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Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children

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IMPORTANCE Multisystem inflammatory syndrome in children (MIS-C) is the most severe pediatric disease associated with severe acute respiratory syndrome coronavirus 2 infection, potentially life-threatening, but the optimal therapeutic strategy remains unknown.

OBJECTIVE To compare intravenous immunoglobulins (IVIG) plus methylprednisolone vs IVIG alone as initial therapy in MIS-C.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study drawn from a national surveillance system with propensity score–matched analysis. All cases with suspected MIS-C were reported to the French National Public Health Agency. Confirmed MIS-C cases fulfilling the World Health Organization definition were included. The study started on April 1, 2020, and follow-up ended on January 6, 2021.

EXPOSURES IVIG and methylprednisolone vs IVIG alone.

MAIN OUTCOMES AND MEASURES The primary outcome was persistence of fever 2 days after the introduction of initial therapy or recrudescence of fever within 7 days, which defined treatment failure. Secondary outcomes included a second-line therapy, hemodynamic support, acute left ventricular dysfunction after first-line therapy, and length of stay in the pediatric intensive care unit. The primary analysis involved propensity score matching with a minimum caliper of 0.1.

RESULTS Among 181 children with suspected MIS-C, 111 fulfilled the World Health Organization definition (58 females [52%]; median age, 8.6 years [interquartile range, 4.7 to 12.1]). Five children did not receive either treatment. Overall, 3 of 34 children (9%) in the IVIG and methylprednisolone group and 37 of 72 (51%) in the IVIG alone group did not respond to treatment. Treatment with IVIG and methylprednisolone vs IVIG alone was associated with lower risk of treatment failure (absolute risk difference, −0.28 [95% CI, −0.48 to −0.08]; odds ratio [OR], 0.25 [95% CI, 0.09 to 0.70]; $P = .008$). IVIG and methylprednisolone therapy vs IVIG alone was also significantly associated with lower risk of use of second-line therapy (absolute risk difference, −0.22 [95% CI, −0.40 to −0.04]; OR, 0.19 [95% CI, 0.06 to 0.61]; $P = .004$), hemodynamic support (absolute risk difference, −0.17 [95% CI, −0.34 to −0.004]; OR, 0.21 [95% CI, 0.06 to 0.76]), acute left ventricular dysfunction occurring after initial therapy (absolute risk difference, −0.18 [95% CI, −0.35 to −0.01]; OR, 0.20 [95% CI, 0.06 to 0.66]), and duration of stay in the pediatric intensive care unit (median, 4 vs 6 days; difference in days, −2.4 [95% CI, −4.0 to −0.7]).

CONCLUSIONS AND RELEVANCE Among children with MIS-C, treatment with IVIG and methylprednisolone vs IVIG alone was associated with a more favorable fever course. Study interpretation is limited by the observational design.

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Supplemental content

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Children account for only 1% to 2% of hospitalized patients with coronavirus disease 2019 (COVID-19).[1] However, in April 2020, severe systemic hyperinflammatory disease was reported in children in Europe and the United States, occurring 2 to 4 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[2-6] This novel entity, named multisystem inflammatory syndrome in children (MIS-C)[7] or pediatric multisystem inflammatory syndrome temporally associated with COVID-19,[8] is associated with a wide range of clinical features including persistent fever, digestive symptoms, rash, bilateral nonpurulent conjunctivitis, mucocutaneous inflammation signs, and frequent cardiovascular involvement.[2,4-6,9] MIS-C is often associated with hemodynamic failure, with acute cardiac dysfunction requiring hemodynamic support in 60% to 75% of cases,[5,6] sometimes associated with death.[2-6]

Many children with MIS-C have received empirical treatment based on Kawasaki disease guidelines, with intravenous immunoglobulin (IVIG) alone or combined with corticosteroids.[2-4,6,10] In some studies, children have required second-line treatment, such as tumor necrosis factor inhibitor or interleukin 1 inhibitor, which underscores the importance of defining optimal initial therapy.[11,12]

However, evidence for the most effective therapies for MIS-C is still lacking.[10,13] In the absence of evidence, a British Delphi consensus study proposed treating MIS-C with IVIG as initial therapy.[14]

The goal of this retrospective cohort study was to compare the outcomes of children with MIS-C associated with SARS-CoV-2 infection treated with IVIG and methylprednisolone vs IVIG alone.

Key Points

Question Is there an association between treatment with intravenous immunoglobulins (IVIG) plus methylprednisolone vs IVIG alone and course of fever in multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2?

Findings This retrospective cohort study included 111 children with MIS-C. After propensity score matching, the rate of treatment failure (defined by the persistence of fever 2 days after the introduction of first-line therapy or recrudescence of fever within 7 days) for those who received IVIG plus methylprednisolone vs IVIGs alone was 9% vs 51%, a difference that was statistically significant.

Meaning Combined treatment with methylprednisolone vs IVIG alone was associated with a better course of fever in MIS-C.

Methods

Ethical Review of Study and Informed Consent of Study Participants

The study was approved by the INSERM ethics committee for evaluation (IRB00003888). A written information form validated by the ethics committee was given to all participants. Oral consent was obtained from study participants; no family members or participants refused to participate.

Patients and Settings

The reporting of all suspected MIS-C cases in France became mandatory since the first descriptions of this entity in April 2020. This reporting was coordinated by the French National Public Health Agency, with a methodology previously published.[5,15] All French pediatric hospitals were mandated to report any suspected case of MIS-C to the French National Public Health Agency, without waiting for the SARS-COV-2 antibody test result.[16] An electronic case report form for each patient was stored in a secure database based on clinical and biological files and shared by each pediatric hospital. The following data were recorded: demographic characteristics, comorbidities, initial symptoms and clinical signs, biological and microbiological parameters, radiography findings, treatments, and course during hospitalization.[17] Then 2 research members (N. O. and F. A.) classified each case as confirmed MIS-C or not following World Health Organization (WHO) criteria (**Box**).[18]

All children with confirmed MIS-C associated with SARS-CoV-2 infection fulfilling WHO criteria up to October 22, 2020, were included in the study. The final date of follow-up was January 6, 2021.

Outcome Measure

The primary outcome was treatment failure, defined as persistence of fever for 2 days (48 hours) after the introduction of initial therapy or recrudescence of fever within 7 days after the initial therapy in children who received IVIG and methylprednisolone vs IVIG alone as first-line therapy. Time was measured from the start of administration of IVIG or methylprednisolone. This outcome was similar to the primary outcome used in therapeutic studies of Kawasaki disease[19-21] and has been associated in Kawasaki disease with increased risk of further cardiovascular complications.[20,21] IVIG and methylprednisolone was considered initial therapy when the beginning of administration of the 2 therapies occurred within 24 hours of one another. Fever was defined as a temperature of 38 °C (ie, ≥100.4 °F) or greater.[22]

Secondary outcomes were second-line therapy, defined by a secondary treatment, such as steroids or biological agents, for MIS-C prescribed at least 24 hours after the initial therapy[14]; hemodynamic support after first-line therapy; occurrence of acute left ventricular dysfunction, defined by left ventricular ejection fraction less than 55% after first-line therapy; and duration of stay in the pediatric intensive care unit (PICU). For hemodynamic support and acute left ventricular dysfunction, only outcomes occurring at least 1 day after the initiation of first-line therapy were considered. Hemodynamic support was defined as vasoactive or inotropic amine but not the escalation of a previously prescribed drug.

Sample Size Calculation

From available data, and prior to any data collection, assuming a risk of treatment failure of 50% in the IVIG alone group[11,12] and that the risk with IVIG and methylprednisolone would be reduced to 20%, with a total of 76 patients, the study was estimated to have 80% power to detect such a difference, assuming 2-sided tests.

Statistical Analysis

The main analysis involved propensity score matching.[23,24] The propensity score was calculated with a multivariable logistic regression model to establish each patient's probability of receiving combination therapy with corticosteroids according to baseline characteristics. The following baseline characteristics were used to generate the propensity score: age, sex, comorbidities, hospital center, gastrointestinal symptoms, lower respiratory tract symptoms, neurological symptoms, initial acute left ventricular dysfunction (left ventricular ejection fraction <55%), intensity of inflammatory syndrome (C-reactive protein level > or ≤150 mg/L), positive SARS-CoV-2 antibody test result, initial PICU care before first-line MIS-C therapy, and initial hemodynamic support before first-line MIS-C therapy (eTable 1 in the Supplement). All of these variables, except the SARS-CoV-2 antibody test result, were assessed at the initial presentation (ie, before the start of the first-line MIS-C therapy).

Patients who received IVIG and methylprednisolone were matched to those who received IVIG alone by their propensity score using nearest-neighbor matching, with a minimum caliper of 0.1. The ratio was 1 patient receiving IVIG and methylprednisolone matched with 2 patients receiving IVIG alone. The balance between the 2 treatment groups for each covariate was assessed with a standardized difference less than 0.1, which was considered acceptable.[23] Conditional logistic regression analysis was performed with the matched cohort to test the association between treatment groups and each outcome, with findings expressed as absolute risk differences, odds ratios (ORs), and 95% CIs. The analysis was also adjusted for center by using random-effects modeling, which involved fitting a mixed-effects logistic regression model.[25]

Six sensitivity analyses were performed to assess the robustness of the study findings. First, the data were analyzed using inverse probability of treatment weighting, an alternative to propensity score matching to account for indication bias in nonrandomized design.[23,24] Unlike propensity score matching, this strategy has the advantage of including all the patients in the final analysis.[24] Second, a propensity score–matched analysis was conducted with center as a fixed effect.[25] Third, a propensity score–matched analysis was conducted with double adjustment on the most likely confounding variables[26] of initial hemodynamic support and initial left ventricular dysfunction. This strategy has been proposed to remove residual confounding after propensity score matching for the main potential confounders and adjusts for these variables both for propensity score calculation and in the final conditional logistic regression analysis with the matched cohort.[26] Fourth, a propensity score–matched analysis was conducted including the duration of fever before first-line MIS-C therapy and the delay between hospital admission and start of first-line MIS-C therapy as an additional baseline covariate to account for potential differences in the delay between disease onset and the start of first-line therapy between the 2 treatment groups. Fifth, a propensity score–matched analysis was conducted including mechanical ventilation and the vasoactive inotropic score[27] as additional baseline covariates to account for potential remaining differences in the initial severity of illness. Sixth, a logistic multivariable regression analysis adjusted on the variables included in the propensity score was conducted.

Box. WHO Criteria for MIS-C[a]

Children and adolescents 0 to 19 years old with fever >3 days

AND 2 of the following:

- Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet)
- Hypotension or shock
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/NT-proBNP)
- Evidence of coagulopathy (by prothrombin time, partial thromboplastin time, elevated D-dimer levels)
- Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

AND elevated markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein level, or procalcitonin level

AND no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes

AND evidence of COVID-19 (RT-PCR, antigen test, or serology positive) or likely contact with patients with COVID-19

Abbreviations: COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro–brain natriuretic peptide; RT-PCR, reverse transcriptase–polymerase chain reaction; WHO, World Health Organization.

[a] Based on WHO criteria.[18]

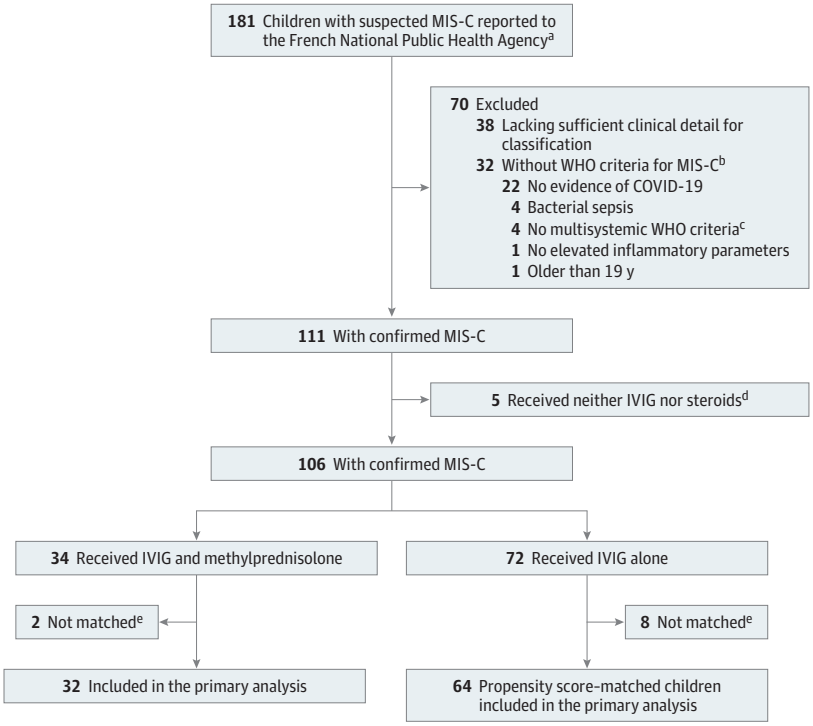
Because of the small sample size, subgroup analyses were conducted with the inverse probability of treatment weighting approach. Prespecified subgroups for analyzing the primary outcomes included presence or absence of initial acute left ventricular dysfunction, defined by left ventricular ejection fraction less than 55%, and age 10 years and older or younger than 10 years. This age categorization was based on the receiver operating characteristic curve to define the optimized cut-off value. To test for significant differences in effect size among subgroups, an interaction term was included in the main propensity score model for each subgroup.[28]

A 2-sided $P < .05$ was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. All analyses were performed with R version 3.6.1 (http://www.R-project.org).

Results

Among the 181 pediatric patients reported to the French National Public Health Agency with suspected MIS-C, 111 fulfilled WHO criteria for MIS-C associated with SARS-CoV-2 infection (**Figure 1**); 70 did not meet the criteria and were not included (eTable 2 in the Supplement). Five children who met the criteria were not included because they did not receive either of the 2 treatments (eTable 3 in the Supplement). The median age of the remaining 106 children was 8.6 years (interquartile range, 4.7 to 12.1), and 58 (52%) were female. Most children (n = 104;

Figure 1. Study Flowchart and Propensity Score Matching of Children With Suspected Multisystem Inflammatory Syndrome in Children (MIS-C)



COVID-19 indicates coronavirus disease 2019; IVIG indicates intravenous immunoglobulins; and WHO, World Health Organization.

[a] The reporting of all suspected MIS-C cases in France became mandatory since the first descriptions of this entity in April 2020. All French pediatric hospital centers were contacted by the French National Public Health Agency in April 2020 to electronically report any case of suspected MIS-C in French children.[5,16]

[b] Details of the characteristics of excluded patients are provided in eTable 2 in the Supplement.

[c] Multisystemic WHO criteria (2 of the following): (1) rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (2) hypotension or shock; (3) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/N-terminal pro-brain natriuretic peptide); (4) evidence of coagulopathy (by prothrombin time, partial thromboplastin time, elevated D-dimers); and (5) acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).

[d] Details about the 5 patients are provided in eTable 3 in the Supplement.

[e] Patients who received IVIG alone were then matched to those who received IVIG and methylprednisolone by their propensity score by using 1:2 nearest-neighbor matching, with a minimum caliper of 0.1. The following baseline characteristics were used to generate the propensity score: age, sex, comorbidities, hospital center, gastrointestinal symptoms, lower respiratory tract symptoms, neurological symptoms, positive severe acute respiratory syndrome coronavirus 2 antibody test result, initial acute left ventricular dysfunction, initial pediatric intensive care unit care, initial hemodynamic support, and intensity of inflammatory syndrome (C-reactive protein level > or ≤150 mg/L).

94%) had gastrointestinal manifestations, and 52 (47%) had initial left ventricular dysfunction. In total, 74 children (67%) were initially admitted to a PICU, 46 (41%) received hemodynamic support, and 29 (26%) received ventilatory support. No deaths were recorded. Among the 111 children, 100 had positive results from SARS-CoV-2 antibody testing or nasopharyngeal reverse transcriptase–polymerase chain reaction and 11 had contact with an individual with SARS-CoV-2 infection. Other baseline characteristics not included in the propensity score are reported in eTable 4 in the Supplement.

Among the 111 children, 34 received IVIG and methylprednisolone and 72 received IVIG alone as first-line therapy. Distribution of children by participating centers is reported in eTable 5 in the Supplement. Among the 106 children who received IVIG and methylprednisolone or IVIG alone, none received any other immunomodulatory treatment before the initial therapy. The dosage of IVIG was 2 g/kg for all patients. A total of 30 of 34 patients in the IVIG and methylprednisolone group received methylprednisolone at 0.8 to 1 mg/kg every 12 hours (maximum of 30 mg for 12 hours) for 5 days; the 4 remaining children received a bolus of 15 to 30 mg/kg/d of methylprednisolone for 3 days. As compared with children who received IVIG alone, those who received IVIG and methylprednisolone had a more severe initial presentation with more frequent initial acute left ventricular dysfunction (22/34 [65%] vs 28/72 [39%]), initial PICU care (31/34 [91%] vs 42/72 [58%]), and initial hemodynamic support requirement (21/34 [62%] vs 23/72 [32%]).

Among the 34 children who received IVIG and methylprednisolone, 3 (9%) did not respond to treatment; among the 72 children who received IVIG alone, 37 (51%) did not respond to treatment.

Among the 34 children who received IVIG and methylprednisolone, 3 (9%) received a second-line therapy (a second IVIG course in 2 children and an interleukin 1 inhibitor in 1 child) (eTables 6 and 7 in the Supplement). Two children had

Table 1. Baseline Characteristics of Children With Multisystem Inflammatory Syndrome in Children (MIS-C) According to First-line Therapy Group

Baseline characteristic[a]	Before propensity score matching, %[b]			After propensity score matching, %[b,c]		
	IVIG and methylprednisolone (n = 34)	IVIG alone (n = 72)	Standard difference	IVIG and methylprednisolone (n = 32)	IVIG alone (n = 64)	Standard difference
Sex						
Male	53	44	0.17	53	48	0.09
Female	47	56	0.17	47	52	0.09
Age, median (IQR), y	9.0 (5.1-12.9)	8.1 (4.6-11.9)	0.14	9.1 (4.7-13.1)	8.7 (4.6-12.0)	0.09
Comorbidities[d]	26	19	0.18	28	23	0.10
Clinical features						
Gastrointestinal manifestations	97	92	0.19	97	97	0.00
Abdominal pain	79	72	0.17			
Vomiting	59	54	0.09			
Diarrhea	50	65	0.31			
Neurological symptoms	50	50	0.00	53	48	0.09
Headache	35	42	0.13			
Altered mental status	8	15	0.20			
Meningeal syndrome	15	4	0.37			
Initial cardiac involvement						
Left ventricular ejection fraction <55%	65	39	0.53	63	58	0.04
Pericarditis	16	15	0.14			
Coronary dilatation[e]	6	4	0.08			
Lower respiratory symptoms	21	28	0.16	22	20	0.04
Dyspnea	15	19	0.13			
Increased work of breath[f]	9	15	0.20			
Oxygen saturation <95%	6	7	0.04			
Duration of fever before first-line therapy, median (IQR), d	5 (4-6)	6 (5-7)	0.35	5 (4-6)	5.5 (5-6)	0.06
Delay between admission and start of first-line therapy, median, d	1 (1-1)	1 (1-1)	0.33	1 (1-1)	1 (1-1)	0.02
Laboratory results at admission						
C-reactive protein >150 mg/L (normally <10 mg/L)	62	49	0.26	70	59	0.23
SARS-CoV-2 identification[g]						
Positive antibody testing	85	72	0.29	84	89	0.10
Positive SARS-CoV-2 RT-PCR	41	36	0.10			
Positive antibody testing or RT-PCR	90	88	0.08			
Contact with an individual with coronavirus disease 2019	46	62	0.06			

(continued)

Table 1. Baseline Characteristics of Children With Multisystem Inflammatory Syndrome in Children (MIS-C) According to First-line Therapy Group (continued)

Baseline characteristic[a]	Before propensity score matching, %[b]			After propensity score matching, %[b,c]		
	IVIG and methylprednisolone (n = 34)	IVIG alone (n = 72)	Standard difference	IVIG and methylprednisolone (n = 32)	IVIG alone (n = 64)	Standard difference
PICU care						
PICU care at any time during MIS-C hospitalization	94	69	0.67			
PICU care before first-line therapy	91	58	0.66	91	89	0.05
Mechanical ventilation	3	11	0.32	3	5	0.07
Hemodynamic support at any time during MIS-C hospitalization[h]	68	56	0.12			
Hemodynamic support before first-line therapy[h]	62	32	0.64	59	56	0.06
Vasoactive inotropic score, median (IQR) (n = 61)[i]	7.5 (5.0-15.0) (n = 23)	10 (5.0-15.8) (n = 38)	0.24	10 (5.0-15.0) (n = 22)	10 (5.0-16.0) (n = 35)	0.09

Abbreviations: IVIG, intravenous immunoglobulins; IQR, interquartile range; PICU, pediatric intensive care unit; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] For additional baseline characteristics not included in propensity score matching, see eTable 4 in the Supplement.

[b] Variables included in the propensity score: age, sex, comorbidities, hospital center, lower respiratory tract symptoms, gastrointestinal manifestations, neurological symptoms, left ventricular ejection fraction less than 55%, duration of fever before first-line therapy, delay between admission and start of first-line therapy, C-reactive protein level greater than 150 mg/L, positive SARS-CoV-2 antibody test result, pediatric intensive care unit care before first-line therapy, mechanical ventilation, and hemodynamic support before first-line therapy. All variables included in the propensity score analysis except SARS-CoV-2 antibody test result were recorded at hospital admission (ie, before first-line MIS-C therapy). Duration of fever before first-line therapy, delay between admission and start of first-line therapy, mechanical ventilation, and vasoactive inotropic score were included only in sensitivity analyses. All clinical features were reported at admission by the physicians.

[c] Patients who received IVIG and methylprednisolone were matched to those who received IVIG alone by their propensity score using nearest-neighbor matching, with a minimum caliper of 0.1. The ratio was 1 patient receiving IVIG and methylprednisolone matched with 2 patients receiving IVIG alone. The balance between the 2 treatment groups for each covariate was assessed with a standardized difference less than 0.1.

[d] Included chronic respiratory disease (n = 13), obesity (n = 6), chronic cardiac disease (n = 3), chronic liver disease (n = 1), heterozygous sickle cell disease (n = 1), and diabetes (n = 1).

[e] Defined by a *Z* score of 2.5 or greater. The maximal *Z* score for the coronary dilation observed in this population was 3.

[f] Grunting, nasal flaring, retractions, or indrawing.

[g] SARS-CoV-2 diagnostics are not mutually exclusive. SARS-CoV-2 identification occurred at any time during hospitalization.

[h] Hemodynamic support defined by vasoactive or inotropic amine requirement.

[i] Following the vasoactive-inotropic score defined by McIntosh et al[27] combining dopamine, dobutamine, epinephrine, milrinone, vasopression, and norepinephrin doses. The score ranges from 0 (no drug used) without an upper limit. The higher the dosage, the higher the score.

Table 2. Primary and Secondary Analyses in the Propensity Score–Matched Cohorts

Outcomes	After propensity score matching				
	No. (%)		Absolute risk difference between groups (95% CI) [reference: IVIG alone]	Odds ratio (95% CI) [reference: IVIG alone]	*P* value
	IVIG and methylprednisolone (n = 32)	IVIG alone (n = 64)			
Primary outcome					
Treatment failure[a]	3 (9)	24 (38)	−0.28 (−0.48 to −0.08)	0.25 (0.09 to 0.70)	.008
Secondary outcomes					
Second-line treatment[b]	3 (9)	20 (31)	−0.22 (−0.40 to −0.04)	0.19 (0.06 to 0.61)	.004
Hemodynamic support[c,d]	2 (6)	15 (23)	−0.17 (−0.34 to −0.004)	0.21 (0.06 to 0.76)	.01
LVEF <55%[c]	2/12 (17)	14/40 (35)	−0.18 (−0.35 to −0.01)	0.20 (0.06 to 0.66)	.007
Duration of PICU stay, median (IQR), d	4 (2 to 5)	6 (4 to 8.5)	Reduction of days: −2.4 (−4.0 to −0.7)		.005

Abbreviations: IQR, interquartile range; IVIG, intravenous immunoglobulins; LVEF, left ventricular ejection fraction; PICU, pediatric intensive care unit.

[a] Treatment failure defined by the persistence of fever 2 days after the introduction of first-line therapy or recrudescence of fever within 7 days after the first-line therapy.

[b] Second-line therapy, defined by a treatment, such as steroids or biological agents, for multisystem inflammatory syndrome in children prescribed at least 24 hours after the initial therapy.

[c] Hemodynamic support defined by the use of a vasoactive or inotropic amine.

[d] Occurring at least 1 day after first-line therapy introduction.

acute left ventricular dysfunction after initial therapy, and 2 required hemodynamic support.

Among the 72 children who received IVIG alone, 33 (46%, all of whom had treatment failure) received second-line therapies: a second IVIG course alone in 14, IVIG and methylprednisolone in 11, methylprednisolone alone in 2, and a biological agent in 6 (an interleukin 1 inhibitor in 4 and an interleukin 6 inhibitor in 2). Sixteen children showed acute left ventricular dysfunction after initial therapy, and hemodynamic support was introduced or added for 17 (24%) (eTables 6 and 7 in the Supplement).

Primary Outcome

Among the 106 treated children, 32 in the IVIG and methylprednisolone group and 64 in the IVIG group were matched based on the propensity score (Figure 1). The treatment groups differed in several baseline characteristics, but after matching, the balance was satisfactory (**Table 1** and the eFigure in the Supplement). There were no missing data for all baseline covariates included in the propensity score.

IVIG and methylprednisolone compared with IVIG alone was associated with a lower rate of treatment failure (3/32 [9%] vs 24/64 [38%]; absolute risk difference, −0.28 [95% CI, −0.48 to −0.08]; OR, 0.25 [95% CI, 0.09 to 0.70]; *P* = .008; **Table 2**).

Secondary Outcomes

Treatment with IVIG and methylprednisolone vs IVIG alone was associated with a lower rate of second-line treatment (3/32 [9%] vs 20/64 [31%]; absolute risk difference, −0.22 [95% CI, −0.40 to −0.04]; OR, 0.19 [95% CI, 0.06 to 0.61]; *P* = .004), secondary acute left ventricular dysfunction (absolute risk difference, −0.18 [95% CI, −0.35 to −0.01]; OR, 0.20 [95% CI, 0.06 to 0.66]), and hemodynamic support (absolute risk difference, −0.17 [95% CI, −0.34 to −0.004]; OR, 0.21 [95% CI, 0.06 to 0.76]) (Table 2). The duration of PICU stay was also significantly shorter (median, 4 vs 6 days; difference in days, −2.4 [95% CI, −4.0 to −0.7]; *P* = .005) (Table 2).

Sensitivity Analyses and Subgroup Analyses

All sensitivity analyses gave similar results (eTable 8 in the Supplement), including the inverse probability of treatment weighting that included all 106 treated children. The association between IVIG and methylprednisolone treatment and lower rate of treatment failure compared with IVIG alone remained similar for children older and younger than 10 years and with or without initial acute left ventricular dysfunction (**Figure 2**, interaction test: *P* = .78 for age and *P* = .74 for initial acute left ventricular dysfunction).

Follow-up

No long-term cardiovascular complication or persistent inflammatory syndrome was reported in patients up to January 6, 2021.

Discussion

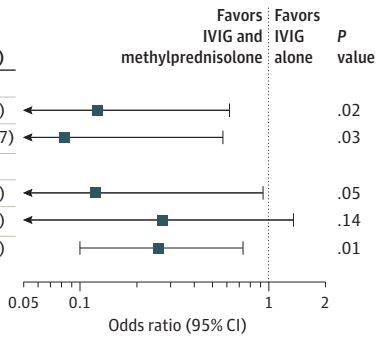
Among children with MIS-C, treatment with IVIG and methylprednisolone vs IVIG alone was associated with a more favorable fever course. The combination therapy was also associated with less severe acute complications, including acute left ventricular dysfunction and hemodynamic support requirement.

A recent research letter[29] reported a single-center experience of cardiac evolution in 40 children with MIS-C and suggested that receiving IVIG plus corticosteroids was associated with a shorter cardiac recovery than receiving IVIG alone. Another single-center study reported that following the implementation of a new local protocol including corticosteroids for MIS-C treatment, hospital length of stay decreased.[30] Recent UK guidelines for MIS-C management,[14] developed using a Delphi method and in the absence of comparative studies, suggested IVIG alone as first-line therapy, or no therapy in some cases. The findings in the current study may warrant reconsidering these recommendations.

A recent prospective surveillance of COVID-19 in children suggested that older children may be at increased risk of developing severe disease.[17] This may reflect an overlap in young children between the classification of MIS-C and Kawasaki disease,[31] which seems less severe than MIS-C.[2,11] In the current study, there were no significant interactions in subgroups based on age 10 years as a cut point. While the subgroup analyses are limited by a small sample size and should be interpreted with caution, they suggest that the association

Figure 2. Association Between First-line Therapy Group and Treatment Failure Depending on Age and Acute Left Ventricular Dysfunction

	Risk of treatment failure						
	Before PS weighting, No. of events/patients (%)		After PS weighting, %		Absolute risk difference between groups (95% CI)	Odds ratio (95% CI)	P value
	IVIG and methylprednisolone	IVIG alone	IVIG and methylprednisolone	IVIG alone			
Age, y							
<10	2/17 (12)	22/39 (56)	12	52	-0.41 (-0.75 to -0.07)	0.12 (0.02 to 0.62)	.02
≥10	1/17 (6)	15/33 (45)	6	40	-0.34 (-0.66 to -0.03)	0.08 (<0.01 to 0.57)	.03
Ventricular dysfunction							
Absent	1/12 (8)	26/44 (59)	8	45	-0.37 (-0.73 to -0.02)	0.12 (0.01 to 0.93)	.05
Present	2/22 (9)	11/28 (39)	9	28	-0.19 (-0.46 to 0.08)	0.27 (0.04 to 1.35)	.14
All patients	3/34 (9)	37/72 (51)	9	38	-0.27 (-0.49 to -0.05)	0.17 (0.04 to 0.61)	.01



Shown are subgroup-specific odds ratios for all patients and those older or younger than 10 years of age and with or without acute left ventricular dysfunction (defined by left ventricular ejection fraction <55%) at baseline. Odds ratios are plotted as squares; the horizontal lines represent 95% CIs. All analyses displayed involved using the propensity score analysis with the inverse probability of treatment weighting approach. Age was transformed into a binary variable using the receiver operating characteristic curve to define the optimized cut-off value. The interaction test *P* value for age ≥ or <10 years was *P* = .78 and for presence or absence of initial acute left ventricular dysfunction was *P* = .74. IVIG indicates intravenous immunoglobulins.

of IVIG and methylprednisolone with better outcomes may be similar in older and younger children. Further studies are required to confirm these findings.

Some recent preliminary mechanistic studies also suggested similarities between MIS-C and acute respiratory distress syndrome related to SARS-CoV-2 infection in adults.[32] Corticosteroid use is currently one of the few validated therapeutics in severe respiratory adult forms of COVID-19.[33,34] The findings in the current study suggest that corticosteroids may also be beneficial in MIS-C, possibly acting systematically as a potent inhibitor of SARS-CoV-2–induced inflammation. Combined with findings of studies reporting MIS-C cases in young adults, there may be common pathways between severe respiratory adult forms of COVID-19 and MIS-C.[32,35] Additional studies are warranted to understand the mechanisms underlying a possible corticosteroid effect in MIS-C and in severe forms of COVID-19.

The main strength of this study was the use of data from a national surveillance system, propensity score–matched analysis to limit selection bias, and consistency of findings using other statistical approaches to control for potential bias.

Limitations

This study has several limitations. First, it was not a randomized trial. While propensity score matching and inverse probability of treatment weighting were used to address limitations in the observation design, confounding by indication due to unmeasured covariates may remain. However, given the rarity and severity of MIS-C, conducting randomized trials may be highly challenging, and observational methods such as these may provide the best level of evidence.

Second, it is not certain that all patients had MIS-C. Patients with Kawasaki disease could have been infected with SARS-CoV-2 given the high prevalence of the pandemic in the general population. To limit this risk, study inclusion was based on WHO criteria for MIS-C.[18] Furthermore, population baseline characteristics, including median age, rate of gastrointestinal symptoms, rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs, were similar to those in other reports of MIS-C.[2,4,6] The clinical features of some patients included in this study have been previously described[3,5,9,11,36] and are consistent with the literature.[2,4]

Third, there was variation in the dosage and routes of steroid treatment used among the 34 children who received IVIG and methylprednisolone as first-line therapy, and the study design did not allow for comparing regimens. In the same way, because no patient received methylprednisolone alone or biological therapy as first-line therapy, other potential therapeutic approaches were not assessed. Further studies are needed to answer these questions.

Fourth, patients in each treatment group may have tended to present to the hospital at a different time in the natural course of this disease. However, the duration of fever before first-line therapy was similar between the 2 groups, and a sensitivity analysis including the duration of fever before first-line therapy as an additional baseline covariate had consistent results.

Fifth, patients with initial MIS-C may show symptoms of septic shock, and initial treatment with IVIG and methylprednisolone has a theoretical risk of worsening an unrecognized bacterial infection. Empirical antibiotic therapy might be initiated until the diagnosis is established to avoid the risk of an untreated infection with corticosteroid exposure.

Sixth, although no deaths occurred in the study population and despite mandatory reporting by the French National Public Health Agency, underascertainment is a possibility.

Conclusions

Among children with MIS-C, treatment with IVIG and methylprednisolone vs IVIG alone was associated with a more favorable fever course. Study interpretation is limited by the observational design.

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