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LEADING ARTICLE

# Multisystem Inflammatory Syndrome in Children Related to SARS-CoV-2

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**Abstract**
Although data on the incidence and severity of new coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection showed more significant disease among adults and the elderly, a clinical manifestation characterized by a multisystem inflammatory syndrome was described in children (MIS-C). It was initially thought to be specific to children, but recent reports have shown that it can also occur in adults. MIS-C is characterized by a number of multisystemic manifestations resembling other known previously described illnesses, mainly Kawasaki disease, especially in cases with shock, toxic shock syndrome, and macrophage activation syndrome. Available literature shows that our knowledge of MIS-C is largely incomplete. Its development in strict relation with SARS-CoV-2 infection seems documented and, in most cases, can be considered a post-infectious manifestation secondary to an abnormal immune response for some aspects, similar to that seen in adults several days after SARS-CoV-2 infection. However, in a minority of cases, a clinical picture with symptoms fulfilling criteria for MIS-C diagnosis develops during the acute phase of SARS-CoV-2 infection. It is highly likely that the criteria currently used to diagnose MIS-C are too broad, meaning that children with different diseases are included. As clarity on the pathogenesis of MIS-C is lacking, different therapeutic approaches have been used, but no specific therapy is currently available. Further studies are urgently needed to improve our definition of MIS-C, to define the real impact on child health, and to elucidate the best clinical and therapeutic approach and true prognosis.

## 1 Introduction

Epidemiological studies conducted during the first weeks of the new coronavirus disease 2019 (COVID-19) pandemic, mainly in hospitalized patients, indicated that children were largely spared from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. The incidence of COVID-19 among children was significantly lower than that reported in adults and the elderly, with no more than 2% of cases diagnosed in the pediatric population. The risk of severe disease was considered very low, as about 90% of cases were asymptomatic or mild or moderate and had a good prognosis with recovery within 1–2 weeks [2, 3]. Hospitalization and admission to the pediatric intensive care unit (PICU) was uncommon, and death was an exceptional event [3].

However, when more data on the epidemiology and clinical features of COVID-19 in children and adolescents were collected, this judgment was revised, at least in part. Although new data on COVID-19 confirmed a higher incidence and severity of disease among adults and the elderly, the total number of pediatric SARS-CoV-2 infections and the risk of severe cases were both frankly greater than initially calculated [4]. A joint report from the American Academy of Pediatrics and the Children's Hospital Association reported that, as at 15 October 2020, a total of 741,891 pediatric COVID-19 confirmed (via a diagnostic molecular test) or probable (via a clinical diagnosis) cases were identified in the USA, representing 10.9% of all disease cases [5]. Throughout the USA, up to 7.2% of all pediatric COVID-19 cases were hospitalized, and up to 0.23% died [5]. Interestingly, among severe cases, a previously unknown SARS-CoV-2-related clinical picture emerged [6]. It was characterized by severe hyperinflammation leading to a number of multisystemic manifestations resembling other previously described illnesses, mainly Kawasaki disease (KD),

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**Key Points**

Severe coronavirus disease 2019 (COVID-19) is uncommon in children. However, a severe manifestation, multisystem inflammatory syndrome in children (MIS-C), can occur.

MIS-C is characterized by a number of multisystemic manifestations resembling other previously described illnesses, mainly Kawasaki disease, although several findings seem to indicate that it is a distinct clinical entity.

As there is no clarity on the pathogenesis of MIS-C, different therapeutic approaches have been used, but no specific therapy is currently available.

Whether a genetic susceptibility to MIS-C exists is unknown, and the long-term prognosis of MIS-C is not completely defined.

Further studies are needed to better define various aspects of MIS-C, with a special focus on discovering the best clinical and therapeutic approach.

toxic shock syndrome (TSS), and macrophage-activation syndrome (MAS). Initially, this condition was considered specific to children as the SARS-CoV-2-associated hyperinflammatory syndrome frequently seen in adults and in the elderly during the third phase of severe COVID-19 had several different characteristics. Unlike children, who generally do not have lung problems, cytokine storm in adults is frequently accompanied by severe respiratory involvement with development of acute respiratory distress syndrome [7]. Moreover, acute illness from COVID-19 often occurs within the first 2 weeks of infection in adults, unlike the disease syndrome, the onset of which usually occurs over 2 weeks after infection. However, cases of multisystem inflammatory syndrome in adults have recently been described, showing that SARS-CoV2 can cause this clinical manifestation in subjects of any age [8]. More than 1000 cases of this SARS-CoV-2-associated syndrome have been reported [9]. Despite this, the spectrum of illness and the clinical course, actual incidence, pathogenesis, and optimal treatment of this condition are not precisely defined [10]. This narrative review summarizes the current knowledge of this disease. We searched PubMed and Scopus for studies published in English from January 2020 to 1 October 2020 using the following keywords: COVID-19 and/or children, pediatric inflammatory multisystem syndrome, multisystem inflammatory syndrome, Kawasaki disease, toxic shock syndrome, macrophage activation syndrome.

## 2 Definition

Only a few weeks after COVID-19 was declared a pandemic, the risk that pediatric SARS-CoV-2 infection could be associated with the development of clinical manifestations resembling KD, TSS, acute abdominal conditions, and encephalopathy was being reported [11–14]. However, the first major call to attention to this problem was in late April 2020 when UK pediatricians warned the national health service of an increase in cases of children with asymptomatic or minimally symptomatic COVID-19 infection who developed a significant systemic inflammatory response with high fever and involvement of more than one organ or body system, a severe course requiring hospitalization, and, although rare, a risk of death. This condition was named pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS), and specific guidelines for its identification and treatment were prepared [15].

When other cases of pediatric COVID-19 associated with hyperinflammation were described, the World Health Organization (WHO) [16], the US Centers for Disease Control and Prevention (CDC), and UK authorities [17] published their own definitions of the syndrome (Table 1) and called it multisystem inflammatory syndrome in children (MIS-C). Unfortunately, despite these definitions all having common elements, such as prolonged fever, multi-organ dysfunction, laboratory evidence of hyperinflammation, and presumed or confirmed infection by SARS-CoV-2, they substantially differed in other criteria. For example, clinical manifestations are significantly more detailed in the WHO definition than in the CDC and UK definitions. Conversely, laboratory tests from which abnormal results could support a diagnosis of MIS-C are much more numerous in the CDC definition than in the UK and WHO definitions. Criteria used to define PIMS-TS can easily lead to complete or incomplete KD diagnosis, which explains why most of the early published studies included several patients with clinical problems fulfilling diagnostic criteria for KD. Obviously, epidemiological evaluations varied significantly according to the criteria used for diagnosis, with broader criteria leading to reports of a higher incidence. However, despite the risk of overdiagnosis in several studies, MIS-C seems to be a relatively uncommon condition that occurs in only a few children infected by SARS-CoV-2. In one of the studies with the greatest number of children with MIS-C, the incidence in those aged < 21 years was 2 per 100,000 compared with 322 per 100,000 individuals of the same age with SARS-CoV-2 infection [18]. However, it is possible that the true incidence of MIS-C is significantly higher. A lack of clinical awareness/diagnosis may have led to some cases being overlooked. Moreover, diagnostic criteria have been based on

**Table 1** Main diagnostic criteria of multisystem inflammatory syndrome in children temporally associated with SARS-CoV-2

| Characteristic | World Health Organization | Center for Disease Control and Prevention | Royal College of Paediatrics and Child Health |
|---|---|---|---|
| Age | < 19 years | < 21 years | Child |
| Fever | ≥ 3 days | > 38 °C (100.4 °F) for 24 h | Persistent > 38.5 °C (101.3 °F) |
| Inflammation | Increased levels of CRP, erythrocyte sedimentation, procalcitonin | At least one of these laboratory results: increased levels of CRP, erythrocyte sedimentation, procalcitonin IL-6, fibrinogen, D-dimer, ferritin, LDH, neutrophils; reduced albumin and low lymphocytes | Increased neutrophils, reduced lymphocytes |
| SARS-CoV-2 infection | SARS-CoV-2 positivity at swab testing or serology, otherwise exposure to a probable COVID-19 case | SARS-CoV-2 positivity at swab testing or serology, otherwise exposure to a probable COVID-19 case | SARS-CoV-2 positive or negative swab tested with molecular biology |
| Exclusion of other diagnoses | No other diagnosis | | |
| Organ dysfunction | At least two of the following organs in failure: circulation, heart, coagulation, gastrointestinal, skin, respiratory | | |

*COVID-19* coronavirus disease 2019, *CRP* C-reactive protein, *IL* interleukin, *LDH* lactate dehydrogenase, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

clinical manifestations in children hospitalized with severe disease. Using these criteria to diagnose MIS-C may omit less serious cases. MIS-C has been reported in many countries and, in addition to the critically ill children in the first reports, a wider spectrum of childhood inflammatory illness has emerged (Table 2). To harmonize reporting tools, the WHO created a research network working group on MIS-C.

## 3 Clinical Manifestations and Laboratory Tests

Given the use of different criteria to define MIS-C, the clinical characteristics of children with this syndrome varied significantly between reports and remained poorly defined (Table 3) [19–36]. This is clearly evidenced by a systematic review of the studies published from 25 April 2020 through 29 June 2020, including preprint manuscripts uploaded to medRxiv and bioRxiv [32]. Eight studies, including 440 patients (59% males, age 7–10 years), were analyzed [13, 26, 31–36]. When all the children were considered together regardless of classification criteria, gastrointestinal and dermatologic/mucocutaneous symptoms were the most common clinical manifestations of MIS-C as they were detected in 87% and 73% of children, respectively. Cardiovascular symptoms were present in 71% of the cases, respiratory symptoms in 47%, and neurologic symptoms in 22%. Conversely, studies that used cardiovascular inclusion criteria had a prevalence of cardiovascular symptoms of 100%, and studies selecting patients with KD included a higher prevalence of neurologic symptoms (55%) but a lower prevalence of respiratory symptoms (14%).

Moreover, as none of the classification systems are specific, it remains possible that they all include patients with a different syndrome. If cases considered MIS-C according to CDC criteria are analyzed and grouped according to signs and symptoms of disease and laboratory tests, three different subgroups of patients with MIS-C can be identified [37]. The first group includes patients with involvement of six or more organ systems, among which cardiovascular and gastrointestinal systems are the most common. However, these patients have little overlap with KD or acute COVID-19 manifestations. The second group is characterized by patients with respiratory symptoms that have a clinical picture resembling classic COVID-19. The last group of children has the highest prevalence of rash and mucocutaneous lesions and has clinical manifestations that fulfill criteria for complete KD disease in most cases. However, the most common description of a child with MIS-C is a school-age patient with persistent fever, skin rash, conjunctivitis, gastrointestinal symptoms, and history of previous asymptomatic or mild COVID-19 or strong epidemiological evidence of SARS-CoV-2 infection [38]. The most common gastrointestinal symptoms are diarrhea, vomiting, and abdominal pain. Peritoneal effusion can be detected. In rare cases, abdominal pain can be severe enough to mimic appendicitis and lead to unnecessary emergency operations [39]. The clinical picture is frequently complicated by signs and symptoms of other organ system functional modifications. Generally, at least four organ systems are involved. However, patients with symptoms involving six or more organ systems have been repeatedly described. Respiratory system symptoms can develop as early manifestations or later when other signs and symptoms of disease are already present.

**Table 2** Definition of childhood inflammatory illnesses associated with SARS-CoV-2

| | |
|---|---|
| MIS-C temporally associated with SARS-CoV-2 | 1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) with additional features. This may include children meeting full or partial criteria for Kawasaki disease<br>2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice)<br>3. SARS-CoV-2 PCR testing may be positive or negative |
| Typical Kawasaki disease, temporally associated with SARS-CoV-2 | 1. Classical criteria for Kawasaki disease<br>2. Evidence of SARS-CoV-2 infection or exposure<br>3. SARS-CoV-2 PCR may be positive or negative, and SARS-CoV-2 antibodies positive or negative |
| Febrile inflammatory syndrome, temporally associated with SARS-CoV-2 | 1. Febrile children with inflammatory blood markers (raised CRP, neutrophilia, lymphopenia, elevated D-dimers, ferritin), in whom other infectious or inflammatory causes cannot be identified<br>2. SARS-CoV-2 may be positive or negative by PCR and antibody |

*CRP* C-reactive protein, *MIS-C* multisystem inflammatory syndrome in children, *PCR* polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

**Table 3** Main clinical manifestations for a diagnosis of multisystem inflammatory syndrome in children

| Involved organ system | Reported prevalence (%) | Main symptom |
|---|---|---|
| Gastrointestinal | 82–87 | Diarrhea, vomiting, abdominal pain |
| Dermatological/ mucocutaneous | 69–73 | Skin rash, conjunctivitis |
| Cardiovascular | 71–100 | Myocardial dysfunction, vasogenic shock, myocardial infarction, coronary artery dilation or aneurysm, arrhythmia |
| Respiratory | 14–47 | Upper respiratory tract infection, shortness of breath, pneumonia, acute respiratory distress syndrome |
| Neurologic | 22–55 | Headache, dysarthria, dysphagia, meningism, cerebellar ataxia, global proximal muscle weakness, reduced reflexes |
| Renal | 3–38 | Acute insufficiency |

Respiratory disease may be limited to the upper respiratory tract or be more severe and characterized by shortness of breath, pneumonia, and acute respiratory distress syndrome. However, in cases requiring mechanical ventilation, the predominant reason was for cardiovascular support [40]. Neurologic manifestations, involving both the central nervous system (CNS) and the peripheral nervous system (PNS), have been described as part of the initial presentation or as a late component of the syndrome. Generally, they are mild and reversible. In the study by Abdel-Mannan et al. [41], 4 of 27 children with clinical manifestations consistent with MIS-C had signs of CNS involvement, with headache, dysarthria or dysphagia, meningism, and cerebellar ataxia. Moreover, PNS disease was evident in all cases, with global proximal muscle weakness and reduced reflexes. Neuroimaging revealed signal changes in the splenium of the corpus callosum in all four patients and T2-hyperintense lesions associated with restricted diffusion in three. No spinal cord involvement or pathological enhancement was observed. Control neuroimaging carried out in one patient showed rapid resolution of the diffusion restriction. Electroencephalography showed a mild excess of slow activity, whereas nerve conduction studies and electromyography revealed mild myopathic and neuropathic changes. Renal involvement is relatively common, with acute insufficiency found in up to 38% of cases. However, less than 0.1% of children required dialysis [37].

Cardiovascular alterations are by far the most important clinical manifestations of MIS-C as they substantially increase the need for PICU admission, the development of potential long-term problems, and the risk of death [42]. They can manifest during the first phase of MIS-C or develop later and generally appear in school-aged, previously healthy children. In a retrospective study that enrolled 35 patients with MIS-C and cardiovascular abnormalities, the median delay from the onset of clinical symptoms to heart failure was 6 days, median age at admission was 10 years, and comorbidities—mainly overweight—were present in only

about one-quarter of cases [36]. No case had underlying cardiac disease. Most patients had significant myocardial dysfunction (left ventricular systolic function with an ejection fraction < 60%, diastolic dysfunction, or regional wall motion abnormalities), vasogenic shock, myocardial infarction, coronary artery dilation or aneurysm, and arrhythmia. Immediate admission to the PICU was required in more than 90% of cases, inotropic drug administration to solve hypotension in 80% of cases, and treatment with extracorporeal membrane oxygenation (ECMO) in 28%. Coronary artery involvement was found in 6–24% of cases and varied from mild generalized dilatation compatible with the hyperinflammatory state to giant aneurysms. As these can appear several days after the disappearance of other MIS-C symptoms and patient discharge from the hospital, it is suggested that all children with MIS-C and cardiac manifestations must undergo long-term follow-up. Rhythm abnormalities have been found in 7–60% of patients. They are non-specific and include ST segment changes, QTc prolongation, and premature atrial or ventricular beats [43].

Laboratory tests generally show a significant increase in inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, and/or ferritin [32, 37, 38]. Other common findings included hyponatremia, increased serum creatinine, and hypoalbuminemia [32, 37, 40]. Increased serum concentrations of troponin and pro-B-type natriuretic peptide (proBNP) is commonly associated with symptoms of cardiovascular involvement, suggesting myocardial damage and heart failure, respectively [38–40]. Reported hematologic abnormalities included neutrophilia, lymphopenia, low to normal platelet levels, elevated D-dimer, and low fibrinogen [39, 40]. Inflammatory cytokines were generally increased, particularly interleukin (IL)-1β, IL-6, IL-10, IL-13, and tumor necrosis factor (TNF)-α [38].

In most cases, clinical manifestations and laboratory values tended to subside rapidly with treatment [43]. Discharge from hospital can be decided once children are afebrile, do not need supplemental oxygen, and have normal blood pressure. However, as long-term outcomes are not precisely defined, especially for children with severe cardiological involvement, close follow-up is recommended [10].

## 4 Pathogenesis

Several conditions characterized by severe inflammation and multiple organ system damage have been associated with previous infections. TSS is thought to be caused by bacterial superantigens (SAGs) secreted from *Staphylococcus aureus* and *Streptococcus pyogenes* [44]. SAGs bypass normal antigen presentation through interaction with class II major histocompatibility complex molecules on antigen-presenting cells and to specific variable regions on the β-chain of the T-cell antigen receptor and activate T cells at orders of magnitude above antigen-specific activation. This results in the massive cytokine release thought to be the cause of all clinical manifestations of TSS [45]. Several factors support the hypothesis that previous infections, mainly those due to respiratory viruses such as adenovirus, rhinovirus, influenza, and bocavirus, may trigger KD development in genetically susceptible children [46, 47]. First, KD can be seasonal and has a greater incidence in late infancy and the preschool years. The epidemiology of KD is quite similar to that of many respiratory viral infections that typically occur during some months of the year. Moreover, it usually occurs in children aged 6 months to 5 years, suggesting maternal antibody protection from the causative agent during the first months of life and the need for a mature immune system to eliminate the infectious agent and avoid uncontrolled responses. Finally, several KD epidemics, as occurs with infectious diseases, have been described [48].

In KD, hyperinflammation is hypothesized to be due to an imbalance between T-helper 17 cells and regulatory T cells [49]. In MIS-C, SARS-CoV-2 is thought to be the trigger [39]. The strict relationship between the virus and MIS-C development is supported by a number of features. Epidemiological studies have shown that clusters of MIS-C mainly occurred in geographic areas with the greatest incidence of SARS-CoV-2 infection [12, 13, 22, 24]. In Bergamo province, an area among those most extensively affected by the COVID-19 pandemic in Italy, the monthly incidence of a disease resembling KD after pandemic development was 30 times greater than monthly reports in the previous 5 years [13]. Similar epidemiological findings were described in the UK [12], France [24], and the USA [22], further confirming the association between MIS-C and SARS-CoV-2 infection. The lack of MIS-C cases in countries such as Japan and China, heavily affected by COVID-19, does not conflict with the association because genetics could explain geographic variations in MIS-C incidence. As demonstrated for KD, hyperinflammation syndromes mainly occur in genetically susceptible children. This supports the hypothesis that the same can also be true for MIS-C. Racial discrepancies in MIS-C incidence, with a higher prevalence among Black, Hispanic, and South Asian populations have been reported [18, 19]. Most of the children (82%) with MIS-C had specific immunoglobulin (IgM) and IgG antibodies against SARS-CoV-2, although only about one-third tested SARS-CoV-2 polymerase chain reaction (PCR) positive on nasopharyngeal swabs [38]. This finding highlights the strict relationship between MIS-C and SARS-CoV-2 and also shows that the new syndrome is not related to the acute early phase of COVID-19 but is a phenomenon that develops during the late post-infectious phase, similar to what is described in adults who experience the so-called cytokine

storm. Evidence that most MIS-C cases are diagnosed 2–6 weeks after SARS-CoV-2 infection confirms this conclusion. It is thought that early infection can trigger macrophage activation followed by T-helper cell activation. This leads to cytokine (TNF-β, IL-1β, IL-4, IL-6, IL-12, IL-23, interferon [IFN]-γ) release; stimulation of macrophages, neutrophils, and monocytes; and activation of B cells and plasma cells with antibody production [50]. Unfortunately, for unknown reasons, a hyperimmune response takes place, as suggested by the fact that children with MIS-C have higher SARS-CoV-2 spike IgG titers than those with severe COVID-19 [51]. Moreover, autoantibodies against endothelial, gastrointestinal, and immune cells are produced [50]. Finally, a hyperimmune response may lead to multisystem damage, as evidenced in animal models infected by coronaviruses with similar characteristics to SARS-CoV-2. In macaques infected with SARS-CoV, the presence of specific anti-spike antibodies before viral clearance is associated with fatal acute lung injury through reductions in the inflammation-resolving response [52].

Furthermore, genetic variations may influence immune system abnormalities. As evidenced in children with KD, genetic variations of genes that regulate clearance of immune complexes or the function of T and B cells can favor hyperinflammation development and explain why only a minority of children with COVID-19 have MIS-C [53]. However, the pathogenesis of MIS-C remains poorly defined, and only further studies can elucidate the mechanisms of inflammation and how they can be modified to avoid the development of MIS-C or reduce its clinical impact.

## 5 Differentiation of MIS-C from Other Known Medical Conditions

The clinical and laboratory similarities between MIS-C and other syndromes characterized by hyperinflammation raises the question of whether this new form could be considered a simple variant of one or is, conversely, an autonomous clinical entity. Differentiation from classic COVID-19 described in children is mainly based on clinical findings and the timing of symptom development versus timing of infection (Table 2).

Pediatric COVID-19 is generally an asymptomatic or mild respiratory disease and develops a few days after infection. Conversely, MIS-C is generally significantly more severe and slowly progresses over days to weeks after initial recovery from COVID-19 illness, although some children do not have prior symptoms of or a positive test for COVID-19 [54]. The greatest doubts have arisen regarding KD for reasons of frequency (i.e., KD, despite being rare, is the most common of the hyperinflammatory syndromes in children) and for the fact that the first cases of MIS-C were described as variants of this syndrome. Although some patients with MIS-C have demographic, clinical, and laboratory characteristics that allow their inclusion among KD cases, a great number differ significantly, suggesting that MIS-C could be a separate entity and not a manifestation of KD. The mean age of children with KD is lower than that of those with MIS-C. About 80% of KD cases involve children aged < 5 years, whereas most MIS-C cases occur in school-age children. Moreover, the incidence of KD is very high in some Asian countries, including China and Japan, whereas MIS-C is not common, despite the high incidence of SARS-CoV-2 infection there. KD mainly affects vessels, particularly coronary arteries, skin, oral, and ocular mucosae, and cervical lymph nodes, although involvement of other organs and body systems has been repeatedly described [55]. The complete KD clinical picture is very different from that found in patients with MIS-C. Gastrointestinal manifestations occur in only about 30% of patients, less than half of that in patients with MIS-C. Similar differences were reported for heart manifestations, which are more frequent and more severe in MIS-C than in KD; ventricular dysfunction and ischemic damage are rare in KD [56]. The only exceptions are coronary artery abnormalities, which are more common in KD (about 35%, roughly double of that of MIS-C cases) [57]. All these differences are clearly reported by a couple of studies showing that cardiovascular manifestations of MIS-C fulfill criteria for KD, including incomplete cases, in only 25% [58] and 66% of patients [54].

Laboratory findings for MIS-C are also quite different from those generally reported in KD [32, 37–40]. Despite leukocytosis with neutrophilia being common in both conditions, leukopenia is rare in KD. Platelet count is increased in KD, ranging from 500,000 to > 1 million/mm$^3$, whereas it remains within normal limits or is slightly reduced in MIS-C. Conversely, several laboratory markers that are significantly increased in MIS-C are within the normal range or only slightly increased in KD. These include markers that suggest heart damage (troponin and proBNP), renal insufficiency (creatinine), and coagulation system alterations (prothrombin time, partial thromboplastin time, and D-dimer serum level) [37–40]. Finally, inflammatory markers such as CRP are increased in both conditions but are higher in MIS-C than in KD [32].

Differentiation of MIS-C from KD can be more difficult when KD is complicated by shock (KDSS) or by MAS. In these children, many clinical and laboratory manifestations are quite similar to those characteristic of MIS-C. KDSS is relatively uncommon in patients with KD, as evidenced by a study that found it in only 138 of 9488 children with KD [59]. However, these patients, like those with MIS-C, frequently present with gastrointestinal symptoms and have

an increased risk of heart complications [60]. Impaired left ventricular systolic function and mitral regurgitations were detected in 31 and 39% of KDSS cases, respectively, compared with 4 and 2% of patients with KD without shock. Moreover, children with KDSS, again like many with MIS-C, have a larger proportion of neutrophils, higher CRP serum levels, lower hemoglobin concentrations and platelet counts, and increased D-dimer serum levels. Finally, responses to first-line therapy are frequently poorer than in children with KD without shock [61]. Even in cases of KD complicated by MAS, clinical and laboratory manifestations can mimic MIS-C [62]: MAS occurs in 2–5% of children with KD and can complicate infectious diseases other than COVID-19 as well as malignancy and rheumatologic diseases. However, when MAS accompanies SARS-CoV-2 infection, development of cytokine storm and related clinical manifestations can occur both in the first phase of COVID-19 and during the post-infection period, as it occurs when it is associated with KD.

In some cases, MIS-C may resemble TSS. Differences in the infectious agent triggering the hyperinflammation is a basic element for differentiation. Most MIS-C cases have negative blood cultures, and no evidence currently suggests that staphylococcal or streptococcal toxins can cause MIS-C [45].

Further elements for differentiation of MIS-C from other similar conditions can be derived by careful study of immune system cells and inflammatory markers during the acute phase of all these syndromes. Lee et al. [58] compared MIS-C cases with historic cohorts of MAS. Despite the significant increase in cytokines in all patients, the increase in sIL-2R was less striking in MIS-C, whereas IL-18 and C-X-C motif chemokine ligand 9 (CXCL9) levels were only mildly elevated in several patients with MIS-C. Diorio et al. [54] prospectively studied children classified as having MIS-C and children with COVID-19 with either minimal or severe disease. They found that concentrations of IL-10 and TNFα could allow differentiation of MIS-C from severe COVID-19. The levels of these cytokines were significantly higher in MIS-C than in severe COVID-19. Consiglio et al. [63] analyzed blood immune cells, cytokines, and autoantibodies in healthy children, children with KD enrolled prior to COVID-19, children infected with SARS-CoV-2, and children presenting with MIS-C. They found that the inflammatory response in MIS-C differed from that in severe acute COVID-19 in adults and was more similar to KD, although with some relevant differences. In particular, IL-17A levels were higher in KD than in MIS-C or in SARS-CoV-2. Moreover, autoantibodies against proteins that play a role in heart and blood vessel formation were more common in MIS-C. Similar findings were reported by Gruber et al. [50] who evaluated eight patients with MIS-C compared with healthy controls, patients with COVID-19, or convalescent individuals and identified enhanced expression of pro-inflammatory cytokines and chemokines in MIS-C. Patients with MIS-C also had reduced numbers of immune cell types such as monocytes and T cells in peripheral blood, likely due to migration of these cells to inflamed sites.

## 6 Treatment

No universally accepted guidelines yet exist for MIS-C treatment, although a group of experts and scientific societies have published clinical guidance for a rational approach to children with suspected SARS-CoV-2-related hyperinflammation syndrome [64–66]. However, all guidelines highlight the importance of early identification of MIS-C so the best therapy for the patient's clinical condition can be prescribed as quickly as possible. The American College of Rheumatology (ACR) [64] states that MIS-C should be suspected in a child with an epidemiological link to SARS-CoV-2, fever > 38 °C (100.4 °F) and at least two of the following suggestive clinical features: rash, gastrointestinal symptoms, edema of hands/feet, oral mucosa changes, conjunctivitis, lymphadenopathy, and neurologic symptoms. If other causes that may explain this clinical picture can be excluded, a full diagnostic evaluation, including laboratory tests, must be performed to demonstrate hyperinflammation (i.e., complete blood count, CRP, procalcitonin) and body system involvement. Cases with clinical manifestations that completely fulfill the definition of MIS-C should be hospitalized for more extensive workup [64–66]. In particular, the ACR suggests hospitalization of children presenting with abnormal vital signs (tachycardia, tachypnea), respiratory distress of any severity, neurologic deficits or change in mental status (including subtle manifestations), evidence of even mild renal or hepatic injury, markedly elevated inflammatory markers (CRP ≥ 10.00 mg/dL), or abnormal ECG, pro-BNP, or troponin [64].

Treatments that are generally recommended for conditions mimicking MIS-C in some aspects, or that have been suggested for COVID-19, are the basis for all protocols (Table 4). The type of supportive care depends on the type and severity of clinical manifestations. According to the recommendations of The Royal College of Paediatrics and Child Health [15], supportive care must be agreed with the experts who should take care of these patients, including PICU, pediatric infectious diseases, immunology, and rheumatology teams. Vital signs, hydration, electrolytes, and metabolic status must be carefully monitored; fluid resuscitation, inotropic support, respiratory support and, in rare cases, ECMO can be used in case of deterioration. Patients with shock should be treated with volume expansion using Plasma-Lyte or Ringers lactate [67]. If hypotension is fluid resistant, vasopressors such as epinephrine or norepinephrine should be added. Given the

**Table 4** Recommended treatment for multisystem inflammatory syndrome in children

| Condition | Therapy |
|---|---|
| If MIS-C is diagnosed | IVIG 2 g/kg (single infusion) ± 3-day intravenous methylprednisolone<br>+ |
| In case of shock | Volume expansion using Plasma-Lyte, Ringers lactate; if fluid-resistant hypotension occurs, add epinephrine or norepinephrine |
| In case of elevated D-dimers | Anticoagulant (no agreement on which drug) |
| In case of specific cytokine storm | Anakinra (IL-1 receptor antagonist), tocilizumab (IL-6 inhibitor), infliximab (monoclonal antibody against TNFα) |
| Most severe cases | Remdesivir |

*IL* interleukin, *IVIG* intravenous immunoglobulin, *MIS-C* multisystem inflammatory syndrome in children, *TNF* tumor necrosis factor

clinical and laboratory similarities with several inflammatory processes, direct care of MIS-C is based on similar protocols. Use of intravenous immunoglobulin (IVIG), steroids, aspirin, and anticoagulation treatment is generally recommended at the same dosages that are usually administered to children with KD. Hennon et al. [65] prepared a guideline based on recommendations from the CDC, the New York State Department of Health, and the Royal College of Pediatrics and Child Health. These guidelines suggest that IVIG 2 g/kg and aspirin 20–25 mg/kg/dose every 6 h (80–100 mg/kg/day) are the first treatment choice for all patients with KD-like illness, evidence of excessive inflammation (ferritin > 700 ng/mL, CRP > 30 g/dL, or multisystem organ failure), or cardiac involvement [65]. Patients with KD-like illness in high-risk categories (infants, KDSS, CRP > 130 g/dL, aneurysms, Asian race) should receive IVIG 2 g/kg as a single infusion with a 3-day pulse methylprednisolone. Similar suggestions were made by a multidisciplinary team from the UK [66], which recommended that children at higher risk (aged < 12 months and those with coronary artery changes) should be given early intravenous methylprednisolone 10–30 mg/kg alongside IVIG. Methylprednisolone remains the second therapeutic choice for children who do not respond to early administration of IVIG alone. However, not all children with MIS-C are treated according to these suggestions. A review of studies published from 1 December 2019 to 31 May 2020 reporting clinical features of children who presented with an inflammatory syndrome related to COVID-19 showed that IVIG and steroids were administered in 63 and 44% of cases, respectively [68]. Immunomodulatory agents effective against single components of the cytokine storm should be considered as a third-line option in children who do not respond to IVIG and methylprednisolone. They were given in a few cases, but no consensus has been reached on how and when these agents should be administered [27, 35]. Use of an IL-1 receptor antagonist (anakinra), an IL-6 inhibitor (tocilizumab), and a chimeric IgG1κ monoclonal antibody specific for human TNFα (infliximab) was reported in 6%, 6%, and 4% of cases, respectively [69]. In the presence of elevated D-dimers, anticoagulants can be suggested, but there is no general agreement on which drug should be prescribed or the duration of treatment.

In the most severe cases, administration of drugs that have been found effective in at least some cases of COVID-19, such as remdesivir, could be considered. Remdesivir is an antiviral that can reduce the duration of COVID-19 illness in adults [69]. Theoretically, this drug could be effective in the minority of children with severe MIS-C, acute SARS-CoV-2 infection, and virus still detectable by PCR. However, no clinical evaluation of remdesivir in children with MIS-C is presently available, and it has been suggested that, to collect reliable data on its true efficacy and safety, it should be given only in the context of a clinical trial. The same conclusions should be drawn for the use of corticosteroids to reduce manifestations of hyperinflammation. Corticosteroids have been effective in reducing 28-day all-cause mortality in critically ill adult patients with COVID-19 [70]; however, although they are frequently used for MIS-C management, no data are yet available in children with MIS-C enrolled in controlled studies.

Antibiotic coverage should be administered in cases resembling severe bacterial sepsis but must be withdrawn when cultures are negative and superimposed bacterial infections are excluded. Metronidazole has been suggested for severe gastrointestinal problems [65]. Although most children with MIS-C are seriously ill, treatment is generally effective and, even if they are admitted to the PICU, they are generally discharged within a week. Although mortality in children with MIS-C is higher than that reported in pediatric patients with COVID-19, it does remain low. In two independent systematic reviews involving 622 [71] and 570 [37] patients, the mortality rate was 1.8 and 1.7%, respectively, compared with < 1% for pediatric patients with COVID-19 [5].

## 7 Conclusions

Currently available results from studies of MIS-C clearly indicate that our knowledge of this new syndrome is grossly incomplete. Several findings seem to indicate it is an autonomous clinical manifestation, but this is not definitively established as in some cases differentiation from COVID-19, KD, TSS, and MAS is not possible. Its development in strict relation with SARS-CoV-2 infection seems documented, and MIS-C can be considered a post-infectious manifestation secondary to an abnormal immune response in most cases. However, in some cases, a clinical picture with symptoms fulfilling criteria for MIS-C diagnosis develops during the acute phase of SARS-CoV-2 infection, and symptoms in these patients could simply be related to the direct damage of the virus. Moreover, in some children, symptoms of disease completely overlap those of KD, TSS, and MAS, making it practically impossible to distinguish MIS-C from these other conditions with hyperinflammation. More knowledge on the pathophysiology of MIS-C compared with that of KD, TSS, and MAS is needed to solve this problem.

It is highly likely that the criteria currently used to diagnose MIS-C are too broad and that this allows inclusion of children with different diseases. Together with cases that overlap with acute COVID-19 cases, several MIS-C cases could be considered KD in children with contemporaneous SARS-CoV-2 infection. Further studies leading to an unbiased analysis of clinical signs and symptoms of MIS-C are needed to definitively establish patients with true MIS-C. Whether a genetic susceptibility to MIS-C exists is unknown, and this is a very important limitation that must be addressed if children who are at greater risk of MIS-C development are to be identified early. Moreover, the long-term prognosis for those with MIS-C is not completely defined, and this requires not only a precise identification of true MIS-C cases but their long-term follow-up after diagnosis. As there is no clarity on the pathogenesis of MIS-C, no specific therapy is currently available.

In conclusion, further studies are urgently needed for a better definition of MIS-C, its true impact on child health, the best clinical and therapeutic approach, and its true prognosis. Much more information is needed for complete comprehension of this new phenomenon.

## Declarations

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