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REVIEW ARTICLE

Multisystem Inflammatory Syndrome In Children (MIS-C) Temporally Associated With COVID-19 - An Update

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Abstract

Introduction: Children are less likely to have severe acute COVID-19, but cases of pediatric multisystem inflammatory syndrome (PIMS) with possible temporal association with previous SARS-CoV-2 infection have been described. **Objectives:** Non-systematic review of the literature on epidemiology, pathophysiology, diagnosis, and treatment of PIMS. **Source of Data:** PubMed database, scientific documents of the Brazilian Society of Pediatrics, World Health Organization, Centers for Disease Control and Prevention (CDC), and Royal College of Pediatrics and Child Health. **Summary of Findings:** PIMS shares characteristics with Kawasaki disease, toxic shock syndrome, bacterial sepsis and cytokine storm syndrome. It is more frequent in Afrodescendants and Hispanics, schoolchildren and adolescents, and in males. It occurs 2-4 weeks after SARS-CoV-2 infection. Pathophysiology involves direct effects of the virus and/or post-COVID-19 immune dysregulation. The clinical presentation is heterogeneous, fever being very frequent, followed by gastrointestinal, cardiovascular, respiratory, neurological, and renal manifestations. Thorough anamnesis and physical examination, as well as complementary exams to assess inflammatory process, organ involvement and the relationship with SARS-CoV-2 infection (RT-PCR and serology), are essential. Diagnostic criteria proposed by the CDC and WHO support the diagnosis. Treatment must be coordinated by a team of specialists, and directed to inflammatory and organic manifestations. **Conclusions:** PIMS is characterized by a broad clinical spectrum, with fever, gastrointestinal, neurological manifestations, shock, and myocardial dysfunction. It requires a high degree of suspicion for early treatment and prevention of potential cardiovascular, respiratory, renal, and neurological complications.

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INTRODUCTION

Since the first cases of COVID-19 were described in Wuhan (China) in 2019, more than 100 million cases had been recorded and 2,501,229 people had died of the disease by February 26, 2021. In Brazil, 10,324,463 individuals had been diagnosed and 247,957 had died of the disease by the same day.[1]

Children are much less likely to develop severe SARS-CoV-2 infection. Studies from several countries enrolling individuals aged 18 years or less have reported severe cases of the disease in only 2% of this population in the United States, 2.2% in China, 2% in Italy, 0.8% in Spain, and 1.8% in Brazil.[2-4] The majority of the children with the disease experience mild or asymptomatic disease, and usually present with coughing and fever, in addition to gastrointestinal (diarrhea, abdominal pain, nausea, and vomiting), cardiovascular, and skin symptoms.[5,6]

In April 2020, at the height of the COVID-19 pandemic, the United Kingdom National Health Service (NHS) published a warning report about a new clinical presentation stemming from COVID-19 in children, with a possible temporal association with prior infection by SARS-CoV-2 confirmed by contact with infected individuals, serology or RT-PCR testing.[7,8] This condition may present signs and symptoms similar to the ones seen in subjects with complete or incomplete Kawasaki disease (KD), toxic shock syndrome, and macrophage-activation syndrome; it involves multiple organs, including the heart, the gastrointestinal tract, the skin, and the eyes; subjects with the condition present with high levels of inflammatory markers; school-age children and adolescents are preferentially affected.

Pediatricians must become acquainted with this condition, since they are usually the first to see patients with the disease. Early diagnosis and treatment may help prevent severe complications.

EPIDEMIOLOGY

There are no updated records of cases of MIS-C in Brazil. In the United States, 1,659 confirmed cases of MIS-C and 26 deaths by the condition (1.7%) had been reported by January 8, 2021.[9] Cases of MIS-C occurred 2-4 weeks after infection by SARS-CoV-2 in children and adolescents aged 1-14 years (mean age: 8 years) and preferentially affected male individuals (57%). More than 70% of the reported cases involved Hispanic and Latino (n=554) or Black non-Hispanic (n=499) children. Most of the patients (99%) had tested positive for COVID-19 and the remaining one percent had been in close contact with someone with the disease.

According to a recent systematic review and meta-analysis including 386 studies and a total of 992 children and adolescents diagnosed with MIS-C,[10] males were slightly more affected than females (1.37:1 ratio of male-to-female cases) and patients had e median age of 7 years (14 days - 20 years). These cases of MIS-C appeared around four weeks after the peak in COVID-19 cases in the general population. Anti-SARS-CoV-2 antibodies were detected in 48% of the patients, 28% had positive RT-PCR tests, and 23% were positive in both tests. Only 10% had a history of contact with individuals suspected for or diagnosed with COVID-19.[10]

Interestingly, differently from KD, few cases of MIS-C have been described in individuals of Asian ethnicity Table 1.[11,12] In the early reports of MIS-C, children of African or African-Caribbean descent were more frequently affected by the syndrome.[13-15] A study published by the United States Centers for Disease Control and Prevention (CDC) with 570 patients with MIS-C showed that 41% were Hispanic/Latinos, 33% were of African descent, and 13% were whites.[16]

In regards to comorbidities, a review published by Panigrahy et al.[7] found baseline conditions in 45% of the 544 patients assessed for comorbidities. The most common comorbidities were obesity (16.4%; 89/544), lung diseases such as asthma and bronchial hyperreactivity (13.4%; 73/544), followed by other comorbidities seen in 15,2% or 83/544 patients (diabetes, systemic lupus erythematosus, and Crohn's disease).[7]

PATHOPHYSIOLOGY

The pathophysiology of MIS-C requires further elucidation, although potential mechanisms have been considered based on the overlapping clinical presentations seen in MIS-C and KD, toxic shock syndrome (TSS), systemic inflammatory response syndrome, and macrophage-activation syndrome (cytokine storm). Several theories have been postulated to explain the pathophysiology of MIS-C despite the knowledge gaps on the subject. In theory, MIS-C may be caused by: a) direct effects from SARS-CoV-2; b) immune deregulation after infection by SARS-CoV-2; c) a combination of the two previously mentioned mechanisms.[17] Below are some of the arguments used to support causation theories.

Direct effect from SARS-CoV-2

The thesis of disseminated viral replication is supported by the detection of SARS-CoV-2 RNA and viral particles in biopsy specimens taken from the heart, brain, kidneys, and gastrointestinal tract of adults with persistent viral infection without respiratory involvement, and from the case of a child with MIS-C who died of heart failure.[18] However, due to the low proportion of patients with positive RT-PCR tests (approximately a third of the cases of MIS-C), this causation theory has not been accepted as the primary explanation for cases of MIS-C.[10]

Immune deregulation after infection by SARS-CoV-2

Most of the cases occur four weeks after infection or contact with someone with the disease, thus indicating that MIS-C is predominantly a post-infection syndrome. Another point in favor of this theory is the high proportion of detection

of anti-SARS-CoV-2 antibodies in these patients when compared to the detection of the virus at the time of symptom onset.[10] In addition, most of the children with MIS-C respond well to therapy with immunomodulators and anti-inflammatory agents and no antivirals, suggesting a pathogenesis mediated by inadequate activation of the immune system.[17]

The inflammatory process may be exacerbated through IgG antibodies (antibody-dependent enhancement) and with the production of immune complexes and cell activation. The production of proinflammatory cytokines (IL-1, IL-6, IL-18, TNF-α, and interferon-γ) is consequently increased, thus triggering the onset of multisystem inflammatory response characterized by fever, increased inflammatory marker levels, shock, Kawasaki-like symptoms, cytokine storm, and multiple organ involvement.[19,20] Proposed physiopathogenesis mechanisms include: a) Molecular mimicry between viral antigens and the host with recognition of self-antigens by antibodies or T cells resulting in antibody activation; b) viral antigens expressed in infected individuals are recognized by antibodies or T cells; c) formation of immune complexes with the activation of the inflammation cascade; d) effect of viral superantigens that activate host immune cells.[19,20]

A second theory involves the cytokine storm caused by the ability of the coronavirus to block types I and III interferon response in patients with high viral loads or individuals unable to deal with viral replication, causing delayed cytokine storm. A third theory is based on susceptibility tied to ethnicity (whites being less susceptible) and gender.[21]

The phenotype similarities seen in some cases of MIS-C and KD indicate the existence of common inflammatory pathways. A number of theories have been proposed to explain the etiology of KD. One of them concerns the development of post-infection inflammatory response causing vasculitis in genetically predisposed individuals. Various bacterial and viral infection agents have been described, including the coronavirus (not SARS-CoV-2). Robust evidence, however, is still lacking. KD and MIS-C share two fundamental characteristics: endothelial damage and upregulation of the IL-1β pathway by activation of the NFκB pathway secondary to the recruitment of endothelial cell receptors and other cells of the innate immune system.[22]

Antibodies also mediate the inflammatory process seen in cases of KD. The presence of immune complexes with the activation of inflammatory response of Fc-gamma (Fcγ) receptors and complement has been documented in cases of coronary injury, while endothelial cell autoantibodies have been described in patients with MIS-C.[22]

High cytokine levels, particularly IL-1 and IL-17, have been associated with coronary artery inflammation and aneurysm formation in individuals with KD. In MIS-C, inflammation appears to be more strongly associated with high levels of IL-1, IL-6, IL-18, TNF-α, and Interferon-γ. Some authors have suggested that Kawasaki disease shock syndrome may be mediated by superantigens, abnormal increase in proinflammatory cytokines, and intestinal bacteria.[19]

CLINICAL SIGNS AND SYMPTOMS

The most frequent form of presentation of MIS-C, the probability of children with mild disease progressing to more severe forms of the disease, and the most relevant risk factors to consider while assessing the chances of disease progression have not been clearly established. The division proposed below is merely didactic and based on the evidence presented in literature to date. It may be changed, as more knowledge about the disease is acquired.

Acute COVID-19 in children presents as follows: 1) asymptomatic disease; 2) mild disease or 3) severe disease (few patients develop severe involvement with respiratory failure, neurlogic symptoms, coagulopathy, and shock; children with severe disease usually have comorbidities and some may develop macrophage-activation syndrome/cytokine storm).[23] Mild disease affects children with predominantly Th2-type immune response due to immune system immaturity. If the virus spreads to other tissues and the patient presents with adaptive immune response, delayed inflammation may occur. Then, IgA immune complexes may lead to systemic inflammation mimicking Th1-type immune response, thus causing MIS-C.[24]

Clinical practice shows that patients with MIS-C produce different presentations of the disease, strengthening the idea that the syndrome produces a broad array of clinical manifestations. A study coordinated by the CDC[25] statistically analyzed the cases of 570 children with the disease and divided them into three subgroups. Despite the limitations inherent to studies based on occasionally incomplete clinical data, similar patterns of disease have been reported in clinical practice. MIS-C was divided into three phenotypes/subgroups of patients with common characteristics (Chart 1).[25]

A systematic review and meta-analysis including 992 children with MIS-C[10] described fever as the most frequent symptom (95% of the cases), followed by gastrointestinal (78%), cardiovascular (75.5%), respiratory (55.3%), and neurlogic (30.6%) alterations, while 19.6% of the patients had acute kidney injury. Of the 992 patients, 225 (22.7%) had Kawasaki-like signs and symptoms such as rash (59%) and conjunctivitis (52%). The same systematic review[10] found that 47% of the patients had significantly elevated troponin or BNP levels (suggestive of myocardial injury) and that 1.4% developed arrhythmia. The echocardiograms of 41% (337/823) of the patients showed left ventricular dysfunction. Myocarditis was seen in 32% (276/870) of the cases and pericardial effusion in 21% (146/709). In regards to coronary alterations, 18% (143/802) had some abnormality, 19.4% (20/103) had dilated coronary arteries, and 17.8% (23/129) had aneurysms. Almost half (49%) of the patients had hypotension with shock, and 9% had congestive heart failure.[10]

The following respiratory manifestations have been described: odynophagia, upper airway congestion, coughing, difficulty breathing, chest pain, pneumonia, pleural effusion, acute respiratory distress syndrome (ARDS). Manifestations consistent with systemic inflammation such as fatigue,

Chart 1. Characteristics of the subgroups of patients with MIS-C identified in the CDC study[25].

Characteristics	Isolated MIS-C	MIS-C with severe symptoms of COVID-19	Kawasaki-like MIS-C
Frequency	35%	30%	35%
Most common signs and symptoms	Cardiovascular and gastrointestinal	Respiratory (coughing, dyspnea, pneumonia or respiratory failure)	Signs/symptoms of complete or incomplete KD. Shock/myocardial dysfunction occurred less frequently
Median age	~ 10 years	~ 9 years (usually with comorbidities)	
Positive PCR test	+/-	+ (majority)	+ (1/3; usually with + serology test)
Positive serology test	+/-	- (majority)	+ (2/3)
Coronary alterations	21%	16%	18%
Death rate	0,5%	5,3%	0%

weakness, lymphadenopathy, and myalgia have also been described.[10,23,27]

Children with severe disease present with clinical signs and symptoms of pneumonia (coughing or difficulty breathing) associated with at least one of the following: central cyanosis or oxygen saturation < 90%; severe respiratory effort; general signs of alarm such as inability to breastfeed or drink, lethargy, unconsciousness, or seizures; tachypnea (breaths/min): aged < 2 months: ≥ 60 bpm; aged 2-11 months: ≥ 50 bpm; aged 1-5 years: ≥ 40 bpm. Diagnosis may be based on clinical criteria, but chest images (X-ray images, computed tomography or ultrasound scans) help identify and rule out lung complications.[10,23,27]

Outside the context of the pandemic, MIS-C and KD share common clinical signs and symptoms, including conjunctivitis, oral cavity changes (erythema and/or cracked lips, strawberry tongue, oropharyngeal hyperemia), skin rash, alterations in the extremities (edema and/or erythema in the hands and feet, scaling), and cervical lymphadenopathy. However, several epidemiological, clinical, and laboratory characteristics of MIS-C are different from KD not associated with SARS-CoV-2 infection:

1) The incidence of MIS-C is higher among individuals of African, African-Caribbean, and Hispanic descent and lower in Asian populations (differently from KD);[26]

2) MIS-C affects a broader age range, produces more gastrointestinal and neurologic symptoms, progresses more frequently with shock, and increases the propensity to heart dysfunction (arrhythmia and ventricular dysfunction) when compared with KD.[26] In classical KD, shock is a rare event;[27]

3) Patients with MIS-C usually have lower platelet counts, lower absolute lymphocyte counts, and higher levels of C-reactive protein (CRP) than individuals with KD. Studies on the epidemiology of MIS-C suggest that younger children are more likely to present signs and symptoms similar to the ones seen in KD, while older children are more likely to develop myocarditis and shock, thus escaping the phenotype seen in KD. It is not known if the incidence of aneurysms differs between MIS-C and KD; however, subjects with MIS-C without signs and symptoms of KD may develop aneurysms.[26]

Table 1. Most common symptoms in individuals with MIS-C[23,26].

Symptoms during disease presentation	Frequency (%)
Persistent fever (4-6 days)	100%
Gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea)	60-100%
Rash	45-76%
Conjunctivitis	30-81%
Mucosal involvement	27-76%
Neurlogic symptoms (headaches, lethargy, and mental confusion)	29-58%
Respiratory symptoms (tachypnea, dyspnea)	21-65%
Odynophagia	10-16%
Myalgia	8-17%
Hand/feet edema	9-16%
Lymph node enlargement	6-16%
Clinical findings	**Frequency (%)**
Myocardial dysfunction (echocardiogram or increased BNP/troponin)	51-90%
Shock	32-76%
Acute respiratory failure (requiring noninvasive or invasive ventilation)	28-52%
Serositis (pleural or pericardial effusion or ascites - usually minor)	24-57%
Criteria for complete Kawasaki disease	22-64%
Arrhythmia	12%
Acute kidney injury	8-52%
Encephalopathy, seizures, coma, or meningoencephalitis	6-7%
Hepatitis or hepatomegaly	5-21%

DIAGNOSIS

In addition to a pediatrician, patients with MIS-C must be managed by a specialist care team that includes a pediatric rheumatologist (for their experience treating and following patients with inflammatory diseases and prescribing immunobiologicals and immunosuppressants); a cardiologist (given the cardiac involvement stemming from the condition); and an infectious disease specialist (to investigate secondary causes and treat complications from secondary infections). Other specialists such as hematologists, intensive care physicians, nephrologists, gastroenterologists might be needed depending

on the patient's clinical signs and symptoms and the severity of involvement.

The Royal College of Pediatrics and Child Health,[28] the Centers for Disease Control and Prevention (CDC),[9] and the World Health Organization (WHO)[29] developed criteria to diagnose patients with MIS-C (Table 2); the criteria proposed by the CDC and the WHO have been adopted more widely.[30]

Given the wide variety of clinical signs and symptoms seen in MIS-C, the condition deserves a special place in the list of diseases analyzed as a part of differential diagnosis. Early diagnosis and treatment may prevent severe complications such as cardiogenic shock and coronary alterations.[31] Although one of the diagnostic criteria for MIS-C requires ruling out other evident causes of infection, which implies considering other diseases in differential diagnosis that may explain the observed signs and symptoms, literature published to date contains reports of viral and bacterial coinfection in patients with MIS-C.[32] Therefore, the decision to prescribe immunomodulators such as intravenous immunoglobulin must always be discussed with specialists and take clinical signs and symptoms (disproportionate inflammatory manifestations vis-à-vis the identified infectious agent) into account, due to the lack of clarity in case definitions and the low levels of certainty inherent to the ongoing construction of knowledge about the disease.

The biggest hurdle is defining whether patients meet the diagnostic criteria for MIS-C, since a positive diagnosis implies immediate initiation of therapy. In clinical practice, MIS-C should be considered in patients with persistent fever (≥3 days). Clinical and laboratory evidence support diagnosis (Figure 1)[23].

Laboratory tests aim to find organ and/or system involvement and measure the intensity of inflammation. Tests help diagnose individuals with MIS-C and assist in differential diagnosis against other conditions and in monitoring patient response to therapy.

Serology and RT-PCR tests are required in the identification of cases of SARS-CoV-2 infection. Specimens for serology tests must be collected before the administration of intravenous immunoglobulin (IVIG).[33] In the American cohort of cases of MIS-C, about two thirds of the patients had RT-PCR, serology, or both tests positive for SARS-CoV-2 infection, while patients with negative tests had been in contact with individuals diagnosed with COVID-19.[4] In clinical practice, contact tracing information is not always available, since some patients may develop asymptomatic disease and are never tested, although they still spread the virus.[34]

The extended panel mentioned in the workflow (Figure 1) includes the following supplementary tests:

- Complete blood count;
- Inflammatory markers (ESR, CRP, LDH, D--dimer, procalcitonin and ferritin);
- Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin and bilirubin fractions, total protein and protein fractions;
- Blood urea nitrogen, creatinine, abnormal elements and urine sediment examination;
- Amylase, lipase, and triglycerides;
- Prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen;
- Creatine kinase (CK), creatinine kinase MB fraction (CK-MB), troponin and proBNP (B-type natriuretic peptide);
- Cultures (blood, urine, and tracheal aspirate if needed);
- RT-PCR and serology tests for SARS-CoV-2;
- Respiratory viral panel;
- Viral serology tests (based on clinical suspicion/differential diagnosis);
- 2D Echo/Doppler study;
- Electrocardiogram;
- Abdomen ultrasound or computed tomography scans (in cases of intense abdominal pain);
- Chest X-ray images or computed tomography scans.
- The association of clinical and laboratory evidence supports the diagnosis of MIS-C. Some patients will meet the criteria for complete or incomplete Kawasaki disease.[35] (Table 3).

Inflammatory markers – C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, D-dimer, and procalcitonin – are used in a combined fashion, since not all are elevated in MIS-C (Table 4). Most patients with MIS-C develop a hyperinflammatory state that manifests with leukocytosis and neutrophilia; elevated ESR, CRP, procalcitonin, D-dimer, and ferritin; hyponatremia and hypertriglyceridemia.[33] Patients with MIS-C usually have low platelet counts and higher levels of ferritin when compared with patients with KD. Lymphopenia has been described in individuals with MIS-C, while leukocytosis with neutrophilia has been reported in subjects with KD.[33]

Macrophage-activation syndrome (MAS) must be considered whenever the patient's clinical condition deteriorates rapidly, with increased CRP, decreased ESR, and, above all, increased ferritin.[33]

The D-dimer, a test rarely ordered for children, gained attention during the COVID-19 pandemic in the care provided to adult patients in particular. Information about the time at which patients are at greater risk of thromboembolism is still not available. Although some studies suggested that thrombosis may be an early sign of disease,[36] others reported the development of thromboembolism after hospital discharge,[37] thus stressing the need to organize further studies on the use of biomarkers such as the D-dimer to allow the early detection of these manifestations.[38]

Tabela 2. Diagnostic criteria for MIS-C[19].

Royal College of Pediatrics and Child Health **(UK [28])**	**Centers for Disease Control and Prevention (CDC [9])**	**World Health Organization (WHO [29])**
Age not specified	Age < 21 years.	Age 0-19 years
Fever	Fever > 38ºC or subjective, for ≥ 24h)	Fever for ≥ 3 days
+	+	+
Increased inflammatory markers (neutrophilia, increased C-reactive protein, and lymphopenia)	Laboratory evidence of inflammation (alterations in one or more of the following tests: C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin 6 (IL-6), neutrophilia, lymphopenia, and hypoalbuminemia	Laboratory evidence of inflammation (erythrocyte sedimentation rate, C-reactive protein or procalcitonin)
+	+	+
Evidence of single-organ injury or multiple organ dysfunction (shock, respiratory, kidney, gastrointestinal or neurologic dysfunction) and additional features*	Evidence of severe disease requiring hospitalization with multisystem involvement (≥ 2 organs): • Heart (e.g.: shock, elevated troponin and proBNP levels, echocardiogram alterations, arrhythmia); • Kidney (e.g.: acute kidney injury or kidney failure); • Respiratory symptoms (e.g.: pneumonia, acute respiratory distress syndrome, pulmonary embolism); • Hematological signs (e.g.: elevated D-dimer, thrombophilia; • Gastrointestinal symptoms (e.g.: elevated bilirubin and liver enzymes; diarrhea); • Neurlogic symptoms (e.g.: stroke, aseptic meningitis, encephalopathy)	At least two of the following: • Rash; bilateral non-purulent conjunctivitis; signs of • mucocutaneous inflammation (oral cavity, hands, feet) Hypotension or shock; • Findings consistent with myocardial dysfunction, pericarditis, • valvulitis or coronary alterations: echocardiogram or elevated • troponin or N-terminal pro–B-type natriuretic peptide (NT-proBNP); • Evidence of coagulopathy (PT, APTT and D-dimer); • Gastrointestinal symptoms (diarrhea, vomiting or abdominal pain).
+	+	+
Rule out infection, including bacterial sepsis, staphylococcal infection or streptococcal toxic shock syndrome, infectious myocarditis, enterovirus infection (The results from the tests for the conditions above should not delay referral to a specialist care team).	No other plausible diagnosis.	No other evident microbiological cause of inflammation, including bacterial sepsis, staphylococcal and streptococcal toxic shock syndrome.
+	+	+
Positive or negative test for SARS-CoV-2	Positive RT-PCR or serology or antigen test for SARS-CoV-2 OR history of exposure to COVID-19 in the four weeks prior to the onset of symptoms.	Evidence of SARS-CoV-2 (RT-PCR, antigen or serology test) OR likely contact with individuals with COVID-19

* Additional features: abdominal pain, altered consciousness (confusion), conjunctivitis, coughing, diarrhea, headaches, lymph node enlargement, mucosal changes, cervical edema, exanthemas, respiratory symptoms, odynophagia, hand/feet edema, syncope or vomiting.

An elevated D-dimer probably indicates the presence of severe inflammatory response accompanied by a secondary state of hypercoagulability. In fact, the D-dimer is also a marker of fibrin deposition in the lungs and is typically elevated in various pulmonary diseases such as acute respiratory distress syndrome (ARDS),[39] a condition often observed in patients with severe COVID-19. D-dimer elevation is accompanied by increases in other inflammatory markers including ferritin, interleukin 6, troponin I, and lactate dehydrogenase.[40] Therefore, the D-dimer may be used in combination with other traditionally used inflammatory markers. Patients suspected for thrombosis should undergo imaging examination of the affected sites.

Patients with MIS-C with severe signs and symptoms generally present more significant alterations in laboratory tests, as noted in some studies. Children diagnosed with shock had higher CRP levels (mean 32.1 vs. 17.6 mg/dL); higher neutrophil counts (16 vs. 10.8 x 10^9/L); lower lymphocyte counts (0.7 vs. 1.3 x 10^9/L); and lower serum albumin levels (2.2 vs. 2.7 g/dL) than children not diagnosed with shock. In

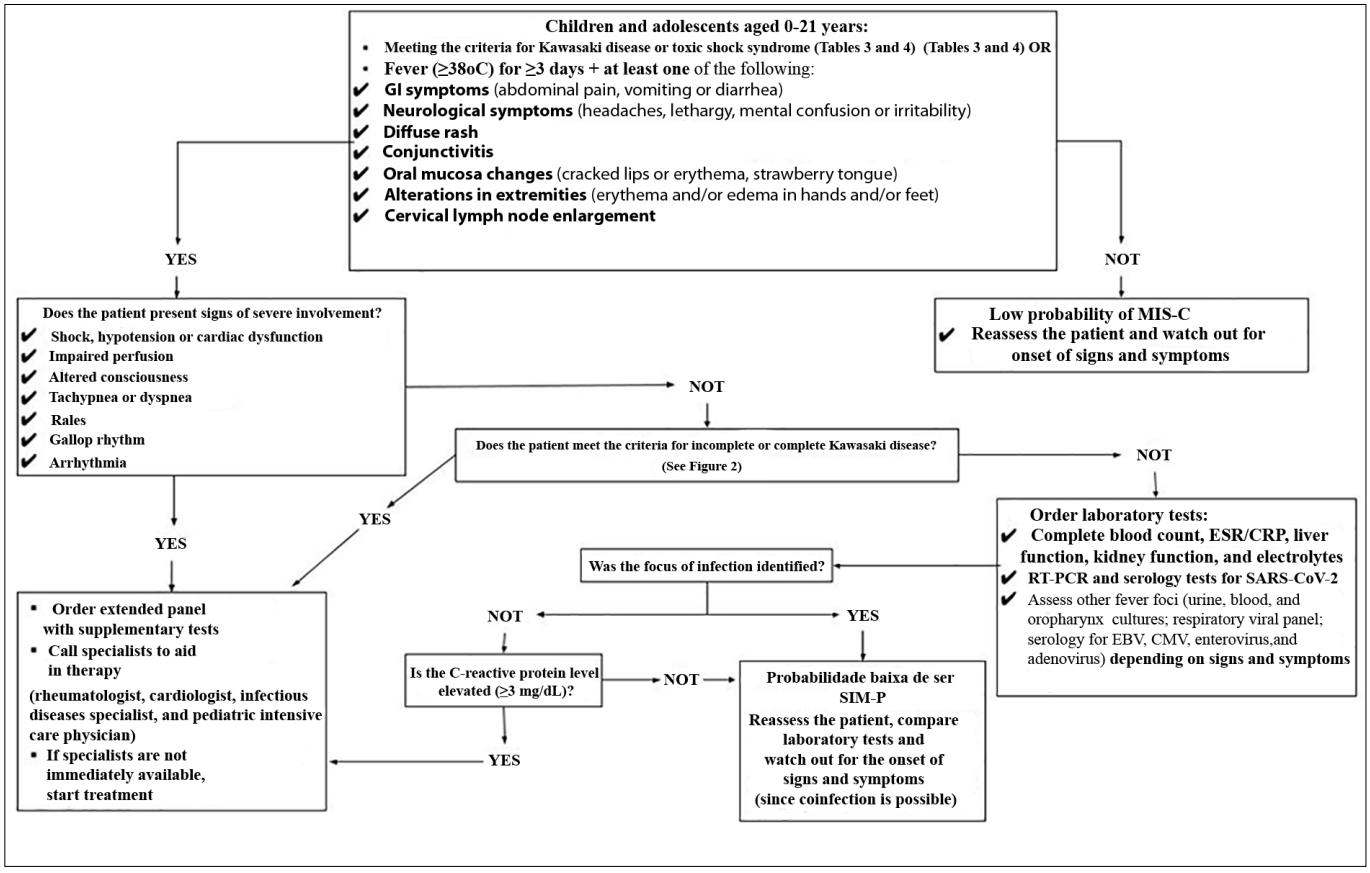

Figure 1. Diagnostic Workflow for MIS-C.[23]

Table 3. Diagnostic criteria for Kawasaki Disease (DK)[35].

Definitions:
• **Complete KD:** unexplained fever for ≥ 4 days + 4/5 clinical criteria;
• **Incomplete KD:** unexplained fever for ≥ 5 days + 2-3/5 clinical criteria.
Clinical criteria:
1. Bilateral bulbar non-purulent conjunctivitis.
2. Alterations in extremities (erythema or edema in hands and/or feet in the acute phase of the disease; periungual scaling during convalescence).
3. Oral mucosa changes (erythema/cracked lips, oropharyngeal hyperemia or strawberry tongue).
4. Polymorphous exanthem (non-vesicular).
5. Cervical lymph node enlargement (at least one lymph node > 1.5 cm in diameter).

addition, children diagnosed with shock had higher levels of cardiac markers.[31,41]

In regards to cardiac alterations, in addition to clinical examination and laboratory testing (for proBNP and troponin levels), patients suspected for or diagnosed with MIS-C should undergo electrocardiographic (for arrhythmia and ischemic alterations) and echocardiographic examination.[13] The main echocardiographic findings are: left ventricular dysfunction; coronary alterations (dilatation and/or aneurysm); mitral regurgitation; and pericardial effusion.[13] The incidence of these alterations varies based on severity of involvement. For example, patients with severe disease have left ventricular dysfunction in 50-60% of the cases and coronary alterations in 20-50% of the cases.[31,41,42]

The need for other diagnostic methods is based on the onset of clinical manifestations. For example, patients with respiratory symptoms require chest X-rays or, in specific cases, chest computed tomography scans. Most patients with MIS-C do not present with alterations in chest imaging, although pleural effusion, focal or diffuse consolidations, and atelectases may occur.[4,43] Abdominal ultrasound or computed tomography must be performed in patients with intense abdominal pain. MIS-C may mimic the symptoms of acute appendicitis. Free fluid, ascites, ileitis, mesenteric adenitis, and pericholecystic edema may be observed in these patients.[44]

DIFFERENTIAL DIAGNOSIS

MIS-C shares clinical manifestations with numerous diseases and differential diagnosis must include every acute febrile condition that produces similar clinical manifestations, including rash, lymph node enlargement, and mucosal changes. Differential diagnosis may be split into infectious and non-infectious diseases.[23]

Table 4. Diagnostic criteria for staphylococcal toxic shock syndrome (CDC)[25].

Clinical Criteria
• **Fever** (≥38.9ºC);
• **Rash** (macular, diffuse, erythrodermic);
• **Scaling** (1-2 weeks after rash onset);
• **Hypotension** (adults: systolic BP ≤ 90 mmHg; children < 16 years: systolic BP < p5 for the age).
Multisystem involvement (3 or more organs affected): • **Gastrointestinal tract** (vomiting or diarrhea at disease onset); • **Mucosal involvement** (intense myalgia or elevated creatine phosphokinase > 2 times the upper normal limit); • **Mucosas** (vaginal, oropharyngeal, or conjunctival hyperemia); • **Kidneys** (increased urea or creatinine > 2 times the upper normal limit, or pyuria > 5 white blood cells per field in the absence of urinary tract infection); • **Liver** (increased bilirubin or transaminase levels > 2 times the upper normal limit); • **Blood parameters** (platelets < 100,000/mm^3); • **Central nervous system** (disorientation or altered consciousness level without focal neurlogic signs outside fever or hypotension).
Laboratory Criteria
• Cultures (blood or cerebrospinal fluid) negative for other infectious agents (except for *Staphylococcus aureus)*; • Negative serology tests (if needed) for spotted fever, leptospirosis or measles.
Case Classification
• **Likely:** laboratory criteria + 4 of 5 clinical criteria; • **Confirmed:** laboratory criteria + 5 clinical criteria (including scaling, unless the patient dies earlier).

Infectious diseases:

• **Bacterial diseases** (scarlet fever, sepsis, meningitis, endocarditis, and toxic shock syndrome) – bacterial sepsis is an important condition to rule out in differential diagnosis, since it also produces fever, shock, and elevated inflammatory markers. For this reason, every patient with MIS-C must have cultures done to rule out infection; doubtful cases must be prescribed empirical broad-spectrum antibiotic therapy. Toxic shock syndrome (staphylococcal or streptococcal) may produce symptoms similar to MIS-C and must be included in differential diagnosis. The early symptoms of MIS-C are often confused with the symptoms of scarlet fever, since patients develop fever, exanthemas, oral mucosa changes, and odynophagia.

• **Viral diseases** (mononucleosis; rubella; measles; dengue; Chikungunya; Zika; hand, foot, and mouth disease; parvovirus infection; enterovirus infection) – exuberant systemic manifestations of these diseases rarely occur in immunocompetent children, although some patients may develop severe inflammatory alterations and cardiac involvement (myocarditis) from viral infection. Serology and molecular tests are useful in differentiating between diseases.

Non-infectious diseases:

• **Dermatitis due to substances taken internally**

• **Vasculitis** (Kawasaki disease, polyarteritis nodosa, and lupus)

• **Appendicitis** – it is not uncommon for patients with MIS-C to present fever and gastrointestinal symptoms, occasionally mimicking acute appendicitis. Imaging examination is needed to rule out this condition.

• **Macrophage-activation syndrome/hemophagocytic lymphohistiocytosis** – this progressively severe and aggressive acute systemic inflammatory disorder occurs secondarily to excessive activation of the immune system and results in persistent inflammation. It is usually triggered by infectious agents, genetic conditions, malignancy, autoinflammatory and autoimmune diseases, or some drugs. Patients often develop cytopenia, liver alterations, and neurlogic symptoms. Cardiac and gastrointestinal manifestations are rare. It is important to remember that SARS-CoV-2 infection in children may trigger this syndrome. The established diagnostic criteria for this condition are not discussed in this article.[30]

TREATMENT

The guidelines published by the American College of Rheumatology in November 2020[26] established the criteria for the hospitalization of patients suspected for MIS-C:

1. Abnormal vital signs (tachycardia, tachypnea)
2. Respiratory distress
3. Neurologic deficits or change in mental status (including subtle manifestations)
4. Evidence of even mild renal or hepatic injury
5. Marked elevations in inflammation markers (e.g.: CRP ≥ 10mg/dL)
6. Abnormal electrocardiogram findings or abnormal levels of BNP or troponin

Despite the above recommendations, we suggest that every patient suspected for MIS-C be hospitalized, even if only for purposes of observation and testing, since this is a potentially severe disease and outpatient follow-up is not always possible.[26]

The management of patients with MIS-C requires not only pediatricians, but physicians from multiple specialties such as rheumatologists, infectious diseases specialists,

cardiologists, intensive care physicians, and hematologists.[25,26] Treatment may be divided into the following steps:

1. Infection spread control

Every patient suspected for MIS-C must be placed in respiratory isolation on account of the risk of COVID-19 coinfection, since 30% have positive RT-PCR tests at the time of disease onset.[16] Patients can only be released from isolation after active infection has been ruled out, so that care teams and other patients are not infected.

2. Hemodynamic support

Acknowledging the signs of shock is essential for these patients, since up to half of them may develop shock according to a recent systematic review and meta-analysis enrolling 992 patients with MIS-C.[10] Patients may present with cardiogenic, distributive, or mixed shock (low cardiac output due to left ventricular dysfunction). Accompanying symptoms include tachycardia, weak pulse, and slow capillary perfusion caused by peripheral vasoconstriction. Introduction of inotropes (e.g.: adrenalin or dobutamine) is needed. Patients with mixed shock present signs of vasoplegia (full pulse and compensatory vasodilation); treatment with norepinephrine (a vasoconstrictor and alpha agonist) is indicated. Pediatricians must watch for the onset of arrhythmia and hemodynamic alterations in these patients. If needed, diuretics may be prescribed with caution. In extreme cases with severe dysfunction, extracorporeal membrane oxygenation (ECMO) has been used.[42]

3. Empirical antibiotics in selected cases

The signs and symptoms of MIS-C may be very similar to the ones observed in individuals with sepsis. For this reason, initiation of antibiotics may be needed until coinfection has been ruled out. Patients may present clinical manifestations similar to the ones seen in gastrointestinal infection, along with skin symptoms (erythrodermic rash) suggestive of toxic shock syndrome. In general terms, empirical antibiotic therapy is meant to cover against gram-positive and gram-negative bacteria.[45] An example of an empirical protocol for community patients is the association of ceftriaxone and oxacillin. Clindamycin may be added if the patient is suspected for toxic shock syndrome.[45] Several empirical protocols have been described, but the choice of therapy must be based on the site of infection and the antimicrobial resistance profile of each particular care center.[45]

4. Treatment of inflammatory manifestations

The main medications used in the management of inflammation are: intravenous immunoglobulin (IVIG), acetylsalicylic acid (in anti-inflammatory doses), and corticosteroids. Treatment is intensified based on patient phenotype/severity of involvement. Patients may change groups and must be reassessed frequently. About 30-80% of the patients do not respond to therapy with IVIG alone and might need adjuvant therapy with corticosteroids to control inflammation.[33] This is not the case for patients with classic KD, in which IVIG resistance has been observed in less than 15% of the patients.[33,35] While defining the course of therapy, patients may be divided into three groups based on clinical manifestations:

Group 1 - Mild MIS-C

This group includes patients with mild fever and symptoms (headaches, fatigue) and elevated inflammatory markers, but no signs of multisystem involvement or manifestations consistent with Kawasaki disease.

Group 2 - Kawasaki-like

This group includes patients with complete or incomplete signs and symptoms, meeting part of or all criteria for Kawasaki disease.

Group 3 - Isolated MIS-C or MIS-C overlapping with KD manifestations

This group includes patients presenting one or more of the following manifestations:

- Shock;
- Cardiac involvement (left ventricular dysfunction, coronary alterations – dilatations and/or aneurysms, arrhythmia, elevated proBNP and/or troponin);
- Other severe manifestations requiring admission to an intensive care unit.

The indications and doses of the medications used in the treatment of inflammatory manifestations are described in Figure 2.[26]

5. Prevention of thrombotic manifestations:

a) Anticoagulation

Patients with severe MIS-C and left ventricular dysfunction (ejection fraction < 35%) and subjects with giant coronary aneurysms (> 8mm or Z-score ≥ 10) are at higher risk of developing thromboembolism (26). These individuals must be prescribed therapeutic doses of enoxaparin (1 mg/Kg/dose, every 12 hours, subcutaneous injection, in order to achieve anti-Xa activity of 0.5-1), if they are not at greater risk of bleeding. Patients prescribed therapeutic anticoagulation due to decreased ejection fraction (< 35%) must be kept on anticoagulants for up to two weeks after discharge.[26] Indications for prolonged anticoagulation therapy are as follows: 1) coronary aneurysm with a Z-score ≥ 10 (undefined length); 2) documented venous thrombosis (minimum of three months, depending on resolution); 3) moderate to severe persistent left ventricular dysfunction.[26]

Prophylactic anticoagulation still requires further analysis; there is no evidence (unlike in adults) indicating that anticoagulants may prevent venous thromboembolism (deep venous thrombosis and/or pulmonary embolism) associated with the state of hypercoagulability seen in COVID-19. The complications seen in hospitalized adolescents are closer to the

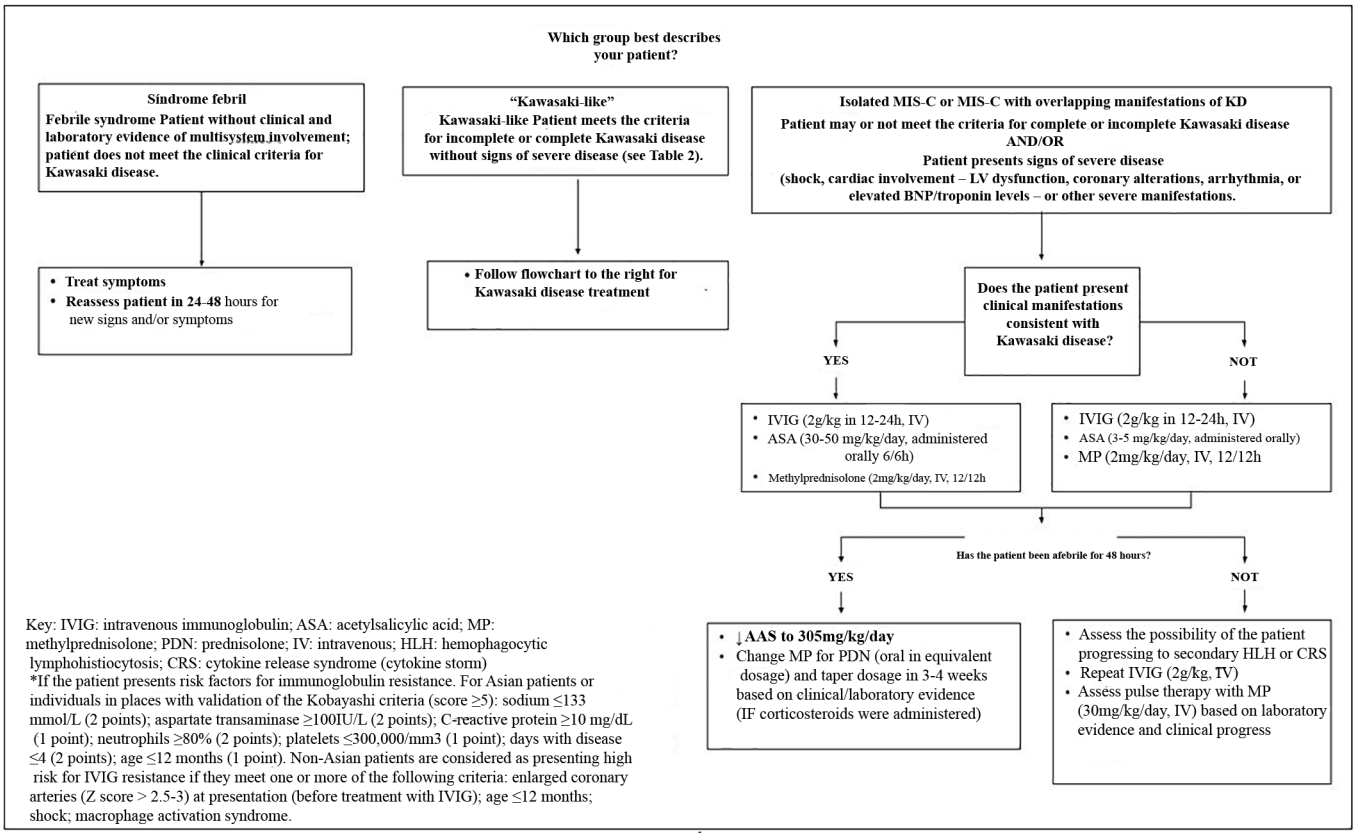

Figure 2. Workflow for MIS-C Treatment.[26]

ones experienced by adults, and prophylactic anticoagulation may be beneficial. Non-pharmacological approaches may be used to prevent venous thromboembolism in hospitalized patients, such as getting patients to walk early on (if possible) and using pneumatic compression devices.[45] Some authors have suggested that prophylactic anticoagulants be administered to hospitalized patients with SARS-CoV-2 infection and the following risk factors:[46] 1) *D-dimer > 5x the maximum reference level* **and/or** *multiple risk factors (≥ 3 risk factors)* for hospital-associated venous thromboembolism (in addition to COVID-19) such as having a central line; mechanical ventilation; prolonged hospitalization (> 3 days); prolonged immobilization (Braden Q score = 1); obesity (BMI > p95); active malignancy; nephrotic syndrome; cystic fibrosis flare-up; sickle-cell disease with vaso-occlusive crisis; inflammatory disease flare-up (lupus, juvenile idiopathic arthritis, or inflammatory bowel disease); congenital or acquired heart disease with venous stasis; history of venous thromboembolism; history or venous thromboembolism in first-degree relatives (before 40 years of age or non-provoked events – without evident risk factors); history of thrombophilia (protein C deficiency, protein S deficiency, or antithrombin III deficiency; Leiden factor V mutation or prothrombin G20210A mutation; persistently positive antiphospholipid antibodies; puberal or post-puberal subject (age > 12 years); use of estrogen-containing oral contraceptives; post-splenectomy or with hemoglobin disorders.[46]

b. Antiplatelet drugs

Prescription of antiplatelet drugs is aimed to prevent coronary artery thrombosis, since MIS-C, in addition to Kawasaki disease, causes endotheliitis and, in some cases, reactive thrombocytosis.[47]

Acetylsalicylic acid (ASA) at a dose of 3-5 mg/Kg/day (maximum dose: 100 mg) must be prescribed to patients with MIS-C until platelet count has gone back to normal levels and absence of coronary involvement has been confirmed based on serial echocardiograms after at least four weeks counting from the day the patient was diagnosed. ASA must be avoided in patients with a history of active bleeding, risk of bleeding, or thrombocytopenia (≤ 80,000/mm³).[26]

Patients with coronary aneurysms and a Z-score of less than 10 must be treated with ASA alone. Subjects with a Z-score ≥ 10 must be prescribed anticoagulation in addition to ASA, as previously mentioned.[26]

Other therapies

Subjects refractory to conventional therapy may be treated with biological medicines (interleukin 1 and 6 inhibitors), although there are no studies validating the efficacy of these medications. The efficacy of convalescent plasma is still uncertain and it should not be prescribed routinely. The efficacy of antivirals such as remdesivir has not been confirmed. Children with MIS-C given this medication had positive RT-PCR tests and developed severe manifestations.[16]

How to assess response to treatment

Patients are expected to become afebrile within 24-36 hours from the end of immunoglobulin administration. If they fail to improve, treatment must be intensified and a pediatric rheumatologist called in to assist. Inflammation parameters must be reviewed daily.

When should the patient be discharged?

Consider the following clinical and laboratory parameters:

a. Clinical parameters

Patients must be afebrile for > 48 hours and show signs of general improvement; they cannot be on support therapies (such as oxygen therapy) and must be able to comply with diet requirements and take oral medicines; cardiac function must be normal (to be discussed with a cardiologist, since some patients may have persistent dysfunction); patients cannot have severe complications and must be available for follow-up in an outpatient setting.[45]

b. Laboratory parameters

Inflammatory markers (CRP, LDH, ferritin, and D-dimer) and proBNP must be decreasing gradually. Troponin must be negative and electrocardiograms without changes. ESR should not be used as a parameter, since immunoglobulin may increase it. ASA in antiplatelet doses (3-5 mg/Kg/day) must be maintained until clinical reassessment on Week 6-8 of disease; platelet count and CRP must be normal and control echocardiograms cannot show coronary alterations.[45]

c. Imaging

Patients with MIS-C and BNP and/or troponin alterations at the time of diagnosis must have these tests monitored until normal results are obtained. Electrocardiographic examination must be performed in every patient; if changes are found, examination must be repeated if requested by a cardiologist. Hospitalized patients should be examined every 48 hours and, if changes such as arrhythmia are found, continuous monitoring should be initiated if possible.[26]

FOLLOW-UP

Clinically stable patients with normal cardiac function and without fever for more than 24 hours may be discharged. A multidisciplinary care team that includes a pediatrician, a pediatric cardiologist, a pediatric rheumatologist, and an infectious disease specialist should be involved in follow-up care. The first follow-up visit should occur 1-2weeks after discharge. Supplementary tests should be ordered and, if all is well, scheduling another visit a month later is recommended.

If changes are found, the cardiologist defines when the patient should be reassessed and whether supplementary tests are needed, since individuals with ventricular dysfunction and coronary aneurysms require closer follow-up care.[26] Echocardiographic examination is recommended at the time of diagnosis and every 7-14 days at first and every 4-6 weeks subsequently. Patients should undergo echocardiography a year after the onset of symptoms to find potential changes (functional or coronary alterations, for example).[26] Chiotos et al. described a case in which a patient had a coronary aneurysm two weeks after discharge.[48]

Specialists have recommended cardiac magnetic resonance imaging (MRI) 2-6 months after diagnosis for patients presenting significant transient ventricular dysfunction in the acute phase of the disease (left ventricular ejection fraction < 50%) or subsequent persistent dysfunction. Cardiac MRI provides for a functional assessment of the myocardium through T1- and T2-weighted scans and T1 mapping with extracellular volume quantification and gadolinium enhancement.[26] Computed tomography angiography of the coronary arteries may be used in subjects suspected for distal aneurysms not easily seen in echocardiography.[26]

OUTCOMES

MIS-C is a potentially deadly condition. The death rates associated with MIS-C have been estimated to range from 0 to 5.3%. Although low, they are higher than the death rates of children with COVID-19 (0.09%).[49] Cardiovascular involvement occurs in 80-85% of the cases and is the primary indicator of disease severity. Hyperinflammatory shock is common, and 60-78% of the patients require resuscitation with fluid and/or vasopressor drugs. Echocardiogram changes are seen in up to 60% of the cases and decreased ejection fraction is the most frequent alteration.[50]

Although they are critically ill, patients respond quickly to shock support therapy and anti-inflammatory drugs, immunoglobulin, and corticosteroids. On average, patients require intensive care for 5-7 days.[49,50]

Ventricular ejection fraction improves within the first 2-5 days and normalizes in most patients within 1-2 weeks, although further long-term follow-up studies are needed. The incidence of coronary aneurysm is 9-25%. Medium and long-term outcomes and sequelae have not been established.[49,50] In the United Kingdom, recommendations dictate that patients with coronary aneurysms, active and regressed, be followed by a cardiologist in the medium and long term.

A few factors have been associated with worse outcomes in retrospective observational series, namely delayed diagnosis; age of less than a year; having chronic disease; and being immunocompromised. Increases in proBNP, troponin and/or procalcitonin have been associated with more severe disease.[49,51] Although the number of patients with MIS-C and deep venous thrombosis or

pulmonary embolism is small, the general risk of thrombosis – a factor that may affect patient outcome – is unknown.

Early diagnosis, special care, and aggressive treatment against inflammatory shock yield better outcomes.

CONCLUSION

Multisystem inflammatory syndrome in children (MIS-C) temporally associated with SARS-CoV-2 infection shares clinical and laboratory characteristics with Kawasaki disease (classic or incomplete), streptococcal and staphylococcal toxic shock syndrome, bacterial sepsis, and macrophage activation syndrome.

MIS-C usually involves children aged five years and older, affects predominantly subjects of African descent, and produces gastrointestinal and myocardial manifestations more frequently. The thesis of a possible temporal association between MIS-C and SARS-CoV-2 infection has been considered, since most children with the first disease were also positive for the latter in RT-PCR or serology tests. These children present with prolonged high fever and prominent gastrointestinal symptoms, conjunctivitis, lymphadenopathy, irritability, and headaches. Some patients develop shock from cardiac dysfunction, with or without coronary artery alteration. Respiratory symptoms may be present and are usually caused by concomitant shock.

Thorough clinical assessment including interviews, physical examination, epidemiological data in cases suspected for or diagnosed with COVID-19 within the past 2-4 weeks, in addition to supplementary tests to assess inflammation and organ involvement, are of paramount importance to establish diagnosis and initiate early treatment.

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