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Multisystem inflammatory syndrome in children: another COVID-19 sequel

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Review

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Abstract

With the rapid expansion of the COVID-19 pandemic, the disease burden and its consequences on the paediatric population has been progressively recognised. Although COVID-19 infection in children presents as asymptomatic to mild illness, instances of hyperinflammation and multi-organ involvement following the viral infection have been described. This condition, known as the multisystem inflammatory syndrome in children (MIS-C), has gained a wide global attention. Despite the global efforts to uncover the disease characteristics and management, a clear pathogenesis and a unified treatment regimen have not been reached yet. This paper tackles the epidemiology of the MIS-C, discusses its suggested pathogenesis, drives through its varying clinical presentations, and evaluates the different treatment regimens employed in managing MIS-C.

Late 2019, a pandemic characterised by the rise of a novel severe acute respiratory syndrome coronavirus, namely SARS-COV-2, has spread globally not sparing a continent nor a particular age group.[1,2] Specifically, the associated respiratory tract infection with that virus was known more widely as COVID-19. The disease appeared to have a spectrum of severity, being critical or even lethal for the eldest and the immunocompromised. Overall, it exhibits decreasing severity when going down the age groups.[2–4] In effect, infections by the SARS-COV-2 were scarce in children and adolescents, whose majority did not require medical intervention.[5,6]

In these younger age groups, the reported incidence of viral infection was the lowest, generally representing only a few percent of the total infections.[7,8] The present literature shows little to no severity in children aged 15 years and below. Similarly, death in this age group represented an insignificant fraction of the total death caused by SARS-COV-2.[5,7,9] Although COVID-19 only followed a mild course of illness in children and adolescents, in the first quarter of 2020, many instances of cardiac and gastrointestinal complications in children were reported in addition to the respiratory ones. Patients admitted to the hospitals showed symptoms of multiple organ inflammations.[3,9–11]

The clinical manifestations, intriguingly mimicking that of Kawasaki disease, involve a severe immune-mediated response characterised by fever, tissue damage, and multiple organ failure.[10,12–14] This condition known as the multisystem inflammatory syndrome in children (MIS-C) was first detected in late April 2020 and is known to occur several weeks after infection by SARS-COV-2.[10,11,15] This specific contiguity has hinted about the role of the virus as the infection agent at cause of MIS-C, possibly correlated with the response of the adaptive immune system.[10,12,16] In fact, most of the patients with MIS-C tested positive for either SARS-COV-2 antibodies, for the virus itself through reverse transcription-polymerase chain reaction (RT-PCR) testing or had a relative positive for the virus at the time of hospitalisation.[6,10,15,16] The large overlap between the clinical manifestations of Kawasaki disease and MIS-C whether they are cardiac or gastrointestinal may show that both conditions are part of one large disease spectrum, rather than two distinct entities.[10,15,16] Overall, MIS-C clinically expresses itself through the involvement and inflammation of more than one system, including cardiac, neurological, gastrointestinal, pulmonary, and haematologic.[3,10,12] This article investigates the epidemiology, pathophysiology, and clinical manifestations of MIS-C. In addition, it examines the employed treatment weapons and the overall prognosis.

Epidemiology

Children and young adults are much less susceptible to SARS-COV-2 infection and constitute only between 1 and 2% of the cases.[17] Clinical symptoms are absent or mild in most of these young patients.[17,18] In April 2020, however, the Pediatric Intensive Care Society of the United

Kingdom alerted the international medical community about the emergence of a severe form of toxic shock syndrome in an increasing number of children following SARS-COV-2 infection.[18] Within a few weeks, children and adolescents presenting with a multisystem inflammatory disease were reported worldwide, more frequently in regions with greater incidence of infections.[12] The term MIS-C was used by the WHO to label this severe disease which was thought to be very similar to Kawasaki disease.[17] Later, each of the Centers for Disease Control and Prevention (CDC) and WHO has issued a case definition for MIS-C (Table 1). The reported incidence of MIS-C was diversely appreciated, ranging from 2 per 100.000 COVID-19 cases in the US study,[6] to 0.8/1000 in the UK series,[17] and 1/1000 during the Bergamo, Italy outbreak.[12]

Children presented with MIS-C between 6 and 51 days following infection with SARS-COV-2, the median being 36 days in the French study[19] and 25 days in a US series including 26 states.[6] The initial COVID-19 infection was symptomatic in 27 to 43% of the cases, reported as an acute febrile or respiratory illness.[18,19] Between 20 and 50% of the patients reported contact with a COVID-19-positive family member.[6,18,19]

Patients ranged between 6 and 20 years of age, with a median age of above 5 years in most cases.[6,15,17,19] Male preponderance was reported by all authors, with a male-to-female ratio of 2–3:1.[6,18,19] However, one unique study from the United Kingdom found no association between MIS-C and patient's gender.[17] Between 57 and 66% of MIS-C patients were of Black/African or Hispanic/Latino ethnicity;[6,17–19] these same ethnic origins were associated with higher instances of hospitalisation, severe disease, and death.[17,18]

Pathophysiology

MIS-C is a newly described rare entity that consists of a severe inflammation targeting more than one organ system, characterised by a fever, multi-organ dysfunction and markedly elevated inflammatory markers.[6,20] This entity has been compared throughout the literature to Kawasaki disease, or even to an "incomplete Kawasaki disease" in practically all reports, as they both present with a wide range of symptoms related to inflammation and overlapping clinical features, without specific and reliable diagnostic tests.[18,20] In fact, 50% of MIS-C patients will present the complete Kawasaki disease symptom and criteria spectrum.[12,19] In addition, Kawasaki disease was described 46 years ago, providing a well-established framework for this puzzling and similar new disease called MIS-C.[21] Thus, it is important to describe what is currently known about the pathophysiology of both these diseases and highlight the specific features of each. Figure 1 summarises the main features of each condition.

Kawasaki disease is usually described as a medium-calibre vessel vasculitis targeting children below 5 years of age in most cases.[12] The cause of Kawasaki disease is still not identified and is thought to be an autoimmune reaction, generated by an unknown pathogen in children with genetic predisposition.[12,18,20] In 5% of the cases, patients may develop shock and haemodynamic instability in the early phase of the disease and demonstrate a clinical picture mimicking macrophage activation syndrome.[15] The underlying pathophysiology in MIS-C is relatively similar to that of Kawasaki disease and is increasingly suspected to also be an unregulated immune reaction triggered by the viral infection with SARS-COV-2.[12,18,19] However, the inflammatory reaction in MIS-C is much more intense, displaying shock in 50% of the patients, macrophage activation syndrome in 20–30%,[12,15] and more than 90% of the patients exhibit a steep elevation of more than four markers of inflammation.[6,20] This unusual "hyperinflammatory" syndrome in MIS-C is thought to be secondary to a sudden cytokine storm and not to a direct viral-induced cell injury.[19,20] This assumption is supported by the absence of viral particles in nasopharyngeal specimen in around 30% of patients with MIS-C, and the presence of SARS-CoV-2 antibodies (IgG3, IgM, and IgA) in 80–100% of the cases.[6,12,18–20] The cytokine storm is primarily mediated by interleukin 6 (IL-6) and IL-8.[12,18–20] IL-6 was increased in virtually all patients with MIS-C and is used as a specific diagnostic test.[18,19] Particularly, IL-6 is increased by SARS-CoV-2 and other viruses through the amplification of IL-6 mRNA transcription, or by stabilisation of IL-6 mRNA.[18]

In contrast to MIS-C, IL-1 and IL-17A are the primary cytokines driving inflammation in children with Kawasaki disease; in MIS-C, IL-17A levels are significantly lower when compared to children with Kawasaki disease,[20] and IL-1 levels are usually around the normal range.[18,19] An imbalance in both directions, between IL-17A-producing T-lymphocytes and regulatory T-lymphocytes, may be the underlying mechanism behind IL-17A levels, both in Kawasaki disease and MIS-C.[15,20]

Along with the established generalised inflammatory reaction, the possibility and extent of additional direct viral cell injury is debated. In Kawasaki disease, this possibility has been disregarded during the last 2 decades. IgA-producing plasma cells and neutrophils infiltrate the arteries in Kawasaki disease and are detected within the walls of the arteries; the resulting arteritis destroys the arterial connective tissue, causing aneurysmal dilatation of the artery wall.[20]

In contrast to Kawasaki disease, patients with COVID-19 and in one child with MIS-C, significant loads of viral particles were found within the endothelial cells of various organs; this may explain the clinical symptoms related to impaired microcirculation in severe COVID-19 illness and may also suggest a direct virus-mediated injury.[18,20] However, these children respond well to anti-inflammatory agents and immuno-regulatory therapies, which supports the first hypothesis of autoimmune disease regarding MIS-C.[20]

The overlap in the pathophysiology of Kawasaki disease, COVID-19, and MIS-C is best illustrated by the research undertaken around the pathogens that triggers Kawasaki disease. A viral trigger had always been considered, including coronavirus subtypes.[19] These studies are particularly interesting today, following the appearance of SARS-COV-2 and MIS-C. However, conflicting results were reported. Concerning the Human Coronavirus isolated in New Haven (HCoV-NH), it was detected in 8 of 11 children with Kawasaki disease in the New Haven study,[22] but in none of 19 Kawasaki disease patients in Japan.[22,23] In another Japanese series, a KD-like disease was associated with another subtype of coronavirus by detecting higher antibodies directed against the HCoV-229E.[12] Thus, coronaviruses will remain prime suspects for Kawasaki disease and MIS-C triggering, as SARS-COV-2 has been confirming its potential to initiate such intense inflammatory and immune reactions during the past 3 years, presenting with clinical features overlapping with Kawasaki disease.[12]

Genetic susceptibility is undoubtedly another important predisposing factor for both MIS-C and Kawasaki disease and is illustrated by race and gender susceptibilities. Kawasaki disease incidence is 12 times higher in Japan than in the United States.[19] In contrast, MIS-C was found to be significantly more prevalent in African/American and Hispanic/Latino patients, with a significant

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Table 1. Case definition of MIS-C[1, 2]

CDC	WHO
All criteria must be met	**All criteria must be met**
Age < 21 years	Age 0–19 years
Presenting with all the following: • Fever of one or more days. It can be documented fever of ≥ 38° C or subjective Laboratory evidence of inflammation: - Can include but not limited to elevated CRP, ferritin, ESR, procalcitonin, LDH, D-dimer, and IL-6 - Severe disease that requires hospital admission - Evidence of multisystem involvement (two or more organ systems)	Fever of ≥ 3 days Evidence of multisystem involvement must include two or more of the following: - Rash, bilateral non-purulent conjunctivitis, or signs of mucocutaneous inflammation - Hypotension or shock - Myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities. This includes findings on echocardiography or elevated cardiac enzymes - Evidence of coagulopathy - Acute gastrointestinal symptoms
Absence of alternative plausible diagnosis	Elevated inflammatory markers No obvious microbiologic cause
Evidence of current or recent COVID-19 infection by: RT-PCR Serology Antigen test Or COVID-19 exposure within the 4 weeks prior to the onset of symptoms	Evidence of SARS-CoV-2 infection by: RT-PCR Serology Antigen test Contact with a known positive COVID-19 patient

CDC = Center for Disease Control and Prevention; CRP = C-Reactive Protein; ESR = Erythrocyte Sedimentation rate; LDH = lactate dehydrogenase; RT-PCR = Reverse Transcription- Polymerase Chain Reaction; WHO = World Health Organization.

[1]Organization WH. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Published 2020. Updated May 15, 2020. Accessed November 1, 2022.

[2]Prevention CfdCa. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). CDC. https://www.cdc.gov/mis/mis-c/hcp/index.html#:~:text=Patients%20with%20MIS%2DC%20usually,cases%2C%20with%20hypotension%20and%20shock. Published 2021. Updated May 20, 2021. Accessed November 1, 2022.

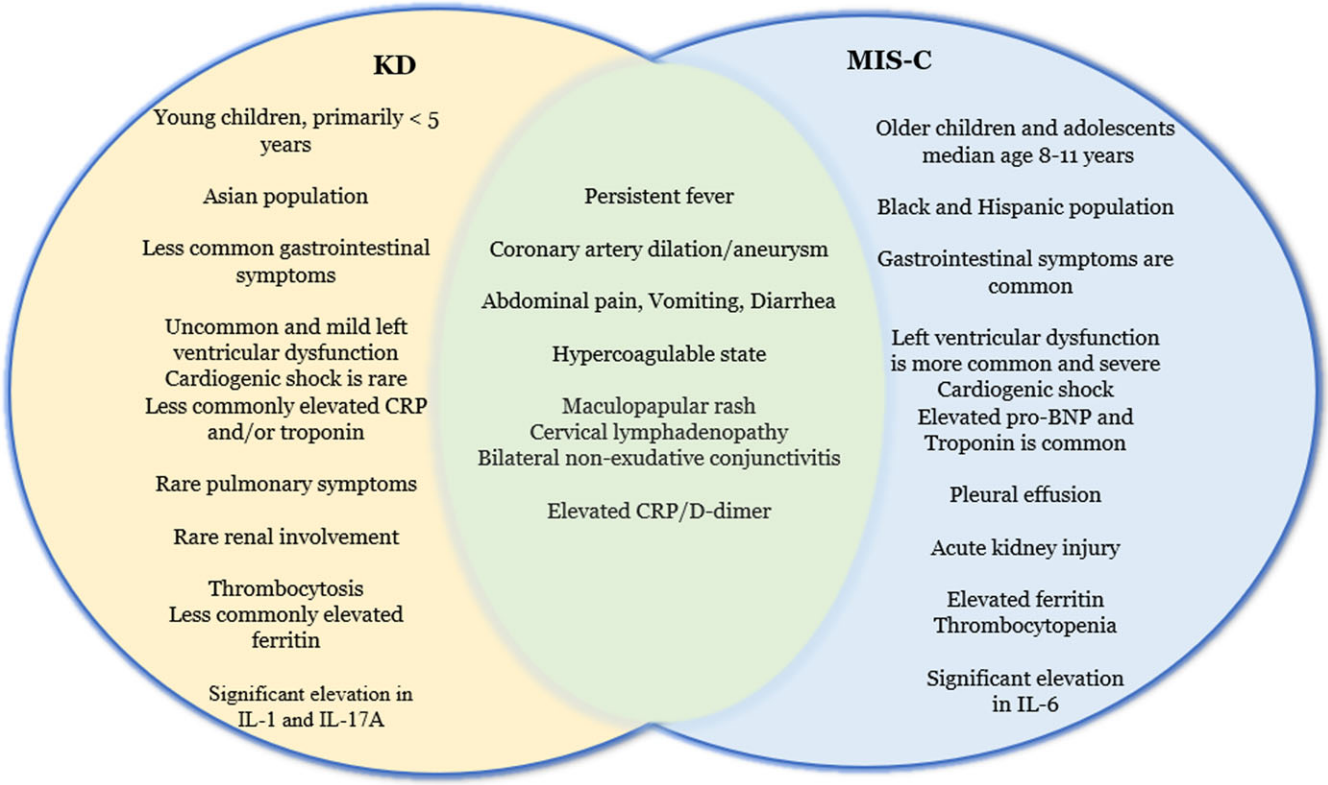

Figure 1. Major differences between KD and MIS-C.[18,68–70] KD: Kawasaki disease.

increase in severe illness and mortality.[17,18] Both MIS-C and Kawasaki disease are more preponderant in male gender, as more than 60% of MIS-C patients are males in most series.[6,12,18,19]

Further, there is a striking difference in the age groups between Kawasaki disease and MIS-C. While Kawasaki disease is generally diagnosed in children below 5 years of age, the median age of

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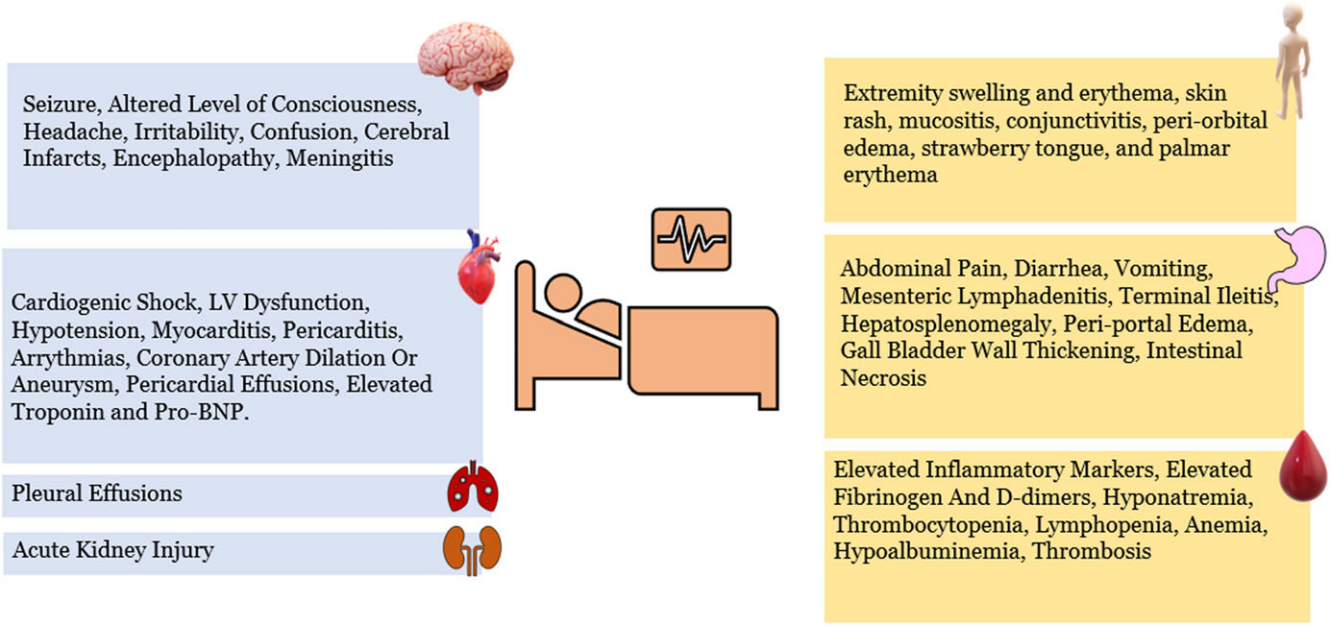

Figure 2. Clinical features of MIS-C.

patients with MIS-C is 7.5 years, ranging from 6 to 20 years in most studies.[12] The reason why younger children seem to be protected against MIS-C may be a "cross-reactive" immunity: These young patients could be protected because they may have been already in contact with another coronavirus during one of their frequent respiratory tract infections.[15] Another explanation involves a common amino-acid sequence between SARS-CoV-2 and measles and rubella viruses; thus, younger children can be protected through the measles, mumps, and rubella (MMR) vaccine.[24] It is also possible that the decreased efficiency of the cell surface enzyme angiotensin-converting enzyme 2 (ACE-2) confers additional protection for children between 4 and 9 years. In fact, ACE-2 is a receptor that promotes cellular infection with SARS-COV-2. Children in this age range exhibit lower gene expression of ACE-2 in the upper respiratory tract epithelium.[25] Finally, a last possible reason for children belonging to a very young age group to be "immune" to MIS-C is the immature immune system, leaving them unable of developing a cytokine storm, presented earlier as one of the physiological factors of MIS-C.[26]

Clinical manifestations of MIS-C

The MIS-C displays a wide range of clinical features and severities (illustrated in Fig. 2). It touches several organ-systems on a full scale of presentations. Children might present in a shock and end-organ damage or might exhibit a minor illness. This is reflected by the vast difference in the initial presentation reported by the varying studies. Table 2 displays the presenting symptoms of children diagnosed with MIS-C along with their frequency, as reported by various investigations.

The gastrointestinal tract appears to be considerably impacted by the hyperinflammatory process of MIS-C. This is mirrored by the high occurrence of such symptoms, reported in 47–100% of children. Diffuse abdominal discomfort, diarrhoea, and vomiting are the most frequently reported symptoms, affecting up to 87% of patients.[18] Paralytic ileus and ascites have also been reported.[18] Notably, growing evidence depicts a subset of patients presenting with acute surgical abdomen. Though, most of these cases are in fact non-surgical and are attributed to varying other reasons such as mesenteric lymphadenitis and terminal ileitis. Nevertheless, due to the alarming initial presentation and the intense pain experienced by children, surgical interventions and exploratory laparotomies were carried in some instances. They were later discovered to be unnecessary.[27,28] A typical presentation would be intense diffuse abdominal pain that is most severe at the right lower quadrant, which would raise high suspicion of appendicitis. However, further laboratory evaluation and imaging would reject this diagnosis. In fact, abdominal imaging has exposed a remarkable variety of findings. Air fluid level, free fluid in the abdominal cavity, ileitis, colitis, bowel wall thickening, lymphadenopathy, and mesenteric fat stranding, especially in the right iliac fossa similar to those seen in inflammatory bowel disease, are all described.[29–31] In addition, hepatosplenomegaly, peri-portal and pericholecystic oedema, enlargement of intra-hepatic bile ducts, and gall bladder wall thickening have also been detected.[32,33] Despite most cases being non-surgical, complications requiring surgical intervention might occur in MIS-C patients. Evidence of venous microthrombi and necrotic lymphadenitis has been discovered.[29] Intra-surgical pathologies revealed intestinal necrosis that required segmental resection.[34] Indeed, one study tried to assess the difference in laboratory values between patients who required surgical intervention and those who presented with acute non-surgical abdomen, in an attempt to minimise unnecessary invasive interventions. Investigators found that laboratory values, inflammatory markers, and biochemical levels were not significantly different among the two groups.[27] To complicate things even more, increasing evidence is suggesting a correlation between MIS-C and appendicitis in children.[35] Therefore, a proper history, physical examination, and imaging are necessary for the assessment of abdominal pain in these patients.

Congruently, the involvement of skin and mucus membrane is frequently common. Extremity swelling and erythema, skin rash, mucositis, conjunctivitis, peri-orbital oedema, strawberry tongue, and palmar erythema are prominent features.[36–38] In one case

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Table 2. Clinical features of MIS-C documented by varying investigators

Study (population size)	Duration, median (range) in days	GI manifestations	Mucocutaneous manifestations	Neurologic manifestations	Cardiac manifestations	Respiratory manifestations	Nephrological manifestations	Constitutional
[1] **(n = 539)**	4 (3–6)	90.2%	66.8%	40%	Cardiac symptoms 67% EF < 55% (33%) Arrythmias 8.5% Coronary artery aneurysm 13% Pericardial effusions 25%	Respiratory symptoms 80% ARDS 10% Pleural effusions 31%		99.4%
[2] **(n = 21)**	5 (2–8)	76% including abdominal pain, loose stools, vomiting	Macular rash 33% Non-purulent conjunctivitis 42%	NA	EF < 55% (43%) Coronary dilatation 24%	Respiratory distress 23%	Oliguria 19%	100%
[3] **(n = 21)**	NA	Vomiting 47% Abdominal pain 52%	Rash 42.9% Conjunctival congestion 38%	47.6% Seizures 23%	LV dysfunction 38%	Respiratory distress 42.9% Shock 48%	NA	100%
[4] **(n = 95)**	4 (3–6)	Abdominal pain 60% Nausea/vomiting 58% Diarrhea 49%	Rash 60% Extremity swelling 9% Conjunctivitis 56$	Headache 29% Altered mental status 2%	Coronary aneurysm 9% Myocarditis 53% Shock 10%	Upper respiratory 27% Lower respiratory 40%	AKI 10%	99%
[5] **(n = 186)**	NA	92% Hepatitis/hepatomegaly 8% Pancreatitis 7%	80%	11%	Cardiac involvement 80% Pericarditis/pericardial effusions 26% EF < 55% (33%) Arrythmias 12%	70%	AKI 8%	100%
[6] **(n = 78)**	11 (8–14)	Abdominal pain 62% Diarrhea 64% Vomiting 63%	Rash 45% Conjunctivitis 29%	NA	Shock 87%	NA	NA	100%
[7] **(n = 15)**	NA	87% including abdominal pain, vomiting, diarrhoea	Rash 47% Conjunctivitis 27% Extremity swelling 27%	NA	Tachycardia and hypotension 87% Depressed LV function 27% Coronary artery abnormality 20% Arrythmia 13%	Cough or dyspnoea 20% Pleural effusions 27%	NA	100%
[8] **(n = 28)**	5 (1–10)	54%	Conjunctivitis 57% Mucositis 25% Rash 36% Extremity swelling 21%	NA	Hypotension/shock 54% EF < 55% (39%) Dilated coronary artery 7% Coronary aneurysm 14%	Pleural effusion 12%	AKI 21%	100%
[9] **(n = 35)**	11 (6–14)	86% (abdominal pain, diarrhoea, vomiting)	Rash 37% Conjunctivitis 26%	NA	78% Pan-carditis 43% Shock 60% Coronary artery aneurysm 20%	Pleural effusions 16%	NA	94%

Table 2. (*Continued*)

[10,11](n = 44)	NA	GI symptoms 84% Hematemesis 2% Hematochezia/melena 4.5%	Mucositis 52% Skin rash 71% Conjunctivitis 52.3%	30%	Shock 50% Any cardiac abnormality 50$	25%	AKI 15.9%	100%
[12](n = 101)	5 (3–7)	GI symptoms 80% Diarrhea 42.5% Vomiting 54% Abdominal pain 80%	Rash 64% Mucositis 59% Conjunctivitis 65%	Headache 36%	Shock 39% Coronary artery aneurysm 5.8% Coronary dilation 22%	44%	17.8 %	100%

ARDS = acute respiratory distress syndrome; AKI = acute kidney injury; EF = ejection fraction; GI = gastrointestinal; LV = left ventricle.

[1]Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of United States of America children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *Jama.* 2021;325(11):1074-1087.

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[11]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 centre experience of 44 cases. *Gastroenterology.* 2020;159(4):1571-1574. e1572.

[12]Ciftdogan DY, Keles YE, Karbuz A, et al. Multisystem inflammatory syndrome in children associated with COVID-19 in 101 cases from Turkey (Turk-MISC study). *J Paediatr Child Health.* 2022;58(6):1069.

series, the duration of mucocutaneous symptoms ranged between 0 and 11 days.[5] Skin rashes were also variable, including morbilliform, maculopapular, urticarial, and petechial rashes.[6]

Neurologic manifestations in MIS-C are largely variable in terms of incidence, severity, and symptoms. Involvement of the neurologic system is not uncommon, reported in almost half of the patients in one study.[37] Children might present in seizure, altered level of consciousness, headache, irritability, or confusion.[31,32,38] Severe neurologic manifestations have been reported such as cerebral infarcts, encephalopathy, status epilepticus, Guillain Barre syndrome or its variant, and even acute fulminant cerebral oedema. Such complications are estimated to occur at a rate of 12%[33,36]. Meningitis was also reported, affecting around 12–56% of children.[31,3841] Brain oedema, diffuse signal changes, acute disseminated encephalomyelitis-like lesions, laminar necrosis, necrotising encephalomyelitis, and atrophy were revealed on MRI.[37]

Cardiac involvement and myocardial insult are frequent and critical. In severe cases, children can present with cardiogenic shock, myocardial dysfunction, hypotension, myocarditis, and pericarditis.[39] Varying degrees of depressed left ventricular function is reported in almost all the studies and in up to 80% of patients in some investigations.[6] Severe depression, defined as ejection fraction of < 30%, is estimated to complicate around 20–30% of cases.[26,28] In a case series of 186 patients, almost half required vasoactive agents on presentation.[31] Intriguingly, in some studies, the left ventricular dysfunction was not present at the time of admission but developed during hospitalisation.[1] Some patients even required extracorporeal membrane oxygenation.[40] Fortunately, affected children are expected to have rapid myocardial recovery. For instance, 100 and 95% of cases described in two separate studies had recovery of the left ventricle documented before hospital discharge.[28,41] Besides left ventricular depression, arrythmias, chest pain, coronary artery dilation, or aneurysm, pericardial effusions and hypotension are relatively common at presentation. Coronary artery involvement is highly evident. Dilatation and aneurysms have been reported in up to 93% of presenting cases.[19,40,42] Furthermore, cardiac involvement is marked on laboratory evaluation by elevation in serum cardiac enzymes, troponin, and pro-BNP.[18,36] Variable Electrocardiogram (EKG) findings including atrioventricular block, bradycardia, tachycardia, ST changes, T-wave changes, ventricular arrythmias, and elongation of QT interval were also reported.[3] Thus, when MISC is suspected, it is of high importance to obtain serum cardiac enzymes, echocardiogram, EKG, and sometimes advanced imaging such as cardiac MRI or CT might be needed.

Luckily, a minority of children present with acute kidney injury.[18] Nevertheless, some studies reported acute kidney failure in up to 70% of patients.[39] However, all of these cases were temporary.[39] Respiratory symptoms are also infrequent and complicate around 9% of presentations.[43] Lung pathologies are not usually reported. On imaging, the most common finding is pleural effusions.[35] Opacities and peribranchial cuffing are also frequently seen.[15,31] Rare cases of diffuse ground glass opacities on chest imaging might be encountered.[28,44] Besides, about 9% of patients might require respiratory support, with peak worsening of respiratory status at around 4 days from the onset of symptoms.[40,45]

From a hematological perspective, laboratory testing is consistently significant for elevated inflammatory markers such as C-Reactive protein (CRP), ferritin, erythrocyte sedimentation rate (ESR), IL-6, and procalcitonin.[6,37,43] At the same time, hyponatremia, thrombocytopenia, lymphopenia, elevated liver enzymes, anaemia, and hypoalbuminemia are also seen.[6,37,41,43] High levels of fibrinogen and D-dimers are also found, reflecting the hypercoagulable state of MIS-C.[43,46] Rare occurrence of aplastic anaemia was reported.[36] Incidence of deep vein thrombosis and pulmonary embolism have been also described by some studies, although rare in the paediatric population compared to adults with multi-system inflammatory syndrome[40]. Hyperglycemia might also complicate the course of illness. It can be severe enough to require transient insulin therapy.[36]

Therapeutic modalities in MISC

The management of MIS-C is not clearly defined until this moment; however, several international health organisations have developed guidelines to approach patients with MIS-C. In addition, multiple pharmacologic therapies have been proposed and used in the management of paediatric MIS-C. In general, a multidisciplinary approach that includes infectious diseases, cardiology, neurology, haematology, and intensive care teams is recruited. Each hospital would develop a specific protocol that would be updated on regular basis. Table 3 represents the guidelines for managing MIS-C patients, developed by the various organisations.

Supportive care should be initiated rapidly at presentation. After providing the proper haemodynamic support, treatment regimen is decided on based on the clinical picture and laboratory evaluation. A significant subset of patients require admission to the ICU.[47] The treatment aims to reduce inflammation in affected organs, prevent permanent damage, and provide prophylaxis against thromboembolic events.[48] Figure 3 depicts the treatment pathway of patients presenting with suspicion of MIS-C. The supportive care needed incorporates hydration, oxygen therapy, and blood pressure regulation.[49] The severity of MIS-C presentation dictates how aggressive the supportive care should be. Children presenting in shock require support with inotropic agents such as epinephrine, norepinephrine, or dobutamine to restore blood pressure and cardiac contractility.[3] Besides, a subset of patients with severe disease requires mechanical ventilation.[50] Extracorporeal membrane oxygenation may also be required in a small number of additional patients.[6]

Pharmacologically, treatment might include coverages with broad-spectrum antibiotics for suspected bacterial aetiology. Some healthcare centres support the use of broad-spectrum antibiotics in all patients with suspected or confirmed MIS-C.[51] Empiric treatment is usually continued until all cultures exclude bacterial infection. The most frequently utilised antibiotics in MIS-C include coverage for gram positive, gram negative, and anerobic organisms.[52] The use of broad-spectrum antibiotics was also endorsed by the Canadian Pediatric Society and by the American Academy of Pediatrics in cases of severe disease.[53,54]

As described above, patients with MIS-C are at a high risk of developing thrombotic complications such as thromboembolisms or apical LV thrombi.[55] Hence, aspirin and/or low-molecular-weight heparin are usually recommended and included in the treatment regimen.[56,57] Low-dose aspirin is advised to counteract the increased risk of blood clots and to provide protective effect in children with coronary artery involvement, thrombocytosis, or Kawasaki disease features. A single daily dose of 3–5 mg/kg/day of aspirin is usually prescribed.[58]

Furthermore, because of its similar presentation to Kawasaki disease and toxic shock syndrome,[59,60] practitioners have chosen immunomodulatory agents that have already shown beneficial

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Table 3. MIS-C management guidelines

Organisation	Last revised	Immunomodulatory agents	Antiplatelet and anticoagulation
American College of Rheumatology[1]	November 2020	For hospitalised patients, 2 g/kg of IVIG is recommended as first-line treatment Addition of 1–2 mg/kg methylprednisolone if the patient presented with shock, or if the disease was refractory If disease remained refractory: Consider 1–3 mg/kg/day methylprednisolone for intensification, if the patient has received high-dose methylprednisolone initially, otherwise high-dose anakinra is suggested	Low-dose aspirin (3–5 mg/kg/day, not to exceed 81 mg) is recommended until the platelet count is normalised and normal coronary arteries are confirmed by imaging at or beyond 4 weeks of diagnosis. Aspirin should not be used if platelet count is below 80,000, and the patients is in active bleed or has high risk of bleeding. Low-dose aspirin is recommended in patients with coronary artery aneurysm of z-score 2.5–10 In patients with coronary artery aneurysm and z-score > 10, low-dose aspirin should be coupled to therapeutic anticoagulation therapy
American Academy of Pediatrics[2]	October 2022	2 g/kg of IVIG, maximum dose of 100 g is recommended as initial therapy. The duration of IVIG therapy is guided by cardiac involvement and the patient's fluid status Patients who fail to show clinical or laboratory improvement or who are admitted to the intensive care should receive 2 to 30 mg/kg/day of methylprednisolone depending on severity and be treated with biologics. This is followed by a 3-week taper of steroids or biologics	All patients should receive low-dose aspirin, unless contraindicated
Canadian Pediatric Society[3]	May 2021	First-line treatment for children with a picture of KD or incomplete KD is 2 g/kg of IVIG (maximum of 70 g/day Steroids to be added if response to initial IVIG was not adequate If severe KD, myocarditis, shock, or macrophage activation syndrome/cytokine storm syndrome 1 to 2 mg/kg/day orally or intravenously as prednisone or methylprednisolone should be added If severe cardiac inflammation, initiation of steroids before IVIG might be considered to reduce inflammation and mitigate fluid overload caused by IVIG For severe disease with organ dysfunction and incomplete response to initial dose of steroids, high dose of pulse steroids of 10 to 30 mg/kg/day (to a maximum of 1000mg) as an infusion over 1 to 3 hours might be administered For cases refractory to pulse steroids (refractory MAS or KDSS) biologic should be considered	Low-dose aspirin (3–5 mg/kg, with maximum of 81 mg) in children with complete or incomplete KD, severe disease, myocarditis, shock, or macrophage activation syndrome/cytokine storm syndrome. Treatment should be continued until normal coronaries are documented by echocardiography > 4weeks after diagnosis in addition to normal inflammatory markers Therapeutic anticoagulation with enoxaparin should be initiated in patients with thrombosis, of EF < 35%
World Health Organization[4]	November 2021	For children with MISC: corticosteroids + standard of care instead of IVIG + standard of care For children with MIS-C + KD picture: corticosteroids + standard of care for KD	
Royal College of Paediatrics and Child Health[5,6]	September 2020	First line is IVIG 2 g/kg in a single or divided doses. A second dose might be considered in those with partial or no response Children less than 12 months or those with evidence of coronary artery involvement should also be given 10–30 mg/kg of methylprednisolone Steroids is the second-line therapy must be considered in children who remain clinically ill 24 hours after IVIG or those who remain febrile. Biologics therapy should be considered in those who fail to respond to IVIG and steroids	Children with Kawasaki-like picture should be treated with antiplatelets according to the local Kawasaki disease management guidelines Low-dose aspirin for at least 6 weeks in all children with MIS-C Initiation and duration of anticoagulation and antiplatelets should be discussed with a haematologist in children with evidence of CAD

KDSS = Kawasaki disease Shock Syndrome; MAS = Macrophage Activation Syndrome.

[1]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 1. *Arthritis & Rheumatology.* 2020;72(11):1791-1805.

[2]Pediatrics AAo. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. American Academy of Pediatrics. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/. Published 2022. Updated October 6, 2022. Accessed October 22, 2022.

[3]Berard RA TH, Scuccimarri R, Haddad E, Morin MP, Chan KJ, Dahdah NS, McCrindle BW, Price VE, Yeung RSM, Laxer RM,. Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (spring 2021 update). Canadian Pediatric Society. https://cps.ca/en/documents/position/pims#Figure%201. Published 2021. Updated May 2, 2021. Accessed October 23, 2022.

[4]Organization WH. Living Guidance for Clinical Management of COVID-19. WHO. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2. Published 2021. Updated November 23, 2021. Accessed November 1, 2022.

[5]Health RCoPaC. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - guidance for clinicians. Royal College of Pediatrics and Child Health. https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance. Published 2020. Accessed October 23, 2022.

[6]Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *The Lancet Child & Adolescent Health.* 2021;5(2):133-141.

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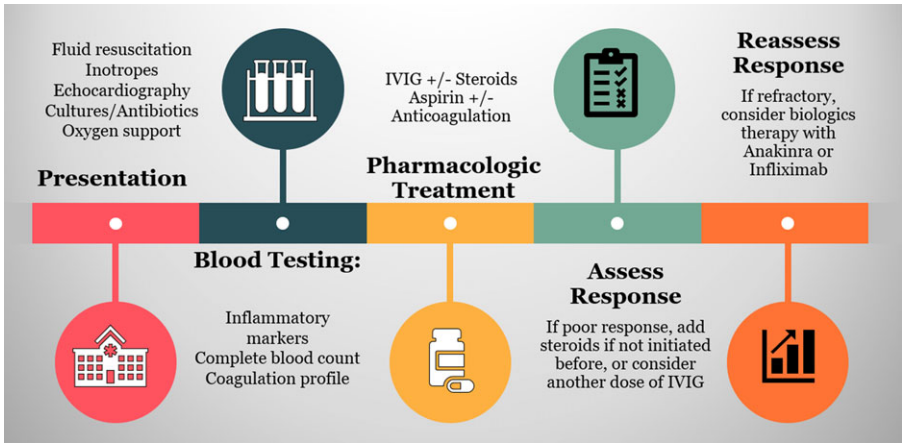

Figure 3. Treatment timeline for children with suspicion of MIS-C. Initial step involves stabilisation through providing supportive care, collecting cultures to assess for any microbial aetiology, and initiating proper antibiotics. It also should include initial echocardiography to evaluate the cardiac function. This is followed by laboratory evaluation. Inflammatory markers, cardiac indicators, and coagulation profile should be assessed. Once the diagnosis is confirmed, the initial treatment starts with IVIG 1-2 mg/kg with or without concomitant steroids therapy. The addition of aspirin and anticoagulation agents should be considered. The initial response is evaluated through clinical improvement and inflammatory markers. A rapid response is usually observed within days form treatment initiation. In refractory cases, a dose of steroids should be considered if not previously given, or a second dose is recommended. If the patient's condition did not improve despite using second-line therapy, the use biologics agents is recommended, including anakinra and infliximab.

results in the treatment of these diseases.[55] Therefore, treatment of children with MIS-C include both intravenous immunoglobulin (IVIG) and anti-inflammatory drugs such as glucocorticoids.[57] First-line treatment in most healthcare centres is IVIG, with a dose of 1–2 g/kg/day depending on severity. The timing of steroids initiation differs among the practitioners. Typically, 2mg/kg/day of methylprednisolone is used. Some studies showed no significant difference in clinical mortality or prognosis between the IVIG and steroid dual therapy and monotherapy with either one of the two.[48] A study conducted on 614 children who met the WHO criteria for MISC, 99 received glucocorticoids alone while 208 received the dual therapy of IVIG and glucocorticoids. The results showed that the adjusted odds ratio for the decrease in disease severity was similar in both groups. Indeed, 93 versus 90% of children receiving glucocorticoids alone versus IVIG + glucocorticoids, respectively, showed a decrease in the severity of their disease.[48] However, other studies show that patients receiving the combination therapy were less likely to experience recurrent fever, had a reduced need for haemodynamic support, and were less likely to have left ventricular dysfunction.[61] In addition, a retrospective cohort was performed in France to investigate the role of IVIG and steroids. It included 111 children who met the WHO criteria of MISC from whom 34 received the dual therapy of IVIG and steroids, in that case methylprednisolone, while 72 received the IVIG monotherapy. The authors measured the rate of treatment failure in that sample defined as the persistence of fever for 2 days after initiation of therapy or the redundancy of fever within 7 days. Nine per cent of children receiving the dual therapy showed a pattern of failure in the treatment received, while 51% of children on IVIG alone showed the same pattern. Moreover, only 5% of children experienced acute left ventricular dysfunction and the need of haemodynamic support in the dual-therapy group, versus 24% in the IVIG alone group.[61] This conclusion was in line with the results of one systematic review and meta-analysis. Authors concluded that children who received dual therapy have significantly lower risks of treatment failure and lower need for adjunct immunomodulator therapy than children receiving IVIG alone. In fact, out of the 756 total children included in the different studies, 44% of children receiving IVIG alone showed a positive result for treatment failure while only 31% of children receiving both IVIG and steroids exhibited treatment failure. These results were statistically significant.[62]

In addition to that, Anakinra (IL1 receptor antagonist) and infliximab (TNF -α receptor antagonist) are used in the treatment of refractory MIS-C in order to further reduce the patients' hyperinflammatory state.[57] Patients are considered refractory if they do not show improvement during the first 24 hours of administration of treatment. Studies also showed that the administration of anakinra as an adjunct therapy to IVIG or before invasive mechanical ventilation is also beneficial.[47] It is also worth mentioning that infliximab is not recommended for use in all the patients and should be only limited to those who did not respond to prior treatments or have other comorbidities like Crohn's disease.[63,64]

Finally, despite the severe and critical presentations of MIS-C, children exhibit excellent prognosis. In fact, clinical improvement is noted within few days of treatment initiation.[6,19] Rapid cardiac improvement and significant drop in inflammatory markers are usually observed following treatment.[39,43] Studies showed that by 6 months, most of the patients treated with the appropriate regimen had normal and clear cardiac MRI imaging,[65,65] and no signs of myocardial oedema or fibrosis were seen with normal left ventricular functioning.[66] The mortality rate is low, estimated at around 1–3%.[6,18,38]

Conclusion

MIS-C is an intriguing new phenomenon observed in the past 2 years and is attributed to COVID-19 infection. It shares overlapping features with Kawasaki disease. The hyperinflammatory storm influences multiple-organ systems and can mark end-organ damage. A clear pathogenesis of this newly arising condition is yet to be confirmed. Although with the appropriate and timely initiation of treatment children are exhibiting excellent prognosis, many questions are yet to be addressed.

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