RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

4th Annual National Conference

September 21–23, 2023

Pediatric IgA Vasculitis

Holly Reid, DNP, RN, CPNP
Instructor – University of Colorado School of Medicine
Section of Pediatric Rheumatology
Children's Hospital Colorado

Accreditation Statement

- All individuals in control of the content of continuing education activities provided by the Annenberg Center for Health Sciences at Eisenhower (ACHS) are required to disclose to the audience all relevant financial relationships related to the content of the presentation or enduring material. Full disclosure of all relevant financial relationships will be made in writing to the audience prior to the activity. All other staff at the Annenberg Center for Health Sciences at Eisenhower and RhAPP have no relationships to disclose.

Faculty Disclosures

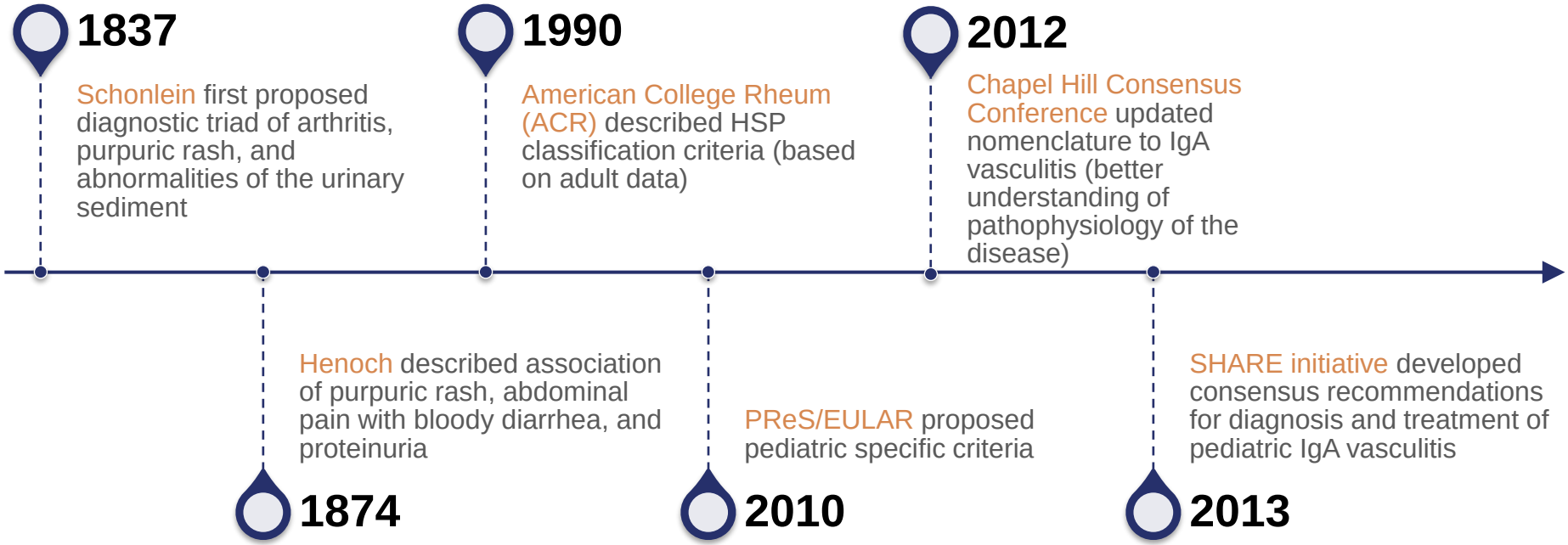
- The speaker has no relevant financial relationships with any commercial interests.

- The speaker will be discussing off-label medication use.

Objectives

- Recognize characteristic clinical manifestations of pediatric IgA vasculitis
- Identify severe complications, atypical presentations, and diagnostic dilemmas of pediatric IgA vasculitis
- Examine SHARE initiative guidelines for treatment of pediatric IgA vasculitis and current pharmacologic treatment options
- Discuss the rheumatology advanced practice provider’s role in managing pediatric IgA vasculitis

History/Nomenclature



Epidemiology

- IgA vasculitis is the most common systemic vasculitis of childhood
- Predominantly a disease of childhood (typically occurs ages 3-15 years)
  - Less common in adults but can have similar presentation (often more severe/worse outcomes)
- Incidence of 3 to 26.7 cases per 100,000 children
  - Peak incidence 70 per 100,000 children between ages 4-6
- More common in boys; male to female ratio 1.2 -1.8:1
- Occurs primarily in Fall, Winter, Spring
  - Approx ½ of infections preceded by URI

Pathogenesis

Immune-mediated vasculitis associated with IgA deposition, complement deposition, neutrophil recruitment

Infectious/chemical triggers recognized but underlying cause unknown

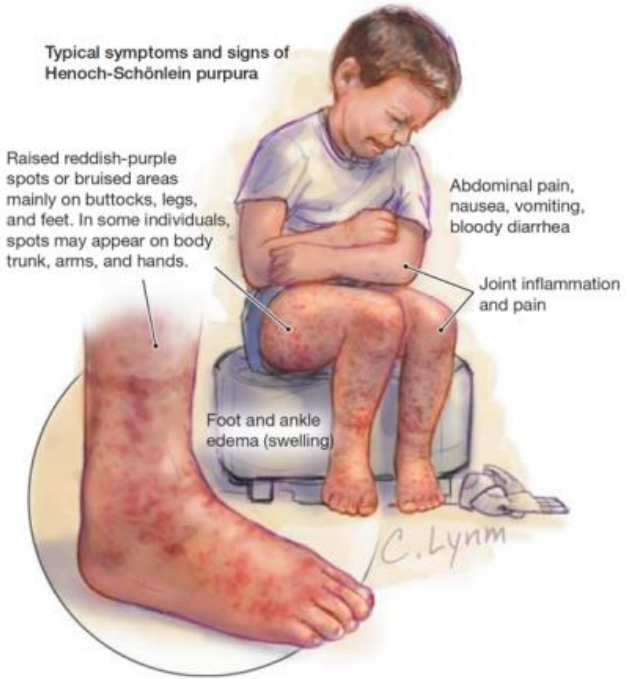
Characteristic finding = leukocytoclastic vasculitis accompanied by IgA immune complexes in affected organs

No causative genetic mutations

Objective #1

RECOGNIZE CHARACTERISTIC CLINICAL MANIFESTATIONS OF PEDIATRIC IGA VASCULITIS

Clinical Manifestations



2010 EULAR and PRES Pediatric Classification Criteria (validated in conjunction with PRINTO):

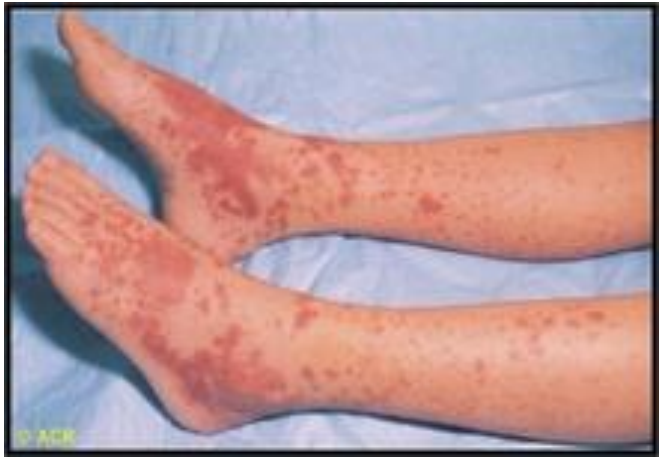
- Mandatory criterion: Palpable purpura or petechiae (lower limb predominance), without thrombocytopenia or coagulopathy
- + one or more of the following:
  - Abdominal pain (usually diffuse, acute onset)
  - Arthritis or arthralgia (acute onset)
  - Kidney involvement (proteinuria, hematuria)
  - Leukocytoclastic vasculitis or proliferative glomerulonephritis, with predominant IgA deposition

Clinical Manifestations

- Symptoms develop over course of days to weeks
- Purpura and joint are typically the presenting symptoms (~ ¾ of patients)
- Abd pain occurs in approximately ½ of patients (GI bleeding in 20-30% of patients)
- Kidney involvement occurs in 21-54% of patients

IgA Vasculitis: Rash

- Erythematous macular or urticarial wheels (can occasionally present with targetoid lesions) → coalesces/evolves into typical ecchymosis, petechiae, palpable purpura
- May be itchy, rarely painful
- Localized subQ edema also common
  - In dependent and periorbital areas



IgA Vasculitis: Joint Involvement

- Typically transient or migratory but can have significant pain/decreased ROM
- Oligoarticular, non-erosive
- Lower extremity large joints most common (hips, knees, ankles)
- Can precede purpura, though usually only by 1-2 days

IgA Vasculitis: GI Involvement

- Ranges from mild (nausea, vomiting, abdominal pain, transient paralytic ileus) to more severe
- Typically develops within 8 days of appearance of rash, though can appear up to months later
- Intussusception most common GI complication

IgA Vasculitis: Kidney Involvement

- Varies from microscopic hematuria to AKI
- Findings on UA w/ micro reflect degree of kidney injury
- Most common presentation is hematuria with or without red blood cell casts and mild or no proteinuria
- 90% of children who develop kidney involvement do so within 2 months of onset (97% within 6 months)

Laboratory Findings

Serum IgA elevated 50-70% patients (Higher levels associated with kidney involvement)

CBC, CMP, UA = nonspecific

(Hematuria, proteinuria may develop over time)

Inflammatory markers generally reflect triggering condition

PT, PTT, INR, Platelets usually normal

Hypocomplementemia often reported

Utility of Biopsy

Skin

- Not necessary for typical purpura lesions that affect lower limbs/buttocks
- Helpful if rash atypical (diffusely distributed or extensive lesions)
  - IgA staining
  - Used to exclude other vasculitides (such as ANCA-vasculitis)

Kidney

- Decision made in conjunction with pediatric nephrologist
- Indicated if severe or persistent proteinuria or impaired eGFR; nephrotic/nephritic syndrome

Differential Diagnoses

- Classic signs = diagnosis straightforward
- Incomplete presentation (lack of rash) = more challenging

- Acute hemorrhagic edema of infancy (AHEI)
- Hypersensitivity vasculitis
- Other small vessel vaculitides (GPA, MPA, EGPA) or medium vessel (PAN)
- SLE
- JIA
- Acute Rheumatic Fever
- Septic or reactive arthritis
- Appendicitis/acute abdomen
- IgA Nephropathy
- Meningococcemia/Sepsis
- Antiphospholipid Antibody Syndrome

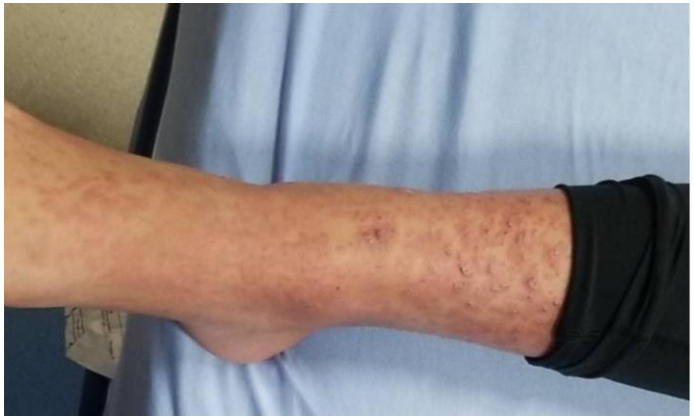
Objective #2

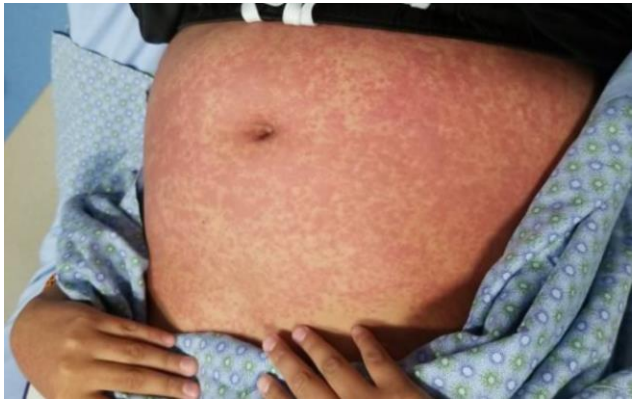
IDENTIFY SEVERE COMPLICATIONS, ATYPICAL PRESENTATIONS, AND DIAGNOSTIC DILEMMAS OF PEDIATRIC IGA VASCULITIS

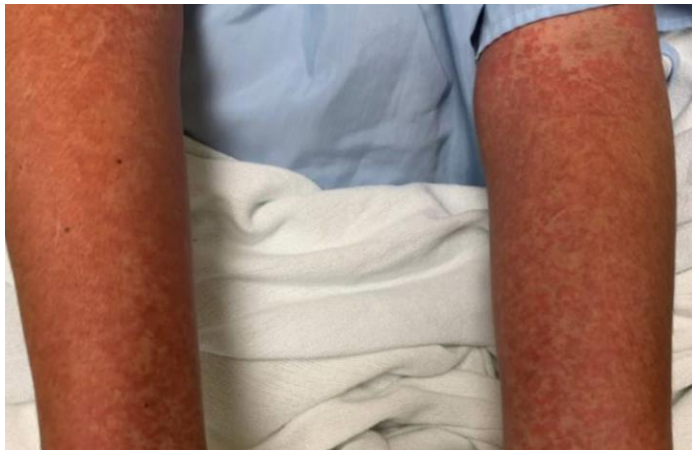
Case Study: RA

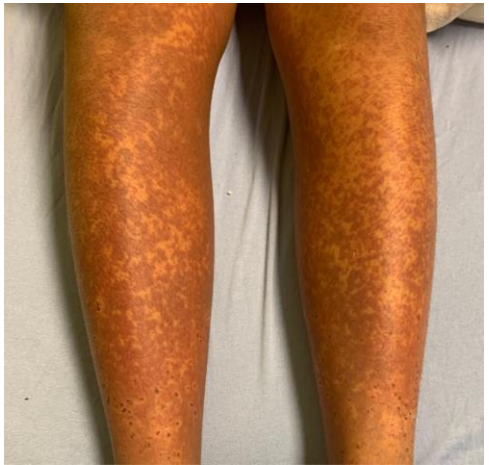
- 14 year old male presented to an Adult ED 3 times in early September for rash. Initially dx with folliculitis, then irritant contact dermatitis.
- 3rd ED visit also complained of significant abdominal pain (in addition to rash), and some foot pain
  - Admitted to hospital

RA rashes upon admission









RA labs upon admission

- **WBC 19.83**
- RBC 5.53
- Hgb 11.8
- Hct 36.6
- Plt 317
- Creatinine 0.58 (rr 0.42 – 0.90)
- **AST 55** (rr 15-40)
- **ALT 32** (rr 11-26)

- **CRP 1.4 mg/dL**
- ESR 10
- C3 126 (rr 86-184)
- C4 26.7 (rr 10-40)
- UA w/ micro: **+ small blood (crenated RBCs),** negative protein
- ASO/DNAase B normal ranges
- Respiratory PCR negative

Rheum consulted next day, additional labs:

- MonoSpot negative
- P-ANCA, C-ANCA negative
- PR3, MPO negative
- Serum IgA, IgG, IgM normal
- ANA (+ ENA) negative
- **Von Willebrand's Antigen 155%** (rr 44-144%)

- 2 days later, continued abdominal pain:
  - U/S for intussusception normal
  - **UA w/micro: + protein**, negative for blood
  - **Urine pr:cr ratio 0.48** (rr 0.0 – 0.20)

RA Hospital Course

- Dermatology consulted, obtained bx
  - Consistent with leukocytoclastic vasculitis
  - Dx IgA vasculitis
- IV methyl pred given, transitioned to oral pred upon discharge

- 3 days later, returned to ED with significantly worsening abdominal pain – readmitted
- CT angiogram abdominal with contrast: normal
  - No medium vessel vasculitis to suggest alternative dx such as PAN
- **UA with micro now with large blood, 100 protein**
- **Urine pr:cr ratio: 8.04** (rr 0 – 0.20)
- Serum cr 0.45
- BP 132/78

RA Hospital Course

- Nephrology consulted
  - Renal biopsy:
  - DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS WITH SEGMENTAL LESIONS INVOLVING 17/26 (65%) OF GLOMERULI:
    - 19% OF GLOMERULI SHOW ACTIVE CRESCENT FORMATION
    - NEUTROPHILIC INFLAMMATION PROMINENT IN THE SEGMENTAL LESIONS
    - 3+ IgA IMMUNE COMPLEX DEPOSITION SEEN IN ALL GLOMERULI WITH LESS EXTENSIVE 2+ C3 DEPOSITS; IgM, IgG, C1Q DEPOSITION NEGATIVE TO SCANT
    - NORMAL TUBULOINTERSTITIAL COMPARTMENT WITH FEW TUBULAR PROTEINACEOUS CASTS.
  - Dx IgAV Nephritis

RA Hospital Course

- Restarted on IV methylprednisolone
- Developed frank hematochezia
  - Peds Surg Consult (unremarkable)

- Due to significant IgAV nephritis: EuroLupus Cyclophosphamide protocol started (500 mg every 2 weeks x3 months)

RA Hospital Course

- s/p CYC:
  - Abd pain and hematochezia resolved, rash improved, foot/joint pain resolved
  - Urine pr:cr ratio improved to 4.01 (rr 0 – 0.20)
- Discharged home on oral pred taper
- Received CYC q2weeks x 3 months (+IV methylprednisolone pulses)
- After completion of CYC, transitioned to azathioprine
- Persistent proteinuria → Nephrology started lisinopril
- 1 year later, incomplete disease control, therefore azathioprine switched to mycophenolate
- 2 years post initial hospital discharge → dx Celiac disease
- Currently doing well on medications, no recent reoccurrence of symptoms

Refractory Disease

Liao *et al. Pediatric Rheumatology* (2020) 18:86
https://doi.org/10.1186/s12969-020-00480-3

Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Onset age is a risk factor for refractory pediatric IgA vasculitis: a retrospective cohort study

Chun-Hua Liao[1], Melody Tsai[1], Yao-Hsu Yang[1], Bor-Luen Chiang[1,2] and Li-Chieh Wang[1*]

Results:

- Renal involvement: more frequent in older children
- Joint symptoms: more frequent in younger children
- Abdominal involvement: no difference in age groups

Conclusion: Pediatric IgAV with different onset ages are associated with distinct clinical manifestations and outcomes. The risk of developing corticosteroid dependence, refractory disease and renal involvement increased with onset age.

Severe Complications: Kidney

Similar presentation to IgA Nephropathy (immunologic and histopathologic)

Severe presentations include nephrotic syndrome, acute nephritic syndrome, hypertension, renal failure

- Risk factors for kidney involvement:
  - Male gender
  - Older age
  - Severe GI symptoms
  - Arthritis/arthralgia
  - Persistent purpura
  - Relapse
  - Raised WBC or platelet count
  - Elevated antistreptolysin titer (ASO)
  - Low C3

Severe Complications: GI

Intussusception most common

- Limited to small bowel in 60% of patients
- Reported overall incidence of 2.3 – 3.5%

More severe/life threatening:

- Bowel ischemia/necrosis/perforation
- GI hemorrhage

Rare GI manifestations:

- Acute pancreatitis
- Gall bladder involvement
- Protein-losing enteropathy

For worsening GI symptoms: serial abdominal exams, hemoccult, advanced imaging, Peds Surgery consult

Severe Complications: Skin

ELSEVIER

Seminars in Arthritis and Rheumatism

Volume 61, August 2023, 152209

Clinical features, treatment and outcome of pediatric patients with severe cutaneous manifestations in IgA vasculitis: Multicenter international study

Mario Sestan [a], Nastasia Kifer [a], Betul Sozeri [b], Ferhat Demir [b], Kadir Ulu [b], Clovis A. Silva [c], Reinan T. Campos [c], Ezgi Deniz Batu [d], Oya Koker [e], Matej Sapina [f], Sasa Srsen [g], Martina Held [a], Alenka Gagro [h], Adriana Rodrigues Fonseca [i], Marta Rodrigues [i], Donato Rigante [j], Giovanni Filocamo [k], Francesco Baldo [k], Merav Heshin-Bekenstein [l], Teresa Giani [m]... Marija Jelusic [a]

- Severe manifestations: hemorrhagic vesicles, bullae, ulcerations, necrosis
- Findings:
  - Patients were older
  - Developed nephritis more frequently (with worse outcomes of renal disease)
  - Higher frequencies of GI complications
  - D dimers higher in these patients
  - More frequent need for steroids

Other Complications of IgA Vasculitis

- Urologic
  - Orchitis (w/o evidence of testicular torsion)
- Ophthalmic (rare)
  - Keratitis, uveitis
- Respiratory (rare)
  - Pulmonary hemorrhage
  - Interstitial pneumonitis
- CNS/PNS
  - Rare: CNS vasculitis, hemorrhage, SZ, encephalopathy, ataxia, neuropathy
  - Headaches without other neurological signs are common

Objective #3

EXAMINE SHARE INITIATIVE GUIDELINES FOR TREATMENT OF PEDIATRIC IGA VASCULITIS AND CURRENT PHARMACOLOGIC TREATMENT OPTIONS

Lack of Guidelines for Pediatric IgA Vasculitis

- Although a common childhood vasculitis, well-designed controlled studies addressing diagnosis, management, and outcomes are lacking
- 2013 → Single Hub and Access point for Pediatric Rheumatology in Europe (SHARE) initiative
  - Panel of 16 international experts in peds rheum and peds nephrology
  - Developed internationally agreed upon consensus recommendations for diagnosis and treatment

Table 3 SHARE recommendations for the treatment of IgAV

Number	Recommendations: Treatment	LoE	SoR
Analgesia			
1.	Adequate analgesia should be prescribed for IgAV-associated arthropathy[a]	4	D
2.	NSAIDs are not contraindicated if renal function is normal in IgAV	4	D
3.	Adequate analgesia should be prescribed for IgAV-associated abdominal pain	4	D
Use of CS			
4.	CS treatment is indicated in case of: • Orchitis • Cerebral vasculitis • Pulmonary haemorrhage • Other severe organ- or life-threatening vasculitis manifestations	4	D
5.	In patients with severe abdominal pain and/or rectal bleeding (in whom intestinal intussusception has been excluded), CS treatment could be considered	4	D
6.	The dose of oral CS (prednisolone/prednisone) should be 1–2 mg/kg/day	4	D
7.	If CS are indicated, pulsed i.v. methylprednisolone (e.g. 10–30 mg/kg with a maximum of 1 g/day on three consecutive days) may be considered for severe cases	4	D
8.	Prophylactic CS treatment to prevent the development of IgAV-associated nephritis is not indicated	1B	A
IgAV nephritis			
9.	When starting treatment of IgAV nephritis, a paediatric nephrologist should be consulted	4	D
10.	In the absence of robust data for evidence supporting the treatment of nephritis, a randomized controlled trial for the treatment of IgAV nephritis is urgently needed	4	D
11.	ACE inhibitors should be considered in IgAV nephritis to prevent/limit secondary glomerular injury for patients with persistent proteinuria	4	D
12.	Oral prednisolone should be used as first-line treatment in patients with mild IgAV nephritis	4	D
13.	AZA, MMF and/or pulsed methylprednisolone can be used as second-line treatment in patients with IgAV nephritis following renal biopsy	4	D
14.	Oral prednisolone and/or pulsed methylprednisolone should be used as first-line treatment in patients with moderate IgAV nephritis	4	D
15.	AZA, MMF or i.v. CYC may be used in the first- or second-line treatment of moderate IgAV nephritis	4	D
16.	Ciclosporin or oral CYC cannot be routinely recommended in moderate IgAV nephritis	4	D
17.	As in other severe systemic small vessel vasculitides, i.v. CYC with pulsed methylprednisolone and/or oral prednisolone are recommended as first-line treatment in patients with severe IgAV nephritis	4	D
18.	In combination with steroid therapy, AZA and MMF may be used as maintenance treatment in patients with severe IgAV nephritis	4	D
19.	One treatment approach for IgAV nephritis is listed below in Fig. 1	4	D

Treatment: Mild to Moderate Pain

- IgA Vasculitis is typically self-limited
- NSAIDs (avoid if GI bleed, evidence of kidney involvement other than microscopic hematuria)
- Acetaminophen

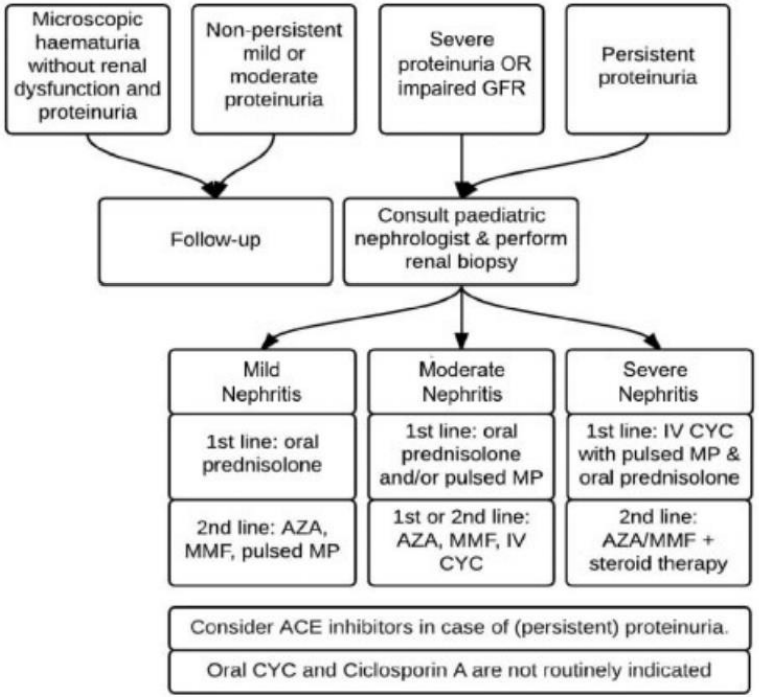
Treatment: Severe Pain

- Corticosteroids (pred 1-2 mg/kg/day – max of 60-80 mg)
  - May shorten duration of abdominal pain, however does not otherwise impact clinical course
  - Recommend slow taper over 3-4 weeks to avoid disease rebound
  - Extra careful monitoring for worsening abdominal disease since steroids can obscure signs/symptoms
- Consider IV methylprednisolone (10-30 mg/kg – max of 1G over 1-3 days) if concerned about oral absorption (due to submucosa gut edema)
- SHARE Guidelines indications: orchitis, cerebral vasculitis, pulmonary hemorrhage, severe GI involvement

Treatment: IgAV Nephritis

- Consult pediatric nephrology
- ACE inhibitors should be considered to prevent/limit secondary glomerular injury
- Oral pred alone for mild disease
- Following renal bx, secondary agents for moderate disease include: MMF, azatioprine, IV methylprednisolone (+/- oral pred taper)
- Consider IV CYC for moderate to severe disease
  - Oral CYC not routinely recommended
- Cyclosporine not routinely recommended

Fig. 1 Guideline for the management of IgA vasculitis-associated nephritis



Objective #4

DISCUSS THE RHEUMATOLOGY ADVANCED PRACTICE PROVIDER'S ROLE IN MANAGING PEDIATRIC IGA VASCULITIS

- Straightforward IgA Vasculitis is often managed by the PCP
  - Typically resolves within one month
  - Adequate oral hydration, bed rest, symptomatic relief of joint/abdominal pain
  - Recommendations include monitoring BP/UA weekly x 1-2 months, then monthly x 1 year

- Reoccurrence of IgAV occurs in about 1/3 of patients (typically within about 4 months)
- Reoccurrence more common in:
  - Patients with nephritis
  - Patients with evidence of acute inflammation (elevated ESR especially)
  - Patients who received tx with steroids

- With complications or reoccurrence, rheumatology is often involved
  - Help guide PCPs with steroid recommendations
  - Help manage patient when steroid-sparing agent is needed
  - Help expand the differential (? correct diagnosis)
  - Collaborate closely with nephrology

Summary

- IgA Vasculitis (formally called HSP) is the most common systemic vasculitis of childhood, with a peak incidence in children ages 4-6
  - Older age associated with more refractory/severe disease course
- Immune-mediated vasculitis likely triggered by variety of antigens (includes various infectious or environmental exposures)
- Tetrad of clinical manifestations includes palpable purpura (without thrombocytopenia or coagulopathy), arthritis/arthralgia, abdominal pain, kidney disease

Summary

- Diagnosis can be more difficult if skin manifestations absent at disease onset
- Treatment depends on severity of disease (NSAIDs → Steroids → MMF/AZA → CYC)
  - SHARE initiative guidelines
- Close monitoring for kidney and GI complications
- Advanced practice rheumatology providers can play a key role in effectively managing complex IgAV patients and collaborating closely with primary care, nephrology and other subspecialities

References

- Brogan, P., Knott, K. Immune Complex Small-Vessel Vasculitis: IgA Vasculitis (Henoch-Schonlein) and Hypersensitivity Vasculitis. In: *Textbook of Pediatric Rheumatology*. Eighth Edition. Petty RE, Laxer RM, Lindsely CB, et al., eds. Philadelphia: Elsevier, Inc.; 2021.
- Dedeoglu, F., Kim, S. IgA vasculitis (Henoch-Schonlein purpura): Clinical manifestations and diagnosis. In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA.
- Dedeoglu, F., Kim, S. IgA vasculitis (Henoch-Schonlein purpura): Management. In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA.
- Liao, Chun-Hua, et al. “Onset Age Is a Risk Factor for Refractory Pediatric IGA Vasculitis: A Retrospective Cohort Study.” *Pediatric Rheumatology*, vol. 18, no. 1, 2020, https://doi.org/10.1186/s12969-020-00480-3.
- Niaudet, P., Appel, G., Hunder, G. IgA vasculitits (Henoch-Schonlein purpura): Kidney manifestations. In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA.
- Ozen, S., Marks, S. D., Brogan, P., Groot, N., de Graeff, N., Avcin, T., Bader-Meunier, B., Dolezalova, P., Feldman, B. M., Kone-Paut, I., Lahdenne, P., McCann, L., Pilkington, C., Ravelli, A., van Royen, A., Uziel, Y., Vastert, B., Wulffraat, N., Kamphuis, S., & Beresford, M. W. (2019). European consensus-based recommendations for diagnosis and treatment of immunoglobulin a vasculitis—the share initiative. *Rheumatology*, *58*(9), 1607–1616. https://doi.org/10.1093/rheumatology/kez041
- Sestan, Mario, et al. “Clinical Features, Treatment and Outcome of Pediatric Patients with Severe Cutaneous Manifestations in IGA Vasculitis: Multicenter International Study.” *Seminars in Arthritis and Rheumatism*, vol. 61, 2023, p. 152209, https://doi.org/10.1016/j.semarthrit.2023.152209.

Thank you!

QUESTIONS?