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Multisystem Inflammatory Syndrome in Children: A Review

An essential guide to this emerging health threat.

ABSTRACT: The coronavirus disease 2019 (COVID-19) pandemic has impacted the health of children worldwide. Although overall mortality from COVID-19 in children remains low, an associated multisystem inflammatory disorder has emerged. The disorder has been recognized and named multisystem inflammatory syndrome in children (MIS-C) by the World Health Organization and the Centers for Disease Control and Prevention. This comprehensive review describes the epidemiology, pathophysiology, signs and symptoms, other potential diagnoses, and treatments relevant to MIS-C. The review also includes patient and family education and anticipatory guidance, and discusses nursing implications for nurses working in various roles and settings, including direct care, research, and public health.

Keywords: coronavirus, coronavirus disease 2019, COVID-19, Kawasaki disease, MIS-C, multisystem inflammatory syndrome in children, pandemic, pediatrics, public health

In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), the disease caused by the novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic.[1] By mid-May, as COVID-19 incidence worsened in many countries, several hospitals in Europe and the United States began to report increasing incidence of a multisystem inflammatory disorder in children and adolescents that in some aspects resembled Kawasaki disease and toxic shock syndrome.[2,3] This emerging disorder was officially recognized and named multisystem inflammatory syndrome in children (MIS-C) by the WHO and the U.S. Centers for Disease Control and Prevention (CDC).[2,3] At the time this journal went to press, the CDC was reporting more than 2,000 confirmed cases of MIS-C, with 69% occurring in children who are Black or Hispanic.[4]

This comprehensive review focuses on several topics in the context of nursing and MIS-C. Given that nurses interact with children and families at many formal and informal health care entry points, including not only hospitals but also ambulatory clinics, tertiary care centers, schools, and communities, an understanding of these topics is vital. This article covers the epidemiology, pathophysiology, signs and symptoms, alternative possible diagnoses, and treatment options of MIS-C. It also addresses patient and family education, offers anticipatory guidance, and provides information relevant to nurses working in various roles and settings. The information presented was cur-

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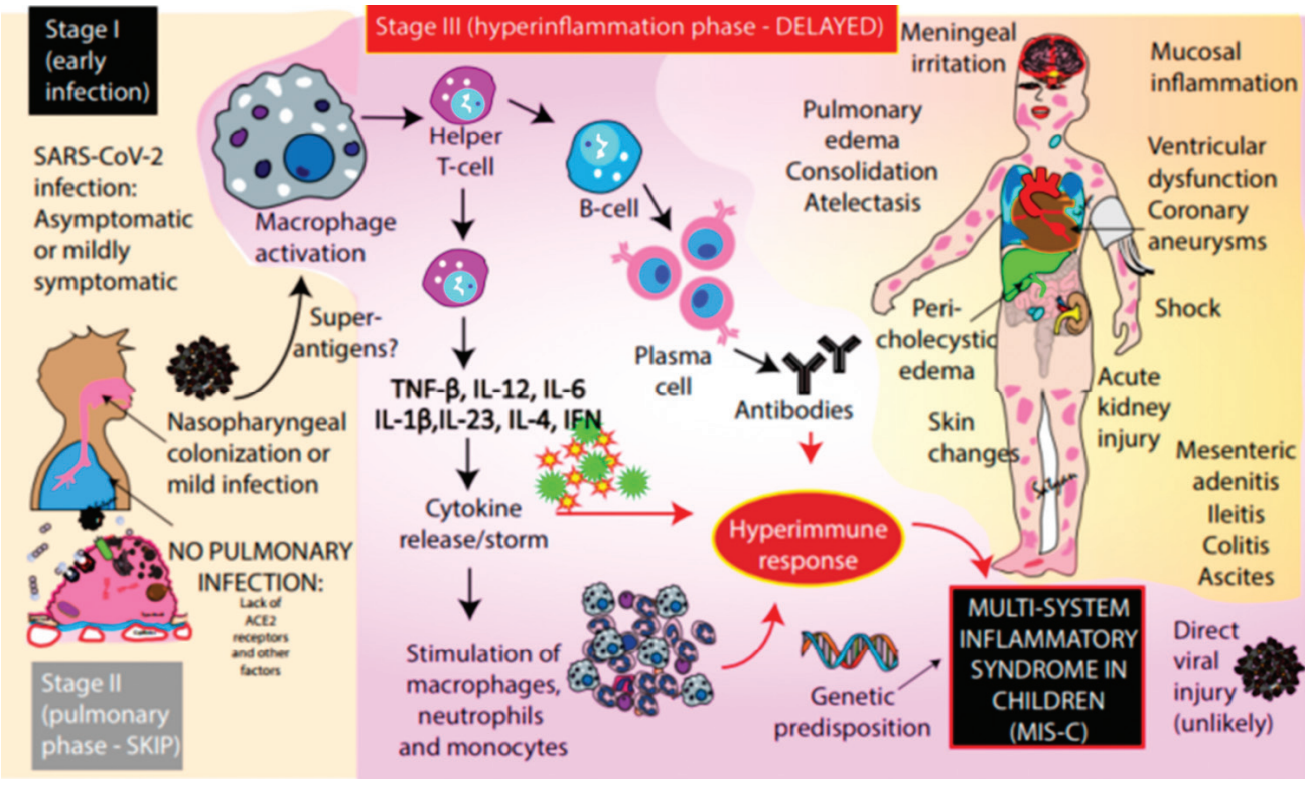
Figure 1. The Presumed Pathogenesis of MIS-C



ACE = angiotensin-converting enzyme; IFN = interferon; IL = interleukin; MIS-C = multisystem inflammatory syndrome in children; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF = tumor necrosis factor.

Reprinted from Nakra NA, et al. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children (Basel)* 2020;7(7):69.

rent at press time. As related research and nurses' experiences continue to produce new evidence and analyses, our knowledge and understanding of MIS-C will continue to evolve.

COVID-19, MIS-C, AND KAWASAKI DISEASE

Brief review of epidemiology. Although COVID-19 and MIS-C share a common viral etiology, they are different disease processes. They vary in terms of populations at risk, clinical presentation, signs and symptoms, illness severity, clinical course, and outcomes.

COVID-19 has been reported in children as young as 30 hours through adolescence and young adulthood.[5-8] There is evidence of bimodal age distribution, at least with regard to more severe illness. DeBiasi and colleagues found that patients younger than one year or older than 15 years accounted for the largest numbers of children and young adults who were hospitalized or became critically ill with COVID-19.[5] Most children who contract COVID-19 are either asymptomatic or have mild symptoms; very few develop severe or critical illness.[5,7] Mortality in children infected with SARS-CoV-2 is low, with reported mortality rates ranging from 0.08% in children age 18 years or younger[7] to up to 4% of those admitted to the hospital.[9,10] A majority of children requiring hospitalization for COVID-19 have had existing comorbidities.[5,9,10]

In contrast, a majority of children admitted with MIS-C have been previously healthy.[11-14] MIS-C has been reported in children as young as three months through adolescence.[11,15,16] No clear gender differences with regard to MIS-C have been established.[11,14,15,17] Findings from case series indicate that MIS-C may impact those of African descent more frequently.[11,12] Indeed, both pediatric COVID-19–related and MIS-C–related hospitalizations occur disproportionately more often among children

from racial and ethnic minorities, as do adverse outcomes.[4, 18] The presentation, symptoms, and radiologic and laboratory findings of COVID-19 and MIS-C vary. For typical findings associated with each disease process, and to help distinguish between them, see Table 1.[5, 7, 9, 10, 12-14, 16, 17, 19-25]

Both COVID-19 and MIS-C vary in epidemiology from Kawasaki disease, which, though more familiar to clinicians, also isn't fully understood. MIS-C shares clinical commonalities with Kawasaki disease, but whether MIS-C and Kawasaki disease are distinctly different entities hasn't yet been resolved.[26] Kawasaki disease primarily affects children under five years of age, has been more prevalent in Japan than in the United States, and is seen more often in children of Japanese ancestry.[27] In the United States, Kawasaki disease is more prevalent in boys than girls, with the highest numbers of cases seen in winter and early spring.[27]

Emergence of MIS-C. In early 2020, the Bergamo province in Italy was extensively affected by COVID-19, reporting the highest rates of infection and death in the country.[16] A significant "severe Kawasaki-like disease outbreak" also occurred at that time.[16] The constellation of symptoms and disease progression shared aspects with several known inflammatory disorders. In April 2020, a British intensive care service specializing in pediatric ICU support reported a case cluster of eight previously healthy children admitted with hyperinflammatory shock.[11] All presentations were similar to those of the Italian children.

The presence of SARS-CoV-2 infection and multiorgan involvement led researchers to propose that these cases reflected a new disease entity. The Royal College of Paediatrics and Child Health soon published a guidance document, *Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19*.[28] In May 2020, the CDC published an official case definition of this new disease phenomenon (see *Case Definition for MIS-C*[29]).[29]

In the spring of 2020, New York City became an epicenter of the COVID-19 outbreak in the United States.[30] In May, Waltuch and colleagues reported on four infected children in that region who developed a "multisystem inflammatory state."[13] They cautioned that children with this postinfectious syndrome "may appear well initially but have a high propensity for acutely decompensating." Subsequent case reports indicated that a higher proportion of cases of a "Kawasaki-like" multisystem inflammatory disorder occurred in children of African ancestry.[12] Interestingly, few such cases have been reported in Asian countries, where the first cases of COVID-19 emerged and Kawasaki disease incidence has historically been high.[12]

A large set of MIS-C cases, involving 186 children in 26 states, was described by Feldstein and colleagues in June 2020.[15] The median age was eight years; 62% were male and 73% had been previously healthy. The percentage of children who were Black or Hispanic was higher than in the general U.S. population. Morbidity was marked, with 80% requiring ICU care, including extracorporeal membrane oxygenation (ECMO) for 4%; the overall death rate was 2%. The researchers noted that significant cardiovascular involvement and its manifestations were common in older children and adolescents, as had been reported in other accounts from France and Switzerland.[31] Their findings suggested but could not establish causality between COVID-19 and MIS-C.[15] It's also unknown whether newer variants of SARS-CoV-2 are associated with changes in either the prevalence or the clinical manifestations of MIS-C.[4]

PATHOPHYSIOLOGY OF MIS-C

The pathophysiology of MIS-C is unknown. Per current understanding, it's best described as a massive systemic inflammatory response that has physiologic correlations to Kawasaki disease, Kawasaki disease shock syndrome, toxic shock syndrome, macrophage activation syndrome, and cytokine release syndrome (see Figure 1). Kawasaki disease and toxic shock syndrome are common alternative diagnoses that are reached following an initial presentation of MIS-C. Macrophage activation syndrome is a complication of systemic inflammatory disorders (most commonly systemic juvenile idiopathic arthritis), and is characterized by an inflammatory reaction secondary to uncontrolled dysfunctional immune response.[32] Cytokine release syndrome is an inflammatory response that can be initiated by multiple factors including infection, certain medications, and immunosuppression, and is currently best described in the literature concerning chimeric antigen receptor T-cell therapies.[33]

SARS-CoV-2 is a betacoronavirus closely related to SARS-CoV.[34] Both use angiotensin-converting enzyme 2 receptors as a means to enter cells. These receptors occur in cardiopulmonary tissues and in some hematopoietic cells, including monocytes and macrophages.[34]

MIS-C was initially characterized as a "Kawasaki-like" disease, as the features of multisystem involvement and rash can be similar. Thus, a short description of the pathophysiology of Kawasaki disease is relevant. The acute febrile phase of Kawasaki disease involves systemic inflammation in all medium-sized arteries and in multiple organs and tissues. Activation of the innate immune system increases the circulating levels of proinflammatory neutrophils and cytokines.[27, 35] These entities may cause both local and systemic damage, resulting in conditions such as hepatitis, interstitial pneumonitis, gastrointestinal (GI) pain, aseptic meningitis,

Table 1. Pediatric COVID-19 vs. MIS-C[5, 7, 9, 10, 12-14, 16, 17, 19-25]

	Pediatric COVID-19	MIS-C
Symptom onset	• Median of 3 days from symptom onset to diagnosis	• Onset of symptoms often occurs after viral prodrome • Hospital admission often occurs on day 4–8 of fever
Most common symptoms	• Majority of symptomatic patients present with upper respiratory symptoms, with or without fever, including: ○ Rhinorrhea, congestion, sore throat, shortness of breath ○ Cough ○ Pharyngeal erythema ○ Tachypnea • Other reported symptoms: ○ Diarrhea ○ Emesis ○ Myalgia ○ Chest pain ○ Loss of taste, smell, or both ○ Tachycardia • In newborns, dyspnea is most common symptom	• Fever occurs in most cases and is often prolonged for 5+ days. • Majority have GI symptoms on presentation or early in illness: ○ Abdominal pain ○ Emesis ○ Diarrhea • Majority present with erythematous or polymorphic rash • Strawberry tongue, cracked lips, mucous membrane involvement • Nonexudative conjunctivitis or conjunctival infection • Cardiac dysfunction or myocarditis • Neurologic symptoms: ○ Headache ○ Vision changes ○ Irritability ○ Altered mental status ○ Meningeal signs • Hypoxia • Cervical lymphadenopathy
Comorbidities	• Majority of those hospitalized or admitted to the PICU have comorbidities and are medically complex: ○ Immunosuppression, malignancy, or oncologic disorders ○ Obesity ○ Neurologic disorders ○ Cardiac disorders ○ Hematologic disorders ○ Chronic lung disease or asthma ○ Others include diabetes mellitus, prematurity, metabolic diseases	• Most are previously healthy • Some have comorbidities: ○ Asthma ○ Neurodisability ○ Epilepsy ○ Sickle cell trait ○ Obesity
Laboratory abnormalities	• Laboratory results are often unremarkable • Lymphopenia is often present on presentation to the hospital • Severe disease is associated with elevated CRP and procalcitonin	• Elevated ESR, CRP, ferritin, procalcitonin • Elevated IL-6, IL-8, TNF-α • Elevated transaminases ALT and/or AST • Lipase > 3 times normal in some patients • Elevated LDH • Hypoalbuminemia • Altered coagulation, increased fibrinogen, elevated D-dimer • Elevated neutrophil percentage • Lymphopenia • Thrombocytopenia • Hyponatremia • Laboratory evidence of transient renal dysfunction • Elevated troponin • Elevated BNP

Table 1. Continued

Radiologic abnormalities	• Chest CT findings are normal in many children with symptomatic COVID-19 • Fewer CT findings of note than are seen in adults, but more peribronchial distribution of opacities and bronchial wall thickening • CT findings in children include ground-glass opacities with peripheral lung distribution (most common), "crazy paving" pattern, and halo and reverse halo signs • Suggestion of a correlation between increasing age and increasing severity of chest X-ray and CT findings • Lung ultrasound findings of subpleural consolidations, confluent B lines • Concordance of ultrasound and radiologic findings	• Some children have normal abdominal imaging • Some have abnormal abdominal imaging, including mesenteric adenitis, biliary sludge, acalculous cholecystitis, ascites, bowel wall thickening • Chest X-ray findings include ground glass opacities, local patchy shadowing, interstitial abnormalities • Some children have cardiomegaly or signs of cardiac dysfunction
Illness severity	• Majority are asymptomatic or have mild or moderate disease • Very few develop severe or critical illness • Low mortality in children	• Majority have developed shock, required ICU admission, or both • Low overall mortality

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CT = computed tomography; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; IL = interleukin; LDH = lactate dehydrogenase; MIS-C = multisystem inflammatory syndrome in children; PICU = pediatric ICU; TNF = tumor necrosis factor.

coronary artery vasculitis, myocarditis, pericarditis, valvulitis, pyuria, pancreatitis, and lymphadenopathy.[27, 35]

The cause of Kawasaki disease remains unknown. One theory, as yet unproven, was offered by Esper and colleagues in 2005.[36] They suggested that coronavirus diseases and Kawasaki disease might be triggered by a common infectious source.[36] Around that time, the disease SARS was emerging. Until then, coronaviruses had been thought to cause only mild-to-moderate upper respiratory illnesses, such as the common cold.

In MIS-C, as in other inflammatory disorders, abnormal laboratory values include significantly elevated levels of interleukin (IL)-6, IL-8, and tumor necrosis factor α. Some MIS-C therapies target these specific cytokines. Increased cytokine levels can lead to high vascular hyperpermeability, and this in turn can lead to multisystem organ failure. The mechanism of action isn't fully understood. Waltuch and colleagues hypothesized that a postinfectious phenomenon—cytokine release syndrome—is related to an antibody-complex mediated reaction.[13] That syndrome had been previously associated with morbidity in patients infected with SARS-CoV or Middle Eastern respiratory syndrome coronavirus (MERS-CoV).[34] Elevated levels of IL-6 and other inflammatory cytokines are documented features of severe MERS-CoV infections.[34]

MIS-C PRESENTATION

The presentation of MIS-C is clinically challenging, as it mimics that of many common pediatric illnesses. Patients may present with fever, GI upset, generalized aches, lethargy, malaise, rash, or a combination of these.[15, 16] A leading feature that distinguishes MIS-C from Kawasaki disease and other known hyperinflammatory disorders is a history of COVID-19 infection or exposure, confirmed by polymerase chain reaction (PCR) or immunoglobulin G antibody testing, or known or highly suspected exposure without confirmatory testing. Other features that help to differentiate MIS-C from other childhood illnesses, inflammatory con-

ditions, and COVID-19 itself include the predominance of GI complaints; neurologic symptoms; and signs of significant cardiac involvement, including hemodynamic instability and poor perfusion.[12, 13, 26] Although presentations of MIS-C share certain commonalities, the number and severity of symptoms vary widely. Few children present with all of the known systemic manifestations.

For a brief review of MIS-C presenting symptoms by system and potential alternative diagnoses, see Table 2.[12, 14-16]

Initial clinical course groupings. There are also differences in the clinical course. When a child's initial presentation suggests possible MIS-C, the ongoing evaluation and progression of signs and symptoms tend to take one of three distinct clinical paths.[37, 38] We discuss these clinical groupings as follows: patients who are evaluated and discharged or referred, patients who require inpatient admission, and severely ill patients who require ICU admission. Nursing physical assessment is integral to placing each child in the optimal grouping. A high level of suspicion and ongoing assessment are essential to timely recognition and reporting of clinical changes, especially in light of case reports indicating that rapid, sudden decompensation is not unusual.[13]

Evaluation with suspicion for MIS-C: subsequent discharge or referral. A child or young adult will often present to their primary care provider's office or an urgent care center when fever or GI symptoms become persistent or worsen. Initial laboratory tests should include a complete blood count with differential, a complete metabolic panel, and C-reactive protein level and erythrocyte sedimentation rate tests to evaluate for the presence of infection and inflammation.[37] If these tests are unavailable, the patient should be referred to a center where such evaluation can be completed. Because recent infection with SARS-CoV-2 appears to be strongly associated with MIS-C, PCR testing in addition to antibody testing to evaluate for persistence of active SARS-CoV-2 infection should be completed on presentation whenever possible.[26] If laboratory and physical assessment results are otherwise reassuring, follow-up should be conducted within 24 to 72 hours to confirm that symptoms have improved or resolved.[38] If the child has presented for multiple visits in recent weeks—and especially if there has been contact with a person known to have tested positive for or become ill with COVID-19—further evaluation and investigation are warranted, given the variable time frame in which MIS-C evolves.

Chest X-ray and pulse oximetry are often included in the initial evaluation and are useful in indicating the extent of multisystem involvement and when considering potential alternative diagnoses. But unlike COVID-19, in MIS-C the results generally aren't consistent with lung disease, although they can suggest cardiac involvement.[39]

Evaluation with suspicion for MIS-C: inpatient admission. If initial laboratory and physical examination findings are abnormal, further evaluation is necessary. Laboratory findings indicative of a potential MIS-C diagnosis include elevated inflammatory markers, lymphopenia, hyponatremia, and thrombocytopenia.[15, 26] If the patient's condition is stable enough to allow further workup before transfer to an inpatient unit, additional laboratory tests and imaging should be considered.[37] These include testing for troponin and B-type natriuretic peptide levels to evaluate for cardiac involvement, which can be present in MIS-C. Cultures should be collected to rule out bacterial or viral infection (or both). These may include blood, urine, respiratory, and cerebral spinal fluid cultures.

Evaluation with suspicion for MIS-C with shock: ICU admission. If the child presents with physical examination findings consistent with shock, such as altered mental status and poor perfusion, resuscitation should begin immediately, along with ICU consultation to establish a plan for rapid admission or transfer. The immediate goal will be to stabilize the patient's hemodynamic status. Multidisciplinary consultation is necessary to identify appropriate treatment options. Additional laboratory tests to consider include assessing levels of serum ferritin, a biomarker of systemic inflammation, and of D-dimer, a bio-

Case Definition for MIS-C[29]

- An individual ages < 21 years presenting with fever,[a] laboratory evidence of inflammation,[b] and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic) **AND**
- No alternative plausible diagnoses **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the four weeks prior to the onset of symptoms

Additional comments.

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C.
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

COVID-19 = coronavirus disease 2019; MIS-C = multisystem inflammatory syndrome in children; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Fever > 38°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours.

[b] Including, but not limited to, one or more of the following: elevations of C-reactive protein, rate of erythrocyte sedimentation, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6; elevated neutrophils; reduced lymphocytes; and low albumin.

marker of coagulopathy (including thrombosis resulting from the endothelial damage associated with MIS-C[40]).[14] Initial echocardiogram (ECHO) and electrocardiogram (ECG) screenings should be done to evaluate overall cardiac function and check for arrhythmias.

When a child with suspected MIS-C has been identified as requiring ongoing acute care, the next considerations will be further evaluation, disease management, and eventual discharge. Clinical priorities include evaluation for potential alternative diagnoses, specialty consultation, and multidisciplinary collaboration.

Further evaluation: differential diagnosis. Although MIS-C is becoming more widely recognized, a differential diagnosis is required to rule out other potential causes of a patient's signs and symptoms. Nurses must have a working knowledge of MIS-C risk factors, presenting signs and symptoms, and suspected pathophysiology and associated inflammatory syndromes to effectively advocate a comprehensive workup.

Specialty consultation. Because MIS-C affects multiple organ systems, many specialists are likely to become involved, and this will inform nursing assessment. The most common specialties consulted include cardiology, infectious disease, hematology, rheumatology, neurology, and critical care.

Cardiology. Significant cardiac dysfunction can occur in MIS-C. Use of ECHO is critical to quantify overall cardiac function. The clinical guidance document published last July by the American College of Rheumatology (ACR) recommends assessment of ventricular and valvar function, pericardial effusion, and coronary artery dimensions.[41] Coronary artery abnormalities have been seen with some MIS-C cases, and coronary artery aneurysm is a known complication of Kawasaki disease.[27, 38] The ACR suggests that ECGs be conducted at least every 48 hours in hospitalized MIS-C patients and postdischarge during follow-up visits.[41]

Infectious disease. Presenting symptoms of MIS-C often overlap with those seen in active bacterial or viral infections. Moreover, the length of time postexposure that a PCR test will show positive results remains unknown.[15] Infectious disease experts can help in distinguishing the source of infection and determining the likely illness trajectory. They can make recommendations as to whether antivirals are needed. Distinguishing between a less acute case of COVID-19 and MIS-C may involve looking at the PCR cycle threshold level,[26] with a higher threshold indicating a less acute COVID-19 infection.[42]

Hematology. Endothelial injury and heightened coagulation activation are potential concerns; biomarkers include elevated fibrinogen, D-dimer, and factor VIII levels.[38] Children with MIS-C are at high risk for multiple thromboembolic events, including deep vein thromboses, pulmonary emboli, arterial thrombosis, microvascular emboli, and stroke.[38] Hematologists can guide both therapeutic and prophylactic anticoagulation therapy.

Rheumatology. Cytokine overproduction, particularly of IL-1 and IL-6, has been implicated in the high, persistent fevers and rashes common in MIS-C presentation.[38] Rheumatologists can guide the selection and progression of the immunomodulatory therapies used in MIS-C treatment.[41]

Neurology. In some cases, neurologic symptoms such as headache, altered mental status, and irritability have been present, suggesting that some degree of inflammation exists throughout the central nervous system.[12, 26] Children with abnormal or worsening findings on neurologic examination would benefit from a neurology consult.

Critical care. Consultation with critical care specialists is essential in all cases of MIS-C. In several published case reports, children presented with or progressed to shock, requiring hemodynamic stabilization and the involvement of pediatric critical care teams.[15, 31]

TREATMENT OF MIS-C

As of press time, no definitive treatment for MIS-C has been established. Research is ongoing, and new evidence relevant to treatment and new professional recommendations are emerging and being published. The following discussion covers some of the treatments now being used. As outlined above, each child's treatment course should be customized in consultation with specialty services.

Supportive care may be sufficient for mild-to-moderate cases of MIS-C.[37] Continuous monitoring of cardiovascular and respiratory status is warranted.

Antibiotics. Because presenting symptoms often mimic those of bacterial infections, initial treatment options often include broad-spectrum antibiotics such as vancomycin and cefepime.[38] Additional antibiotics might include clindamycin if toxic shock syndrome is suspected and doxycycline if rickettsial disease such as Rocky Mountain spotted fever is suspected.[26, 43]

Immunoglobulin and steroids. Intravenous immunoglobulin (IVIG) and steroids are considered first-tier treatment for MIS-C.[41] IVIG is thought to augment antibody production and dampen the inflammatory response, while steroids suppress the immune system.[27] There are data to suggest that treatment with both IVIG and methylprednisolone, as opposed to IVIG alone, was associated with better resolution of fever.[44] Additional dosing of IVIG or steroids may be needed for persistent symptoms.[12, 31, 41] Serial lab-

Table 2. MIS-C Presenting Symptoms and Potential Alternative Diagnoses[12, 14-16]

System / Problem	MIS-C Symptoms	Alternative Diagnoses
Gastrointestinal	Acute pain, vomiting, diarrhea	• Viral gastrointestinal illness • Appendicitis • Surgical abdomen • Abscess
Dermatologic	Rash, erythematous, nonpruritic; may involve cracked lips, mucous membrane involvement, and conjunctivitis	• Stevens–Johnson syndrome • Drug reaction with eosinophilia and systemic symptoms • Viral exanthems
Neurologic	Headache, irritability, meningeal signs	• Meningitis • Viral encephalitis
Cardiac	Lethargy, poor perfusion, hemodynamic instability, abdominal pain	• Myocarditis from other viral sources
Immune: infection	Fever, rash, hemodynamic instability	• Sepsis • Toxic shock syndrome • Rickettsial diseases, including Rocky Mountain spotted fever
Immune: inflammation	Fever, rash, hemodynamic instability	• Kawasaki disease • Macrophage activation syndrome • Cytokine release syndrome • Hemophagocytic lymphohistiocytosis

MIS-C = multisystem inflammatory syndrome in children.

oratory testing and cardiac assessment should be used in assessing immunomodulatory treatment response.[41] Note that some children may require a period of two to three weeks to taper off immunomodulatory medications.[41]

IL antagonists. If no improvement is noted with the use of IVIG or steroids, other immunologic therapies are considered. Anakinra, an IL-1 antagonist, has been used in several cases involving persistent inflammatory states, as well as in children with contraindications to first-tier treatment.[31, 41] Tocilizumab, an IL-6 antagonist, has also been used in such cases.[25, 38] Children receiving tocilizumab may be at greater risk for bacterial and fungal infection, and should be monitored accordingly.

Anticoagulants. Because heightened coagulation activation is a potential concern with MIS-C, anticoagulation agents should be used for both treatment and prophylaxis. Anticoagulation therapies are institution-specific; that said, the ACR clinical guidance document recommends the use of low-dose aspirin and enoxaparin for children with MIS-C and Kawasaki disease–like features, thrombocytosis, or both.[41] Aspirin has been administered in several such cases.[11] As thrombocytopenia is also common in MIS-C,[26] aspirin should be avoided if thrombocytopenia is present.[38] The recommended duration of anticoagulant treatment is contingent upon whether coronary artery abnormalities, left ventricular dysfunction, and thrombosis are present.[41]

Mechanical ventilation. In some cases, noninvasive or invasive mechanical ventilation is needed to support adequate oxygenation and ventilation. In Feldstein and colleagues' multisite study of 186 children with MIS-C, 20% received invasive mechanical ventilation and 17% received noninvasive mechanical ventilation.[15] And in the aforementioned British case cluster, five of eight children received invasive mechanical ventilation and two received noninvasive mechanical ventilation.[11] It's not clear in either study whether the primary intent of respiratory support was to assist cardiac function or to target respiratory impairment.[11, 15]

ECMO and vasoactive support. Children presenting with shock secondary to MIS-C may require additional cardiovascular support, including continuous vasoactive infusions such as epinephrine, norepinephrine, dobutamine, dopamine, and milrinone. The choice of agent is dependent on the child's specific physiology and clinical situation. The need for vasoactive support and continuous infusions has been described in multiple case reports; in severe cases, ECMO was used to support refractory cardiovascular failure.[15, 31]

NURSING IMPLICATIONS

Symptom recognition and care referral. Because its presenting signs and symptoms can be subtle, MIS-C can be mistaken for mild viral illness or gastroenteritis. Children with a viral prodrome of fever, GI upset, irritability, and other nonspecific symptoms should be referred for evaluation by a pediatric provider.[17] Per the CDC, suspected cases of MIS-C should be reported to the local or regional health departments by a nurse or other health care provider.[29]

The discharge planning process should ensure adequate access to long-term medication needs and to primary and specialty care. Follow-up within 24 to 72 hours after discharge is recommended.[38] Some specific aspects of MIS-C follow-up care remain unknown, and the participation of nurses in developing comprehensive MIS-C follow-up protocols will be invaluable.

Long-term follow-up for GI sequelae may be indicated, as some children may require surveillance for inflammatory bowel disease.[17] Cardiac follow-up care can vary. In cases of Kawasaki disease it's recommended that ECHO be repeated one to two weeks and four to six weeks after treatment for an uncomplicated course.[27] Similarly, the ACR clinical guidance document for children with MIS-C recommends repeating ECHO at a minimum of one to two weeks and four to six weeks after presentation; an additional ECHO one year after diagnosis should be considered in cases of MIS-C with associated cardiac abnormalities.[41] More frequent monitoring and imaging may be needed for children with left ventricular dysfunction or coronary artery aneurysm.[41] The American Academy of Pediatrics recommends outpatient pediatric cardiology follow-up beginning two to three weeks after discharge; those with MIS-C–associated myocarditis should have cardiology-directed guidance regarding physical activities.[45]

Anticipatory guidance after a COVID-19 or MIS-C diagnosis. Nurses in all settings should be ready to provide anticipatory guidance to parents and other lay caregivers after a child is diagnosed with or has been exposed to COVID-19, or is diagnosed with MIS-C. Such guidance should include information about which signs and symptoms to monitor and for how long. Ensure that they have the tools and understanding needed to accurately monitor the child's temperature. Resources that can help to reinforce this anticipatory guidance can be found in the section "For parents and other caregivers" of Table 3. The listed websites offer short informational articles and fact sheets on a wide range of topics, and these can be shared either in print or digital form.

When a child diagnosed with COVID-19 is being managed at home, the parents will need information and guidance in several areas. Instruct parents to notify anyone who was exposed to the child in the last week, especially older adults and parents of infants. The child should be separated from others in the household (including pets) as much as possible, and other children in the household should be monitored for signs of infection. Discuss with parents the risk of MIS-C and ensure they know which signs and symptoms to monitor the child for. These include recurrence of fever (usually above 102°F) that lasts more than 24 hours, rash, abdominal pain, vomiting, diarrhea, respiratory distress, lethargy, conjunctivitis, oral mucosal erythema, cracked lips, and "strawberry tongue."[13, 14, 17] Nurses should emphasize that MIS-C is rare. That said, after a child's exposure to or recovery from COVID-19, parents should monitor the child for MIS-C signs and symptoms for four to six weeks and notify the primary care provider immediately if any develop.

For children diagnosed with MIS-C, anticipatory guidance will be based on the severity of illness. Until the long-term sequelae and outcomes of MIS-C are better known and understood, the standard postdischarge guidance given for any hospitalized child should be provided. Parents should monitor the child for indications that recovery isn't progressing, including recurrence of fever (usually above 102°F) that lasts more than 24 hours, decreased activity, poor appetite, or respiratory distress. In particular, nurses should stress the importance of understanding that long-term follow-up with specialty services will be needed and of keeping these appointments.[14, 17] Parents of children who required ICU admission should be taught about pediatric post–intensive care syndrome and should monitor their child for symptoms. These can include learning difficulties, attention deficits, sleep disruptions, behavior changes, persistent weakness, altered appetite, and alterations in vision or hearing.[46] Any concerns should be reported to the primary care provider.

Nursing research is essential if we are to gain an improved understanding of MIS-C. Relevant topics include the pediatric immune response in MIS-C, genetic predisposition to developing MIS-C, the risk and incidence of long-term sequelae, comprehensive disease follow-up, populations at risk for both COVID-19 and MIS-C, and health and health care disparities associated with these higher risks. Nurses' participation in the research will also ensure attention to the related nursing-sensitive outcome measures.

Systems leadership. Given that MIS-C patients may actively be shedding the COVID-19 virus, there is an urgent need for protocols regarding screening, triage, specific patient groups, and patient throughput, as well as for addressing surge.[47-49] MIS-C patients are often cared for in

Table 3. Pediatric COVID-19 and MIS-C Resources

	Internet Link	Description
For health care providers		
American Academy of Pediatrics	https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance	Critical updates on COVID-19 and links to multiple resources Interim guidance on MIS-C
American Nurses Association	www.nursingworld.org/practice-policy/work-environment/health-safety/disaster-preparedness/coronavirus	COVID-19 resource center with multiple resources, including a video education series
Centers for Disease Control and Prevention	www.cdc.gov/mis-c/hcp/index.html	Information on reporting MIS-C cases
Children's Hospital of Philadelphia	www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway	MIS-C clinical pathway
Connecticut Children's Hospital	www.connecticutchildrens.org/clinical-pathways/covid-19	Several COVID-19 clinical pathways re: primary care and ambulatory sites, MIS-C
National Association of Pediatric Nurse Practitioners	www.napnap.org/coronavirus-safety	Multiple resources on COVID-19 and safety strategies
For parents and other caregivers		
Boston Children's Hospital	www.childrenshospital.org/conditions-and-treatments/conditions/c/coronavirus	Information and resources re: COVID-19
Centers for Disease Control and Prevention	www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/mis-c.html	Information about MIS-C
HealthyChildren.org (sponsored by the American Academy of Pediatrics)	www.healthychildren.org/English/health-issues/conditions/COVID-19/Pages/COVID-19-Youth-with-Special-Health-Care-Needs.aspx	Information for parents of children with special health care needs
KidsHealth	https://kidshealth.org/en/parents/coronavirus.html	Information about pediatric COVID-19, including how to talk to kids about the disease
Society of Critical Care Medicine	www.youtube.com/watch?v=-NEDVF_glfg	Video about pediatric post–intensive care syndrome
For children		
Cincinnati Children's Hospital	www.cincinnatichildrens.org/patients/coronavirus-information/videos-for-kids-parents	Series of short videos for children and parents about COVID-19
KidsHealth	https://kidshealth.org/en/kids/coronavirus-kids.html?WT.ac=p-ra	Basic information on COVID-19

COVID-19 = coronavirus disease 2019; MIS-C = multisystem inflammatory syndrome in children.

dedicated COVID-19 units or in special isolation units.[49] There are significant benefits to including nurses in the planning, development, and integration of such units.

Public health policy. Surveillance data trends serve to alert communities and health care systems to surges in COVID-19 cases, which could result in more MIS-C cases. Having a more comprehensive understanding of how COVID-19 spreads among children, the role of asymptomatic carriers, and the mechanisms of transmission will lead to more informed public health policies. For nurses, the implications include collaborating on policy recommendations for reopening schools and day

care centers, resuming youth sports, and supporting risk reduction through social distancing and other measures.[50-53]

CONCLUSIONS

This article presents information that is current at press time; but what we know about COVID-19 and MIS-C is constantly evolving. The nature and impact (immediate and long term) of pediatric COVID-19 and MIS-C continue to be documented and studied. Nurses in all settings and roles have much to contribute by learning and bringing into practice the latest evidence, participating in nursing research, and helping to develop public health policies. Performing thorough patient assessment, maintaining a high index of suspicion for MIS-C, educating patients and families, providing anticipatory guidance according to the clinical course, and identifying areas for further research remain paramount. ▼

For 16 additional nursing continuing professional development activities on the topic of COVID-19, go to www.nursingcenter.com.

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