Who Would Have Predicted Multisystem Inflammatory Syndrome in Children?

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Abstract

Purpose of Review Multisystem inflammatory disease in children (MIS-C) is a novel post-infectious phenomenon following coronavirus disease-19 (COVID-19). Herein, we present an in-depth review of the latest MIS-C literature related to clinical findings, pathophysiology, imaging and laboratory studies, treatment algorithms, and disease outcomes.

Recent Findings With its non-specific presentation of fever, gastrointestinal symptoms, cardiovascular injury and shock, systemic inflammation, and Kawasaki disease (KD)-like features, MIS-C can be a diagnostic challenge, overlapping with KD and active COVID-19 infection. However, common laboratory features, imaging findings, and historical clues can lead to accurate diagnosis and allow for appropriate treatment with a variety of immunomodulatory therapies, including intravenous immunoglobulin (IVIG). Aggressive treatment of MIS-C leads to good outcomes. Longitudinal studies continue to illumine long-term cardiac sequelae and recovery.

Summary MIS-C presents with fever, KD features, gastrointestinal symptoms, cardiac inflammation, and shock. Early recognition and prompt institution of IVIG and glucocorticoids provide for rapid improvement.

Keywords COVID-19 · MIS-C · Inflammation · Pediatric rheumatology · Kawasaki disease · Cytokine

Introduction

Since its appearance in late 2019, the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has infected over 200 million people worldwide and has caused over 4.5 million deaths. Ranging from asymptomatic to mild upper respiratory infectious symptoms to severe clotting abnormalities, shock, and acute respiratory distress syndrome, COVID-19 has had the most severe impact on the adult population, with the pediatric population relatively less affected during acute infection. However, early into the COVID-19 pandemic, a report arose out of the United Kingdom (UK) describing a cohort of 8 patients who presented with hyperinflammatory shock, findings similar to Kawasaki disease (KD), gastrointestinal symptoms, and coronary artery changes, requiring significant cardiovascular support and immunomodulatory therapy [1•]. This was one of the first articles to report a presentation of the novel multisystem inflammatory syndrome in children (MIS-C), which has since affected tens of thousands across the globe. Other reports came from Europe describing a novel pandemic within a pandemic [2•]. This came to most everyone’s surprise, although similar KD-like clusters have been reported previously in association with coronavirus infections, prompting some to postulate the KD should really be Kawasaki syndrome [3, 4]. Over the last year and a half, much has been learned about MIS-C, and herein, we review this influential and novel disease as it continues to affect children both in the United States (US) and abroad.

Definitions of MIS-C

Multiple central agencies have published case definitions and diagnostic criteria for MIS-C (Table 1). The United States Centers for Disease Control defined MIS-C as an individual
Table 1: MIS-C, PIMS-TS, and MIS-A case definitions

|                  | CDC MIS-C case definition [5] | WHO MIS-C case definition [6] | RCPCH PIMS-TS case definition [7] | CDC MIS-A case definition [8] |
|------------------|-------------------------------|-------------------------------|-----------------------------------|-------------------------------|
| **Age**          | <21 years old                 | 0–19 years old               | Child (unspecified age)           | ≥ 21 years old + hospitalized for ≥ 24 h OR with illness resulting in death |
| **Fever**        | Fever ≥38.5 °C (or subjective fever) for ≥24 h | Fever ≥3 days (unspecified degree) | Persistent fever (unspecified degree) | Feversubjects or documented fever ≥38.5 °C for ≥24 h prior to and/or within the first 3 days of hospitalization |
| **Inflammation** | Laboratory evidence of inflammation | Elevated markers of inflammation | Inflammation | Requires 3 of the following clinical criteria (one must be a primary clinical criterion), evidence of inflammation, and SARS-CoV-2 infection: |
|                  | - One or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin | - ESR, CRP, procalcitonin | - ESR, CRP, elevated CRP, and lymphopenia | |
| **System involvement** | Clinically severe illness requiring hospitalization with ≥2 organ systems involved | Two of the following: - Rash or bilateral conjunctivitis or mucocutaneous inflammation - Hypotension or shock - Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities via echocardiography findings or elevated cardiac enzymes - Evidence of coagulopathy by PT, PTT, elevated d-dimers - Acute gastrointestinal problems—diarrhea, vomiting, abdominal pain | Single or multi-organ dysfunction: - Shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder - May include children fulfilling full or partial KD criteria - “Additional features”—broad list of symptoms, lab findings, and imaging in appendix of criteria | - Severe cardiac illness: myocarditis, pericarditis, coronary artery changes, or new-onset RV/LV dysfunction. 2nd/3rd degree AV block, or ventricular tachycardia - Rash and non-purulent conjunctivitis |
| **Rule-out of additional causes** | No alternative plausible diagnosis | No other obvious microbial cause of inflammation - Rule-out bacterial sepsis, staph, or sepsis shock syndromes | Exclusion of other microbial causes - Bacterial sepsis, staph/sepsis shock syndromes, viral myocarditis-related infections | Secondary criteria |
| **COVID-19 link** | Current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to suspected or confirmed COVID-19 case within 4 weeks | Evidence of COVID-19 (RT-PCR, antigen test, serology positive), or likely contact with COVID-19 patient | Positive or negative SARS-CoV-2 PCR testing | Laboratory evidence |

*RT-PCR*, reverse transcription-polymerase chain reaction; *PT*, pro-thrombin time; *PTT*, partial thromboplastin time; *ESR*, erythrocyte sedimentation rate; *CRP*, c-reactive protein; *IL-6*, interleukin-6; *RV*, right ventricle; *LV*, left ventricle; *AV*, atrioventricular
less than 21 years of age presenting with fever, elevated inflammatory markers, and severe illness with greater than two organ systems involved, and positive COVID-19 serology, SARS-CoV-2 antigen test, polymerase chain reaction (PCR), or exposure to COVID-19 within the 4 weeks prior to symptoms, and no alternative diagnoses [5]. The World Health Organization added their slightly varied definition, including patients 0–19 years of age with fever for at least 3 days, elevated markers of inflammation, no other obvious source, evidence of COVID-19 via PCR, antigen testing, serologies, or likely sick contact, and two of the following: rash, conjunctivitis, or mucocutaneous inflammation; hypotensive shock; cardiac dysfunction; coagulopathy; or gastrointestinal symptoms [6]. In the UK, MIS-C is alternatively known as pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and is more broadly defined: a child presenting with fever, inflammation, positive or negative SARS-CoV-2 PCR, and organ system dysfunction with additional possible clinical, imaging, and laboratory features (such as abdominal pain, Kawasaki-like symptoms, gastrointestinal symptoms, cardiac dysfunction), excluding other microbial causes [7]. Regardless of the definition used, the common threads of a pediatric patient presenting with fever, inflammation, multiple organ system dysfunction, and severe illness are present in all criteria.

Starting in June 2020, reports arose of similar hyperinflammatory shock and severe illness in the adult population, leading to the defining of the multisystem inflammatory syndrome in adults (MIS-A) by the Centers for Disease Control. MIS-A is defined in patients greater than or equal to 21 years of age by similar criteria of severe cardiac illness, new-onset neurological symptoms, shock/hypotension, abdominal symptoms, thrombocytopenia, rash or conjunctivitis, evidence of systemic inflammation, and positive SARS-CoV-2 testing [8].

**Epidemiology and Demographics**

During the COVID-19 pandemic, children have been relatively spared in both infection rate, illness severity, and mortality. Since its onset, pediatric patients have accounted for 12.8% of total COVID-19 cases and 0.1% of total deaths, despite accounting for 22.3% of the total US population [9]. However, given that pediatric patients and younger children are more likely to be asymptomatic during their acute COVID-19 infection, it is likely that pediatric COVID-19 cases have been underestimated due to missed infections and underestimating since the appearance of this novel disease.

Comparatively, among the millions of pediatric patients diagnosed with active COVID-19, MIS-C seems to be a rare but serious manifestation. In the largest population study of 1733 MIS-C patients, the incidence was reported to be 2.1 cases per 100,000 children and, in line with the established case definitions and the post-infectious illness theory, peaks in MIS-C cases followed local COVID-19 outbreaks by 2–5 weeks [10]. Incidence seems to differ by age, with an incidence of 2.3–2.9 cases per 100,000 children in 0–9 year olds, decreasing to 0.4–1.5 per 100,000 in 15 to 20-year-old patients [10].

When analyzing the six largest studied (> 100 patients) MIS-C cohorts of international and US children, the median age of the affected patient is 7–8.9 years of age, and data shows a slight male predominance of 54.7–67.8% of cases, similar to KD [10–12, 13•, 14•]. MIS-C patients seem to be overwhelmingly healthy at baseline as 69.1–88.4% of patients did not have any prior medical conditions [12, 13•, 15]. Consistent throughout most US MIS-C studies are broad racial and ethnic differences in prevalence and incidence of MIS-C. Black and Hispanic children are overrepresented in US MIS-C cohorts, making up 25–34.7% and 31–37.4% of patients diagnosed with MIS-C respectively, despite representing 13.4% and 18.5% of the total US population, per the most recent census data [10, 12, 13•, 16]. This discrepancy is likely multifactorial, as Black and Hispanic patients have also been affected by active COVID-19 infection at similar discordant rates. Racial and ethnic minority background and low socioeconomic status has been shown to increase the risk for SARS-CoV-2 infection in both the adult and pediatric population, and increased the risk for morbidity and death in adults [17, 18]. It is unclear what proportion of these racial and ethnic differences in MIS-C development is related to risk for COVID-19 infection and/or appropriate access to medical care; further study needs to be pursued to evaluate the reason for this discrepancy.

**Pathophysiology**

The pathophysiology of MIS-C is a much-debated topic in the literature, with no consensus yet identified. MIS-C is believed to be a post-infectious phenomenon, occurring a number of weeks after a primary COVID-19 infection. National geographic and temporal associations have been found between peaks of MIS-C cases and COVID-19 infection rates in the USA, with MIS-C peaks following peaks in COVID-19 infections by 2–5 weeks [10, 13•, 19•]. This post-infectious hypothesis is given further weight as the majority of MIS-C patients is positive for IgG antibodies against SARS-CoV-2 and has significantly lower SARS-CoV-2 PCR cycle thresholds from nasopharyngeal viral testing as compared to active COVID-19 infection, indicating viral clearance [11, 12, 15, 19•, 20•].

Along with findings of a post-infectious pathogenesis, MIS-C is typified by a specific hyperinflammatory response
and there have been many looking to profile this hyperinflammation with a multitude of biomarkers studied. From a cytokine and chemokine standpoint, high levels of interleukin (IL) 1β, IL-6, IL-8, IL-10, IL-17, interferon-γ (IFN-γ), and CXCL-9 have been identified in MIS-C patients, with some correlated with disease activity and severity [21••, 22••, 23, 24]. Specifically, CXCL-9 (a marker of IFN-γ) levels have been shown to correlate with the level of inflammatory markers and cardiac dysfunction seen in MIS-C [25]. Studies have also shown activation of monocytes and neutrophils, decreased levels of circulating T-cells and natural killer cells, and lower total levels of B cells, highlighting the importance of certain immune cell lines in MIS-C disease activity and the recovery of these cell lines in disease recovery [21••, 23, 26].

Another mechanism of disease activity hypothesized is endothelial dysfunction leading to shock and cardiac injury and pro-coagulation leading to microvascular injury. MIS-C patients have been shown to have elevated levels of angiopoietin-2 (associated with vascular injury) and high angiopoietin-2/angiopoietin-1 ratios correlated with the level of shock severity and heart failure [27]. Additionally, secondary activation of auto-reactive antibodies arises in the MIS-C disease process, with some of these auto-antibodies targeted to antigens expressed in endothelial and cardiac tissues, as well as the gastrointestinal tract [23]. Along with this endothelial activation, thromboelastometry of MIS-C samples demonstrates hypercoagulability within the hyperinflammatory state [28].

Presentation and Clinical Findings

Presenting Symptoms

The presenting symptoms of MIS-C vary significantly in their severity and presence throughout the disease spectrum. Fever is the predominant symptom in MIS-C, usually persisting for 2–4 days prior to diagnosis, and as such is the mainstay of most diagnostic criteria [11, 12, 15, 19•]. Gastrointestinal symptoms of nausea/vomiting, diarrhea, and abdominal pain are common complaints, present in 60–90% of patients in the largest cohorts of patients [11, 12, 15, 19•]. Mucocutaneous and Kawasaki-like symptoms of conjunctivitis, rash, and mucosal changes are also frequent within MIS-C, appearing in 60–70% of all patients and seen in increased frequency in younger MIS-C patients [12, 19•]. Cardiovascular involvement has been reported in a significant proportion of MIS-C patients at 60–80% with tachycardia and hypotension among the most commonly reported symptoms [11, 12, 15, 19•]. Respiratory involvement has been reported variably and inconsistently in the literature, as its definition diverges widely from cough/congestion to respiratory failure requiring invasive mechanical ventilation. It is unclear as to the true respiratory involvement in MIS-C as respiratory failure and ventilatory needs can be due to primary disease activity, pulmonary edema from intensive volume resuscitation, and secondary to cardiovascular shock. Similar variable reporting is seen in neurologic system involvement, as definitions vary from headache and altered mental status to stroke, encephalitis, and demyelinating disorders. Neurologic symptoms have been reported in 11–40% of MIS-C patients dependent on the definition employed [11, 12, 15, 19•]. Other less common findings reported include lymphadenopathy, thrombosis, muscle aches and pains, and joint pain.

MIS-C symptoms are hardly specific and can involve almost any organ system with varying severity and timing. However, there have been important studies that have helped to identify different phenotypes under the MIS-C umbrella and to assist in improved diagnosis and treatment. Godfred-Cato et al. analyzed a 570 patient MIS-C cohort via latent class analysis and identified three distinct groupings of patients [29]. One group was likely active COVID-19 infection that was misclassified, but the other two groups separated MIS-C patients into two different subsets. The first MIS-C subset identified had very high frequency of cardiovascular and gastrointestinal involvement, with a significantly higher prevalence of abdominal pain, shock, myocarditis, inflammatory marker elevation, and SARS-CoV-2 serology positivity. The second MIS-C subset was significantly younger with a higher prevalence of Kawasaki-like mucocutaneous symptoms and rash, frequent coronary changes, and with less shock than the first MIS-C group [29]. Similar findings have been demonstrated by Geva et al., who identified features that cluster patients into a high likelihood of having MIS-C: previously healthy status at baseline, cardiovascular and mucocutaneous involvement, gastrointestinal symptoms, and high levels of inflammation and brain natriuretic peptide (BNP) [30].

Laboratory Values and SARS-CoV-2 Testing

Despite its wide array of clinical characteristics and symptomatology, MIS-C does have some consistent laboratory findings that are seen on presentation. White blood cell (WBC) count is generally normal to elevated with absolute lymphopenia, normal to elevated neutrophil counts, and high neutrophil/lymphocyte ratio, like COVID-19. Platelet count can be normal or depressed, with thrombocytopenia correlating with disease severity, and a post-inflammatory thrombocytosis can be seen, similar to that in KD [11, 12, 15, 19•]. Elevation in liver enzymes and creatinine can be seen in cases with hypotension, severe inflammation, and end-organ hypoperfusion. Inflammatory markers are quite elevated, with high levels of C-reactive protein (CRP), erythrocyte
sedimentation rate (ESR), and ferritin seen in the majority of cases. Coagulation abnormalities are seen with elevation in d-dimer and fibrinogen, and lactate dehydrogenase (LDH) levels are elevated. During the disease course with ongoing vascular leak and third spacing, albumin and hemoglobin levels decrease and slowly normalize with treatment. Finally, those with significant cardiac involvement have elevated levels of troponin and BNP [11, 12, 15, 19•].

As previously discussed, a high percentage of MIS-C patients are positive for SARS-CoV-2 IgG antibodies against the nucleocapsid protein, indicating past infection with COVID-19. Cohorts vary widely in the percentage of MIS-C patients testing positive and range from 60–90% positive for SARS-CoV-2 IgG antibodies [11, 12, 15, 19•]. However, the case definitions allow for PCR positivity to count toward the diagnostic criteria, and studies have shown that MIS-C patients can be simultaneously positive for both SARS-CoV-2 PCR and IgG in 30–40% of cases [11, 12, 15, 19•]. This dual positivity can create a diagnostic dilemma for providers, muddying the picture between MIS-C and active COVID-19. However, it is likely that these dual-positive patients are not actively infectious. As mentioned previously, MIS-C patients have higher PCR cycle thresholds (indicating lower viral RNA levels) than active COVID-19 patients and additional studies have shown that PCR can remain positive in nasopharyngeal samples for a significant amount of time after viral clearance tested in culture [20••, 31].

Cardiac Findings

In patients with cardiovascular involvement, echocardiography, cardiac magnetic resonance imaging (MRI), and electrocardiography demonstrate findings of myocardial dysfunction, coronary dilatation/aneurysms, and conduction abnormalities. EKG is performed in a proportion of MIS-C patients and studies vary widely in the prevalence of abnormalities. Abnormal EKGs have been reported in 35.3–67% of patients on presentation with low QRS amplitudes, transient T wave inversion, and arrhythmias [14, 32]. Studies have found arrhythmias in upwards of 8–21% of patients with AV block seen in 2–20% [12, 14, 33, 34]. Echocardiography in MIS-C patients shows reduced left ventricular systolic function and ejection fraction in 30–40% of patients and can show valvular regurgitation and pericardial effusion [12, 13•, 14, 35, 36]. Similar to KD, MIS-C has been associated with coronary artery aneurysms and dilatation; echocardiography has shown dilatation and/or aneurysm in 13–28% of patients [12, 14, 35]. Cardiac MRI is less frequently performed in acute MIS-C and is most often used to monitor the recovery of patients after hospitalization. However, cardiac MRI in small hospitalized cohorts has found T2 hyperintensity, pericardial effusions, myocardial edema, and late gadolinium enhancement without evidence of focal necrosis or fibrosis [14, 37].

Non-cardiac Imaging

Non-cardiac imaging in MIS-C can show a wide variety of findings that point toward systemic inflammation of multiple organ systems. In children with significant abdominal symptoms, common findings on abdominal computed tomography (CT) were ascites, hepatomegaly, and localized ileitis or diffuse bowel wall edema [38, 39, 40•]. In the setting of predominant gastrointestinal symptoms, those with localized ileitis may be at increased risk for an incorrect diagnosis of appendicitis, especially if imaged only with appendix ultrasound [41]. Chest CT and radiography in MIS-C patients can demonstrate residual ground-glass opacities, pleural effusion, consolidation, and peribronchial thickening [39, 40•, 42]. In patients with neurologic abnormalities, brain imaging can be helpful to differentiate between reversible or fulminant neurologic findings, as MRI has demonstrated a wide variety of findings including ischemic or hemorrhagic stroke, white matter hyperintensities, corpus callosum changes, and demyelination [43•].

Differentiation of MIS-C from KD and Acute COVID-19

MIS-C and KD

MIS-C and KD are very similar in the acute presentation, and the similarity of these two disease processes guided much of the initial treatment algorithms for MIS-C. However, there are some key differences that differentiate the two disease processes, both in their clinical presentation and pathogenesis. Patients with MIS-C are more likely to present with cardiac, gastrointestinal, coagulopathic, and neurologic symptomology than patients with KD and more often require intensive care [44, 45]. KD patients are generally younger at disease onset with a lower prevalence of cytopenias and a lower degree of hyperferritinemia than those with MIS-C [44, 45]. These differences in the clinical presentation can possibly be explained by subtle differences in the inflammatory profiles seen with these two disease processes. Both KD and MIS-C show high levels of inflammatory cytokines and chemokines, including IFN-γ, IL-18, and IL-1α, but differ in the expression of CXCL9, with MIS-C patients expressing higher levels [25, 46].

MIS-C and Active COVID-19

Throughout the pandemic and especially in locations with constant community spread of SARS-CoV-2, peaks of
MIS-C and active COVID-19 infections have significant overlap, creating a diagnostic dilemma for healthcare providers. With somewhat non-specific lab findings and clinical presentations, much work has been done to differentiate active COVID-19 infection and post-infectious MIS-C, as they require different workup and treatment. Patients with active COVID-19 infection are more likely than MIS-C patients to have underlying medical conditions and to be of a racial or ethnic minority [12, 47–49]. On presentation, fever, gastrointestinal involvement, cardiac involvement, and KD-like symptoms were more common in MIS-C patients, where COVID-19 infected patients were more likely to suffer from primary respiratory symptoms [12, 47–49]. Patients with MIS-C have higher neutrophil counts, higher neutrophil to lymphocyte ratios, higher levels of inflammation (CRP and ESR), lower levels of LDH, and lower platelet counts than those with COVID-19 [12, 47–49]. Therapies for MIS-C and COVID-19 are similar, but not identical.

**Treatment**

There are no universally accepted treatment algorithms for MIS-C to date, but many institutions and medical societies have published individual guidelines that have changed and adapted throughout the pandemic. A general treatment algorithm can be found in Table 2.

**Supportive Care**

Initial treatment of MIS-C is focused on immediately treating life-threatening sequelae of the disease process including cardiac dysfunction, respiratory failures, and end-organ injury. The range of illness severity seen with MIS-C is broad, ranging from supportive care measures in mild cases to invasive mechanical ventilator support and extracorporeal membrane oxygenation (ECMO) in severe cases. In the largest cohorts of MIS-C patients, vasoactive/inotropic medications were required in 14.7–45% of cases, invasive ventilatory measures were required in 15.3–23.5% of patients, and ECMO was required in 0.3–4% [11, 12, 13•, 14]. Many children with MIS-C present severely ill, often requiring intensive care. Fortunately, immunomodulatory therapies are typically rapidly effective.

**Immunomodulatory Therapies**

Since the initial reports of MIS-C cases, the mainstays of immunomodulatory treatment have been intravenous immunoglobulin (IVIG) and corticosteroids, given MIS-C’s similarity to KD and its proposed hyperinflammatory pathogenesis. IVIG is well known to prevent coronary aneurysm in KD and is therefore the initial immunomodulatory medication of choice in the most proposed treatment algorithms at 2 g per kilogram (g/kg) dosing [50–53]. The next line medication in most MIS-C treatment algorithms is glucocorticoids, with dosing and timing of administration varying widely. Treatment algorithms generally break up steroid dosing into two groups: lower doses (1–2 mg/kg/day) used for those patients without severe cardiac manifestation or shock and higher doses (10–30 mg/kg/day) reserved for those with severe features, coronary changes, and/or shock [51–53]. In the largest cohorts of MIS-C patients, IVIG was used in 77–89% of patients with steroid use varying more widely at 28–69.4% [11, 12, 13•, 14, 19•]. Early in the pandemic, corticosteroids were used more sparingly and in sequential order after IVIG, but more recent data has shown improved outcomes with early steroid use with or without IVIG. Son et al. reported that IVIG plus steroid treatment was associated with a lower risk of cardiovascular complications and adjunctive therapy requirement as compared to IVIG alone, and Ouldali et al. showed that IVIG plus methylprednisolone versus IVIG alone was associated with lower rates of treatment failure, lower hemodynamic support requirements, and decreased length of ICU stay [54•, 55•]. Smaller studies have shown that corticosteroid use alone can even be superior to IVIG use as a first-line medication, with faster normalization of left ventricular function, fever curve, and shorter ICU stay [56]. This is particularly relevant to resource-poor settings.

Many different adjunctive therapies and immunomodulatory medications have been used with varying efficacy in MIS-C. Treatment algorithms generally recommend biologic agents as third-line medication options after initial treatment with IVIG and steroids. Anakinra is an IL-1 receptor antagonist that has been previously shown to be effective with limited side effects in KD patients [57]. Multiple studies have shown anakinra to be similarly effective in MIS-C, especially when it comes to cardiac function, after failure or poor response to IVIG and steroid treatment [58–60]. In two large cohorts, anakinra was used in 24/186 and 8/183 patients to good effect [11, 13•]. Infliximab is a tumor necrosis factor inhibitor that has long been used in IVIG-refractory KD and has been demonstrated to be similarly effective in refractory cases of MIS-C [59]. Many other therapies have been referenced as possible next-line medications in the literature, including tocilizumab and plasmapheresis.

**Anticoagulation and Thrombosis Risk**

MIS-C has been shown to have pro-thrombotic features with early elevations in d-dimers and fibrinogen, late elevation in platelet count, and evidence of hypercoagulability on thromboelastometry [28]. These findings and the similarity of MIS-C to KD have led to the generally
uniform addition of anti-platelet agents to MIS-C treatment algorithms. In most cases, a low dose of 3–5 mg/kg/day of aspirin (up to 81 mg daily) is recommended in patients with Kawasaki-like findings, coronary changes, and thrombocytosis [51–53]. If patients require both steroids and aspirin treatment, the generally accepted practice is to add gastric prophylaxis medication as well to prevent ulceration. Individual treatment algorithms have differing opinions on the use of anticoagulation in lieu of aspirin in the setting of severe disease with abnormal cardiac function, ventilatory requirements, and ICU admission. Treatment options include low molecular weight heparin, enoxaparin, and/or discussion with hematologists on an individual case basis [51–53].

### Prognosis and Outcomes

Overall, MIS-C patients overwhelmingly do well with appropriate therapy and a vast majority recover from their illness, regardless of severity. However, there are those patients who do not recover and death has been reported in 0.3–2% of MIS-C cases, higher than the mortality of pediatric active COVID-19 infection, reported to be <0.1% of pediatric cases [11, 12, 13•, 14, 63]. Increased risk of death from MIS-C is associated with patients of racial and ethnic minorities, ages 16–20 years and is seen in those with severe cardiac involvement and/or existing underlying medical conditions [64]. In those patients who survive, there is undoubtedly a long road to recovery, especially in those who require significant cardiorespiratory support with vasopressors, ventilation, and ECMO. Unfortunately, there is a lack of longitudinal studies focusing specifically on patients who require intensive interventions, but they are incorporated in other types of longitudinal studies.

Systemic inflammation has been shown to rapidly improve with appropriate treatment, including two studies of 46 and 45 MIS-C patients showing normalization of C-reactive protein, platelet count, liver enzyme levels, albumin levels, and d-dimer levels in the vast majority by 4–6 months, and in some by as early as 6 weeks [65, 66]. Cardiac function abnormalities have been shown to improve in a similar manner. In a study of 50 MIS-C patients, LV systolic dysfunction was seen at diagnosis in 52% of patients, with only 1 patient having persistent dysfunction on echocardiography at 2-week follow-up and complete resolution at 8 weeks [67•]. Additional studies have utilized cardiac MRI at follow up for more specific analysis of cardiac function. In a study of 20 patients referred for follow-up cardiac MRI, 50% had LV ejection fraction <55% during acute MIS-C, but all had complete normalization of all cardiac abnormalities within 2–6 weeks after discharge [68]. Another study of 19 consecutive MIS-C patients with LV ejection fraction <55% showed no persistent cardiac changes at a median follow-up of 99 days post-hospitalization [69]. Finally, a large source of concern for medical providers is the development and persistence of coronary artery dilatation and aneurysm formation in MIS-C patients. Coronary artery dilatation (z > 2) has been reported in 9–24.1% of MIS-C cases [11, 12, 13•, 14]. However, in multiple follow-up studies, coronary changes have been shown to resolve with appropriate treatment—one study reported 7 out of 45 (15.6%) patients with coronary changes on admission, all resolved within 1–4 weeks [66], and another study demonstrated coronary changes in 12 out of 50 (24%) patients that resolved by 8 weeks.
to 6 months [67•]. Overall, those MIS-C patients that are appropriately treated and recover from the initial disease course have promising longitudinal outcomes, with continued research ongoing.

**Conclusion**

MIS-C is a novel, post-infectious manifestation of SARS-CoV-2 with characteristics similar to KD and typified by intense inflammation throughout the body, affecting most organ systems. Although clinical symptoms and laboratory findings can be somewhat non-specific, unique patterns have been identified to aid clinicians in appropriate diagnosis and differentiation from similar disease processes. When treated appropriately with immunomodulatory therapy, early longitudinal data has shown relatively optimistic outcomes for recovery of overall health and cardiac dysfunction. However, current cohorts of MIS-C patients will need to be followed further, to fully grasp the long-term effects of this condition. Further study is also needed into the pathophysiology of MIS-C to develop more targeted therapies and in anticipation of post-infectious inflammatory conditions that may be of public health concern in the future.

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**Code Availability** Not applicable.

**Declarations**

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

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- Of importance
- Of major importance

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