American Journal of Emergency Medicine 49 (2021) 148–152

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Multisystem inflammatory syndrome in children with COVID-19

Michael Gottlieb, MD [a,*], Rachel Bridwell, MD [b], Joseph Ravera, MD [c], Brit Long, MD [b]

[a] Department of Emergency Medicine, Rush University Medical Center, USA
[b] Department of Emergency Medicine, Brooke Army Medical Center, USA
[c] Department of Surgery, Division of Emergency Medicine, University of Vermont, USA

ARTICLE INFO

Article history:
Received 14 March 2021
Received in revised form 19 May 2021
Accepted 28 May 2021

Keywords:
COVID-19
MIS-C
Pediatrics

ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) is a dangerous pediatric complication of COVID-19.
Objective: The purpose of this review article is to provide a summary of the diagnosis and management of MIS-C with a focus on management in the acute care setting.
Discussion: MIS-C is an inflammatory syndrome which can affect nearly any organ system. The most common symptoms are fever and gastrointestinal symptoms, though neurologic and dermatologic findings are also well-described. The diagnosis includes a combination of clinical and laboratory testing. Patients with MIS-C will often have elevated inflammatory markers and may have an abnormal electrocardiogram or echocardiogram. Initial treatment involves resuscitation with careful assessment for cardiac versus vasodilatory shock using point-of-care ultrasound. Treatment should include intravenous immunoglobulin, anticoagulation, and consideration of corticosteroids. Interleukin-1 and/or interleukin-6 blockade may be considered for refractory cases. Aspirin is recommended if there is thrombocytosis or Kawasaki disease-like features on echocardiogram. Patients will generally require admission to an intensive care unit.
Conclusion: MIS-C is a condition associated with morbidity and mortality that is increasingly recognized as a potential complication in pediatric patients with COVID-19. It is important for emergency clinicians to know how to diagnose and treat this disorder.

1. Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a condition among pediatric patients with coronavirus disease of 2019 (COVID-19), resulting in inflammation of a variety of organ systems, including the heart, lungs, brain, kidneys, gastrointestinal system, skin, and eyes. There are a distinct set of clinical criteria, which are displayed in Table 1. The true global incidence of MIS-C is uncertain, but it appears to be rare. The first reported cases occurred in the United Kingdom, followed by reports from Canada, Europe, South Africa, and the United States [1-10]. Reports estimate the incidence in those under age 21 years to be 2 per 100,000 persons with an overall incidence among children with COVID-19 of 322 per 100,000 persons [1-4]. As of May 2021, 3742 cases of MIS-C have been reported in the United States, with 35 deaths related to MIS-C [1,3]. Most studies demonstrate a lag of 2–6 weeks between COVID-19 infection and developing MIS-C [1,2,5]. Over 70% of MIS-C cases occur in previously healthy patients, with obesity and asthma being the most common underlying medical conditions [1,7,11].

While MIS-C and Kawasaki disease (KD) share some overlap in symptoms, the epidemiology of MIS-C differs from that of KD. The median age of confirmed cases in MIS-C is 7–11 years, whereas 80–90% of cases of KD occur in children under age 5 years of age [5,12,13]. Males are more commonly affected in both MIS-C (up to 59%) and KD (up to 60%) [4,5,7,11,14,15]. The rates of MIS-C vary by race, with studies reporting 25–62% of patients being Black, 30–40% being Hispanic, 15–25% being White, and up to 28% being Asian [4,5,7,11,14]. By comparison, KD more commonly affects infants and young children of Asian descent, with an incidence of 30 per 100,000 for those of Asian or Pacific Islander descent compared with the lowest incidence among Caucasians (12 per 100,000) [15-18].

The complications of MIS-C can be severe, including cardiogenic shock or distributive shock with poor vasomotor tone. In one systematic review of 917 patients, 11 (1.9%) patients died [19]. Most patients with cardiac involvement (including depressed ventricular function or arrhythmias) typically recover. However, 20–45% of patients may still have a mildly depressed ejection fraction at the time of hospital discharge [19-22]. Given

* Corresponding author.
E-mail address: michaelgottliebmd@gmail.com (M. Gottlieb).

https://doi.org/10.1016/j.ajem.2021.05.076
0735-6757/

Table 1
MIS-C diagnostic criteria.

Criteria	CDC [3]	WHO [66]	RCPCH [67]
Age	<21 years	<19 years	All children (age not defined)
Fever	≥38C for ≥24 h or subjective fever lasting ≥ 24 h	Fever ≥ 3 days	Persistent fever ≥ 38.5C
Clinical	Evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement (≥2 of the following: cardiac, renal, respiratory, hematologic, GI, dermatologic, or neurologic)	At least 2 of the following: 1) Rash, conjunctivitis, mucocutaneous inflammation 2) Hypotension or shock 3) Cardiac involvement* 4) Coagulopathy 5) Acute GI symptoms	Single or multiorgan dysfunction and additional features**
Inflammation	At least one of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, IL-6, elevated neutrophils, reduced lymphocytes, low albumin	Elevated CRP, ESR, procalcitonin	Neutrophilia, elevated CRP, and lymphopenia
SARS-CoV-2	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or COVID-19 exposure within the 4 weeks prior to symptom onset	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or likely COVID-19 exposure	Positive or negative RT-PCR
Exclusion	No alternative diagnosis	No obvious microbial cause	Exclusion of other infections

CDC, Centers for Disease Control and Prevention; WHO, World Health Organization; RCPCH, Royal College of Paediatric and Child Health; GI, gastrointestinal; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; NT-proBNP, N-terminal pro-brain natriuretic peptide.
* Cardiac involvement defined by the WHO MIS-C case definition: features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin/NT-proBNP).
** Additional features for the RCPCH definition: abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucous membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting.

the significant impact of MIS-C on affected patients, it is important for the emergency clinician to be aware of this condition.

2. Methods

Authors searched PubMed and Google Scholar for articles using a combination of the keywords "MIS-C", "Multisystem Inflammatory Syndrome", "COVID-19", and "pediatric" from inception to May 18, 2021. The literature search was restricted to studies published in English. Authors reviewed all relevant articles and decided which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. A total of 67 articles were selected for inclusion in this narrative review.

3. Discussion

3.1. Pathophysiology and microbiology

The pathophysiology remains incompletely understood. The syndrome has been hypothesized to result from an abnormal immune response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but with a distinct immunophenotype when compared to KD [23-25]. Endothelial dysfunction associated with SARS-CoV-2 and cytokine storm have been proposed as the mechanisms of end organ injury in MIS-C [25]. One study suggests the SARS-CoV-2 spike protein may directly activate the immune system, functioning as a superantigen similar to Staphylococcal enterotoxin B [25,26]. This abnormal immune response may result in multiorgan injury and failure. Myocardial injury may be associated with systemic inflammation, viral myocarditis, cardiomyopathy, hypoxia, and/or coronary vessel involvement resulting in ischemia [25,27]. Autopsy findings have demonstrated evidence of pericarditis, myocarditis, and endocarditis with infiltration of inflammatory cells, as well as the presence of SARS-CoV-2 virus in cardiac tissue [28].

3.2. History and physical examination

The presentation of MIS-C varies and can mimic a variety of other conditions, particularly KD. Table 2 depicts differences between MIS-C and KD. Patients with MIS-C may present with gastrointestinal symptoms (abdominal pain, vomiting, or diarrhea are present in 60–100%), neurocognitive symptoms (headache, decreased mental status, or lethargy are present in 29–58%), respiratory symptoms (21–65%), sore throat (10–16%), and myalgias (8–17%) [1,4,7,10,11,14,19,20,29-31]. Severe cases may present with myocardial dysfunction (55%), cardiogenic shock (66%), multisystemic organ failure, and cytokine storm, which can overlap with presentations of KD, septic shock, secondary hemophagocytic lymphohistiocytosis, and toxic shock syndrome [10,19,32-34].

In one multinational survey of 183 pediatric patients with MIS-C, fever was present in 100% of cases [35]. Shock was present in 43.2% and was more common in older children (mean 9 years vs 7 years) [35]. A meta-analysis demonstrated similar results with 100% of patients presenting with fever, followed by 73.3% patients presenting with diarrhea or abdominal pain, and 68.3% patients presenting with

Table 2
Distinctions between MIS-C and Kawasaki disease [35]

MIS-C	Kawasaki disease
- More commonly affects older children and adolescents (>7 years) - GI symptoms very common - Myocardial dysfunction and shock more common - Inflammatory markers [CRP (12–22 times normal values), ferritin (1–3 times normal values), D-dimer (10–20 times normal values)] more significantly elevated - Absolute lymphocyte count and platelet counts are low	- More commonly affects younger children and infants (<5 years) - GI symptoms not common - Myocardial dysfunction and shock less common - Inflammatory markers (CRP, ferritin, D-dimer) not very elevated - Leukocytosis and thrombocytosis are common

MIS-C, Multisystem Inflammatory Syndrome in Children; GI, gastrointestinal; CRP, C reactive protein.

vomiting [30]. The vast majority of these patients will have fever for a minimum of 3 days, with a median duration of 4–6 days [30].

The physical examination of MIS-C patients can overlap with KD [32]. Conjunctivitis is present in 30–81% of patients with MIS-C, while rash is present in 45–76% [14,30,31,36]. The rash can have a variable appearance, including erythema, morbilliform, purpura, targetoid, or urticarial [37]. The majority of patients with MIS-C will exhibit abdominal tenderness on examination [30]. Multiorgan involvement is common in these patients, and cardiogenic or vasoplegic shock can occur in 32–76% of patients [1,7,11,27,28,32]. Patients may also present with mucous membrane involvement (27–76%), lymphadenopathy (6–16%), and swollen hands or feet (9–16%) [1,4,7,10,11,20,29-32,38-40]. Pleural effusions, pericardial effusions, and ascites can also occur in these patients [41]. Severe neurologic manifestations including seizures, altered mental status, encephalopathy, and meningoencephalitis may occur in 6–15% of patients [1,7,11,27,28,31].

One study compared MIS-C patients with control patients presenting with febrile illnesses from other common outpatient conditions [42]. Between these groups, MIS-C patients reported higher temperatures (40 °C vs 38.9 °C), increased frequency of abdominal pain (odds ratio [OR]: 12.5), neck pain (OR: 536.5), conjunctivitis (OR: 31.3), oral mucosal irritation (OR: 11.8), extremity swelling or rash (OR: 99.9), and generalized rash (OR: 7.4) [42].

3.3. Diagnostic testing

The diagnostic evaluation of suspected MIS-C in a toxic-appearing patient (e.g., shock, dehydration, respiratory distress, neurologic changes) should include a complete blood cell count (CBC), electrolytes, renal and liver function, inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), albumin, coagulation panel, D-dimer, SARS-CoV-2 testing (polymerase chain reaction [PCR] and/or serologies if available), troponin, and brain natriuretic peptide (BNP). Due to the overlapping presentation with sepsis, blood cultures should also be obtained. If available, ferritin, fibrinogen, and procalcitonin can assist the inpatient team.

For patients who are otherwise well-appearing, the American College of Rheumatology recommends a tiered system of testing [43]. In this testing strategy, those who appear well but in whom MIS-C is a consideration should be tested with CBC, electrolytes, renal and liver function, CRP, and ESR [43]. If CRP ≥ 5 mg/dL or ESR ≥ 40 mm/h are found on testing combined with one of the following other laboratory abnormalities (absolute lymphocyte count < 1.5, platelet count < 150,000, sodium < 135 mmol/L, neutrophilia, or hypoalbuminemia), then full testing as described above is recommended [43]. In order to avoid repeat blood draws in this population, it is recommended to obtain extra blood tubes for this additional testing if they are otherwise well-appearing, but MIS-C is suspected.

Elevated inflammatory markers are common, with 92% of patients having at least 4 of the following abnormalities: elevated ESR (75–80%), elevated D-dimer (67–100%), elevated CRP (90–100%), lymphocytopenia (80–95%), neutrophilia (68–90%), elevated ferritin (55–76%), hypoalbuminemia (48–95%), anemia (70%), thrombocytopenia (31–80%), or increased liver enzymes (62–70%) [10,19,35,44-47]. One large study found that inflammatory markers were higher and platelets were lower among those presenting in shock [35]. Cardiovascular involvement is commonly seen, with elevations in BNP/pro-BNP (73–95%) and troponin (50–93%) [10,19,31,35,44-46]. Acute kidney injury can occur in 8–52%, and laboratory evaluation may also reveal elevated lactate dehydrogenase (10–60%) or hypertriglyceridemia (70%) if these laboratory tests are obtained [1,7,11,27,28].

Because of the relatively broad presentations of MIS-C, pediatric emergency departments have sought to screen for these patients using a variety of physical examination and laboratory markers. One tertiary pediatric emergency department found that fever for more than 24 h plus 2 system involvement (gastrointestinal, mucocutaneous, lymphadenopathy) and at least 2 of 4 laboratory criteria above these set thresholds (CRP ≥ 87.5 mg/L, troponin *I* ≥ 17 ng/L, ferritin ≥ 121.6 ng/mL, D-dimer ≥1.07 mg/L fibrinogen equivalent units) had a sensitivity of 92% and a specificity of 83% [48]. Elevated CRP values, higher neutrophil counts, lower lymphocyte counts, elevated troponin, and lower serum albumin are associated with a greater risk of shock [10].

All patients with concern for MIS-C should receive an electrocardiogram (ECG). Arrhythmias are present in 12–21% of patients [1,7,11,27,28,49]. The most common abnormal ECG findings are repolarization abnormalities, ischemic changes, and first-degree atrioventricular block [35]. Other findings include bundle branch blocks, prolonged QT intervals, and high-grade atrioventricular blocks [31]. In an image review of chest radiographs in MIS-C patients, cardiomegaly (63%), cardiogenic pulmonary edema (56%), and atelectasis (56%) were the most common findings [50]. Other findings on chest radiography in this population included pleural effusions (44–82%), pulmonary consolidations (6–73%), and radiographic findings of acute respiratory distress syndrome (13%) [50,51]. If obtained, abdominal imaging may demonstrate small volume ascites, bowel wall thickening, gallbladder wall thickening, or abdominal lymphadenopathy [52,53]. Echocardiograms are performed in the majority of patients with MIS-C due to both concern for coronary artery aneurysmal dilation as well as cardiac dysfunction due to myocarditis [30]. The most common finding is reduced left ventricular ejection fraction, seen in 45–60% of patients [10,11,22,27,54]. Coronary artery abnormalities can be present in 8–50% of patients [10,11,27,30,31]. Echocardiogram may also demonstrate pericardial effusions (28%), mitral regurgitation (43%), or tricuspid regurgitation (6%) [8,31,36,55]. Comprehensive echocardiography can also be used to assess coronary artery diameter, described using the *Z*-score. The Z-score is a measured of the coronary artery diameter compared to the average diameter for a child of the same size body surface area. Normal Z-score values are 0, with values greater than 0 representing coronary artery dilation [56,57].

3.4. Management

The first step in management should be resuscitation and hemodynamic stabilization in those with evidence of shock, which can be present in 32–76% of patients with MIS-C [1,7,11,27,28]. As these patients are often toxic appearing and present similar to those with septic shock, broad spectrum antibiotics are recommended, with blood cultures obtained prior to antibiotic therapy when feasible. Given the potential for cardiogenic versus vasodilatory shock, point-of-care ultrasound should be performed prior to aggressive volume resuscitation [58]. Patients who are volume depleted based on either clinical examination or ultrasound should receive fluid resuscitation [59]. Many children presenting in shock with MIS-C will present with vasodilatory shock, which may be refractory to adequate volume repletion. These patients may require vasopressor support with agents such as epinephrine or norepinephrine. However, epinephrine may be preferred if cardiac dysfunction is present. Further inotropic support can be provided with dobutamine or milrinone. Intubation and mechanical ventilation may be required; however, this is rarely due to a primarily pulmonary indication [6,10].

Once children have been appropriately resuscitated, consultation with pediatric specialists (e.g., cardiology, intensive care, rheumatology, infectious disease, and/or hematology) is recommended. The mainstay of treatment for MIS-C is immunomodulation in those with shock, cardiac involvement, or severe disease manifestations requiring intensive care unit admission [1,4,6-8,10,40,42,59,60]. While there are no prospective studies to date, expert recommendations using data extrapolated from KD advise intravenous immunoglobulin (IVIG) as first-line therapy in doses of 2 g/kg administered every 8–12 h [1,4,6-8,10,40,42,59-61]. Recent retrospective data have also suggested a potential benefit of early initiation of corticosteroids (prednisolone 2 mg/kg/day given intravenous or oral in 3 divided doses for

10 days), particularly in critically ill children and those on multiple vasoactive medications [1,4,7,20,43]. If patients do not respond to corticosteroids and IVIG, high-dose corticosteroids (10–30 mg/kg/day) should be considered [43]. Although not part of the initial management, further immunomodulation with IL-1 blockade (e.g., anakinra, canakinumab) and/or IL-6 blockade (e.g., tocilizumab) may be helpful in refractory cases [7,20,42]. In select cases, an intra-aortic balloon pump or extracorporeal membrane oxygenation may be considered [14,19,62-65].

Due to the proinflammatory state and potential for coronary artery and other thrombotic complications, anticoagulation is recommended. Patients should additionally receive full anticoagulation with either enoxaparin or warfarin if there is evidence of thrombosis, a severely depressed ejection fraction (ejection fraction < 35%), or a *Z*-score > 10 [7,20,43]. Low-dose aspirin (3–5 mg/kg/day; maximum 81 mg/day) is recommended if there is thrombocytosis (platelets ≥ 450,000) or KD-like features on echocardiography [7,20,43]. Aspirin should be avoided in patients with a platelet count of ≤80,000 [43].

3.5. Disposition

Given the complexity of management, patients presenting to non-pediatric centers should be transferred to a pediatric tertiary care center once stabilized [11]. Due to the risk of significant complications and need for close monitoring, most patients (60–80%) with MIS-C will require admission to an intensive care setting [1,5,10,19,20].

4. Conclusion

MIS-C is a complication of COVID-19 which causes a multi-inflammatory syndrome that can affect nearly any organ system. Common signs and symptoms include fever, gastrointestinal symptoms, neurologic symptoms, and dermatologic findings. Most patients will have elevated inflammatory markers and may have an abnormal ECG or echocardiogram. Initial treatment involves resuscitation with careful assessment for cardiac versus vasodilatory shock using point-of-care ultrasound. Treatment includes IVIG, anticoagulation, and consideration of corticosteroids. IL-1 and/or IL-6 blockade may also be considered for refractory cases. Aspirin is recommended if there is thrombocytosis or KD-like features on echocardiogram. Patients will generally require admission to an intensive care unit.

Meetings

None.

Grants

None.

Author contributions

None except listed.

Declaration of competing interest

We have neither conflicts of interest nor financial support to disclose.

Acknowledgements

This review does not reflect the views or opinions of the U.S. government, Department of Defense, U.S. Army, U.S. Air Force, Brooke Army Medical Center, or SAUSHEC EM Residency Program.

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