Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Journal of Emergency Medicine, Vol. 62, No. 1, pp. 28–37, 2022

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2021.07.070

Clinical Review

Multisystem Inflammatory Syndrome in Children

Muhammad Waseem, MD MS,[a] Masood A. Shariff, MD,[b] Ee Tein Tay, MD,[c] David Mortel, MD,[d] Shivraj Savadkar, MD,[d] Horton Lee, MD,[e] Noah Kondamudi, MD MBA,[f] and Tian Liang, MD FAAP[g]

aDepartment of Emergency Medicine, NYC Health + Hospitals/Lincoln, Bronx, New York; Weill Cornell Medicine New York and New York Medical College, Valhalla, New York, bDepartment of Emergency Medicine, NYC Health + Hospitals/Lincoln, Bronx, New York, cDepartment of Emergency Medicine, NYU Langone Health/Bellevue Hospital Center, New York, New York, dDepartment of Emergency Medicine, Harlem Hospital, New York, New York, eDepartment of Emergency Medicine-Pediatrics, NYC Health + Hospitals/Elmhurst Hospital, Queens, New York, fDepartment of Pediatrics, The Brooklyn Hospital Center, Brooklyn, New York, and gDepartment of Emergency Medicine, NYU Langone Health/Bellevue Hospital Center, New York, New York

Reprint Address: Muhammad Waseem, MD, MS, Department of Emergency Medicine, NYC Health + Hospitals/Lincoln, 234 East 149th Street, Bronx, NY 10451.

□ **Abstract—Background: Multisystem inflammatory syndrome in children (MIS-C) is a newly recognized condition affecting children with recent infection or exposure to coronavirus disease 2019 (COVID-19). MIS-C has symptoms that affect multiple organs systems, with some clinical features resembling Kawasaki disease (KD) and toxic shock syndrome (TSS). Objective of the Review: Our goal was to review the current literature and describe the evaluation and treatment algorithms for children suspected of having MIS-C who present to the emergency department. Discussion: MIS-C has a wide clinical spectrum and diagnosis is based on a combination of both clinical and laboratory findings. The exact mechanism of immune dysregulation of MIS-C is not well understood. Physical findings may evolve and do not necessarily appear at the same time. Gastrointestinal, cardiac, inflammatory, and coagulopathy manifestations and dysfunction are seen frequently in MIS-C. Conclusions: The diagnosis of MIS-C is based on clinical presentation and specific laboratory findings. In the emergency setting, a high level of suspicion for MIS-C is required in patients exposed to COVID-19. Early diagnosis and prompt initiation of therapy offer the best chance for optimal outcomes.**

□ **Keywords—multisystem inflammatory syndrome in children; Kawasaki disease; COVID-19; SARS-CoV-2; PMIS**

Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, a newly described hyperinflammatory condition has been reported among children with recent severe acute respiratory syndrome–related coronavirus 2 (SARS-COV-2) infections or exposures. These children presented with fever, systemic illness, and sometimes shock, cardiac involvement, and multi-organ failure. Initially recognized in the United Kingdom, reports of this condition spread subsequently in other parts of Europe and the United States (1–3). The Centers for Disease Control and Prevention (CDC) termed this condition as *multisystem inflammatory syndrome in children* (MIS-C). It shares many clinical features with Kawasaki disease (KD) and toxic shock syndrome (TSS), which can cause considerable diagnostic uncertainty for the treating physician. This review highlights overlapping manifestations between MIS-C and KD and the association of MIS-C with COVID-19.

Discussion

Pathophysiology

SARS-CoV-2 is a single-stranded RNA virus that causes COVID-19 infections in humans (4). It is part of

Received: 28 February 2021; Final submission received: 22 July 2021;
Accepted: 31 July 2021

the β genus of coronavirus that is also found in SARS-CoV and Middle East respiratory syndrome coronavirus (5). The virus invades cells through its "spike" structural protein, binding to the host cell receptors, such as angiotensin converting enzyme 2, during transmission, and is expressed in many organs of the body, including the lung, heart, ileum, kidney, and bladder (5). Severe COVID-19 infection is associated with a massive proinflammatory response and cytokine storm that results in multi-organ dysfunction in adults (6).

The exact mechanism of immune dysregulation of MIS-C is not well understood. The latent period between the peak of initial COVID-19 infection and onset of MIS-C and the observation that most of the children diagnosed with MIS-C are SARS-CoV-2 IgG–positive but polymerase chain reaction (PCR)–negative, suggests a post-infectious etiology (7,8). An uncontrolled cytokine storm involving hyperinflammatory markers, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1b, IL-6, and interferon-alfa, or a superantigen-like motif in the "spike" protein, has been proposed as a mechanism for the development of MIS-C (6,9,10).

Epidemiology

Although initially children were considered less susceptible to severe disease in COVID-19 infections, reports emerged from the United Kingdom in April 2020 that some SARS-CoV-2–positive children were presenting in a hyperinflammatory state with symptoms that overlap those of KD and TSS (1,11,12). Since then, hundreds of additional cases temporally related to COVID-19 infections have been identified in Europe and the United States and were eventually termed *MIS-C* (2,7,13–15). The incidence of MIS-C is rare, occurring in $< 1\%$ of children with COVID-19 infection (7). Children diagnosed with MIS-C were older than the typical age of patients with KD (7,13). There was a predominance of Hispanic and Black children among patients with MIS-C compared with the Asian predominance of children diagnosed with KD (1,7,13,16–18). Up to 40% of cases of MIS-C are in Black and Hispanic patients and $< 10\%$ in patients of Asian decent (7,13). These epidemiologic differences in addition to a family history predilection for KD suggest that the two conditions are separate entities (19,20).

Clinical Presentation of MIS-C

MIS-C is defined by the CDC as an individual younger than 21 years presenting with fever, laboratory evidence of inflammation affecting two or more organs (e.g., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), and exhibiting evidence of severe illness requiring hospitalization without an alternative plausible diagnosis (Tables 1 and 2) (21). The diagnostic clinical features are wide and overlap with KD (20). Children with MIS-C may present with fever, nonpurulent conjunctivitis, polymorphic rash, oral mucosal changes, swollen extremities, abdominal pain, vomiting, and diarrhea (2,7,13–15,22,23). Gastrointestinal symptoms are very common in children with MIS-C, which can help differentiate it from KD or TSS (7). Respiratory distress is not a common feature in children compared with adults (8,18). The diagnosis is made on the basis of a combination of both clinical and laboratory findings. The presentation involves a continuum of severity ranging from mild symptoms to multi-organ failure. Physical findings may evolve and do not necessarily appear at the same time.

Laboratory findings

The vast majority of patients with MIS-C show evidence of inflammation on serum testing (7,8). Commonly elevated inflammatory markers seen in MIS-C include C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), D-dimer, lactic acid dehydrogenase, and ferritin (7,8). Elevated white blood cell count with concomitant lymphopenia is associated with MIS-C (7). Lower levels of platelet counts are seen (8). Elevated cardiac enzymes, such as troponin and brain natriuretic peptide (BNP) are also seen in MIS-C (Table 3) (7,8).

Patients with KD also present with elevated inflammatory markers with several distinctions. Children with KD generally present with lymphocytosis, thrombocytosis, and anemia (24). Compared with MIS-C, patients with KD will usually have lower or normal cardiac enzyme markers (8). Both MIS-C and KD can present with elevated transaminases, CRP, ESR, and D-dimer (8,13,24).

Cardiac manifestations

Cardiac findings are common in MIS-C (7,8). Nearly 50% of patients present with shock and require some form of inotropic support and extracorporeal membrane oxygenation (ECMO) (Table 2) (1,2,7,13–15,18,22). Electrocardiograph abnormalities include atrial and ventricular tachycardia, heart blocks, and isolated changes with ST segment, QT prolongation, and T-wave abnormalities (18). Coronary artery dilatation and, in rare cases, aneurysms have been described in MIS-C (1). Pericarditis and valvulitis have also been reported (18). Aneurysm formation can occur in up to 15% of patients with KD, but occur much less frequently in MIS-C (24–29). Fortunately, heart failure symptoms in MIS-C respond well to treatment (18).

Gastrointestinal manifestations

Gastrointestinal symptoms are common in children with MIS-C (30). Most patients present with abdominal pain, diarrhea, or vomiting, which is a rarer finding in KD (8,24,31). The presence or absence of gastrointestinal symptoms can be helpful in differentiating the

Table 1. Definition of Multisystem Inflammatory Syndrome in Children According to the Centers for Disease Control and Prevention (21)

Case Definition for MIS-C
• An individual younger than 21 years presenting with fever,* laboratory evidence of inflammation,† and evidence of clinically severe illness requiring hospitalization, with multisystem (two or more) organ involvement (e.g., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic); AND • No alternative plausible diagnoses; AND • Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to onset of symptoms

COVID-19 = coronavirus disease 2019; MIS-C = multisystem inflammatory syndrome in children; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome–related coronavirus 2.

* Fever ≥ 38.0°C for ≥ 24 h or report of subjective fever lasting ≥ 24 h.

† Including, but not limited to, one or more of the following: elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin 6, or neutrophils; and reduced lymphocytes and low albumin.

Table 2. Presentations of Multisystem Inflammatory Syndrome in Children

Symptoms of MIS-C	Complications of MIS-C
• Fever	• Myocarditis
• Headache or mental status change	• Coronary artery aneurysm
• Conjunctivitis	• Hypotension and hypoperfusion
• Oral mucosa changes	• Serositis
• Sore throat	• Acute respiratory distress syndrome and respiratory failure
• Cough	• Acute kidney injury
• Abdominal pain	• Hepatic failure
• Vomiting or diarrhea	
• Rash	
• Lymphadenitis	
• Swollen extremities	

MIS-C = multisystem inflammatory syndrome in children.

Table 3. Clinical Features Distinguishing Multisystem Inflammatory Syndrome in Children and Kawasaki Disease (36)

Variable	MIS-C	Kawasaki Disease
Age	Any age	Usually < 5 y
Demographics	Increased incidence in Black and Hispanic patients	Increased incidence in East Asian patients
White blood cell count	Lymphopenia	Lymphocytosis
Platelets	Thrombocytopenia	Thrombocytosis
C-reactive protein	Elevated (> 100 mg/dL)	Elevated but usually < 100 mg/dL
Troponin	Increased	Usually normal
Brain natriuretic peptide	Increased	Usually normal

MIS-C = multisystem inflammatory syndrome.

two conditions. Abdominal imaging findings are numerous and often nonspecific, and can include hepatomegaly, splenomegaly, mesenteric adenitis, ascites, ileocolitis, or inflammation of either the gallbladder or appendix (12,13,32).

Coagulation and fibrinolytic system dysfunction

Hypercoagulability with vascular thrombosis has been reported in children with MIS-C. Prolonged prothrombin times and international normalized ratio, activated partial thromboplastin time, elevated D-dimer levels, and low antithrombin III can be seen. These abnormalities can cause disseminated intravascular thrombosis, venous and arterial thrombi, and development of pulmonary emboli (33).

Management

The treatment objectives for MIS-C are to reduce systemic inflammation, restore organ function, and reverse shock symptoms. Early recognition and prompt management of MIS-C is critical to optimal patient outcomes.

Workup (Laboratory Findings and Ancillary Testing)

Figure 1 presents an algorithm for the evaluation of patients suspected of having MIS-C in the emergency department. Laboratory tests to be considered during the initial evaluation of suspected MIS-C include complete blood count; comprehensive metabolic panel; inflammatory markers, such as CRP and D-dimer, BNP, and COVID-19 testing (PCR and IgG).

At least one laboratory marker of inflammation is required for a CDC case definition of MIS-C. Most children are COVID-19 PCR–positive or IgG antibody–positive (7). Although a blood culture is recommended in the evaluation of children with MIS-C for presumptive sepsis, most children have negative blood cultures (7).

Many institutions have implemented a screening algorithm with minor variations. Children with fever for 3 or more days, symptoms suspicious for MIS-C or KD, or no source of fever can enter the algorithm. Patients who present with symptoms concerning for MIS-C generally receive first-tier laboratory tests that include inflammatory and cardiac markers, such as CRP, D-dimer, and BNP (Figure 1 and Table 4). If these first-tier laboratory test results are abnormal, patients can then have a second-tier of laboratory tests, such as ESR, ferritin, troponin, and fibrinogen, with further evaluation for coagulopathies (Figure 1 and Table 4).

There is no standard set of laboratory cutoff values peculiar to this condition, but many of these biomarkers are often elevated, as in other inflammatory conditions. A careful review of the physical examination findings, laboratory results, and epidemiologic factors should be considered.

Alternative diagnoses should be ruled out before the diagnosis of MIS-C is made. Bacterial infection or sepsis should be duly considered and ruled out with negative cultures. Other viral infections, such as adenovirus, enterovirus, Epstein-Barr Virus, Human Herpesvirus 6 (HHV-6), and rubeola can be ruled out. Respiratory viral panels may be sent in addition to the COVID-19 nasal swab.

Emergency Department Management

Treatment of shock

Children with MIS-C can present in shock or multiorgan failure (7). Vasopressors are often required, as these children may be fluid-resistant (34). Distinction between warm and cold shock should be established, with pressor choice being norepinephrine and epinephrine, respectively (Figure 1). Judicious fluid administration is needed to avoid fluid overload in the setting of severe myocardial dysfunction. Empiric broad-spectrum antibiotics should be administered for patients meeting sepsis criteria or who present in shock.

Cardiac dysfunction

Ill-appearing children should obtain a point-of-care ultrasound or an echocardiogram to evaluate ejection fraction. Supportive care with fluid resuscitation, inotropes, mechanical ventilation, and, in the most severe cases, ECMO support, are essential for some patients during the acute phase. Declining or depressed left ventricular function and ejection fraction may necessitate admission to a pediatric center with ECMO capabilities. Elevations in cardiac enzymes, troponin levels, or pro-BNP should lead to cardiology consultation.

Disposition

If laboratory test results are reassuring and the patient is well-appearing, it is reasonable to discharge the patient home with close follow-up with primary care within 24–48 h (Figure 1). Patients with clinical manifestations and abnormal laboratory findings consistent with MIS-C should be hospitalized for close monitoring. Children with severe MIS-C disease and those with hypotension or shock requiring vasopressor support should be admitted to the pediatric intensive care unit (ICU). A multidisciplinary team approach involving pediatrics, cardiology, infectious disease, immunology, rheumatology, hematology, and intensive care can be helpful in optimizing patient outcomes.

Pharmacological Management of MIS-C

Clinical presentation and clinical course drive the management of the MIS-C patients. Although no universal

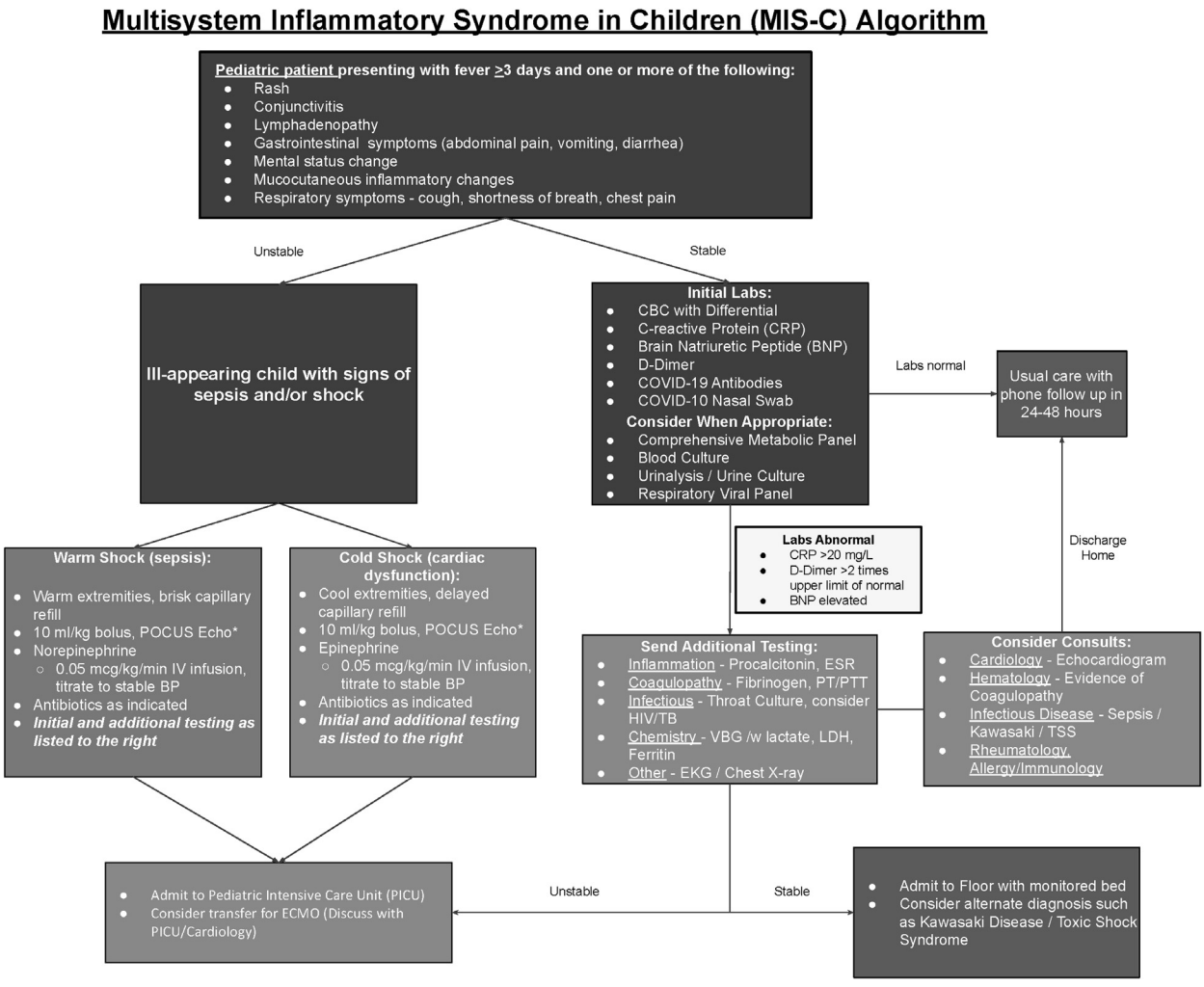

Figure 1. Diagnostic algorithm for suspected multisystem inflammatory syndrome in children. BP = blood pressure; CBD = complete blood count; COVID-19 = coronavirus disease 2019; Echo = echocardiogram; ECMO = extracorporeal membrane oxygenation; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; POCUS = point-of-care ultrasound; PT = prothrombin time; PTT = *partial thromboplastin time; TB = tuberculosis; TSS = toxic shock syndrome; VBG = venous blood gas.* *POCUS Echo.

protocol exists for the management of MIS-C, general guidelines based on current evidence, expert opinion, and anecdotal experiences have been published (35,36). Table 5 lists drugs with clinical considerations for use.

First-tier agents

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) has been used as a first-line treatment for MIS-C patients with KD-like presentation to blunt inflammatory response (35,36). The anti-inflammatory effect of this treatment is via the binding of Fcγ receptors on the IgG molecule and inhibition of cytokine production (IL-1 and IL-6) (37). IVIG has also been associated with an improvement of left ventricular systolic function and disease severity in MIS-C (35,36,38).

Corticosteroids

Corticosteroids have potent anti-inflammatory properties and the potential to blunt cytokine response (39). Dexamethasone use has been shown to reduce death in mechanically ventilated patients with severe COVID-19 infections (40). However, corticosteroids may also inhibit the immune response and potentially increase viral shedding (41). Methylprednisolone has been used successfully in the treatment of MIS-C (42). Treatment of MIS-C with IVIG and methylprednisolone is associated with faster recovery of cardiac function and shorter ICU stays compared with IVIG monotherapy (36). Glucocorticoids should be used with IVIG in patients with MIS-C

Table 4. Common Laboratory Findings in Patients with Multisystem Inflammatory Syndrome

Laboratory Test	Laboratory Test Finding
CBC with manual differential	Lymphocytes: Low ↓ Neutrophils: Low ↑ Platelets: Low ↓
Serum chemistry	Lactate dehydrogenase: Elevated ↑
Hepatic function panel	AST: Elevated ↑ ALT: Elevated ↑ Albumin: Low ↓
Inflammatory markers	C-reactive protein: Elevated ↑ Procalcitonin: Elevated ↑ Ferritin: Elevated ↑ Erythrocyte sedimentation rate: Elevated ↑ Interleukin-6: Normal or elevated ↑
Coagulation panel	D-dimer: Elevated ↑ Fibrinogen: Elevated ↑
Cardiac markers	B-type natriuretic peptide: Normal or elevated ↑ Troponin: Normal or elevated ↑

ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count.

who are ill-appearing, in shock, or have evidence of end-organ involvement (36).

Adjunct therapies

Aspirin

Aspirin is typically given to patients diagnosed with MIS-C who present with cardiac involvement or clinical features of KD (36). In contrast to KD, in which patients are given high-dose aspirin (30–100 mg/kg/d) until clinical improvement, low-dose aspirin (3–5 mg/kg/d) is used in the initial treatment of MIS-C (24,36). Therapeutic anticoagulation is strongly recommended for patients with MIS-C with ventricular dysfunction or large coronary artery aneurysms (18).

Proinflammatory cytokine inhibitors

Proinflammatory cytokine inhibitors, including anakinra (IL-1 receptor antagonist) and tocilizumab (anti–IL-6 receptor monoclonal antibody), have been used as adjunct therapies for MIS-C (37). These medications have been effective in other hyperinflammatory conditions with good safety profiles (41,43). Anakinra can be considered for patients with MIS-C with severe inflammation, those not responding to first-line therapies or who have a contraindication to receiving corticosteroids (36,37). The evidence of benefit for tocilizumab in treating COVID-19 hyperinflammation is less robust and its use should be guided with rheumatology or infectious disease consultation (36).

Remdesivir

Remdesivir is a broad-spectrum antiviral agent that has received emergency approval from the U.S. Food and Drug Administration (FDA) for treatment of selected patients with COVID-19. It is a nucleoside analogue that inhibits viral RNA polymerase causing termination of RNA transcription. This decreases viral RNA production and can reduce the duration of illness (37). Remdesivir treatment can be considered in severely ill SARS-Cov-2 PCR–positive children (42,44). Its use in treatment of an individual patient with MIS-C should be guided by subspecialist consultation.

Hydroxychloroquine

Hydroxychloroquine was found to have anti–SARS-CoV-2 activity in vitro studies and received Emergency Use Authorization (EUA) from the FDA on March 20, 2020 (45,46). However, there is no robust evidence to support its use in COVID-19 infection. On June 15, 2020, the FDA revoked the EUA for hydroxychloroquine and chloroquine (47).

Hypercoagulable Disease Management

Recent studies have found that thrombosis has a lower incidence in children with COVID-19 compared with adults (48). However, children with MIS-C are at greater risk for hypercoagulable events compared to those with asymptomatic COVID-19 infection (49). Anticoagulant use is recommended in patients that have features of KD,

Table 5. Pharmacologic Treatment

Drug	Clinical Consideration
First-tier agents	
IVIG	• Give to patients with MIS-C who fulfill Kawasaki disease criteria • Dose: 2 g/kg in a single dose (ideal body weight) • Adverse effects: fevers, chills, myalgias, nausea, and anaphylaxis (rare)
Corticosteroids	• Give in addition to IVIG in ill-appearing patients, patients in shock, cardiac dysfunction, or with end-organ disease • Dose: methylprednisolone 1–2 mg/kg/d • Toxic effects: Immunosuppression, metabolic changes, hypertension
Adjunctive treatments	
Aspirin	• Give to all patients with MIS-C • Dose: 3–5 mg/kg daily (low-dose) Contraindications: active bleeding, significant bleeding risk, or thrombocytopenia ($<$ 80,000/μL)
Anakinra	• Interkeukin-1 inhibitor. Consider in MIS-C refractory to IVIG and steroid treatment • Dose: 4 mg/kg/d i.v. or s.c. • Adverse effects: nausea, vomiting, and hypersensitivity reactions
Tocilizumab	• Interleukin-6 inhibitor. Consider in severe disease in consultation with infectious disease or rheumatology specialist • Dose: $<$ 30 kg: 12 mg/kg i.v., $>$ 30 kg: 8 mg/kg i.v. • Adverse effects: neutropenia and transaminitis
Remdesivir	• Consider in severely ill SARS-CoV-2 PCR–positive children • Dose: 5 mg/kg/dose i.v. (maximum dose 200 mg) on day 1, followed by 2.5 mg/kg/dose i.v. (maximum dose 100 mg) once daily. • Adverse effects: nausea, vomiting, and transaminitis
Hydroxychloroquine*	• No robust evidence to support its use in COVID-19 infection

IVIG = intravenous immunoglobulin; MIS-C = multisystem inflammatory syndrome; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome–related *coronavirus 2;* s.c. = subcutaneous.

* U.S. Food and Drug Administration revoked the Emergency Use Authorization for hydroxychloroquine and chloroquine in June 2020 and it is no longer indicated as a treatment for COVID-19 infection or multisystem inflammatory syndrome (mentioned above only for historical significance).

evidence of thrombosis, coronary artery involvement, or depressed ejection fraction ($<$ 35%) (18,36). Therapeutic anticoagulation with enoxaparin should be started during the inpatient period and continued after recovery and discharge for 2 weeks (36). Low-dose aspirin (3–5 mg/kg/d, maximum 81 mg/d) should be given until normal platelet counts and normal coronary arteries are confirmed, at least 4 weeks after the diagnosis (36). The D-dimer levels can also aid in assessing the need for anticoagulation, thromboprophylaxis should be considered for patients with D-dimer levels more than five times the upper limit of normal (50). Treatment with antiplatelet and anticoagulation therapy should be avoided for patients with severe thrombocytopenia ($<$ 20,000–80,000/μL) and those with significant bleeding risk or active bleeding (36,50). Overall, choice of therapy should be tailored to the individual risk assessment for the patient.

Conclusions

MIS-C is a new clinical manifestation associated with COVID-19 infection and is likely a distinct entity from KD. The occurrence of MIS-C in older children, predominance of gastrointestinal symptoms, and the extent of myocardial dysfunction differentiates it from KD. The diagnosis of MIS-C is based on criteria involving clinical and laboratory findings without a plausible alternate diagnosis. It is important to maintain a high level of suspicion for this emerging clinical phenomenon. Early recognition,

excellent supportive care, and intervention using a multidisciplinary team approach provides the best chance for improved outcomes.

Acknowledgments

The authors thank Dr. Hina Asad for reviewing the manuscript and her tremendous input into the content structure.

References

1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607–8.
2. 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):1771–8.
3. Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, et al. Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. Pediatr Infect Dis J 2020;39(8):e195–8.
4. Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization. Accessed October 30, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it%0A
5. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020;215.
6. Molloy EJ, Bearer CF. COVID-19 in children and altered inflammatory responses. Pediatr Res 2020;88:340–1.
7. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347–58.
8. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259–69.
9. Tezer H, Demirdağ TB. Novel coronavirus disease (COVID-19) in children. Turk J Med Sci 2020;50(SI–1):592–603.
10. Pang J, Boshier FAT, Alders N, Dixon G, Breuer J. SARS-CoV-2 polymorphisms and multisystem inflammatory syndrome in children. Pediatrics 2020;146(6).
11. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:759–65.
12. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145(6).
13. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334–46.
14. Levin M. Childhood multisystem inflammatory syndrome—a new challenge in the pandemic. N Engl J Med 2020;383:393–9.
15. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr 2020;10:537–40.
16. Goyal MK, Simpson JN, Boyle MD, et al. Racial and/or ethnic and socioeconomic disparities of SARS-CoV-2 infection among children. Pediatrics 2020;146(4).
17. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927–99.
18. Alsaied T, Tremoulet AH, Burns JC, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation 2021;143:78–88.
19. Uehara R, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease in parents and children. Acta Paediatr 2003;92:694–7.
20. Rowley AH. Multisystem inflammatory syndrome in children and Kawasaki disease: two different illnesses with overlapping clinical features. J Pediatr 2020;224:129–32.
21. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Center for Disease Control and Prevention. Accessed December 20, 2020. Available at: https://www.cdc.gov/mis-c/
22. Dallan C, Romano F, Siebert J, Politi S, Lacroix L, Sahyoun C. Septic shock presentation in adolescents with COVID-19. Lancet Child Adolesc Heal 2020;4(7):e21–3.
23. Young TK, Shaw KS, Shah JK, et al. Mucocutaneous manifestations of multisystem inflammatory syndrome in children during the COVID-19 pandemic. JAMA Dermatol 2021;157:207–12.
24. Ramphul K, Mejias SG. Kawasaki disease: a comprehensive review. Arch Med Sci Atheroscler Dis 2018;3:e41–5.
25. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142:429–36.
26. Shulman ST. Pediatric coronavirus disease-2019-associated multisystem inflammatory syndrome. J Pediatric Infect Dis Soc 2020;9:285–6.
27. Stiglic N, Viner RM. Effects of screentime on the health and well-being of children and adolescents: a systematic review of reviews. BMJ Open 2019;9(1).
28. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5 819–8.
29. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: is there a linkage to Kawasaki disease? Trends Cardiovasc Med 2020;30:389–96.
30. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to coronavirus disease 2019: a single center experience of 44 cases. Gastroenterology 2020;159 1571–4.e2.
31. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem inflammatory syndrome in children (MIS-C) associated with SARS–CoV-2: a systematic review. J Pediatr 2020;226:45–54.
32. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatric Infect Dis Soc 2020;9:393–8.
33. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–50.
34. Kache S, Chisti MJ, Gumbo F, et al. COVID-19 PICU guidelines: for high- and limited-resource settings. Pediatr Res 2020;88:705–16.
35. Capone CA, Subramony A, Sweberg T, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr 2020;224:141–5.
36. 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 2. Arthritis Rheumatol 2021;73(4):e13–29.

37. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med 2020;383:1813–26.
38. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children—initial therapy and outcomes. N Engl J Med 2021;385:23–34.
39. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.
40. Horby P, Lim WS, Emberson J, et alRECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693–704.
41. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223):473–5.
42. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020;20:e276–88.
43. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Crit Care Med 2016;44:275–81.
44. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. J Pediatr 2020;223 14–9.e2.
45. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;71:732–9.
46. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020;6:16.
47. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. US Food and Drug Administration. Accessed November 6, 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or
48. Saleh NY, Aboelghar HM, Salem SS, et al. The severity and atypical presentations of COVID-19 infection in pediatrics. BMC Pediatr 2021;21:144.
49. Whitworth HB, Sartain SE, Kumar R, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. Blood 2021;138:190–8.
50. Goldenberg NA, Sochet A, Albisetti M, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. J Thromb Haemost 2020;18:3099–105.

ARTICLE SUMMARY

1. Why is this topic important?

Multisystem inflammatory syndrome in children (MIS-C) is a novel entity affecting children recently exposed to or infected by the severe acute respiratory syndrome–related *coronavirus 2*. Some of these children presented with shock, cardiac involvement, and multi-organ failure. Understanding the nuances and complexities of this new condition will help enhance patient care, contribute to further research, and aid in the development of public health strategies. Formulation of appropriate protocols for early diagnosis and treatment will help achieve optimal outcomes.

2. What does this review attempt to show?

This article reviews the epidemiology, clinical features, laboratory findings, and management options of MIS-C and presents a workup algorithm for patient evaluation.

3. What are the key findings?

MIS-C typically presents with fever, multi-organ symptoms, inflammation on laboratory markers, and recent exposure to or infection with coronavirus disease 2019 (COVID-19). Some clinical features overlap with other hyperinflammatory conditions, such as Kawasaki disease and toxic shock syndrome. This highlights the importance of developing protocols to quickly identify and differentiate MIS-C from other diseases in the emergency setting.

4. How is patient care impacted?

Early identification and treatment of MIS-C can help prevent clinical deterioration, multi-organ failure, shock, and cardiac manifestations. Investigations into long-term sequelae of MIS-C are ongoing and require a multidisciplinary team to streamline the management, treatment, and follow-up of children affected by this condition. The understanding of the etiology and the differentiation of MIS-C from other inflammatory disorders will aid the clinician to efficiently allocate resources early in the disease process.