ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children — Initial Therapy and Outcomes

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ABSTRACT

BACKGROUND

The assessment of real-world effectiveness of immunomodulatory medications for multisystem inflammatory syndrome in children (MIS-C) may guide therapy.

METHODS

We analyzed surveillance data on inpatients younger than 21 years of age who had MIS-C and were admitted to 1 of 58 U.S. hospitals between March 15 and October 31, 2020. The effectiveness of initial immunomodulatory therapy (day 0, indicating the first day any such therapy for MIS-C was given) with intravenous immune globulin (IVIG) plus glucocorticoids, as compared with IVIG alone, was evaluated with propensity-score matching and inverse probability weighting, with adjustment for baseline MIS-C severity and demographic characteristics. The primary outcome was cardiovascular dysfunction (a composite of left ventricular dysfunction or shock resulting in the use of vasopressors) on or after day 2. Secondary outcomes included the components of the primary outcome, the receipt of adjunctive treatment (glucocorticoids in patients not already receiving glucocorticoids on day 0, a biologic, or a second dose of IVIG) on or after day 1, and persistent or recurrent fever on or after day 2.

RESULTS

A total of 518 patients with MIS-C (median age, 8.7 years) received at least one immunomodulatory therapy; 75% had been previously healthy, and 9 died. In the propensity-score–matched analysis, initial treatment with IVIG plus glucocorticoids (103 patients) was associated with a lower risk of cardiovascular dysfunction on or after day 2 than IVIG alone (103 patients) (17% vs. 31%; risk ratio, 0.56; 95% confidence interval [CI], 0.34 to 0.94). The risks of the components of the composite outcome were also lower among those who received IVIG plus glucocorticoids: left ventricular dysfunction occurred in 8% and 17% of the patients, respectively (risk ratio, 0.46; 95% CI, 0.19 to 1.15), and shock resulting in vasopressor use in 13% and 24% (risk ratio, 0.54; 95% CI, 0.29 to 1.00). The use of adjunctive therapy was lower among patients who received IVIG plus glucocorticoids than among those who received IVIG alone (34% vs. 70%; risk ratio, 0.49; 95% CI, 0.36 to 0.65), but the risk of fever was unaffected (31% and 40%, respectively; risk ratio, 0.78; 95% CI, 0.53 to 1.13). The inverse-probability-weighted analysis confirmed the results of the propensity-score–matched analysis.

CONCLUSIONS

Among children and adolescents with MIS-C, initial treatment with IVIG plus glucocorticoids was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIG alone. (Funded by the Centers for Disease Control and Prevention.)

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*A complete list of the Overcoming COVID-19 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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In the spring of 2020, the rapid emergence of multisystem inflammatory syndrome in children (MIS-C)[1-3] — a presumed postinfectious complication of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — necessitated decisions regarding immunomodulatory treatment without an evidence base or an understanding of its pathophysiological characteristics. Patients with MIS-C had prominent cardiovascular involvement, including shock, echocardiographic findings of decreased function, and coronary-artery aneurysms, for which they received urgent intervention.[4] Given the similarities between MIS-C and Kawasaki's disease, a vasculitis of childhood that can cause coronary-artery aneurysms and sometimes a shock-like presentation,[5] most patients with MIS-C were treated with intravenous immune globulin (IVIG),[6] the standard treatment for Kawasaki's disease.[7] Although contemporaneous studies showed clinical and immunophenotypic differences between Kawasaki's disease and MIS-C,[8-10] findings of myocarditis in many patients with MIS-C also supported treatment with IVIG, given its use in clinical practice for viral myocarditis.[11,12] Features of cytokine storm led to the use of dexamethasone in patients with acute Covid-19,[13] and the frequent concurrent finding of a severe shock-like presentation in patients with MIS-C[14] probably encouraged the use of glucocorticoids, in varying doses.[15]

Because MIS-C appeared to be a rare syndrome,[16] with cases following sporadic waves of Covid-19, randomized trials of treatment strategies have been impeded.[17] However, the evaluation of clinical outcomes in patients with MIS-C who were treated with various immunomodulatory therapies could provide insight into their effectiveness. Here, we describe patterns of immunomodulatory medication use in patients with MIS-C in the United States and an assessment of the relative effectiveness of IVIG plus glucocorticoids, as compared with IVIG alone, in the initial treatment of MIS-C.

Methods

Disease Surveillance

The Overcoming COVID-19 surveillance registry was funded by the Centers for Disease Control and Prevention (CDC) to conduct surveillance of Covid-19–related severe complications, including MIS-C as defined according to CDC criteria,[18] in children and adolescents hospitalized in the United States and to collect detailed data. Patients with MIS-C were identified at each site by intensive care unit (ICU) and subspecialty clinicians and through mandated public health reporting. Trained staff at participating facilities abstracted medical records onto a standard form and entered data into a Web-based secure electronic database (Research Electronic Data Capture [REDCap], Vanderbilt University). Data collected included the demographic characteristics of the patients, underlying medical conditions, signs and symptoms at presentation, clinical course, laboratory test results, diagnostic studies, treatments, complications, and outcomes. The surveillance protocol, which is available with the full text of this article at NEJM.org, was approved by the central institutional review board at Boston Children's Hospital, with a waiver of informed consent. It was also reviewed by the CDC, and all activities were conducted in accordance with applicable federal law and CDC policy. The last two authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Case Definition

Cases were adjudicated by the principal investigators at each site and at the central coordinating center. The case definition of MIS-C included six criteria[18]: 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 organ 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 suspected or confirmed Covid-19 within 4 weeks before the onset of MIS-C symptoms. Owing to a lack of SARS-CoV-2 testing in the spring of 2020, cases reported between March 15 and May 31 as suspected or confirmed MIS-C cases that were epidemiologically linked to a Covid-19 exposure were included without the requirement of a positive SARS-CoV-2 test; positive testing was required after May 31.

IMMUNOMODULATORY TREATMENTS

Two approaches were used to categorize patients with MIS-C. First, we categorized patients according to the immunomodulatory treatments they received at any time during their hospital course: IVIG only; IVIG and glucocorticoids; IVIG, glucocorticoids, and a biologic agent; or other treatments (glucocorticoids only, a biologic only, glucocorticoids and a biologic, or IVIG and a biologic). Glucocorticoids included methylprednisolone, prednisolone, and dexamethasone. Biologics included an interleukin-1–receptor antagonist (anakinra), tumor necrosis factor α inhibitors (infliximab and etanercept), and an interleukin-6–receptor antagonist (tocilizumab).

Second, we classified patients according to which of two commonly used[19] treatments they received on day 0, which was termed their "initial treatment": IVIG plus glucocorticoids or IVIG alone. Day 0 was defined as the first day a patient received any immunomodulatory treatment (which was not necessarily the first day of hospitalization). Days 1 and 2 were the first and second calendar days after day 0. Available data included the calendar day for all the treatments but not the calendar time. Glucocorticoids (in patients not already receiving glucocorticoids on day 0), biologics, and second doses of IVIG administered on or after day 1 were considered "adjunctive" treatment. Patients who received a biologic on day 0 were excluded because of small sample size and the use of multiple types of biologics with varying cytokine targets.

OUTCOMES

We report the following outcomes for patients who received any immunomodulatory treatment during hospitalization: admission to the ICU, receipt of supplemental oxygen, receipt of mechanical ventilatory support, use of vasopressor agents, receipt of extracorporeal membrane oxygenation, hospital length of stay, coronary-artery aneurysms, and death. Coronary-artery aneurysms were defined as a z score of at least 2.5 for the left anterior descending coronary artery or the right coronary artery (or both) on echocardiography.[7]

To assess the potential effectiveness of initial treatment with IVIG plus glucocorticoids, as compared with IVIG alone, we prespecified a primary outcome of cardiovascular dysfunction on or after day 2 through the time of discharge, which was based on a composite of left ventricular dysfunction (as defined by a left ventricular ejection fraction [LVEF] of <55% on echocardiography) or shock that resulted in the use of vasopressors. This composite cardiovascular outcome was chosen because, in this MIS-C cohort,[6] low LVEF did not always result in the use of vasopressors and distributive shock was not always associated with low LVEF; however, either finding would influence therapy decisions. Outcomes were measured on or after day 2 to allow for a clinical response after initial treatments.[6] Secondary outcomes were the individual components of the primary outcome, the receipt of adjunctive immunomodulatory treatment on or after day 1, persistent or recurrent fever (body temperature, >38.0°C) on or after day 2, and length of stay in the ICU (counted starting from the day of initial treatment [day 0]). Data on treatment-related adverse events were not collected as part of the registry.

STATISTICAL ANALYSIS

Continuous variables were expressed as medians and interquartile ranges or ranges, and categorical variables were expressed as counts and percentages. To assess the associations between initial treatment with IVIG plus glucocorticoids, or with IVIG alone, and the primary and secondary outcomes, we used propensity-score matching and an inverse-probability-weighted analysis, with adjustment for confounding factors that might have influenced treatment choices.[20]

We modeled the probability of treatment using logistic regression and used the estimated probability as a propensity score. We included relevant baseline variables that might have affected treatment decisions. These included demographic characteristics (age, race or ethnic group, and sex), preexisting conditions, commonly measured laboratory markers of inflammation on the day of admission (neutrophil-to-lymphocyte ratio, C-reactive protein level, and platelet count), and clinical observations at admission (Kawasaki's disease–like features [as defined by American Heart Association guidelines[7]], severe cardiovascular or respiratory involvement, vasopressor use, receipt of mechanical ventilation, pulmonary infiltrates on radiographic imaging, and admission to the ICU). Variables were selected on the basis of clinical experience,[1,21,22] review of paired correlations, and the success of

balancing distributions of treatment groups. We excluded patients who had missing laboratory test results, and we performed a complete-case analysis after covariates were selected.

In the propensity-score–matched analysis, we used "greedy nearest-neighbor" matching without replacement. Here, the matching algorithm first selected a patient who had received IVIG plus glucocorticoids and then selected a patient who had received IVIG alone who had a linear propensity score that was closest to that of the first selected patient. We used a 1:1 ratio within a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Risk ratios and 95% confidence intervals were calculated to quantify the association between the treatment and outcome with the use of log-binomial regression models. We adjusted for treatment site in the propensity-score–matched analysis using generalized estimating equations clustered according to treatment site with an exchangeable correlation structure. We then evaluated the potential effectiveness of treatment on the primary and secondary outcomes using an inverse-probability-weighted analysis to maintain all members of the treatment-comparison cohort by assigning each patient a weight that was based on the propensity score. We used the matching package from R software, version 4.0.2, for the propensity-score–matched analysis and SAS software, version 9.4, for the inverse-probability-weighted analysis.

RESULTS

PATIENT CHARACTERISTICS OF THE COHORT

Of 596 patients with MIS-C who were admitted to 58 participating hospitals between March 15 and October 31, 2020, a total of 518 (87%) received at least one immunomodulatory treatment during hospitalization (Fig. 1 and Table 1). The median age of the patients was 8.7 years (interquartile range, 4.9 to 12.8; range, 0 to 20.9), 217 patients (42%) were female, 183 (35%) were Black non-Hispanic, 174 (34%) were Hispanic or Latino, and 390 (75%) had been previously healthy (i.e., they had no preexisting conditions and had not been receiving any prescription medications). More than half the patients (286 [55%]) had involvement of five or more organ systems, 196 (38%) met complete or incomplete criteria for Kawasaki's disease, 385 (74%) received care in the ICU, and 9 (2%) ultimately died (Table S1 in the Supplementary Appendix, available at NEJM.org). The patients who received IVIG alone were somewhat younger than those in other treatment categories, and half these patients had Kawasaki's disease–like features.

Among the 518 patients who were treated with immunomodulatory therapies during hospitalization between day 0 and discharge, 89 (17%) received IVIG only; 241 (47%) received IVIG and glucocorticoids; 107 (21%) received IVIG, glucocorticoids, and a biologic; and 81 (16%) received other treatments, including glucocorticoids only, a biologic only, glucocorticoids and a biologic, or IVIG and a biologic (Table 1). Methylprednisolone was the most common glucocorticoid prescribed (in 353 patients [68%]); it was administered at a dose of 2 mg per kilogram of body weight per day in 284 of these patients (80%) and in pulse doses of 10 to 30 mg per kilogram per day in 69 of these patients (20%) (Table S2). The most common initial treatments given on day 0 were IVIG alone (in 192 of 518 patients [37%]) and IVIG plus glucocorticoids (in 157 of 518 patients [30%]). Only 34 patients received a biologic on day 0.

CLINICAL OUTCOMES ASSOCIATED WITH TREATMENTS GIVEN DURING HOSPITALIZATION

Overall, in patients who received immunomodulatory treatments at any time during hospitalization, the severity of illness was high with marked treatment heterogeneity; patient characteristics and clinical outcomes differed according to the immunomodulatory treatment combinations received (Table 1). Treatment patterns changed over time (Fig. 2A). Immunomodulatory medications were administered early after hospitalization and in rapid succession; most treatments were given within 2 days after admission (Table S2). The 107 patients in the group that received IVIG, glucocorticoids, and biologic therapy during their hospitalization had the highest illness severity, as evidenced by multiple indicators of critical illness (Fig. 2B). A total of 245 patients (47%) received vasopressors. Among the 501 patients (97%) for whom at least one echocardiogram was obtained during hospitalization, coronary-artery aneurysms were documented in 64 (13%) and 212 (42%) had left ventricular dysfunction during hospitalization.

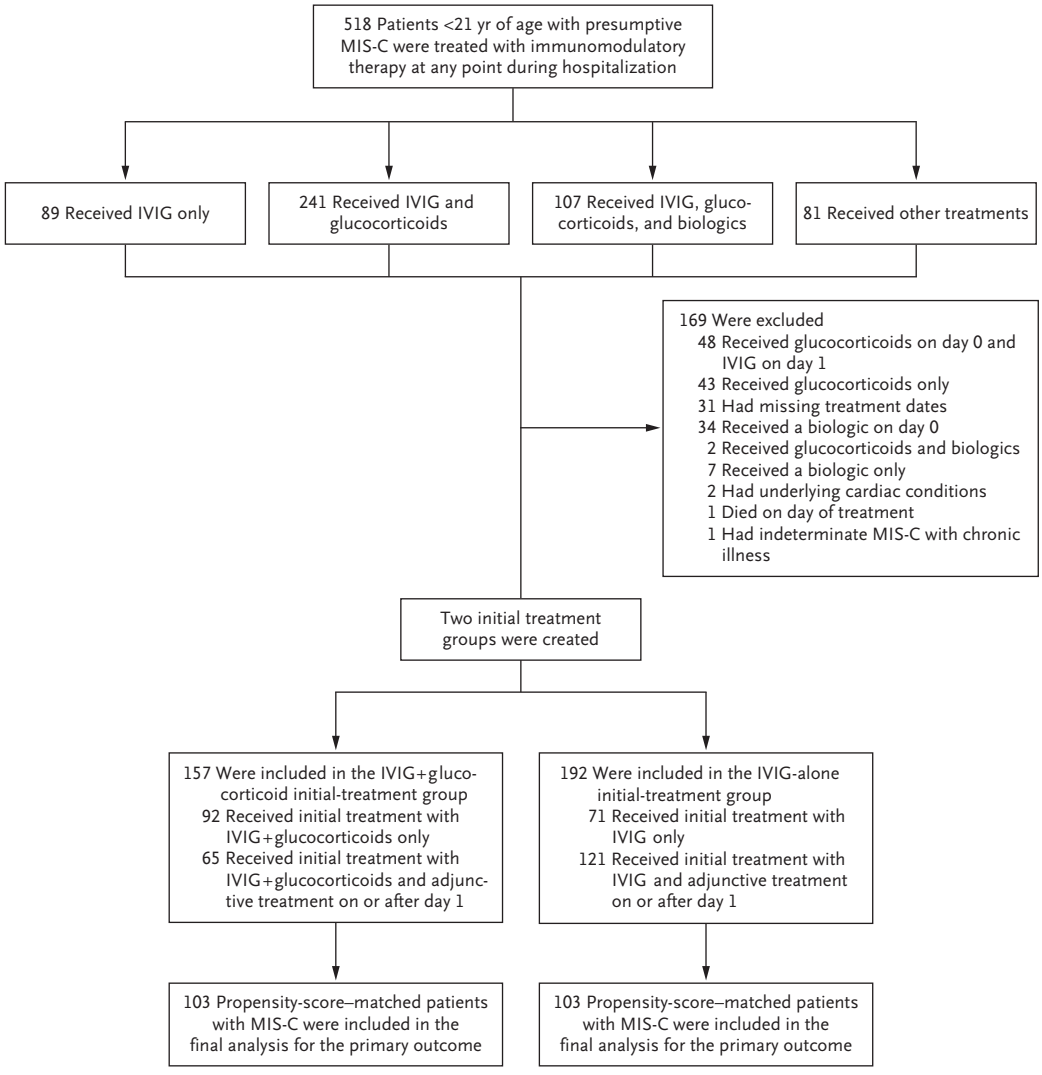

Figure 1. Patients with MIS-C Treated with Immunomodulatory Therapies in the Overcoming COVID-19 Surveillance Registry.

Among the 65 patients who received initial treatment with intravenous immune globulin (IVIG) plus glucocorticoids, followed by adjunctive treatment on or after day 1, adjunctive treatment consisted of a second dose of IVIG in 35 patients, a biologic alone in 16 patients, and a second dose of IVIG plus a biologic in 14 patients. Among the 121 patients who received initial treatment with IVIG alone, followed by adjunctive treatment on or after day 1, adjunctive treatment consisted of glucocorticoids alone in 63 patients; a second dose of IVIG in 15 patients; a biologic alone in 8 patients; glucocorticoids and a second dose of IVIG in 19 patients; glucocorticoids, a second dose of IVIG, and a biologic in 14 patients; and a second dose of IVIG and a biologic in 2 patients. MIS-C denotes multisystem inflammatory syndrome in children.

CLINICAL OUTCOMES ASSOCIATED WITH INITIAL TREATMENT ON DAY 0

Patients who received initial treatment with IVIG plus glucocorticoids, as compared with IVIG alone, differed with respect to demographic and clinical characteristics at baseline, laboratory markers, and severity of illness (Table 2). Among the 349 patients treated with IVIG plus glucocorticoids or IVIG alone on day 0, a total of 206 could be matched according to the propensity score (in a 1:1 ratio of IVIG plus glucocorticoids to IVIG alone); the baseline characteristics were

Table 1. Patient Characteristics and Clinical Outcomes According to Immunomodulatory Treatments Received at Any Time during Hospitalization.*

Variable	Any Treatment (N=518)	IVIG Only (N=89)	IVIG and Glucocorticoids (N=241)	IVIG, Glucocorticoids, and a Biologic (N=107)	Other Treatments† (N=81)
Demographic characteristics					
Male sex — no. (%)	301 (58)	49 (55)	135 (56)	65 (61)	52 (64)
Age — yr					
Median (IQR)	8.7 (4.9–12.8)	5.5 (2.5–10.5)	8.6 (4.6–12.0)	9.0 (5.9–13.5)	10.5 (5.9–15.0)
Range	0–20.9	0.1–19.1	0–20.8	0–19.3	0.9–20.9
Race and ethnic group — no. (%)‡					
White, non-Hispanic	69 (13)	12 (13)	31 (13)	15 (14)	11 (14)
Black, non-Hispanic	183 (35)	27 (30)	94 (39)	41 (38)	21 (26)
Hispanic or Latino	174 (34)	27 (30)	80 (33)	39 (36)	28 (35)
Asian	19 (4)	4 (4)	9 (4)	2 (2)	4 (5)
Other race, non-Hispanic	28 (5)	3 (3)	14 (6)	6 (6)	5 (6)
Unknown	72 (14)	22 (25)	25 (10)	8 (7)	17 (21)
Preexisting conditions					
At least one coexisting condition, excluding obesity — no. (%)	128 (25)	21 (24)	48 (20)	23 (21)	36 (44)
Respiratory condition — no. (%)	67 (13)	14 (16)	24 (10)	9 (8)	20 (25)
Cardiovascular condition — no. (%)	14 (3)	2 (2)	3 (1)	4 (4)	5 (6)
Other preexisting condition — no. (%)§	47 (9)	7 (8)	13 (5)	11 (10)	16 (20)
Clinically diagnosed obesity — no./total no. (%)¶	40/459 (9)	4/72 (6)	19/212 (9)	5/98 (5)	12/77 (16)
Clinical and cardiac characteristics					
Involvement of at least five organ systems — no. (%)	286 (55)	30 (34)	139 (58)	81 (76)	36 (44)
Criteria for Kawasaki's disease — no. (%)‖	196 (38)	45 (51)	91 (38)	43 (40)	17 (21)
Troponin level on admission					
No. of patients	261	30	134	59	38
Median (IQR) — ng/ml	0.11 (0.02–0.74)	0.15 (0.02–7.50)	0.08 (0.02–0.56)	0.12 (0.04–0.70)	0.12 (0.02–3.60)
B-type natriuretic peptide level on admission					
No. of patients	194	18	114	32	30
Median (IQR) — pg/ml	404.0 (87.1–1062.9)	147.0 (50.7–333.3)	483.6 (103.0–1062.9)	833.0 (182.0–2698.4)	375.0 (81.3–504.8)

N-terminal pro–B-type natriuretic peptide level on admission					
No. of patients	122	18	53	42	9
Median (IQR) — pg/ml	1292.5 (227.8–3700.8)	1475.0 (220.2–2121.8)	604.0 (137.0–1921.0)	2024.5 (433.5–7799.2)	2900.0 (630.0–4633.0)
LVEF <55% during hospitalization — no. (%)	212 (41)	25 (28)	99 (41)	62 (58)	26 (32)
Coronary-artery aneurysm — no. (%)**	64 (12)	4 (4)	32 (13)	22 (21)	6 (7)
Interventions and hospital course					
ICU admission — no. (%)	385 (74)	43 (48)	185 (77)	95 (89)	62 (77)
Supplemental oxygen — no. (%)	287 (55)	26 (29)	133 (55)	76 (71)	52 (64)
Mechanical ventilation — no. (%)	91 (18)	7 (8)	25 (10)	42 (39)	17 (21)
Vasopressors — no. (%)	245 (47)	23 (26)	110 (46)	77 (72)	35 (43)
Extracorporeal membrane oxygenation — no. (%)	16 (3)	1 (1)	1 (<1)	10 (9)	4 (5)
Discharged alive — no. (%)	509 (98)	88 (99)	241 (100)	104 (97)	76 (94)
Median hospital length of stay among survivors (IQR) — days	7 (4–10)	5 (4–7)	7 (5–9)	12 (8–17)	6 (4–9)
Died — no. (%)	9 (2)	1 (1)	0	3 (3)	5 (6)

* Among the 518 patients, the percentages of patients corresponding to the numbers of patients in each treatment category were as follows: 17% received intravenous immune globulin (IVIG) only; 47% received IVIG and glucocorticoids; 21% received IVIG, glucocorticoids, and a biologic; and 16% received other treatments. ICU denotes intensive care unit, IQR interquartile range, and LVEF left ventricular ejection fraction.

† Other treatments included glucocorticoids only (40 patients), a biologic only (7 patients), IVIG and a biologic (24 patients), and glucocorticoids and a biologic (10 patients).

‡ Information on race and ethnic group was collected from hospital medical records or was reported by the patient, parent, or caregiver to the site clinicians caring for the patients. Race categories are not mutually exclusive.

§ Other preexisting conditions include neurologic or neuromuscular, oncologic, immunosuppressive, autoimmune, hematologic, renal, urologic, gastrointestinal, hepatic, endocrine, genetic, and metabolic disorders.

¶ The determination of clinically diagnosed obesity was based on reporting by clinicians among patients who were at least 2 years of age. The denominators include all patients who were at least 2 years of age at the time of admission.

‖ This category includes patients who met complete or incomplete criteria for Kawasaki's disease as defined by American Heart Association guidelines.[7]

** Coronary-artery aneurysm was defined as a z score of at least 2.5 for the left anterior descending coronary artery or the right coronary artery (or both) on echocardiography.

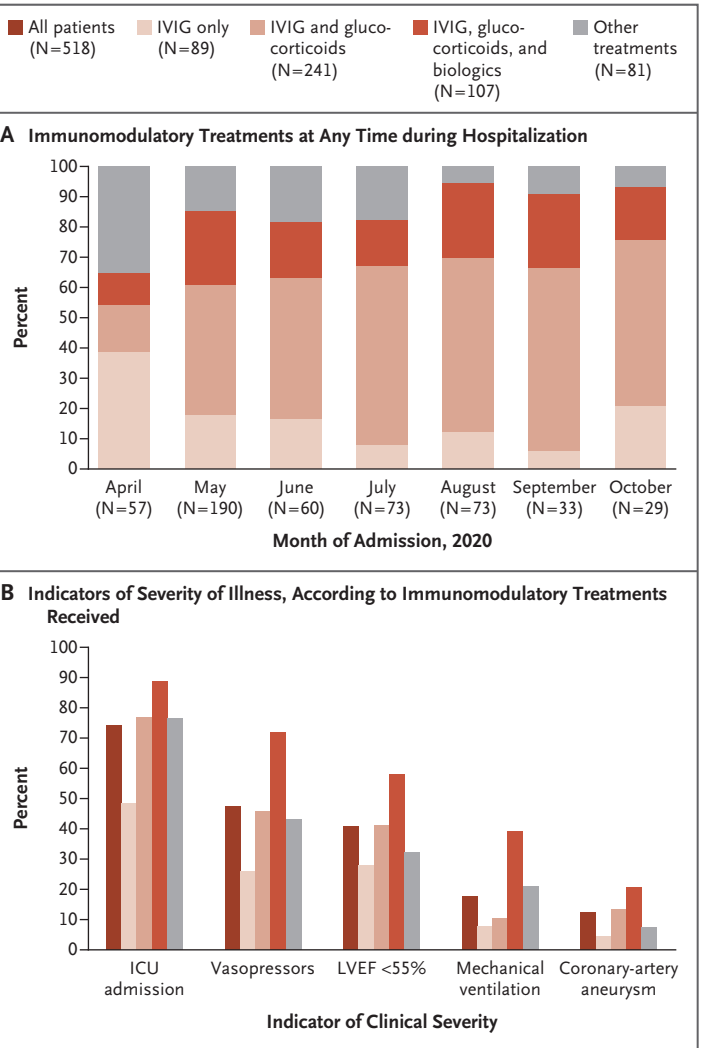

Figure 2. Immunomodulatory Treatments Received during Hospitalization and Indicators of Clinical Severity.

Panel A shows the extent of variability in immunomodulatory treatment that patients with MIS-C received during hospitalization. Panel B shows the distribution of patients whose hospital course included indicators of clinical severity of illness, according to immunomodulatory treatments received during hospitalization. Left ventricular ejection fraction (LVEF) was measured by means of echocardiography. ICU denotes intensive care unit.

well balanced in the propensity-score–matched and inverse-probability-weighted samples (Figs. S1 through S3).

Among the patients in the propensity-score–matched sample who received IVIG alone, 74 (72%) received an adjunctive treatment; 60 patients (58%) received glucocorticoids, 29 (28%) received a second dose of IVIG, and 13 (13%) received a biologic. Among the patients who received IVIG plus glucocorticoids, 30 patients (29%) received a second dose of IVIG and 11 (11%) received a biologic (Table S3).

In the propensity-score–matched analysis, initial treatment with IVIG plus glucocorticoids was associated with a lower risk of the composite outcome of cardiovascular dysfunction on or after day 2 than IVIG alone (18 of 103 patients [17%] vs. 32 of 103 patients [31%]; risk ratio, 0.56; 95% confidence interval [CI], 0.34 to 0.94) (Fig. 3). The risks of the components of the composite outcome were also lower among those who received IVIG plus glucocorticoids than among those who received IVIG alone; left ventricular dysfunction occurred in 8% and 17% of the patients, respectively (risk ratio, 0.46; 95% CI, 0.19 to 1.15), and shock resulting in vasopressor use occurred in 13% and 24% (risk ratio, 0.54; 95% CI, 0.29 to 1.00). Patients treated with IVIG plus glucocorticoids had a lower risk of receiving adjunctive treatment on or after day 1 than those who received IVIG alone (34% vs. 70%; risk ratio, 0.49; 95% CI, 0.36 to 0.65) but did not have a lower risk of fever on or after day 2 (31% vs. 40%; risk ratio, 0.78; 95% CI, 0.53 to 1.13) (Fig. 3 and Table S3). Clustering according to treatment site showed similar results (risk ratio, 0.56; 95% CI, 0.35 to 0.90). Regression estimates for the propensity-score–matched analysis are provided in Table S4, and the results of an analysis that assessed potential unmeasured confounding are provided in Table S5. The median length of stay in the ICU did not differ significantly between the initial-treatment groups after propensity-score matching: 2 days in the group that received IVIG plus glucocorticoids and 3 days in the group that received IVIG alone.

The inverse-probability-weighted analysis confirmed the findings of the propensity-score–matched analysis (Fig. 3). Initial therapy with IVIG plus glucocorticoids was associated with a lower risk of the composite outcome of cardiovascular dysfunction than IVIG alone (20% vs. 24%; risk ratio, 0.65; 95% CI, 0.48 to 0.89), as well as a lower risk of each of the components of the composite outcome; left ventricular dysfunction occurred in 8% and 15% of the patients, respectively (risk ratio, 0.58; 95% CI, 0.32 to 1.02), and shock resulting in vasopressor use occurred in 16% and 20% (risk ratio, 0.59; 95%

Table 2. Characteristics of 349 Patients Who Received Initial Treatment with IVIG plus Glucocorticoids or IVIG alone, before and after Propensity-Score Matching.*

Characteristic	Before Propensity-Score Matching		After Propensity-Score Matching	
	IVIG plus Glucocorticoids (N=157)	IVIG Alone (N=192)	IVIG plus Glucocorticoids (N=103)	IVIG Alone (N=103)
Male sex — no. (%)	90 (57)	114 (59)	58 (56)	59 (57)
Median age (IQR) — yr	8.9 (4.4–12.1)	7.0 (3.6–11.5)	8.8 (3.6–12.0)	7.6 (5.4–12.6)
Race and ethnic group — no. (%)†				
White, non-Hispanic	19 (12)	24 (12)	13 (13)	12 (12)
Black, non-Hispanic	59 (38)	68 (35)	41 (40)	37 (36)
Hispanic or Latino	59 (38)	57 (30)	35 (34)	39 (38)
Other race, non-Hispanic	9 (6)	13 (7)	5 (5)	4 (4)
Unknown	13 (8)	34 (18)	11 (11)	12 (12)
Previously healthy — no. (%)‡	124 (79)	136 (71)	79 (77)	77 (75)
Pulmonary infiltrates on radiography — no. (%)	47 (30)	45 (23)	30 (29)	28 (27)
Kawasaki's disease signs without cardiorespiratory involvement — no. (%)	9 (6)	29 (15)	7 (7)	8 (8)
Median neutrophil-to-lymphocyte ratio (IQR)§	6.8 (3.8–12.9)	5.4 (3.2–9.9)	6.2 (3.0–10.8)	6.6 (4.0–11.6)
Median platelet count (IQR) — $\times 10^{-3}$ per microliter¶	155 (110–219)	181 (116–274)	161 (116–227)	144 (107–222)
C-reactive protein >30 mg/dl — no. (%)‖	13 (8)	11 (6)	7 (7)	9 (9)
ICU admission — no. (%)	113 (72)	100 (52)	69 (67)	71 (69)
Vasopressors — no. (%)	73 (46)	65 (34)	42 (41)	45 (44)
Mechanical ventilation — no. (%)	10 (6)	10 (5)	7 (7)	6 (6)

* Among the 349 patients treated with IVIG plus glucocorticoids or IVIG alone on day 0, a total of 206 patients could be matched according to the propensity score.
† Information on race and ethnic group was collected from hospital medical records or was reported by the patient, parent, or caregiver to the site clinicians caring for the patients. Race categories are not mutually exclusive.
‡ A previously healthy patient was defined as a patient who had no preexisting conditions and was not receiving any prescription medications.
§ Baseline values for neutrophil-to-lymphocyte ratio were available for 330 of the 349 patients (95%).
¶ Baseline values for platelet count were available for 314 patients (90%).
‖ Baseline values for C-reactive protein were available for 260 patients (74%). The values for the remaining 89 patients were considered to be 30 mg per deciliter or lower.

CI, 0.40 to 0.85). Patients treated with IVIG plus glucocorticoids also had a lower risk of receiving adjunctive treatment on or after day 1 than those who received IVIG alone (39% vs. 65%; risk ratio, 0.53; 95% CI, 0.44 to 0.62), and a lower risk of fever on or after day 2 (31% vs. 43%; risk ratio, 0.70; 95% CI, 0.56 to 0.88).

DISCUSSION

Among U.S. children and adolescents hospitalized for MIS-C, a wide variety of immunomodulatory medications were administered early during hospitalization and often with the rapid addition of glucocorticoids, second doses of IVIG, or biologics in critically ill patients. After adjustment for clinical characteristics, including measures of illness severity, IVIG plus glucocorticoids was associated with a lower risk of cardiovascular dysfunction than IVIG alone on or after day 2 following initial treatment, with cardiovascular dysfunction assessed on the basis of a composite outcome of left ventricular dysfunction (as defined by an LVEF of <55%) or shock resulting in vasopressor use. Initial receipt of IVIG plus glucocorticoids was also associated with less use of adjunctive immunomodulatory treatments later in hospitalization, but the risks of persistent or recurrent fever and length of stay in the ICU were not clearly lower with initial

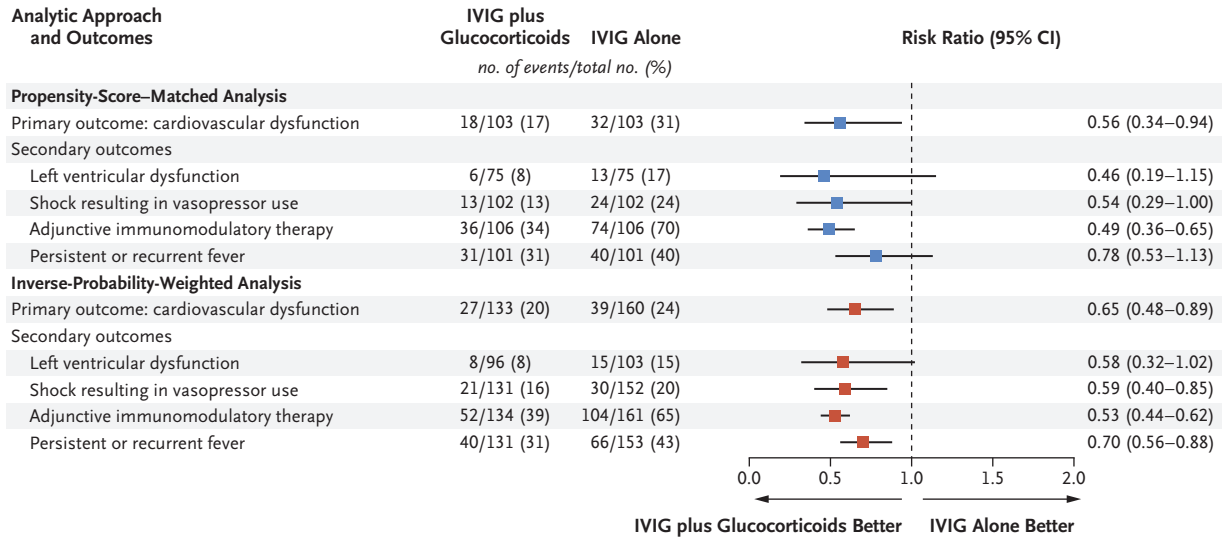

Figure 3. Associations between Initial Treatment with IVIG plus Glucocorticoids, or with IVIG Alone, and Clinical Outcomes.

Cardiovascular dysfunction was based on a composite of left ventricular dysfunction or shock that resulted in the use of vasopressors on or after day 2 after initial treatment. Left ventricular dysfunction was defined as an LVEF below 55%. Medications that met the study criterion of vasopressor use were dobutamine, dopamine, epinephrine, norepinephrine, or a combination of these. Adjunctive immunomodulatory therapy included a second dose of IVIG, glucocorticoids, or biologic treatment on or after day 1. Persistent or recurrent fever was defined as a body temperature of higher than 38.0°C on or after day 2.

treatment of IVIG plus glucocorticoids than with IVIG alone. Until published data that define best practices are available, these data provide clinicians with additional evidence to guide treatment for MIS-C.

Our study builds on earlier studies of MIS-C that also describe the use of glucocorticoids with IVIG[23-25]; these studies suggested that outcomes may be improved with glucocorticoids, although rigorous adjustment for baseline disease severity was not made. Ouldali et al.[26] recently used a propensity-score–matched analysis in an MIS-C cohort in France to compare the effects of initial treatment with IVIG and glucocorticoids (32 children) with those of IVIG alone (64 children). They reported that initial treatment with IVIG and glucocorticoids resulted in a lower risk of fever (the primary outcome) than IVIG alone. Their findings also suggested a lower incidence of receipt of adjunctive treatments and a lower risk of cardiovascular dysfunction. In our larger U.S. cohort, we confirmed that cardiovascular function was better and the incidence of administration of adjunctive treatments was lower among patients who received initial treatment with IVIG plus glucocorticoids than among those who received initial treatment with IVIG alone. We did not identify a strong treatment effect on persistent or recurrent fever, possibly owing to a higher incidence of adjunctive treatments in the U.S. cohort, in which half the patients who were given initial treatment with IVIG alone received glucocorticoids in the subsequent days.

Our study has certain limitations. First, the use of propensity scoring is less likely than randomized trials to balance unmeasured confounders, but on the basis of a sensitivity analysis for unmeasured confounding (i.e., E-value analysis), the introduction of a moderate confounder, independent of the measured confounders we included, would have been needed to change the primary outcome result.[27] More severely ill patients could have been treated more aggressively, but such an approach would have biased the results toward worse rather than better outcomes in the group that received IVIG plus glucocorticoids. Second, our study did not assess criteria for initiating immunomodulatory treatment for MIS-C. Third, although we had a

sufficient sample size to use propensity-score matching for initial treatment with IVIG plus glucocorticoids as compared with IVIG alone, the benefits of other initial treatment regimens could not be analyzed. It is possible that a higher incidence of adjunctive immunomodulatory treatments in the group that received IVIG alone is related to the relative ease of later adding glucocorticoids. However, we did not assess the effect of individual medications (e.g., glucocorticoids alone) in the adjunctive treatment analysis owing to the potential effect of multiple comparisons. Accordingly, we are unable to draw a causal inference regarding the discrete effect of glucocorticoids. Fourth, a lack of baseline echocardiographic data before initial treatment for some patients did not allow for efficient inclusion of baseline left ventricular function in the propensity-score–matched analysis, and echocardiography was not standardized. Lastly, although we report deaths, we did not collect data on adverse events that could have been related to treatment, such as gastrointestinal bleeding, hyperglycemia, or allergic reactions to IVIG, nor did we obtain information regarding the duration or adverse effects of tapering of glucocorticoids in an outpatient setting.

The ongoing transmission of SARS-CoV-2 and the emergence of variants of concern[28] may promote continued outbreaks of MIS-C in the United States and internationally. Additional evidence-based studies are needed to examine the generalizability of our findings across a broad range of geographic regions and practice settings.

In a propensity-score–matched analysis, we found that initial treatment with IVIG plus glucocorticoids for MIS-C was associated with a lower risk of serious short-term outcomes, including new or persistent cardiovascular dysfunction 2 or more days later, than initial treatment with IVIG alone.

The findings and conclusions in this article 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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APPENDIX

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