Pulmonary vasculitis & diffuse alveolar hemorrhage

January 1, 2017 by Josh Farkas

overview of pulmonary vasculitides in the ICU

Common presentations to ICU:

- (1) Diffuse alveolar hemorrhage.
  - May manifest with hemoptysis (easier to diagnose)
  - May manifest solely with hypoxemic respiratory failure (harder to diagnose)
- (2) Renal failure (e.g. requiring emergent hemodialysis).
- (3) Pulmonary-Renal syndromes (#1 + #2).

ANCA-associated vasculitides are by far the most common cause of pulmonary vasculitis, including two in particular:
The most common is Granulomatosis with Polyangiitis (GPA, previously known as Wegener’s Granulomatosis).

The second most common is microscopic polyangiitis, which is similar to GPA but involves fewer organs (mostly: kidney, lung, skin, nerves).

Treatment for GPA & microscopic polyangiitis is identical.

- Don’t worry about sorting out GPA vs. microscopic polyangiitis.
- This chapter will focus on the presentation and treatment of ANCA vasculitis, as this is the most commonly encountered vasculitis.

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### diffuse alveolar hemorrhage

- (1) Hemoptysis can be severe – or entirely absent.
  - ~1/3 of patients *don’t* have hemoptysis upon presentation, despite having blood in the lungs ([Lally 2015](https://www.ncbi.nlm.nih.gov/pubmed/25836645)).
  - Drop in hemoglobin level may be a clue supporting the presence of hemorrhage. Unfortunately, hemoglobin drops are extremely common and therefore *nonspecific*.
- (2) Pulmonary infiltrates & hypoxemia (may mimic pneumonia).

### renal failure

- Can be a dominant feature or may be subclinical.

### other features of GPA

- Patients often have waxing/waning symptoms for weeks or months before presentation. Symptoms may involve a variety of organs as follows:
  - **Constitutional symptoms**: fever, weight loss, arthralgia, myalgia.
  - **HEENT**:
    - Eye: conjunctivitis, scleritis, uveitis.
    - Nose: ulceration, saddle deformity, sinusitis.
    - Ear: otitis media.
    - Pharynx: voice change.
  - **Skin**: palpable purpura, nodules, ulcers.
  - **Neurology**:
    - Multifocal neuropathy (e.g., wrist drop, foot drop).
    - Cranial nerve dysfunction, meningitis, or ischemic stroke can occur.

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### differential diagnosis of diffuse alveolar hemorrhage

- **vasculitis**
  - ANCA-associated vasculitidies, particularly:
    - Granulomatous polyangiitis.
    - Microscopic polyangiitis.
  - Goodpasture’s disease (a.k.a. anti-glomerular basement membrane disease).
  - Connective tissue diseases (especially SLE, which may manifest with DAH).
  - Cryoglobulinemia.
  - IgA vasculitis (a.k.a. Henoch-Schonlein purpura).

- **heart failure**
  - Especially mitral stenosis or mitral regurgitation

- **medications & toxins**
Toxic exposures
- Smoking crack (especially cut with levamisole)
- Vaping (29984031)

Medications (complete listing on Pneumotox.com: [https://www.pneumotox.com/drug/index/](https://www.pneumotox.com/drug/index/))
- Allopurinol
- Amiodarone
- All-trans retinoic acid
- Chemotherapeutic agents (e.g. cytotoxic medications)
- Hydralazine
- Nitrofurantoin
- Penicillamine
- Sirolimus
- Sulfalazine
- Thyroid medications: Methimazole, propylthiouracil
- Tumor Necrosis Factor antagonists

infection
- Any infection (e.g. bacterial, viral).

severe hematologic derangement
- Thrombocytopenia, platelet dysfunction
- Anti-phospholipid antibody syndrome
- Promyelocytic leukemia (especially with differentiation syndrome)

evaluation of diffuse alveolar hemorrhage
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[Renal tubular epithelial cells and RBCs within cast - unspun unstained - phase contrast - patient with DAH and AKI - MPO ab markedly elevated - Renal Bx this am - #UrinarySediment](https://twitter.com/jrseltzer/status/884179416524509697)
**labs**

- Basic labs
  - Falling hemoglobin is supportive of alveolar hemorrhage, but nonspecific.
  - Renal failure may be seen.
  - Check coagulation studies (more relevant to treatment than diagnosis).
- CRP & Erythrocyte sedimentation rate (ESR)
  - Can be useful because it turns around rapidly
  - Very high ESR (>100 mm/hr) supports vasculitis, whereas normal ESR argues against vasculitis.
- Urinalysis
  - **Hematuria** +/- proteinuria is seen in ~85% of patients with GPA. **Hematuria** is more indicative of active nephritis, whereas proteinuria may be seen in between disease flares due to chronic renal damage. Note that urinalysis is roughly as sensitive as an ANCA screen, but much easier and faster to obtain.
  - Urine microscopy showing **glomerulonephritis** (e.g. RBC casts) supports a diagnosis of vasculitis.
- More specific labs
  - **ANCA, anti-myeloperoxidase antibody, anti-Proteinase-3 antibody** (anti-myeloperoxidase & anti-Protease-3 are more specific than ANCA; for critically ill patients it may expedite matters to order all three tests up-front).
  - Anti-GBM antibody.
  - Anti-nuclear antibody (ANA), anti-double-stranded DNA, rheumatoid factor, CH50, C3, C4.
  - Anti-histone antibody if suspect medication-induced SLE.
  - Cryoglobulin.
  - Anticardiolipin antibodies, anti-beta-2-glycoprotein I.
  - Urine toxicology (mostly evaluating for cocaine).
- If pneumonia possible, infectious workup
  - Blood cultures.
  - Influenza testing during season, urine antigens for legionella and pneumococcus.
  - Procalcitonin.

**chest CT scan ASAP**

- i) Diagnosis of diffuse alveolar hemorrhage
  - CXR can be normal in diffuse alveolar hemorrhage; you need a CT ([Lally 2015](https://www.ncbi.nlm.nih.gov/pubmed/25836645)).
  - CT will generally show patchy bilateral infiltrates due to diffuse alveolar hemorrhage.
  - CT may also help *exclude* alternative etiologies of hemoptysis (e.g. focal malignancy).
- ii) Evaluating *cause* of diffuse alveolar hemorrhage
  - GPA may also cause nodules which can cavitate.
  - Septal thickening, bilateral effusions, and dilation of the left atrium may suggest heart failure.

**bronchoscopy with serial lavage**

- Usually an urgent bronchoscopy will be performed with the following goals:
  - (1) Confirm diagnosis of diffuse alveolar hemorrhage with **serial lavage**
    - Three syringes are sequentially flushed into a bronchus and then aspirated.
    - If blood *clears* with repeated lavage, this suggests a **bronchial** source of bleeding.
    - If lavages become sequentially bloodier, this suggests diffuse alveolar hemorrhage.
  - (2) Hemosiderin-laden macrophages
    - May also help clarify the diagnosis of DAH (if >20% macrophages contain hemosiderin).
    - Takes longer to return (compared to lavage which is immediately apparent), but might be useful in equivocal situations. The serial lavage isn't always definitive.
  - (3) Exclude infection: Fluid should be tested for viruses, bacteria, and possibly fungi, depending on presentation.
  - (4) If seen, tracheal ulceration/stenosis supports a diagnosis of GPA.

**tissue diagnosis**
Not required prior to initiation of corticosteroid. Primary role is often clarifying the diagnosis definitively, to guide longer-term treatment strategies (e.g. use of rituximab).

May be unnecessary, depending on the clinical context (e.g., if clinical picture, labs, and bronchoscopy all support GPA).

Renal biopsy or surgical lung biopsy both have high yield (~85%; McGeoch 2016 [https://www.ncbi.nlm.nih.gov/pubmed/26523024]).

- Renal biopsy is safer and less invasive than lung biopsy. It also may provide prognostic information about the likelihood of renal recovery.
- Surgical lung biopsy requires intubation and lung resection ~ making this more invasive & risky. This is usually helpful only in patients with isolated pulmonary involvement (31376892 [https://www.ncbi.nlm.nih.gov/pubmed/31376892]).
- Skin biopsy may be considered if lesions are present (undoubtedly the safest option).

Renal biopsy or surgical lung biopsy both have high yield (~85%; McGeoch 2016 [https://www.ncbi.nlm.nih.gov/pubmed/26523024]).

Antibiotics

- Initially it may not be entirely clear that a patient has vasculitis, rather than pneumonia.
- It is often reasonable to start antibiotics and steroid initially, until additional data is available.
- Antibiotics should ideally be stopped within 24-48 hours, based on culture data +/- procalcitonin.

Steroid

- Steroid should be started once there is a high level of suspicion for vasculitis.
- Patients with severe manifestation (e.g. glomerulonephritis, respiratory failure) are started on pulse-dose steroid (125-250 mg IV methylprednisolone Q6hs for three days).
  - This is a data-free zone. Most experts recommend pulsing with steroid for patients with glomerulonephritis or alveolar hemorrhage, but there is no solid evidence to support this. The dose to use for the pulse is also unclear. According to the Canadian 2016 guidelines for ANCA vasculitis (https://www.ncbi.nlm.nih.gov/pubmed/26523024), the initial pulse may be 500-1000 mg methylprednisolone daily for three days (equal to 125mg q6hr ~ 250mg q6hr).
  - For patients with known vasculitis, pulsing with 1 gram methylprednisolone daily for three days seems reasonable.
  - For patients with suspected vasculitis, a lower dose (e.g. 500 mg methylprednisolone daily) may be reasonable.
  - After the three-day pulse, steroid is reduced to 1 mg/kg prednisone daily with a slow taper.

Plasma exchange (PLEX)

- These are antibody-mediated diseases, so removal of antibody makes some sense. Unfortunately, PLEX does remove rituximab (so these therapies shouldn't be used simultaneously).
- The largest RCT on plasmapheresis (PLEXIVAS) has been released in abstract form only (see figure below). This places us in evidentiary limbo while awaiting review of the full manuscript.
  - On the one hand, PLEXIVAS is the highest quality evidence on this, so we might feel compelled to follow it.
  - However, it's generally unwise to change practice prior to reviewing an entire study manuscript.
- (1) Glomerulonephritis with severe renal failure
  - PLEX is supported by one RCT (Jayne 2007 [https://www.ncbi.nlm.nih.gov/pubmed/17582159]). Patients in this study had severe renal failure (Creatinine > 5.8 mg/dL or 500 uM).
  - However, this indication seems to be soundly refuted by the PLEXIVAS trial.
  - Unclear what to do here; would consult with nephrology.
- (2) Diffuse alveolar hemorrhage due to ANCA vasculitis?
  - 🤷
  - Again, this isn't supported by the PLEXIVAS trial (although this involves subgroup analysis because most patients in the trial didn't have pulmonary hemorrhage).
There is a public schism between UpToDate authors and editors about how to manage this. Recommendations range from plasmapheresis for all patients with pulmonary hemorrhage to reserving this for patients with respiratory failure refractory to steroid. This highlights the level of confusion surrounding this therapy.

(3) Diffuse alveolar hemorrhage or renal failure due to anti-GBM antibodies.

- Currently this might be the strongest indication for plasmapheresis (or perhaps simply the only indication which hasn't yet been refuted).
- Anti-GBM disease is even more rare than ANCA vasculitis, so the evidentiary basis here is very sparse.

Abstract Number: 2788

The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis

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Session Information
Session Date: Tuesday, October 23, 2018
Session Title: ACR Abstract: Plenary Session III
Session Type: ACR Plenary Session
Session Time: 11:00AM-12:30PM

Background/Purpose: It is uncertain whether plasma exchange improves clinical outcomes in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Also uncertain is whether, compared to standard therapy with high-dose oral glucocorticoids, a lower-dose glucocorticoid regimen reduces the risk of infection without increasing the risk of end-stage renal disease or death. The PLEXIVAS clinical trial addressed both of these questions.

Methods: PLEXIVAS was a 2-by-2 factorial, randomized, controlled trial to separately evaluate plasma exchange and two different regimens of oral glucocorticoids in patients with new or relapsing severe ANCA-associated vasculitis, including lung hemorrhage and/or glomerulonephritis (eGFR <50 ml/min/1.73 m2). Participants were randomly assigned to 7 treatments of plasma exchange or no plasma exchange. Participants were also randomly assigned to either a standard-dose oral glucocorticoid regimen or a reduced-dose oral glucocorticoid regimen (0.6) of the standard regimen by 6 months.

All patients received immunosuppression with either cyclophosphamide or rituximab. Patients were followed up for at least up to 7 years for the primary composite outcome of death from any cause or end-stage renal disease.

Results: The trial recruited 704 participants from 15 countries: 397 (56%) men; 289 (41%) PR3-ANCA, 209 (30%) MPO-ANCA, 69 (9%) with renal involvement; 191 (27%) with alveolar hemorrhage, 109 (15%) patients received rituximab and 595 (85%) received cyclophosphamide. Among 704 participants, the primary outcome occurred in 28% of patients allocated to plasma exchange compared to 31% in the no plasma exchange group (hazard ratio 0.86, 95% confidence interval [CI] 0.65 to 1.13; p=0.27). The primary outcome occurred in 26% of patients in the reduced glucocorticoid group and 26% in the standard glucocorticoid group (absolute risk difference 2.3%, 95% CI 3.6% to 8.0%; met non-inferiority hypothesis). Serious infections in the first year occurred less often in the reduced glucocorticoid group compared to the standard group (incidence rate ratio 0.70, 95% CI 0.52 to 0.94; p=0.03). The results were similar for both the plasma exchange and glucocorticoid interventions when the individual outcomes of end-stage renal disease or death were analyzed separately.

Conclusions: Plasma exchange does not reduce the risk of end-stage renal disease or death in patients with ANCA-associated vasculitis. Compared to a standard dose, reduced glucocorticoids did not substantially increase the risk of death or end-stage renal disease and resulted in fewer serious infections. The primary results of PLEXIVAS, regarding both the use of plasma exchange and dosing of glucocorticoids, will have immediate and substantial impact on the standard of care for patients with ANCA-associated vasculitis.

PLEXIVAS is the largest RCT evaluating plasmapheresis in vasculitis. It has been released only in abstract form (above). The study protocol has been published here (https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-14-73). Some slides from this conference presentation are available here (http://www.nephjc.com/news/pexivasearly/).

coagulation management

- If there is active pulmonary hemorrhage, any coagulopathy should be aggressively reversed.
  - See chapter on anticoagulation reversal (https://emcrit.org/ibcc/anticoagulant-reversal/).

- Once hemorrhage has stopped, DVT prophylaxis should be started.

discontinue any offensive medications

- Rarely, drugs may cause an ANCA-positive vasculitis or diffuse alveolar hemorrhage.
- Review drug list and discontinue drugs associated with vasculitis/pneumonitis.
  - Pneumotox.com (https://www.pneumotox.com/drug/index/) may be helpful here.

eventual maintenance immunosuppressive regimen

- After stabilization with steroid +/- PLEX, patients require a maintenance immunosuppressive.
- Rituximab is emerging as the best agent (traditionally cyclophosphamide has been used, but its toxicity profile is considerably greater).
  - The RAVE trial (https://www.wikijournalclub.org/wiki/RAVE) suggested that rituximab has equivalent efficacy (with some trends towards superiority).
  - Retrospective and subset analyses suggest a potential benefit of rituximab over cyclophosphamide (31376892 (https://www.ncbi.nlm.nih.gov/pubmed/31376892)).
  - This will be determined by nephrology or rheumatology consultation after the dust settles.

https://emcrit.org/ibcc/dah/
Complications to beware of:

- (1) DVT/PE
  - Vasculitis increases risk of thromboses.
  - Large series of patients with vasculitis often include one or two patients who die from PE.
  - DVT prophylaxis should be started after alveolar hemorrhage has subsided.
  - Avoid placing hemodialysis catheter in femoral vein for prolonged duration.

- (2) Fungal pneumonia (usually aspergillosis)
  - Pulse-dose steroid renders patients susceptible to fungal pneumonia.
  - Consider this in patients who improve but later deteriorate with signs of pneumonia.

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- Diffuse alveolar hemorrhage (Daniel J Bell et al, Radiopaedia)
- Hemoptysis (IBCC chapter)
The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.

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