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Severe COVID-19 and Multisystem Inflammatory Syndrome in Children in Children and Adolescents

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KEYWORDS

• Pediatrics • Multisystem inflammatory syndrome • MIS-C • COVID-19

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. Acute COVID-19 affects mostly children with underlying chronic conditions. A new disorder emerged early in the pandemic called multisystem inflammatory syndrome in children (MIS-C) that seems to be a postinfectious complication of SARS-CoV-2.[1] Children and adolescents with MIS-C have hyperinflammation and multiple organ system involvements. About half have cardiovascular involvement which can be life-threatening. The diagnostic criteria for these 2 conditions have some overlap, making differential diagnosis challenging in some cases. This review focuses on these 2 severe complications related to SARS-CoV-2 infection in children and adolescents

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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.[2] Other children develop central nervous system (CNS) pathology and/or complications relating to a hypercoagulable state such as thrombosis.[3,4]

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).[5] Infants, those with the history of prematurity and those with immune compromise are also at higher risk of severe disease.[2,6,7]

Incidence of pediatric hospitalization for severe COVID-19 has ranged from 0.1 to 1.4 per 100,000 per week during the pandemic, with a recent increase with the predominance of the B.1.617.2 (Delta) variant.[8,9] 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 at 0.146%; however, it is 16 times higher than for those without COVID-19.[10]

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.[11] 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 to 7 days after viral exposure, peaking 7 to 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 ARDS. COVID-19 ARDS presents similarly in children as it does in adults, though it is less severe in most pediatric patients.[12] 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.[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.[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 preexisting neurologic conditions were at higher risk of developing CNS complications from COVID-19, Recommended Initial Evaluation including the exacerbation of an underlying seizure disorder.[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.[3]

Laboratory and 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 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 examination rather than laboratory studies. Imaging findings vary based on the presenting syndrome.[4] 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 laboratories may also be prolonged, and thrombocytopenia may develop.

Recommended Initial Evaluation

Initial evaluation of children with critical illness is guided by the presentation and is similar to the evaluation of acute respiratory disease from other causes (eg, 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 examination, expedited CNS imaging is indicated with computed tomography (CT), or magnetic resonance imaging (MRI).

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Background

In April 2020, case series emerged from the UK, Italy, and later from the US describing children admitted to the hospital for persistent fever, diffuse inflammation, and shock that seemed similar to Kawasaki disease (KD) or toxic shock syndrome (TSS) which are described in **Table 1**.[14–17] 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 1 month after surges of COVID-19 cases in the general population in a region, so it was

Table 1
Criteria for diagnosis of Kawasaki disease and Toxic Shock Syndrome (TSS)

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

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. https://doi.org/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.

suspected to be a postinfectious complication.[18] 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).[19] There are similarities and differences in these criteria, which are listed in **Table 2**.[20] In the UK, the term "Pediatric Inflammatory Multisystem Syndrome Temporally related to COVID-19" (PIMS-TS) is used to describe the syndrome.[21]

It is important to highlight that children diagnosed with MIS-C must have fever, evidence of inflammation, at least 2 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 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.[19]

Differential Diagnosis

Sepsis is the most common condition to be ruled out before diagnosing a patient with MIS-C. Bacterial pathogens must be screened for using blood and other cultures or rapid testing (**Table 3**). In particular, TSS from *Staphylococcus aureus* or *Streptococcus* spp. should be considered (see **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

Table 2
U.S. Centers for Disease Control and Prevention (CDC) versus World Health Organization (WHO) Diagnostic criteria for Multisystem Inflammatory Syndrome in Children (MIS-C) and adolescents with differences highlighted in bold

Criteria	CDC	WHO
Age	< 21 y	< 20 y
Fever	≥ 1 d	≥ 3 d
Inflammation	Elevated CRP, PCT, ESR, fibrinogen, D-dimer, ferritin, lactate, LDH, IL-6, elevated neutrophils, decreased lymphocytes, decreased albumin	Elevated CRP, PCT, ESR
Multisystem Involvement	≥ 2 of the following: Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) Hematologic (eg, coagulopathy) Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) Dermatologic (eg, erythroderma, mucositis, other rashes) Respiratory (eg, pneumonia, ARDS, pulmonary embolism) Renal (eg, acute kidney injury, renal failure) Neurologic (eg, seizure, stroke, aseptic meningitis)	≥ 2 of the following: Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP); AND/OR Hypotension or shock Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
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 wk prior to the onset of symptoms	Positive by RT-PCR, serology, or antigen test or likely contact with patients with COVID-19
Alternative diagnoses*	No alternative plausible diagnoses	No other obvious microbial cause of inflammation including bacterial sepsis and staphylococcal or streptococcal toxic shock syndromes
Severity	Requires hospitalization	

Data from Royal College of Pediatrics and Child Health. Guidance: Pediatric 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/.

Table 3
Overall differences between severe COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) in the national comparative study from the Overcoming COVID-19 public health surveillance registry

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

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. https://doi.org/10.1001/JAMA.2021.2091.

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 patients with MIS-C will meet diagnostic criteria for KD (see **Table 1**).[18]

Approximately 30% of patients with MIS-C will have a positive respiratory test for SARS-CoV-2.[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 2 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 to 4 or 13 to 17 years of age.[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.[22]

Epidemiology

As of October 4th, 2021, there were 5217 cases of MIS-C reported to US state public health departments.[23] Additionally, many hundreds of cases have been reported in the United Kingdom, continental Europe, and South America.[24–27] There are also MIS-C case reports in the literature from Africa and Asia.[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 less than 21 years of age infected with SARS-CoV-2.[30,31] Incidence after a diagnosis of MIS-C is difficult to determine as 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.[32]

The most common age of onset is 6 to 12 years of age, though there are case reports spanning from the neonatal period to early adulthood.[5,22,30,31] Black and

Hispanic children are overly represented in multiple cohorts, as are males.[5,7,30,33] Most children with MIS-C were previously healthy. Some studies report an elevated prevalence of obesity among patients with MIS-C.[5,34] There is evidence that some children have an underlying genetic predisposition to hyperinflammation that likely explains their MIS-C.[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 postinfectious 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 the criteria for MIS-A versus MIS-C, aside from age, is that the 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 (**Fig. 1**). It typically develops 3 to 6 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 to be overly activated[38,39] One theory hypothesizes that the SARS-CoV-2 spike protein can act as a "superantigen," activating both T- and B-cells, leading to the hyperinflammatory state and a subsequent cytokine storm, and similar to the staphylococcal endotoxin B implicated in TSS.[40]

Clinical Manifestations

MIS-C presents with fever and systemic inflammation that leads to the 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 the criteria for MIS-C. Length of fever before presentation varies but is usually present for at least 24 to 48 hours and most commonly 3 days or more.[18]

Cardiovascular: Acutely, children can present with cardiovascular instability, decreased cardiac function, arrhythmias including heart block, or myocarditis.[41] Approximately 50% to 80% of children present with shock and approximately half require vasoactive support.[17,18] More than 80% of cases have cardiovascular involvement.[18] Severity of these symptoms range from mild, fluid-responsive shock, shock requiring vasoactive agents, to complete cardiovascular collapse requiring extracorporeal support.

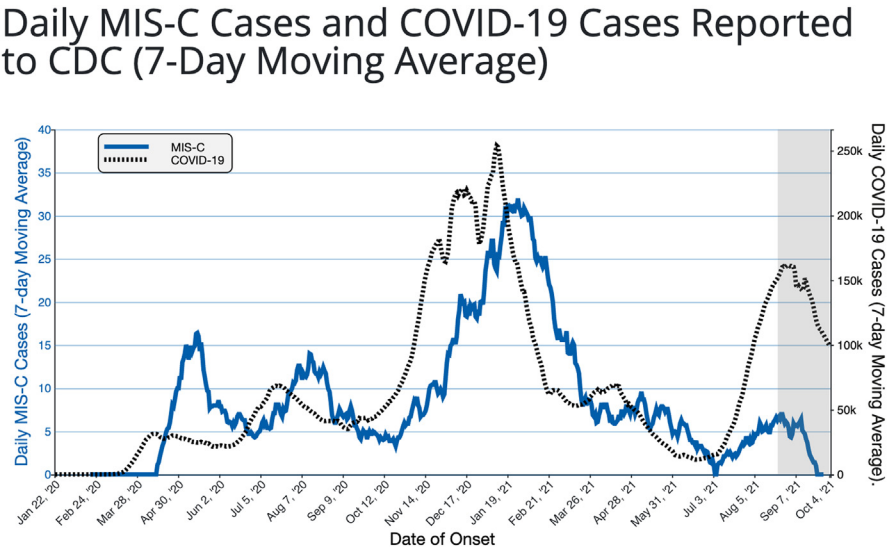

Fig. 1. Daily cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the U.S. reported to the Centers for Disease Control and Prevention (CDC) from the state public health departments in relation to reported pediatric cases of COVID-19. (*From* The Centers for Disease Control & Prevention https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (Accessed 10/9/2021).)

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 $\geq$2.5 in the proximal right coronary artery or proximal left anterior descending coronary artery. The exact mechanism of CAA development is unclear. Multicenter case series suggest that CAA occurs in between 8% and 14% of cases of MIS-C.[5,42] 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.[5] Even in severe MIS-C, CAA in the great majority of patients with MIS-C is likely to resolve by 3 to 6 months after diagnosis and treatment.[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.[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).[5] Some of the respiratory involvement may be

Table 4
Frequency of organ system involvement in patients with Multisystem Inflammatory Syndrome in Children (MIS-C) in published surveillance studies

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]

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.[5,44] Symptoms include severe abdominal pain with or without emesis, peritonitis, mesenteric lymphadenopathy, and diffuse secretory diarrhea.[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.[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. Nonexudative conjunctivitis has also been well-described (see **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 and 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 **Box 1**. 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.[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.[41,42] An echocardiogram may show decreased left ventricular systolic function with an ejection fraction of less than 55%. Myocardial deformation parameters (such as global longitudinal strain) can be present even with persevered ejection fraction. CAAs are seen in approximately 8% of patients, especially in delayed or very severe presentation.[41,42]

Recommended Initial Evaluation

Initial evaluation should be performed as shown in **Table 3**. A thorough patient history should be obtained, with a focus on the presence of fever, close contact with an

Box 1
Common laboratory and diagnostic test abnormalities identified in children presenting with Multisystem Inflammatory Syndrome in Children (MIS-C)[a]

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-a[49,58]

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) or non-specific ST wave changes

Chest radiograph: Pulmonary edema

[a]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.

individual with COVID-19, and occurrence of other symptoms. Careful physical examination 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 noninfectious etiologies should be performed. Other infectious considerations include sepsis, rickettsial illness (particularly Rocky Mountain Spotted Fever), TSS, 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.[50] The Pediatric Infectious Diseases Society suggests the use of a 5-day course of remdesivir in children with severe COVID-19.[51] Pharmacokinetic/pharmacodynamic clinical trials are ongoing to determine optimal dosing strategies (NCT04431453).[52] 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.[53] 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 have also been used in children. Status asthmaticus is managed with standard asthma protocols.[54] 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 antiinflammatory effect and ARDS. IVIG and/or remdesivir may also be used.

Outcomes

An estimated 5% to 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 less than 2% even in a large national multicenter study.[5] 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.[8] Given the ongoing worldwide pandemic and the rarity of MIS-C, data regarding optimal treatment of 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.[55] 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.[56] 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 responded initially to steroids and/or IVIG. A recent single-center study reported quicker recovery in children given IVIG plus infliximab (a TNF-a inhibitor).[57]

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 result 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 patients with MIS-C is 1% to 2%.[5,23] A recent UK case series showed that 6 to 12 months after diagnosis, most patients had a resolution of their hyperinflammatory state.[43] For cardiac outcomes. 4% to 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.[5,39,42] Data are still being collected about long-term outcomes of these children, though data suggest that full recovery typically occurs after aggressive treatment on 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.

SUMMARY

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 of cardiovascular dysfunction, but the optimal treatment of milder cases of MIS-C is unclear.

DISCLOSURE

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