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Multisystem Inflammatory Syndrome in Children and Kawasaki Disease: Parallels in Pathogenesis and Treatment

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Abstract

Purpose of Review Since it first appeared, multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) has been compared to Kawasaki disease (KD). Although there were early parallels between MIS-C and KD, key differences emerged over time. Here, we aim to compare the pathogenesis, clinical presentation, treatment, and outcomes of MIS-C and KD.

Recent Findings In this article, we review and compare MIS-C and KD, highlighting differentiating features. We discuss the epidemiological and immunological factors along with clinical and laboratory features which discern MIS-C from KD. We also compare treatment and our understanding of long-term outcomes.

Summary Though parallels exist between MIS-C and KD, distinguishing the two is important for clinical management of patients, counseling about natural history, and determining long-term monitoring. While both MIS-C and KD are characterized by profound inflammation and inflammatory vasculopathy, further study is needed to determine whether they are distinct immunopathogenic disorders.

Keywords Kawasaki disease · Multisystem inflammatory syndrome in children · Coronary artery aneurysm · Intravenous immunoglobulin

Introduction

Kawasaki disease (KD), one of the most common vasculitides of childhood, was initially described by Dr. Tomisaku Kawasaki in 1967 [1]. Since that time, the medical community's understanding of the condition has advanced, leading to classification criteria based on clinical findings and the widespread recognition of KD by pediatric providers. Recently, reports emerged of an inflammatory vasculopathy resembling KD affecting children who had prior infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The earliest descriptions of affected children appeared in April 2020, occurring shortly after the World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19) a global pandemic in March 2020 [3]. Initial nomenclature varied in the literature, but ultimately, the term multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 has been used to describe the condition and will be used here for the purpose of this review.

Immediately, providers encountering MIS-C recognized the shared clinical features between MIS-C and KD, which both commonly include mucocutaneous and cardiac manifestations in the setting of systemic inflammation. For this reason, early management of MIS-C was largely extrapolated from experiences with treating KD. The significant overlap in clinical features between MIS-C and KD can make distinguishing the two challenging. In both conditions, timely diagnosis and treatment are critical, underscoring the necessity of recognizing key similarities and differences between the two diagnoses. Since the first descriptions of MIS-C, distinguishing features have emerged to aid the provider in

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differentiating MIS-C from KD. Here, we aim to provide a review of MIS-C and KD, comparing their pathogenesis, clinical presentation, treatment, and outcomes with particular attention to highlighting their differing features to help the practitioner in discerning between the two conditions.

Pathogenesis

Kawasaki Disease

The cause of KD remains unknown; however, multiple different hypotheses have been explored. The principal etiologic framework is KD results from an underlying genetic susceptibility and exaggerated immune response to an environmental trigger. There has been long-standing suspicion of an infectious trigger based on observed seasonality patterns in diagnosis as well as clustering of cases in communities, though no single pathogen has been consistently identified. Other environmental triggers such as aeroallergens, toxins, pollutants, and medications have also been of interest, similarly, with no single factor identified [4]. Genetic predisposition has also been explored as a contributing factor, and there are several genes that have been consistently linked to KD susceptibility, coronary artery aneurysm formation, and treatment resistance [4]. One of the stronger associations with KD susceptibility and risk of coronary artery involvement is a single nucleotide polymorphism (SNP) in the inositol 1,4,5-triphosphate 3-kinase C (*ITPKC*) gene (involved in calcium mobilization and activation of the NLRP3 inflammasome) [5]. Given that KD is considered a polygenic disorder, additional susceptibility loci will likely be identified and provide further insight into disease pathogenesis.

Both the innate and adaptive immune systems are involved in the hyperinflammatory response in KD. Elevated levels of interleukin (IL)-1 primarily through activation of the NLRP3 inflammasome are observed which leads to the production of other proinflammatory cytokines [6]. Inflammatory cytokines involved in the hyperinflammatory process in the acute phase of KD include IL-1, IL-2, IL-6, IL-8, interferon (IFN)-α, and tumor necrosis factor (TNF)-α [7]. IL-1 activates coronary artery endothelial cells and results in increased production of IL-6, IL-8, and IL-17 [6, 8].

The adaptive immune system has also been implicated in the pathogenesis of KD. Recently, there has been interest in dysregulated T-cell activation which may contribute to the degree of severity of KD [9]. B-cells are also involved in pathogenesis, demonstrated by elevation of B-cell activating factor (BAFF) in patients with KD which normalizes after treatment [4, 10, 11]. IgA plasma cells have been found in the vessel walls of the coronary arteries in children with KD [11] with one recent mouse model study demonstrating coronary artery involvement was dependent on IgA [12]. The mediators of coronary artery involvement and inflammation remain of great interest, and other implicated mediators in coronary artery pathogenesis include CD8 + T-cells and matrix metalloproteinase (MMP)-9 [8, 13].

MIS-C

Outside of the observation that MIS-C typically develops 2–6 weeks after infection with COVID-19, other underlying risk factors remain largely unknown. Gene sequencing in small MIS-C cohorts has identified potential genetic variants affecting the inflammasome, interferon signaling, the complement system, and adaptive immunity, but these findings need to be validated in larger cohorts [14, 15]. For some individuals, MIS-C may indicate an underlying disorder of immune dysregulation due to a genetic risk factor that is incompletely penetrant. Defects in *SOCS1*, *XIAP*, and *CYBB* have been found among children with MIS-C and are associated with impaired negative regulation of interferon and inflammatory signaling [16•, 17].

Though the pathophysiology of MIS-C has not been fully elucidated, the innate immune system is highly involved, and many different pro-inflammatory cytokines have been implicated. Elevated levels of IL-1β, IL-6, IL-8, IL-10, IL-17, TNF-α, and IFN-γ have been observed in MIS-C patients [18]. Complement activation is also likely involved in the microangiopathy observed in MIS-C; children with MIS-C have elevated levels of soluble C5b-9 as compared to healthy controls [19, 20].

Studies have also investigated the role of B-cells in MIS-C pathogenesis, finding that IgG and IgA autoantibodies occur in MIS-C [21, 22]. Additionally, there is increased expression of FcγR1 on neutrophils and monocytes in patients with MIS-C [22]. One study examining immune profiling of children with MIS-C found increased activation of CX3CR1 + CD8 + T-cells (a mediator of vascular endothelial inflammation) in patients with MIS-C. Patients with this immunological signature had requirement for vasoactive support, elevated D-dimer, and decreased platelets [23]. The proportion of these activated cells in MIS-C patients decreases with clinical improvement, further suggesting a role in their pathogenesis. This is reflective of the other immunological abnormalities which have been observed to resolve at follow-up after a child's recovery from acute illness [18].

There have been few studies comparing the underlying immune dysregulation between MIS-C and KD. One study comparing immunological profiles of children with the two conditions found IL-17A was significantly higher in children with KD as compared to those with MIS-C [24]. The levels of IFN-γ were higher in severe MIS-C presentations as compared to KD or milder MIS-C cases [25•]. Studies have also

compared autoantibody profiles, but further investigation is needed to draw definitive conclusions [24].

Clinical Features

Kawasaki Disease

KD typically affects children younger than 5 years old, with an average age of 3 years [26]. It can also affect infants, and the index of suspicion should remain especially high in this age group, because they are less likely to exhibit all the characteristic clinical features. One large North American study found that 18% of children with KD were under 12 months old [27]. If untreated, KD is typically a triphasic illness with clinical symptoms resolving by an average of 12 days. The first phase is characterized by high fever, mucocutaneous involvement including conjunctivitis and rash, cervical lymphadenopathy, and peripheral extremity changes. The second phase, called the subacute phase, can involve desquamation of the hands and feet. Importantly, this is the phase when coronary artery aneurysms (CAA), the most important determinant of long-term morbidity, typically develop. The final phase, the convalescent phase, is usually asymptomatic [28].

The diagnosis of KD is solely based on clinical criteria. The child should have the mandatory criterion of fever for 5 days and at least 4 of the following criteria: changes in peripheral extremities or the perineal area; polymorphous exanthema; bilateral conjunctival injection; changes of the lips and oral cavity, injection of oral and pharyngeal mucosa; cervical lymphadenopathy (Table 1). Though laboratory studies are not part of diagnostic criteria, supportive findings include elevation in inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Platelet counts may be normal at the time of diagnosis but are typically elevated by the second week of illness.

Coronary artery involvement is the most common cardiac manifestation of KD (Fig. 1). Small CAAs (defined by z-score ≥ 2.5–5) are most common at diagnosis and are observed in 15–20% of children, though 43% of infants younger than 6 months old may have dilatation or aneurysm at baseline [29•, 30]. In KD shock syndrome (KDSS), impaired left ventricular function is commonly observed, but coronary artery abnormalities are often concurrently present. Reports of KDSS are more rare, but larger North American studies have suggested it occurs in 5% of children with KD [31]. If there is suspicion for KD, an echocardiogram is indicated. If a diagnosis of KD is made, then a follow-up echocardiogram is obtained during the subacute phase given this is the time when CAA are most often observed.

Table 1 Comparison of Kawasaki disease classification criteria and multisystem inflammatory syndrome in children case definition

Kawasaki disease (modified from European League against Rheumatism/Paediatric Rheumatology European Society classification criteria)		
Fever persisting for at least 5 days (mandatory criterion) plus 4 of the following: 1.Changes in peripheral extremities or perineal area 2. Polymorphous exanthema 3. Bilateral conjunctival injection 4. Changes of lips and oral cavity: injection of oral and pharyngeal mucosa 5. Cervical lymphadenopathy		
In presence of coronary artery involvement and fever, fewer than 4 of the remaining 5 criteria are sufficient.		
Multisystem inflammatory syndrome in children (modified from CDC case definition)		
Any illness in a person aged less than 21 years old: 1. The clinical AND the laboratory criteria OR 2. The clinical criteria AND epidemiologic linkage criteria		
Clinical criteria:	Laboratory criteria:	Epidemiology linkage:
Subjective or objective fever	Detection of SARS-CoV-2 RNA or specific antigen in testing up to 60 days prior to or during hospitalization	Close contact with a confirmed or probable case of COVID-19 in 60 days prior to hospitalization
Need for hospitalization	Detection of SARS-CoV-2 specific antibodies associated with current illness or hospitalization	
Two organ manifestations •Cardiac involvement •Mucocutaneous involvement •Shock •Gastrointestinal involvement •Hematologic involvement		

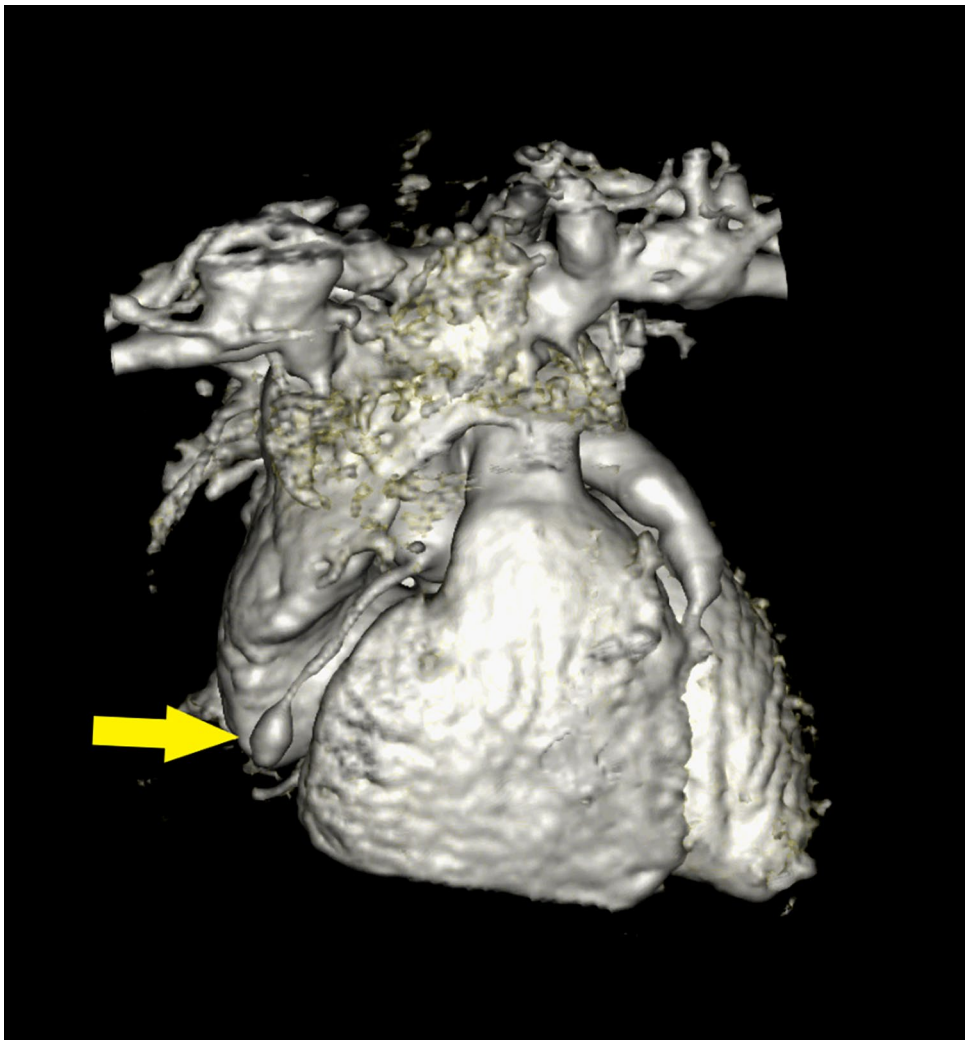

Fig. 1 This is a 3D reconstruction of a cardiac MRI contrast enhanced angiogram. The right coronary artery has a distal saccular aneurysm (arrow)

MIS-C

In contrast to KD, MIS-C predominantly affects older children with reported ages in cohorts typically 6 years old and above, and teenagers are also not uncommonly affected [32–34, 35••]. MIS-C has no diagnostic criteria; however, several case definitions have been developed since the condition was first recognized in 2020 including the development of the case definition by the Centers for Disease Control and Prevention (CDC) commonly used in the USA [36]. The initial CDC case definition included individuals under 21 years old presenting with fever for 24 h or more, laboratory evidence of inflammation, severe illness requiring hospitalization with multisystem organ (2 or more) involvement, no alternative diagnosis, and evidence of current or recent SARS-CoV-2 infection or recent exposure to a person with COVID-19 within the previous 4 weeks. The CDC case definition has undergone modifications as experience has evolved with changes made to fever duration, laboratory requirements, and lengthening the time of COVID-19 exposure from 4 weeks to 60 days (Table 1) [37].

Although initial observations suggested MIS-C resembles KD, differences in clinical presentation emerged over time. By case definition, MIS-C should present with fever, which begs the question of whether a milder disease spectrum has been missed or overlooked. Outside of fever, gastrointestinal symptoms including abdominal pain, vomiting, or diarrhea are the most common clinical manifestation, typically occurring in over 80% of children [35••, 38]. Gastrointestinal symptoms are less common in KD, occurring in approximately 60% or less of children [39]. Mucocutaneous involvement, including rash and conjunctivitis, is also common, occurring in about half of patients [32, 33]. Another way MIS-C is clinically distinct from KD is in cardiovascular complications. Up to 50% of MIS-C can present with sudden and profound cardiogenic shock, requiring intensive care unit (ICU) care in 50–80% of cases [32–34] as compared to KD where shock is uncommon occurring in less than 5% of children [40]. A spectrum of

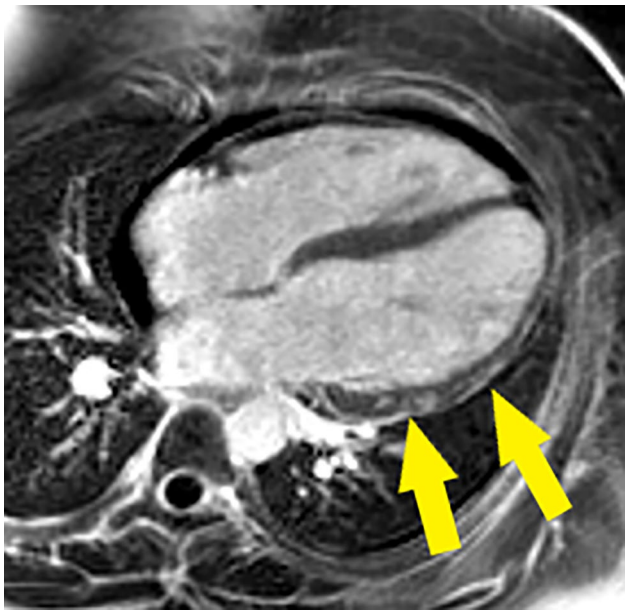

Fig. 2 This is a cardiac MRI late gadolinium enhancement (PSIR) long axis image in a patient with a history of MIS-C. There are areas of hyperenhancement (arrows) in a mid-myocardial pattern consistent with myocarditis. The cardiac MRI was performed in the acute presentation of MIS-C, 4 weeks after COVID-19 infection

other cardiac complications can happen including myocarditis defined as elevated cardiac enzymes and/or imaging evidence of myocardial inflammation (Fig. 2), coronary artery involvement, conduction abnormalities, and arrhythmias [41]. Coronary artery involvement is less common than in KD, observed in less than 10% of affected children at diagnosis [32, 33].

Inflammatory markers, including CRP and ESR, are typically significantly elevated. Median CRP levels are often higher than those observed in KD. In contrast to KD, thrombocytopenia is often observed in MIS-C during the acute presentation [32, 34]. Other hematologic anomalies include lymphopenia, neutrophilia, and anemia [32]. D-dimer is typically significantly elevated, and coagulopathy occurs more often than in KD. Like KD, if MIS-C is suspected, an echocardiogram is indicated given most children will have cardiac involvement [33, 42••]. In addition, obtaining troponin and brain natriuretic peptide (BNP) levels are indicated, and both are elevated in more than 50% of patients [32, 35••] (Table 2).

Treatment

Kawasaki Disease

Intravenous immunoglobulin (IVIG) and aspirin are the cornerstones of first-line therapy for KD. Coronary artery involvement is the leading cause of morbidity in KD, and IVIG has been shown to significantly reduce CAA development nearly fivefold if administered within 10 days of fever onset [40]. This underscores the need for timely diagnosis and initiation of first-line therapy in KD. About 20% of children with KD do not respond to initial treatment, and typically, a second dose of IVIG is administered [43]. Factors that predict IVIG resistance and development of CAA

Table 2 Comparison of clinical and laboratory features of Kawasaki disease and multisystem inflammatory syndrome in children

Comparison/variable	Kawasaki disease	MIS-C
Age at presentation	6 months to 5 years	Older than 5 years
Sex	Boys (~ 1.5:1)	No significant predilection
Affected ethnicity	Japanese	African American Hispanic
Pathogenesis	Possible infectious trigger	2–6 weeks after SARS- CoV-2 infection
Cardiovascular involvement	Coronary arteries Normal troponin and BNP	Myocarditis ↑ Troponin ↑ BNP
Mucocutaneous involvement	Rash, oropharyngeal involvement	Rash
Shock	Uncommon	Common
Gastrointestinal involvement	Can occur, less common	Most common symptom
Hematologic involvement	↑ Platelets ↑ ANC	↓ Platelets ↓ ALC ↑↑ ANC ↑↑ D-dimer
Inflammatory markers	↑ CRP	↑↑ CRP
Immunomodulatory treatment	IVIG (first-line) Consider adjunctive corticosteroid Infliximab in refractory cases	IVIG + corticosteroids (first-line) Anakinra in refractory cases

remain of interest to providers given their influence on treatment decisions which may also include the use of corticosteroids and biologic agents.

Risk factors for IVIG resistance and CAA development that have been identified in the Japanese population have not been generalizable to the North American population [44]. One recent North American risk model identified a left anterior descending or right coronary artery z-score ≥ 2.0, age < 6 months, Asian race, and CRP ≥ 13 mg/dL at baseline all to be predictive of CAA development [29•]. The risk model did not account for differences in treatment regimens, so future study is needed to determine its utility at predicting CAA development with the concomitant administration of corticosteroids and biologic agents for treatment.

Corticosteroids are often used in the management of KD, typically as adjunctive therapy to IVIG or in IVIG-resistant disease. The Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE) initiative recommends the use of corticosteroids when children are IVIG-resistant [45•]. A Cochrane review from 2017 examining corticosteroids in KD found that the addition of corticosteroids reduced the occurrence of CAA, fever duration, time for ESR and CRP normalization, and length of hospital stay. These findings were most notable in children of Asian race, those who had higher risk scores, and individuals who received a longer steroid course as compared to a single dose [43]. Studies from Japan have also shown the benefit of adjunctive corticosteroids [46], but it is unclear if these findings are generalizable to other populations.

Another therapy utilized in resistant cases of KD is TNF-α inhibitor (TNFi) therapy. One double-blind randomized, placebo-controlled trial (RCT) demonstrated that the addition of infliximab to initial therapy led to earlier resolution of fever and improvement in inflammatory markers, but there was no difference in coronary outcomes at 5 weeks [47]. A more recent study, the KIDCARE study, investigated the use of infliximab in IVIG-resistant children versus a second dose of IVIG. The group of children treated with infliximab had shorter duration of fever, less need for additional treatment, and had shorter hospitalization as compared to children who received a second IVIG infusion [48]. Further studies are needed to understand the coronary artery outcomes in KD patients treated with TNFi.

MIS-C

Early treatment of MIS-C was largely extrapolated from first-line treatment of KD, and published literature regarding management was initially limited to case reports and case series. In May 2020, the American College of Rheumatology (ACR) assembled a task force to provide guidance for clinicians focused on evaluating and managing MIS-C. The first guidelines were published in November 2020 and included IVIG and/or corticosteroids to be used as first-line treatment, advocating for a stepwise approach to immunomodulatory treatment [49]. In individuals refractory to IVIG and corticosteroids, anakinra was recommended as a consideration [49].

Subsequent updates in treatment guidelines have been published from the ACR in April 2021 and April 2022 [50, 51••]. The most recent guidelines advocate for treatment with both IVIG and adjunctive corticosteroids as first-line therapy [51••]. One large retrospective study of patients in the USA found that receipt of both IVIG and corticosteroids was associated with a lower risk of cardiovascular dysfunction on or after day 2 after receiving IVIG as compared to receiving IVIG alone without corticosteroids, though another study found no differences in treatment with IVIG alone versus IVIG with adjunctive corticosteroids in outcomes [42••, 52]. If the disease is refractory to an initial dose of IVIG and corticosteroids, then a second dose of IVIG is not recommended given the risk of volume overload and hemolytic anemia. Most recent guidelines recommend an escalation in corticosteroid dose in patients who are resistant to IVIG and moderate dose corticosteroids [51••]. Anakinra and infliximab may be considered in refractory cases [51••].

Outside of immunomodulatory therapy, pressors are often required for treatment since many MIS-C patients present in cardiogenic shock. Cardiac function should be monitored closely, and IVIG may be given in divided doses if patients have significantly depressed cardiac function. Children with MIS-C may also require antiplatelet or anticoagulation therapy depending on presentation. Anticoagulation is typically considered on an individual basis [51••]. The presence of a central venous catheter, age greater than 12 years old, malignancy, ICU admission, and D-dimer levels greater than five times the upper limit of normal were found to be independent risk factors for thrombosis in MIS-C [51••, 53]. These situations may warrant more intensive anticoagulation.

COVID-19 vaccination is now authorized for use in children. One large study found that only 5% of MIS-C patients ages 12 to 18 years old were fully vaccinated since vaccinations have become widely available [54]. All of the MIS-C patients who required life support including mechanical ventilation, vasoactive support, or extracorporeal membrane oxygenation (ECMO) were unvaccinated [54]. The hospital length of stay did not differ between the groups. In addition to vaccination being protective against severe COVID-19 acute sequelae, studies suggest that it may also be beneficial in regard to MIS-C.

Outcomes

Kawasaki Disease

KD is typically a self-limited illness and recurrence is rare. The major cause of morbidity is cardiac sequelae primarily from coronary arteritis during acute illness. KD is the

leading cause of acquired heart disease in the developed world [40]. Despite treatment, about 5% of affected children develop CAA [55]. Long-term follow-up demonstrates aneurysms may regress, remain unchanged, or progress to stenotic or obstructive lesions [56]. Smaller aneurysms more quickly regress and are more likely to have normal luminal diameter at follow-up compared to individuals with large aneurysms [57]. Rarely, there may be coronary artery rupture, though this typically occurs during the acute phase of illness. Children with giant CAA have the greatest risk of cardiac sequelae which can include myocardial infarction (MI). Outside of cardiac sequelae, outcomes are excellent.

MIS-C

Similar to KD, MIS-C has not been observed to commonly recur. CDC surveillance data found median hospitalization to be 5 days, with median ICU stay being 4 days. The duration of hospitalization and ICU stay has decreased over time along with deaths [58]. This could be a result of earlier recognition of the condition and report of milder cases, earlier treatment, variation in SARS-CoV-2 virus, COVID-19 vaccination, or a combination of factors.

Information regarding long-term outcomes in MIS-C will continue to be assimilated as more experience is gained with this condition. Initial reports of outcomes are overall encouraging. Children are often prescribed an oral corticosteroid taper at the time of discharge from the hospital. Laboratory abnormalities normalize, often by the time of the first follow-up in the weeks following hospitalization. Patients with myocarditis typically have recovery of their systolic ventricular function on echocardiogram by the time of discharge from the hospital [35••].

More information is needed about long-term cardiac outcomes. Studies to date have been encouraging in terms of recovery of LV function and resolution of coronary artery abnormalities at 6-month follow-up [59]. Cardiac MRI (CMR) is a helpful imaging modality for the evaluation of myocardial inflammation, fibrosis, and scarring, and may be considered in MIS-C patients based on their presentation and degree of cardiac involvement. Studies examining CMR 6 months after illness have varied in their findings [60, 61]. Long-term follow-up studies such as COVID MUSIC (multisystem inflammatory syndrome in children) are in process and will shed more light on cardiac outcomes [62].

Conclusion

As the world was trying to adjust to the COVID-19 global pandemic, MIS-C was also emerging as a rare but serious condition predominantly affecting children several weeks after COVID-19. MIS-C required providers to quickly assimilate and disseminate information about the condition in order to provide timely diagnosis and treatment to affected children. Understanding of its pathogenesis and characteristic clinical features has rapidly expanded since it first appeared. It was appreciated early that MIS-C resembles KD in several ways. As MIS-C has been further characterized, however, differences between MIS-C and KD have emerged. They are both inflammatory vasculopathies characterized by dysregulated innate and adaptive immune responses. In MIS-C, the infectious trigger is known; however, in the case of KD, a single pathogen has yet to be identified. The incidence of KD is higher in Asian populations, while most children with MIS-C have been of Black/Non-Hispanic and Hispanic/Latino ethnicity. While MIS-C and KD share several overlapping clinical manifestations, a key distinctive feature is cardiac involvement. Coronary arteritis is more common in KD and a significant determinant of long-term morbidity. In contrast, cardiogenic shock, myocarditis, and elevated markers of cardiac inflammation are more common in MIS-C. Treatment of both MIS-C and KD initially involves IVIG and corticosteroids, but somewhat differs for those with more severe presentations or who are treatment refractory. Anakinra has been favored in MIS-C, whereas TNFi may more often be deployed in KD. Outside of the coronary artery involvement in KD, the overall long-term outcomes of MIS-C and KD are favorable, although studies are ongoing that will shed light on the cardiac sequelae of MIS-C. Recognition of these parallels and differences between MIS-C and KD can aid the provider in diagnosis and management, as well as counseling patients regarding follow-up and long-term outcomes.

It has been a humbling experience to witness this medical phenomenon emerge and see how quickly the community was able to share knowledge and experience to advance the care of children affected by MIS-C. We have been privileged to be a medical specialty at the bedside providing care and insight into this rare condition. While we were able to construe parallels between MIS-C and the pre-pandemic KD early, it became apparent over time that perhaps these were two distinct diseases. Despite the rapid gains in knowledge regarding MIS-C, critical gaps remain. For instance, the reasons why MIS-C disproportionately affects children of Black/Non-Hispanic and Hispanic/Latino ethnicity have not been fully elucidated. Long-term studies are also needed to better understand outcomes including cardiac involvement. While on the surface, MIS-C and KD appear to share features of profound inflammation and inflammatory vasculopathy, further study is needed to truly determine whether they are distinct immunopathogenic disorders. A better understanding of these questions will help inform potential preventative measures, development of better diagnostic tools, and disease outcomes.

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Compliance with Ethical Standards

Conflict of Interest Dr. Cannon declares that she has no conflict of interest. Dr. Campbell reports personal fees from Longeveron Inc. and grants from the CDC Clinical Immunization Safety Assessment, outside the submitted work. Dr. Wu reports Advisory Board fees and Speaker honorarium from Pharming Healthcare, Inc. and Advisory Board fees from Enzyvant Therapeutics, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kawasaki T. Kawasaki disease. Int J Rheum Dis. 2014;17(5):597–600. https://doi.org/10.1111/1756-185x.12408.
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607–8. https://doi.org/10.1016/s0140-6736(20)31094-1.
3. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157–60. https://doi.org/10.23750/abm.v91i1.9397.
4. Lo MS. A framework for understanding Kawasaki disease pathogenesis. Clin Immunol. 2020;214:108385. https://doi.org/10.1016/j.clim.2020.108385.
5. Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet. 2008;40(1):35–42. https://doi.org/10.1038/ng.2007.59.
6. Armaroli G, Verweyen E, Pretzer C, Kessel K, Hirono K, Ichida F, et al. Monocyte-derived interleukin-1β as the driver of S100A12-induced sterile inflammatory activation of human coronary artery endothelial cells: implications for the pathogenesis of Kawasaki disease. Arthritis Rheumatol. 2019;71(5):792–804. https://doi.org/10.1002/art.40784.
7. Jia S, Li C, Wang G, Yang J, Zu Y. The T helper type 17/regulatory T cell imbalance in patients with acute Kawasaki disease. Clin Exp Immunol. 2010;162(1):131–7. https://doi.org/10.1111/j.1365-2249.2010.04236.x.
8. Noval Rivas M, Lee Y, Wakita D, Chiba N, Dagvadorj J, Shimada K, et al. CD8+ T cells contribute to the development of coronary arteritis in the Lactobacillus casei cell wall extract-induced murine model of Kawasaki disease. Arthritis Rheumatol. 2017;69(2):410–21. https://doi.org/10.1002/art.39939.
9. Yeung RS. Kawasaki disease: update on pathogenesis. Curr Opin Rheumatol. 2010;22(5):551–60. https://doi.org/10.1097/BOR.0b013e32833cf051.
10. Doi M, Takeda T, Sakurai Y, Kato J, Hayashi T, Fukuda K, et al. Altered immunoglobulin A and M levels associated with changes in BAFF and APRIL after administration of intravenous immunoglobulin to treat Kawasaki disease. J Investig Allergol Clin Immunol. 2010;20(5):413–8.
11. Rowley AH, Eckerley CA, Jäck HM, Shulman ST, Baker SC. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. J Immunol. 1997;159(12):5946–55.
12. Noval Rivas M, Wakita D, Franklin MK, Carvalho TT, Abolhesn A, Gomez AC, et al. Intestinal permeability and IgA provoke immune vasculitis linked to cardiovascular inflammation. Immunity. 2019;51(3):508-21.e6. https://doi.org/10.1016/j.immuni.2019.05.021.
13. Chua PK, Melish ME, Yu Q, Yanagihara R, Yamamoto KS, Nerurkar VR. Elevated levels of matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase 1 during the acute phase of Kawasaki disease. Clin Diagn Lab Immunol. 2003;10(2):308–14. https://doi.org/10.1128/cdli.10.2.308-314.2003.
14. Santos-Rebouças CB, Piergiorge RM, Dos Santos FC, SeixasZeitel R, Gerber AL, Rodrigues MCF, et al. Host genetic susceptibility underlying SARS-CoV-2-associated multisystem inflammatory syndrome in Brazilian children. Mol Med. 2022;28(1):153. https://doi.org/10.1186/s10020-022-00583-5.
15. Abolhassani H, Delavari S, Landegren N, Shokri S, Bastard P, Du L, et al. Genetic and immunologic evaluation of children with inborn errors of immunity and severe or critical COVID-19. J Allergy Clin Immunol. 2022;150(5):1059–73. https://doi.org/10.1016/j.jaci.2022.09.005.
16.• Chou J, Platt CD, Habiballah S, Nguyen AA, Elkins M, Weeks S, et al. Mechanisms underlying genetic susceptibility to multisystem inflammatory syndrome in children (MIS-C). J Allergy Clin Immunol. 2021;148(3):732–8.e1. https://doi.org/10.1016/j.jaci.2021.06.024. **A single-center cohort study demonstrating MIS-C patients were enriched for monogenic susceptibility to inflammation**.
17. Lee PY, Platt CD, Weeks S, Grace RF, Maher G, Gauthier K, et al. Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. J Allergy Clin Immunol. 2020;146(5):1194-200.e1. https://doi.org/10.1016/j.jaci.2020.07.033.
18. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med. 2020;26(11):1701–7. https://doi.org/10.1038/s41591-020-1054-6.
19. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest. 2020;130(11):5967–75. https://doi.org/10.1172/jci140970.
20. Diorio C, McNerney KO, Lambert M, Paessler M, Anderson EM, Henrickson SE, et al. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. Blood Adv. 2020;4(23):6051–63. https://doi.org/10.1182/bloodadvances.2020003471.
21. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183(4):982-95.e14. https://doi.org/10.1016/j.cell.2020.09.034.
22. Sharma C, Ganigara M, Galeotti C, Burns J, Berganza FM, Hayes DA, et al. Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol. 2021;17(12):731–48. https://doi.org/10.1038/s41584-021-00709-9.
23. Vella LA, Giles JR, Baxter AE, Oldridge DA, Diorio C, Kuri-Cervantes L, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to

adult and pediatric COVID-19. Sci Immunol. 2021;6(57). https://doi.org/10.1126/sciimmunol.abf7570.
24. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020;183(4):968-81.e7. https://doi.org/10.1016/j.cell.2020.09.016.
25.• Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumadó V, Fortuny C, et al. Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. J Clin Invest. 2021;131(6). https://doi.org/10.1172/jci144554. **The study performed cytokine profiling in pediatric patients with MIS-C and pre-pandemic KD, and results suggest IFN-γ and inflammatory monocytes are important drivers of inflammation in MIS-C**.
26. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997–2007. Pediatr Infect Dis J. 2010;29(6):483–8. https://doi.org/10.1097/INF.0b013e3181cf8705.
27. Son MB, Gauvreau K, Ma L, Baker AL, Sundel RP, Fulton DR, et al. Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. Pediatrics. 2009;124(1):1–8. https://doi.org/10.1542/peds.2008-0730.
28. Sundel RP. Kawasaki disease. Rheum Dis Clin North Am. 2015;41(1):63–73, viii. https://doi.org/10.1016/j.rdc.2014.09.010.
29.• Son MBF, Gauvreau K, Tremoulet AH, Lo M, Baker AL, de Ferranti S, et al. Risk model development and validation for prediction of coronary artery aneurysms in Kawasaki disease in a North American population. J Am Heart Assoc. 2019;8(11):e011319. https://doi.org/10.1161/jaha.118.011319. **This study aims to develop a risk model predictive of coronary artery aneurysm development, a major determinant of Kawasaki disease morbidity, for North American cohorts**.
30. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, et al. High Risk of Coronary Artery Aneurysms in Infants Younger than 6 Months of Age with Kawasaki Disease. J Pediatr. 2017;185:112-6.e1. https://doi.org/10.1016/j.jpeds.2017.03.025.
31. Gámez-González LB, Murata C, Muñoz-Ramírez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. Eur J Pediatr. 2013;172(3):337–42. https://doi.org/10.1007/s00431-012-1879-1.
32. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347–58. https://doi.org/10.1056/NEJMoa2021756.
33. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383(4):334–46. https://doi.org/10.1056/NEJMoa2021680.
34. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259–69. https://doi.org/10.1001/jama.2020.10369.
35.•• Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA. 2021;325(11):1074–87. https://doi.org/10.1001/jama.2021.2091. **This report is one of the largest case series including 539 children with MIS-C from the Overcoming COVID-19 surveillance registry. The study observed that most cardiovascular involvement resolved over time**.
36. Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr. 2007;19(3):314–20. https://doi.org/10.1097/MOP.0b013e3280dd8c4a.
37. Son MBF, Burns JC, Newburger JW. A new definition for multisystem inflammatory syndrome in children. Pediatr. 2023. https://doi.org/10.1542/peds.2022-060302.
38. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to Coronavirus disease 2019: a single center experience of 44 cases. Gastroenterology. 2020;159(4):1571-4.e2. https://doi.org/10.1053/j.gastro.2020.05.079.
39. Baker AL, Lu M, Minich LL, Atz AM, Klein GL, Korsin R, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. J Pediatr. 2009;154(4):592-5.e2. https://doi.org/10.1016/j.jpeds.2008.10.006.
40. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927–99. https://doi.org/10.1161/cir.0000000000000484.
41. Wu EY, Campbell MJ. Cardiac Manifestations of multisystem inflammatory syndrome in children (MIS-C) following COVID-19. Curr Cardiol Rep. 2021;23(11):168. https://doi.org/10.1007/s11886-021-01602-3.
42.•• Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, et al. Multisystem inflammatory syndrome in children - initial therapy and outcomes. N Engl J Med. 2021;385(1):23–34. https://doi.org/10.1056/NEJMoa2102605. **This study looked at 518 MIS-C patients from the Overcoming COVID-19 surveillance registry and found that initial treatment with IVIG plus corticosteroids was associated with lower risk of cardiovascular dysfunction than IVIG alone**.
43. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2017;1(1):Cd011188. https://doi.org/10.1002/14651858.CD011188.pub2.
44. Son MBF, Gauvreau K, Kim S, Tang A, Dedeoglu F, Fulton DR, et al. Predicting coronary artery aneurysms in Kawasaki disease at a North American Center: an assessment of baseline z scores. J Am Heart Assoc. 2017;6(6). https://doi.org/10.1161/jaha.116.005378.
45.• de Graeff N, Groot N, Ozen S, Eleftheriou D, Avcin T, Bader-Meunier B, et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease - the SHARE initiative. Rheumatology (Oxford). 2019;58(4):672–82. https://doi.org/10.1093/rheumatology/key344. **This report provides international evidence-based recommendations for diagnosing and treated KD in children to facilitate uniformity in care**.
46. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, 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(9826):1613–20. https://doi.org/10.1016/s0140-6736(11)61930-2.
47. Tremoulet AH, Jain S, Jaggi P, Jimenez-Fernandez S, Pancheri JM, Sun X, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet. 2014;383(9930):1731–8. https://doi.org/10.1016/s0140-6736(13)62298-9.
48. Burns JC, Roberts SC, Tremoulet AH, He F, Printz BF, Ashouri N, et al. Infliximab versus second intravenous immunoglobulin for treatment of resistant Kawasaki disease in the USA (KIDCARE):

a randomised, multicentre comparative effectiveness trial. Lancet Child Adolesc Health. 2021;5(12):852–61. https://doi.org/10.1016/s2352-4642(21)00270-4.

49. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol. 2020;72(11):1791–805. https://doi.org/10.1002/art.41454.
50. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. Arthritis Rheumatol. 2021;73(4):e13–29. https://doi.org/10.1002/art.41616.
51.•• Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 3. Arthritis Rheumatol. 2022;74(4):e1-e20. https://doi.org/10.1002/art.42062. **The most recent version of clinical guidance recommendations for MIS-C endorsed by the American College of Rheumatology.**
52. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385(1):11–22. https://doi.org/10.1056/NEJMoa2102968.
53. Whitworth H, Sartain SE, Kumar R, Armstrong K, Ballester L, Betensky M, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. Blood. 2021;138(2):190–8. https://doi.org/10.1182/blood.2020010218.
54. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA vaccination against multisystem inflammatory syndrome in children among persons aged 12–18 years - United States, July-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52–8. https://doi.org/10.15585/mmwr.mm7102e1.
55. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736–54. https://doi.org/10.1161/circulationaha.106.183095.
56. Senzaki H. Long-term outcome of Kawasaki disease. Circulation. 2008;118(25):2763–72. https://doi.org/10.1161/circulationaha.107.749515.
57. Akagi T, Rose V, Benson LN, Newman A, Freedom RM. Outcome of coronary artery aneurysms after Kawasaki disease. J Pediatr. 1992;121(5 Pt 1):689–94. https://doi.org/10.1016/s0022-3476(05)81894-3.
58. Miller AD, Zambrano LD, Yousaf AR, Abrams JY, Meng L, Wu MJ, et al. Multisystem inflammatory syndrome in children-United States, February 2020-July 2021. Clin Infect Dis. 2022;75(1):e1165–75. https://doi.org/10.1093/cid/ciab1007.
59. Capone CA, Misra N, Ganigara M, Epstein S, Rajan S, Acharya SS, et al. Six month follow-up of patients with multi-system inflammatory syndrome in children. Pediatr. 2021;148(4). https://doi.org/10.1542/peds.2021-050973.
60. Chakraborty A, Philip R, Santoso M, Naik R, Merlocco A, Johnson JN. Cardiovascular magnetic resonance in children with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19: institutional protocol-based medium-term follow-up study. Pediatr Cardiol. 2022;43(8):1879–87. https://doi.org/10.1007/s00246-022-02927-8.
61. Barris DM, Keelan J, Ahluwalia N, Jhaveri S, Cohen J, Stern K, et al. Midterm outcomes and cardiac magnetic resonance imaging following multisystem inflammatory syndrome in children. J Pediatr. 2022;241:237-41.e1. https://doi.org/10.1016/j.jpeds.2021.10.009.
62. Truong DT, Trachtenberg FL, Pearson GD, Dionne A, Elias MD, Friedman K, et al. The NHLBI study on long-term outcomes after the multisystem inflammatory syndrome in children (MUSIC): design and objectives. Am Heart J. 2022;243:43–53. https://doi.org/10.1016/j.ahj.2021.08.003.