



# Current Insights Into the Pathophysiology of Multisystem Inflammatory Syndrome in Children

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## Abstract

**Purpose of Review** We highlight the new clinical entity multisystem inflammatory syndrome in children (MIS-C), the progress in understanding its immunopathogenesis, and compare and contrast the clinical and immunologic features of MIS-C with Kawasaki disease (KD).

**Recent Findings** Studies show immune dysregulation in MIS-C including T lymphocyte depletion and activation, T cell receptor Vbeta skewing, elevated plasmablast frequencies, increased markers of vascular pathology, and decreased numbers and functional profiles of antigen-presenting cells.

**Summary** MIS-C is a late manifestation of infection with SARS-CoV-2 associated with marked immune activation and many potential mechanisms of immunopathogenesis. MIS-C and KD have clinical similarities but are distinct. Myocardial dysfunction with or without mild coronary artery dilation can occur in MIS-C but generally corrects within weeks. In contrast, the coronary arteries are the primary target in KD, and coronary artery sequelae can be lifelong. Supportive care and anti-inflammatory therapy appear to hasten improvement in children with MIS-C, and there is hope that vaccines will prevent its development.

**Keywords** MIS-C · Kawasaki disease · Pediatric · SARS-CoV-2 · Inflammatory syndrome

## Introduction

SARS-CoV-2 infection has provided many unexpected events for the medical profession, not the least of which has been the pediatric experience. Unlike other respiratory viral pathogens such as RSV or influenza, this new human virus does not commonly cause severe disease in young children **1**. Moreover, despite children rarely requiring

hospitalization for acute COVID-19, it became clear over time that a small subset of children developed a serious illness at a median of 4 weeks after the acute infection, manifested by prolonged fever, hypotension, myocardial dysfunction, and marked increase in inflammatory markers in the blood. Initially termed pediatric multisystem inflammatory syndrome (PIMS) in Europe **[2]**, this clinical illness became known as multisystem inflammatory syndrome in children (MIS-C) in the USA **[3]**. In this review, we focus on what is presently known about the epidemiology, immunopathogenesis, and treatment of this unique illness. We also describe the differences between MIS-C and Kawasaki disease (KD), a pediatric illness with some clinical similarities to MIS-C.

## Epidemiology

Identifying the precise epidemiology of MIS-C is hampered by the lack of a specific case definition. Current case definitions are very broad; children who recently or previously were infected with SARS-CoV-2 and develop a multisystem illness due to infections or inflammatory conditions

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unrelated to SARS-CoV-2 or due to acute COVID-19 can fulfill current case definitions, resulting in overdiagnosis [3•, 4, 5•]. However, certain epidemiologic features are consistently reported. The median age of children with MIS-C is 9 years [2•, 3•, 4, 6]. MIS-C occurs a median of 27 days (IQR 21–36 days) after preceding SARS-CoV-2 infection [7••], and an increase in cases has occurred about 1 month (range 2–5 weeks) following peaks of COVID-19 in individual geographic areas [7••]. If RT-PCR for SARS-CoV-2 from the respiratory tract is positive in children with MIS-C, the cycle threshold (Ct) values are high, suggesting low viral load at that site at the time of clinical presentation [7••, 8••]. About 60% of affected children in the USA have been reported to be Hispanic or non-Hispanic Black, with a slight male preponderance [7••, 9]. Although the racial/ethnic distribution most likely reflects COVID-19-related health disparities, a genetic predisposition to MIS-C has not been excluded [9].

Adults can develop an illness similar to MIS-C following COVID-19 infection, called multisystem inflammatory syndrome in adults, or MIS-A; it may be underdiagnosed [10, 11].

## Immunology

MIS-C is associated with high levels of inflammation and responds to anti-inflammatory therapies; it is therefore presumed to be immune-mediated. The immunopathogenesis of MIS-C remains unknown, but substantial progress has been made in defining the features of immune dysregulation in MIS-C. Once the syndrome was recognized, global research efforts collected blood samples from patients with MIS-C to assess plasma cytokines, changes in innate and adaptive immune cells, and profiles of antibodies against SARS-CoV-2 and against self-antigens [8••, 12••, 13••, 14••, 15•, 16•, 17•, 18•, 19•]. Studies were undertaken in pandemic conditions and in the setting of an evolving field, and therefore, each had limitations. These included lack of ideal comparator groups (acute COVID-19 subjects or pediatric healthy controls), comparator samples that

were not contemporaneously collected, sample collection after start of immunosuppressive therapies, low numbers of cell events captured, and small sample sizes. Moreover, some studies include a substantial percentage of patients diagnosed with MIS-C who were negative for SARS-CoV-2-specific antibodies, suggesting they may either have had acute COVID-19 if they had a positive respiratory PCR assay, or had an alternative diagnosis. Still, several themes emerged (Table 1).

**Changes in Plasma Cytokine and Protein Profiles** To identify both diagnostic tools and therapeutic targets in MIS-C, multiple groups assessed the profiles of plasma cytokines and other plasma proteins [12••, 13••, 14••, 16•, 17•, 18•, 19•, 20•, 21–23]. Consistent with multisystem inflammation, patients with MIS-C variably demonstrated elevations above the normal range in multiple plasma cytokines, including IL-6, IL-8, IFN $\gamma$ , IL-17, TNF $\alpha$ , IFN $\gamma$ , and IL-10 [13••, 14••, 16•, 17•, 18•, 21, 24], and several groups have identified changes in interferon responsiveness pathways [20•, 25, 26]. Cytokine levels did not clearly sort with patients who remained PCR positive at presentation versus those who were PCR negative [19•], and although some cytokines such as IFN $\gamma$ , IL-10, and TNF $\alpha$  are more prominent in MIS-C and therefore serve as indicators of possible immunopathogenesis, there remains overlap with the cytokine profiles of patients admitted with acute COVID-19 [12••, 14••, 16•, 17•, 18•].

Broader plasma protein measurements have identified candidate markers for MIS-C, serving as potential clues into aspects of disease pathogenesis. A proteomic study of MIS-C found that phospholipase A2 (PLA2G2A) — an enzyme component of many inflammatory pathways — was the plasma protein most elevated in MIS-C compared to healthy controls and typically higher in MIS-C than in acute pediatric COVID-19 [20•]. Increased PLA2G2A was observed in smaller MIS-C cohorts by two other groups [15•, 23] and has been shown to correlate with thrombocytopenia and with elevations in a complement biomarker of the tissue microangiopathy observed in MIS-C, soluble C5B9 [17•, 20•]. As such, elevation of PLA2G2A is one of

**Table 1** Immunologic findings in MIS-C

Immune system component	Consistent findings
Cytokines	Increases in multiple, including IFN $\gamma$ , IL-10, TNF $\alpha$
Proteome	Increased PLA2G2A
Monocytes	Decreased HLA-DR
Dendritic cells	Decreased pDC
B cells	Increased plasmablasts
SARS-CoV-2-specific antibody	Normal quantity and neutralization
Autoantibody	Detected, but no single autoantibody confirmed across studies
T cells	Decreased numbers, increased activation

the more consistent research findings in MIS-C. In addition to insights into disease pathogenesis, assessment of plasma proteins has tremendous potential as a diagnostic tool for MIS-C. Studies that pool larger numbers of subjects, compare across similar febrile presentations, and collect plasma before immune modulation will be required to develop such tools further.

**Changes in Innate Immune Cells** In another consistent finding, children with MIS-C demonstrate decreases in monocyte and dendritic cell subsets, particularly plasmacytoid dendritic cells [8••, 13••, 14••, 15•]. The remaining cells have decreased expression of the class II molecule HLA-DR and the costimulatory molecule CD86 [13••, 15•, 16•]. Of note, changes in monocytes and dendritic cells are not exclusive to MIS-C. Reduced plasmacytoid DC have been described in adult and pediatric COVID-19 [14••, 27] and reduced HLA-DR expression on monocytes is well described in critical illness. In sepsis, reduced HLA-DR on monocytes is considered to be a component of “immunoparalysis” because it reduces the capacity for monocytes to present antigen and correlates with worse outcome [28]. To that end, multiple studies have used activating immune modulation such as granulocyte–macrophage colony-stimulating factor (GM-CSF) to increase HLA-DR expression and/or immune responsiveness in sepsis [28, 29]. It is therefore interesting to consider that monocyte and dendritic cell HLA-DR expression in MIS-C appeared to improve instead in the context of therapeutic immunosuppression [13••]. The changes in monocytes and dendritic cells might therefore fit in a broader concept of immune dysregulation — with both aberrantly increased and decreased inflammatory pathways — rather than immune hyporesponsiveness alone.

**Changes to Antibodies and B cells in MIS-C** The majority of patients diagnosed with MIS-C have been SARS-CoV-2 IgG positive [3•, 18•, 30, 31]. These antibodies are of normal quantity and are able to neutralize virus [18•, 31]. Some quality differences in SARS-CoV-2-specific antibodies have been observed, depending on the comparator group. Patients with MIS-C as compared to children with acute COVID-19 had a greater IgG1:IgG3 ratio of spike-specific antibodies, with enhanced antibody-dependent cellular phagocytosis (ADCP) [18•]. In a separate study, the ADCP ability was on par with convalescent adults [32]. In general, studies of antibody differences between patients with COVID-19 and MIS-C may benefit from convalescent cohorts, as convalescent time periods normalize for the longer time between infection and hospitalization that is a hallmark of MIS-C as compared to acute COVID-19. When compared to convalescent adults, spike-specific antibodies from subjects with severe MIS-C demonstrated an increased ability to activate

monocytes [32]. Together, these data suggest differences in the quality of antibody responses to SARS-CoV-2 in MIS-C, but whether those differences are due to age, time from infection, or are a reflection of aberrant virus-specific immunity remains unclear.

Profiling of B cell responses in MIS-C has shown increases in circulating plasmablasts [8••, 13••, 15•], similar to levels typically seen after severe viral infection or live viral vaccinations [33–35]. Of note, the degree of plasmablast elevation is also similar to that observed in acute adult and pediatric COVID-19 [8••], despite the many weeks from initial infection. Further, plasmablast levels are higher than observed in convalescent adults, in whom plasmablast frequencies return to baseline within weeks [8••]. The absence of samples from children in the week(s) before they develop MIS-C limits our ability to know whether these plasmablast responses are persisting from the initial infection or whether they are a newly developed immune response at the time of clinical illness.

The antigenic targets of circulating plasmablasts ~4 weeks after initial infection have not been identified. A major question is whether these plasmablasts are virus-specific and continuing to expand based on persisting SARS-CoV-2 antigen, reacting nonspecifically to inflammation, or whether they are responding to a non-viral antigen as part of the immunopathogenesis of MIS-C. To understand the potential for autoimmunity as a driver of disease, B cell and antibody responses against self-antigens have been profiled in several MIS-C cohorts [12••, 14••, 15•]. With limited numbers, there is some suggestion that antibodies in MIS-C can bind to activated human cardiac microvascular endothelial cells; however, most samples with this finding were obtained after administration of intravenous immunoglobulin [15•]. Autoantibodies that bound self-antigens including endothelial, cardiovascular, and gastrointestinal antigens were also found to be enriched in MIS-C patients as compared to healthy controls, although these studies also included a mixture of pre- and post-IVIg treated subjects [14••]. The largest set of subjects to undergo autoantibody screens included 12 pre-treatment patients with MIS-C compared with the autoantibody profiles of patients with acute SARS-CoV-2, Kawasaki disease, and healthy subjects and found antibodies that bound to proteins involved in immunologic and cardiovascular pathways [12••]. Future studies would benefit from increased sample sizes, prioritization of sample collection before administration of IVIg, and inclusion of febrile controls with non-SARS-CoV-2 viral or bacterial illnesses [36, 37].

**Changes in T cells** Clinical laboratory measurements highlighted decreased absolute lymphocyte counts in many patients with MIS-C [3•, 8••, 38]. In particular, T cell lymphopenia was observed, with losses in both CD4+ and

CD8+ T cell compartments [8••, 13••]. The remaining T cells demonstrated marked activation, with high-frequency expression of HLA-DR and CD38, particularly in CD8 T cells [8••, 13••]. In addition, deep immune profiling of peripheral blood mononuclear cells directly after isolation demonstrated that the most differentially activated subset was CD8 T cells that express CX3CR1, the fractalkine receptor that enables cells to interact with fractalkine-expressing endothelium [8••]. These activated CX3CR1+ CD8 T cells correlated with elevated D-dimer and decreased platelet count and need for vasoactive support [8••]. Finally, several groups have documented that the T cells remaining in circulation are often enriched for usage of the T cell receptor beta variable gene 11–2 (TRBV11-2), encoding Vbeta(Vβ)21.3, and enrichment is not present in children with acute COVID-19 [15•, 16•, 19•]. These Vβ21.3+ T cells are more likely to be activated and also express CX3CR1 at greater frequencies than T cells without Vβ21.3 [16•]. However, the MHC class that binds the potential superantigen remains incompletely described, and Vβ21.3+ T cell activation is seen in both CD4 and CD8 T cells [16•]. In summary, the picture emerging in MIS-C is one of decreased circulating T cells with those T cells remaining in blood having increased activation, Vβ21.3 gene segment enrichment, and increased frequencies of activated cells that can interact with vasculature. It remains unclear whether these T cells reflect the phenotype of cells that did not exit into tissues and/or whether these activated T cells are directly related to the pathogenesis of disease. Further, while the Vbeta expansion and polyclonality data might suggest that no single classically recognized

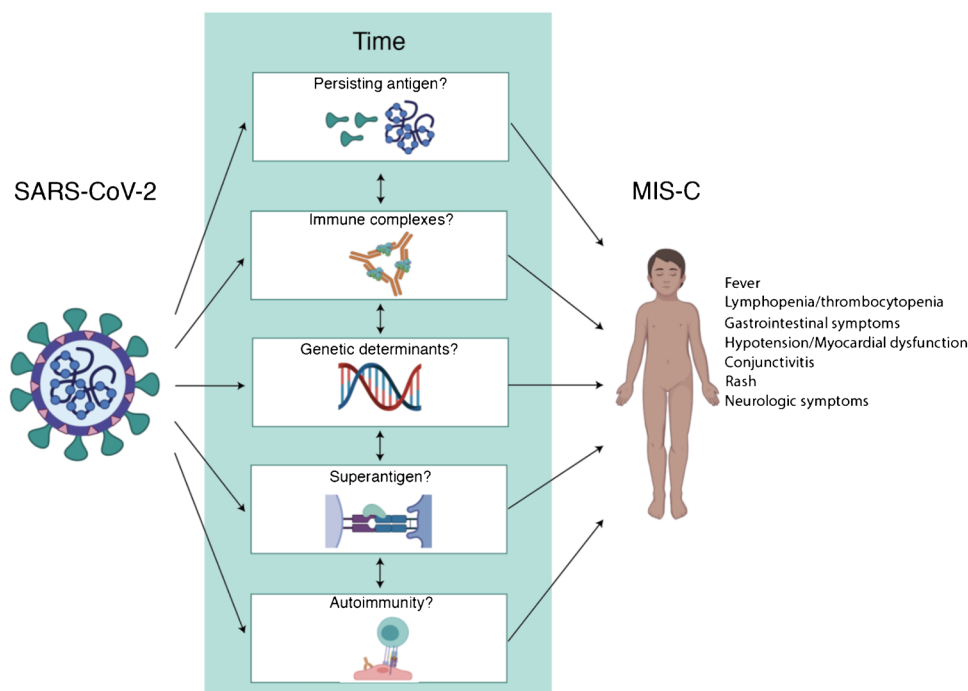
antigen is driving disease [16•], the true specificity of the activated T cells remains unknown.

In summary, MIS-C is manifested by increased cytokine production; increased PLA2G2A protein; decreases in total frequencies of monocytes, dendritic cells, and T cells; and increases in frequencies of activated T cells and plasmablasts.

## Immunopathogenesis

The possibilities for immunopathogenesis of MIS-C remain broad (Fig. 1). The most striking and consistent feature identified by multiple groups has been expansion of Vβ21.3+ T cells [15•, 16•, 19•], although this finding is not present uniformly. The expansion is similar to that observed in superantigenic processes such as streptococcal toxic shock syndrome (STSS), and certainly, some clinical features of MIS-C overlap with STSS [16•]. Still, it remains unclear why such a syndrome would most prominently develop in the school-aged child—with relatively few cases in early childhood and in adulthood—given that a superantigen's ability to bind TCRVbeta segments to MHC alleles is not known to change with age [39]. Second, the 4-week time period between acute infection and disease is inconsistent with the antigen being from viral structures alone [40]. Still, SARS-CoV-2 RNA remains detectable in many patients at the time of hospitalization for MIS-C, and one study has suggested detectable antigen

**Fig. 1** Potential immunopathogenesis of MIS-C. Created with Biorender.com



in circulation [3•, 8••, 41]. Differences in cellular tropism by patient age, viral variant, or other factors remain important avenues of investigation. Other possibilities include immune-activating structures or superantigens resulting from immune complexes formed with persisting antigen [8••, 41], the development of a transient autoimmune response [12••, 14••, 15•], or an otherwise dysregulated immune response that occurs around the time of viral clearance. Future work to evaluate each hypothesis will benefit from collaborative approaches to increase the diversity and sample size of patients as well as the adequacy of control populations.

## MIS-C and KD

KD is a febrile illness of young childhood that can lead to infiltration of inflammatory cells into medium-sized arteries, particularly the coronary arteries, with a risk of myocardial infarction and sudden death. Because the etiology of KD has remained unknown for the past 50 years, the diagnosis has been based upon compatible clinical and laboratory features, and there is a broad differential diagnosis [42]. A subset of children with KD does not have all the clinical features identified in classic KD (so-called incomplete KD) and yet develops severe coronary artery disease, further complicating diagnosis. The existence of incomplete KD led the American Heart Association's Committee on Endocarditis, Rheumatic Fever, and Kawasaki Disease to propose a treatment algorithm for possible incomplete KD [42]. The purpose of the algorithm is to define clinical, laboratory, and echocardiographic features that support a possible diagnosis of incomplete KD when no other diagnosis can be established and to suggest when the benefit of treating for KD to prevent coronary artery aneurysms that could lead to lifelong heart disease likely outweighs the possible risk. It is not intended to provide definite diagnosis of KD, and the diagnosis cannot be considered confirmed in incomplete cases unless coronary artery inflammation with subsequent aneurysm formation develops.

When MIS-C cases were first identified, children with the illness were noted to have some of the clinical features of KD, and some had mild coronary artery dilation in the acute febrile phase of illness. This led to initial speculation that MIS-C was somehow related to KD [43, 44]. However, the epidemiology of the two conditions is markedly different. Table 2 provides distinguishing features of acute COVID-19, MIS-C, and KD. The presence of leukopenia, thrombocytopenia, hypotension, myocardial dysfunction, prominent gastrointestinal symptoms, and presentation at an older age favor MIS-C over KD as the diagnosis [6, 45]. The majority of children with KD are less than 5 years of age, and

children of East Asian ancestry have the highest incidence [42]. In nations with the highest prevalence of KD, such as Japan, China, and Korea, MIS-C cases have been notably absent, and KD prevalence in the USA does not pattern MIS-C prevalence [1•, 46, 47]. Perhaps the most compelling epidemiologic data indicating a lack of association between MIS-C and KD are the worldwide decrease in KD cases during COVID-19 outbreaks and mitigation strategies [1•, 47, 48, 49••, 50, 51]. Masking and social distancing, which have reduced the prevalence of many respiratory viruses, presumably have decreased the prevalence of transmission of the as-yet-unidentified KD respiratory etiologic agent(s) [52].

Children with MIS-C rarely meet classic diagnostic criteria for KD, typically only displaying the KD criteria of conjunctival injection and rash, features observed in many infectious and inflammatory illnesses of childhood. Moreover, the coronary artery dilation occurring in MIS-C is generally mild and is apparent during the initial febrile illness, rapidly resolving on short-term follow-up in most cases [53••, 54••], similar to that observed in systemic onset juvenile idiopathic arthritis and rarely in children with other infections [55, 56]. This is markedly different from the pattern of coronary artery dilation in KD, which generally peaks after resolution of the febrile illness, during a time that the child appears clinically well [42]. This peak of coronary artery dilation in KD has been reported to occur at a median of 35 days after fever onset [57]. The difference in timing and severity of coronary artery dilation in the two conditions is likely related to different pathologic mechanisms. In MIS-C, coronary dilation may be due to increases in circulating cytokines with endothelial cell dysfunction and likely edema with mild dilation of the coronary arteries, while in KD, there is infiltration of the coronary arteries by inflammatory cells, leading to disruption of collagen and elastin fibers, and loss of structural integrity resulting in aneurysms of the arteries [58]. In the very few pathologic studies of the heart in cases of MIS-C or MIS-A published to date, inflammatory cells have been observed in interstitial spaces of the myocardium, without apparent infiltration into the coronary arteries [59, 60]. Fortunately, myocardial function also appears to normalize in almost all children with MIS-C at short-term follow-up [53••]. Because of the difficulties in differentiating MIS-C from KD in individual cases, some patients reported to have had MIS-C likely had KD, and vice versa. Some studies examining the differences between pathogenesis of KD and MIS-C include children with incomplete KD in their studies, many of whom may have had non-KD illnesses. Given these caveats in accurate identification of both MIS-C and KD, it is difficult to know whether studies comparing immune dysregulation in MIS-C to KD are providing accurate data.

In studies performed in the pre-pandemic era, both innate and adaptive arms of the immune system were shown to



**Table 2** Distinguishing features of pediatric acute COVID-19, MIS-C, and KD

	Pediatric acute COVID-19		
	MIS-C	KD	
<b>Epidemiology</b>			
Age	Any age	Median age 9 years	Median age 2 yr, peak age 10 months
Ethnicity	Highest prevalence Black, LatinX	Highest prevalence Black, LatinX	Highest prevalence East Asian
Seasonality/timing	Any season	Median of 4 weeks after acute COVID	Peaks in winter-spring in temperate climates
Association with SARS-CoV-2	Etiologic agent	Delayed presentation of SARS-CoV-2 infection	Unrelated to SARS-CoV-2
<b>Laboratory</b>			
	Mild lymphopenia	Marked lymphopenia	Lymphopenia rare
	Mild thrombocytopenia	Thrombocytopenia	Thrombocytopenia rare
	Acute phase reactants may be elevated	Very high levels acute phase reactants	High levels of acute phase reactants
	Normal troponin	Elevated troponin in cases with severe myocardial dysfunction	Normal troponin
<b>Clinical features</b>			
Organ/tissue most significantly affected	Lung	Myocardium and GI tract	Coronary arteries
Timing and prevalence of coronary artery dilation	Not applicable	Up to 20% in acute febrile phase, normalizes within 2–3 months or sooner	30% in untreated, 5% in treated patients (higher in infants), peaks at ~4 weeks after fever onset, more severe aneurysms persist indefinitely
<b>Cardiovascular pathology</b>			
	Thrombosis, endoathelitis, myocarditis, without evidence of SARS-CoV-2 RNA or antigen in the heart	Inflammatory cells in myocardium without myocyte necrosis, no apparent inflammation of coronary arteries [59, 60]	Marked inflammatory cell infiltration into coronary arteries, thrombosis of inflamed arteries [42]

be activated in acute KD, and the response is more typical of a conventional infectious agent than a superantigen [61]. In particular, early reports of T cell Vbeta skewing in acute KD peripheral blood that suggested a superantigen stimulus were not reproduced in many subsequent studies [62]. The lack of T cell Vbeta skewing in KD was recently reported to be a differentiating feature of KD compared with MIS-C [16•]. One study comparing plasma cytokine profiles in KD to MIS-C suggested a group of proteins differentiating KD, MIS-C, and acute COVID-19 infection [12••]. In this analysis, KD was associated with relative upregulation of CXCL9 and OSM and downregulation of ITGB6. In a separate, pre-pandemic study, CXCL9 was also observed as the most upregulated transcript in inflamed KD coronary arteries compared with childhood control coronary arteries, with OSM upregulation and ITGB6 downregulation also observed [12••, 63]. While these findings appear to suggest consistent cytokine features across KD, one inherent difficulty in direct comparisons of cytokine levels between KD and MIS-C is the significantly different age groups affected by the disorders. For example, IL-17A was reported to be higher in KD compared with MIS-C [12••]; however, another report clearly demonstrated an inverse relationship between IL-17A levels and patient age [64], and KD children are significantly younger than MIS-C patients.

Over time, newer studies are clarifying the clinical and laboratory features that differentiate the two conditions, which should allow for improved pathogenesis studies in the future.

## Treatment

The optimal treatment for MIS-C is unknown. Because of the clinical similarities between KD and MIS-C, treatment was modeled after that used in KD, and intravenous gamma-globulin (IVIG) is often administered. Over time, anecdotal experience suggested that patients who received corticosteroid therapy with IVIG experienced more rapid improvement than those who did not. Several retrospective reviews support the clinical impression that myocardial function normalizes more quickly in children who receive corticosteroid with IVIG [65, 66, 67•]. A single study suggesting a lack of benefit of corticosteroids in MIS-C included a subset of patients who did not meet a standard MIS-C case definition and were negative for SARS-CoV-2 antibody, making a diagnosis of SARS-CoV-2-related illness unlikely in these patients and complicating interpretation of the results [68]. The optimal dose of corticosteroid for MIS-C remains unknown, but in two studies, doses in the 1–2-mg/kg/day range were used [65, 66]; many centers use a tapering dose regimen over a 2–3-week period. The role of IVIG in treatment remains unclear. Some centers have had success with

corticosteroid treatment without IVIG in some patients [45] [69]. Patients who do not appear to respond to IVIG and corticosteroid are often treated with anakinra or infliximab, but the efficacy and role of these agents are also presently unknown. It also should be recognized that milder cases of MIS-C may be self-limited and could improve with supportive care alone [21].

## Conclusions

MIS-C is a new pediatric illness that is a late complication of SARS-CoV-2 infection. KD should be considered in the differential diagnosis of MIS-C but is a separate disorder. The pathogenesis of MIS-C remains incompletely understood, but advances have been made in understanding the immune system components affected by the disorder and the immunomodulatory therapies that may hasten recovery. Continued work to explore potential immunopathologic mechanisms will be needed, with the most pressing question being whether the response is driven by a persisting component of the virus, a modified component of the virus, or whether the process is independent of persisting viral antigens and is, instead, virus-triggered autoimmunity. Most children recover completely, but long-term outcome studies are ongoing. It is hoped that universal vaccination of children against SARS-CoV-2 will prevent pediatric cases of both COVID-19 and MIS-C in the future.

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