



NON-SYSTEMATIC REVIEW

Pediatrics

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

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.

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.¹ 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).² 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 hyperinflammatory syndrome. In the latter half of April 2020, an apparent cluster of children presented with Kawasaki disease (KD)-like symptoms, toxic shock syndrome (TSS) and secondary hemophagocytic lymphohistiocytosis (SHLH)/macrophage activation syndrome (MAS) in Italy, the United Kingdom and the United States.^{3–5} A novel syndrome in children termed “multisystem inflammatory syndrome in children” (MIS-C) associated with SARS-CoV-2 infection was described. The cluster of MIS-C cases lagged behind the peak incidence of COVID-19 among adults by approximately one month. Positive SARS-CoV-2 serological test results has been reported in a greater proportion (80%–90%) of patients with MIS-C than positive polymerase chain reaction test results (20%–40%), which suggests that this syndrome may be post-infectious rather than related to acute early infection. Therefore, MIS-C is a delayed immunological

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.^{4,5}

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.

In the case series from Bergamo, Italy, KD and KD-like illnesses were observed at an incidence rate 30 times higher than that in the previous five years.³ The emergence of clusters of KD and KD-like illnesses in areas that have been heavily affected by COVID-19, such as Italy, the United Kingdom and New York City, clearly suggests a link between SARS-CoV-2 and MIS-C.³⁻⁵ However, only a quarter to around one-half of all reported MIS-C cases meet the full diagnostic criteria for KD.⁸ Published cases showed similarities between patients with MIS-C and those with other well-defined syndromes, including KD, TSS and SHLH/MAS, providing guidance for treatment. MIS-C has several clinical and laboratory features that differ from KD unrelated to SARS-CoV-2 infection. First, the age distribution of patients with MIS-C is between three months and 17 years, while the age of onset of KD is less than five years. Second, hematologic abnormalities are slightly different. Patients with KD have leucocytosis with neutrophil predominance and thrombocytosis, but rarely develop thrombocytopenia. By contrast, lymphopenia and thrombocytopenia are common in patients with MIS-C. Finally, as the most important difference, although both diseases involve coronary artery dilations or coronary artery aneurysms (CAA), left ventricular dysfunction and shock are more common in MIS-C.⁸

Some patients with MIS-C present with clinical and laboratory findings suggestive of SHLH/MAS. Evidence of systemic inflammation, decreased white blood cell count, platelet count and erythrocyte sedimentation rate, increased triglyceride and D-dimer levels, coagulopathy and organ dysfunctions are detected in patients with SHLH/MAS. The presence of fever and hyperferritinemia (> 500 ng/mL) are specific to SHLH/MAS.⁶⁻⁹ We aimed to better understand this cytokine storm syndrome by comparing the initial laboratory findings of MIS-C and MAS in our study with those of a comparative

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, hypoalbuminemia)	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 natriuretic 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, SHLH/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

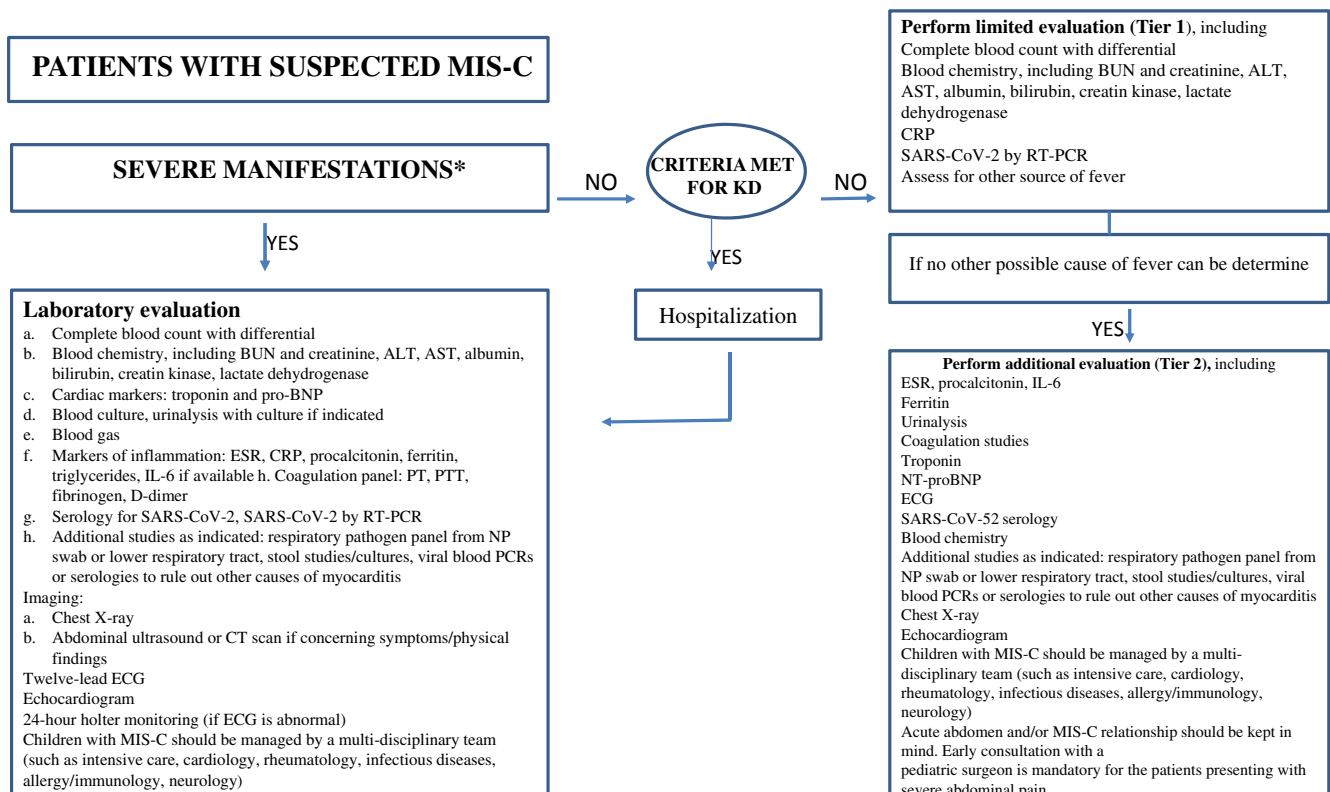


FIGURE 1 Approach for evaluating patients with suspected COVID-19 associated multisystem inflammatory syndrome in children. ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, *c-reactive protein*; CT: computed tomography; pro-BNP, pro-B-type natriuretic peptide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; PT, prothrombin time; PTT, a partial thromboplastin time; 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 injury¹²

symptoms and decreased inflammatory marker levels.¹⁷ Therefore, it would be quite reasonable to use steroids in the treatment of MIS-C, which reflects the hyperinflammatory state associated with SARS-CoV-2 infection in children. Low-to-moderate or high-dose corticosteroid therapy is commonly used for the treatment of KD. Low-to-moderate glucocorticoid doses may be considered in patients who do not respond to first-line therapy. High-dose glucocorticoids may be considered in the treatment of patients with life-threatening complications. Corticosteroids should be considered for high-risk cases according to the KD guidelines that were published in 2019 (fever or persistent inflammation \geq 48 hours after IVIG, defined as a Kobayashi score \geq 5, characteristics of SHLH/MAS [ie, ferritin level $>$ 500 ng/mL], shock, age $<$ 1 year and/or coronary or peripheral aneurysms at diagnosis).¹⁸ Similarly, the use of corticosteroids is recommended as a second-line therapy for nonspecific presentations.

Biological agents are recommended as a third-line therapy for all children with MIS-C whose conditions are refractory to IVIG and/or glucocorticoids.¹⁹ Dysregulation in the interleukin (IL)-1/IL-6 pathway is thought to play an important role in severe COVID-19 complications. Although data on biological treatments in patients with MIS-C are limited, promising results with biologicals have been shown in adult patients with COVID-19.²⁰

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.²¹ 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.²² 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/MAS. 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/MAS. Coronary artery dilatation, CAAs and left ventricular dysfunction were detected in 18 patients during their PICU stay. IVIG and glucocorticoids were given to 33

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.³² 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 diversion from the KD guidelines is the administration of systemic anticoagulants to some patients with MIS-C. This choice might be made potentially 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 managements 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 $\geq 450\,000/\mu\text{L}$) 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

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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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