ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S.J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

ABSTRACT

BACKGROUND

Understanding the epidemiology and clinical course of multisystem inflammatory syndrome in children (MIS-C) and its temporal association with coronavirus disease 2019 (Covid-19) is important, given the clinical and public health implications of the syndrome.

METHODS

We conducted targeted surveillance for MIS-C from March 15 to May 20, 2020, in pediatric health centers across the United States. The case definition included six criteria: serious illness leading to hospitalization, an age of less than 21 years, fever that lasted for at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement, and evidence of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on reverse-transcriptase polymerase chain reaction (RT-PCR), antibody testing, or exposure to persons with Covid-19 in the past month. Clinicians abstracted the data onto standardized forms.

RESULTS

We report on 186 patients with MIS-C in 26 states. The median age was 8.3 years, 115 patients (62%) were male, 135 (73%) had previously been healthy, 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing, and 164 (88%) were hospitalized after April 16, 2020. Organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%). The median duration of hospitalization was 7 days (interquartile range, 4 to 10); 148 patients (80%) received intensive care, 37 (20%) received mechanical ventilation, 90 (48%) received vasoactive support, and 4 (2%) died. Coronary-artery aneurysms (z scores ≥2.5) were documented in 15 patients (8%), and Kawasaki's disease–like features were documented in 74 (40%). Most patients (171 [92%]) had elevations in at least four biomarkers indicating inflammation. The use of immunomodulating therapies was common: intravenous immune globulin was used in 144 (77%), glucocorticoids in 91 (49%), and interleukin-6 or 1RA inhibitors in 38 (20%).

CONCLUSIONS

Multisystem inflammatory syndrome in children associated with SARS-CoV-2 led to serious and life-threatening illness in previously healthy children and adolescents. (Funded by the Centers for Disease Control and Prevention.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Patel at the Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd., MS H24-7, Atlanta, GA 30329, or at mpatel@cdc.gov; or to Dr. Randolph at Division of Critical Care Medicine, Boston Children's Hospital, Bader 634, Boston, MA 02115, or at adrienne.randolph@childrens.harvard.edu.

*Complete lists of members of the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team are provided in the Supplementary Appendix, available at NEJM.org.

Drs. Feldstein and Rose and Drs. Patel and Randolph contributed equally to this article.

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The coronavirus disease 2019 (COVID-19) pandemic has caused catastrophic disease worldwide, although children have been relatively spared.[1,2] Severe lung involvement with acute respiratory failure is the most common complication of Covid-19 in adults, but many have complications in multiple organs, including the heart.[3-5] Adults with severe Covid-19 typically present during the second week of illness, a time coinciding with declining viral loads and increasing markers of inflammation.[3-5] These observations suggest that host tissue damage is mediated by dysregulated innate and adaptive immune responses.[6] In contrast, most children and adolescents with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have mild Covid-19 that does not lead to medical intervention.[1,2] In late April 2020, clinicians in the United Kingdom reported a cluster of eight previously healthy children presenting with cardiovascular shock, fever, and hyperinflammation.[7] On May 14, 2020, the Centers for Disease Control and Prevention (CDC) issued a national health advisory to report on cases meeting the criteria for multisystem inflammatory syndrome in children (MIS-C).[8]

In published case series, many of the pediatric patients with this hyperinflammatory syndrome have had fever and mucocutaneous manifestations similar to those of Kawasaki's disease, a rare vasculitis of childhood that can cause coronary-artery aneurysms.[7,9-14] Some patients have presented with features of toxic shock syndrome, secondary hemophagocytic lymphohistiocytosis, or macrophage activation syndrome.[15,16] Although the cause of Kawasaki's disease remains unknown, a preceding or active infection has been suspected.[17,18] Like Kawasaki's disease, MIS-C is a syndrome with a range of clinical presentations and an absence of pathognomonic findings or diagnostic tests. Unlike Kawasaki's disease, however, MIS-C has been suggested in early reports to predominantly affect adolescents and children older than 5 years of age and to be associated with more frequent cardiovascular involvement.[7,11,12]

Characterizing the epidemiology, spectrum of illness, clinical course, treatments, and prognosis of MIS-C is key for reducing morbidity and mortality. In April 2020, the CDC initiated surveillance for severe Covid-19 in children and adolescents (the Overcoming COVID-19 study).[19] In this report, we summarize the epidemiology and clinical characteristics of 186 cases of MIS-C reported to the Overcoming COVID-19 study and the CDC by clinicians in 26 states.

Methods

Overview

We conducted prospective and retrospective surveillance of patients with MIS-C who were admitted to participating health centers from March 15, 2020, to May 20, 2020. Participating health centers in the Overcoming COVID-19 study were members of the Pediatric Acute Lung Injury and Sepsis Investigators Pediatric Intensive Care Influenza and Emerging Pathogens Subgroup, which was made up of investigators at 38 sites funded by the CDC to conduct surveillance for pandemic surveillance preparedness[20] and at 15 additional sites.[21]

On May 5, clinician investigators at Overcoming COVID-19 surveillance sites were told to report cases of MIS-C that met the case definition. Clinicians at participating sites who had knowledge of patients with MIS-C abstracted medical records onto a standardized form and then into an electronic database (Research Electronic Data Capture [REDCap], Vanderbilt University). The Boston Children's Hospital Institutional Review Board and the CDC Human Subjects Research Protection Office waived the need for informed consent for this study because of the declaration of a public health emergency. The authors vouch for the accuracy and completeness of the data.

Study Definitions

The case definition of MIS-C included six criteria[8]: serious illness leading to hospitalization, an age of less than 21 years, fever (body temperature, >38.0°C) or report of subjective fever lasting at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement (i.e., involving at least two systems), and laboratory-confirmed SARS-CoV-2 infection (positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction [RT-PCR] or antibody test during hospitalization) or an epidemiologic link to a person with Covid-19 (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). An epidemiologic link was defined as exposure to a person with suspected Covid-19 within 4 weeks before the onset

of MIS-C symptoms, determined on the basis of clinician judgment because of differences in testing availability, delays in the manifestation of MIS-C in relation to exposure to the virus, and geographic differences in Covid-19 activity. To address duplicate reporting, we excluded patients who had been included in the New York Department of Health surveillance report[22] and note inclusion of cases reported in previous studies in the Supplementary Appendix (page 5).

Categories of SARS-CoV-2 test results included RT-PCR positivity (with or without a positive antibody test), antibody positivity only (with negative or unknown RT-PCR results), or an epidemiological link with negative RT-PCR results and negative or unknown antibody test results. We also assessed Kawasaki's disease–like signs and symptoms among the patients with multisystem inflammatory syndrome (Table S2).[10]

We described organ-system involvement on the basis of symptoms, clinical findings, and laboratory measures (Table S3). The severity of cardiovascular involvement was specifically evaluated.[7,11,12] Cardiovascular involvement was identified on the basis of any of the following: receipt of vasopressor or vasoactive support, an echocardiogram showing an ejection fraction of less than 55% (based on measurement or qualitative evaluation of decreased left ventricular function) or a maximum z score of the left anterior descending or right coronary artery of at least 2.5 on any echocardiogram,[10] pericarditis or pericardial effusion, elevated levels of troponin or B-type natriuretic peptide (BNP), cardiac arrhythmia, pulmonary edema due to left heart failure, or receipt of cardiopulmonary resuscitation (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We report the frequency of clinical features, relevant laboratory findings, and treatments among patients stratified according to SARS-CoV-2 test results, age groups, and clinical syndromes. Continuous variables were expressed as medians and interquartile ranges or ranges, and categorical variables were expressed as counts and percentages. We did not impute missing data. We analyzed all data using R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

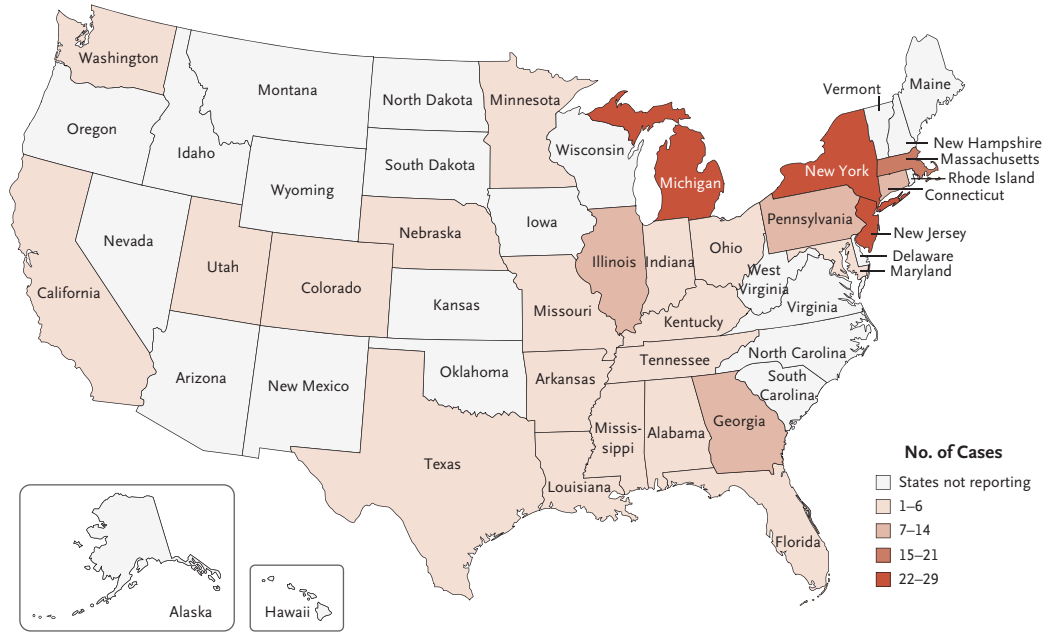
CASE-DEFINING, DEMOGRAPHIC, AND CLINICAL CHARACTERISTICS

Of 234 patients admitted to 53 participating hospitals, we excluded 21 whose condition did not meet the case definition and 27 who were included in the New York State Department of Health report.[22] Among the 186 patients with MIS-C included in our report (Fig. 1A), 22 (12%) were hospitalized between March 16 and April 15, and 164 (88%) were hospitalized between April 16 and May 20; the peak incidence of MIS-C occurred when Covid-19 activity was decreasing (Fig. 1B).

The majority of patients (131 [70%]) tested positive for SARS-CoV-2 infection by RT-PCR, antibody testing, or both, and 55 (30%) had an epidemiologic link to a person with Covid-19 (Table 1). Among the 14 patients with recorded Covid-19 symptoms before the onset of MIS-C, the median interval from Covid-19 symptom onset to MIS-C symptom onset was 25 days (range, 6 to 51). The median age of the patients was 8.3 years (interquartile range, 3.3 to 12.5), 115 (62%) were male, and 135 (73%) had previously been healthy. Overall, 35 patients (19%) were white non-Hispanic, 46 (25%) were black non-Hispanic, 9 (5%) were another race and non-Hispanic, 57 (31%) were Hispanic or Latino, and 41 (22%) were of unknown race (race categories were nonexclusive).

CLINICAL CHARACTERISTICS AND TREATMENT

Most patients (132 [71%]) had involvement of at least four organ systems (Table 1). The most commonly involved organ systems were the gastrointestinal (171 [92%]), cardiovascular (149 [80%]), hematologic (142 [76%]), mucocutaneous (137 [74%]), and respiratory (131 [70%]) systems (Fig. 2 and Table S4). Most patients (148 [80%]) were cared for in an intensive care unit, and 37 (20%) received invasive mechanical ventilation. Eight patients (4%) received extracorporeal membrane oxygenation (ECMO) support. As of May 20, 2020, a total of 130 patients (70%) had been discharged alive, 52 (28%) were still hospitalized, and 4 (2%) had died. The median length of hospitalization was 7 days (interquartile range, 4 to



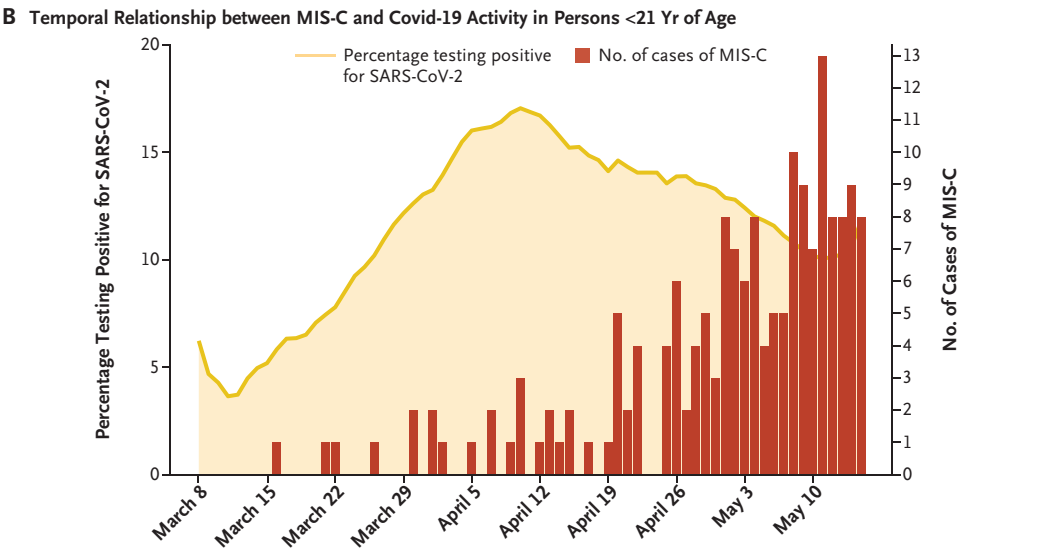


Figure 1. Geographic and Temporal Representation of Cases of Multisystem Inflammatory Syndrome in Children (MIS-C).

Panel A shows the cases of MIS-C included in this report according to state; cases are only from the reporting hospitals and do not reflect all cases in each state.[1] Panel B shows statewide pooled percentages of positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) laboratory testing of respiratory specimens from persons younger than 21 years of age as compared with hospitalization dates for patients with MIS-C included from participating hospitals from March 15 to May 15, 2020.[2] The percentage of positivity for SARS-CoV-2 is based on pooled results from tests reported to the Centers for Disease Control and Prevention from commercial and public health laboratories in 25 of the 26 states in which hospitals in our system that reported cases of MIS-C are located.

Table 1. Demographic and Clinical Characteristics of the Patients According to SARS-CoV-2 Infection Status.

Characteristic	Laboratory Confirmation of SARS-CoV-2 Infection (N=131)		Epidemiologic Link to Person with Covid-19 (N=55)*	All Patients (N=186)
	RT-PCR Positive (N=73)†	Antibody Test Positive, RT-PCR Negative or Unknown (N=58)		
Male sex — no. (%)	43 (59)	36 (62)	36 (65)	115 (62)
Median age (interquartile range) — yr	9.1 (4.8–14.2)	9.1 (4.1–11.7)	3.9 (1.4–11.6)	8.3 (3.3–12.5)
Age group — no. (%)				
<1 yr	6 (8)	0	7 (13)	13 (7)
1–4 yr	13 (18)	19 (33)	21 (38)	53 (28)
5–9 yr	21 (29)	14 (24)	11 (20)	46 (25)
10–14 yr	17 (23)	18 (31)	10 (18)	45 (24)
15–20 yr	16 (22)	7 (12)	6 (11)	29 (16)
Race and ethnic group — no. (%)‡				
White, non-Hispanic	13 (18)	8 (14)	14 (25)	35 (19)
Black, non-Hispanic	17 (23)	18 (31)	11 (20)	46 (25)
Hispanic or Latino	29 (40)	12 (21)	16 (29)	57 (31)
Other race, non-Hispanic	4 (5)	1 (2)	4 (7)	9 (5)
Unknown	11 (15)	19 (33)	11 (20)	41 (22)
Underlying conditions				
Previously healthy — no. (%)§	49 (67)	43 (74)	43 (78)	135 (73)
At least one underlying condition, excluding obesity — no. (%)	24 (33)	15 (26)	12 (22)	51 (27)
Respiratory — no. (%)	16 (22)	12 (21)	5 (9)	33 (18)
Cardiac — no. (%)	2 (3)	2 (3)	1 (2)	5 (3)
Immunocompromising or autoimmune — no. (%)	6 (8)	1 (2)	3 (5)	10 (5)
Other — no. (%)¶	15 (21)	3 (5)	2 (4)	20 (11)
Clinically diagnosed obesity — no./total no. (%)‖	8/62 (13)	3/55 (5)	1/36 (3)	12/153 (8)
BMI-based obesity — no./total no. (%)**	21/62 (34)	15/55 (27)	9/36 (25)	45/153 (29)
Organ-system involvement — no. (%)				
Two systems	5 (7)	1 (2)	12 (22)	18 (10)
Three systems	14 (19)	10 (17)	12 (22)	36 (19)
Four or more systems	54 (74)	47 (81)	31 (56)	132 (71)
Detection of additional virus — no. (%)††	6 (8)	2 (3)	1 (2)	9 (5)
Highest level of care — no. (%)				
Ward	11 (15)	5 (9)	22 (40)	38 (20)
Intensive care unit	62 (85)	53 (91)	33 (60)	148 (80)
Extracorporeal membrane oxygenation	6 (8)	1 (2)	1 (2)	8 (4)
Mechanical ventilation	23 (32)	8 (14)	6 (11)	37 (20)

Table 1. (Continued.)

Characteristic	Laboratory Confirmation of SARS-CoV-2 Infection (N=131)		Epidemiologic Link to Person with Covid-19 (N=55)*	All Patients (N=186)
	RT-PCR Positive (N=73)†	Antibody Test Positive, RT-PCR Negative or Unknown (N=58)		
Outcome — no. (%)				
Still hospitalized as of May 20, 2020	26 (36)	19 (33)	7 (13)	52 (28)
Discharged alive	44 (60)	39 (67)	47 (85)	130 (70)
Died	3 (4)	0	1 (2)	4 (2)

* Patients without laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (i.e., because of negative or unknown test results or lack of testing) were classified as having an epidemiologic link if they had exposure to a person with coronavirus disease 2019 (Covid-19) within 4 weeks before the onset of symptoms of multisystem inflammatory syndrome.

† Of the 73 patients who had SARS-CoV-2 infection confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR), 27 were also antibody positive (see the Supplementary Appendix).

‡ Race and ethnic group were reported by the patient or by the patient's parent or guardian. Race categories are not mutually exclusive.

§ "Previously healthy" was defined as an absence of reported underlying conditions (excluding obesity).

¶ "Other" includes neurologic, hematologic, gastrointestinal or hepatic, renal, endocrine (including diabetes mellitus), metabolic (other than obesity), and genetic conditions.

‖ The determination of clinically diagnosed obesity was based on reporting by clinicians among patients who were at least 2 years of age.

** The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. BMI-based obesity was defined on the basis of national reference standards for BMI and was calculated only for patients who were at least 2 years of age. The category includes patients with clinician-diagnosed obesity.[23]

†† Viral test results were as follows: among the patients with RT-PCR confirmation of SARS-CoV-2 infection, additional viral infections included Epstein–Barr virus (1 patient), Epstein–Barr virus plus parvovirus B19 (1 patient), rhinovirus (2 patients), rhinovirus/enterovirus (1 patient), and human metapneumovirus (1 patient). Among the patients who were antibody-positive for SARS-CoV-2 infection, additional viral infections included rhinovirus (1 patient) and parainfluenza (1 patient). Among the patients with an epidemiologic link to a person with Covid-19, additional viral infections included human metapneumovirus (1 patient).

10) among the patients who were discharged alive and 5 days (range, 2 to 5) among those who died. The 4 patients who died were 10 to 16 years of age; 2 of the patients had diagnoses of underlying conditions, and 3 received ECMO support (Table S5).

Among the patients with MIS-C, 131 of 167 (78%) had fever for 5 or more days, and at least 151 of 167 (90%) had fever for 4 or more days. Overall, 74 patients (40%) had fever for at least 5 days and four or five Kawasaki's disease–like features or two or three Kawasaki's disease–like features plus additional laboratory or echocardiographic findings (Table 2 and Table S2). Treatment with intravenous immune globulin was most common in these two groups (100% and 97%, respectively, vs. 63% among other patients). Almost half the patients (91 [49%]) received glucocorticoids, 14 (8%) received interleukin-6 inhibitors (tocilizumab or siltuximab), and 24 (13%) received an interleukin-1Ra inhibitor (anakinra) (Table 2).

ORGAN INVOLVEMENT AND INFLAMMATORY MARKERS

Cardiovascular involvement was common (in 149 patients [80%]) (Fig. 2A and Table S4), with 90 patients (48%) receiving vasoactive support. The majority of patients had elevated levels of BNP (94 of 128 [73%]), and 50% (77 of 153) had elevated troponin levels. Most patients (170 [91%]) had at least one echocardiogram. Coronary-artery aneurysms identified on the basis of a z score of 2.5 or higher in the left anterior descending or right coronary artery were documented in 8% of the patients (15 of 186) and in 9% of those with echocardiograms (15 of 170). Respiratory insufficiency or failure occurred in 109 patients (59%) (Fig. 2B and Table S6); 85 (78%) of these patients had no underlying respiratory conditions. Overall, 37 patients (20%) received invasive mechanical ventilation and 32 (17%) received noninvasive mechanical ventilation.

Most patients (171 [92%]) had four or more laboratory biomarkers indicating inflammation.

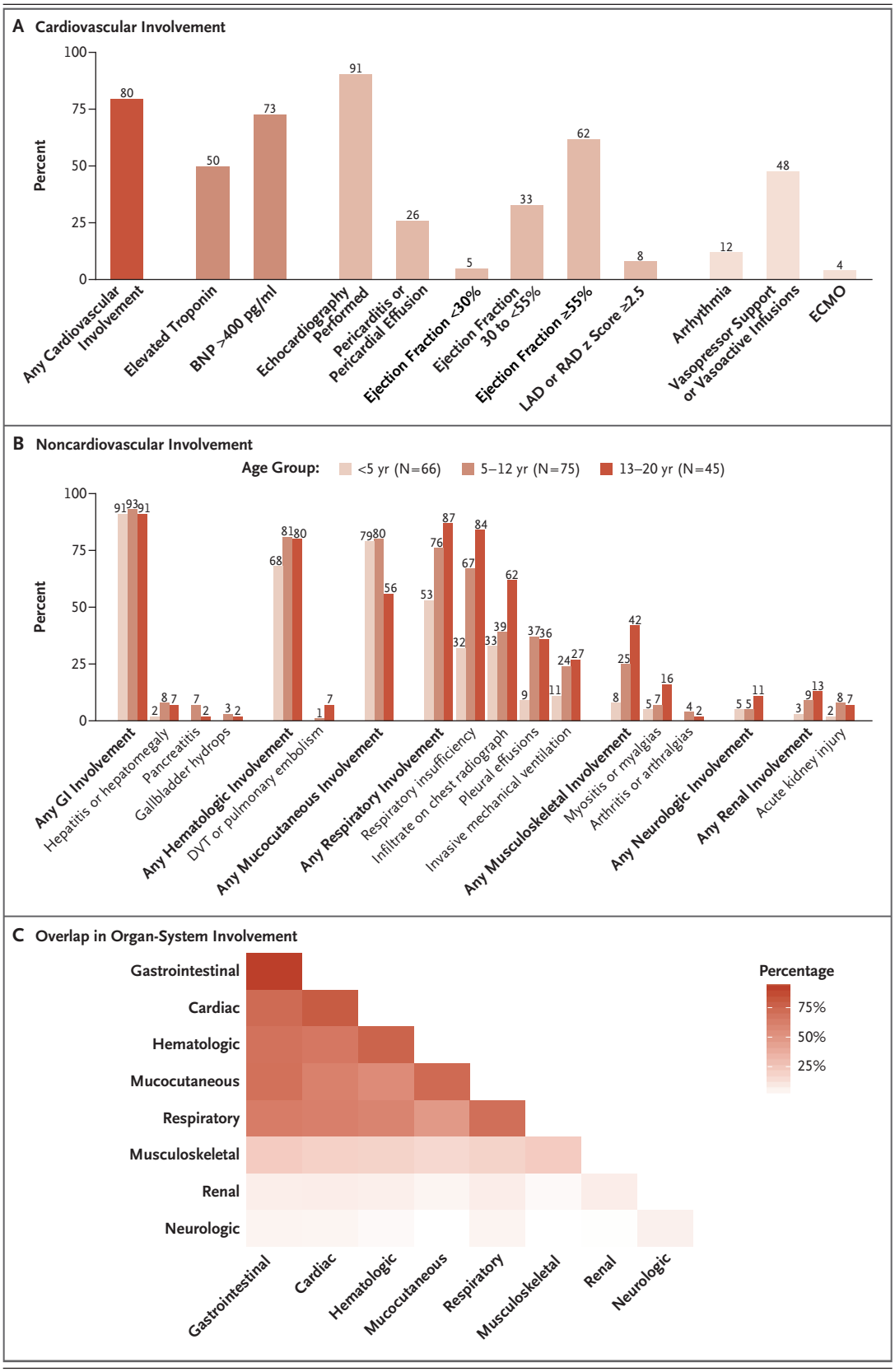


Figure 2 (facing page). Organ-System Involvement in Patients with MIS-C.

Cardiovascular involvement and laboratory and diagnostic findings are shown in Panel A, and noncardiovascular complications and diagnostic findings according to age are shown in Panel B. Numbers on each column represent percentages. The denominator for percentages was the 186 patients included in this report, with the exception of the percentages of patients with elevated troponin and B-type natriuretic peptide (BNP), which were calculated among those with reported values (128 patients and 153 patients, respectively). DVT denotes deep-vein thrombosis, ECMO extracorporeal membrane oxygenation, GI gastrointestinal, LAD left anterior descending, and RCA right coronary artery. Panel C is a heat map illustrating the overlap in organ-system involvement among patients with MIS-C. The diagonal represents the percentage of patients with involvement of each organ system. The intersections of rows and columns beneath the diagonal indicate the percentages of patients with both indicated organ systems involved.

The majority had an elevated erythrocyte sedimentation rate or C-reactive protein level, lymphocytopenia, neutrophilia, elevated ferritin level, hypoalbuminemia, elevated alanine aminotransferase level, anemia, thrombocytopenia and an elevated D-dimer level, prolonged international normalized ratio, or elevated fibrinogen level (Fig. 3 and Table S7).

Table S8 shows a comparison of the results that were obtained with and without the 27 patients who were part of the New York State Department of Health report included in the analysis.[22]

DISCUSSION

We describe 186 patients younger than 21 years of age who met the criteria for MIS-C associated with SARS-CoV-2 infection from across the United States. The majority of patients (70%) had laboratory-confirmed antecedent or concurrent SARS-CoV-2 infection, and most had no documented underlying conditions. Cardiovascular involvement was common, with almost half receiving vasopressor or vasoactive support and 1 in 12 having coronary-artery aneurysms. Most patients were cared for in an intensive care unit, and 20% received invasive mechanical ventilator support. Although most discharged patients survived, 28% were still hospitalized as of May 20, 2020, and 4 patients (2%) died, 2 of whom had previously been healthy.

Evidence supporting a causal link with SARS-CoV-2 includes a strong temporal association with Covid-19 activity, confirmation of SARS-CoV-2 infection through nucleic acid or antibody testing in the majority of patients, and hyperinflammatory manifestations similar to those in adults with Covid-19.[24-26] Almost one third of the patients tested negative for SARS-CoV-2 by RT-PCR but had detectable antibodies. In a small subgroup of the patients in our series, a median interval of 25 days was reported between the onset of Covid-19 symptoms and hospitalization for MIS-C. Although not sufficient to establish causality, these findings suggest that a substantial proportion of the patients in this series were infected with SARS-CoV-2 at least 1 to 2 weeks before the onset of MIS-C.[27]

These patients met a case definition developed by the CDC that was designed to be sensitive.[8] Although more than one third of the patients had Kawasaki's disease–like clinical features, 60% of the patients would not have met complete or incomplete criteria for Kawasaki's disease. Patients with Kawasaki's disease–like features were more likely to be younger than 5 years old, similar to what is seen among patients with Kawasaki's disease reported in the literature.[9,10] Some of the Kawasaki's disease–like features, including fever, erythroderma, and delayed desquamation, are also seen in toxic shock syndrome, which can have manifestations of multiorgan involvement and has been associated with other viruses.[14,28]

Although both Kawasaki's disease and MIS-C can have cardiovascular involvement, the nature of this involvement appears to differ between the two syndromes. We observed cardiovascular involvement leading to vasopressor or vasoactive support as a common and severe subphenotype, most frequently in older children and adolescents. Approximately 5% of children with Kawasaki's disease in the United States present with cardiovascular shock leading to vasopressor or inotropic support,[10] as compared with 50% of the patients in our series. Myocardial dysfunction is a prominent extrapulmonary manifestation of Covid-19 that has been associated with increased mortality in adults.[29,30] Coronary-artery aneurysms are a common feature of Kawasaki's disease, affecting approximately one quarter of patients within 21 days after disease onset.[31] In our series, a maximum z score of 2.5 or higher

Table 2. Clinical Characteristics of the Patients According to the Number of Kawasaki's Disease–like Features Present.*

Characteristic	Patients with 4 or 5 Features (N=38)	Patients with 2 or 3 Features plus Laboratory Findings (N=36)	Other (N=112)†	All Patients (N=186)
Median age (IQR) — yr	5.7 (1.7–8.9)	8.4 (4.2–12.0)	9.1 (3.1–14.1)	8.3 (3.3–12.5)
Signs and symptoms				
Fever‡	38 (100)	36 (100)	112 (100)	186 (100)
Median fever duration (IQR) — days	6 (6–8)	6 (6–8)	6 (4–8)	6 (5–8)
Fever duration — no./total no. (%)				
≤3 days	0	0	16/93 (17)	16/167 (10)
4 days	0	0	20/93 (22)	20/167 (12)
≥5 days	38/38 (100)	36/36 (100)	57/93 (61)	131/167 (78)
Bilateral conjunctival injection — no. (%)	36 (95)	30 (83)	37 (33)	103 (55)
Oral mucosal changes — no. (%)	38 (100)	16 (44)	24 (21)	78 (42)
Peripheral extremity changes — no. (%)	36 (95)	14 (39)	19 (17)	69 (37)
Rash — no. (%)	38 (100)	27 (75)	45 (40)	110 (59)
Cervical lymphadenopathy >1.5 cm diameter — no. (%)§	7 (18)	3 (8)	8 (7)	18 (10)
Echocardiography performed — no. (%)	37 (97)	35 (97)	98 (88)	170 (91)
LAD or RCA z score of ≥2.5¶	3 (8)	8 (23)	4 (4)	15 (9)
Treatment				
Intravenous immune globulin — no. (%)	38 (100)	35 (97)	71 (63)	144 (77)
Median day of illness on which treatment was received (IQR)	6 (6–8)	7 (6–8)	6 (5–8)	6 (5–8)
Second dose received — no. (%)	16 (42)	9 (25)	14 (12)	39 (21)
Systemic glucocorticoid — no. (%)	20 (53)	18 (50)	53 (47)	91 (49)
Interleukin-6 inhibitor — no. (%)‖	1 (3)	1 (3)	12 (11)	14 (8)
Interleukin-1Ra inhibitor — no. (%)**	5 (13)	6 (17)	13 (12)	24 (13)
Anticoagulation therapy — no. (%)††	14 (37)	18 (50)	55 (49)	87 (47)
Highest level of care				
Ward — no. (%)	13 (34)	2 (6)	23 (21)	38 (20)
Intensive care unit — no. (%)	25 (66)	34 (94)	89 (79)	148 (80)

* Kawasaki's disease–like features are listed in Table S2 in the Supplementary Appendix. The number of features excludes fever. IQR denotes interquartile range, LAD left anterior descending, and RCA right coronary artery.
† This category includes patients who had 0 or 1 Kawasaki's disease–like features or 2 or 3 features without additional laboratory findings.
‡ Fever was defined as a body temperature higher than 38.0°C.
§ Data on cervical lymphadenopathy were not collected systematically for patients with fewer than two principal signs of Kawasaki's disease.
¶ The denominator for the calculation of these percentages was the number of patients who had echocardiography performed.
‖ Interleukin-6 inhibitors included tocilizumab and siltuximab.
** The interleukin-1Ra inhibitor given was anakinra.
†† Anticoagulation therapy included heparin, enoxaparin, bivalirudin, warfarin, and argatroban.

in the left anterior descending or right coronary artery was reported in 8% of the patients overall and in 9% of patients with echocardiograms. However, images may have been technically limited in some studies, and we were unable to evaluate the evolution of coronary dimensions after discharge. Cases of fatal and nonfatal myocardial infarction in otherwise healthy young adults have been attributed to undiagnosed Kawasaki's disease during childhood.[32] However, some patients had no Kawasaki's disease findings, which underscores the importance of per-

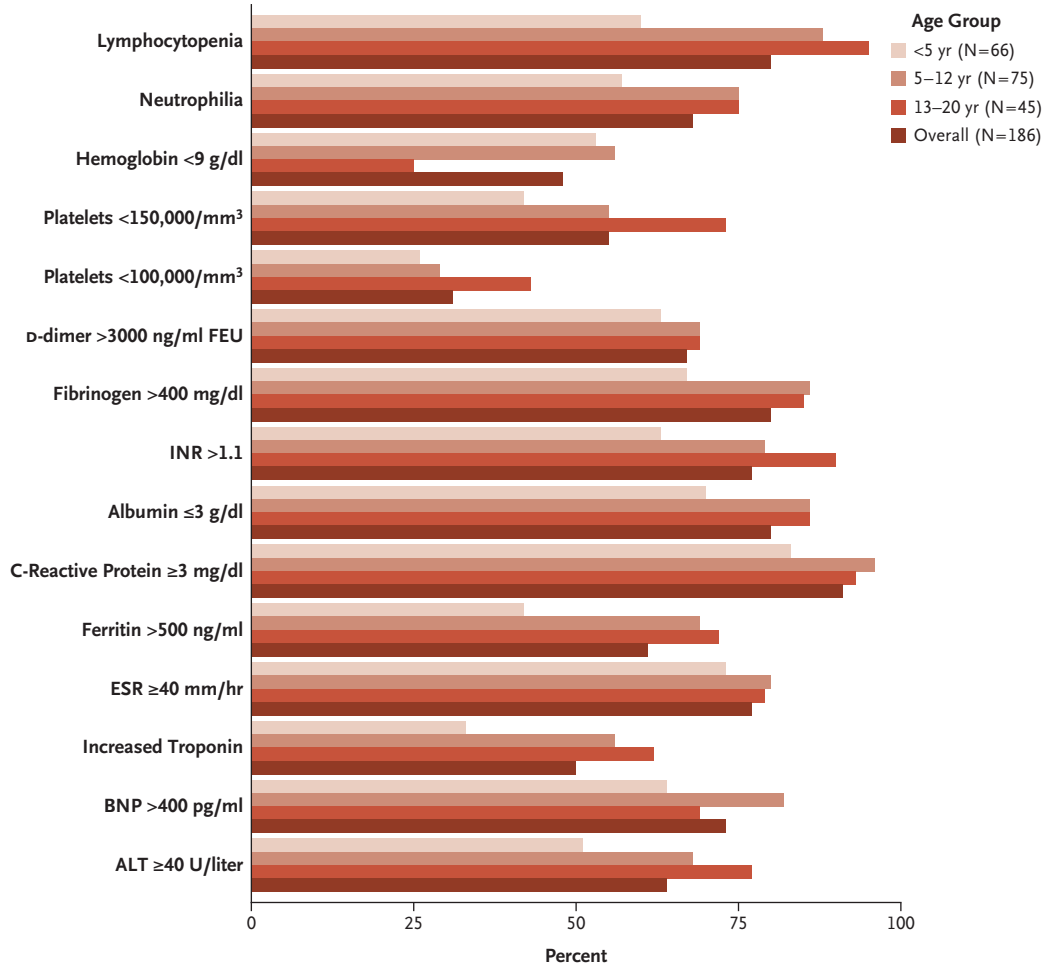


Figure 3. Laboratory Markers in Patients with MIS-C Associated with Covid-19.

Denominators varied and are provided in Table S6 in the Supplementary Appendix. Lymphocytopenia was defined as an absolute lymphocyte count of less than 1500 per microliter in patients 8 months of age or older and of less than 4500 per microliter in patients younger than 8 months of age. Neutrophilia was defined as a maximum absolute neutrophil count higher than 7700 per microliter. Increased troponin was defined on the basis of the hospital cutoff for the upper limit of the normal range. No imputations were made for missing laboratory values. ALT denotes alanine aminotransferase, ESR erythrocyte sedimentation rate, FEU fibrinogen equivalent units, and INR international normalized ratio.

forming echocardiography in all patients presenting with MIS-C. Until more is known about long-term cardiac sequelae of MIS-C, providers could consider following Kawasaki's disease guidelines for follow-up, which recommend repeat echocardiographic imaging at 1 to 2 weeks and 4 to 6 weeks after treatment for patients whose disease course is uncomplicated and more frequent echocardiography for patients with coronary-artery z scores of 2.5 or higher.[10] Long-term monitoring for other potential sequelae of MIS-C will also be critical.

Understanding the pathogenesis of MIS-C will be necessary to inform clinical management and prevention efforts. In our case series, a majority of patients were treated with immunomodulatory drugs, most commonly intravenous immune globulin (77%) and systemic glucocorticoids (49%). Our study was not designed to evaluate or compare the long-term effectiveness of any therapies;

however, most discharged patients survived. The selection of candidate treatment methods must be informed by whether organ damage is mediated by ongoing viral replication in the affected tissues, an exuberant host inflammatory response, or both.[6,33] Antiviral agents may be beneficial in the former situation, whereas immunomodulatory agents are generally preferred for immune dysregulation.[33] In adult patients, the onset of severe Covid-19 coincides with a decline in viral load in the respiratory tract and an increase in markers of hyperinflammation,[3-5] although virus replication in nonrespiratory tissues cannot be ruled out. The clinical and the laboratory features of hyperinflammation, the timing of onset in relation to SARS-CoV-2 infection, and the similarities with the disease pattern in adults with Covid-19[5] support the hypothesis that MIS-C is a consequence of immune-mediated injury triggered by SARS-CoV-2 infection.

Although available data suggest that MIS-C is an uncommon complication of SARS-CoV-2 infection in children and adolescents, an essential question is why MIS-C develops in some patients in this age group and not in others. Potential age-specific differences among patients with MIS-C could result from differences in SARS-CoV-2 infection related to the likelihood of exposure or to differences in nasal expression of angiotensin-converting enzyme 2 (ACE2), the receptor used by SARS-CoV-2 for cell entry.[34] In the sentinel MIS-C case series in London, five of the eight patients were of black or Afro-Caribbean descent.[7] The percentage of patients in our series who were black or Hispanic was also higher than in the U.S. population overall[35] and was similar to the reported percentage of children who are black or Hispanic among those who are 0 to 17 years of age and have Covid-19 in the U.S. population.[36] Susceptibility to Kawasaki's disease and its response to treatment may be influenced by the gut biome,[37] as well as by signaling pathways and genetic variants.[10,38] Exploration of potential host factors is also needed to identify potential determinants of developing MIS-C.[10]

We observed more cases of MIS-C in our sites in April than in March. The recent emergence of reported cases in several countries during the descent of the Covid-19 epidemic in those locations[7,12,22,39] suggests that the increased detection of MIS-C in the later part of our surveillance period reflects a delayed onset after infection rather than an increase in community transmission. Surprisingly, published reports of illness similar to MIS-C occurring in China are lacking, with most reports of hospitalized children with Covid-19 in China indicating that their illness is nonsevere.[1,40] Reasons for this observation are unclear and may involve differences in rates of infection in children, host factors, early treatment with immunomodulators, or incomplete reporting.

Our case series study has certain limitations. The working MIS-C case definition was intended to be sensitive, and as a result, some cases may have had a different underlying cause. Cases of MIS-C were identified only from the reporting hospitals in each state, and the results are not generalizable beyond the surveillance population. In the absence of a comparison group, caution is warranted in interpreting our case-series data to infer risk factors for MIS-C, particularly with respect to factors such as age, sex, and race or ethnic group. Although we used a standardized case report form, clinical management differs among centers, and therefore we may not have captured certain variables completely, including detailed echocardiographic data on coronary-artery outcomes and quality of imaging. Because of the limitations of a retrospective chart review and clinical testing, we were unable to accurately assess the time of onset of SARS-CoV-2 infection or the influence of false negative results on respiratory testing, nor were we able to test nonrespiratory specimens, including stool. Our pooled statewide results for SARS-CoV-2 test positivity may not accurately reflect test positivity or the incidence of Covid-19 in the catchment populations of our participating hospitals. Finally, to avoid duplicate reporting, we excluded 27 patients who had been included in the New York Department of Health report[22]; this resulted in the exclusion of 2 additional previously healthy patients who died, which may have influenced our estimates. We therefore include results based on the entire sample of 213 patients in the Supplementary Appendix. Taken as a whole, the evidence from our investigations, from early reports from New York State and Europe, and from the literature on adult patients suggests that the cases of MIS-C are part of a spectrum of Covid-19–related disease with severe immune-mediated pathology.

We report the emergence of a life-threatening hyperinflammatory syndrome across the United States that involves damage to multiple organ systems in predominantly previously healthy children and adolescents during the Covid-19 pandemic.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Leora R. Feldstein, Ph.D., Erica B. Rose, Ph.D., Steven M. Horwitz, M.D., Jennifer P. Collins, M.D., Margaret M. Newhams, M.P.H., Mary Beth F. Son, M.D., Jane W. Newburger, M.D., M.P.H., Lawrence C. Kleinman, M.D., M.P.H., Sabrina M. Heidemann, M.D., Amarilis A. Martin, M.D., Aalok R. Singh, M.D., Simon Li, M.D., M.P.H., Keiko M. Tarquinio, M.D., Preeti Jaggi, M.D., Matthew E. Oster, M.D., M.P.H., Sheemon P. Zackai, M.D., Jennifer Gillen, M.D., Adam J. Ratner, M.D., M.P.H., Rowan F. Walsh, M.D., Julie C. Fitzgerald, M.D., Ph.D., Michael A. Keenaghan, M.D., Hussam Alharash, M.D., Sule Doymaz, M.D., Katharine N. Clouser, M.D., John S. Giuliano, Jr., M.D., Anjali Gupta, M.D., Robert M. Parker, D.O., Aline B. Maddux, M.D., Vinod Havalad, M.D., Stacy Ramsingh, M.D., Hulya Bukulmez, M.D., Tamara T. Bradford, M.D., Lincoln S. Smith, M.D., Mark W. Tenforde, M.D., Ph.D., Christopher L. Carroll, M.D., Becky J. Riggs, M.D., Shira J. Gertz, M.D., Ariel Daube, M.D., Amanda Lansell, M.D., Alvaro Coronado Munoz, M.D., Charlotte V. Hobbs, M.D., Kimberly L. Marohn, M.D., Natasha B. Halasa, M.D., M.P.H., Manish M. Patel, M.D., and Adrienne G. Randolph, M.D.

The authors' affiliations are as follows: the COVID-19 Response, Centers for Disease Control and Prevention (L.R.F., E.B.R., J.P.C., M.W.T., M.M.P.), and the Division of Critical Care Medicine, Department of Pediatrics (K.M.T.), the Department of Pediatrics, Division of Infectious Diseases (P.J.), and the Department of Pediatrics, Division of Cardiology (M.E.O.), Emory University School of Medicine, Atlanta; Public Health Service Commissioned Corps, Rockville (L.R.F., E.B.R., M.M.P.), and the Department of Anesthesiology and Critical Care Medicine, Division of Pediatric Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore (B.J.R.) — both in Maryland; the Department of Pediatrics, Division of Pediatric Critical Care, Bristol-Myers Squibb Children's Hospital, Robert Wood Johnson Medical School, Rutgers University (S.M. Horwitz), the Department of Pediatrics, Division of Population Health, Quality, and Implementation Sciences (PopQuIS), Rutgers Robert Wood Johnson Medical School (L.C.K.), New Brunswick, the Department of Pediatrics, Division of Pediatric Cardiology, Children's Hospital of New Jersey, Newark Beth Israel, Newark (R.F.W.), the Division of Hospital Medicine, Department of Pediatrics, Hackensack University Medical Center, Hackensack (K.N.C.), and the Division of Pediatric Critical Care, Department of Pediatrics, Saint Barnabas Medical Center, Livingston (S.J.G.) — all in New Jersey; the Department of Anesthesiology, Critical Care and Pain Medicine (M.M.N., A.G.R.), the Division of Immunology (M.B.F.S.), and the Department of Cardiology (J.W.N.), Boston Children's Hospital, and the Departments of Pediatrics (M.B.F.S., J.W.N., A.G.R.) and Anaesthesia (A.G.R.), Harvard Medical School, Boston, and the Department of Pediatrics, Pediatric Critical Care, Baystate Medical Center, Springfield (K.L.M.) — both in Massachusetts; the Department of Pediatrics, Division of Pediatric Critical Care Medicine, Central Michigan University, Detroit (S.M. Heidemann, A.A.M.); the Pediatric Critical Care Division, Maria Fareri Children's Hospital at Westchester Medical Center and New York Medical College, Valhalla (A.R.S., S.L.), Pediatric Critical Care Medicine, Department of Pediatrics, Icahn School of Medicine at the Mount Sinai Kravis Children's Hospital (S.P.Z., J.G.), the Division of Pediatric Infectious Diseases, Departments of Pediatrics and Microbiology, New York University Grossman School of Medicine (A.J.R.), Pediatric Critical Care, New York City Health and Hospitals, Kings County Hospital (M.A.K., H.A.), the Division of Pediatric Critical Care, Department of Pediatrics, SUNY Downstate Health Sciences University (S.D.), and the Department of Pediatrics, Division of Pediatric Critical Care, Maimonides Children's Hospital (A.D.), New York — all in New York; the Division of Critical Care, Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, Philadelphia (J.C.F.); the Department of Pediatrics, Division of Critical Care, Yale University School of Medicine, New Haven (J.S.G., A.G.), and the Division of Critical Care, Connecticut Children's, Hartford (R.M.P., C.L.C.) — both in Connecticut; the Department of Pediatrics, Section of Critical Care Medicine, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora (A.B.M.); the Division of Pediatric Critical Care Medicine, Department of Pediatrics, Advocate Children's Hospital, Chicago (V.H., S.R.); the Department of Pediatrics, Division of Pediatric Rheumatology, MetroHealth Medical Center, Case Western Reserve University (H.B.), and the Division of Pediatric Hospital Medicine, Rainbow Babies and Children's Hospital (A.L.), Cleveland; the Department of Pediatrics, Division of Cardiology, Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, New Orleans (T.T.B.); the Department of Pediatrics, Division of Pediatric Critical Care Medicine, University of Washington, Seattle (L.S.S.); the Pediatric Critical Care Division, Department of Pediatrics, University of Texas Health Science Center at Houston, Houston (A.C.M.); the Department of Pediatrics, Department of Microbiology, Division of Infectious Diseases, University of Mississippi Medical Center, Jackson (C.V.H.); and the Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville (N.B.H.).

REFERENCES

1. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr 2020 April 22 (Epub ahead of print).
2. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663-5.
3. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
4. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis 2020;20:411-2.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
6. Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 2020;20:269-70.
7. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.
8. Centers for Disease Control and Prevention. Emergency preparedness and response: multisystem inflammatory syn-

drome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Health advisory (https://emergency.cdc.gov/han/2020/han00432.asp).
9. Shackelford PG, Strauss AW. Kawasaki syndrome. N Engl J Med 1991;324:1664-6.
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(17):e927-e999.
11. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020 May 17 (Epub ahead of print).
12. 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.
13. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094.
14. MacDonald KL, Osterholm MT, Hedberg CW, et al. Toxic shock syndrome: a newly recognized complication of influenza and influenzalike illness. JAMA 1987;257:1053-8.
15. Crayne C, Cron RQ. Pediatric macrophage activation syndrome, recognizing the tip of the Iceberg. Eur J Rheumatol 2019;7:Suppl 1:1-8.
16. Wang W, Gong F, Zhu W, Fu S, Zhang Q. Macrophage activation syndrome in Kawasaki disease: more common than we thought? Semin Arthritis Rheum 2015;44:405-10.
17. Baker AL, Lu M, Minich LL, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. J Pediatr 2009;154(4):592.e2-595.e2.
18. Benseler SM, McCrindle BW, Silverman ED, Tyrrell PN, Wong J, Yeung RS. Infections and Kawasaki disease: implications for coronary artery outcome. Pediatrics 2005;116(6):e760-e766.
19. Fliesler N. Boston Children's Hospital leads national study on pediatric COVID-19 and MIS-C. Boston: Boston Children's Hospital, June 13, 2020 (https://discoveries.childrenshospital.org/covid-19-in-children-nationwide-study/).
20. Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics 2011;128(6):e1450-e1458.
21. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian Pediatric intensive care units. JAMA Pediatr 2020 May 11 (Epub ahead of print).
22. 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.
23. Centers for Disease Control and Prevention. Clinical growth charts (https://www.cdc.gov/growthcharts/clinical_charts.htm).
24. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372-4.
25. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
26. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020 March 12 (Epub ahead of print).
27. Long Q-X, Liu B-Z, Deng H-J, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26:845-8.
28. Tofte RW, Williams DN. Toxic shock syndrome: evidence of a broad clinical spectrum. JAMA 1981;246:2163-7.
29. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 March 27 (Epub ahead of print).
30. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020 March 25 (Epub ahead of print).
31. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med 2007;356:663-75.
32. Burns JC, Shike H, Gordon JB, Malhotra A, Schoenwetter M, Kawasaki T. Sequelae of Kawasaki disease in adolescents and young adults. J Am Coll Cardiol 1996;28:253-7.
33. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020 April 13 (Epub ahead of print).
34. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;323:2427-9.
35. Data Resource Center for Child & Adolescent Health. Child and adolescent health measurement initiatives (https://www.childhealthdata.org/browse/survey/results?q=7259&r=1).
36. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): cases in the US (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html).
37. Esposito S, Polinori I, Rigante D. The gut microbiota-host partnership as a potential driver of Kawasaki syndrome. Front Pediatr 2019;7:124.
38. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. Nat Genet 2011;43:1241-6.
39. European Centre for Disease Prevention and Control Pediatric. Rapid risk assessment: paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. May 2020 (https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment).
40. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20:689-96.