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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) IN AN ADOLESCENT THAT DEVELOPED CORONARY ANEURYSMS: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract—Background: A small subset of pediatric patients develop a rare syndrome associated with Coronavirus Disease 2019 (COVID-19) infection called multisystem inflammatory syndrome in children (MIS-C). This syndrome shares characteristics with Kawasaki disease. **Case Report:** A 15-year-old girl presented to our Emergency Department (ED) with fevers and malaise. She was diagnosed on her initial visit with an acute viral syndrome and discharged with a COVID polymerase chain reaction test pending, which was subsequently negative. She returned 3 days later with persistent fever, conjunctivitis, and a symmetric targetoid rash over her palms. She had no adenopathy, but her erythrocyte sedimentation rate and C-reactive protein were both significantly elevated at 90 mm/h and 19.61 mg/dL, respectively. The patient was then transferred to the regional children's hospital due to a clinical suspicion for MIS-C, and subsequent COVID-19 immunoglobulin G testing was positive. She had been empirically started on intravenous immunoglobulin in addition to 81 mg aspirin daily. Initial echocardiograms showed mild dilatation of the left main coronary artery, and on repeat echocardiogram, a right coronary artery aneurysm was also identified. Oral prednisone therapy (5 mg) was initiated and the patient was discharged on a continued prednisone taper. **Why Should an Emergency Physician Be Aware of This?:** We present a case of a 15-year-old girl who presented to the ED with MIS-C who developed coronary aneurysms despite early

therapy, to increase awareness among emergency physicians of this emerging condition. © 2020 Elsevier Inc. All rights reserved.

Keywords—COVID; COVID-19; PIMS; MIS-C; Kawasaki; pediatric inflammatory multisystem syndrome; multi-system inflammatory syndrome in children

INTRODUCTION

First described in December of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the newest Coronavirus known to infect humans. Symptomatic infection is designated COVID-19 (CORona VIRus Disease 2019). Due to its highly communicable nature, lack of cross-reactive immunity to extant coronavirus strains, and delay in identification, it quickly spread and was designated a global pandemic by the World Health Organization on March 11, 2020. At the time of submission, COVID-19 is estimated to have infected more than 10 million individuals and deemed responsible for over 500,000 deaths. Although adults more commonly present with symptomatic infection, children are also afflicted, but frequently exhibit a milder disease course (1).

A small subset of pediatric patients develop a rare but newly emerging syndrome associated with COVID-19

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infection. Termed multisystem inflammatory syndrome in children (MIS-C), this syndrome shares characteristics with Kawasaki disease (KD), including fever, elevated inflammatory markers, and multisystem involvement (ocular, dermatologic, mucocutaneous, gastrointestinal, and cardiac). MIS-C can have a protean presentation, creating a diagnostic challenge for emergency physicians. We present this case to increase familiarity among emergency physicians with the clinical manifestations of this syndrome.

CASE REPORT

A 15-year-old girl presented to our Emergency Department (ED) with fevers and malaise. She had been healthy until 2 days prior to arrival, at which point she developed elevated temperature, myalgias, fatigue, and headaches. She also reported mild crampy abdominal pain, nonbilious, nonbloody emesis, and watery diarrhea. She denied upper or lower respiratory tract symptoms, urinary symptoms, or skin rash. Although she denied any known sick contacts, she reported travel to Tijuana, Mexico 3 weeks prior to the onset of her symptoms. Vital signs at the time of examination included a temperature of 38.7°C (101.6°F), heart rate of 128 beats/min, blood pressure of 125/85 mm Hg, respiratory rate of 20 breaths/min, and an oxygen saturation of 99% on room air. Physical examination revealed an overall well-appearing patient. She was tachycardic without any murmurs and had clear lungs to auscultation bilaterally. She had no abdominal tenderness on palpation. A chest radiograph did not have any evidence of infiltrates and her urinalysis was unremarkable. She was diagnosed with an acute viral syndrome and discharged with a COVID polymerase chain reaction test pending. It returned negative the following day.

Three days later, the patient returned to our ED. During this visit she complained of ongoing fevers, was minimally responsive to antipyretics, and had painless, nonpruritic rash, which had erupted on her palms over the last 24 h. Vital signs at this visit were remarkable for a heart rate of 112 beats/min. Physical examination was notable for symmetric perilimbal-sparing conjunctivitis and a symmetric targetoid rash over her palms (Figure 1). The remainder of her dermatologic examination was unrevealing. Oral examination was within normal limits and specifically lacked findings to suggest ulcers, tongue depapillation, or lip hyperemia. She lacked any notable palpable lymphadenopathy, and her extremities were without acral edema or desquamation. Laboratory analysis was remarkable for mild hyponatremia at 135 mmol/L, hypochloremia at 95 mmol/L, with a slight anion gap acidosis at 19. She also had a slight transaminitis at 50 U/L and leukocytosis at 11.1/mm³. Her eryth-



Figure 1. Targetoid rash over palms of patient's right hand on second visit.

rocyte sedimentation rate and C-reactive protein (CRP) were both significantly elevated at 90 mm/h and 19.61 mg/dL, respectively.

The patient was then transferred to the regional children's hospital for further evaluation and treatment with a clinical concern for possible MIS-C given the underlying prevalence of COVID-19. She was admitted to the pediatric hospitalist service with Rheumatology, Cardiology, and Infectious Disease consultations. She received one 120-g dose of intravenous immunoglobulin (IVIG) on day 1 in addition to 81 mg aspirin daily throughout the admission. Her COVID-19 immunoglobulin G returned positive later that same day. Further history noted that the patient had a close family contact who tested positive for COVID-19 approximately 1 month prior. Admission laboratory analysis was remarkable for a CRP of 20.7 mg/dL, a ferritin of 1080 ng/dL, and an interleukin 6 level of 18.8 pg/dL.

During her admission, initial echocardiograms showed mild dilatation of the left main coronary artery. On repeat echocardiogram 3 days later, this dilatation had increased from the previous study and a right coronary artery aneurysm was also identified at this time. These enlarging aneurysms prompted additional therapy with 5 mg of oral prednisone for 5 days. The patient was discharged 5 days after hospital admission on a continued prednisone taper. At the time of discharge, her CRP had decreased to 1.6 mg/dL, her ferritin to 565 ng/dL, and interleukin 6 to 9.48 pg/dL.

DISCUSSION

Available epidemiologic data have described COVID-19 largely as a disease of adults. When present in pediatric patients, COVID is milder and has a mortality rate < 1% (2). Although the reason for the lower incidence of symptomatic disease remains uncertain, it has been postulated that children have fewer angiotensin-converting enzyme 2 receptors, which are required for viral entry (3). It has also been hypothesized that children have less exposure to persons with COVID-19, have lower rates of testing, and may have improved immunity from exposure to other viral respiratory syndromes (4). Nevertheless, recent reports describe a subset of pediatric patients who developed a severe inflammatory response with multiorgan involvement, now recognized as a condition called MIS-C. We report a 15-year-old girl with predominantly dermatologic, ocular, and gastrointestinal (GI) symptoms who later developed multiple coronary artery aneurysms. This particular case illustrates several important concepts for emergency physicians. First, in contrast to KD, where afflicted children are typically under the age of 5 years, adolescents are at risk of developing MIS-C and its consequent cardiac complications. Second, although early reports of MIS-C all involved cardiovascular shock, cardiovascular collapse is not a requirement for diagnosis. This case reminds emergency physicians that MIS-C should be entertained in adolescents with recent COVID exposure and multisystem complaints.

Initial Case Descriptions

The initial description of MIS-C was reported in April 2020 by a group of pediatric intensivists in London who described a hyperinflammatory syndrome in 8 previously healthy pediatric patients ranging from 4 to 14 years old (5). All reported unrelenting fevers, rashes, and GI symptoms and each progressed to vasodilatory shock. Despite significant elevations in inflammatory markers, and many with recent COVID-19 exposures, all tested negative for active infection. Although the majority of these patients required intubation and mechanical ventilation, all fully recovered. Shortly after this sentinel report, a group in Bergamo, Italy described a cohort of 10 pediatric patients with similar hyperinflammatory findings and significant myocardial involvement (6). In both series, the authors discovered that approximately half of patients met criteria for incomplete KD. Of concern, they noted a 30-fold higher rate of cardiovascular complications, including coronary aneurysms and shock, compared with patients with KD.

More recently, a report from New York City in June 2020 provided an analysis of 99 patients with either sus-

pected or confirmed MIS-C (7). The majority of patients tested positive for SARS-CoV-2 infection, and all but one had evidence of immunoglobulin G antibodies to SARS-CoV-2. The most common complaints at the time of admission were GI (80%), dermatologic (62%), mucocutaneous (61%), and lower respiratory (40%). The median time from symptom development to admission was 4 days. Most patients required intensive care unit admission and half required vasoactive medication support. Cardiovascular complications were common, with half having some degree of ventricular dysfunction, a third with pericardial effusions, and a tenth with coronary artery aneurysms. A larger report of 186 children with MIS-C across 26 states found similar characteristics to the New York City cohort of children (8). The median age of affected children was 8 years old and the majority of children with MIS-C had involvement of at least four organ systems, most commonly GI (92%), cardiovascular (80%), hematologic (76%), and mucocutaneous (74%). Eighty percent of children were admitted to the intensive care unit, 20% required mechanical ventilation, and 4% received extracorporeal membrane oxygen support. In children with clear evidence of preceding COVID infection, median time from the start of COVID to development of MIS-C was 25 days (range 6–51 days). In the above case series, children with MIS-C were typically healthy prior to development of disease. Almost all patients had significantly elevated inflammatory markers. Mortality rates were 2% or lower.

Incidence and Diagnostic Criteria

The true incidence of MIS-C is uncertain. In the United States, there have been clusters of MIS-C in New York, Michigan, Washington, California, Louisiana, and Mississippi (8). An initial lack of diagnostic criteria and underreporting, or lack of hospitalization in mild cases, likely contributed to a low disease incidence. Diagnostic criteria for MIS-C have now been provided by the Centers for Disease Control and Prevention and the World Health Organization, and can be found in [Table 1](#). Although slight differences exist between these definitions, there is consensus that the presence of at least 1 day of fever, multisystem involvement, and elevated inflammatory markers are required for the diagnosis. Organs affected include cardiovascular, dermatologic, GI, neurologic, renal, and respiratory.

Comparison between KD and MIS-C/Importance to Emergency Physicians

KD is a childhood systemic vasculitis that affects predominantly the medium- and small-sized vessels, notably

Table 1. CDC and WHO Case Definition of MIS-C

CDC Definition	WHO Definition
<ul style="list-style-type: none"> • An individual aged < 21 years 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 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. 	<ul style="list-style-type: none"> • An individual aged 0–19 years who presents with fever for > 2 days and has evidence of multisystem involvement (at least two systems) being: Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet), Hypotension or shock, Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP), Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer), Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer). • Elevated markers of inflammation (e.g., ESR, CRP, or procalcitonin) <p>No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes. Evidence of SARS-CoV-2 infection via:</p> <ul style="list-style-type: none"> • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

CDC = Centers for Disease Control and Prevention; WHO = World Health Organization; MIS-C = multisystem inflammatory syndrome in children; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; RT-PCR = reverse transcription polymerase chain reaction; BNP = B-natriuretic peptide; PT = prothrombin time; PTT = partial thromboplastin time; COVID-19 = coronavirus disease 2019.

* Fever ≥ 38.0°C for ≥ 24 h, or report of subjective fever lasting ≥ 24 h.

† Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

the coronary arteries. The etiology of KD is uncertain. It is hypothesized that it is triggered by an unrecognized infectious agent in genetically predisposed children. Between 3000 and 5000 cases are diagnosed each year in the United States (9). The mean age of affected children is 3 years old, although KD is not exclusively a disease of young children. Diagnosis of classic KD is clinical and requires fever for at least 5 days and the presence of four of the five criteria: conjunctival injection, oropharyngeal mucous membrane changes, cervical lymphadenopathy (one node at least > 1.5 cm), peripheral extremity changes, and a polymorphous generalized rash (10). Incomplete KD is defined as a patient who is febrile for > 4 days with two or three of the classic clinical criteria, and it is also important to identify as children are at risk for the same cardiovascular sequelae as complete KD (10). Approximately 5% of patients present with clinical signs of hypoperfusion or refractory hypotension, referred to as KD shock syndrome (11). Early treatment with IVIG and aspirin is critical. Prior clinical trials have shown that administration of these therapies within 10 days of fever significantly decreases the incidence of coronary artery aneurysms (12,13).

There is some overlap between KD with MIS-C, however, some important differences exist. Whether MIS-C has a similar cause of KD is unknown at this point. KD disproportionately affects children of Asian descent, whereas the available evidence suggests that MIS-C oc-

curs in children of all racial and ethnic backgrounds and may have higher rates in children of black or Hispanic heritages. Patients with MIS-C are also typically older (8 years old) than those with KD (3 years old), although there have been descriptions of neonates with suspected MIS-C.

Initially considered a Kawasaki variant, likely secondary to uncontrolled inflammation, less than half of MIS-C patients exhibit complete Kawasaki symptoms. In patients older than 13 years, the percentage is around 10%. Children with MIS-C had a higher percentage of GI symptoms and distinct laboratory abnormalities including lymphopenia, thrombocytopenia, and elevated ferritin levels. There was a higher percentage of patients with serious cardiovascular involvement, including both vasoplegic shock and coronary aneurysms than those with KD (14). Importantly, in the report from Italy, children were 30 times more likely to develop coronary aneurysms compared with those afflicted with KD, although it is likely that other children in the region with milder symptoms were not included in this case series (6). Although data suggest that the incidence of coronary artery aneurysms is decreased if IVIG is administered within 10 days of fever for patients with KD, the time-frame for the development of coronary aneurysms is uncertain in children with MIS-C. Finally, coronary aneurysms can develop in children with MIS-C that do not have Kawasaki-like features (15).

Diagnosis and Management in the ED

Identification and early supportive care for patients with MIS-C should be the cornerstone of management in the ED. Figure 2 provides recommendations for a two-tiered diagnostic pathway in patients with potential MIS-C developed by a task force from the American College of Rheumatology (16). Initial evaluation (the first tier) includes laboratory analysis with inflammatory markers, consisting of a complete blood count, a complete metabolic panel, and SARS-2-CoV serology. Consideration for additional work-up should be given to other conditions that may mimic MIS-C, such as bacterial sepsis, based on clinical suspicion. If elevated inflammatory markers and other markers associated with COVID-19 (e.g., lymphopenia, neutrophilia, hyponatremia, or thrombocytopenia) are present, additional evaluation (the second tier), including a screening electrocardiogram and echocardiogram, if available, should be pursued. Importantly, patients with circulatory shock without a clear etiology should undergo extensive evaluation for MIS-C (both tier 1 and tier 2).

Although there have been no randomized trials completed to guide therapy for MIS-C, many patients receive high-dose IVIG (1–2 mg/kg) and low-dose aspirin (3–5 mg/kg, maximum of 81 mg) based on prior experience with KD. A smaller percentage receive low-to mod-

erate-dose corticosteroids. Appropriate fluid resuscitation and vasoactive support is required in patients who present with circulatory shock. Patients may benefit from point-of-care ultrasound to evaluate for a depressed systolic function. Patients with vasopressor-refractory shock may benefit from high-dose corticosteroid administration. Importantly, immunomodulatory and antiplatelet therapies are typically started after consultation with available specialists. Disposition should involve discussion with centers that have experience with KD and can provide multispecialty care, including pediatric rheumatologists, cardiologists, intensivists, infectious disease specialists, and hematologists. Patients with abnormal vital signs, any respiratory distress, neurologic deficit, renal or hepatic dysfunction, profoundly elevated inflammatory markers (e.g., CRP > 10 mg/dL), or elevation in cardiac biomarkers should be admitted or transferred to an appropriate facility. Outpatient evaluation may be appropriate for well-appearing children with suspected MIS-C who have reassuring vital signs and are able to have close clinical follow-up.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

We present a case of a 15-year-old girl who presented with MIS-C and developed coronary aneurysms despite

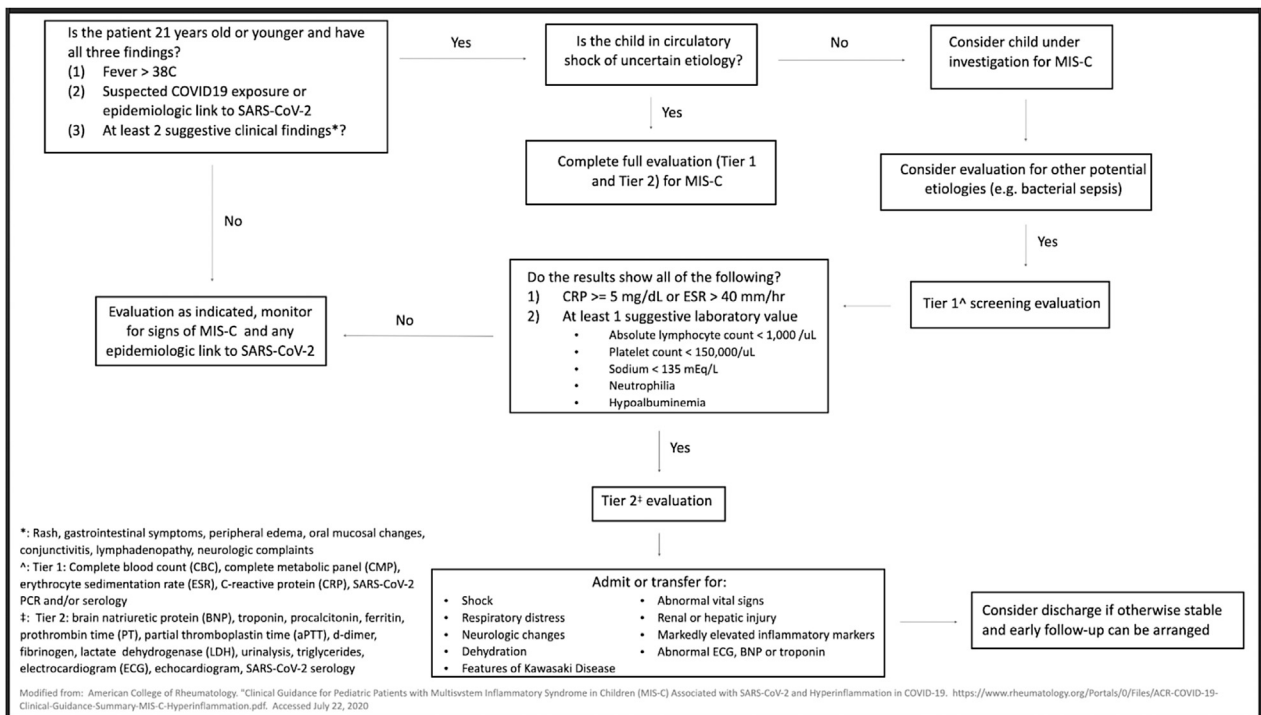


Figure 2. Proposed diagnostic algorithm modified from American College of Rheumatology guidelines. COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; MIS-C = multisystem inflammatory syndrome in children.

early therapy. Originally thought to be a variant of KD, MIS-C is now recognized as a distinct clinical entity associated with SARS-CoV-2, which has been reported in neonates to late adolescents. Early consideration and appropriate diagnostic evaluation in the ED are important, as these children are at high risk of multiple cardiovascular complications, including coronary artery aneurysms. After identification of a patient with MIS-C, emergency physicians should provide appropriate resuscitation, if required, and determine the appropriate disposition based on the severity of illness. Although evidence for providing aspirin, IVIG, and steroids is lacking, these therapies are commonly administered based on prior experience with KD and recommendations from professional societies. This case highlights several differences that emergency physicians should be aware of in the diagnosis of MIS-C and illustrates many of the subtleties in the diagnosis of this new condition.

REFERENCES

1. Giwa AL, Desai A, Duca A. Novel 2019 coronavirus SARS-CoV-2 (COVID-19): an updated overview for emergency clinicians. *Emerg Med Pract* 2020;22:1–28.
2. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment of coronavirus (COVID-19). Available at: <https://www.ncbi.nlm.nih.gov/books/NBK554776/>. Accessed June 18, 2020.
3. Offringa A, Montijn R, Singh S, Paul M, Pinto YM, Pinto-Sietsma SJ. The mechanistic overview of SARS-CoV-2 using angiotensin-converting enzyme 2 to enter the cell for replication: possible treatment options related to the renin-angiotensin system. *Eur Heart J Cardiovasc Pharmacother* 2020;6:317–25. <https://doi.org/10.1093/ehjcvp/pvaa053>.
4. Chang T-H, Wu J-L, Chang L-Y. Clinical characteristics and diagnostic challenges of pediatric COVID-19: a systematic review and meta-analysis. *J Formos Med Assoc* 2020;119:982–9.
5. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;395:1607–8.
6. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771–8.
7. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med* 2020;383:347–58.
8. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020; 383:334–46.
9. Marx JA, Rosen P. Rosen's emergency medicine: concepts and clinical practice. 8th edn. Philadelphia, PA: Elsevier/Saunders; 2014.
10. 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:e927–99.
11. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009;123:e783–9.
12. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984;2:1055–8.
13. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324: 1633–9.
14. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;324:259–69.
15. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multi-system inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation* 2020;142:429–36.
16. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for pediatric patients with multi-system inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. *Arthritis Rheumatol*; <https://doi.org/10.1002/art.41454>. 2020. Available at: <https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf>. Accessed July 21, 2020. [Epub ahead of print].