Multisystem Inflammatory Syndrome in Children Associated With Coronavirus Disease 2019 in a Children's Hospital in New York City: Patient Characteristics and an Institutional Protocol for Evaluation, Management, and Follow-Up

OBJECTIVES: The disease caused by severe acute respiratory syndrome coronavirus 2, known as coronavirus disease 2019, has resulted in a global pandemic. Reports are emerging of a new severe hyperinflammatory syndrome related to coronavirus disease 2019 in children and adolescents. The Centers for Disease Control and Prevention has designated this disease multisystem inflammatory syndrome in children. Our objective was to develop a clinical inpatient protocol for the evaluation, management, and follow-up of patients with this syndrome.

DATA SOURCES: The protocol was developed by a multidisciplinary team based on relevant literature related to coronavirus disease 2019, multisystem inflammatory syndrome in children, and related inflammatory syndromes, as well as our experience caring for children with multisystem inflammatory syndrome in children. Data were obtained on patients with multisystem inflammatory syndrome in children at our institution from the pre-protocol and post-protocol periods.

DATA SYNTHESIS: Our protocol was developed in order to identify cases of multisystem inflammatory syndrome in children with high sensitivity, stratify risk to guide treatment, recognize co-infectious or co-inflammatory processes, mitigate coronary artery abnormalities, and manage hyperinflammatory shock. Key elements of evaluation include case identification using broad clinical characteristics and comprehensive laboratory and imaging investigations. Treatment centers around glucocorticoids and IV immunoglobulin with biologic immunomodulators as adjuncts. Multidisciplinary follow-up after discharge is indicated to manage continued outpatient therapy and evaluate for disease sequelae. In nearly 2 months, we admitted 54 patients with multisystem inflammatory syndrome in children, all of whom survived without the need for invasive ventilatory or mechanical circulatory support. After institution of this protocol, patients received earlier treatment and had shorter lengths of hospital stay.

CONCLUSIONS: This report provides guidance to clinicians on evaluation, management, and follow-up of patients with a novel hyperinflammatory syndrome related to coronavirus disease 2019 known as multisystem inflammatory syndrome in children. It is based on the relevant literature and our experience. Instituting such a protocol during a global pandemic

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is feasible and is associated with patients receiving treatment and returning home more quickly.

KEY WORDS: clinical protocols; coronavirus disease 2019; critical care; pediatric multisystem inflammatory disease, coronavirus disease 2019 related; pediatrics; severe acute respiratory syndrome coronavirus 2

The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the world has led to a global pandemic and a public health emergency, with over 10 million cases of coronavirus disease 2019 (COVID-19) and 500,000 deaths as of June 29, 2020 (1). New York City (NYC) has been at the forefront of the COVID-19 pandemic with over 210,000 cases and 17,000 deaths (2). As a quaternary referral medical center in NYC, our institution has developed unique expertise in the care of COVID-19 patients. During the early stages of the pandemic in NYC, the majority of critically ill patients at our institution were adults. This experience fits with the global understanding of pediatric acute COVID-19: symptoms are generally mild or absent (3, 4).

Starting March 2020, a new pathologic process emerged in pediatric patients related to SARS-CoV-2 in the United States and Europe (5–8). Patients presented with a novel multisystem inflammatory syndrome that is temporally associated with SARS-CoV-2 exposure or infection. The syndrome has pathophysiologic features similar to Kawasaki disease (KD), but affects a broader age range and frequently includes gastrointestinal and neurologic symptoms, myocardial depression, and shock, all of which are rarely seen in KD. The New York State Department of Health (NYSDOH) has reported a case series of 99 patients, highlighting the high prevalence of this syndrome in the region (9). The Centers for Disease Control and Prevention has designated this illness multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 (10). It is also referred to as pediatric multisystem inflammatory syndrome temporally related to COVID-19. Between March 15, 2020, and June 5, 2020, we cared for 54 patients in our institution who were suspected to have MIS-C. Given the complexity, variability, and acuity of illness in MIS-C, we created a clinical protocol to aid in caring for these patients, which was implemented on May 9, 2020. This report provides an explanation of our protocol and its recommendations, as well as a comparison of patient features and measures pre- and post-protocol initiation.

SCOPE OF THE PROTOCOL

The purpose of this protocol (for full details, **Supplemental Digital Content 1**, http://links.lww.com/PCC/B560) is to aid in the evaluation, management, and follow-up of inpatient pediatric patients (< 21 yr old) with suspected MIS-C secondary to SARS-CoV-2. This protocol is not for the management of primary (active) SARS-CoV-2 infection and does not address isolation precautions, transport, airway management, or treatment of suspected active SARS-CoV-2 infection. This protocol is intended as a general guide and should be applied and interpreted with caution. Departure from this protocol may be appropriate and necessary in certain clinical circumstances.

METHODS

We convened a multidisciplinary working group with representation from pediatric cardiology, clinical pharmacy, critical care, dermatology, gastroenterology, hematology, immunology and rheumatology, infectious disease, neurology, and stem cell transplant. Goals of our protocol included: prompt identification of MIS-C cases with high sensitivity, stratification based on clinical presentation, identification of co-infections or co-inflammatory processes, mitigation of risk of coronary artery abnormalities, and control of the hyperinflammatory state to improve or prevent shock and organ injury. Recommendations were based on expert opinion and peer-reviewed literature if present. After consensus was achieved and the protocol was implemented, revisions were made based on provider and subspecialist feedback. The Columbia University Institutional Review Board approved the study with a waiver of informed consent.

MIS-C CLINICAL INSTITUTIONAL PROTOCOL

Case Identification

Our institutional protocol recommends that patients should be screened for MIS-C with NYSDOH case definition criteria in mind (**Supplemental Digital Content 2**, http://links.lww.com/PCC/B561) and

suspected cases should undergo diagnostic testing (11). Specific emphasis was placed on the presence of clinical symptoms and signs suggestive of systemic inflammation with multiple organ system involvement. Fever is a requisite symptom. Symptoms suggesting systemic inflammation include as follows: myalgias, lymphadenopathy or lymphadenitis, and shock evidenced by changes in perfusion, tachycardia, or hypotension. Cardiopulmonary symptoms include chest pain or respiratory distress. Mucocutaneous symptoms include rash (reticular, morbilliform, purpuric, blisters, or erosions), acral swelling or peeling, lip swelling or cracking, strawberry tongue, or conjunctivitis. Gastrointestinal symptoms include nausea, vomiting, diarrhea, or abdominal pain. Neurologic symptoms include headache, altered mental status, meningismus, focal deficits, or seizure. Patients are suspected to have MIS-C if they had a preceding illness consistent with COVID-19 or a COVID-19 sick contact. We recommend treatment for MIS-C be pursued in patients who meet case definition (suspected or confirmed) according to NYSDOH criteria (see "Special Consideration in Mild Cases" below for exceptions) (11). However, the epidemiologic context (i.e., local COVID-19 prevalence) and patient presentation must be carefully considered prior to initiation of treatment in order to avoid misdiagnosis and mismanagement of common severe childhood illnesses (i.e., bacterial sepsis). The Surviving Sepsis Campaign Children's Guidelines should be followed in critically ill patients where sepsis is suspected (12).

Initial Laboratory and Imaging Evaluation

The comprehensive listing of MIS-C initial evaluation is detailed in **Table 1**. Our practice is for all patients with suspected MIS-C to receive SARS-CoV-2 reverse transcription polymerase chain reaction (PCR) testing by nasopharyngeal swab (or institutional equivalent) and SARS-CoV-2 serology testing. Initial evaluations must include necessary testing to exclude other possible etiologies of the patient's presentation. Bacterial blood cultures should be obtained per the Surviving Sepsis Campaign Children's Guidelines (12). Viral studies should be considered if patient presentation is concerning for co-infection. Our practice is to measure Lyme serology in patients with cardiac or neurologic abnormalities and risk of exposure. We measure soluble interleukin-2 receptor level to aid in evaluation for hemophagocytic lymphohistiocytosis (HLH). Additional cytokine levels may be obtained based on the patient's clinical course and in coordination with subspecialist experts. Serum serologies and quantitative immunoglobulins should be sent prior to administration of IV immunoglobulin (IVIG). Ancillary tests include chest radiograph, electrocardiogram (ECG), and transthoracic echocardiogram focused on ventricular function and coronary artery anatomy.

Organ-Specific Evaluations

Symptomatology of patients also warrants targeted studies. For patients with gastrointestinal symptoms, our practice is to send SARS-CoV-2 stool PCR (if available), gastrointestinal pathogen stool PCR panel, *Clostridium difficile* toxin PCR (if diarrhea present), and stool calprotectin. For patients with neurologic symptoms, we pursue head imaging if they present with a focal neurologic deficit, altered mental status, seizure, or severe headache with or without meningeal signs. If a lumbar puncture is indicated, obtaining an opening pressure and cerebrospinal fluid (CSF) cell count, glucose, protein, lactate, culture, and infectious PCR panel is recommended. In some cases, a paraneoplastic CSF panel or autoimmune encephalitis CSF panel may be indicated. Patients with rashes should be documented with photographs in their electronic chart if available. Our practice is for erosions, blisters, or varicella-like lesions to be sampled by PCR for herpes simplex virus, varicella, and enterovirus (if available).

Initial Inpatient Consultations

Our protocol recommends all patients with suspected MIS-C have pediatric cardiology, pediatric infectious disease, and pediatric rheumatology (or appropriate institutional subspecialty) consults (if available). Patients with localized or severe abdominal pain should have pediatric gastroenterology and pediatric general surgery consults. All additional consults should be based on presenting symptoms and clinical indications. Rising or significantly elevated ferritin levels or new cytopenias may indicate evolving HLH. If a patient has suspected HLH or meets HLH criteria, management is beyond the scope of this protocol, and we recommend further management with appropriate institutional HLH expert consultation.

TABLE 1.
Initial Laboratory and Imaging Evaluation for Multisystem Inflammatory Syndrome in Children

Laboratory and Imaging Studies
SARS-CoV-2 testing
SARS-CoV-2 reverse transcription PCR nasopharyngeal swab
SARS-CoV-2 serologies
Systemic inflammation
Complete blood count with differential, C-reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin, D-dimer, lactate dehydrogenase, prothrombin time, partial thromboplastin time, fibrinogen, creatine phosphokinase, triglycerides, quantitative immunoglobulins, soluble interleukin-2 receptor
End-organ function
Basic metabolic panel, liver function panel, blood gas with lactate
Cardiac evaluation
N-terminal-pro B-type natriuretic peptide, troponin
Infectious studies
Blood culture, respiratory pathogen PCR panel, Methicillin-resistant *Staphylococcus aureus* PCR screen
Cytomegalovirus PCR, Epstein-Barr virus PCR, parvovirus PCR, adenovirus PCR, coxsackie immunoglobulin M/immunoglobulin G–if concern for viral co-infection or mimic
Lyme IgM/IgG–if neurologic or cardiac abnormalities and risk of exposure
Urine studies
Urinalysis, urine creatinine, urine protein
Imaging and cardiac studies
Transthoracic echocardiogram focused on ventricular function and coronary arteries
Electrocardiogram
Chest radiograph

PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Classification of Clinical Severity

Cases are classified as mild, moderate, or severe. Classification is determined by Vasoactive-Inotropic Score (VIS), degree of respiratory support, and evidence of organ injury (13). However, the full clinical picture must be considered when deciding on patient classification. Mild cases have no vasoactive requirement, minimal respiratory support, and/or minimal signs of organ injury. Moderate cases have a VIS less than or equal to 10, significant supplemental oxygen requirement, and/or mild or isolated organ injury. Severe cases have a VIS greater than 10, noninvasive or invasive ventilatory support, and/or moderate or severe organ injury including moderate to severe ventricular dysfunction.

Special Consideration in Mild Cases

In some mild cases of MIS-C, patients meet case definition but present with a phenotype that, based on our experience, has a low risk of progressing to a significant hyperinflammatory state. The American College of Rheumatology has released a pathway for initial

evaluation of suspected MIS-C cases, particularly focused on evaluation of mild cases (14). In these patients with minimal signs of inflammation and without signs of cardiac involvement (normal to mildly elevated troponin and/or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) with normal ECG and echocardiogram), we recommend that treatment be deferred on initial evaluation, with serial laboratory and imaging evaluations used to determine need for treatment.

Immunomodulation Management by Clinical Severity

Treatment recommendations as outlined below are based on institutional expert consensus opinion and were revised as our clinical experience grew. Clinical management by severity is summarized in **Figure 1**. Our protocol states that patients fulfilling mild criteria where treatment is indicated should receive 2 mg/kg/d of methylprednisolone (maximum 60 mg/d). Pulse methylprednisolone and/or anakinra should be considered for mild cases with refractory illness (lack of clinical and/or diagnostic test improvement after initial therapy). After clinical improvement, our practice is for steroids to be tapered over 2–3 weeks. Our protocol states that moderate cases should receive at least one dose of methylprednisolone 10 mg/kg (maximum 1 g/d), followed by 2 mg/kg/d (maximum 60 mg/d). A longer pulse methylprednisolone course (up to 3 d) should be considered in moderate cases with limited or no improvement after the initial pulse dose. Our practice is for steroids to be tapered over 6–8 weeks after clinical improvement in moderate cases. Our protocol states that severe cases should receive methylprednisolone 20–30 mg/kg/d for 1–3 days (maximum 1 g/d), followed by 2 mg/kg/d (maximum 60 mg/d). In severe cases, steroids should be tapered slowly and with subspecialty consultation. Anakinra up to 10 mg/kg/dose (maximum 100 mg/dose) every 6 hours should be considered in refractory illness for moderate and severe cases. Other biologic immunomodulators should be considered in severe cases that are refractory to anakinra. We recommend subcutaneous dosing of anakinra in mild cases and IV dosing in moderate and severe cases due to impaired perfusion. In our experience, patients may be refractory to initial steroid treatment but will respond when escalated to pulse doses and longer durations (up to 3 d).

IV Immunoglobulin

Our protocol recommends all patients with MIS-C in whom treatment is indicated receive IVIG 2 g/kg up to 100 g. Serum quantitative immunoglobulins should be obtained before administration of IVIG. A second dose of IVIG should be considered in refractory cases. Patients who meet KD or incomplete KD criteria should receive IVIG even if treatment is otherwise deferred for MIS-C. If IVIG is indicated but unavailable, discuss with relevant subspecialty teams an appropriate alternative therapy.

Other Management Considerations

All patients should receive empiric antibiotics until bacterial infection can be excluded. Antibiotics for first-line empiric coverage should be identified based on local or institutional antibiograms, with consideration for coverage of skin or soft-tissue infection, intra-abdominal infection, and immunocompromised or critically ill patients. Our institutional antibiotic choices are included in Supplemental Digital Content 1 (http://links.lww.com/PCC/B560).

We recommend all patients in whom treatment is indicated receive anticoagulation prophylaxis with either low-molecular-weight heparin (LMWH) or low-dose aspirin (ASA) 3–5 mg/kg/d (maximum dose 81 mg). LMWH is preferred in our protocol for anticoagulation in patients with elevated D-dimer or fibrinogen, patients with significant gastrointestinal symptoms who cannot tolerate ASA, and patients who are critically ill. The full clinical presentation should be considered when deciding on an anticoagulation regimen while monitoring for bleeding, thrombocytopenia, and coagulopathy. Hematology and/or cardiology consultation should be considered in deciding anticoagulation.

We recommend rheumatology and/or immunology consultation for patients with severe, refractory illness when considering immunomodulation beyond pulse steroids and anakinra. Tocilizumab should be used with caution (15). Renal clearance should be considered in the dosing of biologic immunomodulators in discussion with a clinical pharmacist.

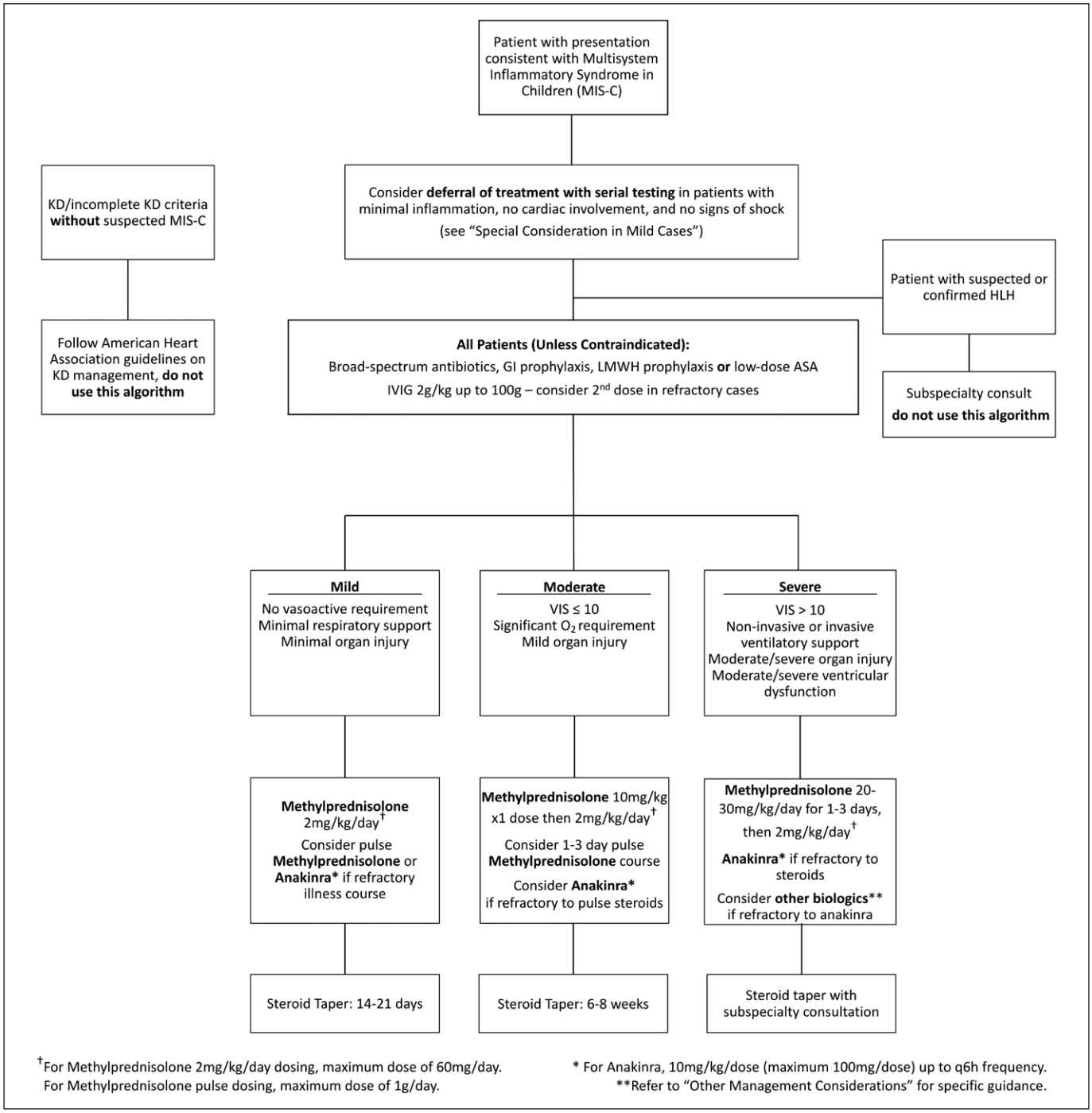

Figure 1. Multisystem inflammatory syndrome in children (MIS-C) management flowchart. ASA = aspirin, GI = gastrointestinal, HLH = hemophagocytic lymphohistiocytosis, IVIG = IV immunoglobulin, KD = Kawasaki disease, LMWH = low-molecular-weight heparin, q6h = every 6 hr, VIS = Vasoactive-Inotropic Score.

Our protocol recommends all patients receive gastrointestinal prophylaxis with a proton pump inhibitor while on steroids and/or ASA. Treatment with high-dose steroids has been associated with gastrointestinal bleeding and perforation in hospitalized patients (16). The risks and benefits of therapy should be carefully considered, particularly in patients with gastrointestinal symptoms.

Repeat Laboratory and Imaging Evaluation While Inpatient

Our protocol recommends patients admitted to the PICU have troponin and NT-proBNP measured every 48 hours, with ECG and echocardiogram performed weekly. General wards patients should have troponin and NT-proBNP measured weekly, ECG performed

weekly, and echocardiogram performed every 2 weeks. Clinical change or abnormal trends may warrant earlier evaluations.

Post-Discharge Follow-Up

Our practice is for all patients who underwent treatment to be discharged home on ASA 5 mg/kg/d (maximum dose 81 mg) unless contraindicated or if there is a clinical indication for other anticoagulation. Follow-up within 2 weeks post discharge with pediatric cardiology and rheumatology (or appropriate subspecialist) is recommended for clinical evaluation, management of steroid taper, and echocardiogram for evaluation of ventricular function and coronary anatomy to determine ASA course. Additional follow-up may be needed based on presenting symptoms and clinical indications.

PATIENT DATA

Statistical Analysis

Reported measures include patient demographics, symptoms, illness features, and laboratory values and were compared pre- and post-protocol initiation. Categorical variables were compared using Pearson chi-square test of independence or Fisher exact test. Continuous variables were compared using the Mann-Whitney *U* test. Statistical analysis was performed using R Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity Analysis

Due to the rapidly evolving nature of this new illness during a pandemic, the initiation of this treatment protocol necessarily occurred very quickly. This may have introduced bias to the statistical analysis, as it is possible that patients hospitalized in the period immediately prior to protocol release may have been treated differently than patients hospitalized in the earliest phases of our hospital's experience with MIS-C. In order to test this source of bias, a sensitivity analysis was performed in which the 24 hours preceding protocol release was considered a rollout period. In the sensitivity analysis, patients who were hospitalized during the rollout were included in the post-protocol period.

RESULTS

From March 15, 2020, to June 5, 2020, our institution admitted 54 patients who met NYSDOH criteria for MIS-C and who did not have an alternative diagnosis for their presentation (i.e., HLH, serious bacterial infection, or other identified autoimmune disorder). One patient who had suspected MIS-C was found to have *Staphylococcus aureus* bacteremia and septic shock. The institutional protocol was put into clinical practice on May 9, 2020. Twenty-six patients were admitted prior to the protocol activation and 28 patients after. Patient demographics, presenting symptoms, and COVID-19 testing status are described in **Table 2**. The median days of fever before admission was 5 days (range, 1–12 d) with no difference in the pre-protocol and post-protocol period. Gastrointestinal symptoms, rash, and conjunctivitis remain among the most common presenting symptoms. Forty-nine patients (49/54, 91%) had laboratory evidence of SARS-CoV-2 infection by PCR and/or serology. Serum laboratory results upon admission prior to treatment as well as results of the admission transthoracic echocardiogram are presented in **Table 3**. Eighteen patients (18/54, 33%) had some degree of left ventricular dysfunction by echocardiogram. Two patients (2/54, 3%) had coronary artery aneurysms (CAAs) by *z* score measurements greater than 2.5 SDs at admission echo. Compared with patients admitted post-protocol, pre-protocol patients had significantly lower absolute lymphocyte count ($p = 0.03$), lower serum sodium ($p = 0.01$), higher C-reactive protein ($p = 0.04$), higher interleukin-6 ($p = 0.03$), and higher NT-proBNP ($p < 0.01$). The majority of patients (50/54, 93%) received some form of immunomodulator as outlined by the protocol (**Table 4**). There was no significant difference in the rate of glucocorticoid or IVIG use between the pre-protocol and post-protocol period. However, there was a significant decrease in the length of time from presentation to first IVIG administration in the post-protocol period compared with the pre-protocol period (33 to 20 hr; $p = 0.02$). While differences were not observed between periods in time to administration of glucocorticoid ($p = 0.05$) or first immunomodulatory therapy (glucocorticoid or IVIG; $p = 0.05$), a sensitivity analysis incorporating a 24-hour rollout period between the pre- and

TABLE 2.
Demographic Characteristics, Presenting Symptoms, and Coronavirus Disease 2019 Testing Status of Patients Admitted With Multisystem Inflammatory Syndrome in Children

Patient Characteristics	All Subjects (*n* = 54)	Pre-Protocol (*n* = 26)	Post-Protocol (*n* = 28)	*p*
Median age (range), yr	7 (0.8–20)	8.5 (0.8–20)	6.0 (0.9–18)	0.33
Male, *n* (%)	25 (46)	11 (40)	14 (50)	0.57
Age group, yr, *n* (%)				
< 1	2 (3)	1 (4)	1 (4)	
1–8	29 (54)	12 (46)	17 (61)	
9–14	15 (28)	8 (31)	7 (25)	
15–21	8 (15)	5 (19)	3 (10)	
Race, *n* (%)				0.69
White	19 (35)	9 (35)	10 (36)	
African American	10 (19)	4 (15)	6 (21)	
Other	8 (15)	5 (19)	3 (11)	
Asian	0 (0)	0 (0)	0 (0)	
Unknown	17 (31)	8 (31)	9 (32)	
Ethnicity, *n* (%)				0.71
Hispanic	16 (30)	9 (35)	7 (25)	
Not Hispanic	20 (37)	10 (38)	10 (36)	
Unknown	18 (33)	7 (27)	11 (39)	
Prior comorbidity (excluding obesity), *n* (%)	7 (13)	4 (15)	3 (11)	0.70
Presenting symptoms, *n* (%)				
Median days of fever (range)	5 (1–12)	5 (1–12)	5 (2–12)	0.76
Gastrointestinal (abdominal pain, vomiting, and/or diarrhea)	45 (83)	21 (81)	24 (86)	0.72
Rash	41 (76)	21 (81)	20 (71)	0.42
Conjunctivitis	31 (57)	15 (58)	16 (57)	0.96
Shock at presentation	30 (56)	18 (69)	12 (43)	0.05
Neurologic (headache, stiff neck, vision change)	22 (41)	11 (42)	11 (39)	0.82
Lip redness/swelling	20 (37)	12 (46)	8 (29)	0.18
Myalgia	17 (31)	10 (38)	7 (25)	0.29
Cervical lymphadenopathy	16 (30)	8 (31)	8 (29)	0.86
Respiratory (cough, dyspnea)	12 (22)	8 (31)	4 (14)	0.15
Hypoxia at presentation	4 (7)	3 (12)	1 (4)	0.34
Skin desquamation	3 (6)	3 (12)	0 (0)	0.10

(*Continued*)

TABLE 2. (*Continued*).
Demographic Characteristics, Presenting Symptoms, and Coronavirus Disease 2019 Testing Status of Patients Admitted With Multisystem Inflammatory Syndrome in Children

Patient Characteristics	All Subjects (*n* = 54)	Pre-Protocol (*n* = 26)	Post-Protocol (*n* = 28)	*p*
Meets KD or incomplete KD criteria, *n* (%)	20 (37)	10 (38)	10 (36)	0.83
History of COVID-19 sick contact, *n* (%)	28 (52)	15 (58)	13 (46)	0.41
COVID-19 testing, *n* (%)				
Severe acute respiratory syndrome coronavirus 2 nasopharyngeal PCR positive	20 (37)	11 (42)	9 (32)	0.44
COVID-19 serology positive	41 (76)	22 (85)	19 (68)	0.35
PCR and serology negative	5 (9)	1 (4)	4 (14)	0.35

COVID-19 = coronavirus disease 2019, KD = Kawasaki disease, PCR = polymerase chain reaction.

post-protocol periods found significant differences in both time measures (p = 0.01 for glucocorticoid, p = 0.01 for first immunomodulatory therapy). In total, 31 patients (31/54, 57%) were admitted to the PICU, with significantly fewer PICU admissions in the post-protocol period (p = 0.02). Both the PICU (p = 0.02) and total hospital lengths of stay (p < 0.01) were significantly shorter in the post-protocol period. None of the patients required invasive mechanical ventilation or mechanical circulatory support. At the time of this article, all patients have been discharged home alive.

DISCUSSION

While guidance in case identification and initial evaluation has been previously released, this institutional protocol provides recommendations for comprehensive MIS-C evaluation and management (11, 17). Given the variability in patient presentation and the possibility of significant short- and long-term morbidity from this disease process, our broad clinical and laboratory diagnostic approach is designed to ensure that MIS-C cases are identified with high sensitivity. We also sought to identify the possibility of co-infection,

TABLE 3.
Study Results for Patients Admitted With Multisystem Inflammatory Syndrome in Children

Patient Characteristics	All Subjects (*n* = 54)	Pre-Protocol (*n* = 26)	Post-Protocol (*n* = 28)	*p*
Echocardiogram at admission[a]				
Left ventricular function, *n* (%)				
Normal	35 (65)	14 (54)	21 (75)	0.07
Any ventricular dysfunction	18 (33)	12 (46)	6 (21)	
Mildly decreased	9 (17)	5 (19)	4 (14)	
Mild-moderately decreased	6 (11)	5 (19)	1 (4)	
Moderately decreased	1 (2)	0 (0)	1 (4)	
Moderate-severely decreased	2 (3)	2 (8)	0 (0)	
Coronary artery *z* score > 2.5	2 (3)	2 (8)	0 (0)	0.23

(*Continued*)

TABLE 3. (*Continued*).
Study Results for Patients Admitted With Multisystem Inflammatory Syndrome in Children

Patient Characteristics	All Subjects (*n* = 54)	Pre-Protocol (*n* = 26)	Post-Protocol (*n* = 28)	*p*
Laboratory studies at admission (normal values), median (range)				
WBC count (×10³/uL)	10.5 (4–35.9)	10.8 (4–35.9)	9.5 (4–34.5)	0.72
Neutrophil (%)	74.3 (25–99)	73.3 (31–95)	74.6 (25–99)	0.47
Lymphocyte (%)	12.3 (1–65)	8.4 (1–51)	17.3 (2–65)	**0.02**
Band (%)	0 (0–38)	2 (0–38)	0 (0–30)	0.15
Absolute lymphocyte count (< 1,500/uL)	1.1 (0.1–8.5)	0.7 (0.1–6.4)	1.8 (0.2–8.5)	**0.03**
Hemoglobin (g/dL)	11.3 (6.5–15.8)	11.5 (7.9–14.3)	11.1 (6.5–15.8)	0.18
Hematocrit (%)	33.9 (20.1–46.5)	34 (23.2–40.7)	32.4 (20.1–46.5)	0.29
Platelet (×10³/uL)	195 (69–892)	173 (69–892)	242 (88–454)	0.22
Serum sodium (137–145 mmol/L)	136 (125–143)	134 (125–142)	138 (125–143)	**0.01**
Serum bicarbonate (19–27 mmol/L)	20 (13–25)	19 (13–25)	20 (16–25)	0.06
Serum creatinine (0.6–1.0 mg/dL)	0.4 (0.2–5.3)	0.4 (0.2–3.6)	0.4 (0.2–5.3)	0.08
Aspartate transaminase (10–37 U/L)	35 (8–167)	36 (18–167)	23 (8–146)	0.44
Alanine transaminase (9–50 U/L)	25 (11–167)	36 (11–167)	34.5 (15–111)	0.16
Albumin (3.2–4.8 g/dL)	3.9 (1.9–4.7)	3.6 (1.9–4.7)	4 (2.8–4.6)	0.06
Prothrombin time (< 12.5 s)	14.9 (11.8–19.6)	15.2 (13.4–19.6)	14.5 (11.8–19.6)	0.06
Activated partial thromboplastin time (< 36.6 s)	34 (23–44.2)	34 (27.5–42.8)	34.4 (23–44.2)	0.93
International normalized ratio (< 1.1)	1.2 (1–1.7)	1.2 (1–1.7)	1.2 (1–1.7)	**0.05**
Fibrinogen (180–400 mg/dL)	565 (140–1,400)	586 (278–875)	548 (140–1,400)	0.30
Lactate dehydrogenase (120–260 U/L)	298 (178–1,295)	321 (178–851)	293 (179–1,295)	0.66
C-reactive protein (10 mg/L)	184.7 (2.5–461.7)	223.7 (3–300)	108.4 (2.5–461.7)	**0.04**
Procalcitonin (≤ 0.08 ng/mL)	1.7 (0.1–127)	2.1 (0.2–127)	1.6 (0.1–100)	0.17
Ferritin (≤150 ng/mL)	475 (69–1,828)	457 (69–1,828)	475.2 (62–1,099)	0.37
D-dimer (≤ 0.5 mg/mL)	3.1 (0.5–20)	3.4 (0.8–11)	2.6 (0.5–20)	0.33
Interleukin-6 (≤ 5 pg/mL)	133 (3–315)	266 (3–315)	76.1 (3.1–315)	**0.03**
Troponin-T, high sensitivity (< 22 ng/L)	17 (6–321)	32 (6–321)	12 (6–315)	0.08
N-terminal prohormone of brain natriuretic peptide (< 207 pg/mL)	2,052 (23–70,000)	5,968 (213–59,291	559 (23–70,000)	**< 0.01**

[a]Admission echocardiogram was not performed in one patient.
Boldface values indicate statistical significance.

co-inflammatory process, or other syndrome mimicking MIS-C with our comprehensive initial laboratory evaluation. The likelihood of MIS-C compared with other common pediatric causes of inflammation (i.e., bacterial sepsis) should be considered according to local epidemiologic and clinical context.

TABLE 4.
Treatment and Outcome for Patients Admitted With Multisystem Inflammatory Syndrome in Children

Patient Characteristics	All Subjects ($n = 54$)	Pre-Protocol ($n = 26$)	Post-Protocol ($n = 28$)	p
Treatment, *n* (%)				0.14
Glucocorticoids only	5 (9)	4 (15)	1 (4)	
IVIG only	9 (17)	4 (15)	5 (18)	
Both glucocorticoids and IVIG	36 (67)	18 (70)	18 (64)	
Supportive treatment only	4 (7)	0 (0)	4 (14)	
Time from admission to initiation of treatment, hr, median (range)				
Glucocorticoids	23 (1–285)	25.5 (1–285)	11 (1–46)	0.05
IVIG	27 (6–319)	33 (12–319)	20 (6–75)	**0.02**
Either glucocorticoids or IVIG	19 (1–285)	23 (1–285)	16.5 (1–46)	0.05
Admission to the PICU, *n* (%)	31 (57)	19 (73)	12 (43)	**0.02**
Disposition				
PICU length of stay, d, median (range)	4 (1–12)	5 (2–12)	3 (1–9)	**0.02**
Hospital length of stay, d, median (range)	4 (1–19)	6 (3–19)	3 (1–14)	**< 0.01**
Alive at discharge, *n* (%)	54 (100)	26 (100)	28 (100)	0.79

IVIG = IV immunoglobulin.
Boldface values indicate statistical significance.

The rationale for our treatment strategy is based on available evidence and our early experience in treating patients with suspected MIS-C. Our guiding principles of treatment were to control the hyperinflammatory state and mitigate coronary artery abnormalities. IVIG is known to improve rates of CAA formation in KD (18). Our early experience with MIS-C, both institutionally and in published literature, indicates patients who do not meet KD criteria are still at risk for CAAs (6, 19, 20). IVIG is theorized to have a general anti-inflammatory effect and has been used successfully with steroids in the treatment of a case of COVID-19 fulminant myocarditis, so it may be beneficial in managing hyperinflammation in MIS-C (21). Given the relatively low risk of IVIG administration and the benefits of CAA prevention and possibly anti-inflammation, we recommend administering IVIG to hospitalized patients with MIS-C, even if KD or incomplete KD criteria are not met. Given the current national shortage of IVIG in the United States, alternative therapies to IVIG must be considered (22). We recommend infliximab or anakinra be considered as alternatives if IVIG is unavailable, given these medications have shown some efficacy in limited studies of IVIG-resistant or severe KD (18). However, we also recommend institutional subspecialty consultation for definitive recommendations in this scenario.

Our approach to steroid use is based on literature indicating the benefits of steroids in diseases similar to MIS-C. Hospitalized adults with COVID-19 often present with a hyperinflammatory state, with D-dimer and interleukin-6 levels correlating with mortality (23–25). In adult patients with COVID-19 and acute respiratory distress syndrome, steroid use has correlated with lower mortality. A possible explanation of this association is the effect of steroids on the hyperinflammatory component of COVID-19 infection (26). The effectiveness of glucocorticoids also applies to severe forms of KD. Pulse steroids have been used in KD shock syndrome with resolution of acute illness (27). In some studies, glucocorticoids, in conjunction with

IVIG, have been shown to lower rates of CAA formation and result in faster resolution of symptoms than IVIG alone in high-risk KD patients, pointing to the ability of steroids to inhibit vascular endothelial inflammation (28, 29). However, overall use of corticosteroids in KD, particularly use of pulse doses, requires further study to definitively determine clinical efficacy (18, 30). Similarly, corticosteroid use in myocarditis has unclear clinical benefit (31). Although adverse events in studies of corticosteroids for KD are rare, corticosteroids are known to have associated risks, including gastrointestinal bleeding and risk of infection (12, 16). The evidence pointing to glucocorticoids as beneficial in severe KD and COVID-19 led us to recommend pulse glucocorticoids for patients with moderate or severe illness and high-dose glucocorticoids for patients with mild illness. We observed clinical improvement in the way of symptom resolution and improvement of shock with the use of steroids in our population. We recommend relatively long steroid tapers given our experience of rebound illness in patients with short steroid tapers (i.e., 5 d). While we recommend anakinra as therapy in patients refractory to pulse glucocorticoids, there is limited evidence to suggest this over other biologic immunomodulators such as infliximab. We use anakinra partially due to its short half-life, which facilitates maintenance of target drug levels in patients with organ injury and discontinuation of therapy in suspected infection reactivation. Although there is limited evidence that tocilizumab may be beneficial in primary COVID-19, it should be used with caution given reports of CAAs with its use in IVIG-refractory KD (32, 15). High-dose ASA was not used as anticoagulation due to lack of demonstrated benefit over low-dose ASA in KD (33).

During peak COVID-19 prevalence in our region, we cared for 54 patients with MIS-C, all of whom survived without the need for invasive ventilatory or mechanical circulatory support. Patients seen in the post-protocol period had fewer admissions to the PICU with shorter lengths of stay, both in the PICU and overall. While this change in outcome is associated with faster administration of immunomodulators (particularly IVIG) in the post-protocol group, potential confounding factors must be considered. Patients in the pre-protocol period had more abnormal inflammatory markers, pointing to a more severe presentation of MIS-C. Greater recognition of MIS-C by healthcare providers and the public in the post-protocol period could have led to earlier patient presentation and lower acuity of illness in the post-protocol period. Finally, instituting our protocol could have created a Hawthorne effect in our hospital, leading to earlier recognition and treatment of MIS-C by providers.

CONCLUSIONS

This institutional protocol seeks to assist providers in caring for patients with a novel, severe inflammatory syndrome in children known as MIS-C. The pathophysiologic process of MIS-C is not known. Given the novelty of this syndrome, the level of evidence needed to create guideline-based recommendations does not exist. This protocol, based on our expert experience, is proposed for the clinician to review. This protocol can be instituted rapidly and is associated with changes in important metrics such as time to treatment and duration of hospitalization. As additional information emerges, more precisely guided clinical evaluation and management can be provided.

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