ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

EDITORIAL
PERSPECTIVA
ARTIGO ORIGINAL
ARTIGO DE REVISÃO
CASO CLÍNICO
IMAGENS MÉDICAS
NORMAS ORIENTAÇÃO
CARTAS

Extracorporeal Membrane Oxygenation in an Adolescent with Multisystem Inflammatory Syndrome in Children

Oxigenação por Membrana Extracorporal num Adolescente com Síndrome Inflamatória Multissistémica Pediátrica

Cristina GAGO✉[1,2], Cristina LORENZO[1], Sara PINTO[1,3], Ana R. SOUSA[4], Cristina CAMILO[1], Francisco ABECASIS[1]
Acta Med Port 2023 Nov;36(11):740-745 ▪ https://doi.org/10.20344/amp.19053

ABSTRACT

Multisystem inflammatory syndrome in children is a rare and potentially life-threatening disease that is associated with SARS-CoV-2 infection, characterized by hyperinflammation and multiorgan involvement. Cardiovascular involvement is common, including myocardial dysfunction often leading to cardiogenic shock. We present the case of a 17-year-old boy with fever, odynophagia, maculopapular rash and abdominal pain who developed a cardiogenic shock. Due to progressive deterioration of cardiac function despite optimized vasoactive support, veno-arterial extracorporeal membrane oxygenation support was initiated 12 hours after admission, with successful decannulation after seven days and discharge after 23 days, with normal cardiac function. The patient received corticosteroids and intravenous immunoglobulin. Early recognition and intensive care support are crucial for ensuring a successful outcome in severe cases of multisystem inflammatory syndrome. In cases of severe cardiogenic shock, extracorporeal membrane oxygenation support can be critical for survival and rapid recovery.
Keywords: Adolescent; COVID-19/complications; Extracorporeal Membrane Oxygenation; SARS-CoV-2; Shock, Cardiogenic; Systemic Inflammatory Response Syndrome

RESUMO

A síndrome inflamatória multissistémica em crianças é uma doença rara e potencialmente fatal, e que está associada à infeção por SARS-CoV-2 e caracterizada por hiperinflamação e pelo envolvimento de múltiplos órgãos. As manifestações cardiovasculares são comuns, incluindo a disfunção miocárdica, podendo apresentar-se como choque cardiogénico. Apresentamos o caso de um rapaz de 17 anos com febre, odinofagia, exantema maculopapular e dor abdominal, que desenvolveu choque cardiogénico. Apesar do suporte vasoativo otimizado, verificou-se a deterioração progressiva da função cardíaca, pelo que 12 horas após a admissão se iniciou o suporte através de oxigenação por membrana extracorporal venoarterial. O doente foi descanulado com sucesso após sete dias e teve alta após 23 dias, com função cardíaca normal, tendo realizado tratamento com corticosteroides e imunoglobulina intravenosa. O reconhecimento precoce e o suporte em cuidados intensivos são cruciais para garantir o tratamento adequado em casos de síndrome inflamatória multissistémica. O suporte por oxigenação por membrana extracorporal pode ser fundamental para a sobrevivência e rápida recuperação perante choque cardiogénico grave.
Palavras-chave: Adolescente; Choque Cardiogénico; COVID-19/complicações; Oxigenação por Membrana Extracorporal; SARS-CoV-2; Síndrome de Resposta Inflamatória Sistémica

INTRODUCTION

Although most children with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appear to be asymptomatic or have a mild clinical course, some cases may have complications such as the multisystem inflammatory syndrome in children (MIS-C) also known, in Europe, as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), which was observed for the first time in April 2020.[1-3] MIS-C is characterized by hyperinflammation and multiorgan involvement and can share clinical features with other syndromes like Kawasaki disease (KD) or toxic shock syndrome.

In these cases, pediatric patients present persistent high-grade fever, skin rash, multisystem organ dysfunction and elevated acute inflammatory markers, which could not be explained by an alternative diagnosis and that was temporally related to SARS-CoV-2 infection, with or without PCR evidence of infection (Table 1).[2,4,5] Despite being rare, severe MIS-C cases can be potentially life-threatening if associated with cardiogenic or distributive shock. Refractory shock may require venoarterial extracorporeal membrane oxygenation (VA-ECMO) for circulatory and respiratory support.[6-12]

Early recognition of this new entity and prompt referral to a pediatric intensive care unit (PICU) in cases of hemodynamic instability is crucial for ensuring a successful outcome. We report a case of an adolescent with severe MIS-C with cardiogenic shock and myocardial dysfunction who required VA-ECMO.

1. Pediatric Intensive Care Unit. Department of Pediatrics. Hospital de Santa Maria. Centro Hospitalar Universitário Lisboa Norte. Lisbon. Portugal.
2. Pediatric Functional Unit. Children Department. Hospital de Cascais Dr. José de Almeida. Lisbon. Portugal.
3. Pediatric Infectious Diseases and Immunodeficiencies Unit. Department of Pediatrics. Hospital de Santa Maria. Centro Hospitalar Universitário Lisboa Norte. Lisbon. Portugal.
4. Pediatric Cardiology Unit. Department of Pediatrics. Hospital de Santa Maria. Centro Hospitalar Universitário Lisboa Norte. Lisbon. Portugal.
✉ **Autor correspondente:** Cristina Gago. cristinapgago@gmail.com
Recebido/*Received*: 11/09/2022 - **Aceite/*Accepted*:** 21/03/2023 - **Publicado *Online*/*Published Online*:** 26/04/2023 - **Publicado/*Published*:** 02/11/2023

Table 1 – Case definitions of Multisystem Inflammatory Syndrome in Children from the World Health Organization and Centers for Disease Control and Prevention.[16,17]

CDC case definition	WHO case definition
4 criteria:	**All 6 criteria must be met:**
1. Age < 21 years	1. Age 0 to 19 years
2. Clinical presentation consistent with MIS-C, including **all** of the following: 1. Fever (> 38º C for ≥ 24 hours) or report of subjective fever lasting ≥ 24 hours 2. Laboratory evidence of inflammation; including, but not limited to, **any** of the following: elevated CRP, elevated ESR, elevated fibrinogen, elevated procalcitonin, elevated D-dimer, elevated ferritin, LDH, elevated IL-6 level, neutrophilia, lymphocytopenia, hypoalbuminemia 3. Multisystem involvement: • **Two or more** organ systems involved: cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia); respiratory (eg, pneumonia, ARDS, pulmonary embolism); renal (eg, AKI, kidney failure); neurologic (eg, seizure, stroke, aseptic meningitis); hematologic (eg, coagulopathy); gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding); dermatologic (eg, erythroderma, mucositis, other rash) 4. Severe illness requiring hospitalization	2. Fever for ≥ 3 days 3. Clinical signs of multisystem involvement (**at least 2** of the following): • Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/ BNP) • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin) 5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/ streptococcal toxic shock syndromes 6. Evidence of SARS-CoV-2 infection • Any of the following: positive SARS-CoV-2 RT-PCR; positive serology; positive antigen test; contact with an individual with COVID-19
3. No alternative plausible diagnosis	
4. Recent or current SARS-CoV-2 infection or exposure	
5. **Any** of the following: positive SARS-CoV-2 RT-PCR; positive serology; positive antigen test; COVID-19 exposure within the 4 weeks prior to the onset of symptoms	

CDC: Centers for Disease Control and Prevention; WHO: World Health Organization; MIS-C: multisystem inflammatory syndrome in children; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; IL-6: interleukin 6; BNP: brain natriuretic peptide; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; COVID-19: coronavirus disease 2019; PT: prothrombin time; PTT: partial prothrombin time.

CASE REPORT

A 17-year-old white boy with irrelevant past medical history presented to the emergency department with a four-day history of persistent high-grade fever, odynophagia, non-pruritic rash and abdominal pain. The physical examination revealed skin pallor, maculopapular rash, and an erythematous throat. Laboratory findings included an elevated C-reactive protein of 143 mg/L and the patient was admitted for monitoring. Nasopharyngeal swab RT-PCR for SARS-CoV-2 and a rapid antigen detection test for group A streptococci were negative. There was a maternal history of SARS-CoV-2 infection seven months earlier and COVID-19 cases in school during the previous weeks.

One day after admission, the patient developed cardiogenic shock (blood pressure 90/60 mmHg with transient improvement after fluid resuscitation of 10 mL/kg) with decreased left ventricular systolic function (LVSF) - ejection fraction (EF) of 45%, and subsequent acute pulmonary edema. Severe hypoxia was evident and invasive mechanical ventilation was necessary. Dobutamine infusion was started due to hemodynamic instability with severe cardiogenic shock. Ceftriaxone and clindamycin were initiated to cover for possible septic shock /toxic shock syndrome and the patient was transferred to the PICU.

On admission, he presented bilateral conjunctival injection, inguinal and cervical lymphadenopathy, bilateral maculopapular rash on the knees, ankles, and elbows, erythematous micropapular rash on the trunk, a petechial rash on his feet and knees and hand edema (Figs. 1 to 3). The echocardiography revealed worsening LVSF (EF 33%) with normal coronary arteries; the electrocardiogram showed negative T-waves (inferior and left precordial leads). Blood tests revealed neutrophilia and lymphopenia, elevated acute inflammatory markers, acute kidney injury, elevated

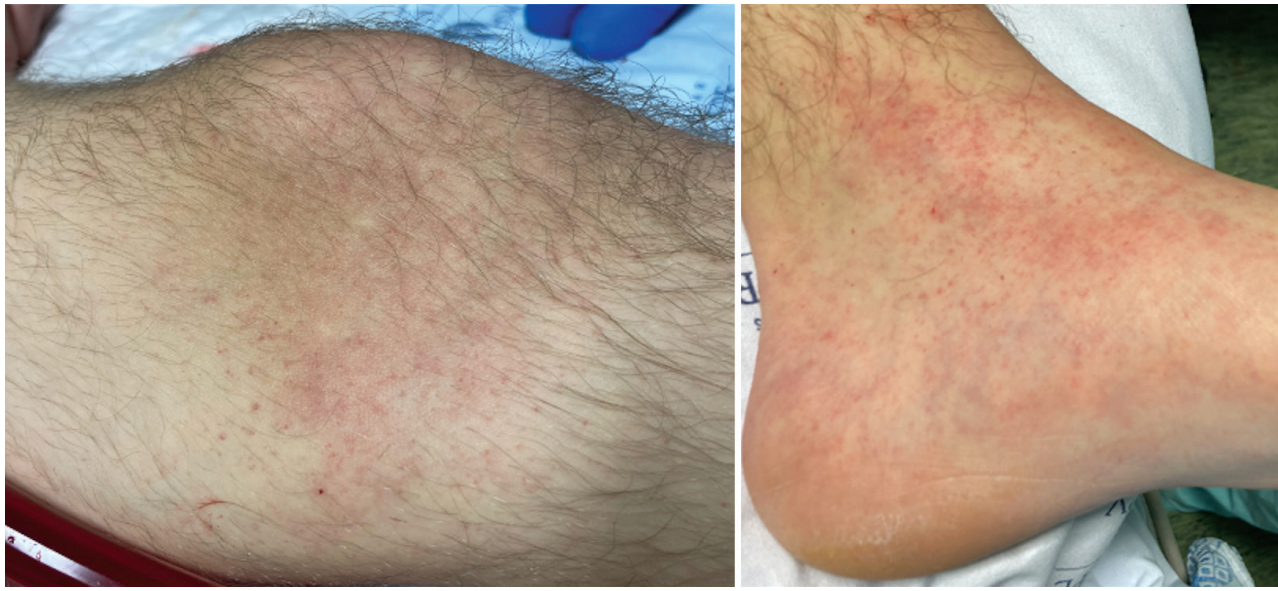

Figure 1 – Maculopapular and petechial rash on PICU day one

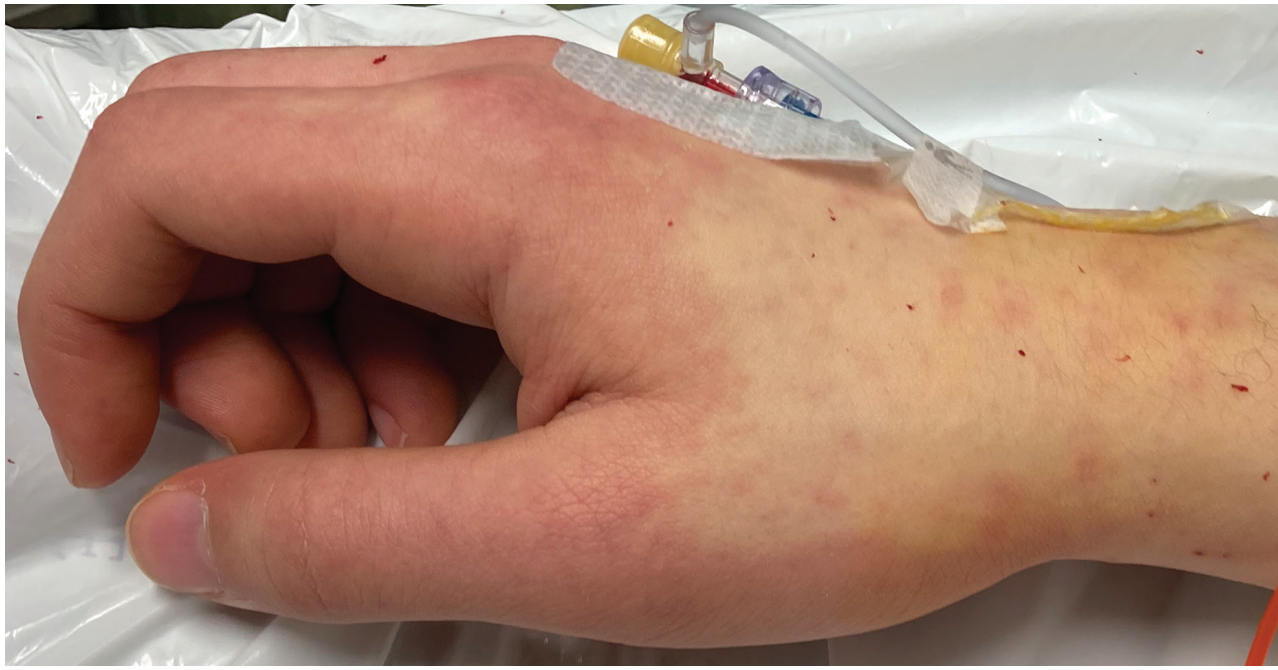

Figure 2 – Hand edema on PICU day one

NT-proBNP and troponin T (Table 2). Due to suspicion of MIS-C, methylprednisolone (1 mg/kg/day) was started shortly after admission. Prophylactic acetylsalicylic acid (100 mg/day) was initiated because of severe left ventricle (LV) dysfunction.

Despite optimized respiratory and inotropic support (dobutamine 10 mcg/kg/min, epinephrine 0.3 mcg/kg/min and norepinephrine 0.05 mcg/kg/min) there was a progressive clinical (blood pressure 82/44 mmHg) and cardiac deterioration (EF 23%, cardiac index 1.69 L/min/m2) with severe lactic acidosis (pH 7.13; lactate 13 mmol/L) and P/F ratio of

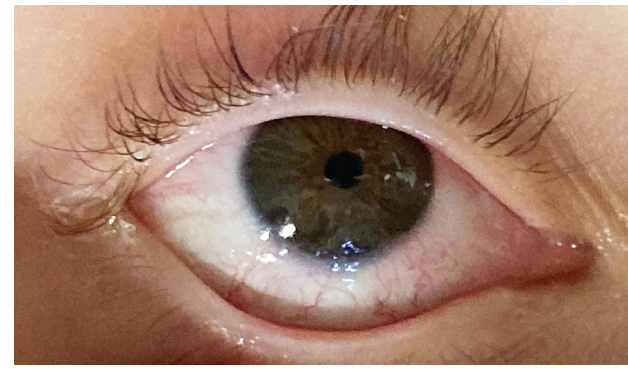

Figure 3 – Conjunctival injection on PICU day one

Table 2 – Laboratory findings

	Normal values	Peak value (PICU day)
NT-proBNP, pg/mL	< 300	34.389 (D1)
Troponin T, ng/L	< 14	119 (D9)
Creatinine kinase, U/L	39 - 308	59 (D4)
D-dimer, ug/mL	0.0 - 0.5	2.76 (D1)
C-reactive protein, mg/L	< 5	315 (D2)
Procalcitonin, ng/mL	< 0.5	4.4 (D2)
Erythrocyte sedimentation rate, mm/h	≤ 10	120 (D6)
Fibrinogen, mg/dL	200 - 400	968 (D1)
Interleukin-6, pg/mL	≤ 1.5	132 (D1)
Ferritin, ng/mL	13 - 110	501 (D1)
Albumin, g/dL	3.5 - 5.2	*2.4 (D3)
Triglycerides, mg/dL	< 150	129 (D6)
Hemoglobin, g/dL	13.0 - 17.5	14.5 (D1)
White blood cell count, x 10^9/L	4 - 11	33.7 (D1)
Neutrophil count, x 10^9/L	1.9 - 7.5	31.6 (D1)
Lymphocyte count, x 10^9/L	1.0 - 4.8	*0.5 (D1)
Platelets, x 10^9/L	150 - 450	*124 (D1)
Serum creatinine, mg/dL	0.7 - 1.2	1.3 (D1)
Blood urea nitrogen, mg/dL	7 - 22	20.5 (D1; D3)
Lactate dehydrogenase, U/L	100 - 250	327 (D1)
Alanine aminotransferase, U/L	0 - 41	146 (D7)
Aspartate aminotransferase, U/L	0 - 40	160 (D7)
Gamma-glutamyltransferase, U/L	0 - 60	164 (D6)
RT-PCR SARS-CoV-2	––	neg (D1)
SARS-CoV-2 IgG, UA/mL SARS-CoV-2 IgM	Cut-off < 0.1	5.2 (D1) neg (D1)
Blood culture	––	neg (D1)

neg: negative; pos: positive; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NT: not tested; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; *nadir value; –– : non applicable

64. Therefore, VA-ECMO was initiated 12 hours after admission. Cannulation was performed uneventfully via left femoral artery and right jugular vein. Immunomodulation therapy was escalated with administration of intravenous immunoglobulin (IVIG, 2 g/kg). The patient improved over the first 48 hours and was gradually weaned from circulatory support. Sustained apyrexy and progressive improvement of skin lesions and conjunctival injection were observed since day two of ECMO run and desquamation of the fingertips since day four. A diagnosis of MIS-C was confirmed after a positive serology for SARS-CoV-2. Blood cultures were negative and antibiotic therapy was stopped after five days. Electrocardiogram normalized by day five. The patient was decannulated on day seven (EF 60% - 70%; NT-proBNP decreasing). The procedure was complicated by femoral artery laceration and hemorrhagic shock requiring fluid resuscitation and transfusion of red cell concentrate. Two days later he was successfully extubated to room air.

Since serial transthoracic echocardiograms revealed increased LV myocardial thickness, carvedilol was started. During hospitalization, changes in the coronary arteries, namely aneurysms, were not visualized. Acetylsalicylic acid was suspended on day 19. Twenty-four-hour Holter monitoring was normal. A cardiac magnetic resonance imaging (MRI) performed at discharge (day 23) showed a non-dilated LV with normal function, mild increase in parietal myocardium thickness, and evidence of acute diffuse myocardial edema consistent with acute myocarditis. One month after discharge the patient only maintained bilateral conjunctival injection. The echocardiogram showed

reduction of parietal myocardial thickness. Corticosteroid therapy was suspended after one month and cardiac MRI was normal eight months later. Currently, the patient has annual follow-up in cardiology, with normal electrocardiogram and echocardiogram.

DISCUSSION

Multisystem inflammatory syndrome in children occurs mainly in previously healthy children and adolescents, although asthma and obesity are common comorbidities.[5,7-9] Unlike KD, patients with MIS-C have a median age of 8 to 11 years and cardiac involvement is more common.[5,9,14] Even though our patient was older than usual for MIS-C diagnosis, both the clinical presentation and the laboratory findings were in agreement with the literature in these cases.[15-17] KD was excluded based on patient age, gastrointestinal symptoms, and elevation of inflammatory and cardiac biomarkers higher than usually seen in KD.

Myocardial dysfunction is frequent and coronary artery dilatation or aneurysm and arrhythmias may develop over time.[8-10] In children, the mechanism of myocardial dysfunction is associated with a dysregulated late inflammatory response.[5,7] A multicenter study in Europe reported 35 cases of MIS-C with cardiogenic shock, LV dysfunction and severe inflammatory state; 28 required inotropic drugs and 10 required ECMO.[7] ECMO has been reported in other series with good outcomes.[5,11-13]

In our case, NT-proBNP was significantly elevated at admission (34.39 pg/mL), which has been shown to correlate with worse clinical outcomes and the need for intensive care support.[10] Due to persistent and severe LV dysfunction despite optimized inotropic support and corticosteroid therapy, VA-ECMO was started shortly after PICU admission. IVIG was only administered after the patient was on VA-ECMO support to prevent fluid overload complications and worsening of pulmonary edema. The use of IVIG and corticosteroids correlates with rapid improvement of LV systolic function (median of two days).[5,7,9] Other studies found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus corticosteroids, or corticosteroids alone.[18] In addition, tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, has been shown to be effective in a cohort of severe COVID-19 adult patients. However, trials including children are ongoing and it is not currently recommended as standard of care.[19]

Since coronary artery involvement may develop in the convalescent stage, there should be close follow-up after discharge in order to optimize cardiac outcomes.[9]

Notwithstanding multisystem organ disfunction seen in MIS-C patients, most children and adolescents show a rapid and full recovery. Death is uncommon, compared with the COVID-19 adult population.[10]

Early diagnosis and immunomodulation therapy are essential to prevent complications such as acute heart failure. In children with prolonged and unexplained fever, NT-proBNP should be evaluated and, if elevated, urgent cardiac evaluation should be performed.[7] IVIG and corticosteroids play an important role and early ECMO support can be critical for survival and rapid recovery from acute heart failure.

PREVIOUS PRESENTATIONS

This case report was presented as a poster at the 31st Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care, on 15th – 18th June 2021.

AUTHOR CONTRIBUTIONS

CG, CL: Data collection, analysis and interpretation, draft and critical review of the paper.

SP, AS, CC, FA: Data analysis and interpretation, critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in china. Pediatrics. 2020;145:e20200702.
2. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J. 2020;39:e340-6.
3. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe acute respiratory syndrome coronavirus 2 (sars-cov-2) infection in children and adolescents: a systematic review. JAMA Pediatr. 2020;174:882-9.
4. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-46.
5. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol. 2021;56:837-48.
6. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G,

et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health. 2020;4:669-77.
7. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global sars-cov-2 pandemic. Circulation. 2020;142:429-36.
8. Sperotto F, Friedman KG, Son MB, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in sars-cov-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307-22.
9. Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation. 2021;143:78-88.
10. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute Cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation. 2021;143:21-32.
11. Badulak J, Antonini MV, Stead CM, Shekerdemian L, Raman L, Paden ML, et al. Extracorporeal membrane oxygenation for COVID-19: updated 2021 guidelines from the Extracorporeal Life Support Organization. ASAIO J. 2021;67:485-95.
12. Di Nardo M, Hoskote A, Thiruchelvam T, Lillie J, Horan M, Belda Hofheinz S, et al. Extracorporeal membrane oxygenation in children with coronavirus disease 2019: preliminary report from the collaborative european chapter of the Extracorporeal Life Support Organization prospective survey. ASAIO J. 2021;67:121-4.
13. Schwartz SP, Walker TC, Kihlstrom M, Isani M, Smith MM, Smith RL, et al. Extracorporeal membrane oxygenation for COVID-19-associated multisystem inflammatory syndrome in a 5-year-old. Am Surg. 2022;88:174-6.
14. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with sars-cov-2. JAMA. 2020;324:259-69.
15. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 2020. [cited 2021 Dec 11]. Available from: https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance.
16. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. 2020. [cited 2021 Dec 11]. Available from: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.
17. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). [cited 2021 Dec 11]. Available from: https://emergency.cdc.gov/han/2020/han00432.asp.
18. McArdle AJ, Vito O, Patel O, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385:11-22.
19. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19(RECOVERY): a randomised, controlled, open-label, platform Trial. Lancet. 2021;397:1637-45.