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REVIEW ARTICLE

Treatment Options for Resistant Kawasaki Disease

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Abstract "Resistant" Kawasaki disease is defined by the American Heart Association as failure to respond within 36 h following the first dose of intravenous immunoglobulin. The optimal management of resistant Kawasaki disease remains uncertain, the outcomes are potentially serious, and the cost of some treatments is considerable. We review the current evidence to guide treatment of resistant Kawasaki disease. Given the relative rarity, there are few trial data, and studies tend to be small and methodologically heterogeneous, making interpretation difficult and limiting generalisability. The literature on resistant Kawasaki disease should be interpreted with reference to current expert consensus guidelines.

Key Points

The reported incidence of resistant Kawasaki disease (KD) varies widely, partly due to inconsistent definitions.

Treatment of resistant KD is important as these patients are at a greater risk of worse outcomes.

The current American Heart Association guidelines suggest that reasonable therapy for resistant KD includes a second dose of intravenous immunoglobulin, a short course of high-dose steroids, or infliximab. The level of evidence for these recommendations varies.

Other agents have been used for resistant KD, but many would require larger studies with standardised methodology to adequately assess efficacy.

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1 Introduction

Kawasaki disease (KD) is an inflammatory vasculitis of medium-sized arteries. It is the leading cause of acquired heart disease in children in industrialised settings [1, 2], and may result in long-term, potentially life-threatening cardiovascular sequelae [2–7]. First described in 1967 by Tomisaku Kawasaki, a Japanese paediatrician, the aetiology of KD is unknown [8]. The consensus is that KD results from an exaggerated immune response to one or more infectious triggers in individuals with a genetic predisposition [2, 9–19]. The management of acute KD aims

to minimise systemic and vascular inflammation to prevent cardiovascular sequelae [4, 5, 20].

Standard primary therapy consists of intravenous immunoglobulin (IVIG) and aspirin [16]. The mainstay of treatment for KD in the acute phase is high-dose IVIG, usually plus aspirin. Treatment is ideally given within the first 10 days of fever [21–23] and reduces the incidence of coronary artery lesions (CALs) from approximately 25% to 5% [16, 24, 25].

The use and dose of IVIG is supported by high-quality randomised controlled trial evidence [16, 24, 25], but its mechanism(s) of action are incompletely understood [24–27]. It is believed that IVIG has a generalised anti-inflammatory effect, reducing pro-inflammatory cytokines, neutralising bacterial superantigens and down-regulating endothelial activation [3, 19, 25, 27–33]. It is worth noting that IVIG preparations and doses vary between centres, making direct comparisons difficult [34]. Aspirin is widely used in conjunction with IVIG, but its use is controversial [35–37]. There is little evidence for its role in CAL prevention and lack of consensus on dosing regimens [3, 23, 35, 36, 38, 39].

Approximately 10–20% of patients do not respond to standard primary therapy. Patients with "resistant" KD are at increased risk of coronary artery damage and associated sequelae [40–49]. There is a lack of high-quality evidence on the optimal management of this group of patients. Infants, particularly those less than 3 months of age, are more likely to present with incomplete KD (i.e. not fulfilling full diagnostic criteria) [16, 50, 51] and are also at greater risk for resistant KD [52–54].

Here we review the current evidence for different management options for resistant KD when primary therapy has failed. Discussion of adjunctive primary therapy, such as concurrent corticosteroids, is outside the scope of this review.

2 Defining Resistant Kawasaki Disease (KD)

Approximately 80% of KD patients defervesce following initial IVIG, together with resolution of clinical signs and symptoms [22, 25]. The remainder have "resistant" KD, although various descriptive terms are used, including refractory, recrudescent, relapsing, recurrent, IVIG-resistant or IVIG non-responsive KD, and recalcitrant systemic inflammation.

The American Heart Association (AHA) defines resistant KD as "recrudescence or persistent fever at least 36 h following completion of the first dose of IVIG" [16]. However, different definitions for resistant KD have been used, both in terms of the timing of recurrence of fever (both whether the time-period begins at the start or end of the initial IVIG and how long the period is) and fever threshold, making comparisons difficult (Table 1). These differences are likely to contribute to the wide range of reported incidence (10–38.3%) of resistant KD [24, 40–42, 49, 55].

3 Second-Line Therapies for Resistant KD

A variety of interventions have been used in the management of resistant KD, including additional IVIG, corticosteroids, biologics, other immunomodulators, and statins. The aim of treatment is to reduce systemic and local vascular inflammation, although there are no robust biomarkers of efficacy, and studies therefore rely on resolution of fever, markers of systemic inflammation, and coronary artery outcomes.

Comparing different studies of second-line treatment is hampered by the variation in nomenclature and definitions for resistant KD (resulting in different thresholds for treatment). In addition, different concomitant or sequential anti-inflammatory agents can confound cause and effect analyses in these studies.

3.1 Further Doses of Intravenous Immunoglobulin

Many authorities suggest a second dose of IVIG at 2 g/kg as the first choice for resistant KD, with its putative dose-response effect [16, 41, 42]. Repeat IVIG has been demonstrated as safe and effective, but has never been tested in an adequately powered randomised trial [16, 41, 42, 56]. There may be a theoretical advantage in using a different IVIG product from that used for initial therapy, as preparations from diverse donor pools may have differing antibody repertoires and/or different amounts and composition and other anti-inflammatory factors [34, 57]. The recommended dose of IVIG for treatment of resistant KD varies, with some suggesting a lower dose of 1 g/kg [41, 42], especially in settings where IVIG is expensive and may not be widely available [58, 59]. An argument against using a second dose of IVIG is that this strategy may delay the initiation of other potentially more potent and effective second-line therapies.

Comparative studies investigating the efficacy of other therapies outlined in the following sections usually compare outcomes with a second dose of IVIG.

3.2 Corticosteroids

The use of steroids as treatment for resistant KD is reasonably well-established, despite the long and chequered history of steroid therapy in KD overall [60–64]. Steroids are relatively inexpensive and widely available [59, 65].

Table 1 Differing definitions for "resistant KD" with accompanying resistance rates

Citation	Specific term(s) used	Definition of "resistant KD"	Reported "resistance" rates
American Heart Association [16]	IVIG resistance	"recrudescent or persistent fever > 36 h after the end of their IVIG infusion"	10–20%
Japanese Society of Pediatric Cardiology and Cardiac Surgery [22]	IVIG-resistant KD	"persistent fever after 48 h of starting IVIG"	20%
Teraguchi et al. [66]	IVIG-resistant KD	"no resolution of fever (> 38 °C) within 36 h after completion of the initial IVIG or no decrease in serum level of C-reactive protein (CRP) by 50% compared with the initial value before IVIG if the temperature was between 37.5 and 38 °C"	17%
Song et al. [98]	Refractory KD	"persistence or reappearance of fever (≥ 38 °C) at least 36 h after the last of more than 2 doses of IVIG therapy and high-dose ASA +/− IVMP pulse therapy (30 mg/ kg/dose/day)"	N/A
Suzuki et al. [114]	Refractory KD	"persistence or recurrence of fever (temp ≥ 37.5 °C) at the end of the second intravenous immunoglobulin (2 g/kg) following the initial one"	8.5%
Tremoulet et al. [113]	IVIG-resistance	"persistent or recrudescent fever (temp ≥ 38 °C) at least 36 h, but not longer than 7 days, after completion of the first IVIG infusion (2 g/kg)"	15–23.6%
Ogata et al. [59]	IVIG-resistant KD	"no clinical response at 36–48 h after initial IVIG treatment" where response was defined by "resolution of fever (< 37.5 °C) and a fall in CRP of more than 50% within 36–48 h after initial IVIG treatment"	16%
Furukawa et al. [58]	IVIG-resistant patients	"persistence or recurrence of KD-associated fever 24–36 h after IVIG administration"	13.3%
Tremoulet et al. [49]	IVIG resistance	"persistent or recrudescent fever (≥ 38 °C) at least 48 h but not longer than 7 days after completion of first IVIG infusion (2 g/kg)"	38.3%
Durongpisitkul et al. [163]	Immunoglobulin failure	"fever that lasted more than 48 h after the initial IVIG treatment or had a return of fever within 2 days to 1 week of initial treatment"	11.6%
Wallace et al., 2000 [55]	IVIG treatment failure	"return of fever and one or more of the initial symptoms that led to the diagnosis of KD within 2–7 days of treatment with IVIG"	23%
Burns et al., 1998 [41]	Persistent or recrudescent fever	Persistent fever: "temperature ≥ 38.3 °C during the 48 h period after IVIG infusion that persisted beyond 48 h after the completion of the infusion"	13.2%
		Recrudescent fever: "temperature < 38.3°C for 48 h after completion of IVIG infusion, followed by temperature ≥ 38.3 °C"	
		Treatment failure: "development of new coronary artery abnormalities after IVIG treatment in a child with a normal baseline echocardiogram"	
Sundel et al., 1993 [42]	Inadequate response to IVIG	"fever (> 38 °C), with or without other signs of mucocutaneous inflammation" with recurrence within at least 72 h following completion of initial IVIG to 4 days of completion	10%

ASA acetylsalicylic acid (aspirin), *CRP* C-reactive protein, *IVMP* intravenous methylprednisolone, *IVIG* intravenous immunoglobulin, *KD* Kawasaki disease, *N/A* not applicable

The controversies regarding the role of steroids as primary adjunctive therapy will not be discussed here.

Table 2 summarises studies investigating the role of steroids in resistant KD [58, 59, 63, 66–70]. It is difficult to draw robust conclusions because of the small numbers in individual studies, heterogeneity in patient groups as well as different treatment preparations and treatment regimens. Overall, the evidence suggests that the use of steroids results in an improvement in inflammatory markers, rapid defervescence and possibly reduction in the incidence of CALs [69, 71–74]. The AHA recommend that a short course of high-dose steroids would be a reasonable alternative to a second dose of IVIG, or a reasonable treatment after failure to respond following two doses of IVIG [16]. The alternative recommendation by the AHA for resistant KD is that in addition to a second dose of IVIG with

Table 2 Summary of studies using steroids for resistant KD

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Teraguchi et al. [66]; prospective study, Japan ($n = 237$); 146 M:91 F; 1 month–10 years	IVIG (2 g/kg) plus ASA (30 mg/kg/day)	"IVIG-resistant KD": no resolution of fever (> 38 °C) within 36 h after completion of initial IVIG; or no decrease in CRP by 50% compared with initial value before IVIG if temperature was 37.5–38 °C ($n = 41$)	IVMP (30 mg/kg/day) for 3 days[a,b] ($n = 14$)	Fever duration 9.5 (7–18) days with recrudescence in 50%	Reduction of CRP by 81.6%	36% incidence of CALs measured at 30 days post-diagnosis	Bloody stool ($n = 1$). 7/14 (50%) had persistent fever/recrudescence of fever resulting in further therapy
			2nd dose of IVIG ($n = 27$)	Fever duration 10 (6–14) days with recrudescence in 22.2%	Reduction of CRP by 49.2%	26% incidence of CALs measured at 30 days post-diagnosis	6/27 (22%) had recrudescence of fever resulting in further therapy
Kobayashi et al. [67]; retrospective review, Japan ($n = 359$); 206 M:168 F; 2–4 years	IVIG (total 2 g/kg[c]) plus ASA (30 mg/kg/day)[d]	"Failed to respond to initial IVIG": persistent fever that lasted for > 24 h (non-response to initial IVIG) or recrudescent fever associated with KD symptoms after an afebrile period (relapse)	2nd IVIG (1 g/kg or 2 g/kg) ($n = 140$)	37.5% still febrile within 24–48 h after initiation of therapy	Baseline CRP measured, but no repeat measurements done	28.7% CALs until 1 month; 15.4% CALs at 1 month[e]	Higher incidence of persistent fever or recrudescent fever in IVIG group > PNL > IVIG + PNL. Day of illness of rescue therapy was later in IVIG group
			IV PNL (2 mg/kg/day in 3 divided doses) until fever resolved[f] ($n = 80$)	31.9% still febrile within 24–48 h after initiation of therapy		30.6% until 1 month; 16.7% CALs at 1 month[e]	
			2nd IVIG plus PNL[f] ($n = 154$)	11.9% still febrile within 24–48 h after initiation of therapy		15.9% CALs until 1 month; 6.6% CALs at 1 month	
Jibiki et al. [68]; prospective study, Japan ($n = 50$); mean age 25.8 months and 28.5 months in control and study groups, respectively	IVIG (1 g/kg/day for 2 days) plus ASA (30 mg/kg/day)	"IVIG non-response": fever lasting > 24 h or recrudescent fever associated with KD symptoms ($n = 38$)	2nd IVIG ($n = 9$)	Median duration 13 days fever (10–28 days)	CRP 10.1 ± 5.7 mg/dL	9/13 (69%) CALs[e] within 1 month, NS; 4/13 (30.8%) after 1 month, NS	Note not all patients who were labelled with "IVIG non-response" received additional therapy. No serious AEs observed. Combined outcomes in control group documented despite differences in regimens received. 4/13 (31%) required 3rd-line therapy in control group. 1/6 (17%) developed recrudescent fever in study group
			2nd IVIG plus 3rd-line PNL ($n = 2$)				
			2nd-line PNL then 3rd-line IVIG ($n = 2$)				
			2nd IVIG (1 g/kg for 2 days) with concurrent IV PNL 2 mg/kg/day in 3 divided doses[g] ($n = 6$)	Median duration 10 days fever (8–23 days); 6/6 (100%) defervescence within 24 h of initiation	CRP 10.9 ± 4.4 mg/dL	1/6 (16.7%) CALs[e] within 1 month, NS; 0/6 (0%) after 1 month, NS	

Table 2 continued

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Ogata et al. [59]; prospective multicentre cohort, Japan ($n = 164$); 2 months–10 years	IVIG (2 g/kg) plus ASA (30 mg/kg/day)	"IVIG-resistant KD": did not have resolution of fever (< 37.5 °C) and a fall in CRP of > 50% within 36–48 h after initial IVIG ($n = 27$)	IVMP (30 mg/kg/day) for 3 days ($n = 13$)	Duration of fever 1 ± 1.3 days	CRP 4.3 ± 1.7 mg/dL, NS	0/13 (0%) with CAAs, NS	Self-resolving bradycardia ($n = 2$)
			2nd IVIG (2 g/kg) ($n = 14$)	Duration of fever 3 ± 2.4 days	CRP 5.9 ± 4.0 mg/dL, NS	3/14 (21.4%) with CAAs, NS	IVIG more expensive than IVMP
Furukawa et al. [58]; retrospective multicentre cohort study, Japan ($n = 411$); 243 M:168 F; 1–141 months of age	IVIG (2 g/kg) plus ASA (30 mg/kg/day)[d]	"IVIG resistance": persistent or recurrent fever 36 h after the initial IVIG treatment ($n = 63$)	IVMP 30 mg/kg/day for 3 days[b,h] ($n = 44$)	34/44 (77%) responded; fever resolved by day 1	CRP only measured at baseline	0% CAAs in those who responded to 2nd-line therapy (IVMP or IVIG)	In all patients who received IVMP (including as 3rd-line therapy), self-limiting AEs reported: hypertension (10%), hypothermia (6%), sinus bradycardia (6%), transient fibular nerve paralysis ($n = 1$). In those who received 3rd-line therapy, 5/10 (50%) IVMP non-responders and 2/7 (29%) IVIG non-responders developed CAAs
			IVIG (1–2 g/kg) ($n = 19$)	12/19 (63%) responded			
Miura et al. [69]; randomised controlled study, Japan ($n = 169$)	IVIG (2 g/kg)	"Refractory KD": persistent or recurrent fever (temp > 37.5 °C) 48 h after initial IVIG ($n = 22$)	IVMP (30 mg/kg/day) for 3 days[b] ($n = 11$)	Superior antipyretic until day 3		3/11 (27%) with CALs	Most common side effects reported: hypertension (91%), NS; transient sinus bradycardia (82%); hyperglycaemia (55%)
			IVIG (2 g/kg) ($n = 11$)	Superior antipyretic on day 2		2/11 (18%) with CALs	Most common side effects reported: hypertension (55%), NS
Hashino et al. [70]; prospective study, Japan ($n = 262$); 2 months–10.6 years	IVIG (2 g/kg) plus ASA (30 mg/kg/day); then 2nd-line IVIG (1 g/kg)	"IVIG-resistant": did not achieve resolution of fever (< 37.5 °C) and a fall in CRP by 50% within 48 h after *initial* IVIG treatment ($n = 35$)	3rd-line IVIG (1 g/kg) ($n = 8$)	Duration of fever 15.4 ± 2.9 days	12.7 ± 4.3 mg/dL	5/8 (63%) CALs including 2/8 (25%) with CAAs at baseline, NS	IVIG more expensive compared with IVMP
			3rd-line IVMP 20 mg/kg ($n = 9$)	Duration of fever 11.2 ± 4.3 days	1.29 ± 0.53 mg/dL	7/9 (78%) had CALs including 4/9 (44%) with CAAs, 3/9 (33%) with transient dilatation, NS	

Table 2 continued

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Wright et al. [63]; case series, USA ($n = 4$); 2 M:2 F; 3–27 months	IVIG (2 g/kg) plus ASA (80–100 mg/kg/day) and ibuprofen; then 2nd-line IVIG (1 g/kg)[i]	"Non-responders": persistent or recrudescent fever at 48–72 h after treatment with IVIG and high doses of ASA	3rd-line IVMP (30 mg/kg/day) for 1–3 days	2/4 (50%) defervesced after 1 dose of IVMP	Not measured	3/4 (75%) CAAs during acute phase with resolution in 2/3 (67%) at most recent follow-up	No AEs reported

AEs adverse effects, *ASA* acetylsalicylic acid (aspirin), *CAAs* coronary artery aneurysms, *CALs* coronary artery lesions, *CRP* C-reactive protein, *g/kg* grams per kilo (of body weight), *IV* intravenous, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *KD* Kawasaki disease, *M:F* male to female ratio, *mg/dL* milligrams per decilitre, *mg/kg/day* milligrams per kilo per day (of body weight), *NS* not significant, *PNL* prednisolone, *U/kg/h* units per kilo (of body weight) per hour

[a]IVMP then switched to oral PNL (1 mg/kg/day) and tapered off within 1 week

[b]Administered concurrently with heparin (10–20 U/kg/h)

[c]IVIG total of 2 g/kg given as single dose or alternatively as 2 doses of 1 g/kg daily for 2 consecutive days

[d]ASA dose then decreased to 5 mg/kg/dose after normalisation of CRP levels

[e]Exclusion of patients with CALs prior to commencement of 1st-line rescue therapy

[f]IVMP then switched to oral PNL until CRP normalised (< 0.5 mg/dL), where dose tapered over 15 days in 5-day steps (2 mg/kg/day for 5 days, 1 mg/kg/day for 5 days, and 0.5 mg/kg/day for 5 days)

[g]IV PNL switched upon resolution of fever and/or CRP < 0.5 mg/dL where PNL then tapered over 15 days in 5 day steps (2 mg/kg/day for 5 days, 1 mg/kg/day for 5 days, 0.5 mg/kg/day for 5 days)

[h]PNL (1 mg/kg/day) administered and tapered over 7 days

[i]ASA continued at high dose until afebrile for 48 h

aspirin, a long duration of steroids could be started [16]. However, there is no clear evidence on the optimal dosing, optimal formulation, timing and duration of corticosteroids [58, 75].

3.3 Tumour Necrosis Factor Alpha Inhibitors

During the acute phase of KD, it is suggested that levels of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α), are elevated, increasing the risk of CALs and resistance to IVIG [29, 33, 61, 76–81]. TNF-α is an inducible pro-inflammatory cytokine produced by T cells and macrophages [22]. Excessive production of TNF-α is associated with chronic inflammation observed in many immune-modulated inflammatory disorders [82, 83]. A Cochrane review is underway reviewing the role of TNF inhibition in both acute and resistant KD [84].

TNF-α inhibitors include infliximab, etanercept and pentoxifylline. Infliximab acts specifically on TNF-α, whilst etanercept is a soluble TNF receptor with a broader action on both TNF-α and lymphotoxins [85]. Pentoxifylline, a methylxanthine derivative, blocks the production of TNF-α and leukotrienes (inflammatory mediators that are part of the arachidonic acid pathway) from monocytes and macrophages [87–89].

Infliximab is a chimeric IgG1 monoclonal antibody with potent anti-inflammatory effects arising from blockade of TNF-α activity [91–92]. Levels of TNF-α and other pro-inflammatory mediators decrease after infliximab in patients with resistant KD who respond, but remain elevated in those who do not [33, 93, 94]. The use of infliximab has also been studied in primary intensification regimens in acute KD [95].

Table 3 outlines studies reporting the use of infliximab in resistant KD [90, 93, 97–100]. The heterogeneity of the populations between Japanese and non-Japanese, as well as differing therapies received pre-infliximab makes the data difficult to compare. Overall, it appears that infliximab causes a rapid defervescence in fever, resulting in a shorter length of hospital stay, and is relatively well tolerated. In the largest randomised trial using infliximab as adjunctive primary therapy with IVIG, there was no evidence that infliximab reduced the rate of KD resistance [95]. Infliximab does not appear to prevent CAL formation nor reverse existing lesions [93, 96, 99–101]. However, relatively small numbers of patients received infliximab in these studies. Also worth noting, half of the studies outlined in Table 3 refer to the use of infliximab as third- or even fourth-line therapy, i.e. following at least a second dose of IVIG.

The AHA recommendation is that infliximab may be substituted for a second dose of IVIG, or steroids, in resistant KD [16]. A multicentre, prospective, randomised study in Shanghai determining the effect of infliximab on development of CALs in resistant KD has been completed, but the results have not yet been published [102].

There is little evidence for the use of etanercept or pentoxifylline in both acute and resistant KD aside from limited case reports [88, 89, 103, 104]. The effect of etanercept on arteritis has previously been investigated in mouse models, where it is most effective in suppressing inflammatory cytokines and reducing the extent of vasculitis [85]. Case reports of anti-TNF-α agents in resistant KD are summarised in Table 6 and the electronic supplementary material (ESM, Table 1).

3.4 Cyclosporin A

Genetic variants in the inositol-trisphosphate 3-kinase C (ITPKC) gene have been implicated in heightened susceptibility to KD and resistance to IVIG [106–107]. ITKPC is also involved in inflammasome activation, a component of the innate immune response that results in interleukin-1 (IL-1) production [109–110]. Defects in this pathway lead to increased inflammation [108].

Cyclosporin A (CsA), a calcineurin inhibitor, suppresses activity of T cells by targeting the Ca^{2+}/NFAT signalling, thus dampening the inflammatory response [105, 111]. A trial in Japan is underway comparing the use of CsA in combination with conventional therapy in acute treatment of KD in high-risk patients [112].

In resistant KD, the limited evidence for CsA predominately comes from case series where it is used as a third-line agent [114–115]. Three case series are outlined in Table 4. These demonstrate that in the majority of patients, fever defervesced within 1–5 days of CsA introduction. The AHA recommend consideration of cyclosporin in patients with refractory KD where a second dose of IVIG, infliximab or a course of steroids has failed [16]. Case reports of where cyclosporin is used in resistant KD are summarised in the ESM.

3.5 Methotrexate

There are a few studies which describe methotrexate use in resistant KD. In patients with rheumatoid arthritis, methotrexate administration leads to a reduction in pro-inflammatory cytokines [116, 117]. Its mechanism of action is incompletely understood, but is thought to be mediated by the intracellular accumulation of polyglutamate metabolites [118]. It is commonly used in inflammatory conditions such as rheumatoid arthritis and both small and large vessel vasculitides as a steroid-sparing immunomodulatory agent. However, the pharmacodynamics of low-dose methotrexate and its putative mechanism of action are such that it is unlikely to have significant

Table 3 Summary of the evidence for the use of infliximab for resistant KD

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Youn et al. [96]; randomised study, Korea ($n = 43$); 28 M:15 F; 3 months–13 years	IVIG (2 g/kg) plus ASA (80–100 mg/kg/day)	"IVIG resistant": indication for retreatment was persistent or recrudescent fever with temp $\geq$ 38 °C beyond 36–48 h after initial IVIG ($n = 43$)	IVIG (2 g/kg) ($n = 32$)	Median fever 17 h (1–154 h); 21/32 (65.6%) "responded"	CRP normalised approx. 3 days post-treatment	4/32 (12.5%) developed CALs	5/32 (15.6%) experienced an infusion reaction. 1/11 (9.1%) developed a skin rash during IFX infusion. 10 days compared with 8 days hospitalisation for IVIG and IFX, respectively. 11/32 (34%) patients required additional therapy in the IVIG group, compared with 1/11 (9%) requiring additional therapy in the IFX group
			IFX (5 mg/kg)[a] ($n = 11$)	Median fever 6 h (1–30 h); 10/11 (90.9%) "responded"	CRP normalised approx. 3 days post-treatment	1/11 (9.1%) developed CALs	
Sonoda et al. [90]; retrospective single-institution only, Japan ($n = 76$); 51 M:25 F	IVIG (1–2 g/kg) then 2nd dose of IVIG (0.5–2 g/kg) plus ASA (30–50 mg/kg/day) ($n = 59$) and flurbiprofen (3–5 mg/kg/day) ($n = 17$)	"Non-responders to additional IVIG": as classified within 24–36 h: (1) temp $\geq$ 37.5 °C; (2) FCs of white cell count, neutrophil count or CRP were positive before and after the additional IVIG therapy; (3) age $\geq$ 1 year with prior BCG vaccination; and (4) exclusion of other infectious diseases and heart failure	3rd-line IFX (5 mg/kg) ($n = 76$)	62/76 (81.6%) defervesced within 2 days of IFX		11/70 (15.7%) CA dilatation; 3/70 (4.3%) CAAs 1 month post-disease onset	All resolved spontaneously; drug eruption and liver dysfunction ($n = 7$); infections ($n = 4$); arthritis ($n = 8$). 6/76 (7.9%) required PE rescue therapy (post-IFX) due to refractory fever and lack of improvements with FC in leukocyte count, neutrophil count, or CRP
Mori et al. [97]; open-label trial, Japan ($n = 20$); 10 M:10 F; 1.9–10.5 years	IVIG (2–4 g/kg) plus ASA ($n = 12$), flurbiprofen ($n = 8$), ulinastatin ($n = 2$)	"Refractory to IVIG": persisting or re-emerging fever > 38 °C and positive FCs of CRP, white cell counts at 48 h after IVIG infusion; within 10 days of disease onset	2nd- or 3rd-line IFX (5 mg/kg) ($n = 20$)	18/20 (90%) rapid defervescence within 24 h of IFX	Normalisation of CRP within 2–3 days of IFX	1/20 (5%) with CAL at 30 days, which resolved within 1 year	18/20 (90%) of patients experienced clinical improvements in symptoms within 3 days of IFX. No serious AEs were recorded during or after IFX treatment. 2/20 (10%) of patients received rescue therapy with PE for persistent high fevers

Table 3 continued

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Son et al. [101]; 2-centre, retrospective study, USA ($n = 106$); 9–57 months	IVIG (2 g/kg) plus ASA (80–100 mg/kg/day)[b]	"IVIG-resistant KD": temp $\geq$ 38 °C beyond 36 h after 1st IVIG completion	IFX 5 mg/kg ($n = 20$)	Median 8 days fever	Measured at baseline, but not later	7/20 (35%) with CAAs within 1st 6 weeks of illness, NS	6/31 (19%) transient hepatomegaly in those who received at least 1 dose of IFX. 3/20 (15%) in the IFX group received subsequent treatment. Hospitalisation duration was shorter in IFX group: 5.5 days compared with 6 days
			2nd dose IVIG ($n = 86$)	Median 10 days fever		29/86 (34%) with CAAs within 1st 6 weeks of illness, NS	Rates of AEs did not differ significantly between the 2 groups. Tachypnoea ($n = 2$), tachycardia ($n = 1$), hypotension ($n = 1$). 21/86 (24%) of patients in the IVIG received subsequent treatment, of whom 12/86 (14%) in the IVIG group were given 3rd-line treatment with IFX
Song et al. [98]; retrospective reviews of patients, Korea ($n = 16$); 13 M:3 F; 0.2–5.8 years	Greater than 2 doses of IVIG (2 g/kg/dose) ± 1–4 doses of IVMP (30 mg/kg) ± PO steroids	"Refractory KD": persistence or reappearance of fever ($\geq$ 38 °C) at least 36 h after the last of more than 2 doses of IVIG therapy and high-dose ASA ± IVMP pulse therapy (30 mg/kg/dose/day)	3rd-line IFX (5–6.6 mg/kg) ($n = 16$) ± further oral steroids ($n = 5$)	13/16 (81%) had "complete" response", i.e. cessation of fever within 12 h of IFX infusion	14/16 (88%) decreased CRP within 72 h of IFX	15/16 (94%) had CAAs at baseline; at follow-up, 4/9 (44%) with CAAs normalised; 3/13 (23%) had persistent dilatation	Acute hepatitis associated with calculous cholecystitis ($n = 1$)

Table 3 continued

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Hirono et al. [93]; retrospective study ($n = 43$)/ 11 total study patients; 6 M:5 F	Greater than 3 doses of IVIG (total 3–6 mg/kg) ($n = 10$), 1–3 doses of IVMP ($n = 8$); ulinastatin ($n = 2$)	"Non-responders": patients whose fever did not subside within 48 h of the 1st IVIG treatment (2 g/kg) but responded to the 2nd IVIG "Refractory KD": persistence or recrudescence of fever at least 48 h after the end of the multiple administrations of IVIG or IVMP infusion ($n = 11$)	4th-line: 2 doses of IFX (5 mg/kg/dose) ($n = 1$); 1 dose of IFX (5 mg/kg/dose) ($n = 10$)	8/11 (73%) cessation of fever within 24–48 h after IFX	CRP decreased in refractory KD, but increased further in non-responders	4/11 (36%) had CALs at baseline; these persisted after IFX	Nil documented AEs. 1 patient required treatment with cyclophosphamide A
Burns et al. [99]; multicentre, RCT, USA ($n = 24$)	IVIG (2 g/kg) plus ASA (80–100 mg/kg/day for 4 doses)[c]	"IVIG-resistant KD": persistent or recrudescent fever ($\geq$ 38 °C) between 48 h and 7 days after completion of the initial IVIG infusion	IFX 5 mg/kg[c] ($n = 12$)	11/12 (92%) defervescence < 24 h	Median CRP 6.2 (2.7–35.8) mg/dL, NS	Median z score max 3.5 (0.3–14.3)	Transient hepatomegaly more common in IFX group, but unclear whether this and other AEs were related to KD or treatment
			2nd dose of IVIG (2 g/kg) ($n = 12$)	8/12 (67%) defervescence < 24 h; 4/12 (33%) persistent or recrudescence	Median CRP 4.8 (< 0.3–23.9) mg/dL, NS	Median z score max 2.2 (0.9–7.7)	

Table 3 continued

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Burns et al. [100]; retrospective case series, USA ($n = 17$); 11 M:6 F; 0.12–13.1 years	Greater than 2 doses of IVIG (2 g/kg) plus ASA (80–100 mg/kg/day) plus 1–3 doses of IVMP (30 mg/kg/dose)	"Refractory KD": persistence or recrudescence of fever (≥ 38 °C) at least 48 h after the end of the IVIG infusion. Treatment for persistent or recrudescent fever ($n = 14$), or fever plus arthritis ($n = 15$), or persistent, severe arthritis without fever ($n = 1$)	3rd- or 4th-line IFX (5 mg/kg) ($n = 15$)	13/16 (81.3%) abrupt defervescence; 2/16 (13%) recurrence of fever	In those who had CRP measured, all had decrease in CRP within 48 h of IFX	12/17 (71%) had CALs at baseline; 4/12 resolved, 3/12 had CALs and 5/12 had ectasia	No infusion reactions. 1 child died at home on day 70 from cardiopulmonary arrest. No autopsy was performed. Prior to receiving IFX, patients were persistently or intermittently febrile for 8–53 days. Resistance to 3rd-line therapy required PE ($n = 1$); re-admission requiring pulse IVMP ($n = 1$)
			3rd-line IFX (10 mg/kg) ($n = 2$)				Dramatic and permanent resolution of arthritis within 12 h of infusion

AEs adverse effects, *ASA* acetylsalicylic acid (aspirin), *CA* coronary artery, *CAAs* coronary artery aneurysms, *CALs* coronary artery lesions, *CRP* C-reactive protein, *FC* fractional change (ratio of post- to pre-therapy laboratory data, i.e. if FC is greater than 0, it is evaluated as positive, and it is negative if smaller than 0), *g/kg* grams per kilo (of body weight), *IFX* infliximab, *IV* intravenous, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *KD* Kawasaki disease, *M:F* male to female ratio, *mg/dL* milligrams per decilitre, *mg/kg/day* milligrams per kilo per day (of body weight), *NS* not (statistically) significant (i.e. p value > 0.05), *PE* plasma exchange, *PO* per oral, *RCT* randomised controlled trial

[a]Given with concurrent paracetamol and chlorpheniramine

[b]Dose of ASA tapered when afebrile for 48 h, to 5 mg/kg/day

[c]Dose of ASA reduced at 1 week to 3–5 mg/kg/day

[d]Pre-treatment paracetamol (15 mg/kg) and diphenhydramine (1 mg/kg PO or IV)

Table 4 Summary of evidence of CsA for resistant KD

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Tremoulet et al. [113]; observational case series, USA ($n = 10$); 4 M:6 F; 2 months–11 years	At least 2 doses of IVIG (2 g/kg) plus ASA (80–100 mg/kg/day); plus IVMP (30 mg/kg/day) ($n = 3$) or IFX (5 mg/kg/day) ($n = 4$) or IVIG plus IFX ($n = 4$)	"IVIG-resistance": persistent or recrudescent fever $\geq$ 38 °C at least 36 h, but no longer than 7 days, after completion of the 1st IVIG infusion (2 g/kg)	3rd-line PO/IV CsA[a] ($n = 9$) or tacrolimus ($n = 1$) for 2 weeks–2 months	6/7 (86%) defervescence of fever within 24 h of CsA	9/10 (90%) decreased CRP 48 h after CsA or tacrolimus	4/10 (40%) had CAAs within the 1st 6 weeks of illness; all 4 patients had subsequent improvement	AEs which occurred following administration of a calcineurin inhibitor included hypomagnesaemia ($n = 2$), transient hirsutism ($n = 2$), flare of arthritis ($n = 1$), otitis media ($n = 1$)
Suzuki et al. [114]; prospective case series, Japan ($n = 28$); 20 M:8 F; 4–93 days of age	2 doses of IVIG (2 g/kg) plus ASA (30–50 mg/kg/day)	"Refractory KD": persistence or recurrence of fever (temp $\geq$ 37.5 °C) at the end of the 2nd IVIG (2 g/kg) following the initial dose ($n = 30$)	3rd-line oral CsA (4–8 mg/kg/day) for 8–50 days ($n = 28$)	Afebrile within 1–13 days (median 2 days); 18/28 (64.3%) defervescence within 3 days	Decreased CRP within 2 days of CsA	3/28 (10.7%) had CAAs; 1/28 (3.6%) had a giant CAA	Hyperkalaemia was observed in 10/28 (35.7%) patients. 4/28 (14.3%) patients who received CsA required re-treatment with a 3rd dose of IVIG
			3rd-line IVIG (2 g/kg) ($n = 2$)			0/2 (0%) had CAAs	
Hamada et al. [115]; prospective case series, Japan ($n = 19$); 11 M:8 F	2 doses of IVIG (2 g/kg) plus ASA (30–50 mg/kg/day)	"Resistant to (initial) IVIG": remained febrile $\geq$ 37.5 °C at the end of 2nd IVIG infusion	3rd-line PO CsA (initial dose 4 mg/kg/day)[b] for 2 weeks	14/19 (73.7%) became afebrile within 5 days; 5/19 (26%) had persistent fever	Only baseline CRP levels collected	3/19 had CALs, of which 1/3 was considered a "responder" to CsA	"Responders" to CsA were defined as those who became afebrile within 5 days. 2/5 (40%) non-responders to CsA developed CALs. 4 received a 3rd dose of IVIG

AEs adverse effects, *ASA* acetylsalicylic acid (aspirin), *CAAs* coronary artery aneurysms, *CALs* coronary artery lesions, *CRP* C-reactive protein, *CsA* cyclosporin A, *g/kg* grams per kilo (of body weight), *IFX* infliximab, *IV* intravenous, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *KD* Kawasaki disease, *M:F* male to female ratio, *mg/kg/day* milligrams per kilo per day (of body weight), *ng/mL* nanograms per millilitre, *PO* per oral

[a]Doses of cyclosporin titrated to (trough) target level 50–150 ng/mL after 3 doses; with max level 600 ng/mL

[b]Doses of cyclosporin adjusted to 4–8 mg/kg/day to maintain trough level 60–200 ng/mL

acute anti-inflammatory activity [119]. Not surprisingly, the AHA does not make any specific recommendations relating to methotrexate for resistant KD [16]. Case series relating to the use of methotrexate in resistant KD are summarised in Table 5 [120, 121]. Further case reports using methotrexate are further described in Table 6 and the ESM.

3.6 Other Agents

There are numerous reports of the use of other agents, including other biologics, cytotoxic agents, ulinastatin, and plasma exchange, in resistant KD. These agents should be reserved for highly refractory patients who have failed other therapies. There is also increasing interest in the role of statins in the long-term management of patients with KD to minimise ongoing vascular inflammation and atherosclerosis [123–125]. Further prospective studies are needed to assess the role, efficacy, and long-term safety of these agents in the management of resistant KD.

Anakinra is a recombinant IL-1 receptor antagonist that inhibits both IL-1α and IL-1β [126, 127]. It has been used in other childhood inflammatory conditions [126, 129–130]. The role of IL-1 in inflammation, and more specifically, in causing coronary artery inflammation, has been demonstrated in both laboratory and animal studies [30, 131, 132]. Notably, the elevated levels of IL-1 that have been observed during the acute phase of KD may be associated with a higher risk of resistance to IVIG, as well as an increased risk of CALs [21, 28, 31, 131, 134–135]. There are currently studies underway investigating the role of anakinra in both acute primary treatment and resistant KD [136, 137]. The only documented use of anakinra in resistant KD is outlined in case reports (summarised in Table 6) [139–140].

Rituximab is a chimeric monoclonal antibody specifically directed against CD20 surface antigen present on B cells [141, 142]. It is increasingly used in other systemic vasculitides in children and is well-tolerated [82, 143, 144]. During the acute phase of KD, B cells are activated,

Table 5 Summary of the evidence for the use of MTX for resistant KD

Citation; study type, country (*n*); M:F ratio; age range	Initial management	Definition of "resistance" (*n*)	Regimen	Effect on fever	Effect on laboratory features	Effect on CAAs	AEs/outcomes
Lee et al. [120]; case-series, Korea ($n = 17$); 4 months–8 years	IVIG (2 g/kg) plus ASA (100 mg/kg/day) ± additional doses of IVIG (1–5 g/kg)	"IVIG-resistant": temp ≥ 37.5 °C persisted or recurred 48 h after initial treatment	PO MTX (10 mg/BSA) once weekly until CRP normalised	4/17 (24%) patients required 2nd or 3rd dose of MTX for fever response	Median CRP decreased 1 week after 1st dose of MTX	13/17 (76.5%) had CALs at baseline; unclear effect on CALs after MTX treatment	No AEs observed. MTX was discontinued in all 17 patients without recurrence of fever. Median cumulative dose of MTX was 20 mg/BSA (range 10–50 mg/BSA)
Ahn and Kim, [121]; case series; Korea ($n = 4$); 1 M:3 F; 8 months–8 years	IVIG (2 g/kg) plus ASA (100 mg/kg/day); ± additional doses of IVIG (2–6 g/kg)[a] with varying courses of IV dexa (0.3 mg/kg)	"IVIG resistant": temp > 37.5 °C persisted or recurred 48 h after initial treatment	PO MTX (10 mg/BSA) once weekly until echocardiogram showed no further progression of CALs	Defervesced within 48/24 h ($n = 3$); defervesced after 2nd dose of MTX ($n = 1$)	CRP normalised 1 month after MTX	2/4 (50%) had CAAs, with no progression following MTX	No AEs observed. Total duration of therapy with MTX ranged from 3 weeks to 7 months

AEs adverse effects, *ASA* acetylsalicylic acid (aspirin), *BSA* body surface area, *CAAs* coronary artery aneurysms, *CALs* coronary artery lesions, *CRP* C-reactive protein, *dexa* dexamethasone, *g/kg* grams per kilo (of body weight), *IV* intravenous, *IVIG* intravenous immunoglobulin, *KD* Kawasaki disease, *M:F* male to female ratio, *mg/kg/day* milligrams per kilo per day (of body weight), *MTX* methotrexate, *PO* per oral

[a]IVIG was administered via regimen of 400 mg/kg/day for 5 days

Table 6 Case reports involving less commonly used agents for resistant KD

Citation, country	Age/sex	Indication(s) for escalating therapy	Therapies used including dose/duration						Reported AEs	Outcome, comments and limitations
			IVIG	ASA	Steroids	IFX	Other novel agents	Other supplementary therapy (including PE/ECMO)		
Sanchez-Manubens et al. [140], Spain	3-year-old F	Recurrence of fever, with associated increase in CRP and platelet count with progressive anaemia	✔ IVIG 2 g/kg (× 3 doses)	✔ ASA (100 mg/kg/day)	✔ IVMP (30 mg/kg) × 4 pulses (?duration) then PO PNL (0.5 mg/kg/day)	X	✔ ANK 2 mg/kg daily S/C for 14 days	X	No side effects or complications during or after use of ANK	No relapses upon cessation of ANK. Echo normalised (initial findings of mild mitral and tricuspid regurgitation, but never CAAs)
Shafferman et al. [138], USA	11-week-old F	KD complicated by MAS; worsening of coronary lesions and rise in inflammatory markers	✔ IVIG 2 g/kg (× 3 doses)	✔ ASA (?dose/?duration) then onto low-dose ASA	✔ IVMP (30 mg/kg) × 3 doses then IVMP (4 mg/kg/dose) TDS-?duration, tapered to PO PNL (1.5 mg/kg/day) over 10 days	✔ IFX 5 mg/kg, single dose	✔ ANK 3 mg/kg BD for 3 days then increased to 3 mg/kg TDS (after 14 days) then decreased to 4 mg/kg BD for 5 months	Propranolol	No infections	Improvement in CALs with persistent CAL at 8-month follow-up echo; administration of ANK associated with improved rash, reduction in inflamed appearance, ↓ CRP, ↑ platelets
de Magalhães et al. [164] Brazil	3-month-old F	Persistent fevers and inflammatory markers with progressive changes on echo including pericardial effusion and CAAs	✔ IVIG (2 g/kg) × 2 doses	✔ ASA (80 mg/kg/day) for 18 days, then ASA 5 mg/kg/day	✔ IVMP (30 mg/kg) for 4 days; PO PNL (2 mg/kg/day), ?duration	X	✔ S/C etanercept (0.8 mg/kg/week), ?duration; PO MTX (0.5 mg/kg/week), ?duration	✔ Broad spectrum ABx (cefepime and vancomycin), anticoagulant-enoxaparin, clopidogrel (3.75 mg/kg/day), alprostadil		Delayed diagnosis at day 14 of illness. Received 1st dose of IVIG at day 14 (not within usual timeframe of 10 days). Clinical remission by day 85 of illness

Table 6 continued

Citation, country	Age/sex	Indication(s) for escalating therapy	Therapies used including dose/duration						Reported AEs	Outcome, comments and limitations
			IVIG	ASA	Steroids	IFX	Other novel agents	Other supplementary therapy (including PE/ECMO)		
Cohen et al. [139], Netherlands	2-year-old M	Respiratory and circulatory failure requiring intubation/ECMO, return of clinical signs	✔ IVIG (2 g/kg) × 2 doses, plus 3rd dose (?amount)	✔ ASA (?dose/?duration)	✔ IVMP × 3 courses (?amount); low-dose PNL	X	✔ ANK 1 mg/kg S/C for 7 days, ANK 1 mg/kg for 10 days, later ANK (?dose) continued for 6 weeks	✔ ABx, warfarin; ECMO		Defervescence after initial ANK, but then recurrence of fever. ECMO required for cardiorespiratory failure. Initial day 9 echo demonstrated nil CAAs, but myocarditis; repeat echo demonstrated dilatation of coronary arteries; but repeat day 53 echo demonstrated giant CAAs. Follow-up 6-month echo showed normalisation of CAAs
Sauvaget et al. [145], France	6-year-old M	Coronary artery changes including development of LAD aneurysm, recurrence of fever, arthritic signs, increase in inflammatory markers	✔ IVIG (2 g/kg) × 2 doses and 3rd dose of IVIG (?amount) and regular supplementation of IVIG (?dose/frequency)	✔ ASA (80 mg/kg/day), ?whether dosage weaned, ceased after 2 months	✔ IV PNL (2 mg/kg/day) for 7 days then weaned to 1–2 mg/kg/day, ceased after 2 months.	X	✔ Rituximab (15 mg/kg/day) for 6 days	✔ Warfarin	Nil AEs with rituximab	Defervescence of fever after rituximab, i.e. day 22 of illness. Improvement on echo on 2/12 follow-up including normalisation of aneurysm. "Regular supplementation" of IVIG (?dose/?frequency) on discharge
Oishi et al. [149], Japan	1-month-old F	Persistent fever, development and progression of CAAs	✔ IVIG (1–2 g/kg), total 4 doses	✔ ASA (30 mg/kg/day), ?duration	✔ IVMP (15 mg/kg/day) for 3 days, PO PNL (1 mg/kg/day), ?duration	✔ IFX (5 mg/kg) infusion	✔ Ulinastatin	✔ Oral aciclovir, cefotaxime	Transient urticaria during IFX infusion	Defervescence of fever within 24 h of IFX with accompanying normalisation of CRP, albumin, LFTs. Follow-up echo 7 months after onset of illness demonstrated normalisation of CAAs and dilatation

Table 6 continued

Citation, country	Age/sex	Indication(s) for escalating therapy	Therapies used including dose/duration						Reported AEs	Outcome, comments and limitations
			IVIG	ASA	Steroids	IFX	Other novel agents	Other supplementary therapy (including PE/ECMO)		
Iino et al. [150], Japan	84 days old (gestational age 31 weeks) M	Persistent fever, progression of clinical signs of KD	✔ IVIG (1.5 g/kg/day) then additional 4 doses of IVIG 1 g/kg/day (1 g/kg/dose)	X	X	X	✔ Ulinastatin (15,000 units/kg/day)	X		Follow-up 4 months after onset of illness demonstrated premature baby with suspected incomplete KD, diagnosed on day 9 of fever. Bilateral coronary aneurysms on echo following discharge
Wallace et al. [55], USA	10-month-old M	Ongoing fever or clinical signs	✔ IVIG (2 g/kg) × 3 doses	✔ ASA (80–100 mg/kg/day) for 2 weeks then ASA 5 mg/kg/day	✔ 4 courses of IVMP (?duration) slowly decreased to 2 mg/kg/day over 2 weeks	X	✔ Cyclophosphamide 2 mg/kg/day (?duration)	X	No short-term AEs reported with cyclophosphamide	Echo normal on follow-up 1.6 years post-illness. No return of fever, conjunctivitis, mucous membrane changes or increase in CRP
	2.7-year-old M	Ongoing fever or clinical signs	✔ IVIG (2 g/kg) × 3 doses	✔ ASA (80–100 mg/kg/day) for 2 weeks then ASA 5 mg/kg/day	✔ 2 courses of IVMP (?duration) slowly decreased to 2 mg/kg/day over 2 weeks	X	✔ Cyclophosphamide 2 mg/kg/day (?duration)	X	No short-term AEs reported with cyclophosphamide	Echo normal on follow-up at 30 days post-illness. No return of fever, conjunctivitis, mucous membrane changes or increase in CRP

? Unknown (information not provided within publication), *ABx* antibiotics, *AEs* adverse effects, *ANK* anakinra, *ASA* acetylsalicylic acid (aspirin), *BD* twice daily, *CAAs* coronary artery aneurysms, *CALs* coronary artery lesions, *CRP* C-reactive protein, *echo* echocardiogram, *ECMO* extracorporeal membrane oxygenation, *F* female, *g/kg* grams per kilo (of body weight), *IFX* infliximab, *IV* intravenous, *IVIG* intravenous immunoglobulin, *IVMP* intravenous methylprednisolone, *KD* Kawasaki disease, *LAD* left anterior descending (coronary artery), *LFTs* liver function tests, *M* male, *MAS* macrophage activation syndrome, *mg/kg/day* milligrams per kilo per day (of body weight), *MTX* methotrexate, *PE* plasma exchange, *PNL* prednisolone, *PO* per oral, *S/C* subcutaneous, *TDS* three times daily

✔ administered

X not administered

↓ decreased

↑ increased

leading to a cytotoxic antibody response, which affects endothelial cells [82]. The use of rituximab in resistant KD has been described in one case report (Table 6) [145].

Ulinastatin is a urinary trypsin inhibitor, which by inhibiting neutrophil elastase may have a dose-dependent effect on endothelial cell injury [15, 147–148]. Its efficacy is questionable, but it is used widely in Japan in both primary and adjunctive management of KD [15, 148]. Its use has been described in two case reports in combination with other agents in resistant KD (Table 6) [149, 150].

The use of plasma exchange in severe resistant KD has been described in case series, with a focus on presumed effects on reducing plasma cytokine levels and reducing CALs [152–156]. All documented case series use plasma exchange as third- or fourth-line therapy for resistant KD [90, 97, 100].

In addition to their lipid-lowering effects, the anti-inflammatory and anti-oxidant properties of statins have long been recognised [122, 125]. In KD, the proposed utility of statins is in reducing endothelial dysfunction and minimising atherosclerosis; however, there are currently insufficient data to inform timing, duration of therapy, and potential long-term side effects [123, 124, 157, 158]. There are currently studies underway investigating the safety and efficacy of atorvastatin in children with KD with persistent CALs [159, 160].

4 Limitations

There are important limitations to the data on the management of resistant KD, which make comparison between treatment options difficult. Importantly, the definition of "resistant KD" differs markedly between studies, with differences in the total number of doses or total cumulative doses of IVIG, the number of hours between the end of the initial IVIG and fever recrudescence, the anatomical site of temperature measurement, the threshold used to define fever, and whether additional features are part of the definition of resistance. Differing thresholds for treatment are a major potential source of bias.

Almost all studies are retrospective, with inherent limitations. These include issues regarding the certainty and timing of the initial KD diagnosis (particularly important if there is poor response to initial therapy). This may be compounded by variation in dosing and administration of initial treatment regimens, and differences in concomitant anti-inflammatory and/or other agents during primary therapy.

CALs and aneurysms are the most important clinical outcome. Importantly, it should be noted that some studies use the Japanese Ministry of Health (JMoH) criteria (based on internal diameter of the coronary arteries), whereas others use the AHA definition (based on coronary artery z scores). This can lead to issues of under-estimation and under-diagnosis of coronary lesions, as coronary artery z scores are considered more sensitive [161, 162]. Of note, some studies excluded patients with coronary artery abnormalities (prior to administration of their second- or third-line therapy) in their analysis. In addition, interpretation of echocardiograms may not be blinded, and these are potentially subject to bias.

Finally, the natural history of KD is that fever usually resolves after 2–3 weeks without specific treatment [16]. Therefore, defervescence after this time period may be falsely attributed to an intervention, when it may reflect the spontaneous resolution of the acute phase of KD.

5 Conclusions

Despite over 5 decades of research, the aetiological trigger and pathogenesis of KD remain poorly understood. It is clear that abnormal inflammation during the acute phase of KD increases the risk of CALs and cardiovascular sequelae. Management of resistant KD has thus focussed on downregulation of the host inflammatory response, aiming to reduce the risk of formation of new CAL and to halt progression of existing lesions.

The current evidence to guide treatment of resistant KD is of moderate to low quality, which is unfortunate given the potential severity of adverse outcomes of both KD itself and the treatments, and the cost of some proposed agents. As suggested by the AHA, [16], it seems reasonable to consider additional IVIG and/or steroids if the initial IVIG does not result in sustained defervescence of fever.

The relative infrequency of resistant KD means a prospective trial is unlikely to be sufficiently powered to provide an evidence base for appropriate treatment. The published data differ substantially between patient groups and treatment approaches, making comparison problematic and robust conclusions difficult. Expert consensus (such as the AHA guidelines) [16] together with accumulating published clinical experience will continue to guide management of resistant KD.

Compliance with Ethical Standards

Conflict of interest Linny Kimly Phuong, Jonathan Akikusa, Peter Gowdie, Nigel Curtis and David Burgner declare that they have no conflicts of interest.

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