Pediatric renal vasculitis

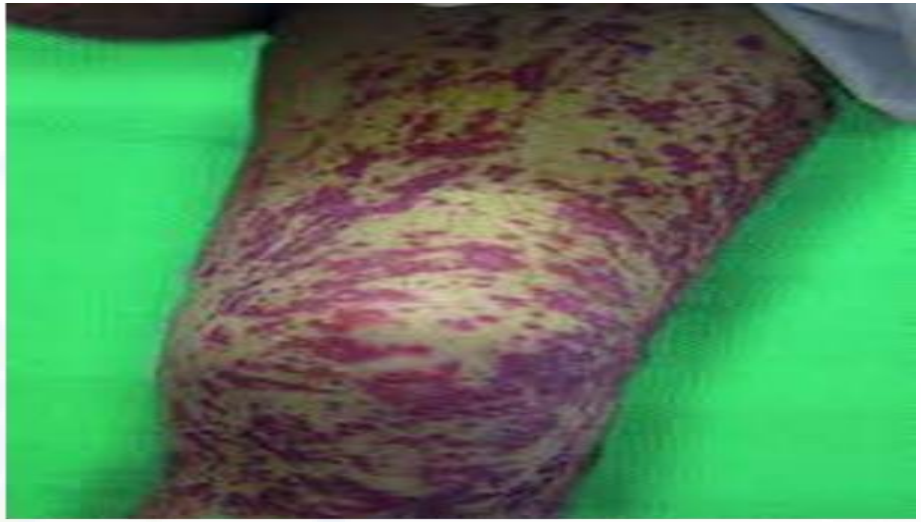
By

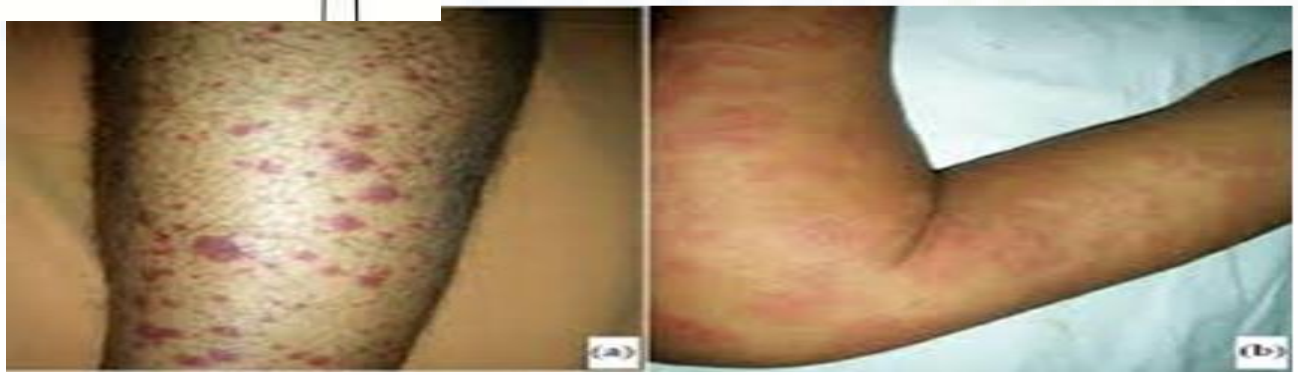
Doaa Youssef

Professor of pediatrics

Zagazig university


why?
why?
why?
why?
why?





Points of this talk

- Introduction
- Major 5 causes of pediatric vasculitis especially with renal affection

1. Background
2. Clinical presentation
3. Lab workups
4. Treatment
5. Prognosis

The definition of the childhood vasculitides is based on

The International Chapel Hill Consensus Conference

Nomenclature of Vasculitides (CHCC2012)

According to the European League Against

Rheumatism, the Pediatric Rheumatology

International Trials Organization, and the Pediatric

Rheumatology European Society

(EULAR/PRINTO/PRES)

- Vasculitis is a challenging disease for pediatricians.
- Certain vasculitis's are quite common in children whereas others are much rarer compared with adults.
- The most common vasculitides in childhood are IgA-associated vasculitis and Kawasaki disease.

Large vessel vasculitis (LVV)
- Takayasu arteritis (TAK)
- Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)
- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small vessel vasculitis (SVV)
- Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (Wegener's) (GPA)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Immune complex SVV
  - Anti–glomerular basement membrane (anti-GBM) disease
  - Cryoglobulinemic vasculitis (CV)
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Variable vessel vasculitis (VVV)
- Behçet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology
- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

1- IgA vasculitis

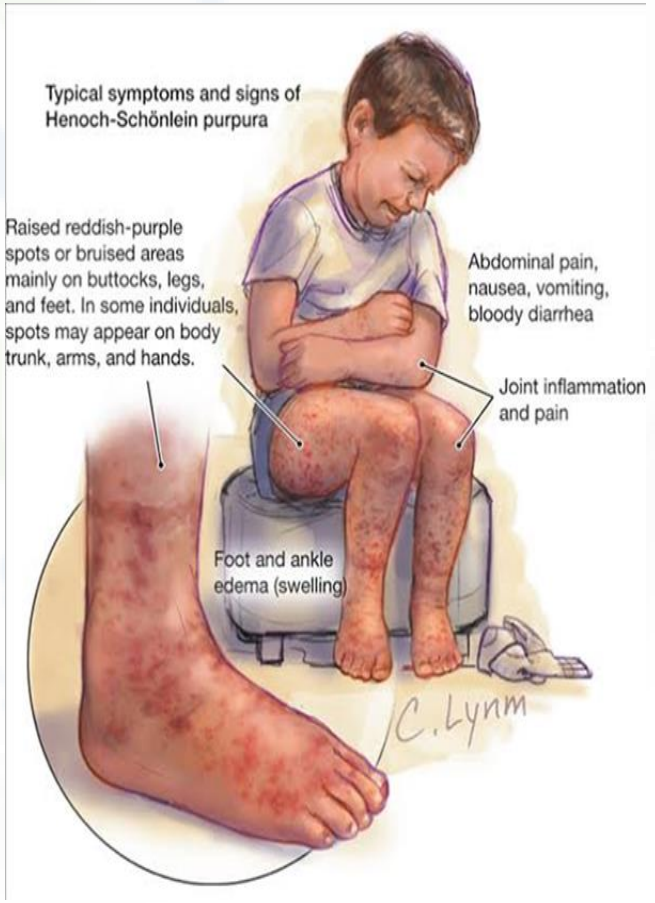
(Henoch-Scho¨nlein purpura)

Electronic databases, including Google Scholar, PubMed, and

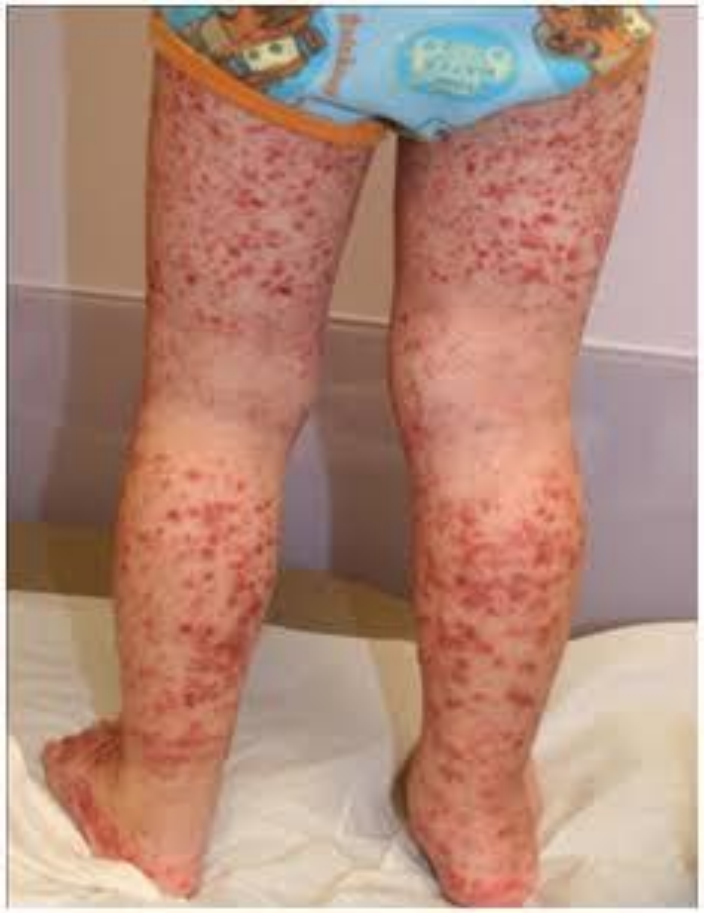
Scopus were used

Abdollahi M, et al. Renal Involvement in Childhood Henoch-schonlein Purpura. J Pediatr Rev. 2021; 9(1):53-60.

- IgAV is the most common primary systemic vasculitis in childhood with an estimated incidence of 29.9/100 000.
- It is a leukocytoclastic vasculitis with the deposition of IgA immune complexes
- in small vessels in skin,
- gastrointestinal tract and kidney *(proteinuria, microscopic or overt haematuria)*
- with arthritis/arthralgia.
- usually a preceding by infection

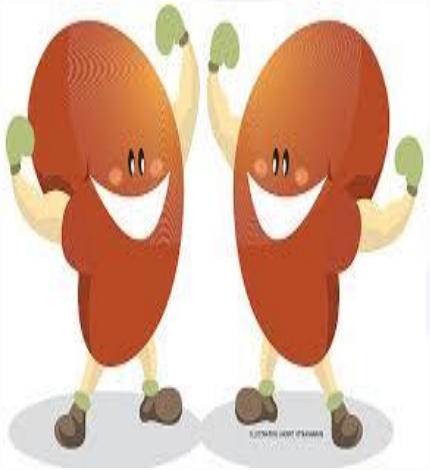


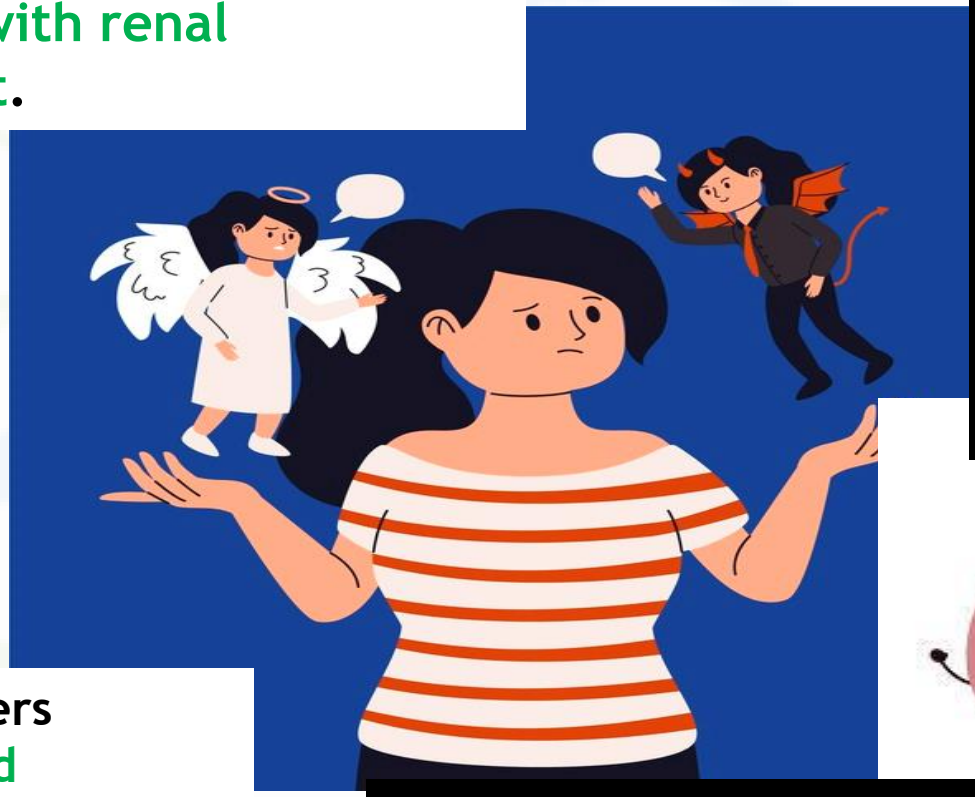
The order of symptoms differs; palpable purpura usually is the first symptom, but GI involvement or arthritis may be prominent as the initial manifestation in some patients.



Clinically

- joint involvement was not associated with renal involvement.





Clinically

- older age at presentation,
- persistent atypical rash,
- gastrointestinal bleeding

were significant risk factors for renal involvement.

Biochemical markers

- peripheral blood immunoglobulin A,
- antinuclear antibody,
- anti-streptolysin O titer,
- ESR,
- C-reactive protein

were not associated with renal involvement.

Biochemical markers

- high red blood cell distribution width
- leukocytosis,
- thrombocytosis,
- or thrombocytopenia

Are risk of renal affection

- pediatric nephrologist should be consulted
- IgA immunofluorescence should be performed on biopsy material, but negative staining does not exclude IgAV.
- eCCL and urinalysis (including urine protein/creatinine ratio or urine albumin/creatinine ratio together with presence of haematuria) should be used for renal involvement detection
- A renal biopsy is recommended for

  - severe proteinuria (>250 mg/ mmol),

  - persistent moderate (100–250 mg/mmol) proteinuria

  - or impaired GFR.

Treatment recommendations

- Supportive analgesia for patients with arthritis and abdominal pain.
- NSAIDs are the first line treatment and their use is not contraindicated unless there is overt IgAV nephritis and active GI bleeding.
- from IgAV nephritis, patients with orchitis, cerebral vasculitis, pulmonary haemorrhage and severe GI involvement should be treated with CSs

[oral prednisolone dose 1–2 mg/kg/day or pulsed intravenous methylprednisolone 10–30 mg/kg/day (maximum 1 g/day) on three consecutive days for severe cases].

- it is not recommended to use prophylactic CS to prevent IgAV nephritis.
- ACE or ARBs are the mainstay treatment to prevent or limit secondary glomerular injury in patients with persistent proteinuria.
- Severe IgAV nephritis management as ANCA-associated vasculitides.

PROGNOSIS

IgAV is usually a self-limited benign disease, but physicians should be alert for GI morbidity in the early stage and renal morbidity in late stages, which need a multidisciplinary approach.

2- Kawasaki disease

Childhood vasculitis Seza Ozen1 and Erdal Sag1, Rheumatology 2020;59:iii95–iii100

- also known as mucocutaneous lymph node syndrome, affects predominantly medium and small sized arteries.
- Coronary arteries are often involved
- The major complication of the disease is coronary artery aneurysm (CAA), which is the leading cause of acquired heart disease in the pediatric population of high-income countries.
- The incidence varies according to geographical distribution, being highest (315/100 000) in Japan and Far East Asia and lower in the non-Asian population (4.5-25/100 000) .

- It is most commonly seen around 1year of age and the incidence gradually decreases with age.
- 80 per cent of KD patients are <5years old.
- There is a male predominance with a ratio of 1.5:1.
- The seasonality of KD, with a peak in January in Japan and winter- spring peaks in the USA, raises speculation about a viral aetiology; however there has been no proof of a specific viral agent driving the condition .

Classification criteria

- There is no specific test to diagnose KD, but according to the American Heart Association, patients are classified as KD if they have a fever persisting for at least 5days (a mandatory criterion) and four of the following five criteria:

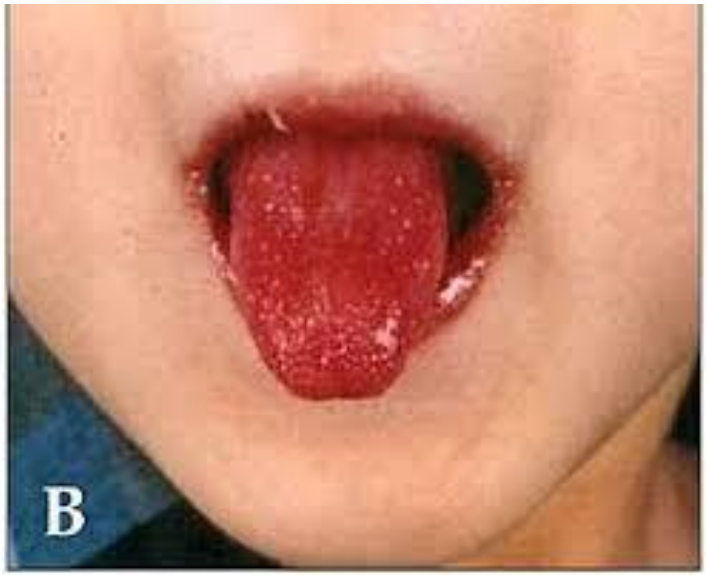
. changes in the peripheral extremities and perianal area,

. polymorphous exanthema,

. bilateral conjunctival injection,

. changes of lips and oral cavity and/or injection of oral and pharyngeal mucosa,

. cervical lymphadenopathy.


B

Treatment

- early treatment in both complete and incomplete KD.
- Treatment should include IVIG (2g/kg as a single infusion) together with aspirin.
- The recommended aspirin dose is 30-80 mg/kg/day until no fever for 48h with improvement of clinical features and CRP, followed by 3-5 mg/kg once daily until the patient has no evidence of coronary changes by 6-8weeks after onset of disease.
- If there is a CAA, aspirin (3-5mg/kg/day) should be continued at least until the aneurysm resolves and longer-term aspirin treatment should be decided on an individual basis.

- About 20-40% of the patients are IVIG resistant, and have ongoing fever and/or persistent inflammation or clinical signs 48h after IVIG infusion .
- For resistant patients, a second IVIG dose may be considered.

PROGNOSIS

- About 4-5% of the patients have recurrent KD.
- The medium and long term prognosis is usually excellent after proper treatment
- The majority of the patients do not have cardiac or other system complications.
- However, long term follow-up is extremely important, especially in patients with cardiac involvement and IVIG resistance .
- Risk factors for poor prognosis are

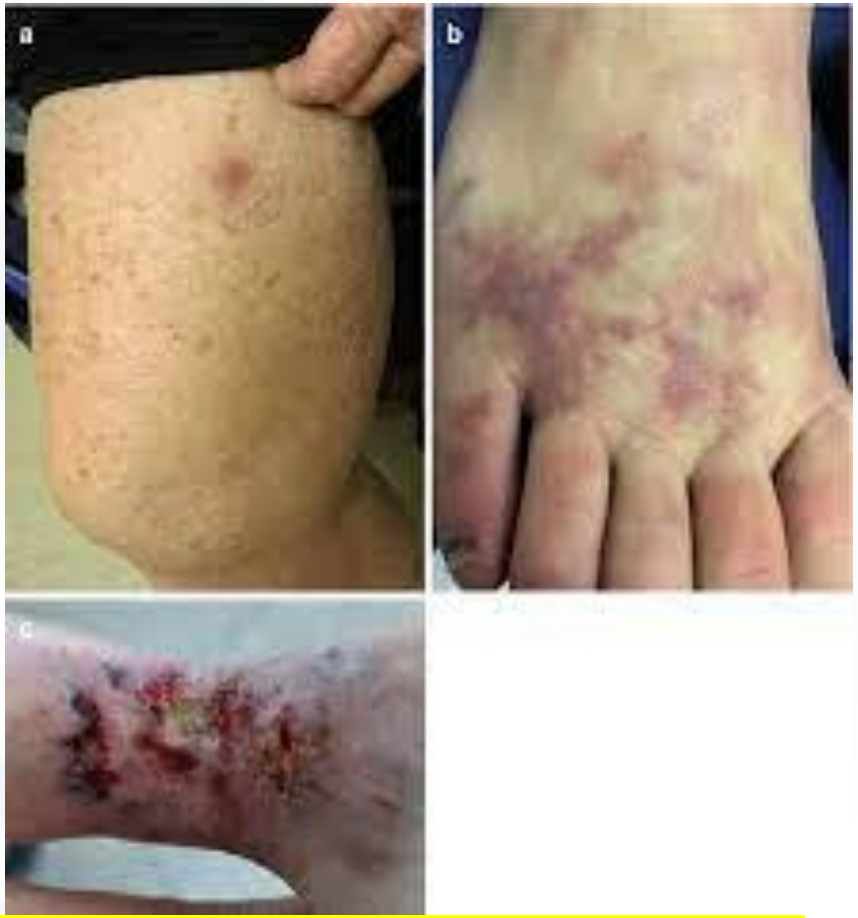
male gender, atypical age, and delayed or absent IVIG

MULTISYSTEM INFLAMMATORY SYNDROME (MIS-C) VS KAWASAKI DISEASE

MIS-C	KAWASAKI DISEASE
Mean age 10-11 y	Mean age 2 y
Individuals with African heritage appear at highest risk	Asians at highest risk
Severe abdominal pain	Less severe GI complaints
Myocardial dysfunction/myocarditis	Coronary artery abnormalities (25%-60% in Kawasaki shock syndrome)
Acute kidney injury	Renal involvement very rare
NT-pro-BNP and troponin ↑↑	Not often reported (myocardial dysfunction less severe) but generally normal to mildly increased
Ferritin, triglycerides, and CRP ↑↑	Same, but less severe
Platelet count ↓ and normalizes with recovery	Marked thrombocytosis by day 10-14
Lymphopenia	Lymphopenia not described
Association with SARS-CoV2 infection (2-4 wk prior)	Specific etiology still unknown; no association with SARS CoV2

Abbreviations: CRP, C-reactive protein; GI, gastrointestinal; NT-proBNP, N-terminal-pro type b natriuretic peptide; SARS-CoV2, severe acute respiratory syndrome coronavirus.

3-Polyarteritis nodosa



Childhood vasculitis Seza Ozen1 and Erdal Sag1, Rheumatology 2020;59:iii95–iii100

- PAN is the third most common vasculitis in childhood
- incidence of <1/100 000
- PAN is defined as a necrotizing vasculitis of medium or small sized arteries that has a tendency to spare glomeruli of the kidney and lungs.
- It is not associated with ANCA.
- Typical clinical features are fever, skin, musculoskeletal, renal (due to vasculitis of arcuate or lobar arteries, not glomerulonephritis), GI and neurological involvement .
- Hepatitis B-associated PAN is no longer seen in children,

- Because of the bleeding risk of aneurysms, percutaneous renal biopsy is not indicated.

ANCA are typically negative
Targeted tissue biopsy (deep skin biopsy) may be needed in patients with suspected PAN; however, due to patchy involvement of the disease, a negative biopsy does not exclude the diagnosis.

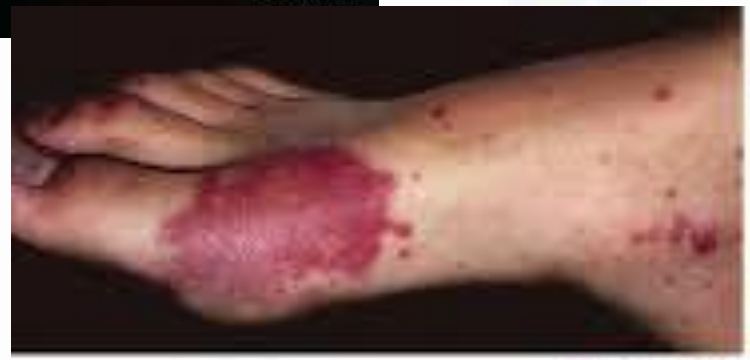
- Catheter digital subtraction angiography is the first line imaging procedure; however, it can be negative in the early course of the disease or after CS treatment.

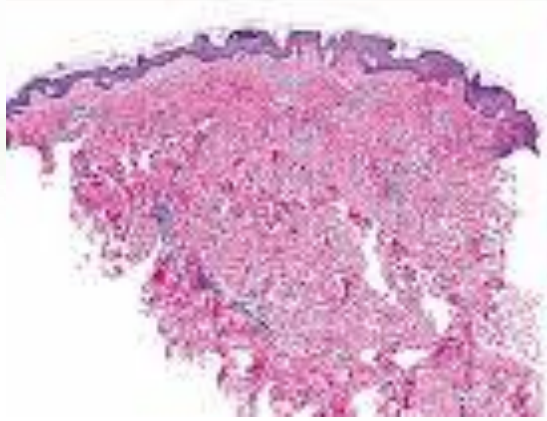
Treatment recommendations

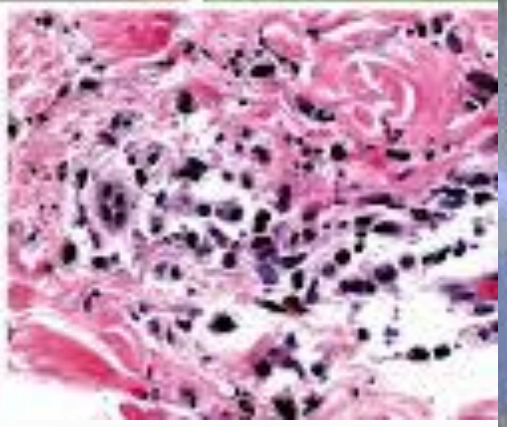
- Treatment of PAN is usually managed according to recommendations for adult onset PAN.
- Isolated cutaneous PAN can be treated with NSAIDs and CSs alone with careful monitoring of clinical and laboratory parameters.
- Patients with systemic disease should be treated with high doses of CSs and intravenous CYC or MMF for remission induction, followed by AZA or MMF as maintenance treatment .

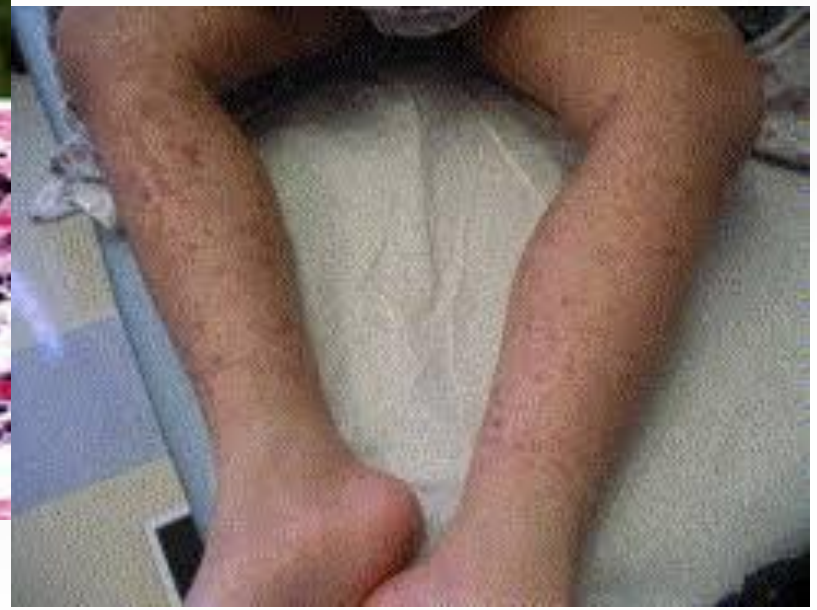
- Overall survival is better and the relapse risk is lower in children compared with adults.
- The overall mortality is about 1-4% and
- Relapse risk about 10-35%

4- ANCA-associated vasculitis









KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

CONFIDENTIAL: DO NOT DISTRIBUTE

PUBLIC REVIEW DRAFT

JUNE 2020

The kidney lesion associated with these conditions is a pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis (NCGN).

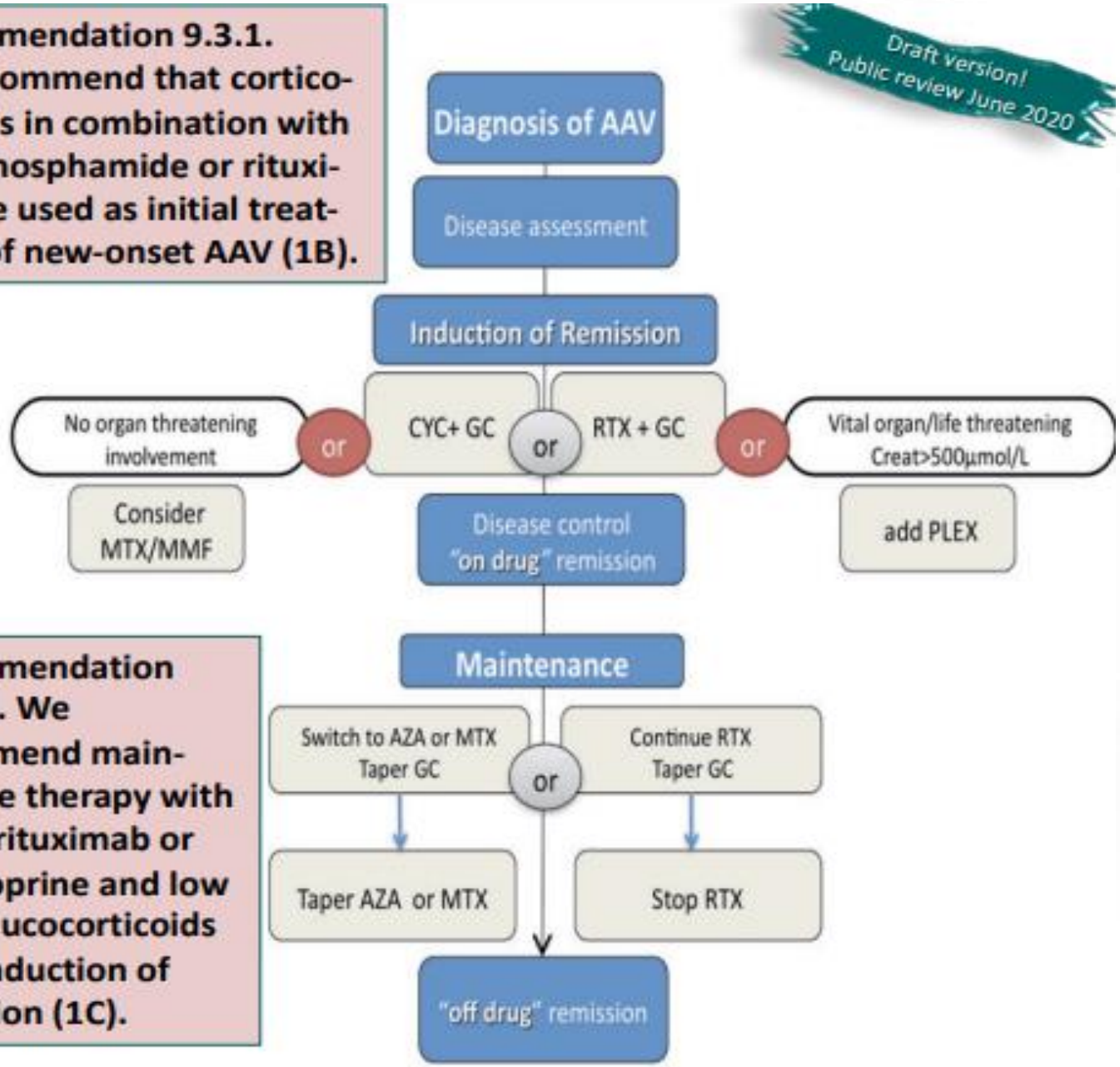
The persistence of ANCA positivity, an increase in ANCA levels, and a change in ANCA from negative to positive are only modestly predictive of future disease relapse and should not be used to guide treatment decisions.

Table ANCA8. Factors that increase relapse risk for AAV

Baseline factors	Factors after diagnosis	Treatment factors
Diagnosis of granulomatosis with polyangiitis	History of relapse	Lower cyclophosphamide exposure
PR3-ANCA subgroup	Antineutrophil cytoplasmic antibody positive at the end of induction	Immunosuppressive withdrawal
Lower serum creatinine	Rise in antineutrophil cytoplasmic antibodies	Glucocorticoid withdrawal
More extensive disease		
Ear, nose, and throat disease		

ANCA, anti-neutrophil cytoplasmic antibodies; PR3, proteinase-3

Recommendation 9.3.1.
We recommend that corticosteroids in combination with cyclophosphamide or rituximab be used as initial treatment of new-onset AAV (1B).



Recommendation 9.3.1.1. We recommend maintenance therapy with either rituximab or azathioprine and low dose glucocorticoids after induction of remission (1C).

Induction treatment

- Cyclophosphamides with Corticosteroids (1A)KDIGO 12 ,(B) KDIGO 20 .

1. KDIGO 12 (oral prednisolone 1 mg/kg/d max 60mg or IV Methyl prednisolone 500 mg daily 3 days doses)
2. with oral (Oral cyclophosphamides 1.5-2 mg/kg/d for 3 m ,continue for ongoing activity to a maximum of 6 m adjust dose to keep leukocyte count >3000/mm3
3. or IV 500mg/m2 monthly 6 doses or 15 mg/kg at weeks 0,2,4,7,10,13,16,19,,21,24 if required .Adjust dose to keep WCC >3000) (B) KDIGO 12

4. or in less severe disease or contraindication to cyclophosphamides as in children Concerned with infertility or in relapsing disease, we recommend rituximab with steroids (375mg/m2/w for 4 w or 1 gm at weeks 0,2)(1B) ,

N.B. IV cyclophosphamide is preferred to oral for patients with

- moderate cumulative dose or
- lower WBC count at risk of further drop to <3000 after start of cyclophosphamides
- or with poor patient adherence,
- and for those with ready access to an infusion center , although relapse rate is higher with IV .

- add PE (seven treatments over a maximum of 2w 60 ml/kg volume replacement, albumin substitution) if pulmonary hemorrhages (2C) or AGBM (2D) .
- Oral Cyclophosphamides to be stopped after 3m or if no extra renal manifestations or if he becomes dialysis dependent. (2C).

*Table ANCA7. Plasma exchange dosing and frequency for AAV**

Antineutrophil cytoplasmic antibody vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-glomerular basement membrane antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-glomerular basement membrane antibodies are undetectable

* If a patient is at risk of bleeding, volume replacement should be with fresh, frozen plasma.

- In children on rituximab with severe disease you may add 2 pulses cyclophosphamides & PE
- (Rituximab 375mg/m2x4w with IV cyclophosphamides. 15mg/kg at w 0,2 or Rituximab 1gm at 0,2 w with cyclophosphamides 500 mg/2w x6) .

Maintenance treatment

- Patients on rituximab) ,taper steroids (to a dose 5 mg/d by 6 m) and keep on rituximab for 18 m
- Patients on cyclophosphamides , taper steroids, shift to azathioprine (1mg/kg/d at remission until 1 y after diagnosis then taper by 25 mg every 3m) (1B) or MMF (600 mg/8h or 12h for 18 m) (2C) for 18 m (2D) KDIGO 12

Treatment of relapse as initial therapy (1c)or increase dose ,agents ,steroids(2c) .

Disease relapse is related to

- more extensive disease ,
- + ANCA or rising titer ,
- low cyclophosphamide exposure ,
- or steroid withdrawal

When to transplant? No TX until complete clinical remission for 6m-1y even if ANCA +

In Anti GBM /GN, Transplant should be delayed till un detectable anti GBM (1D) KDIGO 12

5- Monogenic vasculitides

- These diseases present in early childhood and are often resistant to conventional treatment.
- A number of inherited immune deficiencies may be associated with various features of vasculitis.

Childhood vasculitis Seza Ozen1 and Erdal Sag1, Rheumatology 2020;59:iii95–iii100

Deficiency of adenosine deaminase 2

- DADA is an autosomal recessively inherited disease associated with mutations in the ADA2 gene formerly called CECR1.
- The disease mainly presents with early onset strokes and PAN-like features.
- In fact it is not possible to differentiate the angiographic features nor the histopathology from classical PAN.
- Many patients who were initially diagnosed as early onset PAN have later tested positive for a mutation in the ADA2 gene.

- renal arteries have frequently been affected .
- Early onset livedo reticularis associated with chronic or recurrent signs of systemic inflammation, haemorrhagic/ischaemic stroke/peripheral nervous system involvement associated with systemic inflammation
- These patients have high acute phase reactants and often have fever.
- DADA2 has been now classified as an autoinflammatory disease with vasculitic features.

- testing for ADA2 enzyme levels and the mutation in a patient thought to have PAN if here is

1. a family history of an affected case or
2. consanguineous patients,
3. there is early onset stroke,
4. there are unexplained haematological and immunological abnormalities,
5. the patient is resistant to conventional treatment.

- These patients may have various haematological and immunological abnormalities such as

1. hypogammaglobulinaemia,
2. common variable immune deficiency,
3. lymphoproliferative immune dysregulation,
4. variable cytopenia including leucopenia, thrombocytopenia, lymphopenia and neutropenia

- The patients with PAN-like presentations respond well to anti-TNF agents.
- Anti-TNF therapy probably also prevents strokes.
- However, it is not effective on haematological features, which often necessitate haematological stem cell transplantation

Take home messages

1- Pediatric vasculitis differ than that in adults

2- Detailed history and examination still the golden pillars for diagnosis rather than investigations

3- When the guidelines fails to achieve remission revise type of disease , you should tailor treatment for individual case


The art of medicine consists in amusing the patient while nature cures the disease.
Voltaire

Thank you