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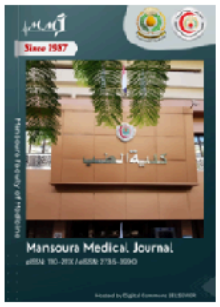

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Pediatric Inflammatory Multisystem Syndrome, temporally associated with SARS-CoV-2 (PIMS-TS)

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Pediatric Inflammatory Multisystem Syndrome, temporally associated with SARS-CoV-2(PIMS-TS)

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- PIMS-TS;
- COVID-19
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- Children
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Abstract

This essay will delve into the knowledge circling the new emerging disease after COVID-19 has spread over the whole world and it affects children for the most part. PIMS-TS symptoms overlapped with Kawasaki Disease (KD) which is hyperinflammatory and multiorgan involvement. PIMS-TS incidence is unknown as of date. Albeit little is known about this disease, reports had shown that this disease is prevalent in the region where KD is not a familiar disease while regions that are famous with KD reported no case of PIMS-TS. While some symptoms overlapped with KD, the difference now is PIMS-TS affect the child of all ages and have a quick and more severe progression of symptoms. Multiorgan involvement such as cardiac, renal, respiratory, haematology, gastrointestinal, neurology, and dermatology coincide with hyperinflammation shows that this disease needs to be attended under emergency cases. To treat PIMS-TS, many experts have shown the steps to manage it by using the culmination of previous KD treatment, the experience of adult COVID-19 treatment, and other types of paediatric hyperinflammatory treatment. Also to prevent other complications that accompany the syndrome needs to be addressed with supplementary therapy and follow-up is a compulsory as the syndrome is newly discovered.

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INTRODUCTION

Since the first case of COVID-19 in Wuhan, China, it has led to a severe pandemic with a worldwide death count of more than 200,000[1]. On the 7th of April 2020, a case report has been published online with the claim of a 6-month-old pediatric patient present with a complete Kawasaki disease (KD) manifestation and potentially linked to COVID-19[2]. In mid-April, 2020, for 10 days, reports in an increasing number of cases of older school-aged children and adolescents presenting with prolonged fever, shock, abdominal pain, and cardiac dysfunction that overlapped with KD after SARS-CoV-2 infections, manifesting as a hyperinflammatory syndrome and multiorgan involvement[3].

Since then, this condition is called Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C). Although the syndrome is still not well defined, the knowledge of the syndrome is evolving rapidly. With the similarities with KD features, some children also exhibit myogenic with cardiogenic shock and features of toxic shock syndrome. The Centre for Disease Control (CDC) has issued an emergency alert[4], as clinical reports have been published recently from United States (US)[5], Italy[6], United Kingdom (UK)[3], France, and Switzerland[7].

Definition criteria for PIMS-TS according to :

1. Royal College of Paediatrics and Child Health :

- A child presenting with inflammation (neutrophilia, elevated C-reactive protein (CRP) and lymphopenia), persistent fever and findings 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[22].
- With exception of any other disease cause by microbes, such as staphylococcal or streptococcal shock syndromes, bacterial sepsis, infections related to myocarditis, such as enterovirus[22].

2. CDC :

- Any individual <21 years old, presenting with fever (≥38.0℃ for ≥24 hours), evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurological), and laboratory evidence of inflammation; **AND**
- No alternative plausible diagnosis[4]; **AND**
- 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[4].

3. WHO :

- Children and adolescents aged ≤19 years old with persistent fever ≥3 days[36]
- **AND** two of the following :
  a) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)[36].
  b) Hypotension or shock[36].
  c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)[36],
  d) Evidence of coagulopathy (by PT, PTT, elevated d-Dimers)[36].
  e) Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)[36].
- **AND** elevation of inflammation markers (ESR, CRP or procalcitonin)[36].
- **AND** no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes[36].
- **AND** evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19[36].

As the knowledge of PIMS-TS is still evolving, we have to know enough data to find a solution for preventing these cases from progressing beyond repair as this involves the futures of children around the world.

Aim of the work

This essay aims to highlight the updates in epidemiology, clinical presentation, and management of PIMS-TS.

Epidemiology

The rate of COVID-19 infection in children appears to lesser but about a total of 230 suspected cases of PIMS-TS have been reported in the UK and European Union (EU) with 2 deaths from UK and France, respectively[8]. An association between SARS-CoV-2 and the new-found multisystem inflammation seems plausible albeit there is no established connection yet as to date[8]. Its incidence is yet unknown[9].

Meanwhile, between 1st March and 17th May 2020, France had launched nationwide surveillance to investigate the temporal relationship between SARS-CoV-2 and PIMS, with the result of 95 out of 156 cases of KD manifestation were confirmed or probable post-COVID cases and the peak incidence of KD manifestation happened 4-5 weeks after the peak of COVID-19 in the country[10]. The number of children admitted to intensive care unit in the UK fulfilling the Royal College of Paediatric and Child Health (RCPCH) case definition of PIMS-TS in 40 days between April and May increase by 11-fold higher than the normal historical trends of paediatric inflammatory conditions after the peak of COVID-19 cases in the UK[11].

In Bergamo, Italy, reports from clinicians of an increase by 30 fold of KD manifestation during the first six weeks after the arrival of COVID-19[6]. The cases of Paris and Bergamo have a similar severe clinical profile and these cases are different from the typical KD profile observed during the surge of the H1N1 swine flu epidemic at Paris in 2009[12]. Interestingly, there is no report regarding the surge of KD or PIMS-TS in Asia. Based on paediatric data from the original outbreak in Wuhan, China, most of the children only show mild course of sickness[13]. The same can be said with paediatric patients in Singapore[14] and South Korea[15]. Although there are a lot of assumptions behind the reason for this difference between Western and Asian, the main basis remains cloudy.

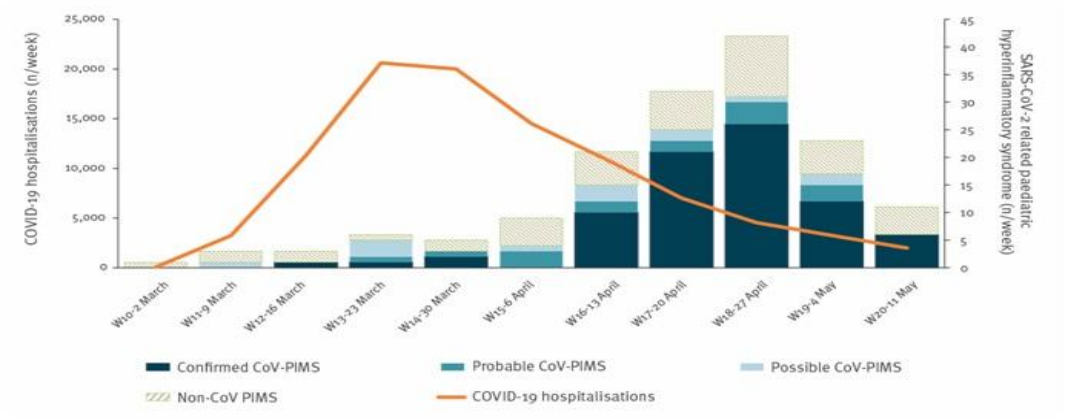

Figure 1 : Temporal distribution of COVID-19 hospitalisations and SARS-CoV2 hyperinflammatory paediatric cases, France, 2 March–17 May (n = 108)[10]

The median age of onset is between 7 to 10 years rather than 2 years for KD that affects children under 5 fundamentally[16]. Across the studies of PIMS-TS, male patients are more prone to be affected which similar case with KD with male to female ratio of 1.5 to 1[16]. Large numbers of the affected patients have no underlying health problems such as autoimmune disorders but a few patients with pre-existing cardiovascular disease or congenital heart disease have been affected[17].

France and UK have release reports that pointing towards a higher risk for children from Afro-Caribbean descent due to a genetic predisposition[18]. Referring to reports from Europe and the US, PIMS-TS affects more children of African, Afro-Caribbean, and Hispanic descent meanwhile KD affects children from East Asian and Pacific Islander ancestry[19].

Characteristics of PIMS-TS

The patient shows the manifestation of fever, extreme inflammation, abdominal symptom, rash, and conjunctivitis[20], but the onset is suggested to be delayed following the primary infection[18]. The inflammation level found in affected children is much more severe

than COVID-19[20]. Research has shown that this disease affects the whole paediatric age groups, from infancy to adolescence[21], despite may having the same diagnostic criteria as KD[22]. Affected children show a negative virus test through reverse transcript polymerase chain reaction (RT-PCR) despite having developed the antibodies to SARS-CoV-2[20].

There is quite a lot of cardiac involvement[16]. Reports of children with positive COVID-19 infection show acute myocarditis on admission to the hospital due to shock[23]. The manifestation of left ventricular dysfunction with ventricular ejection fraction of 60% or less was found among the children reported[24]. Laboratory finding is cytokine storm also reported including high serum interleukin-6 (IL-6) levels and requiring the support of inotropic to increase cardiac output[25]. Coronary artery dilatation or aneurysm appeared in some patients[26].

Although respiratory symptoms are predominant in COVID-19 cases, it is reported far less in the case of PIMS-TS[16]. Respiratory problems such as dyspnea mostly connected to shock[8].

To differentiate from KD, PIMS-TS common presentation includes also vomiting, abdominal pain, diarrhoea, and rash[20]. The unusual presentation that does not point toward KD is also presented in PIMS-TS such as gastrointestinal symptoms and neurological involvement (severe headache and altered mental status)[8]. However, symptoms of KD like lymphadenopathy, mucocutaneous finding (cracked lips, strawberry tongue, and rash), conjunctivitis, and oedema of hands/feet[8]. Also frequently found in affected children is muscle pain and fatigue[20]. Neck and chest pain also possible to present themselves[27]. Notably, some patients require continual intensive care admission due to hypotension and shock either from systemic hyperinflammation/vasodilation or myocardial involvement[17].

Evidence of hyperinflammation constantly appears from reports. Biological markers such as IL6, procalcitonin (PCT), C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin is exceeded normal levels tremendously[17]. Abnormal haematological findings show that there is thrombocytopenia[21], leukocytosis, lymphopenia, neutrophilia with immature forms of neutrophils, normal or reduced count of red blood cells, meanwhile from the coagulation profile, increase in fibrinogen and D-dimer is emphasized[17]. Another suggestive symptom of hyperinflammation that can be found is effusions of pericardial, pleura and peritoneal, hypoalbuminemia, hyponatremia, and acute kidney injury[28].

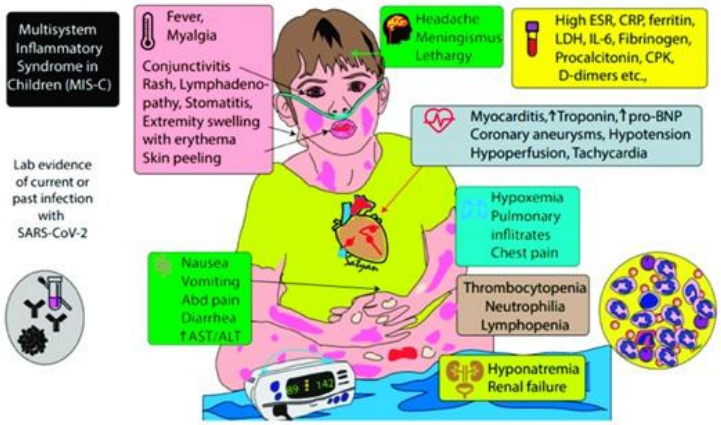

Figure 2 Infographic showing CDC criteria for the diagnosis of PIMS-TS. A combination of fever, evidence of inflammation, involvement of at least two organ systems, and prior evidence of SARS-CoV-2 infection are required to establish the diagnosis.[28]

Management of PIMS-TS

The target of management is to reduce the inflammation and restore organ function. These actions can reduce the chance of long-term damage such as progression towards cerebral amyloid angiopathy (CAA) or chronic cardiac dysfunction[28].

On account of the insufficient amount of knowledge and a little number of reported case to date, the treatment for PIMS-TS is established on experts' opinion, previous KD treatment deduction, other paediatric systemic inflammatory disorders, and adult experience of COVID-19[17]. As different children will show different presentations and clinical courses, it is important to be wary of it and the therapy must be adapted to each case individually with the consultation from a specialist[29]. A variety of approaches has come up since the first case reported, for example, the RCPCH[22], the UK[30], the National Institutes of Health[31], the American College of Rheumatology[8], and the American Academy of Pediatrics[32].

Management strategies seem to revolve around the treatment of inflammation, shock, and thromboprophylaxis[33]. Most of the patients received immunomodulatory treatment of intravenous immunoglobulin (IVIG)[33] as IVIG is the central component for KD treatment[34]. The use of steroids, mostly methylprednisolone also has been seen in the majority of the reports[33]. IVIG received the best response in therapy with positive correction of the vital signs and cardiac dysfunction[29].

Recommended doses of immunomodulatory treatment is 2 g/kg IVIG and 20-25 mg/kg/dose every 6 hour (80-100 mg/kg/day) for every patients presenting with KD-like illness, evidence of excessive inflammation (ferritin >700 ng/mL, CRP >300 g/dL, or multisystem organ failure), or any cardiac involvement[29].

For a successful and beneficial outcome, it is proven that early recognition of shock state, proper and cautious fluid resuscitation, early initiation of invasive monitoring, intubation

and mechanical ventilation, optimization of oxygen delivery (DO_2), minimization of oxygen consumption (VO_2), and appropriate delivery of inotropes and vasopressors is the key factors[29]. Patients should always be reassessed during fluid resuscitation of any evidence of fluid overload as there is a high possibility of underlying cardiac dysfunction[29].

If the first-line treatment has no response, supplementary medication in terms of cytokine blockers such as IL-6 inhibitors (tocilizumab), tumor-necrosis-factor (TNF)-α inhibitors (anakinra, infliximab) is used[17]. In the special case of KD-like presentations or positive evidence of coronary involvement, antiplatelet treatment with aspirin is regularly used[17]. Vasoactive substance and inotropic is often used in case of hypotension or cardiac involvement[35]. Anticoagulation treatment in conjunction with antiplatelet also was recommended as there is a risk of thrombotic complications due to multiple causes[17].

Due to limited knowledge of this disease, follow up is a must, to understand the progression and prognosis of PIMS -TS[17].

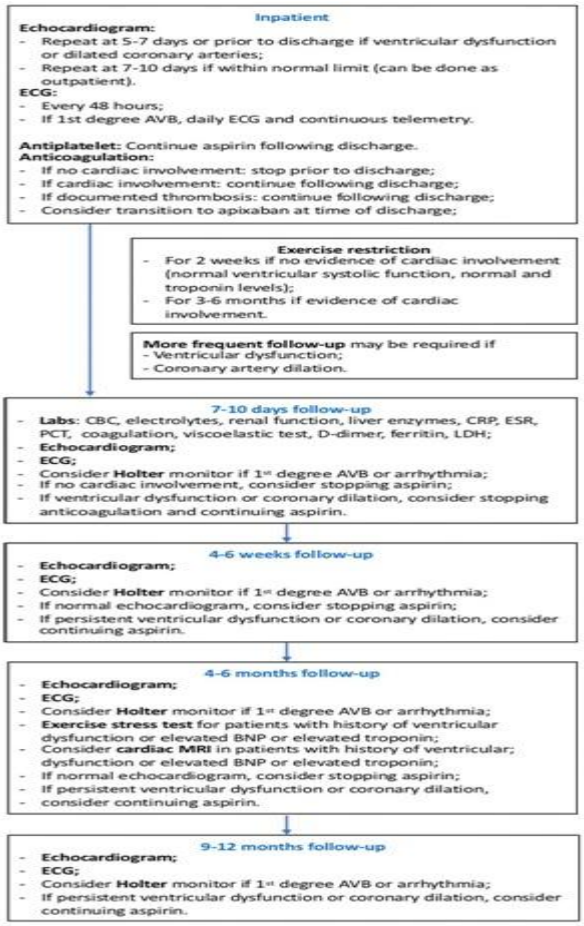

Figure 3 Suggested outpatient follow-up of patients with MIS-C. AVB atrioventricular block, ECG electrocardiogram, CBC complete blood count, CRP C-reactive protein, ESR erythrocyte sedimentation rate, MRI magnetic resonance imaging, PCT procalcitonin, LDH lactic dehydrogenase[17].

Summary and Conclusion

In conclusion, the incidence of PIMS-TS is still inconclusive. Although we can see that the cases increase after the peak of incidence in COVID-19 infection, the real mechanism is still undiscovered, only hypothesis has been shown. With the symptoms mimicking KD, many thoughts of KD in the first place but with other paediatric inflammatory conditions present like toxic shock syndrome and difference in age of incidence, KD has been out listed from the probable cause of PIMS-TS. Despite that, with the clinical appearance of KD and other inflammatory syndrome, we can at least summarize the affected systems and prepare the best treatment to prevent it from progressing further and a plan for follow up is compulsory for all patients.

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