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Diagnosis, Treatment, and Management of Common Childhood Vasculitides

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Abstract

Childhood vasculitides, including immunoglobulin A vasculitis, Kawasaki disease, Behçet disease, and polyarteritis nodosa, are inflammatory disorders affecting varying-sized blood vessels. Their pathogenesis involves immune dysregulation, genetic predisposition, and environmental triggers. While treatment varies based on disease severity, immunosuppressive therapy is often required. Preventing complications depends mainly on early identification of the disease and initiating appropriate management. This review aims to guide clinicians in the early diagnosis and multidisciplinary management of childhood vasculitides by addressing their pathogenesis, clinical features, diagnostic approaches, and treatment strategies.

Keywords: Vasculitides, Behçet disease, Kawasaki disease, IgA vasculitis, polyarteritis nodosa, immunosuppressive agen

Introduction

Vasculitides are a rare group of disorders characterized by inflammation of blood vessel walls, affecting both arterial and venous systems of various calibers. Clinical manifestations are closely related to the size of the involved vessels, their anatomical location, and the intensity of inflammation. According to the 2012 Chapel Hill Consensus, vasculitides are primarily classified based on the predominant size of the affected vessels (**Table 1**)[1]. Although vasculitis may occur in both pediatric and adult populations, childhood-onset forms differ substantially in clinical presentation, disease course, treatment response, and long-term prognosis compared to adult-onset vasculitis[2].

For instance, immunoglobulin A vasculitis (IgAV) and Kawasaki disease (KD) predominantly occur during childhood, and key clinical features of vasculitic disorders may vary according to age group[2]. IgAV typically presents with abdominal pain in children, whereas adults more commonly exhibit purpuric rash and joint symptoms[3-6]. KD is extremely rare in adults, often leading to diagnostic delays; as a result, treatment strategies are mostly adapted from pediatric guidelines[2]. In polyarteritis nodosa (PAN), pediatric patients tend to have a better prognosis, with a more pronounced female predominance compared to adults[2]. In Behçet's disease, children often present with incomplete phenotypes, posing diagnostic challenges, and

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genital ulcers, thrombosis, and vascular involvement are less frequently observed than in adults[7].

The diagnostic process of pediatric vasculitis is more complex than that in adults. The rarity of these diseases, the overlap of symptoms with infections or malignancies, and the gradual evolution of clinical features can lead to significant diagnostic delays. Applying adult classification criteria directly to pediatric patients may be insufficient, as these criteria often fail to reflect the heterogeneity of disease in childhood. Therefore, the 2008 Ankara Consensus developed pediatric-specific classification criteria, and the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative later introduced evidence-based treatment recommendations for childhood vasculitides[8-10].

This review focuses on IgA vasculitis, KD, PAN, and Behçet's disease, with the aim of highlighting their pediatric-specific clinical features and therapeutic approaches to support improved diagnosis, treatment, and disease management strategies (**Table 2**).

Highlights

- Pediatric vasculitides represent a diverse spectrum of inflammatory conditions, with clinical manifestations influenced by the caliber and anatomical site of the involved vessels.
- Common vasculitic disorders observed in children include immunoglobulin A vasculitis, Kawasaki disease, Behçet disease, and polyarteritis nodosa; recognized as the most prevalent subtypes in the pediatric population.
- These vasculitic disorders are primarily driven by underlying genetic factors and disruptions in immune system regulation.
- To ensure the best outcomes, treatment plans should be customized and involve various specialties in the management of pediatric vasculitic conditions.

IgA Vasculitis

The most common type of pediatric vasculitis, IgAV, has historically been referred to as Henoch-Schönlein purpura. Classified as a small-vessel vasculitis, it predominantly involves capillaries, venules, and arterioles, with IgA contributing significantly to its underlying pathogenesis[1]. Clinically, IgAV may present as a skin-limited form or a systemic disease with renal, gastrointestinal, or musculoskeletal involvement[11].

The incidence of IgAV exhibits regional differences, with reported incidence rates between 3 and nearly 56 per 100,000 children[3,9,12,13]. Its distribution is also uneven across populations, with the highest prevalence observed in East Asians, a moderate frequency in Europeans, and the least common occurrence in populations with African genetic backgrounds[3,13]. Most cases are seen in children below the age of 10, especially those aged 4 to 7 years, where the disease is most prevalent[12,13]. The greater prevalence in this age group may stem from their increased tendency to contract pathogenic infections. This is further supported by the seasonal variation in IgAV, with higher occurrence during spring and winter, when infections are more prevalent, and lower incidence in summer. IgAV is slightly more frequent in boys than girls, with an estimated boy-to-girl prevalence ratio of 1.5:1[13].

Multifaceted and intricate biological processes characterize IgAV pathogenesis. These include a complex interplay of immune mechanisms, genetic predisposition, and environmental factors. One of the most distinctive outcomes of these mechanisms is the deposition of IgA1-dominant immune complexes (ICs) within small blood vessels, a defining feature of IgAV.

Table 1. *Vasculitis subtypes according to the 2012 Chapel Hill consensus criteria*

1. Large vessel vasculitis • Takayasu arteritis • Giant cell arteritis	2. Medium vessel vasculitis • Polyarteritis nodosa • Kawasaki disease
3. Small vessel vasculitis	
ANCA-associated vasculitis	• Microscopic polyangiitis • Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis
Immune complex vasculitis	• IgA vasculitis (Henoch-schönlein purpura) • Cryoglobulinemic vasculitis • Anti-glomerular basement membrane disease • Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
4. Variable vessel vasculitis • Behçet's disease • Cogan's syndrome	5. Single-organ vasculitis • Cutaneous leukocytoclastic angiitis • Cutaneous arteritis • Primary CNS vasculitis • Isolated aortitis • Others
6. Vasculitis associated with systemic disease • Lupus vasculitis • Rheumatoid vasculitis • Sarcoid vasculitis • Others	7. Vasculitis with probable etiology • Hepatitis C-associated cryoglobulinemic vasculitis • Hepatitis B-associated vasculitis • Syphilis-associated aortitis • Drug-induced immune complex vasculitis • Drug-induced ANCA-associated vasculitis • Cancer-associated vasculitis • Other

Adapted from Jennette JC, Falk RJ, Bacon PA, et al. *Arthritis Rheum*. 2013;65:1-111. CNS; Central nervous system, ANCA; Anti-neutrophil cytoplasmic antibodies, IgA; Immunoglobulin A

Table 2. *Overview of vessel involvement, clinical features, and treatment strategies in common pediatric vasculitides*

Disease	Vessel involvement	Clinical features	Treatment approach
IgA vasculitis	Small vessels (capillaries, venules, arterioles); IgA1 immune complex deposition	• Palpable purpura (especially on lower limbs) • Arthritis/arthralgia • Abdominal pain • Renal involvement • Orchitis • CNS involvement • Pulmonary involvement	• Supportive care Systemic involvement • Corticosteroids • Immunosuppressants
Kawasaki disease	Medium and small arteries; coronary arteries at high risk of aneurysm	• Fever ≥5 days • Conjunctivitis • Mucosal changes • Extremity desquamation • Rash • Cervical lymphadenopathy • Complications of coronary artery	• IVIG within 10 days (2g/kg) • ASA (high then low dose) • Corticosteroids/biologics (IVIG resistance) • Anticoagulation (for aneurysms)
Behçet disease	Variable-vessel vasculitis (arterial and venous of all sizes)	• Recurrent oral/genital ulcers • Uveitis • Skin lesions • Arthritis • Thrombosis • CNS involvement • GI involvement	• Colchicine Systemic involvement • Corticosteroids • AZA • TNF inhibitors • Apremilast
Polyarteritis nodosa	Medium-sized muscular arteries; necrotizing arteritis	• Livedo reticularis • Nodules • Ulcers • Myalgia • Hypertension • Neuropathy	Induction • High-dose IV corticosteroids • CYC Maintance • AZA • MTX • MMF • bDMARDS

ASA; Acetylsalicylic acid, AZA;Azathioprine, bDMARDS;Biologic disease-modifying anti-rheumatic drugs, CNS; Central nervous system, CYC; Cyclophosphamide, GI; Gastrointestinal involvement, IgA; Immunoglobulin A, IVIG; Intravenous immunoglobulin, MMF; Mycophenolate mofetil, MTX; Methotrexate, TNF;Tumor necrosis factor, bDMARDs; Biologic disease-modifying anti-rheumatic drugs

Among the several mechanisms implicated in IgAV, altered glycosylation of IgA1 plays a prominent role. In most patients with IgAV, IgA1 lacks galactose residues, a condition known as galactose-deficient IgA1 (Gd-IgA1)[14]. IgA1 is typically glycosylated at the hinge region through a process called O-glycosylation. It is proposed that genetic susceptibility and/or mucosal infection, in conjunction with interleukin (IL)-6 production, disrupts the glycosylation process, leading to aberrant glycosylation[15]. In IgAV, abnormal glycosylation leads to the generation of Gd-IgA1, contributing to the formation and accumulation of pathogenic ICs. A key process in IgAV pathogenesis is the development of ICs containing Gd-IgA1. Following the interaction of Gd-IgA1 with specific autoantibodies (IgA1 or IgG), circulating ICs are formed and subsequently deposited in small vessels, particularly in organs such as the skin, kidneys, and gastrointestinal tract, where they trigger localized inflammation[16,17]. Gd-IgA1-rich ICs initiate activation of both the alternative and lectin complement cascades, significantly contributing to the disease process[18]. Higher levels of complement split products, including C3a, C5a, C4, and the terminal complement complex (C5b-9), have been reported in individuals with IgAV, with renal involvement showing a robust correlation with complement-mediated disease severity[19]. Activation of the complement cascade promotes cytokine secretion and attracts inflammatory cells to the injury site, thereby intensifying tissue damage. Gd-IgA1 and its corresponding autoantibodies have emerged as potential biomarkers for disease severity, particularly in cases with renal involvement. Their quantification may aid in risk stratification and personalized treatment approaches. Similarly, complement activation products such as C5a and C5b-9 have been associated with disease activity and therapeutic response. While these biomarkers offer clinical promise, their routine use remains limited, and further validation through large-scale, prospective studies is required before they can be integrated into standard clinical practice.

The genetic background in the pathogenesis of this disorder is indisputable. Genome-wide association studies (GWAS) have identified susceptibility loci within the human leukocyte antigen (HLA) class II region, particularly between HLA-DQ Alpha and DQB1, as well as at the DRB1-11 and DRB1-13 alleles[20]. The DQA1*01:01/DQB1*05:01/DRB1*01:01 haplotype is linked to IgAV pathogenesis; however, this association does not seem to apply to other autoimmune diseases[21]. Additionally, increased frequencies of HLA-A2, A11, and B35 alleles have been reported in affected individuals, suggesting a broader HLA-related predisposition[22].

As an essential finding, the diagnostic criteria emphasize the presence of palpable purpura or petechiae in the absence of thrombocytopenia[9]. In addition, at least one other clinical or histopathological feature is required, such as abdominal pain, joint involvement (arthritis or arthralgia), renal manifestations, or biopsy findings demonstrating leukocytoclastic vasculitis or glomerulonephritis with dominant IgA deposition. Palpable purpura and petechiae most commonly affect the lower extremities; however, atypical manifestations in the head, neck, and upper extremities may also occur. In more critical cases, patients may present with hemorrhagic bullae, ulcerations, or necrotic lesions[23]. Subcutaneous edema is common in the

extremities, scalp, and periorbital region. Involvement of the gastrointestinal tract often presents with sudden abdominal pain, which may coincide with symptoms like hematemesis, melena, and occasionally, bowel intussusception[24]. Kidney-related symptoms may manifest as microscopic or gross hematuria, proteinuria (including nephrotic range), hypertension and, if progressive, renal insufficiency. In pediatric IgAV, kidney involvement is a critical predictor of disease outcome, significantly influencing both morbidity and long-term prognosis[23]. For pediatric patients suspected of having IgAV, comprehensive kidney monitoring-comprising regular blood pressure tracking, urinalysis performed on morning samples, and an assessment of glomerular filtration rate (GFR)-is essential throughout both the acute phase and follow-up period[8]. Persistent, significant proteinuria exceeding 250 mg/mmol for at least four weeks typically necessitates renal biopsy in IgAV, although shorter durations might serve as relative indications depending on the clinical context. Persisting moderate proteinuria (100-250 mg/mmol) and reduced GFR are also considered among the indications for biopsy[8]. In addition, although less common, orchitis[25], penile involvement[26], cerebral vasculitis[27], and pulmonary hemorrhage[28] may also occur. Criteria for hospital admission include testicular pain and tenderness, significant crampy abdominal pain, polyarthritis (involving three or more joints), proteinuria, impaired independent mobility, and macroscopic gastrointestinal bleeding[29].

Based on the SHARE recommendation, IgAV cases limited to skin and joint manifestations are expected to resolve without complications when supported by bed rest, sufficient fluid intake, and analgesic management. Corticosteroids and immunosuppressive drugs are recommended for cases involving the gastrointestinal system, kidneys, or other organs[8]. Patients who develop nephritis, severe gastrointestinal involvement, orchitis, cerebral vasculitis, or pulmonary hemorrhage require treatment with corticosteroids. Oral prednisolone 1 to 2 mg/kg daily is recommended. In more severe presentations, pulse IV methylprednisolone (10-30 mg/kg) may be administered over a the clinical. Persistent proteinuria may warrant treatment with angiotensin-converting enzyme inhibitors to prevent secondary injury to the glomeruli. In cases of mild IgAV nephritis, initial therapy typically consists of oral prednisolone. After histopathological confirmation via renal biopsy, immunosuppressive treatment may be intensified using second-line options like azathioprine (AZA), mycophenolate mofetil (MMF), or pulse steroid therapy. In moderate nephritis cases, oral prednisolone and/or intravenous pulse methylprednisolone are usually initiated. Depending on disease progression and clinical risk, immunosuppressive agents such as AZA, MMF, or intravenous cyclophosphamide (CYC) may be introduced. Patients presenting with severe manifestations are typically treated with corticosteroids (oral or pulse theraphy) alongside CYC, following protocols established for similar vasculitic conditions. For chronic management, the use of corticosteroids together with immunosuppressive agents such as AZA or MMF is advised, targeting both renal preservation and reduction of disease recurrence. While plasmapheresis is not part of standard treatment guidelines, it is applied in high-risk cases when deemed necessary[30].

Kawasaki Disease

First reported by T. Kawasaki in 1967[31], this febrile vascular illness primarily affects early childhood. It is considered the second most common childhood vasculitis after IgAV 31, primarily involving medium- and small-sized blood vessels[32]. Despite various clinical observations and population-based studies implying an infectious contribution, the precise etiology of the disease is still unclear[33].

KD primarily occurs in boys and typically manifests before the age of five[34]. Japan reports the most significant number of KD cases globally, with an incidence nearing 239 per 100,000 children, whereas South Korea and Taiwan follow with rates of approximately 113 and 69 per 100,000, respectively[35]. A family history, especially in parents or siblings, increases susceptibility[36]. The incidence of KD fluctuates with the seasons, reaching its highest levels during winter in Japan. In contrast, in the U.S., a rise is commonly observed throughout winter and into the spring months[37].

There is growing evidence that infections might activate the immune system in genetically susceptible individuals, even though the exact etiology of KD is not determined[38]. Early genetic studies identified HLA-DRB1, HLA-B5, Bw51, and Bw44 as susceptibility factors[39]. KD exhibits autoimmune-like features, with immune dysregulation playing a central role[40]. Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) influences T-cell function and contributes significantly to the immunopathology of the disease. ITPKC dysfunction impairs immune regulation, enhancing T-cell responses and elevating cytokine secretion[41]. Following intravenous immunoglobulin (IVIG) treatment, levels of key proinflammatory cytokines such as IL-6, IL-20, interferon-gamma, and tumor necrosis factor-α (TNF-α) show a marked reduction[42]. A shift toward T helper 17 (Th17) over regulatory T-cells (Treg) promotes cytokine-driven inflammation[43]. Initially secreted by T-cells and later by innate immune cells, TNF-α facilitates endothelial activation and leukocyte attachment[36]. TNF-α enhances endothelial cell activation by upregulating adhesion molecule levels and stimulating chemokine secretion, facilitating leukocyte-endothelial interactions[36]. It also stimulates matrix metalloproteinase-9, leading to elastin degradation and aneurysm formation, making TNF-α inhibitors potential therapeutic agents[41]. Additionally, nitric oxide levels are elevated in KD but decrease rapidly after IVIG therapy[44].

The clinical course of KD is typically divided into acute, subacute, and convalescent phases[45]. KD is diagnosed when a persistent fever of at least five days is accompanied by four or more characteristic signs, including diverse skin eruptions, non-purulent redness in both eyes, mucosal changes in the mouth, alterations in the hands or feet, and swelling of the cervical lymph nodes. A four-day fever may suffice if all criteria are met[46], and experienced clinicians may diagnose cases with a three-day fever based on clinical presentation[46,47].

KD represents one of the leading causes of acquired cardiovascular conditions in the pediatric population, and in the absence of treatment, it may lead to coronary artery aneurysm formation. The American Heart Association (AHA) recommends evaluating for incomplete KD in

infants who exhibit persistent unexplained fever for seven days, or fever lasting five days accompanied by two to three of the characteristic clinical signs. The diagnostic approach includes evaluation of inflammatory markers, relevant laboratory investigations, echocardiographic assessment, and ongoing clinical monitoring. Elevated erythrocyte sedimentation rate and C-reactive protein levels, along with at least three additional lab criteria-including hypoalbuminemia (<3.0 g/dL), anemia, thrombocytosis (≥450,000/mm³), leukocytosis (≥15,000/mm³), elevated alanine aminotransferase, or sterile pyuria (≥10 white blood cell/hpf), support incomplete KD diagnosis (**Figure 1**)[48].

KD presents with a sudden high fever (39-40 °C) that can persist for 1-3 weeks if untreated, though spontaneous resolution within a week may occur. Fever generally resolves within 36 hours following the administration of IVIG treatment. In the early stage of KD, a non-itchy macular skin eruption frequently develops on the torso and limbs and may be associated with peeling in the perineal region[49]. Other findings in the acute phase may involve widespread redness on the palms and soles, along with tender edema affecting the hands and feet[50]. In the subacute phase, periungual desquamation becomes evident, particularly around the fingers, usually within 2-3 weeks of disease onset. Beau's lines may also emerge later in the clinical course.

Ophthalmologic manifestations include bilateral, painless, and non-exudative conjunctivitis, a common finding in KD[50]. Oropharyngeal involvement may present with cracked, desiccated lips, a distinct erythematous 'strawberry tongue,' and non-purulent inflammation of the tongue surface. Cervical lymphadenopathy, typically unilateral and affecting the anterior cervical chain, is frequently observed. Among the less common manifestations are gastrointestinal complaints like vomiting and diarrhea, alongside findings such as sterile pyuria, painful urination, joint inflammation, and non-infectious meningeal irritation[41]. In individuals who have received the Bacillus Calmette-Guérin vaccine, localized redness or scabbing at the inoculation site is recognized as a distinctive clinical indicator[50]. Cardiac complications often emerge in the early stage of KD and can include inflammation of the valves, myocardium, or pericardium, as well as the development of Kawasaki shock syndrome[45]. Kawasaki shock syndrome represents a more severe clinical presentation characterized by vasodilatory shock, hypotension, and impaired tissue perfusion, which may occur with or without underlying myocardial dysfunction[51]. Coronary artery dilatation and aneurysm formation typically develop in the later stages of KD, particularly during the subacute and recovery periods. In the absence of timely intervention, nearly 20% of pediatric patients may progress to coronary artery aneurysm formation[45].

Both the AHA and American Academy of Pediatrics endorse IVIG in combination with acetylsalicylic acid (ASA) as the primary approach to managing acute KD[52]. Administering IVIG at a dose of 2 g/kg over a 12-hour period, preferably during the initial 10 days of illness, is associated with the best clinical response[53]. IVIG is also indicated beyond 10 days if fever persists or inflammatory markers remain elevated[54]. Possible complications-such as sterile meningeal inflammation, red blood cell destruction, and infusion, associated side effects, require close clinical surveillance. In addition, live attenuated vaccines, such as those againtst measles, mumps, and varicella, recommended to be

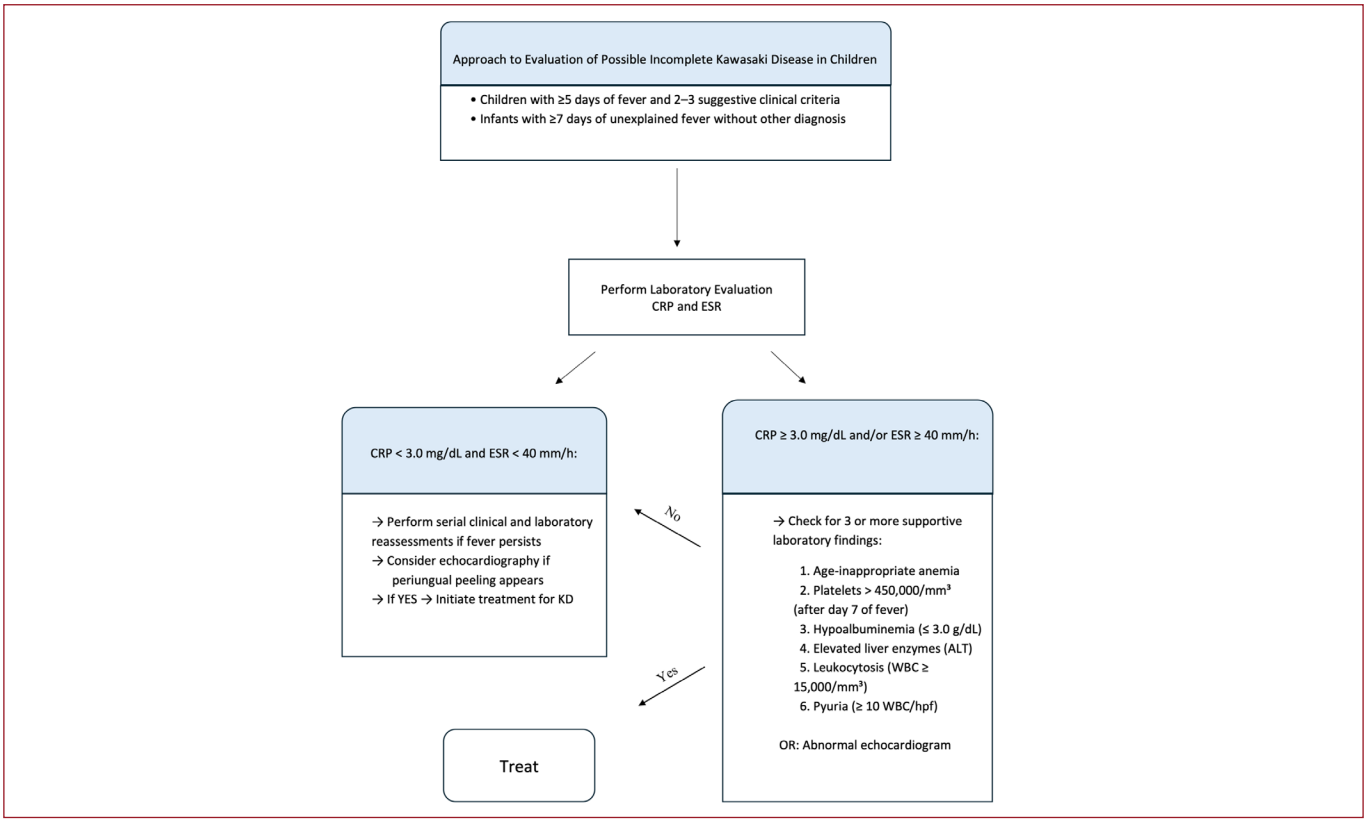

Figure 1. Diagnostic algorithm for incomplete Kawasaki disease

Adapted from Jone P-N, Tremoulet A, Choueiter N, et al. *Circulation*. 2024;150:e481-e500[48]

CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, WBC; White blood cell, ALT; Alanine aminotransferase, KD: Kawasaki disease

delayed for up to 11 months after IVIG administration due to potential interference with vaccine efficacy[46].

ASA is typically administered in moderate to high dosages during the early stages of the illness. After the patient remains afebrile for 48-72 hours, ASA is reduced to a maintenance dose of 3-5 mg/kg/day and generally sustained throughout a 6- to 8-week course[46]. In the presence of varicella or influenza, ASA should be temporarily substituted with agents like clopidogrel due to Reye syndrome risk[46]. Refractory KD refers to fever persisting beyond 36 hours after IVIG treatment[52]. In IVIG-resistant cases, the most frequently used second-line treatments include a repeat IVIG infusion (2 g/kg), systemic corticosteroids in combination with IVIG, and infliximab (5 mg/kg)[46]. Retrospective data suggest that infliximab may reduce the duration of fever and hospitalization, although it appears similar to a second IVIG dose in terms of coronary artery outcomes. No clear superiority has been demonstrated between pulse and prolonged oral corticosteroid regimens. However, some studies suggest that longer steroid courses may improve both clinical outcomes and coronary artery status. For patients unresponsive to these options, additional therapies may include cyclosporine, the IL-1 receptor antagonist anakinra, therapeutic plasma exchange, and the cytotoxic agent CYC in rare cases. Owing to the limited evidence base, treatment strategies should be tailored to the individual, considering prior response and disease severity. For individuals presenting with sizable coronary artery aneurysms, the use of anticoagulants such as low-molecular-weight heparin or warfarin is advised to minimize the risk of thrombosis[53]. Low-dose ASA is continued for six weeks in those without coronary involvement, whereas long-term antiplatelet or anticoagulation therapy is needed for those with aneurysms[46].

Early recognition and prompt intervention in KD are critical for minimizing death rates, reducing disease-related complications, and preventing long-term sequelae.

Behçet Disease

Behçet disease was initially identified in 1937 by Behçet[55], who described it as a syndrome involving recurrent oral and genital ulcers in addition to uveitis. In 1946, the inclusion of superficial thrombophlebitis expanded its clinical spectrum[56].

Behçet disease is a form of variable vessel vasculitis that affects both arterial and venous structures across a wide range of calibers[1]. The disease manifests as a chronic inflammatory condition affecting multiple organ systems, characterized by repeated episodes of oral and genital ulceration. It may also involve the skin, eyes, joints, gastrointestinal tract, and central nervous system. Its heterogeneous presentation poses challenges for definitive diagnosis and classification.

Behçet disease is most frequently reported in populations residing along the ancient Silk Road, notably in East Asia, the Middle East, and the Mediterranean area. Prevalence rates differ widely, reaching 370 per 10,000 in Türkiye, while being significantly lower in regions such as Japan (13.5), Israel (11.9), the U.S. (5.2), the UK (0.64), and Italy (3.8-15.9)[57]. Epidemiological data on pediatric cases remain limited[58]. Data on pediatric Behçet's disease are limited; however, a recent international report indicated childhood onset in 26% of cases, typically between ages 4 and 15[59].

While its precise cause is uncertain, BD is thought to result from immune dysregulation driven by genetic and environmental factors[60]. Infections and alterations in the microbiota are considered important triggers[61,62]. BD has been significantly correlated with the HLA-B5 antigen, particularly the B51 subtype of the HLA-B5 antigen, which is linked to genital, ocular, and cutaneous manifestations, whereas gastrointestinal involvement is less commonly observed[63,64]. GWAS has also implicated variants in major histocompatibility complex class I, IL-10, and IL-23R-IL12RB2 regions in disease susceptibility[65]. A20 protein (HA20) deficiency, which regulates nuclear factor kappa B activation, has been linked to BD-like phenotypes[66,67]. In children, Th17 overactivity appears to coincide with impaired Treg[68]. Genomic studies implicate IL-23 receptor gene variants in the genetic predisposition to BD.

In 1990, the International Study Group (ISG) introduced diagnostic guidelines for adult Behçet's disease, which require recurrent oral ulceration that occur three or more times annually, along with at least two additional findings such as genital ulcers, eye involvement, skin lesions, or a positive pathergy reaction[69]. Cases with only one additional feature are considered incomplete Behçet's disease. Mason and Barnes later introduced broader criteria to capture more diverse clinical presentations[70]. Established in 2014, the International Criteria for Behçet's Disease (ICBD) have shown greater diagnostic sensitivity compared to the earlier ISG guidelines[71]. The ICBD awards 2 points for mucosal and ocular signs, and 1 point for pathergy, neurological, or vascular features. Diagnosis is confirmed with a score of 4 or above. Developed in 2016, the pediatric-Behçet's disease criteria award 1 point for each major feature: Oral or genital ulcers, skin lesions, eye inflammation, neurological findings, and vascular signs; a minimum score of 3 confirms the diagnosis[72].

Behçet disease primarily affects the skin and eyes[73]. Recurrent aphthous ulcers occur in 95-97% of patients and are generally considered the first symptom[74]. Genital ulcers, observed in 50-85% of cases, may heal with scarring[75]. Papulopustular lesions commonly affect the face, chest, and back, but can also appear more diffusely[76]. Erythema nodosum-like nodules are painful and non-ulcerative, usually located on the lower limbs. Musculoskeletal involvement affects around 50% of patients, commonly as non-erosive oligoarthritis in the knees, ankles, hands, and wrists[77]. Ocular involvement, a key contributor to morbidity, is often bilateral and presents as panuveitis or retinitis, though anterior uveitis can occur in isolation[78]. Vascular involvement in Behçet's disease may present as thrombotic events in veins, arterial blockages, or aneurysms, with deep vein thrombosis of the lower limbs being the most observed presentation[79]. Neurological involvement affects around 5% of patients and is categorized into parenchymal and vascular types. Parenchymal involvement impacts the

brainstem and corticospinal tracts, while the vascular form presents as cerebral sinus venous thrombosis. Gastrointestinal manifestations frequently include ulcerative lesions localized to the terminal ileum and cecal region, typically manifesting as abdominal pain, episodes of vomiting, and diarrhea[80]. The pathergy reaction assesses cutaneous hypersensitivity following minimal skin injury; a positive test is characterized by the emergence of a papule or pustule at the puncture site within 24 to 48 hours.

Therapeutic approaches in Behçet's disease vary according to clinical severity and the systems affected. Topical corticosteroids are commonly prescribed to manage mucosal lesions, while systemic formulations are reserved for more serious complications, such as ocular inflammation, vascular pathology, or gastrointestinal involvement[81]. The primary treatment approach includes colchicine for managing mucocutaneous lesions and arthritis, with AZA used in more severe cases affecting the eyes, blood vessels, or gastrointestinal system[82-85]. Methotrexate and MMF are alternative options for neuro-Behçet and mucocutaneous disease. Cyclosporine A is beneficial in managing severe ocular manifestations, whereas CYC is typically employed in critical cases involving the pulmonary arteries or central nervous system[81,86,87].

Treatment of aneurysmal involvement in the pulmonary vasculature or heart typically involves intensive glucocorticoid therapy combined with CYC, while TNF inhibitors may be considered in refractory cases[86]. Anti-TNF therapies-including agents like etanercept, infliximab, and adalimumab-have shown efficacy in managing complex Behçet's disease presentations, such as ocular, neurological, gastrointestinal, vascular, joint, and mucocutaneous involvement[86,88]. Infliximab and adalimumab show particular efficacy in uveitis and severe gastrointestinal disease[88].

For gastrointestinal Behçet's disease, 5-ASA and sulfasalazine are effective in mild cases, while refractory cases require AZA, anti-TNF agents, or immunosuppressants such as thalidomide[89]. Apremilast, a phosphodiesterase-4 inhibitor, has shown efficacy in treating mucocutaneous lesions, arthritis, and overall disease activity, both as monotherapy and in combination with immunosuppressants or TNF inhibitors[90].

Behçet disease is a relapsing-remitting systemic inflammatory condition, with approximately 25% of cases beginning in childhood. While its clinical features resemble those in adults, the entire disease spectrum may take years to develop, often delaying diagnosis

Oral and genital ulcerations frequently emerge during the initial stages of Behçet's disease and can significantly affect patients' quality of life. However, ocular, neurological, and arterial involvement are the primary determinants of morbidity and mortality[91]. Given its **heterogeneous course** and multi-organ involvement, Behçet's disease requires an individualized and multidisciplinary treatment approach based on disease severity and affected systems.

Polyarteritis Nodosa

PAN involves inflammation of medium-sized arteries, with necrotizing changes being the hallmark histopathological feature[1]. This condition is infrequently encountered in the pediatric population, affecting roughly one child per million. Additionally, the current epidemiological data are limited and require further investigation. No sex-related differences have been identified, and the peak age at presentation is between 7 and 11 years[13]. The pathogenesis is not fully understood. Necrotizing vascular inflammation is driven by the coordinated actions of innate and adaptive immune systems[92].

Diagnostic confirmation of PAN is based on defined clinical and pathological criteria. These criteria include either a histological confirmation of necrotizing arteritis or the detection of vascular abnormalities through angiography. To establish a diagnosis, at least one clinical manifestation must be present, such as skin lesions, muscle pain, elevated blood pressure, peripheral nerve dysfunction, or renal involvement,alongside histopathological or angiographic findings[9]. This condition is characterized histopathologically by fibrinoid necrosis in affected vessel walls, with neutrophilic infiltration at the vessel's periphery, and erythrocyte extravasation into the lower dermis subcutaneous adipose tissue. Notably, giant cells and granulomas are absent, and no immune deposition detected[92]. Imaging typically reveals vascular changes such as fusiform or saccular aneurysms and arterial narrowing. Despite the increasing use of non-invasive imaging methods-namely magnetic resonance and computed tomography angiography-conventional angiography remains the preferred standard in radiologic assessment[93]. Skin findings may present as livedo reticularis or racemosa, subcutaneous nodules, or ulcerations. Less commonly, digital ischemia and Raynaud's phenomenon may occur. Renal manifestations vary widely, from isolated hematuria to impaired kidney function. Involves the kidneys, as the disease mainly affects medium and small renal vessels rather than capillaries.

Fever, general weakness, fatigue, weight loss, loss of appetite, muscle pain, muscle tenderness, and high blood pressure are common clinical manifestations of the disease. Fever, mucocutaneous symptoms, and musculoskeletal involvement have been reported as the most frequent clinical features in pediatric PAN cases, as shown in a cohort of 56 patients[94]. Similarly, Eleftheriou et al.[95] reported a higher prevalence of fever, weight loss, fatigue, and musculoskeletal involvement. Additionally, Kasap Cuceoglu et al.[96] found skin and musculoskeletal system involvement to be more frequent in their study. Although less common, studies have also shown cardiac, respiratory, and neurological involvement. In pediatric patients presenting with PAN-like features, differential diagnosis is broad, with monogenic vasculitides, particularly adenosine deaminase 2 deficiency (DADA2),requiring careful exclusion[10]. DADA2 should be strongly considered in cases with early onset, consanguinity, neurological manifestations such as stroke, lymphopenia, and lack of thrombocytosis (**Table 3**)[96].

Table 3. *Key distinctions between polyarteritis nodosa and deficiency of adenosine deaminase 2*

	Poliarteritis nodosa	Deficiency of adenosine deaminase 2
Age on onset	Childhood or adulthood	Typically early childhood
Genetic	None/unknown	*ADA2* gene (formerly known as CECR1)
Inheritance pattern	Sporadic, usually autoimmune	Autosomal recessive
Clinical features	Systemic inflammation Vasculitis Myalgia Peripheral neuropathy	Systemic inflammation Vasculitis Early-onset stroke Immunodeficiency
Laboratory findings	Elevated inflammatory markers (CRP, ESR) Reactive thrombocytosis Autoantibodies absent or low	Elevated inflammatory markers (CRP, ESR) Cytopenias Reduced ADA2 activity
Treatment	Steroids Immunosuppressants	Anti-TNF therapy

CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, TNF; Tumor necrosis factor

Treatment recommendations for rare vasculitis have been established by the SHARE consortium, which includes pediatric rheumatologists and nephrologists from across Europe[10]. The treatment plan usually consists of an initial induction period, followed by extended maintenance therapyadjusted based on the course of the disease. Treatment typically begins with intravenous administration of high-dose corticosteroids (ranging from 10-30 mg/kg/day, provided it does not exceed 1 g/day) for three consecutive days, followed by oral steroids at 1-2 mg/kg/day for maintenance. The dosage is subsequently reduced stepwise and typically discontinued by the end of 12 months. CYC is utilized in induction regimens as periodic infusions (500-1000 mg/m², not exceeding 2 g per dose), administered every few weeks for up to six months, together with steroid therapy. Additionally, therapeutic plasma exchange may be utilized. For maintenance purposes, agents such as AZA, methotrexate, and MMF can be used as first-line therapeutic strategies. For individuals who do not respond to standard induction therapy or present with refractory disease, biologic agents offer an alternative therapeutic option. Although no clear preference is established for the initial biological agent, TNF blockade, B-cell depletion, or IL-6 inhibition are considered potential options[97].

Conclusion

Pediatric vasculitides are complex and heterogeneous disorders that demand timely recognition and individualized, multidisciplinary management.

IgAV, although often self-limiting, requires close follow-up when renal involvement is present, as it significantly influences long-term prognosis. Corticosteroids and immunosuppressive agents play a key role in preventing chronic renal damage in these cases. KD, a leading cause of acquired heart disease in children, necessitates prompt IVIG treatment to reduce the risk of coronary aneurysms. Patients with IVIG resistance or cardiovascular involvement may benefit from adjunctive corticosteroids or biologics. Behçet's disease typically follows a relapsing-remitting course with multisystem involvement. Early identification of mucocutaneous symptoms and monitoring for ocular, neurologic, or vascular manifestations guide escalation to systemic immunosuppressive or biologic therapy. PAN, though rare, can be life-threatening. Early systemic involvement warrants aggressive induction therapy with corticosteroids and CYC, followed by maintenance with steroid-sparing agents. In suspected monogenic mimics such as DADA2, genetic testing and targeted biologics (e.g., anti-TNF) should be considered.

Research should prioritize the development of non-invasive biomarkers for early diagnosis and disease monitoring, the establishment of multicenter pediatric cohorts to better understand disease variability, and the evaluation of steroid-sparing treatment strategies to improve outcomes and minimize long-term toxicity.

Ethics

Informed Consent: The consent form was not needed due to the study design.

Footnotes

Author Contributions: Başer Taşkın B: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Doğru A: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Aktay Ayaz N: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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