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Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (MIS-C): A Multi-institutional Study from New York City

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Objective To assess clinical characteristics and outcomes of severe acute respiratory syndrome coronavirus 2-associated multisystem inflammatory syndrome in children (MIS-C).

Study design Children with MIS-C admitted to pediatric intensive care units in New York City between April 23 and May 23, 2020, were included. Demographic and clinical data were collected.

Results Of 33 children with MIS-C, the median age was 10 years; 61% were male; 45% were Hispanic/Latino; and 39% were black. Comorbidities were present in 45%. Fever (93%) and vomiting (69%) were the most common presenting symptoms. Depressed left ventricular ejection fraction was found in 63% of patients with median ejection fraction of 46.6% (IQR, 39.5-52.8). C-reactive protein, procalcitonin, d-dimer, and pro-B-type natriuretic peptide levels were elevated in all patients. For treatment, intravenous immunoglobulin was used in 18 (54%), corticosteroids in 17 (51%), tocilizumab in 12 (36%), remdesivir in 7 (21%), vasopressors in 17 (51%), mechanical ventilation in 5 (15%), extracorporeal membrane oxygenation in 1 (3%), and intra-aortic balloon pump in 1 (3%). The left ventricular ejection fraction normalized in 95% of those with a depressed ejection fraction. All patients were discharged home with median duration of pediatric intensive care unit stay of 4.7 days (IQR, 4-8 days) and a hospital stay of 7.8 days (IQR, 6.0-10.1 days). One patient (3%) died after withdrawal of care secondary to stroke while on extracorporeal membrane oxygenation.

Conclusions Critically ill children with coronavirus disease-2019-associated MIS-C have a spectrum of severity broader than described previously but still require careful supportive intensive care. Rapid, complete clinical and myocardial recovery was almost universal. (*J Pediatr* 2020;224:24-9).

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The initial reports from China of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children have infrequently described critically ill children.¹ However, reports from the US demonstrate a higher rate of critical illness in children with coronavirus disease-2019 (COVID-19).^{2,3} Reports have begun to emerge of multisystem involvement with circulatory shock and systemic inflammation that has presented predominantly in children with COVID-19. The first report of this syndrome was from the United Kingdom comprising a cohort of 8 children with evidence of severe inflammation and Kawasaki disease-like features.⁴ These reports continued, with subsequent reports from Italy describing 10 children and from France and Switzerland describing 35 children.^{5,6} One patient of 44 hospitalized children in 1 cohort was reported to have a Kawasaki disease-like presentation with a hyperinflammatory state, hypotension, and profound myocardial depression.³ A health alert from the New York State Department of Health described the condition and instituted mandatory reporting of cases and on May 13, 2020, created a case definition.⁷ On May 14, the US Centers for Disease Control and Prevention formally named this entity

COVID-19	Coronavirus disease-2019
ECMO	Extracorporeal membrane oxygenation
IL	Interleukin
IVIG	Intravenous immunoglobulin
LV	Left ventricular
MIS-C	Multisystem inflammatory syndrome in children
PICU	Pediatric intensive care unit
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 and introduced a case definition.⁸ The detailed clinical profile, therapies, interventions, and outcomes in children from the US with MIS-C are lacking. We report a multicenter cohort of children with COVID-19-associated MIS-C from the epicenter of COVID-19 in New York City, describing the spectrum of clinical presentation, hospital course, therapies, and outcomes.

Methods

This is a retrospective observational study of pediatric patients (aged 1 month to 21 years) with a confirmed infection with SARS-CoV-2 who meet criteria for MIS-C admitted from April 23 to May 23, 2020, to 3 New York City tertiary care children's hospitals (Children's Hospital at Montefiore, Mount Sinai Kravis Children's Hospital, and Jacobi Medical Center); the institutional review boards at the 3 institutions have approved this multicenter study. Waiver of informed consent was obtained with only deidentified data transmitted and analyzed. Four patients of the 16 reported from Mount Sinai Kravis Children's Hospital were previously described in a recently published case series.⁹ Additionally, some of the patients' data are being reported to an ongoing Society of Critical Care Medicine's national registry—the Discovery Virus Infection and Respiratory Illness Universal Study COVID-19 Registry.

Definitions

A confirmed case of COVID-19 was defined as a positive result from real-time reverse transcription polymerase chain reaction (RT-PCR) testing of a specimen using a nasopharyngeal swab for SARS-CoV-2 or positive SARS-CoV-2 antibody assay. The Centers for Disease Control and Prevention case definition for MIS-C is used to define a confirmed case of MIS-C, which is as follows: 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 neurologic); and no alternative plausible diagnoses; and positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms.⁸

There were additional suspected patients with similar symptomatology and management without confirmed SARS-CoV-2 infection/exposure who were not included in this analysis because we strictly intended to include only cases confirmed by positive SARS-CoV-2 RT-PCR or antibody assay.

Depressed left ventricular (LV) function was defined as an LV ejection fraction of <50%, and severely depressed LV function as an LV ejection fraction of <30%.

Demographic, clinical, and outcome data were recorded. Race/ethnicity was identified by documentation in the medical record or by surname for some Latino patients when not documented. Laboratory and radiologic results were recorded as well. All tests and treatments were performed at the discretion of the treating physicians.

Statistical Analyses

Statistics for the study were descriptive with data presented as numbers with percentages and continuous data as median with IQR.

Results

Thirty-three children met criteria for confirmed MIS-C among the 3 centers and were included in the final cohort and analyses; demographics and baseline clinical characteristics are presented in **Table I**. The median patient age was 10 years (IQR, 6-13 years); 61% of patients were male. Fifteen patients (45%) were Hispanic/Latino and 13 patients (39%) were black. The median weight was 33.4 kg (IQR, 20.7-60.0 kg) with median body mass index of 18.6 (IQR, 15.9-22.9). Four patients (12%) were overweight, and 2 patients (6%) were obese. Comorbid conditions were present in 16 patients (48%). Common presenting symptoms include fever (93%), abdominal pain (63%), nausea/emesis (69%), and hypotension (63%) with a median duration of symptoms before presentation of 4.5 days (IQR, 3-6 days).

Laboratory test results on admission are presented in **Table II**. The majority of patients (27 [81%]) tested positive only for SARS-CoV-2 antibody; 11 (33%) tested positive on SARS-CoV-2 RT-PCR, and 6 patients (18%)

Table I. Demographic and clinical characteristics of patients (n = 33) with MIS-C

Characteristics	Values
Age, y	10 (6-13)
Male sex	20 (61)
Weight, kg	33.4 (20.7-60.0)
BMI, kg/m ²	18.6 (15.9-22.9)
Race	
Hispanic or Latino	15 (45)
Black	13 (39)
White	3 (9)
Asian	1 (3)
Other	1 (3)
Comorbid conditions	16 (48)
Asthma	5 (15)
Allergic rhinitis/eczema	3 (9)
Obesity (BMI >30 kg/m ²)	2 (6)
Cardiac	2 (6)
Hematologic	2 (6)
Others	3 (9)
Symptoms	
Duration of symptoms before admission, d (n = 35)	4.5 (3-6)
Maximum temperature (n = 31)	39.4 (38.8-40.0)
Fever	31 (93)
Mucocutaneous involvement	7 (21)
Conjunctivitis	12 (36)
Rash	14 (42)
Abdominal pain	21 (63)
Nausea/vomiting	23 (69)
Diarrhea	16 (48)
Shortness of breath	11 (33)
Dizziness	3 (9)
Hypotension	21 (63)
Neurologic involvement	4 (12)
Ill contact	8 (24)
Known COVID+ contact	5 (15)

BMI, body mass index.
Values are median (IQR) or number (%).

tested positive for both RT-PCR and antibodies. The median white blood cell count was 11 000 k/ μ L (IQR, 8450-14 400 k/ μ L). Markers of inflammation were elevated with median C-reactive protein 250 mg/L (IQR, 156-302 mg/L), erythrocyte sedimentation rate of 53 mm/h (IQR, 28.2-77.2 mm/h), procalcitonin of 5.4 ng/mL (IQR, 1.8-16.7 ng/mL), and ferritin 568 ng/mL (IQR, 340-954 ng/mL). The median fibrinogen was 627 mg/dL (IQR, 455-782 mg/dL), and median d-dimer was 3.7 μ g/mL FEU (IQR, 2.4-5.1 μ g/mL FEU). Markers of abnormal cardiac status were elevated with median B-type natriuretic peptide (BNP) levels of 388 pg/mL (IQR, 75-1086 pg/mL) (Mount Sinai Kravis Children's Hospital), median N-terminal pro-BNP levels of 4328 pg/mL (IQR, 2117-13 370 pg/mL) (Children's Hospital at Montefiore and Jacobi Medical Center), and troponin 0.08 ng/mL (IQR, 0.02-0.17 ng/mL). Mixed venous saturation was low, with a median value of 56.5% (IQR, 39.5%-76.7%). IL-6 and IL-8 levels were elevated

with medians of 200 pg/mL (IQR, 56.4-330 pg/mL) and 41.7 pg/mL (IQR, 25.1-54.4 pg/mL), respectively.

Imaging and echocardiogram findings are presented in **Table III**. Cardiomegaly was present in 10 patients (30%). Focal or bilateral pulmonary opacities were noted in 11 patients (33%). To the best of our knowledge, none of the patients had typical lung disease as described in adults with COVID-19 pneumonia, although none of these patients had a computed tomography scan of the chest performed, limiting this evaluation. Echocardiograms were performed in 32 (97%) patients, of whom 21 (65.6%) had a depressed LV ejection fraction (<50%). Of the patients with depressed LV ejection fraction, 4 (12%) had an ejection fraction of <30%, and 17 (53%) had an ejection fraction between 30% and 50%. Twenty-four patients (72%) had a second echocardiogram performed; 20 of 21 with depressed function (95%) had recovery of ventricular function with normal ejection fraction. Details of patients with depressed systolic function are described in **Table IV**.

Medical therapies used are presented in **Table V**. Eighteen patients (54%) received intravenous immunoglobulin (IVIG), 17 (51%) received corticosteroids, 12 (36%) received tocilizumab, 7 (21%) received remdesivir under a compassionate use, 4 (12%) received Anakinra, and 1 (3%) received convalescent plasma therapy. Vasoactive medications were used in 17 patients (51%), with norepinephrine being the most commonly used agent in 10 (30%), followed by dopamine in 9 (27%). The median duration of vasopressor use was 72 hours (IQR-48, 110 hours). Anticoagulation was used in all patients, with prophylactic dosing with enoxaparin in 5 (15%), therapeutic dose enoxaparin in 27 (82%), and therapeutic dose unfractionated heparin in 1 (3%). Empiric antibiotic coverage for <48 hours was given in 14 patients (42%), and antibiotics for >48 hours was used in 15 (45%).

Five patients (15%) required invasive mechanical ventilation. Two patients (6%) required mechanical circulatory support, 1 each by extracorporeal membrane oxygenation (ECMO) and an intra-aortic balloon pump. A 5-year-old with severely depressed LV function and cardiogenic shock was cannulated for venoarterial ECMO within 24 hours of presentation, but developed an ischemic brain infarction

Table II. Admission laboratory test results of all patients with MIS-C

Tests	Value	Reference normal range
SARS-CoV-2 PCR positive	11 (33)	–
SARS-CoV-2 antibody positive	27 (81)	–
SARs CoV-2 PCR and antibody positive	6 (18)	–
WBC, cells/ μ L	11 000 (8450-14 400)	4000-11 000/ μ L
Hemoglobin, g/dL	11.3 (9.55-12.5)	10.5-14 g/dL
Platelets, thousands/ μ L	176 (130.5-282)	150-300 K/ μ L
Absolute lymphocyte count, thousands/ μ L	1.1 (0.6-1.3)	1.0-4.0 K/ μ L
ESR, mm/h	53 (28.2-77.2)	0-10 mm/h
Serum sodium, mEq/L	136 (135-139)	135-145 mEq/L
Albumin, g/dL	3.5 (2.6-3.9)	3.5-4.9 g/dL
BUN, mg/dL	12 (9-16)	6-23 mg/dL
Serum creatinine, mg/dL	0.6 (0.4-1.1)	0.7-1.3 mg/dL
AST, U/L	48 (27-69)	1-35 U/L
ALT, U/L	36 (28-53)	1-45 U/L
Total bilirubin, mg/dL	0.7 (0.4-1.3)	0.1-1.2 mg/dL
C-reactive protein, mg/L	250 (156-302)	0.0-5.0 mg/L
C-reactive protein at peak, mg/L	255 (181-310)	0.0-5.0 mg/L
Procalcitonin, ng/mL	5.4 (1.8-16.7)	<0.1 ng/mL
Procalcitonin peak, ng/mL	6 (2.7-16.5)	<0.1 ng/mL
Fibrinogen, mg/dL	627 (455-782)	162-378 mg/dL
Ferritin, ng/mL	568 (340-954)	80-500 ng/mL
BNP at admission, pg/mL (n = 16)	388 (75-1086)	0-100 pg/mL
Peak BNP at admission, pg/mL (n = 16)	760 (388-1434)	0-100 pg/mL
Pro-BNP at admission, pg/mL (n = 16)	4328 (2117-13 370)	0-450 pg/mL
Peak Pro-BNP, pg/mL (n = 16)	15 000 (9329-15 000)	0-450 pg/mL
Troponin T, ng/mL	0.08 (0.02-0.17)	<0.1 ng/mL
D-Dimer, μ g/mL FEU	3.7 (2.4-5.1)	<0.5 μ g/mL FEU
Lactate, mmol/L	1.9 (1.4-3.0)	0.5-1.99 mmol/L
Mixed venous saturation, % (n = 24)	56.5 (39.5-76.7)	
IL-6, pg/mL	200 (56.4-330)	0-5.0 pg/mL
IL-1, pg/mL	0.8 (0.4-1.2)	0-22 pg/mL
IL-8, pg/mL	41.7 (25.1-54.4)	0-5 pg/mL
Triglycerides, mg/dL	129 (108-191)	<150 mg/dL

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B type natriuretic peptide; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; FEU, Fibrinogen equivalent unit; WBC, white blood cell count. Values are number (%) or median (IQR).

Table III. Imaging and echocardiogram results

Variables	Value
Chest radiograph	
Cardiomegaly	10 (30)
Focal opacity	5 (15)
Bilateral opacities	6 (18)
Echocardiogram	32 (97)
Pericardial effusion	15 (46)
LV ejection fraction on admission	46.6 (39.5-52.8)
LV ejection fraction <30%	4 (12)
LV ejection fraction 30%-50%	17 (53)
LV ejection fraction >50%	11 (34)
Recovered LV function before discharge	20 (95)
Predischarge LV ejection fraction	58 (55-62)

Values are number (%) or median (IQR).

Table IV. Profile of all patients with depressed systolic ventricular function (LV ejection fraction of <50%)

Patients	Age, years/sex	Race	Admission LV ejection fraction	Repeat LV ejection fraction	Peak BNP/Pro-BNP (pg/mL)	Subsequent BNP/Pro-BNP (pg/mL)	Admission troponin (ng/mL)	Peak troponin (ng/mL)	Coronary arteries by ECHO	Treatment
1	11 F	Hispanic	40	57	993	343	0.07	0.07	Prominent RCA	IVIg, Toci
2	13 F	White	46	55	607	306	0.18	5.8	Prominent LMCA	IVIg, Toci
3	17 M	Hispanic	44	58	64.3	NA	27.32	32.51	–	IVIg, Toci
4	3 F	Hispanic	47	58	1364	8.4	0.1	–	Prominent LAD	IVIg, Toci
5	13 M	Hispanic	48	58	3584	230.4	0.75	0.9	–	IVIg, Toci
6	20 M	Hispanic	29	50	431	248	2.7	3.67	–	Conv Plas, MP, IABP
7	5 M	Black	34	50	6758	484	0.06	0.36	–	Toci, ECMO
8	13 M	Black	42	67	1643	4.5	0.02	3.4	–	IVIg, Toci ANK, REM
9	14 F	Black	48	52	1300	10.3	0.47	1.2	–	Toci, REM, ANK
10	0.16 M	Hispanic	25	56	15 000*	138*	0.16	0.19	Prominent LMCA	MP, REM
11	7 F	Asian	47	55	15 000*	60*	0.01	0.03	–	MP, REM
12	8 F	Black	42	59	15 000*	60*	0.03	0.23	Prominent LAD	IVIg, REM, MP, ANK
13	13 F	Black	38	67	15 000*	164*	0.15	0.2	Prominent LMCA	IVIg, MP
14	20 M	Black	44	56	2985*	204*	0.66	0.66	–	MP
15	8 M	Hispanic	36	63	15 000*	793*	0.13	0.13	–	MP
16	6 M	Black	50	58	15 000*	444*	0.01	0.01	–	MP
17	12 F	Black	46	59	2190*	660*	0.1	0.1	–	None
18	14 M	Black	41	68	15 000*	1654*	0.01	2.05	LMCA ectasia	IVIg
19	16 M	Black	18	61	15 000*	428*	0.05	0.09	–	MP
20	7 M	Black	38	55	15 000*	608*	0.08	0.1	LMCA ectasia	None
21	1.3 M	Hispanic	25	27	15 000*	7232*	0.1	0.1	–	MP

Adm, admission; ANK, anakinra; Conv plas, convalescent plasma therapy; IABP, intra-aortic balloon pump; LAD, left anterior descending; LMCA, left main coronary artery; MP, methylprednisolone; RCA, Right coronary artery; REM, remdesivir; Toci, tocilizumab.

Reference ranges: BNP, 0–100 pg/mL; *Pro-BNP 0–450 pg/mL (highest reported value, >15 000); troponin <0.01 ng/mL.

with subarachnoid hemorrhage on day 6 of ECMO. Life-sustaining therapies were withdrawn after neurologic examination consistent with brain death. Support using an intra-aortic balloon pump was used for a 20-year-old male who presented with 3 days of fever, nausea, vomiting, diarrhea, and abdominal pain and was found to have severely depressed LV function. He required inotropic support with epinephrine and dobutamine infusions as well as intubation and mechanical ventilation. Owing to rising serum lactate and troponin levels, he underwent diagnostic cardiac catheterization, which excluded coronary artery stenosis or anatomic abnormality. An intra-aortic balloon pump was inserted with which he was supported for 24 hours. He was treated with methylprednisolone and convalescent plasma. He was weaned off invasive mechanical ventilation by day 3 of hospitalization and was discharged home on day 12.

Thirty-two patients were discharged home with a median duration of pediatric intensive care unit (PICU) stay of 4.7 days (IQR, 4–8 days) and hospital stay of 7.8 days (IQR, 6.0–10.1 days). One patient (3%) died after withdrawal of care secondary to hemorrhagic stroke while on ECMO support, as discussed.

Discussion

The clinical profile of COVID-19 MIS-C in our cohort of 33 children was heterogeneous in severity of illness, ranging from clinically stable patients with normal or mildly depressed myocardial function to decompensated circulatory

shock requiring invasive mechanical ventilation and mechanical circulatory support.

Possible mechanisms of myocardial involvement are speculative and include direct viral invasion of myocytes and systemic inflammatory response triggering myocyte injury, which can be compounded by myocardial ischemia secondary to hypotension.¹⁰ In the absence of myocardial biopsy, it is difficult to discern the exact mechanism of myocardial involvement, but given elevation of inflammatory markers, absence of strong data on coronaviruses being cardiotropic, occurrence after appearance of CoV antibodies in most patients, and the fact that not all critically ill children with shock developed myocardial dysfunction, it is plausible that the myocardial injury and circulatory shock in COVID-19 is secondary to inflammatory mediators.¹¹ Based on the positive antibody status and the elevated cytokines, especially IL-6, seen in our cohort, we hypothesize that this novel COVID-19 MIS-C is predominantly an antibody-mediated of other immune cell-mediated cytokine storm, with some contribution from direct myocardial injury. These findings suggest a potential role for both antiviral and immunomodulatory therapies in the treatment of MIS-C. In our cohort, remdesivir, a nucleoside analog that blocks virus replication, was used for patients with active SARS-CoV-2 infection, as evidenced by positive RT-PCR results.¹² However, for the vast majority of patients who have positive antibodies and cytokine storm, as evidenced by elevated inflammatory markers and IL-6 levels, immunomodulatory therapy has been the mainstay of treatment. IVIG or corticosteroids or both were given to most patients for anti-inflammatory and

Table V. Medical therapies and outcomes of patients with MIS-C

Parameters	(n = 33)
IVIG	18 (54)
Corticosteroids	17 (51)
Tocilizumab	12 (36)
Remdesivir	7 (21)
Anakinra	4 (12)
Hydroxychloroquine	0 (0)
Convalescent plasma therapy	1 (3)
Hydroxychloroquine	0 (0)
Vasopressor/Inotropes	17 (51)
Duration of vasopressor use, h	72 (48-110)
Norepinephrine	10 (30)
Dopamine	9 (27)
Epinephrine	5 (15)
Dobutamine	4 (12)
Vasopressin	4 (12)
Milrinone	3 (9)
Aspirin	8 (24)
Diuretics	21 (63)
Anticoagulation prophylaxis	5 (15)
Anticoagulation therapeutic	27 (81)
Antibiotics <48 h	14 (42)
Antibiotics >48 h	15 (45)
Noninvasive mechanical ventilation	12 (36)
Invasive MV	5 (15)
ECMO	1 (3)
Intra-aortic balloon pump support	1 (3)
Cardiac arrest	1 (3)
PICU LOS, d	4.7 (4-8)
Hospital LOS, d	7.8 (6.0-10.1)
Discharged from PICU	32 (97)
Discharged from hospital	31 (94)
Mortality	1 (3)

LOS, length of stay; MV, mechanical ventilation.
Values are number (%) or median (IQR).

antibody-mediating effects, and tocilizumab, an IL-6 receptor inhibitor, which seems to mediate a significant portion of this cytokine storm and resulting myocardial injury, was used for children with high IL-6 levels.^{13,14}

The reasons for an exaggerated inflammatory response leading to MIS-C after SARS-CoV-2 infection are unclear, although cytokine-mediated storm has been described with other viral infections, though to a lesser degree. Although initially thought to be SARS-CoV-2-associated Kawasaki disease, emerging data have shown MIS-C to be a separate entity with age as a distinguishing feature.⁵ In contrast with the infantile age distribution of Kawasaki disease, MIS-C is predominantly a disease of older children and adolescents, supported by the median age in our cohort of 10 years, which is consistent with other reports of MIS-C.^{4,6} Critical illness with COVID-19 in children is infrequent but reported with younger age and comorbidities being risk factors for severe disease.^{1,2}

In contrast with the European studies, our cohort had lower morbidity with 51% requiring vasopressor support, 15% requiring invasive mechanical ventilation, and only 6% requiring mechanical circulatory support.^{4,6} The median LV ejection fraction in our cohort was 44%, which is higher than that reported by Belhadjer et al in a cohort of 35 children in which almost one-third had severely depressed LV systolic function (LV ejection fraction of <30%).⁶ The use of inotropic support (80%), mechanical ventilatory (62%), cir-

culatory support (28%), therapy with IVIG (71%), and corticosteroids (34%) were all higher in their cohort compared with ours. Expectedly, recovery of LV function was higher in our cohort with 20 of 21 patients (95%) with depressed LV function having recovered LV function at hospital discharge compared with 71% in the report of Belhadjer et al.⁶ Recovery of ventricular function on echocardiogram demonstrated a good correlation to normalization of BNP or pro-BNP level in all patients before discharge. It is unclear why children in other reports were of higher acuity, but 1 hypothesis may be related to a better, evolving understanding of this syndrome and its underpinnings.

Although isolated reports have described COVID-19 associated myocarditis in adults, MIS-C seems to be a separate entity; shock and hemodynamic compromise in MIS-C can occur in the absence of laboratory evidence of myocardial inflammation, and with preserved cardiac function and rapid reversibility.¹⁵ The most common agent used for inotropic support was norepinephrine, consistent with management of inflammatory mediator-induced vasoplegic shock. A median vasopressor duration of 72 hours and median PICU stay of 4.6 days provide insight into the clinical courses of these patients, with improvement in the majority of patients by day 4-5 and discharge from the hospital by day 7. The duration of vasopressor support and PICU stay were similar between patients, suggesting that a majority of patients required close hemodynamic monitoring in PICU and that therapies such as respiratory support are required secondary to hemodynamic derangement. Based on PICU and hospital lengths of stay, it appears that inflammatory markers and myocardial function improved by days hospital 4-7.

Further larger multicenter studies are needed to further elucidate the spectrum of disease, risk factors for more severe illness, and response to supportive and medical therapies including IVIG, corticosteroids, biologic modifying agents, and anticoagulation strategies. Long-term follow-up will be required to determine any sequelae of MIS-C on myocardial function. ■

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References

- Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020;145:e20200702.
- Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. *J Pediatr* 2020;223:14-9.e2.
- DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region. *J Pediatr* 2020;223:199-203.e1.
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;395:1607-8.

5. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, 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;6736:1-8.
6. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation* 2020 [Epub ahead of print].
7. New York State Department of Health. Health advisory: pediatric multi-system inflammatory syndrome temporally associated with COVID-19 interim case definition in New York State. https://health.ny.gov/press/releases/2020/docs/2020-05-13_health_advisory.pdf. Accessed June 14, 2020.
8. Centers for Disease Control and Prevention. Emergency preparedness and response. <https://emergency.cdc.gov/han/2020/han00432.asp>. Accessed May 22, 2020.
9. Waltuch T, Gill P, Zinns LE, Whitney R, Tokarski J, Tsung JW, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. *Am J Emerg Med* 2020 [Epub ahead of print].
10. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. *Int J Cardiol* 2020;309:70-7.
11. Tunuguntla H, Jeewa A, Denfield SW. Acute myocarditis and pericarditis in children. *Pediatr Rev* 2019;40:14-25.
12. Agostino ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio* 2018;9:e00221-18.
13. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020;55:105954.
14. Lünemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology—mode of action and clinical efficacy. *Nat Rev Neurol* 2015;11:80-9.
15. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1-6.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Plus ça Change: Halfway Technologies in Pediatrics

Reinhart JB. The doctor's dilemma: whether or not to recommend continuous renal dialysis or renal homotransplantation for the child with end-stage renal disease. *J Pediatr* 1970;77:505-6.

This commentary by Reinhart was in response to an article previously published in *The Journal* by Fine et al describing transplant outcomes for children in end-stage renal disease (ESRD).¹ They described the psychological and emotional complexity of treating ESRD in children and asked whether children should receive what Lewis Thomas would refer to as a “halfway technology.”² Their solution was to embed psychological support into their program.¹ In contrast, Reinhart “seriously question[ed] the value of chronic dialysis or renal transplant for these patients.”

More striking than the debate of how aggressive physicians should be is Reinhart's comment about the state of pediatrics more generally: “Those of us who live and work in hospitals tend to focus all our efforts on diagnosis and ‘cure.’ We try to avoid dealing with chronic or incurable conditions which thwart our efforts.” Contrast this with current pediatric practice in which many children have chronic conditions and almost two-thirds of all pediatric acute-care hospitalizations involve children with 1 or more chronic conditions.³

Interestingly, the editors published a short retort to Reinhart's commentary by Korsch and Fine in which they reaffirmed their commitment “to the goal of maintaining life and function whenever possible.”⁴ Their persistence has paid off in terms of survival, although “the care of children with end-stage renal disease and earlier stages of CKD [chronic kidney disease] continues to saddle families with significant psychosocial, emotional, and economic stress.”⁵ Organ replacement therapies are still only halfway technologies. ■

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References

1. Fine RN, Korsh BM, Stiles Q, Riddell H, Edelbrock HH, Brennan LP, et al. Renal homotransplantations in children. *J Pediatr* 1970;76:347-57.
2. Thomas L. On the science and technology of medicine. *Daedalus* 1988;117:299-316.
3. Berry JG, Ash AS, Cohen E, Hasan F, Feudtner C, Hall M. Contributions of children with multiple chronic conditions to pediatric hospitalizations in the United States: A retrospective cohort analysis. *Hosp Pediatr* 2017;7:365-72.
4. Korsch BM, Fine RN. Additional comment. *J Pediatr* 1970;77:506-7.
5. Bignall ON 2nd, Goldstein SL. Childhood CKD affects the entire family. *Am J Kidney Dis* 2015;65:367-8.