Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Severe COVID-19 and MIS-C In Children & Adolescents

Allison M. Blatz MD¹ & Adrienne G. Randolph MD, MS²

¹ Department of Pediatrics, Division of Infectious Diseases, Children’s Hospital of Philadelphia; 3401 Civic Center Blvd, Philadelphia, PA 19104
blatza@chop.edu

² Department of Anesthesiology, Critical Care and Pain Medicine, Division of Critical Care, Boston Children’s Hospital; 300 Longwood Ave, Bader 634, Boston, MA 02115
adrienne.randolph@childrens.harvard.edu

Corresponding author: Adrienne Randolph, MD

Disclosure: AMB and AGR have nothing to disclose.

Key Words: pediatrics, multisystem inflammatory syndrome, MIS-C, COVID-19

Synopsis: Severe complications related to COVID-19 occur infrequently in children and adolescents. The two major types of life-threatening complications are acute respiratory failure from acute COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C is a post-infectious complication occurring approximately 3-6 weeks after an asymptomatic or mild SARS-CoV-2 infection. For both types of complications, supportive ICU care is provided. For MIS-C critical illness, immunomodulation is prescribed to reverse hyperinflammation and its cardiac and other sequelae.
Key points

- Severe lung disease due to SARS-CoV-2 is uncommon in children and occurs mostly in children with underlying risk factors such as obesity, chronic lung disease, and other underlying conditions.
- Severe, acute COVID-19 can also present in children as severe CNS disease and rarely as acute myocarditis.
- Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly recognized disorder characterized by systemic hyperinflammation and multisystem involvement and appears to be a post-infectious complication of SARS-CoV-2.
- Usual treatment of critically ill MIS-C patients involves prompt initiation of immune modulation with IVIG and/or corticosteroids.

Introduction

Severe complications related to COVID-19 are fortunately uncommon in children and adolescents, affecting mostly those with underlying conditions putting them at higher risk. A new disorder emerged early in the pandemic called Multisystem Inflammatory Syndrome in Children (MIS-C) that appears to be a post-infectious complication of SARS-CoV-2.¹ Children and adolescents with MIS-C have hyperinflammation and multiple organ system involvement. About half have cardiovascular involvement which can be life-threatening. The diagnostic criteria for these two conditions have some overlap, making differential diagnosis challenging in some cases. This review focuses on these two severe complications related to SARS-CoV-2 infection in children and adolescents admitted to the ICU, including their presentation, epidemiology, diagnosis, and evaluation. We then review therapeutic strategies for each.
Severe, acute pediatric COVID-19

Definition:

The great majority of children infected with SARS-CoV-2 will be asymptomatic, or develop mild COVID-19. However, some children present with severe or critical COVID-19 and this review focuses on those patients. There are multiple acute presentations for severe COVID-19 requiring ICU admission. Most commonly, children present with acute hypoxic respiratory failure. Some patients develop central nervous system (CNS) pathology and/or complications relating to a hypercoagulable state such as thrombosis.

Epidemiology:

Most children with severe acute COVID-19 admitted to the ICU have one or more underlying medical conditions. Teenagers with obesity and/or metabolic syndrome are at increased risk and may present more similarly to adults with COVID-19 acute respiratory distress syndrome (ARDS). Infants, those with history of prematurity and those with immune compromise are also at higher risk of severe disease.

Incidence of pediatric hospitalization for severe COVID-19 has ranged from 0.1-1.4 per 100,000 per week during the pandemic, with a recent increase with predominance of the B.1.617.2 (Delta) variant that is likely due to its higher transmissibility. Fewer than 2% of pediatric COVID-19 cases require intensive care admission and almost all will survive with supportive care. Recent data from the CDC estimate the rate of myocarditis due to COVID-19 to be rare at 0.146%, however, it is sixteen times higher than for those without COVID-19.
**Diagnostic Criteria**

Children and adolescents suspected of having acute COVID-19 should be tested for SARS-CoV-2 with either a PCR or an antigen test from a respiratory specimen. While both tests are highly specific, the PCR test is much more sensitive.\(^1\) In patients with negative testing, retesting should be considered if there is high suspicion such as during a household outbreak. If testing is confirmed negative, alternate diagnoses are likely.

**Pathogenesis**

Children are exposed to SARS-CoV-2 just as adults are – through droplets. Many children are asymptomatic. In those that do develop symptoms, onset is typically 5-7 days after viral exposure, peaking 7-14 days after exposure.

**Clinical Manifestations**

**Respiratory:** Pulmonary symptoms in pediatric patients hospitalized in the pediatric intensive care unit (PICU) can range from mild hypoxemia, status asthmaticus, to acute respiratory distress syndrome (ARDS). COVID-19 ARDS presents similarly in children as it does in adults, though it is less severe in most pediatric patients.\(^2\) Children are less likely to require invasive mechanical ventilation for acute respiratory failure than adults and they have shorter durations of hospital stay. Presentation is usually with gradual onset of symptoms, though may be acute in onset in those with underlying complex conditions.
**Cardiovascular:** Cardiovascular involvement is less common than pulmonary involvement. Critically ill patients can develop shock, acute myocarditis, and acute cardiac dysfunction.\textsuperscript{2,5}

**Neurologic:** Severe neurologic involvement in children related to SARS-CoV-2 is rare, but can manifest with both peripheral and CNS symptoms, including severe encephalopathy, stroke, direct CNS infection, fulminant cerebral swelling, Guillain-Barré syndrome or a demyelinating syndrome.\textsuperscript{13} Patients cannulated for extracorporeal membrane oxygenation (ECMO) for ARDS are at risk of cerebral hemorrhage as a secondary complication. A recent multi-center U.S. public health surveillance registry showed that with pre-existing neurological conditions were at higher risk of developing CNS complications from COVID-19 including exacerbation of an underlying seizure disorder.\textsuperscript{4}

**Hematologic:** Patients with severe, acute COVID-19 are often hypercoagulable. This can lead to deep venous thrombus and/or pulmonary embolus as a presenting symptom or complication of acute COVID-19. Teenagers are more likely than younger children to develop thrombotic events.\textsuperscript{3}

**Laboratory & Imaging Abnormalities**

Baseline laboratory studies may demonstrate lymphopenia and neutrophilia, mild acute kidney injury and/or mild hepatitis. Inflammatory markers are usually modestly elevated.

In the setting of acute respiratory failure due to COVID-19, children develop hypoxia. Chest imaging frequently shows bilateral, diffuse pulmonary infiltrates.
Children with symptoms of cardiovascular shock may have an elevated lactate or other markers of end organ perfusion. Troponin will be elevated in the setting of acute myocarditis. Brain natriuretic peptide (BNP) or pro-BNP may be high in the setting of decreased cardiac function. Echocardiogram can demonstrate decreased function or show signs of pulmonary hypertension, depending on pulmonary disease.

Neurologic manifestations are more likely to be found by physical exam rather than laboratory studies. Imaging findings vary based on the presenting syndrome. These can include delirium, confusion, obtundation, inability to walk, and seizures.

Children may be hypercoagulable with an increased D-dimer, especially in the setting of a thrombus. Other coagulation labs may also be prolonged, and thrombocytopenia may develop.

**Recommended Initial Evaluation**

Initial evaluation of children with critical illness is guided by the presentation and there are not major differences from the evaluation of acute respiratory disease from other causes (e.g. chest radiograph, blood gas, continuous pulse oximetry). Patients should be screened for hypercoagulopathy and markers of inflammation should be followed. If any neurologic deficits are present on exam, expedited CNS imaging is indicated with computed tomography (CT) or magnetic resonance imaging (MRI).
Multisystem Inflammatory Syndrome in Children (MIS-C):

**Background:**

In April 2020, case series emerged from the UK, Italy and later from New York State in the US describing children admitted to the hospital for persistent fever, diffuse inflammation, and shock that appeared similar to Kawasaki disease (KD) or Toxic Shock Syndrome (TSS) which are described in Table 1. These patients presented differently than most children with KD; they were older, had markedly increased frequency of cardiovascular shock and most had gastrointestinal symptoms. Children presented approximately one month after surges of COVID-19 cases in the general population in a region, so it was suspected to be a post-infectious complication. MIS-C has now emerged in many countries across the world, and national and international public health registries have been tracking this life-threatening disease. Early identification and aggressive treatment strategies have become the standard of care, aimed at decreasing the risk of fatal and long-term cardiovascular sequelae.

**Diagnostic Criteria:**

In mid-May of 2020, the U.S. Centers for Disease Control and Prevention (CDC) developed diagnostic criteria for MIS-C as did the World Health Organization (WHO). There are similarities and differences in these criteria, which are listed in Table 2. In the UK, the term “Pediatric Inflammatory Multisystem Syndrome Temporally related to COVID-19” (PIMS-TS) is used to describe the syndrome.

It is important to highlight that children diagnosed with MIS-C must have fever, evidence of inflammation, at least two organs involved, no other active infection that could explain their
condition, and a plausible epidemiologic link to SARS-CoV-2 through a positive laboratory test (PCR, antigen or antibody) or a confirmed exposure. MIS-C is a clinical diagnosis based on symptomology and laboratory features. The CDC definition requires hospitalization, which is used to define the disease as severe, whereas the WHO definition does not.\(^\text{19}\)

Differential Diagnosis:

Sepsis is the most common condition to be ruled out prior to diagnosing a patient with MIS-C. Bacterial pathogens must screened for using blood and other cultures or rapid testing (Table 3). In particular, Toxic Shock Syndrome from *Staphylococcus aureus* or *Streptococcus* spp. should be considered (Table 1) given the acute presentation of shock, fever, diffuse inflammation, hepatitis and skin changes such as erythroderma. Rocky Mountain Spotted Fever due to *Rickettsia rickettsiae* should be another consideration in certain geographic areas in the summertime, especially in patients with hyponatremia, thrombocytopenia and a palmar rash. Overlap exists in the diagnosis of MIS-C and KD, and approximately 40% of MIS-C patients will meet diagnostic criteria for KD (Table 1).\(^\text{18}\)

Approximately 30% of patients with MIS-C will have a positive respiratory test for SARS-CoV-2.\(^\text{5}\) Inflammation and coagulopathy can be features of both acute COVID-19 and MIS-C, and multiorgan involvement is common in critically ill patients with acute COVID-19. The definition of MIS-C is broad, and it is likely that some patients diagnosed with MIS-C have acute COVID-19, especially in those with cardiorespiratory involvement (see Table 3). A comparison of children and adolescents with the two diagnoses showed that patients with MIS-C were overall more inflamed with higher C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR), that thrombocytopenia (<150,000 platelets per microliter) was more common in MIS-C, and patients with acute COVID-19 tended to be more often 0-4 or 13-17 years of age.\(^\text{5}\) In addition, those with
acute COVID-19 were much more likely to have underlying medical conditions whereas the majority of patients with MIS-C were previously healthy.\textsuperscript{22}

\textit{Epidemiology:}

As of October 4\textsuperscript{th}, 2021, there were 5,217 cases of MIS-C reported to US state public health departments.\textsuperscript{23} Additionally, many hundreds of cases have been reported in the United Kingdom, continental Europe and South America.\textsuperscript{24–27} There are also MIS-C case reports in the literature from Africa and Asia.\textsuperscript{28,29}

Overall population incidence estimates for MIS-C range from 2 per 100,000 children in New York State to 3 per 10,000 individuals <21 years of age infected with SARS-CoV-2.\textsuperscript{30,31} Incidence after a diagnosis of MIS-C is difficult to determine since so many children are asymptomatic with their initial infection thus not tested. By definition, children with MIS-C are hospitalized, and over two-thirds require admission to the ICU.\textsuperscript{32}

The most common age of onset is 6-12 years of age, though there are case reports spanning from the neonatal period to early adulthood.\textsuperscript{5,22,30,31} Black and Hispanic children are overly represented in multiple cohorts, as are males.\textsuperscript{5,7,30,33} Most children with MIS-C were previously healthy. Some studies report an elevated prevalence of obesity among MIS-C patients.\textsuperscript{5,34} There is evidence that some children have an underlying genetic predisposition to hyperinflammation that likely explains their MIS-C.\textsuperscript{32,35}

A similar clinical syndrome also exists in adults: Multisystem Inflammatory Syndrome in Adults (MIS-A). It is hypothesized that this is also a post-infectious phenomenon that occurs from a
dysregulated immune response to SARS-CoV-2. The CDC diagnostic criteria for MIS-A are as follows:

1) a severe illness requiring hospitalization in a person aged ≥21 years;
2) a positive test result for current or previous SARS-CoV-2 infection;
3) severe dysfunction of one or more extrapulmonary organ systems;
4) laboratory evidence of severe inflammation;
5) absence of severe respiratory illness. \(^{36}\)

The major difference between criteria for MIS-A vs. MIS-C, aside from age, is that presence of pulmonary symptoms excludes MIS-A, whereas a patient can have pulmonary symptoms as part of multisystem involvement in MIS-C. Given the biphasic course of acute COVID-19 in adults, this criterion exists as to not confuse MIS-A with the hyperinflammatory phase of acute COVID-19. MIS-A is much rarer than MIS-C with only 221 cases described in the literature as of September 2021. Most cases were in younger adults (median age = 21 years). \(^{37}\) Clinical evaluation and treatment strategies are similar to those for MIS-C.

**Pathogenesis:**

The pathogenesis of MIS-C is poorly understood though is hypothesized to be a delayed, overactive immune response to infection with SARS-CoV-2 given its temporal association to SARS-CoV-2 infections in the population (Figure 1). It typically develops three to six weeks after exposure to SARS-CoV-2. The initial SARS-CoV-2 infection may go undetected due to no or mild symptoms. Much research aims to elucidate the precise pathogenesis of MIS-C. Both the innate and adaptive immune systems are thought be overly activated \(^{38,39}\) One theory hypothesized that the SARS-CoV-2 spike protein can act as a “superantigen,” activating both T-
and B-cells, leading to hyperinflammatory state and a subsequent cytokine storm, and similar to the staphylococcal endotoxin B implicated in Toxic Shock Syndrome.  

Clinical Manifestations

MIS-C presents with fever and systemic inflammation that leads to involvement of multiple organ systems, including the cardiovascular, gastrointestinal, neurologic, and mucocutaneous systems (Table 4). Involvement can present as follows:

Fever: Children must have persistent fever to meet criteria for MIS-C. Length of fever prior to presentation varies but is usually present for at least 24-48 hours and most commonly 3 days or more.  

Cardiovascular: Acutely, children can present with cardiovascular instability, decreased cardiac function, arrhythmias including heart block or myocarditis.  

A finding of major concern in MIS-C is the development of a coronary artery aneurysm (CAA) resulting from severe, diffuse inflammation. CAAs in MIS-C are defined as a Z score ≥2.5 in the proximal right coronary artery or proximal left anterior descending coronary artery. The exact mechanism of CAA development is unclear. Multi-center case series suggest that CAA occurs in between 8-14% of cases of MIS-C. The majority of these CAAs resolve within 30 days of
hospital admission, therefore most are unlikely to be vasculitis similar to what is identified in patients with KD.\textsuperscript{5} Even in severe MIS-C, CAA in the great majority of MIS-C patients is likely to resolve by three-to-six months after diagnosis and treatment.\textsuperscript{43} Longer term outcomes of these CAAs related to MIS-C are under study.

**Respiratory:** Respiratory symptoms are common in patients diagnosed with MIS-C, reported in about one third to one half of patients in a national cohort.\textsuperscript{5,22} These range from mild tachypnea and hypoxemia to respiratory failure with pulmonary infiltrates. Lower respiratory symptoms are more common in severe, acute COVID-19 than in MIS-C (62\% vs. 43\%, respectively).\textsuperscript{5} Some of the respiratory involvement may be cardiogenic, and other patients who have positive respiratory testing for SARS-CoV-2 may be misclassified and have acute COVID-19 with multisystem involvement and hyperinflammation.

**Gastrointestinal:** Studies report that up to 90\% of patients with MIS-C have gastrointestinal symptoms.\textsuperscript{5,44} Symptoms include severe abdominal pain with or without emesis, peritonitis, mesenteric lymphadenopathy, and diffuse secretory diarrhea.\textsuperscript{45} Abdominal pain has been so severe that cases have been mistaken for acute appendicitis. Terminal ileitis and diffuse colitis have also been observed.

**Mucocutaneous:** Rashes in MIS-C are variable, and there is not a pathognomonic presentation in MIS-C. More than half of children with MIS-C have a polymorphous exanthem. There have been a variety of lesions described, including maculopapular lesions, annular plaques, and morbilliform eruptions with coalescing papules.\textsuperscript{46 47} Most common rash locations include anterior and posterior trunk and extremities. Erythroderma has also been described, along with facial, palmar, and sole erythema and edema. Additionally cracked, dry, erythematous lips are often
present. Non-exudative conjunctivitis has also been well-described (Table 4). Younger children are more likely to have mucocutaneous findings.⁴⁸

**Neurologic:** CNS involvement can include mild to severe acute encephalopathy, stroke, demyelinating lesions, fulminant cerebral edema, headache, delirium, impaired consciousness, inability to walk or crawl, and neck pain. A recent multicenter study reported that 12% of MIS-C cases had neurologic involvement. CNS findings were generally mild and transient but 8% of patients had severe involvement.⁴ Case reports describe head imaging findings that range from normal to mild, diffuse cerebral swelling. Evaluations of cerebral spinal fluid have demonstrated a range of symptoms from normal CSF parameters to pleocytosis that can mimic acute bacterial or viral meningitis. Neurologic dysfunction is more common in MIS-C than in severe COVID-19.

**Hematologic:** Patients may present with deep venous thrombosis, pulmonary embolus, or coagulopathy. A recent multicenter, retrospective cohort study identified thrombi in 6.5% of patients with MIS-C and found MIS-C to be an independent risk factor for thrombotic events, with most thrombi occurring in children 12 years and over.³

*Laboratory & Imaging Abnormalities*

Multiple laboratory abnormalities are described in MIS-C. Inflammation is required, but other findings need not be present to make a diagnosis. Common laboratory findings are summarized in Table 5. Polymerase chain reaction (PCR) or antigen testing for SARS-CoV-2 is positive in about 30% of reported cases. Most patients are positive for antibody (IgG) testing, and those who are antibody negative should be investigated fully to identify alternate diagnoses. In those patients who are PCR positive, often the cycle threshold from a SARS-CoV-2 PCR is
high, indicating a lower viral load and a later stage of infection, though the utility of this test remains controversial.\textsuperscript{49}

Cardiac studies are frequently abnormal. Case series describe a variety of EKG findings, including normal sinus rhythm, sinus tachycardia, heart block and non-specific ST-wave abnormalities.\textsuperscript{41,42} An echocardiogram may show decreased left ventricular systolic function with an ejection fraction of <55\%. Myocardial deformation parameters (such as global longitudinal strain) can be present even with persevered ejection fraction. Coronary artery aneurysms are seen in approximately 8\% of patients, especially in delayed or very severe presentation. \textsuperscript{41,42}

\textit{Recommended Initial Evaluation}

Initial evaluation should be performed as show in Table 3. A thorough patient history should be obtained, with focus on presence of fever, close contact with an individual with COVID-19, and occurrence of other symptoms. Careful physical exam should be performed with special attention to findings such as meningismus, mental status, conjunctivitis, dry, cracked lips, abdominal pain, extremity swelling, palmar or sole erythema and rash.

Additional testing to rule out other infectious and non-infectious etiologies should be performed. Other infectious considerations include sepsis, rickettsial illness (particularly Rocky Mountain Spotted Fever), Toxic Shock Syndrome, Staph Scalded Skin Syndrome or severe adenovirus infection. Clinicians should consider obtaining a blood culture, urinalysis and culture, group A streptococcus testing, PCRs for other respiratory viral pathogens and Rocky Mountain Fever Syndrome or Ehrlichia serologies (depending on geographic location and season).
Hemophagocytic lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS) should be considered in the appropriate clinical scenario.

**Severe COVID-19 Treatment and Outcomes**

*Treatment:*

Most children with moderate to severe COVID-19 will improve with supportive care alone. Data are lacking regarding optimal treatment strategies of children with COVID-19 as severe disease in children is very uncommon and children were not enrolled in prior published clinical trials. The Pediatric Infectious Diseases Society suggests use of five-day course of remdesivir in children with severe COVID-19. Pharmacokinetic/pharmacodynamic clinical trials are ongoing to determine optimal dosing strategies (NCT04431453). Dexamethasone has been widely used in children with severe disease, given results in adults from the RECOVERY trial, and while considered safe, efficacy data are lacking children. Other immunomodulatory therapies such as tocilizumab, anakinra and baricitinib have also been given to some children following some successful results in adults, but no data exist to support their use.

There is no evidence to support the use of azithromycin, hydroxychloroquine, ivermectin, other antiviral therapies or convalescent plasma in children.

Similar techniques of ICU management including optimal ventilation strategies, proning and other optimal intensive care unit management of ARDS has also been used in children. Status asthmaticus is managed with standard asthma protocols. Fluid management is essential.
Adolescents are often anticoagulated, as are those who are obese or have another coexisting condition.

For treatment and outcomes of the overlapping phenotype between MIS-C and severe COVID-19, these children generally receive hybrid treatment strategies including steroids both for anti-inflammatory effect and ARDS. IVIG and/or remdesivir may also be used.

Outcomes:

An estimated 5-20% of cases require hospitalization, and about 2% of cases require admission to the intensive care unit versus the general pediatric floor. Of those admitted to the intensive care unit, the mortality rate was <2% even in a large national multicenter study. Long term pulmonary outcomes are unknown given that this is a novel disease.

**MIS-C Treatment and Outcomes**

Treatment:

Of the MIS-C cases in the United States, multicenter studies have shown that about two thirds of patients diagnosed with MIS-C require admission to the intensive care unit. Given the ongoing worldwide pandemic and the rarity of MIS-C, data regarding optimal treatment for MIS-C are sparse and largely from observational studies. Current treatment strategies from consensus recommendations focus on immunomodulation similar to the treatment of KD,
typically with intravenous immunoglobulin (IVIG) and/or corticosteroids. Corticosteroids are usually initiated intravenously, then transitioned to an oral regimen with a physiologic taper until after hospital discharge.

A recent US based study of very severe patients in the Overcoming COVID-19 US Network (47% were on vasopressors and 41% had impaired ejection fraction) showed improved outcomes when given IVIG plus steroids on the first day of treatment. Addition of other immunomodulatory treatments after the initial treatment day was also significantly decreased. However, the Best Available Treatment Study (BATS) which was international, showed no difference in recovery from MIS-C when comparing groups given IVIG alone, corticosteroids alone, or IVIG and corticosteroids together. The BATS study population used a broader definition for MIS-C, and their patients were markedly less ill than the US cohort. Therefore, in critically ill patients it is likely prudent to treat more aggressively initially to resolve the cardiovascular complications more quickly. Other immunomodulatory therapies have been trialed such as anakinra, an IL-1 inhibitor, and tocilizumab, an IL-6 inhibitor, though data are lacking whether these are effective. Some institutions have used anakinra for refractory MIS-C that has not respondend initially to steroids and/or IVIG. A recent single-center study reported quicker recovery in children given IVIG plus infliximab (a TNF-a inhibitor).

In addition to immunomodulatory therapies, anticoagulation is typically administered to patients with laboratory markers consistent with a hypercoagulable state, given potential CAA and risk of thrombosis. While hospitalized in the ICU, low-molecular weight heparin is usually initiated. In some centers, patients are also given low-dose aspirin, as is the standard of care in KD. Ultimate duration of optimal anticoagulation remains unclear. Most institutions continue anticoagulants until after discharge when a follow up echocardiogram has been obtained and longer if the patient has a CAA.
Supportive care is always provided, including vasoactive support if needed and careful fluid management. Echocardiograms should be performed serially to follow decreased cardiac function. Antibiotics are usually administered until the blood and other cultures report back as negative as sepsis must be ruled out.

Outcomes:

The great majority of children with MIS-C have recovered. The mortality rate in the US in MIS-C patients is 1-2%. A recent UK case series showed that six-to-twelve months after diagnosis, most patients had resolution of their hyperinflammatory state. For cardiac outcomes, 4-17.5% percent of patients have had coronary aneurysms diagnosed while hospitalized, and at 90-day follow up, the majority of these coronary aneurysms have resolved. Data are still being collected about long-term outcomes of these children, though data suggest that full recovery typically occurs after aggressive treatment upon presentation. Studies are ongoing to determine the longer-term effects on the heart. Children who are diagnosed with MIS-C are often followed by a multidisciplinary team after discharge including rheumatology, cardiology and in some cases, infectious disease specialists.

Conclusions:

Both severe acute COVID-19 and MIS-C can cause life-threatening illness in children and adolescents. Fortunately, the clinical outcomes for severe COVID-19 are markedly better in children than in adults, and mortality is uncommon. Optimal treatment strategies for severe, acute COVID-19 and MIS-C are difficult to study due to the low frequency of these conditions.
and there is a paucity of strong evidence in the pediatric population. Most institutions have applied the evidence gained from adult studies to children with acute COVID-19 critical illness. Consensus guidelines have been developed for the diagnosis and treatment of MIS-C, with treatment algorithms similar to what is used for KD.

**Clinics Care Points:**

- Severe, acute COVID-19 is uncommon in children and adolescents but is most likely to present with pulmonary involvement as it does in adults.
- MIS-C is a novel clinical entity that is driven by systemic inflammation and most commonly affects the cardiovascular and mucocutaneous systems.
- Children with suspected MIS-C are at risk for thrombosis and neurologic complications.
- Immunomodulation, given promptly in children with MIS-C who are critically ill, will shorten the duration cardiovascular dysfunction, but optimal treatment of milder cases of MIS-C is unclear.
References:

1. Levin M. Childhood Multisystem Inflammatory Syndrome — A New Challenge in the Pandemic. *NEJM*. 2020;383(4):393-395. doi:10.1056/NEJME2023158

2. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatrics*. 2020;2019:1-6. doi:10.1001/JAMAPEDIATRICS.2020.1948

3. Whitworth H, Sartain S, Kumar R, et al. Rate of Thrombosis in Children and Adolescents Hospitalized with COVID-19 or MIS-C. *Blood*. 2021;138(2):190-198. doi:10.1182/BLOOD.2020010218

4. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome. *JAMA Neurology*. 2021;78(5):536-547. doi:10.1001/JAMANEUROL.2021.0504

5. Feldstein LR, Tenforde MW, Friedman KG, 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):1074-1087. doi:10.1001/JAMA.2021.2091

6. She J, Liu L, Liu W. COVID-19 Epidemic: Disease Characteristics in Children. *Journal of Medical Virology*. 2020;92(7):747-754. doi:10.1002/JMV.25807

7. Swann O v., Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: Prospective multicentre observational cohort study. *The BMJ*. 2020;370. doi:10.1136/BMJ.M3249

8. Delahoy MJ, Ujamaa D, Whitaker M, et al. Hospitalizations Associated with COVID-19 Among Children and Adolescents — COVID-NET, 14 States, March 1, 2020–August 14,
2021. *MMWR Morbidity and Mortality Weekly Report.* 2021;70(36):1255-1260. doi:10.15585/MMWR.MM7036E2

9. Kim L, Whitaker M, O’Halloran A, et al. Hospitalization Rates and Characteristics of Children Aged 18 Years Hospitalized with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1–July 25, 2020. *MMWR Morbidity and Mortality Weekly Report.* 2020;69(32):1081-1088. doi:10.15585/MMWR.MM6932E3

10. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021. *MMWR Morbidity and Mortality Weekly Report.* 2021;70(35):1228-1232. doi:10.15585/MMWR.MM7035E5

11. Dinnes J, Deeks JJ, Berhane S, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database of Systematic Reviews.* 2021;2021(3). doi:10.1002/14651858.CD013705.PUB2

12. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. *JAMA Network Open.* 2021;4(6):e2111182-e2111182. doi:10.1001/JAMANETWORKOPEN.2021.11182

13. Govil-Dalela T, Sivaswamy L. Neurological Effects of COVID-19 in Children. *Pediatric Clinics of North America.* 2021;68(5):1081. doi:10.1016/J.PCL.2021.05.010

14. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like Multisystem Inflammatory Syndrome in Children During the Covid-19 Pandemic in Paris, France: Prospective Observational Study. *BMJ (Clinical research ed).* 2020;369:m2094. doi:10.1136/BMJ.J2094

15. Verdoni L, Mazza A, Gervasoni A, et al. An Outbreak of Severe Kawasaki-like Disease at the Italian Epicentre of the SARS-CoV-2 Epidemic: an Observational Cohort Study. *The Lancet.* 2020;395(10239):1771-1778. doi:10.1016/S0140-6736(20)31103-X
16. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series. *Journal of the Pediatric Infectious Diseases Society*. 2020;9(3):393-398. doi:10.1093/JPIDS/PIAA069

17. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory Shock in Children During COVID-19 Pandemic. *Lancet*. 2020;395(10237):1607. doi:10.1016/S0140-6736(20)31094-1

18. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *NEJM*. Published online 2020:1-13. doi:10.1056/NEJMoa2021680

19. The Centers for Disease Control & Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Health Alert Network. Published 2020. Accessed July 29, 2020. https://emergency.cdc.gov/han/2020/han00432.asp

20. World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents Temporally Related to COVID-19. Published May 15, 2020. Accessed September 27, 2021. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

21. Royal College of Paediatrics and Child Health. Guidance: Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19. Published online May 2020. Accessed September 26, 2021. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

22. Godfred-Cato S. COVID-19–Associated Multisystem Inflammatory Syndrome in Children — United States, March–July 2020. *MMWR Morbidity and Mortality Weekly Report*. 2020;69(32):1074-1080. doi:10.15585/MMWR.MM6932E2
23. The Centers for Disease Control & Prevention. CDC COVID Data Tracker. Published 2021. Accessed October 3, 2021. https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

24. Flood J, Shingleton J, Bennett E, et al. Paediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS): Prospective, National Surveillance, United Kingdom and Ireland, 2020. *The Lancet Regional Health – Europe*. 2021;3. doi:10.1016/J.LANEPE.2021.100075

25. Lima-Setta F, Magalhães-Barbosa MC, Rodrigues-Santos G, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) During SARS-CoV-2 pandemic in Brazil: A Multicenter, Prospective Cohort Study. *Jornal de Pediatria*. 2021;97(3):354-361. doi:10.1016/J.JPED.2020.10.008

26. Antúnez-Montes OY, Escamilla MI, Figueroa-UrIBE AF, et al. COVID-19 and Multisystem Inflammatory Syndrome in Latin American Children: A Multinational Study. *The Pediatric Infectious Disease Journal*. 2021;40(1). doi:10.1097/INF.0000000000002949

27. García-Salido A, de Carlos Vicente JC, Belda Hofheinz S, et al. Severe Manifestations of SARS-CoV-2 in Children and Adolescents: from COVID-19 Pneumonia to Multisystem Inflammatory Syndrome: a Multicentre Study in Pediatric Intensive Care Units in Spain. *Critical Care*. 2020;24(1):666. doi:10.1186/S13054-020-03332-4

28. Balagurunathan M, Natarajan T, Karthikeyan J, Palanisamy V. Clinical Spectrum and Short-term Outcomes of Multisystem Inflammatory Syndrome in Children in a South Indian Hospital. *Clinical and experimental pediatrics*. Published online August 4, 2021. doi:10.3345/CEP.2021.00374

29. van Heerden J, Nel J, Moodley P, et al. Multisystem Inflammatory Syndrome (MIS): A Multicentre Retrospective Review of Adults and Adolescents in South Africa. *International Journal of Infectious Diseases*. 2021;111:227-232. doi:10.1016/J.IJID.2021.08.042
30. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem Inflammatory Syndrome in Children in New York State. *The New England Journal of Medicine*. 2020;383(4):347-358. doi:10.1056/NEJMOA2021756

31. Payne A, Gilani Z, Godfred-Cato S, et al. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2. *JAMA Network Open*. 2021;4(6). doi:10.1001/JAMANetworkOpen.2021.16420

32. Chou J, Platt CD, Habiballah S, et al. Mechanisms Underlying Genetic Susceptibility to Multisystem Inflammatory Syndrome in Children (MIS-C). *The Journal of Allergy and Clinical Immunology*. Published online July 2021. doi:10.1016/J.JACI.2021.06.024

33. Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. *JAMA Pediatrics*. 2021;175(8):837-845. doi:10.1001/JAMAPEDIATRICS.2021.0630

34. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors Linked to Severe Outcomes in Multisystem Inflammatory Syndrome in Children (MIS-C) in the USA: A Retrospective Surveillance Study. *The Lancet Child & Adolescent Health*. 2021;5(5):323. doi:10.1016/S2352-4642(21)00050-X

35. Lee PY, Platt CD, Weeks S, et al. Immune Dysregulation and Multisystem Inflammatory Syndrome in Children (MIS-C) in Individuals with Haploinsufficiency of SOCS1. *The Journal of Allergy and Clinical Immunology*. 2020;146(5):1194. doi:10.1016/J.JACI.2020.07.033

36. Morris S, Schwartz N, Patel P, et al. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020. *MMWR Morbidity and Mortality Weekly Report*. 2020;69(40):1450-1456. doi:10.15585/MMWR.MM6940E1

37. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review.
JAMA Network Open. 2021;4(9):e2126456-e2126456.
doi:10.1001/JAMANETWORKOPEN.2021.26456

38. Vella LA, Giles JR, Baxter AE, et al. Deep Immune Profiling of MIS-C Demonstrates Marked but Transient Immune Activation Compared to Adult and Pediatric COVID-19. Science Immunology. 2021;6(57). doi:10.1126/SCIIMMUNOL.ABF7570

39. McMurray JC, May JW, Cunningham MW, Jones OY. Multisystem Inflammatory Syndrome in Children (MIS-C), a Post-viral Myocarditis and Systemic Vasculitis—A Critical Review of Its Pathogenesis and Treatment. Frontiers in Pediatrics. 2020;8:626182. doi:10.3389/FPED.2020.626182

40. Rivas MN, Porritt RA, Cheng MH, Bahar I, Arditi M. COVID-19–associated Multisystem Inflammatory Syndrome in Children (MIS-C): A Novel Disease that Mimics Toxic Shock Syndrome—the Superantigen Hypothesis. The Journal of Allergy and Clinical Immunology. 2021;147(1):57-59. doi:10.1016/J.JACI.2020.10.008

41. Niaz T, Hope K, Fremed M, et al. Role of a Pediatric Cardiologist in the COVID-19 Pandemic. Pediatric Cardiology. 2021;42(1):19-35. doi:10.1007/S00246-020-02476-Y

42. Matsubara D, Kauffman H, Wang Y, et al. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. Journal of the American College of Cardiology. 2020;76(17):1947-1961. doi:10.1016/J.JACC.2020.08.056

43. Farooqi KM, Chan A, Weller RJ, et al. Longitudinal Outcomes for Multisystem Inflammatory Syndrome in Children. Pediatrics. 2021;148(2):e2021051155. doi:10.1542/PEDS.2021-051155

44. Chen T-H, Kao W-T, Tseng Y-H. Gastrointestinal Involvements in Children With COVID-related Multisystem Inflammatory Syndrome. Gastroenterology. 2021;160(5):1887. doi:10.1053/J.GASTRO.2020.06.084
45. Assa A, Benninga MA, Borrelli O, et al. Gastrointestinal Perspective of Coronavirus Disease 2019 in Children-An Updated Review. *Journal of Pediatric Gastroenterology and Nutrition*. 2021;73(3):299-305. doi:10.1097/MPG.0000000000003204

46. Blatz AM, Oboite M, Chiotos K, et al. Cutaneous Findings in SARS-CoV-2-Associated Multisystem Inflammatory Disease in Children. *Open Forum Infectious Diseases*. 2021;8(3). doi:10.1093/OFID/OFAB074

47. Naka F, Melnick L, Gorelik M, Morel KD. A Dermatologic Perspective on Multisystem Inflammatory Syndrome in Children. *Clinics in Dermatology*. 2021;39(1):163. doi:10.1016/J.CLINDERMATOL.2020.09.003

48. Young TK, Shaw KS, Shah JK, et al. Mucocutaneous Manifestations of Multisystem Inflammatory Syndrome in Children During the COVID-19 Pandemic. *JAMA Dermatology*. 2021;157(2):207-212. doi:10.1001/JAMADERMATOL.2020.4779

49. DeBiasi R, Harahsheh A, Srinivasalu H, et al. Multisystem Inflammatory Syndrome of Children: Subphenotypes, Risk Factors, Biomarkers, Cytokine Profiles, and Viral Sequencing. *The Journal of Pediatrics*. 2021;237:125-135.e18. doi:10.1016/J.JPEDS.2021.06.002

50. Hwang TJ, Randolph AG, Bourgeois FT. Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19). *JAMA Pediatrics*. 2020;174(9):825-826. doi:10.1001/JAMAPEDIATRICS.2020.1888

51. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *Journal of the Pediatric Infectious Diseases Society*. 2021;10(1):34-48. doi:10.1093/JPIDS/PIAA115

52. ClinicalTrials.gov. Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN). Published June 21, 2020. Accessed September 27, 2021. https://www.clinicaltrials.gov/ct2/show/NCT04431453
53. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *NEJM*. 2020;384(8):693-704. doi:10.1056/NEJMOA2021436

54. Abrams EM, Sinha I, Fernandes RM, Hawcutt DB. Pediatric Asthma and COVID-19: The Known, the Unknown, and the Controversial. *Pediatric Pulmonology*. 2020;55(12):3573-3578. doi:10.1002/PPUL.25117

55. Son MBF, Murray N, Friedman K, et al. Multisystem Inflammatory Syndrome in Children - Initial Therapy and Outcomes. *NEJM*. 2021;385(1):23-34. doi:10.1056/NEJMOA2102605

56. McArdle AJ, Vito O, Patel H, et al. Treatment of Multisystem Inflammatory Syndrome in Children. *NEJM*. 2021;385(1):11-22. doi:10.1056/NEJMOA2102968

57. Cole LD, Osborne CM, Silveira LJ, et al. IVIG Compared to IVIG Plus Infliximab in Multisystem Inflammatory Syndrome in Children. *Pediatrics*. Published online September 21, 2021:e2021052702. doi:10.1542/PEDS.2021-052702

58. McCrindle BW, Rowley AH, Newburger JW, 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-e999. doi:10.1161/CIR.0000000000000484

59. Staphylococcus aureus | Red Book® 2021 | Red Book Online | AAP Point-of-Care-Solutions. Accessed October 8, 2021.
https://redbook.solutions.aap.org/chapter.aspx?sectionid=247326921&bookid=2591

60. Centers for Disease Control. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) | CDC. Published 2020. Accessed October 23, 2020. https://www.cdc.gov/mis-c/hcp/

61. Diorio C, Henrickson SE, Vella LA, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS–CoV-2. *Journal of Clinical Investigation*. 2020;130(11). doi:10.1172/JCI140970
FIGURE AND TABLES

Figure 1. Daily cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the U.S. reported to the Centers for Disease Control and Prevention (CDC) from the state public health departments in relation to reported pediatric cases of COVID-19.

From The Centers for Disease Control & Prevention https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (Accessed 10/9/2021).

Table 1. Criteria for diagnosis of Kawasaki disease and Toxic Shock Syndrome (TSS) (Data from McCrindle BW, Rowley AH, Newburger JW, 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-e999. doi:10.1161/CIR.0000000000000484; and Staphylococcus aureus | Red Book® 2021 | Red Book Online | AAP Point-of-Care-Solutions. Accessed October 8, 2021. https://redbook.solutions.aap.org/chapter.aspx?sectionid=247326921&bookid=2591)

| Kawasaki disease | Toxic Shock Syndrome due to Staphylococcal spp. |
|------------------|-----------------------------------------------|
| **Persistent fever** ≥ 5 days that is otherwise unexplained | Must meet all 5 criteria below to be considered probable and is confirmed if desquamation occurs 2 weeks later: |
| 4 to 5 clinical criteria (complete) or 3 of 5 (incomplete) below: | • Fever |
| • Eyes: Conjunctival injection that is bilateral | • Diffuse macular erythroderma |
| | • Hypotension |
| | • 3 or more organs involved |
| | • Negative microbial testing for other causes |
- Mouth: mucous membrane changes (e.g. cracked lips, fissures, strawberry tongue)
- Hands or feet: erythema, swelling, periungual desquamation.
- Skin: Rash
- Neck: Cervical lymphadenopathy

**Table 2.** U.S. Centers for Disease Control and Prevention (CDC) vs World Health Organization (WHO)

Diagnostic criteria for Multisystem Inflammatory Syndrome in Children (MIS-C) and adolescents with differences highlighted in bold. *(Data from Royal College of Paediatrics and Child Health. Guidance: Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19. Published online May 2020. Accessed September 26, 2021.*

https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-
%20inflammatory%20syndrome-20200501.pdf; and Centers for Disease Control. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) | CDC. Published 2020. Accessed October 23, 2020. https://www.cdc.gov/mis-c/hcp/)

| Criteria       | CDC                  | WHO                  |
|----------------|----------------------|----------------------|
| Age            | < 21 years           | < 20 years           |
| Fever          | ≥ 1 day              | ≥ 3 days             |
| Inflammation   | Elevated CRP, PCT, ESR, fibrinogen, D-dimer, ferritin, lactate, LDH, IL-6, | Elevated CRP, PCT, ESR |
| Multisystem Involvement | ≥ 2 of the following: |
|-------------------------|----------------------|
| elevated neutrophils, decreased lymphocytes, decreased albumin | ≥ 2 of the following: |
| Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) | Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP); AND/OR Hypotension or shock |
| Hematologic (eg, coagulopathy) | Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) |
| Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) | Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) |
| Dermatologic (eg, erythroderma, mucositis, other rash) | Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) |
| Respiratory (eg, pneumonia, ARDS, pulmonary embolism) | |
| Renal (eg, acute kidney injury, renal failure) | |
| Neurologic (eg, seizure, stroke, aseptic meningitis) | **Association with SARS-CoV-2** |
|----------------------------------------------------|--------------------------------|
| Positive by RT-PCR, serology, or antigen test or exposure to a suspected/confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms | Positive by RT-PCR, serology, or antigen test or likely contact with patients with COVID-19 |

| Alternative diagnoses* | Severity |
|------------------------|----------|
| No alternative plausible diagnoses | Requires hospitalization |

No other obvious **microbial cause** of inflammation including bacterial sepsis and staphylococcal or streptococcal toxic shock syndromes.
Table 3. Overall differences between severe COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) in national comparative study from the Overcoming COVID-19 public health surveillance registry. (Data from Feldstein LR, Tenforde MW, Friedman KG, 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):1074-1087. doi:10.1001/JAMA.2021.2091)

| Severe Acute COVID-19 | MIS-C |
|-----------------------|-------|
| Much more likely (70-80%) to affect children with underlying conditions (obesity, type 1 diabetes mellitus, prematurity, immune compromise) | Much more likely (70-80%) to affect previously healthy children |
| More pulmonary involvement and acute respiratory failure | More cardiac dysfunction with 40-50% requiring vasopressors |
| Milder systemic inflammation | Severe systemic inflammation |
| Children 0-4 years old and older teenagers are more likely to be affected | Peak incidence is in children 6-12 years old |
**Table 4.** Frequency of organ system involvement in patients with Multisystem Inflammatory Syndrome in Children (MIS-C) in published surveillance studies.

| Organ System          | Frequency |
|-----------------------|-----------|
| Gastrointestinal      | 80-90%\(^5\) |
| Mucocutaneous         | 74-83%\(^{47,48}\) |
| Cardiovascular        | 66.7-86.5%\(^{5,22}\) |
| Hematologic           | 47.5%\(^5\) |
| Respiratory           | 36.5%\(^5\) |
| Neurologic            | 12.2%\(^{4,5}\) |
Table 5. Common laboratory and diagnostic test abnormalities identified in children presenting with Multisystem Inflammatory Syndrome in Children (MIS-C)*

| Inflammatory markers: Elevated CRP, PCT or ESR. Cytokine panels (if done) may show elevated soluble IL-1, IL-2R, IL-6, IL-8 and TNF-α^49,61 |
| Complete Blood Count with Differential: Lymphopenia with neutrophilia, anemia, thrombocytopenia |
| Complete Metabolic Panel: hyponatremia, elevated creatinine and/or BUN, elevated AST and/or ALT |
| Blood gas: metabolic acidosis |
| Cardiac/Perfusion: Elevated troponin, elevated BNP or pro-BNP, elevated lactate |
| Coagulation: elevated PT, INR and D-dimer |
| SARS-CoV-2: Positive antibody testing |
| Echocardiogram: Impaired ejection fraction of the left ventricle, coronary artery dilations or aneurysms |
| Electrocardiogram: Heart block (first or second degree) |
| Chest radiograph: Pulmonary edema |

*Patients must have elevated inflammatory markers to meet diagnostic criteria; other laboratory derangements may or may not be present. Serial evaluation is often indicated until abnormalities normalize.
Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)