Infection and Immunity Course Special Edition

Kawasaki disease fact check: Myths, misconceptions, and mysteries

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Article type: Annotation, IIC Special Edition

Contributors' Statement Page

Dr Butters drafted the initial manuscript, reviewed and revised the manuscript.

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Prof Curtis reviewed and revised the manuscript.

Funding Source: No funding was secured for this study.

Conflict of Interest: The authors have no conflicts of interest to disclose.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/jpc.15101](https://doi.org/10.1111/jpc.15101)

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Funding Source: No funding was secured for this study.

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Abstract

Kawasaki disease (KD) is an important cause of childhood vasculitis and a common cause of acquired heart disease in children worldwide. The emergence of Paediatric Multisystem Inflammatory Syndrome-Temporally Associated with SARS-CoV-2 (PIMS-TS), a KD-like hyperinflammatory syndrome, and the recent death of Dr Tomisaku Kawasaki, makes this a timely review. Although KD was described by Dr Kawasaki over 50 years ago, there is still no specific diagnostic test and the aetiology remains elusive. This article summarises the latest evidence, highlights important myths and misconceptions, and discusses some of the mysteries that surround this disease.

Keywords: Infectious Diseases, General Paediatrics, Kawasaki disease, Intravenous immunoglobulin, COVID-19.

Key points

1. Kawasaki disease (KD) likely results from the interaction of genetic factors and one or more infectious triggers.
2. PIMS-TS is a KD-like hyperinflammatory syndrome recently recognised in children in countries with a high prevalence of COVID-19 and appears distinct from KD.
3. KD is diagnosed by clinical criteria, together with supplementary investigations when full criteria are not met. Diagnosis of a concurrent infection does not exclude KD.
4. Children with KD should receive IVIG as soon as practicable. There is a lack of evidence to guide further management of children who do not respond to IVIG, and expert advice should be sought.

Introduction

On the 5th of June 2020, Dr Tomisaku Kawasaki died after a career dedicated to the illness he described in 1967 as ‘acute febrile mucocutaneous lymph node syndrome with specific desquamation of the fingers and toes’.^{1,2} He reportedly kept early case notes in a file labelled “GOK”, which he later revealed stood for “God Only Knows”.² Over the subsequent 50 years, there have been many advances in the treatment of Kawasaki disease (KD), but there is still no diagnostic test and the aetiology and pathogenesis remain incompletely understood. This article aims to summarise the latest evidence, highlight areas of uncertainty and debunk some myths.

KD is a vasculitis of predominantly medium and small-sized vessels, capable of causing coronary artery aneurysms (CAA). KD has been reported worldwide but is most common in Asia, particularly Japan (annual incidence 359 per 100 000 children <4 yo) and children of Asian or Japanese descent living elsewhere.^{3,4} In Australia, the incidence varies by ethnic group, but overall is at least 9.34 per 100 000 children <5 yo.⁵

1. Kawasaki disease is caused by a single aetiological agent, possibly SARS-COV-2: *Probably incorrect*

Kawasaki disease (KD) has been linked with variable veracity to a broad range of infectious agents as well as environmental exposures, including carpet shampoo, genetic variants and meteorological patterns.³ The aetiology of KD remains unknown and it is likely that KD results from the interaction of one or more infectious agents and genetic factors.

Epidemiological evidence strongly suggests an infectious trigger for KD: the peak incidence is at an age when children are most at risk of infection (6 months to 5 years) and in winter months, when most childhood infections occur. Numerous single microbial aetiologies have been suggested, but none have been substantiated. Some studies have mapped geotemporal clusters consistent with human transmission and by overlaying wind patterns with KD time series there is an apparent association with the Asia-North Pacific wind pattern, and a possible airborne pathogen.⁶

Epidemiological, genome-wide, and candidate gene association studies highlight a genetic contribution to KD susceptibility. Associated variants include those at loci *FCGR2A*, *BLK* and *ITPKC* involved in immune modulation and vascular remodelling. For example, *ITPKC* is implicated in both innate and T cell immune regulation and linked to susceptibility and CAA formation in both Asian and non-Asian populations.⁷

Paediatric Multisystem Inflammatory Syndrome-Temporally Associated with SARS-CoV-2 (PIMS-TS), also known as Multisystem Inflammatory Syndrome in Children (MIS-C) is a hyperinflammatory disorder recently described in countries with high rates of community transmission of SARS-CoV-2. This syndrome shares some clinical features of KD and with other conditions of immune dysregulation and hyperinflammation, such as macrophage activation syndrome and toxic shock syndrome (TSS). Although PIMS-TS appears to be distinct from KD, occurring in older children with prominent gastrointestinal symptoms, myocardial dysfunction and higher C-reactive protein, CAA or coronary artery dilatation has been reported in 14%.⁸

2. The diagnosis can be made after four days of fever: *Correct*

Clinical criteria are central to the diagnosis of KD as no laboratory parameter in isolation has adequate sensitivity or specificity to 'rule in' or 'rule out' KD. The clinical features occur sequentially over one to two weeks. As cervical lymphadenopathy is the least common clinical feature, and as thrombocytosis and desquamation occur in the sub-acute phase, these are less useful diagnostically.^{3,7}

Recent American Heart Association (AHA) guidelines suggest that in the presence of four or more clinical features the diagnosis can now be made after four days of fever. In children with less than four clinical findings, a diagnosis of incomplete KD is made in the presence of raised inflammatory markers and supporting echocardiographic and/or laboratory findings (*Table 1*). Children <12 months and >5 years are more likely to have incomplete KD. The diagnosis is often delayed in children with culture-negative shock, infants < 6 months with prolonged fever and irritability and those with sterile retropharyngeal or parapharyngeal phlegmon.³

3. Children with KD should have echocardiography done as part of initial assessment:

Correct

Coronary artery dilatation typically begins with changes in the proximal segment. In the majority developing CAA, some abnormality is detectable on echocardiography done within the first 10 days following fever onset.³ Japanese guidelines define CAA by absolute internal vessel diameter or dilatation relative to an adjacent segment. Where height and weight are available, a Z-score may be calculated as a standard deviation of units from the mean based on body surface area. This allows for differences in patient size and avoids underdiagnosis of CAA.³

The current AHA guidelines recommend echocardiography as soon as the diagnosis is suspected, as CAA may develop rapidly and require aggressive management.³ Treatment should not be delayed if echocardiography is not immediately available or is initially normal. In patients with uncomplicated KD, an echocardiogram should be repeated within two weeks and again within 6 weeks of treatment. In patients with coronary artery dilatation, echocardiogram should be done at least twice per week until changes have stabilised.³

4. A viral infection makes KD unlikely: *Incorrect*

A positive respiratory viral PCR, including for SARS-CoV-2, or presence of ‘viral’ symptoms at the time of presentation does not exclude the diagnosis of KD. In a study of 192 children with KD, ninety-three (41.9%) had a positive respiratory viral PCR, which did not correlate

with gastrointestinal or respiratory symptoms. A positive PCR for respiratory viruses, such as adenovirus, may represent asymptomatic shedding or latency in the upper airway.⁹

5. The shocked child may have Kawasaki disease: *Correct*

KD shock syndrome (KDSS) occurs in around 7% of KD and is characterised by haemodynamic instability and end-organ dysfunction requiring fluid resuscitation, inotropes or vasopressors.¹⁰ It has features of both KD and TSS, suggesting a superantigen may be involved in the shared pathogenesis. The mechanism of shock is likely multifactorial, including capillary leak, decrease in peripheral vascular resistance, and myocardial dysfunction due to myocarditis and/or ischaemia. KDSS is a more severe phenotype, with greater inflammation and higher rates of consumptive coagulopathy, IVIG resistance, coronary artery dilatation and persisting myocardial dysfunction; prompt recognition, intensive care support and initiation of IVIG are essential.^{3,10}

6. IVIG resistance is defined as persistent or recrudescent fever 36 hrs after completion of initial infusion of IVIG: *Correct*

As soon as practicable, patients should receive 2 g/kg of IVIG as a single infusion over 10 to 12 hours, with careful monitoring for fluid overload and anaphylaxis, although the latter is rare. In randomised control trials, IVIG reduces the incidence of coronary artery lesions from 25% to ~5%. IVIG has a broad anti-inflammatory effect, including decreasing endothelial activation and increasing regulatory T-cell activity.^{3,7}

Patients who are febrile ≥ 36 hours post-completion of IVIG are considered IVIG-resistant. IVIG-resistance occurs in 20% of patients and is associated with higher risk of CAA.^{4,11} Unfortunately, clinical trial data do not provide compelling evidence for one particular treatment pathway (*Figure 1*).^{3,7,11} Further IVIG and/or corticosteroids are widely used in these patients. Biologic agents include anti-TNF (infliximab, etanercept) and anti-IL1 (anakinra, canakinumab). While anakinra has shown some promise, experience is limited to case-series.¹¹

7. All children should receive high-dose aspirin in addition to IVIG: *Incorrect*

While aspirin (ASA) has been almost universally used in treatment of KD since its first description, it has not been shown in randomised control trials to prevent CAA at any dose.¹² Some centres give high-dose ASA for anti-inflammatory effect during the acute illness, at doses ranging from 30-100 mg/kg/day and for variable duration. All children should receive at least low-dose aspirin (3-5 mg/kg/day) as an anti-platelet agent until follow-up echocardiography confirms normal coronary arteries.³ Children with CAA should continue ASA and/or thromboprophylaxis under specialist supervision. Aspirin carries a small risk of Reye syndrome, especially in association with influenza or varicella infection, however this has never been reported with doses ≤ 5 mg/kg/day. Importantly, nonsteroidal anti-inflammatory drugs should be avoided while taking ASA due to potential antagonism of anti-platelet effect.^{3,7}

8. All children with KD have a potential lifelong risk of cardiovascular disease: *Correct*

Children with KD are at risk of cardiovascular morbidity including valvular regurgitation, coronary artery stenosis, coronary artery thrombosis and myocardial ischaemia. The risk is reliably stratified from echocardiography based on maximal coronary artery Z-score. Follow-up of the original Japanese cohort suggests that those without any coronary artery changes have a risk of cardiovascular disease which may be similar to the general population, although definitive longitudinal data are lacking. Regardless, all patients with KD should manage traditional cardiovascular risk factors including engaging in regular physical activity, maintaining a healthy diet and body mass index, and avoiding smoking. It is reasonable for all patients who have had KD to have their blood pressure and lipid profile checked in mid-childhood.^{3,7}

Conclusion

While recognising areas of uncertainty, clinicians should have a high index of suspicion for KD, particularly in those outside the typical age range of 1-5 years. Treatment with IVIG and aspirin remains the mainstay of treatment. Given the limited evidence, children with IVIG-resistance should be discussed with a specialist team to guide further treatment. Follow-up and long-term cardiovascular morbidity are determined by presence and severity of coronary artery dilatation.

Multiple choice questions

1. In the epidemiology of Kawasaki disease, which one of the following is true:
  - a) Kawasaki disease is most common in children of low socioeconomic background
  - b) Children of Asian ancestry have low incidence if raised outside of Asia
  - c) In the Northern Hemisphere, is more common in the winter months
  - d) Is more common in children aged < 6 months old
  - e) Immunisation is associated with an increased risk
2. Echocardiography in children with Kawasaki disease should be done:
  - a) As a key diagnostic test
  - b) Only in children with persistently raised inflammatory markers
  - c) Two weeks after diagnosis and then yearly for five years
  - d) Only in children meeting all diagnostic criteria
  - e) After diagnosis then in two weeks and again before six weeks. More frequent echocardiography is recommended in children with initial coronary artery changes
3. IVIG-resistance is:
  - a) Defined as persistence or recrudescence of fever 36 hrs after completion of initial infusion of IVIG
  - b) Characterised by increased erythrocyte sedimentation rate post-completion of IVIG
  - c) Predicted using scoring methods validated across different populations
  - d) Best treated with high-dose aspirin and/or plasma exchange
  - e) Not associated with increased rates of coronary artery abnormalities

Multiple choice questions: Answers

1. In the epidemiology of Kawasaki disease, which one of the following is true:

- a) Kawasaki disease is most common in children of low socioeconomic background- Incorrect. There is no known association with socioeconomic status.
- b) Children of Asian ancestry have low incidence if raised outside of Asia- Incorrect. Children of Asian descent have similar risk to children who are born and raised in Asia.
- c) **In the Northern Hemisphere, is more common in the winter months- Correct.** KD is more common in winter months, at least in the Northern Hemisphere, supporting an infectious aetiology.
- d) Is more common in children aged < 6 months old – Incorrect. KD is most common in children aged 1 to 5 years old.
- e) Immunisation is associated with an increased risk- Incorrect. There is no evidence to support a causal association or increased risk.

2. Echocardiography in children with Kawasaki disease should be done:

- a) As a key diagnostic test- Incorrect. Echocardiography may be normal during the initial phase of illness.
- b) Only in children with persistently raised inflammatory markers- Incorrect. All children with KD or atypical KD require follow-up echocardiography.
- c) Two weeks after diagnosis and then yearly for five years- Incorrect. In children with uncomplicated KD, an echocardiogram should be repeated within two weeks and again within 6 weeks of treatment.
- d) Only in children meeting all diagnostic criteria- Incorrect. Patients with atypical KD or high clinical suspicion of KD also require echocardiography.
- e) **After diagnosis then in two weeks and again before six weeks-Correct.** More frequent echocardiography is recommended in children with initial coronary artery changes.

3. IVIG-resistance is:

- a) **Defined as persistence or recrudescence of fever 36 hrs after completion of initial infusion of IVIG- Correct.** This is the most recent definition of IVIG-resistance or IVIG non-response.
- b) Characterised by increased erythrocyte sedimentation rate post-completion of IVIG- Incorrect. Erythrocyte sedimentation rate may be falsely elevated after IVIG.
- c) Predicted using scoring methods validated across different populations. Incorrect. While some scoring systems for IVIG-resistance have been validated in Asian populations, these scoring systems are insufficiently accurate to be used in other populations.
- d) Best treated with high-dose aspirin and/or plasma exchange- Incorrect. There is no clinical trial data to support either of these treatments over other second-line treatment options.
- e) Not associated with increased rates of coronary artery abnormalities- Incorrect. IVIG-resistance is associated with higher rates of coronary artery abnormalities, including formation of aneurysms.

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Table 1 Features of Kawasaki disease.³	
Diagnostic criteria	Supportive laboratory findings
Unexplained fever ≥ 5 days (fever $> 38.5^{\circ}\text{C}$)	Raised inflammatory markers: ESR ≥ 40 mm/hr and/or CRP ≥ 30 mg/L
Changes of the oral mucosa: erythema and/or cracking of the lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa	Sterile pyuria: ≥ 10 white cells/high powered field
Conjunctival injection: bilateral, limbal sparing, and without exudate	Anaemia: normochromic, normocytic anaemia for age
Peripheral changes: Erythema and oedema in acute phase and/or periungual desquamation in subacute phase	Thrombocytosis: platelets $\geq 450 \times 10^9/\text{L}$
Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like	Elevated white cells: $\geq 15 \times 10^9/\text{L}$
Cervical lymphadenopathy: ≥ 1.5 cm diameter, usually unilateral	Elevated ALT
	Low albumin: <30 g/L
ALT alanine aminotransferase, CRP C-reactive protein, ESR erythrocyte sedimentation rate	

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Tables and figures

Figure 1 Treatment options after IVIG non-response.¹¹

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Title:

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Date:

2020-08-08

Citation:

Butters, C., Curtis, N. & Burgner, D. P. (2020). Kawasaki disease fact check: Myths, misconceptions and mysteries. JOURNAL OF PAEDIATRICS AND CHILD HEALTH, 56 (9), pp.1343-1345. <https://doi.org/10.1111/jpc.15101>.

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