EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2022.21114

Literature Review

Multisystem Inflammatory Syndrome in Children: A Year in Review

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Abstract

Centers for Disease Control and Prevention published a case definition for the multisystem inflammatory syndrome in children in May 2020 when reports started pouring in about a clinical syndrome in children which was temporally associated with coronavirus disease 2019 infection. It has also been referred to as pediatric inflammatory multisystemic syndrome temporally associated with severe acute respiratory syndrome coronavirus 2. Most of these patients test positive for severe acute respiratory syndrome coronavirus 2 serology or reverse transcription-polymerase chain reaction, although a small number of patients could test negative which would require an epidemiological link to the coronavirus disease 2019 infection. The initial clinical presentation could overlap with Kawasaki disease, severe coronavirus disease 2019 infection, toxic shock syndrome, and macrophage activation syndrome. While multisystem inflammatory syndrome in children is characterized by multisystem involvement with hyper inflammation and severe clinical presentation initially, the prognosis is generally good. Since it was first described, there have been multiple studies describing the demographic characteristics, laboratory features, and treatment paradigm.

Keywords: Multi-system inflammatory syndrome in children (MIS-C), pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), COVID-19, SARS-CoV-2, hyperinflammatory shock

Introduction

Since the initial report from the United Kingdom was published in 2020 describing a multisystem inflammatory syndrome in children (MIS-C),[1] the Centers for Disease Control and Prevention (CDC) has recorded a total of 3742 MIS-C cases and 35 MIS-C deaths in the United States as of May 9, 2021.[2] This disease was initially thought to be related to Kawasaki disease and toxic shock syndrome,[3] but soon it was clear that while bearing some similarities to these diseases, this was altogether a novel disease entity.[1,3] Multisystem inflammatory syndrome in children was eventually recognized as a possible postinfectious complication temporally related to coronavirus disease 2019 (COVID-19) infection.[4] Our understanding of the nature of this disease is still evolving, but significant strides have been made since the time it was first described.

Epidemiology

A total of 3742 cases of MIS-C were reported by May 9, by the CDC and 63% were of Hispanic/Latino and non-Hispanic black heritage. Non-Hispanic whites also constitute 28% of the total cases, but cases reported in other races and ethnic groups, including Asians, Native Americans, and the native Hawaiian population, are very rare. There is a slight male preponderance, constituting 60% of the total reported cases. Furthermore, the male-to-female ratio seems to increase in the higher age groups, from 1 : 1 in the 0-4 years age group to 2 : 1 in the age group 18-20 years.[5] The median age for the MIS-C affected children seems to be around 9 years. Although 5-17 years age group children constitute only approximately 9.8% of the total population infected with COVID-19,[6] 61% of the total reported cases of MIS-C are in the 5-14 years of age group. Multisystem inflammatory syndrome in children is considered to be a post-COVID-19 infection hyperinflammatory phenomenon that usually happens 2-6 weeks after the initial severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection. In the most extensive cross-sectional study so far,[5] the authors identified 3 peaks of MIS-C, which occurred 2-5 weeks after the peak COVID-19 infections in May, August, and December 2020. Multisystem inflammatory syndrome in children incidence was noted to be 2.1 per 100 000 children in this study, and a considerable variation in the number of cases from different states with the highest number of cases was reported from the northeastern states.

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Cite this article as: Tiwari V, Daniel AA. Multisystem inflammatory syndrome in children: A year in review. Eur J Rheumatol 2022;9(3):167-175.

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Received: June 9, 2021
Accepted: August 10, 2021

Pathogenesis

Pathogenesis of MIS-C is not well understood, but it might involve immune dysregulation, cytokine storm, and autoreactivity.[7] While it is widely accepted that MIS-C is probably a postinfectious autoimmune phenomenon, it is not clear why only some of the children infected with SARS-CoV-2 develop features of MIS-C. One hypothesis is related to the intensity of viral load, with low viral load associated with interferon responses leading to viral clearance and mild infection.[8,9] However, a high viral load could lead to aggressive virus replication, which can delay the interferon response, and the resulting cytokine storm could result in a severe disease phenotype such as MIS-C. On the other side, many MIS-C patients report only mild COVID-19 symptoms during the acute infection. Peripheral immunophenotyping of the leukocytes in the children with MIS-C has shown high levels of cytokines including interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-17, IL-18, and interferon-γ during the acute phase.[10,11] Neutrophils and monocytes also show high CD64 expression, and high Human Leukocyte Antigen- DR (HLA-DR) expression is noted on γδ and $CD4^+CCR7^+$ T cells.[12] A recent study using single-cell RNA sequencing, flow cytometry, and serum proteomics showed increased levels of S100A-family alarmins and decreased antigen presentation pattern, which was suggestive of myeloid dysfunction. Additionally, MIS-C patients also showed increased expression of cytotoxicity genes in natural killer and $CD8^+$ T cells.[12,13] Although acute COVID-19 infection and Kawasaki disease could also be associated with hyperinflammatory states, it seems different from what is seen in MIS-C. Patients with COVID-19 infection tend to have a distinct cytokine profile than children with MIS-C and Kawasaki disease with the predominance of IL-7 and IL-8 activity in COVID-19.[14] Similarly, the levels of IL -17A are significantly higher in patients with Kawasaki disease compared to MIS-C. Another protein secreted by endothelial cells known as DCBLD2 seems to have a higher expression in Kawasaki disease, probably suggesting a different kind of vasculitic involvement with tropism to coronary arteries compared with MIS-C.[14]

Main Points

- Multisystem inflammatory syndrome in children (MIS-C) is a post-coronavirus disease 2019 (COVID-19) hyperinflammatory syndrome in children, predominantly in the age group of 5-14 years that occurs 2-6 weeks after the initial COVID-19 infection, which might be asymptomatic.
- The majority of the reported cases occur in non-Hispanic blacks and Hispanic/Latino populations without any underlying medical co-morbidities.
- Clinical presentation of MIS-C could overlap with diseases like Kawasaki disease, acute COVID-19 infection, sepsis, macrophage activation syndrome, and toxic shock syndrome.
- Treatment consists of supportive measures and immunomodulatory therapies, including intravenous immunoglobulin, corticosteroids, and interleukin-1 inhibition.

Clinical Features and Diagnostic Evaluation

Symptoms and Signs

Patients with MIS-C generally present with fever, gastrointestinal symptoms, mucocutaneous manifestations, and cardiovascular involvement, including shock.[15] One of the initial studies published through CDC Morbidity and Mortality Weekly Report described 3 categories of patients who met MIS-C criteria.[16] The first category patients had the most significant involvement of organ systems, elevated inflammatory markers, and 98% were with positive SARS-CoV-2 serology with or without a positive reverse transcription-polymerase chain reaction (RT-PCR). The second category of the patients had more prominent respiratory system involvement with the highest fatality rates, and 84% tested positive for SARS-CoV-2 RT-PCR. The third group of the patients was younger, with more mucocutaneous involvement and with only 63.1% testing positive by serology and 33.8% by both serology and RT-PCR. One of the first major studies published by Feldstein et al[17] reported on 186 patients from 26 states and 70% of these patients had confirmed SARS-CoV-2 infection by serology and RT-PCR. The rest of the patients were diagnosed with MIS-C based on an epidemiological link through exposure to suspected or confirmed cases of COVID-19, as per the MIS-C case definition from CDC.[18] In this study, the majority of the patients had a fever for 4 days (90%) and predominant involvement of gastrointestinal (92%), cardiovascular (80%), mucocutaneous (74%), hematologic (76%), and respiratory (70%) systems. At least 71% of the patients had 4 organ system involvement. Of these, 40% of the patients had 4 or 5 Kawasaki's disease characteristics, and these patients were likely to be younger than 5 years. Belay et al[5] identified 1733 patients with MIS-C from March 2022 to January 2021, 90.4% of these patients had involvement of at least 4 organ systems, 51.5% of these patients were positive for SARS-CoV-2 RT-PCR, and 82.6% were positive for serology. Apart from fever, gastrointestinal symptoms and mucocutaneous features, including conjunctival injection, were the most prominent symptoms. Cardiovascular involvement was significant with features of myocardial dysfunction (31%), pericardial effusion (23.4%), myocarditis (17.3%), and coronary artery dilatation/aneurysm (16.5%). The respiratory involvement was seen in less than 30% of the patients with the presence of pneumonia (19%), pleural effusion (10.3%), and acute respiratory distress syndrome (ARDS) (6.6%). Additionally, significantly severe involvement of organ systems was observed in patients from higher age groups than younger patients. For example, compared to the patient in the age group of 0-4, the patients in the age group 18-20 were more likely to have myocardial dysfunction (31% vs. 41.5%) and myocarditis (17.3% vs. 30.9%).

Laboratory Features

Currently, the diagnosis of MIS-C is based on evidence of present/past SARS-CoV-2 infection based on positive RT-PCR, serology, or epidemiological link to COVID-19 infection through exposure to a suspected or a confirmed case. Severe acute respiratory syndrome coronavirus 2 reverse transcription-polymerase chain reaction and coronavirus disease 2019 serology should both be checked as patients could be either positive for both or one of them, which would meet the requirements for the MIS-C case definition.[2] This should be carefully considered as a positive RT-PCR in such a setting could also be indicative of an acute COVID-19 infection with hyperinflammation, although the clinical presentation would generally allow the differentiation between the 2 entities.[19,20] Rarely, both the tests could be negative, and in such cases, an epidemiological link through exposure to a COVID-19 infection should be established.

The majority of the patients have a significant elevation in the markers of inflammation, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, D-dimer, procalcitonin, and IL-64.[4,21] Moreover, these patients also have other laboratory characteristics of lymphopenia, neutrophilia, anemia, thrombocytopenia, and hypoalbuminemia.

Role of Echocardiogram and Imaging Studies

Cardiac involvement is a characteristic feature of MIS-C. Patients have been noted to have myocardial dysfunction, myocarditis, coronary

artery abnormalities, pericardial effusion, and rarely valvular abnormalities. In a retrospective study[22] which looked at the echocardiogram of patients with MIS-C, coronary arteries were noted to be relatively spared, but myocardial dysfunction was common. Myocardial injury was observed in 61% of these MIS-C patients. Multisystem inflammatory syndrome in children was reported to have lower left ventricular systolic ejection fraction and worse diastolic dysfunction than 2 control groups, including age-matched healthy children and Kawasaki disease patients. However, coronary artery dilatations have been noted in other studies. In the study by Belay et al[5], coronary artery dilation was found in 18.3% of children in the age group of 0-4 years and 14.6% of children aged 18-20 years. This has been variable in other studies, ranging from 8% to 24%.[23-25] In another study involving 539 patients diagnosed with MIS-C, 13.4% of the 434 patients who had echocardiograms were identified to have coronary artery aneurysm.[20]

A small study[26] analyzed the cardiac magnetic resonance imaging (MRI) of 4 MIS-C patients and found diffuse myocardial edema with no evidence of fibrosis or focal necrosis which corresponds to the finding of myocardial recovery in the majority of such patients. Other imaging studies such as chest x-ray and computed tomography (CT) of the chest and abdomen could reveal the relevant pathologies consistent with the clinical presentation, but there are no specific characteristic imaging findings related to MIS-C. Retrospective studies[27,28] have shown findings of central bronchial wall thickening, ground-glass opacities, pleural effusions, pulmonary edema, acute respiratory distress syndrome, atelectasis, etc. Abdominal imaging studies, including ultrasound and CT, could show features of ascites, hepatomegaly, mesenteric lymphadenopathy, bowel wall thickening, and gallbladder wall thickening.[29]

Case Definitions

Many organizations, including the World Health Organization (WHO) and CDC, have published case definitions for MIS-C, which have been used arbitrarily in various research studies. While mostly similar, there are some differences between the WHO and CDC definitions which are related to the duration of fever (more than 24 hours in CDC definition versus more than 3 days in the WHO definition), and the need for hospitalization (CDC definition requires hospitalization but WHO does not). In the early pandemic, there was a need to devise a diagnostic protocol for MIS-C which was altogether a novel disease entity and the case definitions as devised by these organizations served this purpose well. However, with the increasing recognition of the clinical presentation specific to MIS-C, its overlap with the other more common diseases such as sepsis and, the increasing seropositivity for COVID-19 leading to incidental findings of SARS-CoV-2 antibodies, there is an urgent need to revisit these criteria for an accurate diagnosis of MIS-C.[16,30]

CDC Case Definition for MIS-C

(1) An individual aged <21 years with
- fever >38.0°C for ≥24 hours or subjective fever lasting ≥24 hours;
- laboratory features of inflammation (one or more of the following):
- elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), IL-6 or presence of neutrophilia, lymphocytopenia, and hypoalbuminemia;
- evidence of severe illness requiring hospitalization and multi-system (2 or more) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological)

AND

(2) no alternative diagnoses

AND

(3) evidence of current or recent SARS-CoV-2 infection
- positive RT-PCR,
- positive serology,
- positive antigen test,
- exposure to a suspected or confirmed COVID-19 case within the last 4 weeks.

WHO Case Definition of MIS-C

Children and adolescents 0-19 years of age with fever for more than 3 days AND 2 of the following:

- rash,
- bilateral non-purulent conjunctivitis or mucocutaneous inflammation,
- hypotension or shock,
- myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or NT-pro-brain natriuretic peptide (BNP),
- coagulopathy (elevated prothrombin time, partial thromboplastin time, D-dimer),
- acute gastrointestinal manifestations (diarrhea, vomiting, or abdominal pain)

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other apparent microbial source, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 by:

- positive RT-PCR,
- positive serology,
- positive antigen test,
- exposure to patients with COVID-19.

Distinction from Kawasaki Disease

Multisystem inflammatory syndrome in children and Kawasaki disease frequently share many clinical features, including fever, mucocutaneous manifestations, and lymphadenopathy.

Diagnostic criteria for Kawasaki disease are as follows (need to have 5 out of the following 6 criteria for the diagnosis):

- fever lasting 5 days or more,
- bilateral bulbar conjunctival injection,
- polymorphous rash,
- peripheral extremity changes including features such as erythema of palms and soles, indurated edema, and desquamation in later stages,
- oral mucositis features such as red/cracked lips, strawberry tongue, and injected oral and pharyngeal mucosa, and
- acute cervical lymphadenopathy.

Multisystem inflammatory syndrome in children and Kawasaki disease differ significantly with regards to the demographics, presenting symptoms, signs, and laboratory findings[31] (Table 2). While MIS-C tends to affect older children and adolescents of black and Hispanic races, Kawasaki disease has a greater prevalence in children with Asian ancestry.[32] Mucocutaneous features, gastrointestinal symptoms, neurological involvement, and myocardial dysfunction seem to be more prominent in the MIS-C than the Kawasaki disease. In addition, the markers of inflammation seem to be significantly higher in cases of MIS-C, and thrombocytopenia, lymphopenia, and neutrophilia also seem to be more common in MIS-C compared to Kawasaki disease.[33] A prospective study found that the children with MIS-C had significantly higher SARS-CoV-2 spike receptor-binding domain IgG antibody titers than children with KD. This was also noted to be true when MIS-C patients were compared with the COVID-19 infected children. The presence of coronary artery aneurysms is common in both the disorders, probably more so in Kawasaki disease (16.5% in MIS-C compared to approximately 27% in Kawasaki disease).[20,34,35]

Table 1. Most Common Clinical Features of MIS-C

Symptoms	Signs	Laboratory Findings	Imaging Findings
Fever	Hypotension	Elevated BNP	Myocarditis
Rash	Shock	Elevated troponin	Reduced LVEF
Conjunctival congestion	Conjunctival injection	Significantly elevated CRP and ESR	Pericardial effusion
Lymphadenopathy	Cervical lymphadenopathy	Increased ferritin	Coronary artery aneurysms
Abdominal pain	Congestive heart failure	Elevated fibrinogen and D-dimer	Mesenteric lymphadenopathy
Vomiting/diarrhea	Pneumonia	Lymphocytopenia/neutrophilia	Bowel wall thickening
Shortness of breath/Cough	Pericardial/Pleural effusion	Hypoalbuminemia	Ground glass opacities
Chest pain	Coronary artery dilatation or aneurysm	Elevated transaminases	Pleural effusion

*Summary of clinical features of MIS-C; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LVEF, left ventricular ejection fraction; MIS-C, multisystem inflammatory syndrome in children

Table 2. Comparison of MIS-C with Kawasaki Disease

	MIS-C	Kawasaki Disease
Demographics	• Generally affects older children • Common in African American and Hispanic population • Slightly higher male predominance	• Common in children less than 5 years of age • High prevalence in Asian children • Young males are affected commonly
Clinical features	• Cardiogenic shock more common • Gastrointestinal and neurological symptoms frequent • Risk of coronary artery aneurysm formation but not as high as KD	• Myocardial involvement in a minority of patients • Gastrointestinal or neurological symptoms uncommon • High risk of coronary artery aneurysms
Laboratory features	• Significant lymphocytopenia • Marked elevation of inflammatory markers	• No lymphocytopenia • High inflammatory markers but not as high as in MIS-C

*Salient points of distinction between Kawasaki disease and MIS-C; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children.

Many of the studies have also identified a subgroup of MIS-C patients who presented with the features of incomplete or complete Kawasaki disease.[3,21,36,37] Although these patients had some or all features of Kawasaki disease, they differed from the classical Kawasaki disease in terms of demographics, overall clinical presentation, and response to the treatment. A study of the hospitalized patients with MIS-C[37] revealed half of these children in the age group of 0-5 years of age had a discharge diagnosis of Kawasaki disease, but only around 12% of the adolescents had a similar presentation. These patients were more likely to present with hypotension and be admitted to the intensive care unit (ICU), which is not common in Kawasaki disease. In a targeted surveillance study[21] across the United States, around one-third of the MIS-C patients were noted to have Kawasaki disease features, which were seen especially in the children less than 5 years of age and is the usual pattern with the classical Kawasaki disease. However, even in these patients, organ involvement was different compared with Kawasaki disease. For example, the nature of the cardiac disease in the MIS-C was different with the presence of significant myocardial dysfunction, which is not common with Kawasaki disease.[38]

Distinction from Severe COVID-19 Infection

Acute severe COVID-19 infection could have a similar presentation to MIS-C, especially if it is associated with hyperinflammation. However, there are characteristic features of MIS-C that could help to differentiate it from acute severe COVID-19 infection (Table 3). Fever, prominent gastrointestinal symptoms, mucocutaneous manifestations, and cardiovascular involvement are the hallmark features of MIS-C. Profound pulmonary involvement with acute respiratory failure is a major feature of severe COVID-19 infection, while the respiratory symptoms noticed in MIS-C mainly emanate from cardiovascular involvement. A recent study done by Feldstein et al[20] compared 577 patients with severe COVID-19 infection and 539 patients with MIS-C. In this study, patients with MIS-C were noted to be different in the demographic characteristics with a predominance of younger (median age of 8.9 years compared to 11.7 years) and non-Hispanic Black patients (34.7% compared to 22.7%). Similar symptomatology and findings were noted between the 2 cohorts, with the significant exception of mucocutaneous findings being more prevalent in the MIS-C group (66.8%) compared to the COVID-19 group (10.2%). The severe COVID-19 infection cohort patients were more likely to have underlying medical comorbidities such as obesity, pulmonary, neurological, and cardiovascular conditions. Multisystem inflammatory syndrome in children was more likely to have cardiorespiratory, cardiovascular, and mucocutaneous systems manifestations than the isolated respiratory involvement in patients with severe acute COVID-19 infection. Myocardial involvement was prominently high in the patients with MIS-C with 15.4% with less than 45% of ejection fraction, compared to the patients with COVID-19 where less than 45% of ejection fraction was reported in only 6.3% of total patients. Interestingly, the patients with MIS-C had their ejection fraction normalize in 1-2 weeks, and this finding mirrors what has been found in other studies.[21,22] Similarly, the MIS-C patients had a higher rate of coronary artery aneurysm formation (13.4%) compared to the COVID-19 cohort (0.9%). Regarding laboratory features, patients with MIS-C were more likely to have significantly elevated levels of CRP, thrombocytopenia, neutrophil to lymphocyte ratio of greater than 5, neutrophilia, and hypoalbuminemia compared to the patients with severe acute COVID-19 infection.

Table 3. Comparison of MIS-C with Acute Severe COVID-19

	MIS-C	Acute Severe COVID-19
Demographics	• Older children with age -12 years • Hispanic/Latino and Non-Hispanic blacks • Previously healthy children • Lag of two to four weeks between the COVID-19 infection and MIS-C	• Any age group • Hispanic/Latino and Non-Hispanic blacks • Children with underlying medical conditions • The incubation period of up to 14 days with a median of 4-5 days
Clinical features	• Significant mucocutaneous findings • Gastrointestinal involvement common • Cardiorespiratory involvement common • Higher chances of coronary artery aneurysm	• Mucocutaneous features rare • Gastrointestinal symptoms less common • Severe respiratory involvement • No significant involvement of coronary arteries
Laboratory features	• Positive SARS-CoV-2 RT-PCR, antibody, antigen test, or exposure to COVID-19 case within four weeks • Significantly higher titers of SARS-CoV-2 antibodies • Higher neutrophil to lymphocyte ratio and C-reactive protein level • Lymphopenia and thrombocytopenia are more common	• Positive SARS-CoV-2 RT-PCR • Lower titers of SARS-CoV-2 antibodies • High but lower levels of these laboratory parameters. • Lymphopenia and thrombocytopenia less common compared to MIS-C

*Salient points of distinction between MIS-C and acute COVID-19 infection; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, real-time quantitative polymerase chain reaction; COVID-19, coronavirus disease 2019.

Approach to Diagnostic Evaluation

It is essential to maintain a high index of suspicion for MIS-C when a child presents with consistent clinical features while also considering a broad range of other differential diagnoses which could be presenting similarly. American College of rheumatology recommends a tiered diagnostic approach considering key clinical features and laboratory characteristics.[19] Patients presenting with fever of more than 3 days duration and a possible epidemiological link to the SARS-CoV-2 infection should be considered "under investigation" for MIS-C. These patients should undergo a staged evaluation for possible MIS-C and other similar illnesses. Initially, complete blood count, comprehensive metabolic panel, ESR, CRP, and SARS CoV-2 RT-PCR, and serology should be checked. When appropriate, other tests such as blood, urine, and throat cultures should also be performed. Such tests should be performed in the context of a child's illness rather than as a part of an algorithmic evaluation. In a patient with evidence of recent/remote SARS-CoV-2 infection or an epidemiological link to the infection, elevated ESR or CRP and presence of any other features such as lymphopenia, thrombocytopenia, neutrophilia, hyponatremia, or hypoalbuminemia should prompt further evaluation. Such patients should have further laboratory tests done, including D-dimer, ferritin level, procalcitonin, and LDH. If available, levels of IL-6 and IL-10 could be checked, but these tests are more of academic interest currently and seldom aid in the evaluation and management. Since cardiac involvement is common in MIS-C patients, troponin, BNP levels, a 12-lead electrocardiogram, and an echocardiogram should be checked.[39] Patients with abnormal troponin or BNP levels should have these tests repeated until these are normalized. While some studies have shown that the markers of myocardial injury such as BNP could correlate with the echocardiographic parameters,[22] it is important to consider the value of such tests in the context of the clinical presentation as these are very non-specific and could be elevated in a number of other conditions such as sepsis. Chest x-ray and abdominal imaging are frequently required at the discretion of the treating physicians

Other Diseases to Consider

It should be noted that the case definitions for MIS-C as devised by CDC and WHO are broadly sensitive, and many diseases characterized by infection and inflammation could fulfill these criteria. Due to the relatively rare incidence of MIS-C, a patient presenting with fever, shock, and features of inflammation should prompt a search for etiologies such as sepsis related to a myriad of infections, toxic shock syndrome, and systemic Juvenile idiopathic arthritis (JIA) with or without macrophage activation syndrome, to name a few. Acute severe COVID-19 infection and Kawasaki disease should be considered in the differential diagnosis of MIS-C as the symptoms, and the presentation could be overlapping as described above. Additionally, Kawasaki disease shock syndrome (KDSS) is a complication of Kawasaki disease that can be confused with MIS-C, especially in the patients presenting with the features of complete or incomplete Kawasaki disease and shock. However, KDSS is rare and has been found in only approximately 7% of patients diagnosed with Kawasaki disease.[40] These patients also tend to have a significantly higher level of inflammatory markers and coronary artery abnormalities than Kawasaki disease. One point of distinction with MIS-C could be with the presence of thrombocytosis in the KDSS rather than the commonly found thrombocytopenia in MIS-C.[41] As the COVID-19 pandemic progresses, the seropositivity in the general population is going to increase. In near future, it would be challenging to differentiate patients with Kawasaki disease from MIS-C patients as the pediatric patients with seropositivity for COVID-19 but with classical features of Kawasaki disease would still be classified as MIS-C. Other clinical features could certainly be helpful in the differentiation, but the criterion of positive COVID-19 serology might need to be revisited.

Management

Due to the multisystem involvement in MIS-C, a multidisciplinary treatment team including pediatric cardiologist, rheumatologist, and an infectious disease expert should be involved in the care of these patients. Apart from supportive treatment such as vasopressors in shock, immunomodulatory treatment forms the cornerstone for MIS-C treatment. American College of Rheumatology clinical guidance on MIS-C[19] recommends intravenous immunoglobulin (IVIG) alone for patients with no shock or organ-threatening disease and use of IVIG and steroids

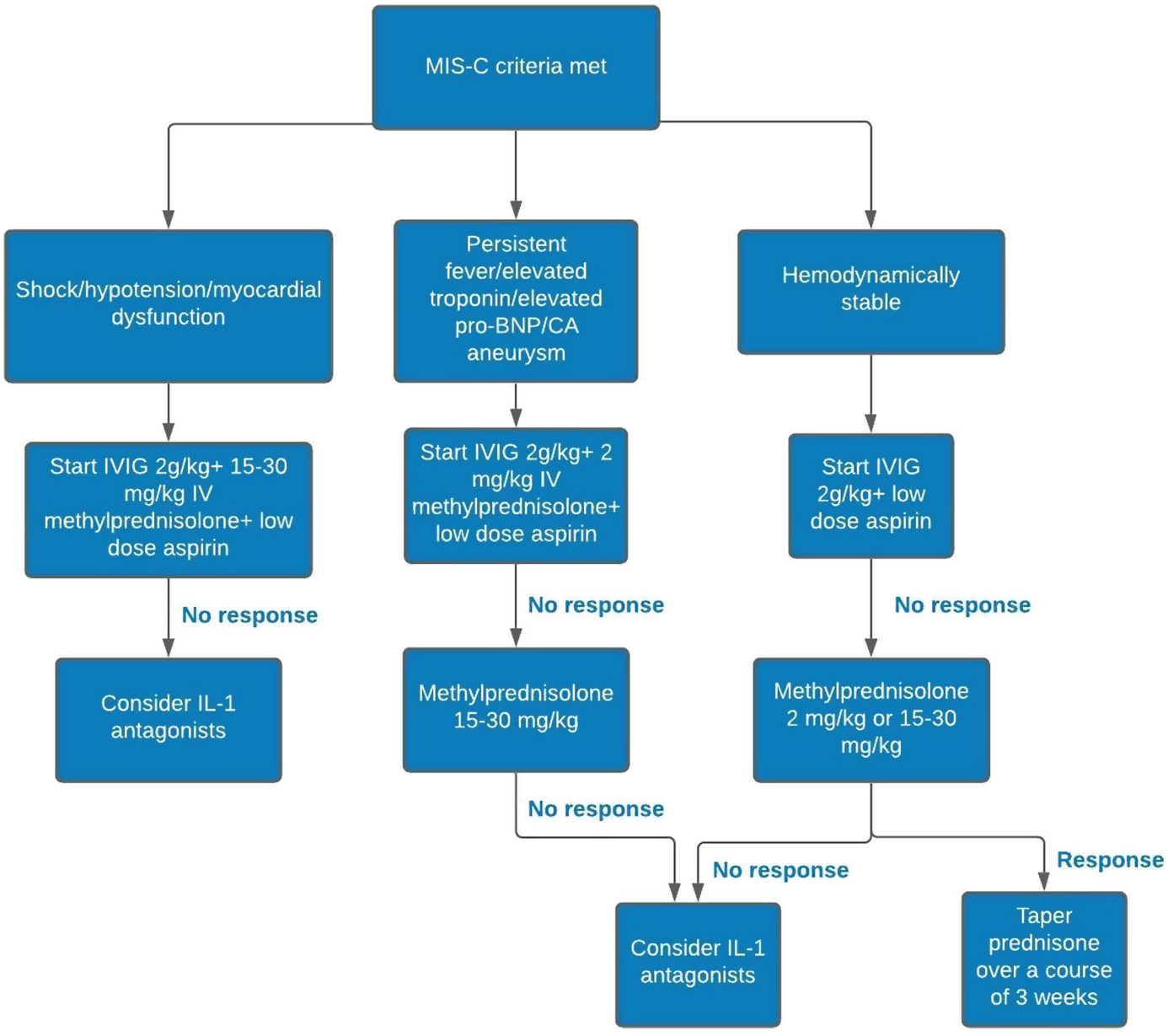

Figure 1. MIS-C immunomodulatory treatment algorithm. Immunomodulatory treatment pathway describing a stepwise approach to MIS-C management. *MIS-C, multisystem inflammatory syndrome in children; IVIG, intravenous immunoglobulin; proBNP, pro-brain natriuretic peptide; CA aneurysm, coronary artery aneurysm; IL-1, interleukin 1. **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 & Rheumatology*. 2021;73(4):e13-e29. doi:https://doi.org/10.1002/art.41616

(1-2 mg/kg/day) only in patients with features of shock or organ-threatening disease. A retrospective cohort study[42] done in France compared the efficacy of treatment with a combination of IVIG and methylprednisolone versus IVIG alone. Treatment with IVIG and steroids was associated with a significantly lower risk of multiple outcome measures, including treatment failure, length of stay in the pediatric ICU, acute myocardial dysfunction, need for hemodynamic support, and use of second-line therapies such as IL-1 inhibitors or IL-6 inhibitors. In this study, 72 out of the 111 children received IVIG alone, and 46% of these patients needed second-line therapies, including a second course of IVIG, a combination of IVIG and methylprednisolone, or biologic therapy. In contrast, among the patients treated with the combination therapy, only 9% needed second-line treatment. A lower incidence of treatment failure was seen in the IVIG and steroid group than in the IVIG group (9% vs. 38%, respectively). Even though this was not a randomized, controlled trial and a retrospective study, it shed light on the stark difference in the treatment efficacy related to combination treatment with IVIG and steroids compared to IVIG alone. In another study,[43] a combination of IVIG and steroids was associated with reduced time in the recovery of myocardial function and pediatric ICU stay compared with the group receiving only IVIG. An argument could be made for watchful observation for the stable patients who have not been hospitalized, but most clinicians would elect to treat such patients too, as the course of the disease could worsen at any time. Intravenous immunoglobulin should be given 2 g/kg of ideal body weight.

When using IVIG in the MIS-C patients with features of myocardial dysfunction, volume

status should be carefully monitored. If there is a concern for volume overload, the IVIG infusion rate should be slowed or given in 2 divided doses, and judicious use of diuretics could be considered to maintain euvolemia. There is no clear recommendation regarding the dosing of glucocorticoids as there are no head-to-head trials comparing the efficacy of different dosing regimens, but generally, the dose of glucocorticoids has been recommended to be around 1-2 mg/kg/day. In the French study mentioned above, most of the patients received a maximum of 0.8-1 mg/kg/day dosing of methylprednisolone, but a few patients were given a bolus of 15-30 mg/kg/day methylprednisolone for 3 days. In the patients who respond to steroids, a tapering regimen of 2-3 weeks should be followed to avoid recurrence.[19] This issue of tapering has not been addressed in a randomized, controlled trial but has been extrapolated from the Kawasaki disease treatment protocol.[44] A repeat course of IVIG has been employed based on the treatment model of Kawasaki disease as well. For refractory disease or in patients with shock and severe organ-threatening illness, a bolus regimen of 15-30 mg/kg/day methylprednisolone could be employed. In such patients, an IL-1 blocking agent such as anakinra should be strongly considered.[19,45] Anakinra is considered to be safe in infections[46] and has been used in cases of sepsis with other inflammatory syndromes such as macrophage activation syndrome. In a retrospective study,[47] the use of anakinra in the patients with COVID-19 infection and ARDS led to clinical improvement in 72% of the patients. It should be emphasized that there has been no published clinical trial of anakinra in MIS-C patients yet, and the available evidence has been extrapolated from different trials in other diseases. Interleukin-6 inhibitors such as tocilizumab have been used in refractory cases,[48] but again, there is no direct evidence of clinical benefit related to these agents. A simplified approach to the immunomodulatory treatment is described in Figure 1.

Based on experience with Kawasaki disease and overlapping clinical features with MIS-C, patients should be considered for additional treatment with antiplatelet therapy with low-dose aspirin (3-5 mg/kg/day). Aspirin should be continued until normal coronary arteries are confirmed at around 4 weeks after the MIS-C diagnosis.[19] Again, on the lines of treatment in Kawasaki disease, patients with large coronary artery aneurysms (coronary artery z-score greater than 10) should receive anticoagulation.[49,50] Similarly, the anticoagulation treatment has also been recommended for MIS-C patients with moderate or severe myocardial dysfunction (Ejection fraction (EF) < 35%). Echocardiograms should be repeated at around 1-2 weeks and then 4-6 weeks after presentation. Patients with Left ventricular (LV) dysfunction or coronary artery abnormalities will require more frequent echocardiograms and a regular follow–up to a cardiologist.

Prognosis

Most of the patients admitted with MIS-C are discharged after clinical improvement, but initially, the presentation can be severe, with approximately 60% of these patients being admitted to ICU with a case fatality of around 2%.[20,21,51] Majority of the patients with cardiac involvement had normalization of the myocardial function and coronary artery aneurysms.[20] In one of the studies, out of all the patients, 80% of children received ICU care, 20% received mechanical ventilation, 48% received vasopressor therapy, and 2% died.[17] In a retrospective study,[51] ICU admissions were more likely in patients in the age group of 6-12 years and 13-20 years and in non-Hispanic black children. The ICU admission predictors included shortness of breath, abdominal pain, and the presence of elevated inflammatory markers. Myocarditis and shock were also noted to be more frequent in a similar group of patients. Coronary artery abnormalities were more frequent in male children and in patients with mucocutaneous and conjunctival involvement. High pro-BNP and IL-6 levels were also associated with the development of coronary artery abnormalities.

Conclusion

Coronavirus disease 2019 pandemic brought forth unprecedented challenges to the world of modern medicine. Since MIS-C was identified for the first time around a year ago, our understanding of the disease process is still evolving. Although most patients with MIS-C have a favorable outcome, significant challenges lie ahead in designing an effective diagnostic and therapeutic strategy. The case definitions would need to be revised as we go further in this pandemic as a significant percentage of the population would turn seropositive for SARS-CoV-2 antibodies. Similarly, although the treatment on the lines of Kawasaki disease has been largely successful, more research is needed to tailor the most effective treatment for MIS-C.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – V.T., A.D.; Design – V.T., A.D.; Supervision – A.D.; Materials V.T., A.D.; Data Collection and/or Processing – V.T., A.D.; Analysis and/or Interpretation – V.T., A.D.; Literature Review – V.T., A.D.; Writing – V.T., A.D.; Critical Review – V.T., A.D.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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