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Review Article

Understanding the enigma of a novel pediatric disease, multisystem inflammatory syndrome in children: when COVID-19 throws a curveball at children's health

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a rare and potentially life-threatening condition that has emerged as a post-infectious complication of COVID-19. MIS-C is characterized by widespread inflammation affecting multiple organ systems, including the heart, lungs, kidneys, and gastrointestinal tract. The condition primarily affects school-aged children and adolescents, with most cases occurring several weeks after a COVID-19 infection. The exact pathophysiology of MIS-C is not yet fully understood, but it is thought to result from an abnormal immune response triggered by the SARS-CoV-2 virus. The clinical presentation of MIS-C is highly variable, and patients may present with fever, rash, conjunctivitis, abdominal pain, vomiting, diarrhea, and cardiac dysfunction. Early recognition and diagnosis of MIS-C are crucial for the prompt initiation of treatment, which typically involves immunomodulatory therapy and supportive care. The diagnosis of MIS-C is based on a combination of clinical and laboratory findings, including elevated inflammatory markers, cardiac biomarkers, and evidence of recent SARS-CoV-2 infection. The management of MIS-C is challenging, and treatment strategies continue to evolve as our understanding of the condition improves. Ongoing research is focused on optimizing diagnostic and therapeutic approaches to improve outcomes for affected children. This review article provides an overview of the current state of knowledge regarding MIS-C, including its epidemiology, clinical presentation, diagnostic evaluation, and management strategies.

Keywords: MIS-C, COVID-19, Pediatric inflammatory multisystem syndrome, SARS-CoV-2 infection

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C), is a clinical syndrome in children and adolescents and was first identified in April 2020 by doctors at children's hospitals in the USA and UK. MIS-C is alternatively being referred to as pediatric inflammatory multisystem syndrome (PIMS), as well. It is also known as PIMS-TS (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection) in European regions. The noteworthy finding associated with this is that most cases were reported to have evidence of recent infection of COVID-19. MIS-C or PIMS shares its common features with the inflammatory conditions known as toxic shock syndrome (due to the symptoms of erythroderma, renal involvement, hypotension) and Kawasaki disease (due to the symptoms of conjunctival and mucosal injection, rash, swelling of hands and feet, coronary artery dilation).[1-4]

HOW COVID-19 PRESENTS IN CHILDREN

Most children with SARS-CoV-2 infection are asymptomatic or have mild symptoms, making diagnosis challenging. Fever, cough, rhinorrhea, and sore throat are the most common symptoms in symptomatic children, but other manifestations such as headache, diarrhea, vomiting, myalgia, fatigue, tachypnea, tachycardia, and rash may

also be observed. Anosmia or ageusia, although not frequently seen, are amongst the strongest predictors of a positive SARS-CoV-2 test. Severe and critical cases are less common in children than adults. Specific symptoms include altered smell or taste, nausea or vomiting, and headache, while cough, nasal congestion, sore throat, and fever are non-specific symptoms. Clinical syndromes observed in children include acute respiratory infection, influenza-like illness, isolated fever, gastroenteritis or vomiting, and episodes of asthma exacerbations.[9]

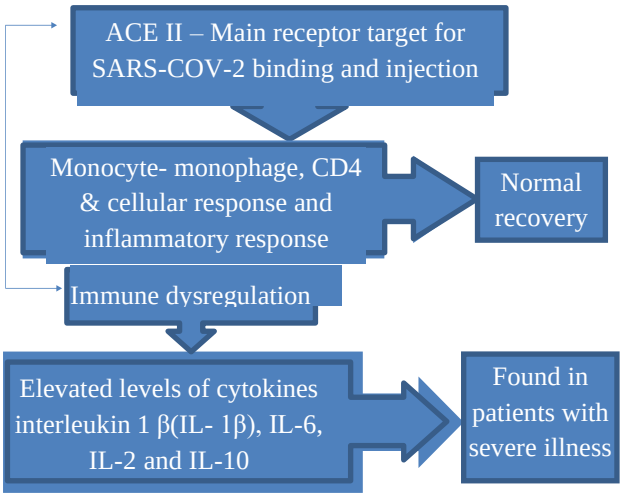

Figure 1: General pathogenesis of the post-COVID19 inflammatory syndrome.

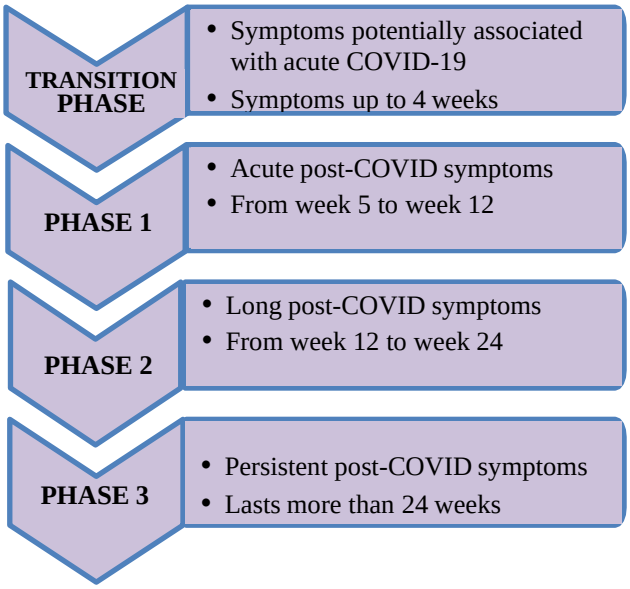

Figure 2: Phases of post COVID-19 infection, Fernández et al 2021.[5]

When reports of various patients were analyzed in other studies, it was elucidated that the pediatric population with a severe infection of COVID-19 may develop neurologic manifestations that could comprise up to 22% of severely affected patients, which were more frequently presented in patients with a pre-existing or underlying neurological condition. Sporadically, conditions of acute disseminated encephalomyelitis, acute transverse myelitis, respiratory failure, myocarditis, shock, ocular manifestations, acute renal failure, multi-organ system failure, intussusception or diabetic ketoacidosis were found to be incident.[9-12]

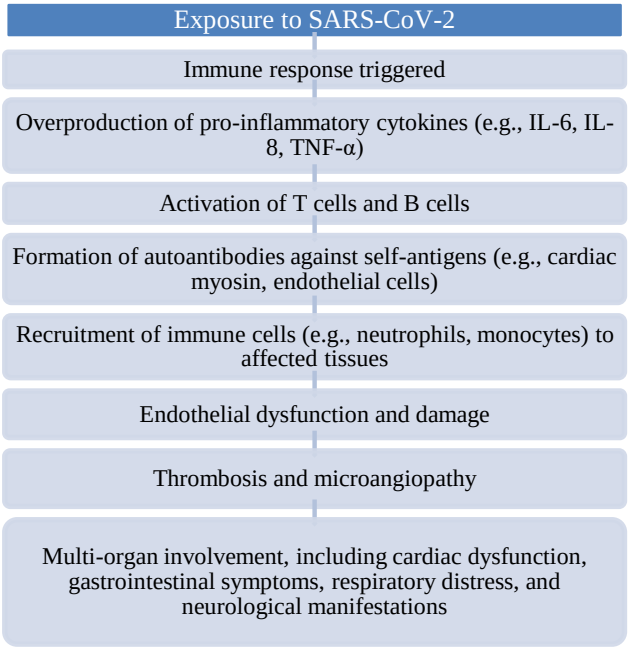

Figure 3: Brief depiction of immune response in MIS-C.[6-8]

Children infected with SARS-CoV-2 are also at risk for developing MIS-C a rare but serious condition associated with COVID-19 that has been reported in children. The significant symptoms include gastrointestinal manifestations, dermatologic/mucocutaneous signs, cardiac dysfunction, shock, and elevated diagnostic markers (C-reactive protein, interleukin-6, and fibrinogen levels).[12] The MIS-C is found to begin weeks after a SARS-CoV-2 infection, either symptomatic or asymptomatic; the median interval between presentation of MIS-C and previous infection being that of 25 days.[9]

CLASSIFICATION OF POST-COVID SYNDROMES

The classification has been summarized in the Tables.

Table 1: Classification based on correlation of development of initial symptoms and duration, to illustrate types of post-COVID manifestations, as elucidated by Helena et al 2021.[13]

Type	Initial symptoms	Duration	Quiescent period	Delayed onset of symptoms
Type 2	Mild	> 6 weeks	No	No
Type 3 A	Mild	3-6 months	Yes	No

Continued.

Type	Initial symptoms	Duration	Quiescent period	Delayed onset of symptoms
Type 3 B	Mild	>6 months	Yes	N/A
Type 1	Variable (correlate with severity)	Variable (correlate with severity)	No	No
Type 4 A	None	Variable	No	Yes, ≥3 months
Type 4 B	None	Variable	No	Yes, ≥6 months
Type 5	None	N/A	N/A	Yes

Table 2: Epidemiological outline of multisystemic inflammatory syndrome across different age groups.[6,14-16]

Disease	MIS-A (in adults)	MIS-N (in neonates)	MIS-C
Age	Adults (18 years and older)	Neonates (0-28 days old)	Children (up to 21 years old)
Epidemiology	Associated with COVID-19 infection	Rare; not clearly associated with COVID-19 infection	Associated with COVID-19 infection
Risk factors	Obesity, diabetes, hypertension, cardiovascular disease, immunocompromised state	Prematurity, maternal COVID-19 infection, neonatal intensive care unit admission, invasive procedures	Obesity, diabetes, Black or Hispanic ethnicity, cardiovascular disease, immunocompromised state
Clinical presentation	Fever, gastrointestinal symptoms, rash, cardiac dysfunction	Fever, irritability, poor feeding, respiratory distress	Fever, abdominal pain, vomiting, diarrhea, cardiac dysfunction
Laboratory findings	Elevated inflammatory markers, lymphopenia, thrombocytopenia	Elevated inflammatory markers, leukocytosis, thrombocytopenia	Elevated inflammatory markers, lymphopenia, thrombocytopenia
Morbidity and mortality	Hospitalization, ICU admission, respiratory failure, shock, death	Hospitalization, respiratory failure, shock, death	Hospitalization, ICU admission, cardiac dysfunction, shock, death
Treatment	Supportive care, immunomodulatory therapy	Supportive care, immunomodulatory therapy	Supportive care, immunomodulatory therapy, anticoagulation for cardiac complications

Table 3: WHO criteria for MIS-C.[17]

S. no.	WHO definition applies to children and adolescents aged 0 to 19 years who meet all of the following clinical criteria
1	Fever for 3 days or longer
2	2 or more of the following
	Rash or bilateral conjunctivitis (non-purulent) or mucocutaneous inflammation of mouth, hands, or feet
	Hypotension or shock
	Features of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities, including evidence found through imaging (echography) and laboratory studies (elevated levels of troponin, NT-proBNP [N terminal–prohormone brain natriuretic peptide])
	Coagulopathy (e.g. elevated prothrombin time/INR, partial thromboplastin time, D-dimer level)
	Acute gastrointestinal symptoms (vomiting, diarrhea) or abdominal pain
3	Elevated levels of nonspecific indicators of inflammation (e.g., erythrocyte sedimentation rate, C-reactive protein, procalcitonin)
4	No obvious alternate microbial cause of inflammation (bacterial sepsis, staphylococcal or streptococcal toxic shock syndrome)
5	Evidence of COVID-19 (positive reverse transcription polymerase chain reaction test result, detectable antigen, or antibody) or likely exposure to COVID-19

CLINICAL PRESENTATION OF PATIENTS WITH MIS-C

There is reportedly the presence of a history of persistent fever, generally lasting 4 days or more, and gastrointestinal symptoms which include diarrhea, vomiting, and abdominal pain. Nonspecific extremity pain, odynophagia, vomiting, headache, myalgia, and rash have also been reported. Respiratory manifestations are relatively

uncommon. Altered mental status (confusion, somnolence) or syncope may occur.[18]

Upon physical examination, the affected patients may appear severely ill with signs of shock. Fever is present and may be towards the high ranges (40 °C or higher). Conjunctival injection is often seen, but purulence and exudate are usually absent. Oral mucosa may be dry and reddened. Meningismus is present in some patients, and cervical lymphadenopathy may be palpable. Cardiac manifestations like tachycardia and irregular rhythms have been noted. Erythema or oedema of palms and soles and rash are commonly noted.[18]

DIAGNOSTIC PROCEDURES RECOMMENDED FOR MIS-C

In the absence of a predefined panel for identifying MIS-C, the general diagnostic tests that could be conducted include CBC, chemistry panel (including kidney and liver function, serum amylase, serum lactate, creatine kinase), inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, or procalcitonin), cytokine panel, coagulation studies (prothrombin time/INR, partial thromboplastin time, D-dimer), ferritin, troponin, NT-ProBNP, and urinalysis. Apart from these, the specific tests that may help correlate observations and clinical findings include SARS-CoV-2 RNA or antigen test and serology; microbiologic evaluation for alternate infectious causes (blood, throat, urine, stool, and cerebrospinal fluid cultures as clinically indicated; viral nucleic acid amplification test panel for Epstein-Barr virus, enteroviruses, and common respiratory viruses). In this case, wherein evaluation for MIS-C is being carried out, it has been seen that the results of tests for SARS-CoV-2 antibodies are often positive, even when polymerase chain reaction and antigen test results are negative.[18]

Chest (may reveal unilateral or bilateral infiltrates), heart (may reveal general features of myocarditis (left ventricular systolic dysfunction) and/or additional changes characteristic of Kawasaki disease (coronary artery dilation, valvulitis, pericardial effusion)) and abdominal imaging studies (may reveal hepatosplenomegaly, lymphadenopathy, bowel wall oedema, or ascites) are indicated for patients presenting with respiratory, cardiac ailments and severe abdominal pain respectively.[18]

The results of the CBC give the impression of the typical presence of neutrophilia and lymphopenia, anemia and/or thrombocytopenia may also be present. Hypoalbuminemia is common; hyponatremia or elevated levels of creatinine, BUN, transaminases, and creatine kinase may be seen. Inflammatory markers C-reactive protein, erythrocyte sedimentation rate, procalcitonin levels, coagulation studies Prothrombin time/INR, partial thromboplastin time, and D-dimer levels are markedly elevated. The fibrinogen in the analysis may be high. Regarding cardiac biomarkers, Troponin and NTProBNP are analyzed, and their levels may also be elevated. SARS-CoV-2 testing Polymerase chain reaction, antigen, or antibody test result has been found to render positive results in almost all patients. Apart from these, the ECG may reveal heart block, increased QT interval, ventricular arrhythmias, and ST-segment elevation in some patients.18

FIGURING OUT IF YOUR PATIENT'S SYMPTOMS ARE DUE TO POST-INFECTIOUS SYNDROME OR PERSISTENT INFECTION

The postulation by Weisberg et al points towards the possibility of younger patients having an increased number of naive T cells in different sites to respond to new pathogens, therefore facilitating a robust T cell response getting rid of an infection in the lung, which in turn prevents severe respiratory disease in children. And apart from that in some patients, a lower level of a persistent infection could build up in other sites over a stipulated period of time, which manifests as a multisystem inflammatory syndrome in children.[19]

Since the receptor binding sites responsible for COVID-19 lie in the ACE-2 receptors, possible infection sites of SARS-CoV-2 infection are present in arterial and venous endothelial cells and arterial smooth muscle cells, and the vascular system. A study by Colmenero et al reports the findings of the presence of viral particles in the dermal vascular endothelium.[20]

Diorio et al report finding extensive burr cells (echinocytes) in the peripheral blood smears of patients with MIS-C. The activated macrophages during this phenomenon could induce nitrosative stress, which leads to the induction of echinocyte formation.[21]

The occurrences of burr cell formation have also been noted in Epstein-Barr virus-triggered secondary hemophagocytic lymphohistiocytosis, and the tumour necrosis factor-α and interleukin-10 elevation. It is speculated that the persistent immune inflammatory response might take place due to the potential of the SARS-CoV-2 particles to block type 1 and type 3 interferon response signaling to the adaptive immune system. This takes place exclusive of cytokine production disruptions. These persistent immune inflammatory responses are facilitated by the immune responses that fail to control an ongoing infection, as seen in the case of MIS-C. These patients have been found to be treated with aspirin, corticosteroids, and immunoglobulin therapy and achieved recovery states.[21,22]

INSIGHTS FROM GLOBAL CASE REPORTS: RELEVANT FINDINGS

A 5-month-old Caucasian boy presented with his chief complaints being the presence of 36 hours of persistent fever, irritability, lip ulceration, and perineal cellulitis. The hematologic examinations revealed nonregenerative anaemia, leukopenia, and severe neutropenia. When a bone marrow aspiration was conducted, it showed

hyperplasia of the granulocyte lineage with notably unbalanced maturation shifted towards promyelocytic and myelocytic forms, whereas neutrophils were very poorly represented. The RT-PCR for COVID-19 tested negative, but the SARS-CoV-2 antibody IgG and IgM tests were positive, pointing towards the working diagnosis of MIS-C secondary to COVID-19. The treatment assigned consisted of filgrastim (10 µg/kg/day for 4 days), empirical broad-spectrum intravenous antibiotic therapy, and immunoglobulin therapy.

Moderate neutropenia persisted for 1 month after discontinuation of filgrastim, and five months later, the neutrophil count was found to be normalized. The overall incidence of neutropenia related to COVID-19 is not as frequently encountered as lymphopenia. Neutrophilia and thrombophilia are the lesser observed findings.[23]

A series of cases report symptoms of acute abdominal pain, mimicking appendicitis which is a common presentation of both COVID-19 and MIS-C. Two cases of patients initially deemed to have appendicitis who presented with or gradually developed shock and were found to have MIS-C. An 8-year-old Hispanic girl whose RT-PCR test for SARS-CoV-2 was positive, presented with fever, abdominal pain, and shock with ultrasound findings consistent with acute appendicitis. She was treated for MIS-C, after which she underwent an appendectomy and her condition improved.[24]

Another report of a 9-year-old girl tells us about her developing post-operative fever and shock, post-laparoscopic appendectomy, as she presented with uncomplicated appendicitis and tested negative for COVID RT-PCR. The antibody testing was done and found to be positive and she responded to the treatment prescribed for MIS-C. Her histology reports revealed lymphohistiocytic inflammation within the muscularis propria, mesoappendix, and serosa without the typical neutrophil-rich inflammation and mucosal involvement of acute appendicitis. The final diagnosis ruled out to be MIS-C, not appendicitis.[24]

A different case of a potential neurological complication with MISC was reported wherein a 7-month-old male child was presented with the chief complaints of fever with a maculopapular rash with 1 episode of abnormal movement at the onset of fever of 2-day duration with conjunctival congestion. After being admitted, the patient suffered one episode of generalized tonic-clonic seizure, not controlled by 1st and 2nd line antiepileptic drugs, therefore he was intubated and on injection midazolam infusion was initiated. Laboratory workup revealed a raised CRP level. In view of the familial history of COVID-19 occurring 20 days ago, the IgG antibody level was measured which yielded positive results. Further, the raised NT Pro-BNP, D-dimer, and ferritin levels led to the diagnosis of MIS-C. Apart from these, the other diagnostic tests for fever under evaluation were: cerebrospinal fluid (CSF) examination and neuroimaging were normal, which ruled out any other causes of status epilepticus. The patient was treated with pulse methylprednisolone therapy and intravenous immunoglobulin (IVIG). The child improved over 48 hours and was discharged.[25,26]

Table 4: Outcomes of a few case reports of MIS-C.[27-31]

Case	Age	Country	Year	Symptoms	Diagnostic tests	Treatment	Outcome
1	10	USA	2020	Fever, abdominal pain, vomiting, rash	RT-PCR, serology, chest X-ray, echocardiography	IVIG, steroids, anticoagulation	Discharged after 3 days
2	7	UK	2020	Fever, lethargy, conjunctivitis, diarrhea	RT-PCR, serology, chest X-ray, echocardiography	IVIG, steroids, antibiotics	Discharged after 7 days
3	12	Spain	2021	Fever, fatigue, headache, abdominal pain	RT-PCR, serology, chest X-ray, echocardiography	IVIG, steroids, anticoagulation	Discharged after 5 days
4	8	Brazil	2021	Fever, cough, abdominal pain, diarrhea	RT-PCR, serology, chest X-ray, echocardiography	IVIG, steroids, antibiotics	Discharged after 10 days
5	11	France	2021	Fever, myalgia, abdominal pain, conjunctivitis	RT-PCR, serology, chest X-ray, echocardiography	IVIG, steroids, anticoagulation	Discharged after 6 days

MIS-C IN COMPARISON WITH KAWASAKI DISEASE

Kawasaki disease, also known as Kawasaki syndrome or mucocutaneous lymph node syndrome, is a rarely occurring acute febrile illness of unknown cause that affects children younger than 5 years of age.[32]

Certain symptoms that are encountered in the case of MIS-C, predominant ones being the presence of persistent fever, gastrointestinal symptoms, cytokine storms, myocardial

dysfunction, and cardiogenic shock with left ventricular dysfunction; are quite similar to the conditions of toxic shock syndrome (TSS) or Kawasaki disease shock syndrome (KDSS), which also may warrant critical care. Some other symptoms like conjunctival injection, oral mucosal changes, and rash when seen in children with infections are also part of features that also resemble symptoms seen in the cases of TSS and incomplete Kawasaki disease. The reason clinicians were led into believing that Kawasaki and MIS-C were the same was because of the mucocutaneous findings being present in Kawasaki disease, and because patients with MIS-C sometimes developed mild coronary artery dilation as well.[32]

On how MIS-C is distinct from Kawasaki disease, studies indicate that coronary artery dilation in patients with MIS-C is mild and transient, similar to other pediatric febrile illnesses like systemic onset juvenile idiopathic arthritis. Unlike in adults with COVID-19 infections, coronary artery inflammation or necrotizing arteritis has not been observed in autopsy studies of MIS-C patients. It is suggested that an endothelial dysfunction associated with SARS-CoV-2 infection, sustained by the cytokine storm, may be a likely contributor to the coronary artery dilation seen in MIS-C.

This mechanism may explain the less severe and more transient dilation found in patients with MIS-C compared to those with Kawasaki disease, where more severe dilation and coronary artery aneurysm formations can lead to serious complications such as myocardial infarction, aneurysm rupture, and sudden death. Additionally, Kawasaki disease tends to occur in infants while the median age of MIS-C is around 9 years.[33,34]

The incidence of Kawasaki Disease is highest among children of Asian, but no cases of MIS- C have been reported from Asia. Additionally, the incidence of lymphopenia is a commonly found laboratory parameter in MIS-C, but it is not characteristic of Kawasaki disease. In the study conducted by Carter et al., when the immunophenotyping of patients with MIS-C from the United Kingdom was performed, it led to the conclusion that MIS-C is an illness that presents as an immunopathogenic illness that is evidently different from Kawasaki disease.[31,35]

Lately, the CDC published initial findings of pediatric patients exhibiting symptoms wherein they were classified into different classes depending on the nature of the involvements. The patients in class 1, who had the highest degree of organ involvement and higher prevalence of presenting with shock and lymphopenia, were deemed to have very little overlap with patients with Kawasaki disease. Whereas, the patients in class 3 mostly met the criteria for Kawasaki disease. Patients in class 2 showed the most respiratory symptoms and the highest prevalence of nasopharyngeal RT-PCR positivity for SARS–CoV-2, and likely had acute COVID-19.[31]

Table 5: Features of three groups of children (non-overlapping classes 1, 2 and 3) reported to CDC as MIS-C and their comparison to Kawasaki disease, as elucidated by Rowley et al 2020.

Disease	Clinical presentation	Features	Signs and symptoms	Pathophysiology	Epidemiology	Diagnosis	Treatment
MIS-C	Multi-system inflammation, rash, fever, abdominal pain, conjunctivitis, mucosal inflammation	Elevated inflammatory markers, recent COVID-19 infection	Fever, abdominal pain, vomiting, diarrhea, conjunctivitis, rash, swollen lymph nodes, cardiac dysfunction	Thought to be an immune response to prior COVID-19 infection, involving cytokine release and endothelial cell activation	Mostly affects children and adolescents, more common in males, most cases reported in North America and Europe	Clinical and laboratory findings, recent or previous COVID-19 infection	Treatment is largely supportive, including intravenous immunoglobulin (IVIG), steroids, and anticoagulants
Toxic shock syndrome	Fever, rash, hypotension, gastrointestinal symptoms	Bacterial infection, most commonly associated with *Staphylococcus aureus*	Fever, headache, muscle aches, vomiting, diarrhea, rash, hypotension	Bacterial toxins, including superantigens, cause a systemic inflammatory response and capillary leak syndrome	Can affect anyone, but more common in females, associated with tampon use and recent skin or soft tissue infections	Clinical findings, cultures of blood or other sites of infection	Treatment includes antibiotics, intravenous fluids, and supportive care

Disease	Clinical presentation	Features	Signs and symptoms	Pathophysiology	Epidemiology	Diagnosis	Treatment
Kawasaki Disease	Fever, conjunctivitis, rash, swollen lymph nodes, redness and swelling of hands and feet, peeling skin	Coronary artery aneurysms, elevated inflammatory markers	Fever, conjunctivitis, rash, swollen lymph nodes, redness and swelling of hands and feet, peeling skin, irritability	Thought to be an autoimmune response triggered by a viral infection or other environmental factor, leading to widespread inflammation and vasculitis	Most common in children under 5 years old, more common in males, most cases reported in Japan and other parts of Asia	Clinical findings, including fever and rash, along with criteria for other features	Treatment includes high-dose aspirin and intravenous immunoglobulin (IVIG)

WHAT ARE THE TREATMENT OPTIONS?

As the patients with MIS-C mimic symptoms of shock and hypoxemia, the approaches may include oxygen administration (and if warranted, mechanical ventilation), cautious fluid replenishment, and vasopressor support.

According to the American College of Rheumatology guidelines, the recommendations suggest the following approach: patients with suspected MIS-C, who suffer from life-threatening manifestations may require immunomodulatory treatment for MIS-C prior to the completion of the full diagnostic evaluation. Whereas in the patients with mild symptoms, close monitoring without immunomodulatory treatment would suffice. The first line of immunomodulatory therapy is IV immunoglobulins, and glucocorticoids may also be used adjunctively depending on the severity of the illness or clinical response to IV immunoglobulin. High doses of IV immunoglobulin (typically 2 g/kg, based on ideal body weight) are recommended for MIS-C patients who are hospitalized or who fulfil Kawasaki disease criteria. It is to be noted that cardiac function and fluid status be analyzed prior to initiating IV immunoglobulin treatment. This is because patients with severely impaired myocardium may require close monitoring and might need diuretics to avoid volume overload in their systems. Another alternate strategy recommended for MIS-C management is to administer IVIg in divided doses (1 g/kg daily over 2 days). The initiation of low to moderate-dose glucocorticoids (for instance, methylprednisolone 1-2 mg/kg/day) with IV immunoglobulin as adjunctive therapy may be done in order to control the MIS-C in patients experiencing shock or organ-threatening disease. The absence to respond to either of the therapies may warrant the consideration of high-dose glucocorticoid pulse therapy (for example, methylprednisolone 10-30 mg/kg/day). This is especially considered in severe illnesses or comorbidities which require high doses or multiple inotropes or vasopressors. A second dose of IV immunoglobulin is not recommended in patients as it has the potential to predispose the patient to develop volume overload and haemolytic anaemia. Hence larger doses must generally be avoided.[15,39]

Corticosteroids when given in low to moderate doses (for example, methylprednisolone 1-2 mg/kg/day) may prove to be beneficial in patients with milder forms of MIS-C, in whom the symptoms of fever and others do not resolve post single dose of IV immunoglobulin. Anakinra, an interleukin antagonist (greater than 4 mg/kg/day IV or subcutaneous) can be considered as an option to treat MIS-C when it does not respond to IV immunoglobulin and glucocorticoids, and also when the patient's diagnostic parameters point towards possible associated macrophage activation syndrome. This is also beneficial as an alternative where the long-term use of glucocorticoids is contraindicated in patients. The tapering of immunomodulating agents may require 2 to 3 weeks or more, and hence must be monitored in correlation with clinical findings and diagnostic lab parameters.[15,39]

Apart from immunotherapy, antiplatelet and anticoagulation therapy are initiated in MIS-C depending on the patient's clinical impressions. A course of low-dose aspirin (at a dose of 3-5 mg/kg/day; with a maximum of 81 mg/day) is recommended to be used continuously until platelet count normalizes and the radiology (echocardiogram 4 or more weeks after diagnosis) shows that the coronary arteries are normal, and aneurysms are resolved. Aspirin is to be avoided in patients with active bleeding, low platelet count, or the ones who possess a risk for developing bleeding tendencies.[15,39]

PIMS temporally associated with COVID-19 (PIMS-TS) National Consensus Management Study Group has come up with recommendations regarding management in children with Kawasaki disease–like phenotype and nonspecific symptoms. When treating children with nonspecific symptoms, the first line of therapy is IV immunoglobulins at a dose of 2 g/kg (based on ideal body weight) which may be administered in a single or divided dose, depending on clinical parameters and cardiac function. The second line therapy is corticosteroids, IV

methylprednisolone (10-30 mg/kg) meant for children who seem to remain unwell and have a persistent fever 24 hours after infusion of immunoglobulin. The third-line therapy recommended for patients who fail to respond to the first- and second-line approaches is a biologic therapy involving the use of either tocilizumab, anakinra, or infliximab. It is also advised that patients aged 12 years and above, wear compression stockings. Adjunct to this, low-dose aspirin may be given for a duration of 6 weeks.[15,39]

For patients who meet Kawasaki disease criteria, Kawasaki disease guidelines the treatment is to be initiated preferably within 10 days of symptom/illness presentation.

Empiric antibiotics may be started in patients with sepsis but in the absence of a definitive culture report. The doses of such may be determined based on laboratory parameters. In case the patient falls into the criteria of toxic shock syndrome, Clindamycin is recommended with broad-spectrum antibiotics. In case an anti-retroviral therapy needs to be initiated to control the existing COVID-19 (detected via positive RT-PCR), Remdesivir remains the first choice.[12,15,39]

MONITORING PARAMETERS

The monitoring parameters are elaborated in Table 8.

Table 8: MIS-C monitoring modalities.[40-44]

Monitoring parameters	Description
Vital signs	Including temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be monitored continuously and assessed for changes
Laboratory tests	Including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, cardiac enzymes, liver and renal function tests. These tests help to evaluate the severity of the inflammatory response and identify organ dysfunction
Echocardiogram	This is a key diagnostic tool for MIS-C and should be performed in all suspected cases. Echocardiography can help to identify myocardial dysfunction, coronary artery abnormalities, and pericardial effusion
Chest X-ray/CT scan	Imaging studies can help to identify pulmonary infiltrates and evaluate the severity of respiratory compromise. Chest X-ray/CT scan should be performed in all patients with respiratory symptoms
Electrocardiogram	This can help to identify arrhythmias and conduction abnormalities in patients with cardiac involvement. Electrocardiography should be performed in all patients with suspected MIS-C.
Inflammatory markers	Serial measurements of CRP, ESR, and ferritin can be used to monitor the inflammatory response and response to therapy
Cardiac biomarkers	Serial measurements of troponin, B-type natriuretic peptide (BNP), and pro-BNP can help to monitor cardiac function and response to therapy
Oxygen saturation	Continuous monitoring of oxygen saturation is important in patients with respiratory compromise

IMPACT

MIS-C, or multisystem inflammatory syndrome in children, can have a significant impact on affected children and their families. The condition can cause a range of symptoms, including fever, rash, abdominal pain, and cardiac dysfunction, and may require hospitalization and intensive care. In some cases, MIS-C can also lead to long-term complications, such as coronary artery aneurysms.

Additionally, the occurrence of MIS-C highlights the ongoing impact of the COVID-19 pandemic, particularly on children who may have been previously thought to be less susceptible to severe illness from the virus. The development of MIS-C appears to be linked to prior COVID-19 infection, and as such, highlights the importance of continued efforts to control the spread of COVID-19 and to vaccinate eligible individuals, including children.

The burden of MIS-C is not yet fully understood, as the condition is relatively new, and ongoing research is needed to determine its long-term impact. However, early reports suggest that MIS-C can be a serious and potentially life-threatening condition, particularly in children with underlying health conditions.[36,40,45]

INTERPRETING THERAPEUTIC OUTCOMES

The CDC declared MIS-C a reportable illness on 14 May 2020. They provided a case definition that includes patients under 21 years old with fever, laboratory evidence of inflammation, severe illness requiring hospitalization, involvement of two or more organ systems, positive testing for SARS-CoV-2, and no other plausible diagnoses. The organ systems involved can include cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological systems.[36]

The Centers for Disease Control and Prevention (CDC) has declared MIS-C a reportable illness with specific diagnostic criteria. MIS-C is diagnosed in patients under 21 years of age who have a fever for at least 24 hours, laboratory evidence of inflammation, and involvement of two or more organ systems with positive testing for SARS-CoV-2.

Clinical, microbiological, and radiological outcomes are important endpoints to assess the efficacy of treatment and determine the duration of therapy in MIS-C patients. Clinical outcome refers to the resolution of all symptoms and signs of inflammation, microbiological outcomes refer to the eradication of the SARS-CoV-2 virus, and radiological outcomes refer to the resolution of pulmonary infiltrates or other radiological abnormalities. These outcomes are used to guide the duration of therapy and monitor the effectiveness of treatment. It is important to note that some patients may have residual symptoms or subclinical inflammation despite achieving a clinical cure, and radiological abnormalities may persist despite clinical and microbiological cures.[3,16,42]

FUTURE DIRECTIONS

Since its initial identification in the early stages of the COVID-19 pandemic, there have been several advances in understanding the pathogenesis and management of MIS-C. However, there is still much to learn about this disease, and research is ongoing to improve diagnosis, treatment, and outcomes for affected children.

One important direction for future research in MIS-C is to understand the long-term effects of the disease. Many children with MIS-C have been found to have persistent symptoms and sequelae even after initial recovery. These may include cardiovascular complications, neurological deficits, and other chronic health problems. Longitudinal studies are needed to better understand the long-term outcomes of MIS-C and identify effective strategies for managing and preventing these complications.

Another important area of research is the development of biomarkers for early diagnosis and risk stratification of MIS-C. While current diagnostic criteria rely on clinical and laboratory parameters, there is a need for more specific and sensitive biomarkers that can identify affected children early in the disease course. Several studies have identified potential biomarkers for MIS-C, including cytokines, chemokines, and other immune system molecules. These biomarkers may also help to identify children at higher risk of developing severe disease and guide treatment decisions.

There is also a need for further investigation into the optimal treatment strategies for MIS-C. Current management of MIS-C involves supportive care and immunomodulatory therapies such as intravenous immunoglobulin (IVIG) and corticosteroids. However, the optimal dosing and duration of these therapies are not yet clear, and there may be a role for newer immunomodulatory agents such as biologics and Janus kinase inhibitors. In addition, there is a need to identify effective strategies for managing the multisystem organ involvement seen in MIS-C, including cardiac, respiratory, and gastrointestinal complications.[40,46,47]

Finally, it is important to continue monitoring the incidence and prevalence of MIS-C, as well as its relationship to SARS-CoV-2 variants and vaccination. As new variants emerge and vaccination programs are rolled out, there may be changes in the epidemiology and clinical characteristics of MIS-C. Surveillance systems will be needed to track these changes and guide public health responses.

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