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European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease – the SHARE initiative

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Abstract

Objectives. The European Single Hub and Access point for paediatric Rheumatology in Europe initiative aimed to optimize care for children with rheumatic diseases. Kawasaki disease (KD) is the most common cause of acquired heart disease in children and an important cause of long-term cardiac disease into adulthood. Prompt diagnosis and treatment of KD is difficult due to the heterogeneity of the disease but is crucial for improving outcome. To date, there are no European internationally agreed, evidence-based guidelines concerning the diagnosis and treatment of KD in children. Accordingly, treatment regimens differ widely. The aim of this study is to provide consensus-based, European-wide evidence-informed recommendations for diagnosis and treatment of children with KD.

Methods. Recommendations were developed using the EULAR's standard operating procedures. An extensive systematic literature search was performed, and evidence-based recommendations were extrapolated from the included papers. These were evaluated by a panel of international experts via online surveys and subsequently discussed in three consensus meetings, using nominal group technique. Recommendations were accepted when $\geqslant$80% agreed.

Results. In total, 17 recommendations for diagnosis and 14 for treatment of KD in children were accepted. Diagnostic recommendations included laboratory and imaging workup for complete as well as incomplete KD. Treatment recommendations included the importance of early treatment in both complete and incomplete KD, use of intravenous immunoglobulin, aspirin, corticosteroids for high-risk cases, and other treatment options for those with resistant disease.

Conclusion. The Single Hub and Access point for paediatric Rheumatology in Europe initiative provides international evidence-based recommendations for diagnosing and treating KD in children, facilitating improvement and uniformity of care.

Key words: childhood/paediatric, Kawasaki disease, systemic vasculitis, SHARE recommendations, treatment

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Rheumatology key messages

- Coronary artery aneurysms in Kawasaki disease may be prevented by early institution of anti-inflammatory therapy, typically IVIG.
- Patients resistant to IVIG are at highest risk of coronary artery aneurysms.
- We provide evidence-based recommendations for the diagnosis and treatment of Kawasaki disease.

Introduction

Kawasaki disease (KD) is the second most common systemic vasculitic illness of childhood after IgA vasculitis [1]. KD is more prevalent in Japanese children (308/100 000) under the age of five years [2], a risk that is independent of geography [3]. In the UK, an indirect epidemiological survey indicated an incidence of 9.2/100 000 children under 5 years, with over-representation of Chinese and Japanese cases [4], but a recent direct British Paediatric Surveillance Unit epidemiological survey suggests an incidence of 4.55/100 000 children under 5 years [5]. In the USA, the incidence is ~25/100 000 children [3].

Importantly, KD is the most common cause of acquired heart disease in children in developed countries, causing coronary artery aneurysms (CAA) in up to 25% of untreated patients due to coronary vasculitis. Clinical trials demonstrate that this declines to ~4% with intravenous immunoglobulin (IVIG) treatment (reviewed comprehensively in [3, 6]) although emerging non-clinical trial 'real-world' studies suggest poorer outcomes despite IVIG, particularly in infants under the age of 12 months (see below). Mortality varies by population: 0.015% in Japan [3]; 0.17% in the USA [3] and 0.36% in the UK [4]. KD remains an important cause of long-term cardiac disease into adulthood [3, 7, 8]. The complexity and heterogeneity of presentation of KD, broad differential diagnosis, and lack of a diagnostic test can be important barriers for making a prompt diagnosis.

In 2012, the European initiative Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) was launched to optimize care for children and young adults with paediatric rheumatic diseases [9]. To date, SHARE recommendations for paediatric antiphospholipid syndrome, juvenile dermatomyositis, familial Mediterranean fever/auto-inflammatory diseases and childhood-onset lupus have been published [10–14]. Although the American Heart Association (AHA) provided updated and detailed guidelines for KD in 2017 [3], there are no internationally agreed, evidence-based recommendations for KD in children. Treatment regimens still differ widely between centres, and internationally. Thus, the SHARE recommendations aim to fulfil this important unmet need to provide a practical tool for optimal care of children with KD.

Methods

A panel of 17 experts in paediatric rheumatology and systemic vasculitides from across Europe was established to develop evidence-based recommendations for diagnosing and treating childhood KD. Experts needed to be senior consultants with at least 10 years' experience working in a major tertiary paediatric rheumatology referral centre routinely looking after children with KD and as part of a multi-disciplinary team. As SHARE was a European Union-funded project, only experts from across Europe were able to be selected, representing a balance between experience and geography, although the panel carefully considered literature and other published recommendations from experts from across the globe. The panel were informed by expert recommendations from paediatric cardiology, infectious diseases and other specialists, but due to the specific scope of the SHARE initiative, the panel did not include directly experts from these specialties in the process. The panel used the previously described [13] SHARE methods and following the EULAR standardized operating procedure for developing best practice recommendations [15].

Systematic literature review and study selection

Based on specific research questions, the PubMed/MEDLINE, EMBASE and Cochrane databases were systematically searched on 20 June 2013 resulting in a set of articles that were then assessed (Supplementary Fig. S1, available at *Rheumatology* online). All systemic vasculitides synonyms were searched using MeSH/Emtree terms, title and abstract, using a validated filter pertaining to children and adolescents only [16] (Supplementary Table S1, available at *Rheumatology* online). Articles were assessed using pre-specified inclusion/exclusion criteria (Supplementary Table S2, available at *Rheumatology* online). The comprehensive literature review was undertaken inclusive of these other forms of systemic vasculitis to ensure no manuscripts including data on KD along with any of these other forms were missed. All articles were screened independently by two reviewers (N.dG., N.G.) and full text assessed when necessary to determine eligibility. Disagreement was resolved by a third reviewer (M.W.B.); agreement was reached in all cases. This literature review was cross-referenced with key articles that had informed a contemporaneous UK national guideline for KD [6].

Additional key KD articles identified between the initial literature search and the final manuscript drafting (May 2018) were identified using the same search strategy. While these latter did not directly inform the recommendations, they were included in the manuscript commentary to provide up-to-date face validity and contextualization, particularly to incorporate updated AHA 2017 guidance [3].

Validity assessment

Papers pertaining to KD were analysed using standardized data extraction and scoring forms by two experts

(P.B. and D.E.); any discrepancies were resolved by a third expert (M.W.B.). Data were extracted using predefined scoring forms for demographics, diagnostic [17] and therapeutic [18] studies. Adapted classification tables for diagnostic [19] and therapeutic [20] studies were used to determine the level of evidence and strength of each recommendation (Supplementary Tables S3 and S4, available at *Rheumatology* online).

Establishment of recommendations

Provisional statements regarding diagnosis and treatment were developed using data from included articles (N.dG., N.G., S.O., S.K., P.B. and M.W.B.). These statements were presented to the expert committee ($n = 14/17$ of the experts) in an online survey (100% response rate). Recommendations were revised according to responses and discussed at three face-to-face consensus meetings in March 2014 (Genoa, $n = 14/17$ expert participants); January 2015 (Utrecht, $n = 10/17$ experts) and March 2015 (Barcelona, $n = 16/17$ experts). Nominal group technique was used to reach consensus [21], with final recommendations accepted with $\geqslant 80\%$ agreement.

Results

Literature search and formulation of recommendations

The literature search yielded 826 articles relating to KD (Supplementary Fig. S1, available at *Rheumatology* online). References concerning rare paediatric systemic vasculitides and IgA vasculitis informed additional recommendations described in separate manuscripts (Supplementary Fig. S1, available at *Rheumatology* online). A total of 31 recommendations were accepted with 100% agreement: 17 relating to diagnosis and 14 concerning treatment of KD.

Diagnosis of Kawasaki disease

Table 1 summarizes the SHARE recommendations for diagnosing KD and incomplete KD.

Diagnostic criteria for KD

There is no diagnostic test for KD; thus, diagnosis rests on clinical criteria and laboratory findings. To establish the diagnosis according to the Diagnostic Guidelines of the Japan KD Research Committee, any five of the six criteria in Table 2 must be present [5]. The AHA (2004) diagnostic criteria are similar, except that fever is mandatory, and four of the remaining five criteria are required [22]. The expert panel assessed the merits and strengths of each, and recommended that the AHA diagnostic criteria should be used for complete KD. Subsequently, the AHA revised their diagnostic criteria, as summarized in Table 2. These are broadly similar to the 2004 criteria, but now acknowledge that diagnosis may be made earlier than day 5 of fever, if fever plus $\geqslant 4$ principal clinical features are present, in line with the SHARE recommendations. However, many patients have some but not all of the clinical features of KD and may still be at risk of CAA (see below). Clinical features may present sequentially, such that an incomplete case can evolve into a complete case [22]. 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 days [6, 22, 23].

Diagnosing KD before day 5 of fever

The SHARE experts acknowledged that the requirement for fever $\geqslant 5$ days may lead to delayed treatment. While fever duration has historically been of importance for the standardization of case definitions, clinicians should not delay diagnosing KD and instituting treatment if five out of six diagnostic criteria of KD are present before day 5 of fever, or if CAA (Z-score $\geqslant 2.5$) or coronary dilatation (Z-score >2, but <2.5) is present [6, 22, 23].

Diagnosing incomplete Kawasaki disease

While the diagnosis of KD is generally straightforward in patients fulfilling all the criteria for KD (complete KD), many patients have only some of the clinical features [3, 6, 22, 23]. However, they may still be at risk of CAA, especially infants who may have prolonged fever alone or fleeting clinical signs. The panel acknowledged that diagnosing KD in patients with incomplete clinical criteria relies on a high index of suspicion, in agreement with other current guidelines [3, 6, 22]. In these situations, early echocardiography is recommended. This may reveal evidence of coronary vasculitis, confirming the diagnosis of KD. Notably, however, a negative echocardiogram does not exclude the diagnosis of KD.

The definition of incomplete KD can cause confusion. As is the case for complete KD, the requirement of fever $\geqslant 5$ days to fulfil current diagnostic criteria may delay treatment unnecessarily. The expert panel recommended that an important research priority is to design and prospectively validate criteria to help diagnose incomplete KD in children. The AHA 2017 recommendations provide some guidance in this respect, defining incomplete KD as children with fever $\geqslant 5$ days and two or three clinical criteria, or infants with fever for $\geqslant 7$ days without other explanation [3]. Thereafter, treatment decisions are determined by laboratory tests including inflammatory markers (Fig. 1). These AHA recommendations offer a practical solution for the diagnosis and treatment of incomplete KD cases, but are not evidence-based, as acknowledged by McCrindle *et al.* [3]

Laboratory work-up of suspected Kawasaki disease

The diagnosis of KD is unlikely in the absence of significant systemic inflammation. Certain laboratory parameters may help stratify the severity of KD and thus help inform therapeutic decisions. Therefore, ESR, CRP, full blood count, electrolytes, renal and liver function (including bilirubin, AST or alanine transaminase, and albumin) should be monitored in all patients [3, 6, 22]. Notably, ESR is only useful prior to IVIG therapy, since this may be elevated post-IVIG as a consequence of binding to red blood cells [24, 25]. It is equally important to rule out severe infections (such as meningitis), and/or

Table 1 SHARE recommendations for the diagnosis and assessment of KD

KD recommendations – diagnosis	LoE	SoR
1. There are different diagnostic criteria for KD. The AHA diagnostic criteria should be used to diagnose complete KD (see Table 2).	4	D
2. The diagnosis of KD should be considered in any child with a febrile exanthematous illness and evidence of inflammation, particularly if it persists longer than 4 days.	4	D
3. KD diagnosis and treatment should not be delayed if: 5/6 diagnostic criteria of KD are present before day 5 of fever. CAAs or coronary dilatation are present. There is evidence of persistent (⩾5 days) elevation of inflammatory markers and/or persistent fever, especially in infants or younger children without other explanation.	4	D
4. In a patient in whom KD is suspected, but all criteria have not yet been fulfilled, the following clinical signs strengthen the suspicion of KD: Irritability New erythema and/or induration at the site of previous BCG immunization.	4	D
5. It is recognized that there are incomplete cases of KD (who do not fulfil the AHA criteria); however, these patients may still be at risk of CAA, particularly infants.	4	D
6. Criteria should be designed and validated to help diagnose incomplete KD[a].	4	D
7. In children presenting with less than five out of six criteria for KD ('incomplete KD'), with evidence of unexplained systemic inflammation (e.g. elevated CRP, ESR or WBC), an echocardiogram should be considered.	3	D
8. The following laboratory values should be determined: ESR, CRP, full blood count and liver function (bilirubin, AST/ALT), albumin, natraemia, renal function and urinalysis. Ferritin and fibrinogen should be considered if there is a concern for macrophage activation syndrome.	3	C
9. Cerebrospinal fluid analysis may be important to rule out infectious meningitis.	4	D
10. The following laboratory values can be important in assessing risk stratification for IVIG resistance: low sodium, raised bilirubin, raised ALT, low platelet count, high CRP, low albumin[b].	3	C
11. The following laboratory values can be important in monitoring inflammation: ESR (prior to IVIG), CRP and full blood count.	2B	C
12. All patients with suspected KD should undergo echocardiography and ECG at baseline, as soon as the diagnosis is suspected.	1A	B
13. An intermediate echocardiogram, 2 weeks after the first IVIG, should be performed in all patients with KD whose initial echo was normal and in whom disease activity has been arrested.	1A	B
14. All patients with KD should undergo echocardiography at 6–8 weeks after disease onset.	2A	C
15. In those with ongoing active inflammation (increasing or persistently elevated CRP and/or persisting signs and symptoms), ECG and echocardiography should be performed at least weekly to monitor the possible development of cardiac sequelae.	2A	C
16. In those with coronary abnormalities detected on initial echocardiography, echocardiography should then be performed at least weekly to monitor progression until there is clinical stabilization.	2A	C
17. In children with CAA, ECG and echocardiography should be performed 3- to 6-monthly, depending on the severity of the CAA[c]	4	D

[a]These SHARE recommendations were formulated prior to publication of the AHA 2017 recommendations [3], which describe an algorithm for the diagnosis and treatment of incomplete KD cases. Although the AHA algorithm is not evidence-based, it provides a useful diagnostic framework (see main text). [b]See also Supplementary Table S5, available at *Rheumatology* online, which provides details of the three main scoring systems used to determine risk of IVIG resistance. [c]Or as otherwise recommended by an expert paediatric cardiologist. AHA: American Heart Association; ALT: alanine transaminase; AST: aspartate transaminase; CAA: coronary artery aneurysm; IVIG: intravenous immunoglobulin; KD: Kawasaki disease; SHARE: Single Hub and Access point for paediatric Rheumatology in Europe; WBC: white blood cell count; LoE: level of evidence; 1A: meta-analysis of cohort studies; 1B: meta-analysis of case–control studies; 2A: cohort studies; 2B: case–control studies; 3: non-comparative descriptive study; 4 expert opinion; SoR: strength of recommendation; A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion.

identify other systemic inflammatory diseases or complications of KD including macrophage activation syndrome (also referred to as secondary haemophagocytic lymphohistiocytosis, HLH) [3, 6]. Thus, consideration of a full septic screen (including consideration of lumbar puncture) and serum ferritin are recommended. Evidence of infection might occur in patients with KD, and should not deter clinicians from treating both entities [26].

Scoring systems to predict high-risk cases

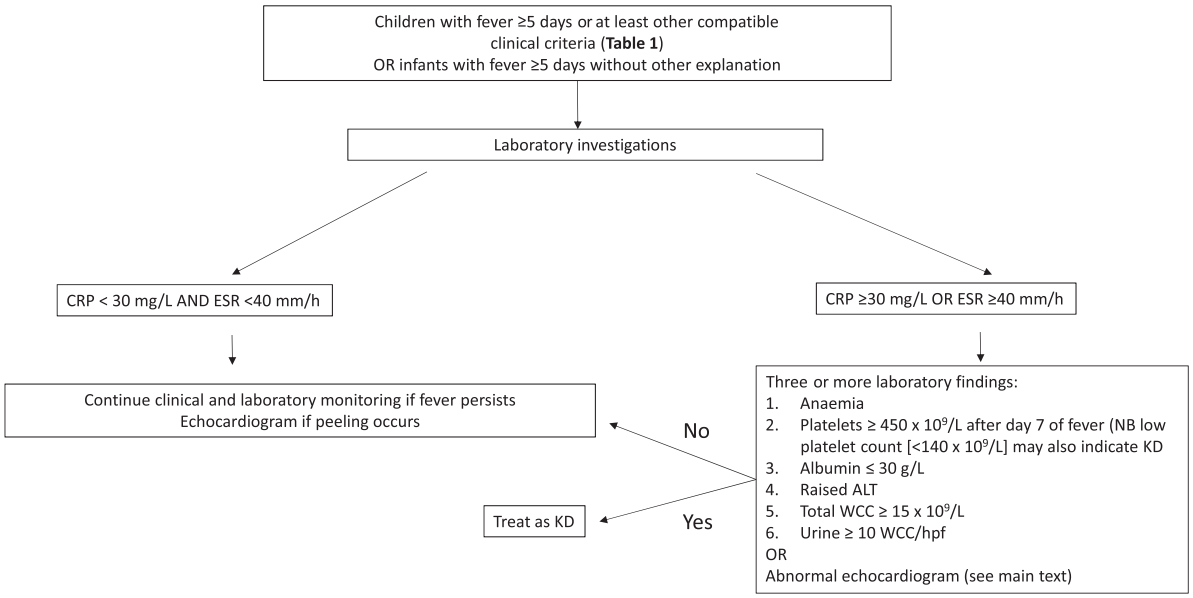
Several scoring systems have been developed to identify children at highest risk of IVIG resistance and hence highest risk of developing CAA [27–29]. Kobayashi *et al.* [28] developed a model to predict unresponsiveness to IVIG in Japanese children with KD based on a cut-off point ⩾4 calculated as per below: sodium ⩽133 mmol/L (2 points); days of illness at initial treatment ⩽4 (2 points); aspartate aminotransferase ⩾100 IU/L (2 points); percentage of

Table 2 Kawasaki disease: diagnostic criteria (AHA 2017 [3])

Criterion	Description
Fever	Duration of 5 days or more, plus four of five of the following:
1. Conjunctivitis	Bilateral, bulbar, conjunctival injection without exudate
2. Lymphadenopathy	Cervical, often >1.5 cm usually unilateral
3. Rash	Maculopapular, diffuse erythroderma or erythema multiforme
4. Changes of lips or oral mucosa	Red cracked lips, strawberry tongue or diffuse erythema of oropharynx
5. Changes to extremities	Erythema and oedema of palms and soles in acute phase and periungal desquamation in subacute phase

KD may be diagnosed with fewer than four of these features if coronary artery abnormalities are detected (Fig.1). KD: Kawasaki disease; AHA: American Heart Association.

Fig. 1 Management of suspected incomplete KD (adapted from AHA 2017 [3])



AHA: American Heart Association; ALT: alanine transaminase; hpf: high power field; KD: Kawasaki disease; WCC: white cell count.

neutrophils ⩾80% (2 points); CRP ⩾100 mg/L (1 point); age ⩽12 months (1 point); platelet count ⩽300 × 10 9/L (1 point) (see Supplementary Table S5, available at *Rheumatology* online). This model was used to define severe cases in a pivotal clinical trial of corticosteroids, because IVIG resistance is known to be a strong risk factor for the development of CAA [27]. The Kobayashi, Egami and Sano scores (see Supplementary Table S5, available at *Rheumatology* online), when tested in North American patients, demonstrated comparably high specificity for predicting IVIG non-response, but with relatively low sensitivity [30]. These data suggested that in non-Japanese children, a positive Kobayashi score might identify a patient at high risk of IVIG resistance, but a negative score may not reliably exclude a high-risk case. More recently, studies from the UK and Germany also demonstrated suboptimal performance of the Kobayashi score for predicting high-risk cases [31, 32]. Therefore, clinicians must adopt a pragmatic approach and synthesize an overall picture of disease severity based on clinical features and laboratory parameters. Factors that increase risk include young age (i.e. <12 months), low serum sodium, high alanine transaminase, low albumin, high bilirubin, high CRP, low platelet count, falling haemoglobin, features of HLH and shock, and these are all important features to consider when assessing risk and hence choice of primary KD treatment modality.

Echocardiography and monitoring systemic inflammation

As up to 25% of untreated KD cases develop CAA, and a significant proportion have other cardiac manifestations, including pericardial effusion, pericarditis, myocarditis, valvular incompetence, cardiac failure and even myocardial infarction, all patients with suspected KD should

undergo echocardiography at baseline, as soon as it is suspected [3, 6, 22, 23]. Treatment should not be delayed while awaiting echocardiography [3, 6, 22, 23]. In view of the potential rapidly evolving nature of this critical complication, all patients with KD should have an intermediate echocardiogram, 2 weeks after administration of the first IVIG, including those whose initial echo was normal and in whom disease activity has been arrested [3, 6, 22, 23, 33–36]. All patients should undergo echocardiography at 6–8 weeks after disease onset [3, 6]. Although not noted as a specific recommendation, it was acknowledged that all patients should have echocardiography undertaken by a paediatric cardiologist or by echocardiographers trained specifically in paediatric cardiology working directly within a paediatric cardiology team. Non-aneurysmal coronary dilatation is defined as internal coronary artery diameter *Z*-score >2 but <2.5; small CAA are defined as $Z \geqslant 2.5$ to <5; medium CAA are $Z \geqslant 5$ to <10; and giant CAA are $Z \geqslant 10$ or absolute internal diameter $\geqslant 8$ mm [3, 35]. Normative data can affect the *Z*-score result (see updated detailed commentary [3]).

Historically, resolution of fever has been used as a metric of therapeutic outcome success in KD. However, some patients may become afebrile but still have significant ongoing systemic inflammation as indicated by elevation of acute phase reactants, including CRP. Indeed, recent clinical trials have employed resolution of fever and normalization of CRP in their therapeutic design [37], emphasizing that temperature alone should not be used to gauge the degree of systemic inflammation, as reflected in recent clinical guidelines [3, 6]. Close monitoring of patients with increasing or persistently elevated CRP and/or persisting signs of systemic inflammation is therefore critical, combined with regular cardiology reviews including at least fortnightly ECG and echocardiography to assess cardiac sequelae [3, 6]. ESR should not be taken into account after IVIG (as an elevation of proteinaemia leads to an elevation of ESR). In those with coronary abnormalities including CAA, at least weekly echocardiography should be considered to monitor progression until clinical stabilization. Among those with CAA, ECG and echocardiography should be performed every 3–6 months (or as specified by a paediatric cardiologist for individual cases), depending on CAA severity [3, 6]. A final important caveat in relation to echocardiography for young children who present with systemic inflammation is that other inflammatory diseases might be associated with transient coronary artery dilatation, particularly systemic-onset juvenile idiopathic arthritis [38].

Treating Kawasaki disease

Table 3 summarizes the SHARE recommendations for treating KD in childhood.

IVIG

Randomized controlled trials and meta-analyses have demonstrated unequivocally that early recognition and treatment of KD with IVIG and aspirin reduces the occurrence of CAA [39, 40]. Therefore, the panel recommended strongly that IVIG and aspirin should be started as soon as a patient is diagnosed with complete or incomplete KD. In keeping with previous guidance [3, 6], treatment should include a dose of 2 g/kg IVIG as a single infusion, in view of greater therapeutic effect in preventing CAA when compared with a lower, divided dose regimen [41]. As the Kobayashi criteria in non-Japanese patients may not reliably exclude IVIG resistance even if negative [30], close monitoring of patients is critical, taking into account temperature, acute phase reactants (particularly CRP post-IVIG), clinical symptoms and signs of systemic inflammation.

Aspirin

All patients should initially receive aspirin at a dose of 30–50 mg/kg/day, in three to four divided doses. Meta-analysis comparing the 30–50 mg/kg/day dose with high-dose (80–120 mg/kg/day), both combined with IVIG, demonstrated no significant difference in the incidence of CAA [42]. Aspirin should be reduced to an antiplatelet dose of 3–5 mg/kg/day, but only after the fever has settled for 48 h, clinical features are improving and CRP levels are falling [3, 6]. Aspirin can be stopped if the echocardiogram at 6–8 weeks remains normal. If CAA persist in the convalescent phase, continuation of low-dose aspirin (3–5 mg/kg/day) is recommended long-term, at least until the aneurysms resolve [3, 6]. In patients with regressed CAA, long-term aspirin (3–5 mg/kg/day) should still be considered, taking into account the risk–benefit ratio for individual patients. It is increasingly recognized that patients with regressed aneurysms may demonstrate coronary artery endothelial function abnormalities comparable to those with persistent CAA [7]. The adverse effects of late KD vasculopathy, even in those with resolved CAA, is increasingly recognized [3, 6]. It should be remembered that ibuprofen and other non-steroidal anti-inflammatory drugs interfere with the antiplatelet effect of aspirin and thus should be avoided if possible, a point emphasized in the recent AHA guidelines [3]. It is possible that future guidance may recommend low-dose aspirin (3–5 mg/kg/day) at all stages of KD, as suggested by data from a retrospective cohort [43]; while the SHARE group acknowledged this recent development, there has never been a prospective controlled clinical trial to support this approach. Another practical consideration highlighted by the AHA regarding children on long-term low-dose aspirin is avoidance of non-steroidal anti-inflammatory drugs such as ibuprofen which can antagonize platelet inhibition induced by aspirin [44]. Low-dose aspirin has not been associated with any documented cases of Reye syndrome and therefore is safe to continue in the event of intercurrent infection [3].

Treatment with corticosteroids

Up to 20–40% of patients are IVIG resistant, and are at increased risk of developing CAA [37, 45–47]. In the UK, CAA rates remain significantly higher (19–29%) despite IVIG, a worrisome complication rate that has remained stable over 25 years of surveillance [4, 48]. Similarly poor outcomes are now recognized in Sweden, Russia and

Table 3 SHARE recommendations for the treatment of KD

KD recommendations – treatment	LoE	SoR
1. As soon as a patient is diagnosed with KD, treatment should be initiated[a]. This applies to both complete and incomplete KD.	1A	A
2. Treatment of KD should include IVIG at a dose of 2 g/kg as a single infusion.	1A	A
3. In non-Japanese patients, the Kobayashi criteria may indicate risk of IVIG resistance if 'positive' (score $\geqslant$4) but may not reliably exclude IVIG resistance if 'negative' (score $<$4).	2A	C
4. All patients diagnosed with KD who are treated with IVIG should be treated with aspirin at a dose of 30–50 mg/kg/day until fever has settled for 48 h, clinical features are improving, and CRP levels are falling.	2A	C
5. The dose of aspirin should subsequently be reduced to an antiplatelet dose of 3–5 mg/kg once daily when fever and inflammation have subsided.	3	D
6. If aneurysms persist in the convalescent phase of KD, antiplatelet therapy in the form of low-dose aspirin (3–5 mg/kg) should be continued long-term, at least until the aneurysms resolve.	3	D
7. In patients with CAA that resolve, long-term aspirin (3–5 mg/kg/day) should be considered, taking into account the risk–benefit ratio for individual patients.	4	D
8. Corticosteroid treatment should be given to patients with severe KD[a]:	1A[b]	A
(a) Who are IVIG resistant, that is, with ongoing fever and/or persistent inflammation or clinical signs $\geqslant$48 h after receiving IVIG as a single dose of 2 g/kg. A second dose of IVIG is at the discretion of the treating physician.	1A 3 4	C C D
(b) Kobayashi score $\geqslant$5 (see Supplementary Table S5, available at *Rheumatology* online)	4	D
(c) With features of HLH	4	D
(d) With features of shock	4	D
(e) Who are under the age of 1 year		
(f) Who present with coronary and/or peripheral aneurysms		
9. If corticosteroids are indicated, the following regimens would be reasonable:	2A	B
Regimen 1: methylprednisolone 0.8 mg/kg BD i.v. for 5–7 days or until CRP normalizes; then convert to oral prednisone/prednisolone 2 mg/kg/day and wean off over next 2–3 weeks. **Regimen 2**: methylprednisolone 10–30 mg/kg (up to maximum of 1g/day) once daily for 3 days followed by oral prednisone/prednisolone 2 mg/kg per day until day 7 or until CRP normalizes; then wean over next 2–3 weeks.		
10. TNF-alpha blockade (e.g. infliximab) should be considered in KD patients with persistent inflammation despite IVIG, aspirin and corticosteroid treatment, after consultation with a specialist unit.	2A	C
11. The use of DMARDs such as ciclosporin, cyclophosphamide and methotrexate, along with anakinra and plasma exchange, cannot be recommended, except on an individual basis after consultation with a specialist unit.	4	D
12. In the presence of giant aneurysms (internal diameter $\geqslant$8 mm, or *Z*-score $\geqslant$10, and/or coronary artery stenosis) warfarin should be administered (in addition to aspirin), after initial heparinization; heparin can be stopped when a stable INR between 2 and 3 is reached. Low molecular weight heparin is a suitable alternative, particularly in young infants where safe warfarinization can be challenging.	2B	C
13. If symptoms of ischaemia or obstruction occur in a patient with KD, a paediatric cardiologist/cardiac surgeon/interventional radiologist (depending on local expertise available) should be consulted immediately	4	D
14. Immunization with all vaccines should be deferred for at least 6 months following an episode of KD treated with IVIG.	4	D

[a]Treatment should not be delayed while awaiting echocardiography. [b]Level of evidence 1A and strength of recommendation A for this overall statement in relation to severe KD. CAA: coronary artery aneurysms; HLH: haemophagocytic lymphohistiocytosis; IVIG: intravenous immunoglobulin; KD: Kawasaki disease; LoE: level of evidence; SHARE: Single Hub and Access point for paediatric Rheumatology in Europe; 1A: meta-analysis of randomized controlled trials; 1B: randomized controlled study; 2A: controlled study without randomization; 2B: quasi-experimental study; 3: descriptive study; 4: expert opinion; SoR: strength of recommendation; A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion.

North America [49–51]. Although therapeutic delay is a major contributing factor to these poor outcomes, some authors speculate that IVIG response may vary across populations [48], perhaps due to genetic differences such as Fc gamma-receptor polymorphisms [3], emphasizing the need for adjunctive primary treatment in some patients. While it is also possible that improved echocardiographic technology has resulted in better detection of CAA and hence seemingly poorer coronary outcomes as compared with historical studies [52], an emerging overall theme is that diagnostic delay remains an important concern in relation to outcome.

While significant equipoise remains regarding the use of corticosteroids for unselected KD patients, the use of corticosteroids as primary adjunctive treatment of patients with severe KD [53], has an increasingly compelling evidence base [37, 45, 46, 54–57]. Meta-analysis of 16 comparative studies involving 2746 KD patients demonstrated that early addition of corticosteroids to conventional IVIG therapy is associated with reduced risk of CAA compared

with IVIG therapy alone (odds ratio: 0.424; 95% CI: 0.270–0.665) [46]. This beneficial effect was only observed when corticosteroids were used as primary therapy rather than rescue therapy for IVIG resistance. It was most beneficial for patients who were determined at baseline to have high risk for IVIG resistance. The authors highlighted the importance of prompt diagnosis and treatment: meta-regression analyses demonstrated that the overall efficacy of corticosteroids was negatively correlated with illness duration before corticosteroid therapy [46]. Thus, the need for more robust clinical risk scoring systems to identify high-risk patients is underlined.

Notwithstanding the ongoing debate regarding the definition of KD severity in non-Japanese patients, it is unclear whether corticosteroids benefit patients with less severe KD [3, 6], and the optimal corticosteroid dosing regimen to use is uncertain [6, 53]. Thus, preventing potentially life-long cardiac sequelae needs to be balanced against careful vigilance for corticosteroid-related complications. In view of this, the expert panel recommended that adjunctive primary corticosteroid treatment should be given to patients: (i) who are IVIG resistant, with ongoing fever and/or persistent inflammation or clinical signs $\geqslant$48 h after receiving a single dose of IVIG [6] (a second dose of IVIG alongside corticosteroids is at the discretion of the treating physician [6]); (ii) have a Kobayashi score $\geqslant$4 [30]; (iii) have features of HLH [58]; and/or (iv) have features of shock [59, 60]. The panel defined additional 'high-risk groups' who are also likely to benefit from primary adjunctive corticosteroids, namely: infants $<$1 year of age [6], and patients who present with coronary and/or peripheral aneurysms at diagnosis [6], although this may impact on damage limitation only [46]. As the meta-analysis of corticosteroid treatment in KD does not provide definite evidence for optimal treatment regimens [45, 46, 53], treating clinicians will need to determine the corticosteroid regimen for individual patients. If corticosteroids are indicated, the panel noted two treatment regimens that in their consensus opinion would be reasonable (Table 3).

TNF-alpha blockade and other treatments

An increasing number of studies have explored the potential use of TNF-alpha blockade in children with IVIG-resistant KD [61–65]. Although these studies have demonstrated no significant differences in cardiac-related outcomes, such as reduction in CAA, they generally demonstrate a significant impact on reducing the acute-phase response, fever and potential length of hospital stay. Therefore, use of anti-TNF-alpha medication (e.g. infliximab) was recommended for consideration in KD patients with persistent inflammation despite IVIG, aspirin and corticosteroid treatment, albeit after consultation with a specialist unit. The panel did not specify dosing or need for additional doses of anti-TNF-alpha medication, which were felt to be beyond the scope of these recommendations. Evidence supporting the use of other treatments, such as ciclosporin, cyclophosphamide, methotrexate, along with anakinra or plasma exchange, was less robust and therefore could not be routinely recommended, apart from on a case-by-case basis after consultation with a specialist unit.

Anti-coagulation and anti-aggregation

Those with medium sized aneurysms (*Z* score 5–10) should also take aspirin at 3–5 mg/kg/day, and consider addition of an antagonist of adenine di-phosphate-mediated activation platelet aggregation such as clopidogrel, at a dose of 0.5–1 mg/kg/daily [3]. Managing patients with giant aneurysms (internal diameter $\geqslant$8 mm; or *Z*-score $\geqslant$10; and/or coronary artery stenoses) includes anti-coagulation as well as antiplatelet therapy with aspirin [66]. Warfarin should be administered in addition to aspirin after initial heparinization, and heparin can be stopped when a stable INR of 2–3 is reached [23, 66, 67]. Low molecular weight heparin is a suitable alternative, particularly in young infants where safe warfarinization can be challenging [3]. If symptoms of ischaemia or vascular occlusion occur in a patient with KD, a paediatric cardiologist/cardiac surgeon/interventional radiologist (depending on local expertise available) should be consulted, if not already closely involved in management [3, 6]. Detailed advice on the use of low molecular weight heparin, clopidogrel and other thienopyridines, thrombolysis and other acute revascularization procedures was not considered in the SHARE process, but these issues have been addressed in the recent AHA guidance, albeit with limited evidence to inform guidance [3].

Immunization

Immunization with all live vaccines should be deferred for at least 6 months following an episode of KD treated with IVIG, mainly due to the potential lack of effectiveness following IVIG [68, 69]. Thereafter, all vaccines should be administered as recommended by national schedules. As IVIG particularly supresses the response to measles vaccine, and in line with recent AHA guidance, we also suggest that mumps, measles and rubella vaccine (and varicella-zoster vaccine, albeit with less supporting evidence) might be deferred for at least 11 months after IVIG administration [3]. However, we acknowledge that children at high risk of exposure to measles should be vaccinated earlier than this 11-month window, with the possibility of re-vaccination if serological response is suboptimal.

Management of other KD scenarios

A wide range of other complex management scenarios arising in the care of children with KD, spanning acute scenarios (such as emergency thrombolysis, calculation of coronary *Z* scores, long-term follow-up strategies and transition to adult care) were beyond the scope of the SHARE process but are covered elsewhere [3, 6]. Recurrent KD is recognized [70], but is rare and should be differentiated from the relatively common and benign re-peeling that can occur with intercurrent infection (such as upper respiratory tract infection) and is not associated with risk of CAA [71]. Secondary HLH (also referred to as macrophage activation syndrome) and Kawasaki shock syndrome, defined as the presence of hypotension and

shock requiring the initiation of volume expanders, are severe complications requiring urgent specialist input. Other treatment (non-mutually exclusive) options may include: high-dose pulsed intravenous methylprednisolone (30 mg/kg daily for at least 3 days); intravenous ciclosporin; and/or more novel therapeutic approaches including IL-1 blockade with anakinra. Whist there is a limited evidence base for these treatments, they may be helpful adjunct therapies, alongside appropriate circulating volume management, and inotropic support and other supportive measures [3].

Conclusions

The SHARE recommendations provide international, evidence-based consensus recommendations among paediatric rheumatologists for the diagnosis and treatment of KD in children, facilitating improvement and uniformity of care. A total of 17 recommendations for diagnosis and 14 for treatment were accepted with 100% agreement. In developing these recommendations, the importance of on-going and future clinical trials/studies in KD was recognized to further improve the diagnosis, treatment and monitoring into adulthood of these patients.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002;360:1197–202.

2 Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K. Epidemiological observations of Kawasaki disease in Japan, 2013–2014. Pediatr Int 2018;60:581–587.

3 McCrindle BW, Rowley AH, Newburger JW *et al*. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927–99.

4 Tulloh RM, Ramanan AV, Brogan P *et al*. Kawasaki disease. Results of the BPSU survey in UK and Ireland. Arch Dis Child 2016;101(Suppl 1):A5.

5 Tulloh RMR, Mayon-White R, Harnden A *et al*. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. Arch Dis Child 2018;doi: 10.1136/archdischild-2018-315087. [Epub ahead of print].

6 Eleftheriou D, Levin M, Shingadia D *et al*. Management of Kawasaki disease. Arch Dis Child 2014;99:74–83.

7 Shah V, Christov G, Mukasa T *et al*. Cardiovascular status after Kawasaki disease in the UK. Heart 2015;101:1646–55.

8 Suda K, Iemura M, Nishiono H *et al*. Long-term prognosis of patients with Kawasaki disease complicated by giant coronary aneurysms: a single-institution experience. Circulation 2011;123:1836–42.

9 Wulffraat NM, Vastert B. Time to share. Pediatr Rheumatol Online J 2013;11:5.

10 Enders FB, Bader-Meunier B, Baildam E *et al*. Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis 2016;76:329–340.

11 Giancane G, Ter Haar NM, Wulffraat N *et al*. Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever. Ann Rheum Dis 2015;74:635–41.

12 Groot N, de GN, Avcin T *et al*. European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative. Ann Rheum Dis 2017;76:1637–41.

13 Groot N, Graeff N, Avcin T *et al*. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Ann Rheum Dis 2017;76:1788–96.

14 Ter Haar NM, Oswald M, Jeyaratnam J *et al*. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis 2015;74:1636–44.

15 Dougados M, Betteridge N, Burmester GR *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis 2004;63:1172–6.

16 Leclercq E, Leeflang MM, van Dalen EC, Kremer LC. Validation of search filters for identifying pediatric studies in PubMed. J Pediatr 2013;162:629–34.

17 Whiting P, Rutjes AW, Reitsma JB *et al*. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med 2004;140:189–202.

18 Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. http://handbook.cochrane.org (15 November 2018, date last accessed).

19 Zhang W, Doherty M, Pascual E *et al*. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1301–11.

20 Zhang W, Doherty M, Bardin T *et al*. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312–24.

21 Delbecq AL, Van de Ven A. A group process model for problem identification and program planning. J Appl Behav Sci 1971;7:466–92.

22 Newburger JW, Takahashi M, Gerber MA *et al*. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747–71.

23 Brogan PA, Bose A, Burgner D *et al*. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. Arch Dis Child 2002;86:286–90.

24 Lee KY, Lee HS, Hong JH *et al*. High-dose intravenous immunoglobulin downregulates the activated levels of inflammatory indices except erythrocyte sedimentation rate in acute stage of Kawasaki Disease. J Trop Pediatr 2005;51:98–101.

25 Salehzadeh F, Noshin A, Jahangiri S. IVIG effects on erythrocyte sedimentation rate in children. Int J Pediatr 2014;2014:981465.

26 Benseler SM, McCrindle BW, Silverman ED *et al*. Infections and Kawasaki disease: implications for coronary artery outcome. Pediatrics 2005;116:e760–6.

27 Egami K, Muta H, Ishii M *et al*. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr 2006;149:237–40.

28 Kobayashi T, Inoue Y, Takeuchi K *et al*. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113:2606–12.

29 Sano T, Kurotobi S, Matsuzaki K *et al*. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr 2006;166:131–7.

30 Sleeper LA, Minich LL, McCrindle BM *et al*. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. J Pediatr 2011;158:831–5.

31 Davies S, Sutton N, Blackstock S *et al*. Predicting IVIG resistance in UK Kawasaki disease. Arch Dis Child 2015;100:366–8.

32 Jakob A, von KR, Horstmann J *et al*. Failure to predict high-risk Kawasaki disease patients in a population-based study cohort in Germany. Pediatr Infect Dis J 2018;37:850–5.

33 Dallaire F, Fournier A, Breton J *et al*. Marked variations in serial coronary artery diameter measures in Kawasaki disease: a new indicator of coronary involvement. J Am Soc Echocardiogr 2012;25:859–65.

34 Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. Pediatr Cardiol 2010;31:242–9.

35 McCrindle BW, Li JS, Minich LL *et al*. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 2007;116:174–9.

36 Ogata S, Tremoulet AH, Sato Y *et al*. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. Int J Cardiol 2013;168:3825–8.

37 Kobayashi T, Saji T, Otani T *et al*. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012;379:1613–20.

38 Binstadt BA, Levine JC, Nigrovic PA *et al*. Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis. Pediatrics 2005;116:e89–93.

39 Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics 1995;96:1057–61.

40 Newburger JW, Takahashi M, Burns JC *et al*. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986;315:341–7.

41 Newburger JW, Takahashi M, Beiser AS *et al*. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991;324:1633–9.

42 Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr 1997;131:888–93.

43 Amarilyo G, Koren Y, Brik SD *et al*. High-dose aspirin for Kawasaki disease: outdated myth or effective aid? Clin Exp Rheumatol 2017;35(Suppl 103):209–12.

44 Catella-Lawson F, Reilly MP, Kapoor SC *et al*. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809–17.

45 Chen S, Dong Y, Yin Y, Krucoff MW. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. Heart 2013;99:76–82.

46 Chen S, Dong Y, Kiuchi MG *et al*. Coronary artery complication in Kawasaki disease and the importance of early intervention: a systematic review and meta-analysis. JAMA Pediatr 2016;170:1156–63.

47 Tremoulet AH, Best BM, Song S *et al*. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr 2008;153:117–21.

48 Dhillon R, Newton L, Rudd PT, Hall SM. Management of Kawasaki disease in the British Isles. Arch Dis Child 1993;69:631–6.

49 Lyskina G, Bockeria O, Shirinsky O *et al*. Cardiovascular outcomes following Kawasaki disease in Moscow, Russia: a single center experience. Glob Cardiol Sci Pract 2017;2017:e201723.

50 Mossberg M, Segelmark M, Kahn R, Englund M, Mohammad AJ. Epidemiology of primary systemic vasculitis in children: a population-based study from southern Sweden. Scand J Rheumatol 2018;47:295–302.

51 Friedman KG, Gauvreau K, Hamaoka-Okamoto A *et al*. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. J Am Heart Assoc 2016;5:e003289.

52 Coon ER, Wilkes J, Bratton SL, Srivastava R. Paediatric overdiagnosis modelled by coronary abnormality trends in Kawasaki disease. Arch Dis Child 2018;103:937–41.

53 Brogan P, Levin M. Intravenous immunoglobulin plus corticosteroids prevent coronary artery abnormalities in Kawasaki disease. Evid Based Med 2013;18:217–8.

54 Furukawa T, Kishiro M, Akimoto K *et al*. Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. Arch Dis Child 2008;93:142–6.

55 Inoue Y, Okada Y, Shinohara M *et al*. A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome. J Pediatr 2006;149:336–41.

56 Okada K, Hara J, Maki I *et al*. Pulse methylprednisolone with gammaglobulin as an initial treatment for acute Kawasaki disease. Eur J Pediatr 2009;168:181–5.

57 Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. J Pediatr 2003;142:611–6.

58 Latino GA, Manlhiot C, Yeung RS, Chahal N, McCrindle BW. Macrophage activation syndrome in the acute phase of Kawasaki disease. J Pediatr Hematol Oncol 2010;32:527–31.

59 Dominguez SR, Friedman K, Seewald R *et al*. Kawasaki disease in a pediatric intensive care unit: a case-control study. Pediatrics 2008;122:e786–90.

60 Kanegaye JT, Wilder MS, Molkara D *et al*. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009;123:e783–9.

61 Burns JC, Mason WH, Hauger SB *et al*. Infliximab treatment for refractory Kawasaki syndrome. J Pediatr 2005;146:662–7.

62 Burns JC, Best BM, Mejias A *et al*. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. J Pediatr 2008;153:833–8.

63 Choueiter NF, Olson AK, Shen DD, Portman MA. Prospective open-label trial of etanercept as adjunctive therapy for Kawasaki disease. J Pediatr 2010;157:960–6.

64 Son MB, Gauvreau K, Burns JC *et al*. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. J Pediatr 2011;158:644–9.

65 Tremoulet AH, Jain S, Jaggi P *et al*. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet 2014;383:1731–8.

66 Sugahara Y, Ishii M, Muta H *et al*. Warfarin therapy for giant aneurysm prevents myocardial infarction in Kawasaki disease. Pediatr Cardiol 2008;29:398–401.

67 Weiss P, Soff GA, Halkin H, Seligsohn U. Decline of proteins C and S and factors II, VII, IX and X during the initiation of warfarin therapy. Thromb Res 1987;45:783–90.

68 Esposito S, Bianchini S, Dellepiane RM, Principi N. Vaccines and Kawasaki disease. Expert Rev Vaccines 2016;15:417–24.

69 Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol 2006;19:3–25.

70 Michie CA, Tulloch R, Davidson S. Recurrent Kawasaki disease. Br Dent J 1999;187:179.

71 Michie C, Kinsler V, Tulloh R, Davidson S. Recurrent skin peeling following Kawasaki disease. Arch Dis Child 2000;83:353–5.