

# Recommendations for the initial management of multisystem inflammatory syndrome temporally related to COVID-19, in children and adolescents

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## ABSTRACT

Multisystem inflammatory syndrome temporally related to COVID-19 in children and adolescents is a clinical presentation of SARS-CoV-2 infection. It shares some features with Kawasaki disease, toxic shock, sepsis, macrophage activation syndrome, and myocarditis. Few publications have addressed its initial management, which is similar to that proposed for septic shock. This review analyzes such approach based on the characteristics typical of multisystem inflammatory syndrome related to COVID-19 in accordance with the paradigm of an "institutional practice guideline" and suggests therapeutic approach strategies, including early detection, stabilization, referral, specific treatment, and process analysis.

**Key words:** patient care bundles, multisystem inflammatory syndrome, COVID-19, sepsis, SARS-CoV-2.

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## INTRODUCTION

Coronavirus disease (COVID-19) was declared a pandemic in 2020.<sup>1</sup> To date, its impact on pediatrics has been small in terms of both severity and frequency, and different clinical presentations have been reported.<sup>2-9</sup>

Cases have been described since May in previously healthy European children, and reports have been made of the onset of a condition associated with COVID-19 characterized by a hyperinflammatory response.<sup>10-14</sup> Such condition is called multisystem

inflammatory syndrome in children (MIS-C) temporally related to COVID-19 and shares clinical characteristics with Kawasaki disease (KD), toxic shock syndrome (TSS), sepsis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis; and it may also occur in association with myocarditis-induced cardiogenic shock.<sup>15-22</sup>

Currently, MIS-C is an uncommon disease overlapping with other conditions; therefore, a high clinical suspicion is required for a timely identification.<sup>10-22</sup> Like sepsis, MIS-C presents with an inadequate immune response to infection leading to different types of organ dysfunction and is life-threatening.<sup>23</sup> In the case of both sepsis and MIS-C, a high diagnostic suspicion is critical and its management may require rapid and timely advanced life support interventions in an adequate setting. MIS-C prognosis is currently good, and mortality has been reported to be low, although a late diagnosis may worsen the outcomes.<sup>10-22</sup>

Although the Surviving Sepsis Campaign (SSC) has recently issued updated clinical practice guidelines (CPGs) for hemodynamic support in septic shock (SSh) in pediatrics, few articles have addressed the initial management of MIS-C.<sup>5,24-27</sup> Several governments, like the Argentine government, have introduced MIS-C as a diagnostic criterion for COVID-19, and this calls for the need to provide care strategies to health care providers.<sup>5,28</sup>

In 2019, *Archivos Argentinos de Pediatría* published updated initial management guidelines for SSh in children and proposed “bundles of measures” to approach it.<sup>29,30</sup> It is worth noting that developing institutional practice guidelines (IPGs) agreed upon by the entire health care team (emergency department, hospitalization ward, critical care unit, pharmacy, laboratory, hemotherapy, pre-hospital practitioners, and primary care physicians, among others) is critical to establish a time-sensitive diagnosis and management where the setting and a joint effort are key.<sup>29</sup>

Our objective is to propose, based on the information available to date, recommendations for the development of institutional bundles of measures (early detection, treatment, stabilization, referral, and process analysis) for the initial management of MIS-C aimed at improving the quality of care provided to children with this condition.

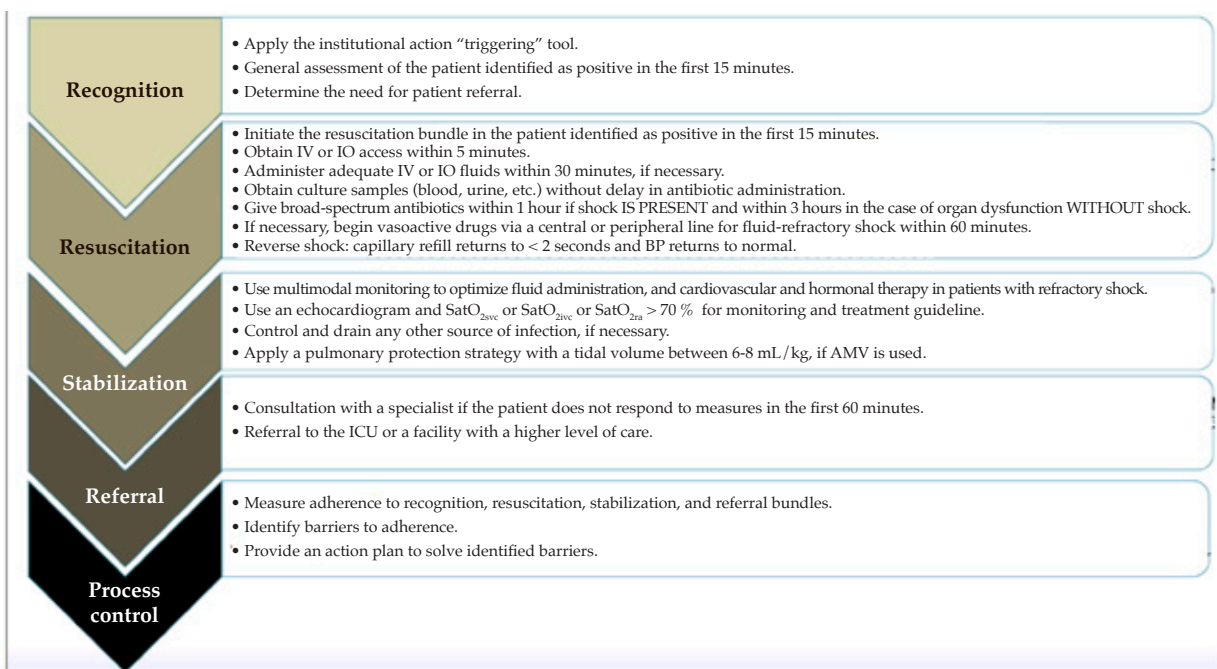
**BUNDLES OF MEASURES**

“Patient care bundles” are diagnostic / therapeutic actions to better address and manage

medical processes.<sup>31</sup> They include practices based on different levels of evidence in relation to a care process that, when developed collectively, result in a synergy that improves care (*Figure 1*). Five care bundles were proposed: early detection, immediate and time-sensitive resuscitation, stabilization, timely referral with the intervention of suitable health care providers in case of inadequate treatment response, and process measurement with corrections.<sup>5,29,32,33</sup> In the case of MIS-C, pediatricians specialized in Emergency Care, Critical Care, Internal Medicine, Infectious Diseases, Immunology, and Rheumatology should be involved.<sup>5,29</sup>

A goal-directed therapy (GDT) protocol should be implemented in MIS-C based on the evidence of its use in pediatric SSh, in spite of the criticism around it in adult care.<sup>34-39</sup> A strict, uniform implementation in all patients and across all institutions does not always result in similar outcomes, probably because it does not involve those who make decisions in close patient care.<sup>40-43</sup> Therefore, it is essential to develop IPGs in accordance with the resources available at each site and to get the entire health care team involved.<sup>29</sup>

FIGURE 1. Bundles of measures for multisystem inflammatory syndrome temporally related to COVID-19 and recognition, resuscitation, stabilization, referral, and process measurement elements (adapted by the authors from Kohn Loncarica et al.)<sup>30</sup>



IV: intravenous; IO: intraosseous; BP: blood pressure; SatO<sub>2svc</sub>: oxygen saturation in the superior vena cava; SatO<sub>2ivc</sub>: oxygen saturation in the inferior vena cava; SatO<sub>2ra</sub>: oxygen saturation in the right atrium; AMV: assisted mechanical ventilation.

## RECOGNITION BUNDLE

An early MIS-C detection is critical for an optimal and time-sensitive treatment; therefore, it is essential to bear clinical criteria in mind. MIS-C is characterized by an ongoing, progressive inflammatory response. It has been referred to with different terms, such as pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TC), and MIS-C, a more rigorous and specific term that we used in this review.<sup>15,16,44</sup> As in the case of other evolving, dynamic entities with inaccurate limits, the use of strict clinical criteria may hinder the initial recognition.<sup>45-47</sup>

The definition by the World Health Organization (WHO) encompasses children and adolescents aged 0-19 years with persistent fever (> 3 days) in association with clinical manifestations in two or more

systems (mucocutaneous, circulatory, cardiac, hematological, and gastrointestinal); elevated markers of inflammation with no other obvious microbial cause; and evidence of COVID-19 (as per reverse transcription polymerase chain reaction [rtPCR], antigen test or positive serology) or contact with COVID-19 patients. In some cases, clinical suspicion may be the only valid tool to assume it is MIS-C.<sup>16</sup>

Recent publications have described the clinical characteristics of MIS-C (please read these for a more comprehensive report) (Table 1).<sup>5,10-22</sup> Cases have been reported across all pediatric age groups and all ethnic origins, in spite of initial reports of a higher incidence among African-Americans and Hispanics.<sup>5,10-22</sup> Most reports point out that MIS-C is prevalent between 6 and 12 years old, although the Critical Coronavirus and Kids Epidemiology (CAKE) study reported that patients with

TABLE 1. Age, clinical manifestations, and course of multisystem inflammatory syndrome temporally related to COVID-19 according to different publications<sup>13-15,20,21</sup>

		Publications (countries where patients were included)					
		Belhadjer et al. (France and Switzerland)	Verdoni et al. (Italy)	González-Dambrauskas et al. (Italy, Spain, Chile, Colombia, USA)*	Duffort et al. (USA) <sup>b</sup>	Feldstein et al. (USA)	Davies et al. (United Kingdom)
		n = 35	n = 10	n = 17	n = 99	n = 186	n = 78
Clinical aspects	Median age, in years	10	7.5	4	0-5 y.o. = 31 p. 6-12 y.o. = 42 p. 13-20 y.o. = 26 p.	8.3	11
	Fever (%)	100	100	76	100	100	100
	Conjunctival injection (%)	NR	20	NR	56	55	29
	Skin involvement (%)	57	80	0	62	74	45
	Gastrointestinal involvement (%)	83	60	35	79	92	90
	Cardiac involvement (%)	80	60	24	53	80	87
	Respiratory involvement (%)	65	NR	35	40	70	85
	Neurological involvement (%)	31	40	17	30	6	NR
Deceased (%)		0	0	6	2	2	2.6

p. = the number of patients in the group is indicated because there is no description of the group's median value.

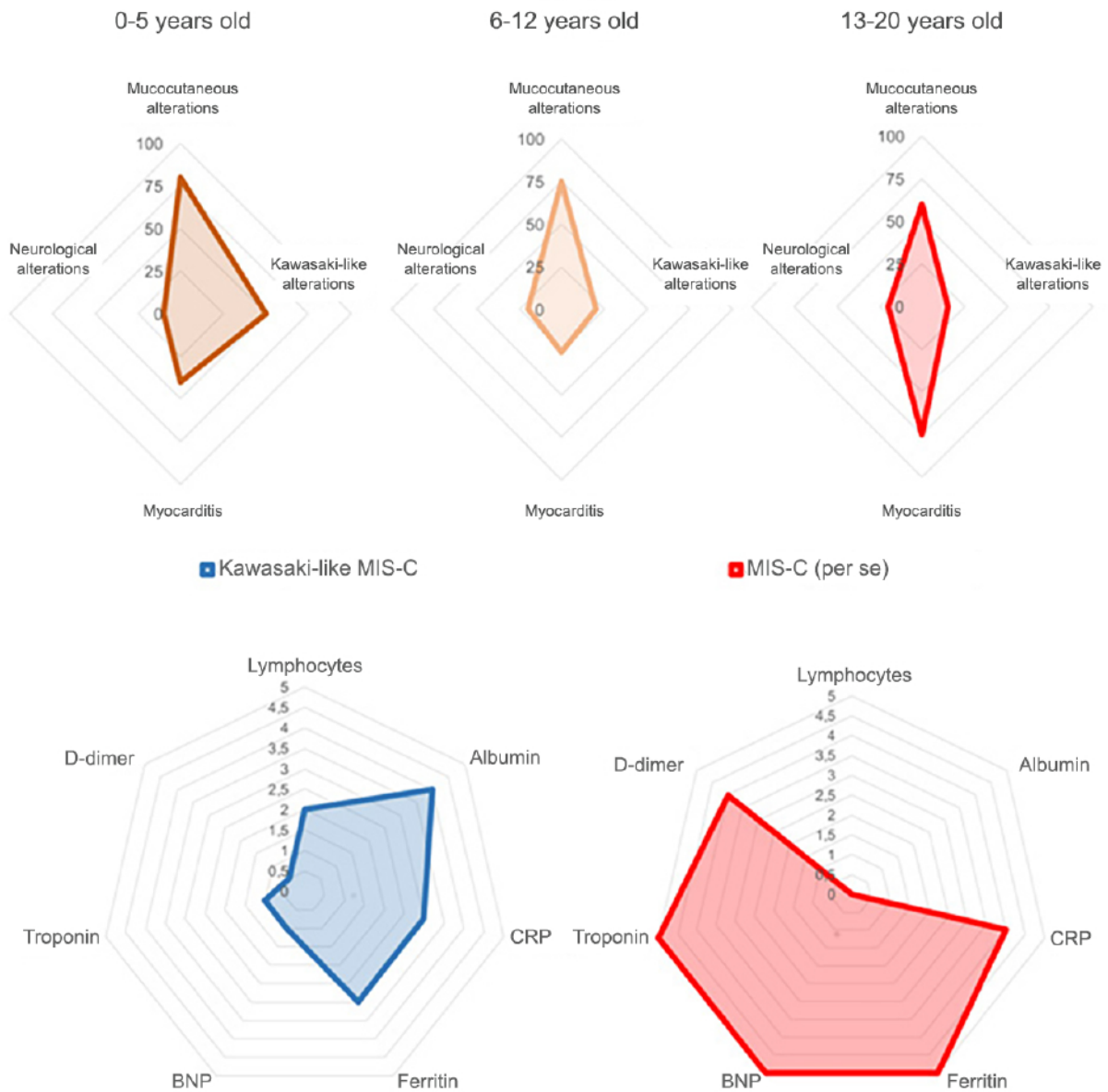
NR: no reference in the report.

The percentage (%) corresponds to the clinical presentation of each sign and symptom in each series.

<sup>a</sup> Data from patients with COVID-19 at the PICU; it is the only publication to date that includes patients from Latin America.

<sup>b</sup> Median age was not reported, only distribution by age group.

FIGURE 2. Clinical and laboratory outcome measures in relation to age and clinical presentations



Radar chart based on Franco Díaz's personal observations in Chile. Each radius size accounts for the value of each outcome measure.

**A.** Clinical manifestations in patients aged 0-5 years. Mucocutaneous manifestations and Kawasaki disease or incomplete Kawasaki disease outcome measures prevail.

**B.** Clinical manifestations in patients aged 6-12 years. Skin manifestations still prevail, although neurological manifestations and myocarditis start to be more common than in A.

**C.** Clinical manifestations in patients aged 13-20 years. Myocarditis and neurological manifestations prevail, unlike mucocutaneous manifestations.

**D.** Biochemical outcome measures in SARS-CoV-2 positive patients and Kawasaki-like clinical presentation, in a scale of 1 (less likely to occur) to 5 (more likely to occur). Elevated CRP and ferritin, with albumin and lymphocyte alterations, prevail.

**E.** Biochemical outcome measures in SARS-CoV-2 positive patients and MIS-C clinical presentation, in a scale of 1 (less likely to occur) to 5 (more likely to occur). A high elevation in troponin, BNP, ferritin, CRP, and D-dimer prevails, with less lymphocytes and albumin alterations.

KD: Kawasaki disease; iKD: incomplete Kawasaki disease; MIS-C: multisystem inflammatory syndrome in children (MIS-C) temporally related to COVID-19; CRP: C-reactive protein.



TABLE 2. Laboratory findings according to different publications<sup>13-15,20,21</sup>

		Publications (countries where patients were included)					
		Belhadjer et al. (France and Switzerland)  n = 35	Verdoni et al. (Italy)  n = 10	González-Dambrauskas et al. (Italy, Spain, Chile, Colombia, USA) <sup>a</sup>  n = 17	Duffort et al. (USA) <sup>b</sup>  n = 99	Feldstein et al. (USA) <sup>c</sup>  n = 186	Davies et al. (United Kingdom)  n = 78
Laboratory finding	<b>Neutrophils</b> Highest value x 10 <sup>3</sup> /mL (IQR) % = patients with neutrophilia in the series	13 (8-19)	84.5 %	NR	0%	68 %	NR
	<b>Lymphocytes</b> Highest value x 10 <sup>3</sup> /mL (IQR) [SD] % = patients with lymphopenia in the series	NR	0.86 [0.4]	47 %	66 %	80 %	0.80 (0.41-1.1)
	<b>Platelets</b> Highest value x 10 <sup>3</sup> /mL (IQR) % = patients with thrombocytopenia in the series	NR	130	NR	155 (105-233) 11 %	133 (88-235) 55 %	151 (93-208)
	<b>CRP</b> Highest value in mg/dL (IQR) [SD] % = patients above the cutoff point	24.1 (15.0-31.1)	25 [15.3]	76 %	21.9 (15.0-30.0) 100 %	17.8 (12.8-25.9) 91 %	25.1 (19.2-30.7)
	<b>Ferritin</b> Highest value in ng/dL (IQR) [SD] % = patients above the cutoff point	NR	1176 [1032]	41 %	522 (305-820) 75 %	639 (332.7-1178.2) 61 %	958 (516-1554)
	<b>Procalcitonin</b> Highest value in ng/dL (IQR) % = patients above the cutoff point	36 (8-99)	NR	35 %	6.2 (2.2-19.7) 92 %	NR	NR
	<b>Troponin</b> Highest value in ng/L (IQR) [SD] % = patients above the cutoff point	347 (186-1267)	1004 [1862]	25 %	71 %	50 %	167 (41-1112)
	<b>Pro-BNP</b> Highest value in pg/mL (IQR) [SD] % = patients above the cutoff point	5743 (2648-11 909)	1255 [829]	NR	90 %	1194.7 (390.8-4833) 73 %	NR
	<b>D-dimer</b> Highest value in ng/mL (IQR) [SD] % = patients above the cutoff point	5284 (4069-9095)	3798 [1318]	41 %	2400 (1200-3700) 91 %	4090 (2240-8404.5) 67 %	3750 (2106-6958)
	<b>Fibrinogen</b> Highest value in mg/dL (IQR) [SD] % = patients above the cutoff point	0	621 [182]	NR	624 (506-764) 86 %	80 %	NR

IQR: interquartile range; SD: standard deviation; CRP: C-reactive protein; pro-BNP: pro B-type natriuretic peptide. Data expressed as per the data reported in the publications: % (n/N), according to the number of patients above the cutoff point. Cutoff points:

<sup>a</sup> Cutoff points: lymphopenia < 1000 (1 x 10<sup>3</sup>)/mL; CRP: > 0.2 mg/L; ferritin: > 200 ng/mL; procalcitonin: 2 ng/dL;

D-dimer: > 500 ng/mL; ferritin: > 300 ng/mL.

<sup>b</sup> Cutoff points in the study by Duffort: lymphopenia < 2.5 % (< 1 month old)/< 4.0 % (1-12 months old)/< 3.0 % (1-2 years old)/< 2.0 % (2-4 years old)/< 1.5 % (4-10 years old)/< 1.2 % (10-16 years old)/< 1.0 % (> 16 years old); thrombocytopenia: < 80 000; CRP (C-reactive protein): ≥ 3 mg/dL, ferritin: > 300 ng/mL; procalcitonin: 0.5 ng/dL; pro-BNP: > 1121 pg/mL (1 month-1 year old)/675 pg/mL (1-2 years old)/391 pg/mL (2-14 years old)/363 pg/mL (> 14 years old); D-dimer: > 550 ng/mL; fibrinogen: > 400 mg/dL.

<sup>c</sup> Cutoff points in the study by Feldstein: thrombocytopenia < 150 000; CRP (C-reactive protein): ≥ 3 mg/dL; ferritin: > 500 ng/mL; pro-BNP: > 400 pg/mL; D-dimer: > 3000 ng/mL; fibrinogen: > 400 mg/dL.

COVID-19 admitted to the pediatric intensive care unit (PICU) had a median age of 4 years.<sup>18</sup> The initial clinical signs include high and persistent fever for > 3 days, maculopapular skin lesions similar to KD, gastrointestinal symptoms (nausea, vomiting, diarrhea or abdominal pain) and myocardial involvement.<sup>5,10-22</sup> If shock is present, it is not possible to clinically differentiate it from SSh.<sup>23-26,28,29</sup> Heart involvement, which is present in a high percentage of patients, includes myocardial dysfunction, coronary artery aneurysms, pericarditis, arrhythmias, refractory shock and/or elevated cardiac biomarkers, including troponin I or brain natriuretic peptide, even in the absence of major cardiac involvement.<sup>10,19,22,48-50</sup>

The CAKE study reported a lower frequency of cardiac involvement than other European studies,<sup>18</sup> which probably pointed out phenotypes of the same disease. Duffort et al.,<sup>19</sup> and Franco Díaz (personal communication about patients with MIS-C in Chile) noted that the presence of clinical and laboratory signs varied depending on age. Skin involvement and similar signs are believed to prevail among patients aged 0-5 years, whereas myocarditis and neurological symptoms are common among those aged 13-20 years<sup>19</sup> (Figure 2).

The most common laboratory findings are leukocytosis, neutrophilia, lymphopenia, anemia, and thrombocytopenia.<sup>2</sup> Inflammatory biomarkers are high (C-reactive protein [CRP], procalcitonin, serum ferritin, interleukin-1, and interleukin-6) (Table 2). As in the case of sepsis, a simultaneous increase in CRP and ferritin is associated with other phenotypes which show a poorer course.<sup>5,10-22,24-27,51</sup>

In MIS-C, there is a procoagulant state evidenced by different biochemical alterations. Although COVID-19-induced coagulopathy shares features with other types of coagulopathy, it may be a new variation.<sup>52</sup> In spite of a high D-dimer value, at baseline, fibrinogen levels are also high, which suggests a predominantly inflammatory response (endotheliitis) rather than a consumptive coagulopathy.<sup>20,21,52</sup> Given that the level of serum hyaluronic acid, a key component in glycocalyx, is higher during childhood, the endothelium may be more protected, with a lower probability of a hypercoagulable state.<sup>53,54</sup>

If MIS-C suspicion is low, it is suggested to order white blood cell count with blood differential test, in addition to platelet count, CRP or erythrocyte sedimentation rate. If MIS-C suspicion is strong or it is confirmed, it is suggested to order more extensive tests:

ferritin, procalcitonin, troponin, D-dimer, coagulation tests, transaminases, and lactate dehydrogenase.<sup>24-27</sup>

The onset of cases 4-6 weeks after the regional pandemic peak and the report of patients with negative rtPCR and positive serology (immunoglobulin G [IgG] or immunoglobulin M [IgM] for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) support the hypothesis of a post-infection inflammatory process related to COVID-19.<sup>10-22</sup>

Given that, signs and symptoms are non-specific and presentation varies, in the context of a pandemic and in accordance with local epidemiological guidelines, if a patient's condition is suspicious, physicians should think: "Could this be MIS-C?"<sup>33</sup> In suggestive cases with normal lab tests, patients should receive specific discharge instructions and follow-up in the following 24-72 hours, either in-person or through telemedicine.<sup>25</sup> The Paediatric Sepsis Six approach proposed by the United Kingdom Paediatric Sepsis Group<sup>55</sup> has been modified for the initial approach of MIS-C (Figure 3).

## RESUSCITATION BUNDLE

### General aspects

As with SSh, resuscitation is targeted at correcting hemodynamic and metabolic alterations.<sup>30,31,56</sup> Local resources should be considered beforehand so that recommendations do not fail because of suggesting unavailable elements (e.g., lab tests, monitoring methods or treatment options) (Figure 4).<sup>57</sup>

### Monitoring

A lack of invasive hemodynamic monitoring is no justification for a delayed management. Non-invasive monitoring includes continuous electrocardiogram and the measurement of respiratory rate (RR), heart rate (HR), blood pressure (BP), shock index (SI), oxygen saturation (SatO<sub>2</sub>), urine flow (UF), rectal or axillary temperature.<sup>30,31</sup> If available, it is advisable to use advanced hemodynamic, in addition to clinical, outcome measures, as guidance for resuscitation (continuous invasive BP, central venous pressure [CVP], and SatO<sub>2</sub> in the superior vena cava [SatO<sub>2svc</sub>]). The target SatO<sub>2svc</sub> is > 70 %; the value obtained for the inferior vena cava (SatO<sub>2ivc</sub>) or the right atrium (SatO<sub>2ra</sub>) is also valid.<sup>24-27,30,31,39,58,59</sup> Although there is no evidence recommending the measurement of tissue/abdominal perfusion pressure (TPP/APP), some experts have pointed

out a mean BP (MBP) between the 5<sup>th</sup> and the 50<sup>th</sup> percentile for age, while others suggested a MBP over the 50<sup>th</sup> percentile.<sup>24,27</sup> If mental status, perfusion, diuresis, and lactate improve, a lower BP may be tolerated.<sup>24,60</sup> At the Emergency

Department, it may be practical to use the SI (HR/systolic BP [SBP]), thus reducing HR and increasing SBP.<sup>61,62</sup>

It is worth performing an echocardiogram to monitor myocardial function because of the

FIGURE 3. Six steps for the initial management of multisystem inflammatory syndrome temporally related to COVID-19 (sepsis)

## MIS-C Six (Sepsis)

### WEAR PERSONAL PROTECTIVE EQUIPMENT

**• Children and adolescents aged 0-19 years with fever > 24 hours (may include patients up to 21 years old):**  
 => If a child has at least shock or myocardial dysfunction  
 PLUS  
 => 2 or more clinical\* or epidemiological characteristics of MIS-C  
 => or body temperature > 38 °C for > 24 h, without a definite source  
 \* Skin rash or bilateral, non-purulent conjunctivitis or signs of mucocutaneous inflammation (mouth, hands or feet), lymphadenopathy, pericarditis characteristics, valvulitis or coronary artery anomalies, coagulopathy, gastrointestinal conditions (diarrhea, vomiting or abdominal pain), known COVID-19 contacts or suspected exposure to COVID-19 or positive test, elevated markers of inflammation (CRP, etc.)

Apply a high suspicion index for children with chronic diseases or immunocompromised children

**THINK:** Time   
 Could this child have MIS-C? (check case definition)\*  
 Request a consultation with an experienced pediatrician or pediatric emergency physician or pediatric intensivist Signature

If you are **highly certain** that it is MIS-C, respond with the MIS-C Six:

Time  Signature

Highly certain that it is NOT MIS-C or unsure

**Complete all steps WITHIN 1 hour** Time  Signature

**1. Give oxygen (titrate as needed: HFNC or NIV or IMV)** Time  Signature

**2. Obtain IV/IO access and take blood tests plus clinical tests** Time  Signature

a. **General:** Cultures (blood, urine, etc.), ABB, WBC count with blood differential test, lactate, C-reactive protein, PT/KPTT.  
 b. **Desirable, if possible:** ferritin, LDH, CPK, troponin, NT-ProBNP, D-dimer, fibrinogen, procalcitonin.  
 c. **Other ancillary tests:** COVID-19 nasal swab, chest X-ray, ECG, echocardiogram, and serology.

**3. Consider giving IV/IO antibiotics** Time  Signature

a. Consider broad-spectrum antibiotics based on local standards (e.g., ceftriaxone or vancomycin)

**4. Consider fluid administration** Time  Signature

Health systems WITH PICU  
 a. Abnormal perfusion **WITH/WITHOUT** hypotension: administer fluid bolus at 10-20 mL/kg up to 40 mL/kg  
Health systems WITHOUT PICU  
 a. Abnormal perfusion **WITHOUT** hypotension: start maintenance fluids  
 b. Abnormal perfusion **WITH** hypotension and NO signs of fluid overload: administer fluid bolus at 10-20 mL/kg up to 40 mL/kg  
 c. Be CAUTIOUS. Control for signs of fluid overload (rales, crepitations, and hepatomegaly)

**5. Consultation with pediatrician or pediatric specialist (specialist in infectious diseases, cardiologist, intensivist or emergency physician)** Time  Signature

**6. Consider administering inotropes and multiple monitoring** Time  Signature

Monitor cardiac function and then decide:  
 WITH cardiac involvement, titrate inotropes (epinephrine, milrinone, dopamine, levosimendan)  
 WITHOUT cardiac involvement, norepinephrine is the first-line drug

NO MIS-C Time  Signature

Unsure Time  Signature

Check in 60 minutes

NO MIS-C Time  Signature

MIS-C Start MIS-C Six Time  Signature

Unsure Time  Signature

Check in 60 minutes

NO MIS-C Time  Signature

MIS-C Start MIS-C Six Time  Signature

Unsure Time  Signature

Check in 60 minutes

**Use your clinical judgment:** Patients with suspected MIS-C may have other conditions.  
 Look for Kawasaki disease or bacterial sepsis or toxic shock syndrome.

Translated and modified by the authors from Tong J, Plunkett A, Daniels R. G218(P) The Paediatric Sepsis 6 Initiative. *Arch Dis Child.* 2014;99(S1):A93.

IV: intravenous; IO: intraosseous; ECG: electrocardiogram.

potential heart dysfunction caused by pulmonary hypertension (in relation to acute respiratory distress syndrome [ARDS], invasive mechanical ventilation [IMV] or pulmonary thromboembolism), myocarditis, and the possibility of coronary artery aneurysms (Z-score adjusted for body surface > 2.5). An echocardiogram also allows to assess hypovolemia by observing if the inferior vena cava has minimum diameter variations throughout the breathing cycle. This allows to reverse shock more rapidly, with a lower fluid overload, a shorter length of stay, and a lower mortality rate compared to those who do not undergo an echocardiogram.<sup>64</sup> The SSC suggests using lactate level trends rather than the baseline lactate level as a supplement to clinical examination.<sup>24</sup>

### Goals

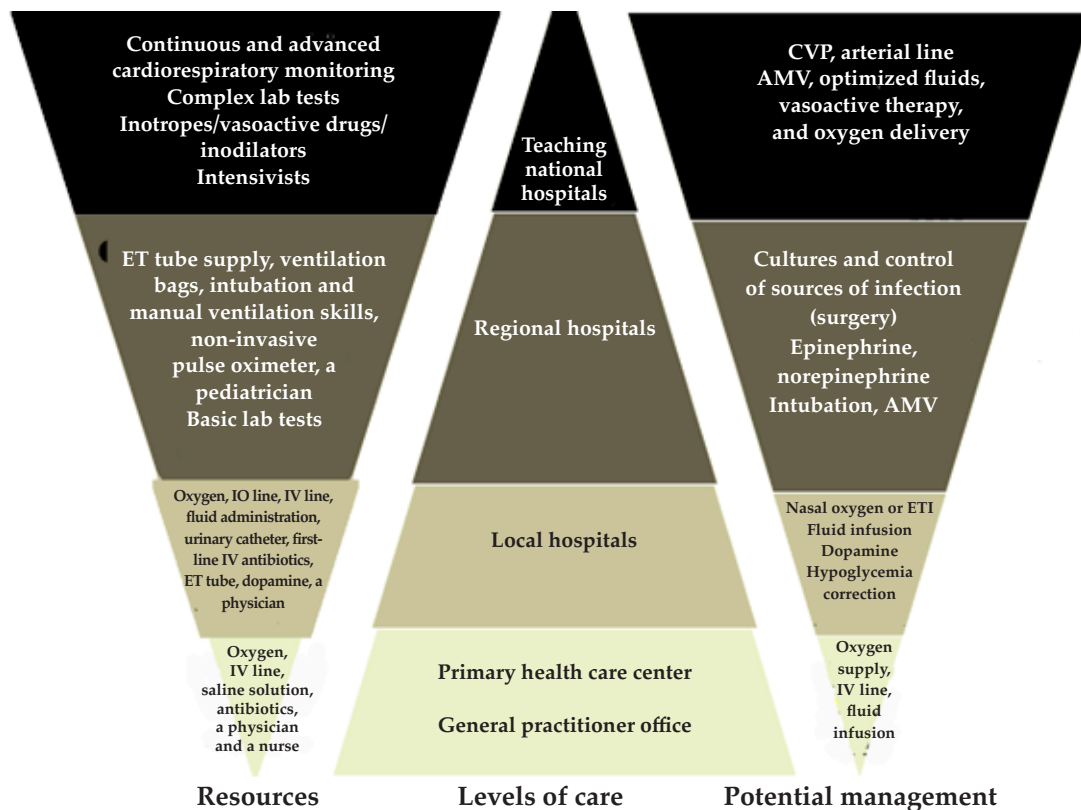
Goals are the same as those described for SSh: obtaining a patent airway, with adequate oxygenation and ventilation; normalizing HR for age, distal and central pulses, capillary refill, skin temperature, and the sensorium; and optimizing urine flow.<sup>30</sup> Achieving these goals

using stepwise treatments has reduced pediatric SSh mortality by 40 %.<sup>37</sup>

### Treatment

- Oxygen therapy: Supplemental oxygen (O<sub>2</sub>) administration should meet the requirement levels based on hypoxemia and work of breathing.<sup>24-27</sup> Given the risk of viral aerosol particles, strict personal protection measures should be followed and, if available, isolation rooms should be used. It is suggested to start with a low-flow nasal cannula if oxygen saturation (SpO<sub>2</sub>) is < 90 % and then escalate, as needed, to a high-flow nasal cannula (HFNC), ventilation with non-invasive positive pressure (NIPPV), continuous positive airway pressure (C-PAP) or bilevel positive airway pressure (BiPAP), and then IMV.<sup>27,66,67</sup> Both hypoxemia and hyperoxia should be prevented.<sup>68</sup>
- Fluids: The recommendations about vascular accesses are the same as for SSh.<sup>24-27,30,33</sup> Patients with MIS-C may develop hypovolemia due to gastrointestinal losses before consultation, and

FIGURE 4. Levels of care, resources, and potential management (modified and translated from the original)<sup>55</sup>



IV: intravenous; IO: intraosseous; ET: endotracheal; CVP: central venous pressure; AMV: assisted mechanical ventilation.



they also frequently have heart dysfunction. The fluid administration strategy should be “adapted” to each patient and available resources.<sup>24,27</sup>

- b.1. In health care systems where a PICU is available (with staff and equipment for an advanced airway management and vasoactive drug administration), balanced crystalloid solutions (Ringer’s lactate) up to 40-60 mL/kg (10-20 mL/kg per bolus) should be given in the first hour, then titrated based on cardiac output clinical markers and stopped if fluid overload signs appear.<sup>24,27</sup>
- b.2. If there is no PICU available and the patient has arterial hypotension, any available crystalloid solution (balanced or unbalanced) should be given up to 40 mL/kg as a bolus (10-20 mL/kg per bolus) in the first hour, then titrated based on cardiac output clinical markers and stopped if fluid overload signs appear.<sup>24,27</sup>
- b.3. If there is no PICU available and the patient does not have arterial hypotension (compensated shock), maintenance fluids should be given, but avoiding bolus administration because it would worsen the outcomes.<sup>24,27</sup> Some CPGs suggest the administration of fluids over 15 minutes, but there is now more evidence of the risk of this type of administration and, in practice, it is difficult to perform.<sup>69,70</sup> Therefore, a goal close to 30 minutes may be more reasonable.<sup>30</sup>
- c. Vasoactive drugs: In the absence of fluid response or in the presence of cardiogenic shock, vasoactive drugs should be infused through a peripheral venous access (PVA) (diluted), an intraosseous access or a central venous catheter (CVC).<sup>24-27,30</sup> The most common MIS-C hemodynamic pattern is warm shock; however, contractile dysfunction is sometimes prevalent. Therefore, norepinephrine or epinephrine are proposed for the initial management based on the patient’s hemodynamic profile. Dopamine, milrinone, levosimendan or vasopressin use has also been reported.<sup>10-22,24-27,30</sup>
- d. Antibiotic therapy: Although MIS-C is a viral condition, in practice, it is very difficult to distinguish among MIS-C, SSh and TSS. At baseline, one or more empiric antibiotics should be administered to cover every probable pathogen (especially, staphylococci and streptococci) and then they should be tailored once the microorganism

has been identified.<sup>24</sup> Antibiotics should be administered as soon as possible, ideally in the first hour.<sup>24,27</sup> It is important to perform a blood culture first, although this should not delay antibiotic administration.<sup>24,27</sup> Sources of infection should be treated as soon as possible.<sup>24,27</sup>

- e. Antiviral therapy: There is not enough evidence to recommend drug therapies in pediatric patients with SARS-CoV-2. Their use should be agreed upon by a multidisciplinary team.<sup>71</sup>

### **STABILIZATION BUNDLE (generally, after 60 minutes)**

An inadequate response to the initial resuscitation measures requires invasive monitoring and PICU-relevant management and, although they exceed the objectives of this study, they deserve some considerations.

#### **Monitoring**

An initial monitoring should be completed and, if available, cardiac output should be measured. It is recommended to monitor for and treat compartment syndrome, pneumothorax, and/or arrhythmias due to potential myocarditis and to maintain glycemia < 180 mg/dL.<sup>24</sup>

#### **Goals**

To continue with the same goals and achieve IMV optimization.

#### **Immunomodulatory therapy**

Given the little evidence available, it should be indicated based on a multidisciplinary approach.<sup>25-27,71</sup> Severe patients may receive it before completing MIS-C confirmation, unlike those without life-threatening involvement.<sup>27,71</sup>

The recommended intravenous immunoglobulin (IVIG) dose is 1-2 g/kg for moderate to severe cases (myocardial involvement, persistent shock or high vasopressor doses), and sometimes two IVIG series are required.<sup>19,20,27,71</sup> Low to moderate doses of methylprednisolone may be considered for all MIS-C patients; however, in the presence of shock or with high vasopressor doses, high pulse dosing may be indicated.<sup>27,71</sup>

In patients refractory to IVIG or corticosteroids, it is necessary to ask for the advice of personnel trained in using anti-inflammatory biological therapies, like anakinra and tocilizumab.<sup>72</sup> However, their use should be

an exception because their indication and safety profile have not been established in pediatrics.

### Hematological considerations

The rate of thrombosis observed in adults has not been reported in children, and it is recommended to document thrombosis in addition to providing a multidisciplinary management.<sup>10-22,73-76</sup>

- a. At risk for venous thrombosis (VT) (with a CVC or indwelling peripheral catheter or severely ill with no hyperinflammatory state and with no risk for thrombosis), subcutaneous enoxaparin should be considered to achieve an anti-Xa factor level of 0.3-0.5 u/mL:<sup>27</sup>
  - < 2 months old: 0.75 mg/kg/dose every 12 h
  - > 2 months old: 0.5 mg/kg/dose every 12 h
- b. At high risk for VT (critically ill, hyperinflammatory state [CRP > 150 mg/L, D-dimer > 1500 ng/mL, IL-6 > 100 pg/mL, ferritin > 500 ng/mL], history of thromboembolic events, echocardiogram ejection fraction < 35 %), subcutaneous enoxaparin should be considered to achieve an anti-Xa factor level of 0.5-1 u/mL:<sup>27</sup>
  - < 2 months old: 1.5 mg/kg/dose every 12 h
  - > 2 months old: 1 mg/kg/dose every 12 h

In patients with thrombocytosis (> 450 000 u/L) or KD-like criteria, the suggestion is to give aspirin: 3-5 mg/kg/day (maximum: 81 mg/day).<sup>72</sup>

Platelet transfusions are not advisable if the patient does not have active bleeding, even if they show an abnormal platelet count. Red blood cell transfusions are indicated for patients with a hemoglobin level < 7 g/dL who are also hemodynamically stable. There is no clear recommendation about hemoglobin levels in hemodynamically unstable patients.<sup>24</sup>

### REFERRAL BUNDLE

Health care teams specialized in critically-ill patients have reduced mortality and improved the clinical course of SSH; which highlights the importance of consulting trained staff for an adequate and timely treatment of MIS-C.<sup>77</sup> A new modality, telemedicine (remote consultation using IT devices, such as mobile phones, computers, etc.) allows an expert to virtually and remotely see a patient.<sup>78-83</sup>

### OUTCOME MEASUREMENT BUNDLE

The implementation of this bundle allows care process improvements.<sup>41-43,84</sup> The suggested items to be measured include bundle adherence,

achievement of goals, barrier description, observed unwanted effects, and adherence to a timely antibiotic administration.<sup>30</sup>

### CONCLUSION

MIS-C is a new form of COVID-19 in children and adolescents about which much remains to be studied. Its low prevalence does not rule out the need to establish its diagnosis and manage it because some patients with COVID-19 with few symptoms may worsen rapidly. Its clinical manifestations, lab test results, and natural course meet the criteria for viral sepsis with organ dysfunction; therefore, its initial management should be very similar. ■

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