

## **Symposium: Connective tissue and bones**

### **Vasculitis in children**

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## **Abstract**

Systemic vasculitis is characterized by blood vessel inflammation which may lead to tissue injury from vascular stenosis, occlusion, aneurysm, and/or rupture. Apart from relatively common vasculitides such as IgA Vasculitis (IgAV; previously referred to as Henoch-Schönlein Purpura [HSP]) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but are associated with significant morbidity and mortality. Classification criteria for childhood vasculitis and a disease activity scoring tool have recently been proposed and validated. The cause of the majority of vasculitides is unknown, although it is likely that a complex interaction between environmental factors such as infections and inherited host responses trigger the disease and determine the vasculitis phenotype. Several genetic polymorphisms in vasculitis have now been described that may be relevant in terms of disease predisposition or development of disease complications. A novel monogenic type of polyarteritis nodosa due to loss of function mutations in *CECR-1* gene has been recently described, and other monogenic inflammatory diseases with a vasculitic component are now recognised. Treatment regimens continue to improve, with the use of different immunosuppressive medications and newer therapeutic approaches such as biologic agents. Randomized control studies involving predominantly adults have recently recruited children with vasculitis too; but rare disease trial design is required for paediatric specific trials such as currently used in an RCT in paediatric polyarteritis nodosa. The SHARE (Single-Hub Access for Pediatric Rheumatology in Europe) project has recently provided guidance on uniform management of rare paediatric rheumatic diseases including the vasculitides. We

herein provide an overview of paediatric vasculitides with emphasis on presenting features, current insights on aetiopathogenesis and treatment advances.

**Key words:** Vasculitis, child, Kawasaki disease, IgA Vasculitis, Henoch-Schönlein Purpura

## **Introduction**

Apart from relatively common vasculitides such as IgA Vasculitis, previously referred to as Henoch-Schönlein Purpura (HSP), and Kawasaki disease (KD), most of the primary systemic vasculitic syndromes are rare in childhood, but when present are associated with significant morbidity and mortality. The general scheme for the classification of paediatric vasculitides is summarized in table 1. An important advance has been the development and validation of a paediatric vasculitis activity assessment (PVAS) tool that systematically quantifies disease activity, and is being used as an outcome measure in two ongoing paediatric vasculitis clinical trials, and other research involving children with vasculitis. Treatment regimens continue to improve with the overall intention of reducing cyclophosphamide and glucocorticoid toxicity for children by exploring different immunosuppressive medications including biologic agents.

Most of the current treatment approaches for paediatric vasculitides are based on evidence from small case series, anecdotal observations, or adult studies. Therefore treatment approaches differ substantially internationally, and even between institutions from the same country. Given that vasculitides are rare, conducting large randomised controlled trials using traditional frequentist statistical method approaches to inform practice may not be feasible. There is however an important unmet need for optimized standard management of these rare paediatric diseases. This review summarizes the epidemiology, aetiopathogenesis, presenting clinical features and advances in current management strategies for paediatric vasculitides including reference to soon-to be-published European management guidance.

## **Predominantly small vessel vasculitis**

### **IgA vasculitis (HSP)**

HSP is the most common childhood primary systemic vasculitis with an estimated annual incidence of 20.4 per 100,000 children in the UK. According to the EULAR/PRINTO/PRES definition a patient is classified as having HSP in the presence of purpura or petechiae with lower limb predominance (mandatory criterion), plus 1 out of 4 of the following criteria:

1. Abdominal pain
2. Histopathology showing typical leucocytoclastic vasculitis with predominant IgA deposit; or proliferative glomerulonephritis with predominant IgA deposit

3. Arthritis or arthralgia

4. Renal involvement (proteinuria or haematuria or presence of red blood cell casts).

In cases with purpura with atypical distribution a demonstration of IgA is required as a mandatory criterion, although in routine clinical practice skin biopsy with immunofluorescence is rarely performed. Another caveat regarding this point is that if the skin biopsy is taken in the centre of the necrotic lesion, IgA deposition may be falsely negative due to the presence of proteolytic enzymes.

#### *Aetiopathogenesis*

As many as 50% of occurrences in paediatric patients are preceded by an upper respiratory tract infection. HSP occurrence following occurring vaccination has also been described, although this remains a contentious issue. Several infectious agents have been implicated, including group A streptococci, varicella, hepatitis B, Epstein-Barr virus, parvovirus B19, *Mycoplasma*, *Campylobacter*, and *Yersinia*.

It is suggested that IgA has a pivotal role in the pathogenesis of the disease, a hypothesis supported by the almost universal deposition of IgA in lesional vascular tissue. Recently, galactose deficiency of O-linked glycans in the hinge region of IgA1 has been reported in adults with IgA nephropathy and children with HSP. IgA immune complexes and activation of complement lead to the formation of chemotactic factors (such as C5a), which in turn recruit polymorphonuclear leucocytes to the site of deposition, resulting in further inflammation and necrosis of vessel walls, with concomitant thrombosis and extravasation of erythrocytes from haemorrhage. The histological endpoint is that of a

typical leukocytoclastic vasculitis that refers to the breakdown neutrophils in lesional tissue resulting in the characteristic nuclear debris or “nuclear dust”.

Several genetic polymorphisms have been linked to HSP in various population cohorts. On the whole however, studies of this nature have been hampered by relatively small patient numbers and lack of power to be definitive or necessarily applicable to all racial groups.

### *Clinical features*

Skin involvement is typically with purpura which is generally symmetrical, affecting the lower limbs and buttocks in the majority of cases, the upper extremities being involved less frequently. Angioedema and urticaria can also occur. Around two thirds of children have joint manifestations at presentation with the knees and ankles most frequently involved; articular symptoms tend to resolve without the development of permanent articular damage. Three-quarters of children develop abdominal symptoms ranging from mild colic to severe pain with ileus and vomiting. Haematemesis and melaena are sometimes observed, due to mesenteric vasculitis. Other serious complications include intestinal perforation and intussusception. The latter may be difficult to distinguish from abdominal colic, and the incidence of intussusception is significant enough to warrant exclusion by ultrasound where suspected. Acute pancreatitis is also described, although is a rare complication.

Other organs less frequently involved include the central nervous system (cerebral

vasculitis), gonads (orchitis may be confused with torsion of the testis) and the lungs (pulmonary haemorrhage). Ureteric obstruction has been reported. Recurrence of symptoms occurs in around one third of cases, generally within four months of resolution of the original symptoms.

Reports of HSP nephritis indicate that between 20-61% of cases are affected with this complication. Renal involvement is normally manifest between a few days and a few weeks after first clinical presentation, but can occur up to 2 months or (rarely) more from presentation. Renal involvement can present with varying degrees of severity. This includes isolated microscopic haematuria, proteinuria with microscopic or macroscopic haematuria, acute nephritic syndrome (haematuria with at least two of hypertension, raised plasma creatinine and oliguria), nephrotic syndrome (usually with microscopic haematuria) or a mixed nephritic-nephrotic picture.

The renal lesion of HSP nephritis is characteristically a focal and segmental proliferative glomerulonephritis with IgA deposition. Severe cases with rapidly progressive glomerulonephritis can demonstrate crescentic glomerular changes on renal biopsy.

Indications for diagnostic renal biopsy in children with HSP are:

- Nephritic/nephrotic presentation (urgent)
- Raised creatinine, hypertension or oliguria (urgent)
- Heavy proteinuria (Ua:Ucr persistently >100 mg/mmol) on an early morning urine sample at 4 weeks. Serum albumin not necessarily in the nephrotic range.
- Persistent proteinuria (not declining) after 4 weeks
- Impaired renal function (GFR <80ml/min/1.73<sup>2</sup>).

### *Management*

There is a very poor evidence base to guide the management of HSP, particularly for those with the severe forms of HSP nephritis (HSPN), and thus very few true therapeutic advances. Early morbidity in the disease is due to GI involvement; late morbidity and the most important overall determinant of poor outcome is renal involvement. In children the management of HSP is mainly conservative because the extra renal manifestations are usually self-limited. Arthritis responds well to non-steroidal anti-inflammatory drugs (NSAIDs). Severe skin lesions and gastrointestinal involvement could require a short course of an oral corticosteroid. Controlled studies have shown that corticosteroids do not prevent renal disease. Despite that, patients with severe renal involvement usually do require corticosteroids combined with other immunosuppressive agents, and sometimes anti-proteinuric and antihypertensive agents.

### *Summary of the SHARE guidelines for HSP*

The SHARE (Single Hub Access for pediatric Rheumatology in Europe) initiative represents an important major therapeutic contribution since it provides consensus guidance for the management of HSP and HSPN, amongst other vasculitides [8]. In anticipation that these will be published imminently, a brief overview of the SHARE management algorithm for HSPN is as follows. Children with microscopic haematuria without renal dysfunction or proteinuria, and those with non-persistent mild-moderate proteinuria usually do not require any specific therapeutic intervention other than a “watchful waiting approach” since the prognosis is excellent. Those with more severe proteinuria and/ or impaired glomerular filtration, and those with persistent proteinuria



should be reviewed by a paediatric nephrologist, and a renal biopsy is usually recommended. Treatment thereafter includes first line therapy with corticosteroids: oral for all; and initially intravenous pulsed methylprednisolone for those with more severe renal involvement. For the severest cases, intravenous cyclophosphamide is usually required (sometimes with plasma exchange: seek expert advice) as additional first line treatment combined with corticosteroids. Immunosuppressants including azathioprine, mycophenolate mofetil (MMF), or intravenous cyclophosphamide may be considered as second-line agents for those with moderate HSPN. It must be emphasised, however, that in the absence of robust data for evidence supporting the treatment of nephritis, even in view of the much anticipated SHARE guidance, a randomised controlled trial for the treatment of HSPN is urgently needed.

### *Outcome*

The majority of children with HSP make a full and uneventful recovery with no evidence of ongoing significant renal disease. Renal involvement is the most serious long term complication of HSP. Renal complications, if they did occur, developed early – by 4 weeks in 85% and by 6 months in nearly all children. Persistent renal involvement (hypertension, reduced renal function, nephrotic or nephritic syndrome) occurred in 1.8% of children overall but the incidence varied with the severity of the kidney disease at presentation, occurring in 5% of children with isolated haematuria and/or proteinuria but in 20% who had acute nephritis and/or nephrotic syndrome in the acute phase. Children with significant renal impairment at presentation, and/or persistent proteinuria should undergo regular assessment of their glomerular filtration rate (GFR)-e.g. at 1, 3 and 5

years after the acute episode of HSP. Some instances of hypertension have been reported many years after normalisation of renal function and urinalysis. An increased incidence of pre-eclampsia has also been reported.

### **ANCA associated vasculitides (AAV)**

#### *Definitions, epidemiology and classification*

Although rare, AAV do occur in childhood and are associated with significant morbidity and mortality. The recently modified classification definition for Granulomatosis with Polyangiitis (GPA; formerly known as Wegener's granulomatosis) requires the presence 3 out of 6 of the following criteria:

- renal involvement (proteinuria or haematuria or red blood cell casts)
- positive histopathology (granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area)
- upper airway involvement (nasal discharge or septum perforation, sinus inflammation)
- laryngo-tracheo-bronchial involvement (subglottic, tracheal or bronchial stenosis)
- pulmonary involvement (chest X ray or CT)
- ANCA positivity (by immunofluorescence, or by ELISA PR3 ANCA or MPO ANCA).

#### *Clinical features of Granulomatosis with Polyangiitis (GPA)*

From a clinical perspective in children it may be useful to think of GPA as having two forms: a predominantly granulomatous form with mainly localised disease with chronic

course; and a florid, acute small vessel vasculitic form characterised by severe pulmonary haemorrhage and/or rapidly progressive vasculitis or other severe vasculitic manifestation. These two broad presentations may co-exist or present sequentially in individual patients. In one case series of 17 children with GPA the frequency of different system involvement was: respiratory 87%, kidneys 53%, sinuses 35%, joints 53%, eyes 53%, nervous system 12%, skin 53%. In the most recent paediatric series of 65 children classified as having GPA, renal involvement was reported up to 75.4% of cases. Dialysis was necessary in 7 patients (10.8%), and end-stage renal disease was present in a single patient of that series. Of note, renal involvement in GPA is recruited with increasing age which could account in part for the variation in reported renal involvement in paediatric GPA.

#### *Treatment of AAV*

Renal morbidity and mortality is a major concern in the AAV, hence therapy aimed at preservation of renal function is a recurring theme for the treatment of AAV in both adults and children. Treatment for paediatric AAV is broadly similar to the approach in adults based on evidence derived from a number of clinical trials conducted by the European Vasculitis Study group (EUVAS). Treatment for paediatric AAV is broadly similar to the approach in adults, with corticosteroids, cyclophosphamide (usually 6-10 intravenous doses at 500-1000 mg/m<sup>2</sup> [maximum 1.2g] per dose given 3-4 weekly; alternatively given orally at 2mg/kg/day for 2-3 months), and in select patients plasma exchange (particularly for pulmonary capillaritis and/or rapidly progressive glomerulonephritis- “pulmonary-renal syndrome”) routinely employed to induce

remission. Anti-platelet doses of aspirin (1-5 mg/kg/day; typically 37.5-75 mg/day) are empirically employed on the basis of the increased risk of thrombosis associated with the disease process. Methotrexate may have a role for induction of remission in patients with limited GPA, but is less commonly used as an induction agent in children with AAV. Recommendations regarding duration of maintenance therapy are based on adult trial data, with no clinical trials in children performed.

Biologic therapy is also increasingly used to treat children with small vessel vasculitis, including AAV and ANCA negative vasculitides. Agents used include rituximab, and anti-TNF $\alpha$  (etanercept, infliximab, and adalimumab. Notably, an ongoing international multicentre study is exploring the efficacy and safety of Rituximab in children with new onset AAV or refractory to standard therapy (the PEPRS study; NCT01750697).

### *Outcome of AAV*

The mortality for paediatric GPA from one recent paediatric series was 12% over a seventeen year period of study inclusion. Another paediatric series of GPA reported 40% of cases with chronic renal impairment at 33 months follow up despite therapy.

## **Predominantly medium vessel vasculitis**

### **Polyarteritis nodosa**

*Definitions, epidemiology and classification criteria*

Polyarteritis nodosa (PAN) is a necrotising vasculitis associated with aneurysmal nodules along the walls of medium sized muscular arteries. The EULAR/PRINTO/PRES classification criteria for PAN are as follows: histopathological evidence of necrotizing vasculitis in medium or small sized arteries or angiographic abnormality (aneurysm, stenosis or occlusion) as a mandatory criterion, plus 1 of the following 5: skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy and renal involvement.

### *Aetiopathogenesis*

The immunopathogenesis leading to vascular injury in PAN is probably heterogeneous. Infections including hepatitis B, parvovirus B19, cytomegalovirus, and HIV have been implicated in the aetiology of PAN. PAN-like illnesses have additionally been reported in association with cancers and hematological malignancies. However, these associations are rare in childhood. Streptococcal infection may be an important trigger, and indirect evidence suggests that bacterial superantigens may play a role in some cases.

Genetic predisposing factors may make individuals vulnerable to develop PAN. Yalcinkaya et al. reported on the prevalence of FMF mutations in 29 children with PAN showing that 38% of the patients were carriers of MEFV mutations.

Deficiency of adenosine deaminase type 2 (DADA2) is an autosomal recessive disease resembling polyarteritis nodosa, caused by homozygous or compound heterozygous mutations in the *CECRI* gene. The cardinal clinical features include livedo racemosa,

neurological involvement including propensity to lacunar (small vessel) stroke, vasculitic peripheral neuropathy, digital ischaemia and cutaneous ulceration, systemic inflammation, and other end organ damage. There is an emerging view that anti TNF alpha is particularly efficacious for this form of monogenic vasculitis; this may be due to the fact that the extracellular enzyme ADA2 functions as an important regulator of immune development. Patients with DADA2 demonstrate skewed macrophage development towards the M1 pro-inflammatory phenotype as opposed to the M2 anti-inflammatory phenotype. M1 macrophages are known to produce TNF alpha, which could explain why this therapeutic approach seems particularly effective in DADA2. Allogeneic haematopoietic stem cell transplantation has been reported to be successful in a few patients; gene therapy may be an option for the future.

### *Clinical features*

The main clinical features of systemic PAN are malaise, fever, weight loss, skin rash, myalgia, abdominal pain and arthropathy. In addition ischaemic heart and testicular pain, renal manifestations such as haematuria, proteinuria and hypertension neurologic features such as focal defects, hemiplegia, visual loss, mononeuritis multiplex and organic psychosis. Skin lesions are variable and may masquerade as those of HSP or multiform erythema but can also be necrotic and associated with peripheral gangrene. Livido reticularis is also a characteristic feature and occasionally subcutaneous nodules overlying affected arteries are present. Systemic involvement is variable but the skin, the

musculoskeletal system, the kidneys and the gastrointestinal tract are most prominently affected with cardiac, neurological and respiratory manifestations occurring less frequently. We recently reported on single centre study of 69 children with PAN. The clinical features at presentation were: fever (87%), myalgia (83%), skin (88%), renal (19%), severe gastrointestinal (GI) (10%), and neurological involvement (10%).

The characteristic histopathological changes of PAN are fibrinoid necrosis of the walls of medium or small arteries with a marked inflammatory response within or surrounding the vessel wall. Indirect evidence of the presence of medium size artery vasculitis affecting the renal arteries may be obtained by demonstrating patchy areas of decreased isotope uptake within the renal parenchyma on Tc 99m dimercapto succinic acid (DMSA) scanning of the kidneys. However, the most valuable investigative procedure is selective visceral catheter digital subtraction arteriography. Findings on catheter arteriography include aneurysms, segmental narrowing and variations in the calibre of arteries together with pruning of the peripheral vascular tree.

Cutaneous polyarteritis nodosa is characterised by the presence of fever, subcutaneous nodular, painful, non-purpuric lesions with or without livedo reticularis occurring predominantly in the lower extremities, with no systemic involvement (except for myalgia, arthralgia and non-erosive arthritis). The condition usually remains localized to the skin although a proportion of cases appear to evolve into full blown systemic PAN in time, and clinicians need to be mindful of this possibility.

### *Management*

The treatment of PAN involves the administration of high-dose corticosteroid with an additional cytotoxic agent such as cyclophosphamide to induce remission, typically for the first 3 to 6 months. Empirically, aspirin has also been given as an anti-platelet agent by some clinicians. When streptococcal infection is implicated penicillin may be effective. Once remission is achieved maintenance therapy with daily or alternate day prednisolone and oral azathioprine is frequently utilized for an additional 18 months. Adjunctive plasma exchange can be used during the induction phase of treatment in life or organ threatening situations. Use of biologic agents, including anti TNF- $\alpha$ , and rituximab is also described for children with systemic PAN, particularly those not responding to standard therapy or because of concern regarding cumulative cyclophosphamide toxicity. An open label, multi-centre randomised controlled trial (RCT) of MMF versus cyclophosphamide for the induction of remission of childhood PAN (the MYPAN trial) is ongoing, and is the first RCT for treatment of systemic PAN in children.

### *Outcome*

PAN, unlike some other vasculitides such as GPA, appears to be a condition where permanent remission can be achieved. However, if treatment is delayed or inadequate, life threatening complications can occur due to the vasculitic process. The relapse rate in



our recent case series was 35%. Gastrointestinal involvement was associated with increased risk of relapse ( $p=0.03$ ); whilst longer time to induce remission ( $p=0.022$ ) and increased cumulative cyclophosphamide dose ( $p=0.005$ ) were associated with lower relapse risk. In comparison to the almost 100% mortality seen in the pre-steroid era mortality rates have reduced to a mortality rate of 4% in our recent case series.

### **Kawasaki disease**

#### *Definitions, epidemiology*

Kawasaki disease is an acute self-limiting systemic vasculitis predominantly affecting young children. It is of world wide distribution with a male preponderance, an ethnic bias towards oriental children, some seasonality, and occasional epidemics. KD is much more prevalent in Japanese children (264.8/100 000 children under the age of 5 years in 2012), a risk which is independent of geography since Japanese patients living in Hawaii have comparable incidence (210/100 000 children under the age of 5) compared with white children from Hawaii (13.7/100 000 children under the age of 5 years). In the UK, a recent 2016 epidemiological survey indicates that the incidence is currently 9.2/100,000 children under 5 years, with overrepresentation of Chinese and Japanese cases in the UK<sup>4</sup>. In the continental United States, the incidence of KD is approximately 25/100,000 children under the age of 5 years.

#### *Aetiopathogenesis*

The aetiology of Kawasaki disease remains unknown. Pronounced seasonality and clustering of KD cases have led to the hunt for infectious agents as a cause. So far, however, no single agent has been consistently identified. Debate regarding the infectious cause of KD has centered around the mechanism of immune activation: conventional antigen versus superantigen (SAg). Several studies have presented evidence supporting super antigen triggered process but others have not confirmed the association. Although uncertainty remains regarding the mechanism(s) of initial immune activation, most authorities believe that one or more potentially ubiquitous infectious agents produces a deleterious host response in a genetically susceptible subject.

Many candidate genes have previously been suggested, either as susceptibility genes for developing KD; or increasing risk of CAA. A number of genome wide association studies (GWAS) of KD have also been published so far. From these studies, several single nucleotide polymorphisms (SNPs) associated with susceptibility to KD, including ITPKC, ABCC4, and FCGR2A; CD40; and a gene region near FAM167A-BLK have been reported.

### *Clinical manifestations*

There is no diagnostic test for KD, thus the diagnosis rests on combinations of clinical criteria and laboratory findings (Table 2). For the diagnosis to be established according to the Diagnostic Guidelines of the Japan Kawasaki Disease Research Committee, five of the six criteria in Table 2 should be present. The North American recommendations for the diagnosis are similar, except that fever is a mandatory criterion, and four of the remaining five criteria are required to establish the diagnosis. However in addition to

patients fulfilling the criteria for complete KD, many patients have some but not all of the clinical features of KD. These patients may still be at risk of CAA. Early echocardiography may reveal evidence of coronary vasculitis, confirming the diagnosis of KD in this patient group.

Irritability is an important sign, which is nearly always present; the exact mechanism of the irritability remains unclear, but it may be related to the presence of aseptic meningitis. Another important clinical sign is the development of erythema and induration at the site of previous BCG immunization. The mechanism of this clinical sign is believed to be due to cross reactivity of T cells in KD patients between specific epitopes of mycobacterial and human heat shock proteins. The diagnostic criteria may present sequentially such that a so called “incomplete” case can evolve with time into a “complete” case. Thus the diagnosis of KD must be considered in any child with a febrile exanthematous illness, particularly if it persists longer than four to five days.

### *Management*

The American Heart Association have recently updated their guidance on diagnosing and managing KD. The SHARE guidance for management of KD is soon to be published too. The general principles of these are discussed below. Early recognition and treatment of KD with aspirin and intravenous immunoglobulin (IVIG) has been shown unequivocally by randomised controlled trials and meta-analysis to reduce the occurrence of CAA. Two g/kg of IVIG is the optimal dose, usually given as a single infusion.

Currently, it is our practice to administer aspirin at a dose of 30-50mg/kg/day during the acute phase of the illness, as this may be better tolerated than higher doses in terms of gastrointestinal and other side effects.

We would recommend that corticosteroids should be considered in the treatment of KD for:

1. Patients who have already declared themselves as IVIG resistant i.e. ongoing fever, and/or persistent inflammation or clinical signs in spite of a single dose of 2g/Kg IVIG.
2. Patients with features of the most severe disease (and therefore the greatest likelihood of developing CAA). In the absence of validated risk scores outside of Japan, we suggest that such patients include the very young; those with markers of severe inflammation, including: persistently elevated C reactive protein despite IVIG, liver dysfunction, hypoalbuminaemia, and anaemia; and the small group who develop features of haemophagocytic lymphohistiocytosis (HLH) and/or shock.
3. Patients who already have evolving coronary and/ or peripheral aneurysms with ongoing inflammation at presentation. It is increasingly recognised echocardiographic studies performed in the first week of KD may already show vessel abnormality including brightness (suggesting inflammation) or dilatation when compared with age related normal ranges and/or extra coronary manifestations including mitral regurgitation and pericardial effusion. Patients with these features may also be at greater risk of CAA and therefore may require corticosteroids.

A randomized control study of corticosteroids as adjunctive therapy to IVIG and aspirin for all patients with KD in the UK is currently being developed.

In addition, there are emerging animal data and case reports suggesting a role for anti-TNF- $\alpha$  in treatment of KD. Burns et al. reported a phase 2 clinical trial including 16 subjects receiving infliximab that demonstrated that this treatment was safe and well tolerated in patients resistant to IVIG. A more recent US retrospective review of IVIG resistant patients treated with either IVIG (n= 86) or infliximab (n= 20) demonstrated that patients treated with infliximab had fewer days of fever and shorter hospitalisation, but with similar coronary artery outcomes. We would recommend that anti-TNF $\alpha$  should be considered in patients with IVIG resistant KD, but not routinely as adjunctive primary therapy.

In the convalescent phase of KD if aneurysms persist, anti-platelet therapy in the form of low dose aspirin should be continued long term until the aneurysms resolve. In the presence of giant aneurysms (>8 mm) warfarin is recommended in addition to aspirin. Heparin should be administered initially for at least 48 hours and only stopped when the INR is stably between 2 and 3 to avoid paradoxical thrombosis due to protein C and S depletion that may occur when warfarin treatment is started. If thrombosis does occur, thrombolytic therapy may be indicated, but expert advice must be sought. If formal catheter coronary arteriography is to be considered, if possible this should be deferred for the first 6 months from the acute illness to avoid procedural related myocardial infarction, of particular concern whilst the coronary endothelium is still actively inflamed.

### *Outcome*

A recent British Paediatric Surveillance Unit (BPSU) study suggested much higher cardiac complication rates despite treatment with IVIG in the UK. This study showed that 28% of 553 children treated with the standard regimen of IVIG and high dose aspirin had cardiac complications; 24% of the total developed CAA. It is suggested that children who have persisting CAA could be routinely followed up according to AHA guidance, recently extensively updated in 2017. From the recent British Paediatric Surveillance of Kawasaki disease, there were approximately 300 incident cases per annum in the UK and Ireland. From this study, we are aware that approximately 10 children per year (10% of all those with CAA) develop giant CAA, defined as Z score  $\geq 10$ . Giant CAA never resolve, and a significant number of these patients (23%) have major adverse coronary events (MACE). A small number of children with intermediate aneurysms (Z score between 5 and 10) may have CAA that persist, but only 3% will have MACE. Very few of those with small CAA (Z score less than 5) persist, and so far none are known to have coronary events in the long term. However, it is increasingly recognized that even those with resolved CAA have abnormal coronary artery function, the long-term prognostic significance of which is currently uncertain.

### **Predominantly large vessel vasculitis**

#### **Takayasu arteritis**

*Definitions, epidemiology and classification*

Onset of Takayasu arteritis TA is most common during the third decade of life but has been well reported in young children. The EULAR/PRES/PRINTO classification criteria for childhood TA are: angiographic abnormalities of the aorta or its main branches (also pulmonary arteries) showing aneurysm/dilatation (mandatory criterion), plus 1 out of 5 of the following criteria:

1. Pulse deficit or claudication
2. 4 limb blood pressure discrepancy
3. Bruits
4. Hypertension
5. Acute phase response

#### *Clinical features*

Clinical diagnosis of TA is commonly challenging for the clinician, especially when it presents in young children. An initial florid inflammatory vasculitic phase is followed by a later fibrotic phase of the illness. It is estimated that one-third of children present with in this late fibrotic/stenotic phase of the disease. It is a misconception that this is in some way an “inactive”, or “burnt-out” stage of the disease, since progressive stenotic disease may be the consequence of persistent but low-level large vessel vasculitic disease activity, but without evidence of conventional laboratory markers of systemic inflammation such as elevated C reactive protein or increased erythrocyte sedimentation rate. The time from onset of symptoms to diagnosis is variable, but this can be several years.

Published case series suggested that the common complaints at presentation were headache (84%), abdominal pain (37%), claudication of extremities (32%), fever (26%), and weight loss (10%). Examination on admission revealed hypertension (89%), absent pulses (58%), and arterial bruits (42%) in the same cohort. Aortic and mitral valve involvement with the vasculitic process are recognized, as is myocardial involvement including the formation of ventricular aneurysms, sometimes with calcification.

#### *Treatment and outcome*

There have been no randomised controlled trials to guide treatment, and few evidence-based therapeutic advances. Biologic therapies are increasingly used in children, particularly anti-TNF $\alpha$  and anecdotally are reported to be efficacious. A major therapeutic challenge, however, is that there remains significant diagnostic delay for TA in children. This leads to significant and sometimes irreversible damage in the pre-diagnostic phase of the illness.

SHARE guidelines for the treatment of TA in the paediatric population will be formally published soon. The general therapeutic approach is that of induction of remission (high dose corticosteroid combined with another immunosuppressant), followed by maintenance of remission therapy (lower dose corticosteroid combined with a maintenance immunosuppressive agent, usually methotrexate), or institution of second line therapy for failed induction. Corticosteroids are the mainstay of first-line treatment



for TA. In addition, methotrexate, azathioprine, MMF, and cyclophosphamide have been used in children as first or second line agents. Ozen, et al. described 6 children with TA, and treatment with steroid and cyclophosphamide induction followed by MTX was suggested as effective and safe for childhood TA. Anti-TNF therapy may be beneficial. Promising results have also been reported with anti-IL6 therapy (tocilizumab) for adults with TA and in some cases children.. Surgical intervention is frequently required to alleviate end-organ ischemia and hypertension resulting from vascular stenosis, although it is preferable to control the vasculitic process before performing revascularisation procedures or other vascular surgery, if possible, since outcomes are worse if these are undertaken when the disease is still active.

The 5 year mortality rate of TA in children has been reported as high as 35%; we recently reported 27% mortality from TA in children. Prognosis is dependent upon the extent of arterial involvement and organ damage at presentation; age of patient at disease onset (children under 5 have poorer prognosis); and on the severity of hypertension.

### **Practice Points**

- Apart from relatively common vasculitides such as IgA Vasculitis (HSP) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but are associated with significant morbidity and mortality.
- Classification criteria for childhood vasculitis and a disease activity scoring tool have recently been proposed and validated.

- The cause of the majority of vasculitides is unknown, although it is likely that a complex interaction between environmental factors such as infections and inherited host responses trigger the disease and determine the vasculitis phenotype. Some vasculitides are now known to be monogenic diseases.
- Treatment regimens continue to improve, with the use of different immunosuppressive medications and newer therapeutic approaches such as biologic agents.

**Table 1 Classification of childhood vasculitides**

**Predominantly small vessel vasculitis**

***Granulomatous:***

Wegener granulomatosis (WG)

Churg Strauss syndrome (CSS)

***Non granulomatous:***

Microscopic polyangiitis

Henoch Schönlein purpura (HSP)

Isolated cutaneous leukocytoclastic vasculitis

Hypocomplementemic urticarial vasculitis

**Predominantly medium-sized vessel vasculitis**

Childhood polyarteritis nodosa (PAN)

Cutaneous polyarteritis

Kawasaki disease.

**Predominantly large vessel vasculitis**

Takayasu arteritis (TA)

**Other vasculitides**

Behçet's disease

Vasculitis secondary to infection (including Hepatitis B associated PAN), malignancies and drugs, including hypersensitivity vasculitis

Vasculitis associated with other connective tissue diseases

Isolated vasculitis of the CNS (Childhood Primary Angiitis of the Central Nervous System: cPACNS)

Cogan's syndrome

Unclassified

**Table 2: Kawasaki disease: diagnostic criteria**

<b>Criterion</b>	<b>Description</b>
Fever	Duration of 5 days or more PLUS 4 of 5 of the following:
1. Conjunctivitis	Bilateral, bulbar, conjunctival injection without exudate
2. Lymphadenopathy	Cervical, often >1.5 c, usually unilateral
3. Rash	Rash: maculopapular, diffuse erythroderma or erythema multiform
4. Changes of lips or oral mucosa	Red cracked lips; "strawberry" tongue; or diffuse erythema of oropharynx
5. Changes of extremities	Erythema and oedema of palms and soles in acute phase and periungual desquamation in subacute phase

**KD may also be diagnosed with fewer than 4 of these features if coronary artery abnormalities are detected.**

**Further reading list:**

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