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REVIEW ARTICLE

Multisystem inflammatory syndrome in children – a literature review

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Mucocutaneous Lymph Node Syndrome, Intensive Care Units Pediatric, Coronavirus Infections.

Abstract

Objectives: This literature review describes the epidemiology, pathophysiology, diagnosis, and management of multisystem inflammatory syndrome in children (MIS-C), assesses economic impacts, and differentiates MIS-C from Kawasaki disease and toxic shock syndrome. **Methods:** It was performed in two stages: a search for articles on PubMed followed by a search for documents from government agencies. Ten articles containing information on the epidemiology, pathophysiology, signs and symptoms, complementary evaluations, diagnostic criteria, clinical management and/or outcomes of MIS-C were selected. Duplicate articles, papers focusing on adult patients, publications that did not include description of changes and approach to MIS-C were excluded.
Results: Patient mean age ranged from 8.5 to 12 years; male gender was the most affected; most of the sample had positive serology for COVID-19; males accounted for the majority of the cases; most patients tested positive for COVID-19; most patients were admitted to an intensive care unit; mortality was low. Pathophysiology of the disease has not been clearly defined yet. The main symptoms were fever, gastrointestinal symptoms, skin rash, and conjunctivitis. The predominant dysfunctions were shock and respiratory failure. Laboratory tests showed increases in inflammatory markers, procalcitonin, IL-6, troponin, and pro-BNP. The most used treatments were ventilatory support, vasoactive drugs, immunoglobulin, and corticosteroids. **Conclusions:** This article allowed a better understanding of MIS-C, despite the lack of studies covering the subject. It described an epidemiological, clinical, workup, and diagnostic profile of the condition. The treatment of the disease still lacks a definitive protocol, although therapies described in most studies were similar. Therefore, further studies and protocols are needed to better understand and treat MIS-C.

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INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen that causes *Coronavirus Disease-2019* (COVID-19), spread rapidly in 2020 to become a global pandemic[1]. The virus causes severe acute respiratory syndrome in adults and has killed more than 800,000 people worldwide.[2] In Brazil, 3,717,156 cases and 117,665 deaths had been recorded as of August 27, 2020[3].

In late April 2020, the UK National Health Service issued an alert about a new complication of COVID-19 in children. Patients presented with signs and symptoms similar to Kawasaki syndrome and toxic shock syndrome coupled with workup changes consistent with intense systemic inflammation[4]. In a warning issued on May 14, the U.S. Centers for Disease Control and Prevention (CDC) called this new clinical presentation multisystem inflammatory syndrome in children (MIS-C)[5].

On May 4, 2020 the New York City Department of Health issued an alert after reports from pediatric intensive care units in the city from April 29 and May 3 told of 15 cases of children between the ages of two and 15 years hospitalized with an illness consistent with the new syndrome.[6] By May 14, the State of New York had reported over 100 cases of the disease and three deaths[7].

On May 6, 2020, eight children reportedly developed exacerbated inflammatory states and shock with features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock in London, UK[8].

The European Center for Disease Control and Prevention reported a total of 224 cases across Europe as of May 12. A group from Bergamo, Italy, published a case series with a 30-fold increase in the incidence of signs and symptoms and laboratory evidence consistent with Kawasaki disease[9,10].

In Brazil, the Brazilian Society of Pediatrics (SBP) issued an alert note on May 20, 2020, in which criteria and clinical management based on the short experience in the rest of the world were described[10]. By July, the Ministry of Health had counted 71 cases and three deaths related to MIS-C in four Brazilian states, namely Ceará, Rio de Janeiro, Pará, and Piauí[11].

Infectious agents can often cause inflammatory and autoinflammatory syndromes that generate acute organ dysfunction due to exacerbated immune system response. SARS-CoV-2 might somehow trigger this multisystem syndrome[12].

MIS-C has similarities with Kawasaki disease and toxic shock syndrome, particularly in terms of the pathophysiology and signs and symptoms of these conditions.[10] Kawasaki disease is a primary vasculitis that affects children, especially boys and girls under five years of age. Its etiology is still unknown, although some suspect it may have an infectious origin. This type of vasculitis causes systemic inflammation of blood vessels, predominantly of medium caliber, and may cause complications such as coronary artery aneurysm[13]. Toxic shock syndrome is a rapidly progressive infection caused in particular by *Staphylococcus aureus*[14].

According to the World Health Organization (WHO), the specific characteristics of this condition are not yet fully understood[15].

The impact of the disease on the lives of patients and the costs it adds to the healthcare system must be taken into consideration. The repercussions MIS-C has on the lives of children are many and include the need for medium- to long-term admission to an intensive care unit (ICU), intensive testing, and invasive procedures. Thus, we need to understand the clinical presentation and management of this new syndrome in order to introduce better approaches directed to this group of patients.

OBJECTIVES

a. Primary Objective

To characterize the epidemiology, pathophysiology, diagnosis, and management of multisystem inflammatory syndrome in children (MIS-C).

b. Secondary objective

To evaluate the economic impacts of MIS-C and establish the differences between this syndrome, Kawasaki disease, and toxic shock syndrome.

METHODOLOGY

The present study is a review of the literature on a new clinical syndrome associated with COVID-19 in children.

The review was performed in two stages: a search for articles on PubMed followed by a search for documents from government agencies published between April and August 2020 (Figure 1).

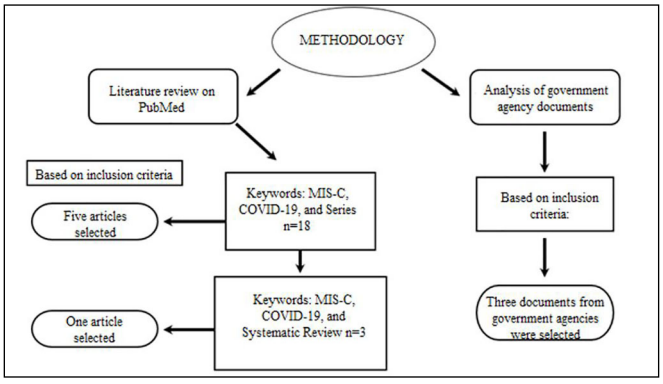


Figure 1. Methodology flowchart.

In the first stage, searches were performed using the keywords "MIS-C" (*multisystem inflammatory syndrome in children*), "COVID-19", "Series", "Systematic Review", with descriptor "AND".

Eighteen articles were found with keywords "MIS-C", "COVID-19" and "Series"; three articles were found with keywords MIS-C, "COVID-19", and "Systematic Review".

Five articles from the first search and one from the second were included. The inclusion criteria for the selected articles were: observational studies, case series or systematic reviews, description of epidemiology, clinical changes, laboratory changes, echocardiogram findings, and clinical management of MIS-C.

In the second stage, we searched for alert notes of the first cases of MIS-C issued by government agencies. Official memos from the United Kingdom, the New York City Department of Health, the World Health Organization (WHO), and the United States Centers for Disease Control and Prevention (CDC) were evaluated. The inclusion criteria for the official notes were: description of clinical changes, laboratory changes, clinical management, and proposed diagnostic criteria for MIS-C. Thus, the official notes from the UK, WHO, and CDC were included.

The exclusion criteria in both stages were: duplicate articles, articles focusing on adult patients, articles that did not include description of changes or management of MIS-C.

Descriptive findings from the statistical analysis of the collected data are shown in Tables.

RESULTS

The seven articles selected comprised a total of 543 cases of MIS-C, one of which was an alert note from the UK[8]. A total of 21 publications were reviewed for inclusion. After applying the inclusion criteria, one systematic review, four case series, one retrospective cohort, and one alert note were included based on epidemiology description, description of signs and symptoms, and treatments performed[4,16-20]. In addition, one article describing the possible pathophysiology[21] and two documents from government agencies proposing diagnostic criteria were included[5,15]. Table 1 shows the study types, publication dates, and populations of the articles describing the cases.

Epidemiology

The mean age of the studied populations ranged from 8.5 to 12 years, with three of the studies having median ages between 7.3 and 10 years. There was a higher prevalence of males over females in most studies, ranging from 16.6% to 73%. Table 2 describes parameters related to race, ethnicity, and presence of comorbidities.

In regard to the diagnostic methods for SARS-CoV-2, a positive nasopharyngeal RT-PCR test was reported in 13% to 69% of the cases. Positive serology test results were described in 27% to 100% of the cases.

Admission to a pediatric intensive care unit (PICU) ranged from 79% to 100% of the cases. Mortality was low in most studies, with no deaths reported in four of them.

Pathophysiology

The precise pathophysiology of MIS-C has not been described to date. One of the established hypotheses addresses three points that might be involved in the development of the syndrome: antiviral response, viral load and *clearance* time, and degree of inflammation. When a high viral load combined with a slow antiviral response slow down *clearance* of the virus, there is a higher probability that intense systemic inflammation and MIS-C may occur[21].

Another point not fully understood yet implied is that MIS-C is a post-infectious syndrome related to IgG immunoglobulins. Although it lacks confirmation, this hypothesis arises from the fact that there is a time lag between the observation of SARS-Cov-2 infection in an area and reports of MIS-C coupled with positive serology in many of the cases[21].

Signs and symptoms

Tables 3 and 4 show the main symptoms and signs present in the studied populations.

Fever was present in 100% of the cases. Other symptoms reported include: gastrointestinal symptoms (abdominal pain, diarrhea, and vomiting), skin rash, and conjunctivitis. Cardiovascular symptoms include hypotension and tachycardia, while respiratory symptoms include cough and dyspnea.

Dysfunctions such as circulatory shock and respiratory failure were respectively observed in up to 100% and 66% of the patients in some of the studies.

Table 1. Description of the studies.

AUTHORS	YEAR	COUNTRY	STUDY TYPE	POPULATION
Abrams J. et al.	2020	USA	Systematic review	440 cases
Riphagen S. et al.	2020	UK	Alert note	8 cases
Chiotos K. et al.	2020	USA	Case series	6 cases
Kaushik S. et al.	2020	USA	Retrospective observational study	33 cases
Capone C. et al.	2020	USA	Case series	33 cases
Blondiaux E. et al.	2020	France	Case series	8 cases
Riollano-Cruz M. et al.	2020	USA	Retrospective observational study	15 cases
Rowley A. et al.	2020	USA	Comment	Not applicable
CDC	2020	USA	Preliminary case definition	Not applicable
WHO	2020	Not applicable	Preliminary case definition	Not applicable

Table 2. The epidemiology of MIS-C.

Epidemiology data	Abrams J. et al.	Riphagen S. et al.	Chiotos K. et al.	Kaushik S. et al.	Capone C. et al.	Blondiaux E. et al.	Riollano-Cruz M. et al.
Age	Median age ranging from 7.3 to 10 years	Mean age 8.8 years	Mean age 8.5 years	Median age 10 years	Median age 8.6 years	Mean age 9.2 years	Mean age 12 years
Sex	59% males 41% females	62% males 38% females	16.6% males 83.4% females	61% males 39% females	61% males 39% females	No data	73% males 27% females
Race/ethnicity	31-62% Blacks 36-39% Hispanics	75% African--Caribbean	33% Whites 33% Blacks 33% no data 0% Hispanics or Latinos	45% Hispanics or Latinos 39% Blacks 16% Other	9% Whites 24% Blacks 73% Non-Hispanics	No data	66% Hispanics or Latinos
Comorbid conditions	No data	None	None	48% had comorbid conditions	21% had comorbid conditions (except for obesity)	No data	33% had comorbid conditions (4 had asthma)
Serologic tests	75-100% positive	No data	83% positive (1 was not tested)	27% positive	73% positive	100% positive	100% positive
Nasopharyngeal RT-PCR test	13-69% positive	25% positive	50% positive (1 was not tested)	33% positive	9% positive	100% negative	60% positive
Serologic + RT-PCR tests	No data	No data	No data	6% positive in both	18% positive in both	No data	No data
ICU admission	No data	100% of the patients	100% of the patients	No data	79% of the patients	100% of the patients	100% of the patients
Death rate	2% of the patients	12% of the patients	0%	0%	0%	0%	6% of the patients

Table 3. Symptoms of MIS-C.

SYMPTOMS	Abrams J. et al.	Riphagen S. et al.	Chiotos K. et al.	Kaushik S. et al.	Capone C. et al.	Blondiaux E. et al.	Riollano-Cruz M. et al.
Fever	No data	100% of the patients	100% of the patients	93% of the patients	100% of the patients	100% of the patients	100% of the patients
Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)	87% of the patients	87% of the patients	100% of the patients	63% abdominal pain 69% nausea and vomiting 48% diarrhea	97% of the patients	100% of the patients	87% of the patients
Skin rash	No data	50% of the patients	33% of the patients	42% of the patients	No data	100% of the patients	47% of the patients
Conjunctivitis	No data	62% of the patients	33% of the patients	36% of the patients	No data	50% of the patients	27% of the patients
Cardiovascular symptoms	71% of the patients	No data	No data	63% of the patients	No data	No data	87% of the patients
Neurocognitive symptoms (headaches, lethargy)	22% of the patients	25% of the patients	50% of the patients	9% lethargy 12% neurologic involvement	58% of the patients	No data	No data
Respiratory symptoms	47% of the patients	37% of the patients	No data	33% of the patients	52% of the patients	No data	33% of the patients
Myalgia	21% of the patients	12% of the patients	No data	No data	No data	25% of the patients	No data
Swollen extremities	No data	No data	33% of the patients	No data	No data	No data	No data
Lymphadenopathy	No data	No data	None	No data	No data	No data	No data

Laboratory alterations

The main laboratory alterations in the studied population were increased inflammatory markers such as C-Reactive Protein, D-Dimer, Ferritin, and Fibrinogen. Elevation of Procalcitonin, Interleukin-6, and myocardial markers Troponin and Pro-BNP was also observed. The other changes are described in Table 5.

Diagnostic Criteria

Criteria have been established to aid in the diagnosis of MIS-C. On May 14, 2020, the *Centers for Disease Control and Prevention* (CDC) of the United States established the criteria described below[5]:

Table 4. Organ dysfunctions in MIS-C.

Organ dysfunction	Abrams J. et al.	Riphagen S. et al.	Chiotos K. et al.	Kaushik S. et al.	Capone C. et al.	Blondiaux E. et al.	Riollano-Cruz M. et al.
Shock	No data	100% of the patients	100% of the patients	No data	76% of the patients	75% of the patients	No data
Met criteria for complete Kawasaki disease	No data	No data	No data	No data	64% of the patients	No data	No data
Respiratory failure	No data	62% of the patients	66% of the patients	No data	No data	25% of the patients	No data
Kidney failure	No data	No data	66% of the patients	No data	No data	No data	No data
Serositis (minor pleural, pericardial, and ascitic effusion)	No data	62% of the patients	No data	No data	No data	No data	No data

Table 5. Laboratory alterations found in patients with MIS-C.

WORKUP FINDINGS	Abrams J. et al.	Riphagen S. et al.	Chiotos K. et al.	Kaushik S. et al.	Capone C. et al.	Blondiaux E. et al.	Riollano-Cruz M. et al.
Lymphocytes	Mean 978	No data	Mean 308	Median 1100	Median 800	Mean 600	No data
Neutrophils	Mean 11460	No data	No data	No data	No data	No data	No data
Hemoglobin	No data	No data	Mean 7.9	Median 11.3	Median 11.2	No data	No data
Platelets	Mean 151400	Mean 145000	Mean 109000	Median 176000	Median 154000	No data	Mean 221666
C-reactive protein	Mean 215 mg/L	Mean 303 mg/L	Mean 21 mg/L	Mean 250 mg/L	Mean 206 mg/L	Mean 309 mg/L	Mean 242 mg/L
Erythrocyte sedimentation rate	Mean 68 mm/h	No data	No data	Median 53 mm/h	No data	No data	No data
D-dimer	Mean 3572 ng/ml	Mean 10.4 ng/ml	Mean 12.1 ng/ml	Median 3.7 ng/ml	Median 1700 ng/ml	No data	Mean 5.5 ng/ml
Fibrinogen	Mean 577 mg/dL	No data	No data	Median 627 mg/dL	Median 736 mg/dL	No data	No data
Ferritin	Mean 714 ng/ml	Mean 1086 pg/ml	Mean 889.5 ng/ml	Median 568 ng/ml	Median 640 ng/ml	No data	Mean 1488 ng/ml
Procalcitonin	No data	Mean 29 pg/L	Mean 49.4 ng/ml	Median 5.4 ng/ml	Median 12.05 ng/ml	No data	Mean 6.4 micro g/L
Interleukin 6	Mean 119 pg/ml	No data	No data	Median 200 pg/ml	No data	No data	Mean 232.3 pg/ml
Troponin	Mean 206 ng/L	Mean 252.5 ng/L	Mean 0.48 ng/ml	Median 0.08 ng/ml	Median 31 ng/L	Median 1404 ng/L	Mean 2.56 ng/ml
NT-pro-BNP	Mean 16694 ng/L	Mean 19960 ng/L	No data	Median 4328 pg/ml	Median 3325 pg/ml	No data	No data
Albumin	Mean 24 g/L	Mean 22 g/L	Mean 2.3 g/dl	No data	Median 3.4 g/dl	No data	Mean 3.13 g/dl
Liver enzymes	No data	No data	Mean 66.8 U/L (ALT)	Median 36 U/L (ALT) Median 48 U/L (AST)	Median 38 U/L (ALT) Median 54 U/L (AST)	No data	No data
DHL	No data	No data	Mean 916 U/L	No data	Median 320 U/L	No data	No data
Leukocytes	Mean 14460	No data	Mean 32300	Median 11000	Median 9140	No data	No data
BNP	Mean 3430 pg/ml	No data	Mean 5755 pg/ml	Median 388 pg/ml	No data	Mean 2394 ng/L	Mean 1438.85 pg/ml
INR	No data	No data	Mean 1.63	No data	Median 1.31	No data	No data

- Individuals under the age of 21 presenting with fever*, laboratory evidence of inflammation**, and evidence of severe clinical illness requiring hospitalization with multiple organ (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic) involvement (>=2); AND
- No other plausible diagnosis; AND
- Currently or recently positive RT-PCR, serology, or antigen test; or exposure to confirmed or suspected cases within four weeks of symptom onset.

*Fever greater than or equal to 38 degrees Celsius or subjective report of fever for a period of 24 hours or more.

**Including but not limited to one or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, pro calcitonin, d-dimer, ferritin, lactic acid, lactate dehydrogenase (LDH) or interleukin-6 (IL-6), elevated neutrophils, decreased lymphocytes, and decreased albumin.

On May 15, 2020, the World Health Organization (WHO) also established the diagnostic criteria described below[15]:

- Child or adolescent aged 0-19 years with fever for three days or more;
- And two of the following:
- Rash or bilateral non-purulent conjunctivitis or signs of muco-cutaneous inflammation (mouth, hands, or feet);
- Hypotension or shock;
- Myocardial dysfunction, pericarditis, valvulitis, or coronary artery anomalies;
- Evidence of coagulopathy (PT, APTT, d-dimer elevation);
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).
- And
- Elevation of inflammatory markers (ESR, CRP, and procalcitonin);
- And
- No other obvious cause of inflammation from infection, including bacterial sepsis and streptococcal or staphylococcal toxic shock syndrome;
- And
- Evidence of COVID-19 (RT-PCR, serology, or antigen test) or contact with patients with COVID-19.

Echocardiogram

Since cardiac involvement has been reported in subjects with MIS-C, ventricular dysfunction and coronary anomalies were analyzed in study populations. Capone et al. analyzed 33 patients and found left ventricular dysfunction in 19 and coronary artery anomalies in 16 of them. Coronary anomalies include dilation and ectasia[18].

Treatment

Several therapeutic options and combinations have been proposed to manage cases of MIS-C, including cardiopulmonary support, intravenous immunoglobulin, corticosteroids, other immunomodulatory therapies such as Tocilizumab, a monoclonal antibody against IL-6, antibiotics, antivirals, and anticoagulants.

Table 7 describes the use and frequency of each intervention evaluated in study populations.

DISCUSSION

Children with COVID-19 generally develop mild to moderate symptoms[12]. However, since mid-April reports of cases of MIS-C have shown that some children may present with a severe syndrome that combines the symptoms of other inflammatory conditions such as Kawasaki and toxic shock syndrome[10].

Kawasaki disease (KD) is an acute febrile illness that primarily affects children under five years of age, peaking between nine and 12 months of age, with a slight predominance in males. It presents in three stages: acute, subacute, and convalescent[22].

The acute phase is marked by high and persistent fever lasting more than five days, elevated inflammatory activity tests, leukocytosis with neutrophilia, and several symptoms such as oral cavity alterations, bilateral conjunctival hyperemia, unilateral enlarged cervical lymph nodes, changes in the extremities, and polymorphic exanthema. Cardiac alterations such as myocarditis, pericardial effusion, arrhythmia, mitral and/or aortic valve involvement, and heart failure may occur in the acute stage of the disease[23,24].

In the subacute stage, after seven to ten days of fever, perineal and periungual scaling begins; ectasia, coronary aneurysms, and thrombocytosis may also occur[23,24].

In the convalescent stage, ESR, CRP, and platelets count normalize, and most aneurysms resolve[22].

Diagnosis is eminently clinical and based on the criteria of the American Heart Association (AHA)[23]:

Presence of fever ≥ 5 days + 4 clinical criteria:

1. Lip and oral cavity alterations: erythema and lip fissures and/or diffuse hyperemia of the oropharyngeal mucosa and/or raspberry or strawberry tongue.
2. Conjunctival hyperemia: bilateral, bulbar and without exudate.
3. Extremity alterations: hand and foot dorsum edema and/or palmar or plantar erythema in the acute phase and/or periungual or perineal scaling in the subacute phase.
4. Polymorphous exanthema.
5. Enlarged cervical lymph nodes ≥ 1.5 cm, usually unilateral.

Treatment of KD is based on intravenous human immunoglobulin in a single dose of 2 g/kg until the tenth day of fever. In cases of patients at high risk of coronary aneurysms, methylprednisolone 2 mg/Kg/day intravenously can be

Table 6. Echocardiogram alterations in patients with MIS-C.

AUTHORS	LEFT VENTRICULAR DYSFUNCTION	BIVENTRICULAR DYSFUNCTION	CORONARY ARTERY ANOMALY
Abrams J. et al.	No data	No data	No data
Riphagen S. et al.	4 of 8 patients	2 of 8 patients	2 of 8 patients
Chiotos K. et al.	3 of 6 patients	1 of 6 patients	1 of 6 patients
Kaushik S. et al.	21 of 33 patients	No data	8 of 33 patients
Capone C. et al.	19 of 33 patients	No data	16 of 33 patients
Blondiaux E. et al.	1 of 8 patients	No data	0 of 8 patients
Riollano-Cruz M. et al.	4 of 15 patients	3 of 15 patients	3 of 15 patients

Table 7. Therapies prescribed to patients with MIS-C.

Authors	Ventilatory support	Vasoactive drugs	Intravenousimmunoglobulin	Corticosteroids	Other immunomodulatory therapies	Antibiotics	Antivirals	Anticoagulants
Abrams J. et al.	32% of the patients (26% intubated; 6% ECMO)	53% of the patient	76% of the patient	52% of the patient	18% of the patient	No data	No data	No data
Riphagen S. et al.	100% of the patients (62.5% mechanical ventilation; 25% noninvasive ventilation; 12.5% catheter)	100% of the patients	100% of the patients	62% of the patients	No data	100% of the patients	No data	No data
Chiotos K. et al.	83% of the patients (50% mechanical ventilation; 33% noninvasive ventilation)	53% of the patients	100% of the patients	83% of the patients	50% of the patients	100% of the patients	No data	No data
Kaushik S. et al.	54% of the patients (36% noninvasive ventilation; 15% mechanical ventilation; 3% ECMO)	51% of the patients	54% of the patients	51% of the patients	48% of the patients	87% of the patients	21% of the patients	85% of the patients
Capone C. et al.	18% mechanical ventilation	76% of the patients	100% of the patients	70% of the patients	24% of the patients	No data	No data	42% of the patients
Blondiaux E. et al.	75% of the patients	75% of the patients	100% of the patients	75% of the patients	No data	No data	No data	No data
Riollano-Cruz M. et al.	53% of the patients (20% mechanical ventilation; 33% noninvasive ventilation)	53% of the patients	80% of the patients	20% of the patients	80% of the patients	100% of the patients	13% of the patients	100% of the patients

associated until fever resolution, followed by oral prednisolone with weaning in 2-3 weeks[22].

It is not exactly clear whether COVID-19 causes KD as an infectious trigger or whether MIS-C arising from COVID-19 is a syndrome mimicking KD. However, the syndrome appears to be related to an abnormal response of the immune system when infected with SARS-CoV-2 due to the emergence of cases 2-3 weeks after peaks in the number of cases of COVID-19 in reporting regions[7].

Furthermore, epidemiologic and clinical data suggest differences between the two diseases[20] with age as a corroborating factor. While in KD 80% of the patients are less than five years old[20], in MIS-C the mean age was greater than eight years in some articles and the median greater than seven years in others[4,8,17,18,19]. Another element is the higher prevalence of KD in Asians[20], which is not observed in MIS-C[4,8,17,18,19].

A large portion of the patients tested positive for SARS-CoV-2 had a negative PCR test, which suggests that MIS-C is a post-infectious complication of COVID-19.

The pathophysiology of the two conditions remains unclear. Clarification of how one syndrome occurs might help understand how the other works and vice versa.

Although well-defined protocols for the treatment of MIS-C have not been developed, cases of the disease have been treated with a range of interventions that include intravenous immunoglobulin and corticosteroids[4,8,16,17,18,19,20]. Thus, even though it is difficult to differentiate the two conditions, prescribed therapies comprehend both.

Toxic shock syndrome (TSS) is an acute toxin-mediated disease characterized by fever, hypotension, organ dysfunction, and diffuse rash. Its main etiological agents are Staphylococcus aureus and Streptococcus pyogenes[14].Like MIS-C and KD, TSS causes exacerbated systemic inflammation that leads to a variety of signs and symptoms such as fever, skin rash, hypotension, and organ dysfunction.[14] Clinically, TSS can be as difficult to differentiate from MIS-C as KD. Blood cultures are ordered for individuals with suspected TSS and may help guide diagnosis,[14] while individuals with MIS-C often have had or, in most cases, still have SARS-CoV-2 infection.

Another point of differentiation is the fact that, unlike MIS-C, TSS does not present with changes in ventricular function or coronary artery anomalies.[4,8,16,17,18,19,20] Echocardiography also helps in differential diagnosis.

Despite the results found in the populations of the studies included in this review, MIS-C affects primarily children between seven and 12 years of age, with Hispanics and African-Caribbeans topping the list of affected ethnicities. The presence of comorbid conditions varied among studies, from none to presence in almost half of the patients.

In most studies, 100% of the patients were referred to pediatric intensive care; in one study, 79% were sent to a PICU.[18]

However, death rates remained low across study populations, which shows that this is a condition that causes high morbidity but low mortality.

Although available data allow the establishment of an epidemiologic profile of MIS-C, further studies are needed to accurately determine the epidemiology of the disease.

Symptoms, signs, and workup alterations show that MIS-C is a highly inflammatory condition, which contributes to the interposition with several other diseases that develop with exacerbated inflammation. Organ dysfunctions are particularly noteworthy. Circulatory shock was present in 75% to 100% of the cases and 25% to 66% of the patients had respiratory failure.

Workup alterations present in MIS-C are also consistent with exacerbated inflammation with increases mainly of markers such as C-Reactive Protein, D-Dimer, Fibrinogen, Ferritin, and Procalcitonin. None of these have yet been shown to be specific for the disease, but they help identify the degree of inflammation.

Myocardial markers troponin and BNP, along with echocardiography, may help in the diagnosis of cardiac dysfunction, although they do not show alterations in every case, nor can they serve as methods to differentiate MIS-C from other conditions. However, alterations in markers and/or imaging findings may help in the identification of patients with more severe involvement.

Treatment protocols for the syndrome are yet to be defined. Nonetheless, specific drug groups have been used in the management of the disease. Intravenous immunoglobulin has almost invariably been used; most studies report prescriptions to 100% of the patients, and the study that used it the least, did so in 54% of the patients. Corticosteroids and especially methylprednisolone were often used along with immunoglobulin,[8,16,17,18], often in the company of other immunomodulatory therapies, especially tocilizumab. The importance of controlling inflammation is clear in MIS-C.

Circulatory and ventilatory support have also been widely prescribed, since most of patients with MIS-C develop significant organ dysfunctions that lead to shock and respiratory failure, often requiring vasoactive drugs and mechanical ventilation.

Although not described in many studies, anticoagulation was prescribed to many patients, reaching 100% in the study by Riollano-Cruz et al.[16]

Given what is known about MIS-C, antivirals and antibiotics are not the first drugs of choice. Stronger evidence and well-defined treatment protocols using them must be developed. Antibiotics might be prescribed in cases of TSS linked to bacterial infection. Antivirals, on the other hand, and particularly Remdesivir,[16,17] still lack evidence of effectiveness, especially in MIS-C, which seems to be a post-infectious syndrome where the virus is no longer present.

The economic impact on public health also deserves consideration due to the costs of the various tests and clinical management required for patients with the disease. Almost all patients with MIS-C require intensive care, extensive testing, invasive procedures, and several drugs so that the condition is properly managed.

A survey was carried out to find out the daily rates of pediatric intensive care units at public and private hospitals in the state of São Paulo. The average rate at a private hospital was BRL 4,886.97, with rates ranging from BRL 4,516.17 to BRL 5,428.75.[25,26,27] In the Brazilian Public Healthcare System, the daily rate for an ICU bed increased from BRL 800 to BRL 1,600 due to the COVID-19 pandemic. These amounts include only accommodation, net of procedures, materials, medications, exams, or healthcare worker fees.[28]

Since children with MIS-C are at higher risk of developing coronary aneurysm, they have to undergo color Doppler echocardiography. For this reason, we looked into the costs of this test in several private clinics in the city of São Paulo, Brazil. The average fee was BRL 323.97, ranging from BRL 226.80 to BRL 431. Considering that patients with MIS-C must have been infected with SARS-CoV-2, diagnostic tests for COVID-19 are required. In the same clinics and laboratories, the mean value for a PCR test for COVID-19 was BRL 287.50, ranging from BRL 240 and BRL 340.[29]

Last but not least, we must compute the cost of intravenous immunoglobulin, one of the medications used in the treatment of MIS-C, which is priced at approximately BRL 3,300 per vial.[30]

Early diagnosis and rigorous management of MIS-C is required to mitigate the economic impacts caused by the condition. Prevention against SARS-CoV-2 infection is equally important to prevent the syndrome from developing, causing significant patient morbidity, and increasing the costs of healthcare.

Further studies are needed to better understand the syndrome itself and its pathophysiology. Differentiation between MIS-C and others such as Kawasaki disease and toxic shock syndrome is utterly important so that clinical management becomes more specific and possibly more affordable.

CONCLUSION

The present study characterized the epidemiologic profile, signs and symptoms, diagnostic criteria, laboratory alterations, and therapy delivered to pediatric patients with MIS-C after SARS-CoV-2 infection.

According to the included studies, the main symptoms are persistent fever and respiratory, circulatory and gastrointestinal symptoms such as vomiting, nausea and abdominal pain. Workup findings include markers of inflammatory activity such as neutrophilia and lymphopenia; and elevated CRP, D--Dimer, Fibrinogen, Ferritin and Procalcitonin in most cases.

Management revolves around the use of immunoglobulin associated with corticosteroids. Circulatory and ventilatory support for stabilization are extremely important.

The pathophysiology of MIS-C is unclear since knowledge on the subject is still scarce.

Since the signs and symptoms of MIS-C are very similar to the ones found in DK and TSS, the elements that differentiate between them become quite relevant. Epidemiologic differences are found mainly in age and race/ethnicity. In addition, patients with MIS-C have tested positive for COVID-19. Blood cultures may also help in the differential diagnosis against TSS, which, differently from MIS-C, is a condition caused by bacteria.

The impacts that MIS-C produces on patients due to the complications arising from the disease and on the healthcare system in relation to the cost of treatment are evident.

Since this is a recently described condition, the number of articles and publications about it is still small, which prompts the need for additional studies and protocols to improve the comprehension and management requirements of MIS-C.

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