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Review Article

Comparison of the Epidemiology, Clinical Features and Treatment of the Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 Infection: Data from Five Countries from Five Continents

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Abstract

Multisystem inflammatory syndrome in children (MIS-C), or pediatric inflammatory multisystem syndrome (PIMS/PIMS-TS), or systemic inflammatory syndrome in COVID-19 (SISCoV), is a rare systemic illness involving persistent fever and extreme inflammation following exposure to SARS-CoV-2. This is a dysregulated autoimmune-mediated illness following COVID-19 with an interval of 2 - 6 weeks. Despite 5 years of intensive study, there is still no widespread definition of this condition. In the majority of studies researchers are using the definition of the Centers for Disease Control and Prevention (CDC) - Multisystem inflammatory syndrome in children (MIS-C). Median age of patients with MIS-C is 6 - 11 years. Most common manifestations are involvement of respiratory and neurological system, gastrointestinal tract, cardiovascular, hematological and mucocutaneous system. Although clinical manifestations vary in different countries. The mortality rate is 1 - 3%, but there is also significant difference between countries. Management of MIS-C are almost similar to that of Kawasaki disease and mostly consisted to intravenous immunoglobulin, corticosteroids and antibiotics, but again in different countries there are different tactique in management of MIS-C. The main aim of this review article is to show difference in clinical presentations and treatment recommendations in different countries from five continents.

Keywords: *SARS-CoV-2; Multisystem Inflammatory Syndrome in Children (MIS-C); Epidemiology; Children; Clinical Manifestation; Treatment*

Introduction

Since December 2019, the global outbreak of New Coronavirus disease (COVID-19), which was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide. Although fever, dry cough, fatigue, and myalgia were the predominant symptoms of acute COVID-19, more serious complications were later registered after initial stage of the disease. Children, similar to adults, can experience significant long-term effects from COVID-19. Pediatric Long COVID-19 can lead to substantial disabilities, even in previously healthy children, and encompasses a range of symptoms from mild to severe infections [1].

Multisystem inflammatory syndrome in children (MIS-C) is a condition that affects children 2-6 weeks after acute SARS-CoV-2 infection. It shows a predominance in male individuals [2-4]. In the first period of pandemic - in 2022 the median age of MIS C patients was 9 years, one year later, in the period of Omicron variant, the median age decreased to 7 years [5]. The first cases of this syndrome were described in

Italy in 2020, when Verdoni and colleagues presented seven boys and three girls aged 5-7 years with a Kawasaki-like disease [6]. In 2020 there were reported more cases of children with a Kawasaki-like disease accompanied by prolonged fever, rash, and conjunctivitis [7].

Similar cases later appeared worldwide, and this potentially life-threatening condition was named multisystem inflammatory syndrome in children (MIS-C) by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). The disease usually begins 2-4 weeks after SARS-CoV-2 infection in children 6 months to 17 years of age. This unexpected presentation in previously healthy children challenges current understanding and highlights the unpredictable nature of SARS-CoV-2, which can lead to severe complications even in those without prior health issues [8].

There is no consensus in MIS-C case definition. This emerging condition has been defined differently (using different names), by the World Health Organization (WHO) - Multisystem inflammatory syndrome (MIS) in children, the Centers for Disease Control and Prevention (CDC) - Multisystem inflammatory syndrome in children {MIS-C) and the Royal College of Pediatrics and Child Health (RCPCH) - Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS).

Diagnoses of MIS-C cases mostly based in CDC and WHO criteria and different countries are using different definitions.

Based on the CDC's initial definition [9], to diagnose MIS C ALL 5 of these things should exist:

1. An individual aged <21 years.
2. Presenting with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours).
3. Laboratory evidence of inflammation (Including one or more of the following: an increased CRP, erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, LDH or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin, and evidence of clinically severe illness, which requires hospital admission and with more than two organs (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) involvement.
4. No alternative plausible diagnoses.
5. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

According to the WHO [10], case definition of MIS C is:

Children and adolescents 0-19 years of age with fever ≥ 3 days

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP).
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive) or likely contact with patients with COVID-19.

Since MIS-C was identified, discussions about pathogenesis, clinical symptoms, diagnostic studies and treatment of MIS-C have continued among professionals worldwide [11-18]. Therefore, the geographic, genomic, and ethnic distribution of children with MIS-C should be considered to identify accurate diagnostic criteria and optimal treatment guidelines.

Africa

Marocco [19]

52 Moroccan children with MIS-C for a 3-year period (March 2020-March 2023) was conducted. The data was collected at the Infectious Diseases and Clinical Immunology Department of the Mother and Children's Abderrahim Harrouchi University Hospital in Casablanca.

The selection of patients for the study adhered to the MIS-C inclusion criteria as outlined by the WHO. Following conditions were selected for inclusion (all criteria must be met): 1. Age from 0 to 19 years, 2. Fever for ≥3 days, 3. Clinical signs of multisystem lesion (at least 2 of the following): Rash, bilateral non-purulent conjunctivitis, or signs of inflammation of the skin and mucous membranes (oral, hands, or feet); Hypotension or shock; Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities; Signs of coagulopathy (prolonged prothrombin time (PT); elevated D-dimer); Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain); Elevated inflammatory biomarkers (ESR, CRP, or Procalcitonin). 5. Signs of previous acute COVID-19.

In this study, the median age was 6 years (IQR: 1-14 years), sex ratio was 1.16 (28 boys and 24 girls). COVID-19 contact was identified in 17 patients (33%). The median duration of hospital admission was 7 days. As for clinical manifestations, this most common was fever in 52 cases (100%), followed by rash in 42 cases (80%), respiratory symptoms in 30 cases (58%), and gastrointestinal symptoms in 23 cases (44%). Shock was diagnosed in 9 cases (17%) and neurological signs were present in 4 cases (8%). In 9 patients signs of macrophage activation syndrome, such as splenomegaly and hepatomegaly were presented. The positive SARS-CoV-2 PCR was shown in 10 patients (19%). Serology study was positive in 42 cases (81%), among them anti-SARS-CoV-2. Ig M positive in 25 cases (48%) and Ig G positive in 31 cases (60%). In echocardiography myocarditis with a reduced left ventricular ejection fraction (25%-30%) in 6 patients (12%) was shown.

The management protocol included intravenous human immunoglobulin (2 g/kg/day) in combination with intravenous methylprednisolone and this method was used for all patients. Boluses of corticosteroids were additionally administered to 17 patients (32%), including 3 cases of myocarditis, 2 cases of acute kidney injury, 3 cases of disturbed consciousness, and 9 cases of macrophage activation syndrome. When clinical signs and inflammatory syndrome persisted a second course of immunoglobulin was administered in 2 patients.

For septic shock patients received intravenous. ceftriaxone. In patients with myocarditis fluid restriction, diuretics, and a converting enzyme inhibitor (captopril) were administered.

Europe

Lithuania [20]

In Lithuania a single-center, partly retrospective, partly prospective observational cohort study was performed from December 2020 to June 2024. Patients were recruited at the Vilnius University Hospital Santaros Klinikos, which was a main hospital for patients with MIS-C in the northeast Lithuania.

The study included patients from 1 month to 18 years who met the national diagnostic criteria of MIS-C, adapted from the WHO and CDC: fever ≥ 38.0°C for ≥24h; new onset manifestations in at least two different organ systems (gastrointestinal, mucocutaneous, cardiovascular, respiratory, renal, neurological and hematological); evidence of COVID-19 (RT-PCR or serology positive); laboratory evidence of inflammation; exclusion of an alternative diagnosis.

The most common signs and symptoms were selected: gastrointestinal (abdominal pain, diarrhea, vomiting, abnormal liver function tests, colitis, ileitis and ascites), mucocutaneous (conjunctivitis, periorbital swelling/redness, mucus membrane changes, strawberry tongue, rash, lymphadenopathy, swollen hands and feet), cardiovascular (tachycardia, high blood pressure, arterial hypotension, shock), respiratory (cough, sore throat, oxygen requirement, patchy infiltrates, pleural effusion), neurological (headache, confusion, irritability, reduced level of consciousness/lethargy, syncope), renal (renal function impairment, decreased diuresis, urine sedimentation abnormalities), other (arthralgia, myalgia).

MIS-C patients were divided into three subgroups based on clinical syndromes: MIS-C with shock; Kawasaki-like disease (KD; patients with fever, lymphadenopathy, mucocutaneous and cardiovascular involvement); undifferentiated MIS-C (patients with fever and inflammation who did not meet either KD criteria or symptoms of shock).

MIS-C diagnose was established in 51 patients. Forty-two children were included in the final analysis. Of these, three patients with comorbidities died.

All enrolled patients were Caucasian, male sex was predominant (73.8%, n = 31). Age ranges from 9 months to 16 years. The median age - 6.5 years. All patients had fever. The predominant symptoms were cardiovascular (88.1%, n = 37), mucocutaneous (85.7%, n = 36) and gastrointestinal (76.2%, n = 32). Two organ systems involved was established in eight patients (19.1%). Majority of patients (69.0%, n = 29) had symptoms involving three or four organ systems and five patients (11.9%) had more extensive involvement.

Most patients were treated with IVIG (92.9%, n = 39) and GCC (81.0%, n = 34). Majority of patients (32 patients, 76.2%) were managed by a combination of IVIG and GCC and 7 patients received intravenous IG alone, 2 patients received steroids alone and in one patient only symptomatic treatment was prescribed. Eleven patients (26.2%) received oxygen therapy for average from 1 to 5 days period. In five patient vasoactive drugs were administered.

America

Peru [21]

In Peru an observational, descriptive and retrospective study was conducted. The study included patients with MIS-C, which were hospitalized between April 2020 and December 2022 at the Instituto Nacional de Salud del Niño-Breña (INSN-B) in Lima, Peru.

MIS-C was diagnosed based on World Health Organization (WHO) criteria.

The following factors were analyzed: age, sex, home contact with SARS-COV-2 infected person, type of SARS-CoV-2 test, comorbidities, time of illness, gastrointestinal symptomatology (abdominal pain, vomiting, diarrhea, nausea), mucocutaneous (polymorphous exanthema, conjunctival injection, edema of palms and soles, desquamation of fingers and cervical lymphadenopathy), respiratory, neurological and clinical phenotype (fever and inflammation, similar to KD and shock).

The variables were analyzed according to the first three waves of COVID-19 (first: March - December 2020, second: January - September 2021, third: December 2021 - January 2022).

The median age of the patients was 6 years. Patients age was higher in the second and third waves. Five participants (6.9%) were less than one year old, 23 (31.5%) one to four years, 32 (43.8%) five to nine years and 13 (17.8%) older than 10 years. Majority were male and 61 (83.6%) patients had home contact with a person infected with coronavirus. Majority of the patients (83.6%) had any positive SARS-CoV-2 test, while 12 had negative tests, but positive home contact to coronavirus. Two patients had comorbidities (one neurogenic bladder and one unilateral hydronephrosis). The median time of illness was longer in the third wave (5 days).

Gastrointestinal and mucocutaneous symptoms were more frequent during all three waves. Similarly, KD-like phenotype was frequent in all three waves, while respiratory and neurological symptoms were frequent during the second wave. The KD-like phenotype was reported in 34 (46.6%) patients followed by the shock phenotype in 21 (28.8%) patients.

Intravenous human immunoglobulin was administered to all patients during the first wave with a dose of 1 to 2 gr/kg (dose range from 9 grams to 100 grams). Methylprednisolone was more frequently used during the second wave. The dose was 1-2 mg/kg for five days. Pulse dose - 10-30 mg/kg for three days was administered in 14 patients with signs of clinical deterioration. Acetylsalicylic acid was used in 69 (94.5%) patients, and in 57 patients (78.1%) antibiotics were administered.

Asia

Iran [13]

In Iran a retrospective study was performed. MIS-C was defined according to the Centers for Disease Control and Prevention (CDC). Three pediatric hospitals were located within the most active COVID-19 pandemic areas (Tehran, Qom and Mazandaran) in Iran.

Patients with MIS-C were distributed into three groups including Kawasaki-like, toxic shock-like and sepsis-like disease. Kawasaki-like disease was defined as the presence of fever for ≥3 days but ≤10 days and who fulfilled ≥4 of 5 diagnostic criteria (rash, conjunctival injection, cervical lymphadenopathy, changes in the oral mucosa and changes in the extremities) or three criteria plus coronary artery abnormalities based on echocardiography. Toxic shock-like disease was diagnosed in patients with cardiovascular dysfunction, included basal systolic blood pressure of at least 20%, or the appearance of signs of peripheral hypoperfusion and sepsis-like was defined as severe organ dysfunction.

Forty-five children who met MIS-C criteria were included in the study, which was performed in period between 7 March and 23 June 2020,

The median age of the patients was 7 years (range from 10 months to 17 years) and majority of them were male. Comorbid conditions were presented in six (13%) patients, included acute lymphocytic leukemia, chronic kidney disease, underlying seizure disorder, cerebral

palsy, cardiovascular disease and Budd-Chiari syndrome. Common symptoms were fever (91%), abdominal pain (58%), nausea/vomiting (51%), mucocutaneous rash (53%), conjunctivitis (51%) and hands and feet oedema (40%). The median duration of symptoms prior to presentation was 5 days.

Most patients with MIS-C showed Kawasaki-like disease (n = 31, 69%), toxic shock-like disease was observed in 11% (n = 5) patients and sepsis-like diseases in 20% of the cases (n = 9). In patients with Kawasaki-like and sepsis-like disease abdominal pain was observed more frequently compared to the toxic shock-like disease.

In twenty-seven patients (60%) methyl prednisone (dose range, 2-30 mg/kg per day) was administered, while in 18 patients (48%) intravenous immunoglobulins (dose range, 2-4 g/kg) was prescribed. Five patients (11%) died; four of them had different underlying diseases. Among these five patients, sepsis-like disease was diagnosed in two cases and toxic shock-like disease in three cases.

Australia

There are no published articles about MIS-C in Australia. Based on information from different web sources, as fir August 2025 there were 213 cases of MIS-C in Australia (in Australian definition - Pediatric Inflammatory Multisystem Syndrome PIMS-TS), Median case age - 7.8 years, youngest case - 3 months, oldest case 16 years; 40% female, 60% Male [22].

We found one Australian guideline "Pediatric Inflammatory Multisystem Syndrome Temporally Associated with COVID-19", published by Children's Health Queensland Hospital and Health Service [23].

In this guideline PIMS-TS described as a patient with persistent fever, elevated inflammatory markers, such are neutrophilia and elevated CRP) and clinical signs and symptoms of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder).

Three different cohorts are selected: Shocked cohort: Median age 10.5 years, clinically abdominal pain, diarrhea +/- rash/erythema, raised inflammatory markers, raised cardiac enzymes, echo - ventricular dysfunction and coronary artery aneurysm. Kawasaki like disease cohort: Median age 8 years, clinically meet American Heart Association criteria - 4/5, mucocutaneous features, raised inflammatory markers, milder increase cardiac markers, echo - rare ventricular dysfunction +/- coronary artery aneurysm. Febrile and inflammatory cohort: Median age 10 years, range of features including abdominal pain, diarrhea, mucocutaneous features, tachycardia common and mild hypotension, raised inflammatory markers and cardiac enzymes, echo - mild ventricular dysfunction +/- coronary artery aneurysm.

For treatment empiric antibiotics should include a toxin mediating antibiotics. For example: Cefotaxime, alternative: Ceftriaxone. Or Lincomycin, Alternative: Clindamycin.

As for Immunomodulatory therapy**:** Any child being considered for immunomodulatory therapy should be discussed at an MDT with immunology, rheumatology, general pediatrics, pediatric infectious diseases specialist and intensive care. There is no evidence so far to suggest that recovery from PIMS-TS is modified by treatment with IVIG alone, IVIG plus glucocorticoids or steroids alone.

First line therapy: Intravenous immunoglobulin 2 gram/kg. In PIMS-TS shock (need for vasoactive support) add: Methylprednisolone 10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days and then Prednisolone oral/enteral 2 mg/kg once daily (maximum 60 mg/day). Reduce dose every 3-5 days over a total of 2-3 weeks.

Note 1: Alternative to IVIG: Methylprednisolone [10 mg/kg IV once daily (Maximum 1000 mg/day) for 3 days] may be used alone as first line in PIMS-TS shock > 5 years and if concern re adverse impact of IVIG fluid volume).

Note 2: Steroids alone may be used as first line treatment in PIMS-TS undefined inflammatory presentation: Methylprednisolone 2 mg/kg IV once daily (Maximum 200 mg/day) for 3 days; after MDT discussion.

Second line therapy: Intravenous steroids should be considered in children unresponsive to intravenous immunoglobulin (continued fever, clinical or laboratory signs of inflammation) 24 hours after administration of IVIG. Methylprednisolone - 10 mg/kg IV once daily (Maximum 1000 mg/day) for 1 to 3 days and then prednisolone oral/enteral 2 mg/kg once daily (maximum 60 mg/day), reduce dose every 3-5 days over a total of 2 to 3 weeks.

Third line therapy: MDT to consider using Infliximab in patients with PIMS-TS refractory to the first- and second-line therapy with IVIG and corticosteroids. Alternative causes should also be excluded. Dose: Infliximab 5 mg/kg IV as a single dose. If deterioration or no improvement and continued signs and symptoms of inflammation: Anakinra 2 mg/kg/dose (maximum 100 mg/dose) by subcutaneous injection every 6 hours on day 1, every 8 hours on day 2, every 12 hours on day 3, every 24 hours days 4 to 5.

Discussion

Although rare, Multisystem inflammatory syndrome in children can be serious condition, with different degrees of severity, from a mild, self-limited systemic inflammation to severe disease with shock or/and cardiac insufficiency, and even death in very rare clinical cases. Despite 5 years of intensive study, there is still no widespread definition of this condition. It's clear that countries are using different definitions of MIS C. In Marocco and Peru are using WHO definition is clinical practice, in Iran - definition of the CDC, in Lithuania - adapted definition based on WHO and CDC recommendations, in Australia - country specific definition. This is not just matter of different definition, this is a matter of timely diagnosis and treatment. For example, if you are using WHO criteria and fever lasts 48 hours, even in case of classical clinical symptoms and lab date, you could not classify this condition as a MIS C, because according to the WHO in patients with MIS C duration of fever should be more than 72 hours. But if you are using CDC criteria, you could classify this case as MIS C and can start appropriate treatment.

In all studies patients were in the same age group: In Marocco - 6 years, in Lithuania - 6.5 years, In Peru - 6 years, In Iran - 7 years and in Australia 7.8 years.

In all studies MIS C was more predominant in male patients.

There was significant difference in clinical manifestations across studies. In Marocco three most involved systems were mucocutaneus manifestations (80%), respiratory symptoms (58%) and gastrointestinal symptoms (44%.). In Lithuania - cardiovascular symptoms (88%), mucocutaneus manifestations (85%) and gastrointestinal symptoms (76%). In Peru - gastrointestinal symptoms, mucocutaneus manifestations and respiratory symptoms. In Iran - gastrointestinal symptoms (58%), mucocutaneus manifestations (53%) and hands and foot oedema (40%).

In some countries MIS-C patients were divided by groups based on clinical duration of illness. In Lithuania - MIS-C with shock; Kawasaki-like disease and undifferentiated MIS-C [20]; in Iran - Kawasaki-like, toxic shock-like and sepsis-like [13]; In Australia - Shocked cohort, Kawasaki like disease cohort, Febrile and inflammatory Cohort [23].

Some differences can be found in treatment options. In Marocco all MIS C patients are managed by combining treatment with intravenous immunoglobulin and intravenous corticosteroids. In Peru - intravenous immunoglobulin was used in 96% of cases. In Iran - intravenous corticosteroids were used in 60% of patients and intravenous immunoglobulin in 48% of patients. In Australia the first line therapy is intravenous immunoglobulin [24].

Conclusion

Multisystem inflammatory syndrome in children associated is a newly emerged pediatric syndrome. Even though the clinical expression of COVID-19 during the Omicron period, became significantly milder over time, no evident changes in the presentation and severity of MIS-C was shown. Therefore it is crucial to have clear knowledge in definition, clinical presentation and treatment of MIS-C. Almost 5 years later after the first case of MIS-S was described, no consensus exists in definition and treatment of this condition and frequency of clinical manifestations varies across countries. Strict international recommendations are required to provide medical workers for timely diagnoses and effective management of this disease.

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