Current Treatment Guidelines of SARS-CoV-2 Related Multisystem Inflammatory Syndrome in Children: A Literature Review and Expert Opinion

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a systemic disorder that seems to be associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since April 2020, there have been multiple reports about children with this new condition worldwide, including Europe, Asia, Latin America, and North America. The symptoms of this syndrome mimic the clinical manifestations of Kawasaki disease; therefore, the treatment of Kawasaki disease, as well as supportive care, was the management of choice in children with MIS-C in the early days of recognizing it. It is important to precisely ascertain the risk of COVID-19 infection and its severity in children and to acknowledge the management of this syndrome, with reliable data from cohorts, trials, and experts' opinions. In the current review, we summarize the current management guidelines for MIS-C and present our own protocol to answer some clinical questions regarding MIS-C management during the COVID-19 pandemic.

Keywords
- COVID-19
- SARS-CoV-2
- multisystem inflammatory syndrome in children
- treatment
- guideline

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread worldwide and led to an emerging pandemic, which has affected all age groups including newborns.[1,2] In the beginning, it was assumed that SARS-CoV-2 causes mild respiratory symptoms in children,[1] but in late April 2020, some reports showed a new clinical syndrome in children resembling Kawasaki disease and toxic shock syndrome.[3,4] Kawasaki disease is an acute medium-vessel vasculitis that causes fever, mucus inflammatory manifestation (e.g., strawberry tongue), skin rash, and lymphadenopathy.[5] The etiology of Kawasaki disease remains unclear, but various theories including viral infection have been proposed.[6,7] Although this new syndrome seems to mimic Kawasaki disease, there are several clinical and laboratory factors that can partly distinguish multisystem inflammatory syndrome in children (MIS-C) from Kawasaki disease.[8,9]

Since MIS-C is a new condition, the benefit and efficacy of various treatments are not fully evident yet.[9] For children with a mild presentation, only supportive care and follow-up are recommended.[10] Other cases with moderate-to-severe clinical manifestations should be admitted to the hospital to receive appropriate treatment and to be monitored closely in case a pediatric intensive care unit (PICU) admission is required.[11]

Various terms have been used to refer to this hyperinflammatory response in pediatrics, including pediatric multisystem inflammatory syndrome, pediatric COVID-19 associated inflammatory disorder, hyperinflammatory shock in children with COVID-19, "Kawashocky," "Coronasacki," and MIS-C. We will use the term MIS-C for the purposes of this review.

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Several children with symptoms indicating Kawasaki disease or MIS-C, according to the criteria provided by the Center for Disease Control and Prevention (CDC), were also referred to the hospitals affiliated to Mashhad University of Medical Sciences. In the current article, we review and summarize several guidelines for MIS-C management. We also render a guideline via advice from pediatric infectious disease specialists, pediatric rheumatologists, and pediatric cardiologists on the management of MIS-C cases in our centers.

Multisystem Inflammatory Syndrome in Children Definitions

Three MIS-C definitions put forth by CDC,[12] World Health Organization,[11] and the Royal College of Pediatrics and Child Health[10] are shown in ►**Table 1**. In all these definitions, the presence of persistent fever in addition to multisystem organ involvement without other possible diagnoses is essential. Furthermore, laboratory evidence of inflammation, SARS-CoV-2 infection confirmation, or recent exposure to a COVID-19 case is the key element in children with MIS-C. All these three guidelines have mentioned that children who present with manifestations resembling those of typical (complete) or atypical (incomplete) Kawasaki disease that also meet the criterial of MIS-C should be considered MIS-C cases. The criteria are slightly different and these definitions may even change, following the new information that is released.

Multisystem Inflammatory Syndrome in Children versus Kawasaki Disease

Kawasaki disease is an acute medium-vessel vasculitis that causes fever in association with signs of mucocutaneous inflammation.[13] The diagnosis of complete Kawasaki

Table 1 Case definition of multisystem inflammatory syndrome in children

		WHO	CDC	NHS The Royal College of Pediatrics and Child Health
Age		<19 y	<21 y	Child
Fever		Fever ≥ 72 h	Subjective persistent fever more than 24 h or documented fever more than 38.0°C for more than 24 h	Persistent fever more than 38.5°C
Clinical presentation		Bilateral nonpurulent conjunctivitis or rash Mucocutaneous inflammation signs (e.g., stomatitis) GI symptoms (e.g., abdominal pain, diarrhea, or vomiting) Hypotension or shock, ventricular dysfunction, pericarditis, valvulitis	Evidence of clinical deterioration requiring hospitalization, in addition to multiorgan dysfunction (≥2)	Single or multiple organ dysfunctions (e.g., cardiovascular, GI, renal, neurologic, or dermatologic) Supplemental oxygen requirements and low blood pressure have been reported in most pediatrics Other features, including GI symptoms (e.g., vomiting, abdominal pain, diarrhea), lymphadenopathy, sore throat, cough, rash, conjunctivitis, confusion, syncope, stomatitis, headache, respiratory symptoms, neck swelling, hand, and feet edema have been seen in some children
Laboratory data		Increased inflammatory factors (e.g., procalcitonin, ESR, or CRP) Abnormal coagulation test (INR, PT, PTT, and D-dimer) Evidence of coronary involvement (including a high amount of NT-proBNP /troponin or echo findings)	Hypoalbuminemia Neutrophilia Lymphocytopenia Elevated LDH, CRP, ESR, D-dimer, fibrinogen, procalcitonin, IL-6, ferritin	High ferritin and D-dimer level Abnormal fibrinogen amount Hypoalbuminemia Some cases present with AKI, high LDH, hypertransaminasemia, anemia, abnormal coagulation test, low platelets, elevated IL-6, as well as IL-10, increased creatine kinase level, high troponin, proteinuria, elevated TG
Evidence of COVID-19 infection (positive for any of the following factors)	Serology	+	+	NR
	Antigen test	+	+	NR
	RT-PCR	+	+	+
	Exposure to COVID-19 patients	+	+	NR
Ruling out alternative plausible diagnoses, including other infectious causes (e.g., toxic shock syndromes, bacterial sepsis)		+	+	+

Abbreviations: +, reported; AKI, acute kidney injury; APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CXR, chest X-ray; echo, echocardiography; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IL, interleukin; LDH, lactic acid dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; NR, not reported; NT-proBNP, N-terminal proB-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TG, triglycerides.

Table 2 Diagnostic criteria for Kawasaki disease

Fever	At least 5 d with no other plausible cause
Presence of ≥4 following criteria	Bilateral conjunctival congestion
	Changes of peripheral extremities (e.g., edema of hands or feet)
	Changes of oral cavity or lips (e.g., strawberry tongue and fissured lips)
	Acute lymphadenopathy (diameter >1.5 cm)
	Polymorphous exanthema

disease, according to the American Heart Association, includes an unexplained persistent fever for 5 days in addition to four out of five clinical criteria. The presence of less than four principal clinical features would be diagnosed as incomplete Kawasaki disease (►**Table 2**).[14] Some case series reported that about one-third to one-half of children with MIS-C met the full clinical criteria of Kawasaki disease.[8,15–18] Furthermore, prominent cardiovascular involvement was seen in children with Kawasaki disease shock syndrome, which refers to a severe form of Kawasaki disease with clinical features of shock, with no evidence of infection.[19] However, some factors help to distinguish between these two similar diseases. The common features of each disease are presented in ►**Table 3.**[8,9,20,21]

Clinical Findings

Based on reports on this syndrome, persistent fever (4–6 days) and gastrointestinal symptoms (e.g., abdominal pain) are the common presentation in almost all children.[22] The following symptoms have occurred in at least half of the patients: rash, conjunctivitis, mucous membrane involvement, neurological symptoms (e.g., headache), cardiac involvement, and respiratory symptoms (e.g., tachypnea and labored breathing). Other clinical manifestations such as sore throat, myalgia, swollen hands/feet, and lymphadenopathy have also been seen in less than 20% of MIS-C patients.[8,23,24] The cardiac manifestations in MIS-C patients are more likely to present with cardiac dysfunction, shock, and hypotension rather than with coronary artery abnormalities.[25,26] Shock was defined as tachycardia in addition to one of the following signs: decrease peripheral pulse, cold extremity, hypotension, oliguria, capillary refill time more than 3 seconds, or arterial blood lactate more than 2 mmol/L.[27]

Management

MIS-C is a new phenomenon and limited studies have been conducted on this subject. Therefore, information about this syndrome, especially its management, is scarce. Due to its

Table 3 The comparison of multisystem inflammatory syndrome in children features with Kawasaki disease

	MIS-C	Kawasaki disease
Age of presentation	Older children and adolescents (usually 8–10 y)	Infants and young children
Gender preference	Male	Male
Race	Black and Hispanic	Asian
Fever	Present	Present
Gastrointestinal symptoms (particularly abdominal pain)	Very common	Less prominent
Lymphadenopathy	Not common	More common
Hypotension	Sometimes	
Rash	Present	Present
Desquamation	Present	Present
Cardiovascular complications and shock	More common	Only in children with Kawasaki disease shock syndrome
Inflammatory markers (especially CRP, ferritin, and D-dimer)	More elevated	Normal to elevated
Absolute lymphocyte and platelet counts	Reduced	Normal
Troponin	Elevated	Normal
Positive SARS-CoV-2 test and exposure history	Yes	

Abbreviations: CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

resemblance to Kawasaki disease, the treatment of children with MIS-C has been based on the management of Kawasaki disease as well as experts' opinions. The coordination of various pediatric specialists in critical care units, infectious disease, rheumatology, and cardiology is necessary to manage these cases. Different treatments have been suggested by experts, but there is no evidence so far to affirm them.

The severity of the disease and its symptoms is the key element in choosing the treatment. Prescribing medications is not recommended for children who do not have severe symptoms, do not seem ill, and who do not need hospitalization. Therefore, the CDC emphasizes the importance of supportive care, including fluid resuscitation and respiratory support, along with close clinical follow-up.[28,29] On the other hand, children with moderate-to-severe clinical manifestations and hemodynamic instability should be admitted to the hospital. Since the progress of MIS-C to hypotension and critical situation may be fast, these children should be managed in a center with PICU. The American Academy of Pediatrics,[30] Tehran Children's Medical Center Protocol,[31] and also the guideline of the Children's Hospital of Philadelphia[32] recommend paraclinical evaluations, including laboratory and imaging assessments, to investigate potential infection and multiorgan involvement. These suggested tests in addition to the evaluation that we recommend are presented in ►**Table 4**. Renal and cardiac functions, as well as respiratory and neurological status, should carefully be monitored. It is also recommended to consider other plausible causes in the absence of a positive PCR test or any exposure to a COVID-19-infected case.[9] The purpose of any treatment in MIS-C is to prevent life-threatening presentations (e.g., shock) and long-term complications such as heart failure.

Different treatment protocols have been presented, but their efficacy has been controversial. These treatment options have been established based on specific clinical manifestations, the management of similar preexisting conditions such as Kawasaki disease, and experts' opinions. The pediatric specialists in our center arranged a guideline, considering the existing literature and worldwide evidence and their experience in managing MIS-C and other similar cases, since the beginning of the COVID-19 pandemic. These data are described in detail in ►**Tables 5** and **6**. Possible drug interactions should be considered before administering these agents.

Antipyretic therapy is an important step of supportive care. For children with fever (more than 38.5°C), paracetamol at a dosage of 10 to 15 mg/kg every 4 to 6 hours is preferred to ibuprofen, especially in dehydrated children (diarrhea or vomiting).[28]

Children who present with shock should immediately be resuscitated with crystalloid fluids. Most of these patients are resistant to volume expansion, so the use of vasopressor is therefore necessary. The first-line agent is epinephrine, and if the shock persists, norepinephrine is also administered. In case of severe myocardial involvement, dobutamine has also been suggested.[27,33] It is also very important to monitor for volume overload. The symptoms and laboratory data (e.g., increased neutrophilia or C-reactive protein) make it hard to rule out a bacterial infection. Therefore, empirical broad-spectrum antibiotics should be initiated in patients with severe clinical presentation and should be stopped once the patient's condition improves and an infection has been ruled out. Some of these children may need intubation or even extracorporeal membrane oxygenation.[27,34,35]

Kawasaki Disease Like Features

As mentioned above, up to 50% of MIS-C cases fulfill the diagnostic criteria of Kawasaki disease. Thus, the standard protocol for the management of Kawasaki disease was performed in most of the reported patients. Some children with MIS-C also present with shock; therefore, supportive care is critical in these cases.[36,37] Both the American Academy of Pediatrics[30] and the American College of Rheumatology guideline[38] suggest that intravenous immunoglobulin (IVIG) at a dose of 2 g/kg, which prevents cardiac dysfunction in Kawasaki disease, would be beneficial in these patients. The fluid status and cardiac functions should be

Table 4 Paraclinical evaluation in children with multisystem inflammatory syndrome in children

Laboratory evaluation	CBC with differential BUN and creatinine, sodium, potassium, calcium, phosphorus, magnesium Coagulation panel: PTT, PT, D-dimer, fibrinogen Creatinine kinase, LDH, C3, C4 AST, ALT, bilirubin, albumin, Amylase pro-BNP and troponin ESR, CRP, procalcitonin, ferritin, TG BC UA Nasopharyngeal swab for SARS-CoV-2 by RT-PCR
Echocardiogram	
12-lead electrocardiogram	
Imaging (if concerning symptoms/physical findings)	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BC, blood culture; BUN, blood urea nitrogen; C3, complement component 3; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; pro-BNP, pro-B-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TG, triglycerides; UA, urinalysis.

Table 5 Suggested doses and other data for agents in the treatment of multisystem inflammatory syndrome in children

Drug	Indication	Mechanism	Dosage	Administration	Adverse effects
Remdesivir	SpO_2 < 94% in a child with a positive PCR test and evidence of active infection	Viral RNA polymerase inhibition	Not on invasivemechanical ventilation: (1) Patients more than 40 kg: 200 mg on day 1 followed by 100 mg on days 2–5 (2) Patients less than 40 kg:5 mg/kg on day 1 followed by 2.5 mg/kg on days 2 to 5 Patients without any improvement after 5 d of treatment and patients on mechanical ventilation or ECMO: duration of therapy should be extended to 10 d	IV infusion over 30–120 min	Acute kidney injury (not recommended for patients with GFR less than 30 mL/min/1.73 m^2) Transaminase elevation (not recommended for patients with amino-transferase 5 times the upper limit of normal) GI symptoms (e.g., nausea, vomiting)
IVIG	Kawasaki disease features Shock Cardiac involvement Admission to PICU	Blocking the immune complex activation	2 g/kg (max. 60 g)	IV infusion over 12 h (over 24–36 h in patients with shock)	Thrombosis Heart failure
Aspirin	Patients with Kawasaki like features	Anti-platelet	30–50 mg/kg	Oral	Not recommended for patients who are receiving Enoxaparin
Enoxaparin	All patients	Anti-thrombin	1 mg/kg B.I.D. (2 mg/kg in patients with symptoms of thrombosis)		Bleeding (not recommended for patients with PLT <50,000 or fibrinogen >100 or active bleeding)
Methylprednisolone	Severe or refractory shock Kawasaki disease like feature in addition to IVIG resistance Persistent fever despite IVIG administration	Immunomodulator	1–3 mg/kg/day B.I.D. 20–30 mg/kg for patients who presented with shock or are irresponsive to IVIG administration (max. 1 g/dose). It can be repeated three times in cases with shock and five times in patients with encephalopathy.	IV (Important note: only methylprednisolone succinate should be used in IV administration)	Exacerbation of lymphopeniaHTN
Tocilizumab	Refractory KD	IL-6 inhibitor	Infants: 8 mg/kg/dose (max. 800 mg/dose) Children: <30 kg: 12 mg/kg/dose > 30 kg: 8 mg/kg/dose Note: In all patients, an additional dose can be repeated 12–24 h after the first administration	IV (over 60 min)	Increased lipid profile Volume retention HTN Hypersensitivity

Abbreviations: ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; HTN, hypertension; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PLT, platelets.

evaluated before IVIG administration. If they are not normal, the IVIG infusion rate should be reduced or the administration should be delayed.[39] The immunomodulatory agents (e.g., corticosteroids and tocilizumab) that showed beneficial outcomes in similar diseases were also administered for children with this syndrome. However, there is no evidence that which drug or what dose is optimal, which necessitates the establishment of randomized clinical trials to investigate the effectiveness of these therapies.[27,40,41]

Cardiac Monitoring

One of the life-threatening organ involvements in MIS-C is cardiac involvement. Many cases present with a high troponin level (~80%) or brain natriuretic peptide (~84%), which indicates myocardial injury and consequently arrhythmia and cardiac dysfunction.[8,15,27,34,35] Both the American Academy of Pediatrics and the Children's Hospital of Philadelphia Guideline advise that children with an abnormal ECG, echocardiogram, or high troponin should be referred to a pediatric cardiologist.[30,32]

Coronary artery dilation and aneurysm have been reported in children with severe MIS-C, but they have also been seen in children with only fever and mild inflammation. Cardiac evaluation and follow-up are therefore necessary for all patients.[8] It is essential to perform echocardiography for all cases and daily electrocardiogram (ECG) monitoring for patients with severe clinical presentation.

Table 6 Supplements that our center recommends for children with multisystem inflammatory syndrome in children

Vitamin C (not recommended for patients with diabetes mellitus or G6PD deficiency)	50–200 mg/kg (IV)
Zinc	5 times of daily requirement
Thiamin	100–300 mg/day
Vitamin D	2,000–3,000 unit/day

The American College of Rheumatology guideline for MIS-C recommends repeating echocardiography at least 1 to 2 weeks and also 4 to 6 weeks after the onset of the syndrome.[38] It should also be repeated 1 year after the onset of MIS-C for the children who had cardiac involvement detected during the previous echocardiograms. Patients with left ventricular (LV) dysfunction should have more echocardiograms. This guideline also recommends performing an MRI at 2 to 6 months after the diagnosis of MIS-C in patients with moderate-to-severe cardiac dysfunction to check for any scarring or fibrosis. An ECG should also be done in each follow-up session. In case of any conduction abnormalities, Holter monitoring is essential.

Coagulopathy Prevention

As coagulopathy is an important issue in dealing with COVID-19-infected cases, anticoagulant therapy, including heparin or low molecular weight heparin (LMWH), is recommended in these patients.[8,27] On the other hand, many children with MIS-C have a high D-dimer level. The American College of Rheumatology and the American Academy of Pediatrics suggest that aspirin at a dose of 3 to 5 mg/kg/day (up to 81 mg per day) is favorable in MIS-C cases with Kawasaki disease features, coronary artery aneurysm, or thrombocytosis.[30,38] In children with coronary artery z-score > 10.0, enoxaparin or warfarin will be more beneficial. However, the Italian Society of Pediatric Infectious Diseases does not recommend prophylaxis with enoxaparin in children, except for patients who are at higher risk for thrombotic complications.[28] The suggested dose for enoxaparin by this guideline is 150 to 300 unit/kg/day in neonates and 100 to 200 unit/kg/day for older pediatric patients.[28]

The Tehran Children's Medical Center Protocol[31] suggests using aspirin at a dose of 30–50 mg/kg/day (the classic Kawasaki treatment) in patients who fulfill clinical criteria for complete Kawasaki disease with confirmed laboratory results. If the patient responds to the medication, the treatment is suggested to continue at a dose of 3 to 5 mg/kg/day plus echocardiography after 2 weeks and 2 months after diagnosis.

The follow-up should be continued via echocardiography to rule out coronary artery aneurysms. The choice of agent, dosage, and duration should be consulted with a pediatric hematologist.[42]

Antivirals

Remdesivir is an intravenous nucleotide prodrug that prevents RNA polymerization of the virus and consequently reduces the replication of viral RNA. It has been shown that remdesivir reduces the duration of SARS-CoV-2 infection in adults. However, most children with MIS-C are not in the acute phase of the disease; therefore, the role of this agent in the management of MIS-C is limited. The guidelines by both the Italian Society of Pediatric Infectious Diseases[28] and the American Pediatric Infectious Diseases Society[43] suggest remdesivir as a preferred antiviral for COVID-19 treatment. In children who were tested positive for PCR and present with severe symptoms, the use of remdesivir could be effective.[44] The protocol of remdesivir administration is summarized in ►**Table 5**, and we also recommend the same protocol.[45]

Lopinavir and ritonavir are other antivirals that are recommended for severe cases by the Italian Society of Pediatric Infectious Diseases.[28] These agents are the protease inhibitors that had been used in China for the treatment of pneumonia following the COVID-19 infection.[46] These drugs are, however, contraindicated in premature neonates and neonates younger than 14 days. The recommended dose for children older than 12 months is 16.4 mg/kg twice a day.

Corticosteroids

Steroids decrease the occurrence risk of coronary artery disorder in children with Kawasaki disease who are resistant to IVIG.[47,48] The American College of Rheumatology reported that steroids at a dose of 1 to 2 mg/kg/day are sufficient in many children with MIS-C. It should be noted that some cases with shock required a high dose of intravenous (IV) glucocorticoids.[38] Furthermore, this guideline and also the American Academy of Pediatrics recommend tapering the dose of steroids over 2 to 3 weeks, regardless of the dosage, to prevent rebound inflammation.[30]

The RECOVERY trial (a large randomized clinical trial) indicated that low-to-moderate doses of dexamethasone are beneficial in patients with severe illness who are on mechanical ventilation. New findings showed that a low dose of dexamethasone may suppress the immune response and reduce the subsequent inflammatory diseases.[44,49,50]

The Italian Society of Pediatric Infectious Diseases recommends methylprednisolone at a dose of 1 to 2 mg/kg/day (maximum 80 mg) for 2 to 5 days, in children with worsening pulmonary function and a high level of inflammatory indicators in the laboratory data.[28] Moreover, in severe cases, the administration of high-dose dexamethasone (30 mg/kg) should be considered. This guideline also recommends considering dexamethasone at a dose of 0.2 to 0.4 mg/kg (maximum 6 mg) in patients who require supplemental oxygen therapy.

Biologic Drugs

The American College of Rheumatology guideline[38] recommends using immunomodulatory agents in severe COVID-19 infected cases, patients with shock or acute respiratory distress syndrome (ARDS), or children with signs of hyperinflammation in the laboratory data, including a high level of LDH (normal range: 140–280 units per liter), ferritin (newborns: 25–200 ng/mL, less than 1 month: 200–600 ng, 2 to 5 months: 50–200 ng, 6 months to 15 years: 7–142 ng), D-dimer (normal range: less than 250 ng/mL), IL-1 (normal range: 0–5 pg/mL), IL-6 (normal range: lower than 6.6 pg/mL), and CRP (normal

range: 0–10 mg/L). However, some contraindications declared by the Italian Society of Pediatric Infectious Diseases[28] are (1) transaminases >5 times the normal level, (2) being allergic to these drugs, (3) severe neutropenia, (4) bowel perforation or diverticulitis, and (5) platelets $<50{,}000$ count.

The American College of Rheumatology guideline suggests that anakinra (an IL-1 receptor inhibitor) at a dose of 10 mg/kg/day might be beneficial in Kawasaki disease patients with a severe condition who are irresponsive to IVIG.[38] An ongoing clinical trial (KAWAKINRA, ClinicalTrials.gov: NCT02390596) showed favorable results when using anakinra in patients with severe manifestations. The preferred dosage of anakinra for patients with cytokine storm syndromes by the panelists of the Italian Society of Pediatric Infectious Disease is 8 to 10 mg/kg/day in two or four divided IV doses for 2 to 3 days. The D-dimer and plasma level of IL-6 should be evaluated after 48 to 72 hours.[28]

Tocilizumab is an IL-6 receptor inhibitor that is used for juvenile idiopathic arthritis. This illness mimics Kawasaki disease in some manifestations, such as rash, arthritis, fever, and high ferritin level. This agent has shown promising results in the management of COVID-19 in adults, and an ongoing clinical trial (CORIMUNO-19, ClinicalTrials.gov: NCT04331808) tested this drug, and the results were encouraging.[51,52] The suggested dosage by the Italian Society of Pediatric Infectious Diseases guideline is 10 to 12 mg/kg for patients <30 kg and 8 mg/kg for >30 kg (maximum 800 mg).[28]

When to Discharge?

Patients who have been afebrile for at least 24 hours can be discharged from the hospital once they are well hydrated and do not require supplemental oxygen. Furthermore, their laboratory data and vital signs should show an improving trend.[42]

Conclusion

The available reports about MIS-C indicated that these patients can deteriorate quickly, and the management of this syndrome requires different pediatric specialists. Therefore, children with moderate to severe conditions should be hospitalized in a well-equipped center with PICU. The choice of treatment and protocol is based on the severity of clinical presentation and the experts' opinions.

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Conflict of Interest
None declared.

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