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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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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, as well as overlapping features with atypical Kawasaki disease (aKD). Our objective was to review and summaries published evidence regarding the

most important aspects of PIMS-TS, with special emphasis on the treatment strategies suggested for middle- and low-income countries.

Methods: A systematic review of the literature was performed in the principal medical databases including PUBMED, EMBASE (OVID) and Google Scholar between December 2019 and August 2020.

Results: A total of 69 articles were identified in the described databases. Altogether, 13 articles met the inclusion criteria and were eligible. The most frequently described symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%), skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-6 weeks after the pandemic appears in the general population. Multisystem inflammatory syndrome in children is presented as a great systemic inflammatory response syndrome (SIRS), which sometimes evolves into septic shock features requiring fluid resuscitation and vasoactive drug support (26%). Several treatment strategies have been used, including immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These general and specific interventions should be guided by an inter- and multi-disciplinary team, especially in settings with limited resources.

Conclusions: PIMS-TS COVID-19 is a new form of SARS-CoV-2 sepsis, with an exaggerated inflammatory response and frequent -*but not exclusive*- digestive and myocardial involvement. It is very similar in its presentation to Kawasaki disease, but should be considered as a new disease. Research is needed to establish the role of biomarkers for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.

Key words: septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease, thrombosis, SARS-CoV-2

What is known about the subject?

-PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times greater need for hospitalization and mortality in children than other COVID-19 presentations.

-It is characterized by fever, shock and gastrointestinal, skin and cardiac involvement, with prior positive RT-PCR or antibody tests.

-The diagnostic and treatment approach should be the same as for sepsis with organ dysfunction and viral septic shock. The specific treatment includes immunomodulators.

What does this study add?

This review summarizes the main PIMS-TS case series, with their clinical characteristics and complications. 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 viral sepsis management and specific immunomodulatory therapy currently recommended based on the available evidence.

INTRODUCTION

In December 2019, a new viral infection was reported for the first time in history, 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 cases are asymptomatic or have a mild infection. However, between 4 -10% 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 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 response[2]. Recently, a new type of presentation of SARS-CoV-2 infection has been described in children, involving this significant inflammatory response. This new disease has been called 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 is a severe presentation of the virus in children and requires early detection to avoid its progression and potentially unsatisfactory outcomes[5]. In this article, we discuss and review the most relevant aspects of PIMS-TS described to date.

METHODS

Search strategy and article selection

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

Eligibility criteria

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

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 throught 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 and Table 2 (supplementary file).*

DISCUSSION

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 communication 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 children (MIS-C).[11,12] In general, they refer to the same entity and the latter name has been the most frequently used in the main descriptions of this disease (*Table 3*).

PIMS-TS is characterized by a very significant ongoing inflammatory response, in crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and WHO (May 15th) definitions (*Table 3*). [11,12] Characteristically, these patients present with

high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.[13] Hoang et al.[14] reported lower expression of circulating CD16+CD56+ natural killer cells and more profound lymphopenia in children with PIMS-TS compare to those without PIMS-TS.

Primarily, there is an initial innate immune response with the macrophages as the principal actors. From the pathophysiological point of view, it is striking that more than 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an acute phase reactant that usually rises after six hours of an inflammatory state and is produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF-α stimulation.[15,16] This acute phase reactant from the pentraxin family identifies phosphatidylserine on the surface of cells that have initiated a programmed cell death pattern of apoptosis by activating the complement system.

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

Author	City, Country	Period	Number	Age	Gender	Comorbidity	Race	IMC kg/m^2
Riphagen et[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 > 75th centile/weight
Verdoni et [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 [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 [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 [45]	France,Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI **below** the 97th 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/m2) 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 [40]	UK	10th April and 9th 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%) 0r other monority 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 fever[1], laboratory evidence of inflammation[2] 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.** [1]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours [2]Including, 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-1β and IL-6 are elevated, which induces thrombocytosis

and hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.[27, 28] D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its early phase.[25] Elevated D-dimer levels can be present in a wide variety of inflammatory and prothrombotic conditions;[29] in COVID-19, these are probably more associated with inflammation than thrombosis.[30] Furthermore, serum hyaluronic acid, a key glycocalyx component, is higher during infancy, progressively diminishing over the years.[19,31] This could explain a more protected endothelium and a lower probability of a hypercoagulable state. In addition, CAC has an overlapping pathophysiology with other coagulopathies like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) / hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type of coagulopathy.[25]

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) [4,5,12,14] (*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.[4,5,9-11] 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.[6,7] 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).[6,7,14] 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-BNP [32-34] (*Table 2*).

With regard to treatment, it is important to keep in mind that PIMS-TS is a viral sepsis, and thus rapid recognition is critical, along with optimal and time-sensitive treatment. An expert consensus recently published in the United Kingdom using the Delphi method provides a good summary of the recommended treatments[34]. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with those of the SCCM sepsis consensus[16], for use in

medium and low-income countries. We believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking these recommendations as a whole could have an impact on the outcomes of PIMS-TS patients in these countries.

From the first presentation to the Emergency Department and / or PICU, two approaches can be assumed, one general and one specific.

a. *General approach:* A comprehensive approach should be used, as with any patient admitted with sepsis with organ dysfunction or septic shock. In this case, the contagiousness of SARS-CoV-2 requires the use of personal protective equipment (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-PCR.

Moreover, the American College of Critical Care Medicine (ACCM) points out the need to give more attention to Institutional Practice Guidelines (IPGs) based on each facility´s capability.[35] Once IPGs are established, diagnostic and therapeutic measures known as "*patient care bundles*" (PCBs) should be developed for a better approach and control of established processes. The PCBs include three to five evidence-based practices related to a health care process that should be performed collectively to achieve a synergistic result that improves care.[36,37] The ACCM Sepsis Bundle includes:

1. Early detection: a comprehensive approach based on a high index of suspicion is critical. This disease may occur with a wide spectrum of symptoms, so it should be suspected in all patients with a fever lasting more than three days associated with the symptoms described in *Figure 2*. Contact with a positive case is not always clear.

2. Immediate, time-sensitive resuscitation:

- Oxygen therapy: This is part of the strategies described in recent sepsis guidelines [16]. High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been considered in many reports,[4,8,14] especially in patients who have a deteriorated respiratory pattern with the use of accessory muscles or an Sa02/Fi02 ratio less than 264. Most series describe respiratory involvement ranging from 20-60% (*Table 2*) and, generally, if endotracheal intubation is required, it is more highly associated with cardiovascular involvement.

- Fluid resuscitation: It is important to consider the recommendations in recently published guidelines.[16] In healthcare systems where staff and equipment for advanced airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour, titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload

develop. In healthcare systems without the availability of intubation, crystalloid boluses may only be given in cases of hypotension (decompensated shock); in these cases, up to 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with titration to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. If the child is not hypotensive, but has compensated shock, only maintenance fluids should be started, avoiding bolus fluids which are associated with worse outcomes.

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

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

3. Stabilization with adequate monitoring:

If possible, advanced hemodynamic monitoring should be instituted. Cardiac ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent guidelines[16] and patients with PIMS-TS.[40]

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

5. Continuous measurement of processes and corrections must be instituted for a continuous quality improvement process.[16, 41, 42]

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 [6,7,11] has been reported in the described series (*Table 2*). The American College of Rheumatology (ACR) recommendations for immunomodulatory therapy[42] have recently been published.

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

⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical course of the disease in adults with severe pneumonia, particularly if they are on

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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REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report. Available in:http://www.who.int/docs/default-source/coronaviruse/situation-reports.2. 28 Jun 2020.

2. Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Epub 2020/02/28. doi: 10.1016/S2213-2600(20)30079-5.

3. Whittaker E, Bamford A, Kenny J et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV2-2. JAMA 2020 Jun8; e2010369. Doi:10.1001/jama.2020.10369.

4. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A, et al. Pediatric critical care and COVID19. Pediatrics. 2020; doi: 10.1542/peds.2020-1766.

5. De Biasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC Metropolitan Region. J Pediatr 2020. https://doi.org/10.1016/j.jpeds.2020.05.007. In press.

6. Riphagen S, Gomez X, Gonzalez-Martinez et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020 May 7. https://doi.org/10.1016/S0140-6736(20)31094-1. S0140-6736(20)31094- 1, ahead of print.

7. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31103-X. ahead of print.

8. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2. pandemic. Circulation 2020 May 17. https://doi.org/10.1161/CIRCULATIONAHA. 120.048360. ahead of print.

9.Grimaud M, Starck J, Levy M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020; 10:69.

10. Royal College of Paediatrics and Child Health. Available in: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims.

11. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp.

12. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID 19 Scientific brief. Available en: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. 15 May 2020.

13. Cheung E, Zachariah P, Gorelik M et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adlescents in New York City. JAMA. Published online June 8, 2020. Doi:10.1001/jama.2020.10374.

14. Hoang A, Chroath K, Moreira A et al., COVID-19 in 7780 pediatric patients: A systematic review, E-Clinical Medicine (2020), https://doi.org/ 10.1016/j.eclinm.2020.100433.

15. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):33. Published 2020 Mar 27. doi:10.1038/s41392-020-0148-4.

16. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46 (Suppl. 1):10–67.

17. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46(5):854–87.

18. Pérez-Toledo M, Faustini S, Jossi S et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Pediatric Inflammatory Multi-system syndrome. Institute of Immunology and Immunotherapy, University of Birmingham UK. Doi: hhtpps://doi.org/10.1101/2020.06.05.20123117. Online 07 June 2020.

19. Fernández-Sarmiento J, Salazar LM, Carcillo J. The endothelial glycocalyx: a fundamental determinant of vascular permeability in sepsis. Ped Crit Care 2020;21e:e291-e300.

20. Carcillo JA, Kernan KK, Horvat CM et al. Why and How Is Hyperferritinemic Sepsis Different from Sepsis Without Hyperferritinemia? Pediatr Crit Care Med. 2020;21(5):509-512. doi:10.1097/PCC.0000000000002285.

21. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, et al: The Hyperferritinemic syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013; 11:185.

22. Jaume M, Yip MS, Cheung CY et al. Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent Fc. R pathway. Journal of virology. 2011;85(20):10582-97. 12.

23. Kam YW, Kien F, Roberts A. et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro. Vaccine. 2007;25(4):729-40.

24. Wang SF, Tseng SP, Yen CH et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochemical and biophysical research communications.* 2014;451(2):208-14.

25. Iba T, Levy JH, Connors JM et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360. Published 2020 Jun 18. doi:10.1186/s13054-020-03077-0.

26. Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology. 2020;132(5):1238–45.

27. Waltuch T, Gill P, Zinns LE et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department [published online ahead of print, 2020 May 8. Am J Emerg Med. 2020; S0735- 6757(20)30403-4. doi:10.1016/j.ajem.2020.05.058.

28. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020;395(10234):1417–8.

29. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis [published online ahead of print, 2020 Jun 10]. J Thromb Thrombolysis. 2020;1-10. doi:10.1007/s11239-020-02171-y.

30. Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. Semin Thromb Hemost. 2012;38(7):673-682. doi:10.1055/s-0032-1326782

31. Trivedi P, Cheeseman P, Mowat AP. Serum hyaluronic acid in healthy infants and children and its value as a marker of progressive hepatobiliary disease starting in infancy. Clin Chim Acta. 1993;215(1):29-39. doi:10.1016/0009-8981(93)90246-z.

32.Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020;309; 7077. doi: 10.1016/j.ijcard.2020.03.063.

33. Tunuguntla H, Jeewa A, Denfield SW. Acute Myocarditis and Pericarditis in Children. PediatrRev. 2019;40(1):14-25. doi:10.1542/pir.2018-0044.

34. Harwood R, Allin B, Jones C et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2020 Published Online September 18 doi.org/10.1016/S352-4642(20)30304-7

35. Davis AL, Carcillo JA, Aneja RK, et al. AmericanCollege of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017; 45(6):1061-93.

36. Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? Curr Open Infect Dis. 2009; 22(2):159-66.

37. Kohn Loncarica G, Fustiñana A, Jabornisky R. Recommendations for the management of pediatric septic shock in the first hour (part I). Arch Argent Pediatr 2019;117(1): e14-e23.

38. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection: A Multi-institutional Study from New York City [published online ahead of print, 2020 Jun 14]. J Pediatr. 2020;S0022-3476(20)30747-239.

39. National Institute for Health and Care Excellence. Sepsis: Recognition, Diagnosis and Early Management. London, 2016;51. [Accessed on: June 27th, 2020]. Available at: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-manage- ment-pdf-1837508256709.

40. Ramcharan, T, Nolan, O, Lai C.Y. et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. *Pediatr Cardiol* (2020). https://doi.org/10.1007/s00246-020-02391-2.

41. Fernández-Sarmiento J, Carcillo JA, Salinas CM, et al. Effect of a sepsis educational intervention on hospital stay. Pediatr Crit Care Med. 2018;19: e321–e328.

42. American College of Rheumatology. Clinical Guidance for Pediatric Patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in covid-19. Available in https://www.rheumatology.org/announcements#PediatricClinicalGuidance. Jun3 17 2020.

43. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [Internet]. RECOVERY (Randomised Evaluation of COVID-19 Therapy) University of Oxford. 2020 [cited 2020 Jun 18]. Available from: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19.

44. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/ sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. Pediatr Crit Care Med 2014;15(5):401–8.

45. Toubiana J, Poiralut C, Corsia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369m2094.

46. Pouletty M, Borocco C, Ouldali N et at. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dise 2020; 0:1-8.

47. Capone CA, Subramony A, Sweberg T et al. Characteristics, Cardiac involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection, The Journal of Pediatrics (2020), doi: https://doi.org/10.1016/ j.jpeds.2020.06.044.

48. Feldstein L.R, Rose E.B, Horwitz J.P et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020 June 29. Doi:10.1056/NEJMoa2021680.

49. Dufort E, Koumnas E, Chow E et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020 Jun 29. Doi:10.1056/NEJMoa2021756

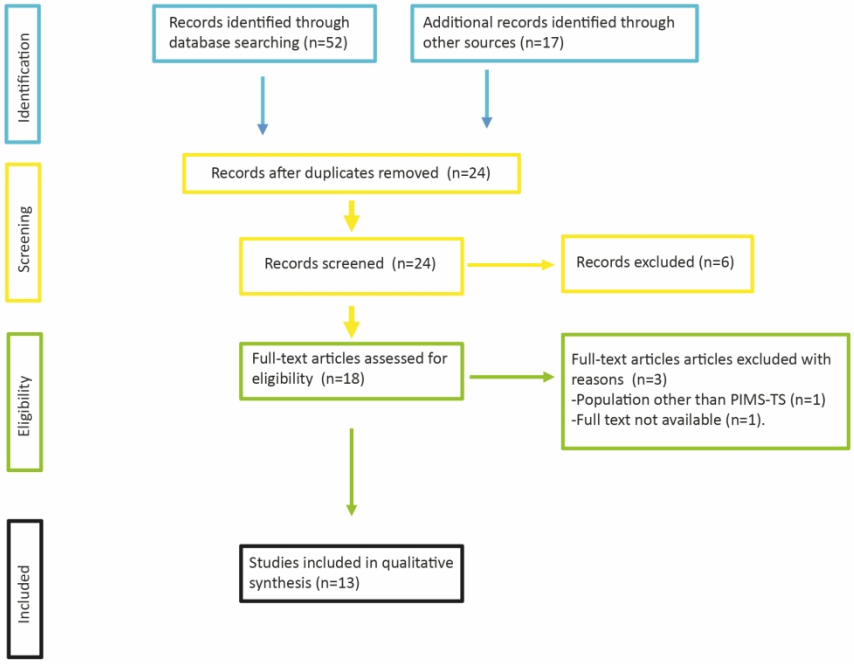
Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses

Table 1. Demographic characteristics of patients with PIMS-TS

Table 2. Clinical and echocardiographic findings, and treatments instituted in the described series of PIMS-TS patients (*(supplementary file)*.

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

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 [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 (arrhytmia with refractory shock, died)	IVIG 8/8,Corticoids 5/58 Aspitin 3/8,Heparin 1/8, Antibiótics 8/8, Infliximab 1/8	1 died 6/8 alive PICU lenght 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
Whittaker et al [3]	Fever 100%, Headache 26%Vomiting 45% Diarrhea52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29%Swollen hands and feet 16%, Respiratory symptons 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% Anakinra5% Infliximab 14%	Death 2%
Grimaud et [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	IVIG100%,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 [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 [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 envolvement 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 dischargr 95%	SARS-CoV-2 antibody + 81% RT-PCR SARS-CoV-2 + 33% 18% tested + for both	NIV 36% IMV 15% ECMO 3% Intra-aortic ballon pump support 3%	IVIG 54%, Corticosteroids 51%, Tocilizumab 36% Remdesivir 21%, Anakinra 12%, Convalescent plasma therapy 3%, Aspirin 24% Anticoagulation, prophylasis 15%, Anticoagulation, therapeutic 81%Antibiotics > 48h 45% Vasopressor/inotrpes 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 craked 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 [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on	13% described typical COVOD-19 symptoms in the previous two	Respiratory support 53% Inotrope or vasopressor	IVIG 67% (10/15), of whom 2 received a second dose Metylprednisolone 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% 2nd 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

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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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 Kawaski disease (aKD) in terms of presenting symptoms, and laboratory and cardiac findings. Our objective was to review

and summarise published evidence regarding the most important aspects of PIMS-TS, with special emphasis on the treatment strategies suggested for middle- and low-income countries.

Methods: A systematic review of the literature was performed in the principal medical databases including PUBMED, EMBASE (OVID) and Google Scholar between December 2019 and August 2020.

Results: A total of 69 articles were identified in the described databases. Altogether, 13 articles met the inclusion criteria and were eligible. The most frequently described symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%), skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-6 weeks after the pandemic appears in the general population. Multisystem inflammatory syndrome in children is presented as a great systemic inflammatory response syndrome (SIRS), which sometimes presents as shock requiring fluid resuscitation and vasoactive drug support (26%). Several treatment strategies have been used, including immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These general and specific interventions should be guided by an inter- and multi-disciplinary team, especially in settings with limited resources.

Conclusions: PIMS-TS COVID-19 is a new type of presentation of SARS-CoV-2 infection, with an exaggerated inflammatory response and frequent -*but not exclusive*- digestive and myocardial involvement. It is important to describe the clinical course and outcomes in countries with limited resources as well as establish the role of biomarkers for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.

Key words: septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease, thrombosis, SARS-CoV-2

What is known about the subject?

-PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times greater need for hospitalization and mortality in children than other COVID-19 presentations.

-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 response[2]. Recently, a new type of presentation of SARS-CoV-2 infection has been described in children, involving this significant inflammatory response. This new disease has been called 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 is a severe presentation of the virus in children and requires early detection to avoid its progression and potentially unsatisfactory outcomes[5]. In this article, we discuss and review the most relevant aspects of PIMS-TS described to date.

METHODS

Search strategy and article selection

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

Eligibility criteria

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

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

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

The largest series described to date is that of the CDC in Atlanta, with 570 patients. Using a latent class analysis (LCA) statistical model, it attempted to divide the cases into three large groups according to their common clinical characteristics.[13] Class I included those with symptoms which could overlap with macrophage activation syndrome, with a large inflammatory response. Class II had predominantly respiratory involvement and signs suggestive of active COVID-19 disease with a high rate of RT-PCR seropositivity (84%). Class III had clinical manifestations that could overlap with Kawasaki disease, and only 2% were RT-PCR positive.[13]

In this regard, most studies report that the patients have a negative RT-PCR and positive antibody or serology tests. In fact, a negative RT-PCR has been found in 40% of patients with positive antibody tests. Although RT-PCR is an imperfect test, it is considered the gold standard today. In the described series, 46% of the cases had a positive serology and a negative RT-PCR, which suggests that, in these patients, the infection occurred possibly weeks earlier. An average of 25% of the patients in the included studies had both positive serology and positive RT-PCR *(supplementary table 2)*.

DISCUSSION

PIMS-TS is characterized by a very significant ongoing inflammatory response, in crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and WHO (May 15th) definitions (*Table 3*). [11,12] Characteristically, these patients present with high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.[13] Hoang et al.[14] reported lower expression of circulating CD16+CD56+ natural killer cells and more profound lymphopenia in children with PIMS-TS compare to those without PIMS-TS.

Primarily, there is an initial innate immune response with the macrophages as the principal actors. From the pathophysiological point of view, it is striking that more than 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an acute phase reactant that usually rises after six hours of an inflammatory state and is produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF-α stimulation.[15,16] This acute phase reactant from the pentraxin family identifies phosphatidylserine on the surface of cells that have initiated a programmed cell death

pattern of apoptosis by activating the complement system. This biomarker is very useful for diagnosis and follow up, especially in middle and low-income countries (given its low cost), and should be considered on admission with subsequent follow up.

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

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.[13] Pérez-Toledo M et al.[22] recently described eight patients with PIMS-TS with a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM. 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.[23-24]. We are not aware of any studies in middle and low-income countries which have described this serological behaviour. Studies are needed to help clear up this aspect, especially when all the diagnostic test options for SARS-CoV-2 are not always available. In these countries with limited resources, we suggest taking an initial RT-PCR. If this is negative and there is a high index of suspicion of PIMS-TS, due to the signs and symptoms, a total antibody or IgM/IgG test should be performed. [24]

For PIMS-TS, most of the series described coagulation disorders. Severe coagulopathy was seen in 70-80% of the cases (very high D-dimers, prolonged PT, PTT).[13] Like inflammation, coagulation is necessary for 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-1β and IL-6 are elevated, which induces thrombocytosis and hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.[27, 28] D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its early phase.[28] Elevated D-dimer levels can be present in a wide variety of inflammatory and prothrombotic conditions;[29] in COVID-19, these are probably more associated with inflammation than thrombosis.[30] Furthermore, serum hyaluronic acid, a key glycocalyx component, is higher during infancy, progressively diminishing over the years.[19,31] This could explain a more protected endothelium and a lower probability of a hypercoagulable state. In addition, CAC has an overlapping pathophysiology with other coagulopathies like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) / hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type of coagulopathy.[32]

Author	City, Country	Period	Number	Age	Gender	Comorbidity	Race	IMC kg/m²
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[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 > 75th centile/weight
Verdoni et [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 [8]	Françe (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/m2) 6%
Ramcharan et [40]	UK	10th April and 9th 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%) 0r other monority ethnic	
Toubiana et [45]	Frânçe,Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI **below** the 97th 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.

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 fever[1], laboratory evidence of inflammation[2] 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.** [1]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours [2]Including, 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-BNP [32-34] *(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 treatments[34]. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with

those of the SCCM sepsis consensus[16], for use in middle and low-income countries. We believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking these recommendations as a whole could have an impact on the outcomes of PIMS-TS patients in these countries.

From the first presentation to the Emergency Department and / or PICU, two approaches can be assumed, one general and one specific.

a. *General approach:* A comprehensive approach should be used, similar to that recommended for patients with sepsis with organ dysfunction or septic shock. In this case, the contagiousness of SARS-CoV-2 requires the use of personal protective equipment (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-PCR.

Moreover, the American College of Critical Care Medicine (ACCM) points out the need to give more attention to Institutional Practice Guidelines (IPGs) based on each facility´s capability.[35] Once IPGs are established, diagnostic and therapeutic measures known as "*patient care bundles*" (PCBs) should be developed for a better approach and control of established processes. The PCBs include three to five evidence-based practices related to a health care process that should be performed collectively to achieve a synergistic result that improves care.[36,37]

1. Early detection: a comprehensive approach based on a high index of suspicion is critical. This disease may occur with a wide spectrum of symptoms, so it should be suspected in all patients with a fever lasting more than three days associated with the symptoms described in *Figure 2*. Contact with a positive case is not always clear.

2. Immediate, time-sensitive resuscitation:

- Oxygen therapy: This is part of the strategies described in recent sepsis guidelines [16,37]. High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been considered in many reports,[38] especially in patients who have a deteriorated respiratory pattern with the use of accessory muscles or an Sa02/Fi02 ratio less than 264. Most series describe respiratory involvement ranging from 20-60% (*Table 2*) and, generally, if endotracheal intubation is required, it is more highly associated with cardiovascular involvement. Cases classified as Class II by the CDC may be classified in these groups.[33,38]

- Fluid resuscitation: It is important to consider the recommendations in recently published guidelines.[16] In healthcare systems where staff and equipment for advanced

airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour, titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. In healthcare systems without the availability of intubation, crystalloid boluses may only be given in cases of hypotension (decompensated shock); in these cases, up to 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with titration to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. If the child is not hypotensive, but has compensated shock, only maintenance fluids should be started, avoiding bolus fluids which are associated with worse outcomes[35-38].

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

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

3. Stabilization with adequate monitoring:

If possible, advanced hemodynamic monitoring should be instituted. Cardiac ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent guidelines[16] and patients with PIMS-TS.[42]

4. Timely referral or transfer is desirable in this context. In middle and low-income countries, it is common for patients to be transferred to higher complexity sites. Patients who are deteriorating or who may need intensive care should be identified. In the PIMS-TS of the CDC group, 84% of the cases had to be transferred to paediatric intensive care.[16,40-42]

5. Continuous measurement of processes and corrections must be instituted for a continuous quality improvement process.[42]

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

College of Rheumatology (ACR) recommendations for immunomodulatory therapy[42] have recently been published. We sought to adapt these recommendations to middle and low-income countries where resources are limited and each intervention must be streamlined according to need.

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

⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical course of the disease in adults with severe pneumonia, particularly if they are on mechanical ventilation.[43-47] In patients with PIMS-TS, low doses could be considered in all cases (used in 70% of the series – *Table 3*). Dosing schemes of 1-2 mg/kg/dose of methylprednisolone or its equivalent three or four times per day have been recommended. The ACR suggests considering high doses in cases of shock or in those with a high need for vasopressors, and we believe this recommendation is very important for middle and low-income countries, especially considering the frequency of late consults with advanced disease.

⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-refractory PIMS-TS.[42] However, in many countries, its use is not approved, or it is not available, and other biological agents are used. Prospective studies are needed to evaluate the efficacy and safety of these medications in PIMS-TS.

⇒ 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.[42,47-50]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%.[43,47] Aspirin would also be recommended in patients with thrombocytosis (> 450,000 u/L) or Kawasaki-like disease criteria.[42,47]

The prognosis of the disease is usually good, with patient survival greater than 95% in different published series.[5,6,42-50] A mortality of 1-2% has been described in the published series, and up to 15% with cardiovascular sequelae, including aneurysms or dysfunction.[33,48-50] These patients should be followed up after discharge by inter and 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]

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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REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report. Available in:http://www.who.int/docs/default-source/coronaviruse/situation-reports.2. 28 Jun 2020.

2. Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Epub 2020/02/28. doi: 10.1016/S2213-2600(20)30079-5.

3. Whittaker E, Bamford A, Kenny J et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV2-2. JAMA 2020 Jun8; e2010369. Doi:10.1001/jama.2020.10369.

4. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A, et al. Pediatric critical care and COVID19. Pediatrics. 2020; doi: 10.1542/peds.2020-1766.

5. De Biasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC Metropolitan Region. J Pediatr 2020. https://doi.org/10.1016/j.jpeds.2020.05.007. In press.

6. Riphagen S, Gomez X, Gonzalez-Martinez et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020 May 7. https://doi.org/10.1016/S0140-6736(20)31094-1. S0140-6736(20)31094- 1, ahead of print.

7. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31103-X. ahead of print.

8. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2. pandemic. Circulation 2020 May 17. https://doi.org/10.1161/CIRCULATIONAHA. 120.048360. ahead of print.

9.Grimaud M, Starck J, Levy M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020; 10:69.

10. Royal College of Paediatrics and Child Health. Available in: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims.

11. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp.

12. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID 19 Scientific brief. Available en: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. 15 May 2020.

13. Golfred-Cato S, Bryant B, Leung J et al. COVID-19- Associated Multiystem Inflammatory syndrome in Children- United States, March-July 2020. Available in https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf.

14. Hoang A, Chroath K, Moreira A et al., COVID-19 in 7780 pediatric patients: A systematic review, E-Clinical Medicine (2020), https://doi.org/ 10.1016/j.eclinm.2020.100433.

15. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):33. Published 2020 Mar 27. doi:10.1038/s41392-020-0148-4.

16. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46 (Suppl. 1):10–67.

17. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46(5):854–87.

18. Jaume M, Yip MS, Cheung CY et al. Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and

cysteine protease-independent Fc. R pathway. Journal of virology. 2011;85(20):10582-97. 12.

19. Fernández-Sarmiento J, Salazar LM, Carcillo J. The endothelial glycocalyx: a fundamental determinant of vascular permeability in sepsis. Ped Crit Care 2020;21e:e291-e300.

20. Carcillo JA, Kernan KK, Horvat CM et al. Why and How Is Hyperferritinemic Sepsis Different from Sepsis Without Hyperferritinemia? Pediatr Crit Care Med. 2020;21(5):509-512. doi:10.1097/PCC.0000000000002285.

21. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, et al: The Hyperferritinemic syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013; 11:185.

22. Pérez-Toledo M, Faustini S, Jossi S et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Pediatric Inflammatory Multi-system syndrome. Institute of Immunology and Immunotherapy, University of Birmingham UK. Doi: hhtpps://doi.org/10.1101/2020.06.05.20123117. Online 07 June 2020.

23. Kam YW, Kien F, Roberts A. et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro. Vaccine. 2007;25(4):729-40.

24. Wang SF, Tseng SP, Yen CH et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochemical and biophysical research communications.* 2014;451(2):208-14.

25. Iba T, Levy JH, Connors JM et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360. Published 2020 Jun 18. doi:10.1186/s13054-020-03077-0.

26. Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology. 2020;132(5):1238–45.

27. Waltuch T, Gill P, Zinns LE et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department [published online ahead of print, 2020 May 8. Am J Emerg Med. 2020; S0735- 6757(20)30403-4. doi:10.1016/j.ajem.2020.05.058.

28. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020;395(10234):1417–8.

29. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis [published online ahead of print, 2020 Jun 10]. J Thromb Thrombolysis. 2020;1-10. doi:10.1007/s11239-020-02171-y.

30. Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. Semin Thromb Hemost. 2012;38(7):673-682. doi:10.1055/s-0032-1326782

31. Trivedi P, Cheeseman P, Mowat AP. Serum hyaluronic acid in healthy infants and children and its value as a marker of progressive hepatobiliary disease starting in infancy. Clin Chim Acta. 1993;215(1):29-39. doi:10.1016/0009-8981(93)90246-z.

32.Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020;309; 7077. doi: 10.1016/j.ijcard.2020.03.063.

33. Cheung E, Zachariah P, Gorelik M et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adlescents in New York City. JAMA. Published online June 8, 2020. Doi:10.1001/jama.2020.10374

34. Harwood R, Allin B, Jones C et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2020 Published Online September 18 doi.org/10.1016/S352-4642(20)30304-7

35. Davis AL, Carcillo JA, Aneja RK, et al. AmericanCollege of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017; 45(6):1061-93.

36. Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? Curr Open Infect Dis. 2009; 22(2):159-66.

37. Kohn Loncarica G, Fustiñana A, Jabornisky R. Recommendations for the management of pediatric septic shock in the first hour (part I). Arch Argent Pediatr 2019;117(1): e14-e23.

38. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection: A Multi-institutional Study from New York City [published online ahead of print, 2020 Jun 14]. J Pediatr. 2020;S0022-3476(20)30747-239.

39. National Institute for Health and Care Excellence. Sepsis: Recognition, Diagnosis and Early Management. London, 2016;51. [Accessed on: June 27th, 2020]. Available at: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-manage- ment-pdf-1837508256709.

40. Ramcharan, T, Nolan, O, Lai C.Y. et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. *Pediatr Cardiol* (2020). https://doi.org/10.1007/s00246-020-02391-2.

41. Fernández-Sarmiento J, Carcillo JA, Salinas CM, et al. Effect of a sepsis educational intervention on hospital stay. Pediatr Crit Care Med. 2018;19: e321–e328.

42. American College of Rheumatology. Clinical Guidance for Pediatric Patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in covid-19. Available in https://www.rheumatology.org/announcements#PediatricClinicalGuidance. Jun3 17 2020.

43. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [Internet]. RECOVERY (Randomised Evaluation of COVID-19 Therapy) University of Oxford. 2020 [cited 2020 Jun 18]. Available from: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19.

44. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/ sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. Pediatr Crit Care Med 2014;15(5):401–8.

45. Toubiana J, Poiralut C, Corsia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369m2094.

46. Pouletty M, Borocco C, Ouldali N et at. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dise 2020; 0:1-8.

47. Capone CA, Subramony A, Sweberg T et al. Characteristics, Cardiac involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection, The Journal of Pediatrics (2020), doi: https://doi.org/10.1016/ j.jpeds.2020.06.044.

48. Feldstein L.R, Rose E.B, Horwitz J.P et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020 June 29. Doi:10.1056/NEJMoa2021680.

49. Dufort E, Koumnas E, Chow E et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020 Jun 29. Doi:10.1056/NEJMoa2021756

50. Prata-Barbosa A, Lima-Setta F, Rodrigues dos Santos G et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. Jornal de Pediatria. 2020:96(5):582-592.

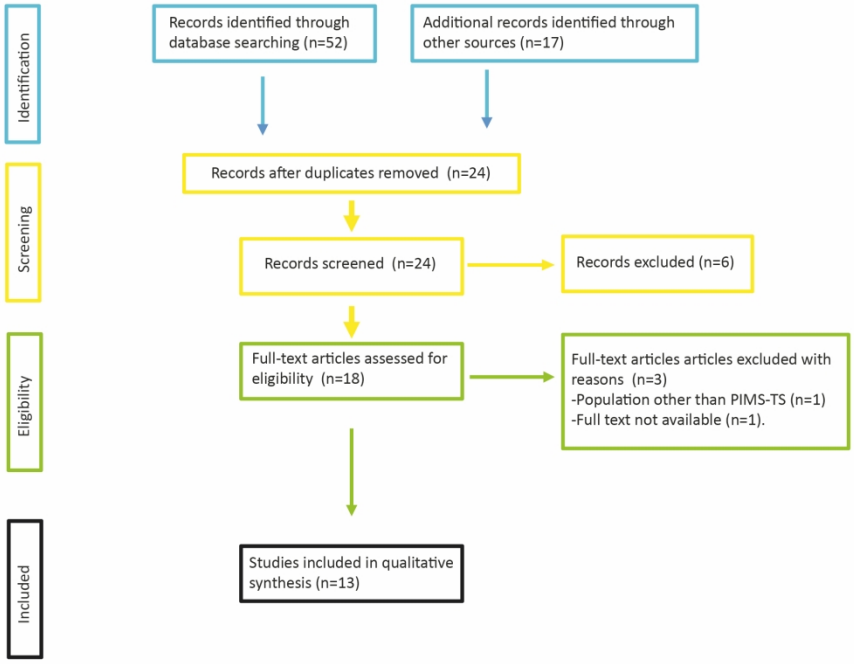
Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses

Table 1. Demographic characteristics of patients with PIMS-TS

Table 2. Clinical and echocardiographic findings, and treatments instituted in the described series of PIMS-TS patients (*(supplementary file)*.

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

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% Diarrhea52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29%Swollen hands and feet 16%, Respiratory symptons 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% Anakinra5% 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 (arrhytmia with refractory shock, died)	IVIG 8/8,Corticoids 5/58 Aspitin 3/8,Heparin 1/8, Antibiótics 8/8, Infliximab 1/8	1 died 6/8 alive PICU lenght 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 [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 sistems involved 4-5 61.6%
Kaushik et [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 envolvement 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, prophylasis 15%, Anticoagulation, therapeutic 81%Antibiotics > 48h 45% Vasopressor/inotrpes 51%	
Ramcharan et [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on admission 51%	13% described typical COVOD-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 [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 craked 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% 2nd 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%

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

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*

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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

and summarize published evidence regarding the most important aspects of PIMS-TS, with special emphasis on the treatment strategies suggested for middle- and low-income countries.

Methods: A systematic review of the literature was performed in the principal medical databases including PUBMED, EMBASE (OVID) and Google Scholar between December 2019 and August 2020.

Results: A total of 69 articles were identified in the described databases. Altogether, 13 articles met the inclusion criteria and were eligible. The most frequently described symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%), skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-6 weeks after the pandemic appears in the general population. Multisystem inflammatory syndrome in children is presented as a great systemic inflammatory response syndrome (SIRS), which sometimes presents as shock requiring fluid resuscitation and vasoactive drug support (26%). Several treatment strategies have been used, including immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These general and specific interventions should be guided by an inter- and multi-disciplinary team, especially in settings with limited resources.

Conclusions: PIMS-TS COVID-19 is a new type of presentation of SARS-CoV-2 infection, with an exaggerated inflammatory response and frequent -*but not exclusive*- digestive and myocardial involvement. It is important to describe the clinical course and outcomes in countries with limited resources as well as establish the role of biomarkers for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.

Key words: septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease, thrombosis, SARS-CoV-2

What is known about the subject?

-PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times greater need for hospitalization and mortality in children than other COVID-19 presentations.

-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 response[2]. Recently, a new type of presentation of SARS-CoV-2 infection has been described in children, involving this significant inflammatory response. This new disease has been called 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 is a severe presentation of the virus in children and requires early detection to avoid its progression and potentially unsatisfactory outcomes[5]. In this article, we discuss and review the most relevant aspects of PIMS-TS described to date.

METHODS

Search strategy and article selection

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

Eligibility criteria

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

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

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

The largest series described to date is that of the CDC in Atlanta, with 570 patients. Using a latent class analysis (LCA) statistical model, it attempted to divide the cases into three large groups according to their common clinical characteristics.[13] Class I included those with symptoms which could overlap with macrophage activation syndrome, with a large inflammatory response. Class II had predominantly respiratory involvement and signs suggestive of active COVID-19 disease with a high rate of RT-PCR seropositivity (84%). Class III had clinical manifestations that could overlap with Kawasaki disease, and only 2% were RT-PCR positive.[13]

In this regard, most studies report that the patients have a negative RT-PCR and positive antibody or serology tests. In fact, a negative RT-PCR has been found in 40% of patients with positive antibody tests. Although RT-PCR is an imperfect test, it is considered the gold standard today. In the described series, 46% of the cases had a positive serology and a negative RT-PCR, which suggests that, in these patients, the infection occurred possibly weeks earlier. An average of 25% of the patients in the included studies had both positive serology and positive RT-PCR *(supplementary table S1)*.

DISCUSSION

PIMS-TS is characterized by a very significant ongoing inflammatory response, in crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and WHO (May 15th) definitions (*Table 2*). [11,12] Characteristically, these patients present with high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.[13] Hoang et al.[14] reported lower expression of circulating CD16+CD56+ natural killer cells and more profound lymphopenia in children with PIMS-TS compare to those without PIMS-TS.

Primarily, there is an initial innate immune response with the macrophages as the principal actors. From the pathophysiological point of view, it is striking that more than 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an acute phase reactant that usually rises after six hours of an inflammatory state and is produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF-α stimulation.[15,16] This acute phase reactant from the pentraxin family identifies phosphatidylserine on the surface of cells that have initiated a programmed cell death

pattern of apoptosis by activating the complement system. This biomarker is very useful for diagnosis and follow up, especially in middle and low-income countries (given its low cost), and should be considered on admission with subsequent follow up.

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

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.[13] Pérez-Toledo M et al.[22] recently described eight patients with PIMS-TS with a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM. 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.[23-24]. We are not aware of any studies in middle and low-income countries which have described this serological behaviour. Studies are needed to help clear up this aspect, especially when all the diagnostic test options for SARS-CoV-2 are not always available. In these countries with limited resources, we suggest taking an initial RT-PCR. If this is negative and there is a high index of suspicion of PIMS-TS, due to the signs and symptoms, a total antibody or IgM/IgG test should be performed. [24]

For PIMS-TS, most of the series described coagulation disorders. Severe coagulopathy was seen in 70-80% of the cases (very high D-dimers, prolonged PT, PTT).[13] Like inflammation, coagulation is necessary for 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-1β and IL-6 are elevated, which induces thrombocytosis and hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.[27, 28] D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its early phase.[28] Elevated D-dimer levels can be present in a wide variety of inflammatory and prothrombotic conditions;[29] in COVID-19, these are probably more associated with inflammation than thrombosis.[30] Furthermore, serum hyaluronic acid, a key glycocalyx component, is higher during infancy, progressively diminishing over the years.[19,31] This could explain a more protected endothelium and a lower probability of a hypercoagulable state. In addition, CAC has an overlapping pathophysiology with other coagulopathies like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) / hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type of coagulopathy.[32]

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[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 > 75th centile/weight
Verdoni et [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 [8]	Françe (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/m2) 6%
Ramcharan et [40]	UK	10th April and 9th 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%) 0r other monority ethnic	
Toubiana et [45]	Frânçe,Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI **below** the 97th 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.

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 fever[1], laboratory evidence of inflammation[2] 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.** [1]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours [2]Including, 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-BNP [32-34] *(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 treatments[34]. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with

those of the SCCM sepsis consensus[16], for use in middle and low-income countries. We believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking these recommendations as a whole could have an impact on the outcomes of PIMS-TS patients in these countries.

From the first presentation to the Emergency Department and / or PICU, two approaches can be assumed, one general and one specific (*Table 3*):

a. *General approach:* A comprehensive approach should be used, similar to that recommended for patients with sepsis with organ dysfunction or septic shock. In this case, the contagiousness of SARS-CoV-2 requires the use of personal protective equipment (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-PCR.

Moreover, the American College of Critical Care Medicine (ACCM) points out the need to give more attention to Institutional Practice Guidelines (IPGs) based on each facility´s capability.[35] Once IPGs are established, diagnostic and therapeutic measures known as "*patient care bundles*" (PCBs) should be developed for a better approach and control of established processes. The PCBs include three to five evidence-based practices related to a health care process that should be performed collectively to achieve a synergistic result that improves care.[36,37]

1. Early detection: a comprehensive approach based on a high index of suspicion is critical. This disease may occur with a wide spectrum of symptoms, so it should be suspected in all patients with a fever lasting more than three days associated with the symptoms described in *Table 2*. Contact with a positive case is not always clear.

2. Immediate, time-sensitive resuscitation:

- Oxygen therapy: This is part of the strategies described in recent sepsis guidelines [16,37]. High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been considered in many reports,[38] especially in patients who have a deteriorated respiratory pattern with the use of accessory muscles or an Sa02/Fi02 ratio less than 264. Most series describe respiratory involvement ranging from 20-60% (*supplementary table S1*) and, generally, if endotracheal intubation is required, it is more highly associated with cardiovascular involvement. Cases classified as Class II by the CDC may be classified in these groups.[33,38]

- Fluid resuscitation: It is important to consider the recommendations in recently published guidelines.[16] In healthcare systems where staff and equipment for advanced

airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour, titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. In healthcare systems without the availability of intubation, crystalloid boluses may only be given in cases of hypotension (decompensated shock); in these cases, up to 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with titration to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. If the child is not hypotensive, but has compensated shock, only maintenance fluids should be started, avoiding bolus fluids which are associated with worse outcomes[35-38].

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

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

3. Stabilization with adequate monitoring:

If possible, advanced hemodynamic monitoring should be instituted. Cardiac ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent guidelines[16] and patients with PIMS-TS.[42]

4. Timely referral or transfer is desirable in this context. In middle and low-income countries, it is common for patients to be transferred to higher complexity sites. Patients who are deteriorating or who may need intensive care should be identified. In the PIMS-TS of the CDC group, 84% of the cases had to be transferred to paediatric intensive care.[16,40-42]

5. Continuous measurement of processes and corrections must be instituted for a continuous quality improvement process.[42]

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

College of Rheumatology (ACR) recommendations for immunomodulatory therapy[42] have recently been published. We sought to adapt these recommendations to middle and low-income countries where resources are limited and each intervention must be streamlined according to need.

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

⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical course of the disease in adults with severe pneumonia, particularly if they are on mechanical ventilation.[43-47] In patients with PIMS-TS, low doses could be considered in all cases (used in 70% of the series – *supplementary table S1*). Dosing schemes of 1-2 mg/kg/dose of methylprednisolone or its equivalent three or four times per day have been recommended. The ACR suggests considering high doses in cases of shock or in those with a high need for vasopressors, and we believe this recommendation is very important for middle and low-income countries, especially considering the frequency of late consults with advanced disease.

⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-refractory PIMS-TS.[42] However, in many countries, its use is not approved, or it is not available, and other biological agents are used. Prospective studies are needed to evaluate the efficacy and safety of these medications in PIMS-TS.

⇒ 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.[42,47-50]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%.[43,47] Aspirin would also be recommended in patients with thrombocytosis (> 450,000 u/L) or Kawasaki-like disease criteria.[42,47]

The prognosis of the disease is usually good, with patient survival greater than 95% in different published series.[5,6,42-50] A mortality of 1-2% has been described in the published series, and up to 15% with cardiovascular sequelae, including aneurysms or dysfunction.[33,48-50] These patients should be followed up after discharge by inter and

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: • 2 gr/kg for moderate to severe cases
2. Immediate, time-sensitive resuscitation a. Oxygen therapy b. Fluid resuscitation c. Vasoactive drugs d. Antibiotic therapy: if bacterial co-infection is suspected	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. Stabilization with adequate monitoring	3. Anakinra: • 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: a. Documented thrombosis b. 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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REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report. Available in:http://www.who.int/docs/default-source/coronaviruse/situation-reports.2. 28 Jun 2020.

2. Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Epub 2020/02/28. doi: 10.1016/S2213-2600(20)30079-5.

3. Whittaker E, Bamford A, Kenny J et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV2-2. JAMA 2020 Jun8; e2010369. Doi:10.1001/jama.2020.10369.

4. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A, et al. Pediatric critical care and COVID19. Pediatrics. 2020; doi: 10.1542/peds.2020-1766.

5. De Biasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC Metropolitan Region. J Pediatr 2020. https://doi.org/10.1016/j.jpeds.2020.05.007. In press.

6. Riphagen S, Gomez X, Gonzalez-Martinez et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020 May 7. https://doi.org/10.1016/S0140-6736(20)31094-1. S0140-6736(20)31094- 1, ahead of print.

7. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31103-X. ahead of print.

8. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2. pandemic. Circulation 2020 May 17. https://doi.org/10.1161/CIRCULATIONAHA. 120.048360. ahead of print.

9.Grimaud M, Starck J, Levy M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020; 10:69.

10. Royal College of Paediatrics and Child Health. Available in: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims.

11. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp.

12. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID 19 Scientific brief. Available en: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. 15 May 2020.

13. Golfred-Cato S, Bryant B, Leung J et al. COVID-19- Associated Multiystem Inflammatory syndrome in Children- United States, March-July 2020. Available in https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf.

14. Hoang A, Chroath K, Moreira A et al., COVID-19 in 7780 pediatric patients: A systematic review, E-Clinical Medicine (2020), https://doi.org/ 10.1016/j.eclinm.2020.100433.

15. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):33. Published 2020 Mar 27. doi:10.1038/s41392-020-0148-4.

16. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46 (Suppl. 1):10–67.

17. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46(5):854–87.

18. Jaume M, Yip MS, Cheung CY et al. Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent Fc. R pathway. Journal of virology. 2011;85(20):10582-97. 12.

19. Fernández-Sarmiento J, Salazar LM, Carcillo J. The endothelial glycocalyx: a fundamental determinant of vascular permeability in sepsis. Ped Crit Care 2020;21e:e291-e300.

20. Carcillo JA, Kernan KK, Horvat CM et al. Why and How Is Hyperferritinemic Sepsis Different from Sepsis Without Hyperferritinemia? Pediatr Crit Care Med. 2020;21(5):509-512. doi:10.1097/PCC.0000000000002285.

21. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, et al: The Hyperferritinemic syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013; 11:185.

22. Pérez-Toledo M, Faustini S, Jossi S et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Pediatric Inflammatory Multi-system syndrome. Institute of Immunology and Immunotherapy, University of Birmingham UK. Doi: hhtpps://doi.org/10.1101/2020.06.05.20123117. Online 07 June 2020.

23. Kam YW, Kien F, Roberts A. et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro. Vaccine. 2007;25(4):729-40.

24. Wang SF, Tseng SP, Yen CH et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochemical and biophysical research communications.* 2014;451(2):208-14.

25. Iba T, Levy JH, Connors JM et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360. Published 2020 Jun 18. doi:10.1186/s13054-020-03077-0.

26. Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology. 2020;132(5):1238–45.

27. Waltuch T, Gill P, Zinns LE et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department [published online ahead of print, 2020 May 8. Am J Emerg Med. 2020; S0735- 6757(20)30403-4. doi:10.1016/j.ajem.2020.05.058.

28. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020;395(10234):1417–8.

29. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis [published online ahead of print, 2020 Jun 10]. J Thromb Thrombolysis. 2020;1-10. doi:10.1007/s11239-020-02171-y.

30. Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. Semin Thromb Hemost. 2012;38(7):673-682. doi:10.1055/s-0032-1326782

31. Trivedi P, Cheeseman P, Mowat AP. Serum hyaluronic acid in healthy infants and children and its value as a marker of progressive hepatobiliary disease starting in infancy. Clin Chim Acta. 1993;215(1):29-39. doi:10.1016/0009-8981(93)90246-z.

32.Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020;309; 7077. doi: 10.1016/j.ijcard.2020.03.063.

33. Cheung E, Zachariah P, Gorelik M et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adlescents in New York City. JAMA. Published online June 8, 2020. Doi:10.1001/jama.2020.10374

34. Harwood R, Allin B, Jones C et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2020 Published Online September 18 doi.org/10.1016/S352-4642(20)30304-7

35. Davis AL, Carcillo JA, Aneja RK, et al. AmericanCollege of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017; 45(6):1061-93.

36. Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? Curr Open Infect Dis. 2009; 22(2):159-66.

37. Kohn Loncarica G, Fustiñana A, Jabornisky R. Recommendations for the management of pediatric septic shock in the first hour (part I). Arch Argent Pediatr 2019;117(1): e14-e23.

38. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection: A Multi-institutional Study from New York City [published online ahead of print, 2020 Jun 14]. J Pediatr. 2020;S0022-3476(20)30747-239.

39. National Institute for Health and Care Excellence. Sepsis: Recognition, Diagnosis and Early Management. London, 2016;51. [Accessed on: June 27th, 2020]. Available at: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-manage- ment-pdf-1837508256709.

40. Ramcharan, T, Nolan, O, Lai C.Y. et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. *Pediatr Cardiol* (2020). https://doi.org/10.1007/s00246-020-02391-2.

41. Fernández-Sarmiento J, Carcillo JA, Salinas CM, et al. Effect of a sepsis educational intervention on hospital stay. Pediatr Crit Care Med. 2018;19: e321–e328.

42. American College of Rheumatology. Clinical Guidance for Pediatric Patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in covid-19. Available in https://www.rheumatology.org/announcements#PediatricClinicalGuidance. Jun3 17 2020.

43. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [Internet]. RECOVERY (Randomised Evaluation of COVID-19 Therapy) University of Oxford. 2020 [cited 2020 Jun 18]. Available from: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19.

44. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/ sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. Pediatr Crit Care Med 2014;15(5):401–8.

45. Toubiana J, Poiralut C, Corsia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369m2094.

46. Pouletty M, Borocco C, Ouldali N et at. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dise 2020; 0:1-8.

47. Capone CA, Subramony A, Sweberg T et al. Characteristics, Cardiac involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection, The Journal of Pediatrics (2020), doi: https://doi.org/10.1016/ j.jpeds.2020.06.044.

48. Feldstein L.R, Rose E.B, Horwitz J.P et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020 June 29. Doi:10.1056/NEJMoa2021680.

49. Dufort E, Koumnas E, Chow E et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020 Jun 29. Doi:10.1056/NEJMoa2021756

50. Prata-Barbosa A, Lima-Setta F, Rodrigues dos Santos G et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. Jornal de Pediatria. 2020:96(5):582-592.

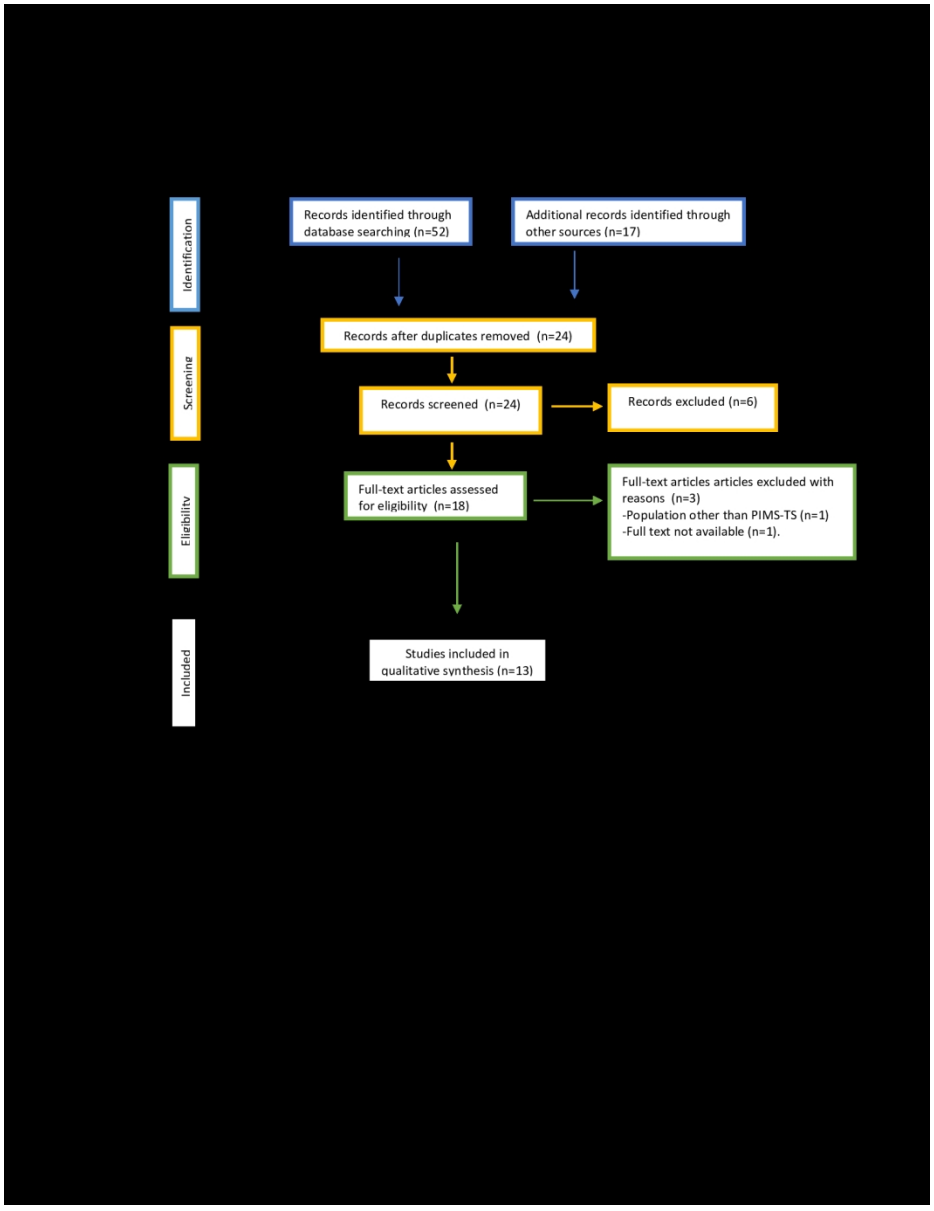
Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses

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.



215x279mm (200 x 200 DPI)

Author	Clinical presentation	ECHO	SARS-CoV-2 test	Organ support	Treatment	Outcome / Died
Whittaker et al [3]	Fever 100%, Headache 26%Vomiting 45% Diarrhea52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29%Swollen hands and feet 16%, Respiratory symptons 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% Anakinra5% 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 (arrhytmia with refractory shock, died)	IVIG 8/8,Corticoids 5/58 Aspitin 3/8,Heparin 1/8, Antibiótics 8/8, Infliximab 1/8	1 died 6/8 alive PICU lenght 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 [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 sistems involved 4-5 61.6%
Kaushik et [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 envolvement 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, prophylasis 15%, Anticoagulation, therapeutic 81%Antibiotics > 48h 45% Vasopressor/inotrpes 51%	
Ramcharan et [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on admission 51%	13% described typical COVOD-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 [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 craked 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% 2nd 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%

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

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

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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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 and summarize published evidence regarding the most important aspects of PIMS-TS, with special emphasis on the treatment strategies suggested for middle- and low-income countries.

Methods: A systematic review of the literature was performed in the principal medical databases including PUBMED, EMBASE (OVID) and Google Scholar between December 2019 and August 2020.

Results: A total of 69 articles were identified in the described databases. Altogether, 13 articles met the inclusion criteria and were eligible. The most frequently described symptoms of PIMS-TS include fever (82%), shock (67%), and gastrointestinal (87%), skin (71%) and cardiac disorders (75%). In most series, it has been observed between 4-6 weeks after the pandemic appears in the general population. Multisystem inflammatory syndrome in children is presented as a great systemic inflammatory response syndrome (SIRS), which sometimes presents as shock requiring fluid resuscitation and vasoactive drug support (26%). Several treatment strategies have been used, including immunoglobulin, steroids, aspirin, anakinra and anticoagulation, among others. These general and specific interventions should be guided by an inter- and multi-disciplinary team, especially in settings with limited resources.

Conclusions: PIMS-TS COVID-19 is a new type of presentation of SARS-CoV-2 infection, with an exaggerated inflammatory response and frequent -*but not exclusive*- digestive and myocardial involvement. It is important to describe the clinical course and outcomes in countries with limited resources as well as establish the role of biomarkers for early diagnosis, effective therapeutic strategies, and outpatient follow-up schemes.

Key words: septic shock, COVID-19, inflammation, immunoglobulin, Kawasaki disease, thrombosis, SARS-CoV-2

Key messages

-PIMS-TS is a type of presentation of SARS-CoV-2 infection which produces a ten times greater need for hospitalization and mortality in children than other COVID-19 presentations.

-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 response[2]. Recently, a new type of presentation of

SARS-CoV-2 infection has been described in children, involving this significant inflammatory response. This new disease has been called 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 is a severe presentation of the virus in children and requires early detection to avoid its progression and potentially unsatisfactory outcomes[5]. In this article, we discuss and review the most relevant aspects of PIMS-TS described to date.

METHODS

Search strategy and article selection

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

Eligibility criteria

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

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

The largest series described to date is that of the CDC in Atlanta, with 570 patients. Using a latent class analysis (LCA) statistical model, it attempted to divide the cases into three large groups according to their common clinical characteristics.[13] Class I included those with symptoms which could overlap with macrophage activation syndrome, with a large inflammatory response. Class II had predominantly respiratory involvement and signs suggestive of active COVID-19 disease with a high rate of RT-PCR seropositivity (84%). Class III had clinical manifestations that could overlap with Kawasaki disease, and only 2% were RT-PCR positive.[13]

In this regard, most studies report that the patients have a negative RT-PCR and positive antibody or serology tests. In fact, a negative RT-PCR has been found in 40% of patients with positive antibody tests. Although RT-PCR is an imperfect test, it is considered the gold standard today. In the described series, 46% of the cases had a positive serology and a negative RT-PCR, which suggests that, in these patients, the infection occurred possibly weeks earlier. An average of 25% of the patients in the included studies had both positive serology and positive RT-PCR *(supplementary table S1)*.

DISCUSSION

PIMS-TS is characterized by a very significant ongoing inflammatory response, in crescendo, which in fact has been the key element in the Atlanta CDC (May 14th) and WHO (May 15th) definitions (*Table 2*). [11,12] Characteristically, these patients present with high leukocytosis, CRP, procalcitonin (PCT), and serum ferritin.[13] Hoang et al.[14] reported lower expression of circulating CD16+CD56+ natural killer cells and more profound lymphopenia in children with PIMS-TS compare to those without PIMS-TS.

Primarily, there is an initial innate immune response with the macrophages as the principal actors. From the pathophysiological point of view, it is striking that more than 90% of children with PIMS-TS have elevated CRP and ferritin. C-reactive protein is an acute phase reactant that usually rises after six hours of an inflammatory state and is produced by hepatocytes and adipose tissue in response to IL-1, IL-6 and TNF-α

stimulation.[15,16] This acute phase reactant from the pentraxin family identifies phosphatidylserine on the surface of cells that have initiated a programmed cell death pattern of apoptosis by activating the complement system. This biomarker is very useful for diagnosis and follow up, especially in middle and low-income countries (given its low cost), and should be considered on admission with subsequent follow up.

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

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.[13] Pérez-Toledo M et al.[22] recently described eight patients with PIMS-TS with a negative RT-PCR but with significant elevation of IgG and IgA, and negative IgM. 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.[23-24]. We are not aware of any studies in middle and low-income countries which have described this serological behaviour. Studies are needed to help clear up this aspect, especially when all the diagnostic test options for SARS-CoV-2 are not always available. In these countries with limited resources, we suggest taking an initial RT-PCR. If this is negative and there is a high index of suspicion

of PIMS-TS, due to the signs and symptoms, a total antibody or IgM/IgG test should be performed. [24]

For PIMS-TS, most of the series described coagulation disorders. Severe coagulopathy was seen in 70-80% of the cases (very high D-dimers, prolonged PT, PTT).[13] Like inflammation, coagulation is necessary for 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-1β and IL-6 are elevated, which induces thrombocytosis and hyperfibrinogenemia, and the angiotensin-converting enzyme 2 (ACE-2) receptor is stimulated by SARS-CoV-2, leading to a massive release of plasminogen activators.[27, 28] D-dimer levels are very high in PIMS-TS, but consumptive coagulopathy is rare in its early phase.[28] Elevated D-dimer levels can be present in a wide variety of inflammatory and prothrombotic conditions;[29] in COVID-19, these are probably more associated with inflammation than thrombosis.[30] Furthermore, serum hyaluronic acid, a key glycocalyx component, is higher during infancy, progressively diminishing over the years.[19,31] This could explain a more protected endothelium and a lower probability of a hypercoagulable state. In addition, CAC has an overlapping pathophysiology with other coagulopathies like hemophagocytic syndrome (HPS) / hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura (TTP) / hemolytic uremic syndrome (HUS), but some unique aspects make it a probably new type of coagulopathy.[32]

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[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 > 75th centile/weight
Verdoni et [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 [8]	Françe (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/m2) 6%
Ramcharan et [40]	UK	10th April and 9th 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%) 0r other monority ethnic	
Toubiana et [45]	Frânçe,Paris	27 April and 11 May	21 children with features of Kawasaki disease	7.9 years (IQR3.7, 16.6)	43% boys	N/R	57% Sub-Saharan Africa/Caribbean islands	76% had a BMI **below** the 97th 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.

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 fever[1], laboratory evidence of inflammation[2] 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.** [1]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours [2]Including, 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-BNP [32-34] *(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 treatments[34]. This approach is recommended for high-income countries. Using the evidence found, we adapted these recommendations, together with

those of the SCCM sepsis consensus[16], for use in middle and low-income countries. We believe that a comprehensive approach to PIMS-TS patients is necessary, and that taking these recommendations as a whole could have an impact on the outcomes of PIMS-TS patients in these countries.

From the first presentation to the Emergency Department and / or PICU, two approaches can be assumed, one general and one specific (*Table 3*):

a. *General approach:* A comprehensive approach should be used, similar to that recommended for patients with sepsis with organ dysfunction or septic shock. In this case, the contagiousness of SARS-CoV-2 requires the use of personal protective equipment (PPE) that prevents the spread of the virus, particularly in patients with a positive RT-PCR.

Moreover, the American College of Critical Care Medicine (ACCM) points out the need to give more attention to Institutional Practice Guidelines (IPGs) based on each facility´s capability.[35] Once IPGs are established, diagnostic and therapeutic measures known as "*patient care bundles*" (PCBs) should be developed for a better approach and control of established processes. The PCBs include three to five evidence-based practices related to a health care process that should be performed collectively to achieve a synergistic result that improves care.[36,37]

1. Early detection: a comprehensive approach based on a high index of suspicion is critical. This disease may occur with a wide spectrum of symptoms, so it should be suspected in all patients with a fever lasting more than three days associated with the symptoms described in *Table 2*. Contact with a positive case is not always clear.

2. Immediate, time-sensitive resuscitation:

- Oxygen therapy: This is part of the strategies described in recent sepsis guidelines [16,37]. High flow nasal cannulas (HFNCs) and non-invasive ventilation (NIV) have been considered in many reports,[38] especially in patients who have a deteriorated respiratory pattern with the use of accessory muscles or an Sa02/Fi02 ratio less than 264. Most series describe respiratory involvement ranging from 20-60% (*supplementary table S1*) and, generally, if endotracheal intubation is required, it is more highly associated with cardiovascular involvement. Cases classified as Class II by the CDC may be classified in these groups.[33,38]

- Fluid resuscitation: It is important to consider the recommendations in recently published guidelines.[16] In healthcare systems where staff and equipment for advanced

airway management are available, up to 40–60 mL/kg (10–20 mL/kg per bolus) of balanced crystalloids (*Ringer's lactate or Plasma-Lyte*) can be given over the first hour, titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. In healthcare systems without the availability of intubation, crystalloid boluses may only be given in cases of hypotension (decompensated shock); in these cases, up to 40 mL/kg of bolus fluid (10–20 mL/kg per bolus) may be infused over the first hour with titration to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. If the child is not hypotensive, but has compensated shock, only maintenance fluids should be started, avoiding bolus fluids which are associated with worse outcomes[35-38].

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

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

3. Stabilization with adequate monitoring:

If possible, advanced hemodynamic monitoring should be instituted. Cardiac ultrasound/echocardiography or S_{cvo2} measurements have been suggested by recent guidelines[16] and patients with PIMS-TS.[42]

4. Timely referral or transfer is desirable in this context. In middle and low-income countries, it is common for patients to be transferred to higher complexity sites. Patients who are deteriorating or who may need intensive care should be identified. In the PIMS-TS of the CDC group, 84% of the cases had to be transferred to paediatric intensive care.[16,40-42]

5. Continuous measurement of processes and corrections must be instituted for a continuous quality improvement process.[42]

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

College of Rheumatology (ACR) recommendations for immunomodulatory therapy[42] have recently been published. We sought to adapt these recommendations to middle and low-income countries where resources are limited and each intervention must be streamlined according to need.

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

⇒ Steroids: Steroids have recently been shown to be useful in modifying the clinical course of the disease in adults with severe pneumonia, particularly if they are on mechanical ventilation.[43-47] In patients with PIMS-TS, low doses could be considered in all cases (used in 70% of the series – *supplementary table S1*). Dosing schemes of 1-2 mg/kg/dose of methylprednisolone or its equivalent three or four times per day have been recommended. The ACR suggests considering high doses in cases of shock or in those with a high need for vasopressors, and we believe this recommendation is very important for middle and low-income countries, especially considering the frequency of late consults with advanced disease.

⇒ Anakinra is suggested by the ACR consensus for use in cases of steroid or IVIG-refractory PIMS-TS.[42] However, in many countries, its use is not approved, or it is not available, and other biological agents are used. Prospective studies are needed to evaluate the efficacy and safety of these medications in PIMS-TS.

⇒ 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.[42,47-50]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%.[43,47] Aspirin would also be recommended in patients with thrombocytosis (> 450,000 u/L) or Kawasaki-like disease criteria.[42,47]

The prognosis of the disease is usually good, with patient survival greater than 95% in different published series.[5,6,42-50] A mortality of 1-2% has been described in the published series, and up to 15% with cardiovascular sequelae, including aneurysms or dysfunction.[33,48-50] These patients should be followed up after discharge by inter and

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*

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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REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report. Available in:http://www.who.int/docs/default-source/coronaviruse/situation-reports.2. 28 Jun 2020.

2. Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Epub 2020/02/28. doi: 10.1016/S2213-2600(20)30079-5.

3. Whittaker E, Bamford A, Kenny J et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV2-2. JAMA 2020 Jun8; e2010369. Doi:10.1001/jama.2020.10369.

4. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A, et al. Pediatric critical care and COVID19. Pediatrics. 2020; doi: 10.1542/peds.2020-1766.

5. De Biasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC Metropolitan Region. J Pediatr 2020. https://doi.org/10.1016/j.jpeds.2020.05.007. In press.

6. Riphagen S, Gomez X, Gonzalez-Martinez et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020 May 7. https://doi.org/10.1016/S0140-6736(20)31094-1. S0140-6736(20)31094- 1, ahead of print.

7. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31103-X. ahead of print.

8. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2. pandemic. Circulation 2020 May 17. https://doi.org/10.1161/CIRCULATIONAHA. 120.048360. ahead of print.

9.Grimaud M, Starck J, Levy M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020; 10:69.

10. Royal College of Paediatrics and Child Health. Available in: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims.

11. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with coronavirus disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp.

12. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID 19 Scientific brief. Available en: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. 15 May 2020.

13. Golfred-Cato S, Bryant B, Leung J et al. COVID-19- Associated Multiystem Inflammatory syndrome in Children- United States, March-July 2020. Available in https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf.

14. Hoang A, Chroath K, Moreira A et al., COVID-19 in 7780 pediatric patients: A systematic review, E-Clinical Medicine (2020), https://doi.org/ 10.1016/j.eclinm.2020.100433.

15. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):33. Published 2020 Mar 27. doi:10.1038/s41392-020-0148-4.

16. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46 (Suppl. 1):10–67.

17. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46(5):854–87.

18. Jaume M, Yip MS, Cheung CY et al. Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent Fc. R pathway. Journal of virology. 2011;85(20):10582-97. 12.

19. Fernández-Sarmiento J, Salazar LM, Carcillo J. The endothelial glycocalyx: a fundamental determinant of vascular permeability in sepsis. Ped Crit Care 2020;21e:e291-e300.

20. Carcillo JA, Kernan KK, Horvat CM et al. Why and How Is Hyperferritinemic Sepsis Different from Sepsis Without Hyperferritinemia? Pediatr Crit Care Med. 2020;21(5):509-512. doi:10.1097/PCC.0000000000002285.

21. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, et al: The Hyperferritinemic syndrome: Macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013; 11:185.

22. Pérez-Toledo M, Faustini S, Jossi S et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Pediatric Inflammatory Multi-system syndrome. Institute of Immunology and Immunotherapy, University of Birmingham UK. Doi: hhtpps://doi.org/10.1101/2020.06.05.20123117. Online 07 June 2020.

23. Kam YW, Kien F, Roberts A. et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro. Vaccine. 2007;25(4):729-40.

24. Wang SF, Tseng SP, Yen CH et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochemical and biophysical research communications.* 2014;451(2):208-14.

25. Iba T, Levy JH, Connors JM et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360. Published 2020 Jun 18. doi:10.1186/s13054-020-03077-0.

26. Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology. 2020;132(5):1238–45.

27. Waltuch T, Gill P, Zinns LE et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department [published online ahead of print, 2020 May 8. Am J Emerg Med. 2020; S0735- 6757(20)30403-4. doi:10.1016/j.ajem.2020.05.058.

28. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020;395(10234):1417–8.

29. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis [published online ahead of print, 2020 Jun 10]. J Thromb Thrombolysis. 2020;1-10. doi:10.1007/s11239-020-02171-y.

30. Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. Semin Thromb Hemost. 2012;38(7):673-682. doi:10.1055/s-0032-1326782

31. Trivedi P, Cheeseman P, Mowat AP. Serum hyaluronic acid in healthy infants and children and its value as a marker of progressive hepatobiliary disease starting in infancy. Clin Chim Acta. 1993;215(1):29-39. doi:10.1016/0009-8981(93)90246-z.

32.Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020;309; 7077. doi: 10.1016/j.ijcard.2020.03.063.

33. Cheung E, Zachariah P, Gorelik M et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adlescents in New York City. JAMA. Published online June 8, 2020. Doi:10.1001/jama.2020.10374

34. Harwood R, Allin B, Jones C et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2020 Published Online September 18 doi.org/10.1016/S352-4642(20)30304-7

35. Davis AL, Carcillo JA, Aneja RK, et al. AmericanCollege of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017; 45(6):1061-93.

36. Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? Curr Open Infect Dis. 2009; 22(2):159-66.

37. Kohn Loncarica G, Fustiñana A, Jabornisky R. Recommendations for the management of pediatric septic shock in the first hour (part I). Arch Argent Pediatr 2019;117(1): e14-e23.

38. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 Infection: A Multi-institutional Study from New York City [published online ahead of print, 2020 Jun 14]. J Pediatr. 2020;S0022-3476(20)30747-239.

39. National Institute for Health and Care Excellence. Sepsis: Recognition, Diagnosis and Early Management. London, 2016;51. [Accessed on: June 27th, 2020]. Available at: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-manage- ment-pdf-1837508256709.

40. Ramcharan, T, Nolan, O, Lai C.Y. et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. *Pediatr Cardiol* (2020). https://doi.org/10.1007/s00246-020-02391-2.

41. Fernández-Sarmiento J, Carcillo JA, Salinas CM, et al. Effect of a sepsis educational intervention on hospital stay. Pediatr Crit Care Med. 2018;19: e321–e328.

42. American College of Rheumatology. Clinical Guidance for Pediatric Patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in covid-19. Available in https://www.rheumatology.org/announcements#PediatricClinicalGuidance. Jun3 17 2020.

43. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [Internet]. RECOVERY (Randomised Evaluation of COVID-19 Therapy) University of Oxford. 2020 [cited 2020 Jun 18]. Available from: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19.

44. Rajasekaran S, Kruse K, Kovey K, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/ sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. Pediatr Crit Care Med 2014;15(5):401–8.

45. Toubiana J, Poiralut C, Corsia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369m2094.

46. Pouletty M, Borocco C, Ouldali N et at. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dise 2020; 0:1-8.

47. Capone CA, Subramony A, Sweberg T et al. Characteristics, Cardiac involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection, The Journal of Pediatrics (2020), doi: https://doi.org/10.1016/ j.jpeds.2020.06.044.

48. Feldstein L.R, Rose E.B, Horwitz J.P et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020 June 29. Doi:10.1056/NEJMoa2021680.

49. Dufort E, Koumnas E, Chow E et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020 Jun 29. Doi:10.1056/NEJMoa2021756

50. Prata-Barbosa A, Lima-Setta F, Rodrigues dos Santos G et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. Jornal de Pediatria. 2020:96(5):582-592.

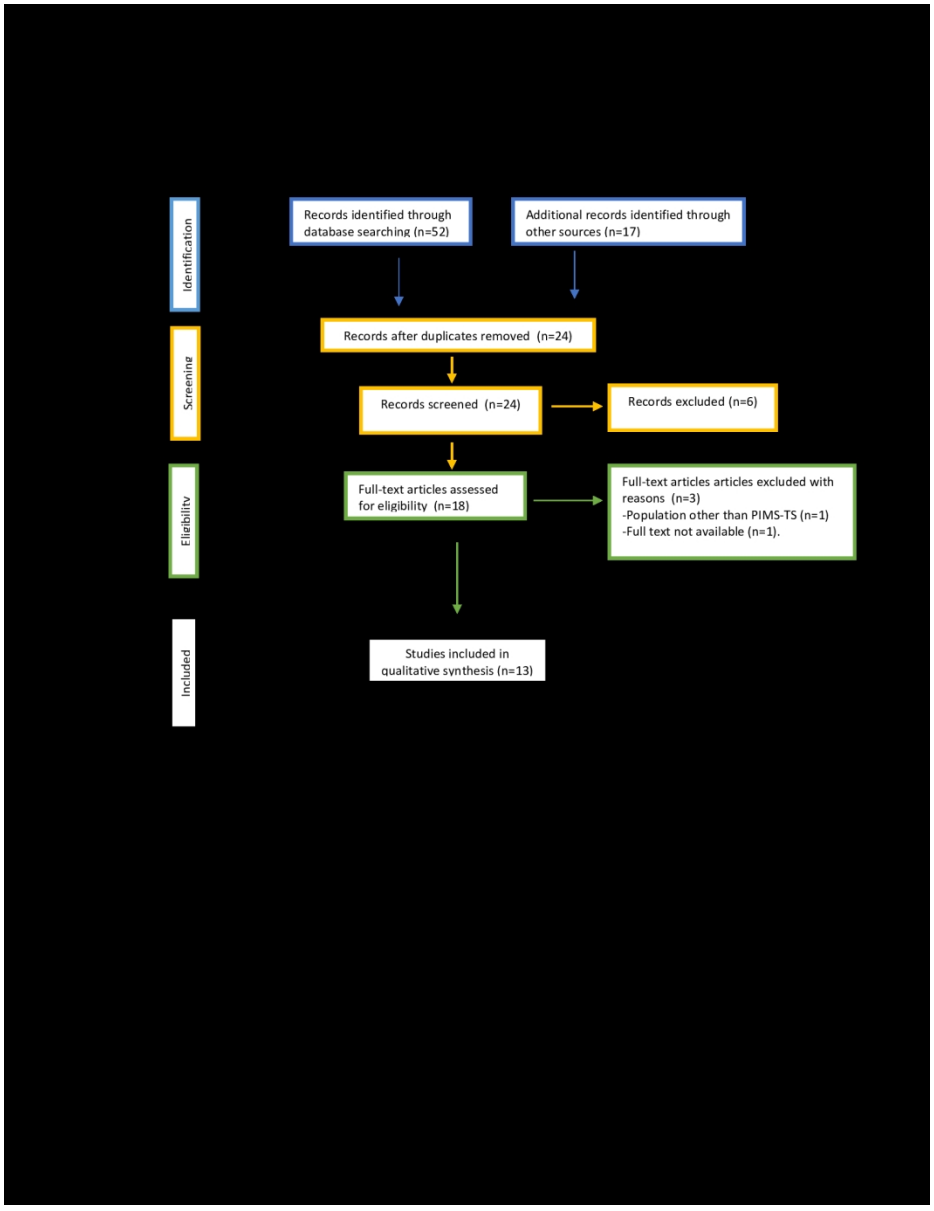
Figure 1. Selection process. We followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses

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% Diarrhea52%, Abdominal pain 53%, Rash 52% Conjunctivitis 45% Lymphadenopathy 16% Mucus membrane, changes/red cracked lips 29%Swollen hands and feet 16%, Respiratory symptons 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% Anakinra5% 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 (arrhytmia with refractory shock, died)	IVIG 8/8,Corticoids 5/58 Aspitin 3/8,Heparin 1/8, Antibiótics 8/8, Infliximab 1/8	1 died 6/8 alive PICU lenght 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 [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 sistems involved 4-5 61.6%
Kaushik et [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 envolvement 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, prophylasis 15%, Anticoagulation, therapeutic 81%Antibiotics > 48h 45% Vasopressor/inotrpes 51%	
Ramcharan et [40]	Fever 100% GI symptoms 87% Incomplete KD 53%	93% coronary artery abnormalities LVEF median on admission 51%	13% described typical COVOD-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 [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 craked 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% 2nd 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%

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

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