MULTISYSTEM INFLAMMATORY SYNDROME in children (MIS-C) is a previously unrecognized and potentially catastrophic illness that appears in children who have been exposed to or diagnosed with COVID-19. In the US as of September 1, 2021, there have been approximately 40,000,000 identified COVID-19 cases related to exposure to the SARS-CoV-2 virus and nearly 640,000 deaths. However, the actual number of cases of COVID-19, particularly early in the pandemic, may not have captured the magnitude of infection because of limited testing that was directed at people who presented with more significant illness.

Children appeared to tolerate infection with COVID-19 well, but in late spring 2020, a hyper-inflammatory process in children similar to Kawasaki disease (KD) began to emerge in the United Kingdom and several other European nations. In mid-May 2020, New York State formulated an interim case definition of MIS-C. Soon after that, the CDC began tracking reports of children meeting the criteria of this novel syndrome.

As of September 1, 2021, 4,044 cases of MIS-C have been identified in the US, resulting in 37 deaths. Waves of new infection are sweeping through the world, heightening concern about people of all ages, including children. In the US, 22% of the population is made up of infants, but in late spring 2020, a hyper-inflammatory process in children similar to Kawasaki disease (KD) began to emerge in the United Kingdom and several other European nations. In mid-May 2020, New York State formulated an interim case definition of MIS-C. Soon after that, the CDC began tracking reports of children meeting the criteria of this novel syndrome.

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In the fall of 2020, approximately 56 million school-aged children returned to school. As healthcare agents and members of the community, nurses are positioned to assist in identifying children who may experience previously unrecognized complications of infection from the SARS-CoV-2 virus and potentially migrate into the inpatient environment.

**Background**

Both MIS-C and other syndromes such as KD share hyperinflammatory states resulting from a viral insult to the body. KD and MIS-C can result in systemic inflammation, leading to
potentially dire physiologic consequences. While inflammation provides a physiologic benefit when functioning normally, it can cause great harm when it becomes dysregulated. The immune system is both innate from birth and adaptive or acquired, emerging as people adapt to their environment (see Innate and adaptive immune systems). This multifaceted system protects individuals against viruses, bacteria, fungi, and parasites, and generates an inflammatory response. Interferons and cytokines are produced by multiple cell types in the immune system, predominately helper T cells and macrophages. These cytokines can either decrease or increase inflammation. Inflammation resulting from cytokine release generates the fever and body aches that are common in COVID-19 and other viral syndromes. Evolving evidence suggests that children and adults produce different types of antibodies (Y-shaped proteins produced by B cells) in response to infection with SARS-CoV-2.

A surge in unrestrained immune responses may explain the emergence of MIS-C in response to COVID-19 infection, but the process is not fully understood. However, as symptoms evolve in suspected cases of MIS-C, diagnosis is aided by excluding other diagnoses. The initial step in this process is to confirm either infection with or exposure to the SARS-CoV-2 virus.

Confirmation of infection with SARS-CoV-2

Confirming infection with SARS-CoV-2 virus presents specific challenges and requires distinct testing mechanisms. Options include molecular, antigen, or antibody testing. The molecular test, known as the polymerase chain reaction (PCR), detects evidence of the virus’ genetic material. The antigen test looks for evidence of specific proteins on the surface of the virus. Both of these testing mechanisms use nasal or throat swabs to identify active infection. The antibody test, which uses a blood sample, reflects evidence of past infection. However, the serologic antibody test may not rule out an active infection if the body has not yet mounted a detectable immune response.

The delayed manifestations of MIS-C syndrome relative to the time of viral insult complicate confirmation of infection. In the general pediatric population, the immune systems of children are often very effective in eliminating the SARS-CoV-2 virus. Symptoms associated with MIS-C most commonly are delayed relative to viral insult, occurring 3 to 6 weeks after exposure or infection. Therefore, confirmation of an infection of SARS-CoV-2 virus by molecular and antigen tests, which only capture evidence of an active infection, may not be helpful. In addition, staffing and supply chain challenges have contributed to deficits in testing nationwide. However, in most cases defined as MIS-C, children display evidence of antibodies to the SARS-CoV-2 virus, confirming past exposure to the virus that causes COVID-19.

KD related to a diagnosis of MIS-C

Because symptoms of other immune disorders in children overlap, specific confirmation of infection with or exposure to SARS-CoV-2 is of particular importance. MIS-C shares many characteristics with other inflammatory syndromes in children, including KD, myocarditis accompanied by cardiogenic shock, and other viral infections such as juvenile idiopathic arthritis and Toxic Shock Syndrome.

MIS-C and KD in particular share many distinct clinical features that make it difficult to form a definitive diagnosis. KD is an inflammatory syndrome presenting as a self-limiting vasculitis that occurs primarily in the middle and small arteries throughout the body, including the coronary arteries in young children, especially those 5 years and younger. KD is disproportionately present in children of East Asian ancestry, whereas MIS-C has presented in greater numbers of Hispanic and Black children.

In KD, self-reactive autoantibodies are produced in response to a viral infection, which may result in the development of coronary artery aneurysms. Clinical features of KD are nonspecific and may include fever of more than 5 days without a focus of infection, a lack of responsiveness to antimicrobial therapy, and at least five of the following six criteria:

- polymorphous rash (face, trunk, extremities, perineum)
- bilateral conjunctivitis
- changes in lip and oral cavity (strawberry tongue)
- changes in peripheral extremities
- polymorphous exanthema
- acute nonpurulent cervical lymphadenopathy

Signs and symptoms of MIS-C

The differentiation of MIS-C from other distinct inflammatory syndromes in children who have COVID-19 is defined by both the character and timing (relative to SARS-CoV-2 infection or exposure) of symptoms associated with each entity. Fully 80% of children diagnosed with MIS-C are admitted to the ICU. In a large cohort study in the early half of 2020, shock was present in 50% of MIS-C patients (particularly in older children), and they required inotropic or vasopressor support. The MIS-C syndrome appears to be concentrated in children ages 7.5 to 11 years, which is older than children who generally experience KD. However, children of all ages should be admitted for observation if they display abnormal vital signs including tachycardia or tachypnea, respiratory distress, changes in mental status, evidence of renal or hepatic injury, or presence of serologic in-
Inflammatory markers. Cardiac abnormalities including echocardiogram changes and lab values should be tracked over time. Echocardiograms should be used to assess ventricular and valvular function, and evidence of pericardial effusion.29

Symptoms associated with MIS-C include shock with accompanying cardiac involvement characterized by elevated markers of cardiac stress or damage such as troponins and N-terminal pro-brain natriuretic peptide (NT-proBNP).26,27 Gastrointestinal symptoms that have presented in up to 84% of cases include diarrhea, vomiting, or pain.27,29 Respiratory symptoms were present in 59% of patients in a large US study, with 20% of patients requiring mechanical ventilation.6

Elevated inflammatory markers are typical and include increased ferritin (an acute phase reactant) and C-reactive protein (produced in the liver in response to inflammation).27,29 Patients frequently present with elevation of four or more inflammatory markers.6 Suspected MIS-C should be investigated through extensive lab workup including complete blood cell counts, electrolytes, and assessments of liver and renal function as well as clotting disorders utilizing plasma levels of D-dimer.

Cutaneous symptoms include skin rashes, which have been present in more than half of observed subjects.30 Neurologic symptoms such as headache, meningeal signs, and alterations in consciousness are often present.9 Of the 570 MIS-C patients admitted from March 2, 2020, to July 18, 2020, 40.5% were Hispanic or Latino, 33.1% were non-Hispanic Black, and only 13.2% were non-Hispanic White. Obesity was the most commonly reported comorbidity.29

The CDC has further refined the diagnosis of MIS-C as:

- An individual less than 21 years of age presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological), AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by real-time quantitative-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the symptoms.24

To further stratify patients and assess for potential patient vulnerabilities, latent class analysis has been used in a population of MIS-C patients reported to the CDC. Three distinct groups of MIS-C patient classes have been identified.29

Class One: This group had the highest number of involved organ systems (48.8% with six or more systems), most frequently cardiovascular (100.0%) and gastrointestinal (97.5%). This group, whose average age was 9 years, had more abdominal pain, shock, myocarditis, elevated inflammatory markers, elevated troponin and proBNP (markers of cardiac failure and/or cardiac damage), and coronary artery aneurysms (21.1%).

Class Two: In this group, whose average age is 10 years, respiratory symptoms were present in 76.3% of cases and included cough, shortness of breath, pneumonia, acute respiratory distress syndrome with a heightened mortality (5.3%) compared with other groups, and coronary artery aneurysms (15.8%).

Class Three: This group, whose average age is 6 years, experienced rash most frequently as well as mucocutaneous lesions, coronary artery aneurysms, and dilation (18.2%).

Pharmacotherapy

MIS-C is a novel syndrome, and clinicians should be aware of treatments that may offer specific benefits to address diverse symptoms. The varied presentation of presumed MIS-C symptoms shares treatment regimens that fall into three categories: 1) treatment of inflammation, 2) treatment of shock, and 3) thromboprophylaxis.31

Children who have a diagnosis of MIS-C typically respond well to anti-inflammatory and immunomodulatory therapies.20 Treatment of the hyperinflammatory syndromes associated with COVID-19 has included the integration of immunomodulatory therapeutics such as Interleukin (II-6) inhibitors and corticosteroids in the adult population.32

When considering a treatment regimen for MIS-C, it is vital to rule out an active infection unrelated to COVID-19. To control the hyperimmune response, modular therapies such as high-dose I.V. immunoglobulin (IVIG) can be used. IVIG has historically been used to treat immune deficiencies and autoimmune processes. Adjustments in dosing regimens with IVIG may be considered for patients with alterations in cardiac function.

In patients with MIS-C and shock, the use of glucocorticoids, which offer immune suppression,
may be indicated in addition to IVIG. Vasoactive agents have been used in more than 50% of cases of MIS-C. Common agents include epinephrine, norepinephrine, dopamine, and milrinone, although milrinone was the subject of a study that cautioned against its use.³⁻¹ The frequency of vasopressor use is consistent with the large proportion of children who present with shock.³³

Specific patients, particularly those with evidence of refractory disease characterized by persistent fever and ongoing end organ involvement, may be candidates for treatment with Anakinra, a biologic that targets specific proinflammatory cytokines. Anakinra traditionally has been used to manage inflammation, and patients should have their liver function monitored during therapy.

Children with MIS-C frequently exhibit widespread endothelial injury and, as a result, activation of coagulation.¹⁸ In the adult COVID-19 population, the incidence of clotting disorders frequently requires anticoagulation therapy. Aspirin is standard treatment for children with MIS-C. Children with documented thrombus formation should receive anticoagulation therapy such as enoxaparin, but their antithrombic therapy should be individualized.¹⁹

**Patient teaching and community education**

Parents and clinicians must seriously consider the COVID-19-related risks to children. Symptoms including fever, gastrointestinal distress, neck pain, rash, fatigue, and bloodshot eyes warrant a visit to a pediatric primary care provider. Caregivers should immediately seek emergency care when children experience trouble breathing, unrelieved chest pain, mental status changes including somnolence, cyanosis, or severe abdominal pain.⁴ Parental concern over potential sources of COVID-19 exposure to their children can range from caution to anxiety to distress. Pre-pandemic common life events such as attending school or a day-care facility, celebrating moments such as holidays and birthdays, and even shopping for basic essentials have now placed added decision-making responsibility and stress on parents. The unintended consequences of actions intended to keep children safe are beginning to emerge fully in the US. Concern about the effects of isolation on children’s learning and psychological health is ongoing.³⁴ As previously noted, the numbers of Hispanic, Latino, and non-Hispanic black children identified in the MIS-C population are disproportionately greater when compared with the general pediatric population.³ The well-documented disparities of financial and health-related resources in the US have the potential to increase the health burdens on the most vulnerable individuals in American society.³⁵ In addition, immigrant families are much more likely to live in intergenerational households, where there is a greater risk of viral transmission.³⁶

Vaccination access for adults in the US is surging, but mistrust of the safety of COVID-19 vaccinations is an unfortunate reality. Parental hesitancy may limit the established public health benefits of a thoroughly tested and protective vaccine.³⁷ As of September 1, 2021, approximately 370,000,000 vaccine doses had been administered to adults in the US, with 53% of the population fully vaccinated. By contrast, phase two and phase three trials of the Moderna vaccine in children have begun, and it is hoped that these will address the delays in vaccinating the pediatric population.³⁸ Screening mechanisms and treatment regimens, including post-acute-care follow-up, must continue to be integrated into practice until vaccinations in children effectively limit the continuing spread of COVID-19.

As the identification of MIS-C in COVID-19–positive children has shown, children are at risk for severe complications, although, thankfully, occurrence is rare. Initial recognition of an inflammatory response with subsequent diagnosis of MIS-C based on the CDC’s methodology is key to implementing an effective treatment regimen, which includes management of inflammation and shock, as well as thromboprophylaxis. Public and especially parental education regarding symptoms is needed, particularly in the presence of a disease that is still commonly perceived as a threat that primarily affects adults. In addition, parents and children alike may benefit from guidance and support in their decision-making when balancing the risks of contracting COVID-19 with their commitments to resume everyday life activities that allow their children to be children again.

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