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CLINICAL PROFILE AND SHORT TERM OUTCOME OF CHILDREN WITH COVID-19 RELATED MULTISYSTEM INFLAMMATORY SYNDROME (MISC) TREATED WITH PULSE METHYLPREDNISOLONE AND/OR IV IMMUNOGLOBULIN : A CASE SERIES FROM TERTIARY CARE PAEDIATRIC HOSPITAL IN BANGALORE

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ABSTRACT **Introduction:** MIS-C in children is a rare, but life threatening complication of covid 19 infection. The complications of MIS-C can be severe, including cardiogenic shock or distributive shock with poor vasomotor tone. Aim: To study the clinical profile and outcome of children treated with methylprednisolone pulse therapy and/or IV immunoglobulin. Materials and methods: Case series of children diagnosed with COVID 19 related MISC admitted to Vydehi Institute of Medical Sciences and Research Centre, Bangalore from march to august 2021 , who met the WHO and CDC criteria were reviewed. Results: The case series describes 11 cases of MISC in our hospital. 3 children were treated with IV immunoglobulin and 8 children were received IV pulse methylprednisolone. All children had fever upon arrival to hospital lasting for atleast 5 days. Children with shock also had higher D-dimer , lower albumin , higher CRP, high lactate and lower ejection fraction compared to other children. Conclusion: We have concluded a favourable role of IV immunoglobulin or pulse methylprednisolone in treatment of MISC.

KEYWORDS : Multisystem inflammatory syndrome, COVID-19, pulse methylprednisolone, IV immunoglobulin, gastrointestinal symptoms.

Introduction:

MIS-C in children is a rare , but life threatening complication of covid 19 infection. Majority of children infected by SARS-COV-2 have been asymptomatic or has mild illness. However, a small proportion of children develop MIS-C post recovery from acute infection.

The true global incidence of MIS-C is uncertain, but it appears to be rare. The first reported cases occurred in the United Kingdom, followed by reports from Canada, Europe, South Africa, and the United States.[1] Reports estimate the incidence in those under age 21 years to be 2 per 100,000 persons with an overall incidence among children with COVID-19 of 322 per 100,000 persons [2].

Most studies demonstrate a lag of 2–6 weeks between COVID-19 infection and developing MIS-C.[3] It is clinically similar to kawasaki disease , toxic shock syndrome and macrophage activation syndrome. MIS-C is defined by inflammation in different organs such as heart, kidneys, lungs, brain, skin, gastrointestinal system etc. Males are more commonly affected in both MIS-C (up to 59%) and KD (up to 60%).[4] The complications of MIS-C can be severe, including cardiogenic shock or distributive shock with poor vasomotor tone. In one systematic review of 917 patients, 11 (1.9%) patients died. Most patients with cardiac involvement (including depressed ventricular function or arrhythmias) typically recover. However, 20–45% of patients may still have a mildly depressed ejection fraction at the time of hospital discharge.[5]

It has been treated empirically with steroids and/or Intravenous immunoglobulin. Some studies have used biologicals like interleukin 1 inhibitor, tumor necrosis factor inhibitor, interleukin 6 receptor antibody etc. Given the significant impact of MIS-C on affected patients, it is important for the emergency clinician to be aware of this condition.

In this study, we aim to review and summarize the clinical presentation and treatment outcome of children treated with pulse methylprednisolone and/or IV immunoglobulin.

Materials and methods:

Case series of children diagnosed with COVID 19 related MISC admitted to Vydehi Institute of Medical Sciences and Research Centre, Bangalore from march to august 2021 , who met the WHO and CDC criteria were reviewed.

Children admitted with MIS-C aged 1 month to 14 years of age from march to august 2021 were included. Children who fulfilled the WHO and CDC criteria for diagnosis of MIS-C during the study period were included in the study. Infective causes like dengue , leptospirosis , scrub and bacterial sepsis were excluded by appropriate investigations. Data were recorded in a standardized form and deidentified. Descriptive statistics were performed and presented as mean and standard deviation (±/SD) for continuous variables or as number and percentages for nominal/categorical variables.

Results:

The case series describes 11 cases of MISC in our hospital. 7 were male and 4 were female. All children were previously healthy and presented at our hospital approximately 4-6 weeks after the peak of covid-19 outbreak in the country.

3 children were treated with IV immunoglobulin and 8 children were received IV pulse methylprednisolone. Mean age of the patients in pulse methylprednisolone group was 9.0313±2.5 and IV IG immunoglobulin group was 12.1667±2.5, p value was 0.074 (not significant) (Table 1 and Graph 1).

All children in our case series who tested for SARS COV-2 antibody were positive at the time of presentation supports the post infectious nature of the disease. Mean day of presentation in pulse methyl prednisolone group was 3.88±0.991, and in IV IG immunoglobulin group was 4.33±1.15 (Table 1 and Graph 1). 45% children in our case series were obese or overweight and all had cardiovascular and gastrointestinal symptoms at the time of presentation.

Clinical presentation in MIS-C patient in our case series were mostly similar to earlier reports with fever and gastrointestinal problems being the most common initial symptoms. All children had fever upon arrival to hospital lasting for atleast 5 days (Table 1 and Graph 1). Mean duration of fever was 5.5 days.

3(37.5%) in pulse methyl prednisolone and 1(33.3%) in IV IG immunoglobulin group had normal nutrition (Table 1 and Graph 1). 3.38±0.91 days in pulse methyl prednisolone and 3.67±1.5 days in IV IG immunoglobulin group were in PICU. Total number of hospital stay in pulse methyl prednisolone group was 9.25±2.5 and in IV IG immunoglobulin group was 10.33±2.8, with no case fatalities. (p-value was not significant). None of the children ventilated. All children responded well. None of the children required any other alternate immunomodulator. All children are fully recovered.

54% children had CVS manifestation . All of them presented with shock and had decreased systolic ventricular dysfunction with Ejection fraction <55% , the most common cardiac abnormalities seen in these childrens. No coronary artery aneurysm or dilatation seen in our case series. All those children who had LV dysfunction after inotropic support were recovered within a short period. 3 patients in each of the group had mucocutaneos manifestation, and Gastrointestinal symptoms were common among these children with

100%,82% and 54% children presenting with vomiting, abdominal pain and loose stools respectively. 63% children in our case series had hepatic involvement 50% in pulse methyl prednisolone and 100% in IV IG immunoglobulin group. Repiratory features in 3 (37.5%) in pulse methyl prednisolone and 1 (33.3%) in IV IG immunoglobulin group. CNS in 1 patient each, serotosis in 4(50%) and 3(100%), introtropic support in 3 patients each, antibiotics was used by all the patients, respiratory support was required by 3 (37.5%) and 1 (33.3%) in pulse methyl prednisolone and IV IG immunoglobulin group respectively. (Table 2 and Graph 2)

Children with shock also had higher D-dimer , lower albumin , higher CRP, high lactate and lower ejection fraction compared to other children. 63% children in our study had neutrophilia and lymphopenia. 36% children had thrombocytopenia. All children's in our study had high D-dimer , ferritin and CRP. Elevated inflammatory marker and evidence of coagulopathy are more common lab finding and are among most important criteria for clinical diagnosis of MISC. (Table 3 and Graph 3)

Outcome measure shows absence of need of biological agents, absence of need of ECMO, improvement in cardiac function, absence of treatment failure and absence of mortality suggesting a favourable role of IV immunoglobulin or pulse methylprednisolone in treatment of MISC.

Discussion:

In this study, all children had fever upon arrival to hospital lasting for atleast 5 days. Gastrointestinal symptoms were common among these children with 100%, 82% and 54% children presenting with vomiting, abdominal pain and loose stools respectively.

In the study by Michael Gottlieb et al., in 2021, Patients with MIS-C may present with gastrointestinal symptoms (abdominal pain, vomiting, or diarrhea are present in 60–100%), neurocognitive symptoms (headache, decreased mental status, or lethargy are present in 29–58%), respiratory symptoms (21–65%), sore throat (10–16%), and myalgias (8–17%).[6]

In one multinational survey of 183 pediatric patients with MIS-C, fever was present in 100% of cases. Shock was present in 43.2% and was more common in older children (mean 9 years vs 7 years).[7] A meta-analysis demonstrated similar results with 100% of patients presenting with fever, followed by 73.3% patients presenting with diarrhea or abdominal pain, and 68.3% patients presenting with vomiting. The vast majority of these patients will have fever for a minimum of 3 days, with a median duration of 4–6 days.[8]

In this study 54% children had CVS manifestation. All of them presented with shock and had decreased systolic ventricular dysfunction with Ejection fraction <55%, the most common cardiac abnormalities seen in these children's. No coronary artery aneurysm or dilatation seen in our case series. All those children who had LV dysfunction after inotropic support were recovered within a short period. Children with shock also had higher D-dimer, lower albumin, higher CRP, high lactate and lower ejection fraction compared to other children. 63% children in our study had neutrophilia and lymphopenia. 36% children had thrombocytopenia. All childrens in our study had high D-dimer, ferritin and CRP. Elevated inflammatory marker and evidence of coagulopathy are more common lab finding and are among most important criteria for clinical diagnosis of MISC.

Elevated inflammatory markers are common, with 92% of patients having at least 4 of the following abnormalities: elevated ESR (75–80%), elevated D-dimer (67–100%), elevated CRP (90–100%), lymphocytopenia (80–95%), neutrophilia (68–90%), elevated ferritin (55–76%), hypoalbuminemia (48–95%), anemia (70%), thrombocytopenia (31–80%), or increased liver enzymes (62–70%).[9] One large study found that inflammatory markers were higher and platelets were lower among those presenting in shock. Cardiovascular involvement is commonly seen, with elevations in BNP/pro-BNP (73–95%) and troponin (50–93%).[10,11] Acute kidney injury can occur in 8–52%, and laboratory evaluation may also reveal elevated lactate dehydrogenase (10–60%) or hypertriglyceridemia (70%) if these laboratory tests are obtained.[12,13]

Elevated CRP values, higher neutrophil counts, lower lymphocyte counts, elevated troponin, and lower serum albumin are associated with a greater risk of shock.[14]

Conclusion:

MIS-C is a complication of COVID-19 which causes a multi-inflammatory syndrome that can affect nearly any organ system. The acute presentation of MIS-C in our study typically includes fever, elevated inflammatory marker, gastrointestinal and cardiac manifestation that require management in the intensive care unit. Elevated inflammatory marker and evidence of coagulopathy are more common lab finding and are among most important criteria for clinical diagnosis of MISC. We have concluded a favourable role of IV immunoglobulin or pulse methylprednisolone in treatment of MISC. Lack of case fatalities in our cohort may indicate that early recognition and prompt medical attention is necessary for a favourable outcome in MISC.

List of tables and figures:

Table 1: Demographic and background characteristics

	Pulse Methyl Prednisolone	IV IG Immunoglobulin	P Value
Age	9.0313±2.5	12.1667±2.5	0.074
Day of presentation	3.88±0.991	4.33±1.15	0.527
Fever(>5days)	8 (100%%)	3 (100%)	-
Nutrition (normal)	3 (37.5%)	1 (33.3%)	0.536
Days in picu	3.38±0.91	3.67±1.5	0.700
Total no of days of hospital stay	9.25±2.5	10.33±2.8	0.558

Graph 1 Demographic and background characteristics

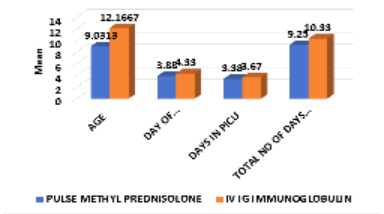


Table 2: Comparison of various symptoms and complications among subjects given Pulse methyl prednisolone or IV IG Immunoglobins

	Pulse methyl prednisolone	IV IG immunoglobulin	P value
Mucocutaneos Manifestation	3 (37.5%)	3(100%)	0.121
GIT Features Abdominal pain Vomiting Loose stools	8 (100%%)	3 (100%)	-
Hepatic Involvement	4 (50%)	3 (100%)	0.212
Respiratory Features	3 (37.5%)	1 (33.3%)	0.536
CNS	1 (12.5%)	1 (33.3%)	0.491
Serotosis	4 (50%)	3 (100%)	0.212
Death	0 (0.0%)	0 (0.0%)	-
Antibiotics	8 (100%%)	3 (100%)	-
Inotropic support	3 (37.5%)	3 (100%)	0.121
Respiratory support	3 (37.5%)	1 (33.3%)	0.536

Graph 2 Comparison of various symptoms and complications among subjects given Pulse methyl prednisolone or IV IG Immunoglobins

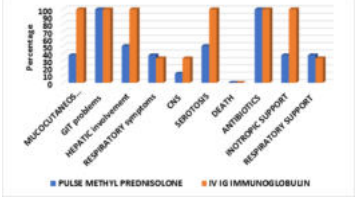
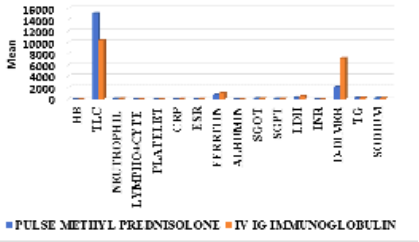


Table 3 Comparison of hematological parameters among subjects given pulse methyl prednisolone or IV IG Immunoglobins

	Pulse methyl prednisolone	IV IG Immunoglobulin	P Value
HB	11±2.21	11.03±0.66	0.981
TLC	15150±5265.25	10400±3642.8	0.190
Neutrophil	67.97±14.44	69.66±20.50	0.879
Lymphocyte	24.45±14.44	25.16±20.64	0.948
Platelet	2.4±0.81	1.5±0.32	0.094
CRP	21.57±6.4	34.46±13.5	0.052
ESR	29.88±26.63	49.33±21.19	0.289
Ferritin	779.50±456.46	1052.67±266.47	0.364
Albumin	2.9±0.477	2.29±0.40	0.065
SGOT	99.38±136.188	82.67±29.95	0.843
SGPT	53.13±41.57	57.67±18.50	0.863
LDH	320.75±302.48	571±186.96	0.221
INR	0.88±0.55	1.23±0.10	0.324
D-Dimer	2154.62±1398	7194±3669	0.007
TG	219.37±203.24	304.33±98.49	0.515
Sodium	137.50±4.4	135.33±5.68	0.519

Graph 3 Comparison of hematological parameters among subjects given pulse methyl prednisolone or IV IG Immunoglobins



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