IN BRIEF

Multisystem Inflammatory Syndrome in Children

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Most children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remain asymptomatic or develop only mild symptoms. However, rare severe cases occur. During spring 2020, a new pediatric syndrome, likely a postinfectious complication of coronavirus disease 2019 (COVID-19), was described. The seminal report discussed 8 children with signs of hyperinflammation and shock and features consistent with Kawasaki disease (KD) or toxic shock syndrome. Initially named pediatric inflammatory multisystem syndrome, it is now commonly called multisystem inflammatory syndrome in children (MIS-C). Alarmingly, patients with MIS-C generally experience more severe disease than children with acute COVID-19, frequently requiring hospitalization and, at times, critical care. Cases of MIS-C have now been reported from many countries. The United States alone has had more than 2,000 cases and 30 deaths meeting the Centers for Disease Control and Prevention (CDC) MIS-C definition (Table).

CDC CASE DEFINITION FOR MIS-C

An individual younger than 21 years presenting with fever (temperature ≥100.4°F [≥38.0°C] for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (including, but not limited to, ≥1 of the following: elevated C-reactive protein level, erythrocyte sedimentation rate, fibrinogen level, procalcitonin level, D-dimer level, ferritin level, lactic acid dehydrogenase level, interleukin [IL]-6 level, and neutrophil count; reduced lymphocyte count; and low albumin level), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement; AND no alternative plausible diagnoses; AND positive for current or recent SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR), serologic testing, or antigen testing; OR exposure to a suspected or confirmed COVID-19 case within the 4 weeks before the onset of symptoms.

Clinical signs and symptoms of MIS-C vary and may include fever, gastrointestinal symptoms, mucocutaneous lesions, hypotension, and shock. Given the clinical overlap among MIS-C, COVID-19, KD, and toxic shock syndrome, and the absence of validated diagnostic tests, recognition can be challenging. The diagnosis of MIS-C requires fever, inflammation, multiorgan involvement, and evidence of infection with or exposure to SARS-CoV-2. Exclusion of other plausible diagnoses is important. Laboratory abnormalities, including leukopenia, lymphopenia,

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Table. CDC Case Definition for MIS-C

- An individual aged <21 years presenting with fever,[a] laboratory evidence of inflammation,[b] and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement; AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

[a]Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.
[b]Including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin.

thrombocytopenia, and elevated transaminase levels, are common, but none is pathognomonic.

MIS-C primarily affects school-age children and adolescents but may occur in younger children. Consistent with local COVID-19 epidemiology, boys are overrepresented in MIS-C cohorts. Just as racial and ethnic minorities worldwide have experienced disproportionate morbidity and mortality from SARS-CoV-2, US data demonstrate that Black and Hispanic children are disproportionately affected by MIS-C. Further study is needed to determine whether these observed differences are mediated by social determinants of health, health-care inequities, genetic predisposition, or other factors.

Although initial reports noted similarities between MIS-C and KD and proposed a shared etiology and pathogenesis, further findings suggest that MIS-C is a distinct entity. Clinically, MIS-C presents with more frequent gastrointestinal symptoms and different cardiac manifestations from KD. Left ventricular dysfunction is more common in MIS-C than the coronary artery dilation more frequently seen in KD. Decline in cardiac function seems more transient in MIS-C versus KD; however, longer-term data are needed to better define outcomes and long-term sequelae. Median ages differ between the 2 syndromes (~8 years for MIS-C versus ~2 years for KD), as do geographic distributions. To date, only sporadic MIS-C cases have been reported from China, Japan, and Korea, despite a high regional burden of COVID-19 and high historical rates of KD.

Based on available data, MIS-C is likely the result of postinfectious immune dysregulation. Although only a minority of reported MIS-C cases are RT-PCR positive for SARS-CoV-2 (consistent with acute infection), most cases are immunoglobulin G (IgG) positive (consistent with previous infection). Furthermore, children with MIS-C with a positive RT-PCR typically have lower nasopharyngeal viral loads than other children with acute COVID-19. Epidemiologically, the lag of 4 to 6 weeks between local COVID-19 peaks and MIS-C presentation is consistent with a postinfectious etiology.

Emerging immunophenotyping data have delineated differences between MIS-C and other disorders, including acute COVID-19 and KD. Evaluation of immune cells, cytokine profiles, chemokines, autoantibodies, lymphocyte activation, and subsets as well as signaling pathways have been published. Study heterogeneity and low numbers of patients in most cohorts limit the development of unified conclusions at this time, but the emerging consensus is that MIS-C represents a distinct immunologic entity.

One study found that both adults and children generated an adaptive immune response to SARS-CoV-2; however, compared with older patients, children developed a reduced breadth of SARS-CoV-2–specific antibodies, primarily generating IgG antibodies to the virus' spike but not to its nucleocapsid protein. This same group noted similar antibody profiles in children with and without MIS-C, with both groups displaying reduced neutralizing activity compared with adults with COVID-19. They theorize that decreased neutralizing activity may expose children to low-level, persistent infection in sites such as the gastrointestinal tract, resulting in MIS-C. An alternative theory suggests that autoreactive antibodies in children with MIS-C may promote aberrant immune responses, leading to generalized inflammation. Cytokine profiling has been used to differentiate MIS-C from KD, but such testing has not been used clinically on a wide scale.

The care of children with MIS-C requires a multidisciplinary approach. Consultation with pediatric rheumatology, infectious diseases, cardiology, and hematology may be helpful, particularly during initial evaluation and treatment. In severe cases, fluid resuscitation, inotropic and respiratory support, and, rarely, extracorporeal membrane oxygenation have all been used. Advanced imaging studies, including echocardiography, may help guide management decisions.

Some patients with MIS-C also meet the criteria for complete or incomplete KD. For these children, regardless of results of SARS-CoV-2 diagnostic testing it is reasonable to proceed with standard therapies for KD, including intravenous immunoglobulin (IVIg) and aspirin. If inflammation persists or coronary artery dilation/aneurysm occurs, glucocorticoids or other immunomodulatory agents may be considered.

For children with MIS-C not meeting the KD criteria, treatment should be based on severity of illness. Children

presenting in shock should be treated with standard resuscitation protocols.

In cases with multisystem involvement, prompt empirical broad-spectrum antibiotics are appropriate until bacterial infection has been excluded. In severe cases, immunomodulatory therapy may be needed before completion of the diagnostic evaluation. If feasible, samples for serologic testing should be obtained before administering IVIg.

Patients with mild, non–life-threatening MIS-C manifestations should undergo thorough diagnostic evaluation and close clinical monitoring to determine the necessity of treatment beyond supportive care. Nearly one-quarter of patients with MIS-C recover with supportive care alone.

The American College of Rheumatology suggests a graded strategy for immune-modulating therapy. IVIg with or without glucocorticoids is frequently used first-line. In the setting of KD, IVIg (2 g/kg) prevents coronary artery abnormalities, but its benefits in treating short- and long-term cardiac manifestations of MIS-C are less clear. Glucocorticoids reduce rates of coronary artery aneurysms in patients with KD at high risk for IVIg resistance, suggesting that they may be beneficial in MIS-C as well. Although many centers use dosing regimens such as intravenous methylprednisolone (1–2 mg/kg per day), some children, especially those with more severe presentation, may require pulse dose glucocorticoids (eg, intravenous methylprednisolone, 30 mg/kg). Recent publications suggest improved outcome with the use of IVIg with intravenous methylprednisolone compared with IVIg alone. Regardless of glucocorticoid dose, a 2- to 3-week-long taper may be necessary to avoid rebound inflammation.

When MIS-C is refractory to IVIg and glucocorticoid treatment, anakinra, a short-acting IL-1 receptor antagonist, has been used, as have other adjunctive therapies, including IL-6 inhibitors (eg, tocilizumab) and convalescent plasma—all in numbers as yet too small to establish efficacy.

COVID-19–induced hypercoagulability has been reported in adults, and children with MIS-C may also be at risk for thrombosis. Coagulopathy, including extreme elevations in D-dimer and fibrinogen levels with variable effects on platelet count, has been described, as have sporadic cases of MIS-C–associated deep venous thrombosis or pulmonary embolism. No robust estimates of thrombosis risk have been reported, and decisions regarding anticoagulation are challenging. The American College of Rheumatology suggests low-dose aspirin (3–5 mg/kg per day; maximum, 81 mg daily) for patients with MIS-C to be continued until the platelet count is normalized and normal coronary arteries are confirmed at 4 weeks or more after diagnosis. Aspirin should be avoided in patients with active bleeding, substantial bleeding risk, and/or a platelet count of $80 \times 10^3/\mu L$ or less ($\leq 80 \times 10^9/L$). For patients with a coronary artery z score greater than 10.0, in addition to low-dose aspirin, anticoagulation with enoxaparin or warfarin is recommended. Therapeutic anticoagulation is also recommended for patients with MIS-C and documented thrombosis or ejection fraction less than 35% until at least 2 weeks after hospital discharge.

Given that MIS-C is a postinfectious condition, in most patients SARS-CoV-2 antiviral therapies (eg, remdesivir) are unlikely to be of benefit. For patients with a positive PCR with or without positive serology and symptoms consistent with active COVID-19, antiviral agents may be considered.

The recent emergence of MIS-C and the consequent lack of long-term follow-up data make its overall prognosis uncertain. In the acute period, the mortality rate of MIS-C has been estimated to be 1% to 2%. With improved recognition of MIS-C and ongoing longitudinal studies, we hope the future will bring a better understanding of the pathogenesis, effective treatment, and long-term sequelae of this novel pediatric inflammatory condition.

COMMENTS: This In Brief was written in the first months of 2021, when, as our authors acknowledge, much was still to be learned about MIS-C: Why does it happen and to whom? How is it best treated? What are the future risks for affected children? How far science took us during the first year of the COVID-19 pandemic, most particularly with vaccine development, is remarkable. But we have miles to go before we can put this infection to sleep, and as useful and timely as the information presented herein certainly is, all of us to need to keep ourselves updated as new insights and recommendations emerge from ongoing experience and research. What should also be clear about this pandemic is that the virus itself is not the most pervasive risk for children: rather, the havoc it has wrought on social interactions and on developmental and educational opportunities and the emotional trauma it has inflicted from the sickness and deaths of loved ones and from the stresses and insecurities families face, all these are affecting children more widely than direct infection. Long after the virus hopefully is gone, we as caregivers will still have much work to do.

–Henry M. Adam, MD
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