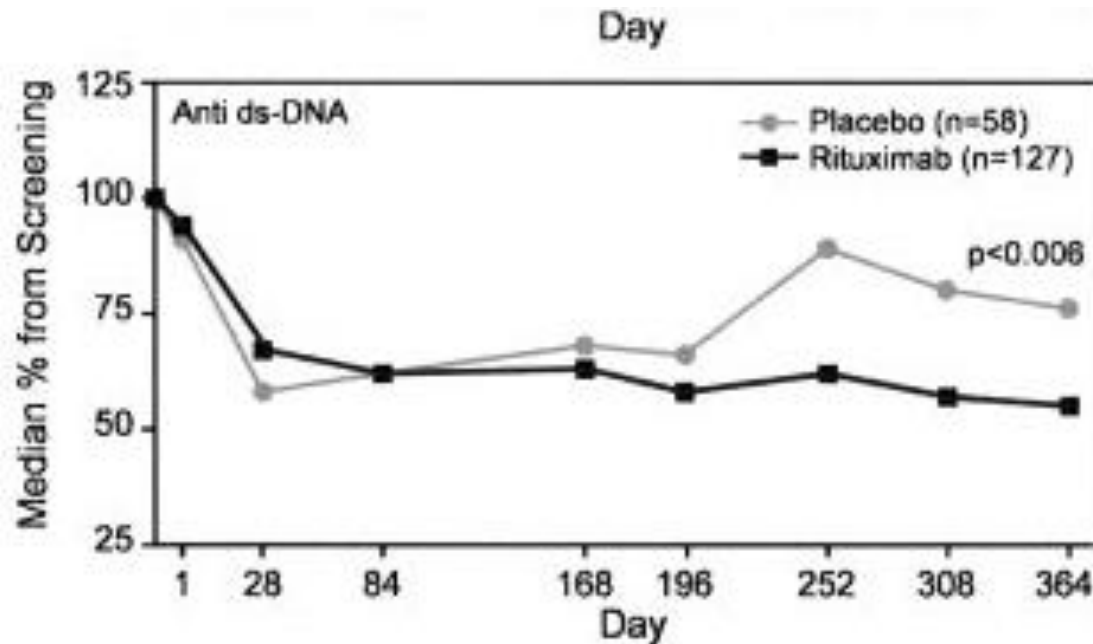
Circulating B-cells with rituximab

EXPLORER - 257 patients



Anti ds-DNA with rituximab

EXPLORER - 257 patients



EXPLORER

Merrill et al. Arthritis Rheum 2010; 62:222-233.

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- Block or clear the plants

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Treatments of ANCA vasculitis

- Block or clear plasma blasts and plasma cells
 - Pulse steroids (plasma blasts)
 - Cytotoxic agents (plasma blasts)
 - Cyclophosphamide
 - Azathioprine, methotrexate
 - Anti-CD19 (plasma blasts)
 - Anti-CD38
 - Bortezomib
 - *Anti-CD20 monoclonals - no effect on plasma cells*

Pathophysiology – simplistic understanding

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- Clear the poison fruit

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Treatments of ANCA vasculitis

■ Antibody Blockade

□ Plasmapheresis / plasma exchange

□ Pexivas trial

- Early benefit for preservation of eGFR

- *Kidney International 107,558-567, 2025*

□ Meta-analysis

- Reduced risk of ESKD at 12 months (RR 0.62 (0.39 to 0.98))
- No significant survival benefit (RR 0.90 (0.64 to 1.27))

- *BMJ 2022;376:e064604*

□ Imlifidase (IgG lysis) (experimental)

Therapeutic approaches to antibody mediated autoimmune disease

Block antibody production

and /or

Block antibody effector mechanisms

Therapeutic approaches to antibody mediated autoimmune disease

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■ Inflammation

- Activate neutrophils
- Alternative complement pathway
- C5a release
- Recruitment and priming of neutrophils

■ Antidote to the poison

■ Disease

- Functional disruption
 - Metabolic destruction
 - Spiral out of control
- dfgsdfgsdgggggggggg

■ Damage

■ Damage

Pathophysiology – simplistic understanding

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■ Block or clear plasma cells

■ Clear the antibodies

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■ Inflammation

- Activate neutrophils
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■ Anti-inflammation

■ Disease

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dfgsdfgsdggggggggggg

■ Damage

■ Damage

Therapeutic approaches to antibody mediated autoimmune disease

Block antibody effector mechanisms (beyond steroids)

- ANCA vasculitis, lupus nephritis, cryoglobulins

- Steroids
- Complement
 - C5
 - C5a

- Myasthenia gravis

- Mestinon
- C5 blockade

- Grave's disease

- Thyroidectomy

- Antiphospholipid antibody syndrome

- Warfarin

- Rheumatoid arthritis

- TNF blockers, etc

- Interstitial lung disease

- Antifibrotics; pirfenidone, nintedanib

Treatments of ANCA vasculitis

- Block priming, recruitment and activation of neutrophils
 - Standard approach
 - Steroids
 - More steroids
 - And more steroids
 - Anti-TNF strategies have not worked
 - (N Engl J Med. 2005, 352:351-61.)
 - (Clin Exp Rheumatol. 2010, 28:661-8.)
- Complement blockade
 - C5 blockade -- eculizumab
 - C5a blockade -- avacopan

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■ Anti-inflammation

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- **ANCA / pathogenic autoantibodies**

■ Stop hydralazine

- anti-CD 20
- *anti-CD 19*
- cyclophosphamide

- steroids
- cyclophosphamide
- methotrexate
- azathioprine
- *anti-CD 19*
- (*anti-CD 38*)

- plasmapheresis
- imlifidase

■ Seeds

■ Plants

- Seedlings
- Annuals
- Perennials, trees

■ Fruit

- Good fruit
- **Poison fruit**

■ Inflammation

- Activate neutrophils
- Alternative complement pathway
- C5a release
- Recruitment and priming of neutrophils

- steroids
- avacopan
- (eculizumab/ravulizum)
- alternate pathway inhib

■ Disease

- Functional disruption
- Metabolic destruction
- Spiral out of control

■ Damage

■ Damage

Treatments of ANCA vasculitis

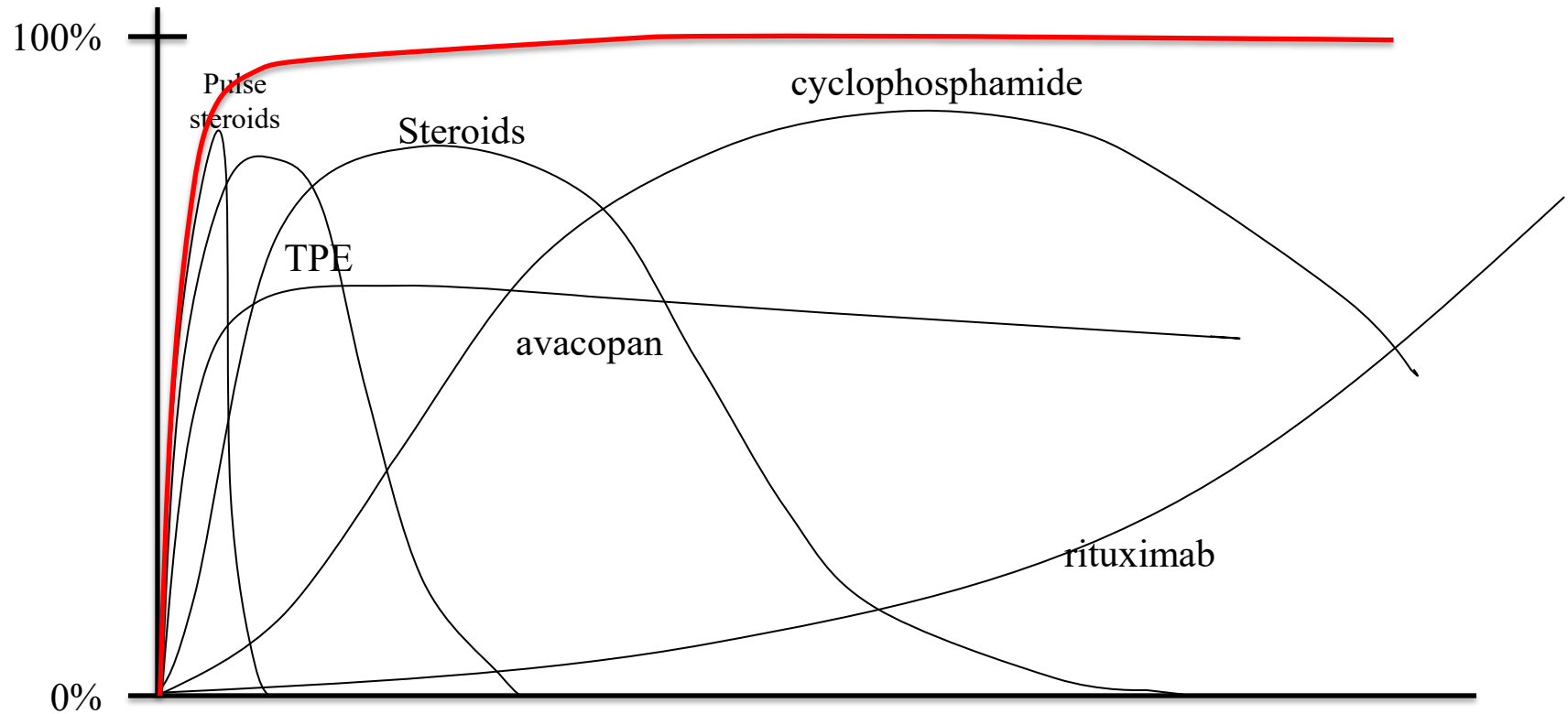
- We have a small set of tools
 - *Steroids*
 - *Cytotoxic agents*
 - *Cyclophosphamide, azathioprine, methotrexate, etc*
 - *Rituximab and other anti-B cell agents*
 - *Plasma exchange*
 - *Block C5, C5a*
 - *Avacopan, Eculizumab*
 - *And*
 - *Other complement agents*
 - *Imlifidase*

Induction treatment combinations

- Steroids alone
 - Average survival 5 monthsWalton 1958
- Steroids and cyclophosphamide
 - Remissions in 79 of 85 patientsFauci, Wolfe, Hoffman 1974, 1983, 1992
- Steroids and methotrexate
 - for not immediately life threatening
 - Remissions in 69% - 71% long term potentialHoffman, Fauci, Langford 1992, 1995, 1997 De Groot, Rasmussen 2005
- IV vs oral cyclophosphamide
 - CyclopsHarper2011
- Rituximab and steroids
 - RAVESpecks 2001
Stone, 2010
- Rituximab, cyclophos and steroids
 - High remission ratesJones, Jayne, 2010 Cortazar, Pendergraft, Niles, 2014, 2017)
- With or without plasma exchange
 - MEPEX PEXIVAS Meta analysisJayne 2007, Walsh 2022
- Ritux avacopan
 - AdvocateSchall, Merkel, Jayne 2021

AAV

Induction treatment combinations



AAV

Induction treatment combinations

■ So my take:

- **Not organ threatening** 
- Subacute organ threatening
 - Microhematuria, otitis, nasal ulcerations
- Acute organ threatening
 - GN, pulmonary lesions, hemorrhage, mononeuritis multiplex, optic neuritis, scleritis
- Critical organ threatening
 - RPGN
- Steroid toxic
- With acute eosinophilia

■ Treatment strategy

- **Steroids**
- **Rituximab**

AAV

Induction treatment combinations

■ So my take:

- Not organ threatening
- **Subacute organ threatening**
 - Microhematuria, otitis, nasal ulcerations
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- Critical organ threatening
 - RPGN, alveolar hemorrhage
- Steroid toxic
- With acute eosinophilia

■ Treatment strategy

- **Steroids**
- **Rituximab**
- **Low dose bridging cyclophosphamide**

AAV

Induction treatment combinations

■ So my take:

- Not organ threatening
- Subacute organ threatening
 - Microhematuria, otitis, nasal ulcerations
- **Acute organ threatening** 
 - GN, pulmonary lesions, hemorrhage, mononeuritis multiplex, optic neuritis, scleritis
- Critical organ threatening
 - RPGN, alveolar hemorrhage
- Steroid toxic
- With acute eosinophilia

■ Treatment strategy

- **Steroids**
- **Rituximab**
- **Short course, low dose, bridging cyclophosphamide**
- **Pulse steroids**
- **Avacopan**

AAV

Induction treatment combinations

■ So my take:

- Not organ threatening
- Subacute organ threatening
 - Microhematuria, otitis, nasal ulcerations
- Acute organ threatening
 - GN, pulmonary lesions, hemorrhage, mononeuritis multiplex, optic neuritis, scleritis
- **Critical organ threatening** 
 - RPGN

■ Treatment strategy

- **Steroids**
- **Rituximab**
- **Short course, low dose, bridging cyclophosphamide**
- **Pulse steroids**
- **Avacopan**
- **Plasmapheresis**

AAV

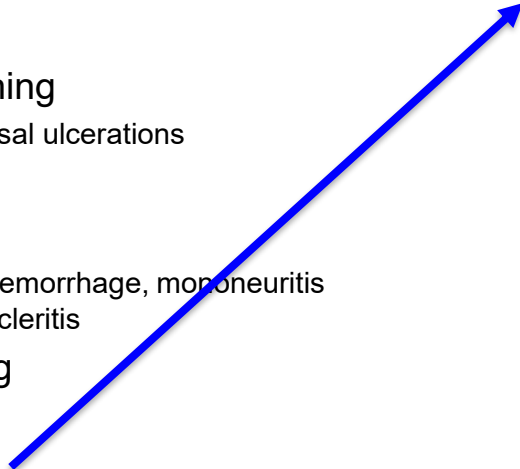
Induction treatment combinations

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- Acute organ threatening
 - GN, pulmonary lesions, hemorrhage, mononeuritis multiplex, optic neuritis, scleritis
- Critical organ threatening
 - RPGN
- **Steroid toxic**

■ Treatment strategy

- ~~**Steroids**~~
- **Rituximab**
- **Low dose bridging cyclophosphamide**
- **Pulse steroids**
- **Avacopan**
- **Plasmapheresis**



AAV

Induction treatment combinations

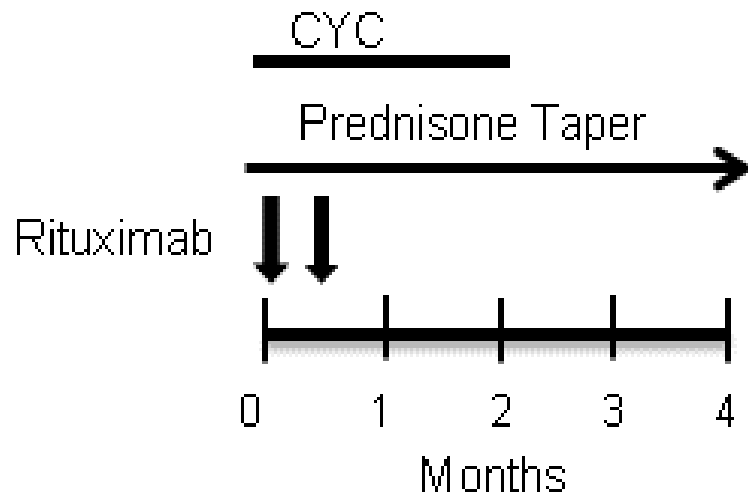
■ So my take:

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- Acute organ threatening
 - GN, pulmonary lesions, hemorrhage, mononeuritis multiplex, optic neuritis, scleritis
- Critical organ threatening
 - RPGN
- Steroid toxic
- **With acute eosinophilia** 

■ Treatment strategy

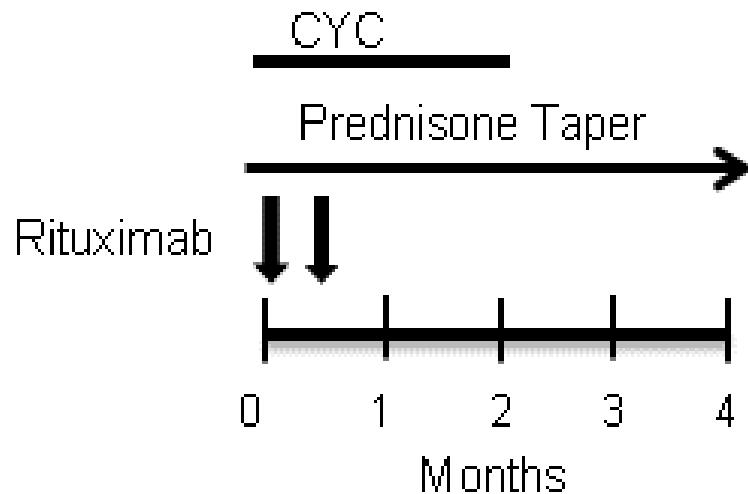
- **Steroids**
- **Rituximab**
- **Low dose bridging cyclophosphamide**
- **Pulse steroids**
- **Avcopan**
- **Plasmapheresis**
- **Mepolizumab**

Triple drug - Steroid sparing - Protocol



- Rituximab
 - 1 gm x 2
- Prednisone
 - Tapered to 15mg by day 30
 - Then tapered by 2.5 mg/month
- Cyclophosphamide
 - 2.5 mg/kg (lean wt) for 1 week
 - 1.5 mg/kg for 7 weeks
 - Adjusted for renal fx
- +/- PLEX

Triple drug - Steroid sparing - Protocol



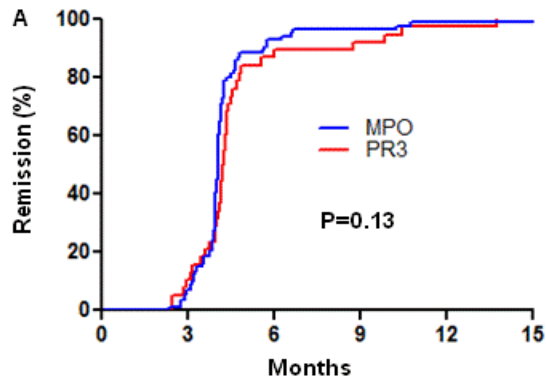
- Rituximab
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 - 1.5 mg/kg for 7 weeks
 - **Adjusted for renal fx**
- +/- PLEX

Adjustment of cyclophosphamide dose for renal function

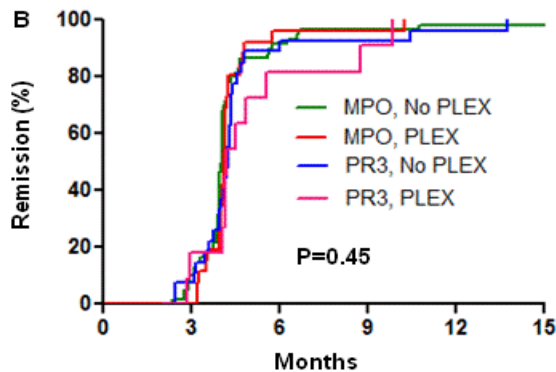
eGFR ml/min/1.72 m²

Dose Adjustment

➤ >90	100%
➤ 60-90	90%
➤ 45-60	75%
➤ 30-45	66%
➤ 15-30	60%
➤ < 15	50%



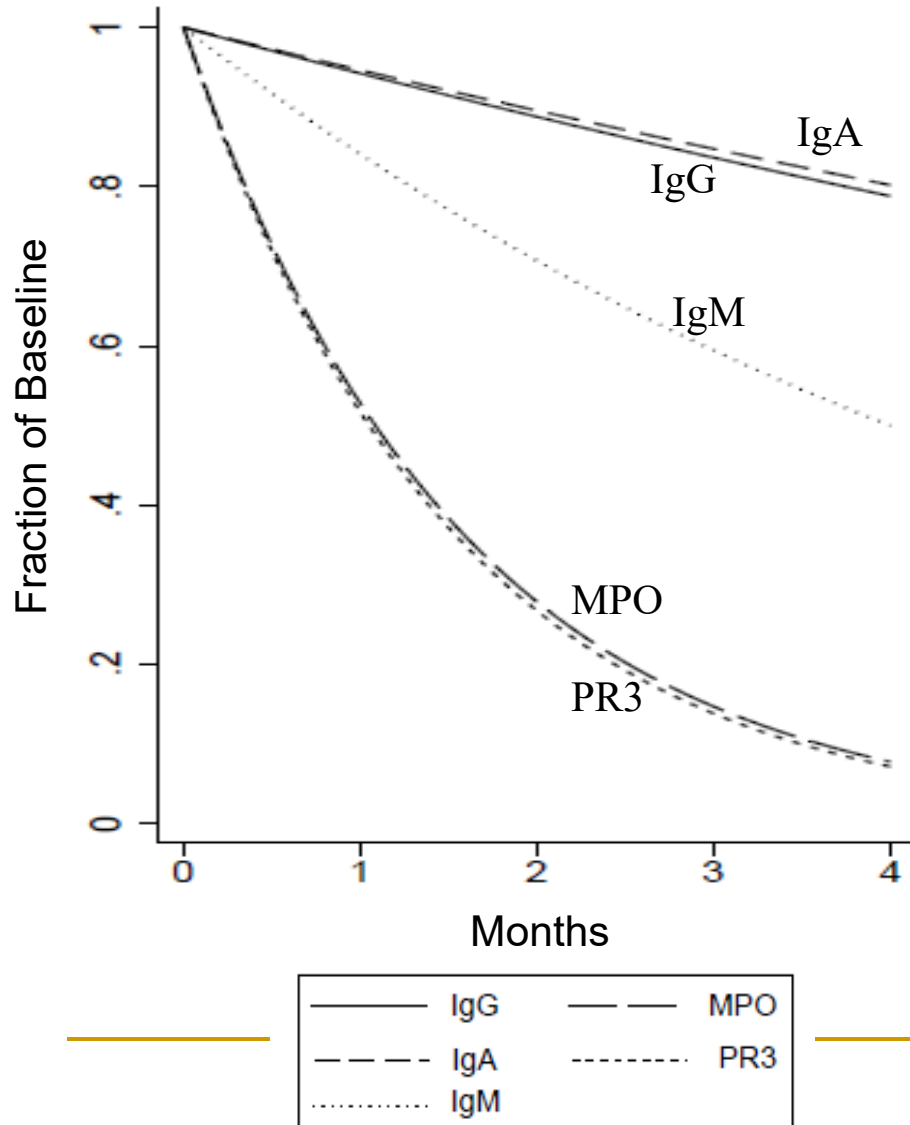
Number at risk						
MPO	90	81	6	3	1	1
PR3	39	34	5	3	1	0



Number at risk						
MPO, No PLEX	62	55	5	2	1	1
MPO, PLEX	28	26	1	1	0	0
PR3, No PLEX	27	25	3	2	1	0
PR3, PLEX	12	9	2	1	0	0

- Remission: BVAS-WG=0 and Pred $\leq$ 7.5 mg/d
- Median (IQR)= 4.1 months (3.9, 4.3)
- Remission by 6 months
 - 5 patients died
 - Survivors: 114/124 (92%)
 - Overall: 114/129 (88%)
- No difference by serotype or PLEX

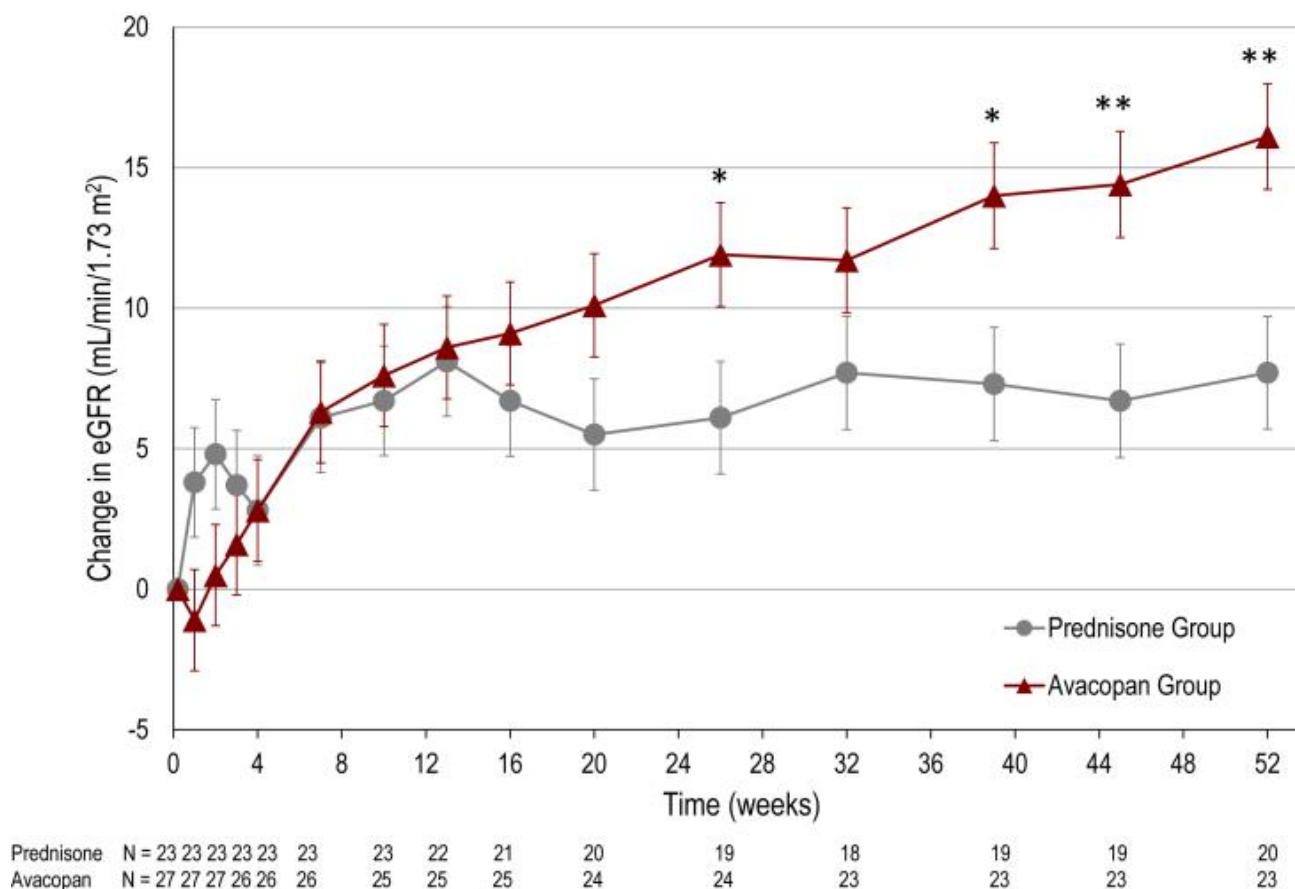
INDUCTION



Antibody	Induction Monthly % Decline (n=52)
IgG	6 (4 to 8)
IgA	5 (2 to 9)
IgM	16 (13 to 19)
Anti-MPO	47 (42 to 52)
Anti-PR3	48 (42 to 54)

Small molecule, oral C5a receptor antagonist ADVOCATE Trial*

■ Phase 3 Trial - subgroup analysis - eGFR <20

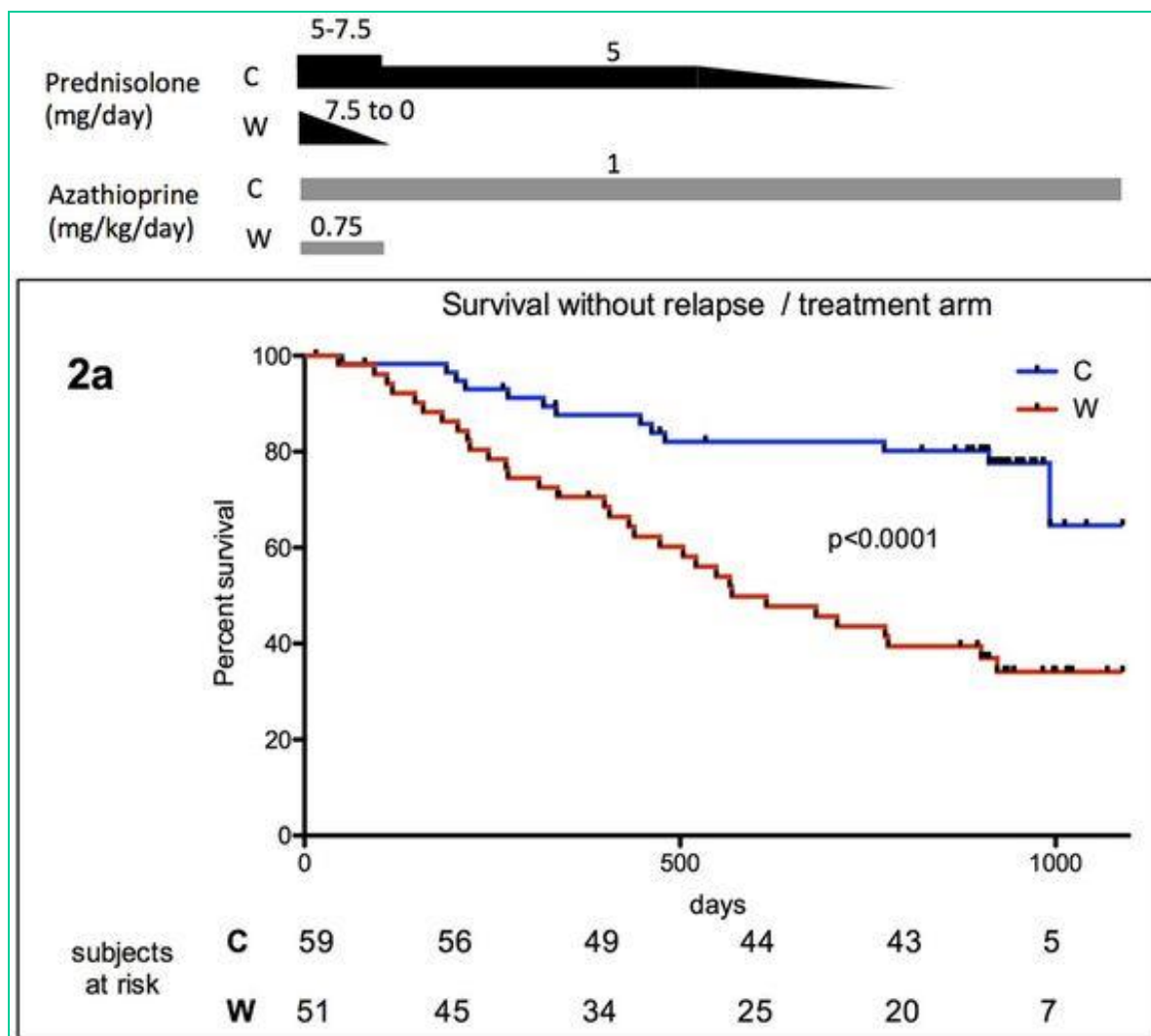


Maintenance therapy for ANCA vasculitis

What do we know ?

- 2017 Oct;76(10):1662-1668.
- 2017 Oct;76(10):1662-1668.
- 2017 Oct;76(10):1662-1668.

REMAIN trial



Continuation
Withdrawal

Relapse rates

MMF vs Aza

Hiemstra et al. Mycophenolate mofetil vs azathioprine for remission maintenance in anti-neutrophil cytoplasmic antibody-associated vasculitis A randomized controlled trial. *JAMA* 2010 304:2381-8

Aza

2 mg/kg/d x 12 mo
1.5 mg/kg/d 12-18 mo
1 mg/kg/d 18-42 mo

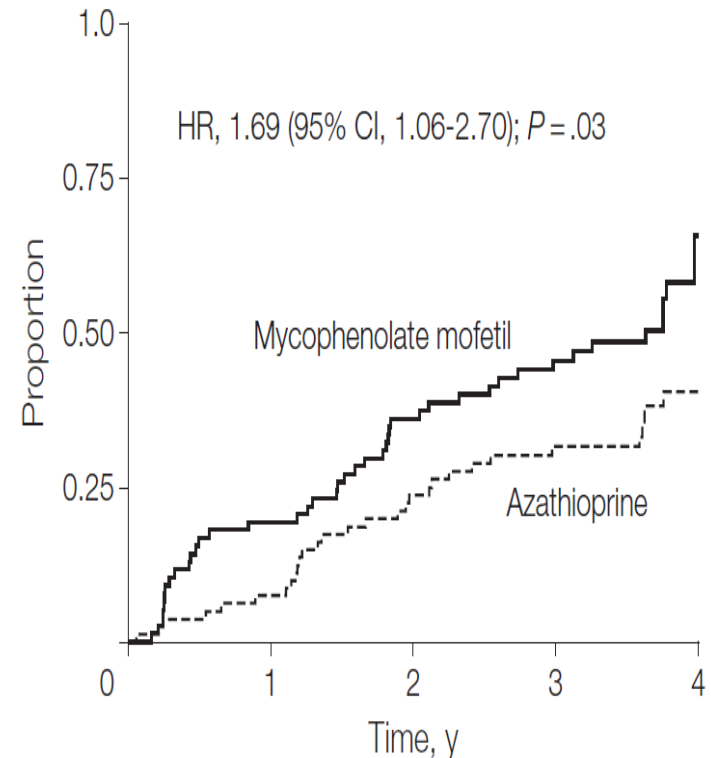
MMF

2000 mg/d x 12 mo
1500 mg/d 12-18 mo
1000 mg/d 18-42 mo

Prednisone

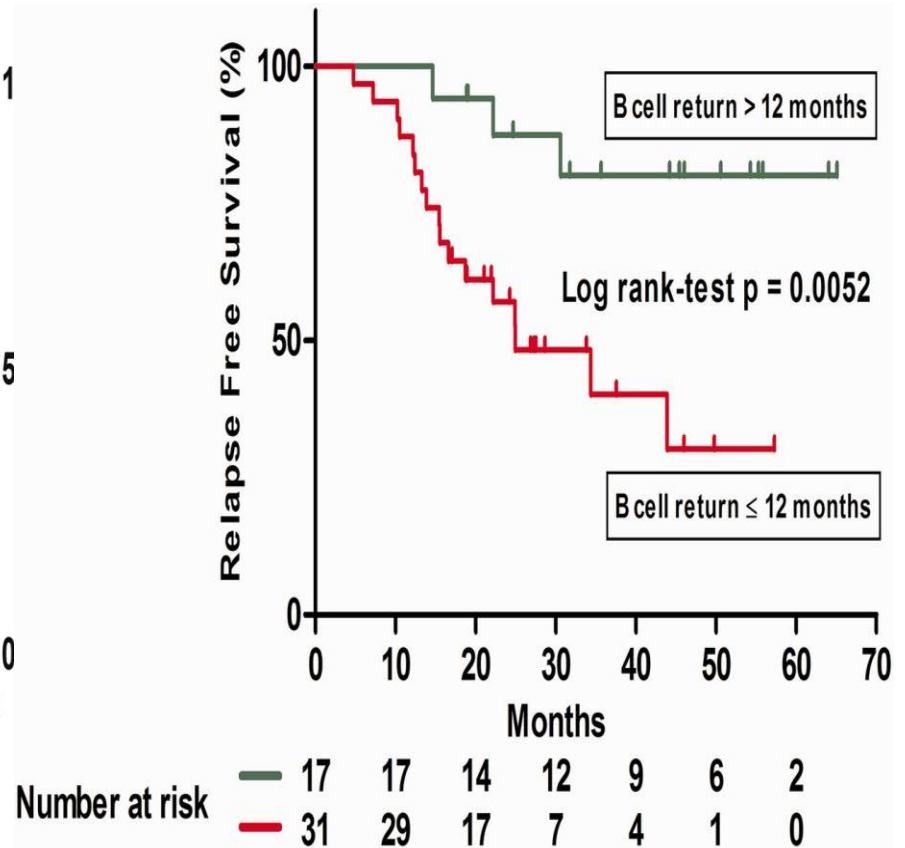
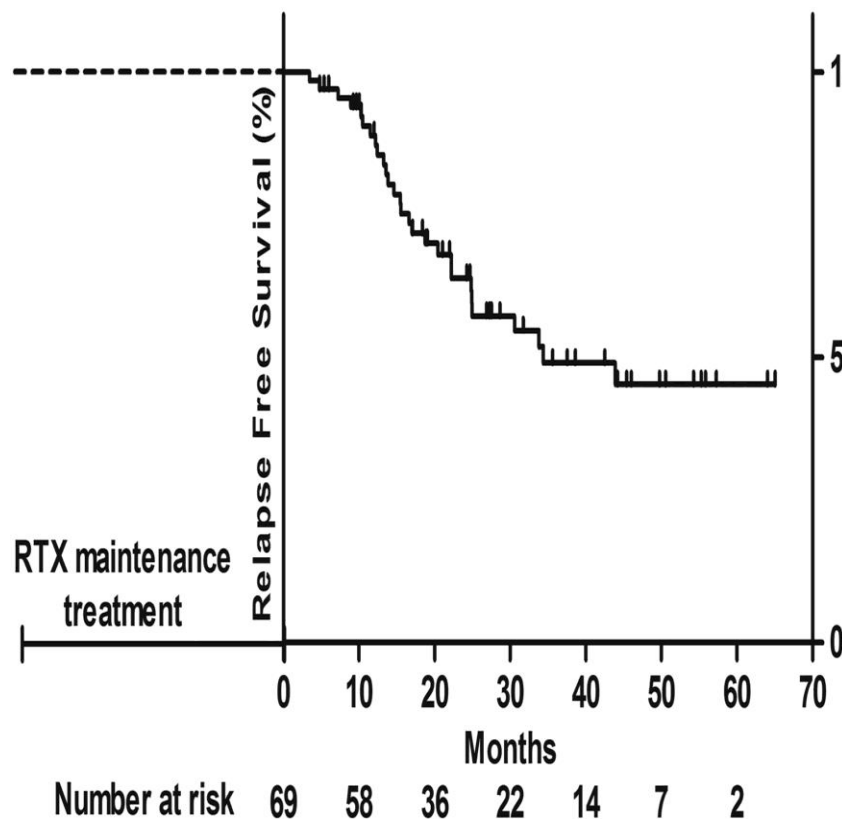
15 tapered to 5 mg/d
over 12 months
5 mg/d 12-24 months
stopped at 24 months

First relapse



No. at risk					
Azathioprine	80	72	57	46	6
Mycophenolate mofetil	76	60	47	37	4

Relapse after Rituximab



Maintenance therapy for ANCA vasculitis

■ Options

- Stop, wait for relapse and retreat
 - Maintenance therapy – **early trials mostly inadequate**
 - **What about rituximab maintenance therapy?**
-

Rituximab maintenance therapy

172 patients followed at MGH

William Pendergraft, MD Frank Cortazar, MD

Eugene Rhee, MD Karen Laliberte, RN

John L. Niles, MD

Treatment

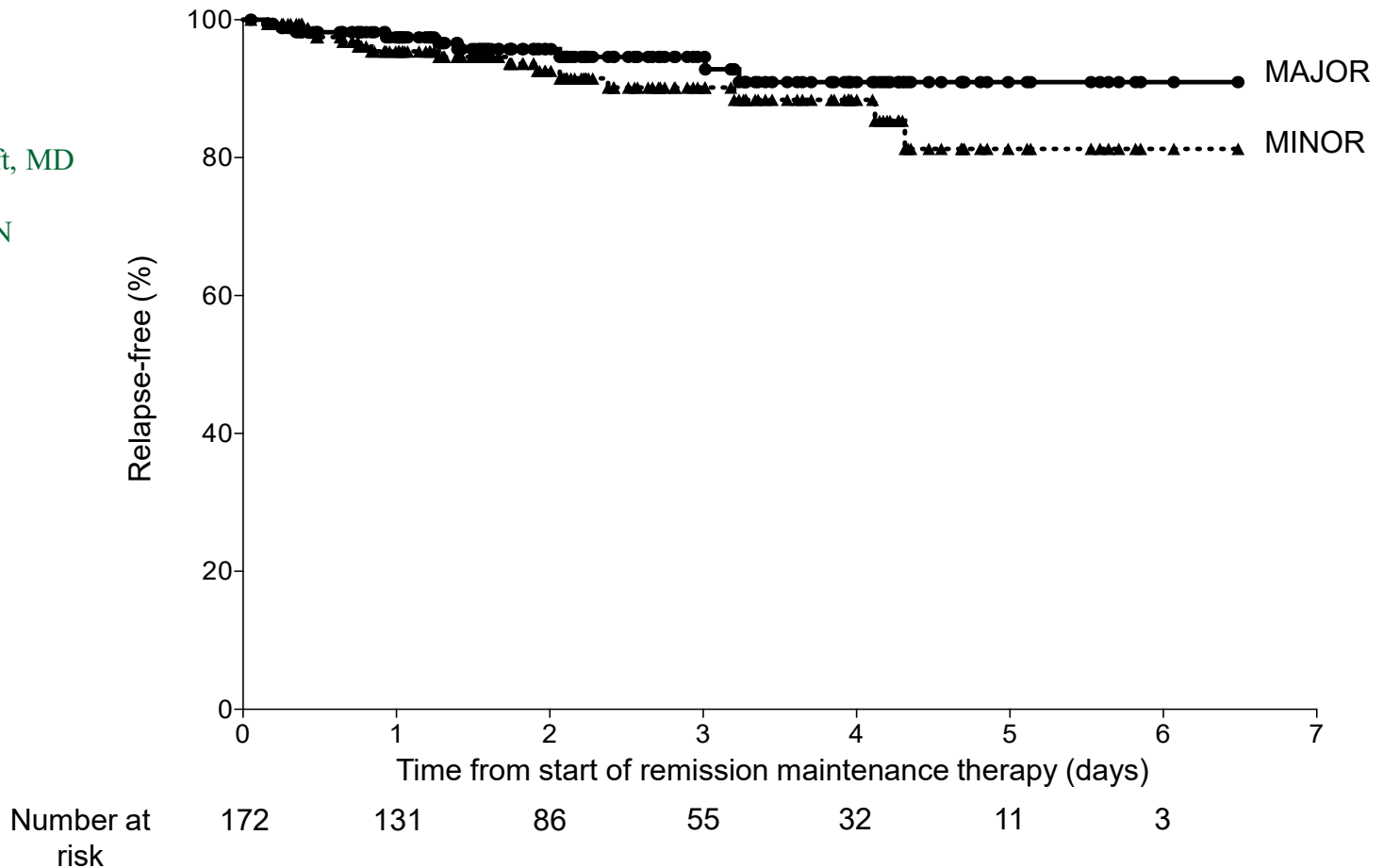
- Rituximab maintenance
 - Continuous B cell depletion
 - Rituximab 1 gm every 4 months
 - After 2 years, dosing interval increased to every 6 months if B cells remain continuously depleted
- Other immunosuppressive medications weaned off
 - Virtually all patients come off steroids
 - (except adrenal insufficiency dosing)

**Strategy for 172
patients on
maintenance
rituximab**

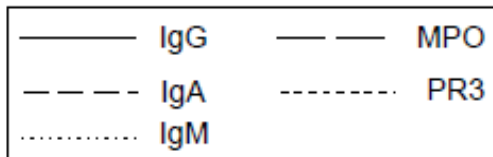
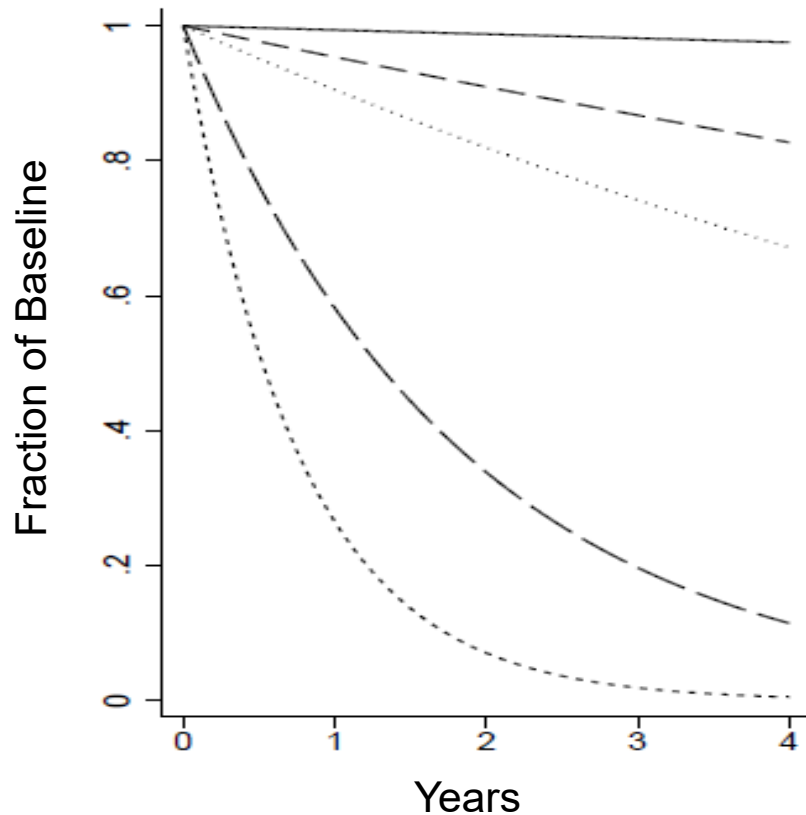
William Pendergraft, MD
Eugene Rhee, MD
Karen Laliberte, RN
John L. Niles, MD

Relapses

Figure 3 Minor and major relapse rates of ANCA vasculitis patients undergoing continuous B cell depletion



MAINTENANCE

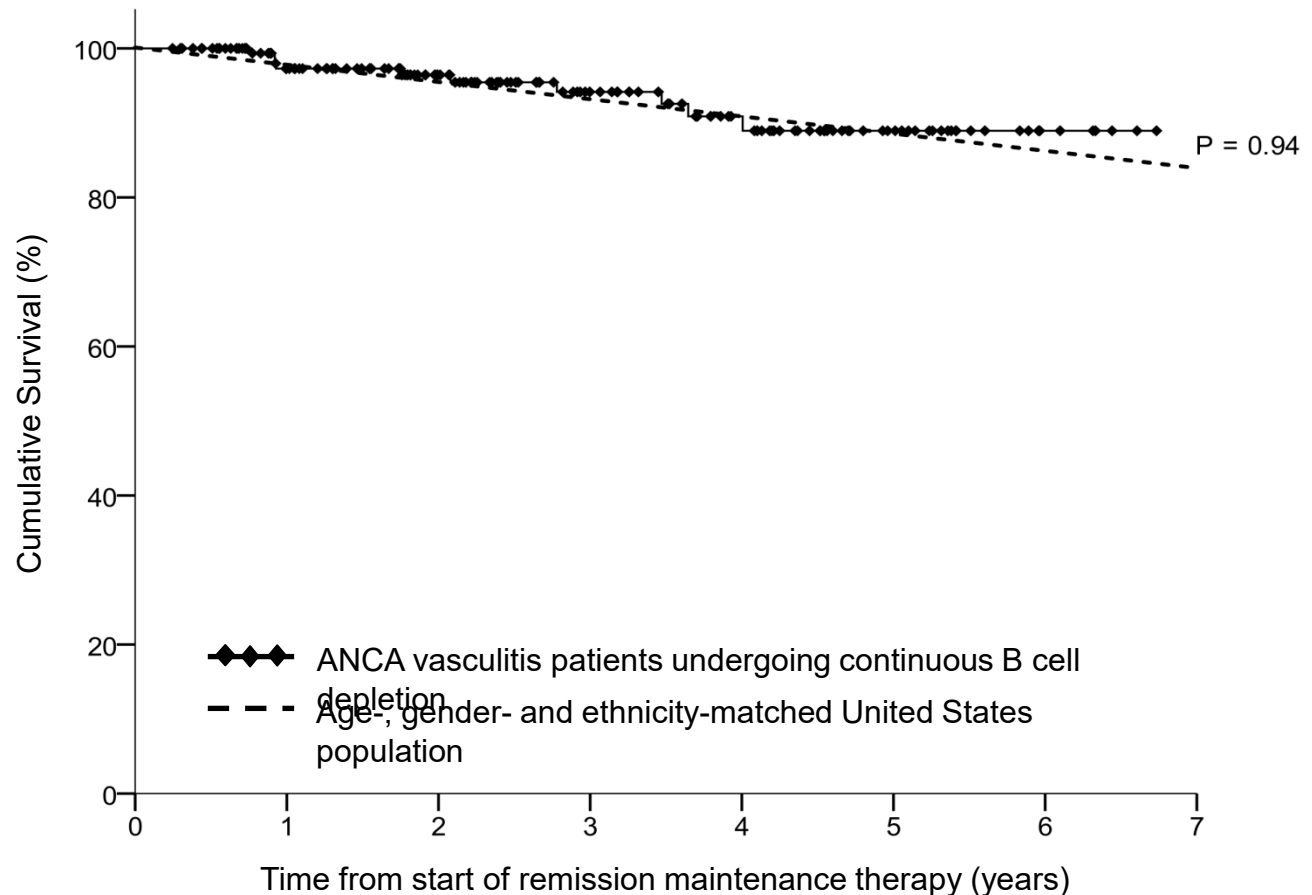


Antibody	*Maintenance Yearly % Decline (n=237)
IgG	0.6 (-0.2 to 1.4)
IgA	5 (3 to 6)
IgM	9 (8 to 11)
Anti-MPO	42 (32 to 50)
Anti-PR3	73 (58 to 83)

**Strategy for 172
patients on
maintenance
rituximab**

William Pendergraft, MD
Eugene Rhee, MD
Karen Laliberte, RN
John L. Niles, MD

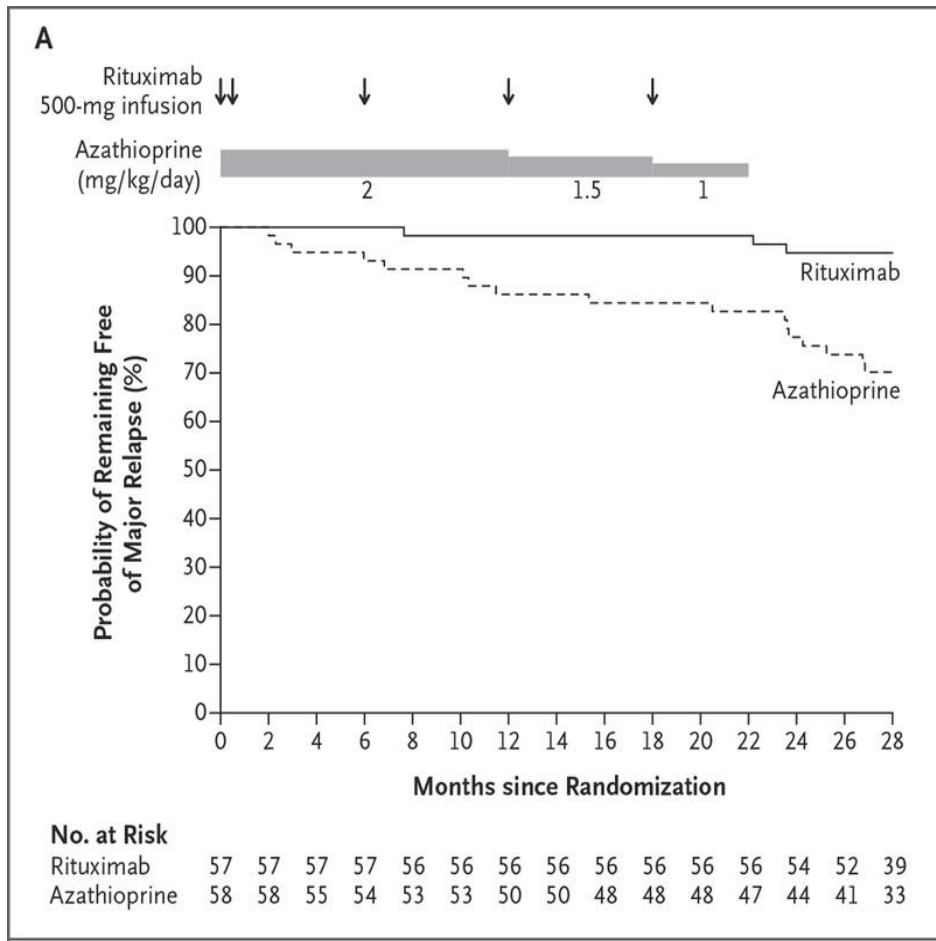
Survival vs age matched general population



Number at risk
172 14 102 69 49 24 7
0

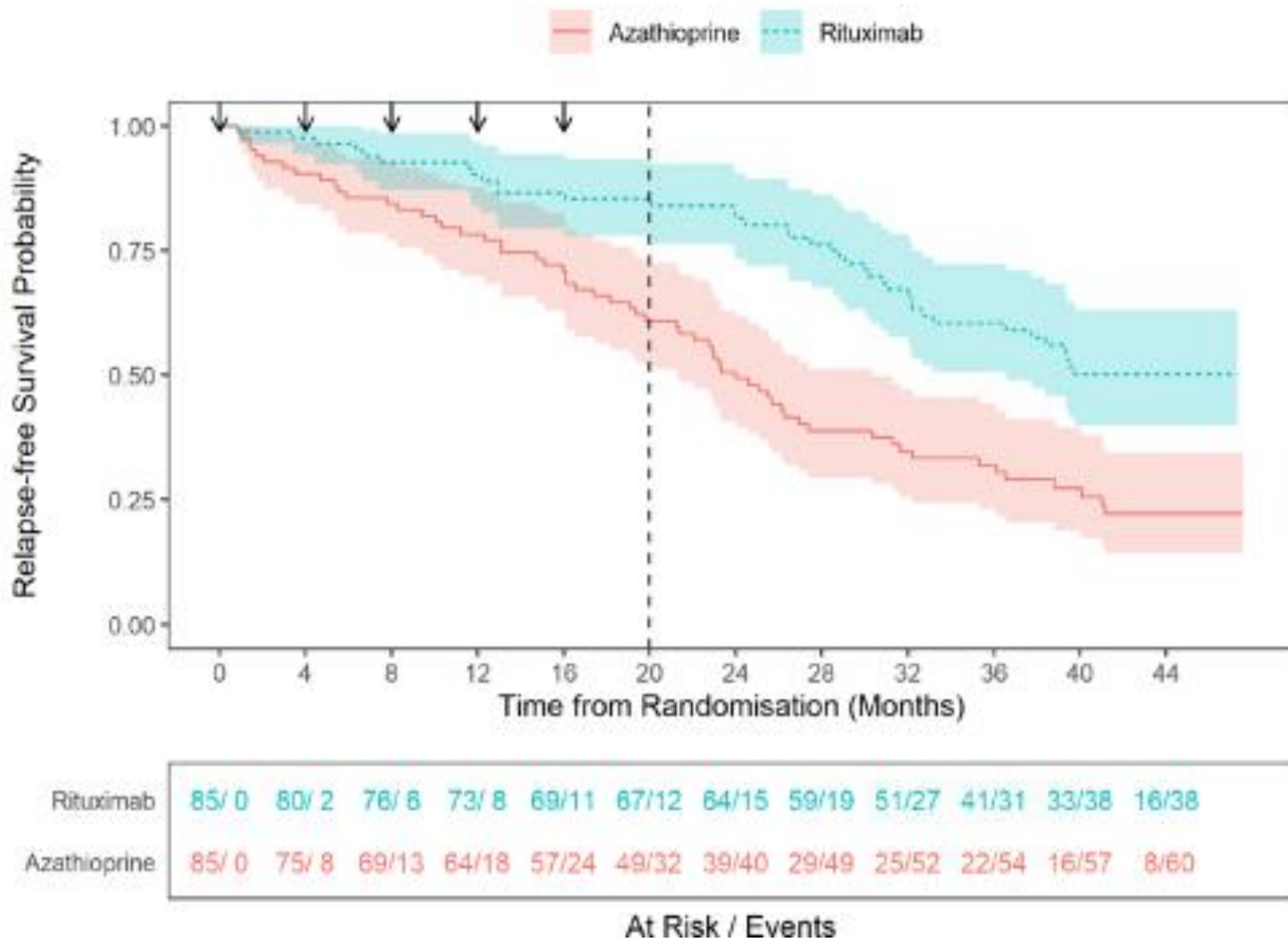
Figure 4 Survival of ANCA vasculitis patients undergoing continuous B cell depletion mirrors the general population

MAINRITSAN Trial



- Rituximab- 5 % Major Relapse
- Azathioprine- 29% Major Relapse
- No difference in adverse events

RITAZAREM

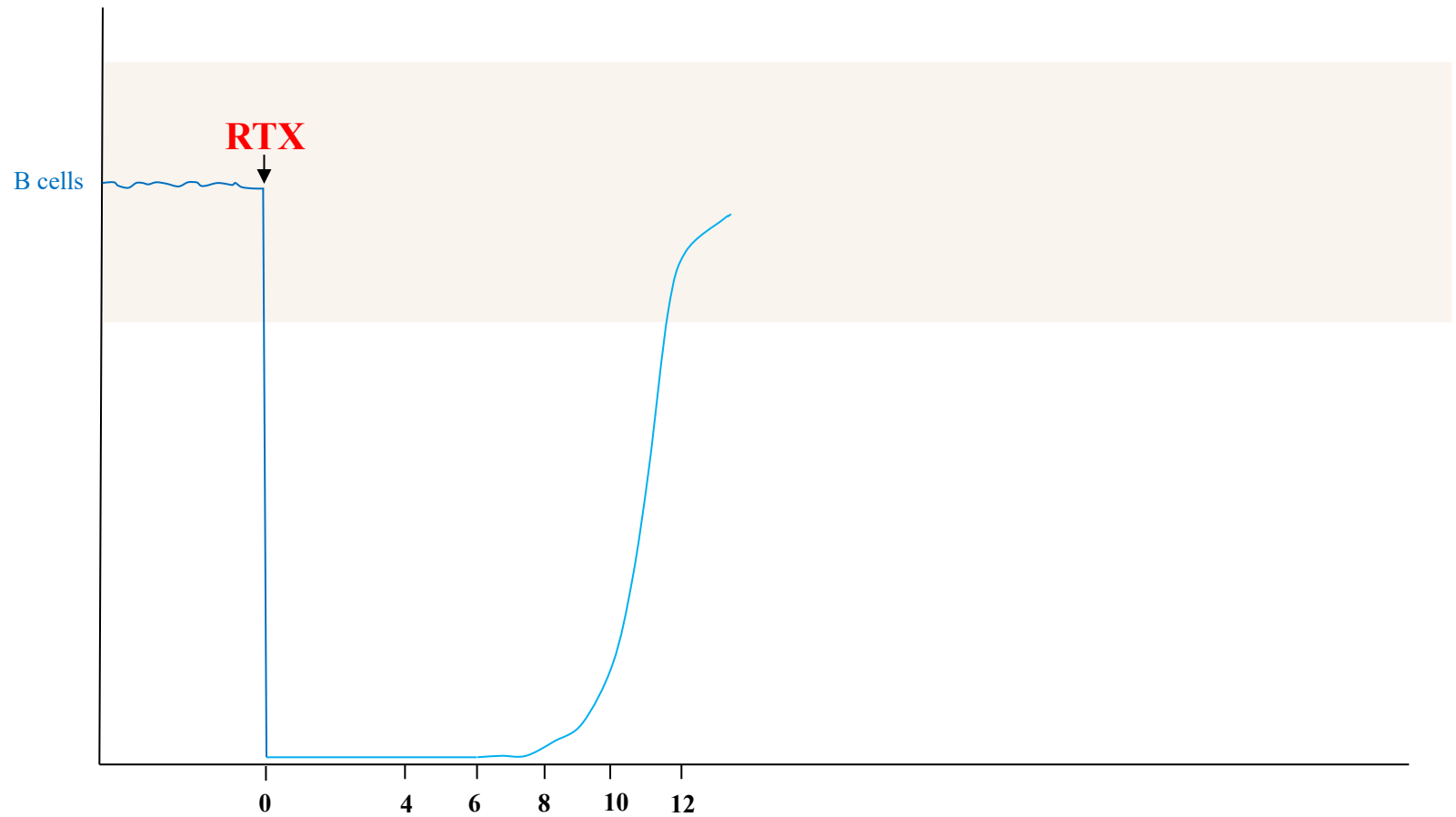


Rituximab vs azathioprine for maintenance of remission for patient with ANCA-associated vasculitis and relapsing disease: an international randomized controlled trial
Ann Rheum Dis: Online 23 March 2023

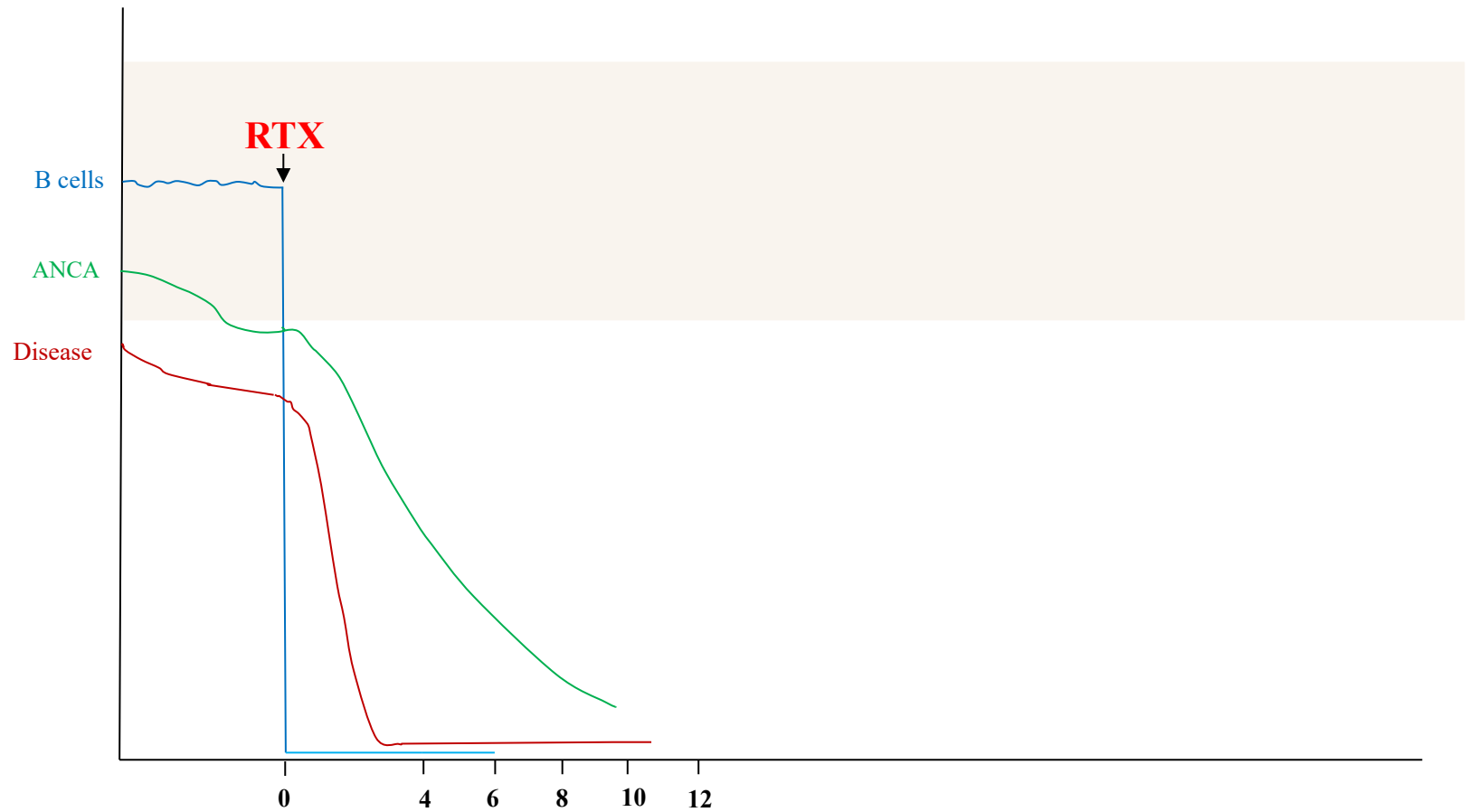
Continuous B cell depletion with rituximab for ANCA vasculitis

- Long term issues
 - Late onset neutropenia
 - Mucosal infections
 - Bronchitis
 - Sinusitis
 - Vaginitis
 - COVID19
-

Anatomy of a relapse

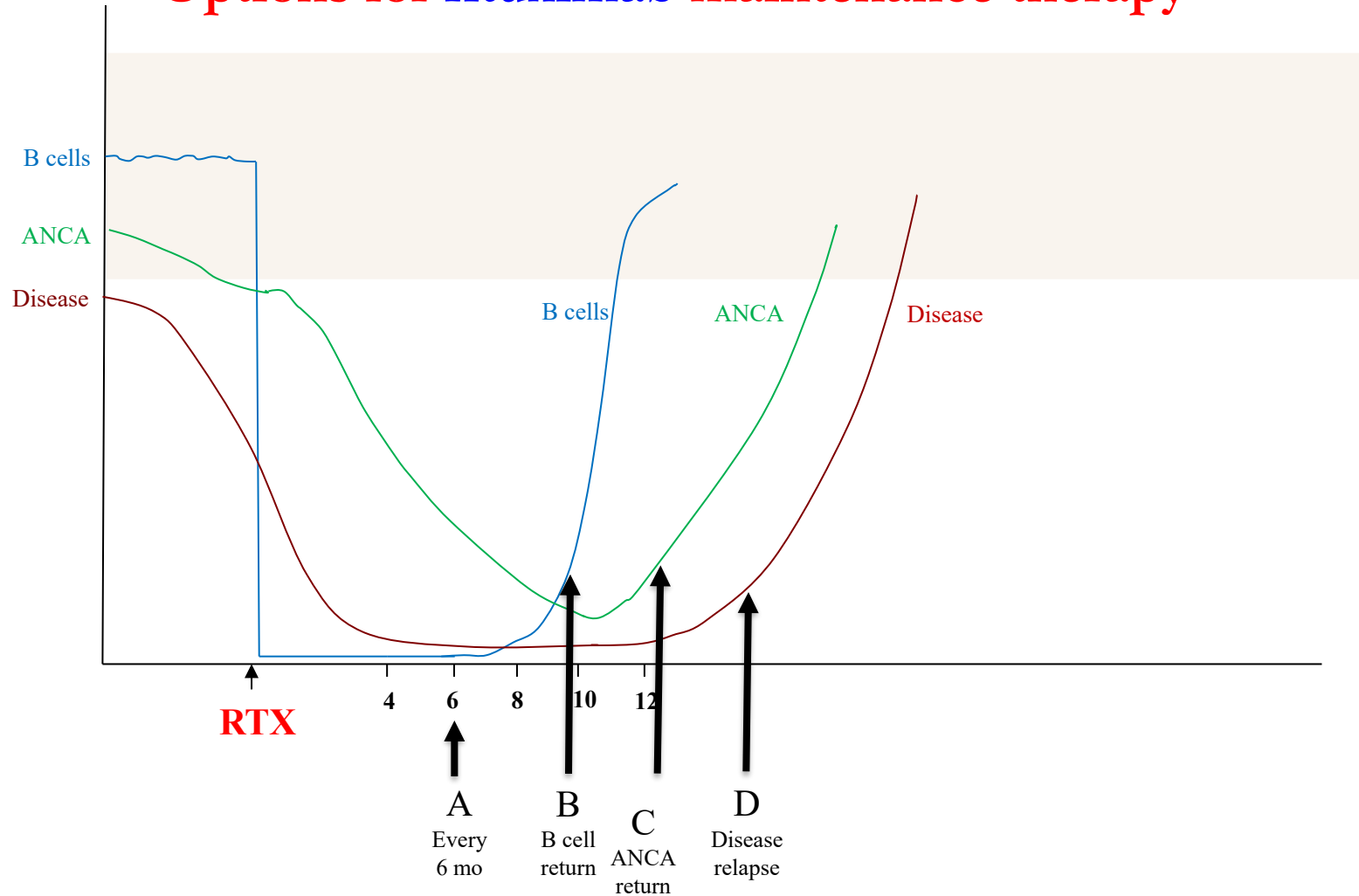


Anatomy of a relapse



Anatomy of a relapse-

Options for rituximab maintenance therapy



Anatomy of a relapse-

Options for maintenance therapy

	Rituximab timing	% major relapse at 5 years	Infections at 5 years
A	Every 6 months	~ 5%	Bronchitis, vaginitis, sinusitis (? colitis)
B	B cell return	?	?
C	ANCA return	?	?
D	Relapse	50-70%	No signal

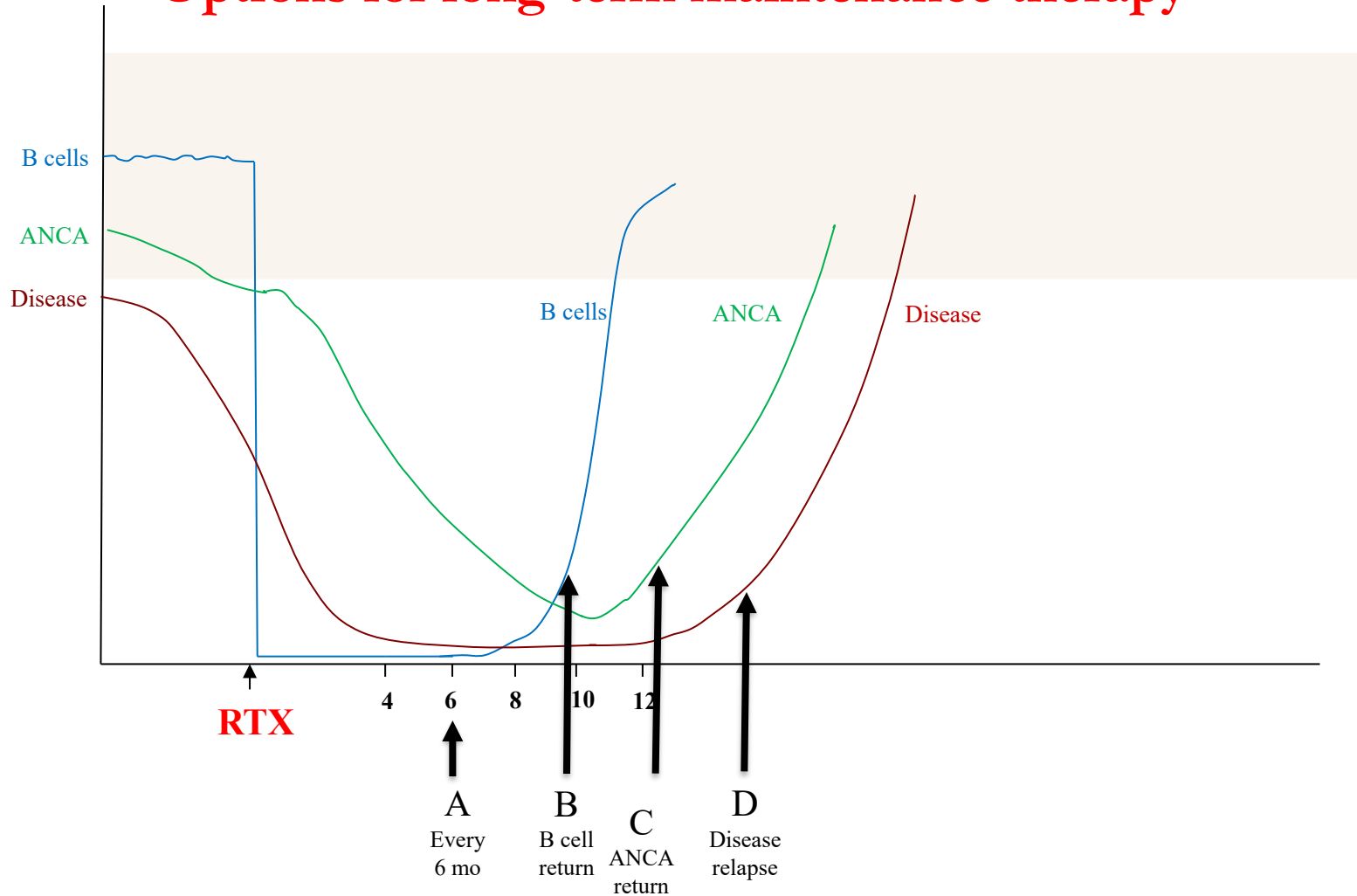
Anatomy of a relapse-

Options for maintenance therapy

	Rituximab timing	% major relapse at 5 years	Infections at 5 years
A	Every 6 months	~ 5%	Bronchitis, vaginitis, sinusitis, (? colitis)
B	B cell return	?	?
C	ANCA return	?	?
D	Relapse	50-70%	No signal

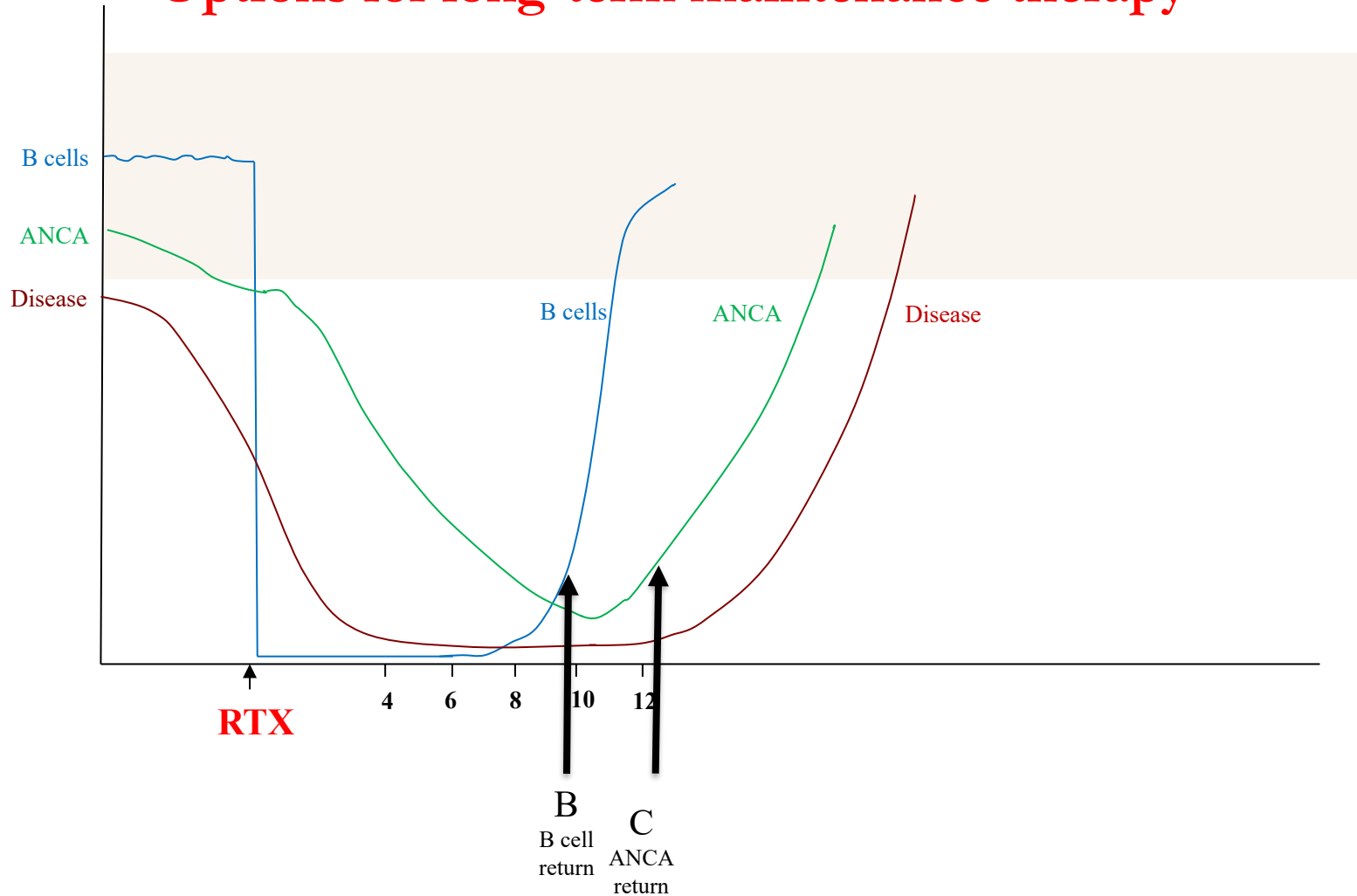
Anatomy of a relapse-

Options for long-term maintenance therapy

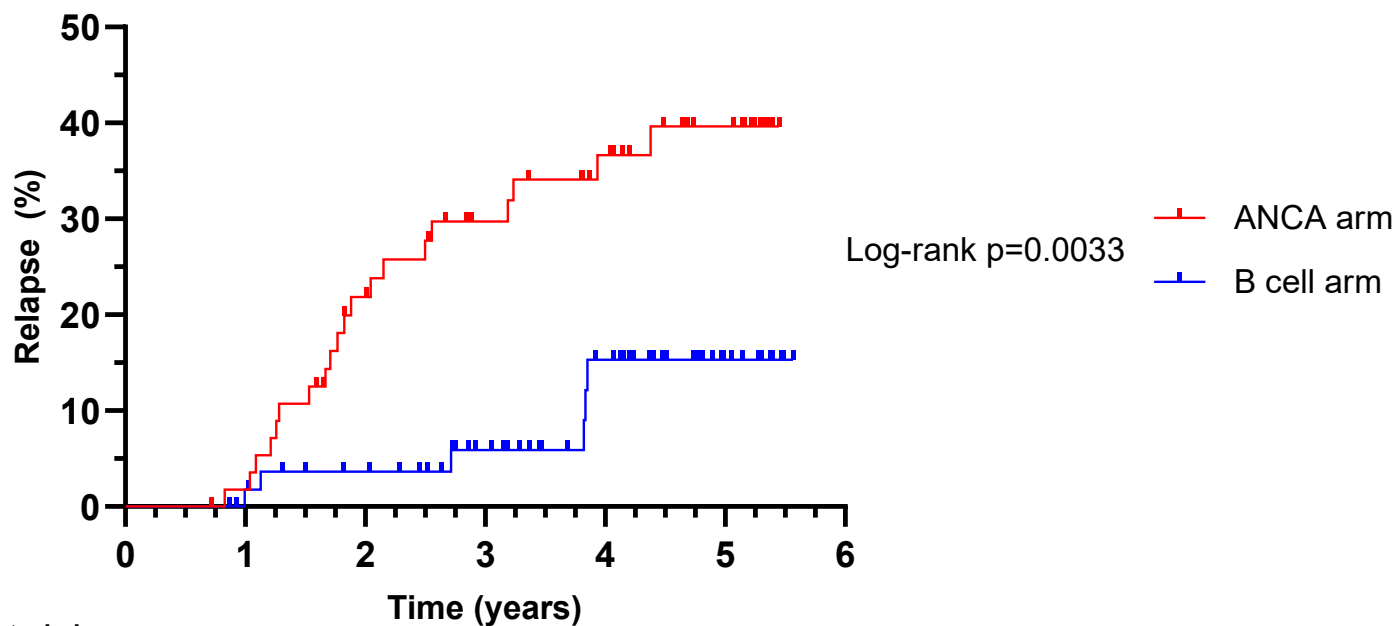


Anatomy of a relapse-

Options for long-term maintenance therapy



Time to clinical or serologic relapse



Number at risk

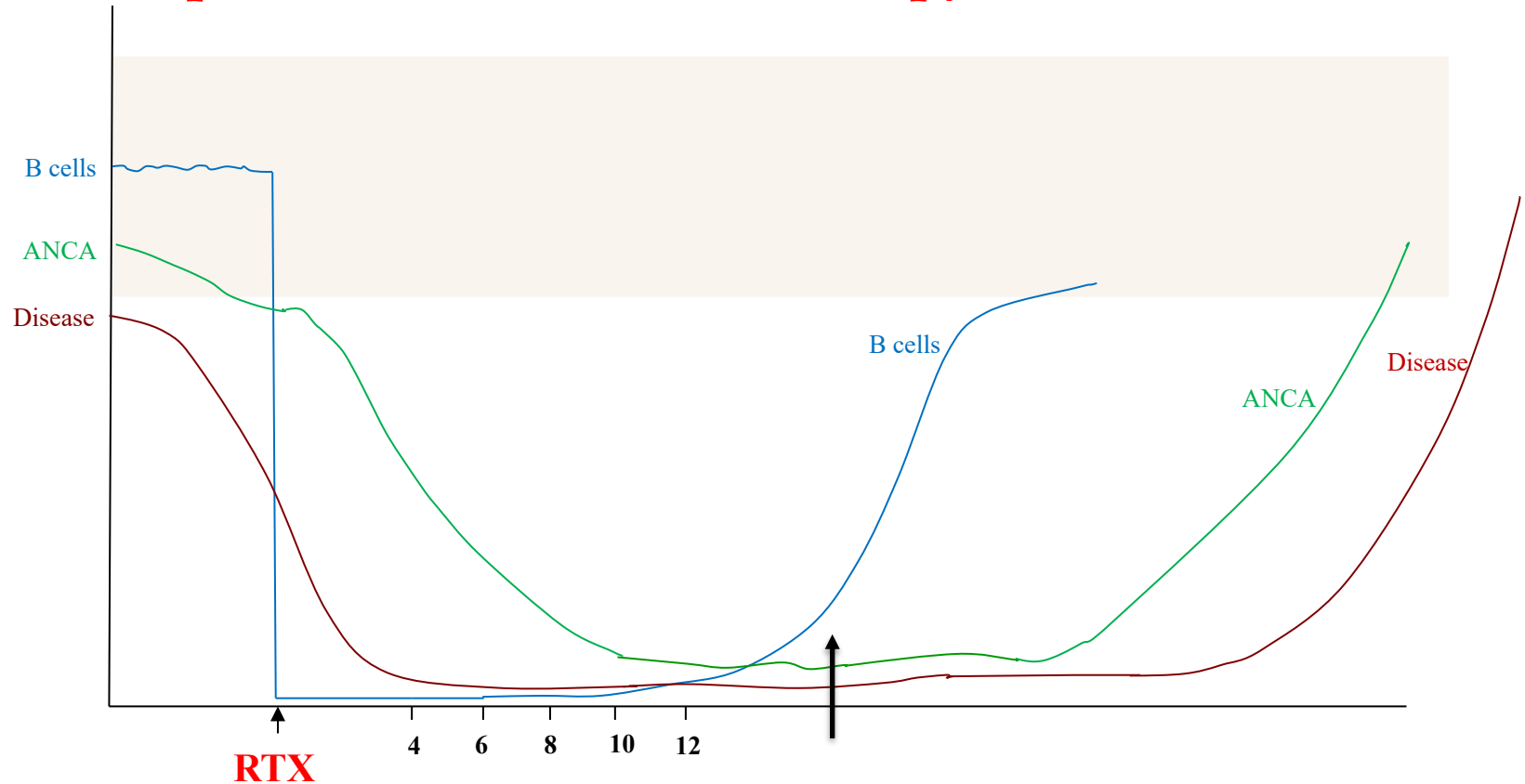
ANCA arm	57	55	41	32	25	15	0
B-cell arm	58	55	49	38	26	11	0

Results – Serious adverse events

	ANCA arm (n = 57)	B cell arm (n = 58)	P-value
Number of events	22	21	NS
Patients with at least one SAE	15 (26%)	12 (33%)	“
Infection (# of events)	6	10	“
Bronchitis	1	1	“
Pneumonia	2	0	“
Genitourinary	2	1	“
Gastrointestinal	0	1	“
Skin and soft tissue	0	1	“
Covid-19	1	6 (2 died)	“
Cancer	0	1	“
Thromboembolic disease	1	0	“
Cardiac events	4	3	“
Pregnancy	0	0	“
Neutropenia	0	1	“
Others	11	6	“

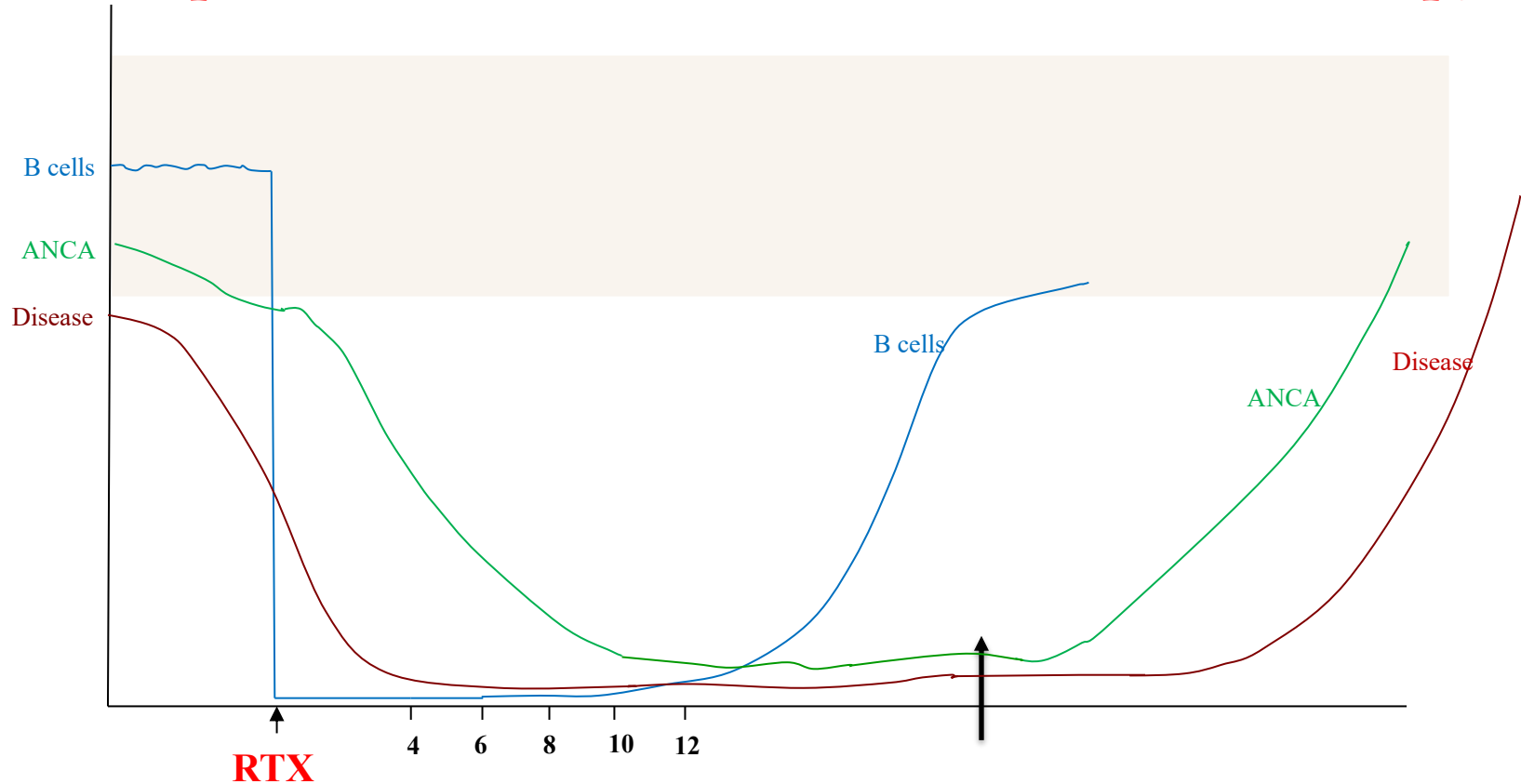
Anatomy of a relapse-

Options for maintenance therapy



Anatomy of a relapse-

Options for extended rituximab maintenance therapy



My dosing strategy

■ Starting strategy

- Early (first 2 years) (q4 mo to q 6mo)
 - Aim to allow no B cell return before next dose
- Next (years 2-4) (typically q 6 to q 9 mo)
 - Allow early and moderate B cell recovery between doses
- Late (by 5 years) (typically q8 to q12 months)
 - Allow moderate to full B cell recovery between doses

■ Adjust

- If relapses occur, then shorten intervals
- If infections occur, then hold and lengthen intervals

■ 15 to 50 year strategy

- In progress

Conclusion

■ Center based care (VGC)

- Availability
- Efficiency
 - Medical
 - Financial
- Comprehensive
- Continuity

■ Early diagnosis, early treatment

- Treatment stops disease activity
- Treatment cannot replace damage

■ Adequate induction

- Rituximab with
 - Steroids
 - Cyclophosphamide
 - Avacopan
 - Plasma exchange in selected patients

■ Long term

- Rituximab maintenance - continuous for 2 years to start
- Long term treatments -- extended rituximab intervals
 - Balancing act -- Disease, ANCA, B cells, infections, and other side effects

Everything Should Be Made as Simple as Possible,
But Not Simpler

Albert Einstein
