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NARRATIVE REVIEW

Pediatric multisystem inflammatory syndrome associated with COVID-19: A review of clinical presentation and pathogenesis

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Abstract

Introduction: Multisystem inflammatory syndrome (MIS) is a hyperinflammatory disorder that has emerged as a significant concern during the COVID-19 pandemic. This syndrome also affects the pediatric population, and notifications of cases of multisystem inflammatory syndrome in children (MIS-C) have increased worldwide. An exceptionally high incidence of Hispanic and Afro-descendant patients is observed, reaching 23% in Latin America. Although a direct link between MIS-C and the SARS-CoV-2 has not been established, research suggests a late immunological connection mediated by an imbalance in the expression of Th17 cells/Thregs, autoantibodies, and immune complexes, especially in genetically susceptible individuals and those with an altered endogenous environment.

Methods: In this theoretical review, an exhaustive bibliographic search was conducted in the MEDLINE, LILACS, and Google Scholar databases. Relevant data were collected on the pathogenic and immunological mechanisms that contribute to the development of MIS-C, as well as information on its clinical presentation and relationship with other childhood inflammatory syndromes.

Results: MIS-C predominantly affects the digestive, cardiovascular, and neurological systems and is associated with fever, significantly elevated inflammatory marker levels, and symptoms of organ dysfunction. This syndrome shares similarities with Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. Research has confirmed that MIS-C patients present unique immune and laboratory profiles, establishing it as a distinct clinical entity.

Conclusions: This review highlights the importance of recognizing multisystem inflammatory syndrome in children infected with SARS-CoV-2. The causal connection has yet to be fully established, but initial data support the existence of MIS-C as a unique clinical entity. Understanding the immunological mechanisms and distinctive clinical characteristics of this disease is essential for its early identification and appropriate management in the pediatric population.

Keywords:

MeSH: COVID-19, child, pediatric multisystemic inflammatory disease, physiopathology, signs and symptoms.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has rapidly spread worldwide [1, 2]. As of June 21, 2021, the World Health Organization (WHO) indicated that COVID-19 had affected approximately 178 million people, with a mortality of 3.8 million; in Ecuador, 446,441 cases were diagnosed [3]. Initial epidemiological studies indicated that, in children, the incidence of COVID-19 was significantly lower than that reported in adults (2%) [4], manifesting as asymptomatic cases or mild symptoms [5]. However, in May 2020, in the United Kingdom, cases of children requiring admission to pediatric intensive care units (PICUs) due to an unknown multisystem inflammatory syndrome were reported [2, 5, 6]. The children presented fever, mucocutaneous inflammation, gastrointestinal symptoms, and cardiac involvement [7- 8] with high levels of IL-6 [9]; adverse reverse transcriptase polymerase chain reaction (RT–PCR) results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but positive antibodies [6]; and an epidemiological link for COVID-19. Initially, given the cardiac involvement of the patients and their hyperinflammatory state, this new entity was mistakenly confused with toxic shock syndrome (TSS), macrophage activation syndrome (MAS), or Kawasaki disease (KD) [10]. Subsequently, increasing numbers of notifications of similar cases in North America and Europe [6] led to a health advisory by the Royal College of Pediatrics and Child Health (RCPCH), Centers for Disease Control and Prevention (CDC), and WHO [11]. These entities named this new clinical manifestation of Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C) [5, 12].

As the incidence of SARS-CoV-2 infection increases, additional data are being obtained from children and adolescents, as is the case for the joint report from the American Academy of Pediatrics and the Children's Hospital Association that was reported on October 15, 2020, indicating an increase in pediatric COVID-19 cases in the U.S. (10.9%) [4]. As of June 2, 2021, the CDC reported 4,018 cases of MIS-C (36 deaths), 63% of which were Hispanic or black [13]. A multinational and multicenter study of pediatric COVID-19 in Latin America, as of August 11, 2020, indicated that the incidence of COVID-19 in Latin children who developed MIS-C was more significant than that described in the European and North American literature but with similar clinical characteristics [14].

At the beginning of the pandemic, children were thought to be largely exempt from severe COVID-19 until the emergence of MIS-C [15]. Although the general incidence of MIS-C is low [12], given its severity, there is an urgent need to elucidate its pathophysiology, establish both clinical and laboratory criteria for accurate early diagnosis, and develop optimal treatments [8, 7] that are key to counteracting the morbidity and mortality of this condition [16].

Given the growing prevalence of COVID-19 and MIS-C, accessing all available updates is challenging [7-8, 17]. Therefore, reliable and concise information is essential. In this theoretical review, a bibliographic search was carried out in the MEDLINE, LILACS, and Google Scholar databases; we critically analyzed and summarized the current evidence to provide descriptive information on the clinical heterogeneity of this emerging syndrome, highlighting its relationship with known childhood inflammatory syndromes. We will also discuss the different pathophysiological hypotheses for MIS-C.

Materials and methods

Type of study

the MEDLINE, LILACS, and Google Scholar databases of COVID-19 and Pediatric Multisystem Inflammatory Syndrome studies from February 1, 2020, to May 31, 2020. 2021 using the terms “pediatric multisystem inflammatory disease”, “child”, “COVID-19”, “SARS-CoV-2”, “PIMS-TS”, and “MIS-C”. Original and review

articles were included in both English and Spanish. For inclusion, research that met the purposes of this review, scientific relevance, methodology quality, and publication date were evaluated.

Table 1. Case definition [20 , 21 , 22] .

	RCPCH [22]	CDC[21]	WHO [20]
Terminology	PIMS-TS	MIS-C	Multisystem inflammatory disorder in children and adolescents
Age	Children (age not specified)	Individual under 21 years of age	Children and adolescents from 0 to 19 years
Clinical findings	*Persistent fever *Evidence of dysfunction of one or more organs (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorders) with additional characteristics.	*Fever > 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours *Evidence of clinically serious illness requiring hospitalization, with organ involvement multisystem (> 2) (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological or neurological).	*Fever > 3 days *2 of the following: a) Bilateral nonpurulent rash or conjunctivitis or signs of mucocutaneous inflammation (oral, hands or feet). b) Hypotension or shock. c) Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including findings of ECO or elevated troponin/NT- proBNP), d) Evidence of coagulopathy (due to elevated PT, PTT or D-dimer). e) Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain).
Inflammation markers	Neutrophilia, elevated CRP and lymphopenia.	Elevated level of CRP, ESR, fibrinogen, PCT, D-dimer, ferritin, LDH, IL-6, elevated neutrophils; reduced lymphocytes and low albumin.	Elevation: ESR, CRP or PCT.
Inclusion criteria	Children who meet full or partial criteria for EK.	*Individuals who meet full or partial criteria for KD, but must be reported if they meet the MIS-C case definition. *Any pediatric death with evidence of SARS-CoV-2 infection.	Children with characteristics of typical or atypical KD or SST.
Exclusion criteria	Any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal TSS, infections associated with myocarditis such as enterovirus.	No plausible alternative diagnoses.	No other obvious microbial causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal TSS.
Evidence of SARS-CoV-2 infection	RT–PCR for SARS-CoV-2 can be positive or negative.	*Positive for current or recent SARS-CoV-2 infection by RT–PCR, serology or antigen test or *Exposure to COVID-19 within 4 weeks prior to symptom onset.	*Evidence of COVID-19 (RT–PCR, antigen test or positive serology) or *Probable contact with patients with COVID-19.

NT-proBNP: *N-terminal probrain natriuretic peptide,* ***TP:*** *prothrombin time,* ***PTT:*** *partial thromboplastin time,* ***CRP:*** *C-reactive protein,* ***ESR:*** *erythrocyte sedimentation rate,* ***LDH =*** *lactate dehydrogenase,* ***IL:*** *interleukins,* ***PCT:*** *procalcitonin,* ***RT–PCR:*** *Reverse transcriptase polymerase chain reaction. Source: Prepared by the authors*

Case definition

A clear definition of any disease is necessary to establish a diagnosis [18]. The RCPCH was the first body to publish a case definition, followed by the CDC and WHO [2, 11]. The proposed diagnostic criteria were developed based on the initial cases described, reflecting clinical and laboratory characteristics [19]. In (Table 1), the case definitions of each health agency are compared; the main difference between them is, if necessary.

Given the evidence of a high probability of SARS-CoV-2 infection, the CDC and WHO definitions require positivity for current or recent infection and exposure to COVID-19 [11]. Moreover, the RCPCH does not need such evidence since its definition of "temporarily associated with SARS-CoV-2" assumes that the risk of exposure to the virus during a pandemic is high. Therefore, patients who meet the other criteria can be included [18]. Overall, the agencies have minor discrepancies in interpreting the required levels of inflammatory response [11, 18]. In this review, we use the term MIS-C.

Characteristics of SARS-CoV-2

SARS-CoV-2 is an enveloped positive single-stranded RNA virus [11, 19]. There are four structural proteins (Figure 1): a) the spike protein (S) is the anchoring point to the host cell; b) the nucleocapsid (N) protein packages the viral RNA into a helical ribonucleocapsid [23]; c) the membrane protein (M) influences the formation of the envelope; and d) the envelope protein (E) is involved in the production and maturation of the virus [24].

SARS-CoV-2 infects host cells through S protein binding to the angiotensin-converting enzyme 2 (ACE-2) receptor on the cell surface [25, 26]. ACE-2 is expressed in type 2 alveolar epithelial cells, ciliated and goblet cells of the airways, stratified epithelial cells of the esophagus, cholangiocytes, enterocytes of the ileum and colon, vascular and myocardial endothelial cells, cells of the proximal tubule of the kidney and bladder urothelial cells [24, 26, 27]. SARS-CoV-2 enters and releases its genome into the cell cytoplasm, where it is translated into ribosomes, and a viral replication and transcription complex is formed [23]. Subgenomic RNA is translated into structural and accessory proteins [28], and genomic RNA constitutes the nucleocapsid by binding to the N protein. In contrast, the S, M, and E proteins enter the endoplasmic reticulum [23]. In the intermediate compartment of the endoplasmic reticulum-Golgi, the nucleocapsid and structural proteins assemble into virions and buds in the form of small vesicles toward the cell membrane, where they are released through exocytosis to the extracellular region [24]. The released virions infect new cells, generating the progression of the infection [23] (Figure 1).

Source: Prepared by the authors

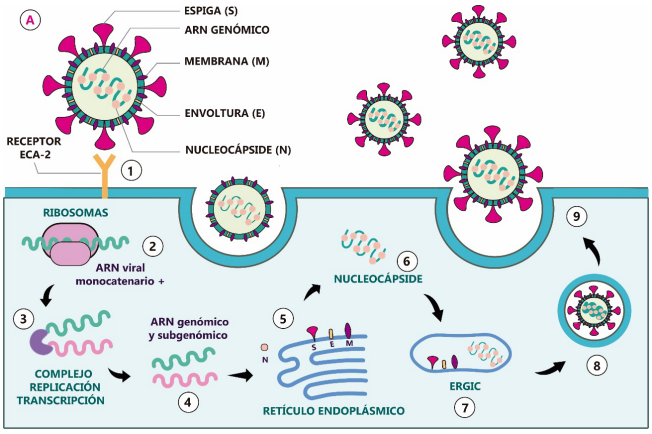


Figure 1. Replicative cycle: (A) Structure of SARS-CoV-2. (1) Fusion and entry of the virus into the host cell. (2) The viral genetic material in the cytoplasm is released, and ribosome translation occurs. (3) Proteolysis and viral replication. (4) Transcription and coding of structural/accessory proteins. (5) Proteins S, M, and E are transferred to the endoplasmic reticulum. (6) The N protein binds to genomic RNA. (7) Assembly of the new virion. (8) Mature virion. (9) Release of the new virus.

Immune response against SARS-CoV-2

Once SARS-CoV-2 penetrates a host cell, the pathogen-associated molecular patterns (PAMPs) of the virus (viral RNA, messenger, and domains) are recognized by host and immune cells (macrophage and dendritic cell)

through different pattern recognition receptors (PRRs) (TLR, RIG - I, MDA5 and NLR) [29] (Figure 2). Intracellular signaling pathways and transcription factors (NF-κB, IRF3-7, MAPK, and JAK/STAT) are activated [26] with subsequent production of type I interferon (INF) and other proinflammatory cytokines (IL-1, IL-6, and TNF-α) that exert antiviral effects [30, 31]; these cytokines also induce changes in the local microcirculation and facilitate the egress of monocytes, neutrophils, natural killer (NK) cells and lymphocytes [32]. The effective activation of these innate immune mechanisms favors the containment and elimination of infection [26, 30, 31]. In the later phases of infection, antigen-presenting cells (APCs) present viral epitopes to T helper lymphocytes (Th) through the major histocompatibility complex (MHC) [32]. Like SARS-CoV and MERS-CoV, SARS-CoV-2 antigen processing is presumed to occur primarily through MHC-I [26, 30]. The microenvironment of previously generated cytokines induces the differentiation of Th1-Th2 cells, which are activated and produce different patterns of cytokines; Th1 cells generate IL-2 and interferon-gamma (IFN-γ), which stimulate cytotoxic lymphocytes ($^{CD8+}$) and NK cells that directly destroy infected cells [32]. On the other hand, Th2 lymphocytes stimulate B lymphocytes (LBs) that produce specific neutralizing antibodies [29], essentially against S and N glycoproteins, to achieve virus clearance [31].

Source: Prepared by the authors.

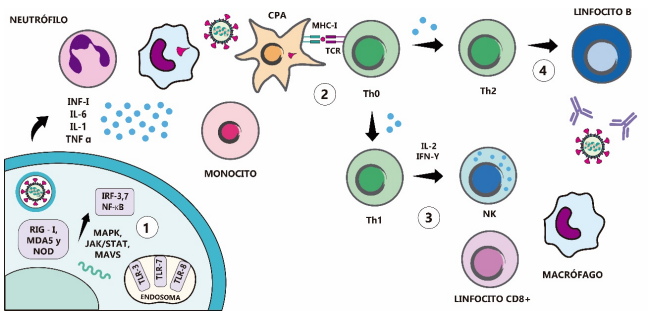


Figure 2. Immune response: (1) Recognition of PAMPs by PRRs and activation of intracellular signaling pathways to produce proinflammatory cytokines. (2) Cell recruitment, antigen presentation, and polarization of naïve helper lymphocytes (Th0). (3) Activate NK cells, cytotoxic lymphocytes, and phagocytes. (4) Neutralizing antibodies for virus clearance.

Virus escape mechanisms

SARS-CoV-2 counteracts the immune response through the inflammation-inducing molecules PAMPs and DAMPs (damage-associated molecular patterns) [31]. They alter the expression of Toll-like receptors (TLR3,7) and cytosolic RNA receptors (RIG-I, MDA5), thus preventing their detection. It also inhibits the activation of mitochondrial antiviral signaling proteins (MAVSs) and counteracts the signaling of transcription factors (IRF3 and NF-κB), which prevents or decreases the production of INF [26]. All of these mechanisms result in altered innate immunity that facilitates replication. Likewise, SARS-CoV-2 causes T-cell exhaustion and overactivation of inflammasome 3 [30].

Immune Response in Children

The difference in the severity of COVID-19 between adults and children is multifactorial [10]. Most children have developed asymptomatic clinical symptoms or mild symptoms [11], which may be due to a) increased levels of cross-neutralizing antibodies against the S protein of coronaviruses (previous exposure to endemic CoVs HCoV-NL63 and HCoV-OC43) [33]; b) reduced expression of the viral entry receptor ACE-2 [8]; c) increased regulatory response of T lymphocytes (immature immune system); and d) decreased production of inflammatory cytokines (IL-6 and TNF-α) [33, 34].

PATHOPHYSIOLOGICAL HYPOTHESIS OF MIS-C

SARS-CoV-2 and MIS-C

The majority of MIS-C notifications occurred between 3 and 6 weeks after the peak of COVID-19 infection in the affected population [11, 35], and many children have positive serological results but negative RT–PCR results for SARS-CoV-2 [10 – 11, 25, 26]. Although a direct link between MIS - C and SARS - CoV - 2 has not yet been established [9], the above findings support the hypothesis that MIS - C is not directly mediated by viral

invasion but develops due to the immune response. Altered latency against SARS-CoV-2 [5, 11, 36, 37].

Patient demographic characteristics

Several publications have shown a higher rate of MIS-C in black and Hispanic children [7, 12, 16]. Jointly, the lack of MIS-C reports is highlighted in Asian countries [5, 35]. It has been described that Afro-descendant children have earlier maturation of ACE-2 and that the ethnicities above suffer from relative vitamin D deficiency (essential for immune modulation) [2]. Based on demographic data and the differences found in the racial distribution, a social effect or genetic predisposition is suspected where Afro-descendant and Latino children seem to have a greater risk of developing MIS-C [2, 10, 12, 25].

Immunological Mechanisms

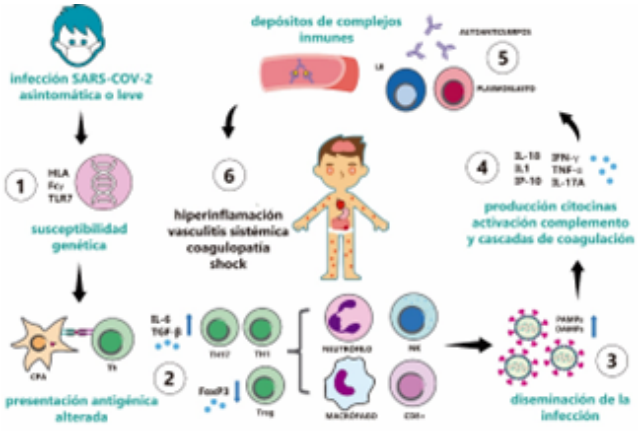
MIS-C is triggered in genetically susceptible children (HLA variant, Fc γ, TLR7) [4, 38] and in an altered endogenous environment (an imbalance of vitamin and microbiota homeostasis) that could compromise the regulatory T-cell (Treg) response [31]. Usually, children infected with SARS-CoV-2 in the convalescent phase recover from infection via efficient adaptive immunity (Th1, Th2) [31]. However, in patients who develop MIS-C, the PAMPs of SARS-CoV-2 initially present an altered signal, producing high levels of IL-6 and TGF-β, mediators of Th17 cells (the main inducers of autoimmune disease) and Th1 cells, which have lower expression of Treg (FoxP3) signaling molecules and other suppressive immune mediators [4, 31]. A greater polarization of Th17 cells does not effectively control viral infection (increase the systemic release of PAMPs and DAMPs) [37], and together with deficient regulatory T activity, inflammation is promoted, inducing the activation and recruitment of macrophages, neutrophils, NK cells, and CD8+ lymphocytes, in addition to generating high levels of IFN-γ, TNF-α, IL-17A, IL-18, IL1, and IP-10 [18, 31] (Figure 3).

Moreover, LBs are activated and differentiate into plasmablasts and antibody-producing plasma cells [37]. However, the immune profile of patients with MIS-C exhibits a decrease in the follicular helper T cells necessary for an optimal BL response [8]. Abnormal expression of neutralizing antibodies has been detected in MIS-C patients in the presence of autoantibodies against specific proteins of endothelial, myocardial, and immune cells (lymphocytes) [4, 5, 18]. This autoantibody theory is also supported by the effectiveness of intravenous immunoglobulin for treating MIS-C [8]. Likewise, the rapid resolution of inflammation in MIS-C patients indicates that if autoimmunity drives this pathology, it is transient and perhaps mediated by short-lived immune cell populations such as plasmablasts [15, 38].

On the other hand, the abnormal antibodies generated can trigger the formation and deposition of immune complexes (ICs) in tissues [26]. IC has been found in the endothelium of an adult patient with SARS-CoV-2 infection. Despite the lack of detectable IC in the serum of patients with MIS-C [19], its possible role and activation of neutrophils in the coronary vasculitis of MIS-C have not been ruled out [15]. A case report revealed the presence of viruses in the myocardium during a fatal presentation of MIS-C due to heart failure, suggesting "second hit" virus-mediated damage to tissues [18, 26], and viral particles have also been observed within the endothelium of pediatric patients with SARS-CoV-2 chilblains [19]. However, the cardiac MRI findings of patients with MIS-C and diffuse myocardial edema (macrophage and neutrophil infiltration) without fibrosis or focal necrosis point to an immune-mediated mechanism and rule out the possibility of viral myocarditis where degeneration occurs of myocardial cells [2, 17]; this finding, in addition to the favorable response of MIS-C to immunomodulatory and anti-inflammatory therapies, excludes the hypothesis of damage mediated by viral replication [26].

As humoral immunity is generated, complement and coagulation cascades are also activated, which, in

addition to the imbalance of Th17/Treg cells, creates the hyperinflammatory response characteristic of MIS-C, systemic vasculitis, coagulopathy, and shock [8, 29, 37].



Source: Prepared by the authors

Figure 3. Immunopathogenesis of MIS-C. (1) A history of SARS-CoV-2 infection in children with a genetic predisposition. (2) Presentation of the viral antigen with an altered signal generating an imbalance in the expression of Th17/Threg lymphocytes and activation of macrophages, neutrophils, NK cells, and CD8+ cells. (3) Systemic spread of infection. (4) Elevation of proinflammatory cytokines, complement activation, and coagulation cascades. (5) B lymphocytes, plasmablasts, and plasma cells express abnormal antibodies associated with immune complex formation [6]. Generation of the hyperinflammatory state characterized by systemic vasculitis, coagulopathy, and shock

MIS-C AND ITS RELATIONSHIP WITH KNOWN SYNDROMES

Significant overlap exists in the clinical presentation of MIS-C and other hyperinflammatory syndromes in children, as differences in etiology, activation, and dysregulation of common inflammatory pathways result in similar clinical conditions [6].

Toxic Shock Syndrome

The initial relationship between MIS-C and TSS seems remote due to the negativity of blood cultures in most MIS-C patients [11]; differences in the infectious agent that triggers hyperinflammation are an essential element of this disease [4]. No evidence exists that staphylococcal or streptococcal toxins are involved in MIS-C etiology [11].

Cytokine Storm

One of the hypotheses raised for MIS-C was that a cytokine storm was caused by the ability of SARS-CoV-2 to block the INF type I and III response [9]. Some features of MIS-C are similar to those described in severe cases of COVID-19 in adults, such as profound lymphopenia and elevated levels of IL-6, IL-10, and IL2 [39]; however, in children with MIS-C, there is no evidence of viremia [12], and their cytokine profiles (lower IL-6 and higher IL-10 and IL-2 levels) are very different from those observed in adults (elevated IL-7 and IL-8 levels) [8, 39]. On the other hand, children who develop MIS-C have higher levels of IL-10 and TNF-**α** than children affected by severe COVID-19 [4. Thus, cytokine storms cannot explain the presentation or immunopathogenesis of MIS-C [18].

Antibody-dependent enhancement (ADE)

Another suggested theory in MIS-C is a postinfectious process caused by nonneutralizing IgG antibodies [2, 18, 9]. ADEs originated when antibodies produced against one virus serotype interact with a second serotype (cross-reactivity) without completely neutralizing it, facilitating viral replication [33]. The Fc**γ** receptor on monocytes, macrophages, and granulocytes has been implicated as the primary receptor to which subneutralizing virus-IgG antibody complexes bind in CoV infections; it has been proposed that possible anti-S IgG binding to Fc**γ**R allows fused virions to invade and infect immune cells [26, 31], thus preventing robust early antiviral responses [26]. However, this presumption of ADE remains unclear due to the absence of reports of

worsening COVID-19 in patients who received convalescent plasma [2].

Macrophage activation syndrome

In the pediatric setting, it is essential to establish whether MIS-C is a new entity or whether SARS-CoV-2 is another trigger of SAM [40]. SAM is a variant of lymphohistiocytosis secondary to hemophagocytosis [41] and is linked to autoimmune and infectious conditions and neoplasia [42]. It is characterized by fever, hemophagocytosis, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, cytopenias, and coagulopathy; cardiac and neurological dysfunction may manifest during clinical presentation [43]. SM-T cells exhibit prolonged hyperfunction of NK and CD8+ cells; these cells produce high levels of IFN-**γ**, which is responsible for the activation of macrophages [44]. Increased circulating IFN-**γ** levels are a hallmark of hemophagocytic syndromes [19]. In MIS-C patients, cytopenias; high levels of IFN-**γ**, IL-18, sIL2R, and IP-[10, 19]; elevated D-dimer, triglyceride, and ferritin; and elevated ferritin are evident characteristics that suggest a possible relationship with SAM [39, 45, 46]. However, most MIS-C patients do not meet the full diagnostic criteria for SAM. Compared to those in historical SAM cohorts, the increases in IL-18, INF-**γ**, sIL2R, and ferritin in MIS-C patients were less prominent [4, 39]. Differences in the degree of hyperferritinemia and distinct cytokine profiles point to the pathogenesis leading to MIS-C differing from MAS [39].

Kawasaki disease

Because MIS-C is compatible with atypical KD [40] and the human coronavirus New Haven has been correlated with KD in Western countries [31], the debate has opened whether MIS-C and KD are the same entity. [5]. EK is a hyperinflammatory febrile vasculitis [37] prevalent in children of Asian descent [31] whose etiology is still unknown [17]; its diagnostic criteria include fever, skin rashes, bilateral conjunctival injection, changes in the oral mucosa, peripheral edema and cervical lymphadenopathy [45]. Several differences between EK and MIS-C have been identified during the pandemic: a) MIS-C affects older children, with an average age of 7 years, compared to children with KD, whose average age is three years [40]. b) MIS-C generates more gastrointestinal and neurological effects and the presence of a rash [19], with greater myocardial involvement [5, 9, 40]. c) In MIS-C, children present with lymphopenia [47], unlike children with KD, who present with leukocytosis and neutrophilia [40]. d) In KD, platelets range between 500,000 and >1 million/mm3, while in MIS-C, they remain within normal limits or decrease [4] and are associated with signs of coagulopathy (increased D-dimers) [47]. e) Inflammatory marker levels are increased under both conditions, but MIS-C patients exhibit more systemic inflammation with drastically increased CRP, IL-6, and ferritin levels [4, 5, 19, 47]. f) In KD patients, 7% of patients are complicated by KD shock syndrome (SSEK), a figure that is offset by the 50% of patients with MIS-C who present with shock [5]. g) According to our immunological profiles, EK is associated with increased levels of IL-17 and decreased levels of adenosine deaminase (ADA), stem cell factor (SCF) and TWEAK (a negative regulator of IFN-**γ** and the immune response Th1 type) [8, 31]; in addition, in SSEK, the levels of IL-6 and IL-10 are increased, while in MIS-C, the levels of IL-10 and TNF-**α** are increased. Thus, MIS-C and EK appear to have similar immune activation pathways but different regulatory pathways [31].

Clinical presentation

MIS-C has a broad spectrum of manifestations [15], predominantly affecting the cardiovascular, gastrointestinal, and neurological systems and only occasionally the respiratory system [5, 6]. It usually develops in previously healthy children [25] without comorbidities [6, 2, 7]. The median age of patients in several studies ranged from 7 to 10 years (three months to 20 years) [17, 31, 6]. The male sex has a slight predominance (53-60%) [5, 35], although the evidence indicates that there is no significant preponderance [17]. A risk factor linked to

MIS-C is obesity since it is present in 30 to 50% of patients; fatty tissue is associated with elevated proinflammatory cytokines and greater expression of ACE-2 [7]. MIS-C generally presents with high fever, organ dysfunction, and significantly elevated inflammatory marker levels [8, 7, 17], with a propensity for coagulopathy and shock [6, 17, 31, 48].

Fever: Fever is a universal characteristic in patients with MIS-C (100%). Most children present with persistent fever for over four days [15], with temperatures varying between 38 and 40°C [2, 17].

Gastrointestinal symptoms: Gastrointestinal involvement was high (80%) in all age groups studied [15] and included abdominal pain, non-bloody diarrhea, and vomiting [4]; all of these symptoms occurred in the initial phase of the disease [2, 6]. The description of abdominal pain has not yet been specified; cases in which the degree of pain is so severe have been reported [2] that patients have undergone exploratory laparotomy for possible acute abdomen (appendicitis) [7, 17]. The most common findings in imaging studies included ascites, intestinal/colonic inflammation, and mesenteric adenopathy [7]. Few patients with peritoneal effusion [2] or pancreatitis secondary to severe acute respiratory syndrome 2 (SARS-CoV-2) [7] have been diagnosed.

Mucocutaneous features: Rashes of varying description [6] have been reported most frequently in children under five years of age (70%) [15]. The most common manifestations were maculopapular rash, conjunctivitis, and cheilitis [2]. Edema of the hands and feet has also been reported [10].

Neurological manifestations: Generally mild and reversible, they are present in variable frequencies in the early and late phases of MIS-C [15]. They include signs of alteration of the central nervous system, such as headache, sensorium disorder, dysarthria, dysphagia, meningism, and cerebellar ataxia [17]. In addition, peripheral nervous system manifestations with global proximal muscle weakness and reduced reflexes were also evident [4].

Cardiovascular involvement: The most prominent complications in patients with MIS-C (50-80% of cases) [17] include severe circulatory failure and myocardial participation [5- 6]. Cardiac dysfunction is the hallmark of MIS-C, including coronary artery dilation and aneurysms, myocarditis, left ventricular dysfunction (decreased LVEF < 55%), pericardial effusion, and shock [2, 10, 12]. Pericarditis and transient valvular insufficiency have also been described [2, 12, 17]. Myocarditis linked to MIS-C is reported to be less severe than other childhood myocarditis and responds better to treatment [15]. Cardiac biomarkers, including NT-pro-BNP and troponin levels, are extremely high [47] and maybe a useful clinical indicator of recovery [17]. Electrocardiographic abnormalities include prolonged PR and QTc interval, premature atrial or ventricular beats [4], ST segment, and T wave changes [17]. Regarding the prognosis, the myocardial injury is milder than in adults, and more than half of the children recover their left ventricular ejection fraction before discharge [15].

Hemodynamic instability: Present in 60-80% of patients [17], most children developed shock refractory to volume resuscitation, requiring vasopressor support (70%) [2]. Warm vasoplegic shock is a common element in MIS-C [7].

Laboratory features: The most common findings are: a) Abnormal blood cell counts: lymphopenia, neutrophilia, thrombocytopenia, and low red blood cell counts [5, 10, 12, 15]. Other reported hematologic abnormalities include elevated D-dimer and low fibrinogen [2, 4]; b) Elevation of inflammatory markers: CRP [5, 10], ESR, ferritin, PCT (without associated bacterial infection) [10, 12, 15]; c) Elevated levels of inflammatory cytokines: IL-6, TNF- α, IL10, IL-1β [4, 10]; d) Elevated markers of heart damage [5, 15], abnormal function tests, hypertriglyceridemia and hyponatremia [15, 17], with elevated LDH [10].

Conclusions

Due to the need for a precise case definition and an accurate diagnostic test, recognizing this disease is

challenging. Currently, MIS-C has three leading names, which can create selection biases in research and incomplete bibliographic coverage that confuses its understanding. In clinical practice, MIS-C terminologies and definition criteria must be unified.

MIS-C is a hyperinflammatory disorder triggered 3 to 6 weeks after SARS-CoV-2 infection. These findings indicate that viral invasion is not the cause of this syndrome; instead, it is triggered by a delayed immune response altered against the virus-mediated by an imbalance in the expression of Th17/Threg, autoantibodies, and ICs.

MIS-C is associated with a phenotype similar to SST, MAS, EK, or SSEK; however, it has unique clinical manifestations and immune and laboratory profiles. It occurs more frequently in older, black, and Hispanic children without comorbidities; has gastrointestinal symptoms, myocardial involvement, and progression to shock; is associated with leukopenia and thrombocytopenia; and has elevated CRP, IL-6, IL10, TNF-α, ferritin, and D-dimer levels, all of which are valuable for its differential diagnosis.

An analysis of published data evaluating serological and inflammatory responses has provided initial data supporting MIS-C as a new entity different from other childhood hyperinflammatory syndromes and the adult hyperinflammatory state. However, elucidating the molecular immune mechanisms of MIS-C will allow the development of preventive strategies and treatment protocols. Future research is needed to address the biological aspects and social determinants that excessively affect some population groups to reduce the burden of the disease.

Abbreviations

MIS: Multisystem inflammatory syndrome.
MIS-C: Pediatric Multisystem Inflammatory Syndrome.
KD: Kawasaki disease.
PAMPs: pathogen-associated molecular patterns.
PRRs: pattern recognition receptors.
MAS: Macrophage activation syndrome.
TSS: Toxic shock syndrome.

Supplementary information

No supplementary materials are declared.

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Isabel Carrasco, Gabriela Carrasco: Conceptualization, critical analysis, argumentation, bibliographic review, preparation, and article writing.
Greta Muñoz: Scientific advice, critical analysis, supervision, and editorial corrections.
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Conflicts of interest

The authors declare that they have no conflicts of interest.

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