1/ This July’s @aspneph pathology webinar was all about pediatric Antineutrophil Cytoplasmic Antibody (ANCA)- associated vasculitis (AAV). Let’s kick off this pediatric AAV tweetorial 🎧 with a quick question #NephTwitter 🤔 What is the role of ANCA antibodies❓

2/
- Diagnostic marker and Pathogenic in nature
- Proteinase-3 (PR3) and Myeloperoxidase (MPO) antigens are sequestered in neutrophil primary granules
- Antigen exposure triggers immune response leading to endothelial activation

https://linkinghub.elsevier.com/retrieve/pii/S0272638619308261
Mechanisms

- Defective neutrophil apoptosis, leading to NETosis
- Inefficient clearance of PR3/MPO
- Antimicrobial antibodies cross reacting with PR3/MPO
- Medication induced

<table>
<thead>
<tr>
<th>Drug classification</th>
<th>Specific drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-thyroid drugs</td>
<td>Benzylthiouracil, Carimazole, Methimazole, Propylthiouracil</td>
</tr>
<tr>
<td>Biological agents</td>
<td>Adalimumab, Etanercept, Infliximab, Golimumab</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Cefotaxime, Minocycline, Nitrofurantoin, Trimethoprim-sulfamethoxazole, Vancomycin</td>
</tr>
<tr>
<td>Anti-tuberculosis drugs</td>
<td>Isoniazid, Rifampicin</td>
</tr>
<tr>
<td>DMARDs</td>
<td>D-Penicillamine, Sulfasalazine</td>
</tr>
<tr>
<td>Psychoactive agents</td>
<td>Clozapine, Thoridazine</td>
</tr>
<tr>
<td>Miscellaneous drugs</td>
<td>Allopurinol, Atorvastatin, Cocaine/Levamisol, Denosumab, Hydralazine, Isotretinoin, Phenytin</td>
</tr>
</tbody>
</table>

ANCA in vasculitis first described in 1982 (PMID: 6297657)
PR3/MPO antigen specificity in 1988 and 1989
ANCA have since been shown to have a role in pathogenesis, diagnosis and prognosis of AAV
Pediatric AAV is a rare, chronic, relapsing, systemic, immunologic small vessel vasculitis with granulomatous inflammation

- Incidence 1-6/1,000,000/yr in children
- Female preponderance
- Median age - 12-14 years, peak 2nd decade
Classification of pediatric ANCA vasculitis

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA) associated with asthma & eosinophilia, seen in adults
- Renal limited vasculitis

PMID: 23045170

GPA and MPA most common AAV seen in children
Presence of PR3 vs MPO antibody determines clinico-pathologic course of disease

<table>
<thead>
<tr>
<th>Type of vasculitis</th>
<th>PR3/c-ANCA AAV Granulomatosis with polyangiitis (GPA)</th>
<th>MPO/p-ANCA AAV Microscopic polyangiitis (MPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody localization</td>
<td>Cytoplasmic distribution</td>
<td>Perinuclear distribution</td>
</tr>
<tr>
<td>Genetic association</td>
<td>HLA-DP and the alpha antitrypsin (SERPINA1, a serine protease inhibitor for which PR3 is one of the substrates)</td>
<td>HLA-DQ</td>
</tr>
<tr>
<td>Clinical</td>
<td>Upper and lower airway disease more common</td>
<td>Pulmonary disease less common, pulmonary hemorrhage and fibrosis can be seen</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Higher relapse rate</td>
<td>Higher mortality</td>
</tr>
</tbody>
</table>

Another question for the think tank: What is the most common renal pathology in pediatric ANCA vasculitis?
Crescentic Glomerulonephritis (GN)

- Rapidly progressive GN (39%) with pauci immune crescentic necrotizing GN on light microscopy (50-60%) is the most common pathology in both pediatric GPA and MPA
- Sclerotic lesions when present, carry the worst prognosis

ANCA vasculitis is one of the most common causes of pulmonary-renal syndrome in children

Other system involvement seen in 30-60% patients

https://doi.org/10.1093/ndt/gfv011
Extrarenal manifestations of Pediatric AAV

- Constitutional - Fever, malaise
- Headache, seizures, peripheral neuropathy (mononeuritis complex)
- Sunglottic stenosis (GPA)
- Pulmonary nodules and infiltrates with necrotising granulomas (GPA > MPA)
- Pulmonary hemorrhage (MPA > GPA)
- Nodular or purpuric rash (GPA > MPA)

- Otitis media (GPA)
- Conjunctivitis (GPA)
- Granulomatous nasal septum infiltration and perforation (GPA)
- Hypertension, Venous Thrombosis, Myocarditis, Heart block
- Mesenteric vasculitis, Hepatitis, Pancreatitis

@Monicavivek #ASPNFOAM group
ANCA vasculitis suspected in any patient with
- Severe/rapidly worsening acute kidney injury (AKI), proteinuria, hematuria
- Signs/symptoms of small vessel vasculitis in other organs
- Prompt evaluation for primary vasculitis syndromes as recommended by #KDIGO

2021 #KDIGO guidelines recommend initiating treatment with clinical suspicion of kidney AAV and/or presence of ANCA in patients with a suspicion of RPGN, while awaiting kidney biopsy #dontwaitforbiopsy
Randomized pediatric studies for treatment not available, data extrapolated from adult studies

- Induction – Cyclophosphamide (CYC) v/s Rituximab (RTX) v/s Steroids
- Plasma exchange (PLEX)
- Maintenance – Steroids w/ additional immunosuppression
Induction

- RTX tolerated, preferable in children, side effects, efficacy = CYC #RAVE #RITUXIVAS
- IV CYC pulses cumulative dose, in severe disease/relapse #CYCLOPS
- dose noninferior to highdose steroids #PEXIVAS @NEJM
- Avacopan noninferior to steroids @landmark_neph
Avacapan for the Treatment of ANCA-Associated Vasculitis

Jayne DRW et al. DOI: 10.1056/NEJMoa2023386

**CLINICAL PROBLEM**
Patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis may have serious complications, decreased quality of life, and side effects from medications (e.g., glucocorticoids) used to treat the condition. Avacapan is an oral small-molecule C5a receptor antagonist that offers a potential treatment option for ANCA-associated vasculitis.

**CLINICAL TRIAL**

**Design:** A phase 3 international, double-blind, randomized, controlled trial compared oral avacapan with oral prednisone in patients with ANCA-associated vasculitis concurrently being treated with immunosuppressive drugs.

**Intervention:** 331 patients were assigned to receive either avacapan (30 mg twice daily) plus prednisone-matching placebo or prednisone (60 mg daily tapered to discontinuation by week 21) plus avacapan-matching placebo. All patients also received cyclophosphamide (followed by azathioprine) or rituximab. The two primary efficacy end points — clinical remission at week 26 and sustained remission at both week 26 and week 52 — were tested for noninferiority (noninferiority margin, 20 percentage points) and superiority.

**RESULTS**

**Efficacy:** Avacapan was noninferior to prednisone with respect to clinical remission at week 26 and was both noninferior and superior to prednisone with respect to sustained remission at week 52.

**Safety:** The percentage of patients who had serious adverse events (excluding worsening vasculitis) was similar in the two groups.

**LIMITATIONS AND REMAINING QUESTIONS**
- Patients in the avacapan group received glucocorticoids, although the mean daily dose was one third that in the prednisone group.
- The trial population was heterogeneous, including patients with newly diagnosed vasculitis and those with relapsing disease.
- The durability and safety of avacapan in patients with ANCA-associated vasculitis need to be assessed in longer-term trials.

**CONCLUSIONS**
Among patients with ANCA-associated vasculitis, avacapan was noninferior to prednisone with respect to remission at 26 weeks and was superior with respect to sustained remission at 52 weeks.

Links: Full Article | NEJM Quick Take | Editorial
PLEX

- Aggressive disease only
- Recent #PEXIVAS trial and a meta-analysis did not show long-term benefits in adults
- However, pediatric RCTs needed - d/t earlier onset, prolonged course & prognosis

@NephroGuy @NEJM @bmj_latest @nephroseeker

16/

- Maintenance
  - RTX is better than Azathioprine (AZA) ([10.1056/NEJMoa1404231](https://doi.org/10.1056/NEJMoa1404231)) (PMID: 28270229)
  - Low dose steroids or Avacopan
  - Duration is 18 - 24 months with first episode, 4 years for relapsing disease ([10.1136/annrheumdis-2017-211123](https://doi.org/10.1136/annrheumdis-2017-211123))

17/

- Poor prognostic factors in pediatric ANCA
  - Severe renal impairment or need for dialysis – strongest predictor
  - Renal histology – sclerosis
  - Severe neurological manifestation
  - Hypertension

https://doi.org/10.2215/CJN.19181220
Kidney transplant

- Clinical resolution for at least 6 months irrespective of ANCA titers
- Continue immunosuppression while on dialysis if other system involvement, awaiting transplant.

https://doi.org/10.1016/j.kint.2021.05.015
Take Home Points Pediatric AAV

- Rare disease, Rx extrapolated from adult RCTs
- Evaluate any RPGN for AAV, including drug induced
- PR3, MPO ANCA IgG+ANCA IFA
- Early aggressive Rx: RTX/CYC + steroids + rarely PLEX awaiting biopsy
- Maintenance 2-4 years - RTX/AZA + steroids

For a case-based clinical discussion on #AAV with a pathologist @trumidor and an expert - login to @ASPNeph website, July 2022 webinar #Membereducation @yardleyjojo @menonshina @aspneph Special thanks to #ASPNFOAM group @nefron1310 @swastithinks @RoshanPGeorgeMD @drM_Sudha

@landmark_neph