Algorithm for the diagnosis and management of the multisystem inflammatory syndrome in children associated with COVID-19

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Abstract
Objective: Although the initial reports of COVID-19 cases in children described that children were largely protected from severe manifestations, clusters of paediatric cases of severe systemic hyperinflammation and shock related to severe acute respiratory syndrome coronavirus 2 infection began to be reported in the latter half of April 2020. A novel syndrome called “multisystem inflammatory syndrome in children” (MIS-C) shares common clinical features with other well-defined syndromes, including Kawasaki disease, toxic shock syndrome and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Our objective was to develop a protocol for the evaluation, treatment and follow-up of patients with MIS-C.

Methods: The protocol was developed by a multidisciplinary team. We convened a multidisciplinary working group with representation from the departments of paediatric critical care, cardiology, rheumatology, surgery, gastroenterology, haematology, immunology, infectious disease and neurology. Our protocol and recommendations were based on the literature and our experiences with multisystem inflammatory
1 | INTRODUCTION

Coronavirus disease (COVID-19) is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It originated in the city of Wuhan, Hubei Province, Central China, in December 2020 and rapidly spread worldwide. Approximately 10%-20% of patients with adult COVID-19 develop a severe or life-threatening disease characterised by acute respiratory distress syndrome (ARDS), septic shock, multiple-organ failure, coagulopathy and/or cytokine release syndrome (CRS). The conditions of these patients deteriorate suddenly in the later stages of the disease or during recovery, a time coinciding with declining viral loads and increasing values of inflammatory markers. These observations suggest that host tissue damage is mediated by an imbalance between proinflammatory and anti-inflammatory mechanisms, the interaction of various cells and cytokines, and dysregulated innate and adaptive immune responses. By contrast, a large proportion of infected children appear to be asymptomatic and less likely to develop severe symptoms. Unfortunately, the view that the disease course of COVID-19 is mild in children is now challenged by reports of children presenting with very severe inflammatory syndrome in children. After an agreement was reached and the protocol was implemented, revisions were made on the basis of expert feedback.

Conclusion: Children may experience acute cardiac decompensation or other organ system failure due to this severe inflammatory condition. Therefore, patients with severe symptoms of MIS-C should be managed in a paediatric intensive care setting, as rapid clinical deterioration may occur. Therapeutic approaches for MIS-C should be tailored depending on the patients’ phenotypes. Plasmapheresis may be useful as a standard treatment to control hypercytokinemia in cases of MIS-C with severe symptoms. Long-term follow-up of patients with cardiac involvement is required to identify any sequelae of MIS-C.

Review criteria

- A comprehensive search strategy using text words and Medical Subject Heading (MeSH) was designed.
- We searched Scopus, PubMed, Embase, and Google Scholar for relevant trials published up to 10 April 2021 with related inclusion and exclusion criteria.
- This review was based on the literature and our experiences with the multisystem inflammatory syndrome in children.

Message for the clinic

- Early diagnosis and treatment are essential for MIS-C.
- TPE may be considered as a therapeutic option in children with severe MIS-C.

phenomenon associated with hyperinflammation following symptomatic or asymptomatic COVID-19 infection.

Although our understanding of COVID-19 in children has shown a remarkable advancement, deficiencies in data and approaches to MIS-C remain owing to the small number of MIS-C cases. Given the severity of MIS-C associated with COVID-19, there is an urgent need for awareness of MIS-C, so that key points in the diagnosis and follow-up of patients and optimal treatment strategies can be designed. We convened a multidisciplinary study group with representation from the departments of paediatric cardiology, rheumatology, critical care, infectious diseases, haematology, pulmonology, immunology, neurology, gastroenterology, nephrology and surgery. The following proposed algorithms were created by the MIS-C Study Group at our centre. Recommendations were based on expert opinion with the experience with approximately 150 patients with MIS-C who were followed up at our centre. In addition, published studies from our centre that included MIS-C data were also included. Here, we present an overview of clinical and laboratory features and complications and propose a plan for the evaluation and management of patients with MIS-C on the basis of our experience and literature review.
2 | METHODS

The protocol was developed by a multidisciplinary team. We convened a multidisciplinary working group. The objectives of our protocol included rapid detection of MIS-C cases, clinical presentation, reduction of the risk of coronary artery abnormalities and control of the hyperinflammatory state to cure or prevent shock and organ damage, and identification of patients suitable for undergoing plasmapheresis. Our protocol and recommendations were based on the literature and our experiences with MIS-C. After an agreement was reached and the protocol was implemented, revisions were made on the basis of expert feedback.

2.1 | Case definition

The World Health Organization and the Centers for Disease Control and Prevention issued case definitions for MIS-C.\(^6,7\) Although the criteria used for case definition vary between the two health agencies, both definitions require the presence of fever, elevated inflammatory markers, at least two signs of multisystem involvement, evidence of SARS-CoV-2 infection or exposure and exclusion of other potential causes (Table 1).

2.2 | Clinical presentation

MIS-C related to SARS-CoV-2 has predominantly been reported in previously healthy children. Fever, severe abdominal pain, cardiac dysfunction, shock, ARDS, neurological changes, dehydration and features of KD may be present.

### TABLE 1 Case definition for multisystem inflammatory syndrome in children

| Case definition for MIS-C (CDC)\(^6\) | Case definition for MIS-C (WHO)\(^7\) |
|-------------------------------------|-------------------------------------|
| All 4 criteria must be met:         | All 6 criteria must be met:         |
| 1. Age < 21 years                   | 1. Age < 20 years                   |
| 2. All of the following:            | 2. Fever for > 3 days               |
|   Fever: Documented fever > 38.0°C (100.4°F) for ≥24 hours | 3. Clinical signs of multisystem involvement (at least 2 of the following): |
|   Laboratory evidence of inflammation (eg, elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6 level, neutrophilia, lymphocytopenia, hypalbuminemia) |   Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) |
|   Multisystem involvement (2 or more organ systems involved) |   Hypotension or shock |
|   Severe illness requiring hospitalisation |   Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) |
| 3. No alternative plausible diagnoses |   Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) |
| 4. Evidence of recent or current SARS-CoV-2 infection or exposure (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) |   Acute gastrointestinal symptoms (diarrhoea, 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, COVID-19 exposure within the 4 weeks prior to the onset of symptoms) |

Abbreviations: CDC: centers for disease control; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; MIS-C: multisystem inflammatory syndrome in children; PT: prothrombin time; PTT: a partial thromboplastin time; SARS-CoV2 RT-PCR: severe acute respiratory syndrome coronavirus 2 real-time reverse-transcriptase polymerase chain reaction; WHO: The World Health Organization.
study published from our centre. Thirteen patients diagnosed as having MAS due to systemic juvenile idiopathic arthritis were compared with 26 patients diagnosed as having MIS-C. The patients with MAS had lower haemoglobin and fibrinogen levels but higher ferritin and lactate dehydrogenase levels at the time of diagnosis. The patients with MIS-C had higher absolute neutrophil counts and C-reactive protein (CRP) values but lower absolute lymphocyte counts at the time of diagnosis. Left ventricle ejection fraction (LVEF) was significantly lower in the patients with MIS-C.10

2.3 | Diagnosis and management of MIS-C

It is recommended that the investigation of children suspected of having MIS-C should be conducted with a multidisciplinary clinical team and stepwise clinical management.6–8 The location of care for patients with suspected MIS-C should be determined according to the severity of the disease. Patients with MIS-C may rapidly progress to critical illness, so children with features of severe disease should be cared for in the paediatric intensive care unit (PICU). The need for vasoactive inotropes, degree of hyperinflammation and presence of shock or cardiac involvement are the main criteria for determining the severity of the disease.

Children under investigation for MIS-C who are not stable and have no other clear cause for their symptoms should be evaluated for generalised inflammation, multisystem involvement and possible infection if appropriate.

Indiscriminate overtesting should be avoided in the evaluation of patients with possible MIS-C, considering the other possible causes of fever. We recommend a tiered diagnostic approach in patients without life-threatening manifestations, including performing an initial screening evaluation (Tier 1) and proceeding to advanced diagnostic workup (Tier 2) only in children with fever whose cause could not be determined in the initial laboratory tests. In addition, children with suspected MIS-C without features of severe disease should be hospitalised for supportive care while completing Tier two testing if abnormal vital signs, significantly elevated inflammatory markers, or signs of cardiac involvement are present, while other possible causes of fever are investigated (Figure 1).

The relationship between acute abdomen and MIS-C should be kept in mind. Early consultation with a paediatric surgeon is mandatory for patients presenting with severe abdominal pain. Initial evaluation should be conducted to determine if urgent surgical interventions are needed. If surgery is required for acute abdomen, whenever possible, it is preferred to delay surgical treatment until the patient’s vital signs normalise. However, conservative treatment with antibiotics may be preferred when the vital signs are unstable.

2.4 | Management of cardiac involvement

Cardiac involvement occurs in some patients with MIS-C, and long-term follow-up of these patients is required after discharge. Abnormalities include left ventricular dysfunction, coronary artery dilatation or CAAs, arrhythmia, valve dysfunction and pericardial effusion. Children with any evidence of cardiac involvement should be cared for in the PICU by clinicians with cardiology expertise. Electrocardiogram, echocardiogram and cardiac laboratory values, especially troponin T and B-type natruretic peptide (BNP)/N-terminal-proBNP levels, are used for cardiac evaluation. Patients with abnormal troponin T and BNP/NT-proBNP levels at diagnosis should be followed up regularly until these laboratory parameters return to normal. Patients with MIS-C without symptoms of KD may also develop coronary artery dilatation, CAAs and left ventricular dysfunction. Cardiac evaluation should be performed in all patients regardless of differences in the clinical presentations of patients with MIS-C and repeated as necessary.

2.5 | Suggested treatment of patients with MIS-C

Therapeutic choices for MIS-C should be tailored to the patient’s phenotype (KD-like or nonspecific presentation, for example, SHHL/MAS or TSS) and severity of the disease (Figure 2). Patients with suspected MIS-C with life-threatening symptoms may require treatment before full diagnostic evaluation for MIS-C can be completed. Intravenous immunoglobulin (IVIG), corticosteroids, aspirin and heparin are widely used in the treatment of MIS-C. The results of a survey of 40 centres of different sizes and experiences with MIS-C showed that IVIG is the most commonly used medication for the treatment of MIS-C. Among these centres, 98% included IVIG in their recommendations and 60% used IVIG regardless of disease severity.11

All patients with MIS-C who meet the criteria for KD should be treated in accordance with the published guidelines for KD.12 First-line therapy for KD includes high-dose IVIG (2 g/day) and aspirin. Cardiac function and fluid status should be evaluated before IVIG therapy is given, and IVIG should be administered after cardiac function has stabilised in patients with MIS-C. For KD, if the patient continues to be febrile 36 hours after completion of the first IVIG dose, a second IVIG administration, high-dose intravenous methylprednisolone and other immunomodulatory agents are considered. IVIG is recommended for all children with a KD-like phenotype, but the decision to use it should be made by a multidisciplinary team for children with a nonspecific presentation and/or those who do not require treatment.9

Steroids are widely used in the treatment of diseases with a hyperinflammatory state, such as MIS-C.13 An exaggerated inflammatory response that leads to MIS-C after SARS-CoV-2 infection has been described, although it can occur to a lesser degree with other viral infections.14 CRS can be controlled with steroids in these patients. Steroid use has been shown to be associated with lower mortality in adult COVID-19 patients with a hyperinflammatory state and ARDS.15,16 Moreover, the use of steroids in IVIG-resistant KD is known to be associated with improvement in coronary artery abnormalities, decreased duration of clinical
Laboratory evaluation
a. Complete blood count with differential
b. Blood chemistry, including BUN and creatinine, ALT, AST, albumin, bilirubin, creatin kinase, lactate dehydrogenase
c. Cardiac markers: troponin and pro-BNP
d. Blood culture, urinalysis with culture if indicated
e. Blood gas
f. Markers of inflammation: ESR, CRP, procalcitonin, ferritin, triglycerides, IL-6 if available
   h. Coagulation panel: PT, PTT, fibrinogen, D-dimer
   g. Serology for SARS-CoV-2, SARS-CoV-2 by RT-PCR
   h. Additional studies as indicated: respiratory pathogen panel from NP swab or lower respiratory tract, stool studies/cultures, viral blood PCRs or serologies to rule out other causes of myocarditis

Imaging:
   a. Chest X-ray
   b. Abdominal ultrasound or CT scan if concerning symptoms/physical findings

Twelve-lead ECG

Echocardiogram

24-hour holter monitoring (if ECG is abnormal)

Children with MIS-C should be managed by a multi-disciplinary team (such as intensive care, cardiology, rheumatology, infectious diseases, allergy/immunology, neurology).

Perform limited evaluation (Tier 1), including
   a. Complete blood count with differential
   b. Blood chemistry, including BUN and creatinine, ALT, AST, albumin, bilirubin, creatin kinase, lactate dehydrogenase
   c. CRP
   d. SARS-CoV-2 by RT-PCR

Assess for other source of fever

If no other possible cause of fever can be determined

Perform additional evaluation (Tier 2), including
   a. ESR, procalcitonin, IL-6
   b. Ferritin
   c. Urinalysis
   d. Coagulation studies
   e. Troponin
   f. NT-proBNP
   g. ECG
   h. SARS-CoV-2 serology
   i. Blood chemistry
   j. Additional studies as indicated: respiratory pathogen panel from NP swab or lower respiratory tract, stool studies/cultures, viral blood PCRs or serologies to rule out other causes of myocarditis
   k. Chest X-ray
   l. Echocardiogram

Children with MIS-C should be managed by a multi-disciplinary team such as intensive care, cardiology, rheumatology, infectious diseases, allergy/immunology, neurology.

Acute abdomen and/or MIS-C relationship should be kept in mind. Early consultation with a pediatric surgeon is mandatory for the patients presenting with severe abdominal pain.

For the subset of patients with severe symptoms, IL-6 expression is likely to be one of the drivers of the hyperinflammatory syndrome. Elevated IL-6 levels have been observed, which suggests that the use of the IL-6 receptor antagonist may be beneficial to patients.

Patients with primary severe or critical COVID-19 cases have been reported to show a rapid reduction in fever and decreased supplemental oxygen requirement within a few days after receiving tocilizumab therapy. Although studies on its safety and effectiveness are needed, tocilizumab therapy primarily plays a role in primary COVID-19 treatment. However, patients treated with tocilizumab may be at higher risks of bacterial and fungal infections.

IL-1 is another primary cytokine involved in hyperinflammation and plays a fundamental role in the development of the cytokine storm in SHLH/MA'S. Anakinra (recombinant human IL-1 receptor antagonist) appears safe and effective in children with hyperinflammatory syndromes. We evaluated the role of biological agents in the treatment of 33 patients with severe MIS-C who were followed up in the PICU and enrolled in an observational and descriptive medical records review study published in our centre. The clinical features of 63.6% of the patients were consistent with KD shock syndrome, and 36.4% were consistent with SHLH/MA’s. Coronary artery dilatation, CAAs and left ventricular dysfunction were detected in 18 patients during their PICU stay. IVIG and glucocorticoids were given to 33
Treatment strategies of patients without severe disease (if necessary)

1. First-line therapy: 2 g/kg IVIG (If they meet KD criteria; typically given in a single dose).
   - Aspirin: If they meet KD criteria: 30–50 mg/kg/d, decrease to 3–5 mg/kg/d (maximum 3.5 g/d), once afebrile 48 h followed by 3.5 mg/kg/d, 6–8 weeks. If they don’t meet KD criteria: 3–5 mg/kg/d, 6–8 weeks.
2. Second-line therapy: Methylprednisolone 10–30 mg/kg IV for 3 d followed by PO prednisone/prednisolone 2 mg/kg/d until d 7 or until CRP normalizes and then wean over 2–3 w OR Methylprednisone 2 mg/kg/d IV for 7 d or until CRP normalizes followed by PO prednisone/prednisolone 2 mg/kg/d with wean over 2–3 w
3. Third-line therapy: Anakinra 2–6 mg/kg/d (dose and length of therapy to be decided with pediatric rheumatology or immunology)
4. Appropriate empirical antibiotic
5. LMWH 100 mg/kg twice a day, and aspirin 3-5 mg/kg/d (maximum 150 mg/d, once a day)

Should plasmapheresis be considered?

Early acute lung injury/ARDS
OR Life threatening situation;
   - Increased respiratory condition
   - Persistent hypotension despite the use of inotropes
   - Progress to multiple organ failure
   - Pulmonary infiltration >50% within 24–48 hours
   - LV dysfunction: EF <50% or acute systolic heart failure (EF <60%) or persistent LV dysfunction (EF <55%)

FIGURE 2 Treatment approach in the intensive care unit of patients with multisystem inflammatory syndrome associated with COVID-19 in children. ACE, angiotensin converting enzyme; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; d, days; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; g, gram; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; kg, kilograms; LMWH, low-molecular-weight heparin; LV, left ventricular; MIS-C, multisystem inflammatory syndrome in children; mg, milligrams; PO, by mouth, RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2. *The severity of the MIS-C was determined by Vasoactive-Inotropic Score (VIS), degree of respiratory support and evidence of organ injury.12

Patients. Anakinra was administered to 69.6% of the patients who were refractory to IVIG and glucocorticoid therapies. Significant increases in lymphocyte and platelet counts and significant decreases in ferritin, BNP and troponin levels were observed at the end of the first week of treatment in patients who were given biological therapy.23 In addition, studies have emphasised the efficacy of anakinra in adult patients with SARS-CoV-2-associated hyperinflammatory conditions.20 After treatment with anakinra, the need for vasopressors decreased and respiratory function improved significantly in eight patients with SARS-CoV-2-associated pneumonia who were followed up in the intensive care unit.24 Langer-Gould et al reported that only 42.3% of patients with COVID-19 and COVID-19-CRS who received tocilizumab treatment and 63.4% of those treated with anakinra responded favourably to their treatments. The importance of recognizing CRS in the earlier course of the disease, ideally before intubation, has been emphasised.25 These studies guide the use of biologicals as a treatment option for patients with IVIG and steroid-resistant MIS-C. To date, data on IL-1 blockade in COVID-19 infection are encouraging and provide a rapid resolution of systemic inflammation and a remarkable improvement of respiratory status.26

As rapid identification and treatment of MIS-C may be more important than the specific type of biological agent, paediatricians should be careful to diagnose possible cases, especially in the period after the peak of the incidence of COVID-19.

Of the 35 documented papers related to MIS-C cases, the characteristics of 783 cases were evaluated. Twelve patients (1.5%) were reported to have died; the cause of death was not stated for most patients, but two died after a stroke, and seven died despite extracorporeal membrane oxygenation, although the cause of each death is not known.26 The mortality risk is higher in patients with severe MIS-C. We think that therapeutic plasma exchange (TPE) may be useful as an initial therapy, especially in patients with severe disease. TPE should preferably be performed in conditions with strong evidence of effectiveness. For the principles of TPE use, the American Apheresis Association regularly publishes categorised and updated evidence-based guidelines. Accordingly, TPE is widely used in some diseases that are characterised by microvascular thrombosis, the presence of autoantibodies, dysregulation of the immune response and immune activation, and some infections.

TPE is an extracorporeal blood purification technique designed to remove inflammatory mediators and various toxins. TPE reverses SHLH/MAS by decreasing the levels of circulating inflammatory cytokines. Successful results have been obtained with TPE in patients with treatment-resistant SHLH/MAS.27 Keith et al demonstrated
improved 28-day survival with adjunct TPE as compared with the standard care alone in adult patients with septic shock and multiple-organ failure.28 In addition, favourable results of using TPE as a strategy to attenuate circulating inflammatory mediators and cytokines have been found in patients with severe COVID-19 who have CRS.29,30 Several case reports have described favourable results from applying TPE to prevent worsening conditions, using less supportive therapy and recovering the lymphocyte count in patients with COVID-19.30,31 We evaluated the effectiveness and role of TPE in the treatment of children with severe MIS-C. Twenty-seven patients with severe MIS-C who were admitted to the PICU were included in this observational, descriptive and retrospective study. Ten (37.0%) of the 27 patients underwent TPE as initial therapy. We found statistically significant differences in vasoactive inotrope score and LVEF between the patients who underwent TPE and those who did not. Moreover, statistically significant differences were found in ferritin, CRP and BNP levels between the patients who received TPE and those who did not. IVIG and corticosteroids were used for treatment in all the patients, and anakinra was used in 51.8% of the patients. In the patients who received TPE, the median Pediatric Logistic Organ Dysfunction score was 21 before TPE and 10 after TPE. Their median LVEF was 52% before TPE and 66.5% after TPE. Early initiation of TPE followed by immunomodulatory therapy in patients with severe MIS-C may help improve clinical and laboratory outcomes.29 Therefore, we speculate that TPE may be useful as a standard modality to control hypercytokinemia in cases of MIS-C with severe symptoms.

The initiation time of TPE is important in patients with COVID-19 and can prevent the need for mechanical ventilation and intensive supportive care. In fact, TPE is recommended not only as a “rescue therapy” but also as part of the earlier treatment phases, so early treatment initiation in patients with severe MIS-C can be lifesaving.

Although treatment of MIS-C is quite similar to the KD recommendations, the large divergence from the KD guidelines is the administration of systemic anticoagulants to some patients with MIS-C. This choice might make potential by paediatricians because of the high D-dimer levels, frequent deep venous thrombosis and pulmonary embolism observed in acutely ill adults with COVID-19.13 In addition, the relationships of MIS-C with deep venous thrombosis and pulmonary embolism have been defined, but the risk of thrombosis in MIS-C is still unknown. The approach to antiplatelet and anticoagulation management should be tailored to the patient’s risk of thrombosis. KD guidelines should be followed in the adjustment of aspirin dosage in children with KD-like phenotypes. Low-dose aspirin (3-5 mg/kg/day) should be continued for a minimum of four to six weeks after diagnosis in all patients with MIS-C (Table 2). The management of children with abnormal coronary arteries, documented thrombosis, or an ejection fraction < 35% should be discussed with a haematologist regarding the use of long-term antiplatelet and anticoagulation therapies.19

Recommendations for hospital discharge are influenced by the many events that occur with the patient’s clinical condition at the time of discharge (Table 2).

### Table 2: Hospital discharge planning of patients with multisystem inflammatory syndrome associated with COVID-19 in children

1. **Antiplatelet and anticoagulation therapy in MIS-C:**
   a. Low-dose aspirin (3-5 mg/kg/day) should be used in patients with KD-like features and/or thrombocytosis (platelet count ≥450,000/μL) and continued until normalisation of platelet count and confirmed normal coronary arteries at ≥4 weeks after diagnosis
   b. Longer outpatient therapeutic LMWH management should be tailored to the patient by haematologists
   c. Patients with MIS-C and documented LV dysfunction should receive LMWH until at least 2 weeks after discharge from the hospital
   d. Patients with MIS-C and CAA, documented thrombosis, or ongoing moderate to severe LV dysfunction should receive LMWH until at least ≥3 months after discharge from the hospital

2. **Outpatient cardiology, infectious diseases, rheumatology/immunology follow-up should be 1 to 2 weeks after discharge**

3. **Families should be informed about to admit to the emergency department in case of palpitation, chest pain, dyspnoea, presyncope or syncope**

4. **Patients with ventricular dysfunction should have cardiac MRI and 24-hour Holter monitoring 2-6 months later**

5. **Exercise should be restricted for 2 weeks in patients without cardiac involvement and at least 6 months in patients with myocarditis**

Abbreviations: CAA, coronary artery aneurysm; KD, Kawasaki disease; LMWH, low-molecular-weight heparin; LV, left ventricular, MIS-C, multisystem inflammatory syndrome in children; MRI: magnetic resonance imaging.

### 3 | CONCLUSION

MIS-C is a life-threatening hyperinflammatory syndrome that mainly damages multiple-organ systems predominantly in previously healthy children during the COVID-19 pandemic. TPE may be useful as an initial therapy, especially in patients with severe manifestations. Larger multicentre studies are needed to elucidate the spectrum of diseases, risk factors of more severe disease and treatment strategies. The long-term implications of the cardiac involvement in MIS-C are unknown but may be important as in KD. Long-term follow-up of patients with MIS-C is required, especially in terms of cardiac effects.

### DISCLOSURES

The authors have no conflicts of interest to declare.

### AUTHOR CONTRIBUTIONS

Algorithms were created following the CDC case definition/WHO case definition with input from specialists in the areas of pediatric infectious diseases, pediatric intensive care unit, pediatric cardiology, pediatric rheumatology, pediatric hematology, pediatric pulmonology, pediatric emergency medicine, pediatric neurology, pediatric nephrology, pediatric allergy/immunology, gastroenterology, pediatric endocrinology and metabolism, pediatric gastroenterology and pediatric surgery. The MIS-C Study Group comprised 18 participants...
including: Serhat Emeksz, Banu Çelikel Acar, Ayşe Esin Kibar, Aslinur Özkaya Parlıkay, Oktay Perk, Gülşüm İslç Bayhan, Güzin Cinel, Namık Özbek, Müjdem Nur Azil, Elif Çelikel, Halise Akça, Emine Dibek Mizriloğlu, Umut Selda Bayrakçı, İbrahim ilker Çetin, Ayşegül Neşe Çıkat Kurt, Mehmet Boyraz, Şamil Hızlı, Emrah Şenel. Serhat Emeksz, Banu Çelikel Acar, Ayşe Esin Kibar, Aslinur Özkaya Parlıkay: An important contribution to the organization of the manuscript, to the writing of the manuscript and the creation of algorithms. Oktay Perk, Gülşüm İslç Bayhan, Güzin Cinel, Namık Özbek, Müjdem Nur Azil, Elif Çelikel, Halise Akça, Emine Dibek Mizriloğlu, Umut Selda Bayrakçı, İbrahim ilker Çetin, Ayşegül Neşe Çıkat Kurt, Mehmet Boyraz, Şamil Hızlı, Emrah Şenel: They discussed the algorithm and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES
1. Felsenstein S, Hedrich CM. SARS-CoV-2 infections in children and young people. Clin Immunol. 2020;220:108588.
2. Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.
3. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet. 2020;395(10239):1771-1778.
4. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the 2019-cov-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
5. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in pediatric hospitals in New York City. JAMA. 2020;324(3):294-296.
6. CDC Health Alert Network. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19); 2020. https://emergency.cdc.gov/han/2020/han00432.asp. Accessed May 14, 2020.
7. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19; 2020. https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed May 15, 2020.
8. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children. 2020;7(7):69-82.
9. Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2021;5(2):133-141.
10. Aydin F, Celikel E, Ekici Tekin Z, et al. Comparison of baseline laboratory findings of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis and multisystem inflammatory syndrome in children. Int J Rheum Dis. 2021;24(4):542-547.
11. Dove ML, Jaggi P, Kelleman M, et al. Multisystem inflammatory syndrome in children: survey of protocols for early hospital evaluation and management. J Pediatr. 2021;229:33-40.
12. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young. American Heart Association. Circulation. 2004;110(17):2747-2771.
13. Jonat B, Gorelik M, Boneparth A, et al. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York City: patient characteristics and an institutional protocol for evaluation, management, and follow-up. Pediatr Crit Care Med. 2021;22(3):e178-e191.
14. Chen J, Wang X, He P, et al. Viral etiology, clinical and laboratory features of adult hemophagocytic lymphohistiocytosis. J Med Virol. 2016;88(3):541-549.
15. Jose RJ, Manuel A. COVID-19 cytokine storm: The interplay between inflammation and coagulation. Lancet Respir Med. 2020;8(6):e46-e47.
16. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763-1770.
17. Wardle AJ, Connolly GM, Seager MJ, Tolloh RM. Corticosteroids for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2017;1(1):CD011188.
18. de Graeff N, Groot N, Ozen S, et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease—the SHARE initiative. Rheumatology. 2019;58(4):672-682.
19. Henderson LA, Canna SW, Friedman KG, et al. American college of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol. 2021;73(4):e13-e29.
20. Dimopoulos G, de Mast Q, Markou N, et al. Favorable Anakinra responses in severe Covid-19 patients with secondary hemophagocytic lymphohistiocytosis. Cell Host Microbe. 2020;28(1):117-123.
21. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2021;110:102452.
22. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci. 2020;117(20):10970-10975.
23. Çelikel E, Tekin ZE, Aydin F, et al. Role of biological agents in the treatment of SARS-CoV-2-associated multisystem inflammatory syndrome in children. J Clin Rheumatol. 2021 Apr 9. https://doi.org/10.1097/RHU.0000000000001734. Epub ahead of print.
24. Tanner T, Wahezi DM. Hyperinflammation and the utility of immunomodulatory medications in children with COVID-19. Paediatr Respir Rev. 2020;35:81-87.
25. Langer-Gould A, Smith JB, Gonzales EG, et al. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. Int J Infect Dis. 2020;99:291-297.
26. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev. 2020;51526–0542(20):3017-3012.
27. Demirkol D, Yıldızdaz B, Bayraki B, et al. Turkish secondary HLH/MAS critical care study group. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macrophage activation syndrome: what is the treatment? Crit Care. 2012;16(2):R52.
28. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care. 2020;24(1):128–130.

29. Luo S, Yang L, Wang C, Liu C, Li D. Clinical observation of 6 severe COVID-19 patients treated with plasma exchange or tocilizumab. Zhejiang Da Xue Bao Yi Xue Ban. 2020;49(2):227-231.

30. Bobek I, Gopcsa L, Réti M, et al. Successful administration of convalescent plasma in critically ill COVID-19 patients in Hungary: the first two cases. Orv Hetil. 2020;161(27):1111-1121.

31. Adeli SH, Asghari A, Tabbarrai R, et al. Therapeutic plasma exchange as a rescue therapy in patients with coronavirus disease 2019: a case series. Pol Arch Intern Med. 2020;130(5):455-458.

32. Emeksiz S, Özcan S, Perk O, et al. Therapeutic plasma exchange: a potential management strategy for critically ill MIS-C patients in the pediatric intensive care unit. Transfus Apher Sci. 2021 Apr 1:103119. https://doi.org/10.1016/j.transci.2021.103119. Epub ahead of print.

How to cite this article: Emeksiz S, Çelikel Acar B, Kibar AE, et al. Algorithm for the diagnosis and management of the multisystem inflammatory syndrome in children associated with COVID-19. Int J Clin Pract. 2021;00:e14471. https://doi.org/10.1111/ijcp.14471