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A Comprehensive Review of SARS-CoV-2-Associated Multisystem Inflammatory Syndrome in Children

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ABSTRACT

The coronavirus disease 2019 (COVID-19) has affected individuals across all age groups, with a notably high rate of morbidity and mortality. Although most children with COVID-19 exhibit mild symptoms, an increasing proportion are developing a novel multisystem inflammatory syndrome (MIS-C), which shares clinical features with Kawasaki disease. MIS-C is a newly recognized hyperinflammatory condition affecting virtually any organ system. The most common symptoms include fever and gastrointestinal disturbances, although neurologic and dermatologic manifestations are well-documented. The clinical presentation of MIS-C overlaps with that of Kawasaki disease, toxic shock syndrome, and other shock syndromes, making accurate diagnosis challenging. Elevated inflammatory markers are frequently observed in MIS-C patients, and abnormalities on echocardiograms or electrocardiograms may be present. Treatment for MIS-C should consider intravenous immunoglobulin, anticoagulation, and corticosteroids. Despite significant cardiovascular involvement in some cases, most patients recover without complications. However, long-term echocardiographic follow-up is essential, as coronary aneurysms have been documented. This narrative review examines the epidemiology, pathophysiology, clinical manifestations, laboratory findings, diagnostic criteria, and treatment strategies for MIS-C to enhance pediatricians' understanding of this emerging syndrome.

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Introduction

Coronavirus disease (COVID-19) was first identified in China and subsequently spread worldwide, affecting individuals across all age groups, including infants and children (1,2). The virus responsible for COVID-19 is named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as designated by the International Committee on Taxonomy of Viruses (3). Early studies indicated that children infected with COVID-19 tend to have a lower mortality rate and exhibit milder symptoms compared to adults (4,5). A novel syndrome, later defined as multisystem inflammatory syndrome in children (MIS-C), was reported in April 2020. A systemic hyperinflammatory response characterizes this syndrome and appears to be associated with COVID-19 infection. MIS-C shares several similarities with Kawasaki disease (KD) (6,7). It is a hyperinflammatory condition in children that leads to inflammation across multiple organ systems, including the brain, lungs, heart, gastrointestinal tract, skin, eyes, and kidneys (8). Studies have shown that MIS-C typically develops 4 to 6 weeks after a COVID-19 infection, suggesting that the virus may act as a trigger in genetically predisposed individuals (9–11).

While specific symptoms, such as strawberry tongue, lymphadenopathy, skin rash, and elevated inflammatory markers, are common to both multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease (KD), MIS-C also exhibits distinct characteristics (12).

This study aims to highlight the differences

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between KD and MIS-C and review the existing evidence on MIS-C, thereby increasing pediatricians' awareness of this emergent and potentially severe syndrome.

Differences between MIS-C and KD:

MIS-C and Kawasaki disease (KD) share several clinical characteristics. The most notable common feature is a febrile illness characterized by blood vessel inflammation and the potential development of coronary artery aneurysms. Additionally, MIS-C patients may exhibit symptoms similar to KDs, including fever, rash, conjunctivitis, and oropharyngeal congestion. However, these non-specific clinical features can also occur in pediatric infectious diseases. As a result, the extent of overlap between KD and MIS-C remains unclear. Despite these similarities, there are distinct differences between the two conditions, including differences in age distribution, ethnic disparities, clinical symptoms, inflammatory markers, and treatment strategies, as outlined in Table 1 (9,11,13–16).

Table 1. Differences between KD and MIS-C.

Variables	KD	MIS-C
Age	Commonly affects infants and younger children (<5 years).	Commonly affects adolescents and older children (>7 years)
Sex (M/F ratio)	1.5:1 - 1.7:1	1:1 - 1.2:1
Ethnicity	Asian descent	Hispanic and Black descent
GI symptoms	Less common (around 20%)	More common (53%-92%)
Multiorgan dysfunction	Not common	Common
Myocardial dysfunction/shock	Less common • 5% get vasoactive treatment	Common • 48% get vasoactive treatment • 50% elevated troponin levels • 73% elevated BNP
Inflammatory markers	• Elevated D-dimer • Elevated CRP • Normal ferritin • Thrombocytopenia is rare	• Highly elevated CRP, ferritin, D-dimer, and procalcitonin • Thrombocytopenia • Lymphopenia
Treatment	• Corticosteroids • IVIG • IL-1 blockers	• Corticosteroids • IVIG • IL-1 blockers • IL-6 inhibitors
Outcome	Mortality rate of 0.01%	Mortality rate of 1.4-1.7%

KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; GI, gastrointestinal; BNP, B-type natriuretic peptide; CRP, C-reactive protein; IVIG, intravenous immunoglobulin.

Epidemiology

The American Academy of Pediatrics reported the first case of multisystem inflammatory syndrome in children (MIS-C) in April 2020, involving a previously healthy child who was diagnosed and treated for Kawasaki disease (KD) while also having a COVID-19 infection (17). Following this, a group of children in the United Kingdom was hospitalized in the critical care unit with symptoms of atypical KD and a multisystem inflammatory state, and testing confirmed the presence of concurrent COVID-19 infection (18). Since then, cases of MIS-C have been reported in children across various countries (19–22).

A comparison of the epidemiological features of multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease (KD) reveals that the majority of MIS-C cases occur in older children and adolescents, with peak prevalence in those aged 5 to 14 years, and a higher male predominance (6,10). In contrast, KD is more commonly seen in newborns and younger children (23). A systematic review of 24 studies involving a total of 270 MIS-C patients reported a male-to-female ratio of nearly

1:1 (24), while another study of 655 MIS-C patients found a ratio of 1.2:1 (25).

In terms of ethnicity, a MIS-C case series (n = 99) from hospitals in New York State found that the majority of patients were Black (40%), followed by White (37%), and Asian (5%) (26). Other studies have shown that Africans, Afro-Caribbeans, and Hispanics/Latinos are among the ethnic groups most affected by MIS-C, in contrast to Kawasaki disease (KD), which is more prevalent in East Asia (8,27,28).

A study from the United Kingdom found that the incidence of MIS-C in children peaked in April 2020, approximately four weeks after the country experienced a significant increase in COVID-19 cases (29). Similar trends were observed in epidemiological investigations conducted in the United States and France (9,30). On the other hand, about one-third of children with MIS-C tested positive for COVID-19, while the majority tested positive for antibodies, indicating past infection (29).

Pathophysiology

The exact pathophysiology of multisystem inflammatory syndrome in children (MIS-C) remains unclear; however, it appears to result from the release of inflammatory mediators and excessive immune system activation, akin to a cytokine storm (31). The causes of end-organ damage in MIS-C have been hypothesized to include endothelial dysfunction associated with SARS-CoV-2 and the cytokine storm (32).

Some studies suggest that the SARS-CoV-2 spike protein may function as a superantigen, directly activating the immune system (32,33). Myocardial injury in MIS-C can result from systemic inflammation, hypoxia, cardiomyopathy, viral myocarditis, or coronary artery involvement, leading to ischemia (32,34). Additionally, autopsy findings have revealed evidence of endocarditis, myocarditis, and pericarditis, with infiltrating inflammatory cells and the presence of the COVID-19 virus in cardiac tissue (35,36).

Clinical presentations

As previously mentioned, MIS-C is characterized by prolonged fever, severe inflammation, and organ dysfunction associated with COVID-19 exposure (8). The clinical presentations of MIS-C may meet some or all of the diagnostic criteria for Kawasaki disease (KD). However, studies have shown that MIS-C is more likely to involve multiple organ systems and present with gastrointestinal symptoms compared to patients with KD (37).

According to published case series, MIS-C cases exhibit similar clinical manifestations, including fever (100%), skin rashes (45-60%), gastrointestinal involvement (diarrhea, abdominal pain, or vomiting in 53-92%), respiratory involvement (21-63%), mucosal changes (29-35%), and conjunctivitis (29-56%) (9,11,13,19,26). In severe MIS-C cases, cardiogenic shock, myocardial dysfunction, cytokine storm, septic shock, toxic shock syndrome, and multisystem organ failure may also occur, which can overlap with the presentation of Kawasaki disease (KD) (38–40).

In a study of 186 patients with MIS-C in the United States, researchers found that 71% involved at least four organ systems. The most commonly affected system was the gastrointestinal, followed by the cardiovascular, hematologic, mucocutaneous, and respiratory systems (9). Additionally, the study found that approximately 40% of MIS-C cases met the diagnostic criteria for incomplete Kawasaki disease (KD) or KD, with the majority of patients experiencing fever for five or more days (9).

A study of 616 MIS-C cases found that 20% of patients had neurologic involvement. Notably, 20 (3.2%) patients experienced life-threatening neurologic disorders, including acute fulminant cerebral edema, Guillain-Barré syndrome, stroke, and severe encephalopathy (41). Cardiac abnormalities are common in MIS-C, with myocarditis, myocardial dysfunction, coronary artery aneurysms or dilatation, and arrhythmias affecting more than 80% of patients (42,43).

Laboratory findings

The hallmark laboratory finding in MIS-C patients is systemic inflammation. Inflammatory markers such as ferritin, procalcitonin, serum IL-6, and C-reactive protein (CRP) are elevated in these patients (9,11,44,45). Additionally, thrombocytopenia and an elevated erythrocyte sedimentation rate (ESR) are common (25,46). MIS-C patients typically exhibit lower lymphocyte and platelet counts and higher procalcitonin and ferritin levels than those with Kawasaki disease (KD) (11,47–49).

The symptoms of MIS-C resemble those of macrophage activation syndrome, with elevated levels of D-dimer, ferritin, and triglycerides, along with a cytokine storm (37,44). However, the cytokines driving the inflammatory processes in Kawasaki disease (KD) and MIS-C appear to differ slightly. In KD, IL-1 seems to be the primary mediator of coronary artery inflammation, whereas in MIS-C, IL-6 and IL-8 appear to play a more prominent role (50). Table 2 presents the laboratory results of MIS-C patients as reported in the published case series (6,8–10,13,19,27,51,52).

Table 2. Laboratory results of MIS-C.

Laboratory findings		Frequency (%) *
Elevated inflammatory markers	ESR	75-80
	CRP	90-100
	Ferritin	55-76
	Fibrinogen	80-100
	D-dimer	67-100
	IL-6	80-100
	Procalcitonin	80-95
Abnormal blood cell counts	Neutrophilia	68-90
	Lymphocytopenia	80-95
	Thrombocytopenia	31-80
	Mild anemia	70
Elevated cardiac markers	BNP or NT-pro-BNP	73-90
	Troponin	50-90
Others	Hypertriglyceridemia	70
	Elevated lactate dehydrogenase	10-60
	Elevated liver enzymes	62-70
	Hypoalbuminemia	48-95

ESR: Erythrocyte sedimentation rate; IL-6: Interleukin 6; CRP: C-reactive protein; NT-pro-BNP: N-terminal pro-BNP; BNP: brain natriuretic peptide.
*The frequencies indicated in this table show the percentage of patients who have each found out of all individuals tested or assessed for it. Not all patients were tested or evaluated for each.

Imaging findings

Most MIS-C cases have normal chest radiographs; however, abnormal imaging findings such as patchy consolidation, atelectasis, focal consolidation, and pleural effusion have been observed. Chest computed tomography (CT) scans showed similar results to those of children with COVID-19, with ground-glass opacification being a common finding (53,54). In a study by Feldstein et al. involving 503 MIS-C patients, echocardiography revealed depressed left ventricular (LV) systolic function in 34% of patients, and 13% had coronary artery aneurysms (9).

Echocardiographic evaluation of 286 MIS-C patients revealed that 28% had pericardial effusion, 6% had tricuspid regurgitation, 42% had mitral regurgitation, and 34% had depressed left ventricular (LV) systolic function (55). Additionally, cardiac magnetic resonance imaging (MRI) showed myocardial edema in 14 patients, with late gadolinium enhancement observed in 6 patients (55). A study by Blondiaux et al. reported that cardiac MRI in MIS-C patients revealed diffuse myocardial edema on T2-STIR sequences, without any evidence of late gadolinium enhancement suggestive of replacement fibrosis or focal necrosis (56).

Diagnosis

The three MIS-C definitions provided by the Royal College of Pediatrics and Child Health (RCPCH) (52)The World Health Organization (WHO) (57), and the Centers for Disease Control and Prevention (CDC) (8), are summarized in Table 3.

Table 3. Case definition of MIS-C by RCPCH, CDC, and WHO.

	RCPCH	CDC	WHO
Age (years)	Children	< 21	0 – 19
Clinical features	• Single or multi-organ failure: ○ Gastrointestinal ○ Cardiovascular ○ Respiratory ○ Renal ○ Neurologic ○ Hematologic	• Multisystem organ involvement (≥ two organs): ○ Gastrointestinal ○ Cardiovascular ○ Respiratory ○ Hematologic ○ Renal	At least **two** of the following are required: • Acute gastrointestinal presentations like abdominal pain, vomiting, and diarrhea. • Coagulopathy

	• **Most** of the patients develop hypotension and require oxygen therapy. • **Some** of the patients suffer from the following symptoms: ○ Cough ○ Confusion ○ Headache ○ Diarrhea ○ Conjunctivitis ○ Abdominal pain ○ Vomiting ○ Mucus membrane changes ○ Lymphadenopathy ○ Sore throat ○ Rash ○ Neck swelling ○ Syncope ○ Swollen hands and feet	○ Neurologic ○ Dermatologic • Evidence of a clinically severe disease that necessitates admission to the hospital.	• Features of coronary abnormalities, valvulitis, pericarditis, or myocardial dysfunction • Hypotension or shock • bilateral non-purulent conjunctivitis, rash, or evidence of mucocutaneous inflammation
Fever	Fever>38.5°C	• A subjective fever that lasts more than 24 hours • Documented fever of >38.0°C for more than 24 hours	Fever ≥ 3 days
COVID-19 infection evidence	The results of SARS-CoV-2 RT-PCR testing might be either negative or positive.	• Positive RT-PCR, serology, or antigen test for present or recent COVID-19 infection • Exposure to COVID-19 patients during the 4 weeks before symptoms	• Positive RT-PCR, antigen test, or serology • Exposure to patients with COVID-19
Laboratory findings	• The following test results would be found in **all** of the patients: ○ High CRP ○ Abnormal Fibrinogen ○ Neutrophilia in most and normal ○ neutrophils in some ○ Lymphopenia ○ Hypoalbuminemia ○ High ferritin ○ High D-dimer • **Some** of the patients may have the following test results: ○ Thrombocytopenia ○ Raised troponin ○ Raised triglycerides ○ Raised LDH ○ Raised CK ○ Proteinuria ○ Neutrophilia ○ High IL-6 ○ High IL-10 ○ Coagulopathy ○ Anemia	• One or more of the following test results: ○ High CRP ○ Elevated ESR ○ High fibrinogen ○ High D-dimer ○ Elevated procalcitonin ○ High ferritin ○ Raised LDH ○ High IL-6 ○ Neutrophilia ○ Lymphopenia ○ Hypoalbuminemia	• Elevated inflammatory markers, including procalcitonin, ESR, or CRP • Evidence of coagulopathy (by INR, PTT, PT, and D-dimer)
Excluding additional microbial sources	• Exclusion of other microbial diseases: ○ Streptococcal or staphylococcal shock syndromes ○ Bacterial sepsis ○ Infectious myocarditis	There are no other plausible diagnoses.	Alternative microbial inflammation causes, such as streptococcal or staphylococcal shock syndromes or bacterial sepsis, must be excluded.

Toxic shock syndrome, Kawasaki disease (KD), bacterial sepsis, myocarditis, macrophage activation syndrome, and various viral infections are among the differential diagnoses for patients with symptoms consistent with MIS-C (53). One of the primary differential diagnoses in patients with prolonged fever and elevated inflammatory markers is bacterial infection, which should be evaluated for localized sources such as meningitis, pneumonia, or soft tissue infections (58).

Treatment

Management and treatment of MIS-C require the involvement of specialists based on the patient's clinical presentation, including pediatric rheumatologists, cardiologists, intensivists, and immunologists (27,29,59). Published recommendations are primarily based on expert consensus due to the lack of robust evidence. In the acute phase, supportive treatments such as mechanical ventilation, inotropes, fluid resuscitation, and extracorporeal membrane

oxygenation (ECMO) may be essential (9,11,19,27,55,60). Immunomodulators are the mainstay of treatment for MIS-C, suggesting that the disorder results from post-infectious immunological dysregulation (61).

Most patients have responded well to high-dose intravenous immunoglobulin (IVIG), alone or combined with corticosteroids. These treatment protocols were based on Kawasaki disease (KD) recommendations, and the combination of IVIG with corticosteroids has been associated with a reduced treatment failure rate (9,11). Treatment with methylprednisolone plus IVIG resulted in better fever control compared to IVIG alone (62). Antiplatelet medications and anticoagulants are also considered first-line therapies (11,19,55).

Monoclonal antibodies targeting the IL-1 receptor antagonist, IL-6 receptor, convalescent plasma therapy, and monoclonal antibodies against TNF-α have been used to treat refractory MIS-C patients (12).

Prognosis and follow-up

The MIS-C mortality rate has been reported as 1.4% in Europe and 1.7% in the United States (25). Despite critical care and significant cardiovascular involvement, the majority of MIS-C patients (70–97%) recover without complications (9,55,62–64). Even in MIS-C patients without cardiovascular involvement, echocardiographic follow-up is essential, as coronary aneurysms have been documented to develop during the convalescent phase of the disease (11). Until more is known about long-term morbidity, it is acceptable to use Kawasaki disease (KD) guidelines to guide outpatient follow-up (9,11). In the study by Sezer et al., 65% of 123 MIS-C patients had echocardiographic abnormalities at admission, and by the third month of follow-up, 2.9% had coronary involvement, 6.7% had left ventricular hypertrophy, 2.9% had left ventricular dysfunction, 8.7% had valve failure, and 7.7% had secundum atrial septal defect (ASD) (65).

Conclusion

MIS-C is a novel pediatric condition associated with COVID-19, characterized by fever, multi-organ involvement, and elevated inflammatory markers. Its clinical features share similarities with Kawasaki disease (KD), and KD recommendations guide treatment. Based on the limited available data, the health of MIS-C patients can deteriorate rapidly, making prompt identification, treatment, and referral essential. As a newly identified disease, much remains to be learned about its long-term prognosis. Further research is needed to establish standardized diagnostic criteria and improve treatment strategies.

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