ACP American College of Physicians
Leading Internal Medicine, Improving Lives | Washington Chapter

Pulmonary Renal Syndromes

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Disclosures

- None

Objectives

- Review the pathophysiology of rapidly progressive glomerulonephritis
- Discuss the evaluation and treatment of immunologic, rapidly progressive kidney diseases
- Describe the natural history and clinical courses of anti-glomerular basement membrane disease and ANCA associated vasculitis
- Review avacopan as a potentially emerging treatment option for ANCA associated vasculitis

Cases

- 64 year old teacher. No PMH, no medications. Smokes 1/2 ppd cigarettes.
- He presented to urgent care with “sinus congestion” and a new onset headache and blurring vision. No cough, no hemoptysis.
- BP 250/155 —> ICU admission
- Creatinine 3.8 mg/dl
- **ESR 102, anti-GBM ++**, negative ANCA, ANA, ASO, anti-cardiolipin
- “Active” urine sediment
- Renal biopsy

- 71 year old retired presents with migratory arthralgia, dyspnea, fatigue and an urticarial rash. PMH hypertension on HCTZ
- BP 155/95
- Creatinine 1.0 —> 3.4 mg/dl
- CXR - RUL infiltrate
- **ESR 94, pANCA (MPO) ++**, negative anti-GBM, ANA, ASO, anti-cardiolipin
- “Active” urine sediment
- Renal biopsy

Which best describes the clinical picture of acute nephritic glomerulonephritis?

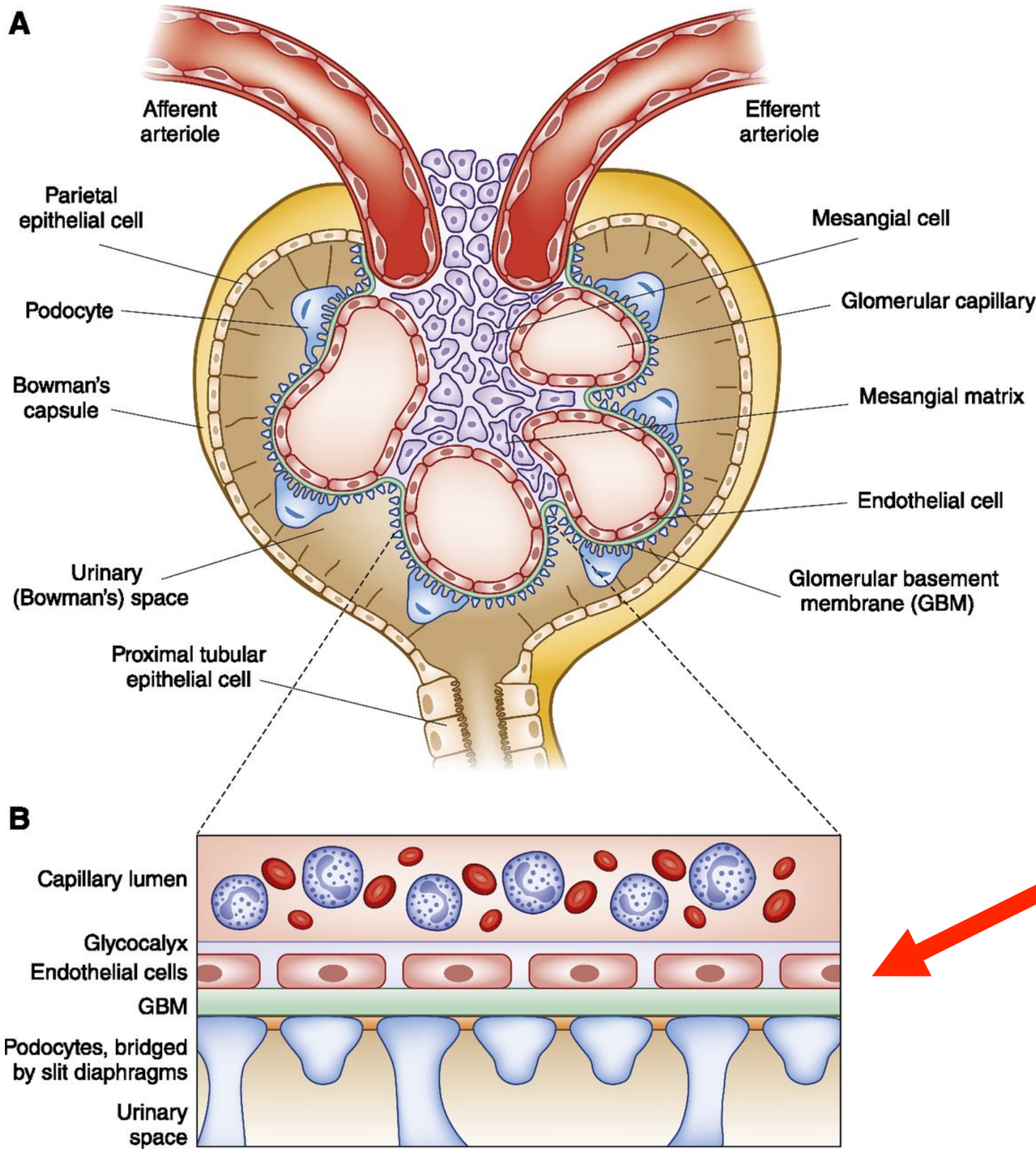
A. 6 grams proteinuria; bland sediment; normal creatinine

B. 1 gram proteinuria; granular casts; increased creatinine

C. 2 grams proteinuria; dysmorphic RBCs; increased creatinine

D. 3 grams proteinuria; bland sediment; increase creatinine

The Glomerulus and the Filtration Barrier



A. Richard Kitching, and Holly L. Hutton CJASN 2016;11:1664-1674

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CJASN

Common Glomerular Disorders

Nephrotic

Proteinuria ~ 3 grams +;
RBC negative

***** Podocyte disorders outside the vasculature***

- Minimal Change
- Foot Process Effacement
- Focal Sclerosis
- Sclerosis
- Membranous
- Subepithelial Deposits
- Post Infectious
- Hypocomplementemia
- MPGN
- Mesangial expansion
- IgA
- *Crescents*
- Rapidly Progressive GN
- ***Anti-GBM***
- ***ANCA vasculitis***
- *SLE Class IV (DPGN)*
- *IgA vasculitis*

- Diabetes
- Amyloid
- Alport's Syndrome

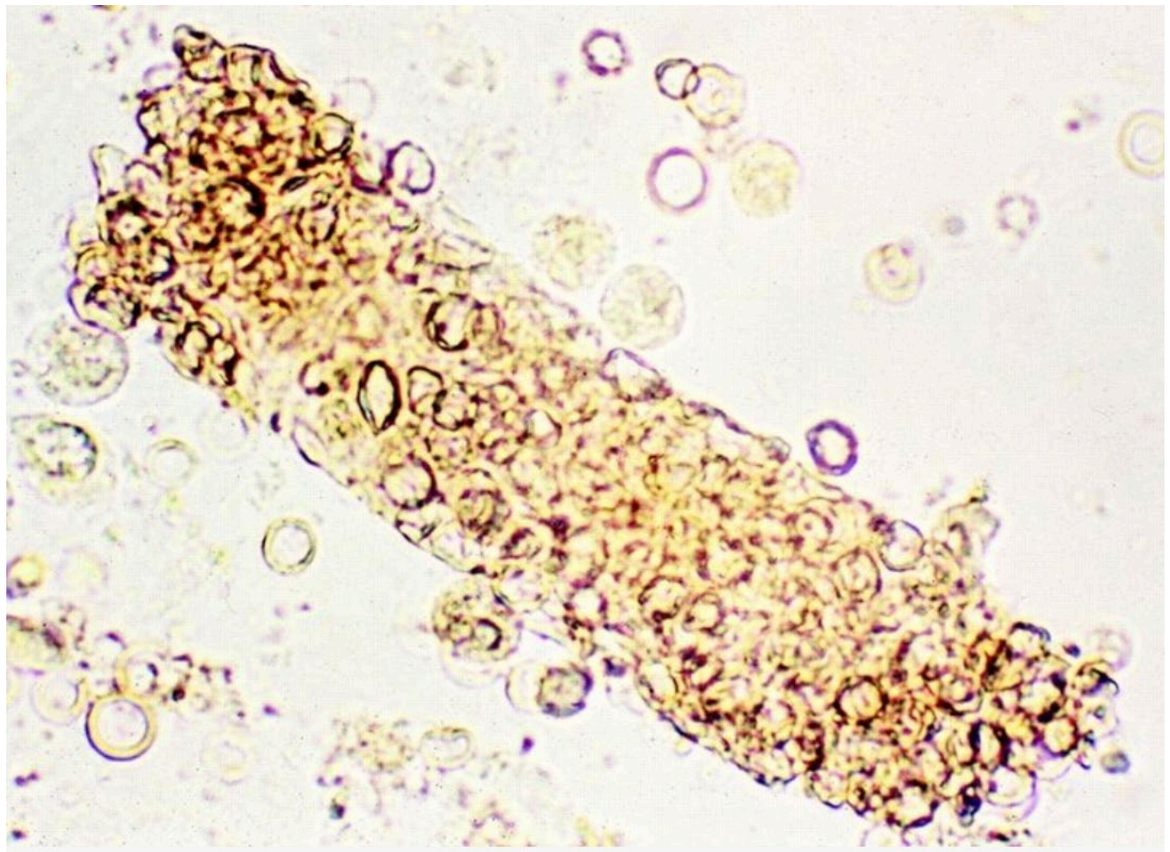
***** Inflammation of vascular endothelium***

Nephritic

Proteinuria ~ 1-3 grams;
RBC positive

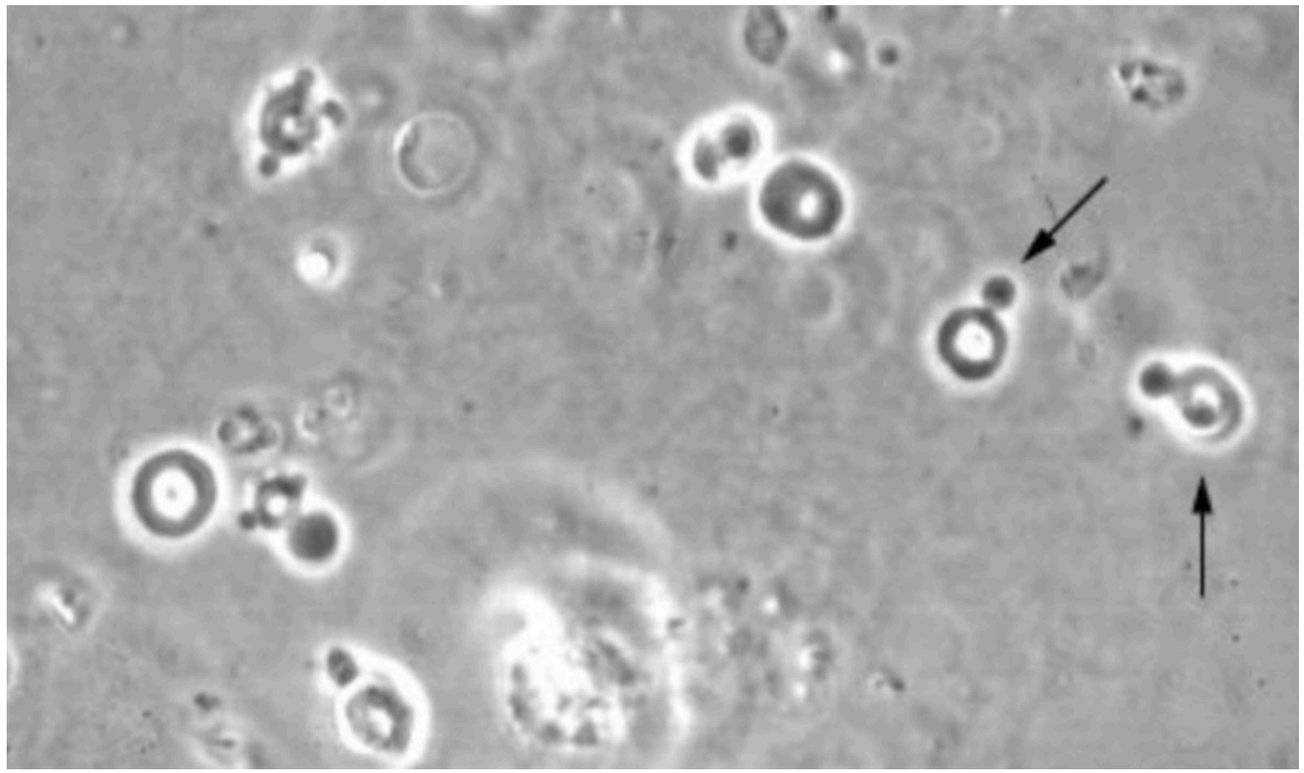
Henry Mroch, MD. 2020

Hints of glomerular bleeding



RBC Cast

Dysmorphic RBCs



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D. 3 grams proteinuria; bland sediment; increase creatinine

Crescentic RPGN by Mechanism

Anti-GBM - 15%

ANCA (AAV) - 60%

Immune complex:

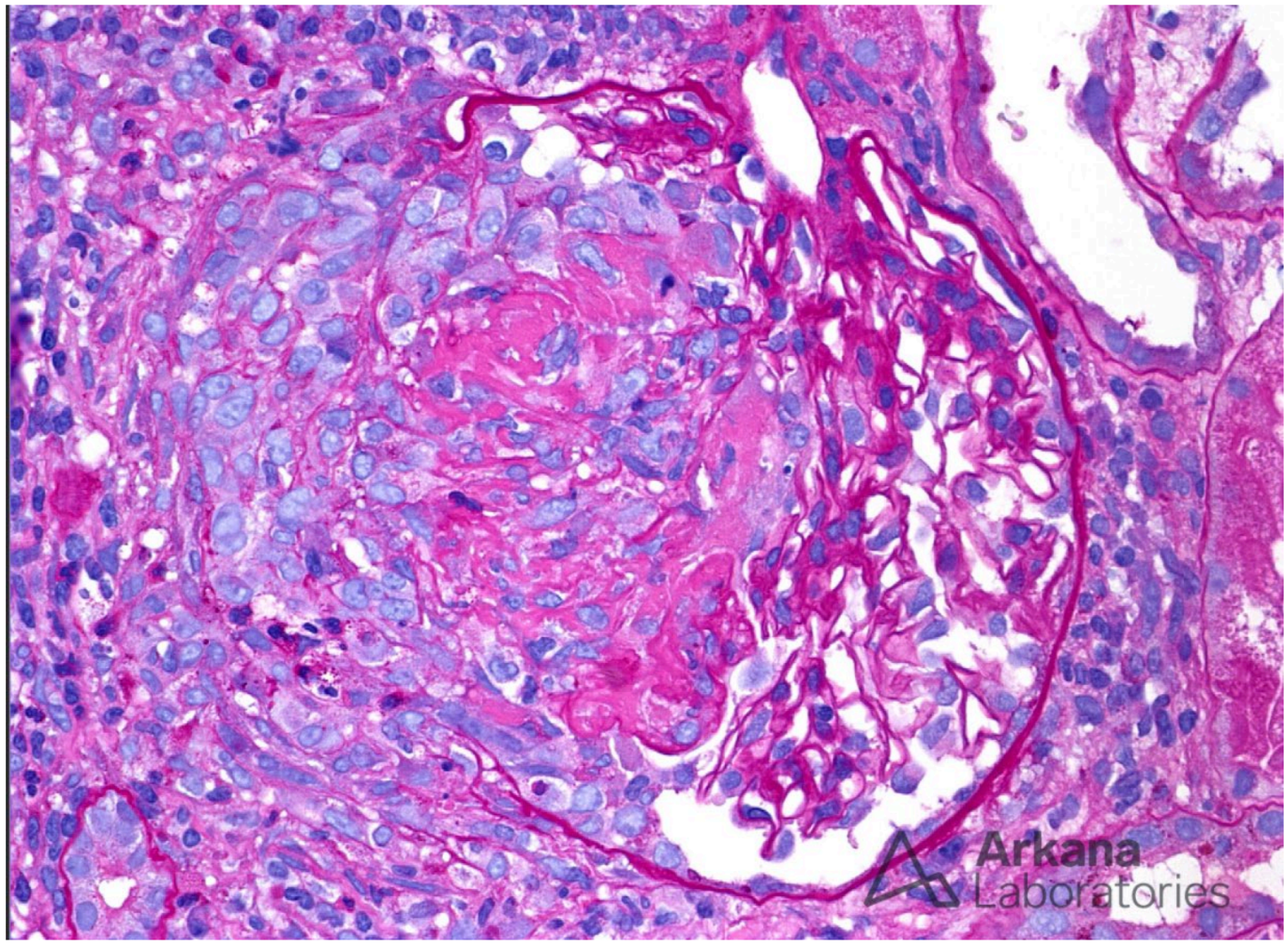
*SLE(Class IV)- **25%***

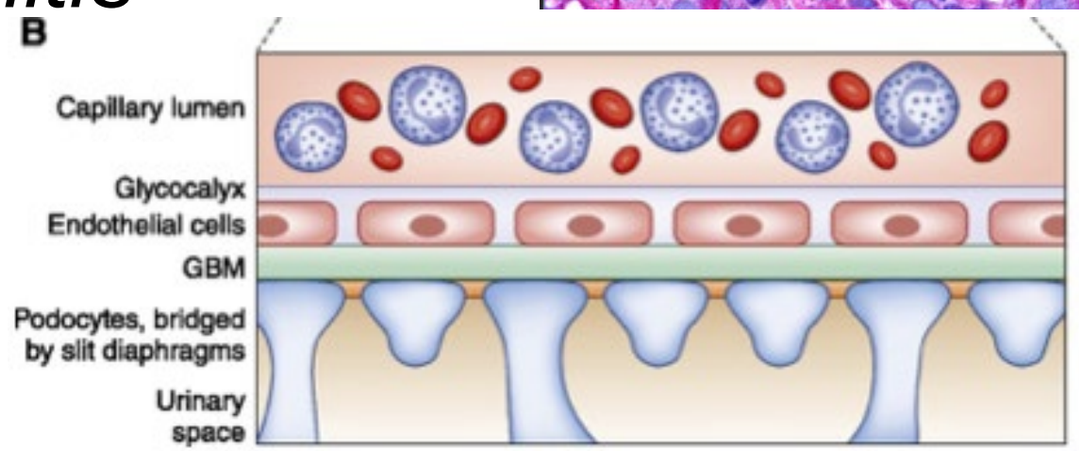
MPGN

Endocarditis

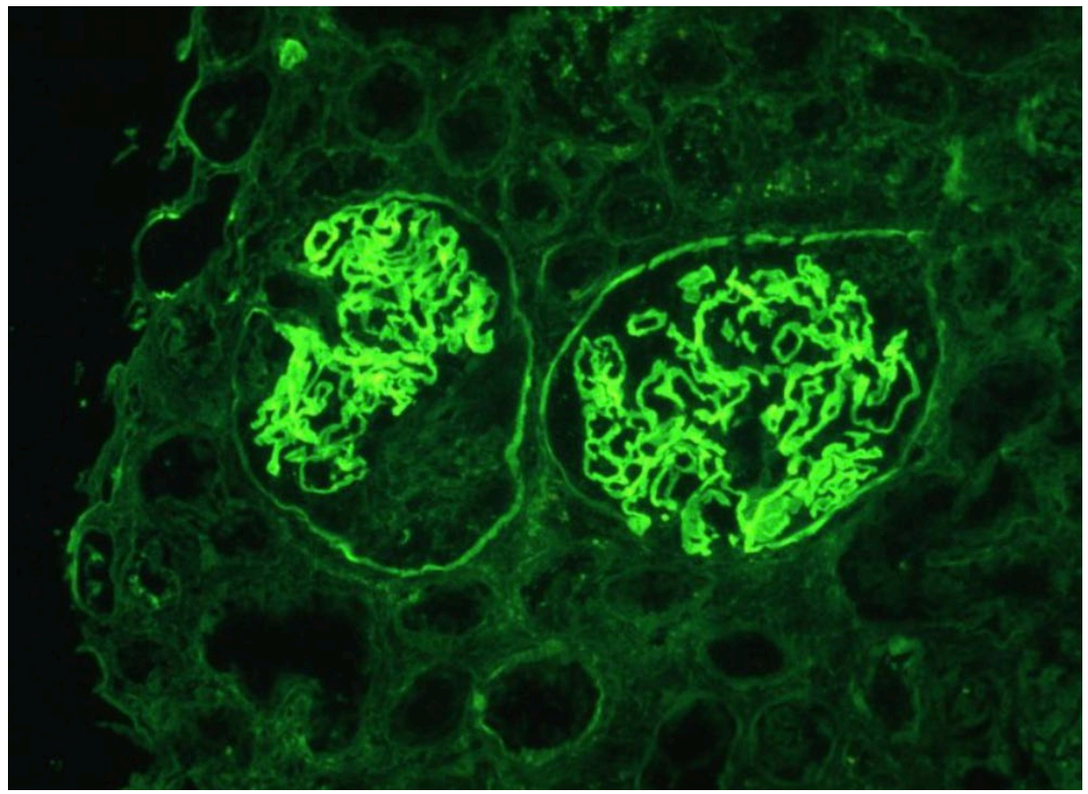
Post infectious

IgA vasculitis





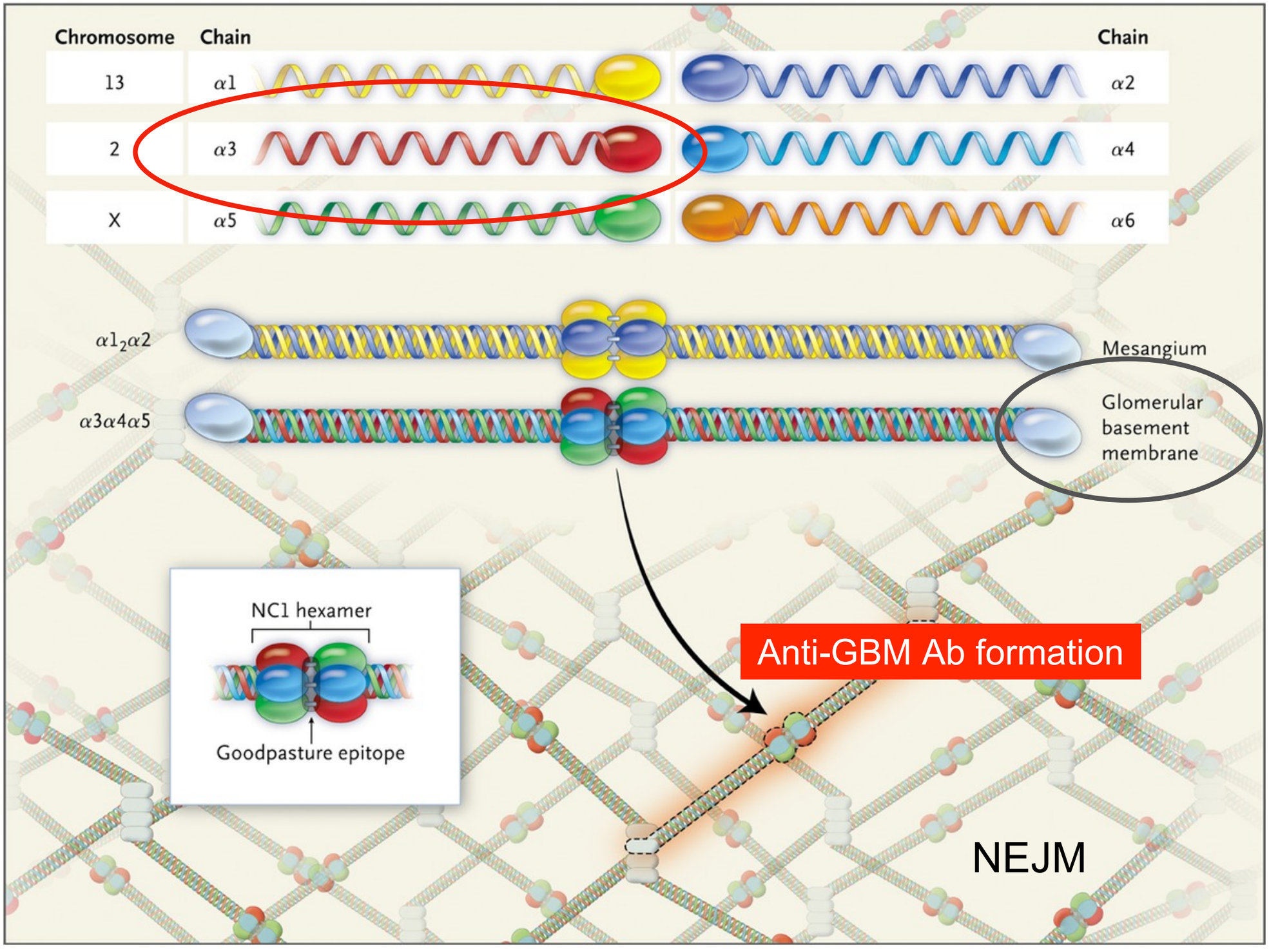
Anti-GBM Disease

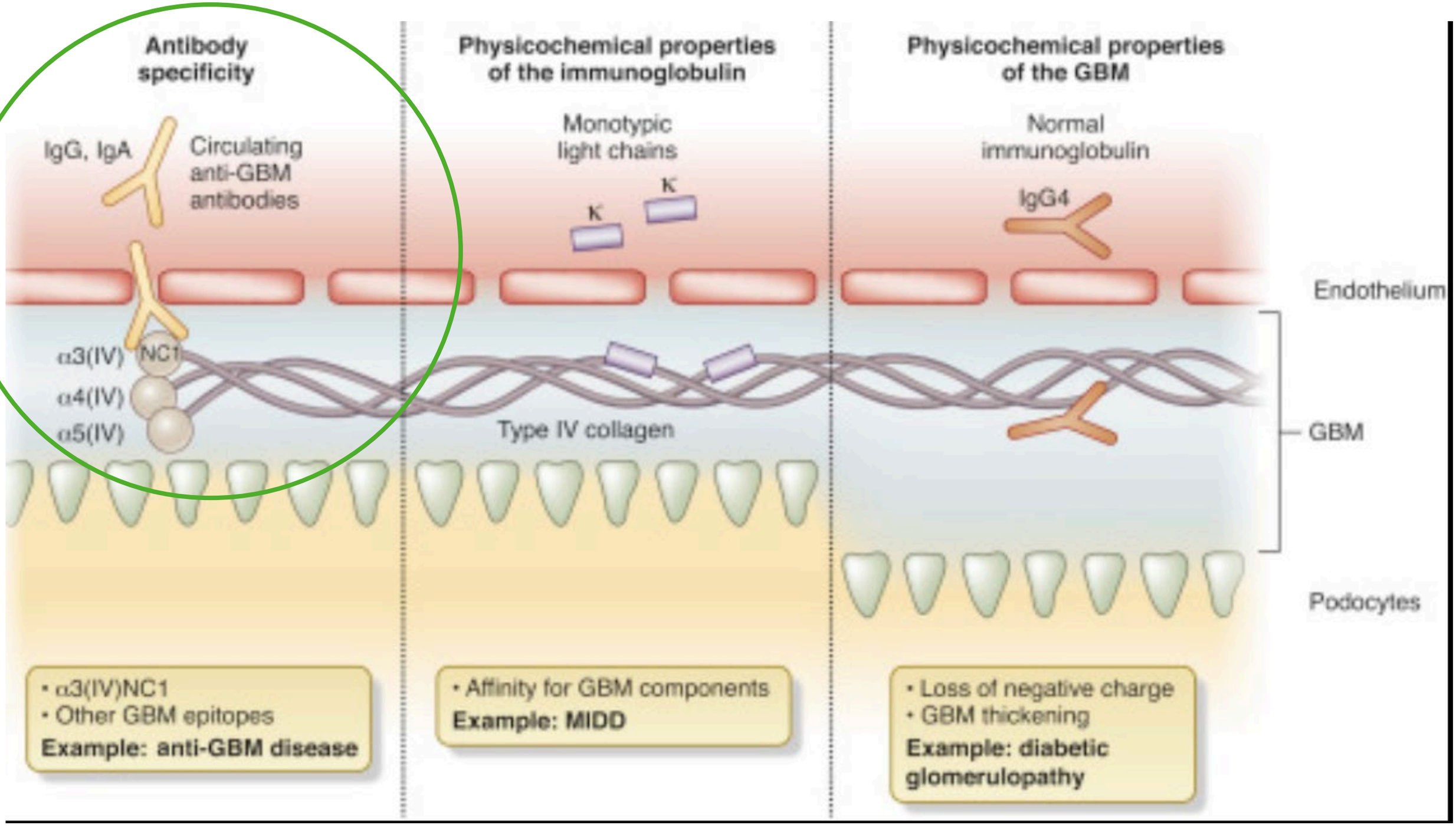


- 1 per million people/year incidence
- Bimodal: 20-40 years and >60 years (*more often renal only*)
- **Linear Ig staining of the basement membrane**
- 15% of all RPGN
- Classic Goodpasture's = Pulmonary hemorrhage + RPGN (90%)
- **Presentation is commonly SEVERE injury**

Exposure of sequestered epitopes within GBM (*lungs* + *kidney*) - *NC1 COL4(3)*

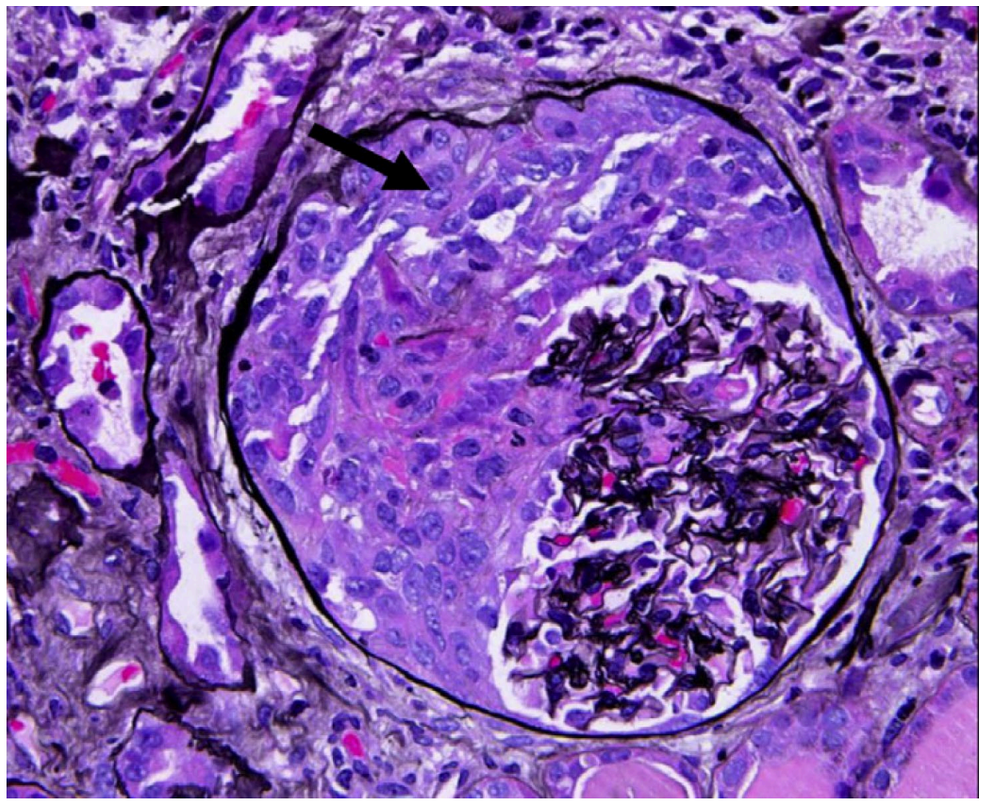
- *Smoking*
- *Infection*
- *Solvents*
- *Other*





Kidney International
Volume 89 Issue 4 Pages 750-752 (April 2016)

ANCA Associated Vasculitis



- 20-40 per million people/year incidence
- 60-80% of RPGN cases
- ~80% will have renal involvement
- **Pauci-immune necrotizing vasculitis with crescents**
- **Immunofluorescence staining will be faint to absent**

Aberrant expression of PR3 and MPO in n

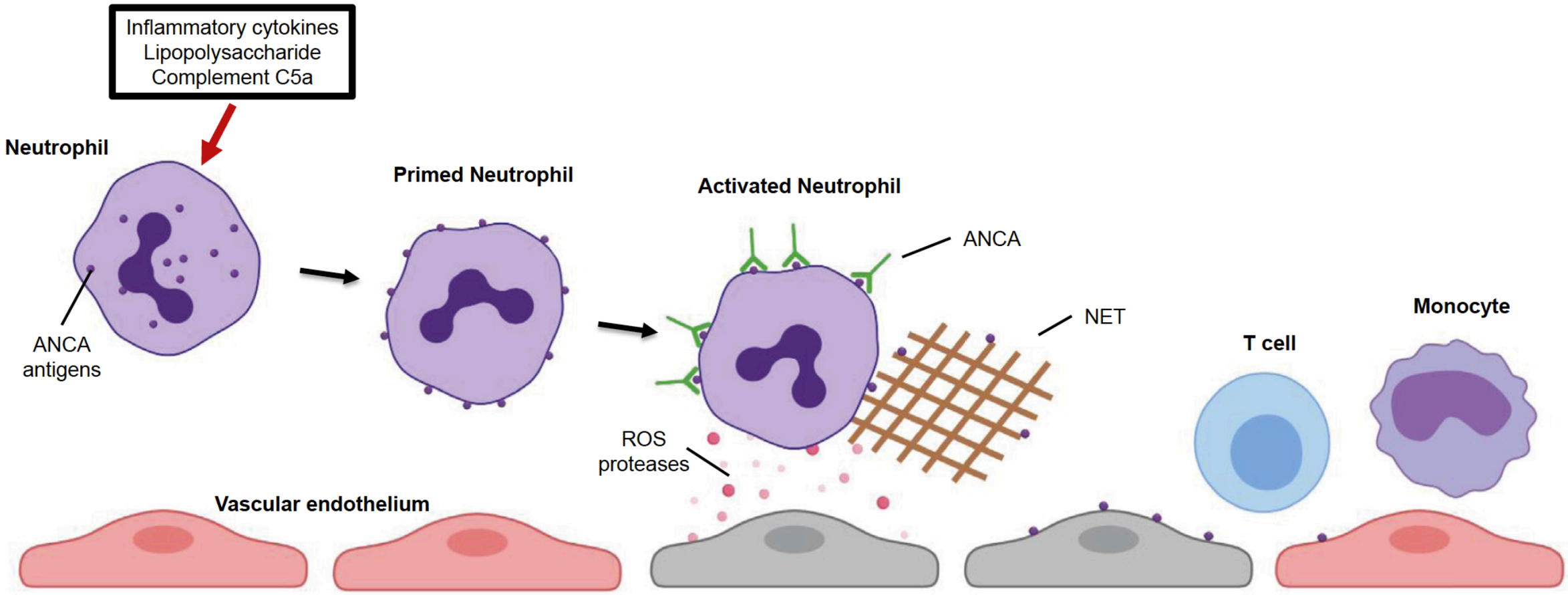
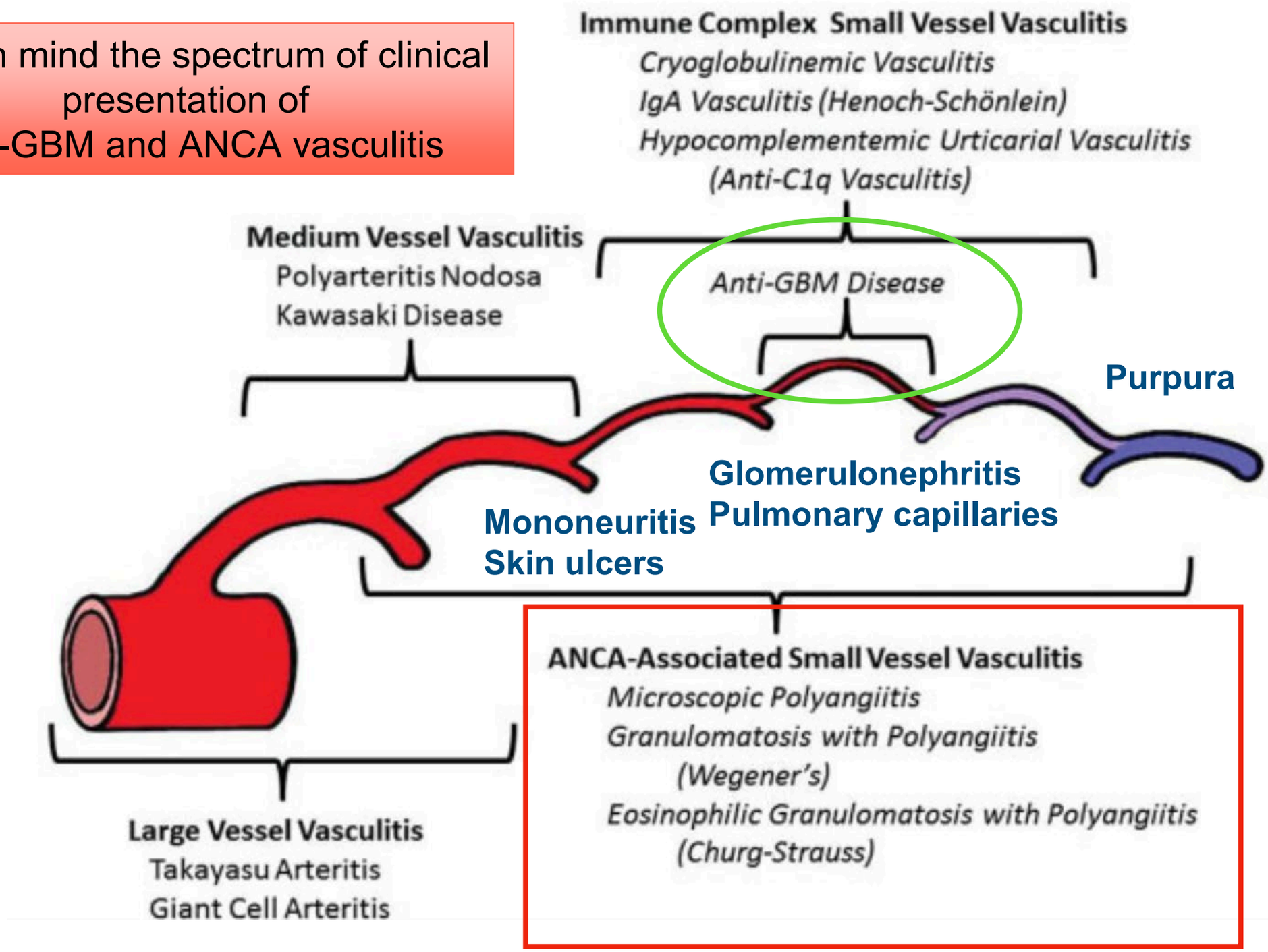


Figure 1. Pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA autoantigens (proteinase 3 [PR3] and myeloperoxidase [MPO]) are normally sequestered in the primary granules of neutrophils. Infection or other environmental stimuli result in neutrophil priming, with movement of PR3 and MPO to the cell surface. Binding of ANCA to these autoantigens results in activation of neutrophils, which adhere to vascular endothelium. Neutrophil degranulation leads to the release of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), damaging the endothelium. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes augmenting tissue injury. Drawings created with BioRender.

JA Jefferson, et al, AJKD, 2020

Chapel Hill Consensus Conference 2012

Keep in mind the spectrum of clinical presentation of anti-GBM and ANCA vasculitis



Arthritis & Rheumatism, January 2013

PR3 and MPO are the ANCA antigens

Table 1. Frequency of ANCA Positivity in Different Conditions

	PR3-ANCA (mostly cANCA)	MPO-ANCA (mostly pANCA)	Other
ANCA-Associated Vasculitis			
GPA	75%	20%	5% ANCA negative
MPA	30%	60%	10% ANCA negative
EGPA	5%	45%	50% ANCA negative
Renal-limited vasculitis	10%	80%	10% ANCA negative
Drug-induced vasculitis	10%	90%	Often high titer, dual positivity for MPO and PR3
Nonvasculitis Conditions			
Systemic lupus	2%	10%	10% atypical ANCA
Endocarditis	15%	5%	
Inflammatory bowel disease	Negative	Negative	Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%)
Primary sclerosing cholangitis	Negative	Negative	Atypical ANCA, various antigens: 60%-80%
Cystic fibrosis	Negative	Negative	Atypical ANCA pattern, directed against BPI (90%)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BPI, bactericidal/permeability-induced protein; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3.

Cocaine, anti-thyroid drugs, TNF inhibitors, hydralazine, plus others

JA Jefferson, et al, AJKD, 2020

Cyclophosphamide and Rituximab are cor

Table 1 Randomized controlled trials for induction of remission in antineutrophil cytoplasmic antibody associated vasculitides with renal involvement and cyclophosphamide-sparing regimens

Name of the Trial (number of patients)	Inclusion criteria	Treatment groups (drug dose)	Primary end points	Outcome
CYCLOPS[7] (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150–500 μmol/L (1.7- 5.66 mg/dL)	Intravenous pulse CYC (15 mg/kg) *vs* Daily oral CYC (2 mg/kg)	Remission, Time to relapse	Pulse CYC not inferior to oral CYC Less leucopenia and trend towards more relapses with pulse CYC
CORTAGE[8] (104)	New diagnosis of MPA, GPA, EGPA, PAN and age > 65 yr	Rapid CCS tapering and reduced-dose intravenous pulse CYC (500 mg) *vs* Standard intravenous pulse CYC (500 mg/m²)	Severe adverse events	Less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates
RAVE[10] (197)	New or relapsing GPA or MPA creatinine ⩽ 353.6 μmol/L (4 mg/dL)	RTX (4 × 375 mg/m² infusions) *vs* Daily oral CYC	Complete remission and cessation of CCS at 6 mo	RTX not inferior to oral CYC, RTX better in patients with relapse than after first diagnosis
RITUXVAS[11] (44)	New diagnosis of AAV and severe renal involvement	RTX (4 × 375 mg/m² infusions) plus two intravenous pulses of CYC *vs* intravenous pulse CYC only	Sustained remission	RTX not inferior to pulse CYC

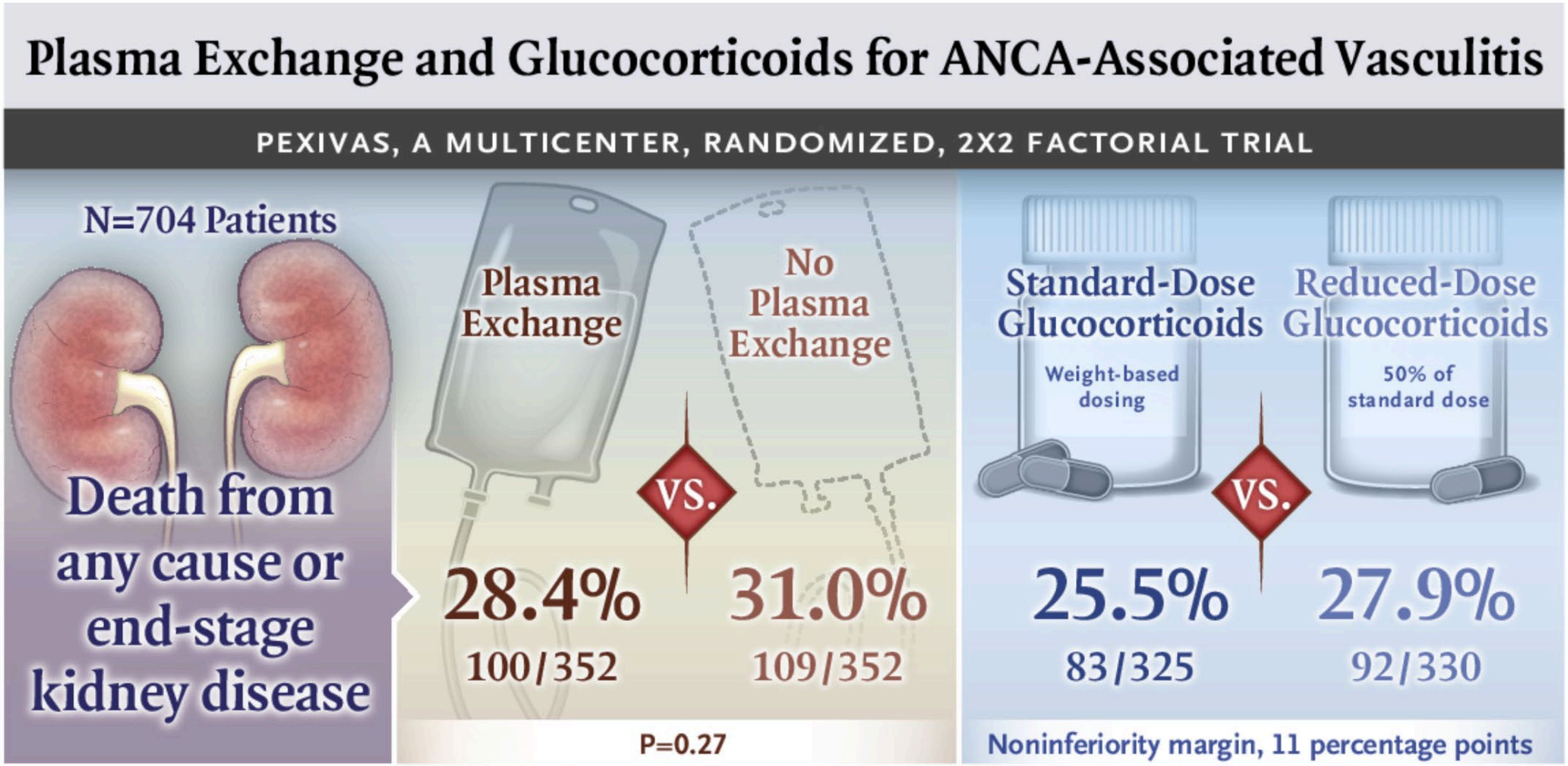
AAV: Antineutrophil cytoplasmic antibody associated vasculitides; CYC: Cyclophosphamide; RTX: Rituximab; CCS: Corticosteroids; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; PAN: Polyarteritis nodosa.

**** IMPROVE Trial 2010** **CYC induction —> MMF vs. AZA maintenance** ***MMF less effective than AZA***

World J Nephrology, May 2018

PEXIVAS Trial
A perPLEXing ANCA Treatment

704 patients
95 centers
16 countries



M. Walsh et al. 10.1056/NEJMoa1803537
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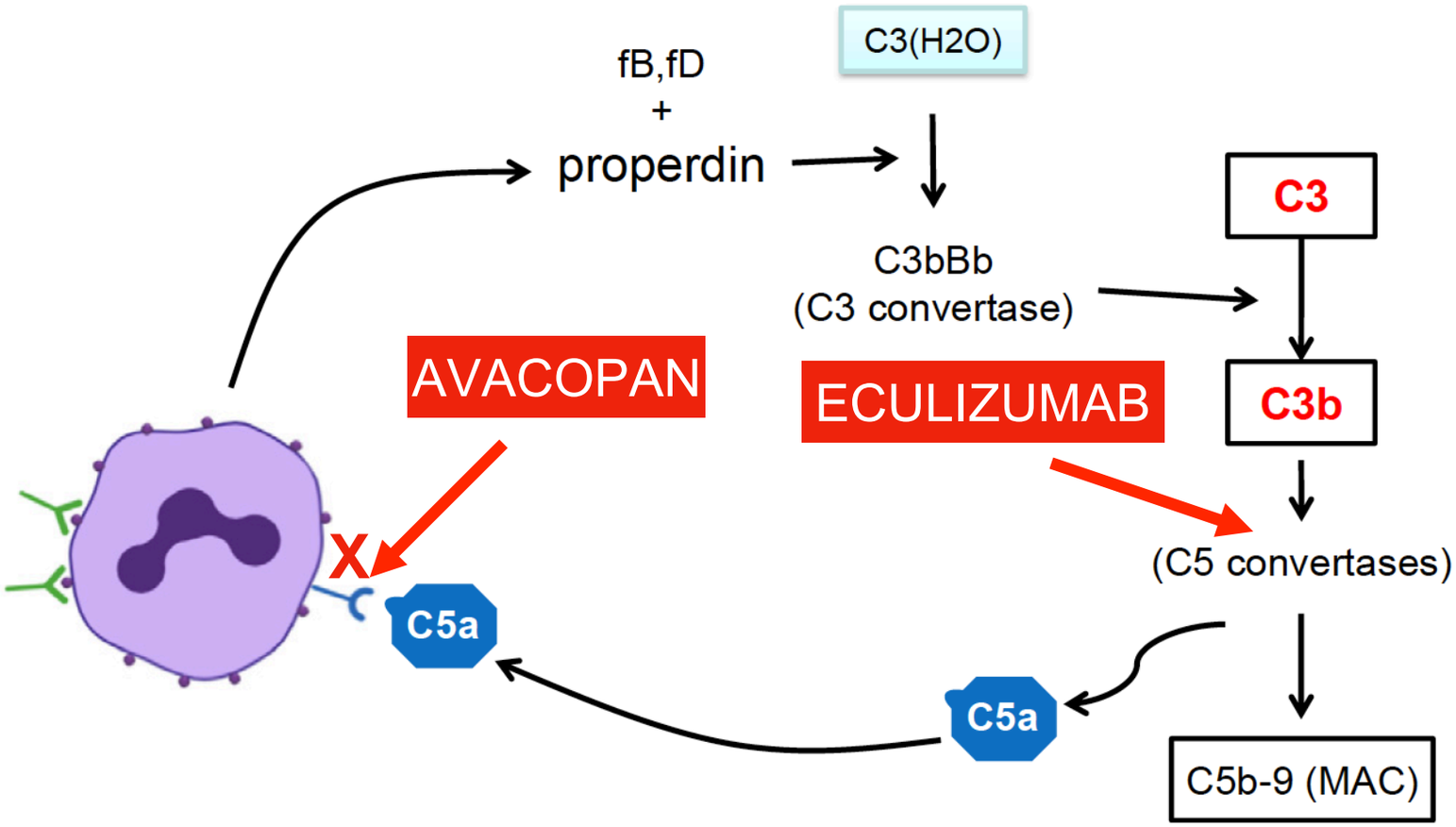
Avacopan treatment for ANCA disease
C5a receptor antagonist

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne, Annette N. Bruchfeld, Lorraine Harper, Matthias Schaier, Michael C. Venning, Patrick Hamilton, Volker Burst, Franziska Grundmann, Michel Jadoul, István Szombati, Vladimír Tesař, Mårten Segelmark, Antonia Potarca, Thomas J. Schall and Pirow Bekker; for the CLEAR Study Group

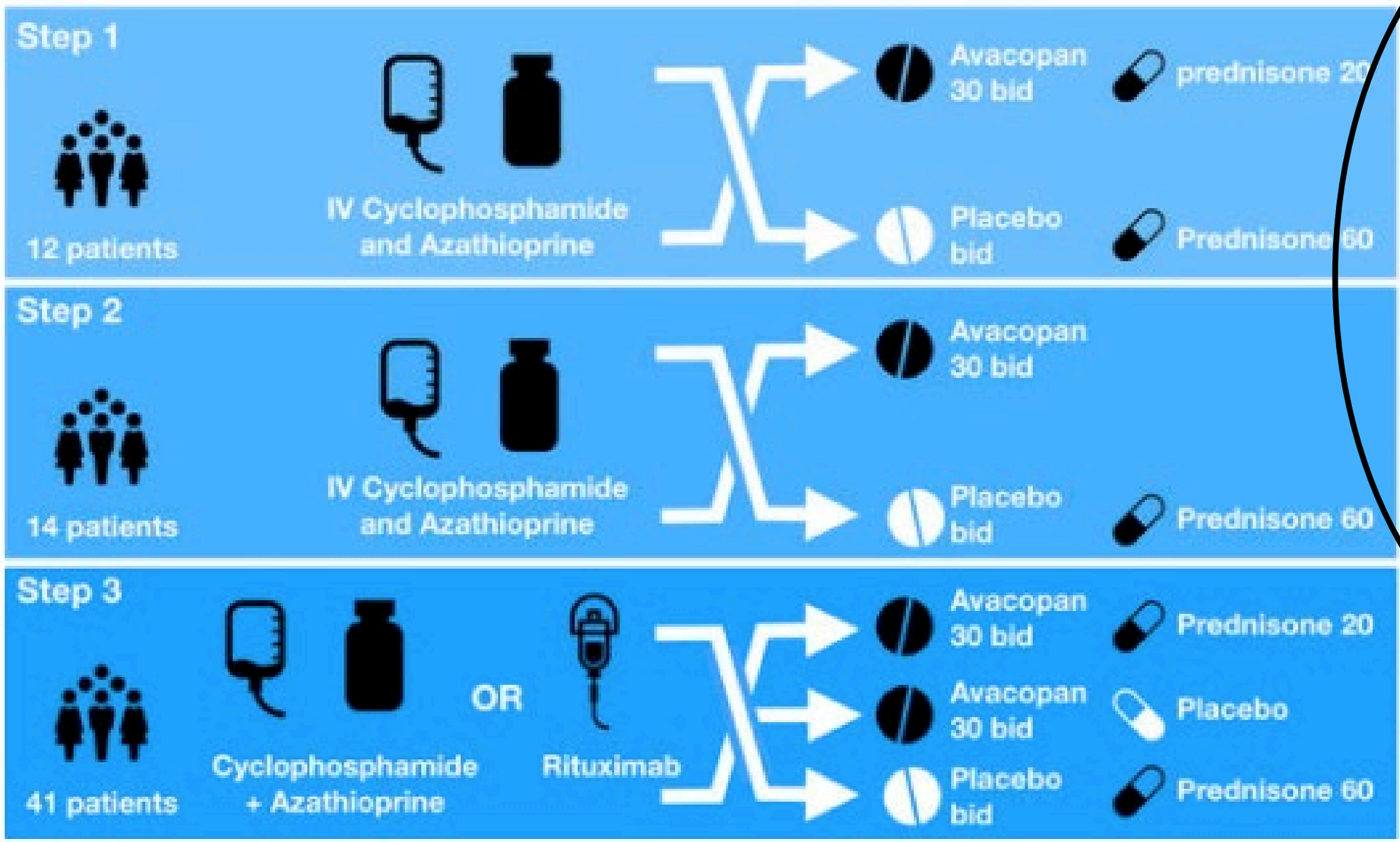
JASN September 2017, 28 (9) 2756-2767; DOI: https://doi.org/10.1681/ASN.2016111179



Avacopan for Steroid Avoidance in ANCA-Associated Vasculitis

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis.
Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Et al. JASN 28; 2017.

#NephJC



Results

≥50% improvement in BVAS score

Avacopan 30 bid	81%
Placebo bid + prednisone 60	86%
Prednisone 60	70%

Both avacopan groups met noninferiority criteria

Adverse effects

incidence of all adverse events and grade 3 or greater adverse events was similar across groups

Dual-positive anti-GBM + ANCA antibodies

- ~30% of anti-GBM test positive for ANCA (almost *MPO exclusively*)
- Speculative mechanism: *ANCA activity exposes sequestered GBM epitopes*
- **Severe disease at presentation**, like anti-GBM with early morbidity and mortality
- **Long term course involves relapses** similar to ANCA associated vasculitis

Epilogue

- 64 year old teacher. No PMH, no medications. Quit smoking. Cr 3.8 mg/dl.
- Renal biopsy showed 16/17 gloms with crescents and necrosis with **linear staining of GBM**
- Tx: Cyclophosphamide, steroids, plasmapheresis
- Cr 3.8 —> 7.5 mg/dl
- ESRD with HD now on CCPD
- **Anti-GBM Ab is now negative**
- Nearing a living donor kidney transplant

- 71 year old retired presents with migratory arthralgia, fatigue and an urticarial rash. Cr 3.4 mg/dl
- Renal biopsy showed 66 gloms (80% necrotizing crescents) with **negative immunofluorescence Ab staining**
- Tx: Rituximab + steroids (she tolerated steroids poorly due to anxiety)
- Creatinine 3.4 —> 1.1 mg/dl
- **pANCA normalized, then relapsed in second year with Cr 3.1 mg/dl**
- Re-Tx: Rituximab + steroids
- Cr 2.4 —> 1.2 mg/dl

Key Points

- Pulmonary-renal syndromes may present with vague or multiple system symptoms
- Check urinalysis and renal biopsy urgently, if possible
- Anti-GBM is typically a “single storm” syndrome not requiring long term maintenance immunosuppression and low transplant recurrence
- ANCA vasculitis with renal involvement presents as RPGN with organ and potentially life-threatening symptoms
- Medications can lead to ANCA antibody formation

Key Points

- First line therapy {cyclophosphamide vs rituximab} + steroids
- PR3 ANCA relapse more frequently than MPO ANCA
- Recurrence of ANCA with previously cleared ANCA antibody is associated 75% relapse
- Avacopan (C5a receptor antagonist) is an emerging non-steroid option with demonstrated non-inferiority to high dose steroids in ANCA patients

Additional References

Anti-Glomerular Basement Membrane Disease;
CJASN July 2017, 12 (7) 1162-1172;
DOI: https://doi.org/10.2215/CJN.01380217

ANCA-Associated Vasculitis: Core Curriculum 2020
Am J Kidney Dis. 75(1): 124-137;
DOI: 10.1053/j.ajkd.2019.04.031

Thank you for all you do ! Be well, be safe!