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Garcia RDJ. Multi-system Inflammatory Syndrome in Children in two private, urban, tertiary hospitals in Metro Manila, Philippines. https://doi.org/10.56964/pidspj20232402006

ORIGINAL ARTICLE

MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) IN TWO PRIVATE, URBAN, TERTIARY HOSPITALS IN METRO MANILA, PHILIPPINES

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ABSTRACT

Background: MIS-C is an infrequent, but serious complication encountered after acquiring COVID-19 illness in children. There is a lack of local data on MIS-C in the Philippines.

Objective: To identify demographic data, co-morbidities, clinical manifestations, laboratory results, 2D-echocardiography findings, acute co-illnesses and complications, treatment, and outcome of children with MIS-C, seen in two, private, urban, tertiary hospitals.

Methodology: This is a retrospective, descriptive study of all consecutive MIS-C cases, using the 2020 US CDC definition, seen between July 2020 to January 2023, by a single infectious disease physician. Demographic, epidemiologic, clinical, and physical examination findings; results of laboratory, 2-DE, and radiologic tests; co-illnesses and complications; and therapeutic and outcome data, were entered in a case report form for each patient.

Results: Thirty-six patients were seen. MIS-C cases had a median age of 6 years, presented with fever in 97%, while one-half had abdominal pain, vomiting, diarrhea and/or rash. CRP, D-dimer, ferritin, LDH and procalcitonin were generally elevated, and thrombocytopenia was seen in 39%. The most common 2-DE abnormalities were pericardial effusion (50%), coronary artery dilatation or aneurysm (39%) and mitral regurgitation (36%); the 2-DE was normal in 22%. The main complications were pneumonia (31%), myocarditis (28%) and hypotension (14%); 8% had ARDS. Treatment was with corticosteroids (89%) and IVIG (84%). Most (94%) recovered, and the hospital stay was five days, or less, in 86%. The two mortalities were a severely wasted adolescent with previously undiagnosed HIV infection; and an adolescent on chemotherapy for AML, who was also being treated for disseminated TB.

Conclusions: There is a need to create a greater awareness of MIS-C as, like Kawasaki disease, it has the potential to be an important cause of acquired heart disease among children.

KEYWORDS: *MIS-C, Filipino, Pediatric*

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INTRODUCTION

Among children, Multisystem Inflammatory Syndrome in Children (MIS-C) is an infrequent, but serious complication encountered after acquiring COVID-19 infection, as it can lead to myocarditis, cardiac dysfunction, coronary artery aneurysms, and in severe cases, multi-organ dysfunction and death.[1-2] The cause of MIS-C is still incompletely understood, but it is thought to result from an abnormal immune response to COVID-19 infection. Endothelial dysfunction and cytokine storm have been mechanisms proposed, that result in end-organ injury.[3]

There is scarce local data on MIS-C. There were 16 MIS-C cases in an interim report of the SALVACION registry, five in one case series, and one newborn (MIS-N) in one case report.[4-6]

There is a need to describe the epidemiology, clinical and diagnostic findings, treatment and outcome of local cases for this important and serious post-COVID-19 complication seen in children.

The purpose of this study is to identify demographic data, co-morbidities, clinical manifestations, laboratory results, 2D-echocardiography (2-DE) findings, acute co-illnesses and complications, treatment and outcome of children, 18 years and younger, diagnosed to have MIS-C, seen in two, private, urban, tertiary hospitals, who were referred to a single pediatric infectious disease physician.

MATERIALS AND METHODS

This is a retrospective, descriptive study of MIS-C cases that were seen between July 2020 to January 2023. Each consecutive inpatient admission or referral of a patient 18 year old and below, with a discharge diagnosis of MIS-C was included in this study. Demographic, epidemiologic, clinical, and physical examination findings; results of laboratory, 2-DE, and radiologic tests; co-illnesses and complications; and therapeutic and outcome data relevant to the MIS-C diagnosis, were entered in a case report form for each patient by the author. The inclusion criteria for MIS-C utilized the 2020 U.S. C.D.C. definition, as follows:[7]

1. An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multi-system (=/>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
2. No alternative plausible diagnoses; AND
3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to onset of symptoms.

Excluded were patients diagnosed with Kawasaki disease with no laboratory or epidemiologic exposure to anyone with COVID-19 in the four weeks prior to illness onset.

This study was approved by each hospital's Institutional Review Board. As all the cases were obtained from the author's personal files in a password-protected, personal computer, no medical records were accessed from the hospitals' medical records department.

RESULTS

Table 1. Demographics & co-morbidities of patients with MIS-C from July 2020 to January 2023 (n=36)

Age	**Years**
Mean	6.4
Median	6
Range	NB[a] to 15
Sex	**n (%)**
Male	23 (64%)
Female	13 (36%)
Comorbidity	**n (%)**
Obese/overweight	3 (8%)
Tuberculosis[b]	2 (6%)
AML[c] on chemotherapy	1 (3%)
HIV infection with severe wasting	1 (3%)
Hemophagocytic lymphohistiocytosis	1 (3%)
Hypothyroidism	1 (3%)

[a]Newborn; [b]Disseminated and pulmonary; [c]Acute myelogenous leukemia

The mean age was 6.4 years; 64% were males. There were three patients who were <4 months of age. The top co-morbidity before the hospital admission was obesity (8%).

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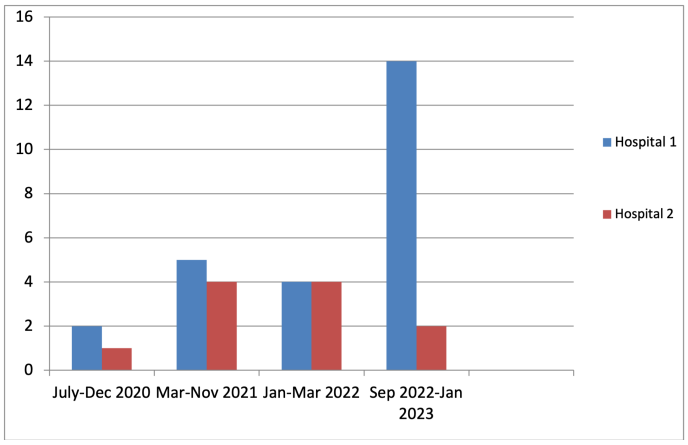

Figure 1: MIS-C cases during different time periods, July 2020 to January 2023 (n=36)

There were four surges in cases between July 2020 to January 2023, with the highest one between September 2022 to January 2023.

Table 2: Signs and symptoms of MIS-C cases, July 2020 to January 2023 (n=36)

Clinical finding	n (%)
Fever	35 (97%)
Vomiting	19 (53%)
Cough	17 (47%)
Abdominal pain	17 (47%)
Rash	15 (42%)
Diarrhea	12 (33%)
Conjunctivitis	12 (33%)
Extremity redness	6 (17%)
Mouth changes	5 (14%)
Difficulty breathing	4 (11%)
Cervical lymphadenitis	2 (6%)

All but one had fever (the only afebrile case was a newborn), while about half of cases had vomiting, cough, abdominal pain, and a rash.

Table 3: Complete blood count and inflammatory parameters of MIS-C cases, July 2020 to January 2023 (n=36)

Laboratory parameter	Result
WBC, lowest value, mean	6,700/mm^3
Hematocrit, lowest value, mean	0.33
Proportion with platelet count <150,000/mm^3	39%
CRP, highest value, mean	71 mg/l
D-dimer, highest value, mean	2,172 ng/ml
Ferritin, highest value, mean	2,246 ug/l
LDH, highest value, mean	532 IU/l
Procalcitonin, highest value, mean	1.6 ng/ml
SGPT, highest value, mean (n=17)	85 U/l

The mean lowest WBC count was within the normal range, while thrombocytopenia was seen in 39% of patients. The inflammatory markers (CRP, D-dimer and ferritin) were generally elevated. The highest recorded value of the inflammatory markers for each patient was recorded, and the mean for these highest values was taken and noted to be elevated. Procalcitonin was elevated in 8 out of 9 patients, or 89%, even as none of the patients were documented to be bacteremic.

Table 4: Proportion of cardiac markers elevated, and highest level, MIS-C cases, July 2020 to January 2023 (n=36)

Cardiac marker	Result
Pro-BNP	**n = 28**
Elevated	22 (79%)
Highest level, mean	2,507 pg/ml
Troponin-I	**n = 21**
Elevated	8 (38%)
Highest level, mean	0.11 ng/ml
CPK-MB	**n = 14**
Elevated	3 (21%)
Highest level	17.9 ng/ml; 52.7 U/L

The pro-BNP was the cardiac marker that was most often elevated among those tested. The unit of measurement of CPK-MB was different for the two hospitals. The mean CPK-MB of 17.9 ng/ml in one hospital was high, as the figure was raised by two outlier measurements of 110 ng/ml and 23 ng/ml from two patients who had severe MIS-C illness, while the rest ranged from 0.4 to 4.5 ng/ml.

Table 5: 2-D echocardiography findings, MIS-C cases, July 2020 to January 2023 (n=36)

Finding	n (%)
Pericardial effusion	19 (50%)
Coronary artery dilatation/aneurysm	14 (39%)
Mitral regurgitation	13 (36%)
Peri-vascular brightness	9 (25%)
Tricuspid regurgitation	6 (17%)
Decreased ejection fraction	4 (11%)
Dilated left ventricle	1 (3%)

The 2-DEs were read by five pediatric cardiologists in the two hospitals. Pericardial effusion (50%), coronary artery ectasia or aneurysm (39%)

and mitral regurgitation (36%) were most commonly seen. A normal 2-DE result was seen in 8 (22%).

Table 6: Acute co-illnesses and complications during the admission (n=36)

Finding	n (%)
Pneumonia	11 (31%)
Myocarditis	10 (28%)
Hypotension	5 (14%)
ARDS	3 (8%)
Dengue fever	2 (6%)
New-onset severe reactive airway disease	2 (6%)
Ventricular arrhythmia	2 (6%)
Pleural effusion	2 (6%)
Rhinovirus PCR-positive bronchiolitis	1 (3%)
Secondary sepsis	0

Myocarditis was documented in 28%; hypotension was noted in 14%, with 8% requiring vasopressors. Acute respiratory distress syndrome (ARDS) occurred in 8%.

Table 7: Treatment and supportive measures given to MIS-C cases, July 2020 to January 2023 (n=36)

Corticosteroid	**89%**
Methylprednisolone 2 mg/kg/day	61%
Methylprednisolone 5 mg/kg/day	3%
Methylprednisolone 10 mg/kg/day	11%
Methylprednisolone 30 mg/kg/day	8%
Dexamethasone	6%
IVIg	**83%**
No IVIg given for:	
Mild disease, 2-DE normal	8%
Refused (DAMA, doctor's choice)	6%
No funds	3%
Others	
Antibacterials	31%
Epinephrine drip	8%
Enoxaparin	8%
Tocilizumab	8%
Mechanical ventilation	6%
Anti-tuberculosis medications	6%
Dobutamine drip	6%
Casirivimab-indevimab monoclonal antibody	3%

Corticosteroids (89%) and IVIG (83%) were most commonly used. All, but one, went home on oral prednisone over 2-4 weeks.

Table 8: Outcome of MIS-C cases, July 2020 to January 2023 (n=36)

Outcome	n (%)
Length of stay ≤5 days	31 (86%)
Discharged on prednisone	35 (97%)
Discharged on digoxin (lanoxin)	2 (6%)
Died	2 (6%)
HIV, severe wasting, shock, ARDS, MODS	
AML, on chemotherapy, died in another hospital after transfer from study hospital	
Home against advice, outcome unknown	1 (3%)

The hospital course was five days, or less, in 86%. The mortality rate was 6%, both occurring in severely immunocompromised individuals.

DISCUSSION

The total number of MIS-C cases seen by one infectious disease physician in the two hospitals was 36. This number is 47% of all the COVID-related cases referred to the author in the same time period (data not shown). In the first hospital, there were 25 cases, while in the second, there were 11. A Swedish population-based study determined a MIS-C rate of 6.8 Swedish children per 100,000-person-years.[8] The reported<20-year-old populations for the two cities in which the study hospitals are located are 181,038 and 39,962.[9-10] If the Swedish MIS-C rate is applied to the two local populations, the expected number of MIS-C cases over three years would be 36.9 children in the first city and 8.2 children in the second, or a total of 45 cases over three years. As there are three other hospitals in the two cities, and other infectious disease doctors in the two hospitals, the number of cases seen in this report (36) is not far from the 45 cases projected, extrapolating from the MIS-C rate reported in Sweden.

There were three cases seen in 2020, when the original Wuhan strain was in circulation; the number of cases increased to nine in 2021, when the alpha, beta and delta strains were seen. There were eight cases in early 2022, when the omicron strain entered the population, and the number spiked sharply to sixteen between September 2022 to January 2023, following the increase of circulating omicron BA.4

and BA.5 cases. Possible reasons for the last spike were the known high transmissibility of the omicron BA.4 and BA.5 sub-variants and the return of children back into schools in June 2022 for face-to-face education after a prolonged lockdown.[11]

The mean age of MIS-C cases was 6.4 years, and the median was 6 years. The mean age among patients (n=12) seen before the COVID-19 vaccine became available for children 5-12 years in October of 2021 was 5.3 years. In the U.S. and Europe, before childhood vaccination became available, the mean age for children who developed MIS-C was 8-9 years.[12-15] In a meta-analysis involving 2,275 MIS-C cases, the mean age was 9 years.[16] MIS-C has been compared to Kawasaki disease, due to the coronary artery involvement in both illnesses;[16-19]the mean age of MIS-C cases (6.4 years) in the present study is higher than the mean age of children with Kawasaki disease (2.8 years) in a previous report from one of the hospitals in the present study.[20]

A few unusual MIS-C occurrences were encountered. Two male siblings in one household developed MIS-C separately, with a one-month interval between each other, even as both acquired the acute COVID-19 illness at the same time. One six-year old male had MIS-C after having had Kawasaki disease four years before. One adolescent had two MIS-C events within a year. This patient was initially diagnosed with hemophagocytic lymphohistiocytosis (HLH), after which, a first MIS-C episode occurred. Shortly after recovering, disseminated tuberculosis (TB) (lymph node, lung, bone marrow) was diagnosed and treated for. Many months later, this patient was diagnosed with acute myelogenous leukemia (AML). The second MIS-C episode occurred after the AML diagnosis, and while undergoing chemotherapy. There have been reports that there may be genetic factors to explain the hyperinflammatory state seen in patients with MIS-C.[21-23]

There were more males (64%) with MIS-C in this study. In the U.S., among 4,107 MIS-C cases, 59.5% were male.[1]

There were 15 COVID-vaccine-eligible children who had MIS-C after COVID-19 vaccination program was started in November 2021. Of these, seven (47%) had not been vaccinated at the time of illness, while two (13%) had received only one vaccine dose. Six (40%) had received two COVID-19 vaccine doses before their MIS-C illness; one of the six had been treated for Kawasaki disease four years before the MIS-C illness occurred. The COMIRNATY monovalent COVID-19 vaccine, the same vaccine that these children received, has been reported to have a vaccine efficacy rate of 91% and 94% in preventing MIS-C.[24-25]

The top co-morbidity before the MIS-C admission was obesity (8%). One had AML during a second admission (this patient had two MIS-C episodes in 12 months), and one severely wasted patient had an undiagnosed human immunodeficiency virus (HIV) infection. Obesity, male sex and asthma are known to be risk factors for MIS-C.[4, 8, 26]

Fever was seen in all but one (97%), with the only afebrile case being a newborn. One 2-year old child presented with prolonged fever of 16 days and a generalized rash, and was managed at another hospital, before being transferred to the study hospital. In a local report, incomplete Kawasaki disease was reported to be a cause of fever of unknown origin in five cases; MIS-C shares many common findings with Kawasaki disease.[27] Otherwise, the present study found the tetrad of symptoms of vomiting, cough, abdominal pain and rash, to be seen in about half (42-53%) of the cases, while diarrhea and conjunctivitis were seen in one-third. Locally, in a report of 16 MIS-C cases, the most common symptoms were fever (100%), decreased appetite (75%), vomiting (56%), diarrhea (50%), abdominal pain (50%) and rash (44%), which are very similar to the present report.[4] In a meta-analysis which included 2,197 children with MIS-C, the most common symptoms were fever (100%), gastrointestinal symptoms (82%), abdominal pain (68%), erythema/rash (59%), non-purulent conjunctivitis (54%) and cough (41%).[16] In another meta-analysis that included 4,475 children with MIS-C, the most common symptoms were fever (91%),

not-specified gastrointestinal symptoms (52%), rash (50%), abdominal pain (49%), conjunctivitis (47%), vomiting (44%), respiratory symptoms (42%) and diarrhea (40%).[18] Compared to children with Kawasaki disease in a report from one of the hospitals in this study, the other classic findings in Kawasaki disease (rash, conjunctival injection, cervical lymphadenopathy, mouth and extremity changes) were more common among the Kawasaki disease patients, in comparison to those with MIS-C, but abdominal symptoms were more common among MIS-C cases (47-53%, vs. 34%).[20]

Two cases presented with very prominent abdominal pain, for which referral to surgery was necessary to rule out a surgical abdomen: one 5-year-old with vomiting, diarrhea and abdominal pain, was found to have small bowel wall thickening, most prominent at the ileum, with gall bladder wall thickening, splenomegaly, and a minimal pelvic effusion, on abdominal ultrasonography; the second case with marked abdominal pain was a COVID-19-vaccinated, 7-year-old male, who was found to have myocarditis and a moderate pericardial effusion, who required an epinephrine drip and mechanical ventilation. He recovered, and the myocarditis and pericarditis were thought to be the likely causes of the severe epigastric pain upon admission. Collectively, gastrointestinal symptoms were the predominant manifestation in MIS-C, after fever. Severe abdominal pain during MIS-C, to the point of surgical intervention, has been well-reported; the most common associated conditions found have been mesenteric lymphadenitis and ascites.[16] In a meta-analysis of 72 children with MIS-C who had acute abdomen, intra-operative findings showed mesenteric adenitis (32%),terminal ileitis/ileocolitis (26%), ascites (11%), and paralytic ileus (4%); laparotomy was done in 49% of acute abdomen cases, and was proven unnecessary in 51%.[28] Appendicitis and obstructive ileus were seen in 24%.[28]

One 17-day old neonate was readmitted after birth, for fever and vomiting, and was treated for MIS-C with myocarditis; the mother had COVID-19 illness at 34 weeks of gestation. This case was reported earlier.[6] One afebrile, 10-hour old, term neonate developed tachypnea, with radiography showing findings seen in transient tachypnea of the newborn. As the mother had COVID-19 illness at 34 weeks of gestation, the newborn was worked up, and showed elevated inflammatory parameters, and a 2-DE that revealed coronary artery dilatation and minimal pericardial effusion. One 3-month-old had MIS-C and PCAP-C, and responded well to treatment. In a systematic review of infants <6 months old who had MIS-C, only 18% of the neonates presented with fever, while cardiovascular dysfunction and respiratory symptoms were the predominant manifestations.[28] Among 84 infants <12 months (median age of 7.7 months) with MIS-C reported to the CDC's MIS-C national surveillance system, pneumonia (21%), hypotension (21%), coronary artery dilatation (14%), shock (13%), and myocarditis (6%) were most often reported. The authors concluded that infants appear to have a milder course of MIS-C than older children, with illness resolution after discharge.[19]

The criteria for Kawasaki disease, other than fever, were seen in only a minority of MIS-C cases (rash in 42%, conjunctivitis in 33%, extremity redness in 17%, mouth changes in 14% and cervical lymphadenitis in 6%). Difficulty of breathing was seen in 11% of MIS-C cases, which is an infrequent finding in Kawasaki disease.[20] In a meta-analysis of 4,475 MIS-C patients, the MIS-C cases were compared to those with Kawasaki disease in nine studies.[18] Children with MIS-C were less likely to develop conjunctivitis (OR 0.27), cervical adenopathy (OR 0.21) and rash (OR 0.44), in comparison with Kawasaki disease patients; while MIS-C cases were more likely to have gastrointestinal symptoms (OR 11.4), mitral regurgitation (OR 6.6), pericardial effusion (OR 1.74) and pleural effusion (OR 19.2).[18]

For the laboratory work-up, the white blood cell counts (WBC) were generally lower than those seen in cases of Kawasaki disease, with a mean of 6,700/mm^3. Platelet counts were less than 150,000/mm^3 in 39% of cases, which has been

reported to be an adverse prognosticator in MIS-C.[30] In the CDC's updated (December 2022) standardized case definition of MIS-C, a platelet count of less than 150,000/mm^3, and an absolute lymphocyte count of less than 1,000/mm^3, are the only abnormal hematologic markers that can be used as criteria for evidence of hematologic dysfunction.[31] The inflammatory markers, C-reactive protein (CRP), D-dimer and ferritin, were generally elevated; all of these markers were included in the 2020 CDC case definition for MIS-C, but in the updated CDC (December 2022) definition, only a CRP of >3 mg/dl is required to satisfy the laboratory evidence of inflammation.[7] Procalcitonin was elevated in 89% when it was requested, with none of these patients having a growth from a blood culture; procalcitonin has also been reported to be elevated in MIS-C.[4] In a meta-analysis of 787 MIS-C patients, MIS-C cases, when compared to non-severe COVID-19 cases, had lower absolute lymphocyte counts and higher CRP and D-dimer levels; severe MIS-C patients had higher WBC, absolute neutrophil count (ANC), CRP, D-dimer and ferritin levels, when compared with patients with non-severe MIS-C.[32]

Among the cardiac markers, the pro-BNP was the most often elevated (79%), while troponin-I and CPK-MB were elevated in 38% and 21%, respectively. In the latest December 2022 case definition of MIS-C, an elevated troponin is the only laboratory test that can be used as evidence of cardiac involvement (or a 2-DE showing coronary artery dilatation or aneurysm, or a left ventricular ejection fraction of <55%), which is one of five systems that have to be involved to make the diagnosis; the others are hypotension/shock, dermatologic manifestation(s), gastrointestinal symptom(s) and hematologic abnormalities.[31] In a meta-analysis involving 1,613 MIS-C cases, the cardiac marker that showed a significant difference between MIS-C patients and non-severe COVID-19 patients, and between severe MIS-C and non-severe MIS-C, was BNP.[34]

Pericardial effusion (50%), coronary artery dilatation or aneurysms (39%) and mitral regurgitation (36%) were the most common 2-DE findings. Most effusions were minimal, with only one case being moderate. This latter case was under consideration for pericardial fluid drainage during the hospital stay, but the effusion decreased with medical treatment, using a higher corticosteroid dose, fluid restriction and diuresis. A decreased ejection fraction was seen in four patients (11%); these cases were managed with vasopressors, while two were given oral digoxin (lanoxin). In a local report, the top 2-DE findings were pericardial effusion (60%), myocardial dysfunction (40%) and coronary arteritis (20%).[4] These findings are similar to those reported in the literature, with coronary artery abnormalities reported from 8% to 50%.[34]

Among acute co-illnesses seen during the admission for MIS-C, two (6%) had concomitant dengue fever. One COVID-unvaccinated, 15-year old had melena, transient hypotension and dengue shock syndrome, and MIS-C at the same time. He did not have evidence of myocarditis during the illness course, but during recovery, a 2nd degree atrio-ventricular heart block was detected, which resolved after three days. A 10-year old COVID-19-vaccinated patient had dengue with warning signs and MIS-C. He was dengue NS-1/IgM/IgG-positive, with a lowest WBC of 2,000/mm^3,lowest platelet count recorded of 40,000/mm^3, SGPT of 210 U/l and SGOT of 500 U/l; he had pericardial effusion and an ejection fraction of 55% on 2-DE. He recovered with standard treatment. There were two other MIS-C cases that tested dengue IgM-positive, but these were assessed to be false-positive results. One MIS-C case was admitted with a bronchiolitis picture, who tested positive for rhinovirus by PCR of nasal swab.

Among complications during the hospital admission, pneumonia was the most common (31%), but these were mostly mild to moderate in severity. Only two patients were mechanically ventilated, one due to mild ARDS, myocarditis and a moderate pericardial effusion; and the other, due to severe anemia, ARDS, cardiogenic and respiratory failure, in a severely wasted, HIV-positive adolescent. The cases with pneumonia were treated with 2nd or 3rd generation cephalosporins, and/or azithromycin.

One case who had prominent abdominal pain and thickened small intestinal walls by ultrasonography, was treated with piperacillin-tazobactam. Otherwise, those with pneumonia were the only ones who received antimicrobials. Two cases (6%) presented with new-onset severe reactive airway disease, and were managed accordingly. Hypotension was seen in five cases (14%) for whom volume and intravenous vasopressors (8%) were given; two (6%) received oral digoxin (lanoxin), due to a decreased left ventricular ejection fraction. No patient developed a secondary healthcare-associated infection.

Treatment for MIS-C was mainly with intravenous (IV) corticosteroids (89%) in the acute phase, and intravenous immunoglobulin(IVIG) (83%). With defervescence, with or without improvement in inflammatory markers, the corticosteroid was stepped down to oral form.

One patient was transferred from outside of Metro Manila; he had received IVIG at the provincial hospital, but the fever recurred nine days after the IVIG was given. This patient was not given a corticosteroid during the first hospitalization, nor upon discharge. When he was admitted to the study institution, he received an IV corticosteroid, and promptly defervesced. Early in the course of the pandemic, when the appropriate corticosteroid doses and duration were not yet well-defined in MIS-C management protocols, two patients in the present study had recurrence of fever after the IV corticosteroid was abruptly stopped after 2-3 days; restarting the corticosteroid, and sending patients home on an oral corticosteroid over 2-4 weeks allowed a continued resolution of the illness, and non-recurrence of fever. In a local report, IVIG was used in 94%,and corticosteroids in 75%, of MIS-C cases.[4]

Hypotension was seen in 14%, for which volume infusion and vasoactive drugs(epinephrine, dobutamine, and dopamine) were used. A decreased ejection fraction was detected by 2-DE in 11%. In a French/Swiss MIS-C study of 35 children, cardiogenic shock with collapse was seen in 80%; left ventricular ejection fraction was found to be 30-50% at baseline in 72%, and <30% in 28%.[26] In the same study, the median delay between the first clinical symptom and heart failure symptoms was six days; 62% were mechanically ventilated, and upon PICU admission, 80% were in shock and needed vasopressors.[26] In a meta-analysis of MIS-C cases, 60% were reported to be hypotensive.[16] Fortunately, we did not see the above rates of cardio-respiratory decompensation in the present report.

Antibacterial(s) (31%) was/were only given for those with evidence of pneumonia, clinically or radiographically, and in one case who had evidence of ileitis. Mechanical ventilation, vasopressors, enoxaparin and tocilizumab were used in 8%, each. Mechanical ventilation was done in two (6%) patients who developed ARDS. Enoxaparin was used, in consultation with the hematology service, when intravascular thrombosis was deemed a risk. Tocilizumab was used in clinically ill patients whose serum interleukin-6 (IL-6) levels were elevated, for which a cytokine storm was suspected, as reported elsewhere.[35]

Unlike in Kawasaki disease, acetyl salicylic (ASA) was not routinely used, because of a concern for upper gastrointestinal bleeding, if corticosteroid and the former were used together; nevertheless, most patients were discharged on low-dose (3-5 mg/kg/dose once daily) ASA, together with an oral corticosteroid. There were no thromboembolic events seen in this report. In a study to evaluate the incidence and risk factors of thrombosis in hospitalized COVID-19 (n=715) and MIS-C (n=138) patients, 6.5% of the MIS-C cases had thrombosis; MIS-C patients aged 12 years and older had the highest thrombosis rate at 19%.[36] Seventy-one percent of thromboembolic events not present on admission, occurred in spite of prophylaxis. Multivariate analysis showed that age of 12 years or older, cancer, presence of a central venous catheter, and MIS-C were significantly associated with thrombosis, and mortality increased from 2.3% for all COVID-19 patients, to 28% for those with thromboembolic events.[36]

The length of stay was generally short, with 86% going home in five days, or less, as most responded well to the usual treatment of IVIG and corticosteroid. This combination is the current standard of treatment for MIS-C, and has shown better outcomes than IVIG alone.[37]

There were two mortalities (6%). One was an adolescent who had received one COVID-19 vaccine dose four weeks prior to the MIS-C illness. The patient had a 7-day fever course and was hypotensive, with premature ventricular contractions in bigeminy, on day 7 of illness upon presenting at the emergency room, necessitating vasopressors, and subsequently, mechanical ventilation. Severe myocarditis progressed to cardiogenic shock and cardio-respiratory arrest. An HIV antibody test was positive, taken a day before demise; this patient was not previously known to be ill with HIV. A second patient was an adolescent who was under treatment for HLH, which was complicated by MIS-C. After treatment for MIS-C, the patient developed disseminated TB within a month of the MIS-C illness, with draining, TB-GeneXpert-positive, supraclavicular lymphadenitis; lung and pleural disease, hepatosplenomegaly, and a bone marrow aspirate which showed granulomas. The course was further complicated by a diagnosis of AML, and while on chemotherapy, a second MIS-C illness occurred a year after the first one. The patient transferred to another hospital due to financial reasons, where death ensued during the course of the second MIS-C episode. Elsewhere, MIS-C mortality rates have been from 1.1 - 4%.[38-39] In a large, population-based U.S. report of 4,107 cases, the authors found that MIS-C outcomes worsened as the number of organ systems affected increased; the inpatient death rate was <1% if 0-2 systems were involved, but increased to 5.8% when 6-8 organ systems were affected.[1] In a local report, the MIS-C mortality was 19%.[4]

This report is limited by the non-inclusion of other MIS-C cases seen by other infectious disease doctors in the two hospitals. The generalizability of the findings from these two hospitals is unclear, because pediatric infectious disease physicians in a government hospital in the same city as one of the study hospitals here, as well as in two other large government hospitals where COVID cases are seen, do not appear to have encountered as many MIS-C cases in the last three years, as has been seen in this report. (personal communication)

CONCLUSION

MIS-C cases had a median age of 6 years, presented with fever in 97%, while one-half had abdominal pain, vomiting, diarrhea and/or rash. CRP, D-dimer, ferritin, LDH and procalcitonin were generally elevated, and thrombocytopenia was seen in 39%. The most common 2-DE abnormalities were pericardial effusion (50%), coronary artery dilatation or aneurysm (39%) and mitral regurgitation (36%). The main complications were pneumonia (31%), myocarditis (28%), hypotension (14%) and ARDS (8%); 6% were mechanically ventilated. Treatment was with corticosteroids (89%), IVIG (84%), fluids and vasopressors (8%), when needed. Most (94%) recovered, with appropriate treatment, and the hospital stay was five days, or less, in 86%.The two mortalities were in an adolescent with previously undiagnosed HIV infection who had severe wasting; and an adolescent undergoing chemotherapy for AML, who was also being treated for disseminated TB.

RECOMMENDATION

There is a need to create a greater awareness of MIS-C as a post-COVID complication in children. MIS-C presents like a common everyday illness, with fever in almost all, and only half will have gastroenteritis-like symptoms and a non-specific rash, which are childhood disease manifestations that many might not place much importance on. In such illnesses, it is important for the health care worker to determine if the patient, or anyone else in the household, has had a COVID-19 illness, whether documented or not, in the preceding 60 days. If such is present, a proper evaluation might be pursued because, similar to Kawasaki disease,[40-41] MIS-C may have the potential to become an important cause of acquired heart disease.

CONFLICT OF INTEREST

None declared.

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