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Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS): The viewpoint of the Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee

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**Paediatric Inflammatory Multisystem Syndrome Temporally
associated with COVID-19 (PIMS-TS): The viewpoint of the *Latin
American Society of Pediatric Intensive Care (SLACIP) Sepsis
Committee***

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Jaime Fernández-Sarmiento MD PhD(c)^{1,6}, Daniela Carla de Souza MD PhD^{2,6}, Roberto Jabornisky MD^{3,6}, Gustavo Ariel González MD^{4,5,6}, María del Pilar Arias López MD^{5,6}, Gladys Palacio MD^{5,6}.

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1 Department of Critical Care Medicine and Pediatrics, Universidad de la Sabana, Fundación Cardioinfantil - Instituto de Cardiología. CES Graduate School. Bogotá Colombia.

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2 Pediatric Intensive Care Unit and Department of Pediatrics, Hospital Universitario da Universidad de São Paulo and Hospital Sírio Libanês, Sao Paulo, Brazil.

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3 Department of Pediatrics. Facultad de Medicina. Universidad Nacional del Nordeste. Argentina.

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4 Pediatric Intensive Care Unit. Hospital Churruca - Visca Medical Complex. Buenos Aires. Argentina.

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5 Pediatric Intensive Care Unit. Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina.

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6 Sepsis Committee. Latin American Society of Pediatric Intensive Care (SLACIP).

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Corresponding author: Jaime Fernández-Sarmiento, MD. Universidad de La Sabana, Campus del Puente del Común, Km 7 Autopista Norte de Bogotá, Chía - Cundinamarca - Colombia - South America. JaimeFe@unisabana.edu.co. + 057-16672727 ext 2204.

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Abstract

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Background: In this review, we discuss some important aspects of Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new syndrome that is temporally related to previous exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This virus has a broad spectrum of presentation, as well as overlapping features with atypical Kawasaki disease (aKD). Our objective was to review and summaries published evidence regarding the

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3 most important aspects of PIMS-TS, with special emphasis on the treatment strategies
4 suggested for middle- and low-income countries.
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8 *Methods:* A systematic review of the literature was performed in the principal medical
9 databases including PUBMED, EMBASE (OVID) and Google Scholar between
10 December 2019 and August 2020.
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15 *Results:* A total of 69 articles were identified in the described databases. Altogether, 13
16 articles met the inclusion criteria and were eligible. The most frequently described
17 symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%),
18 skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-
19 6 weeks after the pandemic appears in the general population. Multisystem inflammatory
20 syndrome in children is presented as a great systemic inflammatory response syndrome
21 (SIRS), which sometimes evolves into septic shock features requiring fluid resuscitation
22 and vasoactive drug support (26%). Several treatment strategies have been used,
23 including immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others.
24 These general and specific interventions should be guided by an inter- and multi-
25 disciplinary team, especially in settings with limited resources.
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35 *Conclusions:* PIMS-TS COVID-19 is a new form of SARS-CoV-2 sepsis, with an
36 exaggerated inflammatory response and frequent *-but not exclusive-* digestive and
37 myocardial involvement. It is very similar in its presentation to Kawasaki disease, but
38 should be considered as a new disease. Research is needed to establish the role of
39 biomarkers for early diagnosis, effective therapeutic strategies, and outpatient follow-up
40 schemes.
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46 *Key words:* septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease,
47 thrombosis, SARS-CoV-2
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51 **What is known about the subject?**

52 -PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times
53 greater need for hospitalization and mortality in children than other COVID-19
54 presentations.
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57 -It is characterized by fever, shock and gastrointestinal, skin and cardiac involvement,
58 with prior positive RT-PCR or antibody tests.
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3 -The diagnostic and treatment approach should be the same as for sepsis with organ
4 dysfunction and viral septic shock. The specific treatment includes immunomodulators.
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8 **What does this study add?**

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10 This review summarizes the main PIMS-TS case series, with their clinical characteristics
11 and complications. For this SARS-CoV2 disease, which mainly affects children, a
12 comprehensive approach is suggested which may be applied under the various healthcare
13 system access conditions, including strategies geared towards middle- and low-income
14 countries. This treatment includes viral sepsis management and specific
15 immunomodulatory therapy currently recommended based on the available evidence.
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22 **INTRODUCTION**

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24 In December 2019, a new viral infection was reported for the first time in history, causing
25 severe respiratory infection and very high mortality. According to its genetic sequencing,
26 this virus belongs to the genus *Beta coronavirus*, closely related to the severe acute
27 respiratory syndrome (SARS) virus. It was named SARS-CoV-2 and its disease COVID-
28 19.^{1,2}
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32 Healthcare systems worldwide have been deeply concerned, given SARS-CoV-2's high
33 transmissibility, severity and lethality, particularly in the population over the age of 60.¹
34 Patients with major comorbidities such as heart disease, diabetes, hypertension, or obesity
35 have an increased risk of dying.^{1,2} Moreover, mortality has been associated with multiple
36 organ failure (MOF) as the common final pathway for pneumonia, sepsis, and acute
37 respiratory distress syndrome (ARDS). COVID-19 is usually less severe in paediatric
38 patients. In general, 80-90% of cases are asymptomatic or have a mild infection.
39 However, between 4 -10% may need to be transferred to a paediatric intensive care unit
40 (PICU), and mortality ranges from 0.1% to 8%.^{3,4} Recently, the Critical Coronavirus and
41 Kids Epidemiology (CAKE) study reported a mortality rate of 5% in five European and
42 American countries (Chile, Colombia, Italy, Spain and USA), with 76% of cases having
43 severe pneumonia as their main manifestation.⁴
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53 Several pathophysiological factors may explain these features. COVID-19 non-survivors
54 have higher serum ferritin, D-dimer and C-reactive protein (CRP) than those who survive,
55 indicating an intense inflammatory response². Recently, a new type of presentation of
56 SARS-CoV-2 infection has been described in children, involving this significant
57 inflammatory response. This new disease has been called Paediatric Inflammatory
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3 Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new
4 syndrome that is temporally related to previous exposure to severe acute respiratory
5 syndrome coronavirus 2 (SARS-CoV-2) infection. This is a severe presentation of the
6 virus in children and requires early detection to avoid its progression and potentially
7 unsatisfactory outcomes⁵. In this article, we discuss and review the most relevant aspects
8 of PIMS-TS described to date.
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13 14 15 **METHODS**

16 17 **Search strategy and article selection**

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20 A systematic review of the literature was performed in the principal medical databases
21 including PUBMED, EMBASE (OVID) and Google scholar, using the MeSH terms
22 (“SARS-CoV-2” OR “Covid-19” OR “coronavirus” OR “infection” OR “sepsis” OR
23 “covid-19” OR “critical care”) AND “Multisystem Inflammatory Syndrome in Children”
24 OR “MIS-C” OR “PIMS-TS” between December 2019 and August 2020. The descriptors
25 were validated in DecS (descriptors in health science) and MeSH (medical subject
26 headings). Grey literature or as yet unpublished documents were not included.
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32 33 **Eligibility criteria**

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35 Articles which reported at least five cases of PIMS-TS, including case series, case reports,
36 and cross-sectional, case-control, cohort (either prospective or retrospective) or clinical
37 trial studies, were included. Studies of critically ill children with COVID-19 were also
38 considered, and the cases of PIMS-TS reported in these studies were explored. The World
39 Health Organization (WHO), Centers for Disease Control (CDC) and Royal College
40 guidelines were consulted for the definitions. Articles which did not provide complete
41 data when reporting general cases of critically ill children with COVID-19, or those for
42 which the full text was not available, as well as narrative reviews, were excluded.
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50 51 **Study selection and data collection process**

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53 First, the inclusion and exclusion criteria for this systematic review were defined, after
54 which one of the researchers (JFS) performed the systematic search of the literature and
55 reviewed the most relevant articles. The established criteria were applied, and the articles
56 were approved by all the SLACIP sepsis committee authors. In case of doubt, or a lack
57 of consensus regarding the inclusion of an article, a second reviewer (RJ) was consulted
58 to decide. Any discrepancies or missing data were resolved by consensus. Preferred
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3 Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were
4 followed. (Figure 1).
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8 **Patient and Public Involvement statement**

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10 No patients participated actively in this review. The data were taken from the most
11 important publications to date on PIMS-TS, including consensus recommendations for
12 high-income countries. It is expected that this information will be disseminated through
13 SLACIP and its various committees for applicability in patients living in middle- and
14 low-income countries.
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20 **RESULTS**

21 **Search and study selection results**

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23 A total of 69 articles were identified in the described databases. After eliminating the
24 duplicates and reviews, 13 articles met the inclusion criteria and were eligible. These
25 articles were included in the qualitative synthesis and the most relevant ones which do
26 not include patients reported in other case series are described by their characteristics in
27 *Table 1 and Table 2 (supplementary file)*.
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34 **DISCUSSION**

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36 Although the main pathogenesis of COVID-19 may be similar to other viruses such as
37 influenza, it has shown some clinical presentations which are different from those usually
38 found in those classical respiratory viruses. On April 24, 2020, a new presentation of
39 SARS-CoV-2 in children was described by Riphagen et al. in the United Kingdom⁶. The
40 first communication described a cohort of eight children with COVID-19 who required
41 hospitalization in intensive care and had an unusual clinical behavior characterized by a
42 severe hyperinflammatory state, with clinical similarity between all eight patients⁷⁻⁹.

43
44 The Royal College of Paediatrics and Child Health called this new entity PIMS-TS.¹⁰
45 Subsequently, the CDC and WHO called it multisystem inflammatory syndrome in
46 children (MIS-C).^{11,12} In general, they refer to the same entity and the latter name has
47 been the most frequently used in the main descriptions of this disease (*Table 3*).
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57 PIMS-TS is characterized by a very significant ongoing inflammatory response, in
58 crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and
59 WHO (May 15th) definitions (*Table 3*).^{11,12} Characteristically, these patients present with
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3 high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.¹³ Hoang et al.¹⁴ reported
4 lower expression of circulating CD16+CD56+ natural killer cells and more profound
5 lymphopenia in children with PIMS-TS compare to those without PIMS-TS.
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8 Primarily, there is an initial innate immune response with the macrophages as the
9 principal actors. From the pathophysiological point of view, it is striking that more than
10 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an
11 acute phase reactant that usually rises after six hours of an inflammatory state and is
12 produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF- α
13 stimulation.^{15,16} This acute phase reactant from the pentraxin family identifies
14 phosphatidylserine on the surface of cells that have initiated a programmed cell death
15 pattern of apoptosis by activating the complement system.
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18 Additionally, a marked elevation of ferritin (2-10 times its normal value) has been
19 observed in more than 90% of the series.^{14,17} Ferritin is a protein that stores iron and
20 releases it in a controlled fashion, but also in pathophysiologic conditions. Its levels can
21 reflect macrophage response to free hemoglobin as well as DNA viruses, intracellular
22 bacterial infections and parasites.¹⁸⁻²⁰ Ferritin can induce positive feedback inflammation,
23 upregulating toll-like receptor 9 (TLR-9) which leads macrophage inflammasome IL-1
24 and IL-18 to feed forward ferritin production. TLR-9 may also be stimulated by viral
25 DNA, other infections and host damage-associated molecular patterns (DAMP).²⁰ This
26 whole process generates a large number of inflammasomes and an enhanced
27 inflammatory pathway, delivering the “cytokine storm.” This precipitate cell death with
28 a pyroptosis pattern and new DAMPs that stimulate TLR-9.²⁰ This was described as
29 “*Hyperferritinemic Syndrome*” by Rosario.
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Author	City, Country	Period	Number	Age	Gender	Comorbidity	Race	IMC kg/m ²
Riphagen et al [6]	London, UK	10 days in mid-April	8	4 – 14 years (range)	5/8 boy	None	6/8 Afro-Caribbean	14 – 33 7/8 > 75 th centile/weight
Verdoni et al [7]	Bergamo, Italy	Feb 18 and April 20	10	7.5 years (SD 3-5)	7/10 boys	N/R	N/R	N/R
Whittaker et al [3]	London, UK	March 23 and May 16	58	9 years (IQR 5.7, 14)	43% boys	7/58 Comorbidities	69% black or Asian	N/R
Grimaud et al [9]	Paris, France	April 15 and April 27	20	10 years (IQR 2.9, 15)	50% boys	N/R	N/R	N/R
Belhadjer et al [8]	France (12 hospitals) and Switzerland (1 hospital)	March 22 to April 30	35	10 years (IQR 8.2, 12.4)	51% boys	Comorbidities 28% (asthma 8.55; lupus 3%)	N/R	Overweight 17%
Cheung et al [13]	New York, US	April 18 and May 5	17	8 years (IQR 1.8, 16)	47% boys	Most were previously healthy (mild asthma in 3)	White 70%	N/R
Toubiana et al [45]	France, Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR 3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI below the 97 th centile
Kaushik et al [38]	New York, US	April 23 to May 23	33	10 years (IQR 6, 13)	61% boys	Comorbidities 48%	45% Hispanic/latino 39% black	Overweight 12% Obesity (BMI > 30kg/m ²) 6%
Pouletty et al [46]	Paris, France	Since April 2020	16	10 (IQR 4.7, 12.5)	50% boys	Comorbidities 37%	N/R	Overweight 25%

Ramcharan et al [40]	UK	10 th April and 9 th May	15	8.8 (IQR 6.4, 11.2) 93% were over 5y	73% boys		100% African/Afr-Caribbean (40%), South Asian, (40%) Mixed (13%) Or other minority ethnic	
Caponi et al [47]	New York, US	April 17 – May 13	33	8.6 years (IQR 5.5, 12.6)	61% boys	Comorbidities 21%	73% non-Hispanic	Overweight 6% Obese 39%
Feldstein L.R et al [48]	Multicenter, US	March 15 to May 20	186	8.3 years (IQR 3.3, 12.5)	62% boys	Comorbidities 27%	31% Hispanic, 25% Black non hispanic	Obesity 29%
Dufort E et al [49]	New York City	March 01 to May 10	95	0-5 years (31%) 6-12 years (42%) 13-20 years (27%)	54% boys	Comorbidities 64%	40% black 36% Hispanic	Obesity 29%

Table 1. Demographic characteristics of patients with PIMS-TS. N/R: not reported.

Royal College of Paediatrics and Health Child (RCPCH) Definition [10]

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative.

Centers for Disease Control and Prevention (CDC) Definition [11]

- 1. An individual aged < 21 years presenting with fever¹, laboratory evidence of inflammation² and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND**
- 2. No alternative plausible diagnoses; AND**
- 3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.**

¹Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

²Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

World Health Organization Definition [12]

Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

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

AND

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

AND

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

AND

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

Table 3. RCPCH, CDC, WHO Definitions Criteria for Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19

Nevertheless, there is evidence of an unusual late adaptive immunity response. It has come to the researchers' attention that PIMS-TS occurred between four and six weeks after the peak of cases reported as positive for SARS-CoV-2 in each country had been reached.^{5,12,14} In fact, negative real-time polymerase chain reaction (RT-PCR) has been found in 40% of patients with positive antibody tests. Pérez-Toledo M et al.¹⁸ recently described eight patients with PIMS-TS with a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM. Although RT-PCR is an imperfect test, it is considered the gold standard today. This suggests that, in these patients, the infection occurred possibly weeks earlier.

Additionally, they found elevated IgG1 and IgG3 in these children, which are immunoglobulin isotypes associated with serum supplement activation. This situation is consistent with highly elevated CRP related to COVID-19, which activates the complement system. The elevation of these immunoglobulins suggests that PIMS-TS occurs due to tissue damage induced by autoantibodies, a situation that has been described in other types of coronavirus infection.²²⁻²⁴

There is evidence that SARS-CoV-2-induced sepsis, presented as PIMS-TS, triggers a procoagulant and antifibrinolytic state evidenced by the different degrees of severe coagulopathy found in 70-80% of the series (very high D-dimers, prolonged PT, PTT).^{8,13} Like inflammation, coagulation is necessary for the host defense. In addition, proinflammatory cytokines, monocytes / macrophages, neutrophil activation, and extracellular neutrophil traps (NETs) can foster local thrombosis. COVID-19 associated coagulopathy (CAC) is complex and in some ways pathophysiologically different from SIC^{25,26}. Cytokine levels of IL-1 β and IL-6 are elevated, which induces thrombocytosis

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3 and hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is
4 stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.^{27, 28}
5 D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its
6 early phase.²⁵ Elevated D-dimer levels can be present in a wide variety of inflammatory
7 and prothrombotic conditions;²⁹ in COVID-19, these are probably more associated with
8 inflammation than thrombosis.³⁰ Furthermore, serum hyaluronic acid, a key glycocalyx
9 component, is higher during infancy, progressively diminishing over the years.^{19, 31} This
10 could explain a more protected endothelium and a lower probability of a hypercoagulable
11 state. In addition, CAC has an overlapping pathophysiology with other coagulopathies
12 like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH),
13 antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) /
14 hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type
15 of coagulopathy.²⁵
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27 From a clinical and laboratory perspective, PIMS-TS has usually been seen in previously
28 healthy and frequently obese (30-60% of the series) children over eight years of age (80%
29 of the cases)^{4, 5, 12, 14} (*Table 1*). Initially, the group from the United Kingdom (UK) found
30 MIS-C in patients of African descent, but it has been described in patients of all
31 origins.^{4, 5, 9-11} Persistent high fever for more than three to five consecutive days,
32 maculopapular skin lesions (50-60%) reminiscent of Kawasaki disease (KD) and,
33 frequently, signs of shock at the time of presentation have been the initial clinical
34 characteristics.^{6, 7} Digestive symptoms (including nausea, vomiting, diarrhea or
35 abdominal pain) usually present in most cases, as well as myocardial involvement (more
36 than 60% of the series).^{6, 7, 14} Cardiac involvement is broad and variable, with features
37 including myocardial dysfunction (100% of the initial UK description - 60% in other
38 series), coronary aneurysms, pericarditis, arrhythmias, refractory shock and elevated
39 troponin I or pro-BNP³²⁻³⁴ (*Table 2*).
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51 With regard to treatment, it is important to keep in mind that PIMS-TS is a viral sepsis,
52 and thus rapid recognition is critical, along with optimal and time-sensitive treatment. An
53 expert consensus recently published in the United Kingdom using the Delphi method
54 provides a good summary of the recommended treatments³⁴. This approach is
55 recommended for high-income countries. Using the evidence found, we adapted these
56 recommendations, together with those of the SCCM sepsis consensus¹⁶, for use in
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3 medium and low-income countries. We believe that a comprehensive approach to PIMS-
4 TS patients is necessary, and that taking these recommendations as a whole could have
5 an impact on the outcomes of PIMS-TS patients in these countries.
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10 From the first presentation to the Emergency Department and / or PICU, two approaches
11 can be assumed, one general and one specific.

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13 a. *General approach:* A comprehensive approach should be used, as with any patient
14 admitted with sepsis with organ dysfunction or septic shock. In this case, the
15 contagiousness of SARS-CoV-2 requires the use of personal protective equipment (PPE)
16 that prevents the spread of the virus, particularly in patients with a positive RT-PCR.
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19 Moreover, the American College of Critical Care Medicine (ACCM) points out the need
20 to give more attention to Institutional Practice Guidelines (IPGs) based on each facility's
21 capability.³⁵ Once IPGs are established, diagnostic and therapeutic measures known as
22 "*patient care bundles*" (PCBs) should be developed for a better approach and control of
23 established processes. The PCBs include three to five evidence-based practices related to
24 a health care process that should be performed collectively to achieve a synergistic result
25 that improves care.^{36,37} The ACCM Sepsis Bundle includes:
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32 1. Early detection: a comprehensive approach based on a high index of suspicion is
33 critical. This disease may occur with a wide spectrum of symptoms, so it should be
34 suspected in all patients with a fever lasting more than three days associated with the
35 symptoms described in *Figure 2*. Contact with a positive case is not always clear.
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39 2. Immediate, time-sensitive resuscitation:

40 - Oxygen therapy: This is part of the strategies described in recent sepsis guidelines¹⁶.
41 High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been
42 considered in many reports,^{4,8,14} especially in patients who have a deteriorated respiratory
43 pattern with the use of accessory muscles or an SaO₂/FiO₂ ratio less than 264. Most series
44 describe respiratory involvement ranging from 20-60% (*Table 2*) and, generally, if
45 endotracheal intubation is required, it is more highly associated with cardiovascular
46 involvement.
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49 - Fluid resuscitation: It is important to consider the recommendations in recently
50 published guidelines.¹⁶ In healthcare systems where staff and equipment for advanced
51 airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of
52 balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour,
53 titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload
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3 develop. In healthcare systems without the availability of intubation, crystalloid boluses
4 may only be given in cases of hypotension (decompensated shock); in these cases, up to
5 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with
6 titration to clinical markers of cardiac output, and discontinued if signs of fluid overload
7 develop. If the child is not hypotensive, but has compensated shock, only maintenance
8 fluids should be started, avoiding bolus fluids which are associated with worse outcomes.

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13 -Vasoactive drugs: According to the clinical condition, most series describe the need for
14 vasoactive drugs in 10 to 60% of the cases with PIMS-TS. Most patients respond to fluid
15 resuscitation. If necessary, epinephrine or norepinephrine should be considered according
16 to the patient's condition.¹⁶ Inotropes like dopamine, milrinone and levosimendan were
17 reported to have been used in PIMS-TS.^{4,8,14,38}

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22 -Antibiotic therapy: If bacterial co-infection is suspected, the first dose is recommended
23 within the first three hours for sepsis associated with organ dysfunction, or within the first
24 hour for children with septic shock.^{16-18,39}

25 26 27 3. Stabilization with adequate monitoring:

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29 If possible, advanced hemodynamic monitoring should be instituted. Cardiac
30 ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent
31 guidelines¹⁶ and patients with PIMS-TS.⁴⁰

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34 4. Timely referral or transfer is desirable in this context, not only for advanced treatment
35 and monitoring but also to cluster COVID-19 patients to decrease the spread of
36 infection.^{16, 40,41}

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39 5. Continuous measurement of processes and corrections must be instituted for a
40 continuous quality improvement process.^{16, 41, 42}

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43 *b. Specific approach:* It is important to emphasize that, in moderate to severe cases, the
44 use of immunomodulatory treatment should be considered. Heterogeneous management
45 including human immunoglobulin, systemic steroids, anakinra, tocilizumab and aspirin
46 ^{6,7,11} has been reported in the described series (*Table 2*). The American College of
47 Rheumatology (ACR) recommendations for immunomodulatory therapy⁴² have recently
48 been published.

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53 ⇒ IVIG: High doses (2 gr/kg) should be considered for moderate to severe cases,
54 particularly those with myocardial involvement. Prior to beginning the infusion,
55 restored heart function must be verified.⁴²

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58 ⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical
59 course of the disease in adults with severe pneumonia, particularly if they are on
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mechanical ventilation.⁴³ In patients with PIMS-TS, low doses could be considered in all cases (used in 70% of the series – *Table 3*) and the RTA suggests considering high doses in cases of shock or a high need for vasopressors.

⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-refractory PIMS-TS.^{43,44} However, in many countries, its use is not approved, or it is not available.

⇒ Anticoagulation and antiplatelet treatment: Anticoagulation has become a fundamental treatment in adults, considering that there is a procoagulant and hypofibrinolytic state in severe SARS-CoV-2 infection.^{17,25,26} In children with PIMS-TS it is recommended only in cases of documented thrombosis or in patients with an echocardiogram ejection fraction less than 35%.⁴³ Aspirin would also be recommended in patients with thrombocytosis (> 450,000 u/L) or Kawasaki-like disease criteria.^{25,34,45,46}

The prognosis of the disease is usually good, with patient survival greater than 95% in different published series.^{5,6,7,38,45-48} However, there are incomplete data from all the cases, along with a knowledge gap regarding mild and moderate cases, the natural course and the clinical behavior of the disease.^{8,49}

Conclusion

PIMS-TS is a new form of SARS-CoV-2 sepsis, with an exaggerated inflammatory response and inadequate inflammatory resolution with frequent *-but not exclusive-*digestive and myocardial involvement. It is very similar in its presentation to KD, but should be considered as a new disease with unique symptoms, a greater variety of clinical courses, and possibly different physiological mechanisms. Research is needed to establish the role of biomarkers for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.

Contributors

JFS, DS, RJ, PA, GG, GP conceptualised and designed the literature search. JFS, DS, RJ initiated the search and a first draft. All authors contributed to subsequent drafts. JFS, as group leader, supervised and moderated the search, initial drafts, the overall collation of the figures and tables and final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

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37 **ORCID:** iD Jaime Fernández-Sarmiento <http://orcid.org/0000-0003-2874-2949116>
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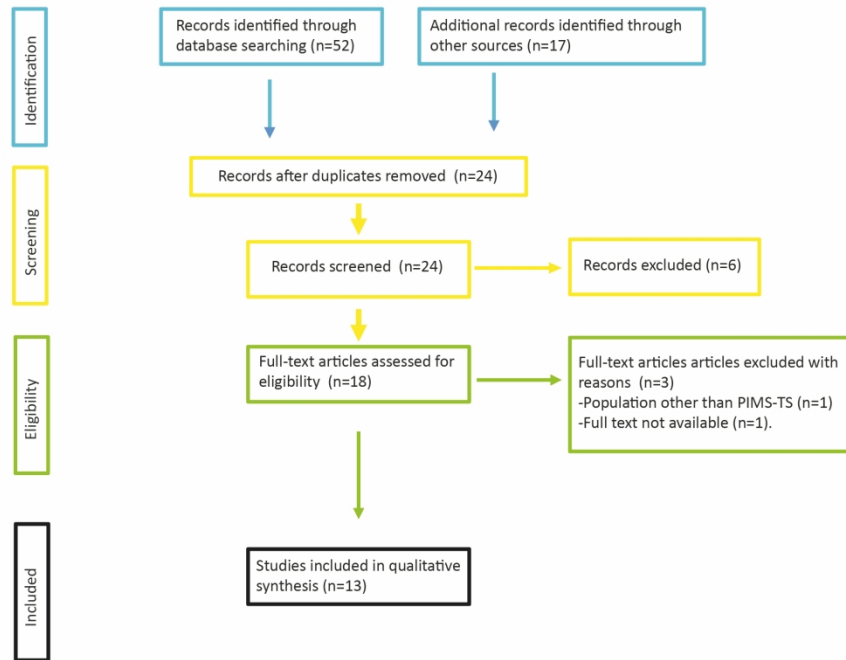
35 *Figure 1.* Selection process. We followed the PRISMA guidelines for reporting in
36 systematic reviews and meta-analyses
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41 *Table 1.* Demographic characteristics of patients with PIMS-TS
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44 *Table 2.* Clinical and echocardiographic findings, and treatments instituted in the
45 described series of PIMS-TS patients (*supplementary file*).
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49 *Table 3.* RCPCH, CDC and WHO Definition Criteria for Paediatric Inflammatory
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Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses



Author	Clinical presentation	ECHO	SARS-CoV-2 test	Organ support	Treatment	Outcome / Died
Riphagen et al [6]	Fever 8/8 Diarrhoea 7/8 Abdominal pain 6/8 Vomiting 4/8 Conjunctivitis 5/8 Rash 4/8 Vasoplegic shock 8/8	7/8 ventricular dysfunction Echobright coronary vessels 1/8 giant coronary aneurysm	SARS-CoV-2 negative 5/8 SARS-CoV-2 positive 2/8 Family exposure 4/8	Inotropic/vasopressor support 8/8, MV 5/8, HFNC 1/8, NIV 3/8, RRT 1/8, VA-ECMO 1/8 (arrhythmia with refractory shock, died)	IVIg 8/8, Corticoids 5/8 Aspirin 3/8, Heparin 1/8, Antibiotics 8/8, Infliximab 1/8	1 died 6/8 alive PICU length of stay 3 – 7 days
Verdoni et al [7]	Classic form of Kawasaki 50%, Incomplete form of Kawasaki disease 50% Kdss and MAS 50% Diarrhoea 60% Meningeal signs 40% Drowsiness 10%	Anormal ECHO 60% Aneurism 10% FEVE < 50% – 50% Mitral valve regurgitation 10% Pericardial effusion 40%	RT-PCR SARS-CoV-2 + 20% Serology for SARS-CoV-2 antibodies – 80% were IgG +, and 3 were also IgM +		Inotropic support 20% Adjunctive steroid treatment 80% IVIg 100% Aspirin 20%	None
Whittaker et al [3]	Fever 100%, Headache 26%, Vomiting 45% Diarrhea 52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29% Swollen hands and feet 16%, Respiratory symptoms 21%. Fever + elevated inflammatory markers – 40%, Shock - 50%	Left ventricular dysfunction 62% (18/29) Abnormally dilated coronary arteries (z score >2) 8/55 Giant coronary artery aneurysms 2 Coronary artery aneurism 14% (n=8)	RT-PCR SARS-CoV-2 + 26% IgG antibody SARS-CoV-2 + 87% 78% had evidence of current or prior SARS-CoV-2 infection	PICU 50% Acute kidney injury 22% Shock + inotropic support 47% MV 43% ECMO 5%	Inotropic support 47% IVIg 71% Corticosteroids 64% Anakinra 5% Infliximab 14%	Death 2%
Grimaud et al [9]	Fever 100%, Abdominal pain 100%, Rash 50%, Conjunctivitis 30%, Adenitis 20%, Tachycardia 100% Hypotension 100% (75% clinical signs of	LVEF 35% (IQR 25-55)	SARS-CoV-nasopharyngeal swabs + 50% SARS-CoV-2 antibodies + 100% (15/15), 95% had identified SARS-CoV-2 infection on PCR	NIV 55%, IMV 40%, HFNO 5%, Respiratory support in all patient was indicated for hemodynamic support	IVIg 100%, Corticosteroids 10%, Anakinra 5%, Tocilizumab 5%, Inotropic/vasopressor support 95%	None

	vasoplegia)		and/or by serology			
Belhadjer et al [8]	Asthenia 100% Fever 100% GI symptoms 83% (2 children underwent emergency operation for suspected appendicitis) Respiratory distress 65% Rhinorrhea 43% Adenopathy 60% Rash 57% Meningism 31% At admission to the ICU, 80% were in cardiogenic shock	Coronary artery dilatation (z score > 2) 17% Aneurysm 0 LVEF < 30% - 28% LVEF 30-50% - 72%	SARS-CoV-2 was confirmed 88.5% RT-PCR-SARS-CoV-2 + 34% Fecal PCR 6% Antibodies + 86%	Respiratory support 94% (IMV 62%; NIV 32%) VA-ECMO 28%	Inotropic support 80% IVIG 71% Corticosteroids 34% Anakinra 8% Anticoagulation with heparin 65%	None
Cheung et al [13]	Fever 100% GI symptoms 88% Shock at presentation 76% Rash 71%, Conjunctivitis 65% Lip redness/swelling 65% Neurologic symptoms 47%, Respiratory symptoms 41%, Myalgia 35%, Lymphadenopathy 35%, Hypoxia 18% Criteria for KD 47% Incomplete Kawasaki 29%	FEVE mildly decreased 29% FEVE mild-moderately decreased 24% FEVE moderate-severely decreased 12% Pericardial effusion 47%	RT-PCR SARS-CoV-2 + 47% Serology for SARS-CoV-2 antibodies -+ 53%	PICU 88%	IVIG 76% Methylprednisolone 71% Hydrocortisone 21% Enoxaparin prophylaxis 59% Enoxaparin treatment 6% Aspirin 24%	None
Toubiana et al [45]	Recent history of viral-like symptoms was report in 43% Median duration between these symptoms and the onset of signs and symptoms of Kawasaki disease was 45 days. Complete presentation of	Myocarditis 76% (LVFE range between 10 and 57%) 38% coronary artery abnormalities: 24% which consisted of dilations (z score between 2.0 and 2.5); 14% with increased	History of recent contact with people with viral-like symptoms was + in 48% Median interval between reported contact and KD was 36 days	PICU 81% Vasoactive agents 71% MV 52%	IVIG 100% (24% needed a second dose) Low dose aspirin (3-5mg/kg/day) 100% Corticosteroids (2-10mg/kg/day) 48% Antibiotic 86%	None

	KD 52%, Abdominal symptoms 95%, Lips and oral cavity changes 76% Conjunctivitis 81% Rash 76%, Changes to extremities 48% Lymphadenopathy 57%	coronary visibility No coronary aneurysms were identified	RT-PCR-SARS-CoV-2 + 38% IgG antibodies SARS-CoV-2 + 90% 9,5% negative Serology and PCR)			
Kaushik et al [38]	Fever 93%, Abdominal pain 63%, Nausea/emesis 69%, Diarrhea 48% Hypotension 63%, Mucocutaneous involvement 21% Conjunctivitis 36% Rash 42%, Shortness of breath 33% Neurologic involvement 12%	Pericardial effusion 46% LVEF median 46.6 (IQR 39.5, 52.8) LVEF < 30%: 12% LVEF 30-50%: 53% Recovered LV function prior to discharge 95%	SARS-CoV-2 antibody + 81% RT-PCR SARS-CoV-2 + 33% 18% tested + for both	NIV 36% IMV 15% ECMO 3% Intra-aortic balloon pump support 3%	IVIG 54%, Corticosteroids 51%, Tocilizumab 36% Remdesivir 21%, Anakinra 12%, Convalescent plasma therapy 3%, Aspirin 24% Anticoagulation, prophylaxis 15%, Anticoagulation, therapeutic 81% Antibiotics > 48h 45% Vasopressor/inotropes 51%	Death 3%
Pouletty et al [46]	Fever 100% Respiratory signs 12% GI signs 81% Anosmia 6% Neurological signs 56% Rash 81% Conjunctivitis 94% Hands and feet edema/erythema 68% Dry cracked lips 87% Lymphadenopathy 37% Haemodynamic failure 69% Complete KD 62% KDSS 44%	Abnormal ECHO 69% Coronary dilatation 19% (median z score 2.6) No aneurysm Myocarditis 44% (median LVEF 35%) Pericarditis 25%	Family c/s COVID-19 infection 75% First infectious exposure-hospitalization 21 days (IQR 21-24) RT-PCR-SARS-CoV-2 all sites + 69% Serology IgG + 87%		IVIG 93% (Second infusion 335) Steroids 25% Anakinra 6% Tocilizumab 6% AAS (30-50mg/kg) 52% AAS anti-aggregant dose 50%	None
Ramcharan et al [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on	13% described typical COVID-19 symptoms in the previous two	Respiratory support 53% Inotrope or vasopressor	IVIG 67% (10/15), of whom 2 received a second dose Methylprednisolone 33%	None

		admission 51%	months 20% related contacted with family member with COVID-19	67%	73% werw discharged on low dose aspirin Antibiotic 100%	
Caponi et al [47]	Fever 100% GI symptoms 97% Neurocognitive symptoms 58% Respiratory symptoms 52% Shock 75% Complete KD 64% HD without shock 76%	Any coronary abnormality 48% (Z score ≥ 2.5 – 15%; Z score 2-2.49 – 9%) Any dysfunction 58%: (LVEF 45-54% - 33%; LVEF 35-44% - 24%)	IgG + and Nucleic acid amplification + 18% IgG + and Nucleic acid amplification negative 73% Nucleic acid amplification +, serology test unavailable 9%	PICU 79% MV 18% Inotrope/vasopressor support 76%	IVIG 100% 2 nd dose IVIG 33% Methylprednisolone 70% Aspirin 88% Anakinra 12% Tocilizumab 9% Infliximab 13% Enoxaparin 42%	None
Feldstein L.R et al [48]	Fever 100% Bilateral conjunctival injection 55% Oral mucose changes 42% Peripheral extremity changes 37% Rash 59%	Abnormal ECHO with coronary-artery aneurysms 9%	RT-PCR or antibody testing 70%	PICU 80% MV 20% Inotrope or vasopressor support 48% ECMO 4%	IVIG 77% Secon dose 21% Systemic glucocorticoid 49% Interleukin-6 inhibitor 8% Interleukin-1Ra inhibitor 13% Anticoagulation 47%	28% were still hospitalized as of May 20, 2020, and 4 patients (2%) died, 2 of whom had previously been healthy.

Abbreviations: MV: mechanical ventilation, HFNC: high flow nasal cannula, NIV:noninvasive ventilation, RRT:renal replacement therapy, VA-ECMO: venu-arterial extracorporeal membrane oxygenation, PCR: protein C reactive, IVIG: immunoglobulin, FEVE: fraction ejection ventricular, RT-PCR: real time polymerase chain reaction, PICU: pediatric intensive care unit, KD:Kawasaki disease

Table 2. Clinical findings, echocardiographic and treatments instituted in the described series of PIMS-TS

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Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS): a narrative review and the viewpoint of the *Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee*

Jaime Fernández-Sarmiento MD PhD(c)^{1,6}, Daniela Carla de Souza MD PhD^{2,6}, Roberto Jabornisky MD^{3,6}, Gustavo Ariel González MD^{4,5,6}, María del Pilar Arias López MD^{5,6}, Gladys Palacio MD^{5,6}.

1 Department of Critical Care Medicine and Pediatrics, Universidad de la Sabana, Fundación Cardioinfantil - Instituto de Cardiología. CES Graduate School. Bogotá Colombia.

2 Pediatric Intensive Care Unit and Department of Pediatrics, Hospital Universitario da Universidad de São Paulo and Hospital Sírio Libanês, Sao Paulo, Brazil.

3 Department of Pediatrics. Facultad de Medicina. Universidad Nacional del Nordeste. Argentina.

4 Pediatric Intensive Care Unit. Hospital Churruca - Visca Medical Complex. Buenos Aires. Argentina.

5 Pediatric Intensive Care Unit. Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina.

6 Sepsis Committee. Latin American Society of Pediatric Intensive Care (SLACIP).

Corresponding author: Jaime Fernández-Sarmiento, MD. Universidad de La Sabana, Campus del Puente del Común, Km 7 Autopista Norte de Bogotá, Chía - Cundinamarca - Colombia - South America. JaimeFe@unisabana.edu.co. + 057-16672727 ext 2204.

Abstract

Background: In this review, we discuss some important aspects of Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new syndrome that is temporally related to previous exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This virus has a broad spectrum of presentation which may overlap with Kawasaki disease (aKD) in terms of presenting symptoms, and laboratory and cardiac findings. Our objective was to review

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3 and summarise published evidence regarding the most important aspects of PIMS-TS,
4 with special emphasis on the treatment strategies suggested for middle- and low-income
5 countries.
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10 *Methods:* A systematic review of the literature was performed in the principal medical
11 databases including PUBMED, EMBASE (OVID) and Google Scholar between
12 December 2019 and August 2020.
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17 *Results:* A total of 69 articles were identified in the described databases. Altogether, 13
18 articles met the inclusion criteria and were eligible. The most frequently described
19 symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%),
20 skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-
21 6 weeks after the pandemic appears in the general population. Multisystem inflammatory
22 syndrome in children is presented as a great systemic inflammatory response syndrome
23 (SIRS), which sometimes presents as shock requiring fluid resuscitation and vasoactive
24 drug support (26%). Several treatment strategies have been used, including
25 immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These
26 general and specific interventions should be guided by an inter- and multi-disciplinary
27 team, especially in settings with limited resources.
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37 *Conclusions:* PIMS-TS COVID-19 is a new type of presentation of SARS-CoV-2
38 infection, with an exaggerated inflammatory response and frequent *-but not exclusive-*
39 digestive and myocardial involvement. It is important to describe the clinical course and
40 outcomes in countries with limited resources as well as establish the role of biomarkers
41 for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.
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46 *Key words:* septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease,
47 thrombosis, SARS-CoV-2
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52 **What is known about the subject?**

53 -PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times
54 greater need for hospitalization and mortality in children than other COVID-19
55 presentations.
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58 -It is characterized by fever, shock and gastrointestinal, skin and cardiac involvement,
59 with prior positive real-time polymerase chain reaction (RT-PCR) or antibody tests.
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3 -The diagnostic and treatment approach should be aimed at initial stabilization and shock
4 management, especially in countries with limited resources. The specific treatment
5 includes immunomodulators.
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10 **What does this study add?**

11 For this SARS-CoV2 disease, which mainly affects children, a comprehensive approach
12 is suggested which may be applied under the various healthcare system access conditions,
13 including strategies geared towards middle- and low-income countries. This treatment
14 includes general stabilization and shock management measures as well as the specific
15 immunomodulatory therapy currently recommended based on the available evidence.
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22 **INTRODUCTION**

23 In December 2019, a new viral infection was reported, causing severe respiratory
24 infection and very high mortality. According to its genetic sequencing, this virus belongs
25 to the genus *Beta coronavirus*, closely related to the severe acute respiratory syndrome
26 (SARS) virus. It was named SARS-CoV-2 and its disease COVID-19.^{1,2}
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29 Healthcare systems worldwide have been deeply concerned, given SARS-CoV-2's high
30 transmissibility, severity and lethality, particularly in the population over the age of 60.¹
31 Patients with major comorbidities such as heart disease, diabetes, hypertension, or obesity
32 have an increased risk of dying.^{1,2} Moreover, mortality has been associated with multiple
33 organ failure (MOF) as the common final pathway for pneumonia, sepsis, and acute
34 respiratory distress syndrome (ARDS). COVID-19 is usually less severe in paediatric
35 patients. In general, 80-90% of children with SARS-CoV-2 infection are asymptomatic
36 or have a mild infection. However, between 4 -10% of hospitalized children may need to
37 be transferred to a paediatric intensive care unit (PICU), and mortality ranges from 0.1%
38 to 8%.^{3,4} Recently, the Critical Coronavirus and Kids Epidemiology (CAKE) study
39 reported a mortality rate of 5% in children hospitalized in critical care in five European
40 and American countries (Chile, Colombia, Italy, Spain and USA), with 76% of cases
41 having severe pneumonia as their main manifestation.⁴
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53 Several pathophysiological factors may explain these features. COVID-19 non-survivors
54 have higher serum ferritin, D-dimer and C-reactive protein (CRP) than those who survive,
55 indicating an intense inflammatory response². Recently, a new type of presentation of
56 SARS-CoV-2 infection has been described in children, involving this significant
57 inflammatory response. This new disease has been called Paediatric Inflammatory
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3 Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new
4 syndrome that is temporally related to previous exposure to severe acute respiratory
5 syndrome coronavirus 2 (SARS-CoV-2) infection. This is a severe presentation of the
6 virus in children and requires early detection to avoid its progression and potentially
7 unsatisfactory outcomes⁵. In this article, we discuss and review the most relevant aspects
8 of PIMS-TS described to date.
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13 **METHODS**

14 **Search strategy and article selection**

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17 A systematic review of the literature was performed in the principal medical databases
18 including PUBMED, EMBASE (OVID) and Google scholar, using the MeSH terms
19 (“SARS-CoV-2” OR “Covid-19” OR “coronavirus” OR “infection” OR “sepsis” OR
20 “covid-19” OR “critical care”) AND “Multisystem Inflammatory Syndrome in Children”
21 OR “MIS-C” OR “PIMS-TS” between December 2019 and August 2020. The descriptors
22 were validated in DecS (descriptors in health science) and MeSH (medical subject
23 headings). Grey literature or as yet unpublished documents were not included.
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33 **Eligibility criteria**

34 Articles which reported at least five cases of PIMS-TS, including case series, case reports,
35 and cross-sectional, case-control, cohort (either prospective or retrospective) or clinical
36 trial studies, were included. Studies of critically ill children with COVID-19 were also
37 considered, and the cases of PIMS-TS reported in these studies were explored. Other
38 inclusion criteria were articles which described important outcomes such as mortality,
39 complications, laboratory findings and treatment received. In addition, articles in English,
40 Spanish or Portuguese were included. No reports of PIMS-TS in low and middle-income
41 countries were found in indexed journals. The World Health Organization (WHO),
42 Centers for Disease Control (CDC) and Royal College guidelines were consulted for the
43 definitions. Articles which did not provide complete data when reporting general cases
44 of critically ill children with COVID-19, or those for which the full text was not available,
45 as well as narrative reviews, were excluded. Adult cases have already been described, but
46 these were not included in this review.
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Study selection and data collection process

First, the inclusion and exclusion criteria for this systematic review were defined, after which one of the researchers (JFS) performed the systematic search of the literature and reviewed the most relevant articles. The established criteria were applied, and the articles were approved by all the SLACIP sepsis committee authors. In case of doubt, or a lack of consensus regarding the inclusion of an article, a second reviewer (RJ) was consulted to decide. Any discrepancies or missing data were resolved by consensus. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. (*Figure 1*).

Patient and Public Involvement statement

No patients participated actively in this review. The data were taken from the most important publications to date on PIMS-TS, including consensus recommendations for high-income countries. It is expected that this information will be disseminated through SLACIP and its various committees for applicability in patients living in middle- and low-income countries.

RESULTS

Search and study selection results

A total of 69 articles were identified in the described databases. After eliminating the duplicates and reviews, 13 articles met the inclusion criteria and were eligible. These articles were included in the qualitative synthesis and the most relevant ones which do not include patients reported in other case series are described by their characteristics in *Table 1*.

Although the main pathogenesis of COVID-19 may be similar to other viruses such as influenza, it has shown some clinical presentations which are different from those usually found in those classical respiratory viruses. On April 24, 2020, a new presentation of SARS-CoV-2 in children was described by Riphagen et al. in the United Kingdom.⁶ The first report described a cohort of eight children with COVID-19 who required hospitalization in intensive care and had an unusual clinical behavior characterized by a severe hyperinflammatory state, with clinical similarity between all eight patients.⁷⁻⁹

The Royal College of Paediatrics and Child Health called this new entity PIMS-TS.¹⁰ Subsequently, the CDC and WHO called it multisystem inflammatory syndrome in

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3 children (MIS-C).^{11,12} In general, both terms refer to the same entity and the latter name
4 has been the most frequently used in the main descriptions of this disease (*Table 3*).

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6 The largest series described to date is that of the CDC in Atlanta, with 570 patients. Using
7 a latent class analysis (LCA) statistical model, it attempted to divide the cases into three
8 large groups according to their common clinical characteristics.¹³ Class I included those
9 with symptoms which could overlap with macrophage activation syndrome, with a large
10 inflammatory response. Class II had predominantly respiratory involvement and signs
11 suggestive of active COVID-19 disease with a high rate of RT-PCR seropositivity (84%).
12 Class III had clinical manifestations that could overlap with Kawasaki disease, and only
13 2% were RT-PCR positive.¹³
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22 In this regard, most studies report that the patients have a negative RT-PCR and positive
23 antibody or serology tests. In fact, a negative RT-PCR has been found in 40% of patients
24 with positive antibody tests. Although RT-PCR is an imperfect test, it is considered the
25 gold standard today. In the described series, 46% of the cases had a positive serology and
26 a negative RT-PCR, which suggests that, in these patients, the infection occurred possibly
27 weeks earlier. An average of 25% of the patients in the included studies had both positive
28 serology and positive RT-PCR (*supplementary table 2*).
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38 **DISCUSSION**

39 PIMS-TS is characterized by a very significant ongoing inflammatory response, in
40 crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and
41 WHO (May 15th) definitions (*Table 3*).^{11,12} Characteristically, these patients present with
42 high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.¹³ Hoang et al.¹⁴ reported
43 lower expression of circulating CD16+CD56+ natural killer cells and more profound
44 lymphopenia in children with PIMS-TS compare to those without PIMS-TS.
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46 Primarily, there is an initial innate immune response with the macrophages as the
47 principal actors. From the pathophysiological point of view, it is striking that more than
48 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an
49 acute phase reactant that usually rises after six hours of an inflammatory state and is
50 produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF- α
51 stimulation.^{15,16} This acute phase reactant from the pentraxin family identifies
52 phosphatidylserine on the surface of cells that have initiated a programmed cell death
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3 pattern of apoptosis by activating the complement system. This biomarker is very useful
4 for diagnosis and follow up, especially in middle and low-income countries (given its low
5 cost), and should be considered on admission with subsequent follow up.
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8 Additionally, a marked elevation of ferritin (2-10 times its normal value) has been
9 observed in more than 90% of the series.¹³⁻¹⁷ Ferritin is a protein that stores iron and
10 releases it in a controlled fashion, but also in pathophysiologic conditions. Its levels can
11 reflect macrophage response to free hemoglobin as well as DNA viruses, intracellular
12 bacterial infections and parasites.¹⁸⁻²⁰ Ferritin can induce positive feedback inflammation,
13 upregulating toll-like receptor 9 (TLR-9) which leads macrophage inflammasome IL-1
14 and IL-18 to feed forward ferritin production. TLR-9 may also be stimulated by viral
15 DNA, other infections and host damage-associated molecular patterns (DAMP).²⁰ This
16 whole process generates a large number of inflammasomes and an enhanced
17 inflammatory pathway, delivering the “cytokine storm.” This precipitate cell death with
18 a pyroptosis pattern and new DAMPs that stimulate TLR-9.²⁰ This was described as
19 “*Hyperferritinemic Syndrome*” by Rosario²¹.
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30 Nevertheless, there is evidence of an unusual late adaptive immunity response. It has
31 come to the researchers attention that PIMS-TS occurred between four and six weeks
32 after the peak of cases reported as positive for SARS-CoV-2 in each country had been
33 reached.¹³ Pérez-Toledo M et al.²² recently described eight patients with PIMS-TS with
34 a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM.
35 Additionally, they found elevated IgG1 and IgG3 in these children, which are
36 immunoglobulin isotypes associated with serum supplement activation. This situation is
37 consistent with highly elevated CRP related to COVID-19, which activates the
38 complement system. The elevation of these immunoglobulins suggests that PIMS-TS
39 occurs due to tissue damage induced by autoantibodies, a situation that has been described
40 in other types of coronavirus infection.²³⁻²⁴ We are not aware of any studies in middle
41 and low-income countries which have described this serological behaviour. Studies are
42 needed to help clear up this aspect, especially when all the diagnostic test options for
43 SARS-CoV-2 are not always available. In these countries with limited resources, we
44 suggest taking an initial RT-PCR. If this is negative and there is a high index of suspicion
45 of PIMS-TS, due to the signs and symptoms, a total antibody or IgM/IgG test should be
46 performed.²⁴
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3 For PIMS-TS, most of the series described coagulation disorders. Severe coagulopathy
4 was seen in 70-80% of the cases (very high D-dimers, prolonged PT, PTT).¹³ Like
5 inflammation, coagulation is necessary for host defense. In addition, proinflammatory
6 cytokines, monocytes / macrophages, neutrophil activation, and extracellular neutrophil
7 traps (NETs) can foster local thrombosis. COVID-19 associated coagulopathy (CAC) is
8 complex and in some ways pathophysiologically different from SIC.^{25,26}
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15 Cytokine levels of IL-1 β and IL-6 are elevated, which induces thrombocytosis and
16 hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is
17 stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.^{27, 28}
18 D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its
19 early phase.²⁸ Elevated D-dimer levels can be present in a wide variety of inflammatory
20 and prothrombotic conditions;²⁹ in COVID-19, these are probably more associated with
21 inflammation than thrombosis.³⁰ Furthermore, serum hyaluronic acid, a key glycocalyx
22 component, is higher during infancy, progressively diminishing over the years.^{19,31} This
23 could explain a more protected endothelium and a lower probability of a hypercoagulable
24 state. In addition, CAC has an overlapping pathophysiology with other coagulopathies
25 like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH),
26 antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) /
27 hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type
28 of coagulopathy.³²
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Author	City, Country	Period	Number	Age	Gender	Comorbidity	Race	IMC kg/m ²
Whittaker et al [3]	London, UK	March 23 and May 16	58	9 years (IQR 5.7, 14)	43% boys	7/58 Comorbidities	69% black or Asian	N/R
Riphagen et al [6]	London, UK	10 days in mid-April	8	4 – 14 years (range)	5/8 boy	None	6/8 Afro-Caribbean	14 – 33 7/8 > 75 th centile/weight
Verdoni et al [7]	Bergamo, Italy	Feb 18 and April 20	10	7.5 years (SD 3-5)	7/10 boys	N/R	N/R	N/R
Belhadjer et al [8]	France (12 hospitals) and Switzerland (1 hospital)	March 22 to April 30	35	10 years (IQR 8.2, 12.4)	51% boys	Comorbidities 28% (asthma 8.55; lupus 3%)	N/R	Overweight 17%
Golfred-Cato S et al [13]	Multicenter US	March 01 to July 29	570	8 (IQR 4,12)	55.4% boys	Comorbidities 8%	40.5% Hispanic and 33.1% Black Non-hispanic	Obesity 25.6%
Cheung et al [33]	New York, US	April 18 and May 5	17	8 years (IQR 1.8, 16)	47% boys	Most were previously healthy (mild asthma in 3)	White 70%	N/R
Kaushik et al [38]	New York, US	April 23 to May 23	33	10 years (IQR 6, 13)	61% boys	Comorbidities 48%	45% Hispanic/latino 39% black	Overweight 12% Obesity (BMI > 30kg/m ²) 6%
Ramcharan et al [40]	UK	10 th April and 9 th May	15	8.8 (IQR 6.4, 11.2) 93% were over 5y	73% boys		100% African/Afr-Caribbean (40%), South Asian, (40%)	

							Mixed (13%) Or other minority ethnic	
Toubiana et al [45]	France, Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR 3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI below the 97 th centile
Pouletty et al [46]	Paris, France	Since April 2020	16	10 (IQR 4.7, 12.5)	50% boys	Comorbidities 37%	N/R	Overweight 25%
Caponi et al [47]	New York, US	April 17 – May 13	33	8.6 years (IQR 5.5, 12.6)	61% boys	Comorbidities 21%	73% non-Hispanic	Overweight 6% Obese 39%
Feldstein L.R et al [48]	Multicenter, US	March 15 to May 20	186	8.3 years (IQR 3.3, 12.5)	62% boys	Comorbidities 27%	31% Hispanic, 25% Black non hispanic	Obesity 29%
Dufort E et al [49]	New York City	March 01 to May 10	95	0-5 years (31%) 6-12 years (42%) 13-20 years (27%)	54% boys	Comorbidities 64%	40% Black 36% Hispanic	Obesity 29%

Table 1. Demographic characteristics of patients with PIMS-TS. N/R: not reported.

Review Only

Royal College of Paediatrics and Health Child (RCPCH) Definition [10]

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative.

Centers for Disease Control and Prevention (CDC) Definition [11]

- 1. An individual aged < 21 years presenting with fever¹, laboratory evidence of inflammation² and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND**
- 2. No alternative plausible diagnoses; AND**
- 3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.**

¹Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

²Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

World Health Organization Definition [12]

Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

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

AND

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

AND

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

AND

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

Table 3. RCPCH, CDC, WHO Definitions Criteria for Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19

From a clinical and laboratory perspective, PIMS-TS has usually been seen in previously healthy and frequently obese (30-60% of the series) children over eight years of age (80% of the cases) (*Table 1*). Initially, the group from the United Kingdom (UK) found MIS-C in patients of African descent, but it has been described in patients of all origins.^{4,32,33} Persistent high fever for more than three to five consecutive days, maculopapular skin lesions (50-60%) reminiscent of Kawasaki disease (KD) and, frequently, signs of shock at the time of presentation have been the initial clinical characteristics.³³ Digestive symptoms (including nausea, vomiting, diarrhea or abdominal pain) usually present in most cases, as well as myocardial involvement (more than 60% of the series).^{14,33} Cardiac involvement is broad and variable, with features including myocardial dysfunction (100% of the initial UK description - 60% in other series), coronary aneurysms, pericarditis, arrhythmias, refractory shock and elevated troponin I or pro-BNP³²⁻³⁴ (*supplementary table 2*).

Guidelines for PIMS-TS management in middle and low-income countries

With regard to treatment in middle and low-income countries, it is very important to maintain a high index of suspicion. Therefore, in these countries, it is important to use a systematic approach including early recognition and a bundle similar to those recommended for patients with other serious diseases. An expert consensus recently published in the United Kingdom using the Delphi method provides a good summary of the recommended treatments³⁴. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with

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3 those of the SCCM sepsis consensus¹⁶, for use in middle and low-income countries. We
4 believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking
5 these recommendations as a whole could have an impact on the outcomes of PIMS-TS
6 patients in these countries.
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11 From the first presentation to the Emergency Department and / or PICU, two approaches
12 can be assumed, one general and one specific.
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15 a. *General approach*: A comprehensive approach should be used, similar to that
16 recommended for patients with sepsis with organ dysfunction or septic shock. In this case,
17 the contagiousness of SARS-CoV-2 requires the use of personal protective equipment
18 (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-
19 PCR.
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24 Moreover, the American College of Critical Care Medicine (ACCM) points out the need
25 to give more attention to Institutional Practice Guidelines (IPGs) based on each facility's
26 capability.³⁵ Once IPGs are established, diagnostic and therapeutic measures known as
27 "patient care bundles" (PCBs) should be developed for a better approach and control of
28 established processes. The PCBs include three to five evidence-based practices related to
29 a health care process that should be performed collectively to achieve a synergistic result
30 that improves care.^{36,37}
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36 1. Early detection: a comprehensive approach based on a high index of suspicion is
37 critical. This disease may occur with a wide spectrum of symptoms, so it should be
38 suspected in all patients with a fever lasting more than three days associated with the
39 symptoms described in *Figure 2*. Contact with a positive case is not always clear.
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43 2. Immediate, time-sensitive resuscitation:

44 - Oxygen therapy: This is part of the strategies described in recent sepsis guidelines^{16,37}.
45 High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been
46 considered in many reports,³⁸ especially in patients who have a deteriorated respiratory
47 pattern with the use of accessory muscles or an SaO₂/FiO₂ ratio less than 264. Most series
48 describe respiratory involvement ranging from 20-60% (*Table 2*) and, generally, if
49 endotracheal intubation is required, it is more highly associated with cardiovascular
50 involvement. Cases classified as Class II by the CDC may be classified in these
51 groups.^{33,38}
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56 - Fluid resuscitation: It is important to consider the recommendations in recently
57 published guidelines.¹⁶ In healthcare systems where staff and equipment for advanced
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3 airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of
4 balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour,
5 titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload
6 develop. In healthcare systems without the availability of intubation, crystalloid boluses
7 may only be given in cases of hypotension (decompensated shock); in these cases, up to
8 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with
9 titration to clinical markers of cardiac output, and discontinued if signs of fluid overload
10 develop. If the child is not hypotensive, but has compensated shock, only maintenance
11 fluids should be started, avoiding bolus fluids which are associated with worse
12 outcomes³⁵⁻³⁸.

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21 -Vasoactive drugs: According to the clinical condition, most series describe the need for
22 vasoactive drugs in 10 to 60% of the cases with PIMS-TS. Most patients respond to fluid
23 resuscitation. If necessary, epinephrine or norepinephrine should be considered according
24 to the patient's condition.^{16,39} Inotropes like dopamine, milrinone and levosimendan were
25 reported to have been used in PIMS-TS.³⁸⁻⁴⁰

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29 -Antibiotic therapy: If bacterial co-infection is suspected, the first dose is recommended
30 within the first three hours for sepsis associated with organ dysfunction, or within the first
31 hour for children with septic shock.³⁹⁻⁴¹

32 33 34 3. Stabilization with adequate monitoring:

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36 If possible, advanced hemodynamic monitoring should be instituted. Cardiac
37 ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent
38 guidelines¹⁶ and patients with PIMS-TS.⁴²

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41 4. Timely referral or transfer is desirable in this context. In middle and low-income
42 countries, it is common for patients to be transferred to higher complexity sites. Patients
43 who are deteriorating or who may need intensive care should be identified. In the PIMS-
44 TS of the CDC group, 84% of the cases had to be transferred to paediatric intensive care.
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5. Continuous measurement of processes and corrections must be instituted for a
continuous quality improvement process.⁴²

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b. Specific approach: It is important to emphasize that, in moderate to severe cases, the
use of immunomodulatory treatment should be considered. Heterogeneous management
including human immunoglobulin, systemic steroids, anakinra, tocilizumab and aspirin
^{40,42-45} has been reported in the described series (*supplementary table 2*). The American

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2
3 College of Rheumatology (ACR) recommendations for immunomodulatory therapy⁴²
4 have recently been published. We sought to adapt these recommendations to middle and
5 low-income countries where resources are limited and each intervention must be
6 streamlined according to need.
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- 10 ⇒ IVIG: High doses (2 gr/kg) should be considered for moderate to severe cases,
11 particularly those with myocardial involvement. Prior to beginning the infusion,
12 restored heart function must be verified.⁴²
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14 ⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical
15 course of the disease in adults with severe pneumonia, particularly if they are on
16 mechanical ventilation.⁴³⁻⁴⁷ In patients with PIMS-TS, low doses could be
17 considered in all cases (used in 70% of the series – *Table 3*). Dosing schemes of
18 1-2 mg/kg/dose of methylprednisolone or its equivalent three or four times per
19 day have been recommended. The ACR suggests considering high doses in cases
20 of shock or in those with a high need for vasopressors, and we believe this
21 recommendation is very important for middle and low-income countries,
22 especially considering the frequency of late consults with advanced disease.
23
24 ⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-
25 refractory PIMS-TS.⁴² However, in many countries, its use is not approved, or it
26 is not available, and other biological agents are used. Prospective studies are
27 needed to evaluate the efficacy and safety of these medications in PIMS-TS.
28
29 ⇒ Anticoagulation and antiplatelet treatment: Anticoagulation has become a
30 fundamental treatment in adults, considering that there is a procoagulant and
31 hypofibrinolytic state in severe SARS-CoV-2 infection.^{42,47-50} In children with
32 PIMS-TS it is recommended only in cases of documented thrombosis or in
33 patients with an echocardiogram ejection fraction less than 35%.^{43,47} Aspirin
34 would also be recommended in patients with thrombocytosis (> 450,000 u/L) or
35 Kawasaki-like disease criteria.^{42,47}
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52 The prognosis of the disease is usually good, with patient survival greater than 95% in
53 different published series.^{5,6,42-50} A mortality of 1-2% has been described in the published
54 series, and up to 15% with cardiovascular sequelae, including aneurysms or
55 dysfunction.^{33,48-50} These patients should be followed up after discharge by inter and
56 multidisciplinary teams including infectious disease, rheumatology and paediatrics.
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3 However, there are incomplete data from all the cases, along with a knowledge gap
4 regarding mild and moderate cases, the natural course and the clinical behavior of the
5 disease.^{8,47-50}
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10 **Conclusion**

11 PIMS-TS is a new type of presentation of SARS-CoV-2 infection, with an exaggerated
12 inflammatory response and inadequate inflammatory resolution with frequent *-but not*
13 *exclusive-* digestive and myocardial involvement. It should be considered as a new
14 disease with unique symptoms, a greater variety of clinical courses, and possibly different
15 physiological mechanisms. In middle and low-income countries, studies should be
16 performed to learn more about this disease in these regions and determine if they have
17 different phenotypic behaviors. In addition, the real role of some inflammatory
18 biomarkers and cost-effective therapeutic strategies should be determined.
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27 **Contributors**

28 JFS, DS, RJ, PA, GG, GP conceptualized and designed the literature search. JFS, DS, RJ
29 initiated the search and a first draft. All authors contributed to subsequent drafts. JFS, as
30 group leader, supervised and moderated the search, initial drafts, the overall collation of
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32 submitted and agree to be accountable for all aspects of the work
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56 **Data are available statement:** no data are available.
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ORCID: iD Jaime Fernández-Sarmiento <http://orcid.org/0000-0003-2874-2949116>

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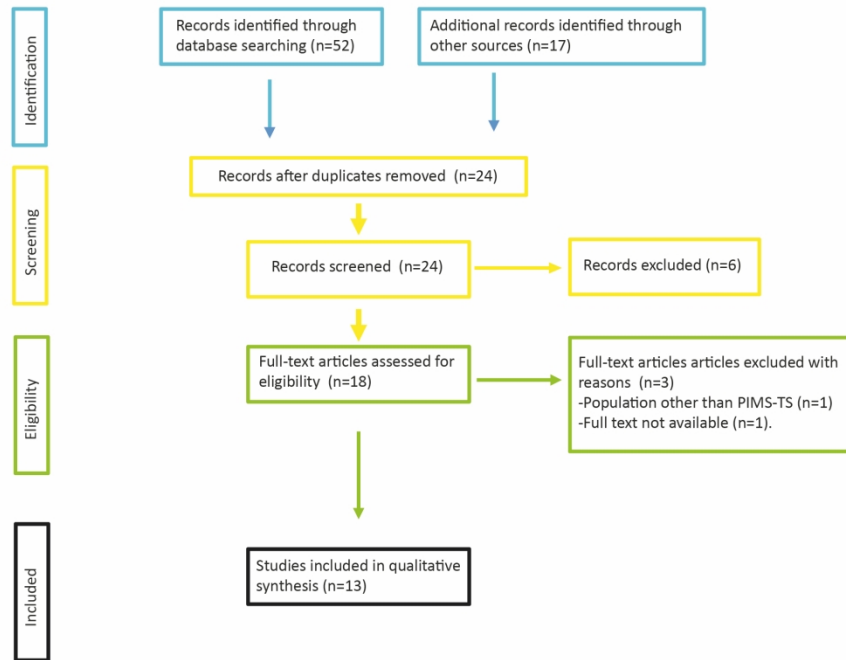
26 *Figure 1.* Selection process. We followed the PRISMA guidelines for reporting in
27 systematic reviews and meta-analyses
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32 *Table 1.* Demographic characteristics of patients with PIMS-TS
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35 *Table 2.* Clinical and echocardiographic findings, and treatments instituted in the
36 described series of PIMS-TS patients (*supplementary file*).
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40 *Table 3.* RCPCH, CDC and WHO Definition Criteria for Paediatric Inflammatory
41 Multisystem Syndrome Temporally associated with COVID-19
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Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses



Author	Clinical presentation	ECHO	SARS-CoV-2 test	Organ support	Treatment	Outcome / Died
Whittaker et al [3]	Fever 100%, Headache 26% Vomiting 45% Diarrhea 52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29% Swollen hands and feet 16%, Respiratory symptoms 21%. Fever + elevated inflammatory markers – 40%, Shock - 50%	Left ventricular dysfunction 62% (18/29) Abnormally dilated coronary arteries (z score >2) 8/55 Giant coronary artery aneurysms 2 Coronary artery aneurism 14% (n=8)	RT-PCR SARS-CoV-2 + 26% IgG antibody SARS-CoV-2 + 87% 78% had evidence of current or prior SARS-CoV-2 infection	PICU 50% Acute kidney injury 22% Shock + inotropic support 47% MV 43% ECMO 5%	Inotropic support 47% IVIG 71% Corticosteroids 64% Anakinra 5% Infliximab 14%	Death 2%
Riphagen et [6]	Fever 8/8 Diarrhoea 7/8 Abdominal pain 6/8 Vomiting 4/8 Conjunctivitis 5/8 Rash 4/8 Vasoplegic shock 8/8	7/8 ventricular dysfunction Echobright coronary vessels 1/8 giant coronary aneurysm	SARS-CoV-2 negative 5/8 SARS-CoV-2 positive 2/8 Family exposure 4/8	Inotropic/vasopressor support 8/8, MV 5/8, HFNC 1/8, NIV 3/8, RRT 1/8, VA-ECMO 1/8 (arrhythmia with refractory shock, died)	IVIG 8/8, Corticoids 5/8 Aspirin 3/8, Heparin 1/8, Antibiotics 8/8, Infliximab 1/8	1 died 6/8 alive PICU length of stay 3 – 7 days
Verdoni et [7]	Classic form of Kawasaki 50%, Incomplete form of Kawasaki disease 50% Kdss and MAS 50% Diarrhoea 60% Meningeal signs 40% Drowsiness 10%	Anormal ECHO 60% Aneurism 10% FEVE < 50% – 50% Mitral valve regurgitation 10% Pericardial effusion 40%	RT-PCR SARS-CoV-2 + 20% Serology for SARS-CoV-2 antibodies – 80% were IgG +, and 3 were also IgM +		Inotropic support 20% Adjunctive steroid treatment 80% IVIG 100% Aspirin 20%	None
Belhadjer et al [8]	Asthenia 100% Fever 100% GI symptoms 83% (2 children underwent emergency operation for suspected appendicitis) Respiratory distress 65%	Coronary artery dilatation (z score > 2) 17% Aneurysm 0 LVEF < 30% - 28% LVEF 30-50% - 72%	SARS-CoV-2 was confirmed 88.5% RT-PCR-SARS-CoV-2 + 34% Fecal PCR 6% Antibodies + 86%	Respiratory support 94% (IMV 62%; NIV 32%) VA-ECMO 28%	Inotropic support 80% IVIG 71% Corticosteroids 34% Anakinra 8% Anticoagulation with heparin 65%	None

	Rhinorrhea 43% Adenopathy 60% Rash 57% Meningism 31% At admission to the ICU, 80% were in cardiogenic shock					
Grimaud et al [9]	Fever 100%, Abdominal pain 100%, Rash 50%, Conjunctivitis 30%, Adenitis 20%, Tachycardia 100% Hypotension 100% (75% clinical signs of vasoplegia)	LVEF 35% (IQR 25-55)	SARS-CoV-nasopharyngeal swabs + 50% SARS-CoV-2 antibodies + 100% (15/15), 95% had identified SARS-CoV-2 infection on PCR and/or by serology	NIV 55%,IMV 40%, HFNO 5%,Respiratory support in all patient was indicated for hemodynamic support	IVIg100%,Corticosteroids 10%, Anakinra 5%, Tocilizumab 5%, Inotropic/vasopressor support 95%	None
Cheung et al [33]	Fever 100% GI symptoms 88% Shock at presentation 76% Rash 71%, Conjunctivitis 65% Lip redness/swelling 65% Neurologic symptoms 47%, Respiratory symptoms 41%, Myalgia 35%, Lymphadenopathy 35%, Hypoxia 18% Criteria for KD 47% Incomplete Kawasaki 29%	FEVE mildly decreased 29% FEVE mild-moderately decreased 24% FEVE moderate-severely decreased 12% Pericardial effusion 47%	RT-PCR SARS-CoV-2 + 47% Serology for SARS-CoV-2 antibodies → 53%	PICU 88%	IVIg 76% Methylprednisolone 71% Hydrocortisone 21% Enoxaparin prophylaxis 59% Enoxaparin treatment 6% Aspirin 24%	None
Golfred-Cato S et al [13]	Fever 100% Bilateral conjunctival injection 48.4% Oral mucose changes 23% Rash 55.3%	Abnormal ECHO with coronary-artery aneurysms 18.6%	RT-PCR 25.8% Serology positive 46.1% RT-PCR and serology positive 27.2%	PICU 63.9% MV 13.1% Vasoactives 44.9%	IVIg 80.5% Steroids 62.8% Antiplatelet medication 58.6% Anticoagulation 44.2%	Died 1.8% Organs systems involved 4-5 61.6%
Kaushik et al [38]	Fever 93%, Abdominal pain 63%, Nausea/emesis 69%, Diarrhea 48%	Pericardial effusion 46%	SARS-CoV-2 antibody + 81%	NIV 36% IMV 15% ECMO 3%	IVIg 54%, Corticosteroids 51%, Tocilizumab 36%	Death 3%

	Hypotension 63%, Mucocutaneous, involvement 21% Conjunctivitis 36% Rash 42%, Shortness of breath 33% Neurologic involvement 12%	LVEF median 46.6 (IQR 39.5, 52.8) LVEF < 30%: 12% LVEF 30-50%: 53% Recovered LV function prior to dischargr 95%	RT-PCR SARS-CoV-2 + 33% 18% tested + for both	Intra-aortic ballon pump support 3%	Remdesivir 21%, Anakinra 12%, Convalescent plasma therapy 3%, Aspirin 24% Anticoagulation, prophylaxis 15%, Anticoagulation, therapeutic 81% Antibiotics > 48h 45% Vasopressor/inotropes 51%	
Ramcharan et al [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on admission 51%	13% described typical COVID-19 symptoms in the previous two months 20% related contacted with family member with COVID-19	Respiratory support 53% Inotrope or vasopressor 67%	IVIG 67% (10/15), of whom 2 received a second dose Metylprednisolone 33% 73% werw discharged on low dose aspirin Antibiotic 100%	None
Toubiana et al [45]	Recent history of viral- like symptoms was report in 43% Median duration between these symptoms and the onset of signs and symptoms of Kawasaki disease was 45 days. Complete presentation of KD 52%, Abdominal symptoms 95%, Lips and oral cavity changes 76% Conjunctivitis 81% Rash 76%, Changes to extremities 48% Lymphadenopathy 57%	Myocarditis 76% (LVFE range between 10 and 57%) 38% coronary artery abnormalities: 24% which consisted of dilations (z score between 2.0 and 2.5); 14% with increased coronary visibility No coronary aneurysms were identified	History of recent contact with people with viral-like symptoms was + in 48% Median interval between reported contact and KD was 36 days RT-PCR-SARS-CoV-2 + 38% IgG antibodies SARS- CoV-2 + 90% 9,5% negative Serology and PCR)	PICU 81% Vasoactive agents 71% MV 52%	IVIG 100% (24% needed a second dose) Low dose aspirin (3- 5mg/kg/day) 100% Corticosteroids (2- 10mg/kg/day) 48% Antibiotic 86%	None
Pouletty et al [46]	Fever 100% Respiratory signs 12% GI signs 81% Anosmia 6%	Abnormal ECHO 69% Coronary dilatation 19% (median z score 2.6)	Family c/s COVID-19 infection 75% First infectious exposure-		IVIG 93% (Second infusion 335) Steroids 25% Anakinra 6%	None

	Neurological signs 56% Rash 81% Conjunctivitis 94% Hands and feet edema/erythema 68% Dry cracked lips 87% Lymphadenopathy 37% Haemodynamic failure 69% Complete KD 62% KDSS 44%	No aneurysm Myocarditis 44% (median LVEF 35%) Pericarditis 25%	hospitalization 21 days (IQR 21-24) RT-PCR-SARS-CoV-2 all sites + 69% Serology IgG + 87%		Tocilizumab 6% AAS (30-50mg/kg) 52% AAS anti-aggregant dose 50%	
Caponi et al [47]	Fever 100% GI symptoms 97% Neurocognitive symptoms 58% Respiratory symptoms 52% Shock 75% Complete KD 64% HD without shock 76%	Any coronary abnormality 48% (Z score ≥ 2.5 – 15%; Z score 2-2.49 – 9%) Any dysfunction 58%: (LVEF 45-54% - 33%; LVEF 35-44% - 24%)	IgG + and Nucleic acid amplification + 18% IgG + and Nucleic acid amplification negative 73% Nucleic acid amplification +, serology test unavailable 9%	PICU 79% MV 18% Inotrope/vasopressor support 76%	IVIG 100% 2 nd dose IVIG 33% Methylprednisolone 70% Aspirin 88% Anakinra 12% Tocilizumab 9% Infliximab 13% Enoxaparin 42%	None
Feldstein L.R et al [48]	Fever 100% Bilateral conjunctival injection 55% Oral mucose changes 42% Peripheral extremity changes 37% Rash 59%	Abnormal ECHO with coronary-artery aneurysms 9%	RT-PCR or antibody testing 70%	PICU 80% MV 20% Inotrope or vasopressor support 48% ECMO 4%	IVIG 77% Secon dose 21% Systemic glucocorticoid 49% Interleukin-6 inhibitor 8% Interleukin-1Ra inhibitor 13% Anticoagulation 47%	28% were still hospitalized as of May 20, 2020, and 4 patients (2%) died, 2 of whom had previously been healthy.
Dufort E et al (49)	Fever 100%, abdominal pain 61%, rash 60%,conjunctivitis 56%	Abnormal ECHO with coronary-artery aneurysm 9%	RT-PCR 51%, IgG antibodies 99%	PICU 80%, MV 10%, Vasopressor support 62%, ECMO 4%	IVIG 48% Systemic glucocorticoids 64%	Death 2%, shock 10%, myocarditis 53%

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4 *Abbreviations: MV: mechanical ventilation, HFNC: high flow nasal cannula, NIV:noninvasive ventilation, RRT:renal replacement therapy, VA-*
5 *ECMO: venu-arterial extracorporeal membrane oxygenation, PCR: protein C reactive, IVIG: immunoglobulin, FEVE: fraction ejection*
6 *ventricular, RT-PCR: real time polymerase chain reaction, PICU: pediatric intensive care unit, KD:Kawasaki disease*
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8 *Supplementary File. Table 2. Clinical findings, echocardiographic and treatments instituted in the described series of PIMS-TS*
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Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS): a narrative review and the viewpoint of the Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee

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Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS): a narrative review and the viewpoint of the *Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee*

Jaime Fernández-Sarmiento MD PhD(c)^{1,6}, Daniela Carla de Souza MD PhD^{2,6}, Roberto Jabornisky MD^{3,6}, Gustavo Ariel González MD^{4,5,6}, María del Pilar Arias López MD^{5,6}, Gladys Palacio MD^{5,6}.

1 Department of Critical Care Medicine and Pediatrics, Universidad de la Sabana, Fundación Cardioinfantil - Instituto de Cardiología. CES Graduate School. Bogotá Colombia.

2 Pediatric Intensive Care Unit and Department of Pediatrics, Hospital Universitario da Universidad de São Paulo and Hospital Sírio Libanês, Sao Paulo, Brazil.

3 Department of Pediatrics. Facultad de Medicina. Universidad Nacional del Nordeste. Argentina.

4 Pediatric Intensive Care Unit. Hospital Churruca - Visca Medical Complex. Buenos Aires. Argentina.

5 Pediatric Intensive Care Unit. Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina.

6 Sepsis Committee. Latin American Society of Pediatric Intensive Care (SLACIP).

Corresponding author: Jaime Fernández-Sarmiento, MD. Universidad de La Sabana, Campus del Puente del Común, Km 7 Autopista Norte de Bogotá, Chía - Cundinamarca - Colombia - South America. JaimeFe@unisabana.edu.co. + 057-16672727 ext 2204.

Abstract

Background: In this review, we discuss some important aspects of Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new syndrome that is temporally related to previous exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This virus has a broad spectrum of presentation which may overlap with Kawasaki disease (aKD) in terms of presenting symptoms, and laboratory and cardiac findings. Our objective was to review

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3 and summarize published evidence regarding the most important aspects of PIMS-TS,
4 with special emphasis on the treatment strategies suggested for middle- and low-income
5 countries.
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10 *Methods:* A systematic review of the literature was performed in the principal medical
11 databases including PUBMED, EMBASE (OVID) and Google Scholar between
12 December 2019 and August 2020.
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17 *Results:* A total of 69 articles were identified in the described databases. Altogether, 13
18 articles met the inclusion criteria and were eligible. The most frequently described
19 symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%),
20 skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-
21 6 weeks after the pandemic appears in the general population. Multisystem inflammatory
22 syndrome in children is presented as a great systemic inflammatory response syndrome
23 (SIRS), which sometimes presents as shock requiring fluid resuscitation and vasoactive
24 drug support (26%). Several treatment strategies have been used, including
25 immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These
26 general and specific interventions should be guided by an inter- and multi-disciplinary
27 team, especially in settings with limited resources.
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37 *Conclusions:* PIMS-TS COVID-19 is a new type of presentation of SARS-CoV-2
38 infection, with an exaggerated inflammatory response and frequent *-but not exclusive-*
39 digestive and myocardial involvement. It is important to describe the clinical course and
40 outcomes in countries with limited resources as well as establish the role of biomarkers
41 for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.
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46 *Key words:* septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease,
47 thrombosis, SARS-CoV-2
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51 **What is known about the subject?**

52 -PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times
53 greater need for hospitalization and mortality in children than other COVID-19
54 presentations.
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57 -It is characterized by fever, shock and gastrointestinal, skin and cardiac involvement,
58 with prior positive real-time polymerase chain reaction (RT-PCR) or antibody tests.
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3 -The diagnostic and treatment approach should be aimed at initial stabilization and shock
4 management, especially in countries with limited resources. The specific treatment
5 includes immunomodulators.
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10 **What does this study add?**

11 For this SARS-CoV2 disease, which mainly affects children, a comprehensive approach
12 is suggested which may be applied under the various healthcare system access conditions,
13 including strategies geared towards middle- and low-income countries. This treatment
14 includes general stabilization and shock management measures as well as the specific
15 immunomodulatory therapy currently recommended based on the available evidence.
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22 **INTRODUCTION**

23 In December 2019, a new viral infection was reported, causing severe respiratory
24 infection and very high mortality. According to its genetic sequencing, this virus belongs
25 to the genus *Beta coronavirus*, closely related to the severe acute respiratory syndrome
26 (SARS) virus. It was named SARS-CoV-2 and its disease COVID-19.^{1,2}
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29 Healthcare systems worldwide have been deeply concerned, given SARS-CoV-2's high
30 transmissibility, severity and lethality, particularly in the population over the age of 60.¹
31 Patients with major comorbidities such as heart disease, diabetes, hypertension, or obesity
32 have an increased risk of dying.^{1,2} Moreover, mortality has been associated with multiple
33 organ failure (MOF) as the common final pathway for pneumonia, sepsis, and acute
34 respiratory distress syndrome (ARDS). COVID-19 is usually less severe in paediatric
35 patients. In general, 80-90% of children with SARS-CoV-2 infection are asymptomatic
36 or have a mild infection. However, between 4 -10% of hospitalized children may need to
37 be transferred to a paediatric intensive care unit (PICU), and mortality ranges from 0.1%
38 to 8%.^{3,4} Recently, the Critical Coronavirus and Kids Epidemiology (CAKE) study
39 reported a mortality rate of 5% in children hospitalized in critical care in five European
40 and American countries (Chile, Colombia, Italy, Spain and USA), with 76% of cases
41 having severe pneumonia as their main manifestation.⁴
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53 Several pathophysiological factors may explain these features. COVID-19 non-survivors
54 have higher serum ferritin, D-dimer and C-reactive protein (CRP) than those who survive,
55 indicating an intense inflammatory response². Recently, a new type of presentation of
56 SARS-CoV-2 infection has been described in children, involving this significant
57 inflammatory response. This new disease has been called Paediatric Inflammatory
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3 Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new
4 syndrome that is temporally related to previous exposure to severe acute respiratory
5 syndrome coronavirus 2 (SARS-CoV-2) infection. This is a severe presentation of the
6 virus in children and requires early detection to avoid its progression and potentially
7 unsatisfactory outcomes⁵. In this article, we discuss and review the most relevant aspects
8 of PIMS-TS described to date.
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13 14 15 **METHODS**

16 17 **Search strategy and article selection**

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20 A systematic review of the literature was performed in the principal medical databases
21 including PUBMED, EMBASE (OVID) and Google scholar, using the MeSH terms
22 (“SARS-CoV-2” OR “Covid-19” OR “coronavirus” OR “infection” OR “sepsis” OR
23 “covid-19” OR “critical care”) AND “Multisystem Inflammatory Syndrome in Children”
24 OR “MIS-C” OR “PIMS-TS” between December 2019 and August 2020. The descriptors
25 were validated in DecS (descriptors in health science) and MeSH (medical subject
26 headings). Grey literature or as yet unpublished documents were not included.
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33 34 **Eligibility criteria**

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36 Articles which reported at least five cases of PIMS-TS, including case series, case reports,
37 and cross-sectional, case-control, cohort (either prospective or retrospective) or clinical
38 trial studies, were included. Studies of critically ill children with COVID-19 were also
39 considered, and the cases of PIMS-TS reported in these studies were explored. Other
40 inclusion criteria were articles which described important outcomes such as mortality,
41 complications, laboratory findings and treatment received. Only articles in English,
42 Spanish or Portuguese were considered. No reports of PIMS-TS in low and middle-
43 income countries were found in indexed journals. The World Health Organization
44 (WHO), Centers for Disease Control (CDC) and Royal College guidelines were consulted
45 for the definitions. Articles which did not provide complete data when reporting general
46 cases of critically ill children with COVID-19, or those for which the full text was not
47 available, as well as narrative reviews, were excluded. Adult cases have already been
48 described, but these were not included in this review.
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Study selection and data collection process

First, the inclusion and exclusion criteria for this systematic review were defined, after which one of the researchers (JFS) performed the systematic search of the literature and reviewed the most relevant articles. The established criteria were applied, and the articles were approved by all the SLACIP sepsis committee authors. In case of doubt, or a lack of consensus regarding the inclusion of an article, a second reviewer (RJ) was consulted to decide. Any discrepancies or missing data were resolved by consensus. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. (Figure 1).

Patient and Public Involvement statement

No patients participated actively in this review. The data were taken from the most important publications to date on PIMS-TS, including consensus recommendations for high-income countries. It is expected that this information will be disseminated through SLACIP and its various committees for applicability in patients living in middle- and low-income countries.

RESULTS

Search and study selection results

A total of 69 articles were identified in the described databases. After eliminating the duplicates and reviews, 13 articles met the inclusion criteria and were eligible. These articles were included in the qualitative synthesis and the most relevant ones which do not include patients reported in other case series are described by their characteristics in Table 1.

Although the main pathogenesis of COVID-19 may be similar to other viruses such as influenza, it has shown some clinical presentations which are different from those usually found in those classical respiratory viruses. On April 24, 2020, a new presentation of SARS-CoV-2 in children was described by Riphagen et al. in the United Kingdom.⁶ The first report described a cohort of eight children with COVID-19 who required hospitalization in intensive care and had an unusual clinical behavior characterized by a severe hyperinflammatory state, with clinical similarity between all eight patients.⁷⁻⁹

The Royal College of Paediatrics and Child Health called this new entity PIMS-TS.¹⁰ Subsequently, the CDC and WHO called it multisystem inflammatory syndrome in

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3 children (MIS-C).^{11,12} In general, both terms refer to the same entity and the latter name
4 has been the most frequently used in the main descriptions of this disease (*Table 2*).

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6 The largest series described to date is that of the CDC in Atlanta, with 570 patients. Using
7 a latent class analysis (LCA) statistical model, it attempted to divide the cases into three
8 large groups according to their common clinical characteristics.¹³ Class I included those
9 with symptoms which could overlap with macrophage activation syndrome, with a large
10 inflammatory response. Class II had predominantly respiratory involvement and signs
11 suggestive of active COVID-19 disease with a high rate of RT-PCR seropositivity (84%).
12 Class III had clinical manifestations that could overlap with Kawasaki disease, and only
13 2% were RT-PCR positive.¹³
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22 In this regard, most studies report that the patients have a negative RT-PCR and positive
23 antibody or serology tests. In fact, a negative RT-PCR has been found in 40% of patients
24 with positive antibody tests. Although RT-PCR is an imperfect test, it is considered the
25 gold standard today. In the described series, 46% of the cases had a positive serology and
26 a negative RT-PCR, which suggests that, in these patients, the infection occurred possibly
27 weeks earlier. An average of 25% of the patients in the included studies had both positive
28 serology and positive RT-PCR (*supplementary table S1*).
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38 **DISCUSSION**

39 PIMS-TS is characterized by a very significant ongoing inflammatory response, in
40 crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and
41 WHO (May 15th) definitions (*Table 2*).^{11,12} Characteristically, these patients present with
42 high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.¹³ Hoang et al.¹⁴ reported
43 lower expression of circulating CD16+CD56+ natural killer cells and more profound
44 lymphopenia in children with PIMS-TS compare to those without PIMS-TS.
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46 Primarily, there is an initial innate immune response with the macrophages as the
47 principal actors. From the pathophysiological point of view, it is striking that more than
48 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an
49 acute phase reactant that usually rises after six hours of an inflammatory state and is
50 produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF- α
51 stimulation.^{15,16} This acute phase reactant from the pentraxin family identifies
52 phosphatidylserine on the surface of cells that have initiated a programmed cell death
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3 pattern of apoptosis by activating the complement system. This biomarker is very useful
4 for diagnosis and follow up, especially in middle and low-income countries (given its low
5 cost), and should be considered on admission with subsequent follow up.
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8 Additionally, a marked elevation of ferritin (2-10 times its normal value) has been
9 observed in more than 90% of the series.¹³⁻¹⁷ Ferritin is a protein that stores iron and
10 releases it in a controlled fashion, but also in pathophysiologic conditions. Its levels can
11 reflect macrophage response to free hemoglobin as well as DNA viruses, intracellular
12 bacterial infections and parasites.¹⁸⁻²⁰ Ferritin can induce positive feedback inflammation,
13 upregulating toll-like receptor 9 (TLR-9) which leads macrophage inflammasome IL-1
14 and IL-18 to feed forward ferritin production. TLR-9 may also be stimulated by viral
15 DNA, other infections and host damage-associated molecular patterns (DAMP).²⁰ This
16 whole process generates a large number of inflammasomes and an enhanced
17 inflammatory pathway, delivering the “cytokine storm.” This precipitate cell death with
18 a pyroptosis pattern and new DAMPs that stimulate TLR-9.²⁰ This was described as
19 “*Hyperferritinemic Syndrome*” by Rosario²¹.
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30 Nevertheless, there is evidence of an unusual late adaptive immunity response. It has
31 come to the researchers attention that PIMS-TS occurred between four and six weeks
32 after the peak of cases reported as positive for SARS-CoV-2 in each country had been
33 reached.¹³ Pérez-Toledo M et al.²² recently described eight patients with PIMS-TS with
34 a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM.
35 Additionally, they found elevated IgG1 and IgG3 in these children, which are
36 immunoglobulin isotypes associated with serum supplement activation. This situation is
37 consistent with highly elevated CRP related to COVID-19, which activates the
38 complement system. The elevation of these immunoglobulins suggests that PIMS-TS
39 occurs due to tissue damage induced by autoantibodies, a situation that has been described
40 in other types of coronavirus infection.²³⁻²⁴ We are not aware of any studies in middle
41 and low-income countries which have described this serological behaviour. Studies are
42 needed to help clear up this aspect, especially when all the diagnostic test options for
43 SARS-CoV-2 are not always available. In these countries with limited resources, we
44 suggest taking an initial RT-PCR. If this is negative and there is a high index of suspicion
45 of PIMS-TS, due to the signs and symptoms, a total antibody or IgM/IgG test should be
46 performed.²⁴
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3 For PIMS-TS, most of the series described coagulation disorders. Severe coagulopathy
4 was seen in 70-80% of the cases (very high D-dimers, prolonged PT, PTT).¹³ Like
5 inflammation, coagulation is necessary for host defense. In addition, proinflammatory
6 cytokines, monocytes / macrophages, neutrophil activation, and extracellular neutrophil
7 traps (NETs) can foster local thrombosis. COVID-19 associated coagulopathy (CAC) is
8 complex and in some ways pathophysiologically different from SIC.^{25,26}
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15 Cytokine levels of IL-1 β and IL-6 are elevated, which induces thrombocytosis and
16 hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is
17 stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.^{27, 28}
18 D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its
19 early phase.²⁸ Elevated D-dimer levels can be present in a wide variety of inflammatory
20 and prothrombotic conditions;²⁹ in COVID-19, these are probably more associated with
21 inflammation than thrombosis.³⁰ Furthermore, serum hyaluronic acid, a key glycocalyx
22 component, is higher during infancy, progressively diminishing over the years.^{19,31} This
23 could explain a more protected endothelium and a lower probability of a hypercoagulable
24 state. In addition, CAC has an overlapping pathophysiology with other coagulopathies
25 like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH),
26 antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) /
27 hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type
28 of coagulopathy.³²
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Author	City, Country	Period	Number	Age	Gender	Comorbidity	Race	IMC kg/m ²
Whittaker et al [3]	London, UK	March 23 and May 16	58	9 years (IQR 5.7, 14)	43% boys	7/58 Comorbidities	69% black or Asian	N/R
Riphagen et al [6]	London, UK	10 days in mid-April	8	4 – 14 years (range)	5/8 boy	None	6/8 Afro-Caribbean	14 – 33 7/8 > 75 th centile/weight
Verdoni et al [7]	Bergamo, Italy	Feb 18 and April 20	10	7.5 years (SD 3-5)	7/10 boys	N/R	N/R	N/R
Belhadjer et al [8]	France (12 hospitals) and Switzerland (1 hospital)	March 22 to April 30	35	10 years (IQR 8.2, 12.4)	51% boys	Comorbidities 28% (asthma 8.55; lupus 3%)	N/R	Overweight 17%
Golfred-Cato S et al [13]	Multicenter US	March 01 to July 29	570	8 (IQR 4,12)	55.4% boys	Comorbidities 8%	40.5% Hispanic and 33.1% Black Non-hispanic	Obesity 25.6%
Cheung et al [33]	New York, US	April 18 and May 5	17	8 years (IQR 1.8, 16)	47% boys	Most were previously healthy (mild asthma in 3)	White 70%	N/R
Kaushik et al [38]	New York, US	April 23 to May 23	33	10 years (IQR 6, 13)	61% boys	Comorbidities 48%	45% Hispanic/latino 39% black	Overweight 12% Obesity (BMI > 30kg/m ²) 6%
Ramcharan et al [40]	UK	10 th April and 9 th May	15	8.8 (IQR 6.4, 11.2) 93% were over 5y	73% boys		100% African/Afr-Caribbean (40%), South Asian, (40%)	

							Mixed (13%) Or other minority ethnic	
Toubiana et al [45]	France, Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR 3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI below the 97 th centile
Pouletty et al [46]	Paris, France	Since April 2020	16	10 (IQR 4.7, 12.5)	50% boys	Comorbidities 37%	N/R	Overweight 25%
Caponi et al [47]	New York, US	April 17 – May 13	33	8.6 years (IQR 5.5, 12.6)	61% boys	Comorbidities 21%	73% non-Hispanic	Overweight 6% Obese 39%
Feldstein L.R et al [48]	Multicenter, US	March 15 to May 20	186	8.3 years (IQR 3.3, 12.5)	62% boys	Comorbidities 27%	31% Hispanic, 25% Black non hispanic	Obesity 29%
Dufort E et al [49]	New York City	March 01 to May 10	95	0-5 years (31%) 6-12 years (42%) 13-20 years (27%)	54% boys	Comorbidities 64%	40% Black 36% Hispanic	Obesity 29%

Table 1. Demographic characteristics of patients with PIMS-TS. N/R: not reported.

Review Only

Royal College of Paediatrics and Health Child (RCPCH) Definition [10]

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative.

Centers for Disease Control and Prevention (CDC) Definition [11]

- 1. An individual aged < 21 years presenting with fever¹, laboratory evidence of inflammation² and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND**
- 2. No alternative plausible diagnoses; AND**
- 3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.**

¹Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

²Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

World Health Organization Definition [12]

Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

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

AND

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

AND

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

AND

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

Table 2. RCPCH, CDC, WHO Definitions Criteria for Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19

From a clinical and laboratory perspective, PIMS-TS has usually been seen in previously healthy and frequently obese (30-60% of the series) children over eight years of age (80% of the cases) (*Table 1*). Initially, the group from the United Kingdom (UK) found MIS-C in patients of African descent, but it has been described in patients of all origins.^{4,32,33} Persistent high fever for more than three to five consecutive days, maculopapular skin lesions (50-60%) reminiscent of Kawasaki disease (KD) and, frequently, signs of shock at the time of presentation have been the initial clinical characteristics.³³ Digestive symptoms (including nausea, vomiting, diarrhea or abdominal pain) usually present in most cases, as well as myocardial involvement (more than 60% of the series).^{14,33} Cardiac involvement is broad and variable, with features including myocardial dysfunction (100% of the initial UK description - 60% in other series), coronary aneurysms, pericarditis, arrhythmias, refractory shock and elevated troponin I or pro-BNP³²⁻³⁴ (*supplementary table S1*).

Guidelines for PIMS-TS management in middle and low-income countries

With regard to treatment in middle and low-income countries, it is very important to maintain a high index of suspicion. Therefore, in these countries, it is important to use a systematic approach including early recognition and a bundle similar to those recommended for patients with other serious diseases. An expert consensus recently published in the United Kingdom using the Delphi method provides a good summary of the recommended treatments³⁴. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with

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3 those of the SCCM sepsis consensus¹⁶, for use in middle and low-income countries. We
4 believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking
5 these recommendations as a whole could have an impact on the outcomes of PIMS-TS
6 patients in these countries.
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11 From the first presentation to the Emergency Department and / or PICU, two approaches
12 can be assumed, one general and one specific (*Table 3*):
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15 a. *General approach*: A comprehensive approach should be used, similar to that
16 recommended for patients with sepsis with organ dysfunction or septic shock. In this case,
17 the contagiousness of SARS-CoV-2 requires the use of personal protective equipment
18 (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-
19 PCR.
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24 Moreover, the American College of Critical Care Medicine (ACCM) points out the need
25 to give more attention to Institutional Practice Guidelines (IPGs) based on each facility's
26 capability.³⁵ Once IPGs are established, diagnostic and therapeutic measures known as
27 "patient care bundles" (PCBs) should be developed for a better approach and control of
28 established processes. The PCBs include three to five evidence-based practices related to
29 a health care process that should be performed collectively to achieve a synergistic result
30 that improves care.^{36,37}
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36 1. Early detection: a comprehensive approach based on a high index of suspicion is
37 critical. This disease may occur with a wide spectrum of symptoms, so it should be
38 suspected in all patients with a fever lasting more than three days associated with the
39 symptoms described in *Table 2*. Contact with a positive case is not always clear.
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43 2. Immediate, time-sensitive resuscitation:

44 - Oxygen therapy: This is part of the strategies described in recent sepsis guidelines^{16,37}.
45 High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been
46 considered in many reports,³⁸ especially in patients who have a deteriorated respiratory
47 pattern with the use of accessory muscles or an SaO₂/FiO₂ ratio less than 264. Most series
48 describe respiratory involvement ranging from 20-60% (*supplementary table S1*) and,
49 generally, if endotracheal intubation is required, it is more highly associated with
50 cardiovascular involvement. Cases classified as Class II by the CDC may be classified in
51 these groups.^{33,38}
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55 - Fluid resuscitation: It is important to consider the recommendations in recently
56 published guidelines.¹⁶ In healthcare systems where staff and equipment for advanced
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3 airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of
4 balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour,
5 titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload
6 develop. In healthcare systems without the availability of intubation, crystalloid boluses
7 may only be given in cases of hypotension (decompensated shock); in these cases, up to
8 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with
9 titration to clinical markers of cardiac output, and discontinued if signs of fluid overload
10 develop. If the child is not hypotensive, but has compensated shock, only maintenance
11 fluids should be started, avoiding bolus fluids which are associated with worse
12 outcomes³⁵⁻³⁸.

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21 -Vasoactive drugs: According to the clinical condition, most series describe the need for
22 vasoactive drugs in 10 to 60% of the cases with PIMS-TS. Most patients respond to fluid
23 resuscitation. If necessary, epinephrine or norepinephrine should be considered according
24 to the patient's condition.^{16,39} Inotropes like dopamine, milrinone and levosimendan were
25 reported to have been used in PIMS-TS.³⁸⁻⁴⁰

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29 -Antibiotic therapy: If bacterial co-infection is suspected, the first dose is recommended
30 within the first three hours for sepsis associated with organ dysfunction, or within the first
31 hour for children with septic shock.³⁹⁻⁴¹

32 33 34 3. Stabilization with adequate monitoring:

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36 If possible, advanced hemodynamic monitoring should be instituted. Cardiac
37 ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent
38 guidelines¹⁶ and patients with PIMS-TS.⁴²

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41 4. Timely referral or transfer is desirable in this context. In middle and low-income
42 countries, it is common for patients to be transferred to higher complexity sites. Patients
43 who are deteriorating or who may need intensive care should be identified. In the PIMS-
44 TS of the CDC group, 84% of the cases had to be transferred to paediatric intensive care.
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5. Continuous measurement of processes and corrections must be instituted for a
continuous quality improvement process.⁴²

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b. Specific approach: It is important to emphasize that, in moderate to severe cases, the
use of immunomodulatory treatment should be considered. Heterogeneous management
including human immunoglobulin, systemic steroids, anakinra, tocilizumab and aspirin
^{40,42-45} has been reported in the described series (*supplementary table S1*). The American

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3 College of Rheumatology (ACR) recommendations for immunomodulatory therapy⁴²
4 have recently been published. We sought to adapt these recommendations to middle and
5 low-income countries where resources are limited and each intervention must be
6 streamlined according to need.
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- 10 ⇒ IVIG: High doses (2 gr/kg) should be considered for moderate to severe cases,
11 particularly those with myocardial involvement. Prior to beginning the infusion,
12 restored heart function must be verified.⁴²
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14 ⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical
15 course of the disease in adults with severe pneumonia, particularly if they are on
16 mechanical ventilation.⁴³⁻⁴⁷ In patients with PIMS-TS, low doses could be
17 considered in all cases (used in 70% of the series – *supplementary table S1*).
18 Dosing schemes of 1-2 mg/kg/dose of methylprednisolone or its equivalent three
19 or four times per day have been recommended. The ACR suggests considering
20 high doses in cases of shock or in those with a high need for vasopressors, and we
21 believe this recommendation is very important for middle and low-income
22 countries, especially considering the frequency of late consults with advanced
23 disease.
24
25 ⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-
26 refractory PIMS-TS.⁴² However, in many countries, its use is not approved, or it
27 is not available, and other biological agents are used. Prospective studies are
28 needed to evaluate the efficacy and safety of these medications in PIMS-TS.
29
30 ⇒ Anticoagulation and antiplatelet treatment: Anticoagulation has become a
31 fundamental treatment in adults, considering that there is a procoagulant and
32 hypofibrinolytic state in severe SARS-CoV-2 infection.^{42,47-50} In children with
33 PIMS-TS it is recommended only in cases of documented thrombosis or in
34 patients with an echocardiogram ejection fraction less than 35%.^{43,47} Aspirin
35 would also be recommended in patients with thrombocytosis (> 450,000 u/L) or
36 Kawasaki-like disease criteria.^{42,47}
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53 The prognosis of the disease is usually good, with patient survival greater than 95% in
54 different published series.^{5,6,42-50} A mortality of 1-2% has been described in the published
55 series, and up to 15% with cardiovascular sequelae, including aneurysms or
56 dysfunction.^{33,48-50} These patients should be followed up after discharge by inter and
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multidisciplinary teams including infectious disease, rheumatology and paediatrics. However, there are incomplete data from all the cases, along with a knowledge gap regarding mild and moderate cases, the natural course and the clinical behavior of the disease.^{8,47-50}

General approach	Specific approach
1. Early detection	1. Human immunoglobulin: <ul style="list-style-type: none"> • 2 gr/kg for moderate to severe cases
2. Immediate, time-sensitive resuscitation <ol style="list-style-type: none"> Oxygen therapy Fluid resuscitation Vasoactive drugs Antibiotic therapy: if bacterial co-infection is suspected 	2. Steroids: <ul style="list-style-type: none"> • 1-2 mg/kg/dose of methylprednisolone three or four times per day • High doses in cases of shock with high vasopressor requirement
3. Stabilization with adequate monitoring	3. Anakinra: <ul style="list-style-type: none"> • Only in cases refractory to steroids and IVIG. Not available in all countries.
4. Timely referral or transfer according to the context and available resources	4. Anticoagulation is recommended for: <ol style="list-style-type: none"> Documented thrombosis Echocardiogram with an EF of less than 35%
5. Continuous measurement of processes	5. Antiplatelet treatment: recommended for thrombocytosis > 450,000 u/L.

Table 3. Summary of recommendations for management of PIMT-TS in countries with limited resources.

Conclusion

PIMS-TS is a new type of presentation of SARS-CoV-2 infection, with an exaggerated inflammatory response and inadequate inflammatory resolution with frequent *-but not exclusive-* digestive and myocardial involvement. It should be considered as a new disease with unique symptoms, a greater variety of clinical courses, and possibly different physiological mechanisms. In middle and low-income countries, studies should be performed to learn more about this disease in these regions and determine if they have different phenotypic behaviors. In addition, the real role of some inflammatory biomarkers and cost-effective therapeutic strategies should be determined.

Contributors

JFS, DS, RJ, PA, GG, GP conceptualized and designed the literature search. JFS, DS, RJ initiated the search and a first draft. All authors contributed to subsequent drafts. JFS, as group leader, supervised and moderated the search, initial drafts, the overall collation of the figures and tables and final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

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ORCID: iD Jaime Fernández-Sarmiento <http://orcid.org/0000-0003-2874-2949116>

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21 *Figure 1.* Selection process. We followed the PRISMA guidelines for reporting in
22 systematic reviews and meta-analyses
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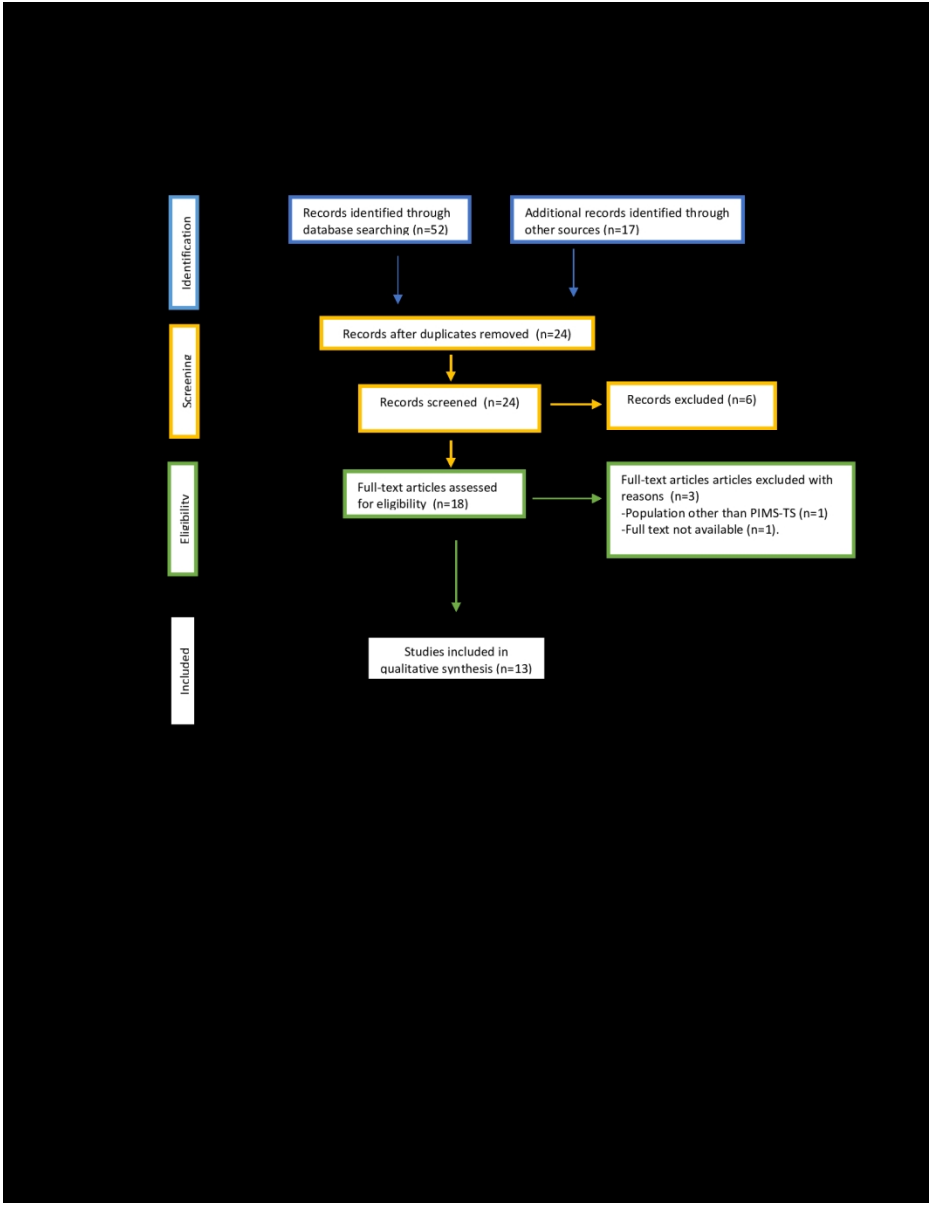
27 *Table 1.* Demographic characteristics of patients with PIMS-TS
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30 *Table 2.* RCPCH, CDC and WHO Definition Criteria for Paediatric Inflammatory
31 Multisystem Syndrome Temporally associated with COVID-19
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35 *Table 3.* Summary of recommendations for management of PIMT-TS in countries with
36 limited resources.
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40 *Supplementary table S1.* Clinical and echocardiographic findings, and treatments
41 instituted in the described series of PIMS-TS patients.
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Author	Clinical presentation	ECHO	SARS-CoV-2 test	Organ support	Treatment	Outcome / Died
Whittaker et al [3]	Fever 100%, Headache 26% Vomiting 45% Diarrhea 52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29% Swollen hands and feet 16%, Respiratory symptoms 21%. Fever + elevated inflammatory markers – 40%, Shock - 50%	Left ventricular dysfunction 62% (18/29) Abnormally dilated coronary arteries (z score >2) 8/55 Giant coronary artery aneurysms 2 Coronary artery aneurism 14% (n=8)	RT-PCR SARS-CoV-2 + 26% IgG antibody SARS-CoV-2 + 87% 78% had evidence of current or prior SARS-CoV-2 infection	PICU 50% Acute kidney injury 22% Shock + inotropic support 47% MV 43% ECMO 5%	Inotropic support 47% IVIG 71% Corticosteroids 64% Anakinra 5% Infliximab 14%	Death 2%
Riphagen et al [6]	Fever 8/8 Diarrhoea 7/8 Abdominal pain 6/8 Vomiting 4/8 Conjunctivitis 5/8 Rash 4/8 Vasoplegic shock 8/8	7/8 ventricular dysfunction Echobright coronary vessels 1/8 giant coronary aneurysm	SARS-CoV-2 negative 5/8 SARS-CoV-2 positive 2/8 Family exposure 4/8	Inotropic/vasopressor support 8/8, MV 5/8, HFNC 1/8, NIV 3/8, RRT 1/8, VA-ECMO 1/8 (arrhythmia with refractory shock, died)	IVIG 8/8, Corticoids 5/8 Aspirin 3/8, Heparin 1/8, Antibiotics 8/8, Infliximab 1/8	1 died 6/8 alive PICU length of stay 3 – 7 days
Verdoni et al [7]	Classic form of Kawasaki 50%, Incomplete form of Kawasaki disease 50% Kdss and MAS 50% Diarrhoea 60% Meningeal signs 40% Drowsiness 10%	Anormal ECHO 60% Aneurism 10% FEVE < 50% – 50% Mitral valve regurgitation 10% Pericardial effusion 40%	RT-PCR SARS-CoV-2 + 20% Serology for SARS-CoV-2 antibodies – 80% were IgG +, and 3 were also IgM +		Inotropic support 20% Adjunctive steroid treatment 80% IVIG 100% Aspirin 20%	None
Belhadjer et al [8]	Asthenia 100% Fever 100% GI symptoms 83% (2 children underwent emergency operation for suspected appendicitis) Respiratory distress 65%	Coronary artery dilatation (z score > 2) 17% Aneurysm 0 LVEF < 30% - 28% LVEF 30-50% - 72%	SARS-CoV-2 was confirmed 88.5% RT-PCR-SARS-CoV-2 + 34% Fecal PCR 6% Antibodies + 86%	Respiratory support 94% (IMV 62%; NIV 32%) VA-ECMO 28%	Inotropic support 80% IVIG 71% Corticosteroids 34% Anakinra 8% Anticoagulation with heparin 65%	None

	Rhinorrhea 43% Adenopathy 60% Rash 57% Meningism 31% At admission to the ICU, 80% were in cardiogenic shock					
Grimaud et al [9]	Fever 100%, Abdominal pain 100%, Rash 50%, Conjunctivitis 30%, Adenitis 20%, Tachycardia 100% Hypotension 100% (75% clinical signs of vasoplegia)	LVEF 35% (IQR 25-55)	SARS-CoV-nasopharyngeal swabs + 50% SARS-CoV-2 antibodies + 100% (15/15), 95% had identified SARS-CoV-2 infection on PCR and/or by serology	NIV 55%,IMV 40%, HFNO 5%,Respiratory support in all patient was indicated for hemodynamic support	IVIG100%,Corticosteroids 10%, Anakinra 5%, Tocilizumab 5%, Inotropic/vasopressor support 95%	None
Cheung et al [33]	Fever 100% GI symptoms 88% Shock at presentation 76% Rash 71%, Conjunctivitis 65% Lip redness/swelling 65% Neurologic symptoms 47%, Respiratory symptoms 41%, Myalgia 35%, Lymphadenopathy 35%, Hypoxia 18% Criteria for KD 47% Incomplete Kawasaki 29%	FEVE mildly decreased 29% FEVE mild-moderately decreased 24% FEVE moderate-severely decreased 12% Pericardial effusion 47%	RT-PCR SARS-CoV-2 + 47% Serology for SARS-CoV-2 antibodies → 53%	PICU 88%	IVIG 76% Methylprednisolone 71% Hydrocortisone 21% Enoxaparin prophylaxis 59% Enoxaparin treatment 6% Aspirin 24%	None
Golfred-Cato S et al [13]	Fever 100% Bilateral conjunctival injection 48.4% Oral mucose changes 23% Rash 55.3%	Abnormal ECHO with coronary-artery aneurysms 18.6%	RT-PCR 25.8% Serology positive 46.1% RT-PCR and serology positive 27.2%	PICU 63.9% MV 13.1% Vasoactives 44.9%	IVIG 80.5% Steroids 62.8% Antiplatelet medication 58.6% Anticoagulation 44.2%	Died 1.8% Organs systems involved 4-5 61.6%
Kaushik et al [38]	Fever 93%, Abdominal pain 63%, Nausea/emesis 69%, Diarrhea 48%	Pericardial effusion 46%	SARS-CoV-2 antibody + 81%	NIV 36% IMV 15% ECMO 3%	IVIG 54%, Corticosteroids 51%, Tocilizumab 36%	Death 3%

	Hypotension 63%, Mucocutaneous, involvement 21% Conjunctivitis 36% Rash 42%, Shortness of breath 33% Neurologic involvement 12%	LVEF median 46.6 (IQR 39.5, 52.8) LVEF < 30%: 12% LVEF 30-50%: 53% Recovered LV function prior to discharge 95%	RT-PCR SARS-CoV-2 + 33% 18% tested + for both	Intra-aortic balloon pump support 3%	Remdesivir 21%, Anakinra 12%, Convalescent plasma therapy 3%, Aspirin 24% Anticoagulation, prophylaxis 15%, Anticoagulation, therapeutic 81% Antibiotics > 48h 45% Vasopressor/inotropes 51%	
Ramcharan et al [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on admission 51%	13% described typical COVID-19 symptoms in the previous two months 20% related contact with family member with COVID-19	Respiratory support 53% Inotrope or vasopressor 67%	IVIG 67% (10/15), of whom 2 received a second dose Methylprednisolone 33% 73% were discharged on low dose aspirin Antibiotic 100%	None
Toubiana et al [45]	Recent history of viral- like symptoms was report in 43% Median duration between these symptoms and the onset of signs and symptoms of Kawasaki disease was 45 days. Complete presentation of KD 52%, Abdominal symptoms 95%, Lips and oral cavity changes 76% Conjunctivitis 81% Rash 76%, Changes to extremities 48% Lymphadenopathy 57%	Myocarditis 76% (LVEF range between 10 and 57%) 38% coronary artery abnormalities: 24% which consisted of dilations (z score between 2.0 and 2.5); 14% with increased coronary visibility No coronary aneurysms were identified	History of recent contact with people with viral-like symptoms was + in 48% Median interval between reported contact and KD was 36 days RT-PCR-SARS-CoV-2 + 38% IgG antibodies SARS- CoV-2 + 90% 9.5% negative Serology and PCR)	PICU 81% Vasoactive agents 71% MV 52%	IVIG 100% (24% needed a second dose) Low dose aspirin (3- 5mg/kg/day) 100% Corticosteroids (2- 10mg/kg/day) 48% Antibiotic 86%	None
Pouletty et al [46]	Fever 100% Respiratory signs 12% GI signs 81% Anosmia 6%	Abnormal ECHO 69% Coronary dilatation 19% (median z score 2.6)	Family c/s COVID-19 infection 75% First infectious exposure-		IVIG 93% (Second infusion 335) Steroids 25% Anakinra 6%	None

	Neurological signs 56% Rash 81% Conjunctivitis 94% Hands and feet edema/erythema 68% Dry cracked lips 87% Lymphadenopathy 37% Haemodynamic failure 69% Complete KD 62% KDSS 44%	No aneurysm Myocarditis 44% (median LVEF 35%) Pericarditis 25%	hospitalization 21 days (IQR 21-24) RT-PCR-SARS-CoV-2 all sites + 69% Serology IgG + 87%		Tocilizumab 6% AAS (30-50mg/kg) 52% AAS anti-aggregant dose 50%	
Caponi et al [47]	Fever 100% GI symptoms 97% Neurocognitive symptoms 58% Respiratory symptoms 52% Shock 75% Complete KD 64% HD without shock 76%	Any coronary abnormality 48% (Z score ≥ 2.5 – 15%; Z score 2-2.49 – 9%) Any dysfunction 58%: (LVEF 45-54% - 33%; LVEF 35-44% - 24%)	IgG + and Nucleic acid amplification + 18% IgG + and Nucleic acid amplification negative 73% Nucleic acid amplification +, serology test unavailable 9%	PICU 79% MV 18% Inotrope/vasopressor support 76%	IVIG 100% 2 nd dose IVIG 33% Methylprednisolone 70% Aspirin 88% Anakinra 12% Tocilizumab 9% Infliximab 13% Enoxaparin 42%	None
Feldstein L.R et al [48]	Fever 100% Bilateral conjunctival injection 55% Oral mucose changes 42% Peripheral extremity changes 37% Rash 59%	Abnormal ECHO with coronary-artery aneurysms 9%	RT-PCR or antibody testing 70%	PICU 80% MV 20% Inotrope or vasopressor support 48% ECMO 4%	IVIG 77% Secon dose 21% Systemic glucocorticoid 49% Interleukin-6 inhibitor 8% Interleukin-1Ra inhibitor 13% Anticoagulation 47%	28% were still hospitalized as of May 20, 2020, and 4 patients (2%) died, 2 of whom had previously been healthy.
Dufort E et al (49)	Fever 100%, abdominal pain 61%, rash 60%,conjunctivitis 56%	Abnormal ECHO with coronary-artery aneurysm 9%	RT-PCR 51%, IgG antibodies 99%	PICU 80%, MV 10%, Vasopressor support 62%, ECMO 4%	IVIG 48% Systemic glucocorticoids 64%	Death 2%, shock 10%, myocarditis 53%

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4 *Abbreviations: MV: mechanical ventilation, HFNC: high flow nasal cannula, NIV:noninvasive ventilation, RRT:renal replacement therapy, VA-*
5 *ECMO: venu-arterial extracorporeal membrane oxygenation, PCR: protein C reactive, IVIG: immunoglobulin, FEVE: fraction ejection*
6 *ventricular, RT-PCR: real time polymerase chain reaction, PICU: pediatric intensive care unit, KD:Kawasaki disease*
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8 *Supplementary File. Table S1. Clinical findings, echocardiographic and treatments instituted in the described series of PIMS-TS*
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BMJ Paediatrics Open

Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS): a narrative review and the viewpoint of the Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee

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**Paediatric Inflammatory Multisystem Syndrome Temporally
associated with COVID-19 (PIMS-TS): a narrative review and the
viewpoint of the *Latin American Society of Pediatric Intensive Care*
(SLACIP) Sepsis Committee**

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Jaime Fernández-Sarmiento MD PhD(c)^{1,6}, Daniela Carla de Souza MD PhD^{2,6}, Roberto Jabornisky MD^{3,6}, Gustavo Ariel González MD^{4,5,6}, María del Pilar Arias López MD^{5,6}, Gladys Palacio MD^{5,6}.

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1 Department of Critical Care Medicine and Pediatrics, Universidad de la Sabana, Fundación Cardioinfantil - Instituto de Cardiología. CES Graduate School. Bogotá Colombia.

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28

2 Pediatric Intensive Care Unit and Department of Pediatrics, Hospital Universitario da Universidad de São Paulo and Hospital Sírio Libanês, Sao Paulo, Brazil.

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30
31

3 Department of Pediatrics. Facultad de Medicina. Universidad Nacional del Nordeste. Argentina.

32
33
34

4 Pediatric Intensive Care Unit. Hospital Churruca - Visca Medical Complex. Buenos Aires. Argentina.

35
36
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5 Pediatric Intensive Care Unit. Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina.

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6 Sepsis Committee. Latin American Society of Pediatric Intensive Care (SLACIP).

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Corresponding author: Jaime Fernández-Sarmiento, MD. Universidad de La Sabana, Campus del Puente del Común, Km 7 Autopista Norte de Bogotá, Chía - Cundinamarca - Colombia - South America. JaimeFe@unisabana.edu.co. + 057-16672727 ext 2204.

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Word count 3008

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Abstract

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Background: In this review, we discuss some important aspects of Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new syndrome that is temporally related to previous exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This virus has a broad spectrum of presentation which may overlap with Kawasaki disease (aKD) in terms of

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3 presenting symptoms, and laboratory and cardiac findings. Our objective was to review
4 and summarize published evidence regarding the most important aspects of PIMS-TS,
5 with special emphasis on the treatment strategies suggested for middle- and low-income
6 countries.
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12 *Methods:* A systematic review of the literature was performed in the principal medical
13 databases including PUBMED, EMBASE (OVID) and Google Scholar between
14 December 2019 and August 2020.
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19 *Results:* A total of 69 articles were identified in the described databases. Altogether, 13
20 articles met the inclusion criteria and were eligible. The most frequently described
21 symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%),
22 skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-
23 6 weeks after the pandemic appears in the general population. Multisystem inflammatory
24 syndrome in children is presented as a great systemic inflammatory response syndrome
25 (SIRS), which sometimes presents as shock requiring fluid resuscitation and vasoactive
26 drug support (26%). Several treatment strategies have been used, including
27 immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These
28 general and specific interventions should be guided by an inter- and multi-disciplinary
29 team, especially in settings with limited resources.
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39 *Conclusions:* PIMS-TS COVID-19 is a new type of presentation of SARS-CoV-2
40 infection, with an exaggerated inflammatory response and frequent *-but not exclusive-*
41 digestive and myocardial involvement. It is important to describe the clinical course and
42 outcomes in countries with limited resources as well as establish the role of biomarkers
43 for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.
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49 *Key words:* septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease,
50 thrombosis, SARS-CoV-2
51

52 53 **Key messages**

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55 -PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times
56 greater need for hospitalization and mortality in children than other COVID-19
57 presentations.
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-It is characterized by fever, shock and gastrointestinal, skin and cardiac involvement, with prior positive real-time polymerase chain reaction (RT-PCR) or antibody tests.

-The diagnostic and treatment approach should be aimed at initial stabilization and shock management, especially in countries with limited resources. The specific treatment includes immunomodulators.

What does this study add?

For this SARS-CoV2 disease, which mainly affects children, a comprehensive approach is suggested which may be applied under the various healthcare system access conditions, including strategies geared towards middle- and low-income countries. This treatment includes general stabilization and shock management measures as well as the specific immunomodulatory therapy currently recommended based on the available evidence.

INTRODUCTION

In December 2019, a new viral infection was reported, causing severe respiratory infection and very high mortality. According to its genetic sequencing, this virus belongs to the genus *Beta coronavirus*, closely related to the severe acute respiratory syndrome (SARS) virus. It was named SARS-CoV-2 and its disease COVID-19.^{1,2}

Healthcare systems worldwide have been deeply concerned, given SARS-CoV-2's high transmissibility, severity and lethality, particularly in the population over the age of 60.¹ Patients with major comorbidities such as heart disease, diabetes, hypertension, or obesity have an increased risk of dying.^{1,2} Moreover, mortality has been associated with multiple organ failure (MOF) as the common final pathway for pneumonia, sepsis, and acute respiratory distress syndrome (ARDS). COVID-19 is usually less severe in paediatric patients. In general, 80-90% of children with SARS-CoV-2 infection are asymptomatic or have a mild infection. However, between 4 -10% of hospitalized children may need to be transferred to a paediatric intensive care unit (PICU), and mortality ranges from 0.1% to 8%.^{3,4} Recently, the Critical Coronavirus and Kids Epidemiology (CAKE) study reported a mortality rate of 5% in children hospitalized in critical care in five European and American countries (Chile, Colombia, Italy, Spain and USA), with 76% of cases having severe pneumonia as their main manifestation.⁴

Several pathophysiological factors may explain these features. COVID-19 non-survivors have higher serum ferritin, D-dimer and C-reactive protein (CRP) than those who survive, indicating an intense inflammatory response². Recently, a new type of presentation of

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3 SARS-CoV-2 infection has been described in children, involving this significant
4 inflammatory response. This new disease has been called Paediatric Inflammatory
5 Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS), a new
6 syndrome that is temporally related to previous exposure to severe acute respiratory
7 syndrome coronavirus 2 (SARS-CoV-2) infection. This is a severe presentation of the
8 virus in children and requires early detection to avoid its progression and potentially
9 unsatisfactory outcomes⁵. In this article, we discuss and review the most relevant aspects
10 of PIMS-TS described to date.
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19 **METHODS**

20 **Search strategy and article selection**

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23 A systematic review of the literature was performed in the principal medical databases
24 including PUBMED, EMBASE (OVID) and Google scholar, using the MeSH terms
25 (“SARS-CoV-2” OR “Covid-19” OR “coronavirus” OR “infection” OR “sepsis” OR
26 “covid-19” OR “critical care”) AND “Multisystem Inflammatory Syndrome in Children”
27 OR “MIS-C” OR “PIMS-TS” between December 2019 and August 2020. The descriptors
28 were validated in DecS (descriptors in health science) and MeSH (medical subject
29 headings). Grey literature or as yet unpublished documents were not included.
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36 **Eligibility criteria**

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38 Articles which reported at least five cases of PIMS-TS, including case series, case reports,
39 and cross-sectional, case-control, cohort (either prospective or retrospective) or clinical
40 trial studies, were included. Studies of critically ill children with COVID-19 were also
41 considered, and the cases of PIMS-TS reported in these studies were explored. Other
42 inclusion criteria were articles which described important outcomes such as mortality,
43 complications, laboratory findings and treatment received. Only articles in English,
44 Spanish or Portuguese were considered. No reports of PIMS-TS in low and middle-
45 income countries were found in indexed journals. The World Health Organization
46 (WHO), Centers for Disease Control (CDC) and Royal College guidelines were consulted
47 for the definitions. Articles which did not provide complete data when reporting general
48 cases of critically ill children with COVID-19, or those for which the full text was not
49 available, as well as narrative reviews, were excluded. Adult cases have already been
50 described, but these were not included in this review.
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Study selection and data collection process

First, the inclusion and exclusion criteria for this systematic review were defined, after which one of the researchers (JFS) performed the systematic search of the literature and reviewed the most relevant articles. The established criteria were applied, and the articles were approved by all the SLACIP sepsis committee authors. In case of doubt, or a lack of consensus regarding the inclusion of an article, a second reviewer (RJ) was consulted to decide. Any discrepancies or missing data were resolved by consensus. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. (*Figure 1*).

Patient and Public Involvement statement

No patients participated actively in this review. The data were taken from the most important publications to date on PIMS-TS, including consensus recommendations for high-income countries. It is expected that this information will be disseminated through SLACIP and its various committees for applicability in patients living in middle- and low-income countries.

RESULTS

Search and study selection results

A total of 69 articles were identified in the described databases. After eliminating the duplicates and reviews, 13 articles met the inclusion criteria and were eligible. These articles were included in the qualitative synthesis and the most relevant ones which do not include patients reported in other case series are described by their characteristics in *Table 1*.

Although the main pathogenesis of COVID-19 may be similar to other viruses such as influenza, it has shown some clinical presentations which are different from those usually found in those classical respiratory viruses. On April 24, 2020, a new presentation of SARS-CoV-2 in children was described by Riphagen et al. in the United Kingdom.⁶ The first report described a cohort of eight children with COVID-19 who required hospitalization in intensive care and had an unusual clinical behavior characterized by a severe hyperinflammatory state, with clinical similarity between all eight patients.⁷⁻⁹

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3 The Royal College of Paediatrics and Child Health called this new entity PIMS-TS.¹⁰
4 Subsequently, the CDC and WHO called it multisystem inflammatory syndrome in
5 children (MIS-C).^{11,12} In general, both terms refer to the same entity and the latter name
6 has been the most frequently used in the main descriptions of this disease (*Table 2*).
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10 The largest series described to date is that of the CDC in Atlanta, with 570 patients. Using
11 a latent class analysis (LCA) statistical model, it attempted to divide the cases into three
12 large groups according to their common clinical characteristics.¹³ Class I included those
13 with symptoms which could overlap with macrophage activation syndrome, with a large
14 inflammatory response. Class II had predominantly respiratory involvement and signs
15 suggestive of active COVID-19 disease with a high rate of RT-PCR seropositivity (84%).
16 Class III had clinical manifestations that could overlap with Kawasaki disease, and only
17 2% were RT-PCR positive.¹³
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25 In this regard, most studies report that the patients have a negative RT-PCR and positive
26 antibody or serology tests. In fact, a negative RT-PCR has been found in 40% of patients
27 with positive antibody tests. Although RT-PCR is an imperfect test, it is considered the
28 gold standard today. In the described series, 46% of the cases had a positive serology and
29 a negative RT-PCR, which suggests that, in these patients, the infection occurred possibly
30 weeks earlier. An average of 25% of the patients in the included studies had both positive
31 serology and positive RT-PCR (*supplementary table S1*).
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41 DISCUSSION

42 PIMS-TS is characterized by a very significant ongoing inflammatory response, in
43 crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and
44 WHO (May 15th) definitions (*Table 2*).^{11,12} Characteristically, these patients present with
45 high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.¹³ Hoang et al.¹⁴ reported
46 lower expression of circulating CD16+CD56+ natural killer cells and more profound
47 lymphopenia in children with PIMS-TS compare to those without PIMS-TS.
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53 Primarily, there is an initial innate immune response with the macrophages as the
54 principal actors. From the pathophysiological point of view, it is striking that more than
55 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an
56 acute phase reactant that usually rises after six hours of an inflammatory state and is
57 produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF- α
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3 stimulation.^{15,16} This acute phase reactant from the pentraxin family identifies
4 phosphatidylserine on the surface of cells that have initiated a programmed cell death
5 pattern of apoptosis by activating the complement system. This biomarker is very useful
6 for diagnosis and follow up, especially in middle and low-income countries (given its low
7 cost), and should be considered on admission with subsequent follow up.

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11 Additionally, a marked elevation of ferritin (2-10 times its normal value) has been
12 observed in more than 90% of the series.¹³⁻¹⁷ Ferritin is a protein that stores iron and
13 releases it in a controlled fashion, but also in pathophysiologic conditions. Its levels can
14 reflect macrophage response to free hemoglobin as well as DNA viruses, intracellular
15 bacterial infections and parasites.¹⁸⁻²⁰ Ferritin can induce positive feedback inflammation,
16 upregulating toll-like receptor 9 (TLR-9) which leads macrophage inflammasome IL-1
17 and IL-18 to feed forward ferritin production. TLR-9 may also be stimulated by viral
18 DNA, other infections and host damage-associated molecular patterns (DAMP).²⁰ This
19 whole process generates a large number of inflammasomes and an enhanced
20 inflammatory pathway, delivering the “cytokine storm.” This precipitate cell death with
21 a pyroptosis pattern and new DAMPs that stimulate TLR-9.²⁰ This was described as
22 “*Hyperferritinemic Syndrome*” by Rosario²¹.

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34 Nevertheless, there is evidence of an unusual late adaptive immunity response. It has
35 come to the researchers attention that PIMS-TS occurred between four and six weeks
36 after the peak of cases reported as positive for SARS-CoV-2 in each country had been
37 reached.¹³ Pérez-Toledo M et al.²² recently described eight patients with PIMS-TS with
38 a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM.
39 Additionally, they found elevated IgG1 and IgG3 in these children, which are
40 immunoglobulin isotypes associated with serum supplement activation. This situation is
41 consistent with highly elevated CRP related to COVID-19, which activates the
42 complement system. The elevation of these immunoglobulins suggests that PIMS-TS
43 occurs due to tissue damage induced by autoantibodies, a situation that has been described
44 in other types of coronavirus infection.²³⁻²⁴ We are not aware of any studies in middle
45 and low-income countries which have described this serological behaviour. Studies are
46 needed to help clear up this aspect, especially when all the diagnostic test options for
47 SARS-CoV-2 are not always available. In these countries with limited resources, we
48 suggest taking an initial RT-PCR. If this is negative and there is a high index of suspicion
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3 of PIMS-TS, due to the signs and symptoms, a total antibody or IgM/IgG test should be
4 performed.²⁴
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8 For PIMS-TS, most of the series described coagulation disorders. Severe coagulopathy
9 was seen in 70-80% of the cases (very high D-dimers, prolonged PT, PTT).¹³ Like
10 inflammation, coagulation is necessary for host defense. In addition, proinflammatory
11 cytokines, monocytes / macrophages, neutrophil activation, and extracellular neutrophil
12 traps (NETs) can foster local thrombosis. COVID-19 associated coagulopathy (CAC) is
13 complex and in some ways pathophysiologically different from SIC.^{25,26}
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20 Cytokine levels of IL-1 β and IL-6 are elevated, which induces thrombocytosis and
21 hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is
22 stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.^{27, 28}
23 D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its
24 early phase.²⁸ Elevated D-dimer levels can be present in a wide variety of inflammatory
25 and prothrombotic conditions;²⁹ in COVID-19, these are probably more associated with
26 inflammation than thrombosis.³⁰ Furthermore, serum hyaluronic acid, a key glycocalyx
27 component, is higher during infancy, progressively diminishing over the years.^{19,31} This
28 could explain a more protected endothelium and a lower probability of a hypercoagulable
29 state. In addition, CAC has an overlapping pathophysiology with other coagulopathies
30 like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH),
31 antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) /
32 hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type
33 of coagulopathy.³²
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Author	City, Country	Period	Number	Age	Gender	Comorbidity	Race	IMC kg/m ²
Whittaker et al [3]	London, UK	March 23 and May 16	58	9 years (IQR 5.7, 14)	43% boys	7/58 Comorbidities	69% black or Asian	N/R
Riphagen et al [6]	London, UK	10 days in mid-April	8	4 – 14 years (range)	5/8 boy	None	6/8 Afro-Caribbean	14 – 33 7/8 > 75 th centile/weight
Verdoni et al [7]	Bergamo, Italy	Feb 18 and April 20	10	7.5 years (SD 3-5)	7/10 boys	N/R	N/R	N/R
Belhadjer et al [8]	France (12 hospitals) and Switzerland (1 hospital)	March 22 to April 30	35	10 years (IQR 8.2, 12.4)	51% boys	Comorbidities 28% (asthma 8.55; lupus 3%)	N/R	Overweight 17%
Golfred-Cato S et al [13]	Multicenter US	March 01 to July 29	570	8 (IQR 4,12)	55.4% boys	Comorbidities 8%	40.5% Hispanic and 33.1% Black Non-hispanic	Obesity 25.6%
Cheung et al [33]	New York, US	April 18 and May 5	17	8 years (IQR 1.8, 16)	47% boys	Most were previously healthy (mild asthma in 3)	White 70%	N/R
Kaushik et al [38]	New York, US	April 23 to May 23	33	10 years (IQR 6, 13)	61% boys	Comorbidities 48%	45% Hispanic/latino 39% black	Overweight 12% Obesity (BMI > 30kg/m ²) 6%
Ramcharan et al [40]	UK	10 th April and 9 th May	15	8.8 (IQR 6.4, 11.2) 93% were over 5y	73% boys		100% African/Afr-Caribbean (40%), South Asian, (40%)	

							Mixed (13%) Or other minority ethnic	
Toubiana et al [45]	France, Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR 3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI below the 97 th centile
Pouletty et al [46]	Paris, France	Since April 2020	16	10 (IQR 4.7, 12.5)	50% boys	Comorbidities 37%	N/R	Overweight 25%
Caponi et al [47]	New York, US	April 17 – May 13	33	8.6 years (IQR 5.5, 12.6)	61% boys	Comorbidities 21%	73% non-Hispanic	Overweight 6% Obese 39%
Feldstein L.R et al [48]	Multicenter, US	March 15 to May 20	186	8.3 years (IQR 3.3, 12.5)	62% boys	Comorbidities 27%	31% Hispanic, 25% Black non hispanic	Obesity 29%
Dufort E et al [49]	New York City	March 01 to May 10	95	0-5 years (31%) 6-12 years (42%) 13-20 years (27%)	54% boys	Comorbidities 64%	40% Black 36% Hispanic	Obesity 29%

Table 1. Demographic characteristics of patients with PIMS-TS. N/R: not reported.

Review Only

Royal College of Paediatrics and Health Child (RCPCH) Definition [10]

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative.

Centers for Disease Control and Prevention (CDC) Definition [11]

- 1. An individual aged < 21 years presenting with fever¹, laboratory evidence of inflammation² and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND**
- 2. No alternative plausible diagnoses; AND**
- 3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.**

¹Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

²Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

World Health Organization Definition [12]

Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

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

AND

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

AND

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

AND

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

Table 2. RCPCH, CDC, WHO Definitions Criteria for Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19

From a clinical and laboratory perspective, PIMS-TS has usually been seen in previously healthy and frequently obese (30-60% of the series) children over eight years of age (80% of the cases) (*Table 1*). Initially, the group from the United Kingdom (UK) found MIS-C in patients of African descent, but it has been described in patients of all origins.^{4,32,33} Persistent high fever for more than three to five consecutive days, maculopapular skin lesions (50-60%) reminiscent of Kawasaki disease (KD) and, frequently, signs of shock at the time of presentation have been the initial clinical characteristics.³³ Digestive symptoms (including nausea, vomiting, diarrhea or abdominal pain) usually present in most cases, as well as myocardial involvement (more than 60% of the series).^{14,33} Cardiac involvement is broad and variable, with features including myocardial dysfunction (100% of the initial UK description - 60% in other series), coronary aneurysms, pericarditis, arrhythmias, refractory shock and elevated troponin I or pro-BNP³²⁻³⁴ (*supplementary table S1*).

Guidelines for PIMS-TS management in middle and low-income countries

With regard to treatment in middle and low-income countries, it is very important to maintain a high index of suspicion. Therefore, in these countries, it is important to use a systematic approach including early recognition and a bundle similar to those recommended for patients with other serious diseases. An expert consensus recently published in the United Kingdom using the Delphi method provides a good summary of the recommended treatments³⁴. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with

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3 those of the SCCM sepsis consensus¹⁶, for use in middle and low-income countries. We
4 believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking
5 these recommendations as a whole could have an impact on the outcomes of PIMS-TS
6 patients in these countries.
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11 From the first presentation to the Emergency Department and / or PICU, two approaches
12 can be assumed, one general and one specific (*Table 3*):
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15 a. *General approach*: A comprehensive approach should be used, similar to that
16 recommended for patients with sepsis with organ dysfunction or septic shock. In this case,
17 the contagiousness of SARS-CoV-2 requires the use of personal protective equipment
18 (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-
19 PCR.
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24 Moreover, the American College of Critical Care Medicine (ACCM) points out the need
25 to give more attention to Institutional Practice Guidelines (IPGs) based on each facility's
26 capability.³⁵ Once IPGs are established, diagnostic and therapeutic measures known as
27 "patient care bundles" (PCBs) should be developed for a better approach and control of
28 established processes. The PCBs include three to five evidence-based practices related to
29 a health care process that should be performed collectively to achieve a synergistic result
30 that improves care.^{36,37}
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36 1. Early detection: a comprehensive approach based on a high index of suspicion is
37 critical. This disease may occur with a wide spectrum of symptoms, so it should be
38 suspected in all patients with a fever lasting more than three days associated with the
39 symptoms described in *Table 2*. Contact with a positive case is not always clear.
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43 2. Immediate, time-sensitive resuscitation:

44 - Oxygen therapy: This is part of the strategies described in recent sepsis guidelines^{16,37}.
45 High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been
46 considered in many reports,³⁸ especially in patients who have a deteriorated respiratory
47 pattern with the use of accessory muscles or an SaO₂/FiO₂ ratio less than 264. Most series
48 describe respiratory involvement ranging from 20-60% (*supplementary table S1*) and,
49 generally, if endotracheal intubation is required, it is more highly associated with
50 cardiovascular involvement. Cases classified as Class II by the CDC may be classified in
51 these groups.^{33,38}
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55 - Fluid resuscitation: It is important to consider the recommendations in recently
56 published guidelines.¹⁶ In healthcare systems where staff and equipment for advanced
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3 airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of
4 balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour,
5 titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload
6 develop. In healthcare systems without the availability of intubation, crystalloid boluses
7 may only be given in cases of hypotension (decompensated shock); in these cases, up to
8 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with
9 titration to clinical markers of cardiac output, and discontinued if signs of fluid overload
10 develop. If the child is not hypotensive, but has compensated shock, only maintenance
11 fluids should be started, avoiding bolus fluids which are associated with worse
12 outcomes³⁵⁻³⁸.

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21 -Vasoactive drugs: According to the clinical condition, most series describe the need for
22 vasoactive drugs in 10 to 60% of the cases with PIMS-TS. Most patients respond to fluid
23 resuscitation. If necessary, epinephrine or norepinephrine should be considered according
24 to the patient's condition.^{16,39} Inotropes like dopamine, milrinone and levosimendan were
25 reported to have been used in PIMS-TS.³⁸⁻⁴⁰

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29 -Antibiotic therapy: If bacterial co-infection is suspected, the first dose is recommended
30 within the first three hours for sepsis associated with organ dysfunction, or within the first
31 hour for children with septic shock.³⁹⁻⁴¹

32 33 34 3. Stabilization with adequate monitoring:

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36 If possible, advanced hemodynamic monitoring should be instituted. Cardiac
37 ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent
38 guidelines¹⁶ and patients with PIMS-TS.⁴²

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41 4. Timely referral or transfer is desirable in this context. In middle and low-income
42 countries, it is common for patients to be transferred to higher complexity sites. Patients
43 who are deteriorating or who may need intensive care should be identified. In the PIMS-
44 TS of the CDC group, 84% of the cases had to be transferred to paediatric intensive care.
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5. Continuous measurement of processes and corrections must be instituted for a
continuous quality improvement process.⁴²

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b. Specific approach: It is important to emphasize that, in moderate to severe cases, the
use of immunomodulatory treatment should be considered. Heterogeneous management
including human immunoglobulin, systemic steroids, anakinra, tocilizumab and aspirin
^{40,42-45} has been reported in the described series (*supplementary table S1*). The American

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3 College of Rheumatology (ACR) recommendations for immunomodulatory therapy⁴²
4 have recently been published. We sought to adapt these recommendations to middle and
5 low-income countries where resources are limited and each intervention must be
6 streamlined according to need.
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- 10 ⇒ IVIG: High doses (2 gr/kg) should be considered for moderate to severe cases,
11 particularly those with myocardial involvement. Prior to beginning the infusion,
12 restored heart function must be verified.⁴²
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14 ⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical
15 course of the disease in adults with severe pneumonia, particularly if they are on
16 mechanical ventilation.⁴³⁻⁴⁷ In patients with PIMS-TS, low doses could be
17 considered in all cases (used in 70% of the series – *supplementary table S1*).
18 Dosing schemes of 1-2 mg/kg/dose of methylprednisolone or its equivalent three
19 or four times per day have been recommended. The ACR suggests considering
20 high doses in cases of shock or in those with a high need for vasopressors, and we
21 believe this recommendation is very important for middle and low-income
22 countries, especially considering the frequency of late consults with advanced
23 disease.
24
25 ⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-
26 refractory PIMS-TS.⁴² However, in many countries, its use is not approved, or it
27 is not available, and other biological agents are used. Prospective studies are
28 needed to evaluate the efficacy and safety of these medications in PIMS-TS.
29
30 ⇒ Anticoagulation and antiplatelet treatment: Anticoagulation has become a
31 fundamental treatment in adults, considering that there is a procoagulant and
32 hypofibrinolytic state in severe SARS-CoV-2 infection.^{42,47-50} In children with
33 PIMS-TS it is recommended only in cases of documented thrombosis or in
34 patients with an echocardiogram ejection fraction less than 35%.^{43,47} Aspirin
35 would also be recommended in patients with thrombocytosis (> 450,000 u/L) or
36 Kawasaki-like disease criteria.^{42,47}
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53 The prognosis of the disease is usually good, with patient survival greater than 95% in
54 different published series.^{5,6,42-50} A mortality of 1-2% has been described in the published
55 series, and up to 15% with cardiovascular sequelae, including aneurysms or
56 dysfunction.^{33,48-50} These patients should be followed up after discharge by inter and
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multidisciplinary teams including infectious disease, rheumatology and paediatrics. However, there are incomplete data from all the cases, along with a knowledge gap regarding mild and moderate cases, the natural course and the clinical behavior of the disease.^{8,47-50}

A. General approach

1. Early detection
2. Immediate, time-sensitive resuscitation
 - a. Oxygen therapy
 - b. Fluid resuscitation
 - c. Vasoactive drugs
 - d. Antibiotic therapy: if bacterial co-infection is suspected
3. Stabilization with adequate monitoring.
4. Timely referral or transfer according to the context and available resources.
5. Continuous measurement of processes.

B. Specific approach

1. Human immunoglobulin: 2 gr/kg for moderate to severe cases
2. Steroids:
 - ⇒ 1-2 mg/kg/dose of methylprednisolone three or four times per day
 - ⇒ High doses in cases of shock with high vasopressor requirement
3. Anakinra:
 - ⇒ Only in cases refractory to steroids and IVIG. Not available in all countries.
4. Anticoagulation is recommended for:
 - a. Documented thrombosis
 - b. Echocardiogram with an EF of less than 35%
5. Antiplatelet treatment: recommended for thrombocytosis > 450,000 u/L

Table 3. Summary of recommendations for management of PIMT-TS in countries with limited resources.

Conclusion

PIMS-TS is a new type of presentation of SARS-CoV-2 infection, with an exaggerated inflammatory response and inadequate inflammatory resolution with frequent *-but not*

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3 *exclusive-* digestive and myocardial involvement. It should be considered as a new
4 disease with unique symptoms, a greater variety of clinical courses, and possibly different
5 physiological mechanisms. In middle and low-income countries, studies should be
6 performed to learn more about this disease in these regions and determine if they have
7 different phenotypic behaviors. In addition, the real role of some inflammatory
8 biomarkers and cost-effective therapeutic strategies should be determined.
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15 **Contributors**

16 JFS, DS, RJ, PA, GG, GP conceptualized and designed the literature search. JFS, DS, RJ
17 initiated the search and a first draft. All authors contributed to subsequent drafts. JFS, as
18 group leader, supervised and moderated the search, initial drafts, the overall collation of
19 the figures and tables and final manuscript. All authors approved the final manuscript as
20 submitted and agree to be accountable for all aspects of the work
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60 **ORCID:** iD Jaime Fernández-Sarmiento <http://orcid.org/0000-0003-2874-2949116>

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Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses

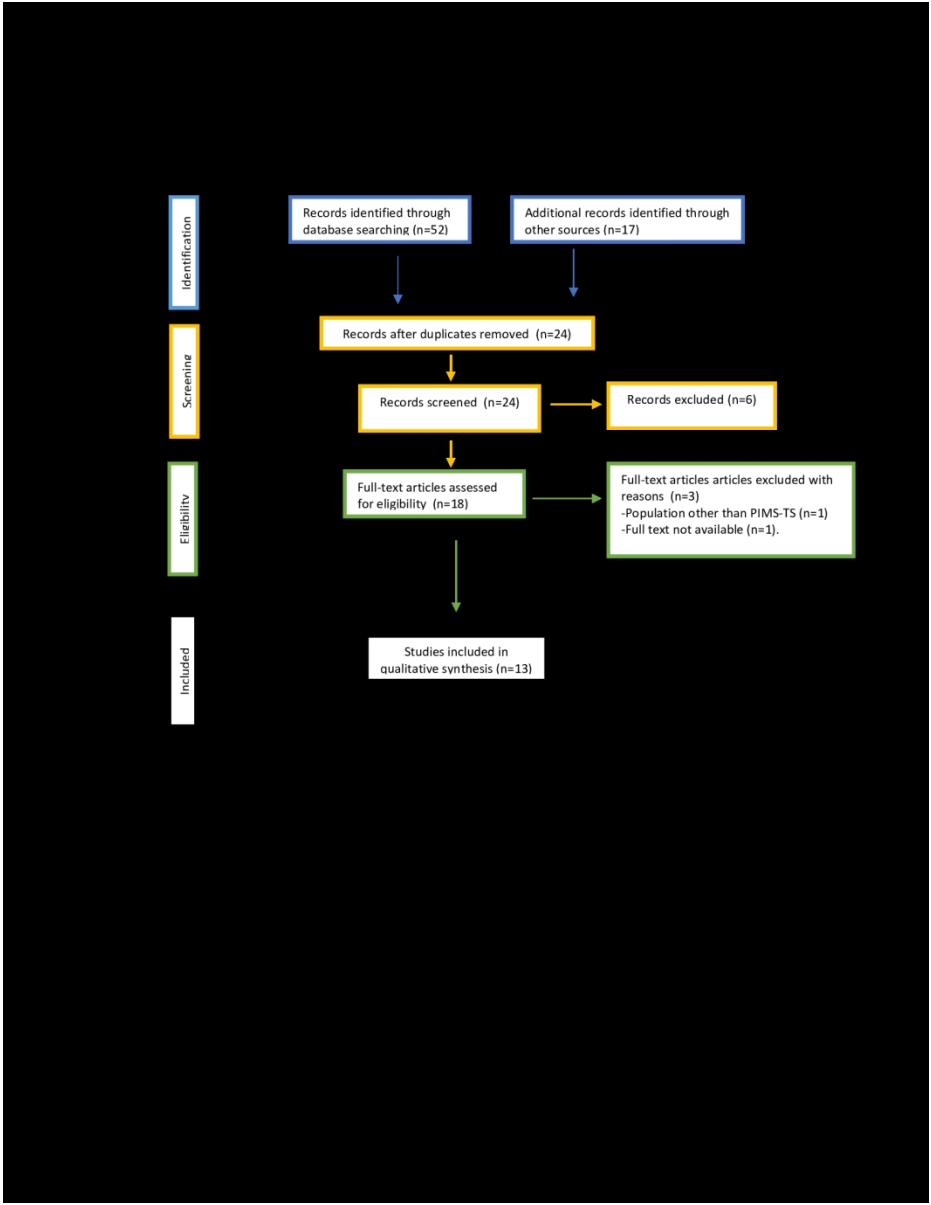
Table 1. Demographic characteristics of patients with PIMS-TS

Table 2. RCPCH, CDC and WHO Definition Criteria for Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19

Table 3. Summary of recommendations for management of PIMT-TS in countries with limited resources.

Supplementary table S1. Clinical and echocardiographic findings, and treatments instituted in the described series of PIMS-TS patients.

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Author	Clinical presentation	ECHO	SARS-CoV-2 test	Organ support	Treatment	Outcome / Died
Whittaker et al [3]	Fever 100%, Headache 26% Vomiting 45% Diarrhea 52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29% Swollen hands and feet 16%, Respiratory symptoms 21%. Fever + elevated inflammatory markers – 40%, Shock - 50%	Left ventricular dysfunction 62% (18/29) Abnormally dilated coronary arteries (z score >2) 8/55 Giant coronary artery aneurysms 2 Coronary artery aneurism 14% (n=8)	RT-PCR SARS-CoV-2 + 26% IgG antibody SARS-CoV-2 + 87% 78% had evidence of current or prior SARS-CoV-2 infection	PICU 50% Acute kidney injury 22% Shock + inotropic support 47% MV 43% ECMO 5%	Inotropic support 47% IVIG 71% Corticosteroids 64% Anakinra 5% Infliximab 14%	Death 2%
Riphagen et al [6]	Fever 8/8 Diarrhoea 7/8 Abdominal pain 6/8 Vomiting 4/8 Conjunctivitis 5/8 Rash 4/8 Vasoplegic shock 8/8	7/8 ventricular dysfunction Echobright coronary vessels 1/8 giant coronary aneurysm	SARS-CoV-2 negative 5/8 SARS-CoV-2 positive 2/8 Family exposure 4/8	Inotropic/vasopressor support 8/8, MV 5/8, HFNC 1/8, NIV 3/8, RRT 1/8, VA-ECMO 1/8 (arrhythmia with refractory shock, died)	IVIG 8/8, Corticoids 5/8 Aspirin 3/8, Heparin 1/8, Antibiotics 8/8, Infliximab 1/8	1 died 6/8 alive PICU length of stay 3 – 7 days
Verdoni et al [7]	Classic form of Kawasaki 50%, Incomplete form of Kawasaki disease 50% Kdss and MAS 50% Diarrhoea 60% Meningeal signs 40% Drowsiness 10%	Anormal ECHO 60% Aneurism 10% FEVE < 50% – 50% Mitral valve regurgitation 10% Pericardial effusion 40%	RT-PCR SARS-CoV-2 + 20% Serology for SARS-CoV-2 antibodies – 80% were IgG +, and 3 were also IgM +		Inotropic support 20% Adjunctive steroid treatment 80% IVIG 100% Aspirin 20%	None
Belhadjer et al [8]	Asthenia 100% Fever 100% GI symptoms 83% (2 children underwent emergency operation for suspected appendicitis) Respiratory distress 65%	Coronary artery dilatation (z score > 2) 17% Aneurysm 0 LVEF < 30% - 28% LVEF 30-50% - 72%	SARS-CoV-2 was confirmed 88.5% RT-PCR-SARS-CoV-2 + 34% Fecal PCR 6% Antibodies + 86%	Respiratory support 94% (IMV 62%; NIV 32%) VA-ECMO 28%	Inotropic support 80% IVIG 71% Corticosteroids 34% Anakinra 8% Anticoagulation with heparin 65%	None

	Rhinorrhea 43% Adenopathy 60% Rash 57% Meningism 31% At admission to the ICU, 80% were in cardiogenic shock					
Grimaud et al [9]	Fever 100%, Abdominal pain 100%, Rash 50%, Conjunctivitis 30%, Adenitis 20%, Tachycardia 100% Hypotension 100% (75% clinical signs of vasoplegia)	LVEF 35% (IQR 25-55)	SARS-CoV-nasopharyngeal swabs + 50% SARS-CoV-2 antibodies + 100% (15/15), 95% had identified SARS-CoV-2 infection on PCR and/or by serology	NIV 55%,IMV 40%, HFNO 5%,Respiratory support in all patient was indicated for hemodynamic support	IVIg100%,Corticosteroids 10%, Anakinra 5%, Tocilizumab 5%, Inotropic/vasopressor support 95%	None
Cheung et al [33]	Fever 100% GI symptoms 88% Shock at presentation 76% Rash 71%, Conjunctivitis 65% Lip redness/swelling 65% Neurologic symptoms 47%, Respiratory symptoms 41%, Myalgia 35%, Lymphadenopathy 35%, Hypoxia 18% Criteria for KD 47% Incomplete Kawasaki 29%	FEVE mildly decreased 29% FEVE mild-moderately decreased 24% FEVE moderate-severely decreased 12% Pericardial effusion 47%	RT-PCR SARS-CoV-2 + 47% Serology for SARS-CoV-2 antibodies → 53%	PICU 88%	IVIg 76% Methylprednisolone 71% Hydrocortisone 21% Enoxaparin prophylaxis 59% Enoxaparin treatment 6% Aspirin 24%	None
Golfred-Cato S et al [13]	Fever 100% Bilateral conjunctival injection 48.4% Oral mucose changes 23% Rash 55.3%	Abnormal ECHO with coronary-artery aneurysms 18.6%	RT-PCR 25.8% Serology positive 46.1% RT-PCR and serology positive 27.2%	PICU 63.9% MV 13.1% Vasoactives 44.9%	IVIg 80.5% Steroids 62.8% Antiplatelet medication 58.6% Anticoagulation 44.2%	Died 1.8% Organs systems involved 4-5 61.6%
Kaushik et al [38]	Fever 93%, Abdominal pain 63%, Nausea/emesis 69%, Diarrhea 48%	Pericardial effusion 46%	SARS-CoV-2 antibody + 81%	NIV 36% IMV 15% ECMO 3%	IVIg 54%, Corticosteroids 51%, Tocilizumab 36%	Death 3%

	Hypotension 63%, Mucocutaneous, involvement 21% Conjunctivitis 36% Rash 42%, Shortness of breath 33% Neurologic involvement 12%	LVEF median 46.6 (IQR 39.5, 52.8) LVEF < 30%: 12% LVEF 30-50%: 53% Recovered LV function prior to dischargr 95%	RT-PCR SARS-CoV-2 + 33% 18% tested + for both	Intra-aortic ballon pump support 3%	Remdesivir 21%, Anakinra 12%, Convalescent plasma therapy 3%, Aspirin 24% Anticoagulation, prophylaxis 15%, Anticoagulation, therapeutic 81% Antibiotics > 48h 45% Vasopressor/inotropes 51%	
Ramcharan et al [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on admission 51%	13% described typical COVID-19 symptoms in the previous two months 20% related contacted with family member with COVID-19	Respiratory support 53% Inotrope or vasopressor 67%	IVIG 67% (10/15), of whom 2 received a second dose Metylprednisolone 33% 73% werw discharged on low dose aspirin Antibiotic 100%	None
Toubiana et al [45]	Recent history of viral- like symptoms was report in 43% Median duration between these symptoms and the onset of signs and symptoms of Kawasaki disease was 45 days. Complete presentation of KD 52%, Abdominal symptoms 95%, Lips and oral cavity changes 76% Conjunctivitis 81% Rash 76%, Changes to extremities 48% Lymphadenopathy 57%	Myocarditis 76% (LVFE range between 10 and 57%) 38% coronary artery abnormalities: 24% which consisted of dilations (z score between 2.0 and 2.5); 14% with increased coronary visibility No coronary aneurysms were identified	History of recent contact with people with viral-like symptoms was + in 48% Median interval between reported contact and KD was 36 days RT-PCR-SARS-CoV-2 + 38% IgG antibodies SARS- CoV-2 + 90% 9,5% negative Serology and PCR)	PICU 81% Vasoactive agents 71% MV 52%	IVIG 100% (24% needed a second dose) Low dose aspirin (3- 5mg/kg/day) 100% Corticosteroids (2- 10mg/kg/day) 48% Antibiotic 86%	None
Pouletty et al [46]	Fever 100% Respiratory signs 12% GI signs 81% Anosmia 6%	Abnormal ECHO 69% Coronary dilatation 19% (median z score 2.6)	Family c/s COVID-19 infection 75% First infectious exposure-		IVIG 93% (Second infusion 335) Steroids 25% Anakinra 6%	None

	Neurological signs 56% Rash 81% Conjunctivitis 94% Hands and feet edema/erythema 68% Dry cracked lips 87% Lymphadenopathy 37% Haemodynamic failure 69% Complete KD 62% KDSS 44%	No aneurysm Myocarditis 44% (median LVEF 35%) Pericarditis 25%	hospitalization 21 days (IQR 21-24) RT-PCR-SARS-CoV-2 all sites + 69% Serology IgG + 87%		Tocilizumab 6% AAS (30-50mg/kg) 52% AAS anti-aggregant dose 50%	
Caponi et al [47]	Fever 100% GI symptoms 97% Neurocognitive symptoms 58% Respiratory symptoms 52% Shock 75% Complete KD 64% HD without shock 76%	Any coronary abnormality 48% (Z score ≥ 2.5 – 15%; Z score 2-2.49 – 9%) Any dysfunction 58%: (LVEF 45-54% - 33%; LVEF 35-44% - 24%)	IgG + and Nucleic acid amplification + 18% IgG + and Nucleic acid amplification negative 73% Nucleic acid amplification +, serology test unavailable 9%	PICU 79% MV 18% Inotrope/vasopressor support 76%	IVIG 100% 2 nd dose IVIG 33% Methylprednisolone 70% Aspirin 88% Anakinra 12% Tocilizumab 9% Infliximab 13% Enoxaparin 42%	None
Feldstein L.R et al [48]	Fever 100% Bilateral conjunctival injection 55% Oral mucose changes 42% Peripheral extremity changes 37% Rash 59%	Abnormal ECHO with coronary-artery aneurysms 9%	RT-PCR or antibody testing 70%	PICU 80% MV 20% Inotrope or vasopressor support 48% ECMO 4%	IVIG 77% Secon dose 21% Systemic glucocorticoid 49% Interleukin-6 inhibitor 8% Interleukin-1Ra inhibitor 13% Anticoagulation 47%	28% were still hospitalized as of May 20, 2020, and 4 patients (2%) died, 2 of whom had previously been healthy.
Dufort E et al (49)	Fever 100%, abdominal pain 61%, rash 60%,conjunctivitis 56%	Abnormal ECHO with coronary-artery aneurysm 9%	RT-PCR 51%, IgG antibodies 99%	PICU 80%, MV 10%, Vasopressor support 62%, ECMO 4%	IVIG 48% Systemic glucocorticoids 64%	Death 2%, shock 10%, myocarditis 53%

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4 *Abbreviations: MV: mechanical ventilation, HFNC: high flow nasal cannula, NIV:noninvasive ventilation, RRT:renal replacement therapy, VA-*
5 *ECMO: venu-arterial extracorporeal membrane oxygenation, PCR: protein C reactive, IVIG: immunoglobulin, FEVE: fraction ejection*
6 *ventricular, RT-PCR: real time polymerase chain reaction, PICU: pediatric intensive care unit, KD:Kawasaki disease*
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8 *Supplementary File. Table S1. Clinical findings, echocardiographic and treatments instituted in the described series of PIMS-TS*
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