Are Steroids Always Necessary in Multisystem Inflammatory Syndrome in Children (MIS-C)?

Anna Camporesi[1,*], Elena Zoia[1], Irene Raso[2], Stefania Ferrario[1], Veronica Diotto[1], Francesca Izzo[1], Massimo Garbin[2] and Giorgio E.M. Melloni[3]

[1]*Department of Pediatric Anesthesia and Intensive Care, "V. Buzzi" Children's Hospital, University of Milan, Milan, Italy*

[2]*Department of Pediatric Cardiology, "V. Buzzi" Children's Hospital, University of Milan, Milan, Italy*

[3]*TIMI Study Group, Department of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard medical School, Boston, US*

Abstract: Multisystem Inflammatory Syndrome in Children (MIS-C) treatment is still under debate and involves Intravenous Immunoglobulins (IVIG) and/or steroids. We retrospectively analysed data from the patients admitted to Our Institution during the year 2020 to investigate whether prompt IVIG treatment conditions cardiac dysfunction and need for support and if addition of steroids in different doses correlates with outcomes.

Days of fever, time between fever appearance and IVIG treatment, left ventricular ejection fraction (LVEF%) at admission and Cardiac Function Recovery Time (time between worst LVEF and resume of LVEF >55%) were used as outcomes.

38 patients were admitted with MIS-C. All except one received IVIG; 24 received also different Methylprednisolone dosages. Time to IVIG treatment, adjusted for age and sex, correlated with global duration of fever (Coefficient: 1.2; 95% CI:0.73-1.68) and with Vasoactive Inotropic Score (VIS) (Coefficient: 0.09; 95% CI 0.02-0.15), with pericardial effusion (Coefficient: 2.37; 95% CI: 0.45-4.2). Global duration of fever was associated with time to IVIG (Coefficient: 0.8; 95% CI :0.49-1.13) and positive Covid-19 swab (Coefficient: 1.71; 95% CI 0.21-3.22). Cardiac Function Recovery Time did not show differences with different steroid dose regimens. High-dose steroids did not show any benefit in our cohort.

Keywords: Immunomodulation, Immunoglobulins, Fever, COVID-19, Critical care.

INTRODUCTION

Children and adolescents constitute a low percentage of Coronavirus disease 2019 (COVID-19) cases [1].

Since late April 2020, reports from Europe [2] and North America described clusters of children and adolescents with a previous exposure to SARS-CoV-2 who develop a multisystem inflammatory condition leading to multiorgan failure.

This novel entity, named Multisystem Inflammatory Syndrome in Children (MIS-C) or Pediatric Multisystem Inflammatory Syndrome Temporally associated with Sars-CoV-2 (PIMS-TS), includes persistent fever, digestive symptoms, bilateral non purulent conjunctivitis, mucocutaneous inflammation signs, and frequently cardiovascular involvement [3]. MIS-C is associated with hemodynamic failure, acute cardiac dysfunction requiring inotropic support in 60% to 75% of cases, and sometimes with death [4, 5].

The United States Centers for Disease Control (CDC) case definition of MIS-C is based on one day of fever, clinical presentation, evidence of severe illness and multisystem (two or more) organ involvement. A positive test for current or recent SARS-CoV-2 infection or COVID-19 exposure within 4 weeks before the onset of symptoms is required as part of the diagnostic criteria (Centers for Disease Control, 2020). The World Health Organization (WHO) case definition includes presence of fever for at least 3 days, elevated markers of inflammation, evidence of infection or contact with patients with COVID-19, and exclusion of other obvious microbial causes of inflammation (World Health Organization, 2020).

Optimal treatment regimens for MIS-C have been studied as the knowledge of the disease was getting deeper. Initially, a British Delphi consensus study proposed treating MIS-C with Intravenous Immunoglobulins (IVIG) as initial therapy [6]; soon other papers suggested the adjunct of steroids according to clinical severity [7]. Recently, the American College of Rheumatology (Henderson *et al*, 2022) has suggested treatment with IVIG and steroids be instituted in all MIS-C hospitalized children, with

*Address correspondence to this author at the Department of Pediatric Anesthesia and Intensive Care, "V. Buzzi" Children's Hospital, University of Milan, Via Castelvetro 32, Milan, Italy; Tel: +39 347 7513638;
E-mail: anna.camporesi@gmail.com

second line immunomodulatory treatments reserved to refractory cases.

During the first year of pandemic, our Institution, a tertiary-level Pediatric Centre, has admitted children with MIS-C since the very first days, as our region was immediately hit by Covid-19. Treatment of these patients evolved in our Institution too together with experience and current literature.

AIM

To investigate whether the global duration of fever and Cardiac Function Recovery Time (defined as time between worst Left Ventricular Ejection Fraction, LVEF%, and resume of LVEF >55%) were associated with time elapsed between fever appearance and IVIG administration and/or use of steroids with different dosages.

METHODS

Retrospective observational study conducted at our tertiary pediatric hospital in Milano, Italy. After Institutional Review Board (IRB) approval (Number hidden due to anonymisation), the clinical charts of all patients admitted from 1st of March to 31st of December 2020 with a diagnosis of MIS-C according to CDC guidelines (Centers for Disease Control, 2020) were reviewed. We recorded demographic data, symptoms at admission, lung and abdominal ultrasound (US), chest x-ray, laboratory tests at admissions and worst laboratory values during stay for every patient. Additionally, we noted admission to pediatric intensive care unit (PICU), Pediatric Index of Mortality 2 (PIM2), days of PICU stay, need for respiratory or inotropic support and relative duration, Vasoactive Inotropic Score (VIS), medications received, results of Covid-19 swab (Real-Time PCR ELITe InGenius® System) and antibodies anti-SARS-CoV-2 (ELISA IgG, Euroimmun, Lübeck Germany).

Admission echo was recorded before IVIG administration (Affinity70, Philips). Left ventricular ejection fraction (LVEF%) was calculated using Simpson's biplane method. Cardiac function was classified as: normal (LVEF ≥ 55%), mildly reduced (LVEF 45%-54%), moderately reduced (LVEF 35%-44%), severely reduced (LVEF <35%) (Kucera F, 2020). Coronary artery z- score were derived from Boston z-score system, values >2 but < 2,5 were defined as coronary ectasia (dilation without focal aneurisms), Z score ≥ 2,5 were classified as aneurisms.

Over 2020, in line with published papers [7], a new protocol for MIS-C diagnosis and treatment was implemented in our Institution, which comprised use of methylprednisolone (MP) together with IVIG, in different dosages according to degree of heart failure, organ involvement, oxygen requirement:

- If no vasoactive requirement, minimal oxygen support, LVEF 45-55%: MethylPrednisolone 2 mg/kg for 5 days then taper (*MP low dose group*)
- If significative oxygen requirement, mild organ injury, LVEF 35-45%: MethylPrednisolone 10 mg/kg one day then 2 mg/kg for 5 days then taper (*MP middle dose group*)
- If invasive or non-invasive respiratory support, need for inotropic support, moderate to severe organ damage, LVEF < 35%: MethylPrednisolone 10-30 mg/kg x 3 days then 2 mg/kg for 5 days then taper (*MP high dose group*)

Patients who presented with mildly depressed cardiac function and a more predominant lung involvement have been treated with Dexamethasone [8].

DATA COLLECTION AND MANAGEMENT

All patients' data have been collected by A.C., V.D., F.I., S.F., anonymised and recorded on an Excel worksheet (Excel, Microsoft 365, 2020) which was hosted in the hospital's informatic system with no access from outside.

All patients admitted with diagnosis of MIS-C in the given period were enrolled in the study with parental written consent. No patient was excluded.

STATISTICAL ANALYSIS

For every patient, total number of days with fever (total duration of fever), time between fever appearance and start of treatment with IVIG, LVEF at admission and worst LVEF recorded were used as outcomes for generalized linear models; all these have been tested both unadjusted and adjusted for age and sex. Duration of fever and cardiac recovery time (time between worst LVEF recorded and resume of LVEF >55%) have been tested also adjusted for age, sex, admission LVEF and worst LVEF and compared among the subgroups of different steroid regimes received. Throughout the article, mean(±SD) or median (IQR) is reported for every continuous covariate

according to its distribution, and n/N(%) for discrete values. The p-value of a two-sided Wald's test was reported for every variable of interest, along with the per 1-SD increase or decrease in the outcome and 95% confidence interval (CI) in the case of continuous variables. Difference in mean and 95% CI was reported for the most significant contrast for discrete variables. Statistical analysis was carried on using R version 3.6.

RESULTS

Patients' Description

A total of 38 children - (27Males/11 Females), median age 8 (IQR 3-12) years, weight 33.65 (IQR 15.5-48) kg, height ‡135.5(IQR 111-157) cm, Body Mass Index (BMI) 18.21 (IQR 16.4-20.2) kg/m^2- have been admitted to our institution from March to December 2020 with diagnosis of MIS-C; of these, 11/38 (29%) have been admitted in spring (1st wave) and 27/38 (71%) in November-December (2nd wave). There was no significant difference in age, weight, and ethnicity between the two waves.

Table **1** summarizes clinical characteristics of the cohort and necessary support.

Table 1: Clinical Characteristics and Therapy/Support of Cohort

	Total n (%)
Patients	38 (100%)
Comorbidities	10 (26%)
- Of which obesity	3 (8%)
Admitted to ICU	25 (66%)
Fever	38 (100%)
Skin Rash	22 (58%)
Extremity hyperaemia/oedema/desquamation	11 (29%)
Cervical lymph	7 (18%)
Oral changes	14 (37%)
Conjunctivitis	23 (60%)
Abdominal symptoms	36 (95%)
- pain	16 (42%)
- vomiting	21 (55%)
- diarrhea	27 (71%)
Neurological symptoms	6 (16%)
Respiratory symptoms*	15 (39%)
Lobar consolidations (Chest X-ray)	
- monolateral	7 (18%)
- bilateral	9 (24%)
Pleural effusion (chest x- ray)	11 (29%)
-monolateral	9 (23%)
-bilateral	2 (5%)
Respiratory support	11(29%)
- Continuous positive airway pressure (Cpap)	8/9 (88%)
- High Flow Nasal Cannula (HFNC)	1/9 (12%)
Shock	9 (23%)
Inotropes	13 (34%)
- one	8/13 (61.5%)
- more than one	5/13 (38%)
Coronary involvement	2 (5%)
Pericardial effusion	9 (23.6%)
Mitral regurgitation	25 (66%)
- moderate/severe	4/25 (16%)
Covid swab positivity	9/37 (24%)
Covid antibodies detected	29/29 (100%)
Diuretics	24 (63%)
Antibiotics	35 (92%)
IVIG	37 (97%)
Steroids	24 (63%)
Dexamethasone	3 (8%)
MP low dose	6 (16%)
MP middle dose	11 (29%)
MP high dose	4 (10.5%)
Low molecular weight heparin, prophylaxis	22 (58%)
Low molecular weight heparin, treatment	8 (21%)
High dose acetylsalicylic acid	2 (5%)

*Respiratory symptoms are defined as tachypnea/desaturation <92% in room air.

Ten patients (26%) had comorbidities

Six (16%) patients showed IgM positive for Coxsackie and one (3%) for Mycoplasma. Blood cultures, urine cultures, other viral investigations (DNA/RNA Polymerase-Chain Reaction – PCR – on nasal aspirate for respiratory viruses; fecal antigenic research for Rota/Adenovirus) were negative in all patients. Antibodies anti SARS-CoV-2 were detected in all those who underwent the test (twenty-nine patients); for the earliest patients a serological test was still not available but history of contact with Covid-19 infected people was present in all subjects. Covid-19 swab was performed in all patients but one and was positive in nine (24%). 31/38 (82%) patients were tested with both swab and serology and five (13%) patients were positive in both.

Twenty-five (66%) patients have been admitted to PICU [median PIM 2: 6.6 (IQR: 6.6-9.4)]; mean PICU stay 4.24days (±2.38) mean hospital stay 12.08 (±3.85) days.

Mean LVEF at admission was 50.84 % (±12.97); mean worst LVEF recorded was 46.60 (±12.78)~~—%~~; mean SvO2 at admission 61.71 % (±11.62).

Twelve patients (31%) presented with repolarization anomalies on ECG at admission; of these, one patient presented with QTc prolongation and one with Brugada-like pattern. Two patients developed arrhythmias (atrial fibrillation and junctional rhythm) during hospital stay. Nineteen children (50%) presented with mild mitral regurgitation (MR), 4 with moderate, and 2 with severe MR. Z-scores for LV end diastolic diameters were <2 in all patients. Two patients had coronary artery ectasia (first patient: Z-score in Left Main Coronary Artery: 2.44; second patient: Z-score in Left Descending Artery: 2.56). Ectasia was transient and recovered by the end of hospital stay. No patient had coronary aneurism.

Eleven patients (29%) required respiratory support (mean duration 2.6 days ±1.43); 34% (n=13) required inotropic/vasoactive support (mean duration 21.6 ± 35.01 h)- mean Vasoactive Inotropic Score (VIS) 12.75 (±9.23); of these, five (38%) required multiple inotropic/vasoactive agents. 63% of patients (n=24) required diuretic therapy (mean duration 3.38 ±1.38 days).

All patients except one received IVIG, 2 g/kg, in 12-24 hours (depending on clinical tolerance of volume load); 24 patients also received steroids: three received dexamethasone 6 mg, six received MP low dose, 11 received MP middle dose and 4 MP high dose. One patient received MP high dosage but no IVIG because of acute kidney injury.

We did not observe any significant difference in the distribution of comorbidities over the population who received MP. All but three received broad spectrum antibiotic therapy.

Twenty-two patients received low molecular weight heparin (enoxaparin, 0,5 mg/kg twice a day) and eight received enoxaparin in therapeutic dosages, 1 mg/kg twice a day, according to degree of ejection fraction and risk factors for venous thrombosis (Goldenberg *et al*, 2020). With the reduction of the D-dimer or at the normalization of LV function, heparin was shifted to low-dose aspirin for 3-4 weeks.

Cardiac Outcomes

Median cardiac function recovery time was two days (IQR 2-5). At discharge, all patients had an LVEF >55%.

Linear regression, unadjusted and adjusted for age and sex, has been conducted for four primary outcomes: LVEF at admission, time from fever appearance to IVIG administration, total duration of fever, cardiac function recovery time (defined as time from worst LVEF recorded and resume of LVEF >55%).

The associations between the four variables in object and laboratory blood exams' results, clinical and instrumental parameters and therapies are reported in Tables **2** and **3** (Supplementary Material) with relative significance.

LVEF: When adjusted for age and sex, LVEF at admission was significantly reduced with Afro-Caribbean ethnicity, with presence of shock, respiratory symptoms and, among abdominal symptoms, presence of vomiting. LVEF was also reduced in presence of neurological symptoms, of lung parenchymal consolidations on lung US at admission, and mitral regurgitation; it was associated with repolarization alterations, with cardiac function recovery time and with total duration of fever ($p < 0.001$) and with hospital length of stay (Table **2**).

Worst LVEF recorded during hospital stay, adjusted for age and sex, had similar statistically significant associations.

Time from fever appearance to IVIG administration, adjusted for age and sex, was associated with Vasoactive-Inotropic Score (VIS), presence of pericardial effusion, total duration of fever and was inversely correlated with neurological symptoms (Table **2**).

Total duration of fever, adjusted for sex and age, was associated with quality of abdominal symptoms, in particular with vomiting, with VIS, with time from fever to IVIG administration and was inversely correlated with LVEF at admission and worst LVEF. When also adjusted for admission LVEF, it was associated with positive Covid-19 swab.

Cardiac Function Recovery Time, adjusted for age and sex, was associated with weight, BMI, presence of shock, presence of respiratory symptoms, duration of respiratory support (negative correlation), mitral regurgitation and inotrope use (Table **2**).

Table 2: Associations Between Variables of Interest and Admission and Worst Laboratory Values

		LVEF at admission	Time from fever to IVIG[1]	Total duration of fever	Cardiac Function Recovery Time[2]
WBC, 10^3/mmc	Coefficient (95%CI)	-4.99 (-8.97, -1.02)	-0.17 (-0.77, 0.43)	-0.29 (-1.02, 0.44)	0.54 (-0.17, 1.25)
Lymphocytes, % of WBC	Coefficient (95%CI)	5.03 (0.14, 9.91)	0.49 (-0.2, 1.18)	0.62 (-0.27, 1.51)	-0.43 (-1.3, 0.45)
PCT, ng/mL,	Coefficient (95%CI)	-0.1 (-0.18, -0.02)	0.01 (-0.61, 0.64)	0 (-0.02, 0.01)	0.49 (-0.25, 1.24)
IL 6, pG/mL	Coefficient (95%CI)	-5.46 (-10.64, -0.29)	-1.04 (-2.15, 0.08)	-1.55 (-2.5, -0.61)	0.36 (-0.77, 1.49)
NT-pro-BNP, pg/mL	Coefficient (95%CI)	-7.23 (-11.04-3.42)	0.13 (-0.52-0.78)	-0.29 (-1.11-0.53)	0.77 (0.1-1.45)
LDH, U/L	Estimate (95%CI)	-0.03 (-0.06, -0.01)	-0.11 (-0.77, 0.56	-0.43 (-1.21, 0.36	0.82 (0.1, 1.55)
D-Dimer, mcg/L	Coefficient (95%CI)	-4.9 (-9.25, -0.55)	-0.06 (-0.72, 0.6)	-0.27 (-1.08, 0.54)	0.65 (-0.07, 1.37)
ALT, U/L	Coefficient (95%CI)	-0.06 (-0.12, -0.01	-0.03 (-0.66, 0.61)	-0.19 (-0.96, 0.58)	0.55 (-0.16, 1.26)
Albumin, mg/dl	Coefficient (95%CI)	9.26 (1.16, 17.36)	1.22 (0.19, 2.26)	1.2 (-0.15, 2.55)	-0.99 (-2.34, 0.36)

[1] Time elapsed between fever appearance and intravenous immunoglobulins administered
[2] Time elapsed between worst LVEF recording and resume of LVEF greater than 55%

Table 3: Significant Associations Between LVEF at Admission, Worst LVEF, Fever Duration, Time Between Fever Appearance and IVIG Administration and Cardiac Function Recovery Time, Adjusted for Age and Sex

		LVEF at admission	Time from fever to IVIG[1]	Total duration of fever	Cardiac function recovery time[2]
Ethnicity (Afro-Caribbean)	Coefficient (95%CI)	-31.25 (-56.09, -6.41)	3.22 (-0.26, 6.7)	-1.25 (-3.04, 0.55)	3.69 (-0.55, 7.92)
Weight	Coefficient (95%CI)	- 0.46 (-0.91, -0.02)	-0.04 (-0.11, 0.03)	-0.02 (-0.1, 0.05)	0.13 (0.05, 0.2)
BMI, kg/m^2	Coefficient (95%CI)	-0.71 (-2.00, 0.56)	-0.10 (-0.29-, -0.08)	0.02 (-0.19, 0.24)	0.22 (0.02, 0.42)
Presence of Shock	Coefficient (95%CI)	-17.67 (-25.68, - 9.66)	0.41 (-1.01, 1.83)	-0.54 (-2.2, 1.12)	1.72 (0.25, 3.2)
Presence of respiratory symptoms	Coefficient (95%CI)	- 8.29 (-15.68, -0.91)	-0.41 (-1.75, 0.92)	-2.7 (-7.31, 1.91)	1 (0.37, 1.63)
Vomiting	Coefficient (95%CI)	-17.15 (-30.02,- 4.28)	-2.17 (-4.5, 0.15)	-2.92 (-5.21, -0.62)	2.59 (-0.36, 5.54)
Neurological symptoms	Coefficient (95%CI)	-29.57 (-55.56,- 3.59)	-1.64 (-3.3, 0.02)	-2.66 (-7.25, 1.92)	3.35 (-1.08, 7.79)
Lung consolidations at ultrasound	Coefficient (95%CI)	-25.78 (-47.95,- 3.62)	2.24 (-1.1, 5.58)	4.05 (0.22, 7.88)	-5.29 (-13, 2.43)
Mitral Regurgitation	Coefficient (95%CI)	-32.74 (-46.85, - 18.63)	0.51 (-1.68, 2.71)	-2.98 (-6.24, 0.29)	3.31 (0.26, 6.35
Vasoactive-Inotropic Score (VIS)	Coefficient (95%CI)	-0.08 (-1.14, 0.99)	0.09 (0.02, 0.15)	0.18 (0.05, 0.3)	0.09 (-0.13, 0.3)

**adjusted for LVEF at admission*				0.18 (0.09, 0.27	
Inotrope use	Coefficient (95%CI)	-14.4 (-21.34, -7.46)	3.84 (-0.05, 7.73)	-2.61 (-4.57, -0.65)	4.84 (0.68, 8.99)
**adjusted for LVEF at admission*				3.77 (-0.23, 7.77)	4.06 (0.85, 7.26)
Pericardial effusion	Coefficient (95%CI)	-16.99 (- 45.41, 11.43)	2.37 (0.45, 4.29)	-0.32 (-0.67-0.03)	-1.71 (-4.83, 1.41)
Duration of fever	Coefficient (95%CI)	3.3 (1.6, 5)	1.2 (0.73, 1.68)		-0.02 (-0.37, 0.34)
Duration of respiratory support	Coefficient (95%CI)	0.32 (-5.23, 5.87)	-0.43 (-0.64, -0.22)	0.51 (-0.3, 1.33)	-0.43 (-0.66, -0.2)
Cardiac Function Recovery Time	Coefficient (95%CI)	-3.68 (-5.62, -1.74)	-0.17 (-0.49, 0.14)	-0.32 (-0.67, 0.03)	
Time from fever to IVIG	Coefficient (95%CI)	1.44 (-1.08, 3.95)		0.81 (0.49, 1.13)	-0.16 (-0.51, 0.19)
Hospital Stay	Coefficient (95%CI)	-1.44 (-2.53, - 0.35)	-0.07 (-0.23, 0.09)	-0.14 (-0.33, 0.05)	0.02 (-0.67, 0.72)
Covid-19 positive swab	Coefficient (95%CI)	-10.12 (-20.05, - 0.19)	0.2 (-1.32, 1.71)	0.81 (-1.02, 2.63)	0.41 (-1.24, 2.06)
**adjusted for LVEF at admission*	Coefficient (95%CI)			1.71 (0.21, 3.22)	
Low MP dose	Coefficient (95%CI)		-0.22 (-3.13, 2.68)	0.57 (-2.03, 3.17)	-1.29 (-3.93, 1.34)
Middle MP dose	Coefficient (95%CI)		0.49 (-1.01, 2)	-0.59 (-2.33, 1.14)	-0.3 (-2.16, 1.55)
High MP dose	Coefficient (95%CI)		0.05 (-2.61, 2.72)	-1.33 (-3.8, 1.15)	-1.04 (-3.40, 1.32)

[1] Time elapsed between fever appearance and intravenous immunoglobulins administered.
[2] Time elapsed between worst LVEF recording and resume of LVEF greater than 55%
LVEF: Left Ventricular Ejection Fraction; *adjusted for LVEF at admission: the Coefficient of linear regression takes into account also the LVEF value at admission.

Methylprednisolone and Outcomes

Multivariate analysis of MP at different dosages adjusted by age, sex, admission LVEF and worst LVEF shows no effect of different dosages on duration of fever (Coefficient: -1.31, 95% CI: -2.77, 0.14) and cardiac function recovery time (Coefficient: 1.66, 95% CI: -0.011, 3.34).

DISCUSSION

Our results show a linear association between the time elapsed between fever appearance and IVIG administration, as well as with Vasoactive-Inotropic Score, presence of pericardial effusion, and global duration of fever. This linear association show a specific role of timing in therapy of MIS-C, suggesting that not only days of fever before start of therapy increase inflammation, but they also worsen patient's condition, increase the need for support, and the global duration of fever. In particular, the association with VIS even when adjusted for admission LVEF could indicate that fever duration adds the need for vasopressors to that for inotropes, as if the global cardiovascular status of the patient was more decompensated and thus requiring more pharmacological support to restore and maintain perfusion. We were among the first ones in the world to receive cases of this new syndrome, whose name and features had yet to be described. After collegial consultation, we decided to treat it with immunomodulators, empirically. After some time, reports appeared and also papers proposing an escalation of treatment according to severity [7]. We followed these suggestions, as the new disease was yet poorly described and therapy to be found. However, we later analysed retrospectively our results in order to establish if the higher doses of steroids were really necessary to "switch off" the pathological process.

With our results, we show that tempestive diagnosis and start of IVIG therapy can have an impact on

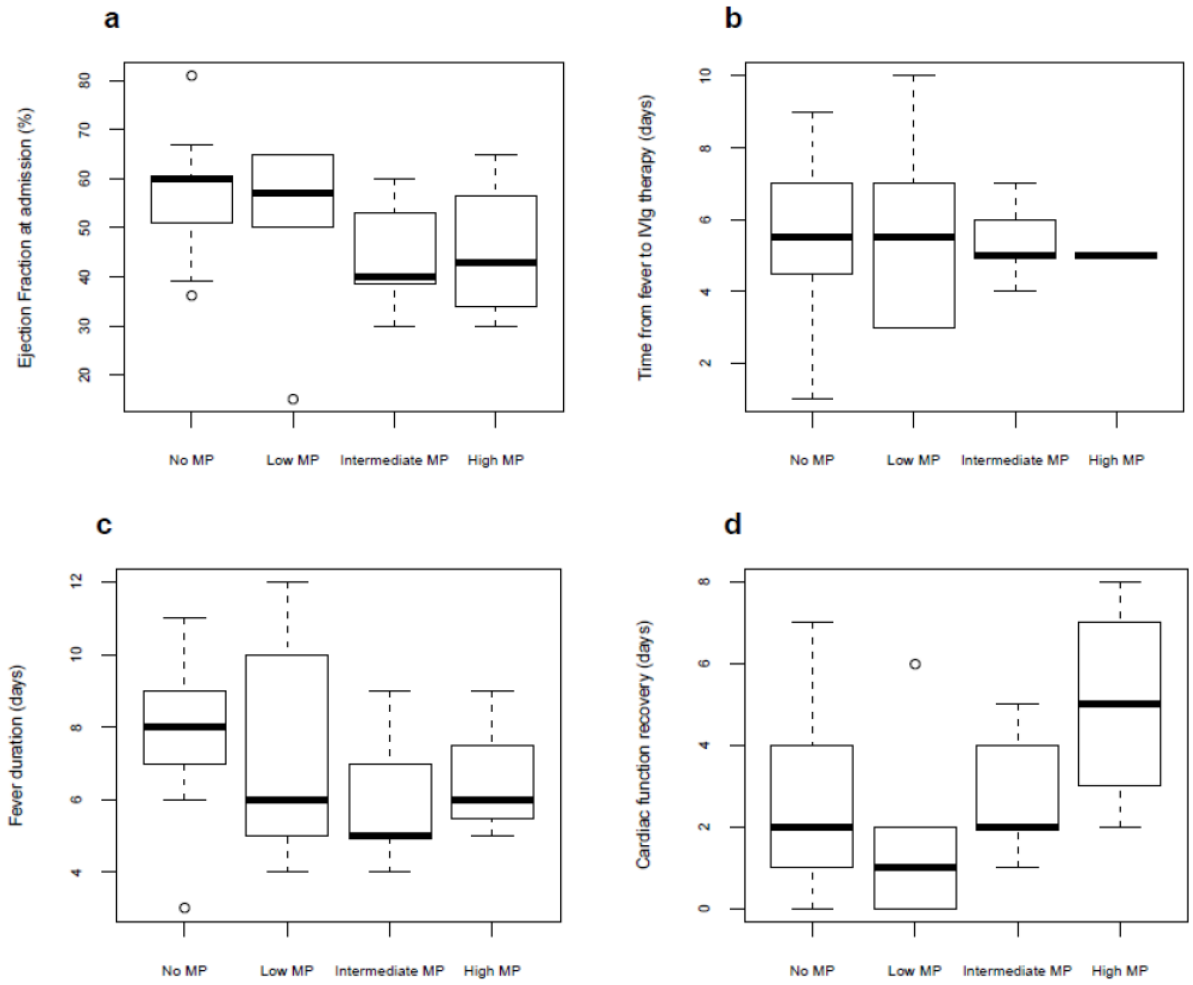

Figure 1: Distribution of LVEF values (**a**), time from fever to IVIG therapy (**b**), duration of fever (**c**) and cardiac function recovery time (**d**) across MP dosages.

cardiovascular function and global duration of the disease. Something similar is proposed by the American Heart Association in the Guidelines for Kawasaki disease [9]. Under this regard, the CDC definition of MIS-C seems to be more helpful in diagnosis and prompt treatment of patients, because it includes subjects after only 24 hours of fever, while the WHO definition requires 3 fever days for diagnosis (Centers for Disease Control, 2020; World Health Organization, 2020). We decided to adhere to CDC criteria as soon as they have been available, in order not to risk any delay in treatment of patients.

Choice of IVIG was made at the very beginning since the first subset of patients admitted were categorized as having an atypical form of Kawasaki disease - this new entity was still unknown and we suspected immediately it could be related to COVID-19, because our region was at the time the epicentre of Covid in Europe, but we were somehow looking for similarities to other better known diseases in order to find a reasonable treatment. Kawasaki-like patients included both the classic type (fever for ≥5 days plus four or more clinical criteria, including bilateral bulbar non-exudative conjunctivitis, changes of the lips or oral cavity, non-suppurative laterocervical lymphadenopathy, polymorphic rash, erythema of the palms and soles, firm induration of the hands or feet, or both) and incomplete types (fever for ≥5 days plus two or three of the aforementioned clinical criteria plus the values of C-reactive protein (CRP), anaemia, thrombocytosis after 7 days of fever, hypoalbuminaemia, hypertransaminasaemia, leucocytosis, sterile pyuria, or an echocardiogram showing coronary aneurysms or cardiac dysfunction (ie, left ventricular function depression, mitral valve regurgitation, or pericardial effusion) [9]. In fact, only one patient of our cohort could completely fulfil the definition of Kawasaki disease but similar features of the new disease prompted us to institute the same therapy before literature was available.

Physiopathology of Kawasaki Disease has been postulated to be triggered by several viruses in genetically predisposed individuals (and this syndrome has been also reported in association with H1N1 influenza virus infection which caused an epidemic in previous years too [10]. Under this point of view, we believe our initial treatment with IVIG in the majority of patients with MIS-C (before the availability of treatment protocols) was prudent and justified.

Later on, other reports appeared on this entity, and steroids therapy was implemented according to evolving literature [11]. Pathophysiological mechanism of MIS-C was still incompletely understood, but its clinical evidence of hyperinflammation favours steroid use.

Some of our patients, also, received steroids because of neurological involvement such as encephalitis, which is a manifestation which has been described not rarely in MIS-C [12, 13].

The optimal steroid dose and timing is still under debate. In a large observational study, no evidence was found that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone [14]. Other, more recent, studies highlighted the better outcome of patients treated with both IVIG and steroids [15]. Dosage of steroids in adjunct to IVIG treatment, also, has varied in different case series. Belhadjer used a MP dosage of 0.8 mg/Kg/day for 5 days and showed a quicker recovery time in children treated with steroids plus IVIG compared to those treated only with IVIG [16]. Ouldaly [17] demonstrated a reduction in treatment failures (defined as fever persistence or recrudescence after therapy) with the association of methylprednisolone and IVIG; dosages in their study have been variable between 0.8-1 mg/kg/day and 30 mg/kg/day with no sub analysis for different dosages. Also, steroids have been recommended in adults' severe Covid cases by WHO. Steroids are known to have associated risks, including hyperglycemia, gastrointestinal bleeding and risk of infection [18]. For this reason we decided to follow the Jonat protocol [7], which suggested increasing doses of steroids, according to clinical severity, rather than approaches that postulated same dose for all kinds of severity.

Our study, although retrospective and consisting of a relatively small cohort, showed no effect of different dosages of steroids on duration of fever and cardiac function recovery time even when adjusted for age, sex, LVEF at admission and worst LVEF during stay, and no better outcome was demonstrated for MP high doses, which are not devoid of side effects. Our results therefore point to the need of rapid institution of IVIG treatment and to the discussion of different steroids regimens according to severity, with particular focus on the need for the highest MP doses. The BATS Trial (Best Available Treatments), an international platform which enrolled children with MIS-C from all over the world into an observational study on treatments and outcomes, since the second half of 2020, has recently produced results which are concordant with ours, showing that recovery rates were similar in patients treated with IVIG only and in those treated with steroids alone or steroids plus IVIG. However, IVIG therapy is an expensive therapy which could be not reachable in all countries of the world.

MIS-C presents high levels of inflammatory markers and cytokines; our population did not differ from other studies in terms of these markers (Carte MJ *et al*, 2020). Similar markers are present also in other pathologies, such as toxic shock syndrome and sepsis. For this reason, our protocol involved broad-spectrum antibiotic therapy up to negativity of cultures in progress, as per Italian guidelines proposed by the Rheumatology Study Group of the Italian Society of Pediatrics [19].

Interestingly, some symptoms had significant associations that were not expected. For instance, abdominal symptoms, which are very common in MIS-C patients, differed between those with worse LVEF at admission, who presented also vomiting and not only diarrhoea and abdominal pain.

Lung ultrasound patterns in children with MIS-C haven't been studied extensively yet, possibly because the focus has more been on heart function or abdominal symptoms. Musolino has described ten patients under this aspect, finding B lines and pleural irregularities as the most common feature, together with pleural effusion [20]. Their work, however, does not correlate with LVEF, possibly also because of a milder clinical presentation of these patients and a less important cardiac involvement, as reflected by their BNP and Troponin mean values. Presence of lung consolidations at lung ultrasound, on the opposite, were noted soon in our cohort and have been associated with reduced LVEF at admission in MIS-C patients [21]. In patients with acute heart failure as the MIS-C patients are, a different lung ultrasound phenotype would have been expected (images of "wet lung" due to left ventricular dysfunction, with diffuse B-

lines). It is possible that these images are part of a more complex clinical picture in patients with both cardiac dysfunction and viral persistence as shown by the association between LEVF and admission and positive swab, which approximates statistical significance. Similarly, patients with positive swab at time of admission had a longer recovery from fever.

With the limitation of a small sample, our results show a correlation between BMI and cardiac function recovery time, which has been described in literature [22]. Even though a precise mechanism is difficult to hypothesize, this particular population, unfortunately growing in our societies, could suffer even more the metabolic side effects of steroids, also in consideration of the metabolic impairments that MIS-C has been shown to create even in normal-weight children [23].

Long term outcome of MIS-C patients, particularly regarding the degree of heart dysfunction, is still under investigation given the relative novelty of the syndrome. Patients from our Institution are currently being followed up and maintain normal heart function at 6 months [24]. Role of different therapeutic regimens on long-term outcomes is also to be described.

LIMITATIONS

We acknowledge the relatively small cohort of patients studied and the retrospective nature of this study can constitute a limitation. Also, we could not apply a propensity matched analysis of the cohort due to the small sample. We present however a particular population, including the very first patients, who have been treated before literature suggestions and whose treatment constitutes intrinsically, under this aspect, a comparison. The different periods of patients' enrolment – that is, the two different "waves" of patients' admission due to MIS-C - could also be different under a clinical aspect due to mutation of SARS-CoV-2, although an official virus "variant" was still not described, that could have led to different immunologic responses to it [25]. Also, a detailed analysis of ethnical subgroups was not possible due to small sample. However, strengths of the work reside in the different dosages of steroids that were tested in our cohort and the detailed laboratory, clinical and functional associations that were established with analysis.

IMPLICATIONS FOR PRACTICE

Tempestive intravenous immunoglobulins, when available, are a good option for initial treatment of MIS-C patients. Adjunct of steroids, and in particular of high doses of MethylPrednisolone, should be discussed case by case in view of the many side effects they present. The choice of the CDC definition for the diagnosis of the disease "MIS-C" is therefore more useful as it includes only one day of fever in the criteria thus allowing a more tempestive diagnosis.

CONCLUSIONS

In a retrospective study on use of IVIG and steroids in different dosages in management of MIS-C, no better outcome was found with use of different doses of MethylPrednisolone, which are not free of potential side effects. Rapid institution of IVIG treatment, on the other side, is advisable and has proven beneficial in our cohort. When available, IVIG should be started promptly in order to shorten the disease course and improve cardiac function. Adhering to the CDC definition for MIS-C can help diagnose patients sooner and therefore institute therapy sooner with benefit.

ETHICS APPROVAL

This study has received IRB Approval (2021/ST/005).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Received on 05-05-2024 Accepted on 10-06-2024 Published on 13-06-2024

DOI: https://doi.org/10.12974/2311-8687.2024.12.09