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SPECIAL FEATURE: SPECIAL ARTICLE

Anesthesia in the Time of COVID-19

# Multisystem inflammatory syndrome in children during the coronavirus disease pandemic of 2019: a review of clinical features and acute phase management

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## Abstract

The current coronavirus disease of 2019 (COVID-19) pandemic has presented unique health challenges in the pediatric population. Compared to adults, the most significant change in viral disease manifestation is encompassed by the multisystem inflammatory syndrome in children (MIS-C). MIS-C is a new inflammatory syndrome which develops 2–4 weeks after COVID-19 exposure, with evidence suggesting it is a post-infectious immune reaction. We describe its epidemiology, pathophysiology, diagnosis (which varies based on definition used) and treatment options based on published recommendations. A systematic literature search we conducted through MEDLINE yielded 518 abstracts and identified five studies that reported more than 100 cases of MIS-C and their mortality. Most cases developed multiorgan dysfunction, including cardiovascular, dermatologic, neurological, renal, and respiratory issues, and required intensive care unit (ICU) admission. Many patients admitted to the ICU needed inotrope support and invasive mechanical ventilation, and the most severe cases required extracorporeal membrane oxygenation support. Most clinicians treated MIS-C with intravenous immunoglobulin, systemic steroids, and biological therapies. Overall mortality was low (2–3%) in all studies. Further research is needed to: understand if early intervention can prevent its progression; optimize its treatment; and improve outcomes of this new syndrome for the patients who develop MIS-C.

**Keywords** MIS-C · COVID-19 · Shock · Children

## Introduction

The current coronavirus disease of 2019 (COVID-19) pandemic has presented unique health challenges in the pediatric population [1]. Compared to adults, the most significant change in viral disease manifestation is encompassed by the multisystem inflammatory syndrome in children (MIS-C). The syndrome consists of a collection of primarily hyperinflammatory pathologies that can involve multiple organs, but most significantly affects the cardiovascular, hematologic, and gastrointestinal systems [2]. Riphagen et al. first reported MIS-C cases in eight previously healthy children with hyperinflammation and shock, who presented with symptoms similar to those of Kawasaki disease, including coronary vasculitis [3]. Given the non-specific constellation of symptoms and lab findings involved in the syndrome (and the need for a positive COVID-19 test), both diagnosis and treatments, including resuscitation, have presented

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challenges. This special article describes the epidemiology, pathophysiology, diagnosis, and detailed treatment of MIS-C based on published studies and case reports. We also present updated evidence of clinical outcomes in children with MIS-C based on a systematic literature search, and discuss future clinical and research implications.

## Epidemiology

Overall incidence of COVID-19 in children has been reported to be low (5%, 36 pediatric cases out of 661 adult and pediatric cases with COVID-19) [4]. Beyond a lower overall incidence, lower respiratory tract infection also tends to manifest less severe symptoms in children compared to adults [4–7]. While only a small percentage of pediatric patients require ICU admission (1.7%) [6], a large portion of children that do require ICU care possess comorbidities (83%), including medical complexity, immune suppression/malignancy, and obesity [7].

A strong epidemiologic association exists between COVID-19 and a hyperinflammatory response which develops in some children, defined as MIS-C. Clinically, MIS-C manifests 2–4 weeks after COVID-19 exposure, although the percentage of cases where the virus was detected by reverse transcriptase polymerase chain reaction is low (14.5–51%), while the percentage of positive serology is high (31–99%) [2, 8–12]. Based on a New York State study, the total incidence of MIS-C was low at 2 per 100,000 persons, while laboratory-diagnosed COVID-19 in children was 322 per 100,000 persons [8], illustrating the relative rarity of the hyperinflammatory condition. Most children who develop MIS-C have been previously healthy (78%), yet a majority of cases required ICU admissions (21–80%) [2, 8–12].

## Pathophysiology

The pathophysiology of MIS-C is not yet completely established. The initial phase starts with the virus invading into the respiratory tract through the angiotensin-converting enzyme-2 (ACE-2) receptor. Often, COVID-19 fails to progress beyond asymptomatic or minimal symptoms in children, probably due to lower expression of ACE-2 receptor (compared to adults) [13]. Given the time delay to presentation (2–4 weeks after viral symptoms), MIS-C is likely related to a post-infectious immune response, rather than a direct pathology of the virus. Several hypotheses of the pathophysiology of MIS-C have been advocated, including a delayed dysregulated immune response and superantigen activity. MIS-C may result from coronaviruses' ability to block type I and type III interferon responses [14], leading to a profound cytokine storm. One study noted that elevated interleukin (IL)-10 and tumor necrosis factor-α (TNF-α) levels were more common in MIS-C patients, over those with just severe COVID-19 disease [15]. This same study found that MIS-C patients were more likely to have burr cells present on peripheral blood smears. A study of structure-based computational models by Cheng et al. demonstrated that the severe acute respiratory syndrome coronavirus 2 spike glycoprotein is similar to the bacterial superantigen staphylococcal enterotoxin B [16].

The pathophysiology of damage across affected organ systems (cardiovascular, dermatologic, neurological, renal, and respiratory systems) can be multifactorial, including secondary to hypovolemia, low cardiac output state, vasculitis, microthrombus, edema, or inflammation. Most common cardiovascular involvement is shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation [17]. Cardiac involvement can result from a combination of inflammation, microthrombus, and myocardial edema. Acute kidney injury is secondary to hypovolemia or a low cardiac output state, or directly related to vasculitis or inflammation [18]. Respiratory failure can result from a combination of pulmonary edema and acute respiratory distress syndrome secondary to inflammation. With multiple organ systems often involved, MIS-C usually develops a mixed shock clinical picture, consisting of components of cardiogenic, hypovolemic, and distributive shock.

## Diagnosis

The most common symptoms of MIS-C at presentation are fever, gastrointestinal manifestations (i.e., pain, nausea, vomiting, and diarrhea), oral mucosa changes and rash, although many cases have presented directly with vasodilatory shock [2, 19]. Most patients show remarkably elevated inflammatory makers, including C-reactive protein (CRP), ferritin, and procalcitonin [8]. There are four different definitions of MIS-C from national and international agencies, including the World Health Organization (WHO) [20], the United States Centers for Disease Control and Prevention (CDC) [21], the Royal College of Pediatrics and Child Health (RCPCH, UK) [22], and The Canadian Paediatric Surveillance Program (CPSP) [23] (Table 1). Although slightly different, these definitions rely on a combination of physiological and laboratory findings, in most cases requiring the finding of a COVID-19 infection (past or current). Given the lack of a specific marker or diagnostic test for MIS-C, all definitions require the exclusion of other probable causes. As mentioned, the generalized inflammation can affect multiple organ systems, and a broad scope needs to be used to discover the presence of involvement in any one individual. Cardiac involvement is high, with the potential for life-threatening dysfunction. A large proportion of patients

**Table 1** Comparison of the definitions for multisystem inflammation syndrome in children among four organizations

| | WHO [20] | CDC (US) [21] | RCPCH (UK) [22] | CPSP (Canada) [23] |
|---|---|---|---|---|
| Age | 0–19 years | < 21 years | Child<br>Age not specified | < 18 years |
| Length of fever | ≥ 3 days | ≥ 24 h | Not specified | ≥ 3 days |
| Elevated makers of inflammation[a] | Yes | Yes | Yes | Yes |
| Number of organs involved | ≥ 2 | ≥ 2 | ≥ 1 | Not specified |
| Exclusion of other causes | Yes | Yes | Yes | Yes |
| RT-PCR positive or serology positive or contact with case | Necessary | Necessary | Not necessary | Necessary |

*CDC* Centers for Disease Control and Prevention (US), *CPSP* Canadian Paediatric Surveillance Program (Canada), *RCOCH* Royal College of Paediatrics and Children Health (UK), *RT-PCR* reverse transcription polymerase chain reaction, *UK* The United Kingdom, *US* The United States of America, *WHO* World Health Organization

[a]Markers of inflammation may include C-reactive protein, procalcitonin and ferritin

(39%) develop acute coronary artery abnormalities [10]. Echocardiography to assess heart function and coronary artery anatomy is essential, especially when a patient has known cardiac dysfunction or elevated troponin I and B-type natriuretic peptide (BNP). There is no current understanding if longitudinal follow-up with echocardiography is needed if the initial assessment is negative (as with Kawasaki disease, more below).

Excluding other potential causes of hyperinflammatory illness is essential. MIS-C has overlapping clinical findings with Kawasaki disease, and features similar to septic shock, toxic shock syndrome, macrophage activation syndrome, and enterovirus-causing myocarditis. Excluding ongoing infectious disease is critical since anti-immunomodulating therapy such as systemic steroid and biologic therapies is an important treatment for MIS-C [24]. Kawasaki disease is a syndrome that causes vasculitis in young children (76% of the cases are in children less than 5 years). The diagnosis of Kawasaki disease is based on clinical features, including fever, erythema, strawberry tongue, bulbar conjunctival injection, rash, edema of the hands and feet in the acute phase, periungual desquamation in the subacute phase, and cervical lymphadenopathy [25–27]. The main difference between MIS-C and Kawasaki disease is that individuals with MIS-C are older; more likely to present with shock; have higher white blood cells, CRP, and troponin; have a higher likelihood of cardiac involvement and have a proximal diagnosis of or exposure to COVID-19 [10, 28].

## Treatment

MIS-C is a new syndrome, and there is no standard-of-care treatment yet. Based on clinical experience in the treatment of other disorders with hyperinflammation and vasculitis, assessed treatments include intravenous immunoglobulin (IVIG), systemic steroids, and biological therapies. The latter can include treatments that specifically target IL-1 (anakinra), IL-6 (tocilizumab), and TNF-α (infliximab) [29], or have wider anti-inflammatory effects like convalescent plasma or stem cell injections.

Since MIS-C may involve a variety of organ systems, treatment should be tailored to each case, and a multi-disciplinary approach is crucial. Medications recommended for MIS-C are summarized in Table 2. A local guideline from a pediatric specialty hospital in NY, U.S. recommends treatment with a single dose of IVIG (2 g/kg) and aspirin (20–25 mg/kg/dose every 6 h) for all patients with Kawasaki disease-like illness [30]. The American College of Rheumatology recommends high-dose IVIG (2 g/kg) and low-to-moderate-dose intravenous methylprednisolone (1–2 mg/kg/day) as first-line therapy for MIS-C patients with shock or organ-threatening disease, even before completion of the full diagnostic evaluation. When the disease is refractory to these first-line treatments, high-dose intravenous methylprednisolone (10–30 mg/kg/day) or high-dose anakinra (> 4 mg/kg/day intravenous or subcutaneous) has been used [31]. In a recent systematic review, 76% of patients received IVIG, and 11% required multiple IVIG doses [32]. When a patient is at a high risk of developing coronary aneurysms, it has been suggested that high-dose intravenous methylprednisolone (30 mg/kg/day) should be administered [30]. If the first-line treatments fail, a second dose of IVIG or biological therapies should be considered [30, 33]. However, there is controversy regarding a second dose of IVIG. The American College of Rheumatology does not recommend a second dose of IVIG due to the risk of volume overload and hemolytic anemia associated with high-dose IVIG [31].

A high percentage of children who are admitted to the ICU with MIS-C present in shock (87%), making initial hemodynamic resuscitation efforts key to improving outcomes [9]. Resuscitation can include fluid resuscitation, inotropic support, and invasive mechanical ventilation, with the most severe cases requiring extracorporeal membrane

**Table 2** Summary of treatment for MIS-C proposed by three groups

| | The Rheumatology Study Group of the Italian Society of Pediatrics [33] | American College of Rheumatology [31] | Western New York [30] |
|---|---|---|---|
| IVIG | 2 g/kg/day (up to 70–80 g)[a] | 2 g/kg/day[b] | 2 g/kg/day[c] |
| Corticosteroids | 1) mPSL 1 mg/kg/dose q12h IV[d]<br>2) mPSL 30 mg/kg/dose (max 1 g) q24h IV for 1–3 days<br>3) Dexamethasone 10 mg/m$^2$ q24h | 1) mPSL 1–2 mg/kg/day[e]<br>2) mPSL 10–30 mg/kg/day | Pulse mPSL with taper[f] |
| Aspirin | 5 mg/kg/day for at least 6–8 week[g] | 3–5 mg/kg/day, maximum 81 mg/day[h] | 20–25 mg/kg/dose q6h[i] |
| Anakinra | 1) 4–6 mg/kg/dose q24h SC[j]<br>2) 2 mg/kg/dose (max 100 mg/dose) q6hIV<br>3)2 mg/kg/dose (max 100 mg) IV pulse followed by continuous infusion at a total daily dose of no more than 12 mg/kg or 400 mg | > 4 mg/kg/day IV or SC[k] | Consider when there was a failure of first-line treatment |
| Tocilizumab | In case of acute kidney failure and evidence of microangiopathy | There is insufficient evidence | Not mentioned |
| Infliximab | Dose not mentioned | There is insufficient evidence | Consider when there is a failure of first-line treatment |

*IVIG* intravenous immunoglobulin, *mPSL* methylprednisolone, *IV* intravenous injection, *SC* subcutaneous injection, *MIS-C* multisystem inflammatory syndrome in children, *sHLH* secondary hemophagocytic lymphohistiocytosis

[a]Recommended to be administered over at least 12 h, a second dose of IVIG should be considered in case of inadequate response

[b]A second dose of IVIG is not recommended

[c]Recommend for all patients with KD-like illness, consider a second dose when there is a failure of first-line treatment

[d]1) or 2) should be chosen depending on disease severity, based on clinical/laboratory features, 3) in case of sHLH or central nervous system involvement

[e]1) for the child with shock or organ-threatening disease, 2) for patient requires high-dose or multiple inotropes and/or vasopressors

[f]For myocarditis/cardiogenic shock and/or distributive shock

[g]In case coronary abnormalities are found

[h]Should be used in patients with MIS-C and continues until the platelet count in normalized and normal coronary arteries are confirmed at 4 > weeks after diagnosis

[i]Recommend for all patients with Kawasaki disease-like illness

[j]1) to be used SQ as second line treatment, in case of persistent disease activity 48 h after first-line treatment or in case of sHLH, 2)–3) to be used IV in adjunction to corticosteroids and IVIG in case of severe sHLH or shock with cardiac failure

[k]For patients with refractory to IVIG and glucocorticoids and features of macrophage activation syndrome or for patients with contraindications to long-term use of glucocorticoids

oxygenation support (3.8%) [9]. At this time, no data are available to determine if the use of aggressive non-invasive ventilation can prevent intubation and the need for invasive mechanical ventilation. Given the prevalence of gastrointestinal symptoms, non-invasive ventilation potentially risks aspiration for the patient.

## Summary of clinical outcomes of MIS-C

We conducted a systematic literature search through MEDLINE on December 9, 2020 with an updated search on April 2, 2021, containing sets of terms reflecting our topic of interest, including the disease (COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)), MIS-C, pediatric patients, and large cohort studies, which yielded 518 abstracts (Supplementary online resource 1). From those 518 abstracts, we identified five studies that reported more than 100 cases of MIS-C and their mortality (Table 3).

Three studies used CDC criteria to diagnose MIS-C [2, 34, 35] while other studies applied modified CDC criterion [36], and modified CDC and RCPCH [17]criterion. This variance in diagnostic criteria complicates comparison between studies. That said, most patient cohorts had high rates of cardiovascular involvement, and 30–48% of the cases required inotrope support (Table 3). The most utilized advanced therapy was the administration of IVIG and, despite disease severity, overall mortality was low (0.3–2%) in all studies.

## Future implications

MIS-C is a newly characterized syndrome, and optimal treatment is currently unknown. Whether early intervention (and exactly which intervention) can prevent severe

**Table 3** Summary of identified 5 large cohort studies reporting demographic and clinical outcomes of multisystem inflammatory syndrome in children (MIS-C)

| | Feldstein et al. [2] | Bautista-Rodriguez et al. [36] | Valverde et al. [17] | Feldstein et al. [34] | Abrams et al. [35] |
|---|---|---|---|---|---|
| Study cohort | 53 hospitals across the US | 33 hospitals in European, Asian, and American countries | 55 centers in 17 European countries | 66 US hospitals in 31 states | State and local health departments in the US |
| Study period | March 15–May 20, 2020 | March 1-June 15, 2020 | February 1–June 6, 2020 | March 15–October 31, 2020 | March 11–Oct 10, 2020 |
| Number of MIS-C patients | 186 | 183 | 286 | 539 | 1080 |
| Age (years) (median/mean) | 8.3 (IQR 3.3–12.5) | 7 ± 4.7 | 8.4 (IQR 3.8–12.4) | 8.9 (IQR 4.7–13.2) | 8 (IQR 4–12) |
| Coexisting conditions[a] *N* (%) | 51 (27) | 48 (26) | 16 (6) | 167 (31) | 286 (26) obesity |
| Diagnostic definition | CDC | CDC age ≦ 18 years | Modified CDC and RCPCH, age < 18 years | CDC | CDC |
| Diagnostic method | | | | | |
| RT-PCR positive *N* (%) | 73 (39) | 43/114 (38) | 90/268 (34) | 281 (52) | NA |
| Serology positive *N* (%) | 58 (31) | 95/110 (86) | 41/260 (16) IgM<br>116/260 (44) IgG | 409 (76) | NA |
| Contact with case *N* (%) | 55 (30) | NA | NA | NA | NA |
| Organ involvement | | | | | |
| Any cardiovascular *N* (%) | 149 (80) | 79 (43)[a] | 286 (100) | 359 (67) | 392 (36) shock |
| Any gastrointestinal *N* (%) | 171 (92) | 117 (64) | 204 (71) | 486 (90) | 693 (64) pain<br>684 (63) vomiting<br>573(53) diarrhoea |
| Any respiratory *N* (%) | 131(70) | 71 (39) | 97 (34)[b]<br>62 (22)[c] | 432 (80) | 287 (27) shortness of breath |
| Any dermatologic *N* (%) | 110 (59) | 120 (66) | 179 (63) | 360 (67) | 584 (54) |
| Any neurologic *N* (%) | NA | 22 (12) | NA | 218 (40) | NA |
| Acute kidney injury *N* (%) | NA | NA | NA | 9 (2) | NA |
| Thrombus *N* (%) | NA | NA | NA | 11 (2) | NA |
| Coronary artery abnormality *N* (%) | 15/170 (9) | 38 (21) | 69 (24) | 57/424 (13) | 185 (17) |
| ICU admission *N* (%) | 148 (80) | 26 (14) | 162 (57) | 398 (74) | 648 (60) |
| Therapy | | | | | |
| IVIG *N* (%) | 144 (77) | 163 (89) | 367 (78) | 415 (77) | NA |
| Systemic steroid *N* (%) | 91 (49) | 105 (57) | 80 (28) | 374 (69) | NA |
| Biologic therapies *N* (%) | 38 (21) | NA | NA | 32 (6) Tocilizumab | NA |
| Antiplatelet (Aspirin) *N* (%) | NA | 124 (67) | 212 (74) | 308 (57) | NA |
| Anticoagulation *N* (%) | 87 (47) | 78 (43) | 108 (38) | 337 (63) | NA |
| Inotropic support *N* (%) | 90 (48) | 72 (39) | 80 (30) | 244 (45) | NA |
| HFNC *N* (%) | NA | NA | NA | 114 (21) | NA |

**Table 3** (continued)

| | Feldstein et al. [2] | Bautista-Rodriguez et al. [36] | Valverde et al. [17] | Feldstein et al. [34] | Abrams et al. [35] |
|---|---|---|---|---|---|
| Non-invasive MV *N* (%) | 32 (17) | NA | NA | 192 (36) | NA |
| Invasive MV *N* (%) | 37 (20) | 43 (24) | NA | 95 (18) | NA |
| ECMO *N* (%) | 8 (4) | 4 (2) | NA | 18 (3) | NA |
| Outcomes | | | | | |
| ICU LOS (days) | NA | NA | NA | 4 (2–7) | NA |
| Death *N* (%) | 4 (2) | 3 (2) | 1 (0.3) | 10 (2) | 18 (2) |

Each cell presents number and percentage unless otherwise specified

*MIS-C* multisystem inflammatory syndrome in children, *RT-PCR* reverse transcription polymerase chain reaction, *IVIG* intravenous immunoglobulin, *HFNC* high flow nasal cannula, *MV* mechanical ventilation, *ECMO* extracorporeal membrane oxygenation, *IQR* interquartile range, *ICU LOS* intensive care unit length of stay, *RCPCH* Royal College of Paediatrics and Children Health, *CDC* The Centers for Disease Control and Prevention, *WHO* World Health Organization, *NYSDOH* New York State Department of Health

[a]Coexisting conditions such as chronic lung disease obesity, and immunocompromising conditions

[b]Upper respiratory tract infection

[c]Lower respiratory tract infection

disease progression and invasive treatment is a particularly pressing question. This includes if early non-invasive respiratory support can prevent future intubation. It is not known if emerging viral variants are able to induce a similar set of symptoms, or how they may affect patient outcomes. For those who have recovered, the long-term sequelae, especially among patients who experienced cardiac dysfunction and coronary aneurysms, is not known. Long-term outcomes are particularly critical to understand with the pediatric population of MIS-C.

## Conclusions

MIS-C is a new clinical syndrome that has emerged as a result of the COVID-19 pandemic. Although a minor proportion of children who are infected with COVID-19 progress to MIS-C, the clinical manifestations can be severe. As second and third waves of COVID-19 are progressing worldwide, anesthesiologists and intensivists are likely to treat an increasing number of children with MIS-C. As research into treatments is ongoing [37], pragmatic trials and investigations are needed that will provide more rapid answers to important clinical treatment questions.

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## Declarations

**Conflict of interest** The authors declare that they have no competing interests related to this publication.

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