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21 Tweets • 2022-08-30 08:21:04 UTC • See on Twitter

rattibha.com

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 ❓

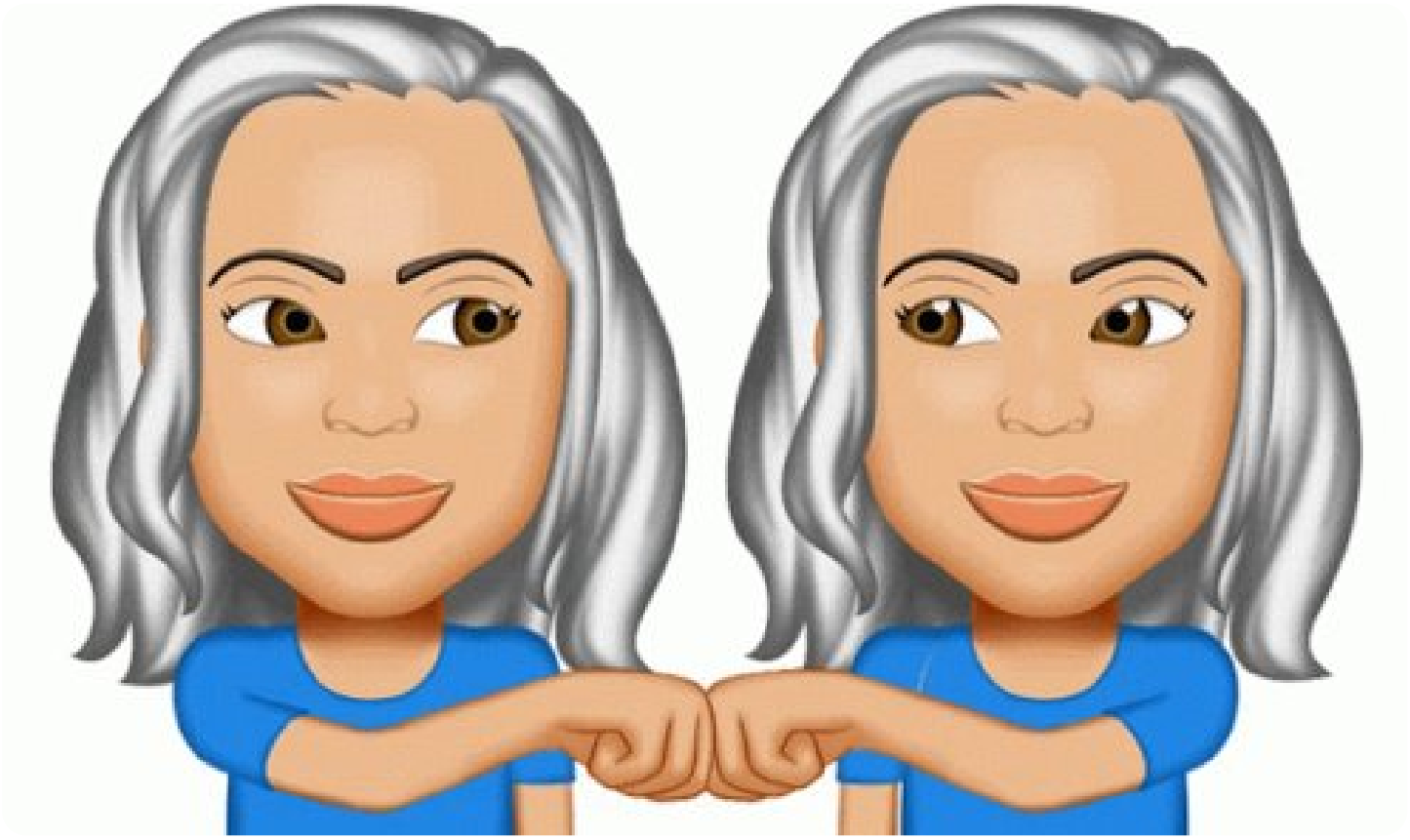
2/

✅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



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Mechanisms

📌Defective neutrophil apoptosis, leading to NETosis

📌Inefficient clearance of PR3/MPO

📌Antimicrobial antibodies cross reacting with PR3/MPO

📌Medication induced

Drug classification	Specific drugs
Anti-thyroid drugs	Benzylthiouracil, Carbimazole, Methimazole, Propylthiouracil
Biological agents	Adalimumab, Etanercept, Infliximab, Golimumab
Antibiotics	Cefotaxime, Minocycline, Nitrofurantoin, Trimethoprim-sulfamethoxazole, Vancomycin
Anti-tuberculosis drugs	Isoniazid, Rifampicin
DMARDs	D-Penicillamine, Sulfasalazine
Psychoactive agents	Clozapine, Thioridazine
Miscellaneous drugs	Allopurinol, Atorvastatin, Cocaine/Levamisol, Denosumab, Hydralazine, Isotretinoin, Phenytoin

AAV: ANCA-associated vasculitis; ANCA: Anti-neutrophil cytoplasmic antibody; DMARDs: Disease-modifying anti-rheumatic drugs.

PMID: 31856057

4/

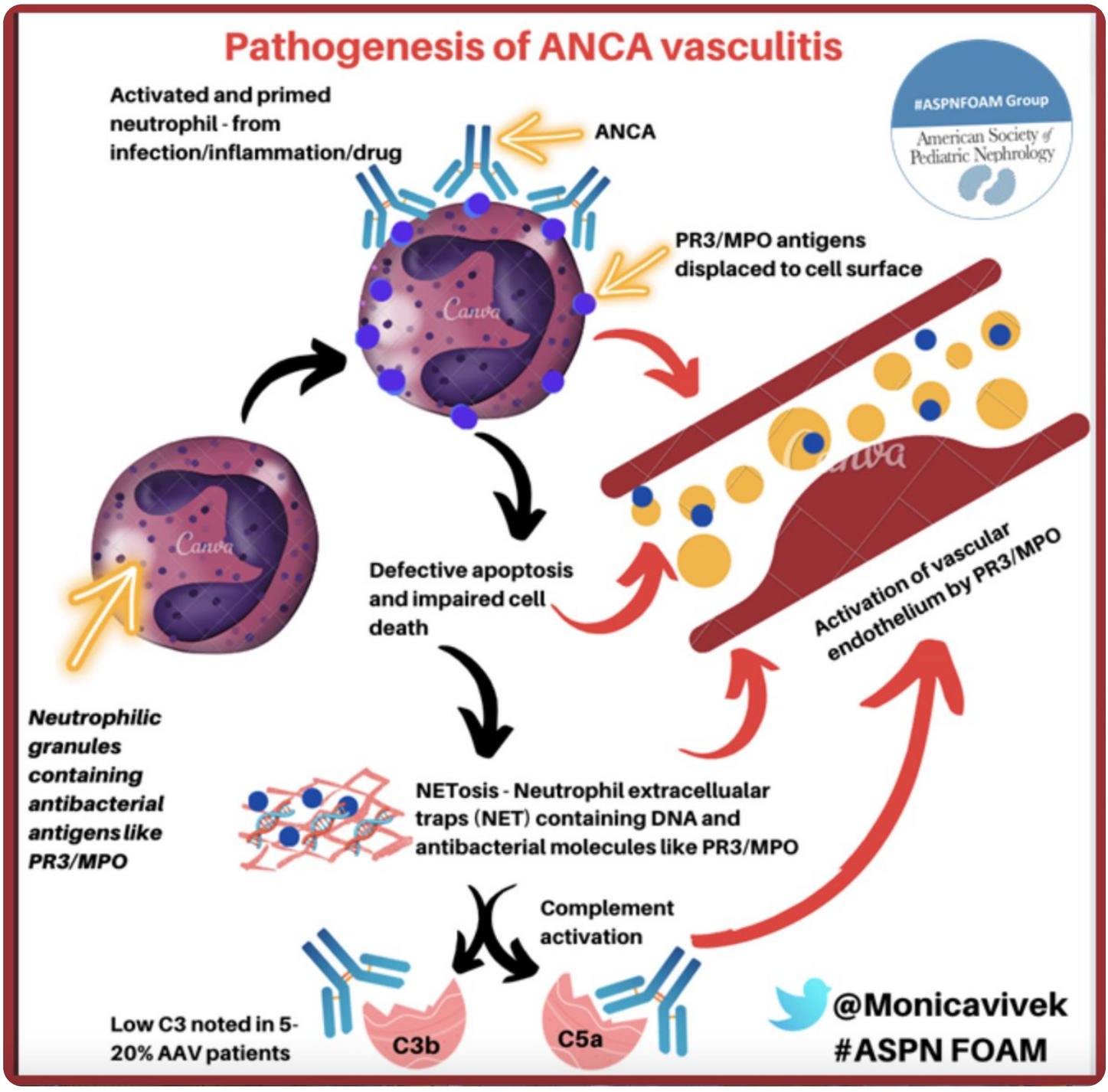
🔵 ANCA in vasculitis🧐first described in 1982 (PMID: 6297657)

🔵 PR3/MPO antigen specificity in 1988 and 1989

🔵 ANCA have since been shown to have a role in pathogenesis, diagnosis and prognosis of AAV

https://doi.org/10.1182/blood.V75.11.2263.2263

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



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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

https://doi.org/10.3389/fped.2018.00226

6/
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

7/
🔵 GPA and MPA most common AAV seen in children
🔵 Presence of PR3 🆚 MPO antibody determines clinico-pathologic course of disease

	PR3/c-ANCA AAV Granulomatosis with polyangiitis (GPA)	MPO/p-ANCA AAV Microscopic polyangiitis (MPA)
Type of vasculitis	Small and medium sized vessels	Small vessels
Antibody localization	Cytoplasmic distribution	Perinuclear distribution
Genetic association	HLA-DP and the alpha antitrypsin (SERPINA1, a serine protease inhibitor for which PR3 is one of the substrates)	HLA-DQ
Clinical	Upper and lower airway disease more common	Pulmonary disease less common, pulmonary hemorrhage and fibrosis can be seen
	Rapidly progressive glomerulonephritis, less sclerotic glomeruli	Rapidly progressive glomerulonephritis, with sclerosis seen more frequently
Prognosis	Higher relapse rate	Higher mortality

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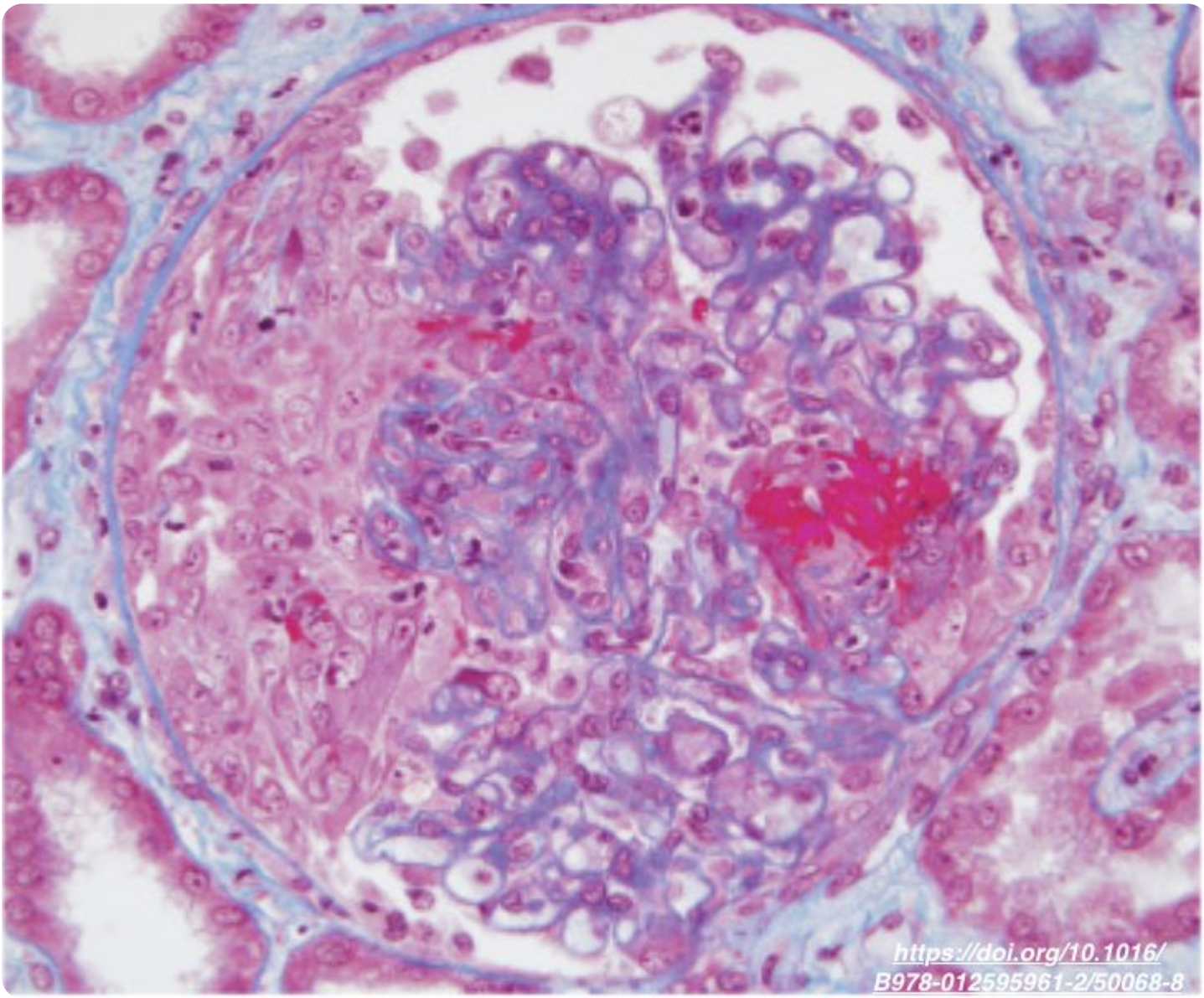
8/
🤔Another question for the think tank🧠‼️
What is the most common renal pathology in pediatric ANCA vasculitis❓

9/

✅ 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



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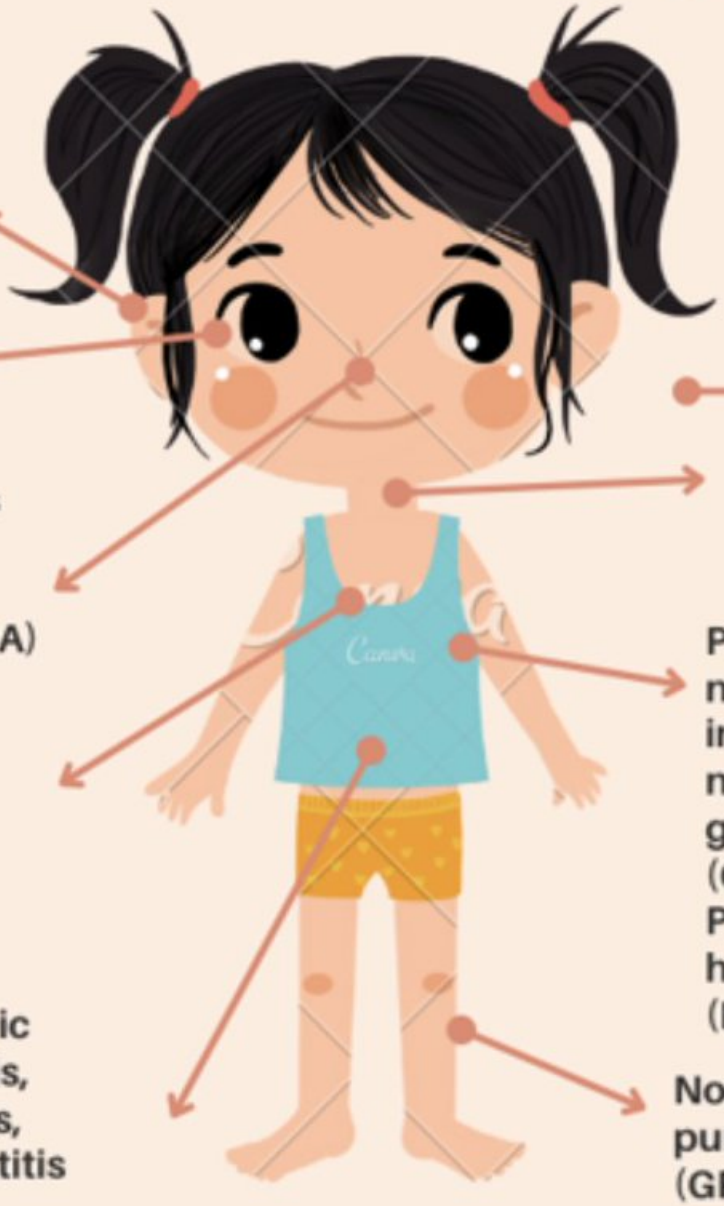
🔶 ANCA vasculitis is one of the most common causes of pulmonary-renal syndrome in children

🔶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 (mono-neuritis complex)

Otitis media (GPA)

Conjun ctivitis (GPA)

Granulamatous nasal septum infiltration and perforation (GPA)

Sunglottic stenosis (GPA)

Pulmonary nodules and infiltrates with necrotising granulomas (GPA >MPA) Pulmonary hemorrhage (MPA > GPA)

Hypertension, Venous Thrombosis, Myocarditis, Heart block

Mesentric vasculitis, Hepatitis, Pancreatitis

Nodular or purpuric rash (GPA >MPA)

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11/

📌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

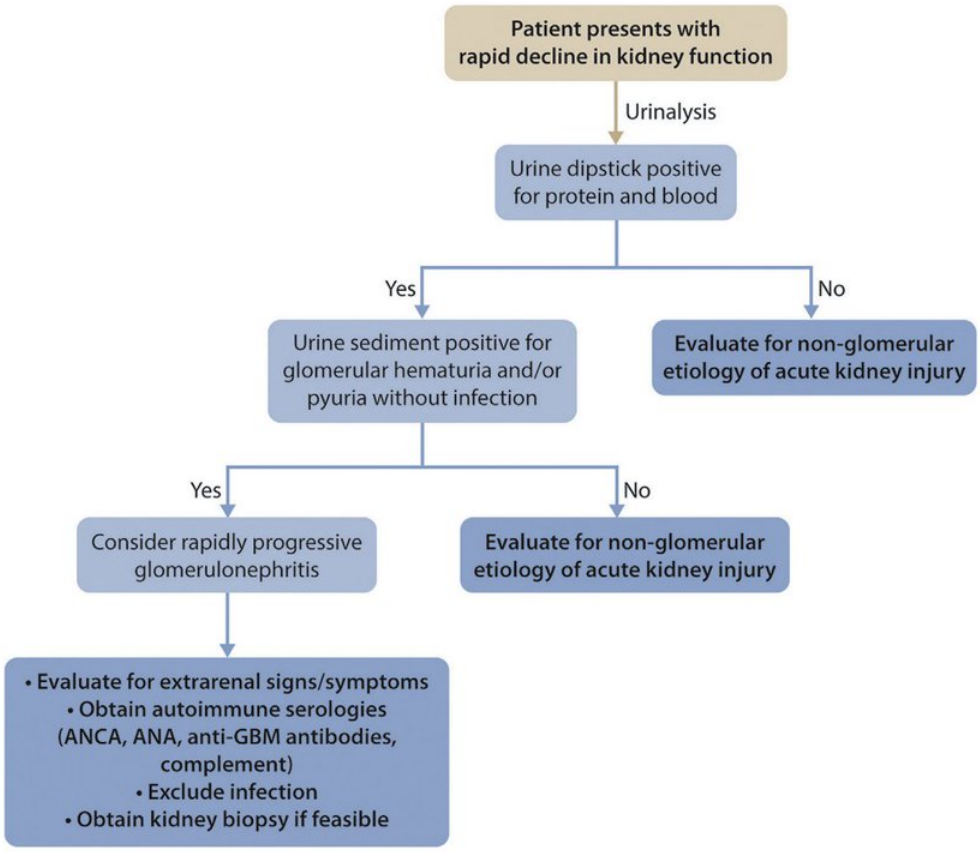


Figure 21 | Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

https://doi.org/10.1016/j.kint.2021.05.015

12/

📌 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

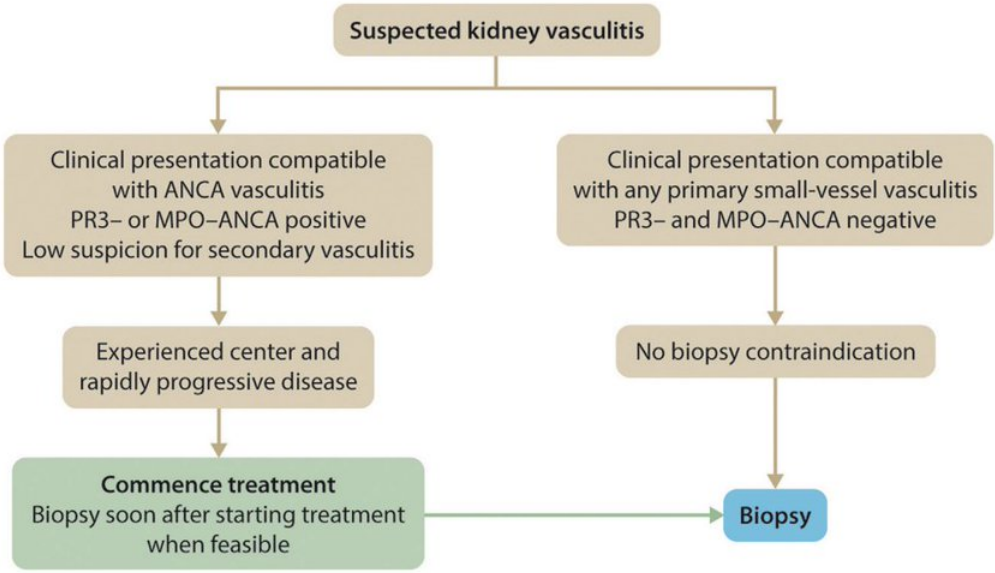


Figure 22 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.
https://doi.org/10.1016/j.kint.2021.05.015

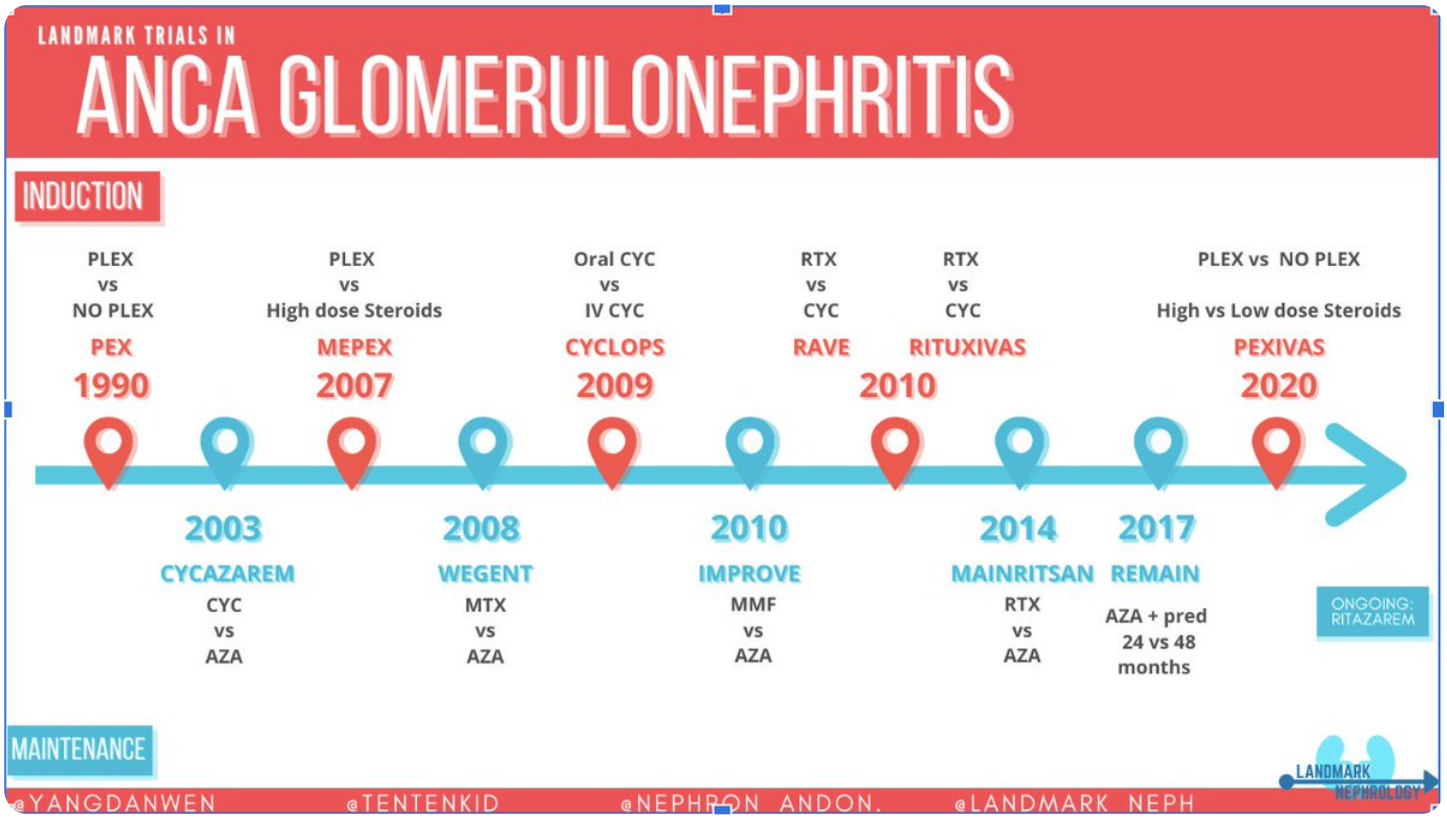
13/

📌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



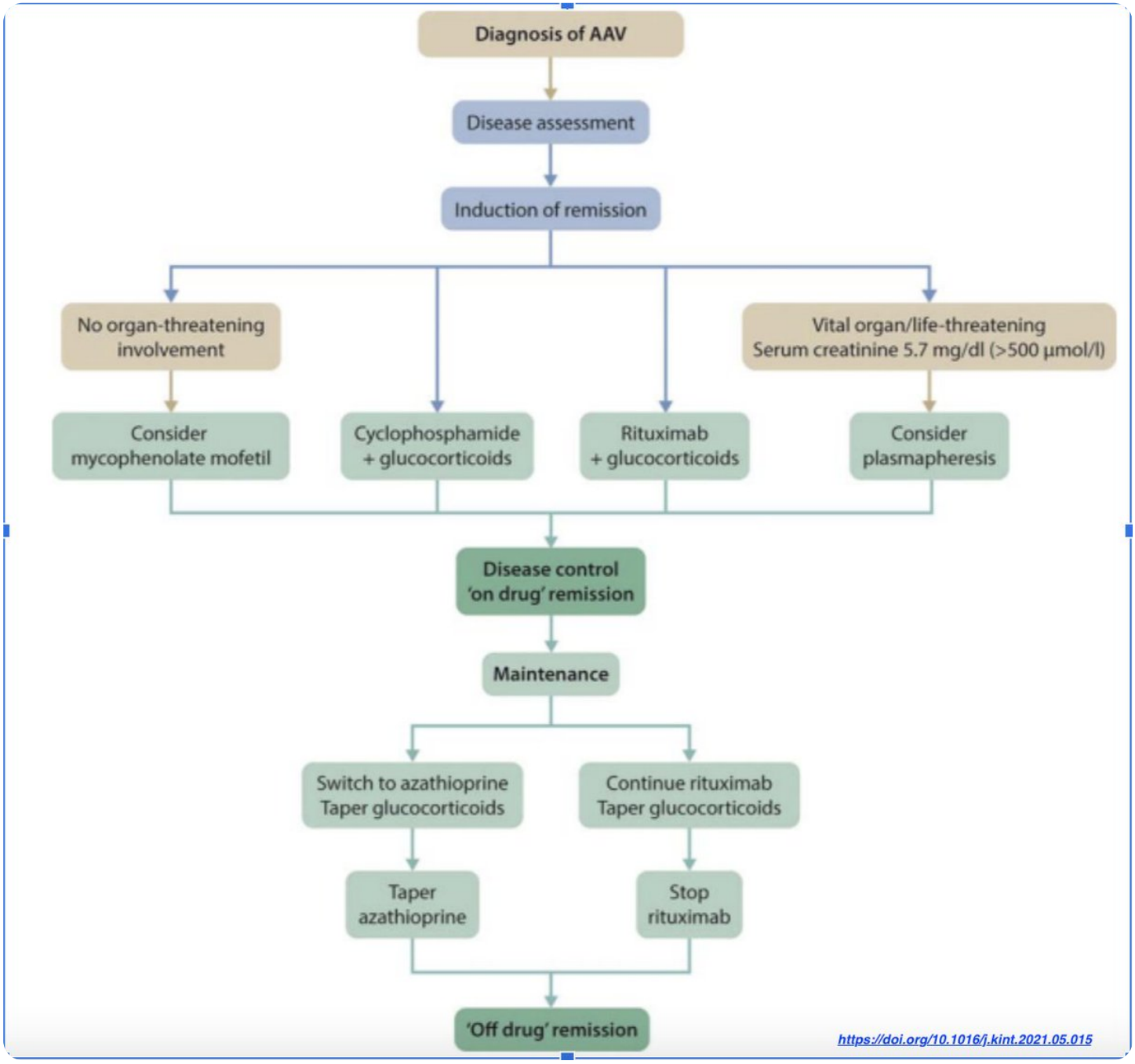
14/📌Induction

🔶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



RESEARCH SUMMARY

Avacopan 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. Avacopan 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 avacopan with oral prednisone in patients with ANCA-associated vasculitis concurrently being treated with immunosuppressive drugs.

Intervention: 331 patients were assigned to receive either avacopan (30 mg twice daily) plus prednisone-matching placebo or prednisone (60 mg daily tapered to discontinuation by week 21) plus avacopan-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

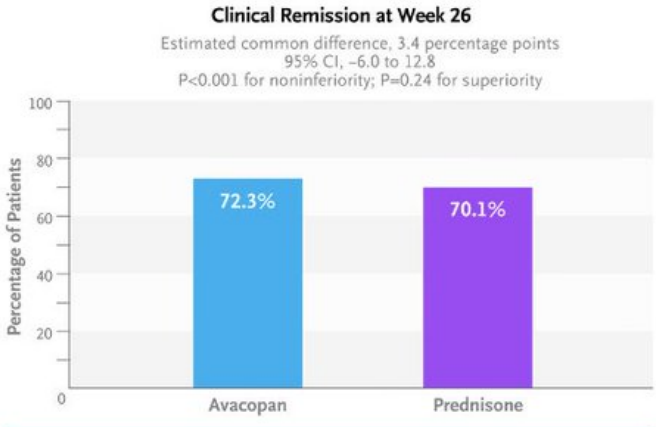
Efficacy: Avocapan was noninferior to prednisone with respect to clinical remission at week 26 and was both noninferior and superior to prednisone with respect to sustained remission at week 52.

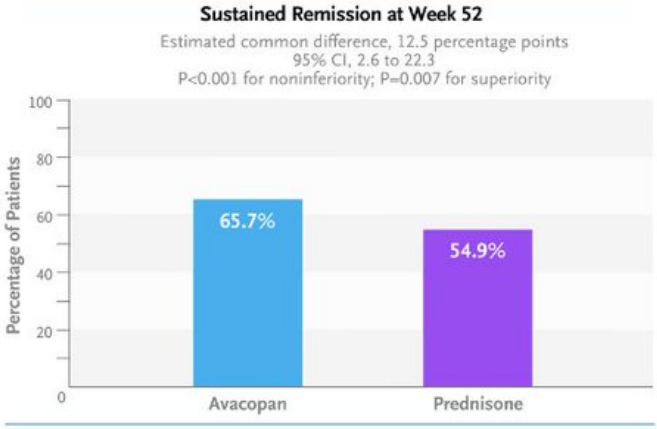
Safety: The percentage of patients who had serious adverse events (excluding worsening vasculitis) was similar in the two groups.

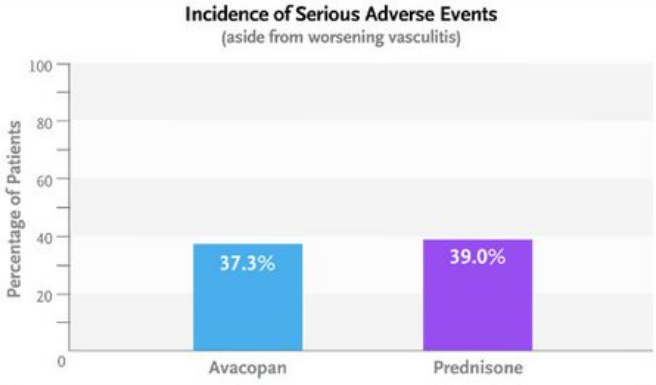
LIMITATIONS AND REMAINING QUESTIONS

- Patients in the avacopan 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 avacopan in patients with ANCA-associated vasculitis need to be assessed in longer-term trials.

Links: Full Article | NEJM Quick Take | Editorial







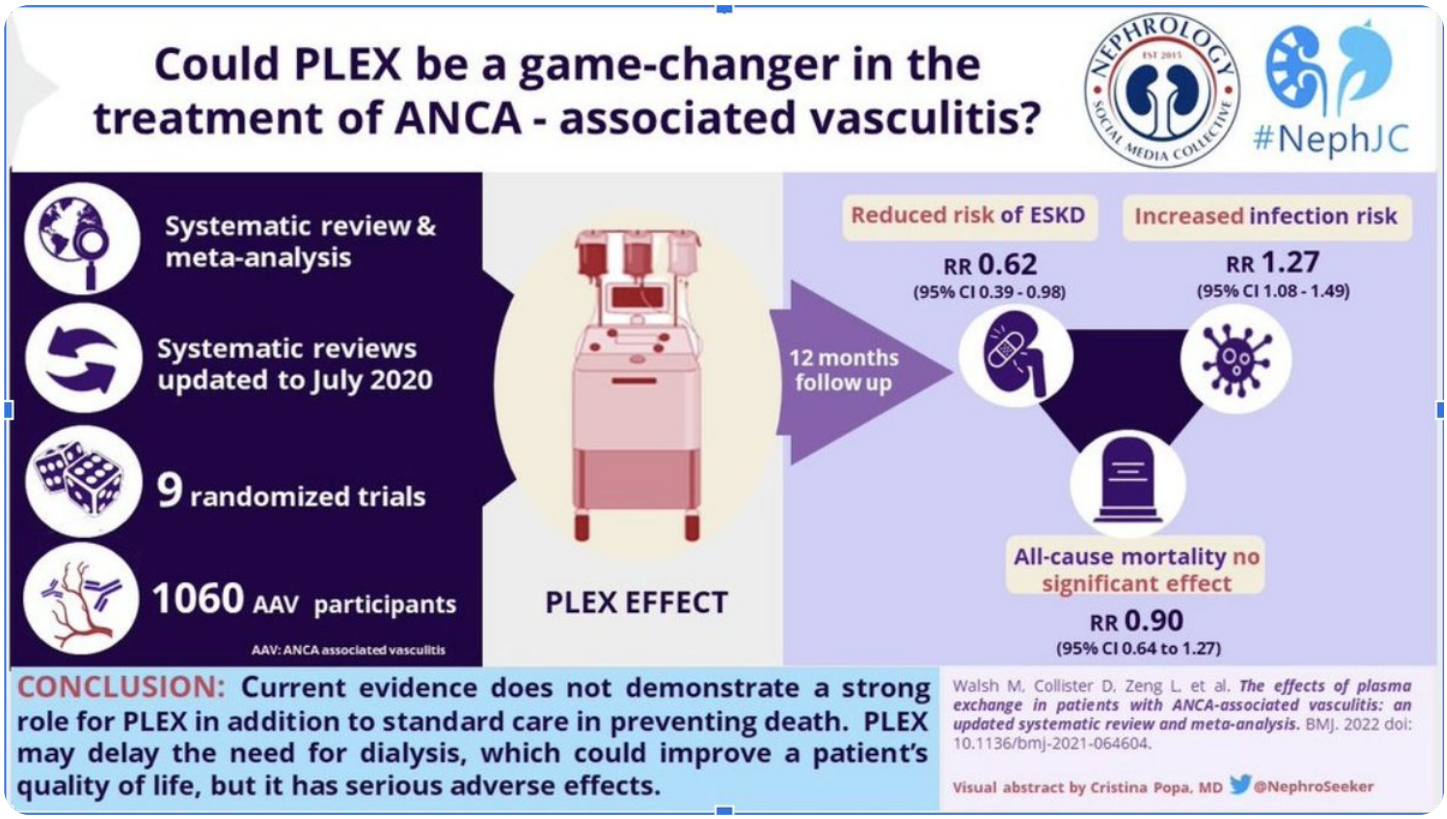
CONCLUSIONS

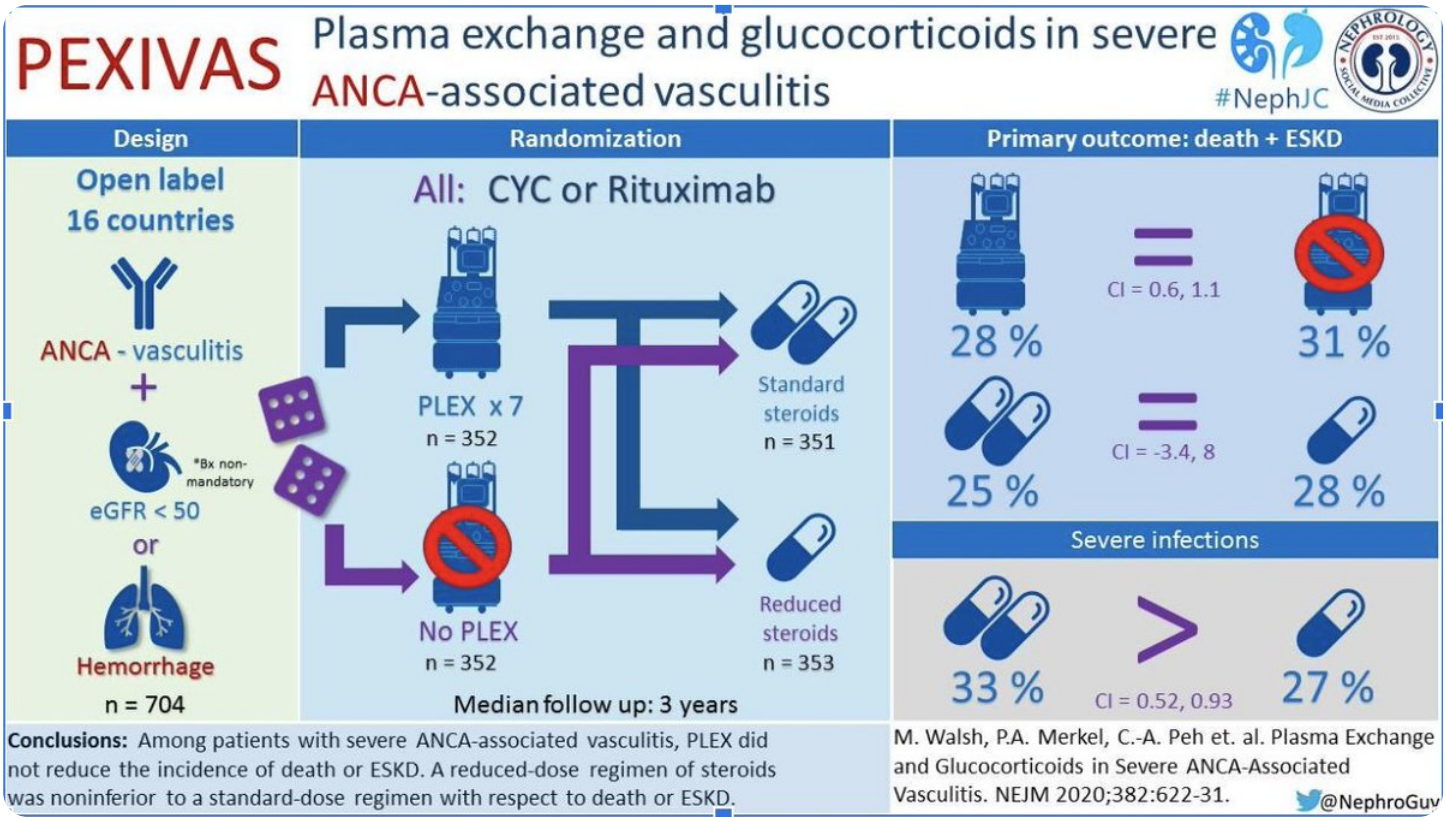
Among patients with ANCA-associated vasculitis, avacopan was noninferior to prednisone with respect to remission at 26 weeks and was superior with respect to sustained remission at 52 weeks.

15/
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

https://www.nejm.org/doi/full/10.1056/nejmoa1803537





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📌Maintenance

🔶 RTX is better than Azathioprine (AZA) (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)

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

18/

📌Kidney transplant

🔶 Clinical resolution for at least 6 months irrespective of ANCA titers

🔶 Continue immunosuppression while on dialysis if other system involvement, awaiting transplant.

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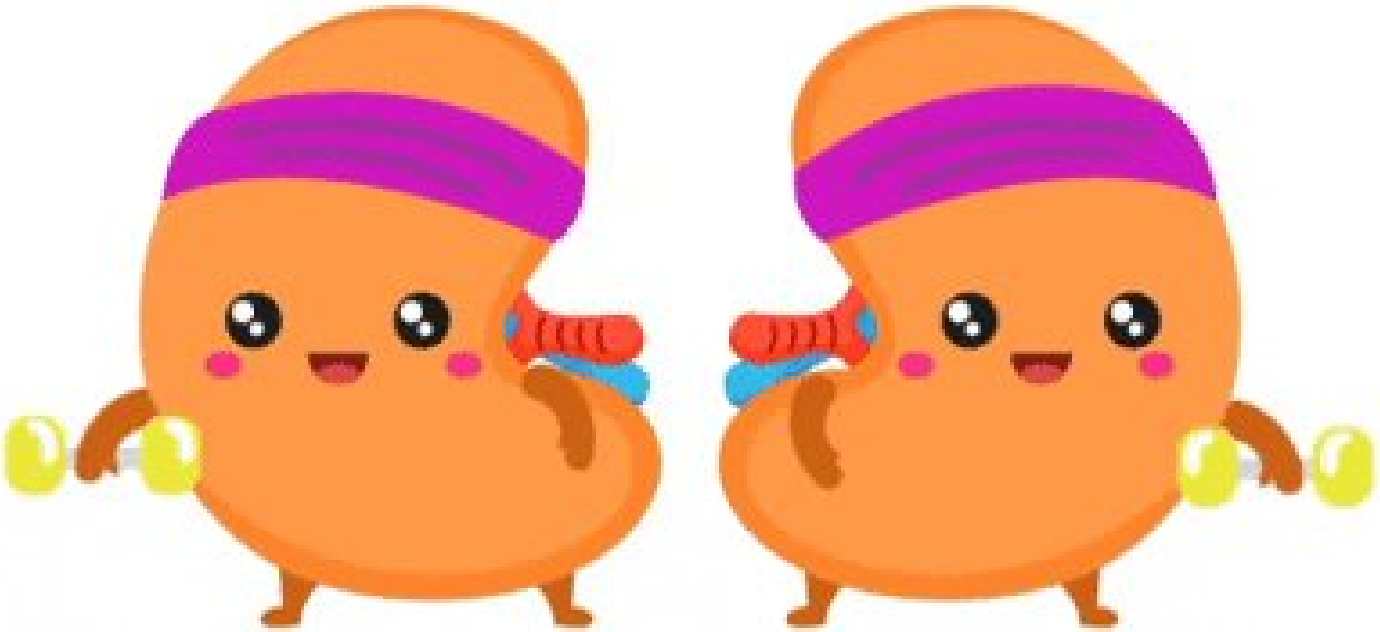
https://doi.org/10.1016/j.kint.2021.05.015



19/📌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

20/

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

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