

## CASE PRESENTATION

# Cardiac Implication in Pediatric Multisystemic Inflammatory Syndrome – Three Case Reports and Review of the Literature

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### Abstract

Pediatric multisystem inflammatory syndrome (PMIS) appears to be a relatively rare complication of COVID-19 in children, occurring in less than 1% of children with confirmed SARS-CoV-2 infection. This condition can appear several weeks after the acute SARS-CoV-2 infection and is assumed to be a delayed immune response to coronavirus disease 2019 which can lead to a severe cardiovascular involvement.

In this retrospective study, our main purpose was to summarize the clinical data from three types of onsets in patients diagnosed with PMIS and report the experience to the known data in the literature. We put the emphasis on the course of management considering the three different presenting faces of the PMIS in children. All patients received IV immunoglobulin and antiplatelet treatment, 66% (2 of 3) necessitated inotropic support, corticosteroid therapy (methylprednisolone), anticoagulation, 33% (1 of 3) received Anakinra (antagonist of the interleukin 1 receptor). All of them received cardiac remodeling treatment with Lisinopril and Bisoprolol (associated or not with Spironolactone and Furosemide). Evolution was good with discharge in approximately 2 weeks from admission, without symptoms, and with cardiac improvement at echocardiography.

PMIS is an alarming situation that necessitate multidisciplinary approach and a complex management. The cardiac evaluation is crucial in risk evaluation and guidance for a correct approach of the disease.

**Keywords:** SARS-CoV-2, children, pediatric multisystem inflammatory syndrome, Kawasaki-disease.

### ABSTRACT

Sindromul inflamator multisistem pediatric (PMIS) pare a fi o complicație relativ rară a infecției COVID-19 la copii, care apare la mai puțin de 1% dintre copiii cu infecție confirmată cu SARS-CoV-2. Această afecțiune poate apărea la câteva săptămâni după infecția acută cu SARS-CoV-2 și se presupune că este un răspuns imun întârziat, care poate duce la o implicare cardiovasculară severă.

În acest studiu retrospectiv, scopul nostru principal a fost de a rezuma datele clinice din trei tipuri de debut la pacienții diagnosticați cu PMIS și de a raporta experiența la datele cunoscute în literatură. Punem accent pe management luând în considerare trei tipuri de prezentare diferită ale PMIS la copii. Toți pacienții au primit imunoglobulină IV și tratament antiagregant plachetar, 66% (2 din 3) au necesitat suport inotrop, terapie cu corticosteroizi (methylprednisolon), anticoagulare, 33% (1 din 3) au primit Anakinra (antagonist al receptorului interleukinei 1). Toți pacienții au primit tratament de remodelare cardiacă cu Lisinopril și Bisoprolol (asociat sau nu cu Spironolactonă și Furosemid). Evoluția a fost bună fiind externati în aproximativ 2 săptămâni de la internare, fără simptome, și cu ameliorare ecocardiografică.

PMIS este o situație alarmantă care necesită o abordare multidisciplinară și un management complex. Evaluarea cardiacă este crucială în evaluarea riscului și ghidare pentru o abordare corectă a bolii.

**Cuvinte cheie:** SARS-CoV-2, copii, sindrom inflamator multisistem pediatric, boala Kawasaki.

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## INTRODUCTION

The incidence of severe cases of SARS-CoV-2 infection in children is much lower compared to adults. However, the pediatric population may be severely affected by the onset of multisystemic inflammatory syndrome (MIS-C) which is related to immune dysregulation occurring after the acute infection has passed. Pediatric multisystemic inflammatory syndrome (PMIS) associated with SARS-CoV-2 infection has similar symptoms to septic shock or Kawasaki disease.

The onset of delayed symptoms relative to the acute SARS-CoV-2 infection is variable. In children who have a well-known history of documented or suspected COVID-19, the usual duration between acute infection and onset of MIS-C symptoms is two to six weeks. However, rare cases of MIS-C occurring in more than 6 weeks after the acute SARS-CoV-2 infection have been reported<sup>1</sup>.

The criteria used for case definition vary slightly between different health agencies. The case definitions of both the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) are summarized in Table 1. According to WHO, the onset of a case with post COVID-19

multisystem inflammatory syndrome in children require all 6 criteria, as following: patient age under 19, persistent fever for more than 3 days, clinical signs of multisystem involvement (at least two of the following) – rash or bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs, hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, evidence of coagulopathy, acute gastrointestinal symptoms, elevated markers of inflammation, no other obvious microbial cause of inflammation, evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 (Table 1)<sup>2</sup>.

Management strategies reported in the literature fall into 3 categories: (i) treatment of inflammation, (ii) treatment of shock, and (iii) thromboprophylaxis (Figure 1)<sup>3</sup>.

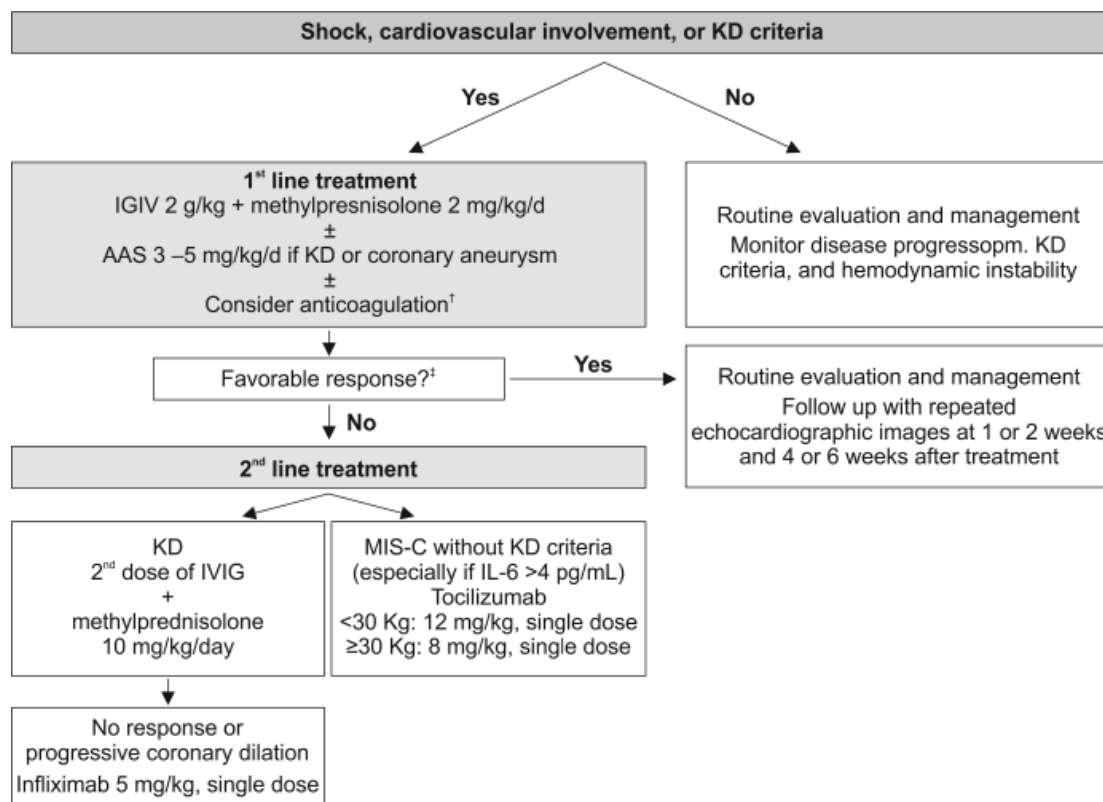
In Figure 2 we can see the treatment algorithm for children with multisystem inflammatory syndrome. Immunomodulatory treatment with high-dose intravenous immunoglobulin (IVIG) (2g/kg) in association with corticosteroids (Methylprednisolone 1 mg/kg/dose every 12 hours) is considered the first-line treatment. Current evidence supports the combination of

**Table 1. World Health Organization and Centers for Disease Control and Prevention definitions of the multisystem inflammatory syndrome in children. AEPC position paper<sup>2</sup>**

MIS-C definition of WHO (required: all six criteria)	MIS-C definition of CDC (required: all 4 criteria)
1. Children's age 0 – 19 years	1. Age <21 years
2. Fever for ≥3 days	2. Fever: documented ≥38.0°C ≥24 hours or reported subjective fever lasting ≥24 hours
3. Clinical signs of multisystem involvement (at least two of the following): <ul style="list-style-type: none"> <li>• Rash or bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)</li> <li>• Hypotension or shock</li> <li>• Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/ NT-proBNP).</li> <li>• Evidence of coagulopathy (prolonged prothrombin time or partial thromboplastin time, elevated D-dimer).</li> <li>• Acute gastrointestinal symptoms (diarrhoea, vomiting, or abdominal pain)</li> </ul>	3. Clinical presentation consistent with MIS-C, including all of the following: <ul style="list-style-type: none"> <li>• Evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement.</li> <li>• Cardiovascular, renal, neurologic, haematologic, gastrointestinal, or dermatologic system.</li> </ul>
4. Elevated markers of inflammation such as C-reactive protein, erythrocyte sedimentation rate, or procalcitonin.	4. Laboratory incidence of inflammation including, but no limited to any of the following: <ul style="list-style-type: none"> <li>• Elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, interleukin 6, neutrophils.</li> <li>• Reduced lymphocytes, low albumin.</li> </ul>
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/ streptococcal toxic shock syndromes.	5. No alternative plausible diagnoses.
6. Evidence of COVID-19 (RT-PCR, antigen test, or serolog positive), or likely contact with patients with COVID-19.	6. 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 4 weeks prior to the onset of symptoms.

Treatment of shock
<ul style="list-style-type: none"> <li>It is reasonable to anticipate that patients with MIS-C may be presenting with ventricular dysfunction. Therefore, consider 10 cc/kg fluid boluses, along with careful reassessments between each administration</li> <li>If there is persistent hypotension or evidence of poor perfusion despite fluid resuscitation consider inotropic support.</li> </ul>
Anti-inflammatory treatment
<ul style="list-style-type: none"> <li>Patients with mild symptoms, no significant ventricular dysfunction, and no coronary artery involvement may not require any immunomodulatory therapy but would warrant close monitoring.</li> <li>IVIg should be considered in patients with KD features and/or coronary artery involvement, but it could be considered in all MIS-C patients. Monitor patients closely when administering IVIG due to associated volume load in setting of potential ventricular dysfunction.</li> <li>Consider addition of steroids in patients with more severe presentations, including those requiring intensive care and/or presenting in shock, and in those who do not respond to IVIG.</li> <li>Biologic agents, such as Anakinra, could be considered as second-line agents.</li> </ul>
Thromboprophylaxis
<ul style="list-style-type: none"> <li>Refer to the 2017 American Heart Association guidelines for KD when considering antiplatelet and/or anticoagulation therapies in patients with KD features or coronary artery involvement.</li> <li>Low dose aspirin (3-5 mg/kg, maximum 81 mg daily) is reasonable to consider in patients with KD-like presentations and/or coronary artery involvement, with consideration of use in all MIS-C patients.</li> <li>Consider prophylactic dosing of anticoagulation, such as enoxaparin, in patients at higher baseline risk of venous thromboembolism (ex: patients ≥ 12 years old with altered mobility, obesity, known thrombophilia or history of thrombus, critical presentation, etc.), along with pneumatic sequential compression devices.</li> <li>Consider therapeutic dosing of anticoagulation in patients with the following: <ul style="list-style-type: none"> <li>Giant coronary aneurysms</li> <li>At least moderately diminished ventricular systolic function</li> <li>Thrombosis concerns.</li> </ul> </li> </ul>

**Figure 1.** Best practices for the management of MIS-C, based on literature review and IKDR survey responses<sup>3</sup>. IKDR, International Kawasaki Disease Registry; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children.



**Figure 2.** Treatment algorithm for children with multisystem inflammatory syndrome associated with COVID-19. †Prophylactic anticoagulation was considered if D-dimer was >1,000 ng/dL or progressively increasing; treatment was 1 mg/kg/d of low molecular weight heparin (Enoxaparin). When thrombosis was suspected or confirmed, the dose was increased to 1 mg/kg every 12 hours and adjusted with anti-Xa factor activity. ‡Favorable response was considered absence of fever for 48 hours, hemodynamic stability, and improvement of inflammatory parameters. AAS, acetylsalicylic acid; APTT, activated partial thromboplastin time; COVID-19, coronavirus disease; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MIS-C, pediatric inflammatory multisystem syndrome temporally associated with coronavirus disease; PCT, procalcitonin; pro-BNP, pro-brain natriuretic peptide; PT, prothrombin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2<sup>3</sup>.

Methylprednisolone with IVIG that work better than immunoglobulins given in monotherapy as first-line treatment. Resolution of fever and inflammatory markers can indicate the transition to oral steroids with gradually decreasing the doses in 2-6 weeks. Patients with toxic shock syndrome require inotropic support. The ideal inotrope remains to be decided by the clinician according to the clinical data, but there is a study that comments on the need to avoid Milrinone due to the counterproductive effect of peripheral vasodilation<sup>4</sup>.

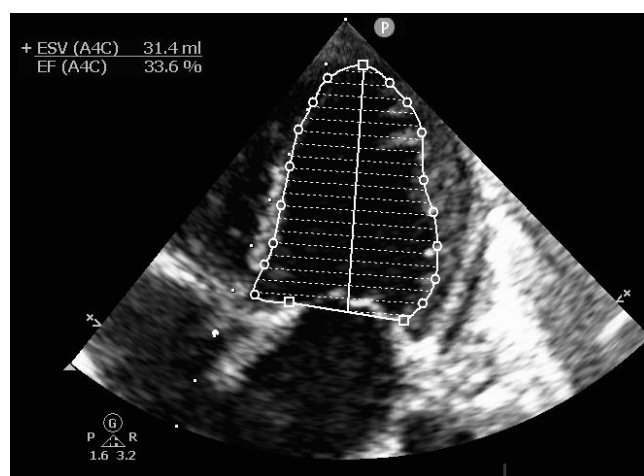
The need for antiplatelet therapy depends on the presence of the coronary artery aneurysms or dilatation (Kawasaki-like disease may be associated). The need for anticoagulation of these patients is also discussed, in prophylactic rather than therapeutic dose (Figure 1).

The second-line of treatment depends on whether or not Kawasaki-like disease exists. If the presentation is most consistent with KD and there is failure of first line treatment, a second dose of IVIG associated with Methylprednisolone could be considered or Infliximab (a tumor necrosis factor - alpha inhibitor) may be used. In case of an inflammatory syndrome that does not meet the criteria of KD, then Tocilizumab - a recombinant humanized anti-IL-6 receptor monoclonal antibody may be used<sup>5</sup>. In addition to the immunosuppressive therapy, opportunistic infections treatment may be considered.

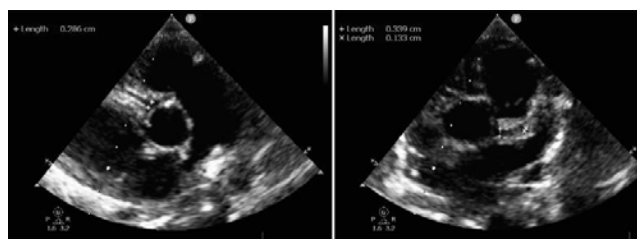
## CASE REPORTS

### Case 1

A 6-year-old patient, male, was admitted with suspicion of cardiogenic shock associated to multisystem



**Figure 3.** Echocardiography showing cardiac dysfunction – ejection fraction measurement by Simpson's method.



**Figure 4.** Coronary artery dilation and increased perivascular echogenicity in a child diagnosed with multisystem inflammatory syndrome.

inflammatory syndrome post COVID-19. The onset was with fever, headache and apathy. In the next days, he developed respiratory distress, hypotension associated with bradycardia and some of the diagnostic elements of Kawasaki disease were highlighted: febrile patient with generalized maculo-papulo-erythematous rash, bilateral conjunctival hyperemia and small latero-cervical lymphadenopathy. Laboratory findings showed positive inflammatory markers (leukocytosis = 25.310 per mm<sup>3</sup>, C-reactive protein = 137,92 mg / L, procalcitonin = 1,92 ng / mL, ferritin 605 mcg/L (6 times the upper reference number) and increased IL-6 (40,36 pg/mL), the SARS-CoV-2 PCR test was negative, but the IgG antibodies were positive.

Correlating the negative result of blood cultures and viral serology with transthoracic echocardiography which showed severe systolic dysfunction (LVEF = 35%) (Figure 3) with dilated coronary arteries (Figure 4), diastolic dysfunction and increased filling pressures, thin layer of pleuro-pericardial effusion accompanied by increased values of NTpro-BNP (48.793 pg/mL) and D-Dimers (7 mg/L) we were able to confirm Kawasaki-like heart disease in the context of PMIS.

Therapeutic strategy was completed with immunomodulator Anakinra (2 mg/kg/day), iv immunoglobulins (0.5 g/kg for 5 days), inotropic support with Adrenaline (0.1 micrograms/kg/min for 5 days) then Dopamine (3 micrograms/kg/min for one week), anticoagulation with Enoxaparin, and treatment of heart failure followed by favorable evolution (Lisinopril 1 mg/kg/day, Spironolactone 1 mg/kg/day and after the resolution of bradycardia we added Bisoprolol 0.08 mg/kg/day). The electrocardiogram showed sinus bradycardia (50-60 bpm) under two inotropic agents in the beginning and negative T waves in leads DI, aVL, VI-4. The treatment was adapted to his clinical condition. So, at 15 days after hospitalization in our clinic, respectively at about one month after the onset of symptoms, the patient was discharged with the indication to receive antiplatelet therapy (Aspirin 3 mg/kg/

day) and preventive treatment for cardiac remodeling (Lisinopril, Spironolactone, Furosemide and Bisoprolol 0.08 mg/kg/day after the resolution of bradycardia which happened in the 10<sup>th</sup> day of hospitalization) with follow-up evaluation according to current recommendations. At three months from discharge, the medication was gradually discontinued having normal clinical and echocardiographic parameters.

### Case 2

An 8-year 4-month-old male presented at the emergency department with fever for about 4 days (maximum body temperature = 38°C) and watery diarrhea associated with respiratory distress and altered general condition without having any past medical history. At the time of admission, the patient had polypnea and oxygen saturation showed a level of 88%, increasing to 98% with 3L/min oxygen via simple face mask. Laboratory tests revealed mild thrombocytopenia (141.000/uL), mild neutrophilia (92.40%), without leukocytosis (13.890/mm<sup>3</sup>) severe inflammatory syndrome (C-reactive protein = 231.68 mg / L, procalcitonin = 5.06 ng / mL, ferritin = 1518 ng / mL, IL-6 = 350.60 pg/mL) and high levels of NT-proBNP = 15,802 pg / mL. Viral serology detects high levels of anti-SARS-CoV-2 IgG antibodies.

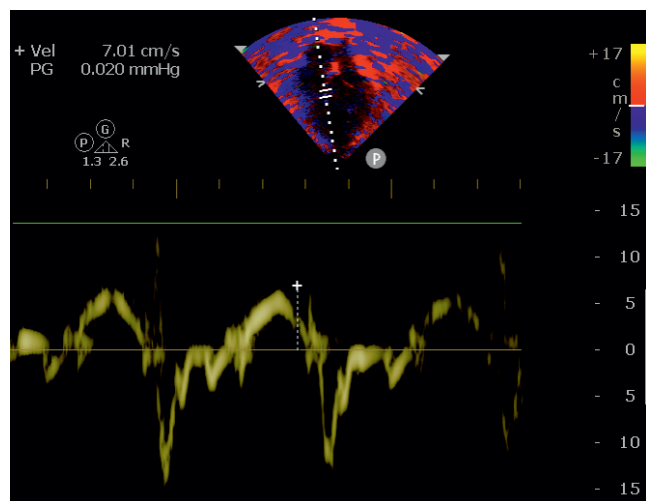
The cardiac evaluation showed a bradycardic (55 bpm), and hypotensive patient (83/39 mmHg), and the echocardiography detected moderate systolic dysfunction (LVEF = 45%) with a thin layer of pericardial effusion, with reduced contractility at Tissue Doppler Imaging (Figure 5). A differential diagnosis with myocarditis was made, the patient being negative tested for the viral panel. Treatment was initiated with Do-

butamine (5 micrograms/kg/min), Dopamine (3 micrograms/kg/min) and iv immunoglobulins (0.5 g/kg/day for three days). Cardiac contractility has progressively improved together with disappearing of bradycardia, which allowed weaning of the inotropic support after 10 days of treatment. The clinical condition of the patient improved remarkably, which allowed the patient to be discharged after 13 days with antiplatelet therapy (Aspirin 75 mg/day) and angiotensin-converting enzyme – inhibitor (Lisinopril 0.45 mg/kg/day).

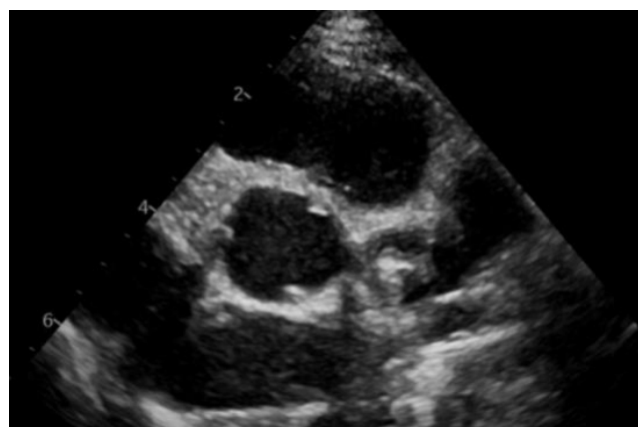
### Case 3

A 2-year-old boy who presented at the hospital for high fever, semi-consistent stools, vomiting and decreased appetite, which started three days before. At the time of arrival, the patient developed microerythematous eruption at the trunk and limbs, accompanied by macular perioral erythema. Laboratory test showed severe inflammatory syndrome (C-reactive protein = 161.25 mg / L, procalcitonin = 3.51 ng/mL, fibrinogen 567.9 mg/dL), increased levels of ferritin (670.32 ng/mL), IL-6 (42.42 pg/mL), NT-proBNP (2752 pg/mL), and also high levels of anti-SARS-CoV-2 IgG antibodies (52.81 RU/mL). Echocardiography showed circumferential pericardial effusion, left coronary artery dilatation – left main coronary artery was about 3.4 (z score +3.8). ECG showed negative T-waves in anterior territory (in precordial leads from V1 to V4).

Based on anamnesis, clinical examination (high persistent fever, skin rash), laboratory investigations (non-specific inflammatory syndrome, increased values of D-Dimers and NT-proNPB, as well as detection of positive values of anti-SARS-CoV2 IgG antibodies) and imaging examinations (circumferential pericardial effusion, left coronary artery dilation, ischemic changes on ECG, and presence of pleural fluid) a diagnosis



**Figure 5.** Tissue Doppler Imaging at septal wall showing reduced velocity of the S' septal wave of 7 cm/s in Case 2.



**Figure 6.** Dilatation of the left coronary artery with both anterior descending artery and circumflex artery aneurisms.

of post-Covid-19 Kawasaki-like inflammatory syndrome was made.

Treatment was established with 2 g/kg IV immunoglobulins, 2 mg/kgc Methylprednisolone, Aspirin, initially at 30 mg/kgc and subsequently decreased to 4 mg/kgc, subcutaneous anticoagulant (Enoxaparin), antibiotherapy (Ceftriaxone for seven days) and symptomatic treatment.

In the course of the disease, skin pallor was noticed, and repeated laboratory tests detected severe anemia with reticulocytosis, direct positive Coombs test, normal bilirubin, leukocytosis and thrombocytosis. The patient received iso-group, iso-Rh transfusion therapy, and the result of specific blood test indicated the diagnosis of cold agglutinin-mediated autoimmune hemolytic anemia associated with Covid-19 infection. A few days later, the patient’s clinical condition visibly improved and he was discharged after 12 days of hospitalization with gradually low-dose oral steroid treatment, antiplatelet therapy and gastric protection. Coronary artery aneurisms developed in medium follow up (Figure 6) in anterior descendant artery (ADA) and left circumflex artery (LCX), as progression of the disease towards potentially life-threatening complications.

## DISCUSSION

In children, the innate immune response acts earlier and promptly than in adults and this was considered as a “protective factor against SARS-CoV-2 infection in children”<sup>6</sup>. At the moment of reinfection with the same viruses, the immune response appears earlier and is more powerful due to memory cells<sup>7-9</sup>. Another factor that may contribute to a lower susceptibility of children to coronavirus disease-2019 include the fact that children have fewer pro-inflammatory cyto-

kines secretion than adults, and less lifetime exposure to toxins such as cigarette smoke and air pollution, factors which may affect the health of an individual’s epithelium<sup>10</sup>.

In April 2020, the National Health Service in the United Kingdom alerted the medical community of children presenting critically ill with findings like Kawasaki disease (KD) or toxic shock syndrome in the setting of recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection<sup>11</sup>. This syndrome was later referred to as pediatric multisystem inflammatory syndrome and multisystem inflammatory syndrome in children.

Initially, PMIS took place in clusters, occurring in approximately 4 weeks after the peak incidence of COVID-19 in heavily affected regions, initially in Western Europe and subsequently throughout North America. The initial report from England included 8 patients<sup>12</sup>. Afterwards larger series were reported from France/Switzerland (35 cases), England (58 cases), multiple series from New York (33 cases, 17 cases) and across the United States (186 cases)<sup>13-16</sup>. Most of the cases (79-95%) occurred in previously healthy children, with the most common preexisting comorbidities being asthma and obesity<sup>17</sup>.

In early stages of the pandemic, this disease was considered to be Kawasaki disease caused by COVID-19, because there are many symptoms of KD, such as rash, conjunctival congestion, chapped lips, and lymphadenitis. Although there are some phenotypic similarities between MIS-C and KD, there are still many differences between the two diseases, such as the age of onset for KD being less than 5 years old, and the median age in this study was over 5 years old. In KD, platelet count generally increased, while

**Table 2. Comparative view of the laboratory findings for all three patients**

Parameters	Case 1	Case 2	Case 3	Reference values
Leukocytes (/uL)	25.310	13.890	7.600	5.000–14.500
Neutrophils (%)	88,2%	92,4%	82,9%	30–75%
Thrombocytes (/uL)	178.000	141.000	186.000	150.000–450.000
C-reactive protein (mg/L)	137,92	231,68	161,25	0–5
Procalcitonin (ng/mL)	1,92	5,06	3,51	<0,05
Ferritin (mcg/L)	605	1518	670,32	14–124
IL-6 (pg/mL)	40,36	350,6	42,42	<7
NT-proBNP (pg/mL)	48,793	15.802	2.752	<125
D-dimers (ug/mL)	1,32	1,55	0,96	0–0,5
SARS-CoV2 Ig G antibodies	Positive	Positive	Positive	–



**Table 3. Comparative view of the treatment received by all three cases presented above**

Medication	Case 1	Case 2	Case 3
Corticotherapy (Methylprednisolone)	✓	✓	✓
Imunoglobulin	✓	✓	✓
Immunomodulator Anakinra	✓	–	–
Inotropic support:	+	+	–
• Dobutamine	x	✓	x
x Dopamine	✓	✓	x
x Adrenaline	✓	x	x
Anticoagulation (Enoxaparin)	✓	✓	✓
Antiplatelet therapy (Aspirin)	✓	✓	✓
Antibiotherapy	✓	✓	✓
ACE-inhibitor (Lisinopril)	✓	✓	–
Diuretic			
x Furosemide	✓	–	–
x Spironolactone	✓	–	–
Beta-blocant	✓	–	–

thrombocytopenia accounted for 26.42% of MIS-C cases. A systematic review of the literature published this year reported that gastrointestinal symptoms in KD and the degree of myocardial dysfunction are also rare, while myocarditis, coronary artery dilatation, cardiac systolic function affects, and gastrointestinal symptoms accounted for 35.97%, 17.83%, 56.32%, and 82.72% of cases, respectively, in MIS-C<sup>18,19</sup>.

In our cases, clinical manifestations of PMIS have started with fever and gastrointestinal symptoms. These nonspecific symptoms at the time of disease onset can lead to misdiagnose this syndrome but after investigations were performed such as laboratory tests, echocardiography and screening of COVID-19 we could easily met all the diagnostic criteria.

We couldn't establish the exact duration between the acute infection and onset of MIS-C symptoms because all patients had initial asymptomatic SARS-CoV2 infection, in fact all the affected children were previously healthy.

Laboratory tests (Table 2) showed leukocytosis (one case), neutrophilia presented in all cases and thrombocytopenia (one patient). All patients had significant increase in various inflammatory indicators such as C-reactive protein, procalcitonin, ferritin, interleukin-6 and, also, evidence of coagulopathy by increased levels of D-dimers.

In our study, all PMIS patients received IVIG at a dose varying between 0.5 and 2 g/kg as the first-line treatment. Because of shock or organ threatening

event, methylprednisolone (1-2 mg/kg/day) was added to all patients (Table 3). To the refractory case number 1, high dose anakinra was given as the second-line treatment. Moreover, all the patients who had dilated coronary arteries received acetylsalicylic acid, initially, and for those with increased prothrombotic risk (elevated levels of D-dimers), anticoagulation therapy in prophylactic dose was added.

All patients had cardiovascular complications, as follows: coronary artery abnormalities, pericarditis, systolic or diastolic dysfunction which required inotropic support. All children received intravenous immunoglobulins and corticosteroids, treatment which seemed to improve symptoms and decrease inflammatory responses. Immunosuppressive therapy with Anakinra was needed only for the first patient because for the other two first-line treatment worked from the beginning. The average duration of hospitalization was 13.3 days. Aneurismal dilatation of the coronary arteries appeared only in the case of prolonged corticoid therapy (case 3), but implications and correlations are difficult to be concluded.

## CONCLUSION

The multisystemic inflammatory syndrome may develop even after an asymptomatic SARS-CoV2 infection, all presented patients having positive SARS-CoV2 antibodies and no past history of infection.

Cardiac evaluation is mandatory in order to establish the type of cardiac implication with direct con-

sequences to treatment. Immunomodulatory therapy, after IVIG and corticosteroid therapy may be needed, and the algorithm should be followed.

All patients need medium to long-term followed-up closely in order to elucidate the potential sequelae of this condition, including coronary aneurism with potential thrombosis and myocardial infarction.

Pediatric multisystem inflammatory syndrome may have a much more severe cardiovascular impact than acute SARS-CoV-2 infection. Most pediatric patients with post-Covid-19 cardiovascular disease have a complete resolution of symptoms associated with PMIS.

### Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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