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Management of Kawasaki disease

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ABSTRACT

Kawasaki disease (KD) is an acute self-limiting inflammatory disorder, associated with vasculitis, affecting predominantly medium-sized arteries, particularly the coronary arteries. In developed countries KD is the commonest cause of acquired heart disease in childhood. The aetiology of KD remains unknown, and it is currently believed that one or more as yet unidentified infectious agents induce an intense inflammatory host response in genetically susceptible individuals. Genetic studies have identified several susceptibility genes for KD and its sequelae in different ethnic populations, including FCGR2A, CD40, ITPKC, FAM167A-BLK and CASP3, as well as genes influencing response to intravenous immunoglobulin (IVIG) and aneurysm formation such as FCGR3B, and transforming growth factor (TGF) β pathway genes. IVIG and aspirin are effective therapeutically, but recent clinical trials and meta-analyses have demonstrated that the addition of corticosteroids to IVIG is beneficial for the prevention of coronary artery aneurysms (CAA) in severe cases with highest risk of IVIG resistance. Outside of Japan, however, clinical scores to predict IVIG resistance perform suboptimally. Furthermore, the evidence base does not provide clear guidance on which corticosteroid regimen is most effective. Other therapies, including anti-TNF α , could also have a role for IVIG-resistant KD. Irrespective of these caveats, it is clear that therapy that reduces inflammation in acute KD, improves outcome. This paper summarises recent advances in the understanding of KD pathogenesis and therapeutics, and provides an approach for managing KD patients in the UK in the light of these advances.

INTRODUCTION

Kawasaki disease (KD) affects 8.1/100 000 children under the age of 5 years in the UK, and is the commonest cause of acquired heart disease in children in developed countries.^{1–3} KD probably represents an aberrant inflammatory host response to one or more as yet unidentified pathogen(s), occurring in genetically predisposed individuals.^{2 4 5} KD is associated with systemic vasculitis particularly affecting the coronary arteries, causing coronary artery aneurysms (CAA) in 15–25% of untreated patients while 2–3% of untreated cases die as a result of coronary vasculitis.^{6–9} In view of the frequency and severity of coronary artery complications, there has been intense interest in treatments to reduce the risk of CAA.^{6 10–14} KD is also potentially an important cause of long-term cardiac disease in adult life.^{6 7} Notably, as more children with KD are advancing into adulthood, further studies are needed to (1) improve our understanding of long-term cardiac sequelae, (2) optimise therapy in childhood to minimise risks in adulthood and to ensure the continuation of quality, evidence-based

care for KD patients as they transit to adult services.

The purpose of this article is to summarise recent advances in our understanding of the pathogenesis and treatment of KD, and to provide an approach to managing KD in the UK in the light of these advances. The updated guidelines are based on evidence from meta-analyses and randomised controlled trials (RCTs), and will highlight areas of practice where evidence remains weak. Last, suggestions for future research are outlined.

EPIDEMIOLOGY

KD is the second commonest vasculitic illness of childhood after Henoch Schönlein purpura and the commonest cause of acquired heart disease in children in developed countries.^{3 6 9 15} The disease has a world-wide distribution with a male preponderance, an ethnic bias towards Asian children (particularly East Asian), seasonality and occasional epidemics.^{6 9 16} The incidence in Japan is 138/100 000 in children younger than 5 years, whereas in the USA, it is 17.1/100 000, and in the UK 8.1/100 000.^{1 3 15 17} Variation in awareness among clinicians of KD, and differences between countries and regional referral patterns may contribute to some of these epidemiological differences, however, the majority of these differences are likely to be the result of ethnic and racial differences in susceptibility and in exposure to a presumed pathogen.¹⁸ Approximately 85% of children with KD are younger than 5 years of age, with peak age incidence at 18–24 months; patients aged less than 3 months, or more than 5 years are encountered less commonly, but are at increased risk for CAA formation.^{1 3 15 17}

AETIOPATHOGENESIS

Infectious trigger

The aetiology of KD 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.^{19–21} Many published reports implicate a number of bacterial and viral pathogens, including retroviruses, Epstein–Barr virus, coronavirus, propionibacterium acnes, staphylococcal and streptococcal superantigens, and unidentified virus particles as infectious triggers of KD.^{2 5} To date, no single pathogen has been confirmed in subsequent studies. The debate regarding the infectious cause of KD has centred around the mechanism of immune activation: conventional antigen versus superantigen (SAg).^{22 23} Superantigens seemed a plausible cause of the disorder in view of the clinical and immunological similarity between KD and staphylococcal and streptococcal superantigen-mediated disorders. Several studies have presented

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Table 1 Genome-wide association studies in Kawasaki disease (KD)

Gene	Locus	Population	Biological significance	References
FCGR2A (encodes low-affinity immunoglobulin gamma Fc region receptor II-a)	1q23	European, Asian	The involvement of <i>FCGR2A</i> in susceptibility to KD highlights the importance of IgG receptors in the pathogenesis of this inflammatory disease and provides a biological basis for the use of intravenous immunoglobulin for treatment.	37
ITPKC (inositol 1,4,5-trisphosphate 3-kinase C)	19q23	Japanese, American	ITPKC acts as a negative regulator of T-cell activation through the Ca ²⁺ /NFAT signalling pathway, and the C allele may contribute to immune hyper-reactivity in KD. This finding provides new insights into the mechanisms of immune activation in KD and emphasises the importance of activated T cells in the pathogenesis of this vasculitis	36
ABCC4 (ATP-binding cassette, subfamily C, member 4)	13q32	European, American, Australian	ABCC4 is a multifunctional cyclic nucleotide transporter that stimulates the migratory capacity of dendritic cells and a mediator of prostaglandin efflux from human cells inhibited by non-steroidal anti-inflammatory medications such as aspirin.	38
Intergenic region between FAM167A and BLK	8p22-23	Japanese	Variations in the FAM167A/BLK region have been associated with several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis. <i>BLK</i> encodes B-lymphoid tyrosine kinase, a Src family tyrosine kinase downstream of the B-cell receptor. Mechanism in KD pathogenesis unknown.	34
CD40	20q12-q13.2	Taiwanese, Japanese	CD40 L is expressed on the surface of CD4 T-cells and platelets, and engages with CD40 expressed on the surface of antigen-presenting cells or endothelial cells. Transduces signals related to cell activation or development. Elevated expression of CD40 L during acute-phase KD, and significantly higher expression in KD patients with CAA have been reported.	34

CAA, coronary artery aneurysms; NFAT, nuclear factor of activated T cells.

evidence supporting superantigen-triggered process, but others have not confirmed the association.^{5 22 24} One explanation for the inconsistent finding is that KD is triggered by a range of different superantigens, and animal studies suggest the possibility that both superantigen, and Toll-like receptor agonists may need to act synergistically.^{5 25} Against a superantigen (SAg)-mediated process is the report by Rowley *et al*²⁶ of three fatal cases of KD in which IgA plasma cell infiltration into the vascular wall during the acute phase of the illness was observed. By examining the clonality of this IgA response using reverse transcriptase (RT)-PCR in lesional vascular tissue, these researchers observed that the IgA response was oligoclonal, suggesting a conventional antigenic process rather than a superantigen-driven one.²⁶ 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.^{2 5 9}

Genetics

A genetic contribution to the risk of KD is suggested by the much higher risk of the disease in Asian children, particularly the Japanese and Koreans, which persists when patients of these ethnicities migrate to other countries²⁷; from the observed increased relative risk to siblings of index cases compared with the general population, from twin studies and from well documented multicase families.²⁸

Many candidate genes have previously been suggested, either as susceptibility genes for developing KD; or increasing risk of CAA.²⁹⁻³¹ These are summarised elsewhere.³¹ Most of these earlier studies, however, failed to identify definitive genetic associations, emphasising the difficulties of the candidate gene approach for a disease where the pathogenesis is poorly understood.³² By contrast with the candidate gene approach, genome-wide association studies (GWAS) have the advantage of identifying disease-associated genes without requiring prior knowledge of the mechanisms involved.³² A number of GWAS of KD have been published so far.³³⁻³⁹ 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 (table 1). Furthermore, other genes have been associated with non-response to intravenous immunoglobulin (IVIG) and risk of CAA, including CASP3, FCGR3B and genes of the TGF- β signalling pathway.^{40 41} It is likely that many other genetic factors have yet to be identified, as the GWAS methodology has so far only identified the most significant associations.³² Whole exome sequencing studies applied to individual KD cases of extreme phenotype, such as those with giant CAA, could clarify the contribution of rarer genetic variants in these extreme cases. Thus, the study of the genetic contribution to KD remains an intense area of research worldwide, and still very much a work in progress.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

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 KD Research Committee, five of the six criteria in table 2 should be present.⁴² The North American recommendations for the diagnosis are similar, except

Table 2 Kawasaki disease: diagnostic criteria. KD may be diagnosed with fewer than 4 of these features if coronary artery abnormalities are detected

Criterion	Description
Fever	Duration of 5 days or more PLUS 4 of 5 of the following:
1. Conjunctivitis	Bilateral, bulbar, non-suppurative
2. Lymphadenopathy	Cervical, often >1.5 cm
3. Rash	Polymorphous, no vesicles or crusts
4. Changes in lips or oral mucosa	Red cracked lips; 'strawberry' tongue; or diffuse erythema of oropharynx
5. Changes of extremities	Initial stage: erythema and oedema of palms and soles Convalescent stage: peeling of skin from fingertips

that fever is a mandatory criterion, and four of the remaining five criteria are required to establish the diagnosis.⁶ 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, or are, at risk of CAA. Diagnosis of these 'incomplete KD' cases depends on a high level of suspicion in children presenting with some of the KD features and evidence of systemic inflammation (such as elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or leucocytosis). Early echocardiography may reveal evidence of coronary vasculitis, confirming the diagnosis of KD in this patient group. A negative echocardiogram does not exclude the diagnosis of KD. In addition to the diagnostic challenge of incomplete cases, the requirement within the existing diagnostic criterion for a fever of greater than 5 days may also lead to delayed treatment. While duration of fever has historically been of importance for the standardisation of case definitions, clinicians should not delay in making a diagnosis of KD and instituting treatment (see below) if: (1) 5/6 diagnostic criteria of KD are present before day 5 of fever; (2) CAA or coronary dilatation are present, or (3) evidence of persistent elevation of inflammatory markers with no other explanation in patients where there remains clinical suspicion of KD.^{2 6 9} We recommend seeking early expert advice in such cases.

Irritability is an important sign which is nearly always present, although interestingly not included as one of the diagnostic criteria.^{9 43} The exact mechanism of the irritability is unclear, but it may be related to the presence of aseptic meningitis.^{9 43} Another important clinical sign is the development of erythema and induration at the site of previous *Bacillus Calmette–Guérin* (BCG) immunisation.^{9 44} 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.^{9 44} The diagnostic criteria may present sequentially, such that a so-called 'incomplete' case can evolve with time into a 'complete' case.⁶ Thus, the diagnosis of KD must be considered in any child with a febrile exanthematous illness and evidence of inflammation, particularly if it persists longer than 4–5 days.

Other relatively common clinical findings in KD include arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis and dysuria and otitis.^{2 9} Relatively uncommon abnormalities include, hydrops of the gallbladder, gastrointestinal

ischaemia, jaundice, cranial nerve palsy, renal involvement (pyuria, proteinuria, tubular disturbances, tubulointerstitial nephritis and renal failure), petechial rash, shock syndrome, febrile convulsions and encephalopathy or ataxia.^{2 9} Additional rare complications of KD include macrophage activation syndrome (secondary haemophagocytic lymphohistiocytosis), and syndrome of inappropriate antidiuretic hormone secretion resulting in hyponatraemia.^{45 46}

Vascular involvement

The main sites of clinically important vascular involvement are the coronary arteries, although other vessels such as the axillary arteries can be involved. CAA occur in 15–25% of untreated cases, with additional cardiac features in a significant proportion of these including pericardial effusion, electrocardiographic abnormalities, pericarditis, myocarditis, valvular incompetence, cardiac failure and myocardial infarction.⁶ When systemic arterial injury (major limb arteries, renal and other visceral vessels) occurs, it is rarely seen in the absence of CAA.²

Laboratory findings

KD is invariably associated with an inflammatory process, with elevation of ESR, CRP and white cell count.^{2 6 9} In the absence of significant inflammation, the diagnosis of KD is unlikely.^{2 6 9} Not all the inflammatory markers may be abnormal at first presentation, and repeat blood testing should be undertaken if there is diagnostic uncertainty. Thrombocytosis occurs towards the end of the second week of the illness and, therefore, may not be helpful, diagnostically, in the early stages.^{2 6 9} Acute thrombocytopenia or low/normal platelet count may occur and may be associated with a poorer prognosis (see below).^{2 6 9 47} Liver function may be deranged and some patients present with jaundice and elevation of transaminases.^{2 6 9} Hypoalbuminaemia is common; sterile pyuria and cerebrospinal fluid (CSF) pleocytosis (predominantly lymphocytes) representing aseptic meningitis also occur.^{2 6 9 48}

Predicting IVIG resistance/high CAA risk

Several scoring systems have been developed to identify children at highest risk of IVIG resistance and, hence, highest risk of developing CAA (table 3).^{47 49 50} Kobayashi *et al*⁴⁷ developed a model to predict unresponsiveness to IVIG in Japanese children with KD. This was used to define severe cases in a pivotal

Table 3 Scoring systems for predicting IVIG resistance

	EGAMI ⁴⁹	KOBAYASHI ⁴⁷	SANO ⁵⁰
	≤4 days of illness (1 point)	Na ≤133 (2 points)	Total bilirubin ≥0.9 mg/dl (1 point)
	ALT >100 U/L (1 point)	≤4 days of illness (2 points)	
	≤300 ×10 ⁹ /L platelets (1 point)	ALT ≥ 100 U/L (1 point)	AST ≥200 U/L (1 point)
	CRP ≥8 mg/dL (1 point)	≤300×10 ⁹ /L platelets (1 point)	
	Age ≤6 months (2 points)	CRP ≥10 mg/dL (1 point)	CRP ≥7 mg/dL (1 point)
		Age ≤12 months (1 point)	
		≥80% neutrophils (2 points)	
High risk	≥3 points	≥5 points	≥2 points
<i>Test performance in Japanese vs non-Japanese</i>			
Japanese cases			
Sensitivity (%)	78	86	77
Specificity (%)	76	67	86
Non-Japanese cases ⁵¹			
Sensitivity (%)	42	33	40
Specificity (%)	85	87	85

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IVIG, intravenous immunoglobulin.^{47 49–51}

clinical trial of corticosteroids (see below), because IVIG resistance is known to be a strong risk factor for the development of CAA. The Kobayashi, Egami and Sano scores when tested in a USA study demonstrated comparably high specificity for predicting IVIG non-response in non-Japanese patients, but had low sensitivity.⁵¹ The clinical implication of this is that if the risk score is 'positive' in a non-Japanese patient (eg, ≥ 5 for the Kobayashi score) then IVIG resistance is likely; however, a negative score does not reliably exclude IVIG resistance. Attempts to develop a more sensitive and specific score for patients outside of Japan have thus far been unsuccessful.⁵²

TREATMENT

IVIG

Early recognition and treatment of KD with aspirin and IVIG has been shown unequivocally by randomised controlled trials and meta-analysis to reduce the occurrence of CAA.^{6 53} Two g/kg of IVIG is the optimal dose, usually given as a single infusion.^{6 53} Meta-analysis of randomised controlled trials comparing divided lower doses of IVIG (400 mg/kg/day for four consecutive days) versus a single infusion of high-dose IVIG (2 g/kg over 10 h) has shown that even though the 4-day regimen has some benefit, the single-dose regimen has a greater therapeutic effect in the prevention of CAA.⁵⁴

Aspirin

Meta-analysis comparing anti-inflammatory doses of aspirin (30–50 mg/kg/day) with high-dose aspirin (80–120 mg/kg/day) combined with IVIG found no significant difference in the incidence of CAA between the groups.⁵⁵ Currently, aspirin at a dose of 30–50 mg/kg/day is recommended during the acute phase of the illness, as this may be better tolerated than higher doses in terms of gastrointestinal and other side effects. The dose should be reduced to an antiplatelet dose of 3–5 mg/kg once fever and inflammation have subsided.

Corticosteroids for the primary treatment of severe KD

IVIG resistance occurs in up to 20% of cases, and these patients are at increased risk of developing CAA unless they receive additional treatment.^{2 6 9} Recently, the findings of the published RAISE study that selected patients at high risk of IVIG non-response emphasised this point as treatment of the control arm with IVIG/ aspirin was still associated with a CAA complication rate of 23%.¹⁴

Corticosteroids are effective treatment for other forms of vasculitis, but early retrospective analyses suggested that corticosteroids were associated with increased risk of CAA.⁵⁶ However, this almost certainly reflected selection bias as the sickest patients received steroids.

Clinical trials evaluating the use of corticosteroids plus IVIG have produced seemingly confusing results.^{10 11 14 57–59} Chen *et al*⁶⁰ recently reported a meta-analysis comparing the frequency of CAA in patients treated with IVIG plus corticosteroids or IVIG alone for the primary treatment of KD. They followed standard guidelines for conduct of meta-analyses, and used defined criteria for trial quality assessment, including evaluation of criteria for diagnosis; study design; follow up and blinding.⁶⁰ They identified nine clinical studies meeting their quality criteria, involving 1011 patients. Six out of nine were prospective RCTs; two were non-randomised controlled studies; and one was a retrospective report.⁶⁰ Of the 1011 patients included, 536 received IVIG+corticosteroids and 475 IVIG alone.⁶⁰ They found that significantly fewer patients receiving IVIG+corticosteroids developed CAA than those receiving IVIG

alone (7.6% vs 18.9%; OR: 0.3; 95% CI 0.20 to 0.46).⁶⁰ The benefit was found in several subgroup analyses including the six prospective RCTs, and studies using prednisolone or intravenous methylprednisolone.⁶⁰ They found no significant differences in frequency of severe adverse events between the steroid and non-steroid treatment groups.⁶⁰ Chen's meta-analysis provides convincing evidence that steroids combined with IVIG as initial treatment reduces overall risk of CAA in severe KD.⁶⁰ However, neither the meta analysis nor the RAISE study provides clear answers as to whether all children in the UK should be treated with corticosteroids, and what dose, duration and route of corticosteroids should be used.

Heterogeneity in corticosteroid dosing in the published trials is an important consideration when translating the results of Chen's meta-analysis into clinical practice, as different corticosteroid regimens were used in each of the trials. This is illustrated when two of the methodologically strongest studies, the American Paediatric Heart Network study¹⁰ and the recently reported Japanese RAISE study¹⁴ are considered in more detail. The American study evaluated the use of intravenous methylprednisolone (30 mg/kg) given as a single dose in unselected patients with KD.¹⁰ By contrast, RAISE evaluated lower-dose (2 mg/kg) intravenous prednisolone given for 5 days; if fever settled, this was then converted to oral prednisolone which was subsequently tapered over 15 days only after the CRP normalised.¹⁴ Moreover, patients were included in RAISE only if they were at high risk of IVIG resistance based on the Kobayashi score.¹⁴ Perhaps unsurprisingly then, these two studies have produced conflicting results, with steroids conferring significant benefit in the Japanese RAISE study, but a lack of overall benefit in the American study.

Second, as seven of the nine studies in the meta-analysis were undertaken in Japan and only two in the USA, the results may not be applicable outside of Japan. There is some concern that KD in Japan may behave differently from the disease in non-Japanese populations, highlighted by the failure of the Kobayashi and other scores used to predict IVIG non-response in Japan to accurately predict non-response to IVIG in the USA.^{14 47 51} The meta-analysis may say more about the beneficial effect of steroids in Japanese patients meeting the criteria for predicted IVIG resistance than about an overall benefit in unselected patients.

Third, while the meta-analysis has not revealed any increase in severe adverse events associated with corticosteroid use, the total number of patients receiving steroids was only about 500.⁶⁰ Most paediatricians who routinely use corticosteroids for the treatment of other systemic inflammatory diseases will probably be comfortable with a modest dosing regimen of prednisolone weaning over 3 or 4 weeks, if this truly will spare some children from potentially lifelong cardiac sequelae, although vigilance during follow-up for the presence of corticosteroid-related complications, such as hypertension, behavioural changes, secondary infection, hyperglycaemia and bone necrosis is required.

As 80% of patients with KD respond to aspirin and IVIG, and CAA are most commonly seen in those who fail to respond to IVIG, we urgently need a means of predicting IVIG resistance so that corticosteroids can be included in primary treatment of selected patients at risk of IVIG non-response. However, the Kobayashi score, used by Japanese investigators had low sensitivity (but good specificity, table 3) for the prediction of IVIG non-response in studies in the USA.^{14 51} Therefore, a low Kobayashi score does not reliably exclude IVIG resistance. With these caveats in mind, we propose a pragmatic treatment

approach (below) based on the current data, while advocating further research to provide the evidence base, which is currently lacking.

Recommended indication for corticosteroids in KD

We suggest that corticosteroids should be considered for

1. Patients who have already declared themselves as IVIG-resistant, that is, with ongoing fever, and/or persistent inflammation or clinical signs ≥ 48 h after receiving IVIG as a single dose of 2 g/kg.
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 (<1-year-old); those with markers of severe inflammation, including: persistently elevated CRP despite IVIG, liver dysfunction, hypoalbuminaemia, and anaemia; and the small group who develop features of haemophagocytic lymphohistiocytosis (HLH)⁶¹ and/or shock.
3. Patients who already have evolving coronary and/or peripheral aneurysms with ongoing inflammation at presentation. It is increasingly recognised that 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 extracoronary manifestations, including mitral regurgitation and pericardial effusion.⁶² Patients with these features may also be at greater risk of CAA and, therefore, may require corticosteroids.⁶²

What corticosteroid regimen to use?

Chen's meta-analysis does not provide us with an evidence base for optimal corticosteroid dose/duration.⁶⁰ From the studies included, an intravenous preparation equivalent to 2 mg/kg prednisolone for 5–7 days, or until CRP normalises, followed by oral prednisolone weaning over 2–3 weeks seems logical. However, in the absence of a robust evidence base, flexibility of the steroid regimen ultimately used for individual patients is recommended, and should ultimately be determined by treating clinicians: the updated guideline provides two suggested regimens (figure 1).

Should a second dose of IVIG be given to patients who fail to respond to the initial dose?

In patients who have shown some but not complete response, we suggest that a second dose of IVIG is given at the same time as commencing steroids if they have not already been commenced for signs of severe disease (see above). A second dose may not be beneficial if there was little response to the first dose. Vigilance during follow-up for the presence of corticosteroid-related complications, such as hypertension, secondary infection, hyperglycaemia and bone necrosis is required.

Role of antitumour necrosis factor- α

There are emerging animal data case reports suggesting a role for anti-tumour necrosis factor (TNF)- α therapy for the treatment of KD.^{63–66} Serum TNF- α is elevated in KD patients, and higher levels correlate with the development of CAA.⁶⁷ The most commonly used agent is infliximab, a chimeric murine/human IgG1 monoclonal antibody specifically binding TNF- α .^{63–66} In one retrospective study of 17 children with IVIG-resistant KD, infliximab was used successfully with abrupt defervescence in 13/16 febrile patients, with no infusion reactions.¹² Burns *et al*⁶⁸ reported a phase 2 clinical trial including

16 patients receiving infliximab that demonstrated that this treatment was safe and well tolerated in patients resistant to IVIG. Response to therapy with cessation of fever occurred in 13 of 16 patients. CRP level was elevated in all but one patient before infliximab infusion, and the level was lower following infusion in all 10 patients in whom it was remeasured within 48 h of treatment.⁶⁸ There were no infusion reactions to infliximab, and no complications attributed to infliximab administration in any of the patients.⁶⁸ 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.⁶⁹

Etanercept (soluble TNF- α receptor) is an alternative TNF antagonist, and has been reported to be safe and well tolerated in 15 children with KD when given at a dose of 0.8 mg per kilogram weekly for three doses, and may be beneficial.⁷⁰ A recent multicentre study in the USA comparing IVIG and aspirin to IVIG/aspirin plus infliximab as initial therapy in an unselected group of KD patients has been completed and showed no significant reduction in CAA, although the trial was underpowered for this endpoint. There was, however, faster resolution of the acute-phase response in the infliximab group. (Burns JC *et al*, personal communication and manuscript submitted). Thus, anti-TNF α should be considered in patients with IVIG-resistant KD, and further study is required of its role as first-line therapy.

Other therapies

Other immunosuppressive agents such as ciclosporin, cyclophosphamide, methotrexate, and plasma exchange, have occasionally been used to treat patients who do not respond to IVIG, steroids and anti-TNF α .^{2–6} Genome-wide association studies have identified polymorphisms of ITPKC, a negative regulator of T-cell activation, and other T cell signalling pathway genes associated with KD susceptibility, IVIG resistance, and increased risk of CAA in Asian and US children.^{36–40} This suggests that calcineurin inhibitors (such as ciclosporin) may be applicable for the treatment of KD.^{71–72} These initial reports need to be tempered by the knowledge that calcineurin inhibitors can also be toxic to the endothelium; for example, in Behçet's disease it is recommended that these are avoided in those with cerebral vasculitis since there is a concern that this class of drug may exacerbate vasculitic complications in some scenarios.^{6–73} The use of these agents cannot be recommended routinely but can be considered on a case-by-case basis after consultation with specialist units.

Management of KD in the convalescent phase

In the convalescent phase of the condition, if aneurysms persist, antiplatelet therapy in the form of low-dose aspirin (2–5 mg/kg) should be continued long-term until the aneurysms resolve.⁶ Clopidogrel is an alternative antiplatelet agent that could be considered.⁶ In the presence of giant aneurysms (>8 mm) warfarin is recommended in addition to aspirin.⁷⁴ Heparin should be administered initially for at least 48 h and only stopped when warfarin has been commenced and the international normalised ratio (INR) is stable between two and three to avoid paradoxical thrombosis due to protein C and S depletion that may occur when warfarin treatment is started.⁹ If thrombosis does occur, thrombolytic therapy may be indicated, but expert advice must be sought.^{6–9} Some patients may require coronary angioplasty or a revascularisation procedure should ischaemic symptoms arise or evidence of obstruction occur.⁶ 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

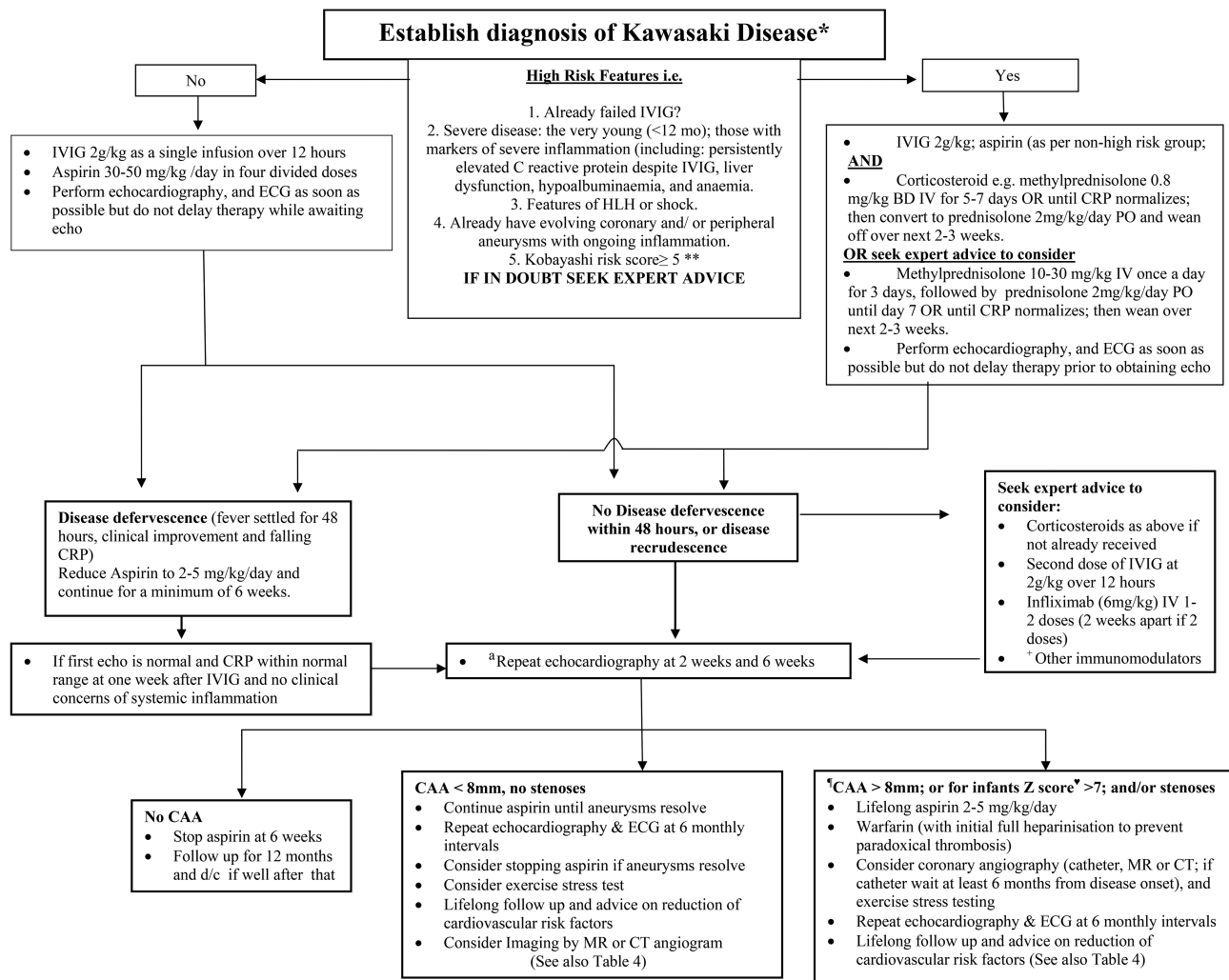


Figure 1 Recommended clinical guideline for the management of Kawasaki disease in the UK. Since risk scores for IVIG resistance perform sub-optimally in non-Japanese patients (Table 3), we cannot recommend their use to define high risk definitively; clinicians may, however, choose to consider the clinical and laboratory parameters listed to identify “high risk” patients. If the Kobayashi risk score is “positive” in a non-Japanese patient (eg, ≥ 5) then IVIG resistance is likely; however a score < 5 does not reliably exclude IVIG resistance. The aim of treatment is to switch off the inflammatory process that is damaging the coronary arteries as rapidly as possible. In the absence of a strong evidence base favouring a specific corticosteroid regimen, two suggested corticosteroid regimens for high-risk cases are provided for clinicians to choose from. For those on low dose aspirin, we also recommend avoiding the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) as these interfere with the anti-platelet effect of low dose aspirin. *Treatment can be commenced before 5 days of fever if sepsis excluded; treatment should also be given if the presentation is > 10 days from fever onset if there are signs of persistent inflammation; **Kobayashi risk score ≥ 5 points ^aRefer to paediatric cardiologist; [†]Other specific interventions such as positron emission tomography (PET) scanning, addition of calcium channel blocker therapy, and coronary angioplasty at discretion of paediatric cardiologist. + Other immunomodulators may include ciclosporin. ♥For infants, Z score for internal coronary artery diameter > 7 based on Montreal normative data: <http://parameterz.blogspot.co.uk/2010/11/montreal-coronary-artery-z-scores.html>.

procedural-related myocardial infarction, of particular concern, while the coronary endothelium is still actively inflamed.⁶

Immunisation following KD

The recommendation regarding timing of immunisations after KD remains unchanged from our 2002 guideline.⁹ Immunisation with all vaccines should be deferred for at least 3 months following an episode of KD treated with IVIG, mainly due to the potential lack of effectiveness of live vaccines following IVIG⁷⁵ and due to the potential for any vaccine to induce potentially detrimental immune activation during the convalescent phase of KD. The evidence for this latter recommendation is anecdotal. Thereafter, all vaccines should be administered as recommended by national schedules.

Patients who require long-term aspirin for persistent CAA should be considered for immunisation with varicella zoster virus (VZV) vaccine in view of the association of VZV and aspirin with Reye’s syndrome.

CARDIAC COMPLICATIONS OF KD

Prognosis is largely determined by cardiac sequelae of KD.^{2 6 9} The outlook for KD patients who have normal coronary echocardiographic findings or only mild dilation on assessment 6 weeks after the onset is generally good.^{2 6 9} However, those patients with persistent coronary artery dilatation and aneurysms are at risk of coronary artery stenosis or thrombosis. In 1993, a British Paediatric Surveillance Unit (BPSU) study indicated a mortality rate of 3.7% in the UK for KD⁷⁶; at the time of this writing, a repeat BPSU survey is ongoing, and will

provide more up-to-date outcome data for the UK. Angiographic resolution 1–2 years after onset of disease has been observed in 50–70% of vessels with coronary aneurysms; giant aneurysms never resolve completely.^{77–79} In a study exploring the long-term outcomes of a cohort of 6576 patients with KD enrolled between 1982 and 2004, the mortality rate for patients without cardiac sequelae in the acute phase of the disease, and for female patients with sequelae, did not differ from the normal population.⁸⁰ The all-cause mortality rate of males with cardiac sequelae was, however, 2.4 times higher than the normal population.⁸⁰

All patients with KD should undergo echocardiography at diagnosis and 6–8 weeks after the onset of the disease.^{6 9} An intermediate echocardiogram at 10–14 days of disease onset should be performed if the initial echo was normal and the disease activity has been arrested.^{6 9} Echocardiography should be performed at least weekly in those with aneurysms detected on initial echocardiography (ECHO) and those with ongoing active inflammation to monitor aneurysm size progression, or the development of thrombus formation.^{6 9} Long-term aspirin at 2–5 mg/kg/day is recommended for those with persisting aneurysms on echocardiography.^{6 9} This can be discontinued if the aneurysms resolve. Depending on the size of the aneurysms, electrocardiography and echocardiography performed 6–12 monthly is recommended.^{6 9}

In patients with persistent aneurysms beyond 6 weeks, long-term cardiovascular follow-up into adult life is required.^{6 9} There may be echocardiographic resolution of the aneurysm over time.^{6 9} This is due to vessel remodelling, with fibrosis, and proliferation of subendothelial tissues.^{6 9} The lesion may remain thickened and abnormal even after echocardiographic resolution.^{6 9}

The prognosis is guarded for those with giant aneurysms.^{6 9} A recent single-centre study described a cohort of 76 Japanese KD patients with giant aneurysms (>8 mm internal diameter) who had a 30-year survival rate of 88%, and a cumulative intervention rate (catheter or surgical) of 59%, 25 years postacute KD⁸¹; 16% developed myocardial infarction.⁸¹ As more patients with a history of KD and coronary aneurysms reach young adulthood, acute myocardial infarction due to thrombosis of aneurysms, or due to progressive arterial stenosis from aneurysm remodelling is of increasing concern.^{82 83} Of note, percutaneous transluminal coronary angioplasty is associated with a high rate of restenosis or occlusion in KD patients, thus rotational ablation or bypass surgery may be advisable as an alternative procedure.⁸³ Intravascular ultrasound (IVUS) can play an important role during interventions in patients with a history of KD by helping to determine the extent of arterial calcification, and by evaluating intervention results to ensure proper stent sizing and placement.^{83 84} Coronary artery bypass graft (CABG) surgery is also used in patients after KD for severe obstructive lesions, and results have generally been good, especially when the internal thoracic artery is used.^{83 85 86} In the setting of giant coronary aneurysms without significant obstruction, CABG may be ineffective in preventing myocardial infarction, as graft patency may be compromised by competing flow from the native coronary artery.^{83 85 86}

Recommendations for long-term cardiac management

A detailed review of this area is beyond the scope of this article. A statement of the American Heart Association committee on rheumatic fever, endocarditis and KD published in 2004 provided detailed guidance on the stratification of KD patients according to their relative risk of myocardial ischaemia.⁶

Risk-level categories are summarised in table 4. This stratification allows for patient management to be individualised with respect to medical therapy to reduce the risk of thrombosis, physical activity, frequency of clinical follow-up and diagnostic testing, and indications for cardiac catheterisation and coronary, CT and MR angiography.⁶ Stress echocardiography when considered safe by cardiologists, should be performed on all patients with persistent structural abnormalities of the coronary arteries.⁶ If there is evidence of inducible ischaemia, then invasive angiography is indicated.⁶ For these patients, bi-annual follow-up and aggressive management of traditional cardiovascular risk factors is also recommended for all patients.⁶ CT coronary artery calcium scores are linked to mortality in atherosclerosis; it has been suggested that this imaging modality could have an important role in the late follow-up of KD.⁸⁷ Adolescents and young adults may develop coronary calcification that is detectable only more than 10 years after the acute KD episode; while promising as a potential means of stratifying patients for a long-term follow-up, it is not yet known in KD exactly how coronary artery scores relate to late morbidity or mortality.

At the time of this writing, a long-term follow-up study of premature atherosclerosis/late KD vasculopathy is ongoing in the UK; it is anticipated that this study will help guide clinicians regarding long-term follow-up after KD.

UPDATED CLINICAL GUIDELINE FOR THE MANAGEMENT OF KD

Since the recognition that IVIG could reduce the morbidity and mortality of KD, treatment of this condition has been largely protocol driven. Although authorities differ in their advocacy for a variety of treatment protocols, it is likely that the success of therapeutic intervention in KD is due to modulation of the causes and/or propagators of inflammation. As such we have re-evaluated the current prescriptive approach to the management of KD in the light of the published literature, adding corticosteroids into primary therapy for severe and IVIG unresponsive cases; and suggesting a role for anti-TNF- α if systemic inflammation persists despite IVIG, aspirin and corticosteroids. Repeated protocol-driven administration of IVIG in patients with little evidence of clinical and/or laboratory improvement may be detrimental, and treatment with corticosteroids and/or anti-TNF α considered. Unchecked inflammation damages the vasculature in KD; the acute-phase response, particularly CRP, combined with clinical response can be used to assess the efficacy of any intervention. A minimum of three echocardiograms should be performed in the first 6 weeks of the illness. The justification for this is: (1) some patients (albeit a minority) can develop CAA in the first week of the illness,⁶ and early detection of these should prompt more aggressive primary management; (2) early echocardiography (in the first week) may detect extracoronary manifestations, such as mitral regurgitation or pericardial effusion, that may be associated with increased risk of CAA⁶² (3) early detection of CAA progression and/or development of thrombus might be detected that could result in intensification of anti-inflammatory and/or additional anticoagulation therapy. With this philosophy in mind, and in light of the therapeutic advances discussed above, we present an updated clinical guideline⁹ for the management of KD in the UK (figure 1).

AREAS FOR FUTURE RESEARCH AND CONCLUSIONS

The therapeutic uncertainties raised by the recent studies and are highlighted above, can only be answered by further

Table 4 Risk stratification and follow-up recommendations for children with Kawasaki disease⁶

Risk level	Pharmacological therapy	Physical activity	Follow-up and diagnostic testing	Invasive testing
Level I (no coronary artery changes at any stage of illness)	None beyond first 6–8 weeks	No restrictions beyond first 6–8 weeks	Cardiovascular risk assessment, counselling at 5-year intervals	None recommended
Level II (transient coronary artery ectasia that disappears within 6–8 weeks)	None beyond first 6–8 weeks	No restrictions beyond first 6–8 weeks	Cardiovascular risk assessment, counselling at 3-year to 5-year intervals	None recommended
Level III (one small-medium coronary artery aneurysm/major coronary artery)	Low-dose aspirin (3–5 mg/kg aspirin per day), at least until aneurysm regression documented	For patients <11y old, no restriction beyond 1st 6–8 weeks; patients 11–20 years old, physical activity guided by biennial stress test, myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents	Annual cardiology follow-up with echocardiogram +ECG, combined with cardiovascular risk assessment, counselling; biennial stress test/evaluation of myocardial perfusion scan; consider CAA imaging using CT or MR angiography	Angiography, if non-invasive test suggests ischaemia
Level IV (>1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without obstruction)	Long-term antiplatelet therapy combined with warfarin (target INR 2.0–2.5) or low molecular-weight heparin (target: antifactor Xa level 0.5–1.0 U/mL) should be considered in all patients with giant aneurysms	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/evaluation of myocardial perfusion scan outcome	Biannual follow-up with echocardiogram +ECG; annual stress test/evaluation of myocardial perfusion scan 1st angiography at 6–12 mo or sooner if clinically indicated; repeated angiography if non-invasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances; consider CAA imaging using CT or MR angiography	1st angiography at 6–12 months or sooner if clinically indicated; repeated angiography if non-invasive test, clinical, or laboratory findings suggest ischaemia; elective repeat angiography under some circumstances
Level V (coronary artery obstruction)	Long-term low-dose aspirin; warfarin or low molecular-weight heparin if giant aneurysm persists; consider TPA to dissolve clot; consider use of β -blockers to reduce myocardial O ₂ consumption; consider statins and/or ACE inhibitors	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/myocardial perfusion scan outcome	Biannual follow-up with echocardiogram and ECG; annual stress test/evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options; consider CAA imaging using CT or MR angiography intermittently to monitor

CAA, coronary artery aneurysms;; TPA, tissue plasminogen activator.

randomised trials and immunopathological studies to address the issues of patient selection, dose, route and safety of corticosteroid and/or other anti-inflammatory agents. The ongoing BPSU study will provide important data regarding current epidemiology, CAA rates, and mortality of KD in the UK. Studies are also needed to identify biomarkers and clinical scores that work outside of Japan to identify patients at highest risk of CAA and, hence, the need for the addition of corticosteroids and/or anti-TNF in the primary treatment. Concerted international efforts aiming at improving our understanding of the potential infectious trigger, and genetic contribution to KD disease susceptibility or complications are of utmost importance. Whether or not KD predisposes to premature atherosclerosis, or more correctly, late-KD vasculopathy, is the subject of an ongoing UK study, and will help provide an evidence base to inform long-term management strategies in the UK. Last, a significant challenge that remains is to coordinate transitional care of KD patients into adulthood. In the UK, this is currently done suboptimally, and the development of local networks to transition cardiac care from paediatrics through adolescence and into adulthood are urgently required.

In conclusion, in addition to the worldwide effort to understand the genetics of KD, it is time for a concerted drive to improve the evidence base for acute and lifelong management of this important childhood disease in the UK. As KD is a rare disorder, research to improve understanding of the aetiology, pathogenesis, treatment and outcome requires multicentre collaboration as in, for example, a recent and ongoing National Institute for Health Research (NIHR) multicentre study of KD in the UK.

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Management of Kawasaki disease

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