BRIGHAM AND WOMEN'S HOSPITAL

The Lung Center

Bells at the Fire Station

Kate Phillips MD
Pulmonary and Critical Care Fellow

HARVARD MEDICAL SCHOOL

Disclosures

- I have no conflicts of interest to disclose

HPI

30 yo man presents with hemoptysis x 2 weeks

- Associated symptoms:
  - Cough x 4 weeks
  - Hemoptysis, now ~1tsp x 2 weeks
  - Nightly fevers up to 102 F x 2 weeks
  - Diffuse myalgias
  - Fatigue
  - Dyspnea on exertion
  - Night sweats
  - 10-15lb unintentional weight loss

HPI

- Bilateral eustachian tube dysfunction (2 mo prior)
- L chronic otitis media and L Bell's palsy (1 mo prior)
  - S/p prednisone 60mgx1 wk followed by taper (total 3 wk) and augmentin x14 d with return of facial nerve function.
  - Fevers started shortly after prednisone taper complete
- Denies chest pain, LE edema, rash, abdominal pain, diarrhea/constipation, abdominal pain, dysuria, hematuria (did note dark urine), joint swelling, focal weakness or numbness (aside from L facial nerve), headaches, nasal/oral/genital lesions. Rare epistaxis. Denies h/o VTE.

HPI

- PCP evaluation: Covid negative, CXR c/w multifocal pneumonia, outpatient azithromycin w/o relief
- Hospitalized at OSH x4 days for pneumonia with 2LNC requirement, treated with IV antibiotics. Ruled out for PE.
- Re-presented to ER 2 d later
- Received pre-hospital solumedrol 125mg

History

Past Medical History:

- GERD
- Recent ENT issues as per HPI

Past Surgical History:

- R knee patellar tendon repair
- Bilateral eustachian tubes and L myringotomy

Medications:

- Flonase
- Tobradex ear drops

Social History:

- Never smoker, no vaping or drug use
- Lives with wife and two dogs
- Works as a firefighter, denies exposure to active fire for >1 mo

Family History:

- Lymphoma – father
- RCC – mother
- No family hx of pulmonary nor autoimmune disease

Initial Exam

T 37.2 HR 125 BP 100/50 SpO2 98% 10LNC

- General: ill appearing, diaphoretic, pale
- HEENT: No nasal polyps or oral ulcers
- Cardiac: tachycardic, normal S1/S2, no murmurs appreciated
- Pulm: tachypneic with increased WOB on arrival -> improved on HFNC 60% 30lpm. Able to speak in short sentences. Crackles bilaterally. Coughing up dark blood
- Abd: soft, nontender, nondistended
- Ext: warm, no edema, no e/o synovitis
- Neuro: alert and oriented, no focal deficits, no facial weakness appreciated
- Skin: no rash

Initial Labs

Cr 1.2 (baseline 0.9-1.07)
UA – 3+ blood, 1+ protein
UMIC – 23 RBC, 10 WBC/hpf

Hgb 7.6 (from 12.9 2 months prior)
WBC 10.9 (84% PMN, 3% eos)
Plt 541

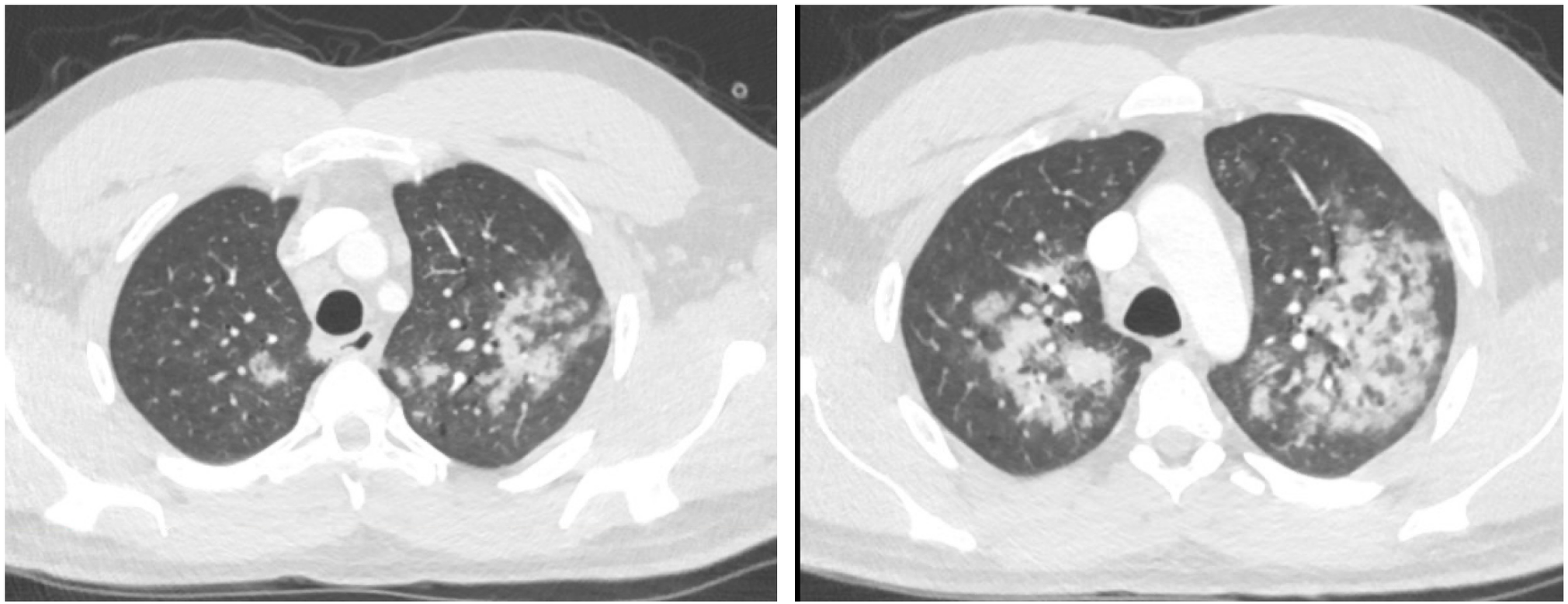
D bili 0.6, albumin 2.8, other LFTs wnl
Lactic Acid 1.1
CK wnl

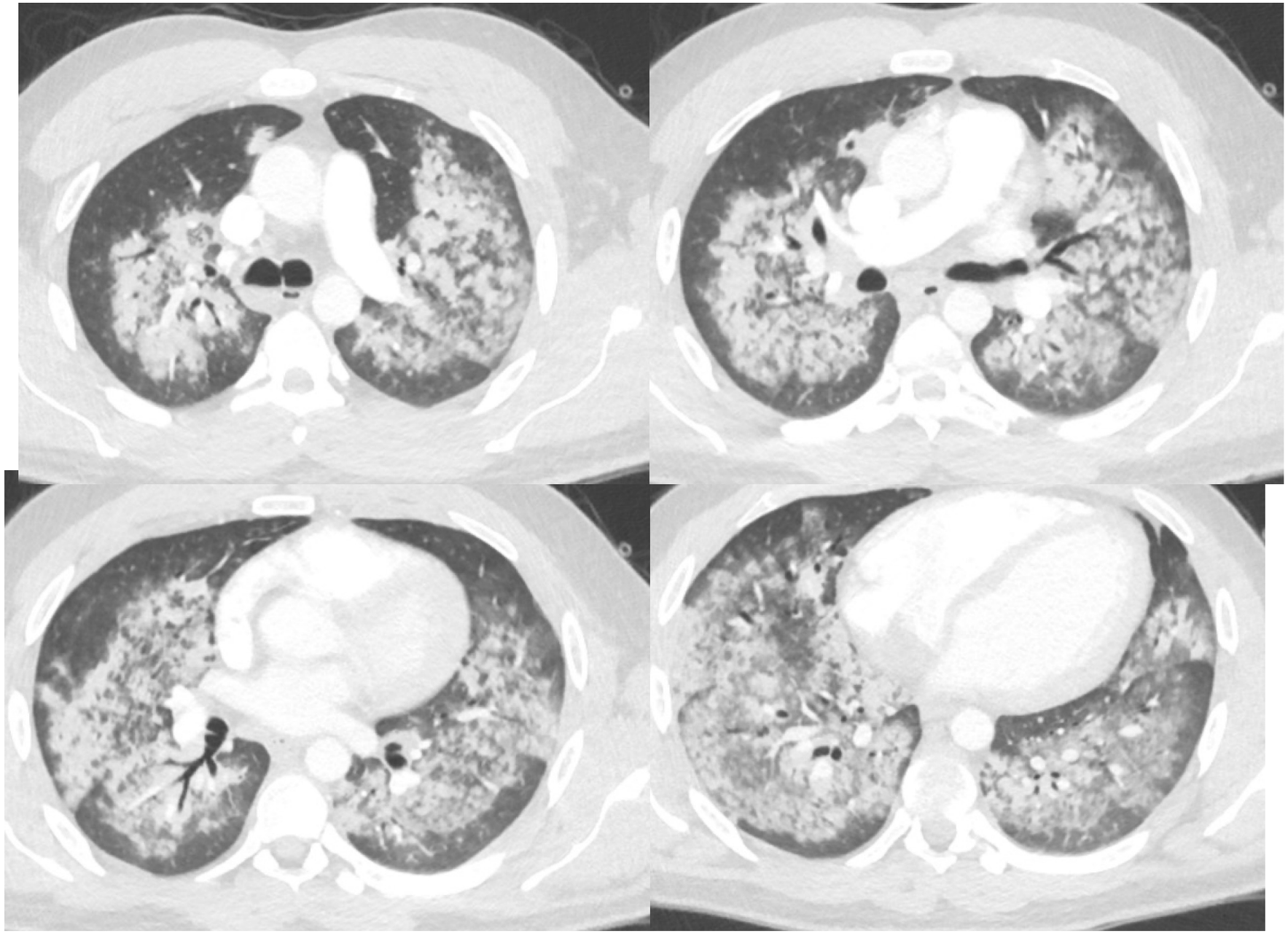
INR 1.4, fibrinogen 852

CRP above assay, ESR 88

Covid negative x2; respiratory viral panel negative
Urine strep/legionella negative

EKG – sinus tachycardia
POCUS - unremarkable





Differential Diagnosis?

Additional Lab Results

- C3, C4 normal
- RF 22
- dsDNA, Sm, ANA RNP, SSA, SSB negative
- Cryoglobulins negative
- APLAS panel negative
- Hep B/C, HIV, antistreptolysin O, T spot, lyme titers negative
- Urine strep/legionella negative
- Serum beta D glucan and galactomannan negative
- ER blood cx ¼ Staph epi, follow up blood cx NG

Additional Lab Results

- C-ANCA positive 1:1280
- PR3 above assay (>2500)
- MP3 negative
- GBM negative

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%)

Geetha et al. ANCA Associated Vasculitis: Core Curriculum 2020. AJKD.

Table 1 | **Comparison of the specificity and sensitivity for different ANCA assays**

Study population	IIF		Immunoassay	
	C-ANCA	P-ANCA	PR3-ANCA	MPO-ANCA
Specificity in disease controls				
Hagen *et al.* (*n* = 184)	95%	81%	86–89%	91%
Damoiseaux *et al.* (*n* = 924)	97–98%	81–96%	98–99%	96–99%
Sensitivity in 'newly diagnosed' GPA				
Hagen *et al.* (*n* = 97)	64%	21%	65–67%	24%
Damoiseaux *et al.* (*n* = 186)	65–77%	11–15%	77–81%	9–12%
Sensitivity in 'newly diagnosed' MPA				
Hagen *et al.* (*n* = 44)	23%	58%	25–27%	58%
Damoiseaux *et al.* (*n* = 65)	5–6%	85–89%	5–9%	71–88%

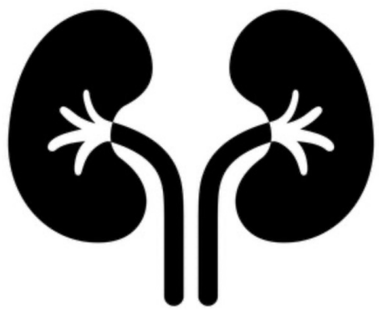
Likelihood ratio of test positivity increases with higher titers for MPO and PR3

Bossuyt et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017.

Discussion Questions

1. Would you send patient for a biopsy?
   a) Yes
   b) No

2. If pursuing, where would you biopsy?

A 

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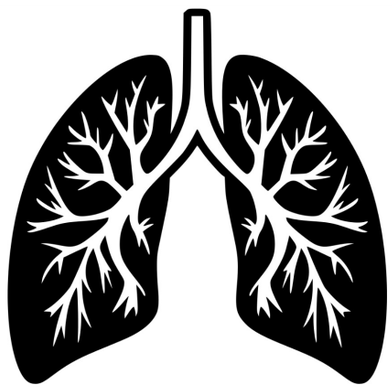
C 

	MPA	GPA	EGPA
Histology	Necrotizing vasculitis without granulomas	Necrotizing granulomas and vasculitis	Eosiniophilic tissue inflammation and vasculitis
	small to medium vessel vasculitis		
Prodrome	Constitutional prodrome x weeks		Years prodrome of allergic rhinitis, asthma
ANCA	Usually a/w MPO	Usually a/w PR3	~50% ANCA negative
Renal involvement	~80%		25%
Cutaneous involvement	~30%	~35%	~50%
Pulmonary involvement	25-55%. Most commonly alveolar hemorrhage. Ccan develop fibrosis	Nodules (cavitary) (40-70%), alveolar hemorrhage (~30%)	Asthma, fleeting infiltrates

	MPA	GPA	EGPA
HEENT/Upper airway involvement	Less common - mild epistaxis, sensorineural hearing loss	**90%** - nasal ulcers, "saddle nose" deformities, conductive/sensorineural hearing loss, subglottic stenoses (~20%), retro-orbital masses	Nasal polyps, chronic allergic rhinitis, conductive hearing loss, chronic otitis media
Neurologic involvement	~70%, most commonly mononeuritis multiplex or distal symmetric polyneuropathy. CNS involvement less common	~10%, most commonly cranial neuropathies	Up to 70%, usually mononeuritis multiplex
Other organs	HEENT lesions/granulomas much more common in GPA		Myocardial involvement is feared complication

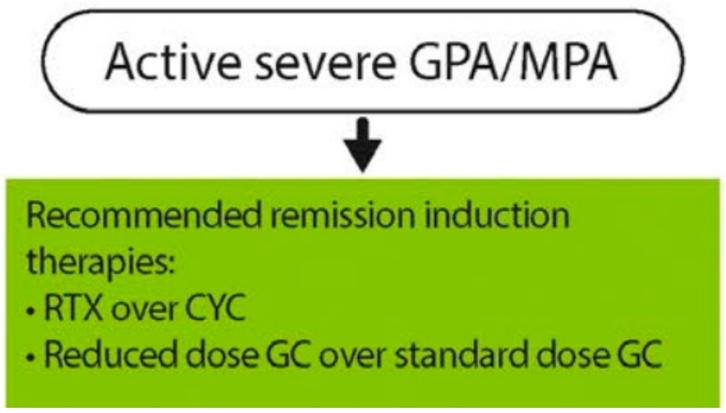
Micheletti et al. Cutaneous Manifestations of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Rheumatol. 2020.
Geetha et al. ANCA Associated Vasculitis: Core Curriculum 2020. AJKD.
Chung et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis . Arthritis Rheumatol. 2021
Seo P et al. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med 2004.
Chung et al. Microscopic Polyangiitis. Rhuem Dis Clin North Am 2010.
Egan A et al. Eosinophilic Granulomatosis with Polyangiitis Renal Disease. Abstract from Proceedings of the ASN 2019.
Ananthakrishnan et al. Wegener's Granulomatosis in the Chest: High-Resolution CT Findings. AJR 2009.

Discussion Questions

3. How would you treat?
    a) High dose glucocorticoids and rituximab
    b) Plasma exchange
    c) IV cyclophosphamide
    d) High dose glucocorticoids

RAVE Trial

- Double blind RCT, 200 MPA+GPA patients
- Excluded: Cr >4, alveolar hemorrhage requiring intubation
- Ritux+GC vs cyc+GC
- Rituximab noninferior
  - Prespecified subgroup: ritux possibly better for relapsing disease
- Given toxicities/tolerance, ACR conditionally recommends rituximab



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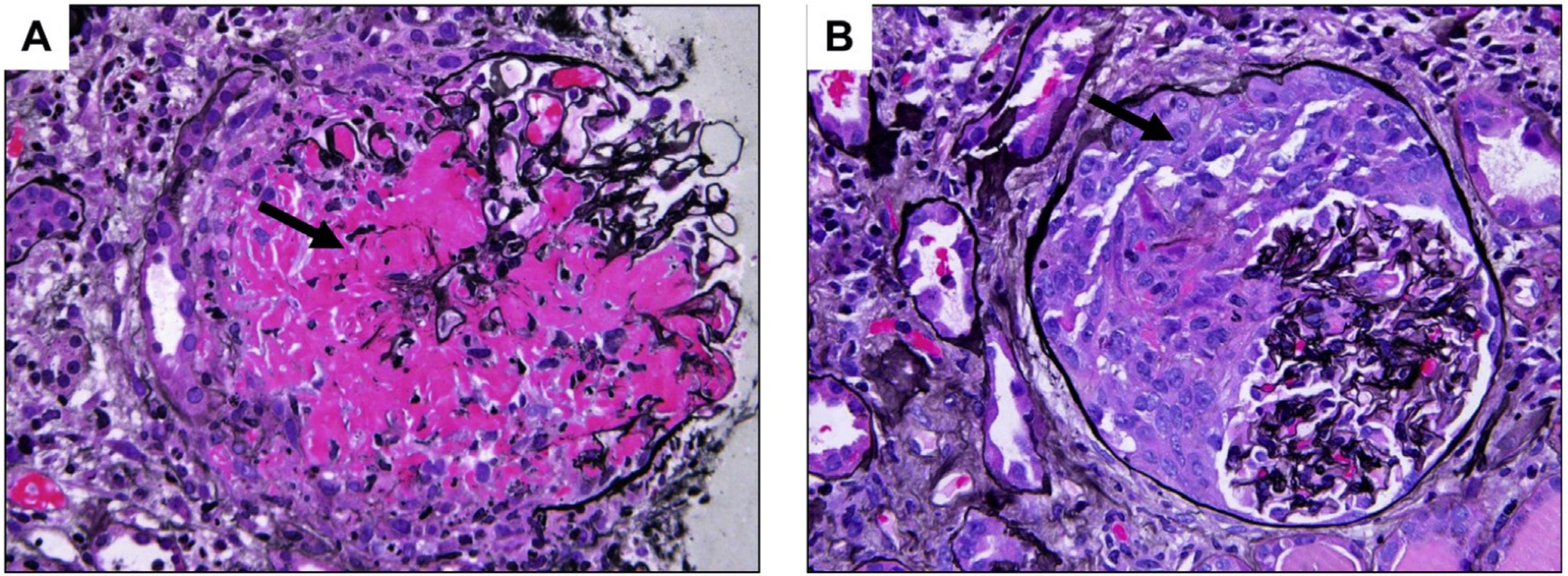
Stone J et al Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. NEJM 2010.
Jones et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. NEJM 2010.

Hospital Course

- Pulse dose steroids 1g x5d followed by prednisone 1mg/kg/d with taper
- Started rituximab
- Weaned to 4LNC
- Rising Cr (1.5) and persistent RBC in urine on hospital day 6 despite treatment
- Renal biopsy: “cellular crescents, necrotizing lesions in most glomeruli, RBC casts, some tubular injury, no immune complex deposits seen”

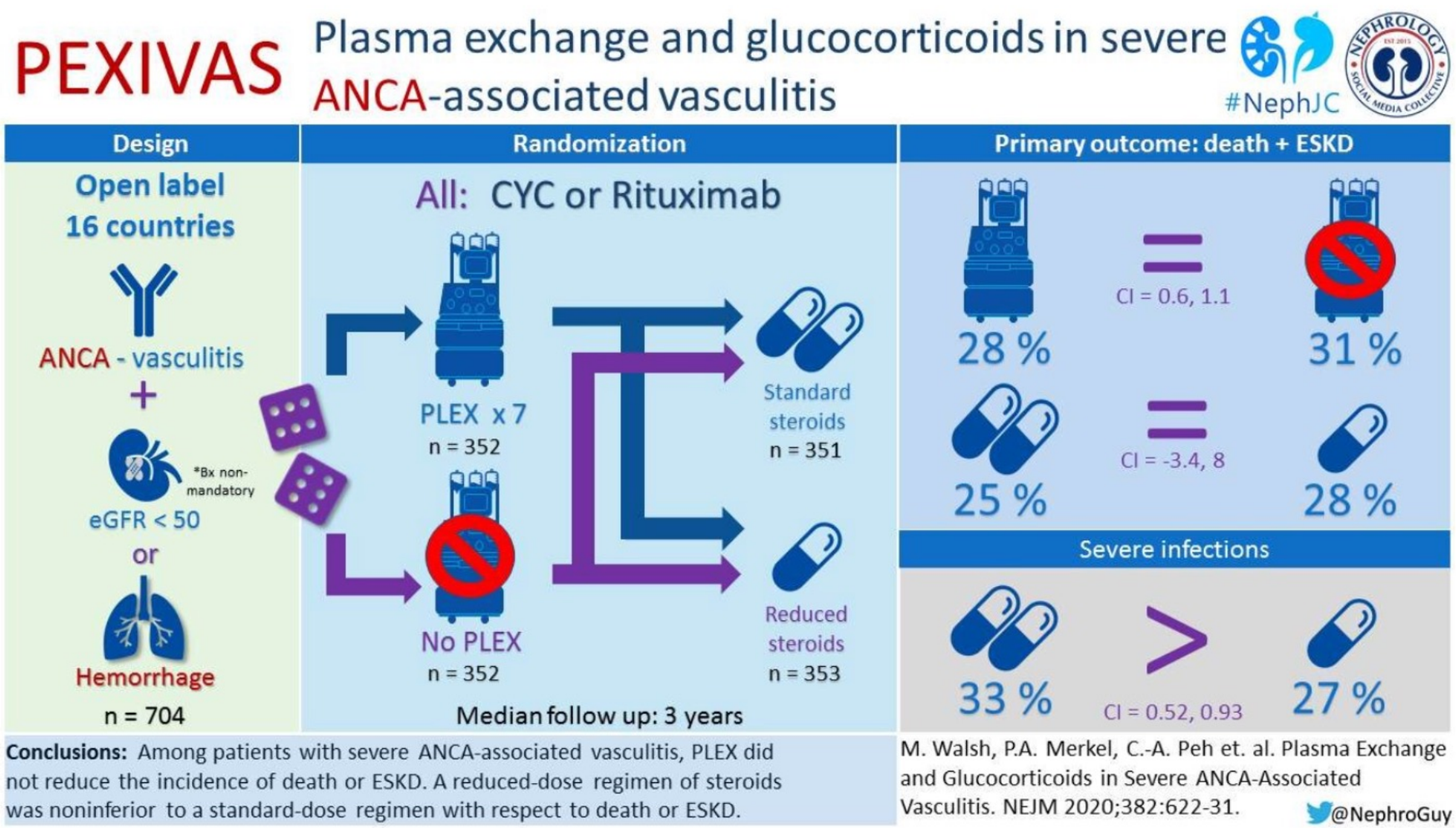


Geetha et al. ANCA Associated Vasculitis: Core Curriculum 2020. AJKD.

Hospital Course (continued)

- Started plasma exchange
- Cr peak 2.5, subsequently downtrended
- Weaned off O2
- Started avacopan prior to discharge

Plasma Exchange for AAV

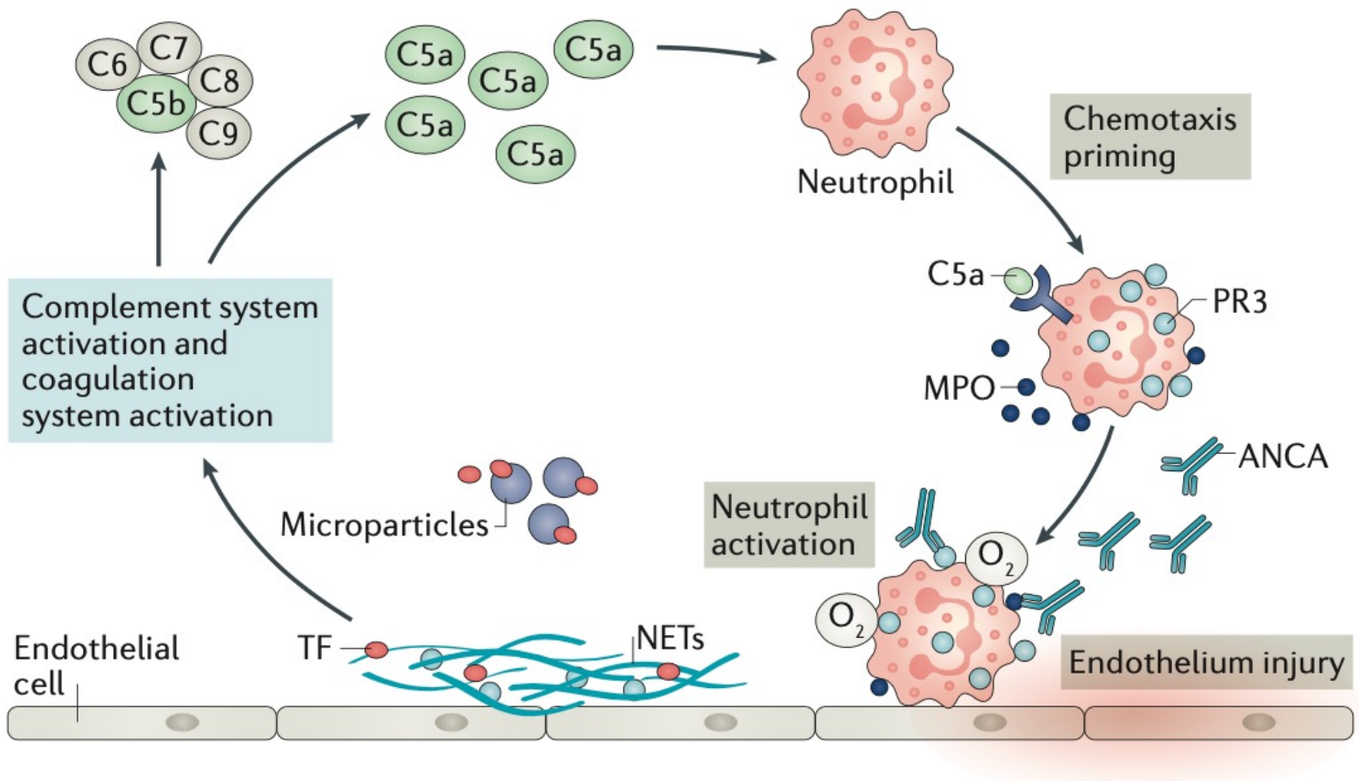


Plasma Exchange for AAV

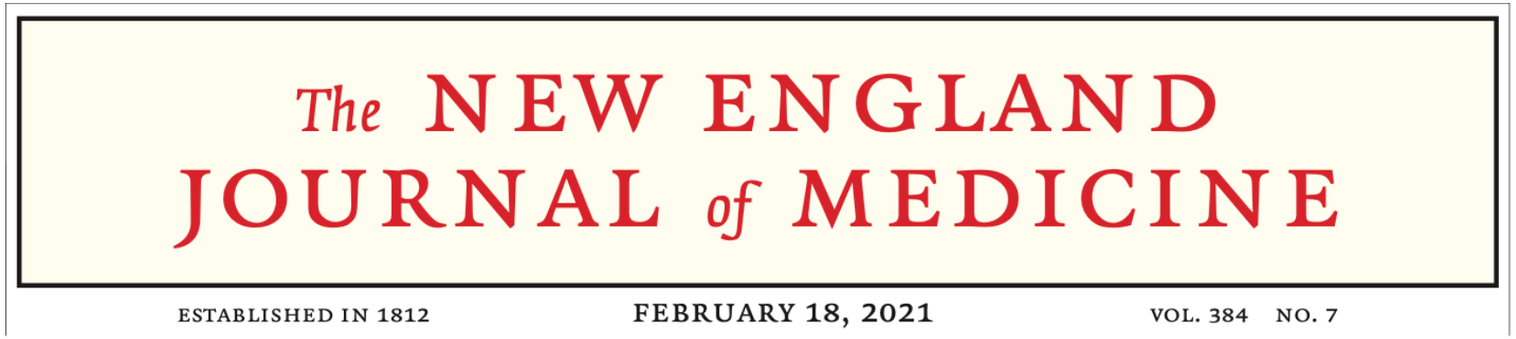
- Single center historical cohort study in patients with AAV and DAH
  - Plasma exchange was not associated with 6 month remission compared to standard therapy
  - However, patients who received plasma exchange had more acute baseline characteristics (more renal failure, mechanical ventilation)
- 2022 meta-analysis: reduced risk of ESKD at 12 months with plasma exchange [RR 0.69; 0.39-0.98] and increased risk of serious infection [RR 1.27; 1.08-1.49]

Cartin-Ceba et al. Diffuse Alveolar Hemorrhage Secondary to Antineutriphil Cytoplasmic Antibody-Associated Vascultiits: Predictors of Respiratory Failure and Clnical Outcomes. ACR 2016.
Jayne et al. Randomized **Trial** of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis. JASN 2007.
Walsh M et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int 2013.
Walsh et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ 2022.

Avacopan



Chen et al. Complement in ANCA-associated vasculitis: mechanisms and implications for management. Nat Rev Nephrol 2017.



Avacopan for the Treatment of ANCA-Associated Vasculitis

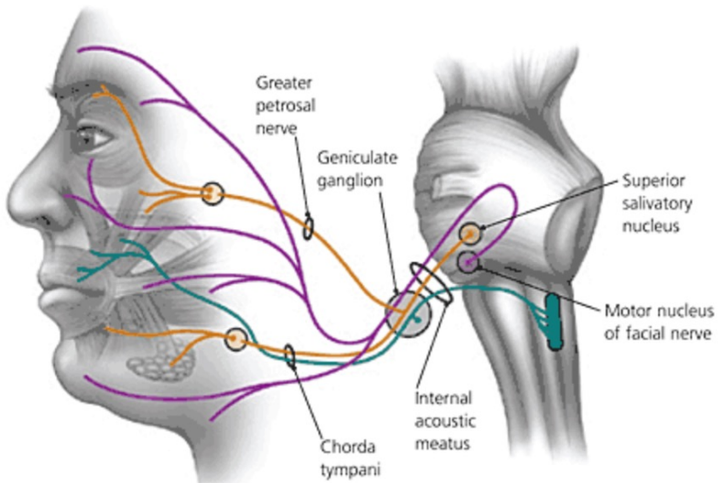
David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

- C5a receptor antagonist
- Noninferior to prednisone for remission at 26 weeks; superior to prednisone for sustained remission at 1 year

High yield points

- GPA classically associated with granulomatous lesions, HEENT lesions
- AAV can cause mononeuritis or cranial nerve involvement
- Anti-GBM disease can be present along with AAV
- Renal involvement common in AAV, often presents as a rapidly progressive GN
- Avacopan is a new treatment for AAV that targets complement pathway
- (Be aware of pre-hospital steroid administration in MA)
- Sometimes patients read the textbook!

Discussion



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