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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Inaugural National Conference

December 3 – 5, 2020

VIRTUAL CONFERENCE

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Vasculitis

Naomi Amudala, RN, FNP-BC
Penn Vasculitis Center
University of Pennsylvania
Philadelphia, PA

Katie Springer PA-C
Northwestern Medical Group
Lake Forest, IL

Disclosure

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Faculty Disclosures

Naomi Amudala, RN, FNP-BC:

- There are no financial relationships to disclose

Katie Springer, PA-C:

- Speaker’s Bureau: Amgen

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Vasculitis Updates and Review

Naomi Amudala, RN, FNP-BC
Penn Vasculitis Center
University of Pennsylvania
Philadelphia, PA
vasculitis.upenn.edu

Case Presentation

34 year old woman presents to your clinic with the following symptoms:

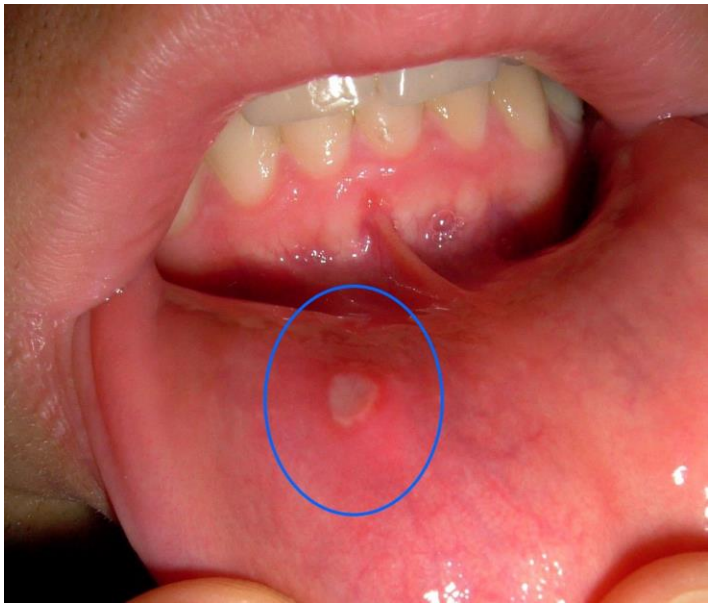
- Multiple sinus infections
- Migratory joint pain
- Oral ulcers
- Shortness of breath
- Couple episodes of blood streaked sputum

Physical Examination

Vital Signs: weight 124 pounds, temp 98.9 degrees F, blood pressure 122/74, HR 108, and SpO2 94% on room air

Relevant Findings:

- Oral ulcer on inner lower lip
- Extensive bloody nasal crusting in the nasopharynx with maxillary sinus tenderness
- Lung sounds are diminished in the bases bilaterally
- Left knee is warm and tender to palpation. + popliteal fullness



Investigational Studies – Laboratory

Creatinine *0.64 - 1.27 mg/dL*	0.79

SEDIMENTATION RATE *0 - 20 mm/h*	16
CRP Non-Cardiac *<=0.80 mg/dL*	0.50

White Blood Cells *4.0 - 11.0 THO/uL*	12.3 (H)
Red Blood Cells *4.30 - 5.80 MIL/uL*	4.87
Hemoglobin *13.5 - 17.5 g/dL*	14.1
Hematocrit *40 - 52 %*	42
RDW *11.5 - 14.5 %*	14.1
MCH *27 - 33 pg*	29
MCHC *31 - 36 g/dL*	34
MCV *80 - 100 fL*	86
Platelets *150 - 400 THO/uL*	303

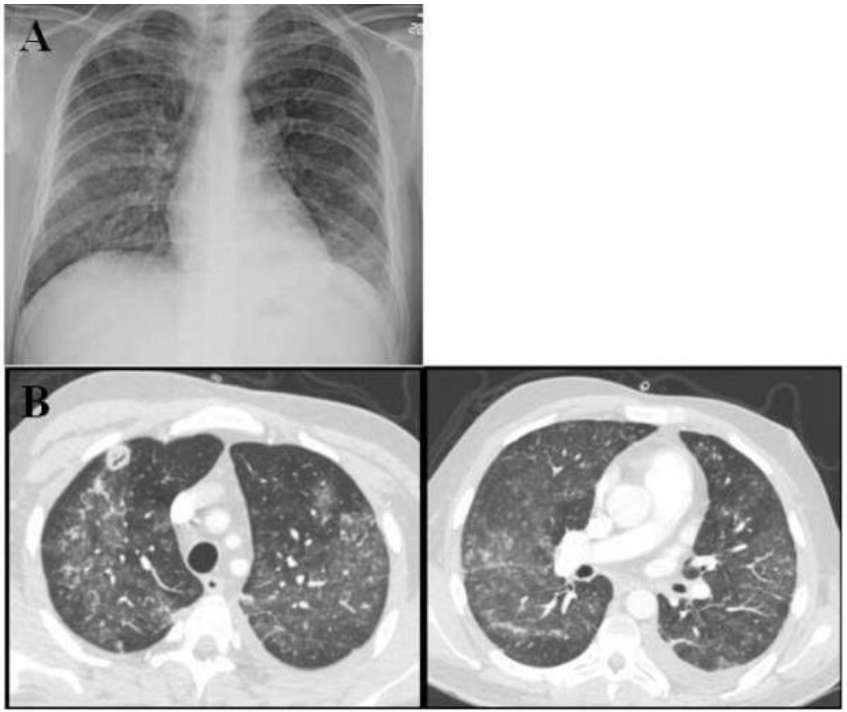
UA Color *<=Dk Yel*	Yellow
UA Appearance *<= Clear*	Clear
UA Glucose *Negative mg/dL*	Negative
UA Bilirubin *Negative mg/dL*	Negative
UA Ketones *Negative mg/dL*	Negative
UA Specific Gravity *1.010 - 1.030*	1.014
UA Blood *Negative mg/dL*	Moderate (A)
UA pH *5.0 - 7.0*	6.0
UA Protein *Negative mg/dL*	100 (A)

Component *Latest Ref Rng & Units*	10/18/2019
UA RBC *0 - 2 /hpf*	20-50 (A)
UA WBC *0 - 2 /hpf*	5-10 (A)
BACTERIA *none-rare /hpf*	Occasional (A)
SQUAMOUS EPITHELIAL *0 - 20 /hpf*	0-2
MUCUS *none - few /hpf*	Few

Investigational Studies – Laboratory

ANCA SLIDE EVAL	C-Anca Abnormal	Negative	Final
SERINE PROTEASE 3 AN	27 High	0 - 20 unit(s)	Final
MYELOPEROXIDASE ANTI	4	0 - 20 unit(s)	Final
Reference range Anti MPO: 0 - 20 U NEGATIVE.			

Investigational Studies – Imaging



Chest x-ray: Bilateral patchy infiltrates

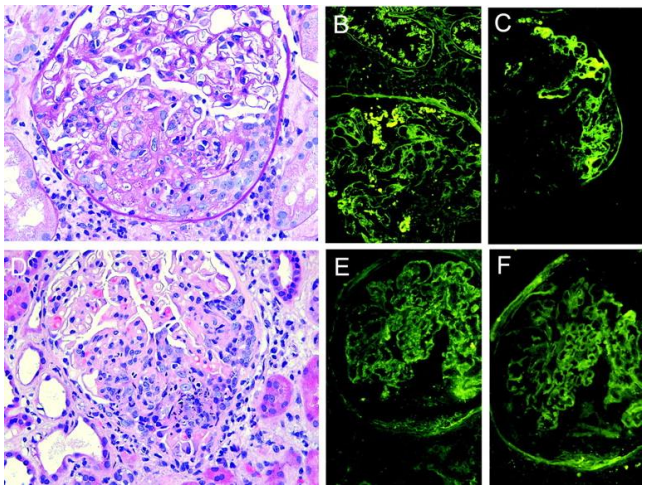
Chest CT WO Contrast: Bilateral ground glass infiltrates with necrotizing nodule

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483562/bin/nihms-400475-f0002.jpg

Investigational Studies – Pathology

Renal Biopsy:

Necrotizing crescentic glomerulonephritis with few/absent immune complexes on immunofluorescence



www.researchgate.net%2Ffigure%2FHistopathologic-findings-in-atypical-anti-GBM-disease-A-C-Patient-2-A-IgG_fig2_298433055&psig=AOvVaw0tSo-7vAHbN8N_S1Y-qWNJ&ust=1604973901715000&source=images&cd=vfe&ved=2ahUKEwiZ78brr_TsAhWLbTABHV08CkAQr4kDegUIARCmAQ

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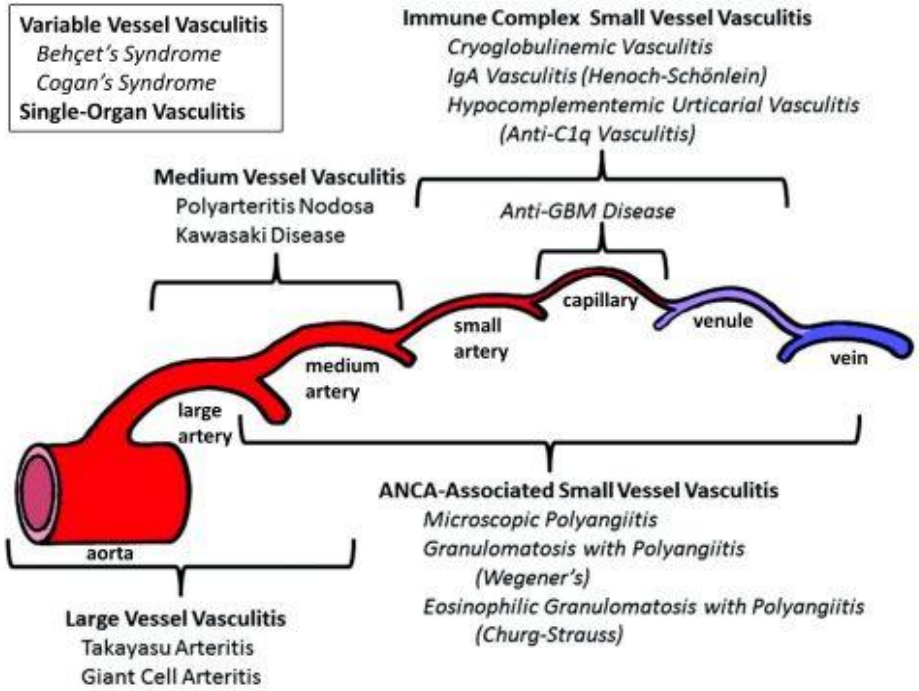
What Is ANCA-Associated Vasculitis (AAV)?

Vasculitis Classification

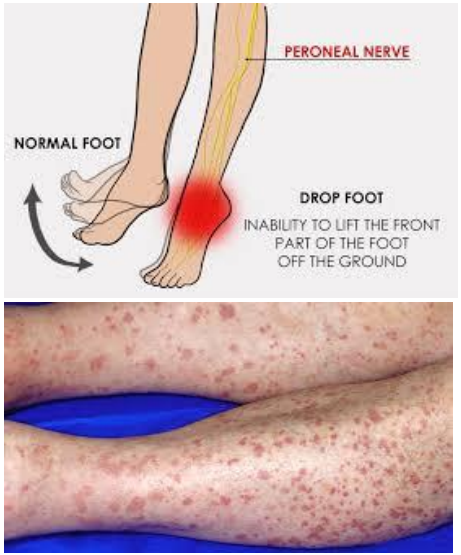


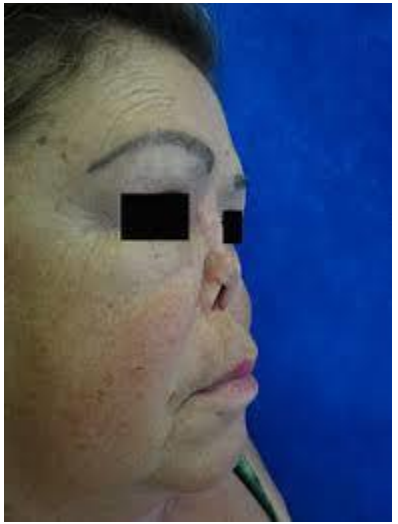
https://onlinelibrary.wiley.com/doi/full/10.1002/art.37715.

ANCA-Associated Vasculitis

- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis

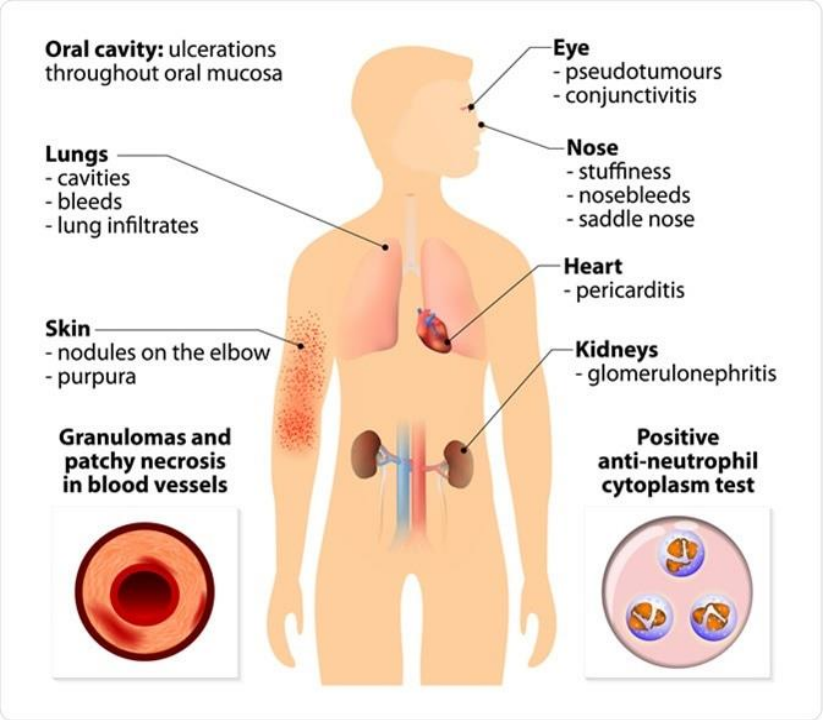
Granulomatosis With Polyangiitis (GPA)





1. www.webmd.com%2Feye-health%2Fscleritis-facts&psig=AOvVaw1jhi6YKrPHUQ2h-CHaFR_6&ust=1604974413669000&source=images&cd=vfe&ved=2ahUKEwjZkNbfsfTsAhVCCN8KHYxFCEsQr4kDegUIARDJAQ;
2. https://walnutmedical.in/wp-content/uploads/2016/09/footdrop-1024x662.jpg;
3. https://post.healthline.com/wp-content/uploads/2019/12/Leukocytoclastic-vasculitis-1296x728-gallery_slide1.jpg;
4. https://en.wikipedia.org/wiki/Saddle_nose

Our Patient



- Chronic Sinusitis
- Nasal Crusting
- Diffuse Alveolar Hemorrhage
- Arthralgias
- Glomerulonephritis

https://www.news-medical.net/health/What-is-Granulomatosis-with-Polyangiitis.aspx

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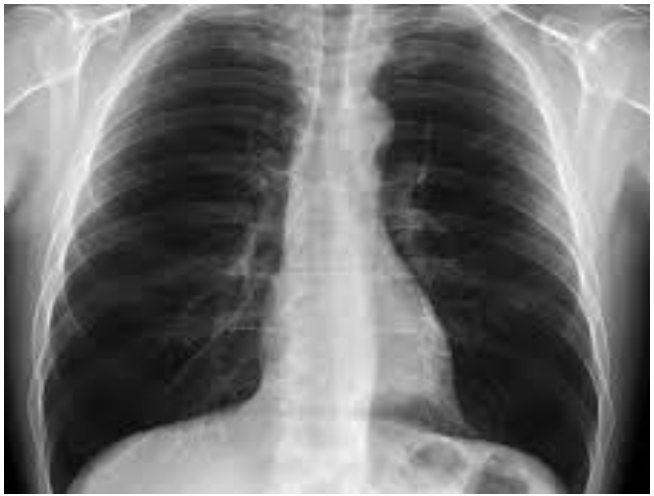
Clinical Pearls in Vasculitis

Diffuse Alveolar Hemorrhage

- **Always a medical emergency**
- Almost always requires hospitalization for close monitoring
- Treat with pulse dose steroids and/or high dose oral corticosteroids

Diffuse Alveolar Hemorrhage

Negative chest x-ray



Stable CBC

Component *Latest Ref Rng & Units*	9/17/2019	10/16/2019
White Blood Cells *4.0 - 11.0 THO/uL*	9.3	14.2 (H)
Red Blood Cells *4.30 - 5.80 MIL/uL*	4.74	4.34
Hemoglobin *13.5 - 17.5 g/dL*	13.9	12.0 (L)
Hematocrit *40 - 52 %*	41	37 (L)
Platelets *150 - 400 THO/uL*	280	355

https://stanfordmlgroup.github.io/projects/chexnet/img/chest-example.png

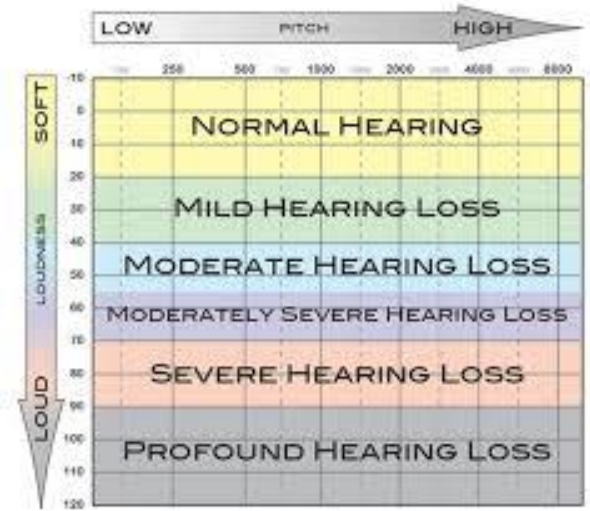
Rapidly Progressive Glomerulonephritis

- Requires prompt treatment
- Patient often asymptomatic
- Always check urinalysis

https://en.wikipedia.org/wiki/Urine_test_strip

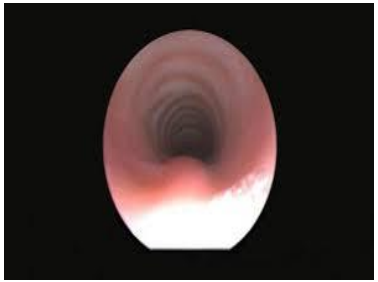
Other GPA Manifestations

Conductive and sensorineural hearing loss

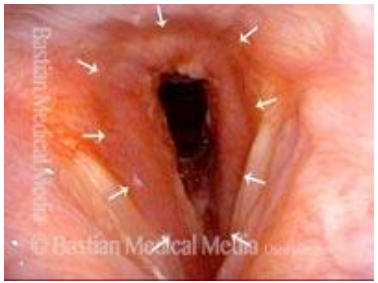


https://buildingmomentuminschools.blog/2018/06/12/hearing-loss-in-school/;

Subglottic Stenosis



Normal Subglottis



Inflammed Subglottis

https://www.researchgate.net/figure/A-Bronchoscopic-view-of-subglottic-stenosis-B-Endoscopic-view-after-treatment-with_fig1_43147775

Other GPA Manifestations

Pulmonary Embolism

https://www.hopkinsmedicine.org/health/conditions-and-diseases/pulmonary-embolism

Peripheral Nerve

https://www.livescience.com/27975-human-body-system-the-nervous-system-infographic.html

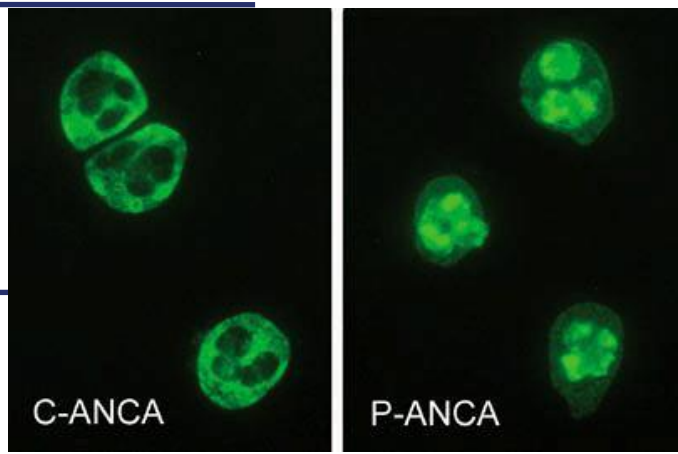
ANCA Interpretation

Perinuclear staining pattern (P-ANCA)

- Myeloperoxidase (MPO) antigen

Cytoplasmic staining pattern (C-ANCA)

- Proteinase 3 (PR3) antigen



Atypical ANCA

- Stains against other antigens
- Dual positive PR3 and MPO

https://www.vasculitis.org.uk/about-vasculitis/what-is-anca

Our Patient

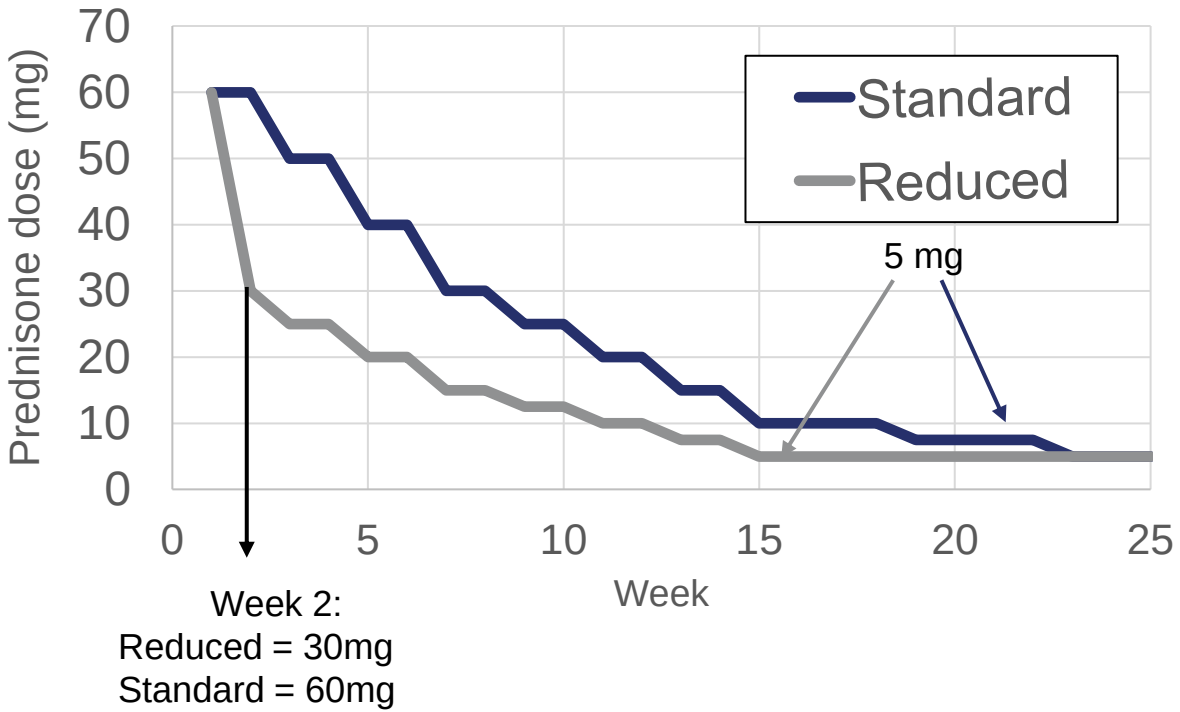
- Admitted and received methylprednisolone 1000 mg x 3 doses followed by high dose oral glucocorticoids
- Rituximab induction therapy 375 mg/m2 x 4 doses (once a week for 4 weeks)
- Bactrim SS once daily for PCP prophylaxis
- Calcium plus vitamin D.
  Consider bisphosphonate

Brief Update on Treatments – PEXIVAS

- 704 patients enrolled
- Severe and active AAV (kidney or pulmonary involvement)
- Everyone was started on cyclophosphamide or rituximab
- Randomized to PLEX versus no PLEX
- Additionally randomized to standard glucocorticoid dosing or reduced glucocorticoid dosing

Standard vs reduced glucocorticoid dosing

55% reduction in cumulative glucocorticoid exposure in first 6 months



Walsh M, et al. Trials 2013

PEXIVAS

Primary Outcomes

- **End Stage Renal Disease**
- **Death**

PEXIVAS – Results

- No difference in PLEX arms for primary outcomes
- No difference in the glucocorticoid dosing arms
  - Fewer serious infections in the reduced glucocorticoid dosing arm

PEXIVAS – Conclusions

- Adding plasma exchange does not reduce the risk of death or ESRD
- Reduced dose glucocorticoids was non-inferior to standard dosing and was associated with a reduction in risk of infection

Resources for Your Patients With Vasculitis

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- -qWNJ&ust=1604973901715000&source=images&cd=vfe&ved=2ahUKEwiZ78brr_TsAhWLbTABHV08CkAQr4kDegUIARCmAQ
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- https://www.vasculitis.org.uk/about-vasculitis/what-is-anca

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GPA: Considerations for Therapy During the COVID-19 Pandemic

Katie Springer PA-C
Northwestern Medical Group
Lake Forest, IL

Rituximab for GPA

- Induction dose
- 1g 14 days apart x 2 or 375 mg/m2 weekly x 4
- Maintenance doses 500mg Q 6 months

Rituximab in COVID-19

- Data from European League against Rheumatism COVID-19 registry
- n= 37 treated with RTX
- No clear worsening of outcomes

Rituximab in COVID-19 Theoretical Risks

- B cell depletion with anti-CD20 monoclonal antibodies
- Could compromise anti-viral immunity, including the development of SARS-CoV-2 antibodies therefore increase risk of reinfection and impair vaccine efficacy

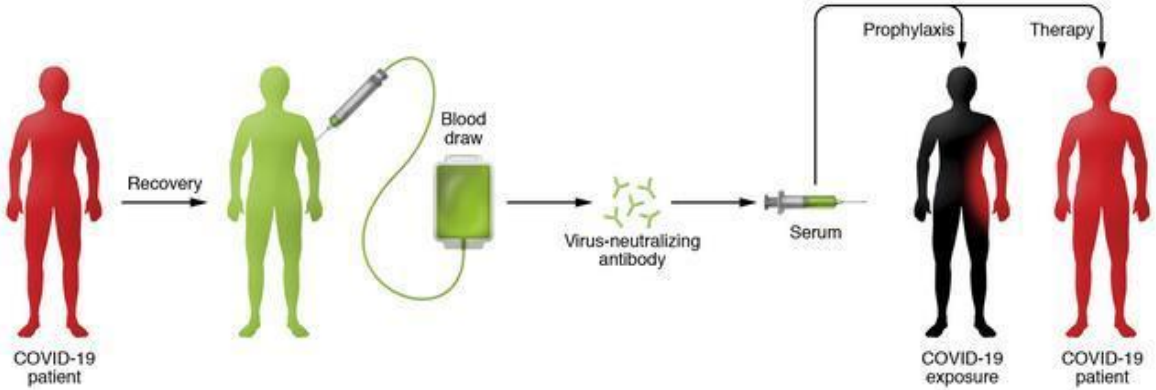
Do We Need Antibodies for a Good Clinical Course of COVID-19?

- COVID-19 in 7 multiple sclerosis patients in treatment with ANTI-CD20 therapies (RTX & ocrelizumab)
- Patients treated with anti-CD20+ have adequate resolution of COVID-19 despite the fact that the presence of antibodies against SARS-CoV-2 was not detected in all cases. It is possible that the presence of humoral immunity is not always necessary for a good clinical course of SARS-CoV-2 infection

Virginia Meca-Lallana, Clara Aguirre, Beatrizdel Río, Laura Cardeñoso, Teresa Alarcon, José Vivancos. *Multiple Sclerosis and Related Disorders*. Elsevier. September 2020.

Rituximab in COVID-19 Theoretical Risks

- Hypogammaglobulinemia
  - Would convalescent serum show particular benefit as a therapeutic option in the patients?



COVID-19 Vaccine

- Rituximab reduces humoral responses following influenza vaccination in RA patients, with a modestly restored response 6-10 months after rituximab administration

Van Assen S, Holvast A, Benne CA, Posthumus MD, van Leeuwen MA, Voskuyl AE, Blom M, Risselada AP, de Haan A, Westra J, Kallenberg CG, Bijl M. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum*. 2010 Jan;62(1):75-81. doi: 10.1002/art.25033. PMID: 20039396.

Could Rituximab Be Beneficial in Severe Cases of COVID-19?

- COVID-19 associated thromboses, severe lung pathology and hyperinflammation share similarities with disease we already treat

Could Rituximab Be Beneficial in Severe Cases of COVID-19?

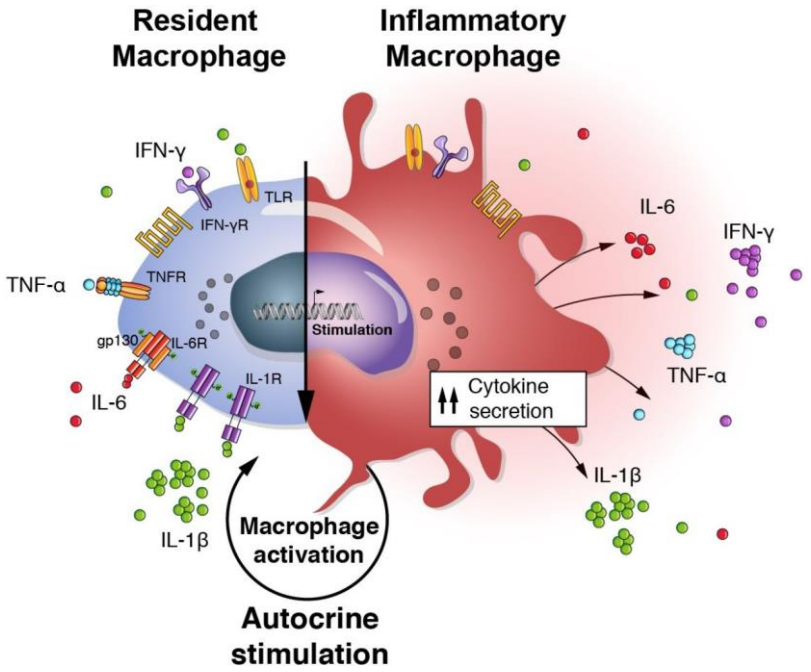
- Antiphospholipid antibodies have also been reported in COVID-19 patients with thrombosis though it is unclear whether these antibodies are pathogenic in this context

Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020; 382: e 38

- COVID is similar to rheumatic lung diseases
- MDA-5 anti synthetase syndrome[1]
- Fibrotic Organizing Pneumonia[2]

1. Rituximab for refractory rapidly progressive interstitial lung disease related to anti-MDA5 antibody-positive amyopathic dermatomyositis. AU So H, Wong VTL, Lao VWN, Pang HT, Yip RML SO. *Clin Rheumatol*. 2018;37(7):1983. Epub 2018 Apr 30;
2. Successful Rituximab Therapy in Steroid-Resistant, Cryptogenic Organizing Pneumonia: A Case Series. AU Shitenberg D, Fruchter O, Fridel L, Kramer MR SO. *Respiration*. 2015;90(2):155-9. Epub 2015 6 3.

- COVID is also similar to Macrophage Activation Syndrome



- Avoiding or pausing Rituximab may lead to higher disease activity requiring more steroids. And we have seen evidence that steroids can worsen outcomes in COVID-19
  - EULAR registry Pred >10mg
  - Global Rheum Alliance Pred >10mg (OR = 2.05; 95%CI, 1.06-3.96)

- When it is appropriate to skip induction?
- Absence of organ-threatening or life-threatening disease:
  - Active GN
  - Pulm hemorrhage
  - Cerebral vasculitis (mood changes, ataxia, memory loss, HA)
  - Progressive peripheral or cranial neuropathy (ie 6th nerve palsy)
  - Orbital pseudotumor (exophthalmos)
  - Scleritis
  - GIB
  - Cardiac disease due to vasculitis (pericarditis, myocarditis)

- So what else can we use for maintenance?
  - Methotrexate
  - Azathioprine

WEGENT trial AZA= MTX

IMPROVE trial AZA > MMF

Thank You!

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Questions?