Diagnosis and Treatment of ANCA-associated Vasculitis

The long-term view

Comprehensive management of a difficult disease

John L. Niles, MD

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

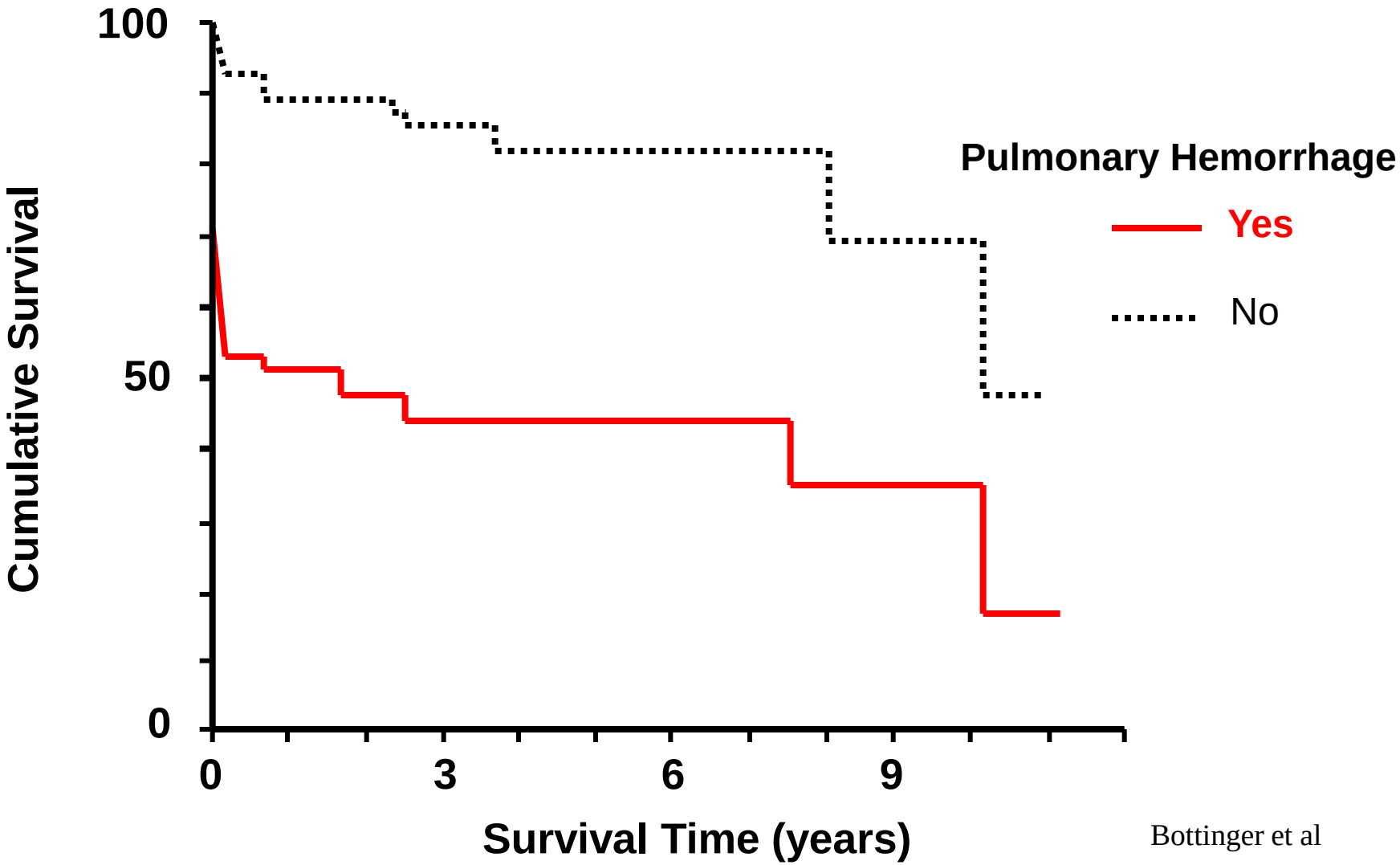
ANCA negative ANCA vasculitis (rare)

~~Other ANCA vasculitis~~

ANCA

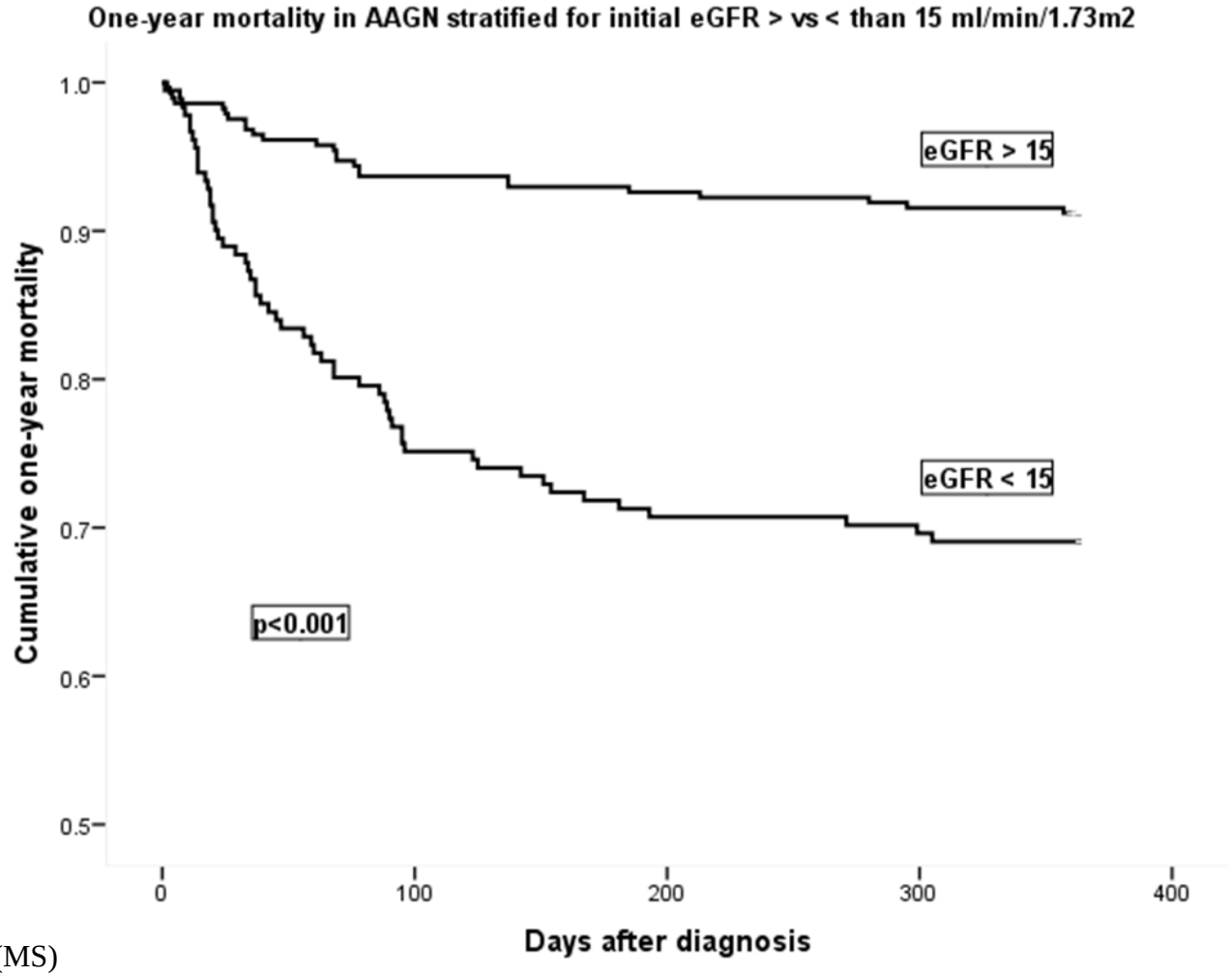
Pulmonary Hemorrhage

MGH 1981-1994



Bottinger et al

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



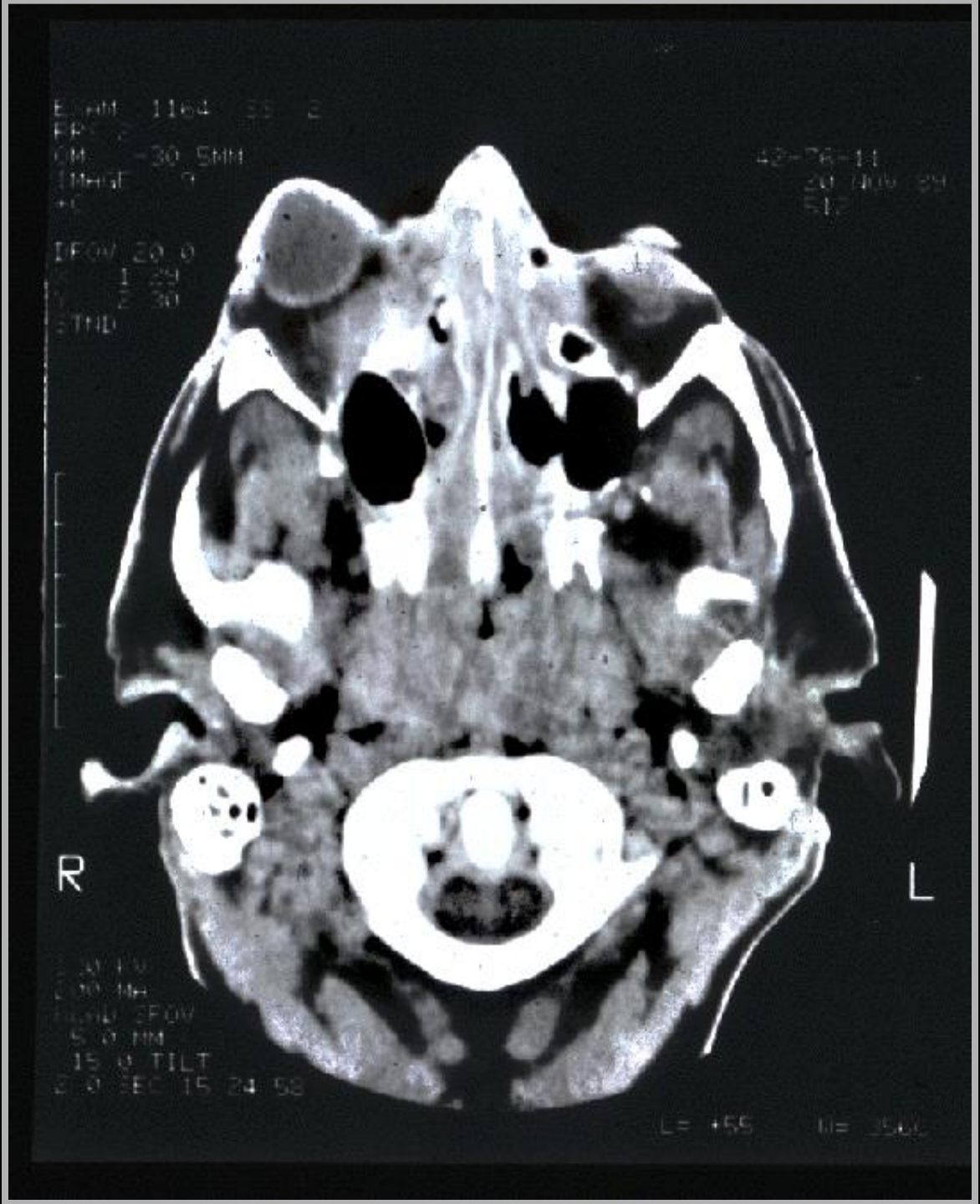
Sanjeevan Sriskandarajah (MS)
Renal Research Group
University of Bergen 2015

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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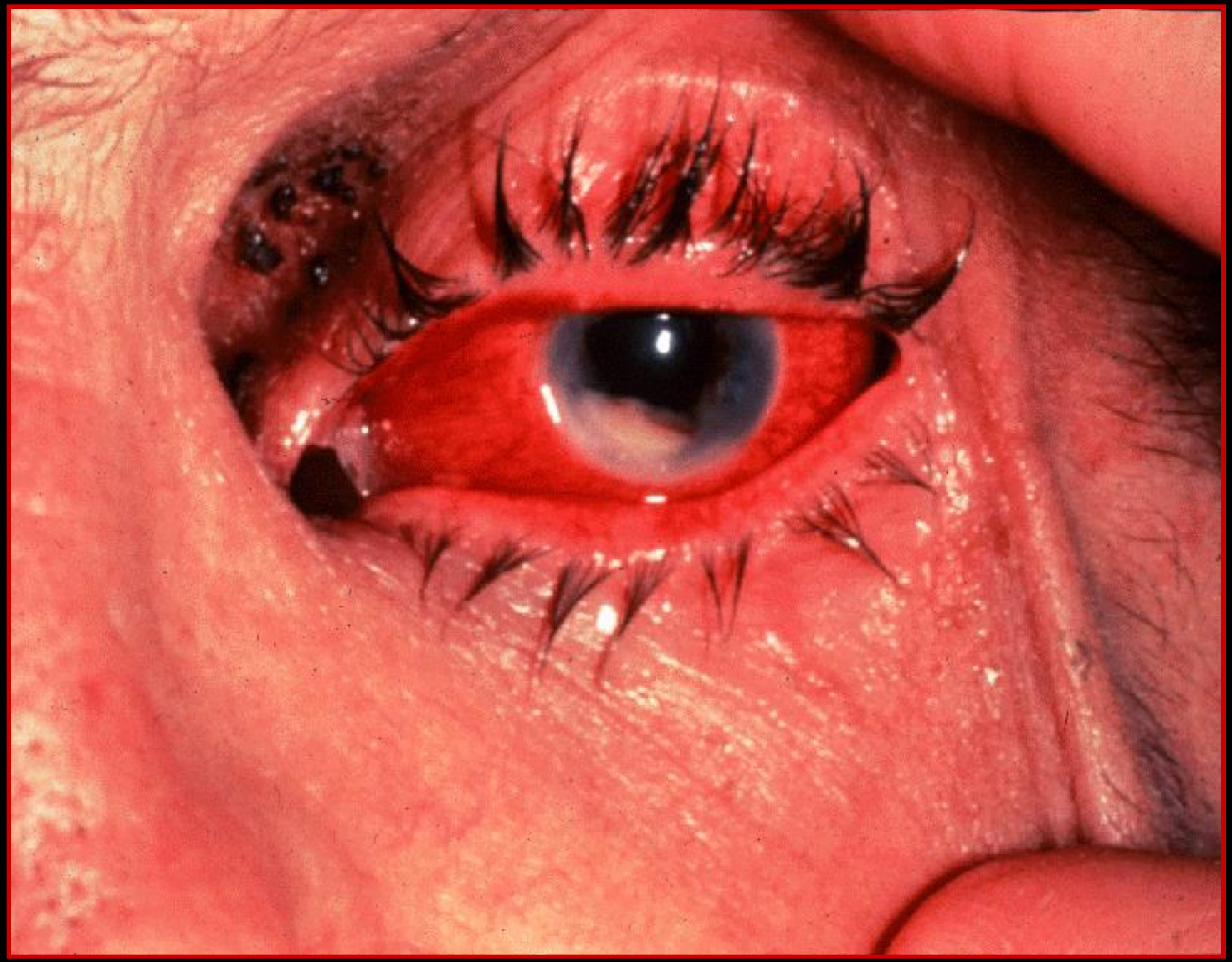
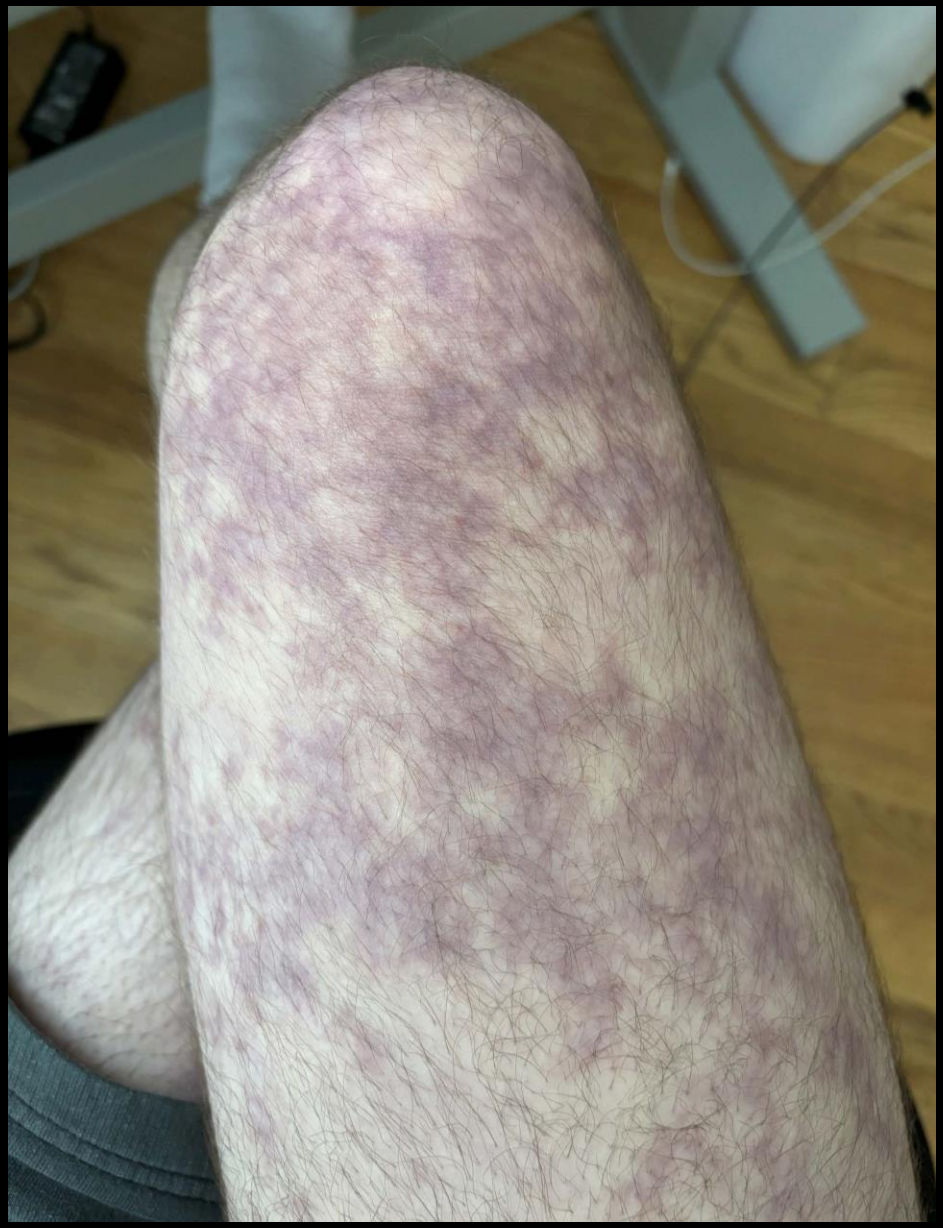
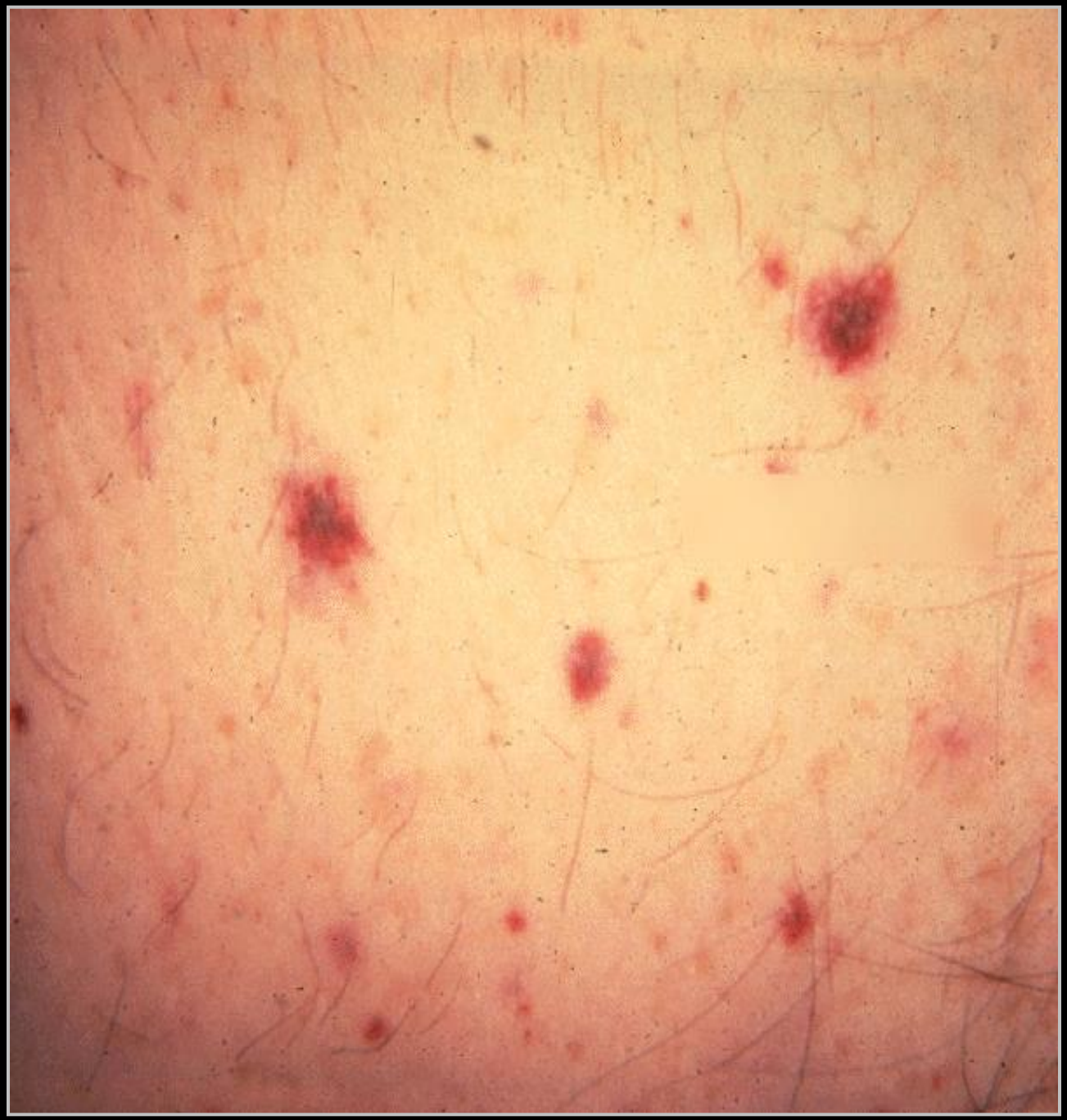
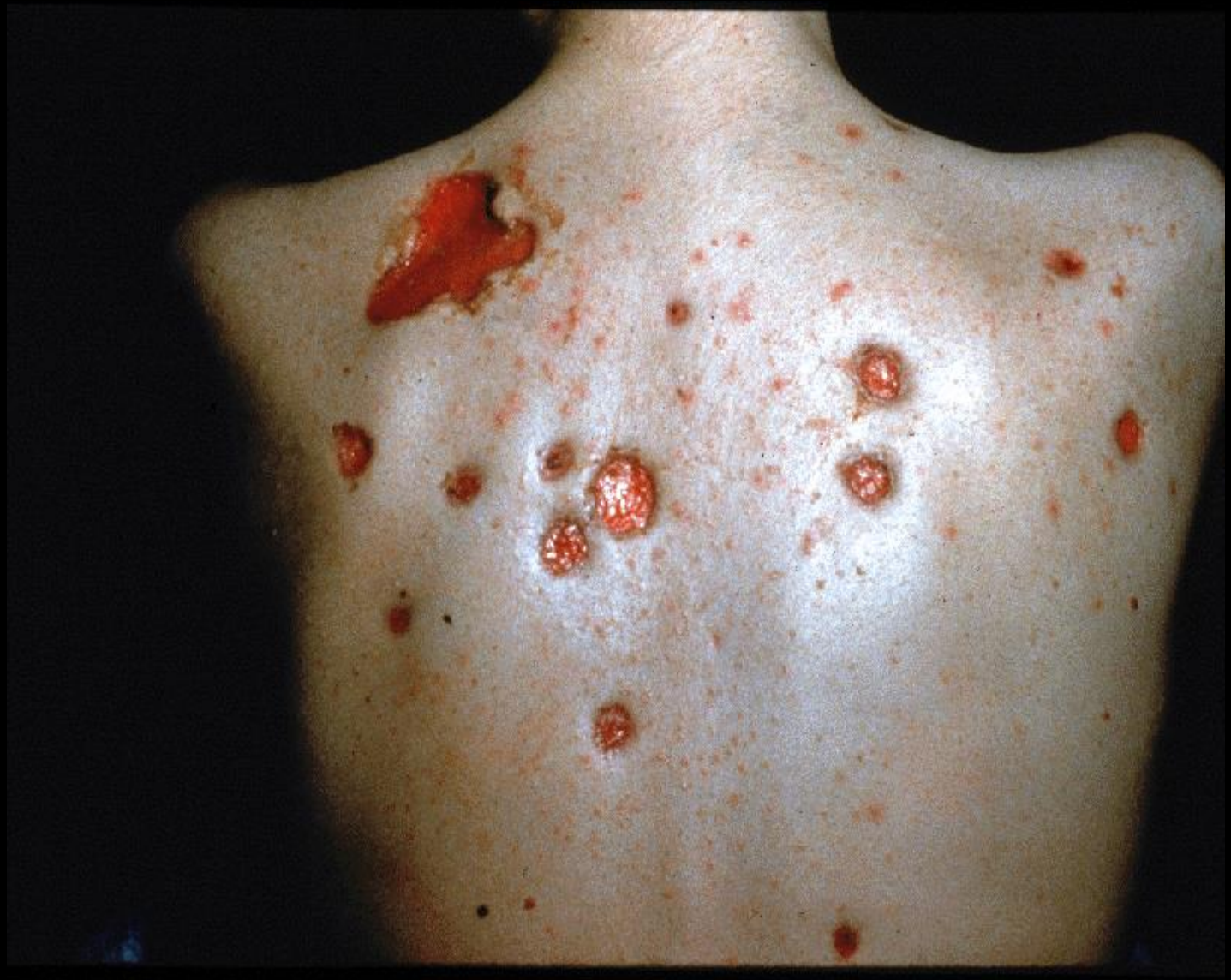


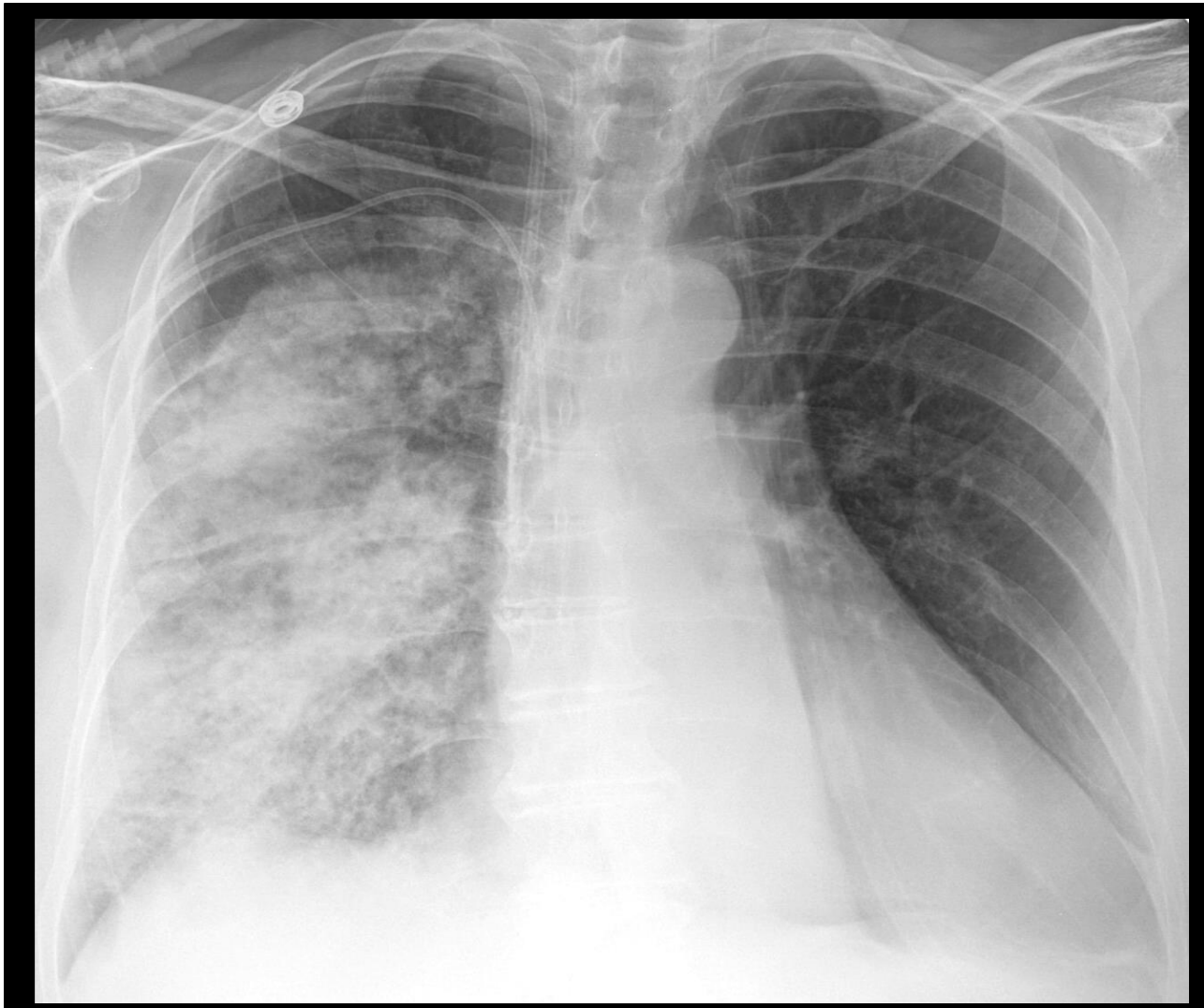






ANCA
Alveolar Hemorrhage

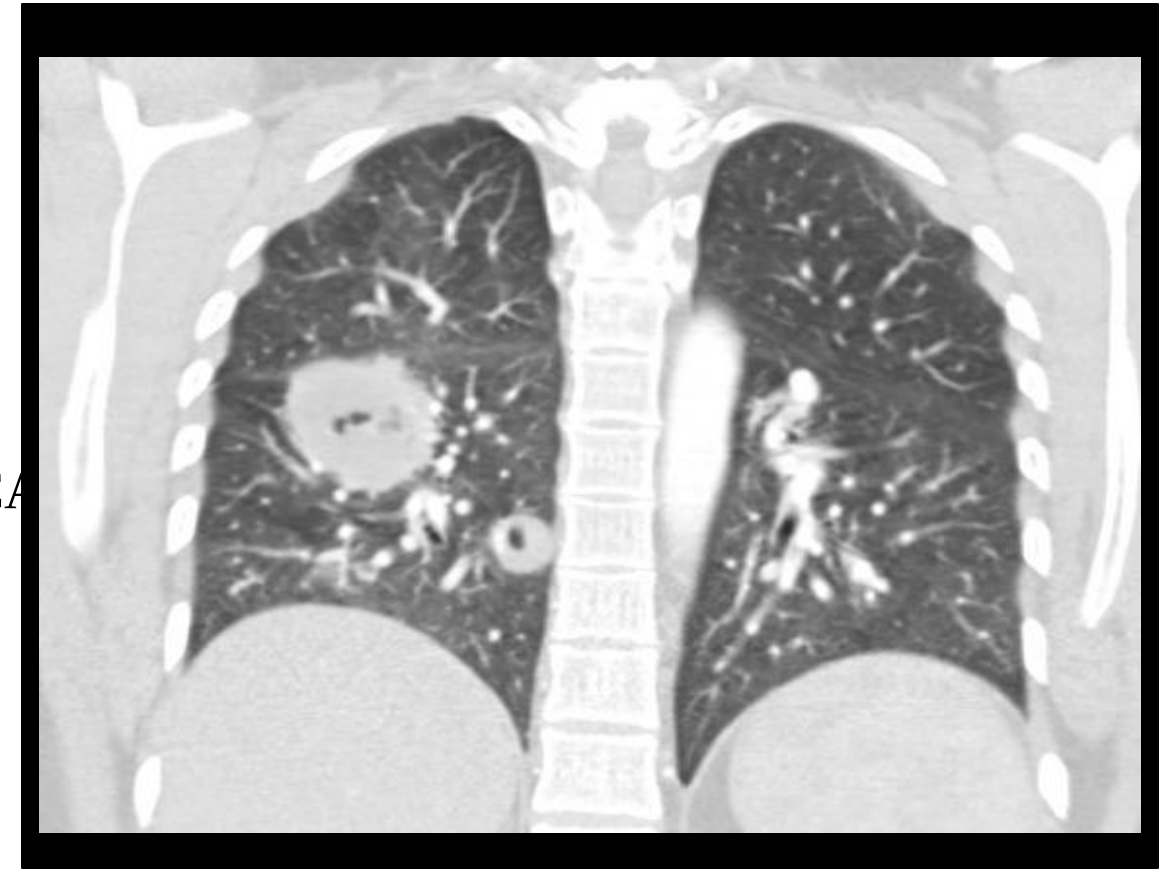
- Alveolar hemorrhage
- Typically
  - High titer MPO
    - or
  - High PR3 ANCA
    - Often very high titer.



ANCA
Cavitary Lung Masses

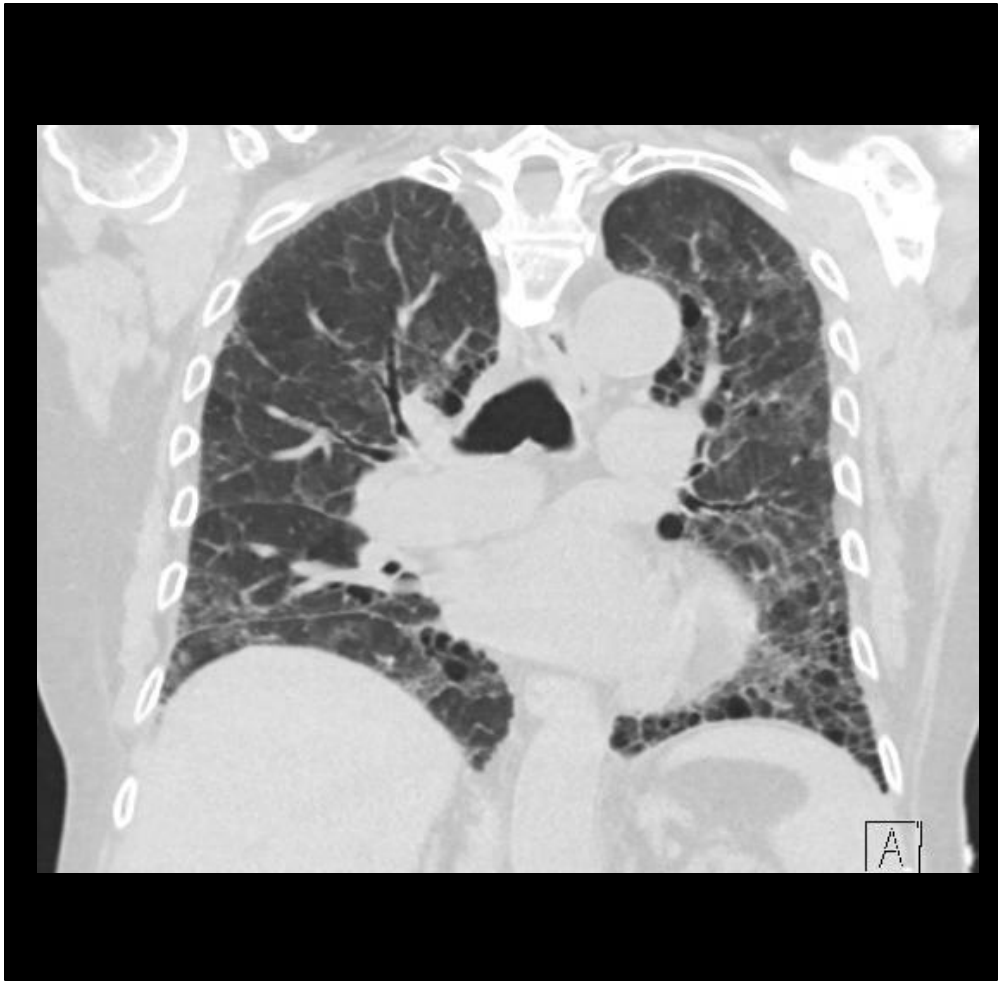
- Nodules
- Cavitary nodules

- Typically
  - Medium titer PR3 ANCA
  - Rarely MPO ANCA



Pulmonary presentations of ANCA associated vasculitis

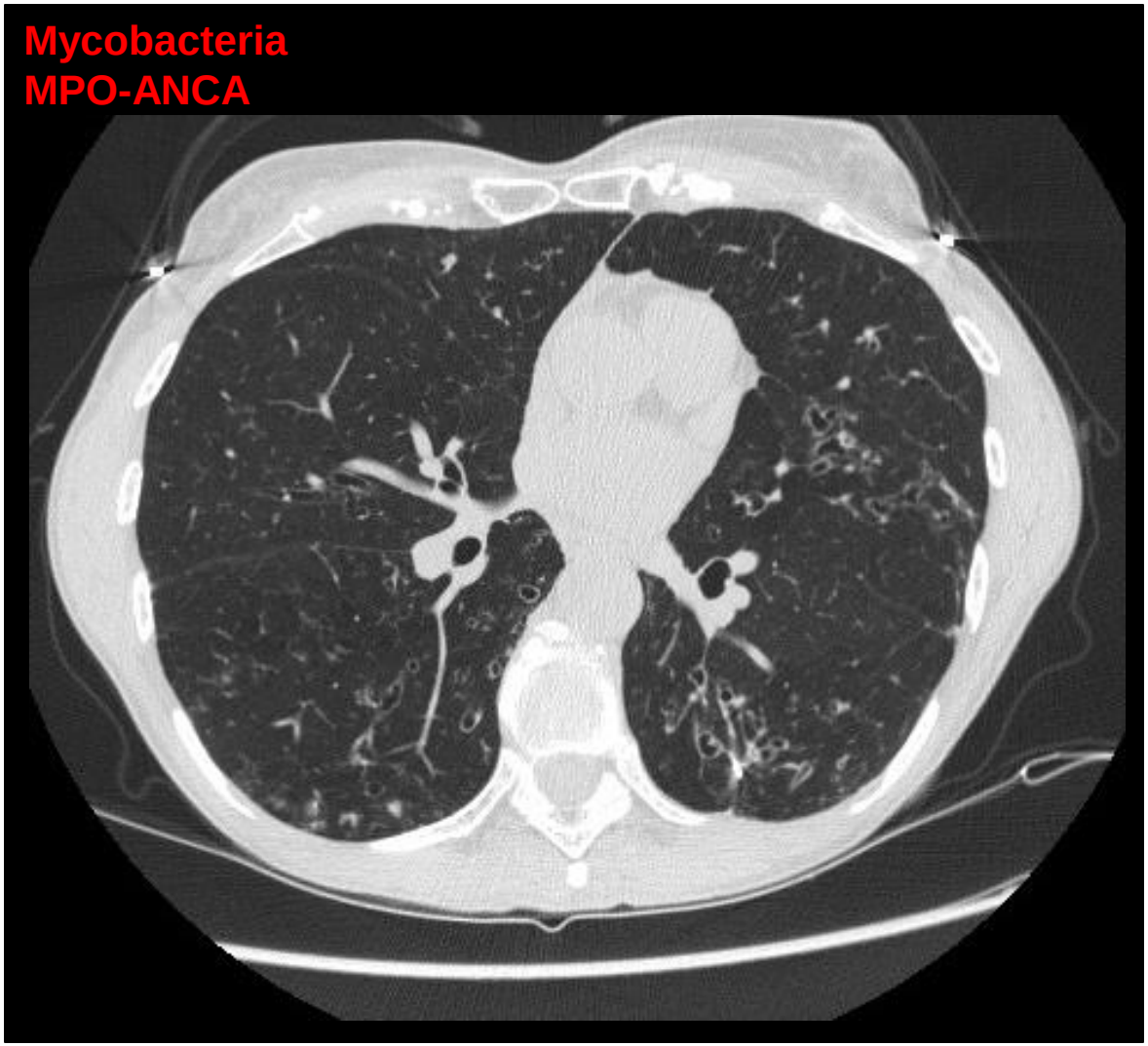
- Interstitial lung disease
  - GGO
  - Fibrosis
    - UIP
    - NSIP
- Typically
  - Almost exclusively MPO



Pulmonary presentations of ANCA associated vasculitis

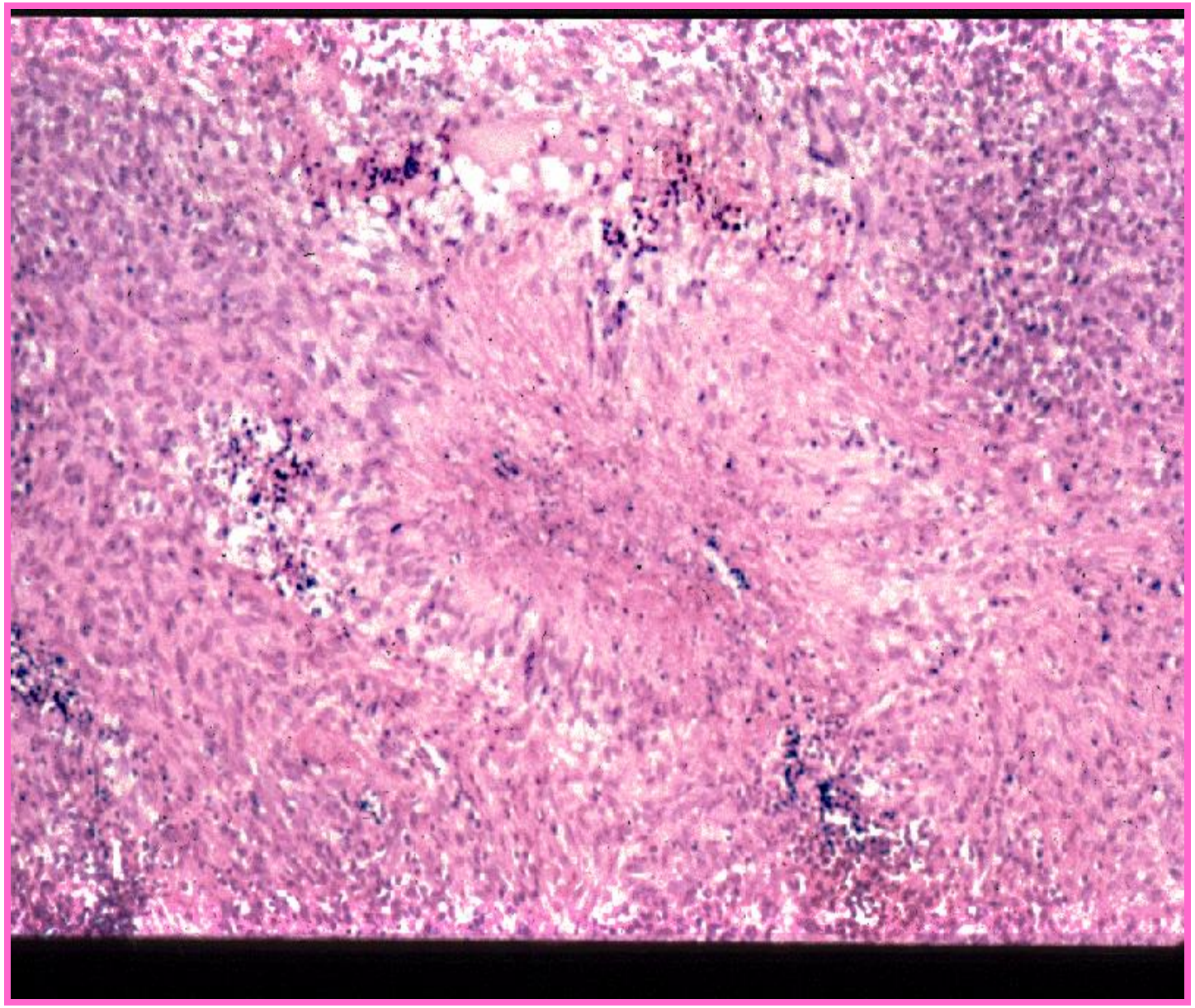
- Bronchiectasis
  - Includes a subset with mycobacterial infection

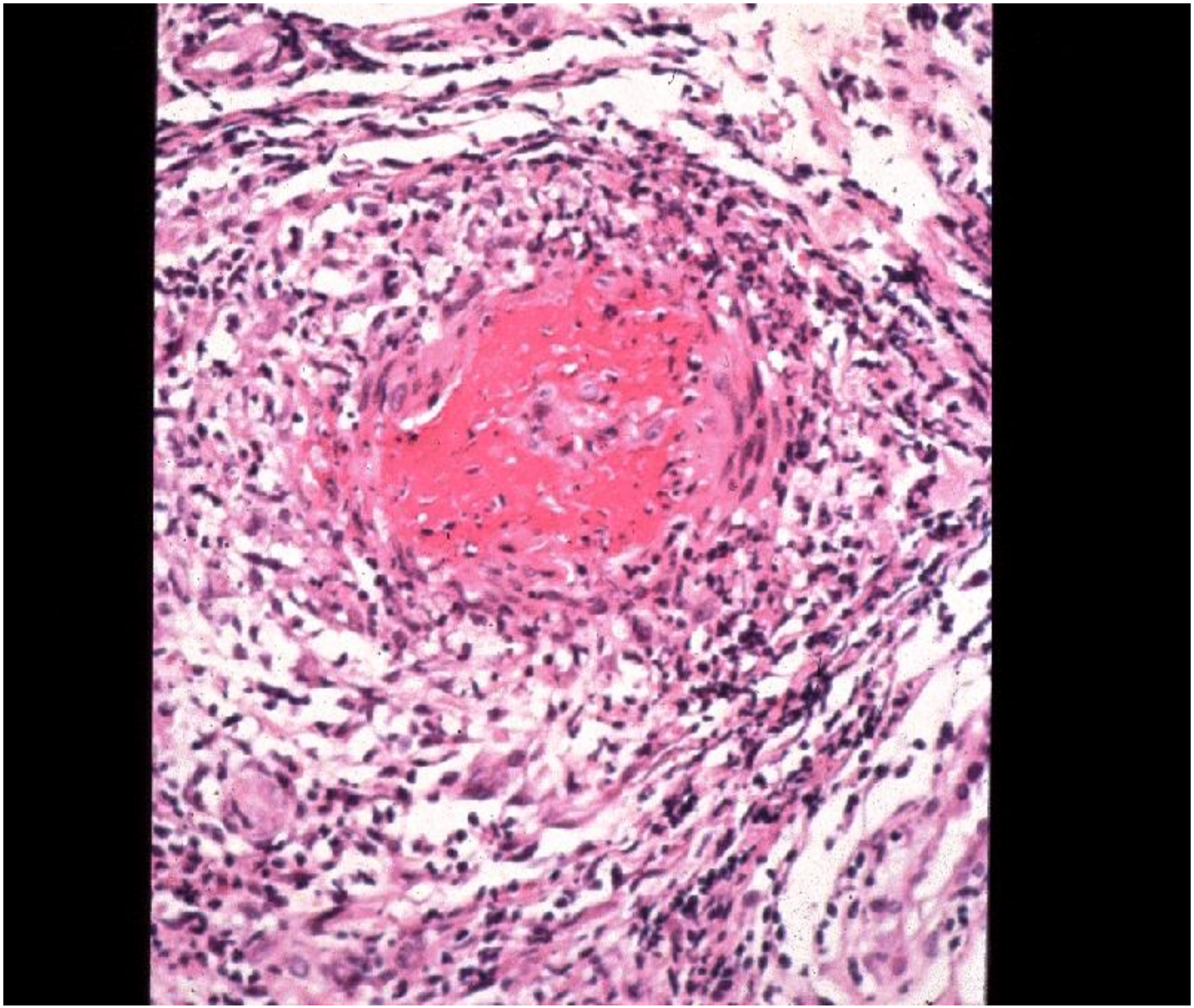
- Exclusively MPO ANCA
  - Moderate titers.

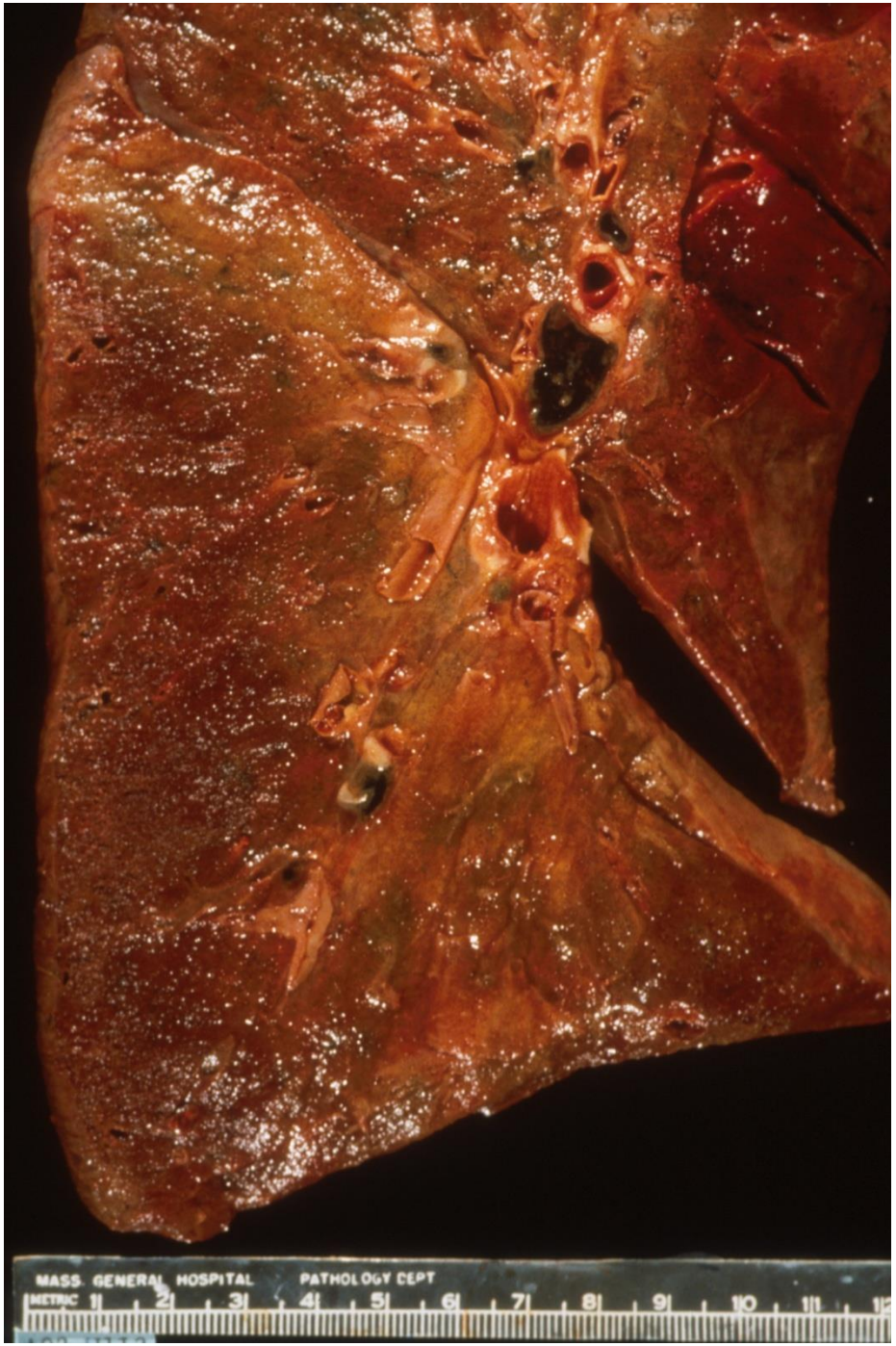


Spectrum of pulmonary ANCA vasculitis

- Diffuse alveolar hemorrhage
  - High titer MPO or PR3 ANCA
    - Often very high titer.
- Nodules and cavitary nodules
  - Low, medium or high titer PR3 ANCA
    - Rarely MPO
- Subglottic or other large airway stenosis
  - **Isolated** stenosis low titer MPO
    - May even be ANCA negative at presentation.
  - Stenosis with MPO or PR3 at low to moderate titers as part of a broader presentation
- Pulmonary fibrosis / interstitial lung disease
  - Almost exclusively MPO ANCA, usually low to medium titer
  - smoldering NSIP may be part of active ANCA
  - Isolated, relentless UIP pattern even after treatment and ANCA resolved
- Bronchiectasis
  - Almost exclusively low to medium titer, smoldering, MPO ANCA
  - Includes a subset with MPO ANCA and Mycobacterium avium complex (MAC)



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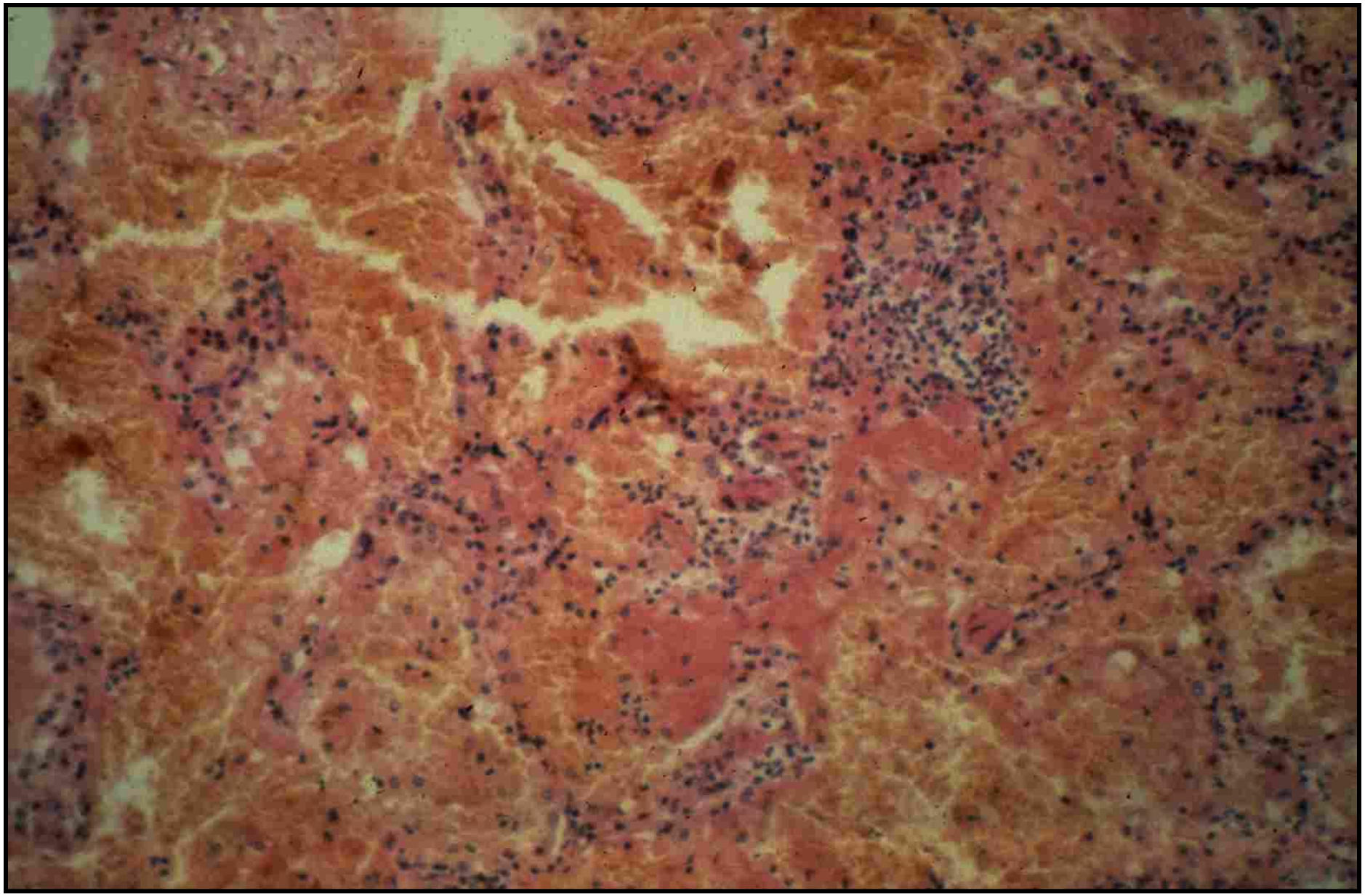
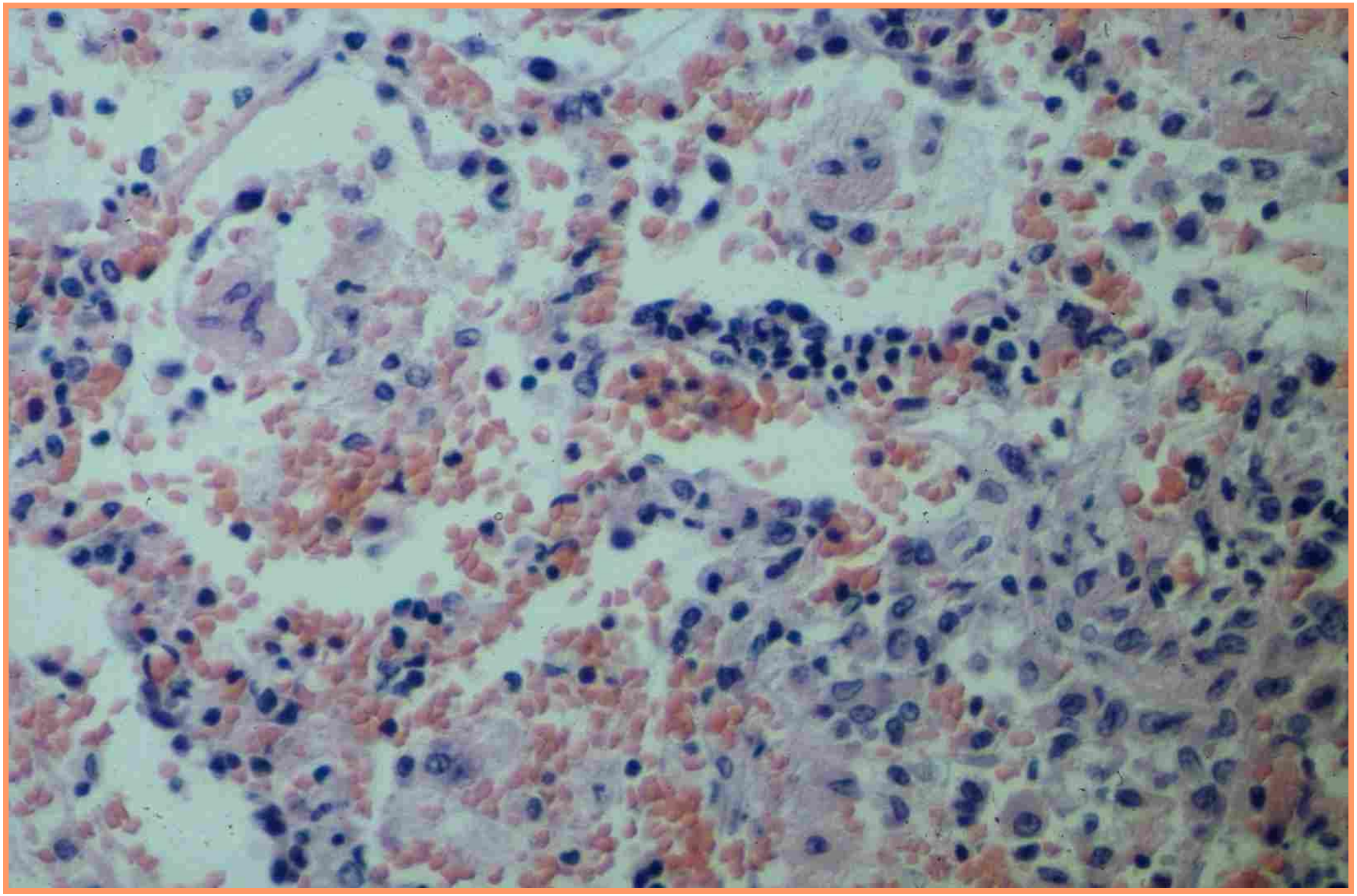
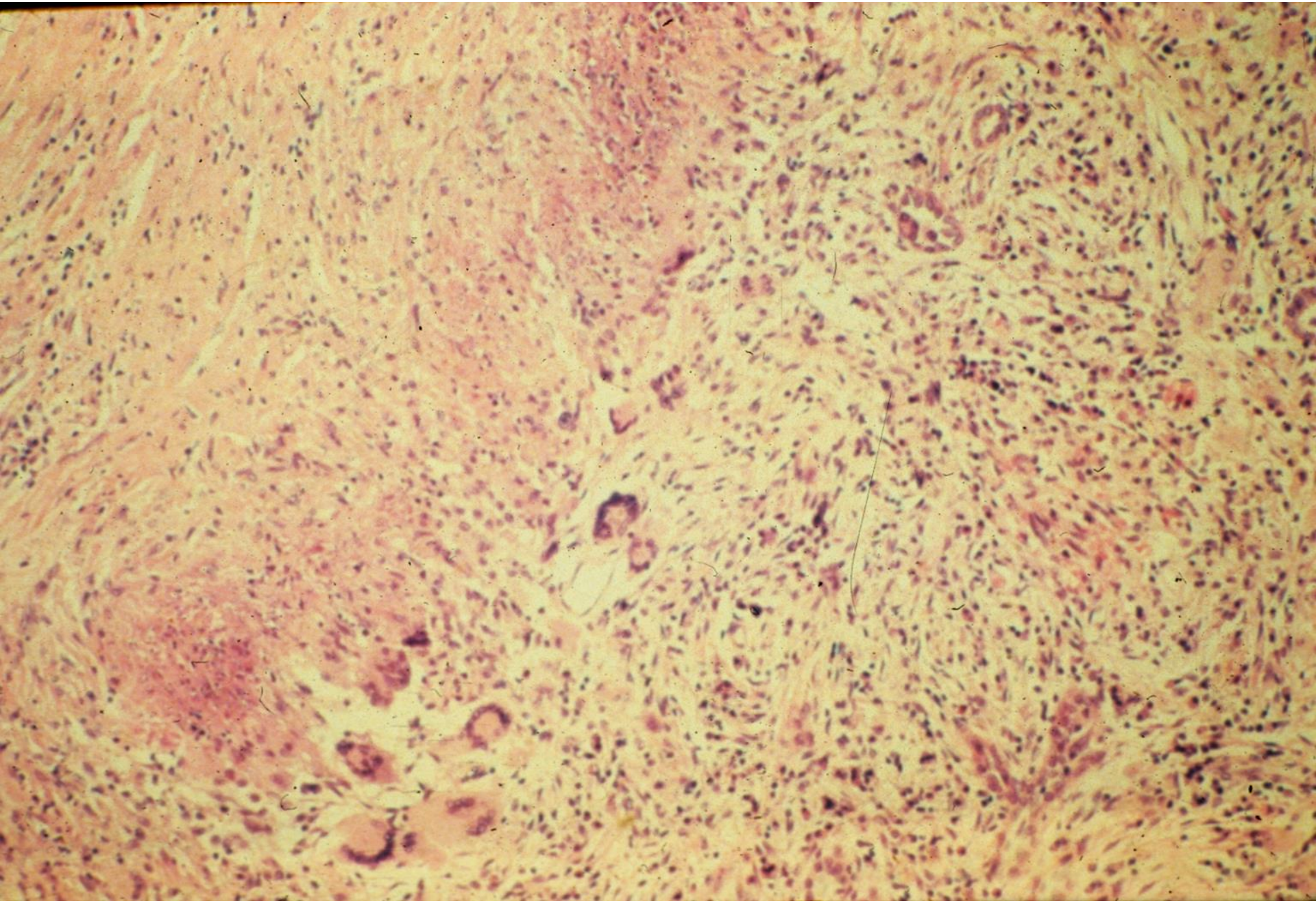
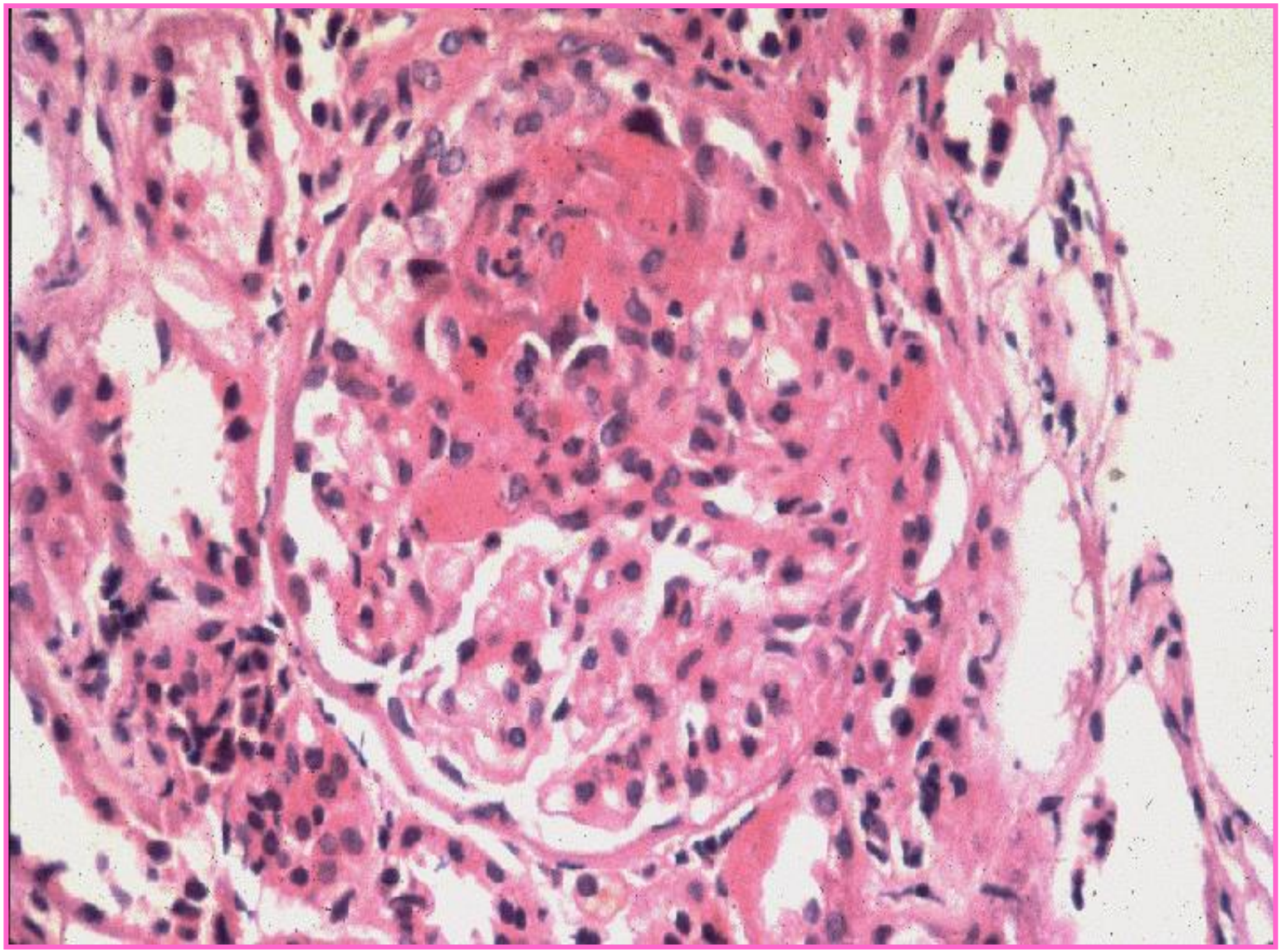
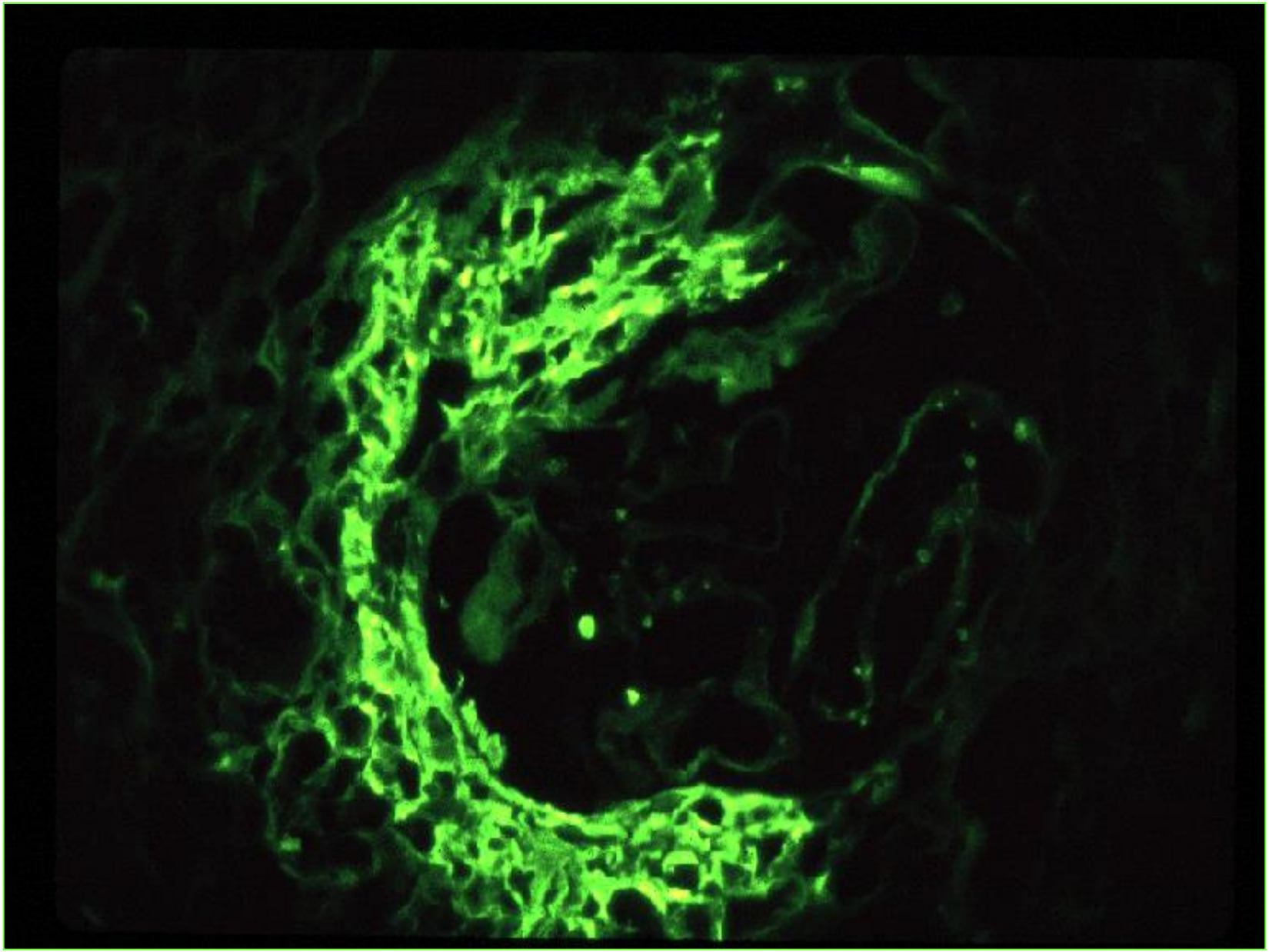
METRIC











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

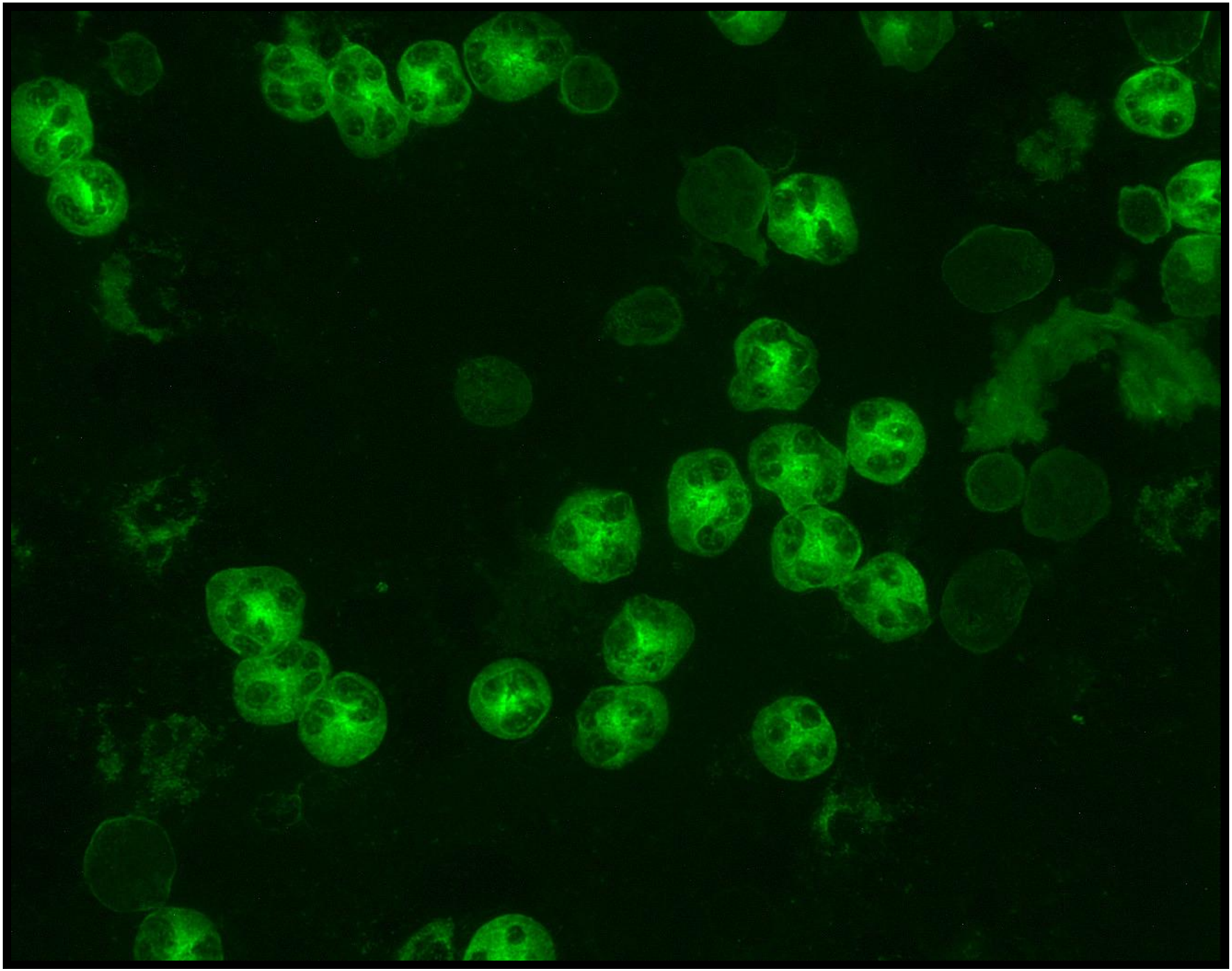
Early Treatment is Dependent on Early Diagnosis

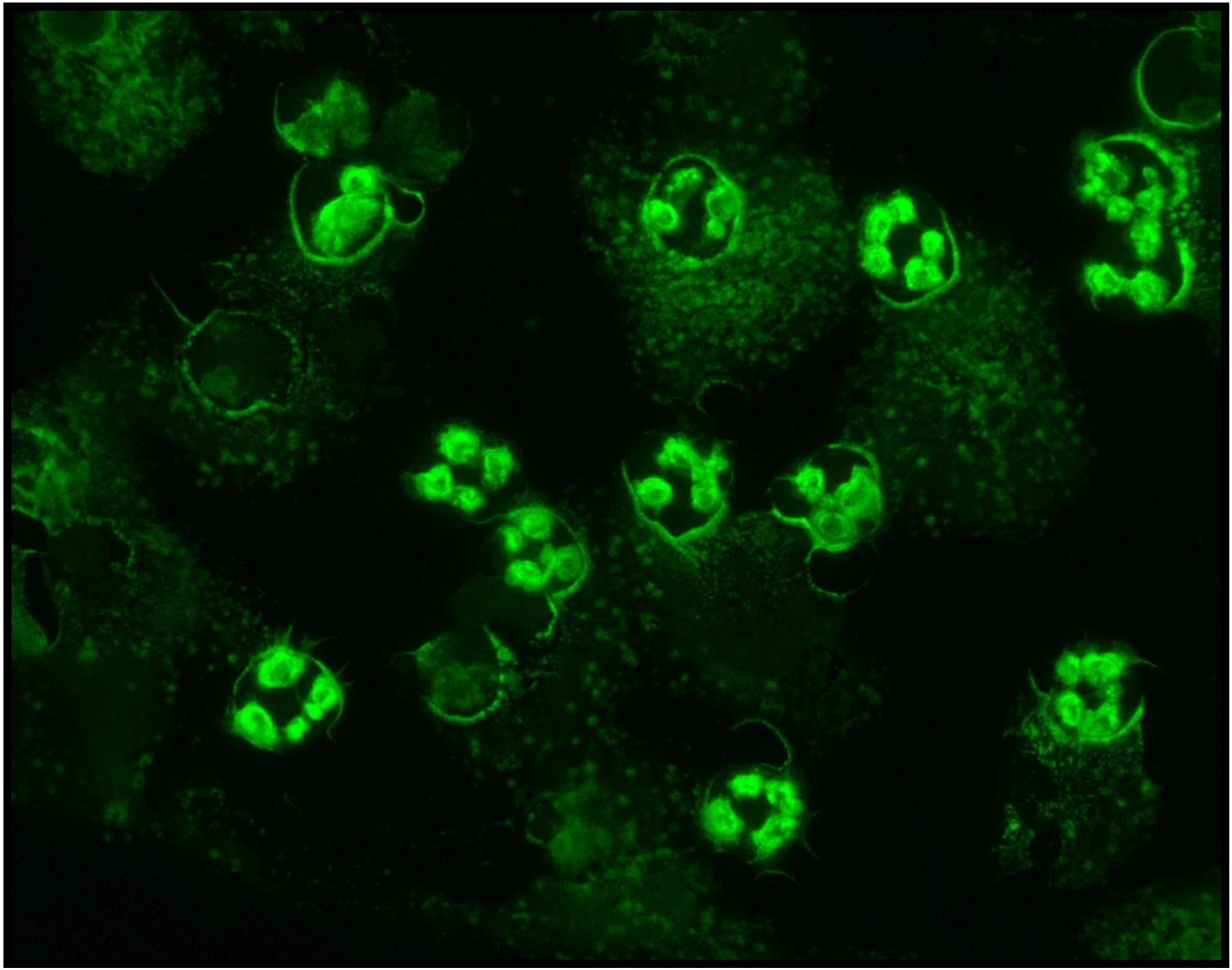
Early diagnosis is dependent on:

- **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 diagnositic 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 %**

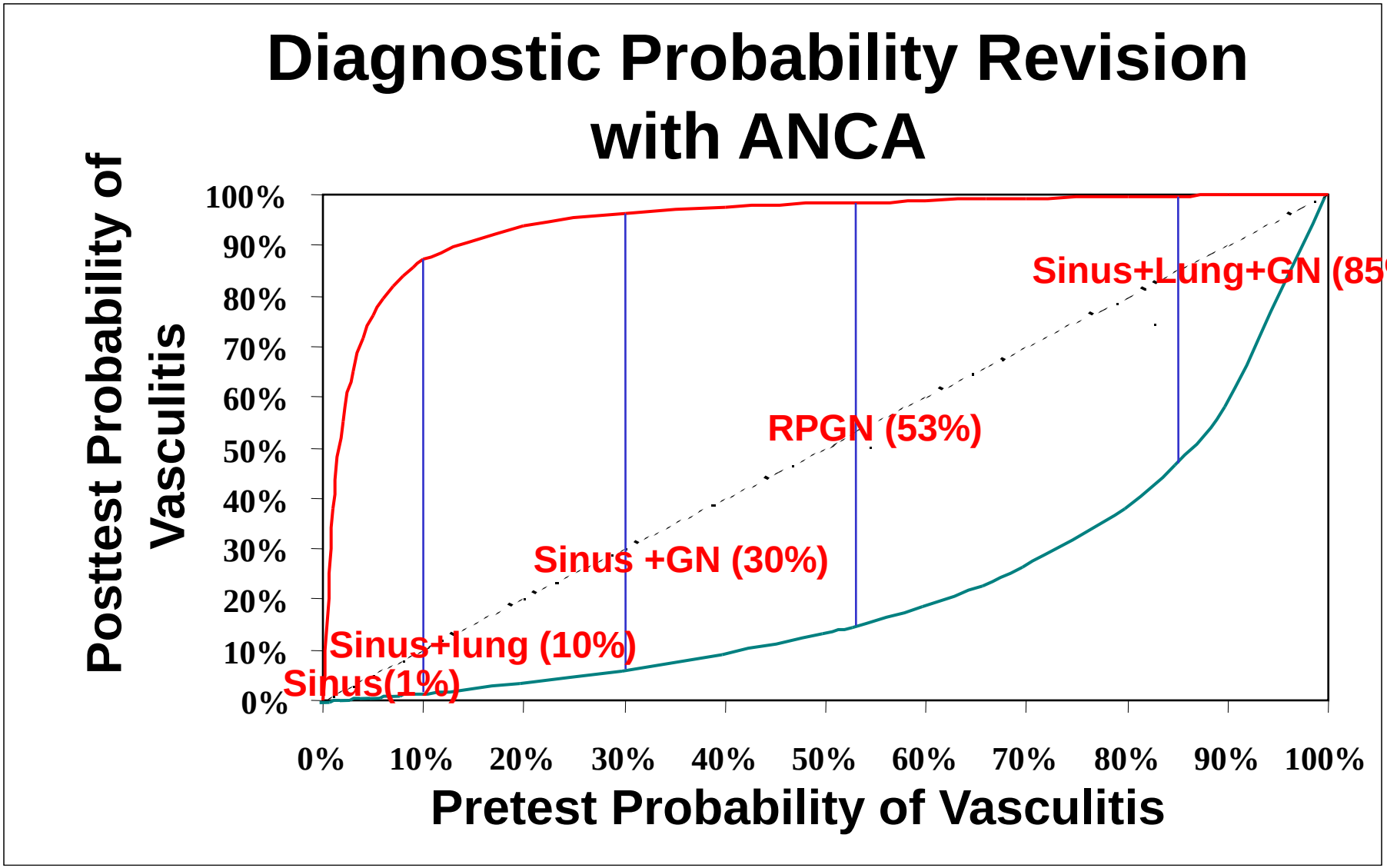
- **Predictive value of ANCA very high in the appropriate clinical setting**

*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



Choi, Hyon et al

Diagnosis with ANCA

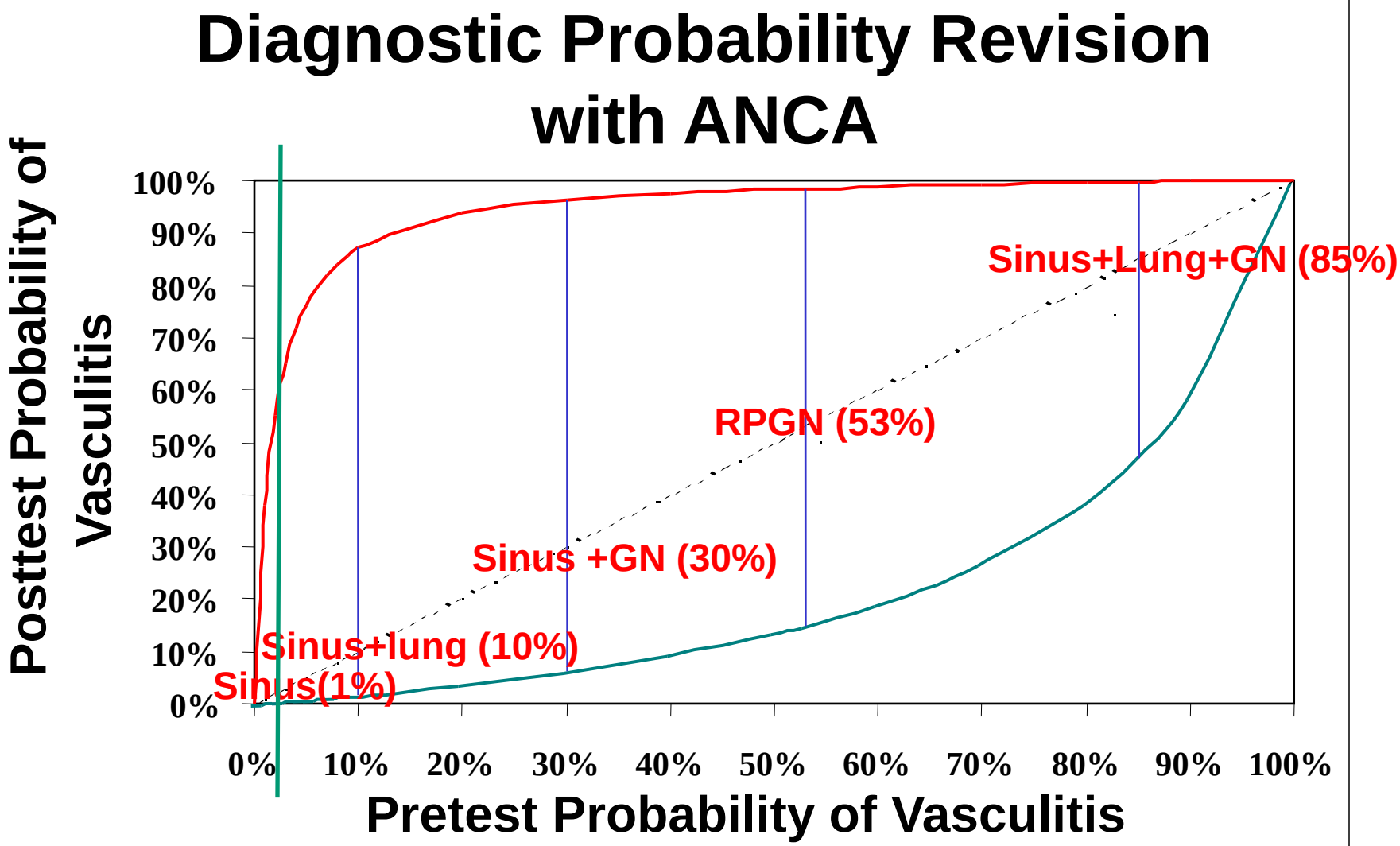
		1990 to 1995	2020 to 2025
MPO	median titer	72 units	28 units
	(n)	(222)	(643)
PR3	median titer	181 units	102 units
	(n)	(115)	(405)

Positive samples as % of tested samples

8% 2.8%

Trend to more early testing and earlier diagnosis

Comments: Application



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

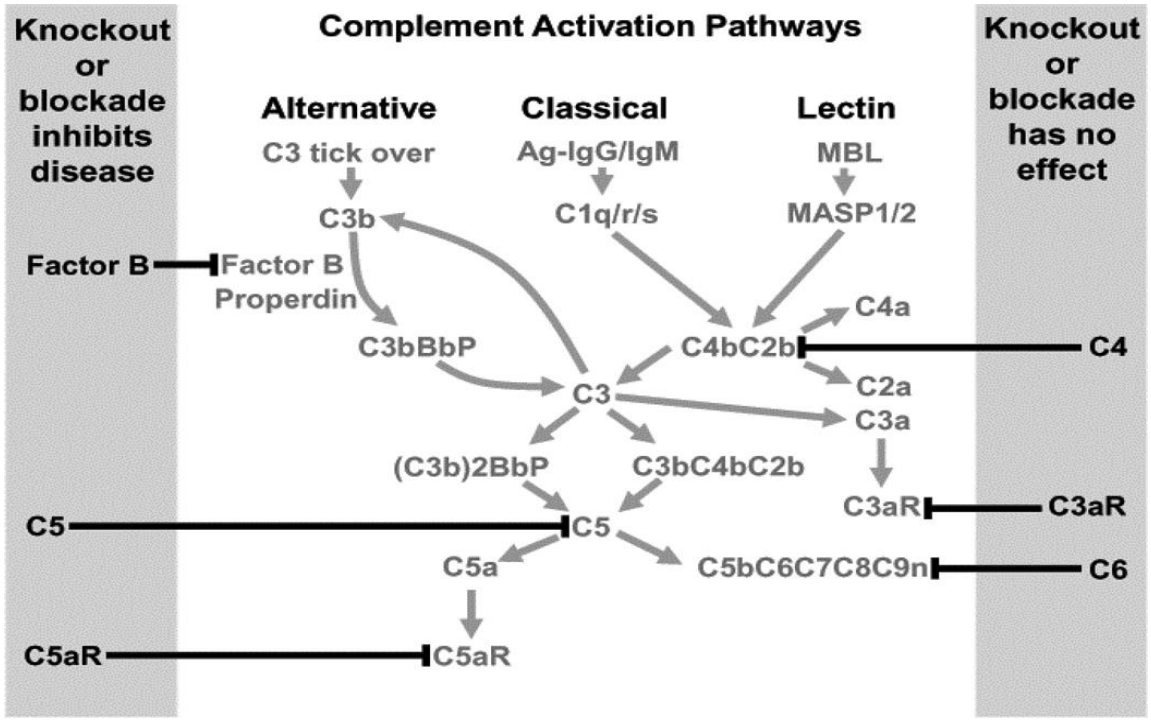
- Triggers
- B cells
- Plasma cells
  - Activated B cell (CD19, CD20)
  - Plasma blast (CD19, CD20)
  - Long lived plasma cell (no CD19/20)
- Antibodies
  - Good antibodies
  - **Pathogenic autoantibodies, ANCA**
- Inflammation
  - Activate neutrophils
  - Alternative complement pathway
  - C5a release
  - 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

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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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- Eliminate triggers

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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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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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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
     (Arthrtitis 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
     (Arthrtitis 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

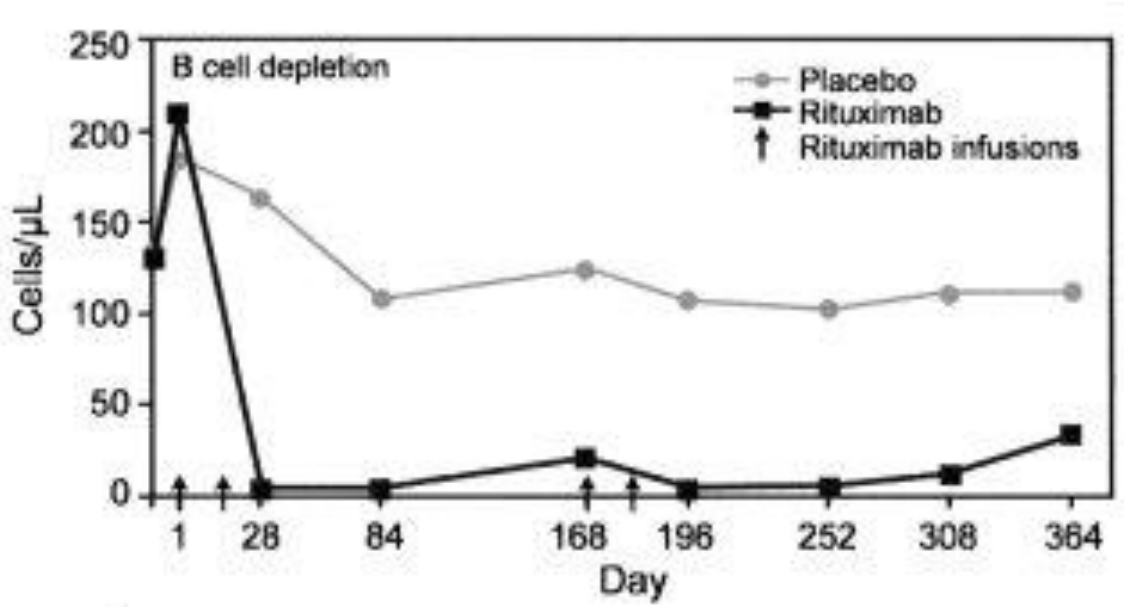
- Rapid clearance of B-cells does not correlate
  - with rapid antibody response or
  - rapid clinical response

- 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

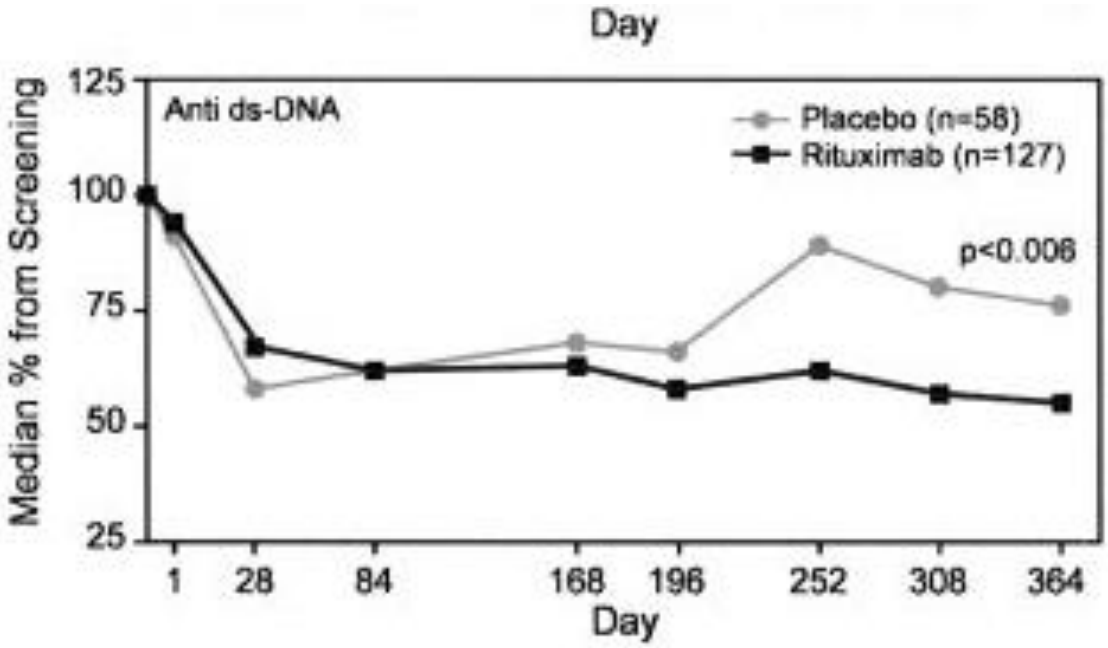
EXPLORER - 257 patients



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

Anti ds-DNA with rituximab

EXPLORER - 257 patients



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- Eliminate triggers
- Clear the B cells
- Block or clear the plants

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

- Eliminate triggers
- Clear the B cells
- Block or clear plasma cells

- Seeds
- Plants
  - Seedlings
  - Annuals
  - Perennials, trees
- Fruit
  - Good fruit
  - **Poison fruit**
- Disease
  - Functional disruption
  - Metabolic destruction
  - Spiral out of control
- Damage

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

- Triggers
- B cells
- Plasma cells
  - Activated B cell (CD19, CD20)
  - Plasma blast (CD19, CD20)
  - Long lived plasma cell (no CD19/20)
- Antibodies
  - Good antibodies
  - **ANCA / pathogenic autoantibodies**
- Inflammation
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  - Alternative complement pathway
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- Clear the B cells
- Block or clear plasma cells
- Clear the poison fruit

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- Plants
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- Clear the B cells
- Block or clear plasma cells
- Clear the antibodies

- Seeds
- Plants
  - Seedlings
  - Annuals
  - Perennials, trees
- Fruit
  - Good fruit
  - **Poison fruit**
- Disease
  - Functional disruption
  - Metabolic destruction
  - Spiral out of control
- Damage

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

Block antibody production

and /or

Block antibody effector mechanisms

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
  - **ANCA / pathogenic autoantibodies**

- Eliminate triggers
- Clear the B cells
- Block or clear plasma cells
- Clear the antibodies

- Seeds
- Plants
  - Seedlings
  - Annuals
  - Perennials, trees
- Fruit
  - Good fruit
  - **Poison fruit**

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

- Antidote to the poison

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

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
  - ANCA or pathogenic autoantibodies

- Eliminate triggers
- Clear the B cells
- Block or clear plasma cells
- Clear the antibodies

- Seeds
- Plants
  - Seedlings
  - Annuals
  - Perennials, trees
- Fruit
  - Good fruit
  - Poison apples

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

- Anti-inflammation

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

*Wegener Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener granulomatosis. N Engl J Med. 2005; 352:351-61.

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
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- Eliminate triggers
- Clear the B cells
- Block or clear plasma cells
- Clear the antibodies

- Seeds
- Plants
  - Seedlings
  - Annuals
  - Perennials, trees
- Fruit
  - Good fruit
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- Inflammation
  - Activate neutrophils
  - Alternative complement pathway
  - C5a release
  - Recruitment and priming of neutrophils
- Damage

- Anti-inflammation

- Disease
  - Functional disruption
  - Metabolic destruction
  - Spiral out of control
- Damage

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
  - **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
- Damage

- steroids
  avacopan
  eculizumab/ravulizumab
  alternate pathway inhib

- Disease
  - Functional disruption
  - Metabolic destruction
  - Spiral out of control
- 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*

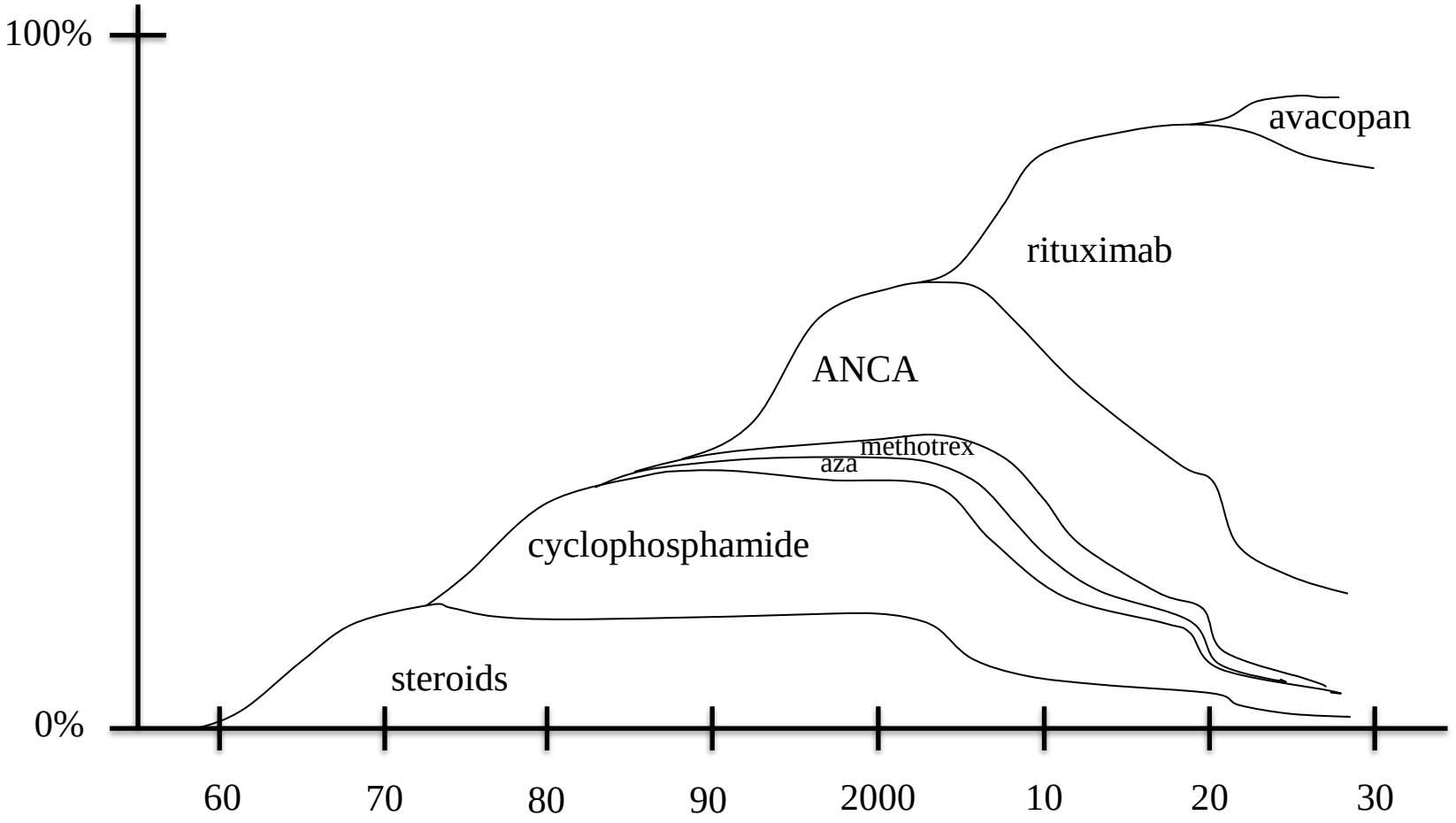
AAV

Induction treatment combinations

- Steroids alone — Walton 1958
  - Average survival 5 months
- Steroids and cyclophosphamide — Fauci, Wolfe, Hoffman 1974, 1983, 1992
  - Remissions in 79 of 85 patients
- Steroids and methotrexate — Hoffman, Fauci, Langford 1992, 1995, 1997 De Groot, Rasmussen 2005
  - for not immediately life threatening
  - Remissions in 69% - 71% long term potential
- IV vs oral cyclophosphamide — Harper2011
  - Cyclops
- Rituximab and steroids — Specks 2001
  - RAVE — Stone, 2010
- Rituximab, cyclophos and steroids — Jones,Jayne, 2010 Cortazar,Pendergraft,Niles, 2014, 2017)
  - High remission rates
- With or without plasma exchange
  - MEPEX PEXIVAS Meta analysis — Jayne 2007, Walsh 2022
- Ritux avacopan — Schall, Merkel, Jayne 2021
  - Advocate

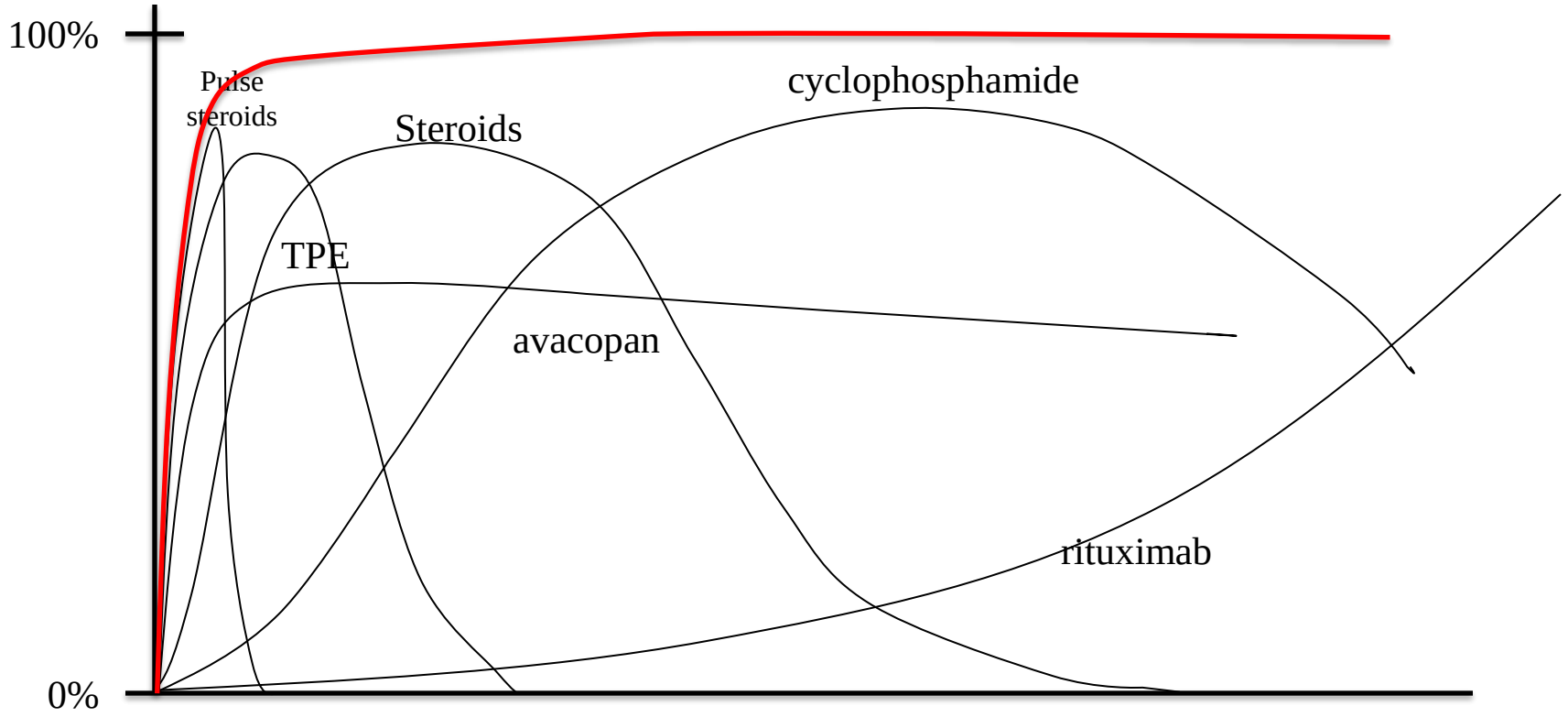
AAV

Induction treatment evolution



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
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  - With acute eosinophilia

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

AAV

Induction treatment combinations

- So my take:
  - Not organ threatening
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    - 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
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  - **Steroids**
  - **Rituximab**
  - **Short course, low dose, bridging cyclophosphamide**
  - **Pulse steroids**
  - **Avacopan**
  - **Plasmapheresis**

AAV

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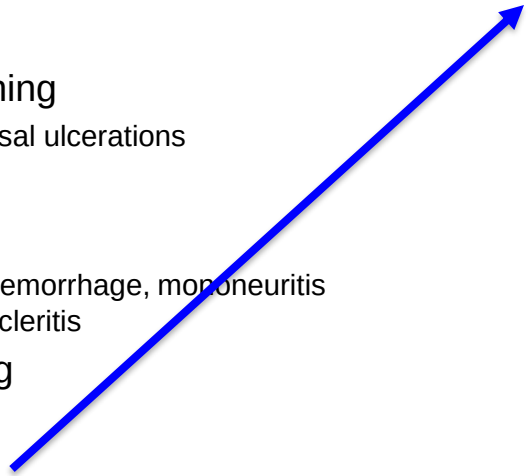
  - **Steroid toxic**



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

AAV

Induction treatment combinations

- So my take:
  - Not organ threatening
  - Subacute organ threatening
    - Microhematuria, otitis, nasal ulcerations
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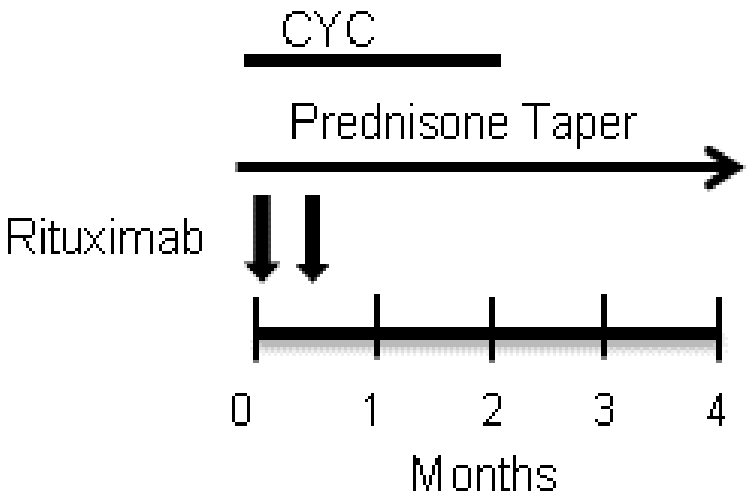
  - Critical organ threatening
    - RPGN
  - Steroid toxic
  - **With acute eosinophilia** 
- Treatment strategy
  - **Steroids**
  - **Rituximab**
  - **Low dose bridging cyclophosphamide**
  - **Pulse steroids**
  - **Avcopan**
  - **Plasmapheresis**
  - **Mepolizumab**

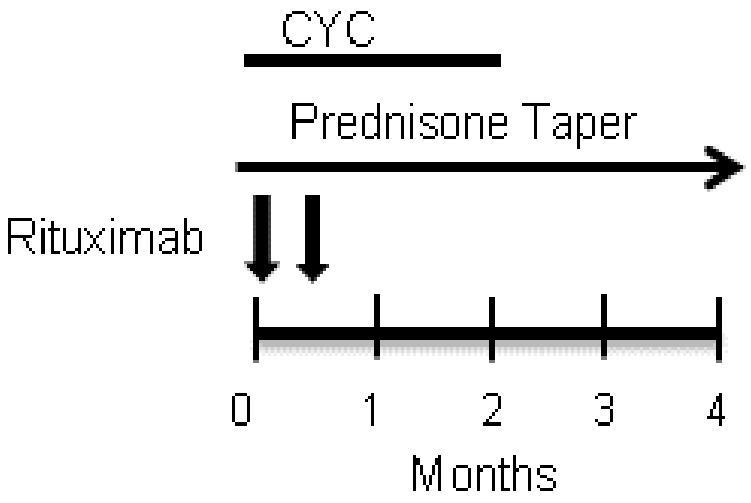
Triple drug - Steroid sparing - Protocol



- 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

Cortazar F, Pendergraft W, Owens C, Cosgrove K, Laliberte K, Niles J. 2016

Triple drug - Steroid sparing - Protocol



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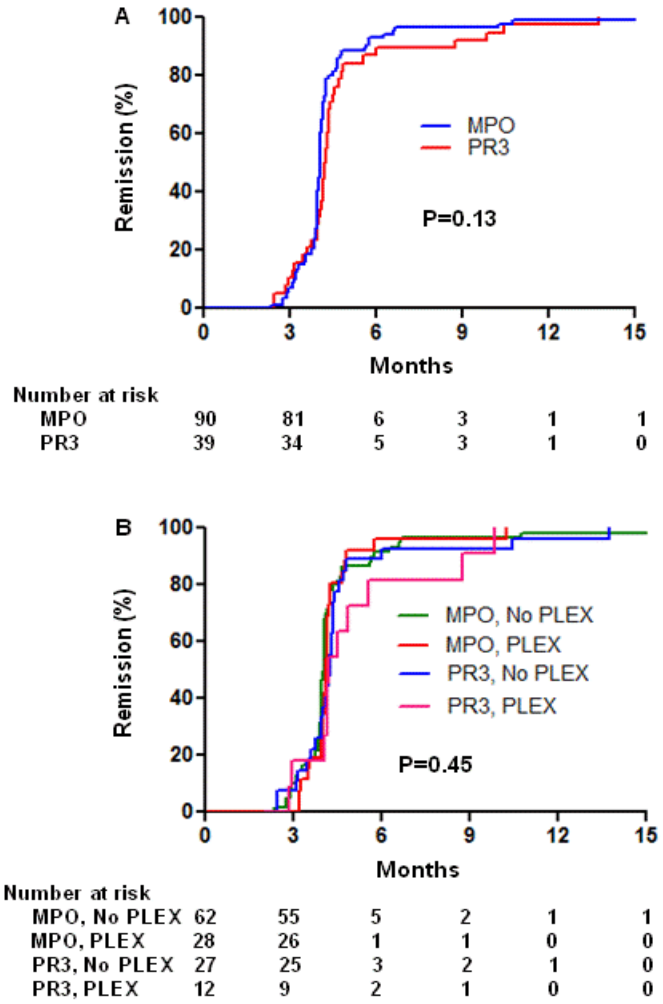
  - 1.5 mg/kg for 7 weeks
  - **Adjusted for renal fx**
- +/- PLEX

Cortazar F, Pendergraft W, Owens C, Cosgrove K, Laliberte K, Niles J. 2016

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%

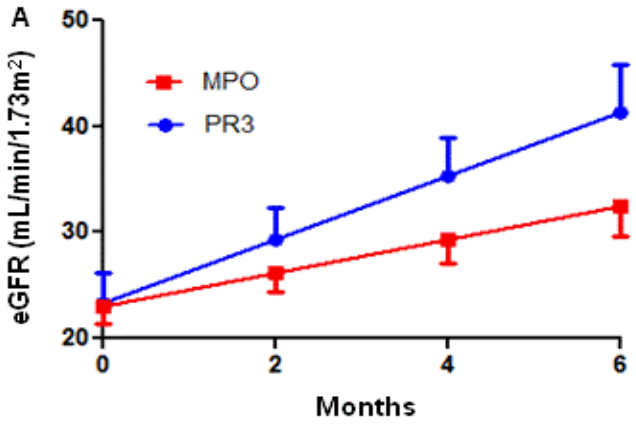
Cortazar F, Pendergraft W, Owens C, Cosgrove K, Laliberte K, Niles J. 2016

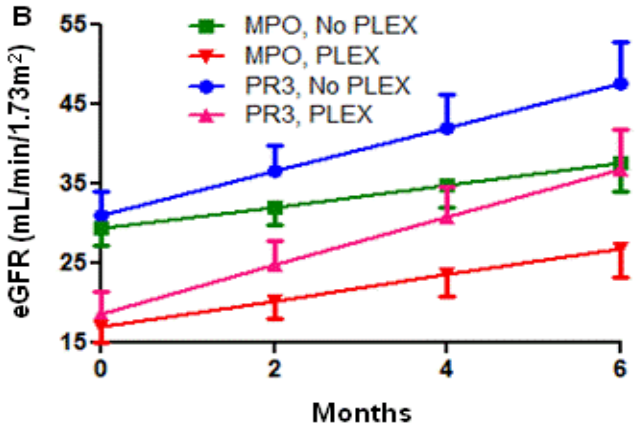


- Remission: BVAS-WG=0 and Pred ≤ 7.5 mg/d
- Median (IQR)= 4.1 months (3.9, 4.3)
- Remission by 6 months
  - 5 patients died
  - Survivors: 114/124 (92%)
  - Overall:114/129 (88%)
- No difference by serotype or PLEX

Cortazar F, Pendergraft W, Owens C, Cosgrove K, Laliberte K, Niles J. 2016

Renal Outcomes





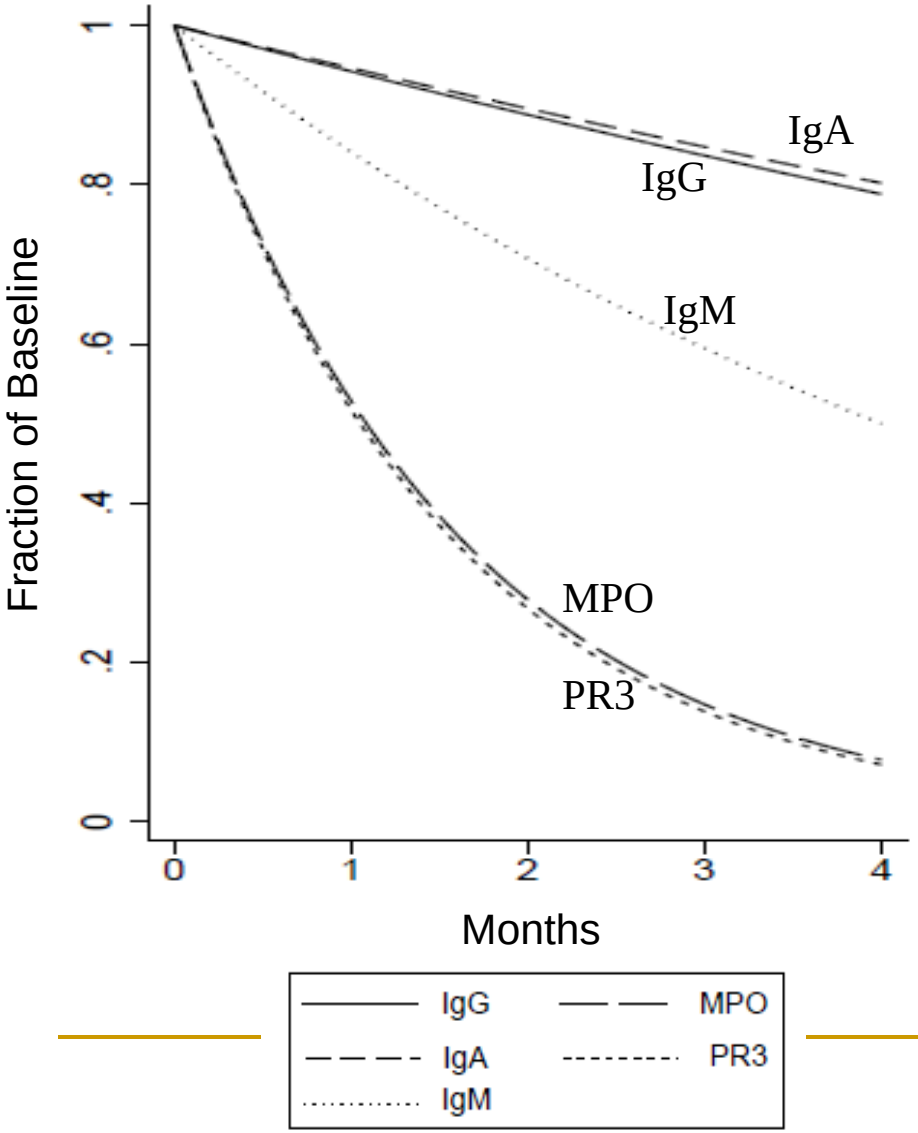
Change in eGFR with treatment

MPO: 1.5 ml/min/1.73m^2/month (95% CI 0.8 to 2.7)

PR3: 2.9 ml/min/1.73m^2/month (95% CI 1.7 to 4.2)

Difference: 1.4 ml/min/1.73m^2/month [95% CI -0.04 to 2.9]; *P*=0.056

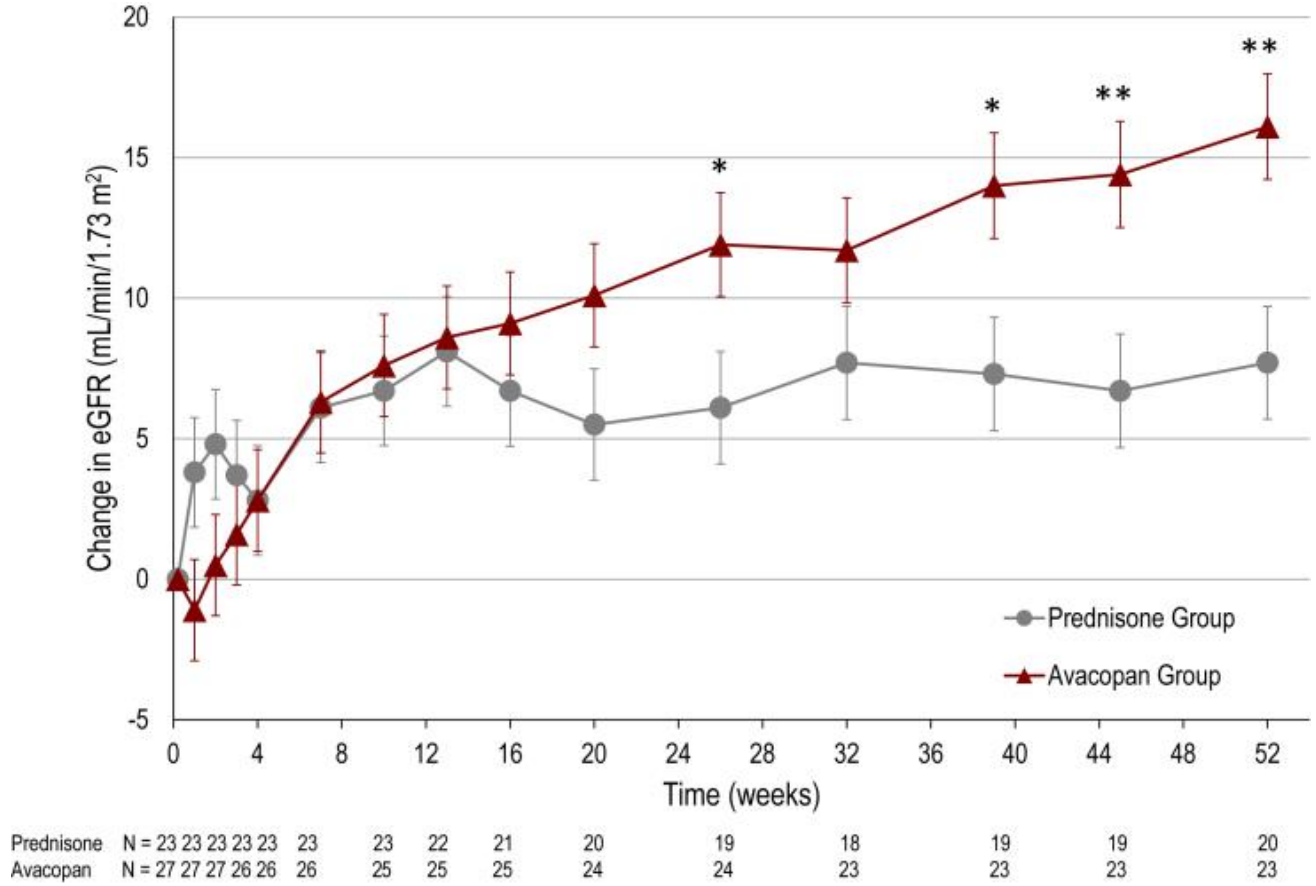
INDUCTION



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



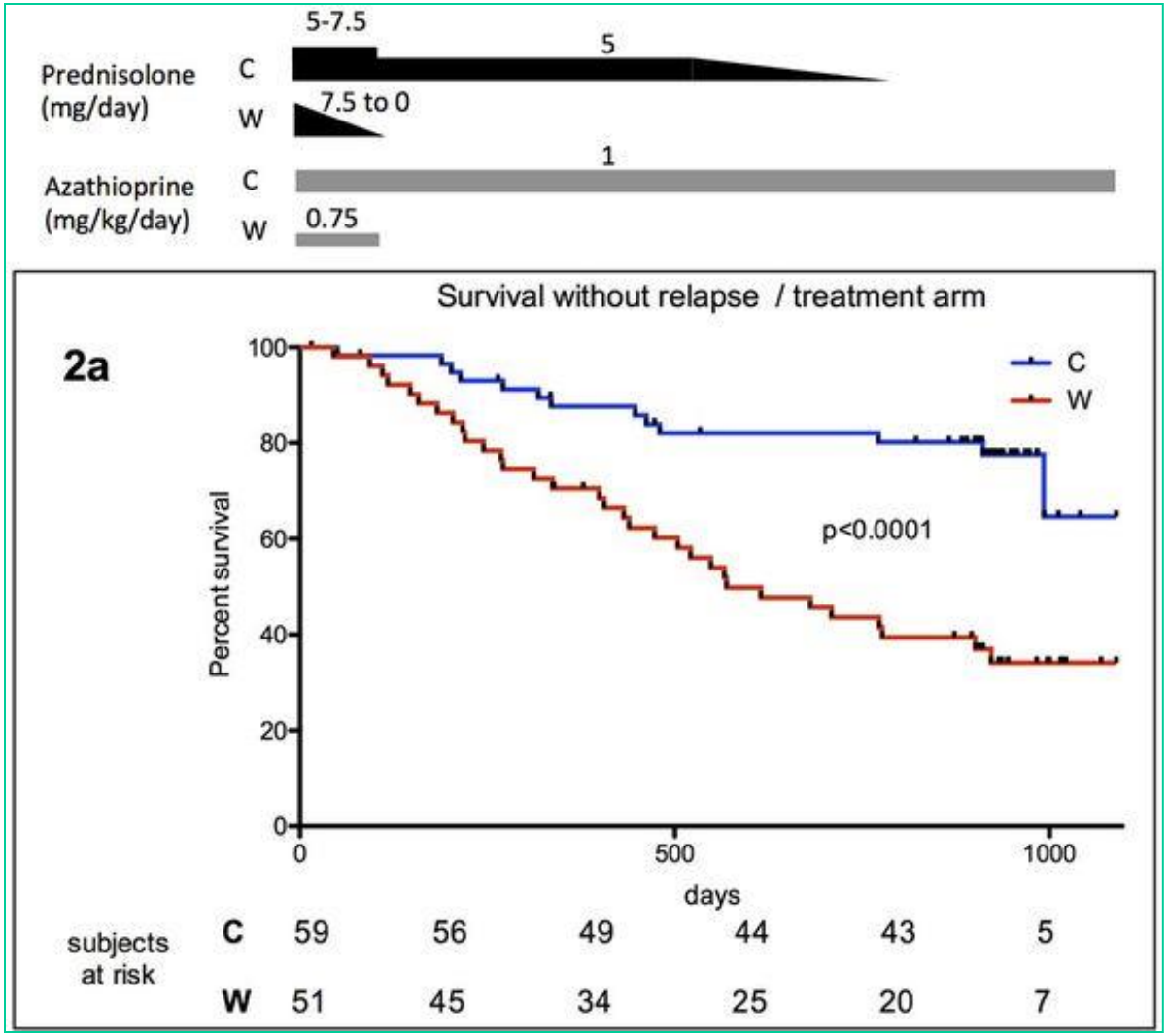
Kidney Int Rep. 2023 Apr; 8(4): 860–870.

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

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

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

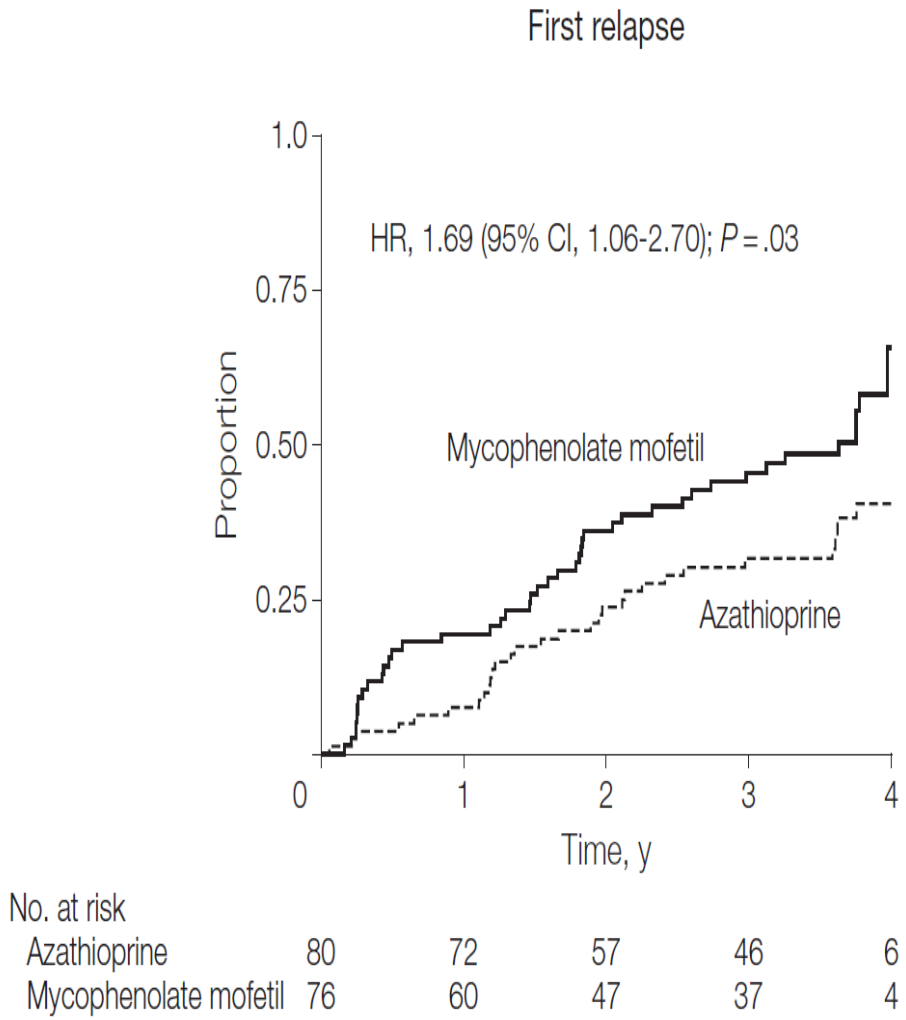
2 mg/kg/d x 12 mo
1.5 mg/kg/d 12-18 mo
1 mg/kg/d 18-42 mo

MMF

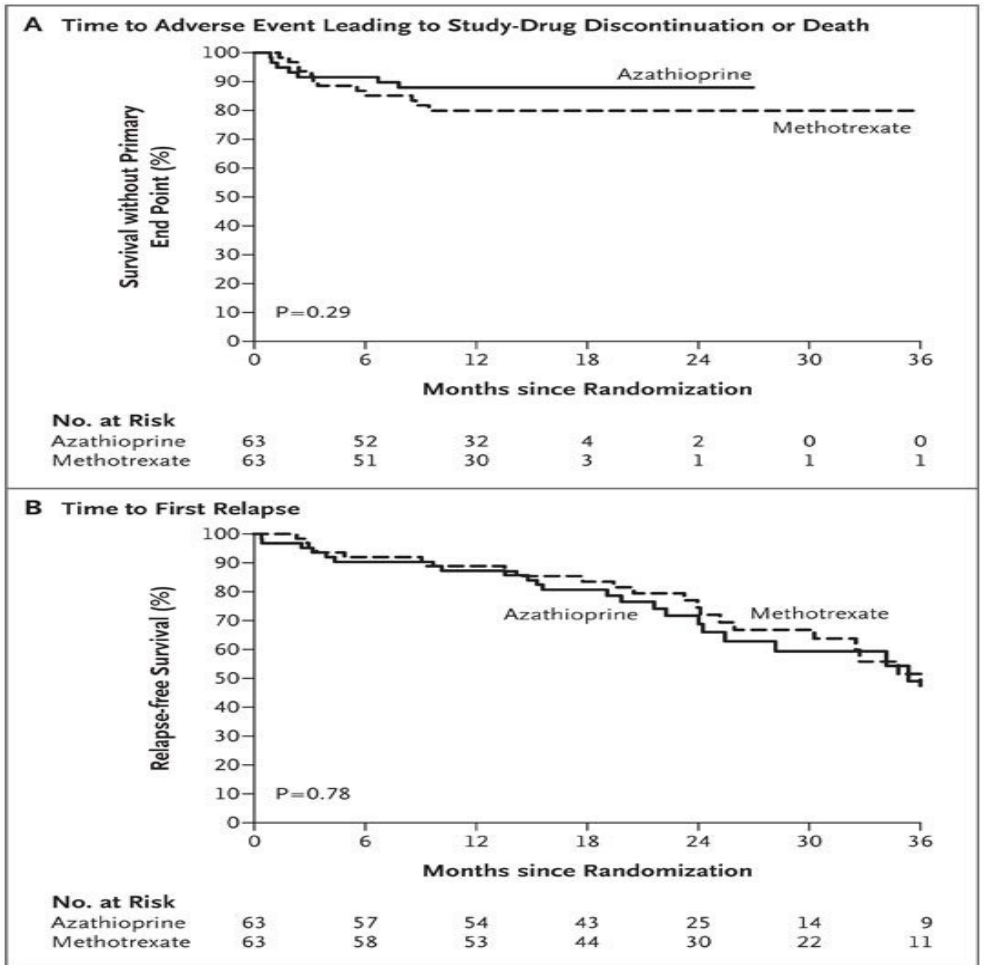
2000 mg/d x 12 mo
1500 mg/d 12-18 mo
1000 mg/d 18-42 mo

Prednisone

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



Methotrexate vs Azathioprine



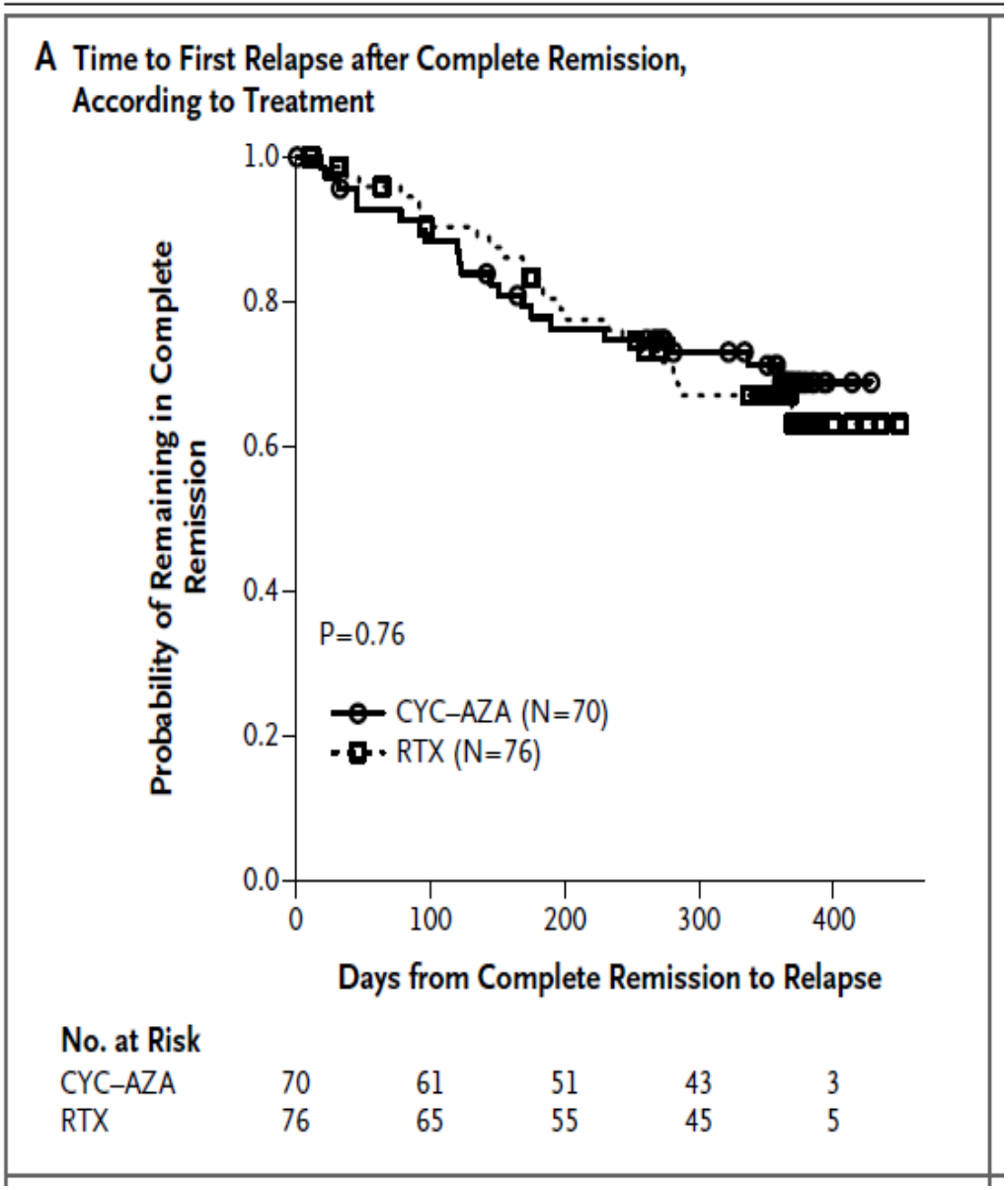
N Engl J Med. 2008 Dec 25;359(26):2790-803

Relapse rates Rave trial

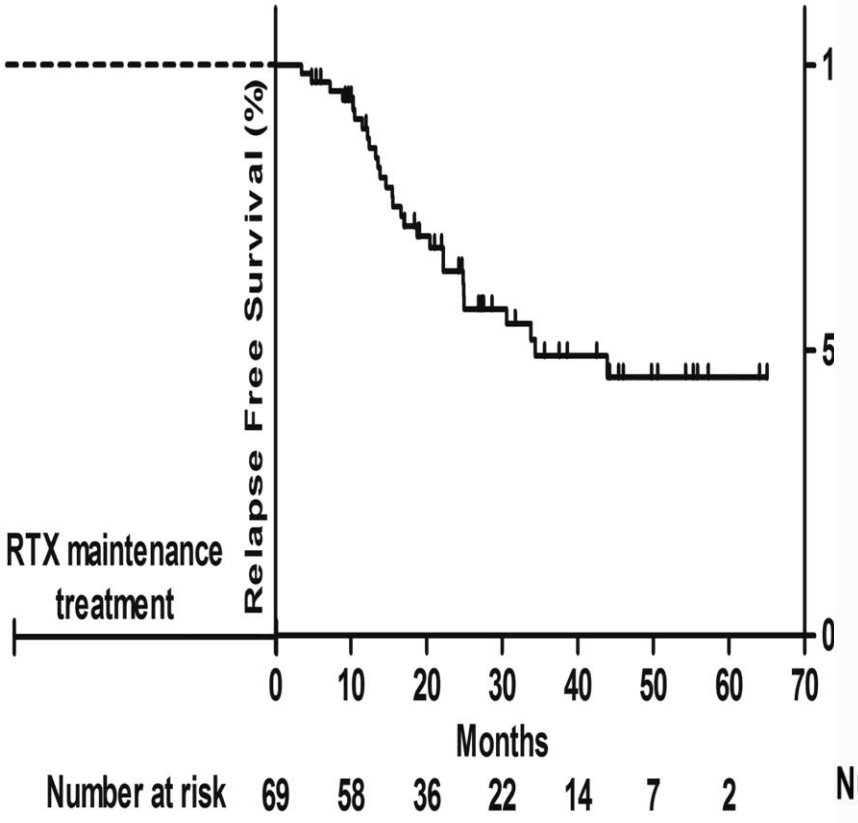
Specks et al. Efficacy of remission-induction regimens for ANCA vasculitis. N Engl J Med 2013; 469:417-27.

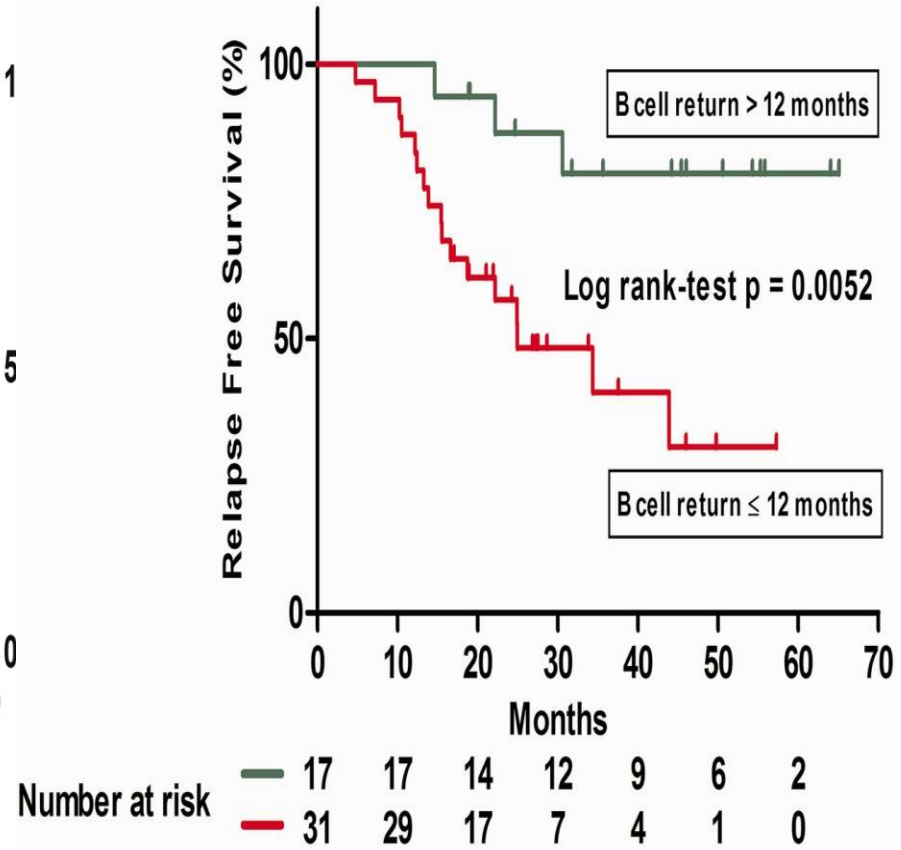
Rituximab
32% relapses by
18 mo

Azathioprine
29% relapses by
18 mo



Relapse after Rituximab





Federico Alberici et al. Rheumatology 2015;54:1153-1160

Maintenance therapy for ANCA vasculitis

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

MGH

Renal Unit

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)

Clin J Am Soc Nephrol 2014 9:736.

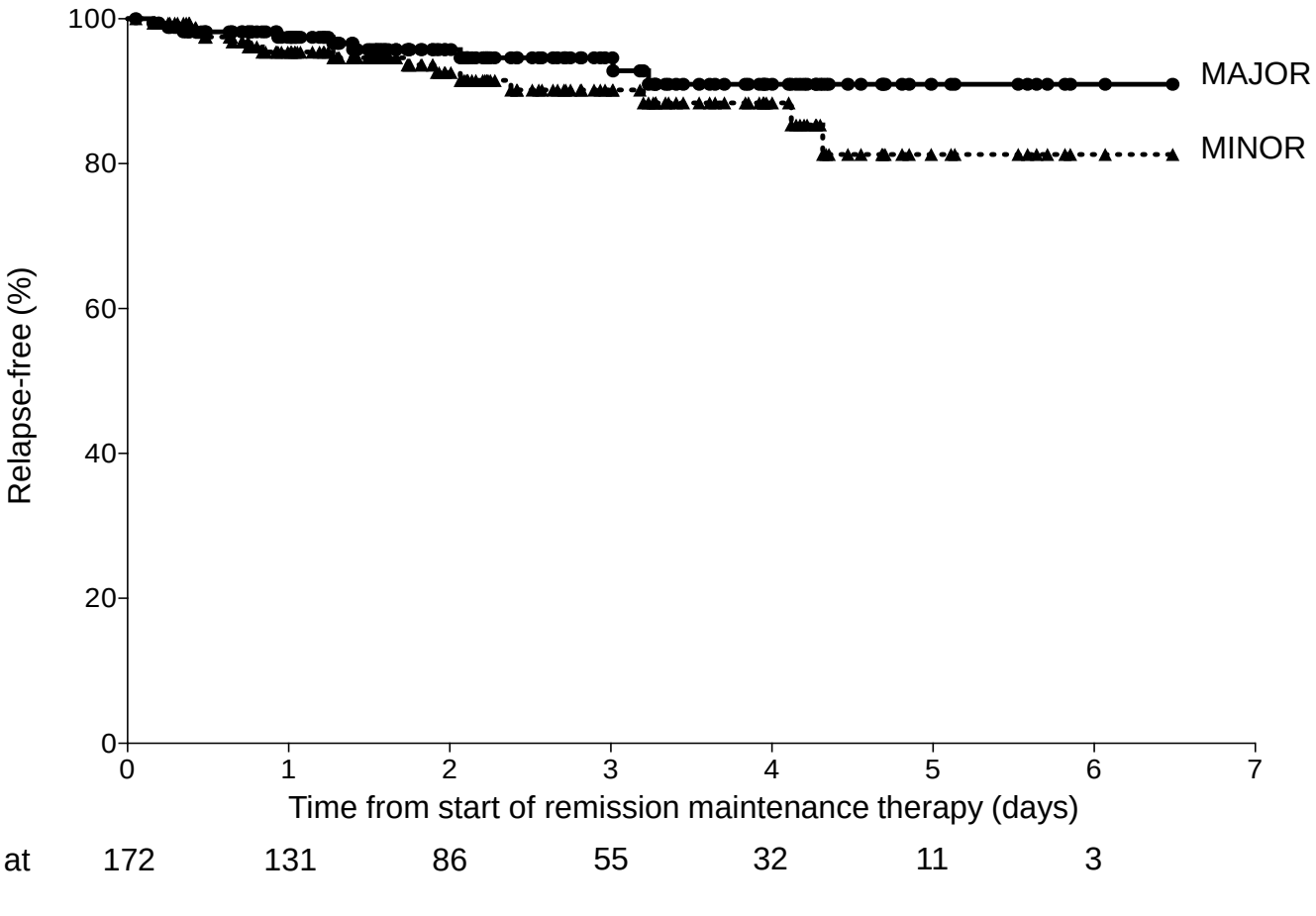
MGH
Renal Unit

Relapses

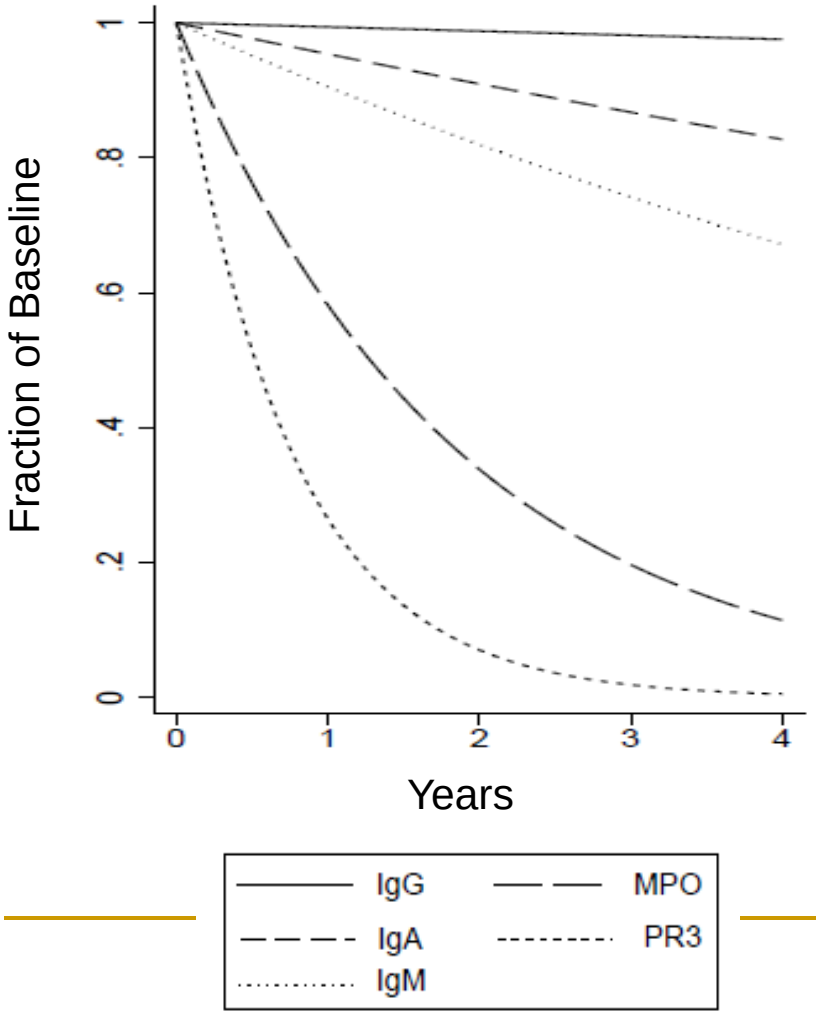
Strategy for 172 patients on maintenance rituximab

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

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



MAINTENANCE



Antibody	[1]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)

MGH

Renal Unit

Survival vs age matched general population

Strategy for 172 patients on maintenance rituximab

William Pendergraft, MD
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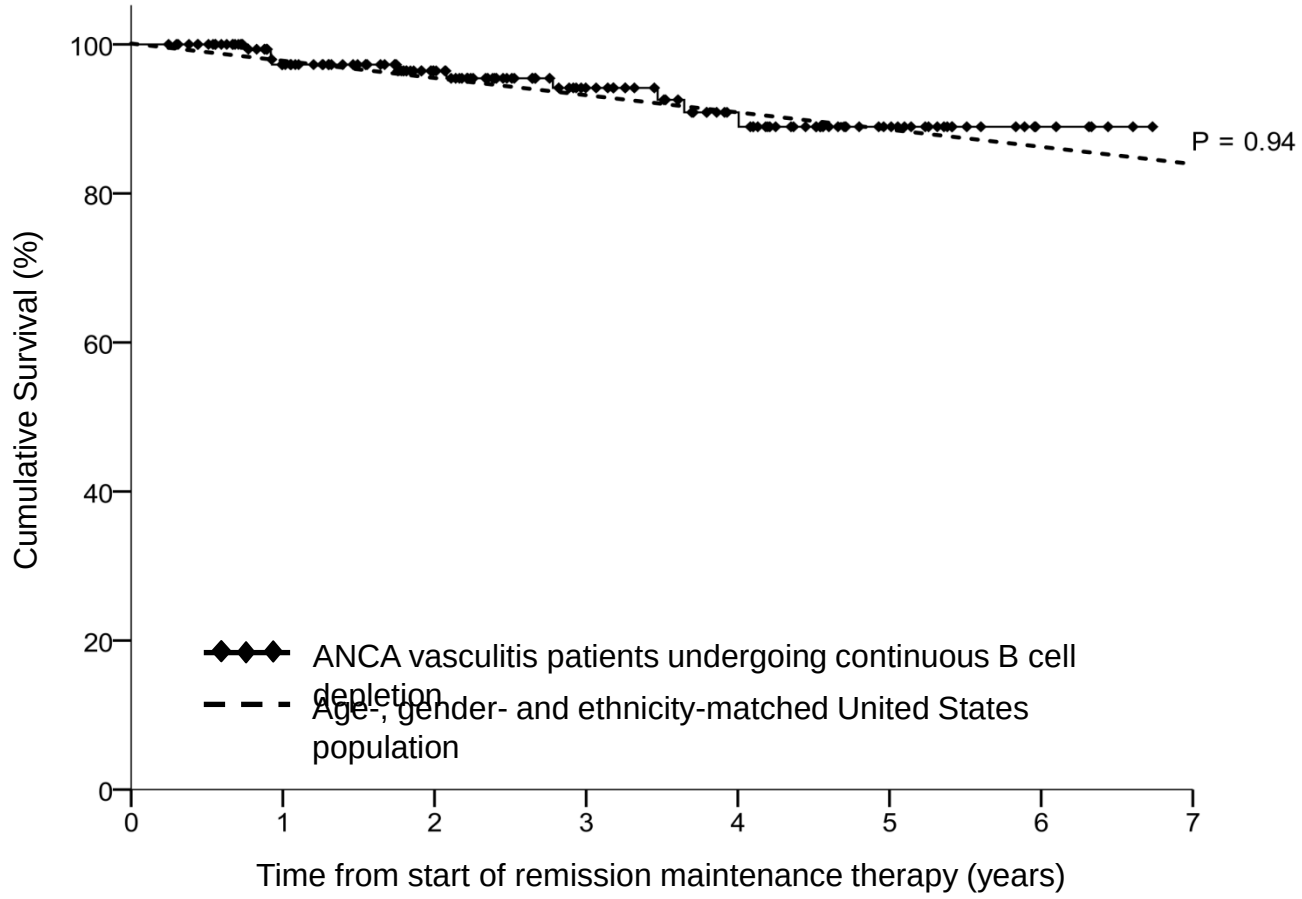
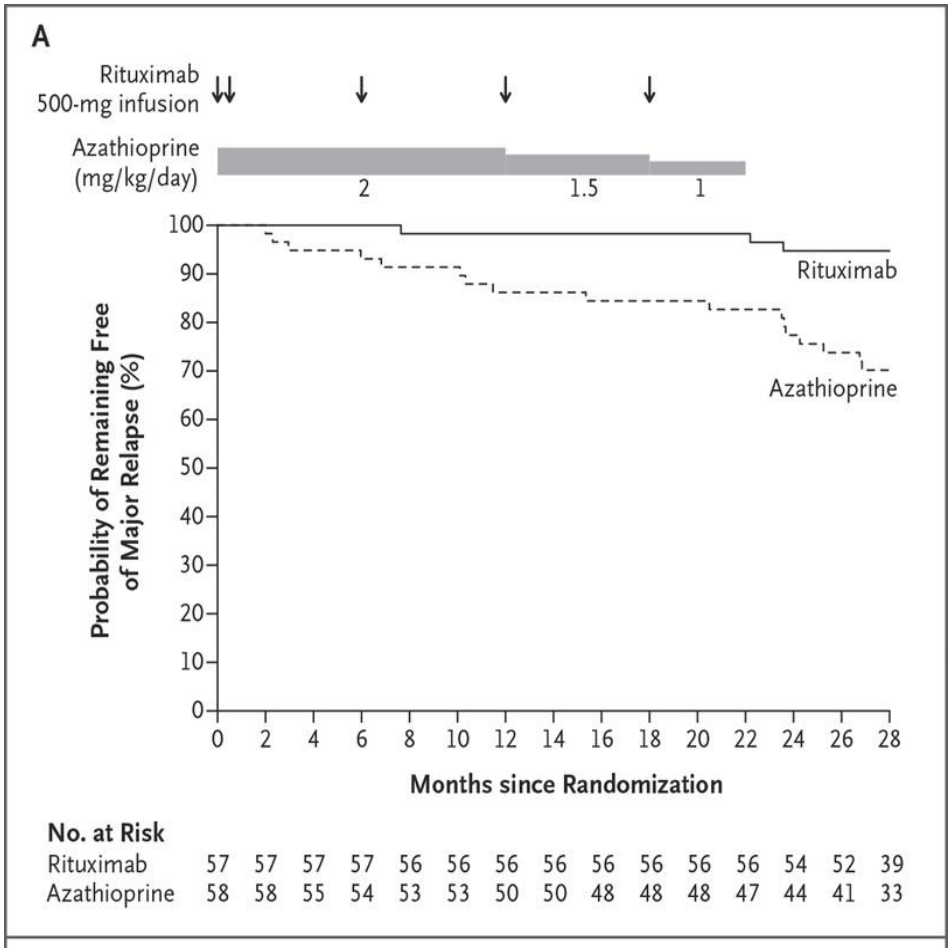


Figure 4 Survival of ANCA vasculitis patients undergoing continuous B cell depletion mirrors the general population

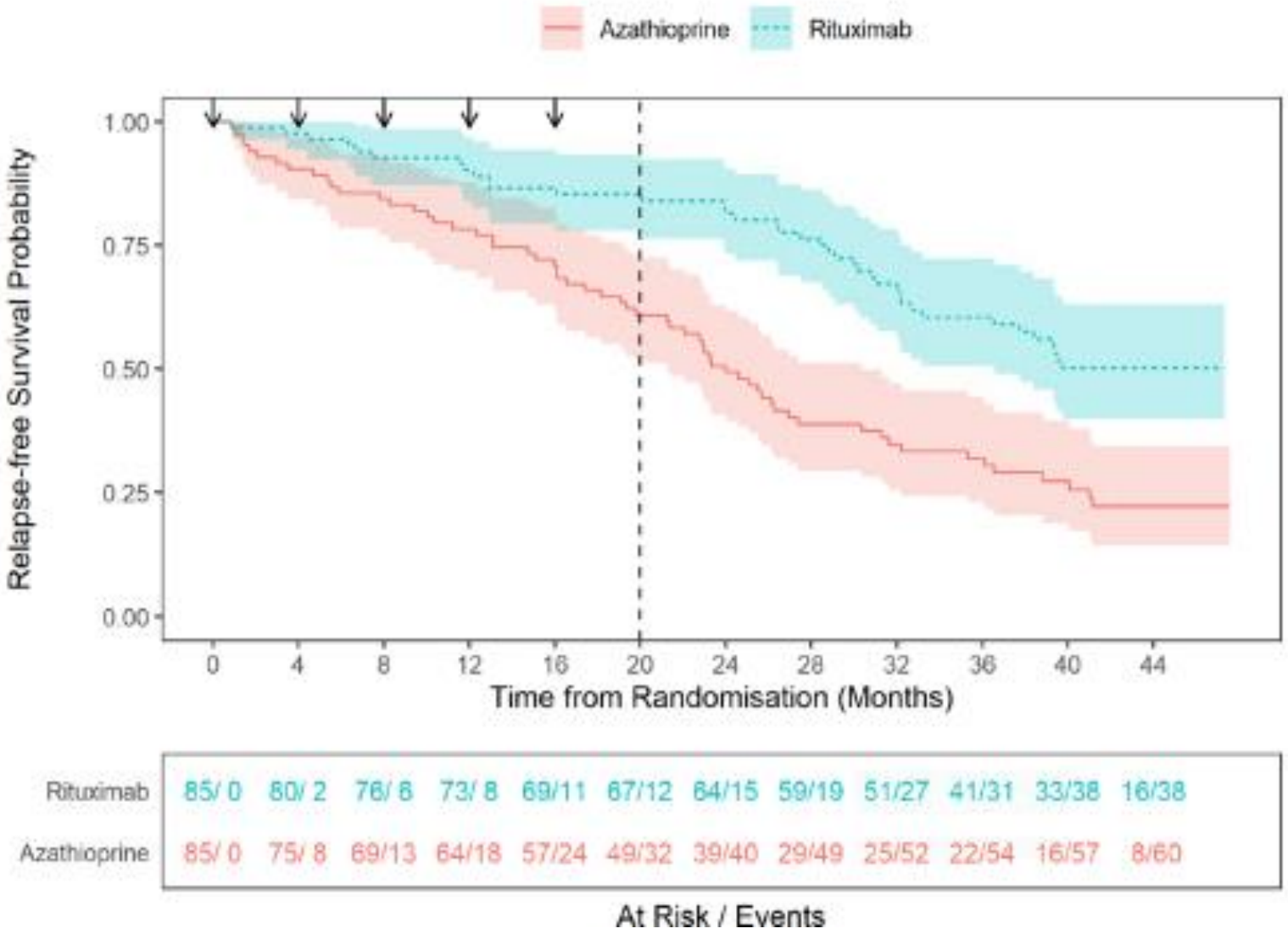
MAINRITSAN Trial



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

N Engl J Med 2014;371:1771-1780.

RITAZAREM



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

Continuous B cell depletion with rituximab for ANCA vasculitis

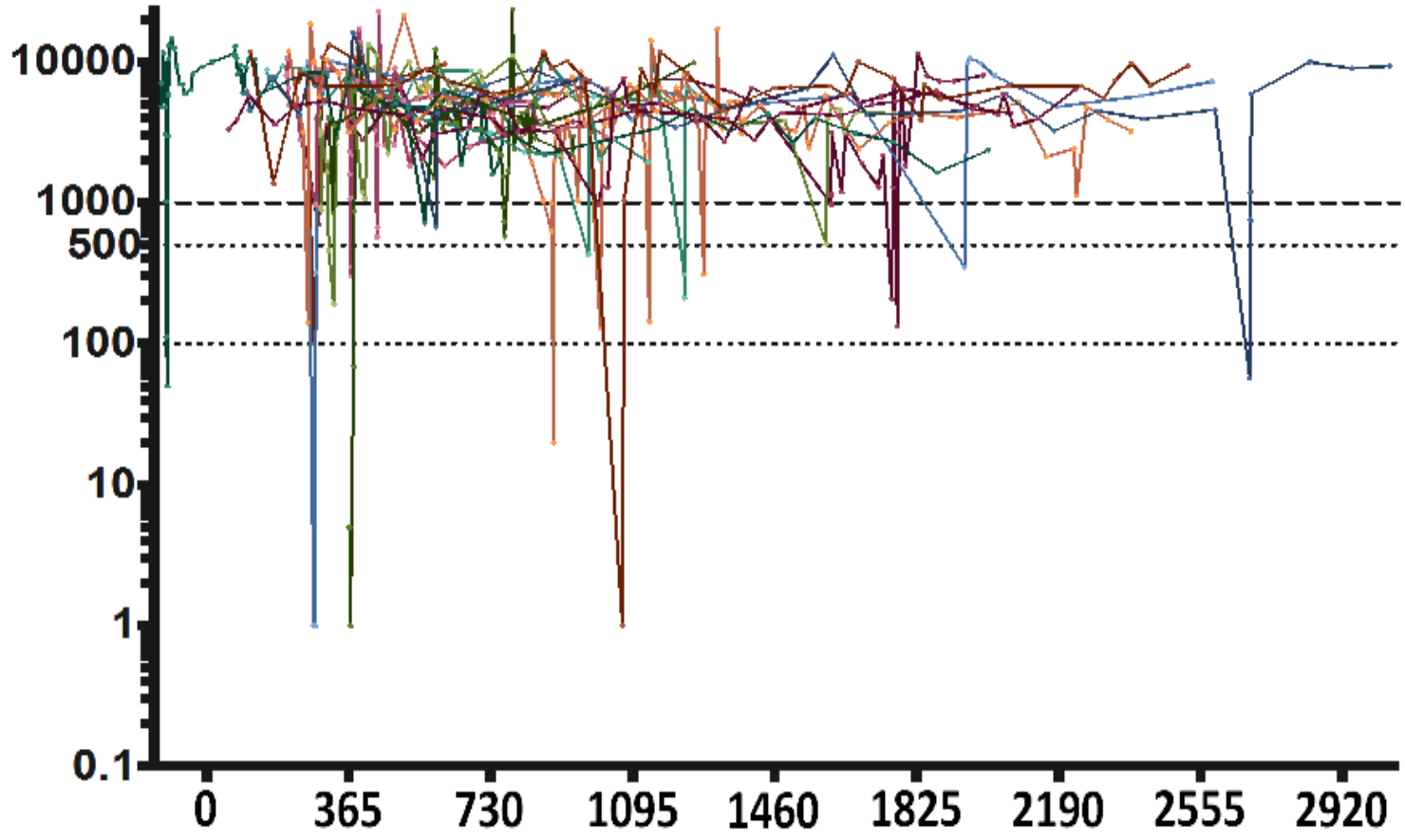
- Efficacy high
  - Most patients with sustained remission, while weaning off all other therapy
    - Most get completely off steroids.

- Toxicity low, but,
  - Late onset neutropenia of rituixmab
  - Late development of
    - Hypogammaglobulinemia
    - Functional hypogammaglobulinemia
  - Rising rate of infection
    - Bronchitis, bronchiectasis
    - Vaginitis (usually unrecognized by vasculitis team)

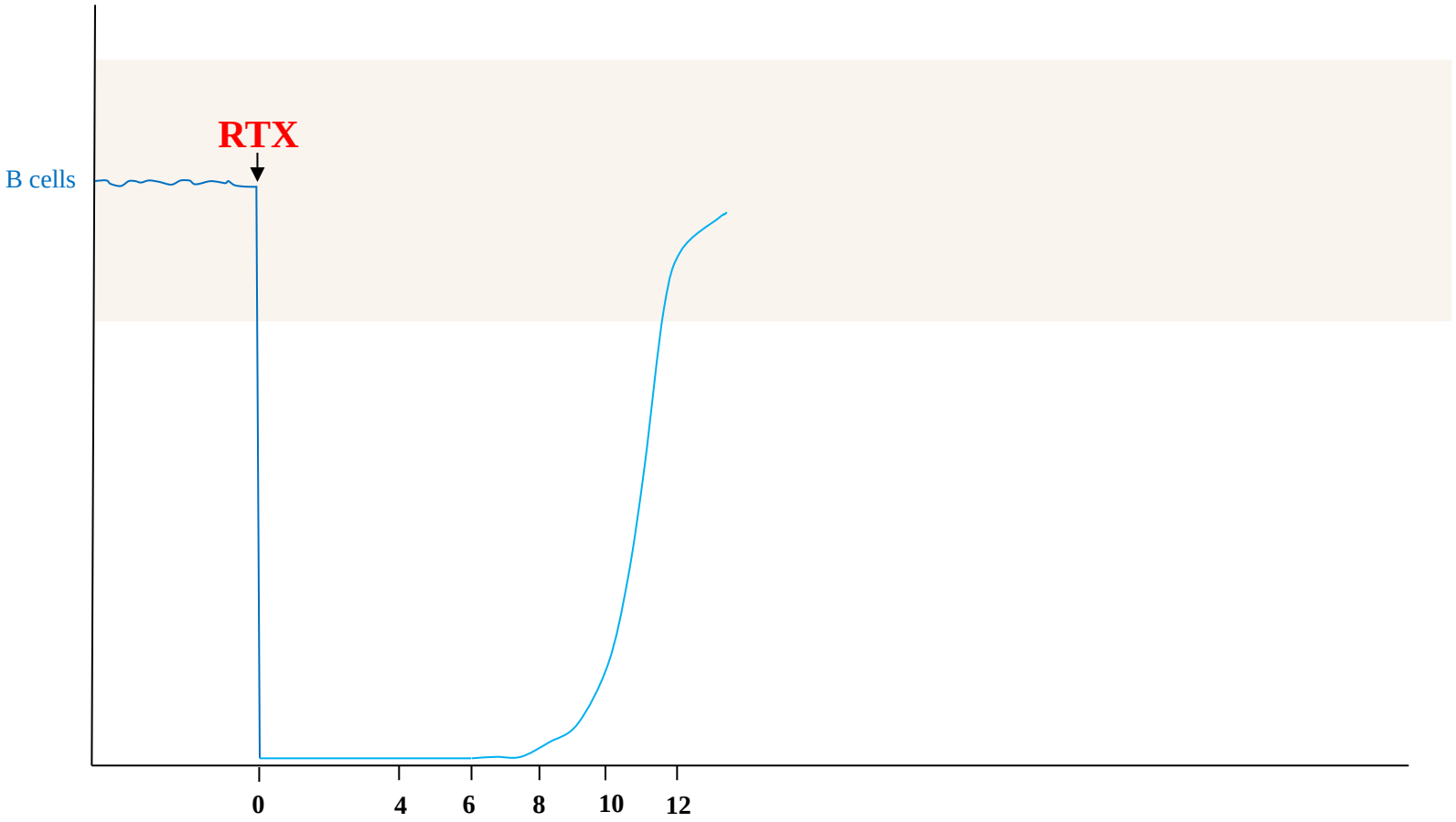
Continuous B cell depletion with rituximab for ANCA vasculitis

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

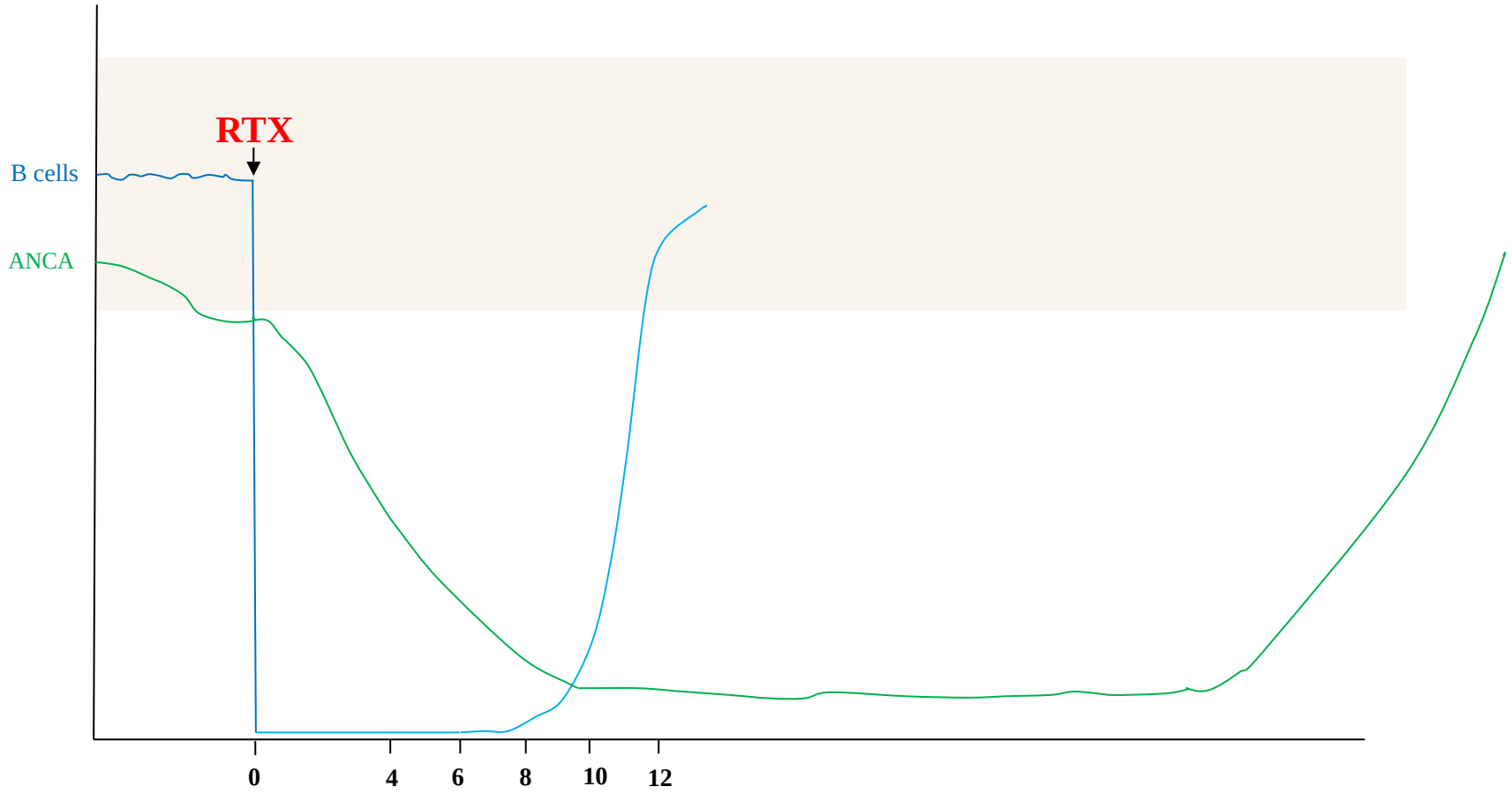
Late-onset Neutropenia



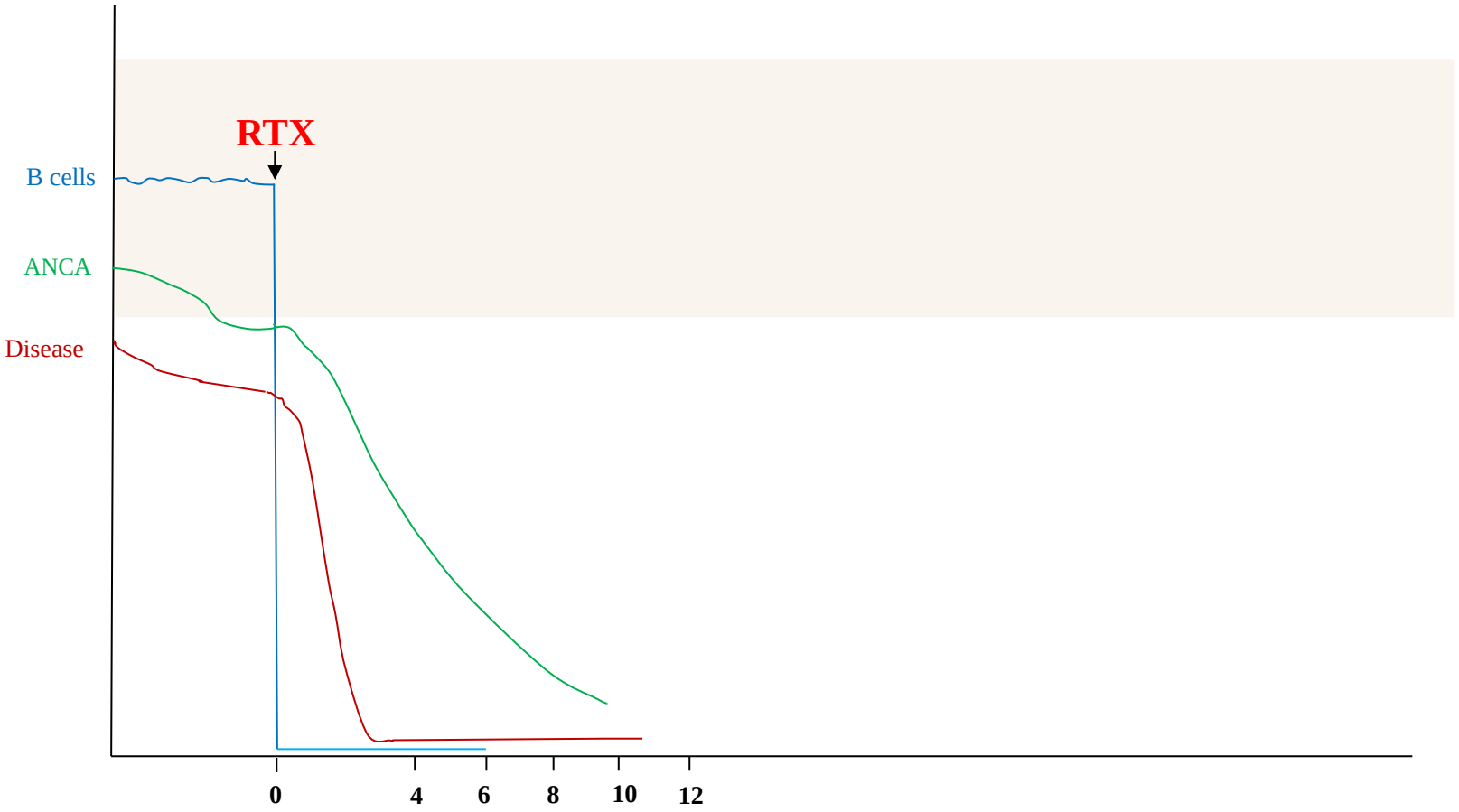
Anatomy of a relapse



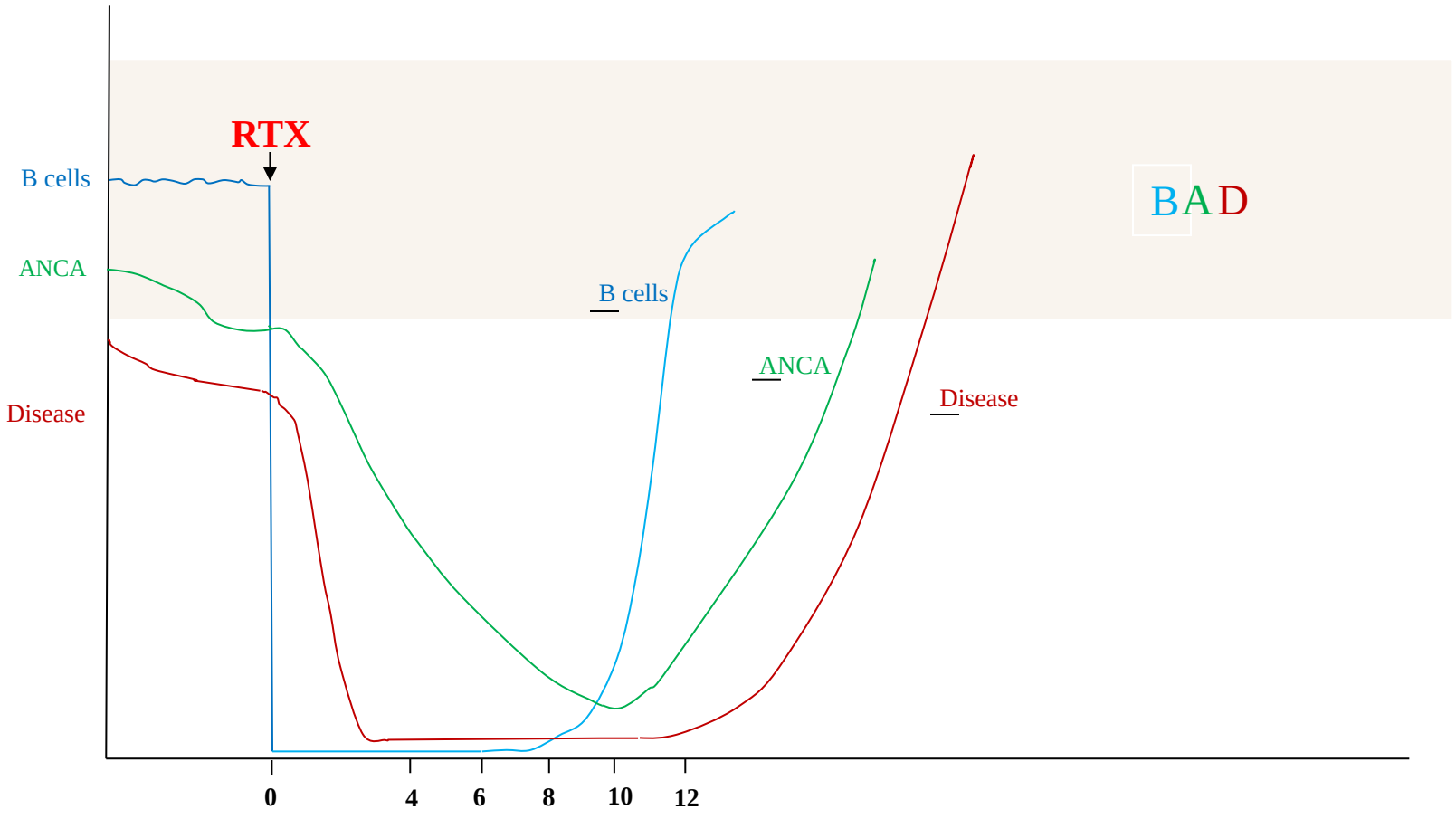
Anatomy of a relapse



Anatomy of a relapse

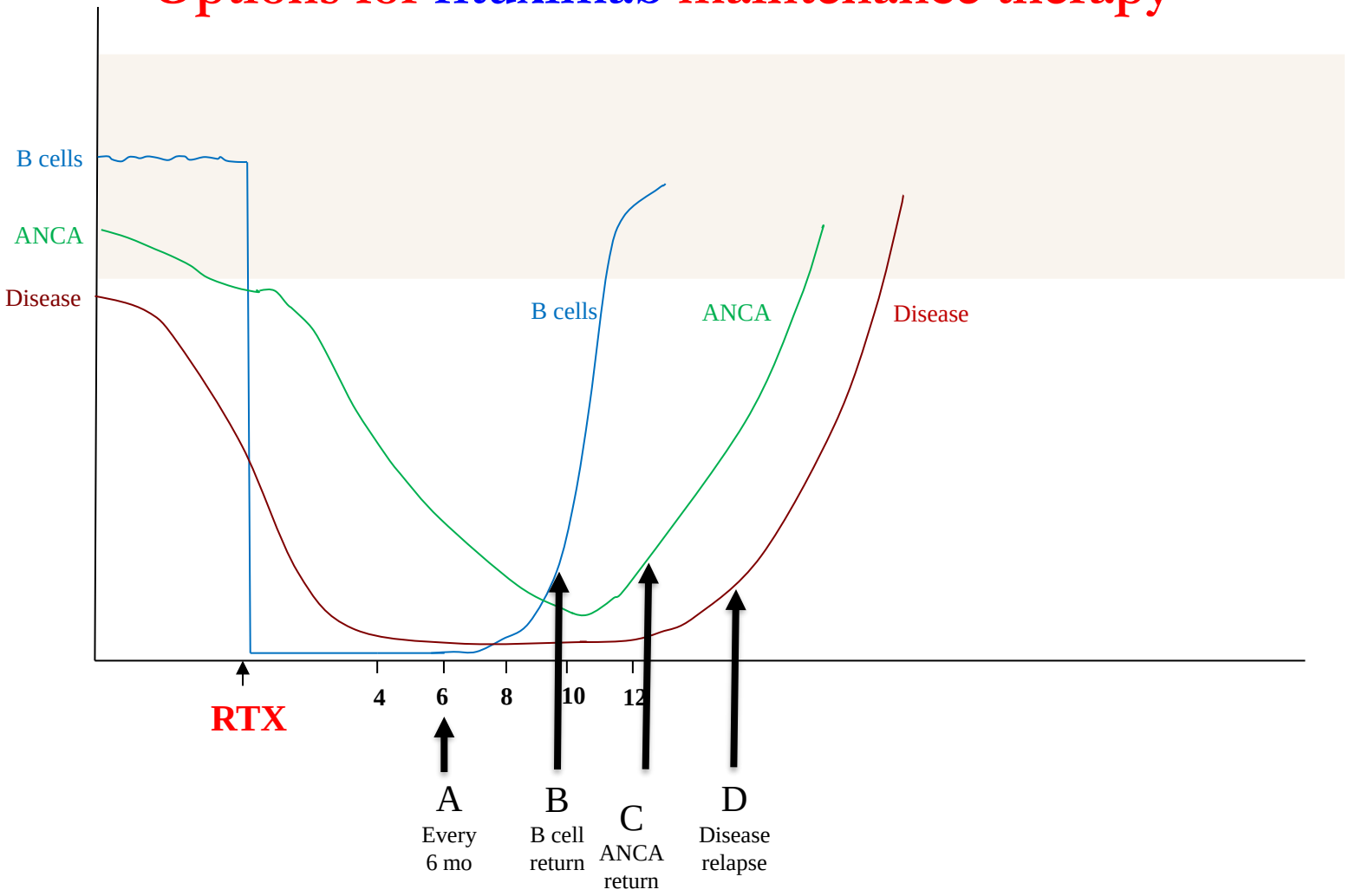


Anatomy of a relapse



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

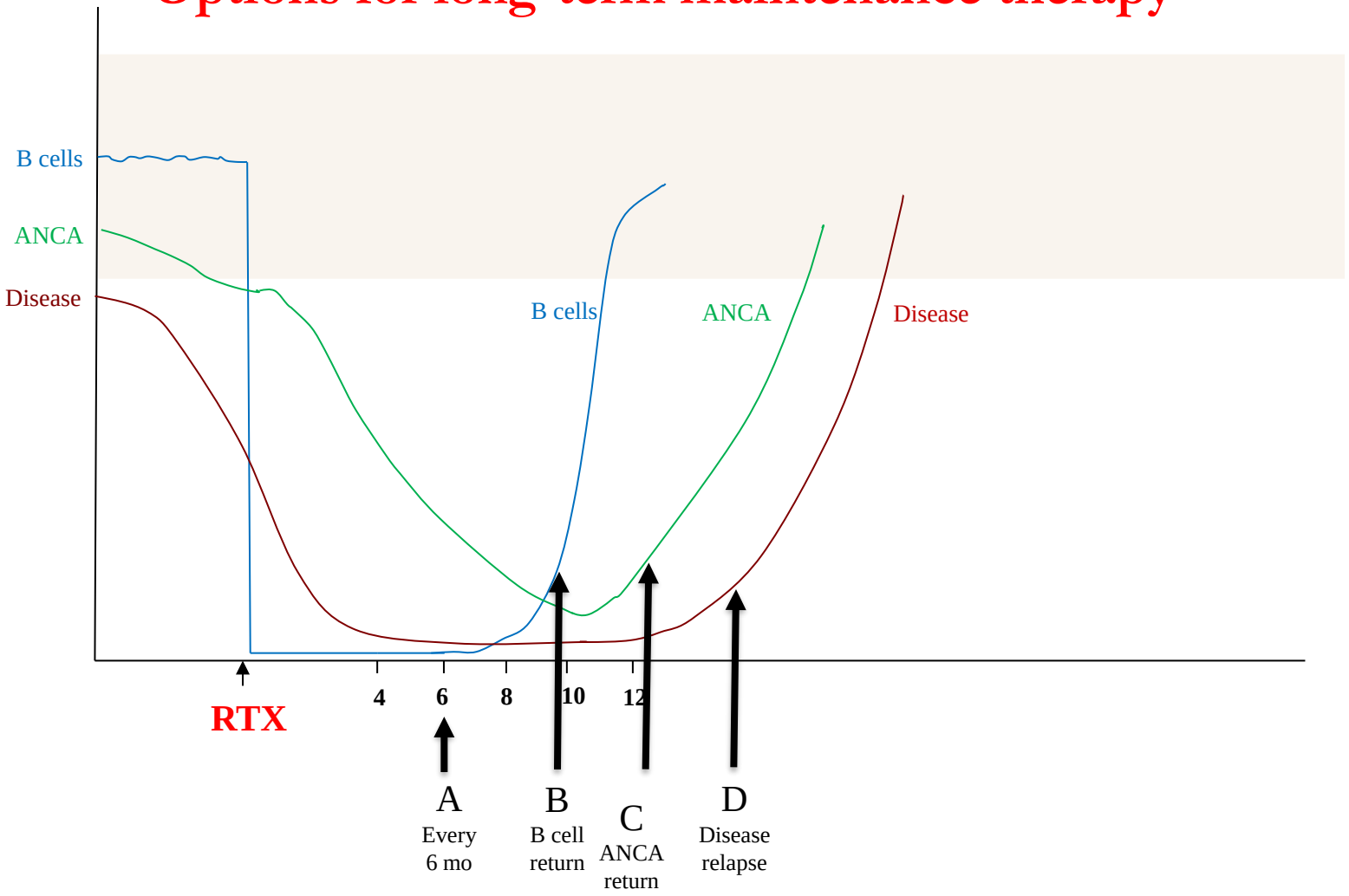
Anatomy of a relapse-

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

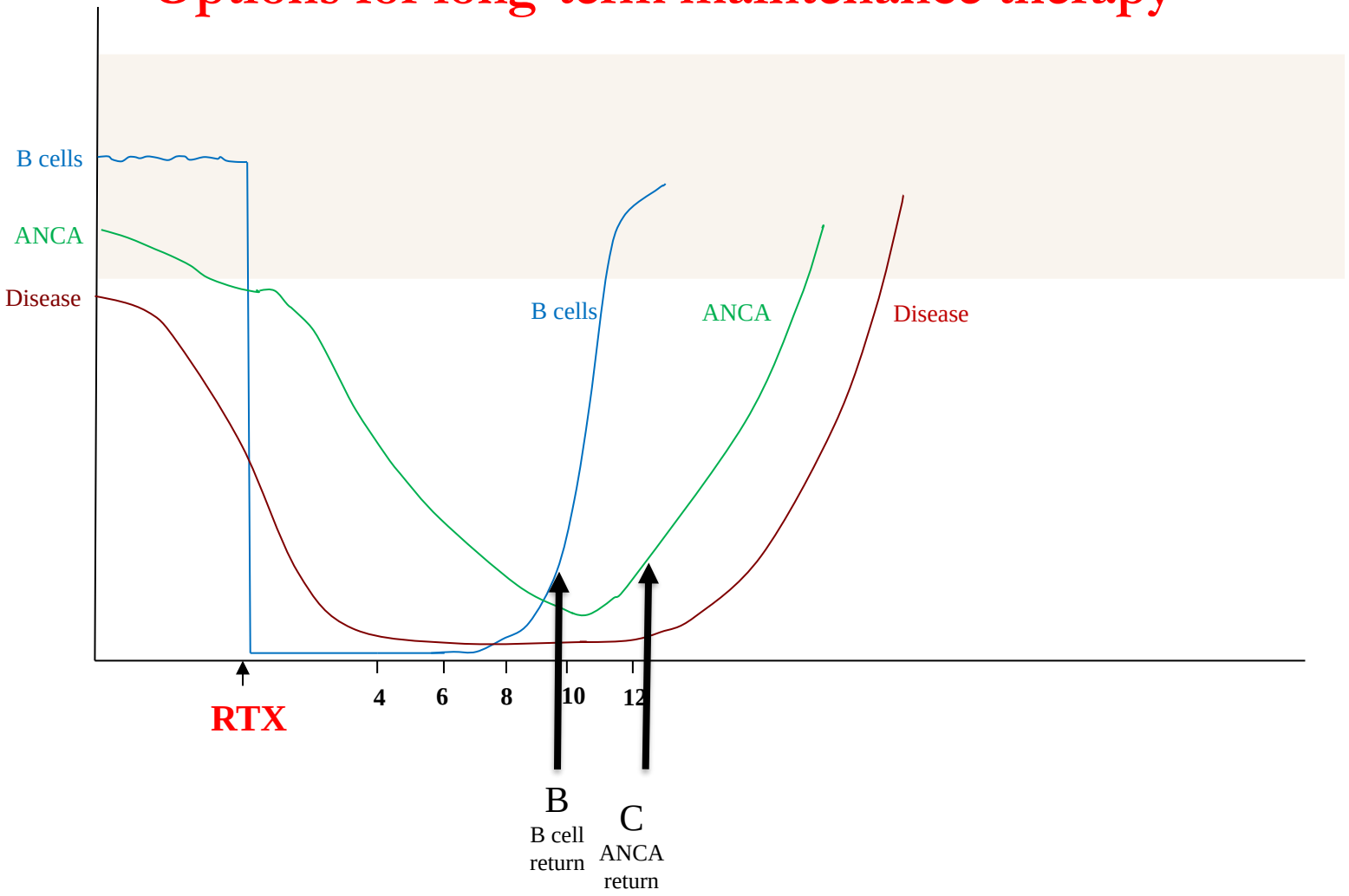
Anatomy of a relapse-

Options for long-term maintenance therapy

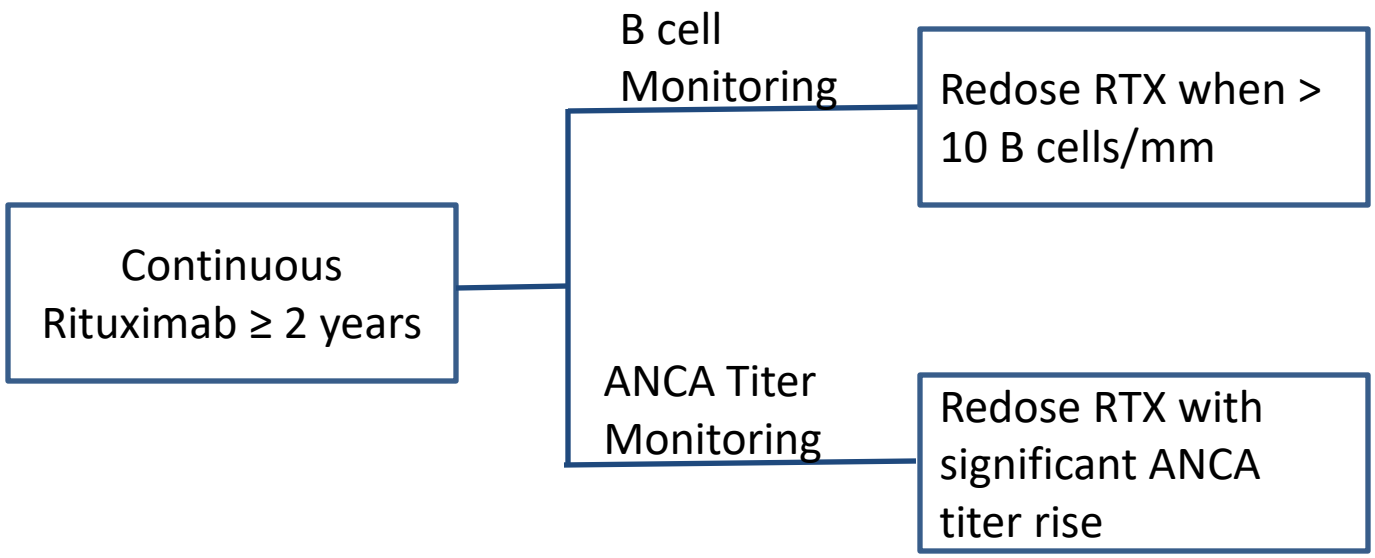


Anatomy of a relapse-

Options for long-term maintenance therapy

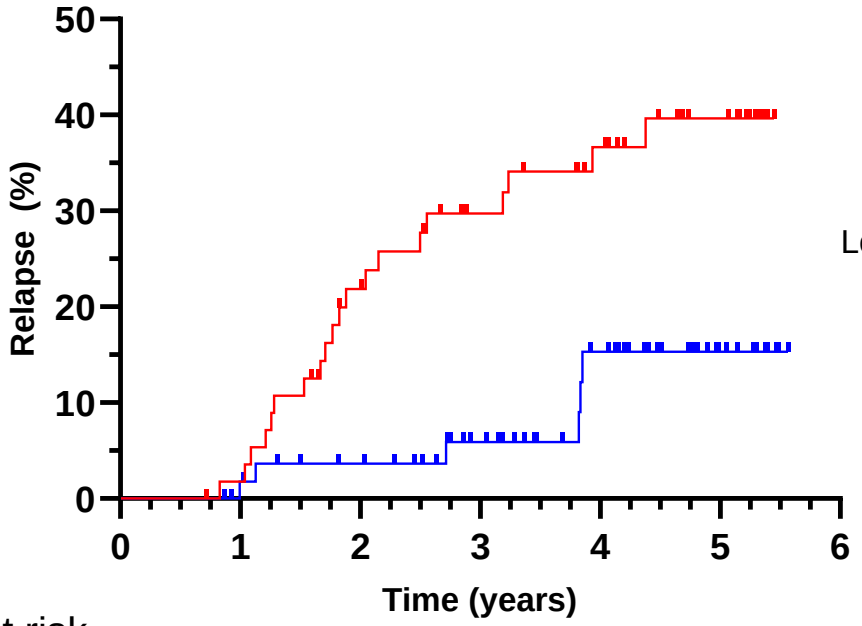


MAINTANCAVAS TRIAL



- Key Outcomes: Relapse, Adverse Events, and RTX utilization
- Projected Enrollment: 180 patients over 2 years
- Common Closeout 3 years after last patient enrolled

Time to clinical or serologic relapse



Log-rank p=0.0033

ANCA arm

B cell arm

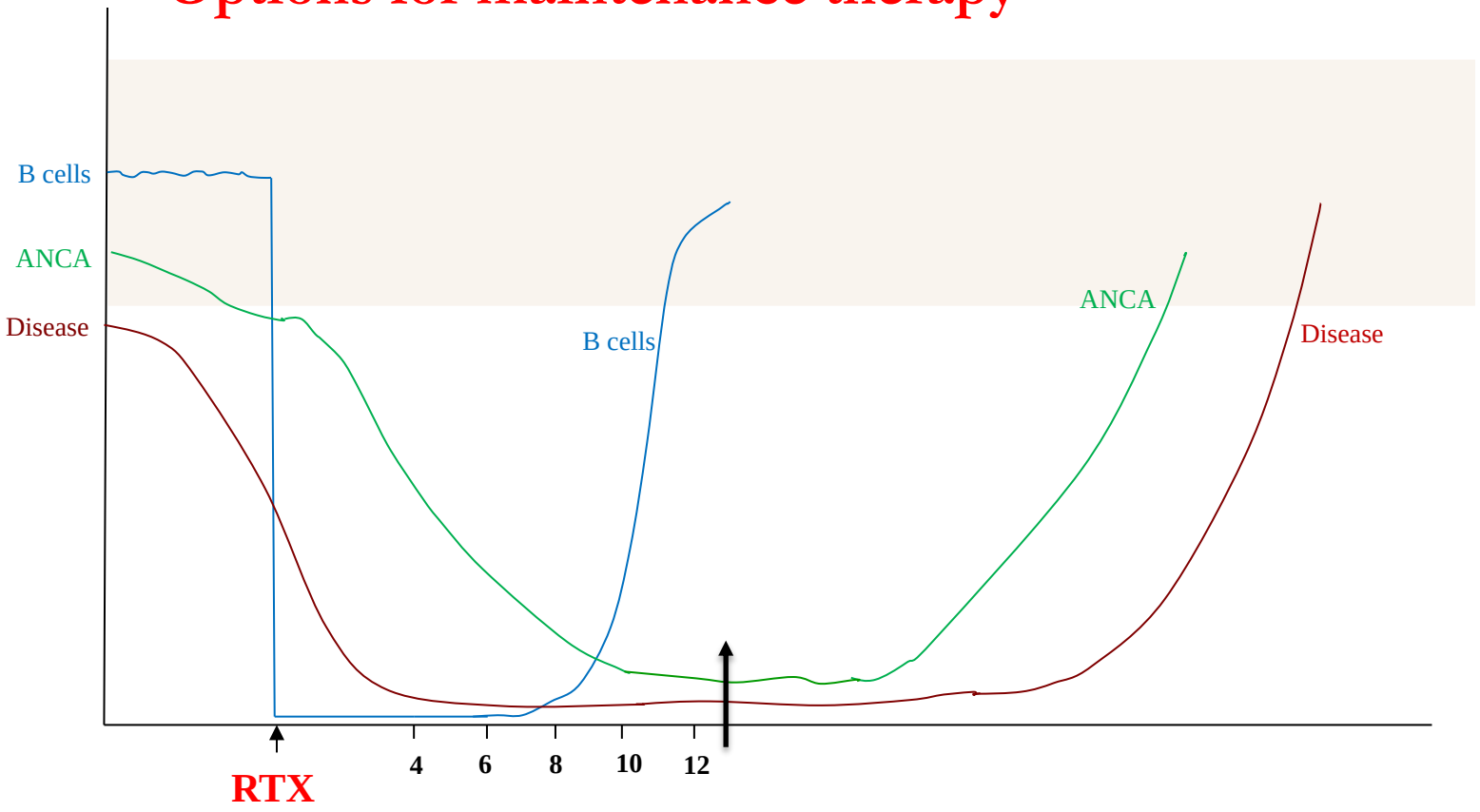
Number at risk							
ANCA arm	57	55	41	32	25	15	0
B-cell arm	58	55	49	38	26	11	0

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	"

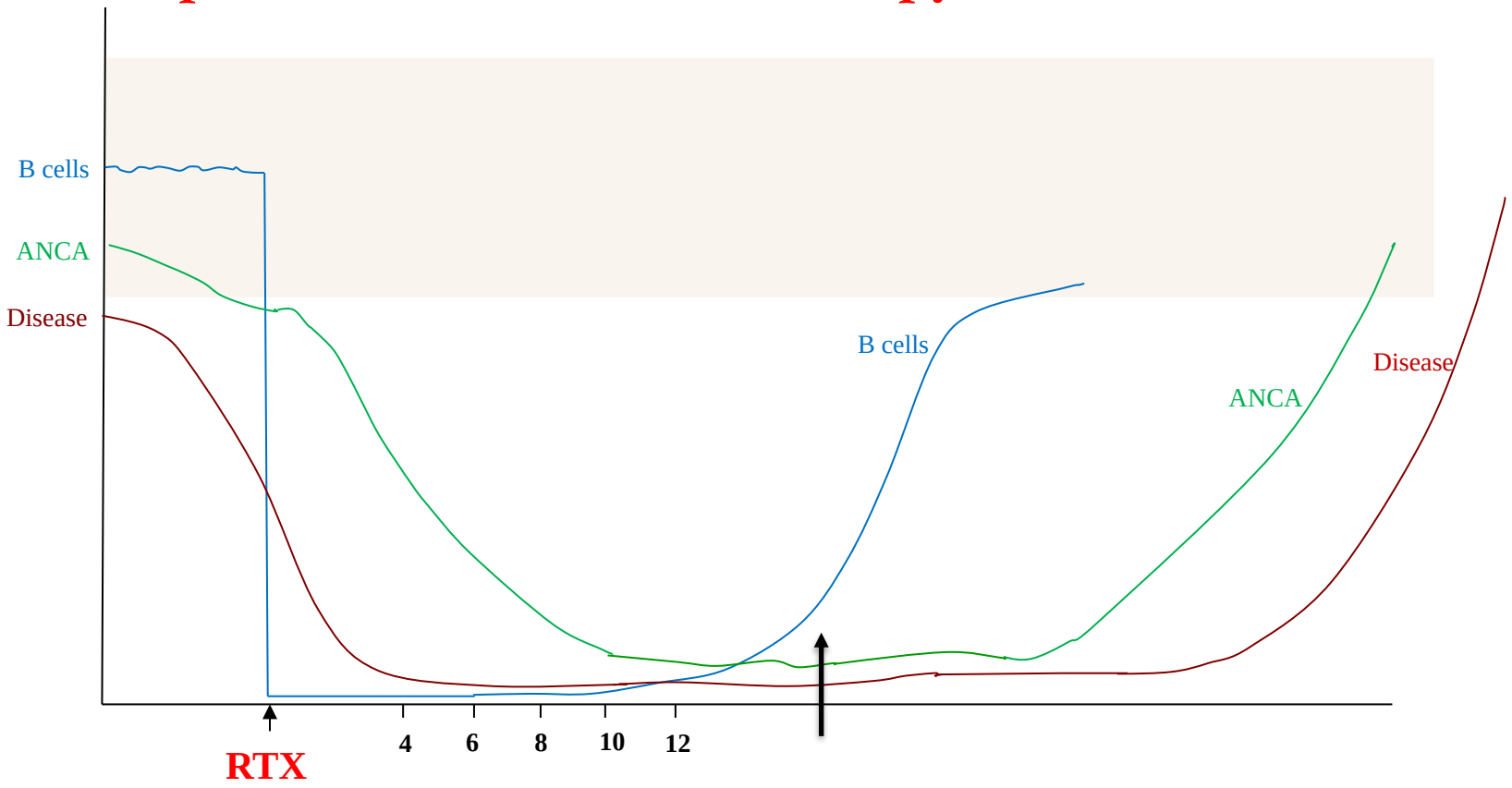
Anatomy of a relapse-

Options for maintenance therapy



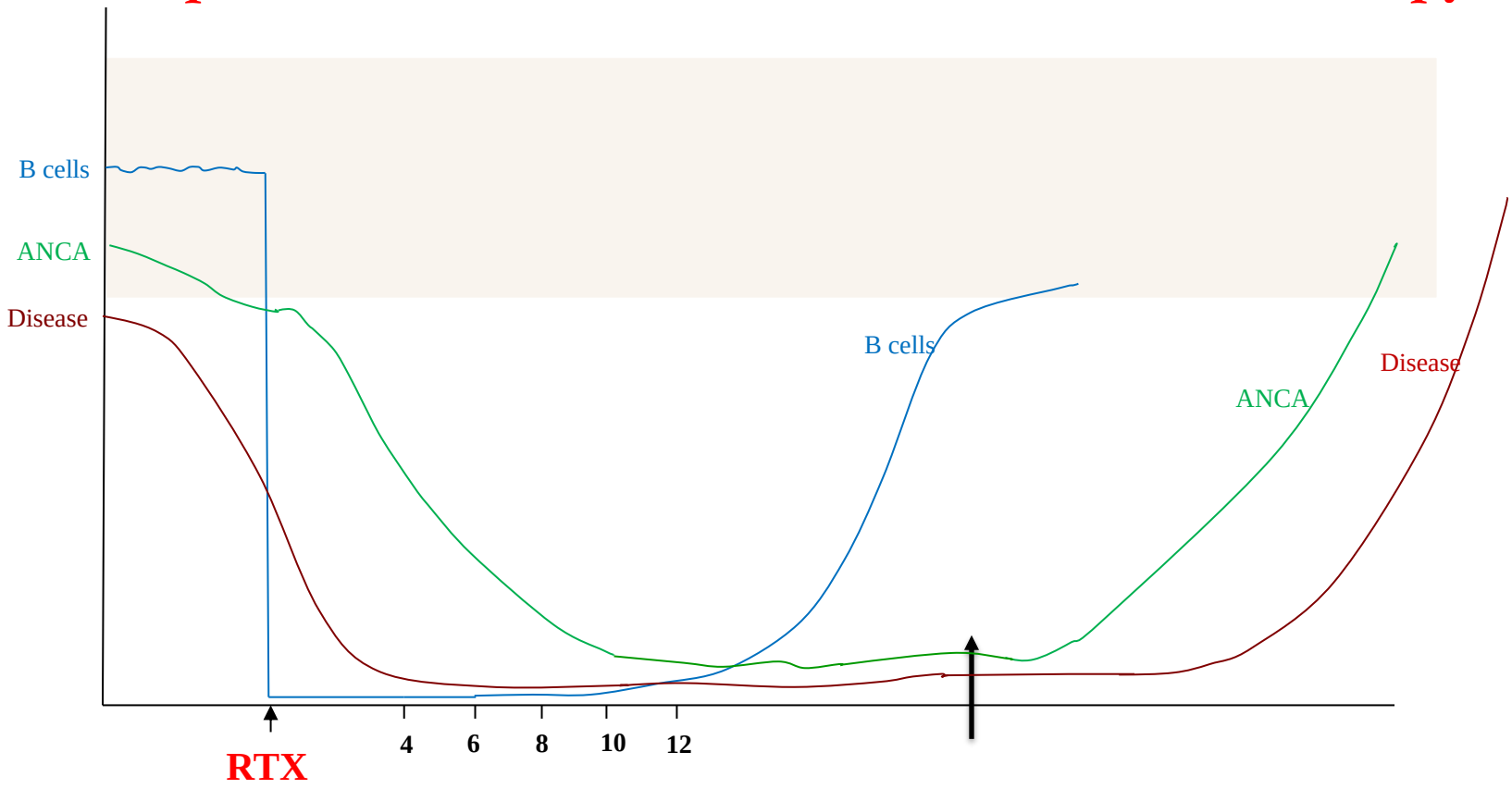
Anatomy of a relapse-

Options for maintenance therapy



Anatomy of a relapse-

Options for extended rituximab maintenance therapy



My dosing strategy

- Starting strategy
  - Early (first 2 years)
    - Aim to allow no B cell return before next dose
  - Next (years 2-4)
    - Allow early and moderate B cell recovery between doses
  - Late (by 5 years)
    - 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

ANCA Vasculitis

Special Senarios

Persistent B cell depletion

MAC
Vaginitis
ILD
COVID

Persistent B cell depletion

- Defined as: zero B cells extending beyond 2 years after the last dose of rituximab

  - ~2% of rituximab patients
    - Typically, those with prolonged and recurrent underlying disease necessitating
    - high cumulative doses of cytotoxic therapies with repeat cycles of immunosuppression.

  - Characterized by
    - quiescent disease course
    - at the expense of complication risk from B cell depletion, including:
      - recurrent infections,
      - inflammatory vaginitis
      - late-onset neutropenia
    - Eventual partial B cell recovery in some

  - Management
    - Ig replacement was key in controlling infectious or inflammatory complications in one-third of the patients

MAC and ANCA

Mycobacterium avium complex

- Combination is too common to be a coincidence
- Features
  - Always MPO ANCA
  - Usually women
  - ANCA disease features usually restricted to lungs
- Management
  - May respond to treatment targeting ANCA
  - May partially respond to treatment targeting MAC
  - Or treatment for both

Vaginitis of rituximab

DIV (desquamative inflammatory vaginitis)

- Vaginitis of rituximab
  - Features
    - Heavy vaginal discharge and pain
    - Typically, minimally responsive to antibiotics, antifungals or steroids
    - Usually not discussed with nephrology or rheumatology or pulmonary
  - Setting of several years (>3) of continuous B cell depletion with rituximab
    - With or without hypogammglobulinemia
  - Management
    - Usually responds well to IVIG
    - Usually resolves after several months of full B cell recovery

Protracted COVID pneumonia of rituximab

- Key points
  - B cell depletion completely blocks anti-covid antibodies
    - zero antibodies in setting of sustained B cell depletion.
  - B cell depletion should trigger a high index of suspicion despite
    - Vaccinations and prior covid infections
  - Routine COVID testing frequently inadequate
    - nasal swabs may be negative
    - sputum or bronch testing may be necessary
  - Apparent excellent response to combination of
    - Extended Paxlovid or Remdesivir
    - With IVIG

ANCA ILD

- ANCA lung disease
  - Setting of acute ANCA disease (MPO and PR3)
  - Variety of pulmonary features are common
  - May include NSIP pattern
  - Responds to standard treatment for ANCA

- ANCA ILD
  - Isolated UIP pattern
  - Emerges in setting of remission
  - MPO >>> PR3
  - Treatment
    - Poor response or no response to increased immunosuppression
    - May respond to antifibrotics as for other UIP ILD

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
    - Cyclophoshamide
    - 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