

# Multi-system inflammatory syndrome in children during the coronavirus disease 2019 in Saudi Arabia

## Clinical perspective from a case series

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### Abstract

Most of the reports about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children reported mild-to-moderate disease manifestations. However, recent reports explored a rare pediatric multisystem syndrome possibly associated with SARS-CoV-2 infection termed multisystem inflammatory syndrome in children (MIS-C).

The study prospectively enrolled 5 patients with clinical and laboratory evidence of MIS-C associated with SARS-CoV-2 infection. They were admitted to the pediatric intensive care unit (PICU). Their clinical presentation, laboratory, and outcome were described.

All patients shared similar clinical presentations such as persistent documented fever for more than 3 days, respiratory symptoms, gastrointestinal involvement, and increased inflammatory markers (CRP, ESR, and ferritin). Three patients had concurrent positive coronavirus disease 2019 (COVID-19) infection, and the other 2 patients had contact with suspected COVID-19 positive patients. They were all managed in the PICU and received intravenous immunoglobulin, systemic steroid, and hydroxychloroquine. The hospital stays ranged between 3 and 21 days. One patient died due to severe multiorgan failures and shock, and the other 4 patients were discharged with good conditions.

Pediatric patients with SARS-CoV-2 are at risk for MIS-C. MIS-C has a spectrum of clinical and laboratory presentations, and the clinicians need to have a high index of suspicion for the diagnosis and should initiate its early treatment to avoid unfavorable outcomes. Long-term follow-up studies will be required to explore any sequelae of MIS-C, precisely the cardiovascular complications.

**Abbreviations:** ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CT = computed tomography, IVIG = intravenous immunoglobulin, MIS-C = multi-system inflammatory syndrome in children, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

**Keywords:** children, coronavirus disease 2019, multi-system inflammatory syndrome in children, PICU, severe acute respiratory syndrome coronavirus 2

## 1. Introduction

The Wuhan Municipal Health Commission in Wuhan City, Hubei province, China, reported a cluster of pneumonia cases of

unknown etiology in December 2019.<sup>[1,2]</sup> The causative organism was recognized later as a “2019 novel coronavirus” that has not been isolated previously. The virus was named severe acute

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Written consent was obtained from the patients' family and documented in their medical chart before the creation of this report.

The authors have no conflicts of interests to disclose.

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respiratory syndrome coronavirus 2 (SARS-CoV-2), as it is similar to the previous novel coronavirus that caused SARS (1). The World Health Organization named the disease caused by SARS-CoV-2 as coronavirus disease 19 (COVID-19).<sup>[3]</sup> Since then, most of the reports about SARS-CoV-2 in children reported mild-to-moderate disease manifestations.<sup>[3]</sup> However, recent reports explored a rare pediatric multisystem syndrome possibly associated with SARS-CoV-2 infection.<sup>[4–6]</sup>

In early May 2020, a novel hyperinflammatory syndrome was described in 8 healthy children in the United Kingdom who presented with multiorgan involvements, including fever, shock, and mucocutaneous involvement. This syndrome shares clinical features with toxic shock syndrome, Kawasaki disease, and Kawasaki disease shock syndrome.<sup>[7]</sup> Also, the New York City Department of Health described 15 pediatric cases with the same clinical features.<sup>[8]</sup> A week later, the Centers for Disease Control and Prevention published a case definition for this hyperinflammatory syndrome, termed multisystem inflammatory syndrome in children (MIS-C).<sup>[9]</sup>

Recently, around 200 pediatric patients with MIS-C were fully described, with the main involved systems being gastrointestinal, mucocutaneous, hematology, and cardiac; the mortality was less than 1%.<sup>[4,10]</sup> Here, we describe the clinical features, laboratory findings, and outcomes of 5 children with MIS-C who were admitted to the pediatric intensive care unit (PICU) at our hospital. To the best of the authors' knowledge, this is the first report of MIS-C cases from Saudi Arabia.

## 2. Material and methods

Between May 15, 2020, and July 25, 2020, 5 MIS-C patients were prospectively enrolled. For each patient, demographics, clinical, laboratory, management, health status at discharge and after discharge were presented. Association with COVID-19 was assessed by both history of exposure to confirmed cases and laboratory confirmation.

### 2.1. Diagnosis and laboratory testing

All patients underwent screening for SARS-CoV-2 infection using the reverse-transcriptase polymerase chain reaction (RT-PCR) test in a nasopharyngeal swab specimen. The diagnosis of MIS-C follows the CDC guidelines, which included severe illness necessitating hospitalization, fever  $\geq 38^{\circ}\text{C}$  lasting at least 24 hours, age between 0 to 21 years, 2 or more organ systems affected (e.g., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, and neurological), laboratory evidence of inflammation (1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, neutrophilia, lymphopenia, and low albumin), and evidence of SARS-CoV-2 infection (Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms).<sup>[9]</sup>

The diagnosis of MIS-C was made by a committee of pediatric subspecialty experts including rheumatologist, infectious disease specialist, and cardiologist after excluding alternative diagnoses such as sepsis, septic shock, and autoimmune diseases.

Patients who shared features of Kawasaki disease was labeled as MIS-C with Kawasaki phenotype. Pediatric cardiologist performed detailed echocardiography for all patients; the cardiac involvement was identified based on using vasopressors, presence of low ejection fraction of less than 55%, and evidence of

coronary dilation (maximum z score of the left anterior descending or right coronary artery of at least 2.5 z scores).<sup>[4]</sup> Acute kidney injury was defined when serum creatinine level exceeded the upper limit value for age. Blood samples were drawn for complete and differential blood counts, complete metabolic panel, inflammatory markers (CRP- ESR-procalcitonin), and blood cultures. Pediatric radiologist read the chest x-ray and CT-chest and documented the detailed reading in the medical records of the patients.

The treating physicians continued to follow the patients together with rheumatologists, hematologists, and cardiologists 3 to 4 weeks after discharge and 4 to 6 months later. In each visit, full clinical examination was performed, and inflammatory markers, complete blood count, and echocardiography were evaluated.

## 3. Results

### 3.1. Case 1

A 9-year-old Saudi female child who was fully immunized and had a negative past medical history presented with fever for 4 days and vomiting and diarrhea for 2 days. She had a history of contact with a family member who was suspected of being COVID-19-positive.

Upon arrival to the emergency room, her vitals revealed a temperature of  $38^{\circ}\text{C}$ , respiratory rate (RR) of 22 breaths/min, heart rate (HR) of 100 beats/min, and  $\text{SpO}_2$  97% on room air. She had moderate dehydration with the otherwise normal systemic examination. The initial laboratory work-up showed elevated C-reactive protein (CRP) level 90 mg/dL. The patient was admitted to the general pediatric ward and started on intravenous fluids and antipyretics. On the second day of admission, the patient suddenly developed severe respiratory distress and unexplained hypotension. Chest X-ray and computed tomography (CT)-chest showed bilateral opacities and diffused bilateral air consolidations with ground glass appearance, respectively. A complete blood count revealed marked lymphopenia and thrombocytopenia (Table 2). Echocardiography showed dilated coronary arteries and mild mitral regurgitation with normal cardiac function. The patient was transferred to PICU with a diagnosis of severe acute respiratory distress syndrome (ARDS) and suspected MIS-C. She was ventilated and started on inotropic support due to fluid-resistant hypotension. Despite receiving 2 doses of intravenous immunoglobulin (IVIG), pulse steroid, and high frequency ventilation, the patient died due to severe ARDS and likely MIS-C with multiorgan failures. Nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test was upon admission and reported negative. After respiratory deterioration, another SARS-CoV-2 PCR was sent and came back positive.

### 3.2. Case 2

A 12-year-old Saudi boy presented to the emergency room with a 1-week history of intermittent fever, sore throat, myalgia, anorexia, and progressive rash (Table 1 and Fig. 1).

He had high-grade intermittent fever that was relieved using antipyretics. He presented with sore throat, painful neck lymph nodes, generalized body ache, joint pain, and loss of appetite, vomiting, and poor oral intake with progressive weakness and lethargy as he was unable to walk properly. Progressive feet erythematous rash appeared first on the dorsum of hands and

**Table 1****Initial clinical characteristics of the patients.**

Clinical Features	Case 1	Case 2	Case 3	Case 4	Case 5
Age in yrs/sex	9/F	12/M	2/F	10/F	11/M
Presenting symptoms					
Fever	+	+	+	+	+
Diarrhea	+	+	+	–	+
Abdominal pain	+	+	+	+	+
Rash	–	+	–	+	+
Conjunctivitis	–	+	–	+	+
Lymphadenopathy	–	+	–	+	+
Altered mental status	+	–	–	–	+
Hypoxia	+	+	+	–	–
Hypotension	+	+	–	–	+
Mucous membrane involvement	–	+	–	+	+
Hepatomegaly	+	–	–	–	–
Respiratory failure	+	+	+	–	–
Underlying chronic disease	–	–	+ <sup>a</sup>	–	–
Known SARS-CoV-2 exposure	–	–	+	–	+
Nasopharyngeal SARS-CoV-2 PCR	Positive	Positive	Positive	Positive	Negative

<sup>a</sup>Chronic lung disease. +=Yes, –=No, F = female, M = male.

later involved the trunk, mostly on the back and buttocks. On clinical examination, he looked ill with moderate dehydration, generalized maculopapular blanching erythematous rash, bilateral conjunctivitis, tender cervical lymphadenopathy, cracked lips, and inflamed tonsils. Vital signs revealed temperature of 38.5°C, tachycardic of 165/min and hypotensive of 85/55 mm Hg, capillary refill time (CRT) of 2 sec, RR of 32/min, and SpO<sub>2</sub> 88% to 89% on room air. Other systemic examination was unremarkable.

His hematology workup showed leukopenia with elevated inflammatory markers (Table 2). ECG showed ischemic changes initially but was found normal when repeated at 12 hours. His ultrasound of the abdomen and chest X-ray were normal.

COVID-19 infection was confirmed and the patient was diagnosed as COVID-19 with MIS (Kawasaki disease-like features), he was managed with a single dose of IVIG 2gm/kg, dexamethasone, enoxaparin, IV antibiotics with a 5-day course of azithromycin and oseltamivir (Tamiflu). His condition improved gradually with improvement in inflammatory markers; D-Dimer and troponin also decreased to 854 and 8.5 pg/mL, respectively.

He was discharged home after 4 days but continued aspirin and oral corticosteroids with follow-up in pediatric and cardiology clinics. The patient was seen 4 weeks after discharge, and his laboratory workup and echocardiography were normal. Therefore, steroid and aspirin were stopped. The last follow-up was

**Table 2****Initial laboratory and chest X-ray data of the patients.**

Laboratory and imaging results	Reference range	Case 1	Case 2	Case 3	Case 4	Case 5
C-reactive protein	0.0–0.9 mg/dL	90	7.15	48	0.8	32
Erythrocyte sedimentation rate	0.0–15 mm/hr	25	51	75	10	110
Ferritin	13.7–78.8 ng/mL	> 3000	1004	490	190	>1500
Troponin	28–39 pg/mL	199	59	ND	ND	ND
D-dimer	0.0–500 pg/mL	700	1647	ND	ND	1733
White blood cell count	4.3–11.0 × 10 <sup>3</sup> /μL	3.7	4.46	5.6	4.17	8.4
Platelets	150–400 × 10 <sup>3</sup> /μL	45	224	275	162	125
Lymphocyte count	970–3960/μL	570	981	1700	730	450
Coronary Artery Dilatation		+	–	–	–	–
Mitral Regurgitation		+	–	–	–	+
Chest X-ray		ARDS	Normal	Bilateral Opacities	Normal	Normal
Initial sodium	136–145 mm/L	135	132	140	138	127
Alanine aminotransferase	10–35 U/L	114	12	22	13	18
Albumin	3.7–5.6 g/dL	2.3	3.5	3	3.2	2.6
Total Bilirubin	0.3–1.0 mg/dL	0.5	0.5	1	0.6	0.9
Lactic dehydrogenase	420–750 U/L	1037	336	1062	286	ND
International normalized ratio		2	1.46	0.98	1.13	1.6
Acute kidney injury		+	–	–	–	+
Procalcitonin	0.0–0.1 ng/mL	ND	0.5	ND	ND	10.9

+ = Yes, – = No, ARDS = acute respiratory distress syndrome, ND = not done.



**Figure 1.** Dermatological manifestations (Cases 2 and 4).

6 months after the initial presentation, and the patient was completely recovered.

### 3.3. Case 3

A two-year-old Saudi female child with known chronic lung disease on home oxygen (0.5L per minute) presented to the emergency room with fever and cough for 3 days. Her initial ER vitals showed temperature of 39°C, HR of 140 beats/min, RR of 52 breaths/min, and SpO<sub>2</sub> 95% with 5 L O<sub>2</sub> via face mask. Chest examination revealed decreased air entry bilateral with bilateral expiratory wheezes. Other systemic examination was normal. Initial laboratory work-up revealed high inflammatory markers and normal coagulation profiles. The patient was admitted as a case of pneumonia and suspected MIS-C due to COVID-19 and started on IV antibiotics and bronchodilators. However, she was later transferred to PICU due to severe distress and persistent hypoxia.

On the second day, her COVID-19 test was positive, and the patient underwent CT-chest, which revealed bilateral ground glass appearance. Infectious and Rheumatology teams recommended starting hydroxychloroquine, methylprednisolone, IVIG, and antiviral (favipiravir) treatments, given her rapid respiratory deterioration and hyperinflammatory manifestations (Table 2).

Echocardiography showed normal heart without evidence of pulmonary hypertension or coronary involvement. She required high flow nasal cannula for ten days and was then discharged to the general ward. She was discharged home after 3 weeks of hospital stay and was back to her baseline, continuous 0.5 liters per minute of oxygen to maintain saturation at 95% and azithromycin for 3 times per week. During the follow up visits (after 3 weeks), the patient was weaned successfully from the systemic steroid. She was also seen around 5 months after the admission and was doing well

without evidence of cardiac involvement, and all inflammatory markers returned to normal levels.

### 3.4. Case 4

A 10-year-old Saudi female with no chronic medical conditions presented with a 6-day history of fever, 2-day history of mouth ulcers, and diffuse erythematous skin rash (Fig. 1). Nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test was positive. She had no respiratory symptoms, and her initial vital signs were normal. The mother reported a history of bilateral conjunctivitis and decreased oral intake. Examination of the patient revealed left submandibular lymph nodes enlargement, diffuse erythematous skin rash, and otherwise normal systemic examination. Notable laboratory findings on admission revealed lymphopenia, normal ESR and CRP, and normal renal and liver functions (Table 2). An echocardiogram demonstrated normal function and the coronary artery. She was started on broad-spectrum antibiotics, a single dose of IVIG 2 g/kg for possible MIS-C Kawasaki phenotype, as well as aspirin. After 5 days of hospital stays, she was discharged home in good condition (absence of fever and skin rash). As per the cardiology plan, she continued aspirin (4 mg/kg/day) and to be seen in the clinic in 3 weeks.

At the first outpatient clinic (3 weeks after discharge), she underwent echocardiography which showed normal result. The aspirin was stopped. The last follow echocardiography was done 5 months after the initial presentation and was within normal.

### 3.5. Case 5

An 11-year-old Yemeni male with no chronic medical conditions presented with a 5-day history of fever; headache; a diffuse, erythematous rash; and a 1-day history of altered mental status. His lowest documented blood pressure within 24 hours of admission was 79/39 mmHg. Notable laboratory findings on admission included elevated inflammatory markers, lymphopenia, hyperferritinemia, hyponatremia, high procalcitonin, and acute kidney injury. Nasopharyngeal SARS-CoV-2-PCR testing was negative (Table 2). The patient had contact with his older brother, who had confirmed COVID-19 disease around 4 weeks before his current illness. Echocardiography demonstrated mild mitral regurgitation and diminished left ventricular (LV) function. He received multiple normal saline boluses at the emergency room, and his blood pressure responded partially. He was then admitted to PICU and started on vasoactive infusions.

Vancomycin and ceftriaxone were started empirically for concern of toxic shock syndrome and underlying bacterial septic shock. He was also treated with IVIG 2 g/kg, methylprednisolone 2 mg/kg/day, and low-dose aspirin. His fever resolved and weaned off vasoactive infusions by hospital day 5. He was transferred out of PICU on hospital day 8 and discharged home after 10 days with a normal examination and normalized laboratory results. Follow-up visits at the fourth week and fourth month revealed normal examination with normal inflammatory markers. The systemic steroid was weaned over 3 weeks, and aspirin was stopped after 4 weeks when echocardiography revealed a normal study.

## 4. Discussion

In this study, we describe 5 pediatric patients with clinical and laboratory evidence of MIS-C. Four patients out of 5 were

**Table 3**  
**Treatments and complications of the patients.**

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Complications					
Arrhythmias	—	—	—	—	—
Congestive Heart failure	+	—	—	—	—
Myocarditis	+	—	—	—	+
ARDS	+	—	+	—	—
Meningitis	—	—	—	—	—
Pulmonary hemorrhage	+	—	—	—	—
Outcome	Died	Home	Home	Home	Home
Treatments					
High flow nasal cannula	+	—	+	—	—
Mechanical ventilation	+	—	—	—	—
Vasopressors	+	+	+	—	+
Steroids	+	+	+	—	+
Number of IVIG doses (2 g/kg)	Single	Single	Two	Two	Two
Aspirin	—	+	—	+	+

+ = Yes, — = No, ARDS = acute respiratory distress syndrome, IVIG = intravenous immunoglobulin.

confirmed to have SARS-CoV-2 infection, and 1 patient with a positive history of exposure to confirmed SARS-CoV-2 subject. To the best of our knowledge, this is the first prospective report of MIS-C cases from Saudi Arabia. One patient died due to severe multiorgan failures and shock, while the remaining 4 patients were discharged home once their conditions were normal. All patients shared similar clinical presentations, including persistent documented fever for more than 3 days, respiratory symptoms, gastrointestinal involvement, and increased inflammatory markers (CRP, ESR, and ferritin). They were managed in the intensive care unit using IVIG, systemic steroid, and hydroxychloroquine. The hospital stays of the patients ranged between 3 and 21 days.

Constellation of multisystem involvements increased inflammatory markers, and concurrent SARS-CoV-2 infection (cases 2, 3, and 4) matched the criteria for MIS-C.<sup>[7,8,11]</sup> A wide variety of systems are involved in MIS-C, whose presentations include mild symptoms to severe symptoms with life-threatening complications such as hypotensive shock and ventricular dysfunction that can lead to heart failure and cardiogenic shock<sup>[4,10,12–16]</sup> (Table 3).

One of our cases (case 1) had a catastrophic course and died within 2 days of hospital admission because of severe hypotension that was resistant to inotropic support and fluids. In addition, the patient had severe ARDS that led to respiratory failure and arrest. Various similar reports have correlated deaths to ventricular dysfunction and likely inflammatory vasculopathy.<sup>[10,13–15]</sup> The patient was initially admitted to the general pediatric ward and then transferred to PICU when she developed increased work of breathing and sudden unexplained hypotension that later required inotropic support. Despite the absence of mucocutaneous manifestations, coronary dilatation and circulatory collapse supported the diagnosis of MIS-C. Based on a large cohort of patients who were diagnosed with MIS-C, the dermatological and mucocutaneous manifestations represent around half of the patients, and their prevalence decreased with age.<sup>[4,10]</sup> The initial SARS-CoV-2 nasopharyngeal swabs was negative while the repeated sample after deterioration was positive.

Cases 2, 3, and 4 met the clinical and laboratory criteria of MIS-C as per the published CDC case definition. Cases 2 and

5 had high D-Dimer and ferritin with Kawasaki disease phenotypes. So, they received IVIG, aspirin, dexamethasone, enoxaparin, and broad-spectrum antibiotics. Patients received extensive immunomodulatory therapy as they presented with life-threatening illnesses and had the risk of end-organ damage. Most of the published cases received a similar approach, especially for those patients who presented with hypotension and evidence of hyper inflammation.<sup>[4,5,10,12,14,15]</sup> On the other hand, case 4 shared certain clinical and epidemiological features of cases 2 and 5, but she only received the usual Kawasaki disease treatment, including IVIG and aspirin.

Due to the lack of well-controlled clinical trials to guide this condition's treatment, we follow the best available evidence of therapeutic strategies, which included supportive measures, broad-spectrum antibiotics to treat coexistent bacterial infections, steroids and IVIG. These regimens have been used in different health care facilities and were recommended in various published review articles.<sup>[4,5,10,15,16]</sup>

This study has few limitations. Drawing a generalizable conclusion from this study is difficult since it involved only 5 patients. In addition, the unavailability of SARS-CoV-2 serology is another limiting factor.

## 5. Conclusion

MIS-C has a spectrum of clinical and laboratory presentations, and the clinicians need to have a high index of suspicion for the diagnosis and should initiate its early treatment to avoid unfavorable outcomes. Further larger multicenter studies are required to clarify the different clinical and pathobiological phenotypes, risk factors for severe disease, and the response to different treatment strategies. Long-term follow-up studies are required to explore any sequelae of MIS-C, precisely the cardiovascular complications.

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