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Pederm Insights

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In this Issue

Editor's Prologue

Dear Colleagues,

Season's greetings!

As we leaf through the pages of the new year, we sail toward horizons brimming with fresh possibilities and nascent vistas. Before embarking on this journey, I wish to acknowledge the exceptional work of Dr. Resham Vasani and the editorial team, whose efforts curated such insightful and well-received issues over the past year. Following the path carved by capable hands is both an honour and a quiet challenge, and I hope to build upon what has been thoughtfully laid, for lasting work is the continuation of many ripples merging to become the current of change.

I am delighted that the newsletter format has been upheld, crafted to condense the torrent of information into clear, engaging capsules, enlightening and inspiring the mind, best savoured during a reflective pause.

*This issue focuses on **PEDIATRIC VASCULITIS**, a field challenging diagnostic acumen and rewarding vigilance, while the Journal Review section captures recent advances, translating research into practical strategies. Meanwhile, the Clinical Vignette guides us through the labyrinthine corridors of Rickettsial vasculitis with encephalopathy, reminding us that uncommon presentations sharpen clinical discernment and foster interdisciplinary collaboration. To tickle the grey matter, we present an exciting Photo quiz.*

In the Therapeutics section, Rituximab emerges as a molecule of promise, with expanding applications in pediatric dermatology and valuable clinical pearls. For residents and early-career clinicians, the Resident's Column, "Approach to Pediatric Vasculitis – From Bench to Bedside" bridges the chasm between research and practice.

I extend my heartfelt gratitude to all contributors, whose dedication infused spirit and substance into the idea, making it a collective achievement.

*Your feedback is always welcome and can be sent to **jetabuch@gmail.com**.*

Happy reading!

Warm regards,
Editor-in-Chief
Jeta Buch

Journal Review

In this section, we review five key clinical conundrums on evolving insights in pediatric vasculitis.

CLINICAL CONUNDRUM 1: Henoch Schonlein Purpura (HSP) / IgA vasculitis (IgAV)

Submitted by Dr Sirisha Varala

Given the ongoing burden of childhood IgA vasculitis (IgAV), three pivotal clinical questions emerge to guide our practice:

1. How can the distribution of purpura help us anticipate specific system involvement in IgAV?
2. Which clinical features and high risk factors should heighten our suspicion for gastrointestinal involvement?
3. What are the recommended guidelines for renal monitoring in IgAV?

EDITOR's OVERVIEW

Purpura may serve as a clinical compass—directing attention beyond IgA vasculitis toward mimickers that share its surface appearance yet diverge in systemic depth.

Consider the following associated features while evaluating a child with purpura:

- Is the child experiencing severe abdominal pain or rapidly progressive renal dysfunction? Such features raise suspicion for *systemic vasculitis*, distinguished by ANCA positivity and a pauci-immune biopsy.

- Do you observe purpura in conjunction with hematuria, arthralgia, or neuropathy? This constellation raises suspicion of *cryoglobulinemic vasculitis*, confirmed through cryoglobulin assays and hepatitis serology.

- Was there recent drug exposure, but no hematuria or gastrointestinal involvement? This pattern is characteristic of *hypersensitivity vasculitis*, supported by routine laboratory studies.

- Is purpura accompanied by fever and systemic toxicity? This should prompt evaluation for *bacterial endocarditis or meningococcemia*, confirmed via blood cultures and microbiologic testing.

- Are there clinical features of arthritis, Raynaud's phenomenon, or multisystem involvement? These signs may indicate a *connective-tissue disease*, further delineated by disease-specific autoantibodies.

- Does the purpura appear fine and non-palpable? This points toward *thrombocytopenia,* where a low platelet count, rather than true vasculitic inflammation, explains the cutaneous findings.

- Finally, in pediatric patients, ask: Is the purpura palpable and polymorphic? This remains a defining feature of *IgA vasculitis*, serving as a crucial diagnostic clue that guides the clinician toward—or away from—the correct diagnosis.

ARTICLE 1:

Characteristics of cutaneous manifestations in immunoglobulin A vasculitis and their relationships with system involvement and treatment needs. Kaplan MM, Ekici Tekin Z, Çelikel E, Güngörer V, Karagöl C, Polat MC et al. Eur J Pediatr. 2024 Nov 15;184(1):17.

This was a retrospective observational study conducted in 489 immunoglobulin A vasculitis (IgAV) patients who were followed-up for at least 6 months between 2013 and 2024. Patients were divided into subgroups based on the presence or absence of vesicles / bullae, necrosis/ulcer, rash spreading above the buttocks and persistence and were analyzed in relation to systemic involvement and treatment. Diagnosis of IgAV was made according to EULAR / PRINTO /PRES criteria.

Of 489 patients, mean age at diagnosis was 6.8±3.2 years with males constituting 53.8%. Palpable purpura was present in all patients (100%) with vesicles / bullae seen in 36 (7.4%) and necrosis/ ulcer in 22 patients (4.5%). Lesions were limited to lower extremities/buttocks in 345 patients (70.6%) with spread above buttocks (to trunk/upper extremities/face) seen in 144 (29.4%). Persistent rash, defined as >1 month was seen in 7.4%.

Salient findings of this study are as follows :
Systemic associations -

- patients with necrosis/ulcers had more persistent rash and genital tract involvement (p=0.02, p=0.04, respectively);
- patients with rash spreading above the buttocks had more GI tract and genital tract involvement (p=0.014, p=0.003, respectively)
- patients with a persistent rash had more renal involvement (p=0.05)

Treatment correlations-

- Increased steroid usage was seen in those with severe cutaneous manifestations like vescicale/ bullae (p=0.003), necrosis/ulcer (p=0.00), spreading rash (p<0.001) and persistent rash (p=0.03).

Limitations - Single centre, retrospective, no objective method of assessing the severity of the disease.

Conclusion - Morphology of skin lesions, distribution and persistence of the rash are important in predicting the systemic involvement and thereby the need for intensive treatment.

ARTICLE 2:

Analysis of Clinical Features and High-Risk Factors of Gastrointestinal Involvement in Children With IgA Vasculitis. Cao D, Liu X. Clin Pediatric (Phila). 2025 Nov 6:99228251389785.

This is a single-center retrospective analysis of 195 hospitalized children (aged <18 years) diagnosed with IgA Vasculitis as per EULAR /PRINTO /PRES criteria from June 2019 to April 2024. The study was aimed to compare clinical and laboratory profiles between IgA Vasculitis children with and without GI involvement, and identify independent risk factors for GI complications. Patients were stratified into those with GI envolement (n=62, 31.8%) vs. non-GI (n=133) involvement. GI involvement was defined by symptoms such as abdominal pain, vomiting, diarrhea, bleeding, intussusception or perforation. Demographics, clinical manifestations and laboratory parameters (complete blood count, inflammatory markers, immunoglobulins, uric acid) were looked into.

Salient findings are as follows :

- 31.8% had GI involvement, 7.2% developed renal involvement, 53.3% experienced arthritis or arthralgia.
- 14 children (22.6%) experienced abdominal symptoms before the onset of purpura, with skin lesions appearing 1 week after abdominal symptoms in 1 case and within 1 week in the other cases.
- GI bleeding or positive fecal occult blood was the commonest presentation seen in 74.2% of the cases followed by multiple GI ulcers.
- Children with GI involvement had significantly lower rates of arthritis/arthralgia ($P<0.05$).
- Multivariate logistic regression analysis has shown that, elevated neutrophil-to-lymphocyte ratio, platelet count, and uric acid levels, and decreased IgG levels, are independent predictors of GI involvement.

Strengths of the study: Large cohort, robust statistics

Limitations: Single-centre (potential selection bias), retrospective design (missing data risk), no long-term outcomes measured (e.g., chronic renal risk).

ARTICLE 3:

National recommendations for the management of children and young people with IgA vasculitis: a best available evidence, group agreement-based approach. Oni L, Platt C, Marlais M, McCann L, Barakat F, Hesseling M et al, Arch Dis Child. 2024 Dec 13;110(1):67-76.

This project by Oni et al from UK was designed to use best available evidence and group-agreement based approach to develop national recommendations for the initial management and associated complications in children and young people with IgA vasculitis. Using accredited methodology and an inclusive, multiprofessional, representative working group, evidence was generated based on key topics and recommendations were given.

Over 14 months, a 28-member Guideline Development Group (GDG)—comprising pediatricians, nephrologists, rheumatologists, general practitioners (GPs), surgeons, and patient representatives—employed a hybrid methodology blending systematic evidence synthesis with expert consensus. Key questions were classified across two domains: initial management (aimed for GPs and pediatricians) and management of complications (for subspecialists). A systematic review of 82 eligible articles focusing on pediatric population between 2002–2022 was done. Evidence was appraised using a modified GRADE system (1- strong, 2- weak recommendation; A–D: quality of evidence), supplemented by international guidelines where gaps persisted.

Key recommendations are as follows :
Diagnosis and classification:

- Disease diagnosis was done using 2010 EULAR /PRINTO /PRES criteria. For atypical presentations (e.g., non-palpable purpura or isolated organ involvement), skin biopsy with immunofluorescence to confirm IgA deposits was recommended.
- "Persisting" disease was defined as rash lasting >1 month and "recurrent" as re- emergence of rash after >1 month of remission.

Initial Management and Screening:
Specialist Referral Recommendations in IgAV
Strong Recommendation (Grade 1):

- Unremitting abdominal pain, protein-losing enteropathy, and/or GI bleeding → pediatric gastroenterology/pediatric rheumatology.
- Significant nephritis (proteinuria, UP:UC ratio >250 mg/mmol, nephrotic/nephritic syndrome, and/or kidney insufficiency) → pediatric nephrology.
- CNS involvement (cerebral vasculitis with neurological symptoms/signs) → pediatric neurology/pediatric rheumatology.
- Pulmonary hemorrhage (pulmonary vasculitis with acute respiratory tract bleeding) → pediatric respiratory/pediatric rheumatology.

Specialist Advice (Grade 2):
- Scrotal/testicular involvement (orchitis) → Pediatric surgeon/urology.
- Severe skin manifestations (intense subcutaneous oedema, blistering, and/or necrotic features) → Dermatology/pediatric rheumatology.
- Severe, unremitting musculoskeletal involvement (arthropathy requiring hospital admission) → Pediatric rheumatology.

Nephritis Screening in IgAV
Strong Recommendation: Frequent urinalysis over 6 months (weekly for first 4–6 weeks, then monthly).
Weak Recommendation: Blood pressure assessment at diagnosis and if evidence of nephritis (grade 2C).

Musculoskeletal involvement in IgAV
- Appropriate analgesia and rest preferred over oral corticosteroids in view of lack of long term morbidity due to musculoskeletal involvement.

Management of Complications:
Renal (IgAV Nephritis)
- A strong recommendation for renal biopsy in cases of persistent and severe proteinuria (>250 mg/mmol for ≥4 weeks), moderate proteinuria (100–250 mg/mmol for ≥3 months), AKI (stage ≥1), or nephrotic syndrome (grade 1C);

Nephritis Treatment in IgAV (with pediatric nephrologist):
- Corticosteroids: For moderate-severe disease, oral prednisolone 1–2 mg/kg/day for 2–4 weeks with gradual tapering; or pulsed IV methylprednisolone for severe nephritis, rapidly progressive glomerulonephritis, or compromised oral absorption.
- Refractory cases: Azathioprine, mycophenolate mofetil, or cyclophosphamide.
- Residual proteinuria: (>100 mg/mmol at 3 months or >50 mg/mmol at 6 months) → Introduce RAAS inhibitors (ACE inhibitors/ ARBs).

Gastrointestinal Involvement
- Admit for severe pain or bleeding; exclude intussusception via ultrasound/clinical assessment.
- Empiric prednisolone 1–2 mg/kg/day for 1–2 weeks, started within 3 days of severe abdominal pain or acute GI bleed.
- Surgical/radiological input essential for suspected perforation or obstruction.

Testicular Involvement
- Suspect acute orchitis in boys with painful scrotal edema and palpable purpura.
- Treatment: Corticosteroids (prednisolone 1–2 mg/kg/day for 1–2 weeks) after specialist referral for surgical advice.

Follow-Up and Long-Term Monitoring:
Follow up of atleast 3 years for biopsy-proven nephritis to vigilantly track for hypertension, proteinuria relapse, or CKD.

COMMENTS:

IgA vasculitis or Henoch Schonlein purpura is the most common vasculitis seen in Pediatric age group. The most common presentation is palpable purpura affecting the lower limbs. Severe cutaneous features—such as vesicles/bullae, necrosis/ulcers, rash extending above the buttocks, or prolonged persistence of rash signal higher risks for systemic issues. Persistent rash (> 1 month) correlates with renal problems, often prompting steroid treatment. Short term complication includes GI involvement which determines the early prognosis of the disease. It is of importance to note that GI manifestations can precede the onset of rash leading to a delay in diagnosis and unnecessary surgical interventions and can be predicted by markers like elevated neutrophil-to-lymphocyte ratio, platelets, and uric acid alongside low IgG levels. UK national guidelines advocate routine urinalysis and blood pressure monitoring frequently post-diagnosis along with appropriate specialist referrals wherever indicated. The long term prognosis depends on renal involvement with a minority of them progressing to CKD or end stage renal disease due to lack of proper monitoring and treatment.

The following nephritis screening recommendations will be useful for monitoring children with IgAV.*

1. Investigations recommended in all patients with IgAV- Initial blood pressure recording, estimated glomerular filtration rate (eGFR), urinalysis for hematuria and proteinuria, urine protein: urine creatinine ratio in an early morning urine sample.
2. If there is hypertension, macroscopic hematuria or significant proteinuria, investigations to consider - complete blood count with platelet and differential counts, urea, serum creatinine, electrolyte levels, albumin and coagulation studies.
3. Indications for Renal biopsy –
   - Impaired eGFR (<80 mL/min/1.73 m2)
   - Severe proteinuria – urine protein : urine creatinine ratio (UP:UC ratio) > 250 mg/ mmol in an early morning urine sample
   - Persistent moderate proteinuria - UP:UC ratio 100-250 mg/mmol for 3 months or >50 mg/mmol for 6 months.
   - Nephritic or nephrotic syndrome and rapidly progressing glomerulonephritis (relative indication)

4). Follow up guidelines -
   - All patients with IgAV should be followed-up for at least 6–12 months even if the initial blood pressure measurements and urinalysis are normal.

- In the case of normal findings - weekly urinalysis in first month, monthly once during next 6 months, and then once every 6 months.
- Longer and more frequent follow up (3-5 years) is required in proven IgA nephritis.
- Although there are no consensus recommendations, it is suggested that longer follow-up might be useful in older children with the onset of GI symptoms before other IgAV symptoms, severe GI form of IgAV, as well as those who develop ulcerations and necroses and persistent purpura, since they may be at higher risk for the later development of nephritis.

**Sestan M, Jelusic M. Diagnostic and Management Strategies of IgA Vasculitis Nephritis/Henoch-Schönlein Purpura Nephritis in Pediatric Patients: Current Perspectives. Pediatric Health Med Ther. 2023 Mar 7;14:89-98.*

EDITOR's NOTE:

Although the rash of IgAV commonly affects the extensor aspects of lower extremities and buttocks, it is not uncommon to see involvement of upper extremities and trunk. Purpura can rarely affect the face, ears and abdomen but never in isolation. Initially, the skin lesions manifest as clusters of erythema, urticaria and maculopapular rash, and then turn into petechiae and ecchymosis. Atypical presentations include bullae, necrosis and ulcers. In some cases, subcutaneous oedema over the dorsum of hands, feet and face may also occur.

Along with gastrointestinal symptoms, oedema, rash above the waist, a high neutrophil-to-lymphocyte ratio, and low mean platelet volume (MPV) are risk factors for GI involvement.

Musculoskeletal involvement in IgA vasculitis manifests as acute, oligoarticular, non-migratory arthritis, predominantly targeting the joints of lower extremities such as the knees and ankles due to their susceptibility to mechanical stress and microvascular inflammation. It affects up to 80% of patients and is typically self-limiting, with symptom improvement occurring within 3 to 12 days in most cases.

Renal involvement is seen in 30–50% of patients overall in IgAV. The spectrum of renal disease ranges from mild urinary abnormalities to nephritic and nephrotic syndromes and ultimately to chronic renal failure. Nephritic syndrome (characterized by haematuria plus at least two of the following: hypertension, elevated plasma creatinine, or oliguria) or nephrotic syndrome (characterized by oedema, hypoalbuminemia, and heavy proteinuria) develops in approximately 20% of patients with renal involvement. Children with isolated microscopic hematuria and no evidence of renal dysfunction or proteinuria typically require no specific therapeutic intervention beyond a "watchful waiting approach", given their excellent prognosis. Children with IgAV but without initial renal involvement should undergo monitoring for at least 6 months, as this is the timeframe in which pathological urinary findings usually emerge—although IgAV nephritis can sometimes manifest even later. Children presenting with significant renal involvement and/or persistent proteinuria should receive regular assessments of their glomerular filtration rate (GFR). It is important to note that hypertension may develop even after normalization of renal function and urinalysis.

Certain red flag signs that override UPCR include:
• Severe colicky abdominal pain
• GI bleeding
• Pulmonary haemorrhage
• CNS symptoms (seizures, focal deficits, severe headache)
• Rapid oedema or oliguria require immediate Pediatric/nephrology consultation

Mild disease is treated with symptomatic acetaminophen or NSAIDs (for abdominal pain or arthritis). Steroids (Prednisolone 1–2 mg/kg/day, 1–2 weeks, tapering dose) are indicated in cases of severe abdominal pain (due to bowel wall oedema, bleeding, intussusception prevention), severe arthritis/arthralgia, testicular involvement, severe skin disease (ulcerative and necrotic), and renal involvement (steroid pulse). NSAIDs are contraindicated in active gastrointestinal bleeding or renal involvement, except in cases of microscopic haematuria.

In most children, IgAV is a mild disease that lasts for 2–3 weeks on an average. 15–40% of the patients have at least one recurrence of the disease, most commonly as purpura with abdominal pain, generally within 4 months of resolution of the original symptoms. Recurrences are more frequent in children over 8 years and in those with renal involvement. Long term follow up with proper monitoring guidelines plays a major role in timely diagnosis and management of systemic involvement.

CLINICAL CONUNDRUM 2: Kawasaki disease (KD) and Multisystem inflammatory syndrome in children (MIS-C)

Submitted *by Dr. Divya Gupta*

COVID-19 has introduced a new entity into our clinical armamentarium—Multisystem Inflammatory Syndrome in Children (MIS-C)—a condition that demands distinction from Kawasaki disease. Against this backdrop, two key questions merit careful consideration.

1. KD and MIS-C — are they truly the same spectrum, or distinct entities after all?
2. When it comes to intensifying treatment for KD, what's new and what really works?

1. EDITOR's OVERVIEW

COVID-19–associated MIS-C is a rare, post-infectious hyperinflammatory syndrome that usually appears a few weeks after a child has had SARS-CoV-2. It affects multiple systems—most often the cardiac, gastrointestinal, hematologic, and cutaneous or mucosal systems. What drives this reaction? A cytokine storm triggered by the virus, disruption of normal immune balance, and possibly an autoimmune response through molecular mimicry. Kawasaki disease (KD) may look similar, but its cause is different, arising from immune activation against unknown pathogens. So the question arises: are they really the same, or different conditions? And if they are different, how can we, as clinicians, tell them apart early and accurately?

ARTICLE 1:

Naka F, Melnick L, Gorelik M, Morel KD. A dermatologic perspective on multisystem inflammatory syndrome in children. Clin Dermatol. 2021 Jan-Feb;39(1):163-168.

In this article, the authors present and overview of MIS-C in children and highlight the salient similarities and differences between MIS-C and Kawasaki Disease (KD). The salient points in summary are as follows:

MIS-C is a post-infectious hyperinflammatory syndrome occurring 2–6 weeks after SARS-CoV-2 infection. Children typically present with persistent fever, gastrointestinal symptoms, mucocutaneous changes, and varying degrees of shock or cardiac dysfunction. While it shares overlapping features with Kawasaki disease (KD), it represents a distinct clinical entity with different epidemiology, systemic involvement, and outcome patterns.

Key Clinical Features of MIS-C

- **Epidemiology**
  - Median age 8–12 years; contrasts sharply with KD where most children are <5 years.
  - Higher incidence among non-Hispanic Black, Hispanic/Latino, and Ashkenazi Jewish children in US cohorts.

- **Timing with COVID-19**
  - Occurs weeks after initial SARS-CoV-2 exposure.
  - PCR often negative, while antibody positivity high (75–100%).
  -
- **Systemic Presentation**
  - High fever is universal.
  - GI symptoms—severe abdominal pain, vomiting, diarrheal—are among the most consistent and striking features, often mimicking appendicitis.
  - Cardiovascular involvement typically manifests as myocardial dysfunction/left ventricular dysfunction, not coronary aneurysms (common in KD).
  - Shock at presentation is frequent.

- **Mucocutaneous Manifestations**
  Mucocutaneous changes are highly prevalent in MIS-C (60–80%) and are often the first clue for dermatologists. Conjunctivitis is seen in 27–93%; Diffuse nonspecific rash in 47–81% (Usually maculopapular; polymorphous; occasionally urticarial or EM-like); Oral cavity changes in 25–87% (Red, cracked lips, mucosal erythema); Acral findings in 27–68% (Hand/foot erythema and oedema; periungual desquamation less consistent than KD).

  It is important to note that the rash in MIS-C is usually diffuse and nonspecific, lacking the classic features of KD (e.g., perineal and periungual peeling). Skin involvement is more common in younger MIS-C patients and declines with age.

- **Laboratory Profile**
  - Marked inflammation: elevated CRP, ferritin, ESR, IL-6.
  - Lymphopenia and thrombocytopenia—more typical of MIS-C than KD.
  - Coagulopathy (high D-dimer) is common.

Differentiation of MIS-C from Kawasaki Disease (KD)

Shared features: fever, conjunctivitis, mucosal changes, rash, extremity alterations, systemic inflammation.

Features	MIS-C	Kawasaki Disease
Age	8–12 years	<5 years
Ethnic Predisposition	Blacks, Hispanics	Asian (especially Japanese, Korean)
GI Symptoms	Very common, severe	Uncommon
Cardiac	LV dysfunction, myocarditis	Coronary artery aneurysms
Platelets	Thrombocytopenia	Thrombocytosis (subacute phase)
Lymphocytes	Lymphopenia	Normal/lymphocytosis
COVID - 19 Link	Strong (mostly antibody-positive)	None

COMMENTS:

1. MIS-C should be suspected in any child with persistent fever, rash, conjunctivitis, and severe GI symptoms in the setting of recent COVID-19.
2. Cutaneous findings are common but nonspecific—recognizing conjunctivitis, cracked lips, diffuse rash, and acral erythema helps prompt early diagnosis.
3. Cardiac involvement differs fundamentally from KD: myocarditis rather than coronary vasculitis predominates.
4. Younger MIS-C patients display more pronounced mucocutaneous features.
5. Negative PCR does not rule out MIS-C; antibody positivity is typical.
6. Differentiating MIS-C from KD, TSS, DRESS, SJS/TEN, MIRM/RIME, and viral exanthems remains essential—dermatologists often play a pivotal diagnostic role.
7. Timely multidisciplinary care (PICU, cardiology, rheumatology) is crucial, as many children present in shock.
8. Treatment usually includes IVIG ± systemic steroids, with escalation to biologics (IL-1, IL-6 inhibitors) in severe cases.

EDITOR's NOTE:

MIS-C and Kawasaki disease (KD) are distinct, infection-triggered syndromes that share overlapping immune pathways, explaining their similar response to IVIG ± corticosteroids and the benefit of IL-1 blockade (e.g., Anakinra). MIS-C affects older children (median 7–11 years) compared with KD (<5 years), likely due to differences in immune memory, MMR cross-protection, ACE2 expression, and immature immunity in younger children.

Mucocutaneous findings in MIS-C include morbilliform, erythrodermic, urticarial, reticular, petechial, purpuric, erythema multiforme–like, chilblain-like, and occasional vesiculo-bullous eruptions, reflecting immune-mediated microvascular and endothelial injury. KD rash is polymorphous but lacks vesicles or bullae. MIS-C conjunctivitis is bilateral with bulbar or limbic involvement, whereas KD conjunctivitis typically spares the limbus. Oral changes are milder in MIS-C; KD commonly shows strawberry tongue and cracked lips. MIS-C lymphadenopathy is multifocal, while KD usually has unilateral cervical nodes. Extremity changes occur less often in MIS-C.

Despite some overlap, their trajectories diverge. MIS-C presents more aggressively with systemic inflammation, myocardial dysfunction, and cardiogenic shock, and its long-term cardiac outcomes remain under investigation. KD predominantly affects the coronary arteries and may progress to arterial remodelling with myofibroblast proliferation, leading to stenosis, ischemia, and myocardial fibrosis—well-recognized chronic complications.

2. EDITOR's OVERVIEW

Kawasaki Disease (KD) remains the leading cause of acquired heart disease in children. While intravenous immunoglobulin (IVIg) and aspirin are standard treatments, why do some patients remain resistant or develop coronary artery abnormalities (CAAs), and how have evolving insights into immune dysregulation influenced the shift from uniform therapy to a risk-adapted, combination-based management approach targeting key inflammatory pathways?

ARTICLE 2:

Jone PN, Tremoulet A, Choueiter N, Dominguez SR, Harahsheh AS, Mitani Y, et al. Update on Diagnosis and Management of Kawasaki Disease: A Scientific Statement From the American Heart Association. Circulation. 2024 Dec 3;150(23): e481-e500.

In this article, the authors discuss the management of KD, with focus on recent updates in management. The salient summary points are as follows:

- KD remains a clinical diagnosis—no pathognomonic test exists.
  Early recognition (ideally by day 4–5 of fever) is critical to prevent coronary artery aneurysms (CAA).
- Echography remains the primary imaging tool.
- Normal echo early in the disease does not rule out future CA involvement. Children with Z ≥2.5 need frequent inpatient echo (twice weekly) until lesions stabilize.
- IVIG 2 g/kg remains standard of care.
- Persistent fever ≥36 hr post-IVIG = IVIG resistance.
- High-risk patients benefit from intensified primary therapy (IVIG + corticosteroids). This category includes age < 6 months, initial coronary Z score ≥ 2.5, Asian race, CRP >13 mg/dl.
- Increasing evidence supports targeted biologics for refractory cases (e.g., infliximab, anakinra)
- Children with no coronary involvement or transient dilation (Z <5) have excellent long-term outcomes, often requiring no imaging beyond 4–6 weeks.

COMMENTS:

The AHA recommendations re-inforce that early recognition and timely IVIG administration remain central to preventing coronary complications in KD. Coronary changes may evolve despite an initially normal study, hence serial ECHO with z-scores are crucial in guiding and informing treatment. High risk children can be identified at baseline and if required, corticosteroids can be added. Biologics are increasingly being used in refractory cases. Children without coronary involvement or with only transient dilation have excellent long-term outcomes.

EDITOR's NOTE:

Kawasaki Disease (KD) is now seen as a cytokine-driven immune vasculitis, mainly involving IL-1, TNF-α, and IL-6 pathways. Genetic factors, such as ITPKC and CASP3 variants, influence disease severity and response to IVIg, highlighting the importance of early recognition and targeted therapy in high-risk children. Current management strategy favours moderate-dose aspirin (30–50 mg/kg/day) instead of traditional high-dose aspirin (80–100 mg/kg/day) regimens during the acute phase, tapered to 3–5 mg/kg/day after 48–72 hours of defervescence, reflecting its supportive role while IVIg and targeted immunomodulators driving outcomes. Early recognition of high-risk patients—including infants <6 months, older children >10 years, males, those with delayed diagnosis, incomplete presentations, elevated CRP/ALT/neutrophils, KD shock syndrome, macrophage activation, early coronary changes (Z ≥2.5), or genetic susceptibility—is crucial. In high-risk cases, upfront intensification with IVIg plus corticosteroids, with selective addition of infliximab or ciclosporin for predicted non-responders and anakinra for refractory hyperinflammatory disease, provides stronger control, while statins offer endothelial protection.

Practical approach:

- Standard KD: IVIg 2 g/kg + aspirin 30–50 mg/kg/day (then 3–5 mg/kg/day). Escalate to corticosteroid or biologic if fever persists beyond 36 hours.
- High-Risk KD: Upfront combination therapy – IVIg with corticosteroid ± infliximab or ciclosporin. Consider anakinra in refractory cases. Statins may aid long-term vascular protection.

NOTE: Although KD is primarily managed by Pediatricians / Pediatric rheumatologists dermatologists must remain well-versed in current evidence and treatment strategies—**WE NEED TO UNDERSTAND IT, EVEN IF WE NEED NOT TREAT IT**—to ensure timely recognition and contribute to prevention of coronary complications.

CLINICAL CONUNDRUM 3: Behcet's disease

Submitted by Dr. Shibhani S. Hegde

With **PEDIATRIC BEHÇET'S DISEASE (BD)** marked by diagnostic uncertainty, phenotypic overlap, and organ-specific complexity, three focused questions highlight emerging advances:

1. When should Pediatric BD prompt evaluation for a monogenic mimic?
2. Is common femoral vein thickness (CFVT) a reliable new marker in the diagnostic assessment of Pediatric BD?
3. What is the recommended stepwise therapeutic approach for mucocutaneous manifestations of Behçet's disease?

1. EDITOR's OVERVIEW

Before delving into Behçet's disease (BD) and its monogenic mimics, it is important to clarify the foundation of our discussion: What exactly is a monogenic disorder?

Genes serve as the blueprint of life, and a defect in even a single gene can disrupt normal biological functions and lead to disease. Disorders caused by mutations in a single gene are known as monogenic or single-gene disorders. These follow Mendelian inheritance patterns; transmitted from parent to offspring via autosomes, sex chromosomes, or mitochondrial DNA and may involve a single organ system or multiple systems. The Online Mendelian Inheritance in Man (OMIM) database remains the most comprehensive source of information on these conditions. Although individually rare, monogenic disorders cumulatively affect more than 6% of the global population, representing a significant clinical and public-health challenge.

Understanding monogenic disorders helps explain why, with the expansion of genomic testing, our perspective on BD has evolved. Rather than a single, uniform entity, BD is now recognised as a clinical continuum with considerable genetic and phenotypic diversity.

This evolving understanding has highlighted an important reality: a subset of Pediatric patients who appear to have BD may, in fact, have an underlying monogenic autoinflammatory disorder. The following article provides key insights into this spectrum and its clinical implications.

ARTICLE REVIEW 1:

Kul-Cinar O, Romano M, Guzel F, Brogan PA, Demirkaya E. Pediatric Behçet's Disease: A Comprehensive Review with an Emphasis on Monogenic Mimics. J Clin Med. 2022;11(5):1278.

BD is a polygenic condition with a complex immune-pathogenetic background. Although rare in Pediatric population, various monogenic mimics of BD have come to the forefront warranting genetic testing in patients with atypical features or in early-onset cases. This study by Kul-Cinar *et al.* is a comprehensive narrative review summarizing clinical presentation, immune-pathogenetic associations and disease mechanisms in Pediatric BD and BD-related phenotypes.

Disease expression varies geographically, suggesting environmental and epigenetic influences. Mean age of onset is 4.9 to 12.3 years; equal female-to-male ratio, with males more often presenting with vascular and ocular involvement, females with genital ulcers. Initial symptoms often do not fulfil classical BD criteria, delaying diagnosis by 3 to 5-years.

The 2015 Pediatric Behçet's disease (PED-BD) criteria classify Pediatric BD based on six equally weighted features: oral ulcers, genital ulcers, ocular lesions, skin lesions, neurological signs, and vascular involvement; with a score of ≥3 defining a definitive case, without requiring a mandatory criterion of recurrent oral ulcers or inclusion of pathergy.

Non-specific gastrointestinal and neurological symptoms, arthralgia, and positive family history are more common in children, whereas genital ulcers, ocular symptoms, and vascular involvement predominate in adults.

Common Pediatric manifestations include recurrent oral ulcers, less frequent genital ulcers, and diverse skin lesions (acneiform and necrotic folliculitis in boys; erythema nodosum in girls). Musculoskeletal involvement is usually non-erosive oligo-or polyarticular arthritis affecting knees and ankles. Ocular involvement occurs in 8.7–66.2%, vascular involvement in 6.5–32%, and less common systemic features include central nervous system (CNS), gastrointestinal, cardiopulmonary, and constitutional symptoms. Long-term, multidisciplinary follow-up is essential.

A number of monogenic disorders can mimic Pediatric BD and should be considered when the presentation is unusually early, severe, or syndromic:

- **Haploinsufficiency A20 (HA20):** Early onset, strong family history, recurrent fevers; Behçet-like oral/genital ulcers, pathergy, vascular thrombosis, neurological and gastrointestinal involvement.
- **Otulipenia:** Neonatal-onset fever, neutrophilic dermatosis or panniculitis, failure to thrive; although no primary immunodeficiency is noted.
- **Deficiency of adenosine deaminase 2 (DADA-2):** Early vasculopathy, lacunar strokes, livedoid rash, hematologic involvement, immunodeficiency; may show oral aphthae, genital ulcers, erythema nodosum, recurrent fever and arthralgia.
- **Systemic autoinflammatory diseases (Cryopyrin associated periodic syndromes - CAPS, Hyper-IgD syndrome - HIDS):** Early-childhood onset with oral ulceration and gastrointestinal symptoms; uveitis overlaps with CAPS, TNF receptor associated periodic fever syndrome (TRAPS) and Blau syndrome.
- **Chronic granulomatous disease:** Primary immunodeficiency characterized by impaired oxidative burst with abscesses and granulomatous lesions in skin, lungs, lymph nodes and liver; mucocutaneous lesions or unusual infectious complications may resemble BD.
- **NF-κB pathway defects:** Familial BD or BD-like mucocutaneous ulceration, colitis, dermatitis, or neuromyelitis optica.
- **Periodic Fevers, Intestinal inflammation, and Terminal stomatitis (PFIT):** Severe auto inflammation with early fever, recurrent perianal ulceration, and scarring oral aphthae leading to microstomia.
- **Trisomy 8:** BD-like inflammatory phenotype linked to NF-κB activation.
- **Fabry disease:** Fever of unknown origin, recurrent oral ulcers, myalgia, colitis, panniculitis-like rash; venous thrombosis may be the diagnostic clue.

In practice, early-onset disease with orogenital ulceration and systemic involvement, with or without familial clustering or immunodeficiency, should always raise suspicion of monogenic disorders resulting in BD-like syndromes.

COMMENTS:

This is a comprehensive narrative review and not a systematic review. Rarity, heterogeneity and multisystem involvement of BD in Pediatric population makes Pediatric specific studies scarce. With the advent of affordable genetic testing, newer genes are constantly reported expanding the BD spectrum of disorders. BD with its clutches in autoinflammatory diseases, vasculitis, neutrophilic disorders and immunodeficiency states will continue to evolve. Early recognition ensures reduced morbidity and mortality. Recent consensus states early presentation (<5-years of age), strong family history and/or incomplete or atypical clinical features (even in older patients) of BD should be screened for monogenic AID and primary immunodeficiency.

EDITOR'S NOTE:

Distinguishing true polygenic BD from its monogenic mimics has become essential for clinicians owing to the expanding spectrum. The implications are substantial: treatments may vary markedly, and establishing a monogenic diagnosis; whether or not the condition is directly treatable, can still guide regarding prognosis, inform genetic counselling, and help avoid unnecessary immunosuppression. While combined whole exome sequencing (WES) based testing and human leucocyte antigen (HLA) genotyping can be valuable, a tiered approach with precise phenotyping and basic laboratory evaluation, followed by targeted genetic testing when red-flag features point to a monogenic mimic is more practical in the Indian setting.

2. EDITOR's OVERVIEW

Recurrent oral ulcers (ROU) can arise from a spectrum of conditions, ranging from idiopathic lesions to autoimmune or autoinflammatory disorders; but how do we identify those that signal BD? This question is crucial, as ROU are almost universally present in children with BD, reflecting patterns seen in adults, and often represent the first clinical manifestation. Characteristic features: multiple ulcers of variable size surrounded by erythema, and involving lips, tongue, cheeks, palate, soft palate, uvula, or oropharynx, typically healing without scarring over ~10 days can help differentiate BD-related ROU from conventional recurrent aphthous stomatitis (RAS), though the distinction is not always straightforward.

In children with BD, ROU may herald systemic manifestations and the interval from initial symptoms to fulfilment PED-BD criteria can extend from 2 to 5 years. This highlights the importance of a meticulous history, systemic examination and vigilant longitudinal monitoring. Due to the absence of a distinct laboratory tool that can discern which children merit heightened surveillance and early intervention, findings from certain adult BD studies have revealed common femoral venous wall thickness as a potential contender for objective measurement.

Studies have demonstrated an increased venous wall thickness (VWT) in BD when compared with healthy controls, even in the absence of clinically apparent vasculitis. These findings support chronic immune-mediated venous inflammation as a central pathogenic mechanism, rather than a secondary post-thrombotic or pressure-related phenomenon. The consistent elevation of VWT across BD subgroups, regardless of overt vascular involvement, reinforces venulitis as a fundamental feature of BD pathogenesis and a potential early marker of disease.

Could Doppler-derived VWT complement clinical assessment for diagnosing childhood-onset Behçet's disease?

ARTICLE REVIEW 2:

Atalay E, Oguz B, Sener S, Ozcan HN, Sag E, Akca KU, et al. A new tool supporting the diagnosis of childhood-onset Behçet's disease: venous wall thickness. Rheumatology (Oxford). 2023;62(SI2): SI181-8.

Diagnosis of BD is challenging with its heterogeneous presentation and absence of a pathognomonic laboratory test. It is classified under variable wall vasculitis in the revised Chapel Hill consensus classification of vasculitis. Increased VWT detection by ultrasonography or MRI have reported that VWT in the lower extremity veins are significantly more in adult BD patients, even in those without thrombosis. With pediatric BD representing around 15.5% of all BD patients; a similar study was undertaken in pediatric BD when compared to healthy controls.

Using the PED-BD criteria, 35 pediatric BD cases are classified are 'definitive' and 'incomplete' BD with the fulfilment of three and two criteria respectively. An age- and gender-matched control cohort of 27 children was also taken. Thickness of all lower limb vessels: common femoral vein, femoral vein, popliteal vein, great and small saphenous vein were calculated using high resolution ultrasound (USG) in all cases and controls taking into account anatomical identifying points for each vein and inter-observer variability. Intima-media thickness was measured to evaluate VWT in a longitudinal view on a minimum of 10mm length of a venous segment and five measurements were recorded for each vein, followed by calculation of mean values.

The median VWT values of BD patients were significantly higher than the control group in all veins on both lower limbs and although these measurements were higher in 'definite' BD patients, difference in measures when compared to the 'incomplete' BD patients were not significant in most vessels, except for the borderline significance for left femoral vein.

The BD cohort did report vascular symptoms with 3 patients having a history of lower limb thrombosis, 2 patients with a history of upper limb thrombosis, 1 patient with pulmonary artery thrombosis and 7 patients having neurological signs and thrombosis of superior sagittal veins. The reminder had no vascular event. The median VWT values of 11 patients with vascular disease were similar to those without vascular involvement highlighting similar reports in adult BD patients where presentation of vascular disease is not a perquisite for increased VWT values and subclinical vascular inflammation in BD. There was no association between the two disease activity assessment criteria used and the corresponding VWT measurements. **This study also reports that VWT is reportedly 86% sensitive and 89% specific over right common femoral vein**. Sensitivity rates for most veins measured in VWT were between 63–86%, and specificity rates were 71–100% with PPV values for best cut-off values of all lower extremity veins detected by receiver operating characteristic (ROC) curve analysis between 82–100%.

COMMENTS:

BD is categorized as a variable vessel vasculitis involving arteries and veins of any calibre, although venous involvement is more predominant. Early recognition of disease, particularly in smaller veins, is crucial, as timely management can prevent serious complications such as neurological involvement, which are often associated with delayed diagnosis.

The 2015 PED-BD criteria serve primarily as classification criteria rather than diagnostic tools. They are designed to identify groups of patients with shared features for research purposes, rather than to guide individual patient diagnosis. This underscores the need for objective, quantifiable markers to detect early vascular involvement.

VWT is emerging as a promising tool in this context. Studies have shown that VWT values are increased in paediatric BD patients, both definitive and incomplete cases alike compared with healthy controls, even in the absence of clinically documented vasculitis. This suggests that VWT can enable the detection of subclinical venulitis and early vascular involvement, allowing timely diagnosis of the condition.

USG is a practical, fast, non-invasive, and widely accessible method for assessing VWT, making it suitable for both paediatric and adult patients. Incorporating it into routine evaluation may allow clinicians to identify subclinical venous inflammation, monitor early vascular changes, and initiate management before complications set in.

Given that BD exhibits geographical and ethnic variations, and that the current study was conducted in children in the USA, further research in multi-ethnic populations is necessary to validate appropriate cut-off values. Additionally, longitudinal studies and long-term follow-up are essential to establish the predictive value of VWT and confirm its utility as a diagnostic marker.

EDITOR'S NOTE:

In the early evaluation of paediatric, incomplete, and atypical Behçet's disease, traditional tools remain limited; HLA-B51 offers little diagnostic value, and the pathergy test has low sensitivity. In this context, venous wall thickness measurement emerges as a novel, reliable, objective ultrasonographic marker for early assessment.

The common femoral veins are particularly suitable, being consistently well-visualized on Doppler USG. A thickness above 0.5 cm demonstrates over 90% sensitivity, while values exceeding 0.75 cm indicate a very high probability of disease. These associations hold true regardless of acute phase reactants, disease activity, organ involvement, patient age, sex or disease duration. Incorporating common femoral vein assessment into early diagnostic protocols is therefore the need of the hour to generate population-specific data and validate its long-term reliability.

Reference: *Alibaz-Oner F, Ergelen R, Yıldız Y, Aldag M, Yazici A, Cefle A, et al. Femoral vein wall thickness measurement: A new diagnostic tool for Behçet's disease. Rheumatology (Oxford). 2021 Jan 5;60(1):288-296.*

3) **EDITOR's OVERVIEW**

In BD, while colchicine, topical corticosteroids, and sucralfate often suffice to control mucocutaneous flares, truly refractory cases demand a more vigilant reassessment because what lies on the surface may simply be a reflection of profound systemic immune activation. If we overlook this systemic inflammation, the disease risks extending beyond the skin and mucosa to involve other vital organs. Moreover role of cytokines - IL-1β, IL-6, IL-17, IL-23, TNF-α, and IFN-γ, orchestrating the complex inflammatory milieu cannot be discounted in BD pathogenesis.

Is it not therefore both prudent and clinically imperative to maintain heightened awareness, even when disease appears confined to mucocutaneous involvement, since early detection may permit timely escalation of therapy or prompt referral?

ARTICLE 3:

Giani T, Luppino AF, Ferrara G. Treatment Options in Paediatric Behçet's Disease. Pediatr Drugs. 2023;25:165-91.

Although a quarter of the BD cases are paediatric, yet most evidence for treatment of paediatric BD is derived from adult studies and experience and extrapolation of data is necessary. Systemic corticosteroids frequently represent the mainstay for management of the initial acute and severe disease phases for short periods as bridging therapy. For mucocutaneous disease, topical therapy is adequate. Disease-modifying anti-rheumatic drugs (DMARDs) like azathioprine, cyclosporine, cyclophosphamide, methotrexate, 5-aminosalicylic acid or sulphasalazine and biological agents (against IL-1, IL-6, and IL-17) have long been used with small molecules like phosphodiesterase 4 (PDE-4) and Janus kinase (JAK) inhibitors emerging as newer therapeutic agents.

A multi-disciplinary care involving personalized management protocol tailored to the specific organ disease is more appropriate than a 'one-size-fits-all' approach. The treatment should focus on symptomatic relief, reducing inflammation and prevention of relapses and complications to reduce morbidity and mortality. As in children with other autoimmune and autoinflammatory diseases requiring long-term immunosuppressive therapy, age-appropriate vaccines are recommended during should ideally be administered during disease quiescence, particularly live-attenuated vaccines. Seasonal influenza vaccines, pneumococcal conjugate severe acute respiratory syndrome coronavirus 2 vaccination are also recommended. In BD mimickers, potential flare us after vaccinations are reported so they need monitoring for potential disease flare ups.

Mucocutaneous BD entails topical treatment with triamcinolone acetonide in orabase as first line management. However, RAO can be painful affecting nutrition and quality of life. Oral hygiene and pain management must be ongoing to ensure oral intake by younger BD patients. Chlorhexidine oral rinses/gel applications reduce ulcer severity, pain and maintains oral hygiene. Lidocaine spray/gel (2%) also help with pain. Hyaluronic acid gel/mouth washes (0.2%) help in ulcer healing. Sucralfate and pentoxifylline gel are also effective in shortening ulcer healing time in addition to providing pain relief. With the use of topical steroids, routine monitoring of secondary infections must be done. Non-steroidal anti-inflammatory mouthwash/sprays like diclofenac 3%, amlexanox oral paste 5%, enzydamine hydrochloride 0.15%, and choline salicylate 8.7% can also be used. Systemic therapy is usually reserved for severe mucosal disease, recurrent episodes, in cases unresponsive to topical therapy or in the presence of orogenital and cutaneous lesions. Colchicine is still the first-line treatment. It is FDA approved for treatment of familial Mediterranean fever (FMF) in ages >4-years The EULAR dosage recommendations for pediatric FMF are ≤0.5 mg/day in <5 years of age, 0.5–1.0 mg/day in 5–10 years of age, and 1.0–1.5 mg/day in >10 years of age. In refractory mucocutaneous lesions, thalidomide, apremilast, pentoxyphylline, dapsone, azathioprine and biological agents have been used. IL, TNF-α inhibitors (etanercept, adalimumab), ustekinumab and secukinumab have been tried with varying results.

Azathioprine has been effective in orogenital aphthae. Thalidomide at a dose of 1–3 mg/kg/day has been effective in aphthae of pediatric BD. Since EULAR and Japanese recommendations document apremilast as an effective treatment of oral ulcers in patients with BD; an ongoing (NCT04528082) to analyze the efficacy and safety of apremilast in children (2–17 years of age) with active oral ulcers associated with BD in underway. Anti-TNF-α agents are effective in inducing remission of orogenital and skin lesions. Etanercept, and adalimumab was effective in treating mucocutaneous lesions and recalcitrant lesions respectively. IL-1 blockers have also showed promise in the resolution of mucocutaneous lesions. Ustekinumab has also been reportedly effective in colchicine resistant mucocutaneous lesions. Although the data is limited, encouraging data has been reported by a few case reports although trials are lacking owing to the rarity of pediatric BD.

For musculoskeletal disease, intra-articular corticosteroid injections and non-steroidal anti-inflammatory drug cycles is considered first line treatment with colchicine as a maintenance drug. Methotrexate, TNF-α inhibitors, and azathioprine are used in resistant, more aggressive articular involvement. Secukinumab is also effective when other treatments fail.

Ocular, gastrointestinal tract, central nervous system, or vasculature involvement is associated with a higher-risk prognosis; requires systemic therapy tailored to the specific organ system and coordinated through a multidisciplinary approach.

COMMENTS:

Due to the rarity of BD in children, heterogeneity of disease expression and lack of randomised controlled studies in the this population, there are currently no consensus management guidelines for paediatric BD but extrapolation of data from adult trails can be done. Systemic colchicine and topical corticosteroids with sucralfate are the classic options for treating orogenital lesions and any escalation is organ-specific using DMARDs. In refractory cases or cases of severe organ involvement, biological agents have also been used with varied success. Cost effective colchicine still seems to headline the therapeutic armamentarium and in addition to being effective in orogenital ulceration is also effective in skin and musculoskeletal complaints. Individualised treatment should be undertaken based on age, sex, organ involvement, susceptibility to infections and tolerability.

EULAR recommends that for neurological, gastrointestinal and vascular manifestations, initial bridging steroid dose can ensure a choice of steroid sparing and organ-specific immunosuppressive therapy. Duration of treatment is still undefined but should be long enough that relapses do not occur on tapering or stopping therapy.

EDITOR'S NOTE:

Paediatric BD care largely mirrors adult management but requires weight-based dosing, vigilant monitoring of growth and development, age-appropriate vaccines during quiescence and before starting therapy, attention to contraception and reproductive counselling in adolescents, extremely careful escalation of therapy with a strict red-flag on thalidomide due to neurotoxicity, judicious use of biologics for severe or refractory disease, and coordinated multidisciplinary input (rheumatology, ophthalmology, dermatology, neurology, and gastroenterology), with early detection of major organ involvement critical to preventing long-term morbidity.

CLINICAL CONUNDRUM 4: Urticarial vasculitis

Submitted by Dr. Preeti Sheth

Urticarial vasculitis, positioned at the intersection of urticaria and small vessel vasculitis, exhibits characteristics of both entities and therefore challenges clinicians. Addressing two key questions helps delineate this complex entity:

1. Chronic spontaneous urticaria (CSU) and urticarial vasculitis (UV)— two faces of the same coin?
2. What is the current consensus on the diagnosis and management of urticarial vasculitis?

EDITOR's OVERVIEW

In clinical practice, we frequently encounter patients—often children—with recurrent wheals persisting beyond six weeks, accompanied by itching, occasional burning, and mild arthralgia—symptoms that blur the boundary between chronic spontaneous urticaria and urticarial vasculitis. The picture is familiar, yet the diagnosis often is not, isn't it? This difficulty is especially pronounced in Pediatric patients, where a skin biopsy may not always be feasible and, even when performed, may yield inconclusive results.

This ambiguity creates a therapeutic dilemma: should treatment begin with conventional therapies such as antihistamines, escalate to targeted agents like cyclosporine or omalizumab, or proceed to immunosuppressive strategies? This scenario raises a critical question: Is there a validated scoring system that can reliably guide therapeutic decision-making in these complex cases?

ARTICLE 1:

Krause K, Bonnekoh H, Jelden-Thurm J, Asero R, Gimenez-Arnau AM, Cardoso JC, Grattan C, Kocaturk E, Lippert U, Maurer M, Metz M, Staubach P, Goncalo M, Kolkhir P. Differential diagnosis between urticarial vasculitis and chronic spontaneous urticaria: An international Delphi survey. Clin Transl Allergy 2023; e12305.

Urticarial vasculitis (UV) is a chronic inflammatory disorder characterised by wheals persisting for more than 24 hours, with or without angioedema, typically resolving with post-inflammatory hyperpigmentation and often accompanied by systemic symptoms. Histopathology usually demonstrates leukocytoclastic vasculitis. UV is subclassified according to complement consumption resulting from complement activation and immune-complex deposition: normocomplementemic UV (NUV), which accounts for nearly 80% of cases, and hypocomplementemic UV (HUV), which is associated with a more severe systemic disease burden including fever, abdominal pain, and musculoskeletal involvement.

Diagnostic distinction between UV and chronic spontaneous urticaria (CSU) can be challenging because a subset of CSU patients may develop long-lasting, painful wheals accompanied by post-inflammatory hyperpigmentation and systemic symptoms, creating clinical overlap or brief evolution between CSU and UV. Nevertheless, differentiating UV from CSU remains essential due to significant differences in treatment strategies and prognosis.

To address persistent uncertainty and the inconsistent use of biopsy—despite its role as the most reliable means of demonstrating leukocytoclastic vasculitis—the Delphi consensus aimed to standardise indications for skin biopsy in chronic wheals, define clinical and histopathological criteria for UV, and clarify the extent of overlap between NUV and CSU. The panel recommended performing a biopsy in patients with CSU when wheals persist beyond 24 hours, when bruising or post-inflammatory hyperpigmentation is present, or when systemic features such as fever, arthralgia, or abdominal pain occur; any two of these pointers were deemed sufficient to justify biopsy. When biopsy is not feasible, the presence of long-lasting wheals with bruising, purpura, or post-inflammatory hyperpigmentation constitutes a major criterion suggestive of UV in patients with recurrent wheals.

On histopathology, definite urticarial vasculitis is characterised by leukocytoclasia and fibrin deposition within vessel walls**,** with erythrocyte extravasation increasingly recognised as an additional supportive feature. In contrast, during transient overlap episodes—where CSU-like and UV-like features briefly coexist—the biopsy may reveal only subtle vascular aggression **or** minimal, fleeting erythrocyte extravasation**,** falling short of the full vasculitic picture. These overlap episodes are clinically limited, self-resolving, and lack sustained vasculitic activity and hence further extensive Investigation may not be necessary. ANA and CRP should be also assessed alongside biopsy to evaluate for associated autoimmune conditions such as systemic lupus erythematosus, Sjögren's syndrome, or autoimmune thyroid disease.

HUV is clinically characterised by a more severe phenotype, with persistent tender wheals resolving with hyperpigmentation, systemic manifestations such as fever, abdominal pain, and arthralgia, low complement levels (C3, C4), and potential pulmonary or renal involvement. These features facilitate clinical suspicion and targeted investigations.

Pitfalls:
The article does not identify the appropriate lesion to biopsy, nor distinguish histopathological differences between early and late lesions or specify the preferred anatomical site, creating uncertainty in sampling and interpretation. Complement testing—central to differentiating NUV from HUV—is not addressed, and routine components of UV evaluation such as ESR, urine routine, C1q, and CH50 are omitted. Reliance on a Delphi consensus rather than evidence-based data, combined with participation restricted solely to dermatologists, introduces specialty bias and excludes rheumatological perspectives.

Additionally, the European-only panel limits global applicability and does not address diagnostic and management nuances pertinent to Pediatric populations.

COMMENTS:

The real challenge is to differentiate the subset of patients of CSU who occasionally manifest with long standing wheals that leave behind post inflammatory hyperpigmentation. The closest differential is normocomplementemic urticarial vasculitis which manifests similar manifestations but displays more severe symptoms.

Hence, in a patient of recurrent wheals of more than 6 weeks, there is an occurrence of long-standing wheals of more than 24 hours that resolve with post inflammatory hyperpigmentation and systemic symptoms, we need to determine if these manifestations are occasional or persistent. If occasional, then it is considered as CSU. If persistent, then a skin biopsy, ANA, CRP and complement levels of C3, C4 are advised. Presence of leukocytoclastic vasculitis on histopathology confirms diagnosis of UV. Normal C3, C4 levels is observed in hypocomplementemic vasculitis and low C3, C4 are seen in hypocomplementemic vasculitis. Positive ANA and CRP warrants search for an underlying systemic disease.

If skin biopsy cannot be undertaken, presence of wheals of more than 24 hours with post inflammatory hyperpigmentation/bruise/purpura on resolution are major criteria to consider UV.

Neutrophilic urticarial dermatosis is another rare condition that is characterized by recurrent transient wheals, that often do not itch and don't leave behind any pigmentation. It is associated with autoinflammatory conditions. A histopathological confirmation is important to rule out UV. Perivascular and diffuse infiltrate of neutrophils without any damage to the vessel wall on histopathology sets it apart.

ARTICLE 2:

Rothermel ND, Ayala CV, Gonçalo M, Fok JS, Herzog LS, Kocatürk E, et al. Managing Urticarial Vasculitis: A Clinical Decision-Making Algorithm. Based on Expert Consensus. American Journal of Clinical Dermatology 2025; 26: 61–75.

This review summarises the current evidence base for systemic treatment of urticarial vasculitis (UV) and introduces a practical clinical decision-making algorithm structured around the Urticarial Vasculitis Activity Score assessed over 7 days (UVAS7). The UVAS7 captures the five cardinal symptoms of UV—wheals, burning or pruritus, post-inflammatory hyperpigmentation, arthralgia, and systemic features such as fever and fatigability. Each symptom is scored daily, the mean of the five values yields a UVAS between 0 and 10, and the sum of daily scores across seven consecutive days produces a final UVAS7 ranging from 0 to 70.

A key distinction proposed in this review is between chronic spontaneous urticaria (CSU) patients who intermittently display UV-like lesions and patients with UV whose manifestations remain confined to the skin, with or without mild malaise or arthralgia—typically corresponding to a UVAS7 < 7/70. These patients can be managed similarly to CSU, using a stepwise approach with second-generation antihistamines, followed by omalizumab and cyclosporine A (used off-label in UV). Patients with UV whose scores exceed 7 but whose disease remains cutaneous can follow the same escalation pathway. More severe or systemic presentations—reflected by UVAS7 > 7/70 accompanied by extracutaneous complaints—necessitate a more aggressive strategy. Here, evaluation for underlying systemic diseases becomes essential, and treatment may include corticosteroids, dapsone, hydroxychloroquine, or anti-IL-1 therapies, chosen according to clinical severity, drug availability, cost, and safety considerations.

The therapeutic landscape remains constrained by limited evidence: across 136 predominantly retrospective studies, treatment data for UV are sparse and heterogeneous. Nonetheless, several patterns emerge. Systemic glucocorticoids consistently provide rapid control of both cutaneous and systemic disease and remain the most dependable short-term option, generally combined with steroid-sparing immunosuppressants such as cyclosporine, methotrexate, azathioprine, cyclophosphamide, or mycophenolate mofetil. Among biologics, monoclonal antibodies—particularly omalizumab, canakinumab, anakinra, and rituximab—demonstrate substantial benefit in refractory or systemic disease, with omalizumab supported by the strongest body of evidence. Dapsone and hydroxychloroquine continue to be effective and well-tolerated options, with hydroxychloroquine being especially valuable in hypocomplementemic UV. Colchicine offers modest benefit, mainly in combination regimens,

while IVIG has produced complete responses only in isolated reports. Conversely, second-generation H1 antihistamines and multiple other agents—including NSAIDs, H2 blockers, leukotriene antagonists, and miscellaneous immunomodulators—show little or no meaningful efficacy.

Proposed Clinical Algorithm

1. Identify and eliminate potential triggers ie. drugs and co-morbidities ie. infections, malignancies, systemic lupus erythematosus. Investigations advised include complete blood count, erythrocyte sedimentation rate, urine and stool routine. Thyroid antibodies, ANA, complement levels may be advised when systemic involvement is suspected.
2. Calculate UVAS7.
3. UVAS7 ≤ 7/70 (skin-limited or CSU-like): sgAHs → omalizumab → cyclosporine A.
4. UVAS7 > 7/70 but still skin-limited: same escalation pathway.
5. UVAS7 > 7/70 with systemic symptoms: evaluate thoroughly for underlying systemic disease; treat with short-course corticosteroids and escalate to dapsone, hydroxychloroquine, immunosuppressants, or IL-1 inhibitors based on severity and safety.
6. Reassess UVAS7 every 4 weeks and de-escalate therapy when possible to minimize adverse effects

Limitations

pediatric UV is poorly represented in the literature, limiting the generalisability of this algorithm; its use in children therefore requires age-appropriate adjustments in safety and dosing.

COMMENTS:

- **sgAHs:** Limited efficacy in UV but may be used in mild disease, in CSU with occasional long-lasting painful wheals, and as adjuvant therapy with immunomodulators/biologics. Preferred first line due to excellent safety.

- **Omalizumab:** FDA-approved for sgAH-refractory CSU ≥12 years (300 mg SC every 4 weeks). Off-label <12 years (150–300 mg SC every 4 weeks). Effective and well tolerated in pediatric UV[1].

- **Corticosteroids:** For acute flares—**0.5–1 mg/kg/day** for 2 weeks, then taper.

- **Colchicine:** 0.5–0.6 mg TID; escalate every 3 days if tolerated.
  - <5 years: 0.5 mg/day
  - 5–10 years: 0.5 mg BID
  - 10 years: 0.5 mg TID

- **Dapsone:** Alternative to colchicine in children with normal hemoglobin and normal G6PD.

- **Immunosuppressants:** Cyclosporine, methotrexate, azathioprine, and MMF reserved for systemic UV; require strict monitoring.

- **Refractory UV:** Anakinra and rituximab only when other options fail (high cost, limited evidence).

- **Special situations:** IVIG is useful when UV is complicated by infection.

  There are no specific guidelines or step ladder approach to treat urticarial vasculitis in children. At our institution, we begin with sgAHs, most commonly with levocetrizine for 2 weeks. If less or no response, it is given twice a day for another two weeks. Subsequently, colchicine is added, escalating the dose according to the weight of the child. If no response, corticosteroids are advised for a short duration and tapered accordingly. Cyclosporine is considered when the treatment is envisioned to be a long term plan.

EDITOR's NOTE:

- Increasing evidence suggests that normocomplementemic UV may not be a discrete entity but rather part of a broader inflammatory continuum with chronic spontaneous urticaria, reminding us that disease boundaries are often more fluid than categorical.

- Accurate diagnosis of UV hinges on timing and technique: a fresh lesion sampled within 24–48 hours and extending deep into the dermis and superficial subcutis offers the best opportunity to demonstrate the hallmark features of leukocytoclasia, fibrin deposition, and variable erythrocyte extravasation. Once confirmed, severity assessment through UVAS7 allows therapy to be aligned with disease burden—ranging from antihistamines, omalizumab, and cyclosporine in skin-limited presentations to corticosteroids, dapsone, hydroxychloroquine, and rituximab in more systemic forms.

- In children, the differential broadens further. Daily, non-pruritic, figurate rashes with circadian fluctuation, accompanied by fever or arthropathy, should raise early suspicion for CAPS. These autoinflammatory syndromes, defined by specific gene mutations and neutrophilic dermal infiltrates, respond dramatically to IL-1 blockade, underscoring the value of timely recognition.

- Taken together, the essential message is clear: thoughtful clinical appraisal, judicious biopsy, and tailored therapy—while remaining vigilant for mimics such as CAPS—form the cornerstone of reducing morbidity in patients with UV across all ages.

CLINICAL CONUNDRUM 5: Polyarteritis Nodosa (PAN) and ANCA associated vasculitis

Submitted by Dr. Rashmi Agarwal

Systemic vasculitides constitute a heterogeneous group of rare disorders in which timely recognition is crucial to prevent irreversible damage. Anchoring the narrative around two pivotal questions provides a focused lens for therapeutic direction -

1. PAN and DADA2 — shared genealogy or generations apart?
2. What are the cutaneous manifestations of ANCA-associated vasculitis?

1.EDITOR's OVERVIEW

Polyarteritis nodosa (PAN) is a necrotizing vasculitis primarily involving medium-sized arteries, sparing arterioles, venules, and capillaries, and typically sparing the glomeruli. It is often associated with hepatitis B infection and demonstrates characteristic aneurysms or occlusions on angiography. *Now, when you compare this with ANCA-associated vasculitis (AAV), what key distinctions come to mind?* In contrast, AAV affects small vessels—including arterioles, venules, and capillaries—with frequent lung and kidney involvement, ANCA positivity, and absence of HBV association or arteriographic changes.

In children, PAN presents in two major forms—cutaneous and systemic. *When you think of cutaneous PAN, which clinical clues would help you differentiate it from other vasculitides?* Cutaneous PAN is characterized by painful, non-purpuric subcutaneous nodules, livedo reticularis, ulceration, infarction, or necrosis, typically limited to the lower limbs, with minimal systemic features such as myalgia, arthralgia, or non-erosive arthritis. *And do you recall the common trigger in children?* It may follow streptococcal infection and often runs a relapsing–remitting course over years.

The paradigm of childhood PAN has been redefined by the discovery of deficiency of adenosine deaminase 2 (DADA2), a monogenic vasculitis that closely mimics PAN. *So, whenever you see a PAN-like picture in a child, which condition should now be high on your differential?*

ARTICLE 1:

Zhengping Huang, Tianwang Li, Peter A. Nigrovic, Pui Y. Lee, Polyarteritis nodosa and deficiency of adenosine deaminase 2 – Shared genealogy, generations apart, Clinical Immunology, Volume 215, 2020, 108411,ISSN 1521-6616,

Polyarteritis nodosa (PAN) is a systemic necrotizing medium-vessel vasculitis traditionally described in adults, but pediatric cohorts have expanded understanding of childhood-onset disease. The discovery of deficiency of ADA2 (DADA2), a monogenic vasculitis often indistinguishable from PAN, has redefined many early-onset and familial cases previously labelled as PAN. PAN is usually sporadic, can occur secondary to infections, drugs, or inflammatory conditions such as familial Mediterranean fever, with limited genetic susceptibility, whereas DADA2 presents in childhood, frequently in familial clusters, and now accounts for a substantial number of PAN-like phenotypes worldwide. Distinguishing PAN from DADA2 is essential because of their differing diagnostic markers and therapeutic implications.

Childhood PAN vs DADA2: Clinical Overlaps, Key Differentiators, and Targeted Management

- **PAN and DADA2 share** systemic constitutional symptoms, medium-vessel necrotizing vasculitis histology, and frequent skin, neurologic, renal, and GI involvement, making them often clinically indistinguishable.
- **DADA2 typically presents in childhood**, often with a family history.
- **Cutaneous involvement is generally more common** in childhood PAN and DADA2 compared to adult PAN. The frequency of livedo ranges from 20% in adult PAN to over 70% of DADA2 patients. Compared to childhood PAN, DADA2 cases show a higher rate of livedo racemosa and cutaneous vasculitis.
- **Neurologic manifestations**, especially CNS involvement like recurrent ischemic/hemorrhagic strokes, are much higher in DADA2 (50% CNS and 40% PNS involvement) than in childhood PAN (10% CNS and 30% PNS involvement). Adult-onset PAN more commonly has peripheral neuropathy.
- **Hematologic and immunologic abnormalities** (anaemia, leukopenia, thrombocytopenia, pure red cell aplasia, bone marrow failure, immunoglobulin deficiencies such as IgA, IgM, and IgG) strongly favour DADA2 over classic PAN. Thrombocytosis and panniculitis are less frequent in DADA2 patients.

- **Ozen S et al. (2019)** suggested **lower platelet count** as a distinguishing feature of DADA2 compared with PAN.[1]

- **Diagnostic approach -** Childhood PAN (EULAR/PRINTO/PRES criteria) requires biopsy evidence of small- or medium-artery necrotizing vasculitis or angiographic aneurysms/occlusions, along with at least two of the following: skin involvement, myalgia or muscle tenderness, hypertension (>95th percentile for height), peripheral neuropathy or renal involvement. Whereas DADA2 is diagnosed by markedly reduced or absent ADA2 activity or biallelic ADA2 mutations, with enzyme testing serving as an efficient first-line screen that also aids interpretation of variants of uncertain significance.

- **Treatment strategies** - Immunosuppressive therapies—corticosteroids, cyclophosphamide and MMF—remain the mainstay for PAN, with biologics introduced for refractory or severe disease. DADA2 responds poorly to classical immunosuppressants, making TNF inhibitors the treatment of choice with marked reduction in stroke risk and disease activity, though their benefit for non-vasculitic features is uncertain, additional immunosuppression in humoral deficiency heightens infection risk, and HSCT is reserved for severe hematologic involvement.

COMMENTS:

DADA2 should be suspected in children with PAN – like vasculitis, especially with parental history of consanguinity, early-onset, familial, or refractory, accompanied by ischemic or haemorrhagic stroke, cytopenias, or immunodeficiency, lack of thrombocytosis during active disease. Confirmation relies on ADA2 enzyme assay or genetic testing, and TNF-α inhibitors represent a targeted, life-saving therapy that can profoundly modify disease course. Recognition of DADA2 has changed pediatric vasculitis diagnosis and highlights the need for tailored genetic and immunologic workup in children presenting with PAN-like features.

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EDITOR's NOTE:

Targeted panel testing and/or ADA2 enzyme activity assessment (the latter commercially available at Metropolis Laboratories) is warranted in idiopathic PAN, as TNF inhibition has demonstrated proven effectiveness in DADA2 – not a conventional therapy for PAN.

2. EDITOR's OVERVIEW:

What precisely are we defining when we refer to ANCA-associated vasculitis (AAV)? AAV denotes a group of primary vasculitides characterised by necrotising, pauci-immune inflammation of small- to medium-calibre vessels—including capillaries, venules, arterioles, and small arteries—frequently accompanied by circulating MPO- or PR3-ANCA. Although intrinsically systemic, why should its recognition remain firmly within the dermatologic purview? The imperative for early identification stems from its prognostic gravity: renal morbidity and mortality are substantially higher in MPA (29–40%) compared with GPA (~10%), and diagnostic delay predisposes to irreversible sequelae such as saddle-nose deformity and subglottic stenosis in GPA, asthma and chronic sinusitis in EGPA, and peripheral neuropathy and progression to chronic or end-stage renal disease across the AAV spectrum.

ARTICLE 2:

Marzano AV, Raimondo MG, Berti E, Meroni PL, Ingegnoli F. Cutaneous manifestations of ANCA-associated small vessels vasculitis. Clinical reviews in allergy & immunology. 2017 Dec;53(3):428-38.

In pediatric patients, although ANCA-associated vasculitis (GPA, MPA, EGPA), reflecting small- and medium-vessel inflammation, is uncommon, cutaneous manifestations —occurring in approximately 44% of GPA[1], 50% of MPA[2], and 60–70% of EGPA[3]—often herald disease onset, and their early recognition, integrating clinical presentation, histopathology, and ANCA serology, is essential for timely and accurate diagnosis.

FEATURE	GRANULOMATOSIS WITH POLYANGITIS (GPA)	MICROSCOPIC POLYANGITIS	EOSINOPHILIC GPA (EGPA)
Epidemiology	Rare, severe; early adolescence; > females[1]	Rare in Childhood[2]	Rare in children[3]
Most common cutaneous lesion	Palpable purpura[4]	Palpable purpura[7]	Palpable purpura
Other morphologies	Nodules (deep subcutaneous nodules), vesicles/bullae, PG-like ulcers[5]; acneiform/ folliculitis – like papules (~25%)[4]; eyelid oedema; "IgG4-related" orbital pseudotumor[6]	Maculopapular/ erythematous-purpuric lesions on face/elbows/ knees/legs[7]; necrotizing ulcers, gangrene, PG-like lesions[2]	Subcutaneous nodules (~25-30%)[10]; macular/ maculopapular (25-30%); urticarial lesions (~14%)[9,] necrotic/ulcerative lesions, vesicles/pustules, EM-like eruptions, oral ulcers, Raynaud, livedo [11]
Distribution	Extremities; face/trunk for acneiform papules; eyelids[4,6]	Lower limb predominance[7]	Extremities > trunk/scalp[9]
ENT manifestation	Frequent, crusting rhinitis, destructive sinusitis, saddle nose deformity, nasal septum deformity, otitis media	Rare, not specific, not destructive and not granulomatous	Allergic rhinitis, nasal polyposis, not destructive
Asthma	No	No	Yes (>90%)
Lung involvement	Lung nodules (can be excavated), alveolar haemorrhage, bronchial and/or subglottic stenosis	Alveolar haemorrhage, interstitial lung disease[8]	Transient patchy infiltrates, eosinophilic pleural effusion, rarely nodules
Peripheral neuropathy	Infrequent	Frequent	Infrequent
Renal involvement	Frequent (~80%), glomerulonephritis (necrotizing extracapillary)	Very frequent (94-100%), glomerulonephritis (necrotizing extracapillary)[8]	Not frequent, glomerulonephritis (necrotising extracapillary)
Eosinophilia in peripheral blood	Possible (minor)	No (or minor)	Yes (>10%)
Granuloma on histopathology	Yes (frequent)[4,5]	No[7]	Yes, including eosinophils (frequent)
Direct Immunofluorescence	Pauci-immune[1]	Pauci -immune[7]	Pauci-immune dominated by eosinophilic infiltrates[9]
ANCA Profile	~80% c-ANCA/PR3 ANCA; can be negative	60-80% MPO-ANCA/p-ANCA; correlates with disease activity[2]	30-40% MPO-ANCA/p-ANCA positive[9]
Diagnostic Pointers	Purpura, acneiform papules, PG-like ulcers + ENT/ airway/ocular disease evaluate for GPA[4,5]	Purpura or necrotic leg ulcers + RPGN + MPO-ANCA strongly suggests MPA[2,7]	Asthma + eosinophilia + purpura/eosinophil-rich nodules suggests EGPA[9,10]
KEY LEARNING POINTS	Skin lesions may precede systemic disease; biopsy crucial when ANCA negative	Skin disease often accompanies systemic involvement; skin activity may mirror MPO-ANCA[2]	Skin biopsy often diagnostic; may show eosinophilic rather than fully vasculitic phase[9]

COMMENTS:

- *Palpable purpura* is the unifying presentation across all pediatric AAVs.
- Distribution favours *extremities*, with necrotic or ulcerative variants more frequent in GPA and MPA.
- *Eosinophilic infiltrates and systemic atopy* point toward EGPA, while *acneiform, PG-like, or ocular skin lesions* suggest GPA.
- *ANCA status*, though supportive, is not mandatory—histopathologic and systemic correlation remain critical.
- Early dermatologic recognition combined with multisystem assessment can significantly reduce diagnostic delay in pediatric AAV.
-

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EDITOR's NOTE:

Dermatologists often serve as the crucial first point of recognition for ANCA-associated vasculitides (AAV), as cutaneous manifestations frequently precede clinically overt systemic involvement. A detailed understanding of the multisystem pathophysiology of AAV facilitates appropriate early diagnostic testing, acknowledging that while ANCA positivity significantly supports the diagnosis, a negative result does not exclude AAV, particularly in pediatric patients who may remain ANCA-negative, as is frequently observed in EGPA; furthermore, rare dual PR3 and MPO positivity should heighten suspicion for drug-induced vasculitis. Histopathologic assessment via skin biopsy is essential for diagnostic confirmation, and once AAV is suspected, dermatologists play a key role in directing comprehensive systemic evaluation—including chest radiography for all patients, chest CT when pulmonary infiltrates are identified, CT or MRI of the paranasal sinuses when GPA is suspected, and ECG with echocardiography in EGPA—thereby enabling timely, coordinated, multidisciplinary management.

Photoquiz 6

Author: Dr Manjyot Gautam, Dr Rushikesh Aundhekar

Case History: A 3-year-old boy presented with multiple, red, itchy, raised lesions over the face, trunk, extremities and scalp (on/off) since the past 6 months. The lesions appeared in crops and gradually spread to involve the entire body. There was no history of fever associated with the lesions. No h/o any joint pain, abdominal pain, diarrhea, chest pain or neurological complaints. There was no history of recent vaccination or drug intake prior to the appearance of the lesions. Personal and family history were non-contributory.

Clinical examination: Cutaneous examination revealed a generalized involvement with multiple, bilaterally symmetrical, papulonecrotic lesions with central hemorrhagic crusts distributed over the face and scalp (FIGURE-1), trunk, upper & lower limbs and buttocks [FIGURE - 2 (A,B,C) & FIGURE - 3] Deep dermal tenderness was noted over the lesions. Some of the lesions healed with atrophy and post inflammatory hypopigmentation.

Investigation	**Results**
CBC	Hb - 13.8 TLC - 6.48 x 10^3 mL Platelet - 268 x 10^3 mL
LFT	SGOT - 35 U/L SGPT - 16 U/l
RFT	Serum Creatinine - 0.25 mg/dl
ESR	8 mm/hr
IHC	Not done due to financial constraints

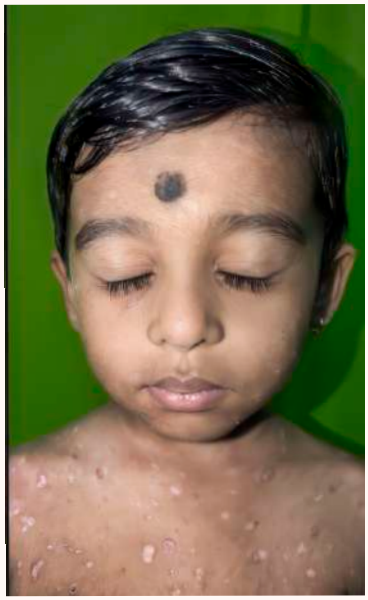


Figure 1

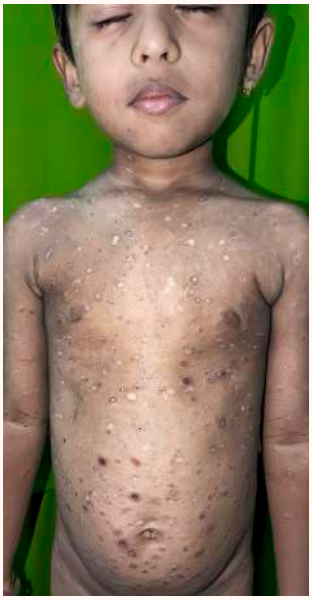


Figure 2 (A)

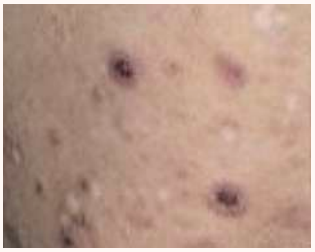


Figure 2 (B)

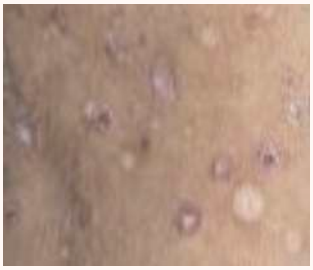


Figure 2 (C)

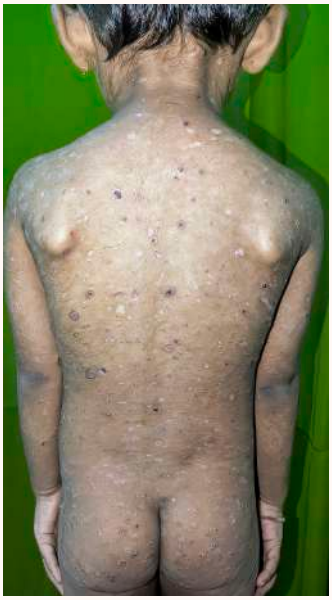
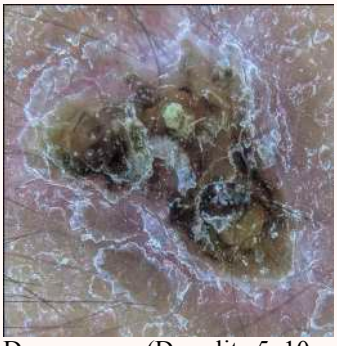


Figure 3



Dermoscopy (Dermlite 5, 10x, polarized) was done (FIGURE - 4). Punch biopsy was taken and sent for histopathological examination (FIGURE – 5 (A,B)].

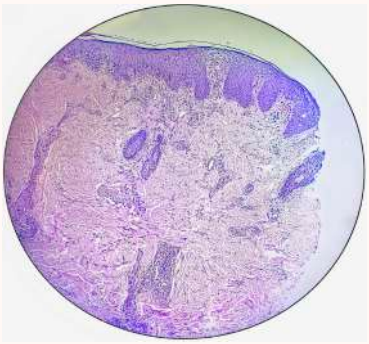


Figure 5 (A) 10X
Hematoxylin and Eosin stain

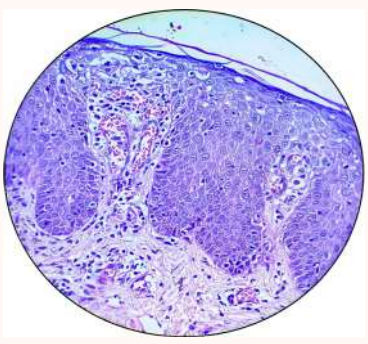


Figure 5 (B) 40X
Hematoxylin and Eosin stain

What is your diagnosis?

Kindly mail your answers along with your affiliation to jetabuch@gmail.com before 1st June 2026. The winners of Photoquiz 6 will be announced in the next issue.

Genetoon

Submitted by Dr Jeta Buch

Our Ancestors must have left a trail of breadcrumbs…….

Though they certainly forgot to leave a GPS

The brain behind the rash – a rare case of rickettsial meningoencephalitis

Author: Dr. Vasudha Belgaumkar

A 2.5-year-old male child hailing from rural Maharashtra was brought with fever since 10 days, rash since 8 days, and seizures since 1 day. The fever was sudden in onset, high-grade, with chills. History revealed frequent exposure to wild rabbits, grey francolins, and hens. Seizures were generalized tonic-clonic, three episodes in 24 hours, each lasting 5–10 minutes.

On general examination, the child was drowsy, tachycardic (161 beats/min), tachypnoeic (30 cycles/min), and hypoxemic (SpO2 80%), with pallor, and altered sensorium. Muscle tone was increased with exaggerated deep tendon reflexes.

On dermatologic examination, there were multiple stellate, non-blanchable purpuric patches with central necrotic areas coalescing to form large geographic ecchymotic lesions over the face, trunk, extremities, gluteal region, palms, and soles. (Fig 1) Scrotal swelling was noted with overlying skin showing ecchymotic areas with central necrosis (Fig 2). Ear pinna involvement was present (Fig 3). There was peri-lesional erythema and tenderness. Gluteal region showed eschar at few places. There were no bullae and mucosae were spared.

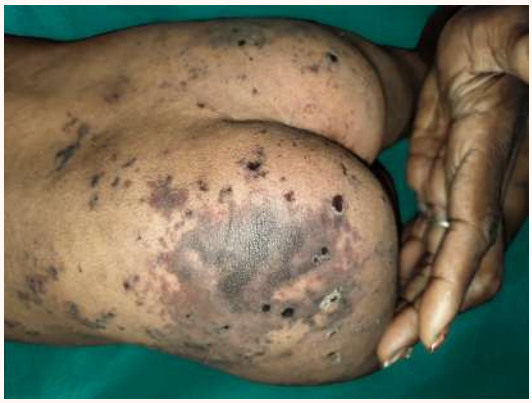


Fig 1 Multiple stellate, non-blanchable purpuric patches with central necrotic areas coalescing to form large geographic ecchymotic lesions over the face, trunk, extremities, gluteal region, palms, and soles.

Fig 2. Scrotal swelling with overlying skin showing ecchymotic areas with central necrosis

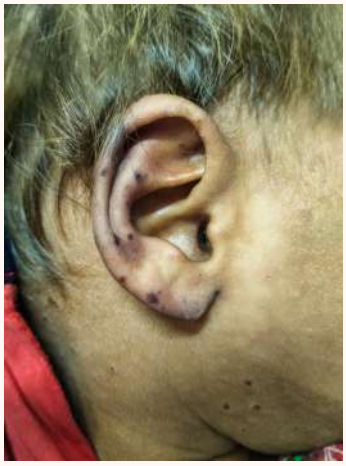


Fig 3 Ear pinna involvement

Initial laboratory investigations showed anemia (hemoglobin 7.3 g/dL), leucocytosis (total leucocyte count 27,170/µL) and thrombocytopenia (platelets 60,000/µL). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) were markedly elevated. In view of suspected disseminated intravascular coagulation (purpura fulminans) secondary to sepsis and possible meningococcemia, he received packed red cells and fresh frozen plasma. However, a normal coagulation profile and negative fibrin degradation products and D-dimer ruled out purpura fulminans. Hemoglobin (9 g/dL) and platelets improved transiently but fluctuated, necessitating repeat transfusions. Cerebrospinal Fluid (CSF) analysis revealed pleocytosis (110 cells, neutrophils 55%, lymphocytes 40%). Dengue NS1 was negative.

Weil-Felix test for OX19 was positive in significant titres (1:160) whereas OX- and OX-K were negative.

Broad-spectrum antibiotics, antivirals, and anticonvulsants were initiated empirically without discernable improvement, but the turning point came with doxycycline therapy (5 mg/kg/day) for 14 days, leading to sustained stabilization of vital parameters, progressive neurological recovery and complete resolution of the rash. A skin biopsy confirmed cutaneous necrotising vasculitis.

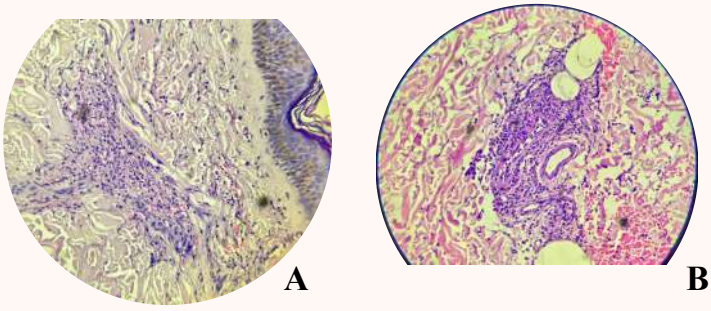


Fig 4 Photomicrogram of skin lesion **(A). 10x, H & E (B).40x, H & E** Superficial and deep dermis shows extravasated RBCs, endothelial swelling with fibrinoid necrosis, perivascular and periadnexal neutophilic infiltrate with karyorrhexis consistent with necrotising small vessel vasculitis

Thus epidemiological context, rash morphology, a positive Weil Felix test and dramatic response to doxycycline supported the final diagnosis of rickettsial meningoencephalitis.

DISCUSSION

Vasculitis is uncommon in children, with incidence rates reported between 12 to 53 cases per 100,000 individuals under 17 years of age. However, despite its rarity, pediatric vasculitis exhibits significant heterogeneity. Although the classification and differential diagnosis of vasculitis is similar, infectious causes are more predominant in children as compared to adults.[1]

Rickettsial infections are common tick, flea, or mite-borne illnesses caused by obligate intracellular *cocco-bacilli* belonging to the family of Rickettsiae. They are re-emerging zoonoses in India, often overlooked due to their nonspecific clinical picture and limited diagnostic facilities. Rickettsial fever has been reported to be endemic in the Himalayan belt, Maharashtra, Karnataka and many other states in India among the adult population. pediatric data is limited in India and other developing countries. Rickettsia are divided into four biogroups namely spotted fever group (SFG) comprising Rocky Mountain spotted fever, Rickettsial pox, Indian Tick Typhus or Mediterranean spotted fever or Boutonneuse fever; Typhus group comprising Epidemic louse borne typhus, Brill–Zinsser disease and Endemic/Murine flea borne typhus; Scrub typhus group and miscellaneous group comprising Ehrlichiosis, Anaplasmosis, TIBOLA (tick borne lymphadenopathy) and DEBONEL (dermacentor borne necrosis eschar lymphadenopathy). Diffuse endothelial infection (infective vasculitis) leading to microvascular leakage and vascular lumen obstruction are basic pathogenetic mechanisms, which explain various clinical features of these infections. The most abundant surface protein of the rickettsia is OmpB and antibodies to OmpB could be a novel treatment tool in future.[2]

Clinical presentation of rickettsial diseases may vary from mild to very severe, with the case fatality rate for highly virulent rickettsiae ranging from 2% to 30%.The most frequent presenting symptoms include fever, headache, rash, and myalgias. While fever and rash are classical features, central nervous system involvement is rare in children. Studies found that the most common neurological features of rickettsial fever include meningitis, encephalitis, and acute disseminated encephalomyelitis which can mimic meningococcemia or viral encephalitis.[3]

Though rash is considered as a hallmark of these infections, it may be absent in some children. Rash of SFG appears on day 2 to 5 of illness, can be pruritic, is evolving (initially macular, becoming maculopapular, petechial, purpuric or gangrenous), has centripetal spread, and can involve palms and soles (considered typical of rickettsial diseases).While several diseases (meningococcemia, infective endocarditis, adverse drug reactions, enteroviral diseases and syphilis) can cause rashes on the palms and soles, the other clinical signs, such as the *speed of onset*, *rash progression*, *presence of an eschar (rickettsial fever)*, and *associated symptoms* (e.g., tender ecchymoses in meningococcemia, heart murmur and signs of embolic phenomena in endocarditis, gastrointestinal symptoms in typhoid, characteristic mucocutaneous lesions in secondary syphilis), are essential for differentiation. Definitive diagnosis often requires specific laboratory tests or serology. Rash in scrub typhus is maculopapular, uncommon than SFG, seen in 30 to 43% cases. The rash in typhus group is quite atypical, initially appearing on trunk, spreading centrifugally and usually sparing palms and soles. Eschar is a crusty necrotic lesion with or without surrounding erythematous halo, which suggests the location of the vector bite. It is painless, non-pruritic and about 1 cm in diameter. Although usually single, multiple eschars may occur. It resembles the skin burn of a cigarette butt and is associated with regional lymphadenopathy. In fact, one should search for eschar in the draining area of regional lymphadenopathy, if the latter is discovered, as regional lymphadenopathy is a marker of hidden or developing eschar. It is recommended that eschars be carefully looked for, as those in intertriginous area may be missed. Although eschar is considered as pathognomonic of rickettsial diseases, it can be seen in anthrax, bacterial ecthyma, spider bite and rat bite fever. It is uncommon in SFG as compared to scrub typhus (7-97%).[4]

Delay in recognition of rickettsial diseases may prove fatal, yet timely doxycycline therapy is often curative. This case illustrates a child with fever, rash, seizures, and hematological instability, whose clinical course highlights the importance of epidemiological context and early therapeutic intervention. The extensive stellate-shaped geographic purpuric rash with central necrosis along with characteristic eschar and involvement of ear pinna pointed to the diagnosis of ricketssial infection as the cause of the meningo-encephalitis. The lack of proper clinical diagnostic techniques in many countries contributes to a delay in starting treatment. This is mainly due to the fact that the only test commonly available is the Weil-Felix test, which does not lead to a definitive diagnosis. Elevated OX K, OX2 and OX19 titres are considered suggestive of scrub typhus, spotted fever group and typhus group respectively though there is a lot of cross-reactivity between the various species. The Immuno-Fluorescence Assay (IFA) is the gold standard test available for diagnosis. [5,6]

CONCLUSION

Vasculitis should be considered as a differential diagnosis in children presenting with unexplained systemic inflammation or multi-organ involvement.

This case highlights the diagnostic challenge of rickettsial encephalopathy, particularly when complicated by haematological instability resembling meningococcemia.

In endemic regions, a child presenting with fever, vasculitic rash, seizures, and zoonotic exposure warrants a strong suspicion of rickettsial infection. Early initiation of doxycycline—even before confirmatory test results—can be lifesaving.

Our patient's course underscores three key lessons: maintain a broad differential with correlation of the characteristic rash with the clinical findings, recognize atypical rickettsial manifestations, and act early with definitive therapy. Awareness of such presentations is essential for improving outcomes in vulnerable pediatric populations from resource-limited settings.

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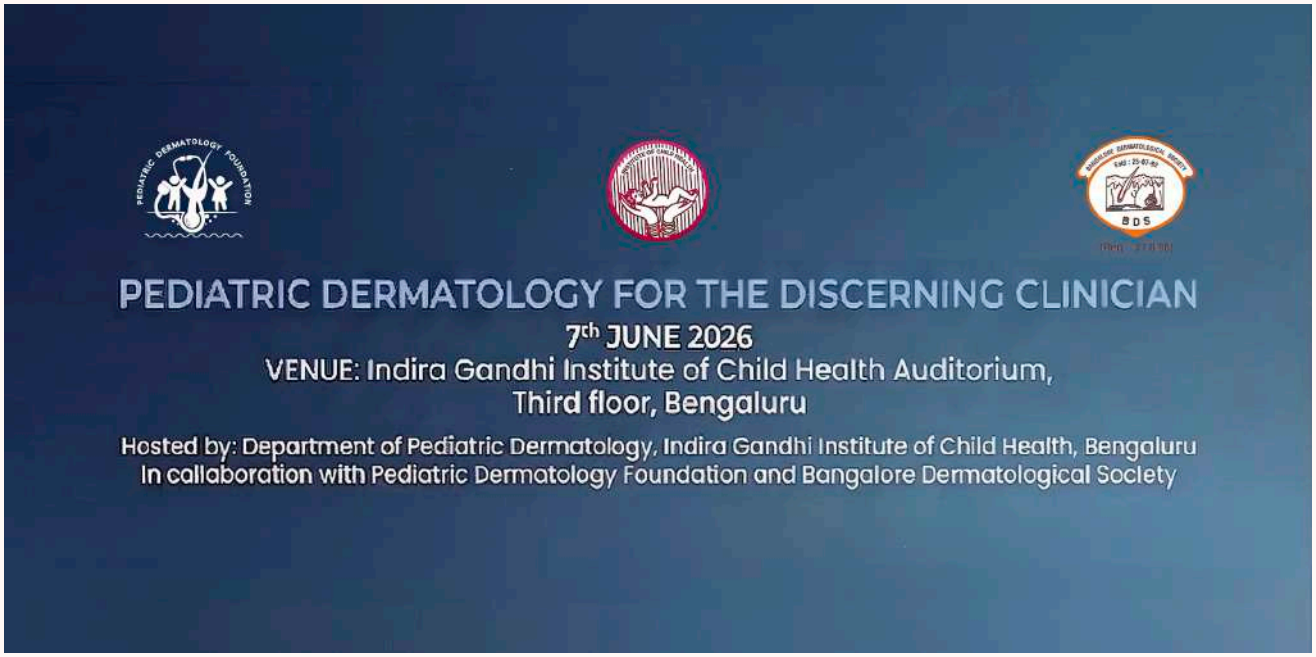

Rituximab in Pediatric Dermatology

Author: Dr. Rashmi Mary Philip

INTRODUCTION

Rituximab is a chimeric monoclonal antibody first approved by the U.S. Food and Drug Administration in 1997 for the treatment of CD20-positive B-cell non-Hodgkin lymphoma. Over the years, its indications have expanded to include chronic lymphocytic leukemia, rheumatoid arthritis, and pemphigus vulgaris refractory to conventional therapies in adults[1]. Although most clinical data focus on adult populations, the use of rituximab in pediatric dermatology is increasing. Case reports and series have demonstrated efficacy in a range of dermatologic disorders; however, a comprehensive pediatric-focused review remains limited.

Rituximab is a chimeric murine-human IgG1 monoclonal antibody (145 kDa) composed of murine-derived variable (Fab) regions fused with human constant (Fc) regions [1]. It selectively targets CD20, a non-glycosylated integral membrane protein expressed on pre-B cells, plasmablasts, mature B cells, memory B cells, and short-lived plasma cells, but not on hematopoietic stem cells, pro-B cells, or long-lived plasma cells [2].

MECHANISM OF ACTION [1,3]

- Fab portion binds CD20 on B cells; Fc portion recruits immune effector cells (mainly NK cells)
- B-cell depletion mechanisms:
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-mediated cytolysis
  - Apoptosis
- Secondary T-cell effects:
  - Reduced costimulatory molecule expression on CD4+ T cells
  - Decreased memory T-cell populations
  - Increased regulatory T cells
- B-cell depletion occurs within 2–3 weeks, lasts ~6 months, and full recovery occurs after ~12 months

PHARMACOKINETICS [4,5]

- Mean half-life: ~3 weeks
- Serum levels increase with multiple infusions
- Age, weight, sex do not significantly affect pharmacokinetics
- 100% bioavailability with IV administration
- Metabolized by proteases and hepatic CYP450 enzymes
- Eliminated via formation of antidrug monoclonal antibody immune complexes mediated by reticuloendothelial systems.
- Dose adjustments in hepatic or renal impairment are undefined

INDICATIONS

FDA-Approved:[6]

- Granulomatosis with Polyangiitis (GPA) – ≥2 years, with glucocorticoids
- Microscopic Polyangiitis (MPA) – ≥2 years, with glucocorticoids
- CD20-positive B-cell malignancies (Diffuse Large B-Cell Lymphoma, Burkitt/Burkitt-like Lymphoma, Mature B-Cell Acute Leukemia) – 6 months–18 years, with chemotherapy

Strong Off-Label/Established Use [4,7,8,9]

- Pemphigus Vulgaris (PV)
- Pemphigus Foliaceus (PF)
- Systemic Lupus Erythematosus (SLE)
- Juvenile Dermatomyositis (JDM)
- Mixed Cryoglobulinemia (MC)
- Graft-versus-Host Disease (GVHD)

Other Off-Label Use (Case Reports/Series)
- Juvenile Bullous Pemphigoid (BP)
- Chronic Bullous Disease of Childhood (CBDC)
- Polyarteritis Nodosa (PAN)
- Sjögren's Syndrome (SS)
- Kawasaki disease
- Atopic dermatitis
- Alopecia universalis
- Refractory urticarial vasculitis

FORMULATIONS, ADMINISTRATION, AND STABILITY OF RITUXIMAB [4,5]

- Formulations:
  - Intravenous (IV): 100 mg/10 mL; 500 mg/50 mL
  - Subcutaneous (SC): Hyaluronidase-enhanced formulation (infusion time 5–7 minutes; currently not available in India)
- Dilution:
  - Can be diluted in 0.9% sodium chloride (NaCl) or 5% dextrose
- Storage and Stability:
  - Reconstituted infusion: Physically and chemically stable for 24 hours at 2–8°C, as it is free of preservatives
  - Post reconstitution at room temperature: Stable for 12 hours
  - Total allowable time post reconstitution: Use within 36 hours
- Administration:
  - IV infusion only; do not administer as IV bolus or push
  - Start infusion slowly to reduce the risk of rapid cytokine release, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)

PEDIATRIC DOSING PROTOCOLS

There are no established rituximab therapy protocol for pediatric patients and there are no recommendations for maintenance treatment. The dosing schedule used in various dermatoses in children is heterogenous and are based on various case reports and case series; as no large randomized trials exists in case of pediatric dermatoses [4].

Two adult dosing protocols are commonly used in pediatrics [4,10]

- Rheumatoid Arthritis Protocol: 1000 mg IV, 2 weeks apart (Most commonly used)
- Lymphoma Protocol: 375 mg/m² IV weekly × 4 doses

  Many pediatric reports use these standard adult regimens with weight adjustment. Evidence does not yet define a single pediatric standard regimen.

Other commonly used regimens in pediatric literature are.

- Combination Therapy: Rituximab (either protocol) + IVIG + dexamethasone pulse[10]
- Low-Dose Regimens [11]
  - 300/350/375 mg/m² × 2 doses (2–4 weeks apart)
  - 500 mg/100 mg × 2 doses (2 weeks apart)

Which protocol is to be followed in children?

The lymphoma protocol was more frequently used, but over time many dermatologist prefer the RA protocol in adults and children due to the following advantages.

a. Fewer infusions
b. Lower costs
c. Earlier peak rituximab concentration[12]

EVIDENCE OF USE OF RITUXIMAB IN PEDIATRIC DERMATOSES

A) Autoimmune blistering disease(AIBD)[13,14]

a.Pemphigus vulgaris

Pemphigus vulgaris and Pemphigus foliaceous has the strongest evidence for the use of rituximab in pediatric dermatology. Evidence reveals that patients achieved complete or partial remission with minimal side effects after rituximab. The indications for the initiation of rituximab were treatment failure in cases of refractory or recalcitrant PV and relapse despite prolonged treatment

with conventional immunosupressants. Protocols used for treatment for pediatric pemphigus reveal considerable heterogeneity, hence a most efficient dosing schedule cannot be ascertained presently. Further testing and comparison of clinical parameters are needed to establish a standard treatment protocol for rituximab in pediatric pemphigus.

b. Bullous pemphigoid[15]

There is evidence of the efficacy of rituximab in treatment of refractory infantile and childhood bullous pemphigoid, when the standard drugs like corticosteroids, cyclosporine and IVG fail to bring an adequate response. There are no fixed protocols that can be used, all rituximab protocols show equal efficacy. A recent article reveals a single dose 375mg/m^2 with additional dose when CD19 count rebounds, gives good response.

Rituximab has been found to be effective in other blistering diseases in children, as an alternative in cases that are refractory to the conventional treatment based on the evidence obtained from single case reports.

- Childhood ocular MMP[16]
- Chronic bullous disease of childhood [17]
- Epidermolysis bullosa acquisita[18]

B) Autoimmune connective tissue diseases

a. Childhood SLE [19,20]

Rituximab for childhood SLE may be considered for the following indications:

1. Refractory lupus nephritis in combination with DMARD
2. Second line therapy for refractory autoimmune haematological disease
3. Few case reports shows its benefit in childhood onset panniculitis
4. Neuro psychiatric disease

b. Chronic cutaneous lupus erythematosus (DLE)[21]

Although there are reports of beneficial effects of rituximab in cutaneous lupus erythematous , overall data suggest poor outcome , with improvement in skin lesions in less than one third of patients suggesting B cells do not play a pathogenic role in the development of skin lesions in DLE.

c. Juvenile dermatomyositis [22,23]

There are conflicting results on the use of rituximab in JDM. It has been used in case of -

- Refractory, or rapidly progressive interstitial lung disease associated with myositis antibodies (anti MDA5)
- Children with refractory calcinosis cutis may benefit with rituximab (conflicting results)
- Refractory cutaneous and myositis that do not respond to standard treatment.

d. Systemic sclerosis [24]

Rituximab shows promising treatment option in severe rapidly progressing juvenile systemic sclerosis in small studies often combined with mycophenolate mofetil. It is found to improve -

- Induration, pigmentation , skin ulcers
- Raynaud's phenomenon
- Joint pain
- Pulmonary and cardiac functions

C) Vasculitis

a. Granulomatous polyangitis and Microscopic polyangiitis [4]

Rituximab was approved by FDA in 2019 for the treatment of GPA and MPA in pediatric

dermatology along with glucocorticosteroids at a dose of 375mg/m^2/weekly BSA for a period of 4 weeks. During follow up period, patient can receive further doses. Complete remission was attained during follow up, Rituximab was found to be superior to other immunosuppressants in ANCA associated vasculitidis.

b. IgA vasculitis [25]

Systemic reviews and reports reveals that rituximab can induce remission in refractory pediatric cases in some children, however evidence is heterogenous. It is highly recommended in HSP nephritis not responding to steroids or immunosuppressants.

D) Graft Vs host disease[4]

Rituximab showed promising results in management of GVHD with improvement of mucocutaneous and musculoskeletal manifestations. However, it did not prevent the development of GVHD when it was used as a prophylactic agent. Hence its use in pediatric steroid resistant chronic GVHD is limited.

BASELINE INVESTIGATIONS [3]

1. Routine Hematology & Chemistry
   - Complete blood count (CBC) with differential
   - Liver function tests (LFTs)
   - Renal function tests (RFTs)
2. Infection Screening
   - HIV serology
   - Hepatitis B: HBsAg, anti-HBc
   - Hepatitis C antibody
   - Tuberculosis screening: Mantoux or IGRA + chest X-ray
3. Immunologic Evaluation
   - Serum immunoglobulins: IgG, IgA, IgM
   - Baseline CD19/CD20 B-cell counts
4. Disease-Specific Tests
   - Anti-desmoglein 1/3 antibodies (pemphigus)
   - ECG
5. Vaccination Review
   - Assess immunization status and ensure age-appropriate inactivated vaccines are administered before therapy

PREMEDICATION & INFUSION MANAGEMENT [3]

- Premedication :
  - Hydrocortisone: 2 mg/kg IV (maximum 100 mg)
  - Pheniramine maleate: 0.1 mg/kg IV (maximum 22.75 mg)
  - Paracetamol: 15 mg/kg orally (maximum 500 mg)
  - Administer all agents 30 minutes prior to the infusion.
- Infusion protocol :
  - First infusion: Begin at 50 mg/h, increasing by 50 mg/h every 30 minutes to a maximum rate of 400 mg/h.
  - Total infusion duration: Approximately 5–6 hours.
- Subsequent infusions: Start at 100 mg/h, escalating every 30 minutes by 50 mg/h up to 400 mg/h.
- In pediatric patients: Initiate the infusion at the lowest practical rate to minimize cytokine-release–associated reactions.
- There are no established maintenance protocols in the pediatric population, likely reflecting both limited evidence and the heightened susceptibility of children to infections during prolonged immunosuppression.

- Management of infusion reactions :
  - Stop the infusion immediately.
  - Administer hydrocortisone and an antihistamine using weight-based dosing.
  - Resume after 30 minutes at a significantly slower rate than previously tolerated.
  -

ADVERSE EFFECTS [4,5]

Common (Most Frequent)

- Mild infusion-related reactions — the predominant adverse events in children, usually brief and easily managed.
- Transient, mild infections — mainly respiratory or urinary tract infections.

Less Common

- Hypogammaglobulinemia — may develop gradually and can be associated with declining vaccine titers.
- Late-onset neutropenia — typically reversible.

Rare

- Severe infections — septicemia, hepatitis B reactivation, herpes zoster, CMV, enteroviral encephalitis.
- Cardiopulmonary reactions — arrhythmias or bronchospasm.

Very Rare (Least Frequent)

- Progressive multifocal leukoencephalopathy (PML) — extremely uncommon but the most serious neurologic complication.

pediatric-Specific Observations

- Children experience more frequent mild infusion reactions.
- They carry a lower overall risk of severe infections compared with adults.

CONTRAINDICATIONS [4]

- Hypersensitivity to murine proteins
- Active infections
- Severe cardiac disease
- CD4 <50 cells/mm³

VACCINE CONSIDERATIONS WITH RITUXIMAB [26]

- Vaccination blunts both humoral and cellular responses. Plasma cells initially produce antibodies, but prolonged B cell depletion reduces overall antibody production.
- Vaccines are unlikely to be fully effective until B cell repopulation occurs.

NOTE: All household contacts must receive up-to-date age-appropriate vaccines to reduce risk of exposure to the patient.

TIMING OF VACCINATION

Before Therapy:

- Live vaccines: ≥4 weeks prior
- Inactivated vaccines: 1–4 weeks prior
- Household contacts: Up to date

During Therapy:

- Live vaccines: Contraindicated
- Inactivated vaccines: Immunogenicity may be reduced

After Therapy:

- Routine vaccination (live & inactivated) ≥6 months after immune recovery

SPECIFIC VACCINE GUIDANCE:

Vaccine Type	Recommendation
Influenza (inactivated)	Continue Rituximab. Give influenza vaccination on schedule (because of seasonal nature of influenza which offers some protection during the relevant season). Delay any subsequent vaccination for at least 2 weeks after vaccination if disease activity allows.
Hepatitis B	Booster dose 2 weeks prior to starting Rituximab. Even after completed HBV vaccination series, a percentage of individuals may not produce adequate antibody levels.

PJP PROPHYLAXIS [27]

Rituximab treated children are at risk of *Pneumocystis jirovecii* pneumonia (PJP), particularly with high-dose corticosteroids (>20 mg/day ≥4 weeks) or additional immunosuppressants. Risk is further increased by lymphopenia (<500 cells/mm³), hypogammaglobulinemia, and renal or pulmonary involvement.

Preferred regimen: Trimethoprim–sulfamethoxazole 5 mg/kg/day (TMP component), 3 days/week, continued for ≥6 months post-Rituximab or until immune recovery. Alternatives: Dapsone, Atovaquone, Pentamidine.

Rationale: B-cell depletion and steroid-induced immune suppression heighten susceptibility; PJP mortality reaches 30–60%, while prophylaxis is safe and effective.

CONCLUSION

Rituximab is an effective, targeted therapy for complex pediatric dermatologic diseases, offering sustained and often transformative disease control where conventional treatments may fail. With careful patient selection, meticulous baseline screening, weight-based premedication, forward-planned vaccination strategies, and vigilant monitoring, rituximab continues to evolve as a safe and increasingly indispensable therapeutic option in children.

EDITOR's NOTE:

- *Rituximab depletes $CD20^+$ B cells, blocking formation of short-lived IgM-secreting plasma cells and causing early, prolonged IgM deficiency. IgG declines later, as long-lived $CD20^-$ plasma cells partially preserve it; IVIG restores IgG but not IgM, leaving patients—especially children with delayed B-cell recovery—vulnerable to infections.*

  Clinical monitoring : Prior to each cycle, assess IgG, IgA, and IgM; which may also unmask underlying primary immunodeficiency; consider IVIG replacement or deferring rituximab if hypogammaglobulinemia persists.

  Remember : IVIG may not fully prevent infections due to IgM deficiency, short half-life (~30 days), and other risks such as neutropenia. Randomized trials are needed to define its prophylactic role in pediatric rituximab therapy.

- *In pediatric patients, rituximab is generally well tolerated; monitoring is essential because infusion reactions—predominantly mild and occurring with the first dose—are most common, while infections peak within six months and include bacterial pathogens such as Streptococcus*, *Staphylococcus*, and *Escherichia coli*, *and viral pathogens such as herpes simplex virus, varicella-zoster virus, and cytomegalovirus, with severe events remaining rare.*
- *Individualize PJP prophylaxis and vaccination schedule based on overall risk–benefit assessment.*

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Approach to Pediatric Vasculitis – From Bench To Bedside

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Why Pediatric Vasculitis Matters?

Pediatric vasculitis may begin as a deceptively simple cutaneous finding—such as transient purpura—but in some children it represents the earliest signal of a systemic disorder, an evolving undifferentiated connective tissue disease, an overlap syndrome, or or even the stark presenting sign of a fully developed connective tissue disorder. This breadth of presentation highlights that vasculitis should therefore be viewed not merely as an isolated vascular event but a potential sentinel of systemic pathology.

Understanding the *pattern, size, and distribution* of vascular involvement is central to accurate diagnosis and rational management.

Epidemiology at a glance

- Most common: Henoch Schonlein Purpura/ IgA vasculitis (IgAV) and Kawasaki disease (KD)
- Sex predilection: Male predominance in Henoch Schonlein Purpura/ IgAV and KD
- All other vasculitides: Rare in childhood

A) Cutaneous Approach (First & Most important step)

➡ **When to Suspect Childhood Vasculitis?**

Childhood vasculitis should be considered in children with cutaneous manifestations that correlate with the calibre of the affected vessels, occurring with or without constitutional symptoms (fever, fatigue, weight loss, arthralgia).

Cutaneous Clues by Vessel Size[1] -

- **Small vessel (SVV):** palpable purpura, petechiae, persistent urticaria with bruising, vesiculobullous or targetoid lesions.
- **Medium vessel (MVV):** livedo, painful or painless nodules, ulcers, infarcts, pitted scars, gangrene.
- **Large vessel (LVV):** secondary ischemic livedo, ulcers, digital necrosis.

➡ ***Vasculitis or Vasculopathy?[2]***

Vasculitis denotes inflammation of the blood vessel wall. The inflammatory infiltrate may be predominantly neutrophilic, eosinophilic, or mononuclear, resulting in structural damage to the vessel.

In contrast, vasculopathy refers to non-inflammatory vascular injury, most commonly due to thrombosis, occlusion, embolism, or coagulopathy, with absence of inflammatory infiltrate within the vessel wall.

Although certain clinical patterns may suggest one entity over the other, histopathological examination remains definitive.

FEATURE	VASCULITIS	VASCULOPATHY
CLINICAL PATTERN	Palpable purpura, nodules, ulcers, livedo reticularis/racemose	Retiform purpura, sharply demarcated necrosis, painful ulcers
PATHOLOGY	Inflammatory infiltrate with vessel wall destruction	Non-inflammatory occlusion (thrombotic/structural)

➡ ***Cutaneous Examination[3]***

- Palpable purpura localised to dependent areas remains the classic cutaneous signature of cutaneous small-vessel vasculitis (CSVV).

- Persistent urticarial wheals lasting beyond 24 hours, often involving the trunk and extremities, with or without angioedema, point strongly toward urticarial vasculitis.
- Acute haemorrhagic oedema of infancy (AHEI) typically begins with erythematous or urticarial plaques that evolve into annular or targetoid lesions over the face and extremities, accompanied by tender, non-pitting oedema of the face, ears, scrotum, and limbs—features that are highly characteristic of this entity.
- In Kawasaki disease, rash (80–90%) is typically erythematous maculopapular, EM-like or scarlatiniform, may be pruritic, uncommonly urticarial or erythrodermic, and never bullous, vesicular, or ulcerative.

➡ ***Dermoscopy–HPE Correlation***

A) Chronic urticaria (CU) vs Urticarial vasculitis (UV)[4]

- Chronic urticaria (CU)
  - Diffuse structureless areas → intense dermal edema obscuring vessels
  - Red reticular lines → ectatic, horizontal subpapillary vessels
- Urticarial vasculitis (UV)
  - Purpuric globules/dots → extravasated, degraded red blood cells

B) Leukocytoclastic vasculitis vs Livedoid vasculopathy

- Leukocytoclastic vasculitis[5]
  - Red globules and red blotches in a mottled pattern on a milky-red or livedoid (blue-gray) background, with absence of scales.
- Livedoid vasculopathy[6]
  - Ivory-white centre → dermal fibrosis (post-vasculitic healing)
  - Reticular pigmentation → basal hyperpigmentation / dermal melanophages
  - Linear & glomerular vessels → dilated, proliferating upper-dermal capillaries

B) General Approach

➡ ***History***

- Presenting: Onset, duration, recurrence; skin lesions, fever, fatigue, arthralgia, abdominal pain, vomiting, hemoptysis, hematuria, edema, melena, photosensitivity, oral ulcers, proximal muscle weakness
- Past: Recent infections, new drugs, vaccinations
- Family: Autoimmune/autoinflammatory disorders, malignancy

➡ ***General and Systemic Examination[3]***

General:

High-yield examination signs are summarized **(TABLE 1)**

TABLE 1

Site	***Findings***	***Interpretation***
Scalp	Diffuse hair loss, telogen effluvium	Systemic disorder, immunosuppressants
Eyes	Conjunctival congestion	KD
	Proptosis	GPA
	Red eye, scleritis, episcleritis	HUVS
Nose	Nasal mass, septum deviation, saddle nose deformity	GPA
Oral Cavity	Ulcer, induration, perforation of hard palate, gingival hyperplasia	GPA
Nails	Clubbing	AAV, HUVS
Lymph Node	Lymphadenopathy	Infection eg. Strep, EBV, Parvo, malignancy
Pulse and Blood Pressure	BP - >140/90	PAN
	Asymmetry in all four limbs	Large vessel vasculitis

Systemic :

A focussed systemic review should guide targeted investigation (TABLE 2)

SYMPTOM	DIAGNOSTIC/PROGNOSTIC VALUE
Constitutional	
Fever	Non – specific. Almost all forms of vasculitis can present with fever. Persistent or prolonged fever in a child with purpura should prompt evaluation for systemic involvement.
Arthralgia	• Transient arthralgia without swelling → hypersensitivity vasculitis, urticarial vasculitis (UV) • Arthritis with swelling in UV → consider Hypocomplementemic Urticarial Vasculitis (HUVS) • Non-migratory oligoarticular arthralgia/arthritis (ankles → knees/wrists/elbows/ hands) → IgAV. • Persistent, frank arthritis with sustained swelling → vasculitis linked to primary rheumatic disease or cryoglobulinemic vasculitis (CryoVas)
Weight loss	Significant weight loss – Polyarteritis nodosa (PAN), ANCA associated vasculitis, vasculitis associated with primary rheumatic disorder, CryoVas
Gastrointestinal	
Abdominal pain, diarrhoea	
Anorexia and jaundice	• Post-prandial pain / ischaemic bloody diarrhoea → IgAV • Unexplained acute abdomen → PAN • Anorexia / jaundice → HBV-PAN, HCV- CryoVas • Abdominal pain, diarrhoea, GI bleeding → Microscopic polyangiitis (MPA), Eosinophilic Granulomatosis with Polyangiitis (EGPA)
Melena and hematochezia	
Renal	
Hematuria	• HUVS (± SLE-associated) in UV child • IgAV • CryoVas • ANCA-associated vasculitis (AAV) (MPA > Granulomatosis with Polyangiitis (GPA) > EGPA) • PAN (microaneurysm rupture → hematuria; glomeruli usually spared)
Frothy urine (s/o proteinuria)	
Oedema	
Upper Respiratory Tract	
Nasal blockage/discharge	GPA
Epistaxis	
Nasal deformity	
Allergic rhinitis, nasal polyposis	EGPA
Lower Respiratory Tract	
Cough	EGPA GPA HUVS in UV
Dyspnea	
Chest pain	
Hemoptysis	
Ophthalmic	
Non conjunctival conjunctival congestion sparing limbus	Kawasaki disease
Episcleritis / scleritis	HUVS, GPA
Auditory	
Otitis media	GPA, EGPA
Sensorineural hearing loss	PAN
Reproductive	
Testicular pain	PAN, IgAV
Vascular system	
Raynaud's phenomenon	PAN, GPA, EGPA, MPA, CryoVasc
Acrocyanosis	
Digital ulcer/gangrene	
Central Nervous System	
Headache, mood change, disturbance of consciousness, vision loss, convulsions, ataxia	Cerebral vasculitis in – IgAV
Peripheral Nervous System	
Cranial nerve palsies	GPA
Paraesthesia	PAN, EGPA, MPA, CryoVas, IgAV (rare)
Neuritic pain	
Motor weakness	

C) When to suspect systemic vasculitis and extend evaluation – RED FLAGS

- Recurrent or persistent purpuric crops
- Necrotic, ulcerative, or atypical cutaneous lesions
- Systemic symptoms such as fever, arthralgia, or weight loss
- Organ-specific involvement, including renal, pulmonary, ENT, gastrointestinal, or neurologic manifestations

D) Secondary Vasculitis & Mimics[2]

Primary vasculitis must be distinguished from secondary causes and non-inflammatory mimics.

A. Infections

Pathogen	Mechanism	Vasculitis Pattern
Bacterial		
Infective endocarditis	a) Vasculitic mechanism - Direct invasion of endothelium Immune complex mediated injury b) Embolic mechanism – Septic infarcts	SVV, ANCA associated vasculitis
Neisseria meningitidis	Direct endothelial invasion	SVV
Mycobacterium tuberculosis	Granulomatous inflammation	EN, panarteritis, thrombophlebitis
Mycobacterium leprae	Immune complexes; vasa vasorum involvement	ENL, large-vessel disease
Treponema pallidum	Endarteritis	Aortitis
Rickettsiae	Endothelial tropism → direct endothelial injury	SVV, purpura fulminans
Viral		
HBV	Direct toxicity + immune complex injury	PAN
HCV	Cryoglobulin deposition	CryoVas
HIV	Immune dysregulation; endothelial effects	PAN; small/medium/large vessel; CNS vasculitis
Parvovirus B19	Immune complex–mediated	PAN, IgAV
VZV	Viral vasculopathy	Meningoencephalitis, retinitis
CMV	Endothelial infection	Retinitis, colitis, PAN

B. Malignancy-Associated Vasculitis

Hematological malignancies

- Leukemia
- Lymphoma

C. Drug-Induced Vasculitis

- Leflunomide → IgAV, AAV
- Anti-TNF agents → IgAV, SVV
- Antithyroid drugs → AAV
- Recreational drugs
  - Cocaine AAV
  - Marijuana

D. Autoimmune & Inflammatory Conditions (AICTD)

- Systemic lupus erythematosus
- Systemic sclerosis
- Dermatomyositis
- Sarcoidosis
- Inflammatory bowel disease

E. Monogenic vasculitis mimics

Monogenic disorders are caused by a mutation in a single gene and follow Mendelian patterns of inheritance, including autosomal dominant, autosomal recessive, X-linked, or mitochondrial.[7]

Key Clinical Clues and Associated Diseases[8]

- Non-classical vasculitic phenotype → Otulipenia, CINCA/NOMID
- Infantile or early-onset presentation → Otulipenia, SAVI, CINCA/NOMID
- Recurrent/periodic fever with purpuric or urticarial rash → TRAPS, DADA2, FMF, MKD
- PAN-, IgAV-, Behçet- or ANCA-like atypical patterns → DADA2, FMF, TNFAIP3 (A20) deficiency, SAVI
- CNS ischemia, lung disease, or severe vascular complications → DADA2, SAVI
- Cytopenias or immunodeficiency → DADA2, Otulipenia
- ANCA-negative small-vessel vasculitis → SAVI, FMF, TRAPS
- Poor response to conventional therapy → TRAPS, CINCA/NOMID, PAPA, SAVI

F. Other Vasculitis Mimickers / Associations

- Thrombocytopenia
- Antiphospholipid antibody syndrome (APLA)
- Embolic disorders
- Coarctation of the aorta

E) Investigations

Baseline Screening[9,10]

- CBC: Leukocytosis (infection), thrombocytopenia (purpura)
- ESR & CRP: Assess inflammatory activity
- Urine routine + microscopy: Hematuria/proteinuria → renal involvement
- Renal function tests: Urea, creatinine
- LFTs: Usually normal; helps exclude systemic causes

Autoimmune Work-up (as indicated):

- ANA: Suspect SLE if cutaneous vasculitis is presenting feature
- ANCA:
  - c-ANCA (PR3) → GPA (~90%)
  - p-ANCA (MPO) → MPA, EGPA (~60%)
  - c-ANCA & p-ANCA → Drug-induced AAV
  - Stepwise testing: IIF → ELISA (PR3/MPO)

Complement & Immunoglobulins:

- C3, C4, serum IgA

Infection Screen:

- Hepatitis B/C serology, HIV
- ASO titre, throat culture if infection suspected

Vessel-Specific Investigations

- Small vessel:
  - Skin biopsy & Direct Immunofluorescence (DIF)
  - IgA deposition → diagnostic of IgA vasculitis
  - C3, IgM, IgG → other immune complex vasculitides
- Medium vessel:
  - PAN → Angiography
  - KD → ECHO for coronary aneurysms
- Large vessel:
  - Doppler / CT / MR angiography

Skin Biopsy – Key Practical Points
- Site: Fresh, active lesion (preferably palpable purpura)
- Timing: Within 24–48 hours of lesion appearance
- Number: One each for H & E and DIF from the lesion

Histopathology:
- Early lesions (<24 h):
  - Neutrophils around post-capillary venules
  - Leukocytoclasia (nuclear dust)
  - Fibrinoid necrosis, RBC extravasation
- Late lesions (>24 h):
  - Fewer neutrophils, lymphocytes/macrophages predominate
- Core diagnostic features:
  - Inflammatory infiltrate
  - Vessel wall damage (endothelial necrosis, fibrinoid change)
  - "Smudgy" vessel wall

Direct Immunofluorescence (DIF):
- Best performed within <48 hours
- Immune complex vasculitis:
  - Ig deposition early
  - Complement (C3) may persist >72 hours
- Older lesions may be DIF-negative → can give false reassurance

Common Pitfalls
- Biopsying old or ulcerated lesions
- Single biopsy only (missing DIF)
- Interpreting ANCA positivity without clinical correlation
- Missing renal involvement without urine examination

Genetic testing
- Whole exome sequencing (WES) in suspected single-gene autoinflammatory or vasculitic syndromes

F) Treatment

A) General Measure
Remove trigger (drug/infection)

Rest, limb elevation, compression stockings

Analgesics, antihistamines

Wound care for ulcerated/necrotic lesions

Watch for systemic complications

If mild, treatment is not necessary

B) Specific Measures
- Hypersensitivity Vasculitis
  - Remove precipitating agent.
  - Mild: antihistamines, NSAIDs.
  - Severe/systemic: glucocorticoids.
  - Usually acute and self-limited.
- IgA Vasculitis (IgAV)
  - Supportive: hydration, nutrition, electrolytes.
  - Pain: acetaminophen; control hypertension if needed.
  - Glucocorticoids reduce joint/skin severity, usually not required.
  - Systemic involvement to be managed by a multidisciplinary team
- Urticarial Vasculitis (UV)
  - Mild/skin-limited (UVAS <7): antihistamines, omalizumab, cyclosporine A.
  - Moderate–severe/systemic (UVAS >7): corticosteroids, dapsone, hydroxychloroquine, rituximab.

- Kawasaki Disease (KD)
  - Managed by pediatrician or pediatric rheumatologist.
  - IVIG + high-dose aspirin; follow-up with low-dose aspirin.
- ANCA-Associated Vasculitis (AAV)
  - Managed by rheumatologist.
  - Glucocorticoids + cyclophosphamide or rituximab; maintenance with azathioprine, methotrexate, or rituximab.
- Monogenic Vasculitis
  - DADA2: Anti-TNF therapy
  - FMF, PAPA: IL-1 blockade
  - SAVI: JAK inhibitors

G) Monitoring

- Regular urinalysis, BP, ESR/CRP
- Most cutaneous-limited vasculitides are self-limiting (HSP, Hypersensitivity Vasculitis)
- Systemic necrotizing forms (PAN, AAV, Takayasu arteritis) require lifelong follow-up
- Echocardiography follow-up in Kawasaki disease
- Angiographic monitoring for Takayasu arteritis/PAN

H) Course and Prognosis

- Hypersensitivity vasculitis: Usually self-limiting; prognosis depends on systemic/end-organ involvement
- HSP: Mostly full recovery; risk of progression to end-stage renal disease is between 1 and 15%
- KD: Good prognosis; early IVIG reduces mortality
- PAN: Systemic PAN better than adults; cutaneous PAN good, relapsing remitting course; penicillin prophylaxis if frequent triggers
- AAV: Renal morbidity and mortality major concern; mortality low in pediatric AAV; usually does not exceed 5-10%[11,12]

TAKE HOME MESSAGE

- Diagnostic continuum: Vasculitis in children is not a fixed diagnosis; relevance depends on potential progression.
- Lesion chronology: Onset, persistence, recurrence, and healing provide critical diagnostic insight beyond morphology.
- Longitudinal reassessment: Even skin-limited disease may later evolve systemically, requiring ongoing monitoring.
- Clinicopathologic integration: Histopathology and serology must always be interpreted within the clinical context.
- Multidisciplinary care: Systemic involvement mandates coordinated management across specialties.
- Early recognition: Enables proactive surveillance, reducing preventable end-organ morbidity.

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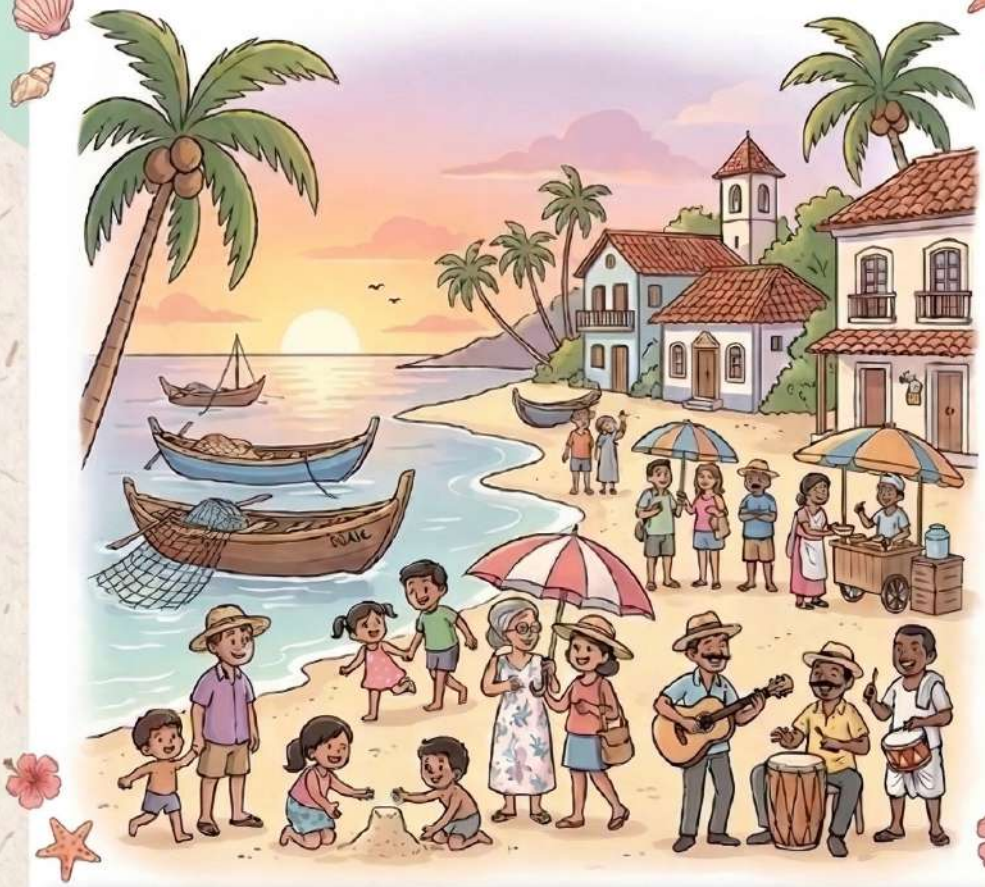

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