Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach

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Abstract
Initial reports on COVID-19 described children as largely spared from severe manifestations, with only 2–6% of children requiring intensive care treatment. However, since mid-April 2020, clusters of pediatric cases of severe systemic hyperinflammation and shock epidemiologically linked with COVID-19 have been reported. This condition was named as SARS-Cov-2-associated multisystem inflammatory syndrome in children and showed similarities to Kawasaki disease. Here, we present a narrative review of cases reported in literature and we discuss the clinical acute and follow-up management of these patients. Patients with SARS-Cov-2-associated multisystem inflammatory syndrome frequently presented with persistent fever, gastrointestinal symptoms, polymorphic rash, conjunctivitis, and mucosal changes. Elevated inflammatory markers and evidence of cytokine storm were frequently observed. A subset of these patients also presented with hypotension and shock (20–100%) from either acute myocardial dysfunction or systemic hyperinflammation/vasodilation. Coronary artery dilation or aneurysms have been described in 6–24%, and arrhythmias in 7–60%. Cardiac support, immunomodulation, and anticoagulation are the key aspects for the management of the acute phase. Long-term structured follow-up of these patients is required due to the unclear prognosis and risk of progression of cardiac manifestations.

Conclusion: Multisystem inflammatory syndrome is a novel syndrome related to SARS-CoV-2 infection. Evidence is still scarce but rapidly emerging in the literature. Cardiac manifestations are frequent, including myocardial and coronary involvement, and need to be carefully identified and monitored over time.

What is Known:
- Multisystem inflammatory syndrome in children (MIS-C) has been described associated with SARS-CoV-2.

What is New:
- Patients with MIS-C often present with fever, gastrointestinal symptoms, and shock. Cardiac involvement is found in a high proportion of these patients, including ventricular dysfunction, coronary artery dilation or aneurysm, and arrhythmias.
- Management is based on expert consensus and includes cardiac support, immunomodulatory agents, and anticoagulation. Long-term follow-up is required due to the unclear prognosis and risk of progression of cardiac manifestation.

Electronic supplementary material
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Introduction

Initial reports during the early phase of the COVID-19 pandemic indicated that children were relatively spared from severe manifestations, with 2–6% of children presenting with severe illness [1–3]. However, since mid-April 2020, clusters of pediatric cases of severe systemic hyperinflammation and shock epidemiologically linked with COVID-19 were reported. Riphagen et al. first described a case series of 8 previously asymptomatic children presenting with hyperinflammatory shock, ventricular dysfunction, and multiorgan involvement [4]. This was followed by other reports of patients with Kawasaki disease (KD) and KD-like syndrome, frequently complicated by significant cardiac involvement [5–9].

The increasing number of reported cases led to a health advisory from the Royal College of Pediatrics and Child Health (RCPCH), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO), which identified these cases as a novel condition named multisystem inflammatory syndrome in children (MIS-C), also called pediatric multisystem inflammatory syndrome (PMIS) [10–12]. For the purpose of this review, the term MIS-C will be used. Here, we aim to review the published case reports and case series of patients with MIS-C, summarize the existing evidence on its cardiac manifestations in a form of narrative review, and propose a consensus-based approach for the management of MIS-C. Methods of the review process are reported as Supplemental material.

Definition of MIS-C

The RCPCH’s, CDC’s, and the WHO’s definitions of the novel syndrome are shown in Table 1 [10–12]. All three definitions include presence of fever, laboratory evidence of inflammation, and multisystem organ involvement without alternative plausible diagnoses, as well as evidence of COVID-19 infection or recent exposure to a COVID-19 case. The duration of fever, criteria for organ involvement, and need for documentation of SARS-CoV-2 infection vary between definitions.

Clinical presentation

Clinical symptoms

Children with MIS-C commonly present with persistent fever, asthenia, diffuse erythematous polymorphic rash, non-purulent conjunctivitis, and prominent gastrointestinal symptoms (Table 2) [4–9, 13–29]. Other commonly reported symptoms are mucosal changes and peripheral edema, which, along with the rash and conjunctivitis, resemble the clinical characteristics of KD [5–9, 13–31]. In contrast with adults, odynophagia and respiratory symptoms were rarely seen [4, 9, 14, 15, 22–27]. Notably, a subset of patients presents with hypotension and shock from either acute myocardial involvement or systemic hyperinflammation/vasodilation, frequently requiring intensive care admission, circulatory, and respiratory support (Tables 2 and 3) [4, 5, 8, 9, 13–20, 22–25, 27].

Factors associated with MIS-C

Although comorbidities have been associated with more severe disease in both adults and children with severe COVID-19 [2], their role in MIS-C remains unclear. While Belhadjer, Dufort and Feldstein et al. hypothesize that overweight patients may have a higher risk to
present MIS-C [24, 25, 27], patients overall were reported to be previously healthy, and only occasionally had a baseline chronic condition such as asthma or autoimmune disorders (Table 2) [4, 8, 15, 19, 20, 25, 27, 28]. Interestingly, none of the reported patients had known congenital heart disease or preexisting cardiovascular disease. Finally, several case series have described a high proportion of African ethnicity or ancestry [4, 18, 20, 24, 25], as well as Hispanic subjects [23–25]. Future studies may help better understand the role of genetic and socioeconomic status in the pathophysiology of MIS-C.

Table 1 Case definitions for SARS-CoV-2-associated multisystem inflammatory syndrome in children

| Royal College of Paediatrics and Child Health, UK | Centers for Disease Control and Prevention (CDC, USA) | World Health Organization (WHO) |
|------------------------------------------------|---------------------------------------------------|--------------------------------|
| A child presenting with persistent fever (≥38.5 °C), inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features**. This may include children fulfilling full or partial criteria for KD. 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). SARS-CoV-2 RT-PCR test results may be positive or negative. Additional features: Clinical: Most: oxygen requirement, hypotension Some: abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope vomiting; Laboratory: All: abnormal fibrinogen, high D-dimers, high ferritin, hypoalbuminemia; Some: acute kidney injury, anemia, thrombocytopenia, coagulopathy, high IL-10, high IL-6, elevated neutrophils, reduced lymphocytes and low albumin. Imaging: Echo and ECG: myocarditis, valvulitis, pericardial effusion, coronary artery dilation; CXR: patchy symmetrical infiltrates, pleural effusion; Abdo USS: colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly; CT chest: as for CXR. May demonstrate coronary artery abnormalities if with contrast. | An individual aged < 21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND No alternative plausible diagnoses; AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or COVID-19 exposure within 4 weeks prior to the onset of symptoms. *Fever ≤ 38 °C for ≥ 24 h, or report of subjective fever lasting ≥ 24 h. **Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes and low albumin. Additional comments: Some individuals may fulfill or partial criteria for KD but should be reported if they meet the case definition for MIS-C; Consider MIS-C in any pediatric death with evidence of SARS-Cov-2 infection. | 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 procalcitinin. 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. Consider this syndrome in children with features of typical or atypical KD or toxic shock syndrome. |

*APTT activated partial thromboplastin time, CK creatine kinase, COVID-19 coronavirus disease 2019, CXR chest X-ray, CRP C-reactive protein, echo echocardiography, ESR erythrocyte sedimentation rate, IL interleukin, KD Kawasaki disease, LDH lactic acid dehydrogenase, MIS-C multisystem inflammatory syndrome in children, NT-proBNP N-terminal pro-B-type natriuretic peptide, PT prothrombin time, PTT partial thromboplastin time, RT-PCR reverse transcriptase–polymerase chain reaction, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, TG triglycerides
| Author, year  | Study design, setting, and period | N | Age, gender | Other patients’ baseline characteristics | Symptoms | Cardiac involvement | SARS-CoV-2 test |
|--------------|----------------------------------|---|-------------|------------------------------------------|----------|-------------------|----------------|
| Jones 2020   | Case report, Palo Alto, USA, April 2020 | 1 | 6 months, F | Previously healthy | Persistent fever, nsh, conjunctivitis, mucosal changes, peripheral edema, minimal respiratory symptoms, irritability | Normal | Normal coronary arteries | Pos |
| Riphagen 2020| Case series, London, UK, April 2020 | 8 | Range 4–14 years, 5M, 3F | 6/8 previously healthy, 1/8 allergic rhinitis and alopecia areata, 1/8 autism, 6/8 Afro-Caribbean | Persistent fever, 7/8 GI symptoms, 5/8 conjunctivitis, 4/8 nsh, 3/8 odynophagia, 2/8 headache, 1/8 myalgia, 8/8 Hypertension/shock | 6/8 (4/8 mild to severe LV dysfunction, 1/8 RV dysfunction, 1/8 BIV dysfunction) | 1/8 in context of refractory shock, requiring ECMO; other ECGs non-specific | ↑ ↑ proBNP |
| Rivera-Figueroa 2020 | Case report, Jackson, USA, April 2020 | 1 | 5 years, M | Previously healthy, African-American | Persistent fever, GI symptoms, nsh, conjunctivitis, mucosal changes, peripheral edema, shock | Normal | Normal coronary arteries | ↑ |
| Balasubramanian 2020 | Case report, Chennai, India, April 2020 | 1 | 8 years, M | Previously healthy, Indian | Persistent fever, odynophagia, nsh, conjunctivitis, mucosal changes, peripheral edema, mild respiratory distress, hypotension | Normal | Normal coronary arteries | ↑ |
| Verdoni 2020 | Case-control study, Bergamo, Italy, 2015-2020 | 10 | Mean 7.5 years (SD 3.5), 7M, 3F | Previously healthy, Caucasian | Persistent fever, nsh, conjunctivitis, peripheral edema, 6/10 GI symptoms, 4/10 mucosal changes, 4/10 meningeal signs, hypotension | 5/10 LVEF < 50% | 2/10 coronary aneurysms (> 4 mm) | ↑ ↓ proBNP |
| Belladjer 2020 | Case series, France and Switzerland (14 centers), March–April 2020 | 35 | Median 10 years (range 1–16 years), 18 M, 17F | 31/35 previously healthy, 3/35 asthma, 1/35 SLE, 6/35 overweight (BMI > 25) | Persistent fever, asthma, 28/35 (80%) GI symptoms, 23/35 respiratory distress, 20/35 mucosal changes, 11/35 meningeal signs, 6/35 chest pain, 3/35 hypotension/shock | 35/35 LVEF < 50% (inclusion criteria), 10/35 LVEF < 30%, 31/35 global LV hypokinesis, 3/35 segmental wall hypokinesis, 1/35 Takotsubo | 6/35 mild coronary dilatation (≥ score ≥ 2), 1/35 ST elevation at onset, 1/35 venricular arrhythmia | ↑ ↑ 35/35 proBNP |
| Licciardi 2020 | Case report, Turin, Italy, April 2020 | 2 | 7 years, M, 12 years, M | Previously healthy, 1/2 PFAPA syndrome | Persistent fever, GI symptoms, nsh, conjunctivitis, peripheral edema, hypotension/shock | 2/2 Ventricular dysfunction | Normal coronary arteries | ↑/2 ↓ proBNP |
| Deza Leon 2020 | Case report, Detroit, USA, April 2020 | 1 | 6 years, F | Previously healthy | Fever, rash, conjunctivitis, peripheral edema, hypotension/shock | Mildly diminished LVEF at onset, severe dysfunction requiring ECMO | Normal coronary arteries | ↑ |
| Dolinger 2020 | Case report, New York, USA, May 2020 | 1 | 14 years, M | Crohn disease | Persistent fever, GI symptoms, nsh, hypotension | - | Normal coronary arteries | ↑ |
| Labé 2020   | Case report, Argenteuil, France, | 2 | 6 years, M, 3 years, M | Previously healthy | Rash, conjunctivitis, mucosal changes; 1/2 persistent fever, cervical lymphadenopathy | - | Functional cardiac rhythm | ↑ |

N: number of patients; N: number of patients; S: number of patients; M: number of patients; F: number of patients; GI: gastrointestinal; LV: left ventricle; RV: right ventricle; BIV: biventricular; Notation ↑ indicates increased values compared to baseline; ↓ indicates decreased values compared to baseline; ↑↑ indicates markedly increased values compared to baseline; ↓↓ indicates markedly decreased values compared to baseline; Pos: positive; Neg: negative; ↑↑↑ indicates extremely increased values compared to baseline; ↓↓↓ indicates extremely decreased values compared to baseline.

Table 2: Demographic, clinical characteristics and cardiac involvement in published cases of patients presenting with possible MIS-C.
| Author, year | Study design, setting, and period | N | Age, gender | Other patients’ baseline characteristics | Symptoms | Cardiac involvement | SARS-CoV-2 test |
|-------------|----------------------------------|---|-------------|----------------------------------------|----------|-------------------|----------------|
| **Table 2 (continued)** | | | | | | | |
| Rauf 2020 | Case report, Kerala, India, April 2020 | 1 | 5 years, M | Previously healthy | Persistent fever, GI symptoms, pyuria, conjunctivitis, peripheral edema, hypotension | Moderate LV dysfunction (FE = 35%), LV global hypokinesia | † proBNP Neg |
| Chiotos 2020 | Case series, Philadelphia, USA, April-May 2020 | 6 | Range 5–14 years, 1M, 5F | Previously healthy, 2/6 African-American, 2/6 Caucasian | Persistent fever, 5/6 GI symptoms, 2/6 conjunctivitis, 3/6 mucosal changes, 1/6 peripheral edema, 1/6 headache, 2/6 irritability, 4/6 respiratory failure, 6/6 shock | 4/6 Mild-Moderate LV dysfunction | † 3/5 † proBNP 3/6 Pos |
| Waltuch 2020 | Case series, New York, USA, April 2020 | 4 | Range 5–13, 3M, 1F | 2/4 previously healthy, 1/4 hypothyroidism, 1/4 asthma | Persistent fever, GI symptoms, 3/4 conjunctivitis, 2/4 rash, 2/4 cough, 2/4 fatigue, 1/4 myalgia, hypotension | Moderately depressed LV function | † 1/4 † proBNP 0/3 Pos |
| Woller 2020 | Case series, Milan, Italy, March-April 2020 | 5 | Mean 84 m, range 2–168, 2M, 3F | Previously healthy | Persistent fever, GI symptoms, 3/4 rash, 1/5 conjunctivitis, 1/5 respiratory distress, 5/5 hypotension/shock | 5/5 Mild-moderate heart dysfunction, 3/5 LVEF < 50% | ST, T waves anomalies, 1/5 atrial fibrillation | † proBNP 5/5 Pos |
| Grimaud 2020 | Case series, Paris, France (4 centers), April 2020 | 20 | Median 10 years (IQR 3–15), 10M, 10F | - | Persistent fever, GI symptoms, 10/20 rash, 6/20 conjunctivitis, 5/20 mucosal changes, 2/10 lymphadenopathy, 20/20 hypotension/shock | 20/20 Cardiogenic/vasoplegic shock (inclusion criteria), LVEF 35% (IQR 25–55) | Normal coronary arteries | † BNP 10/20 Pos, others neg |
| Toubiana 2020 | Case series, Paris, France, April-May 2020 | 21 | Median 8y (range 4–17), 9M, 12F | 12/21 African ancestry | Persistent fever, GI symptoms, 16/21 rash, 17/21 conjunctivitis, 16/21 mucosal changes, 12/21 cervical lymphadenopathy, 12/21 irritability, 12/21 serous diffusion, 15/21 hypotension/shock | 16/21 myocarditis 5/21 moderately dilated coronary arteries (z score 2–2.5), 3/21 echobright coronaries | 2/16 increased QT interval, ventricular arrhythmias or diffuse ST segment elevation | † 17/21 † 14/18 8/21 19/21 IgG+ |
| Whitaker 2020 | Case series, UK (8 centers), March-May 2020 | 58 | Median 9 years (IQR 6–14), 25M, 33F | 7/58 comorbid: 3/58 asthma, 1/58 neuro-disability, 1/58 epilepsy, 1/58 sickle cell trait, 1/58 alopecia; 22/58 Black; 18/51 Asian | Persistent fever, GI symptoms, 30/58 rash, 26/58 conjunctivitis, 17/58 mucosal changes, 12/58 respiratory symptoms, 9/58 peripheral edema, 9/58 lymphadenopathy, 6/58 | 18/29 LV dysfunction 8/58 coronary artery dilation (z score > 2), 7/58 z score > 2.5, giant | 4/58: 1/58 1st-degree AV block, 1/58 intractable broad complex tachycardia, N-† proBNP 29/29 15/58 Pos |
Table 2 (continued)

| Author, year | Study design, setting, and period | N | Age, gender | Other patients' baseline characteristics | Symptoms | Cardiac involvement | Coronary involvement | Arrhythmia/ECG changes | Troponin proBNP | SARS-CoV-2 test |
|--------------|----------------------------------|---|-------------|----------------------------------------|----------|---------------------|----------------------|-----------------------|-----------------|-----------------|
|              |                                  |   |             |                                        |          |                     |                      |                       |                 |                 |
| Blondiaux 2000 | Case series, Paris, April 2000 | 4 | Median 9 y (range 6 – 12), 1 M, 3 F | No history of cardiovascular disease | Persistent fever, GI symptoms, rash, conjunctivitis | 4/4 transient systolic dysfunction, 1/4 LVEF < 30% | Normal coronary arteries | 1/4 ST depression, 1/4 T waves abnormalities | ↑ 4/4 | 0/4 Pos | 4/4 IgG+, 1/4 IgM+ |
| Cheung 2020 | Case series, New York, April–May 2020 | 17 | Median 8 years (range 2 – 16), 8 M, 9 F | Previously healthy, 3/17 mild asthma; 6/17 Ashkenazi Jewish, 4/17 Asian | Persistent fever, 14/17 GI symptoms; 1/17 rash, 11/17 conjunctivitis; 9/17 mucosal changes, 3/17 respiratory symptoms, 13/17 shock | 11/17 normal-mild LV dysfunction | 6/17 moderate-severe LV dysfunction | 7/17 echobright coronaries, 1/17 medium-sized aneurysm (z score 5.2) | ↑ 14/17 | 10/17 | ↑ proBNP 15/29 |
| Ramcharan 2020 | Case series, Birmingham, April–May 2020 | 15 | Median 9 (IQR 7 – 11), 11 M, 4 F | 6/15 African/Afro-Caribbean, 6/15 Asian | Persistent fever, 13/15 GI symptoms; 8/15 Kawasaki-like symptoms; 4/15 myalgia, 4/15 lethargy | 8/15 Reduced LV fractional shortening, 12/15 LVEF < 55% | 14/15 coronary artery abnormalities: 1 aneurysm, 6 ectasia, 7 prominent coronary artery abnormalities; 1 aneurysm, 6 ectasia, 7 prominent | 9/15 abnormal PR interval, abnormal T waves | ↑ 15/15 | ↑ proBNP 15/15 | 2/15 Pos | 12/12 IgM/IgG/IgA+ |
| Pouletty 2020 | Case series, Paris (multicenter), April–May 2020 | 16 | Median 10 years (IQR 5 – 12), 8 M, 8 F | 10/16 Previously healthy, 2/16 asthma, 4/16 overweight | Persistent fever, 13/16 GI symptoms; 13/16 rash, 15/16 conjunctivitis; 14/16 mucosal changes; 9/16 neurological signs; 6/16 lymphadenopathy; 2/16 respiratory symptoms; 1/16 arthritis; 1/16 anosmia | 7/16 Myocarditis, LVEF 35% (IQR 32 – 46) | – | – | ↑ 11/16 | ↑ proBNP 11/16 | 11/16 | 7/8 IgG+ |
| Kaushik 2020 | Case series, New York (3 centers), | 33 | Median 10 years (IQR 5 – 12), 15/33 Hispanic or Latino, 13/33 black | 17/33 Previously healthy, 5/33 asthma, 4/33 overweight, 15/33 Hispanic or Latino, 13/33 black | Persistent fever, 23/33 GI symptoms; 14/33 rash, 12/33 conjunctivitis; 11/33 respiratory symptoms, 7/33 | 21/32 LVEF < 50%, 4/32 LVEF < 30% | 6/21 prominent coronary arteries, 2/21 | – | N-1 | ↑ BNP, proBNP | 11/33 Pos | 27/33 IgM/IgG+ |
Table 2 (continued)

| Author, year | Study design, setting, and period | N | Age, gender | Other patients' baseline characteristics | Symptoms | Cardiac involvement | SARS-CoV-2 test |
|--------------|----------------------------------|---|-------------|-----------------------------------------|----------|---------------------|-----------------|
|              |                                  |   |             |                                         |          | Ventricular function | Coronary involvement | Arrhythmia/ECG changes | Troponin proBNP/BNP | RT-PCR | Serology |
| Greene 2020  | Case report, New York, May 2020  | 1 | 11 years, F | Previously healthy                       | Persistent fever, GI symptoms, sore throat, rash, leg pain, malaise, shock | Decreased LV function | Normal coronary arteries | - | † | † | Pos | - |
| Dufort 2020  | Case series, New York (multicenter), March–May 2020 | 99 | 31/99 0–5 years, 42/99 6–12 years, 26/99 13–20 years; 53M, 46F | 36/95 pre-existing condition, 29 of them obesity; 31/78 black, 31/78 Hispanic, 29/78 white | Persistent fever or chills, 79/99 GI symptoms, 59/99 rash, 60/99 mucosal change, 40/99 lower respiratory symptoms, 30/99 neurologic symptoms, 27/99 upper respiratory, 11/99 chest pain, 61/99 hypotension, 10/99 shock | 51/99 some degree of ventricular dysfunction, 52/99 myocarditis | 9/99 coronary artery aneurysm (4/99 z score > 2.5) | † | 63/89 | † 74/82 | 50/94 | 76/77 IgG+, 3/77 IgM+ |
| Feldstein 2020 | Case-series, United States (multicenter), March–May 2020 | 186 | Median 8 years (IQR 3–12), 115M, 71F | 135 previously healthy, 51/186 at least one underlying condition excluding obesity (resp 33/186, cardiac 5/186, immunocompromising or autoimmune 10/186, 45/153 BMI-based obesity; 46/186 Black, 57/186 Hispanic or Latino) | Persistent fever, 171/186 GI symptoms, 103/55 conjunctivitis, 78/186 oral mucosal changes, 37/186 peripheral edema, 18/186 lymphadenopathy, 13/186 respiratory symptoms, 149/186 cardiovascular symptoms | 90/186 Myocardial dysfunction | 15/170 Coronary artery aneurysm (z score ≥ 2.5) | † 50/128 | † 73/153 | 73/186 | 85/186 | IgM/IgG+

AVatrio-ventricular, BiV biventricular, ECG electrocardiogram, ECMO extracorporeal membrane oxygenation, F female, GI gastrointestinal, IQR interquartile range, LV left ventricle, LVEF left ventricular ejection fraction, M male, RV right ventricle, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, SD standard deviation, VT ventricular tachycardia
Evidence of SARS-CoV-2 infection

While a small number of MIS-C patients have positive SARS-CoV-2 reverse-transcriptase protein chain reaction (RT-PCR) (Table 3), the majority have either known family exposures or serologic evidence of prior infection. Time from infection to onset of MIS-C symptoms varies among studies, from a few days to months [17, 18, 25, 27]. Overall, a variable percentages of subjects, from 0 [15, 30] to 100% [16] had positive RT-PCR; however, in most of the reports, SARS-CoV-2 positivity varies between 20 and 53% (Table 2) [4, 5, 14, 17, 18, 20, 22–25, 27]. Generally, a higher percentage (75–100%) had evidence of IgG antibodies (Table 2) [5, 15, 17, 18, 20–25, 27, 30] and suggest that a postinfectious immune response may be responsible for this condition [32].

Laboratory findings

Elevated inflammatory markers and evidence of hyperinflammation were widely reported and consistently found in patients with MIS-C [4–9, 13–33]. Supplemental Table 1 summarizes the main laboratory characteristics of the existing cases in the literature. Overall, C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR) are highly elevated, as well as ferritin and IL-6. A significant increase in D-dimer and fibrinogen are key features of the coagulation profile, while the hematologic aspect of the disease is characterized by leukocytosis, neutrophilia with immature forms, lymphopenia, normal or decreased red blood cell count and normal or decreased platelet count.

Cardiac involvement

Myocardial dysfunction

Left ventricular (LV) systolic dysfunction has been described in a large proportion of children diagnosed with MIS-C in both the initial reports and subsequent case series. Cardiac findings in children with MIS-C are summarized in Table 2 and Table 3. In the first MIS-C case series reported from the UK, cardiac dysfunction was present in 6/8 patients (75%) [4]. In subsequent case series, ventricular dysfunction has been reported in 35–100% of children with MIS-C, depending on definition and inclusion criteria (Table 2) [4, 5, 8, 9, 13–25, 27, 30, 31].

Two of the published case series described selected cohorts of patients with myocardial dysfunction as inclusion criteria [17, 27]. Belhadjer et al. reported a selected cohort of 35 MIS-C patients who developed acute LV failure (LV ejection fraction (LVEF) < 50%) or shock, fever, and elevated inflammatory markers [27]. Management of these patients included mechanical ventilation and inotropic support in 80% of patients, and extracorporeal membrane oxygenation (ECMO) support in 28%. All patients successfully weaned off ECMO and none had died at the time of publication. [27]. Grimaud at el. reported 20 patients admitted with cardiogenic/vasoplegic shock and a median LVEF of 35% (IQR 25–55%). Nineteen out of 20 patients required inotropes/vasopressors but no ECMO support was needed. All patients had a full recovery of the LV function prior to discharge [17].

A high proportion of patients also had elevated troponin level or B-type natriuretic peptide (BNP)/pro-BNP values (Table 2), which may be a useful marker for myocardial involvement. Most patients had recovery of ventricular function, but 6–14% of patients had persistent dysfunction at discharge (Table 3).

The mechanism underlying myocardial dysfunction in MIS-C has not been yet fully elucidated. Possible causes of myocardial injury in adults with COVID-19 include acute myocarditis, hypoxic injury, ischemic injury caused by cardiac microvascular damage or coronary artery disease, right heart strain (acute cor pulmonale), stress cardiomyopathy (Takotsubo), and systemic inflammatory response syndrome [3, 34–37]. The variable timing and modality of presentation with ventricular dysfunction suggests that different pathophysiological mechanisms may be responsible: while the acute infection may explain the occurrence of acute myocardial damage, a second phase characterized by a post-viral immunological reaction and systemic hyperinflammation may explain the occurrence of myocardial inflammation and dysfunction in predisposed subjects. In this second phase, a combination of cardiogenic and distributive shock may be observed. Advanced cardiac imaging in patients with MIS-C and ventricular dysfunction may help us better understand the underlying mechanism of injury, and presence of long-term scar or myocardial damage.

Coronary involvement

Coronary artery dilation or aneurysms have been described in 6–24% of patients (Table 2) [4, 5, 14, 15, 18–25, 27]. Most cases described mild coronary artery dilation with z-scores 2–2.5. As coronary artery z-scores are based on healthy, nonfebrile children, some of the findings in the acute phase may be related to coronary vasodilation in the setting of fever and inflammation. However, there have also been reports of large and giant coronary artery aneurysms [4, 20], and progression of coronary aneurysm following discharge raising concerns for coronary artery intimal disruption [4, 5, 19, 20]. The late development of coronary artery aneurysm highlights the need for ongoing follow-up of those patients.

Arrhythmia

Studies focusing on arrhythmic manifestations have described 7–60% of patients having rhythm abnormalities of variable
severity (Table 2). The most frequently reported electrocardiogram (ECG) anomalies were non-specific and included ST segment changes, QTC prolongation, and premature atrial or ventricular beats. First- and second-degree atrioventricular blocks were reported in one series, while atrial fibrillation was described in two reports [9, 20]. However, there have also been reported cases of sustained arrhythmias leading to hemodynamic collapse and need for ECMO support [4, 20].

Hyperinflammatory state and resemblance to Kawasaki disease

MIS-C overlaps with many features of KD [5, 20, 32]. KD is an acute pediatric vasculitis involving medium-sized vessels typically affecting children <5 years of age [38, 39]. The etiology of KD is still unknown, but it has been considered an inflammatory syndrome likely resulting from an infectious or other environmental trigger in a genetically susceptible host. While no specific infectious trigger has been confirmed, several viruses have been implicated, including coronaviruses [40, 41]. Clinical diagnostic criteria include a persistent fever (>5 days) and at least 4 of 5 clinical symptoms including mucocutaneous involvement, non-purulent conjunctivitis, polymorphous rash, unilateral lymphadenopathy, and palmar/plantar erythema and desquamation. An incomplete form of KD is defined by persistent fever and presence of <4 of classical symptoms with suggestive laboratory data and/or echo findings [38, 39]. In the acute phase of the disease, about 7% of patients manifest hemodynamic instability, a condition known as KD shock syndrome (KDSS) [39, 42]. Compared with KD patients without any signs of shock, KDSS patients were more frequently female, had a larger proportion of bands, higher CRP, and lower hemoglobin and platelet counts [42].

The small case series from Bergamo, Italy, reported a 30-fold increase in the incidence of KD or KD-like illness during the height of COVID-19 outbreak in the region (uncorrected for seasonal incidence), with many patients testing positive for IgG antibody and negative RT-PCR [5]. When these cases were compared with 19 classical KD, COVID-19-associated cases were found to be older (7.5 ± 3.5 vs 3.0 ± 2.5 years), more likely to present in shock (50% vs 0%), to have more cardiac involvement (abnormal echocardiogram in 60% vs 10%), and more likely to have elevation in troponin or BNP. Similarly, Whittaker et al. compared patients meeting the MIS-C definition with classical KD or KDSS patients [20], reporting that patients with MIS-C were generally older, had higher white blood cell count, neutrophil count, CRP, fibrinogen levels and higher troponin, as well as more profound lymphopenia, anemia, and lower platelet counts.

While generally self-limited, KD can have a number of long-term sequelae, the most important of which are cardiovascular. In addition to ventricular and valvular dysfunction, patients with KD can develop persistent coronary aneurysms, occurring in 20–25% of untreated children [38, 43, 44]. Coronary dilation or aneurysms have been reported in up to 25% of MIS-C patients, suggesting a pathophysiologic similarity with KD. Even if MIS-C patients have different clinical characteristics and laboratory findings compared with classical KD, the similarity in clinical features and the development of coronary artery aneurysms in both disorders may represent a key point for the future understanding of underlying pathophysiologic mechanisms [32]. Further studies will be needed to deeply understand the pathophysiology of this disorder.

Management

Management of patients with MIS-C is reported in Table 3. Overall, admission to the intensive care unit (ICU) for management of shock was described in 20–100% of the patients, most often for inotropic support (Table 3) [4, 5, 8, 9, 13–25, 27, 30, 31]. More rarely, patients required V-A ECMO support (0–28%) [4, 9, 20, 23–25, 27]. Most patients received immunomodulatory treatment with intravenous immunoglobulin. The use of corticosteroids was less consistent and ranged from low-dose treatment to high-dose methylprednisolone pulses [4, 5, 8, 13, 14, 16–25, 27, 30, 31]. The use of anti-inflammatory dosages of aspirin has been also occasionally reported [5, 6, 21, 22]. Not infrequently, cytokine blockers have been added as a supplemental therapy, with a preference for IL-6 inhibitors (tocilizumab), but also IL-1 or tumor-necrosis-factor (TNF)-α inhibitors (anakinra, infliximab) [4, 14–17, 19, 20, 22, 23, 25, 27, 28, 31, 33]. Antiplatelet treatment with aspirin was frequently adopted, especially in patients with KD-like clinical presentations, or in those with evidence of coronary involvement. A therapeutic or prophylactic anticoagulation approach was less frequently used, except for a few case series [16, 19, 23, 25, 27, 31].

Due to the scarce knowledge and the small number of reported cases so far, the management of patients with MIS-C has been largely based on expert opinion and extrapolated from KD treatment, adult experience with COVID-19, and other systemic inflammatory disorders in children. Here, we describe a consensus-based approach for the acute and medium-term management of children with MIS-C, as well as a follow-up algorithm, developed within our Institution. However, it is necessary to emphasize that there are currently no approved therapies for MIS-C patients, and data from
higher-evidence studies may quickly lead to changes in clinical practice.

**Proposed clinical approach**

A multidisciplinary team should be involved in the management of patients with MIS-C, including cardiology, rheumatology, intensive care, and infectious disease specialists. Given the lack of established treatment, possibility of harm, and limited drug supply, treatment is currently not recommended for (a) prevention or postexposure prophylaxis or (b) non-hospitalized patients.

**Cardiac support**

As described above, a high proportion of patients will present with shock and require acute resuscitation. Pediatric resuscitation guidelines should be followed [45]. In patients with suspicion or evidence of ventricular dysfunction, smaller fluid boluses (10 mg/kg) should be administered with careful reassessment for signs of fluid overload between each. Extracorporeal membrane oxygenation should be considered if medical support fails.

**Immunomodulatory therapy**

There may be a benefit of immunomodulatory therapy in patients with MIS-C, severe disease, and evidence of cytokine storm syndrome and/or those with cardiac involvement. Due to recent emergence of MIS-C, no randomized trials or comparative effectiveness studies have evaluated treatment strategies, but the benefits of immunomodulatory therapy are well established in KD [39], and they are often used for the treatment of infective myocarditis [46–48] and other systemic inflammatory diseases [49, 50]. Therefore, based on the experience in similar conditions, it appears reasonable to suggest an immunomodulation approach based on intravenous immunoglobulins (IVIGs). Slower IVIG administration should be considered in patients with myocardial dysfunction to decrease the risk of fluid overload. Low-dose corticosteroids should be considered in sicker patients, in patients with known baseline conditions which can benefit from steroid treatment, or based on clinical judgment. The use of biologic drugs (tocilizumab, anakinra, infliximab) could be considered in patients with severe or critical illness, especially if they did not respond to first-line treatments.

**Antiplatelet treatment and anticoagulation**

Children with MIS-C are at risk of thrombotic complications from multiple causes, including hypercoagulable state, possible endothelial injury, stasis from immobilization, ventricular dysfunction, and coronary artery aneurysm. For these reasons, antiplatelet and/or anticoagulation treatment is recommended. Decisions about anticoagulation should be based on coagulation tests, viscoelastic testing [51, 52], and clinical presentation. Patients with evidence of myocardial involvement or coronary artery dilation may benefit from antiplatelet therapy and prophylactic anticoagulation. In addition, therapeutic anticoagulation may be considered in patients with very abnormal coagulation profile (i.e., D-dimer ≥ 3 mg/mL), documented thrombosis, arrhythmia, ventricular dysfunction greater than moderate, or giant coronary artery aneurysm. However, it should be emphasized that this is based on experts’ opinion, with no evidence to support recommendations.

**Antiviral therapy**

The role of antiviral therapies (e.g., remdesivir) in the management of children with MIS-C is uncertain [53, 54]. Evidence suggests that MIS-C represents a postinfectious complication rather than an active infection. Although we did not include antiviral therapies as an established step in our algorithm, antiviral therapy may be considered in patients with severe manifestations and concerns for ongoing infection with positive RT-PCR. A consultation with specialists in infectious disease is highly recommended in this case.

**Outpatient follow-up**

Cardiac manifestations often improve and/or normalize prior to hospital discharge, but some patients have shown residual cardiac lesions. Additionally, some series reported progression of coronary artery aneurysm following discharge, highlighting our limited knowledge of this disease and the potential for long-term complications. Therefore, it is essential to guarantee an adequate medium and long term follow-up to these patients.

At this point of knowledge, we recommend follow-up for at least a year after initial diagnosis (Fig. 1). At initial visits, laboratory testing should be obtained to document normalization of inflammatory markers and resolution of hematologic anomalies. Laboratory testing may also guide weaning of corticosteroids if used in the acute phase. Echocardiograms should be obtained at regular intervals for evaluation of ventricular function and coronary artery dimensions. ECGs should also be obtained due to reports of arrhythmias including atrioventricular block, which may progress after initial diagnosis. If anomalies are identified on ECG, Holter monitors may be useful as further investigation. In patients with a history of ventricular dysfunction, cardiac magnetic resonance imaging (MRI) may be considered 2–6 months after initial diagnosis for evaluation of ventricular function, edema, diffuse fibrosis, and scar.

While the prothrombotic risk is greatest in the acute phase, the optimal duration of antiplatelet and anticoagulation
| Author, year | Cardiac support treatment | Anti-inflammatory/immunomodulatory treatments | Antiplatelet/anticoagulation treatment | Outcomes |
|--------------|---------------------------|---------------------------------------------|----------------------------------------|----------|
|              | Inotropes/vasopressors    | ECMO                                        | IVIG                                    | Steroids |
|              |                           |                                             | Biologic drugs                          | Aspirin  |
|              |                           |                                             |                                        | Heparin  |
|              |                           |                                             |                                        | At discharge | Follow-up |
| Jones 2020   | No                        | No                                          | 2 g/kg                                  | No        | 20 mg/kg ×4/day, then 3 mg/kg/day |
|              |                           |                                             |                                        | No        | Complete recovery |
|              |                           |                                             |                                        |           | Planned at 2 weeks after discharge |
| Riphagen 2020| 8/8                       | 1/8                                         | 8/8                                     | 5/8       | 1/8 infliximab |
|              |                           |                                             |                                        |           | 6/8 50 mg/kg |
| Rivera-Figueroa 2020 | No | No | 1.8 g/kg | Premed only | No | 40 mg/kg/day |
| Balasubramanian 2020 | No | No | 2 g/kg | No | Tocilizumab 8 mg/kg |
| Verdoni 2020  | 2/10                      | No                                          | 10/10                                   | 2 g/kg    | 2 mg/kg/day × 5 |
|              |                           |                                             |                                        | 10/10     | 7/10 30 mg/kg/day; then 3–5 mg/kg/day |
| Belhadjer 2020 | 28/35                     | 10/35                                       | 25/35                                   | 12/35     | 3/35 anakinra |
|              |                           | (1/25 s dose)                               |                                        |           | 28/35 |
|              |                           |                                             |                                        | 23/35 Therapeutic dosage | |
| Licciardi 2020 | 1/2                       | No                                          | 1/2                                     | 2/2 MTPD  | No |
|              |                           |                                             |                                        | 2 mg/kg/ide | - |
| Deza Leon 2020 | 1/1                       | 1/1                                         |                                        | No        | 1/1 |
| Dolinger 2020 | No                        | No                                          | No                                      | Infliximab 10 mg/kg |
| Labé 2020    | No                        | No                                          | No                                      | No        | 1/1 on ECMO |
| Rauf 2020    | 1/1                       | No                                          | 2 g/kg                                  | MTPD 30 mg/kg/day ×3 |
| Chiotos 2020 | 5/6                       | No                                          | 4/6 2 g/kg, 2/6 s dose                 | 5/6 MTPD  | 1/10 anakinra |
|              |                           |                                             |                                        | 2/6 MTPD  | 4 mg/kg/day |
|              |                           |                                             |                                        |            | 3/6 “low dose” |
|              |                           |                                             |                                        | No        | 5/6 complete recovery |
|              |                           |                                             |                                        |           | discharged at day 8–17, 1/6 still in |
|              |                           |                                             |                                        |           | |

Note: MTPD: maintenance therapy; ECMO: extracorporeal membrane oxygenation; IVIG: intravenous immunoglobulin; Biologic drugs: infliximab, tocilizumab, anakinra; Aspirin, Heparin, Outcomes: Complete recovery, Planned at 2 weeks after discharge, 1/8 developed 1 giant coronary aneurysm 1 week after discharge, 1/8 died for large cerebrovascular infarct; ongoing surveillance for coronary arteries; Complete recovery confirmed at 2 weeks; Complete recovery confirmed at 8 weeks, including echocardiogram; Recovery, 7/35 residual LV dysfunction at last follow-up (median 12 days); Recovery - ECMO decannulation at day 6, organs recovery day 12.
| Author, year | Cardiac support treatment | Anti-inflammatory/immunomodulatory treatments | Antiplatelet/anticoagulation treatment | Outcomes |
|-------------|--------------------------|---------------------------------------------|----------------------------------------|----------|
|             |                          | Inotropes/vasopressors | ECMO | IVIG | Steroids | Biologic drugs | Aspirin | Heparin | At discharge | Follow-up |
| Waltuch 2020 | 3/4 No                  | 3/4 No                  | 30/mg/kg/day x3 | 2/4 tocilizumab, 1/4 tocilizumab and anakinra | No | No | PICU at moment of submission |  |
| Woller 2020 | 4/5 No                  | 4/5 2 g/kg            | 1/5 | 1/5 tocilizumab | - | 4/5 LMWH prophylaxis | Complete recovery |  |
| Grimaud 2020 | 19/20 No                | 20/20 2 g/kg         | 2/20 | 1/20 tocilizumab | - | No | Full left ventricular function recovery |  |
| Toubiana 2020 | 15/21 No                | 21/21 2 g/kg, 5/21 s dose | 10/21 steroids 2–10 mg/kg/ day | No | 21/21 3–5 mg/kg/day | No | Complete recovery, discharged at day 5–17 |  |
| Whittaker 2020 | 27/58 3/58             | 41/58 3/58           | 37/58 | 3/58 anakinra, 8/58 infliximab | - | - | 1/58 died |  |
| Blondiaux 2000 | 3/4 No                  | 4/4 No                 | 3/4 | - | - | - | Complete recovery, discharged at day 13–23 |  |
| Cheung 2020 | 10/17 No                | 13/17 2–4 g/kg       | 14/17 MTPN 2–30 mg/kg/ day, HC 2 mg/kg/day | 1/17 tocilizumab | 4/17 Enoxaparin 10/17 prophylaxis, 1/17 treatment | Most patients had improved LV function at day 2–18, 1/17 mildly decreased function | At day 3–18 of follow up, all patients at home, no fatalities |
| Ramcharan 2020 | 10/15 No                | 10/15, 3/15 s dose | 5/15 MTPN | - | 2/15 high dose, 11/15 low dose | No | All patients discharged home with normal/improving cardiac parameters | Planned at 1 week, including ECG and echocardiogram |
| Pouletty 2020 | 6/16 No                 | 15/16, 5/16 s dose | 4/16 1/1 tocilizumab, 1/1 anakinra | 15/16 Aspirin | 7/16 | 30–50 mg/kg/day, | Complete recovery, all discharged at median follow-up of 14 days |  |
| Author, year | Cardiac support treatment | Anti-inflammatory/immunomodulatory treatments | Antiplatelet/anticoagulation treatment | Outcomes |
|-------------|---------------------------|---------------------------------------------|--------------------------------------|----------|
|             | Inotropes/vasopressors    | IVIG | Steroids | Biologic drugs | Aspirin | Heparin | At discharge | Follow-up |
| Kaushik 2020 | 17/33 | 8/16 antiaggregant dose | 12/33 tocilizumab, 4/33 anakinra | 8/24 | 28/33 therapeutic | UHF/enoxaparin, 5/33 prophylactic | 32/33 complete recovery, discharged at day 6–10, 20/21 complete LV function recovery, 1/33 died on ECMO |
| Greene 2020 | 1/1 | No | 1/1 | Tocilizumab | - | Therapeutic dose enoxaparin | Complete recovery | Planned at 2 weeks |
| Dufort 2020 | 61/99 | 4/99 | 69/99 | 63/99 | 91/186 | 14/186 tocilizumab or siltuximab, 24/186 anakinra | 130/186 discharged, 4/186 died as of May 20, 2020 |
| Feldstein 2020 | 90/186 | 8/186 | 144/186 | 91/186 | 14/186 tocilizumab or siltuximab, 24/186 anakinra | 87/186 (heparin, enoxaparin, bivalirudin, warfarin, argatroban) | 130/186 discharged, 4/186 died as of May 20, 2020 |

ECMO extracorporeal membrane oxygenation, HC hydrocortisone, IVIG intravenous immunoglobulins, LMWH low molecular weight heparin, MTPD methylprednisolone, Premed premedication, VA veno-arterial
remains unclear. Patients with documented thrombosis should be continued on anticoagulation for at least 3 months after discharge. Coagulation, D-dimer, and viscoelastic testing may help guide discontinuation of anticoagulation. Moreover, patients with persistent ventricular dysfunction and/or coronary artery aneurysm may also benefit from long-term antiplatelet and/or anticoagulation depending on the severity of cardiac involvement.

Exercise restriction

Due to the high prevalence of myocardial involvement with MIS-C, the safety to return to physical activity and exercise after discharge is unanswered. While the etiology of the myocardial involvement remains unknown, it is clear that there are similarities to acute myocarditis. Thus, one can argue that guidelines for return to sport participation after myocarditis should be followed in those patients [48, 55]. After acute myocarditis, restriction from physical activity for at least 6 months following diagnosis is recommended. Preparticipation evaluation with echocardiograms and exercise testing may be beneficial to document the safety of exercise participation.

Conclusion

MIS-C is a novel syndrome related to SARS-CoV-2 infection characterized by fever, signs of inflammation, and organ dysfunction. Evidence is still scarce but rapidly emerging from literature. Myocardial involvement, due to either acute myocarditis or secondary hyperinflammation, is frequent in children with MIS-C. Coronary dilation or aneurysm and arrhythmias may develop and evolve over time. Cardiac support, immunomodulation, and antplatelet/anticoagulation treatments are part of the management of acute MIS-C. Finally, follow-up of MIS-C patients is essential to better understand the evolution and prognosis of this disease. Future studies are needed to define evidence-based management of this novel condition.

Authors' contributions F.S. and A.D conceptualized the review, systematically reviewed the literature, evaluated articles for eligibility, extracted relevant data, interpreted the results, and drafted the manuscript. K.F., J.N., M.B.S., and C.J.V. critically revised the first draft of the manuscript and contributed with important intellectual content. All the authors approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement This is a review article. No ethical approval is required.
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