Post COVID-19 paediatric inflammatory syndrome (PIMS-TS/MIS-C): what have we learned?

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Abstract

During the early phase of the COVID-19 pandemic, PIMS-TS emerged as a new hyper-inflammatory disorder affecting children. These children were often unstable requiring admission to critical care. Children with PIMS-TS displayed symptoms mimicking other inflammatory processes but it was quickly apparent this was a novel condition requiring its own treatment regime. Through international co-operative resource sharing, agreement grew over several treatment options including biological agents, IVIG and steroids leading to consensus guidance based on anecdotal and limited observed data. As our understanding of COVID-19 grew with each wave of the pandemic, so has our understanding of PIMS-TS. Several large trials, including the RECOVERY and BATS trials, are now able to provide an evidence base for the treatment of this condition, and challenge some of the management practices that were widely utilized. IV Immunoglobulin, for example, has been shown not to change outcomes and would therefore no longer be recommended for treatment, whereas methylprednisolone did show some improvements over usual supportive care. Epidemiology data shows PIMS-TS to have been a temporally limited condition, reducing in prevalence with each variant of COVID-19. Looking at overall outcome data, this was thankfully a condition with overall very low mortality and limited long term morbidity.

Keywords Hyper-inflammation; MIS-C; PIMS-TS

Introduction

First identified in April 2020, during the first wave of the COVID-19 pandemic caused by SARS-COV-2, a number of children started to present to paediatric intensive care units (PICUs). These children presented with some symptoms similar to Kawasaki Disease (fever, rash, lymphadenopathy), but also with marked increased rates of myocardial dysfunction and shock.[1,2] Though initially thought to be a Kawasaki mimic, it quickly became apparent that this was a separate hyper-inflammatory disease process. The new disease process had several names including Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV2 (PIMS-TS, named by the UK Royal College of Paediatrics and Child Health (RCPCH)), Multisystem Inflammatory Syndrome in Children (MIS-C, named by the US Centre for Disease Control (CDC)) and Multisystem Inflammatory Disorder in Children and Adolescents (named by the World Health Organization (WHO)). Although it was initially identified in the UK, it quickly became apparent that this was a worldwide phenomenon.[3,4]

Over the last 4 years, a growing amount of data has been published about these cases, with several high-profile studies looking at treatment options. Some studies have also started to demonstrate the long-term implications of these conditions. As our knowledge about this condition has increased, we have also witnessed a dramatic decline in the prevalence of new cases of PIMS-TS. For those of us who witnessed and were involved in those early cases, we now have an opportunity for reflection on our practice.

Case definitions

Three different case definitions emerged — the RCPCH published its criteria for PIMS-TS,[5] the CDC publishing its definition of MIS-C (Multisystem Inflammatory syndrome in Children) a few weeks later[6] - this has since been updated in 2023 to the revised definition.[7] The WHO following with its definition of Multisystem Inflammatory Disorder in Children and Adolescents.[8] All three case definitions continue to overlap but no international unifying diagnostic criteria has emerged. As a result, any search for papers on these conditions continues to require searching for both PIMS-TS and MIS-C — a challenge when PubMed lists 1923 results for PIMS-TS and 2120 results for MIS-C as of October 2024. See Table 1.

Epidemiology

When PIMS-TS first emerged, the COVID-19 pandemic was spreading rapidly and was able to be characterized into distinct waves of infection corresponding to different variants of the virus — i.e. SARS-COV-2, alpha, delta and omicron.[9] Live tracking data through the CDC[10] (Figure 1) was able to identify that following each peak of COVID-19 infection, there was a spike of cases of MIS-C, supporting the temporal association between the two. However, the same USA live data shows that whilst COVID-19 cases have continued, there has been a marked drop in the prevalence of new cases of MIS-C since the end of 2022.

Several factors have been proposed as to the reduced prevalence seen in MIS-C (and PIMS-TS) over time. First are the extensive vaccination programs undertaken by many world countries. For example, the UK started its vaccination program in December 2020 and by August 2022, greater than 70% of adults and children aged 12 years and older had received three or more COVID vaccines.[11] With more adults and older children vaccinated, the likelihood of both new and severe COVID-19 infections reduces due to herd immunity. One Danish study undertaken during the delta wave suggested a reduction in cases of PIMS-TS due to vaccination.[12] Though a small study, it adds to similar results from both French and US studies.[13,14]

There are also data to support ongoing reductions in cases of PIMS-TS with each wave/COVID-19 variant. One team had

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Comparison of updated CDC criteria for MIS-C against the criteria for PIMS-TS as per the RCPCH and Multisystem inflammatory syndrome in children and adolescents with COVID-19 as per the WHO

	PIMS-TS	MIS-C (CDC 2023)	WHO
Age	Child (RCPCH defines as <18 yrs)	<21 yrs	0—19 yrs
Fever	Persistent ≥38.5 °C	≥38°C	Fever ≥3 days
Clinical features	Single **or** multi-organ dysfunction (e.g. Shock, cardiac, respiratory, renal, neurological) **With** additional features (e.g. Abdominal pain, confusion, cough, conjunctivitis, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting)	Clinical severity requiring hospitalization or resulting in death **AND** **≥ two** of **(a)** cardiac involvement (left ventricular ejection <55%, coronary artery dilatation or aneurysm, elevated troponin) **(b)** mucocutaneous involvement **(c)** shock **(d)** gastrointestinal involvement **(e)** haematologic involvement (decreased platelets <150,000 cells/μL or lymphocytes <1,000 cells/μL)	**≥ two** of **(a)** Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs **(b)** Hypotension or shock **(c)** Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities **(d)** Evidence of coagulopathy **(e)** Acute gastrointestinal problems
Laboratory	Inflammation (e.g. Elevated neutrophils, CRP, ferritin or decreased lymphocytes)	Evidence of systemic inflammation indicated by C-reactive protein ≥3.0 mg/dL	Inflammation (e.g. Elevated ESR, CRP or Procalcitonin)
COVID-19	SARS-CoV-2 PCR testing may be positive or negative		Evidence of COVID-19 (PCR, antigen or serology +ve) or likely contact with COVID-19 patient
Exclusion	Any other microbial cause	A more likely alternative diagnosis	Other obvious microbial cause of inflammation

Table 1

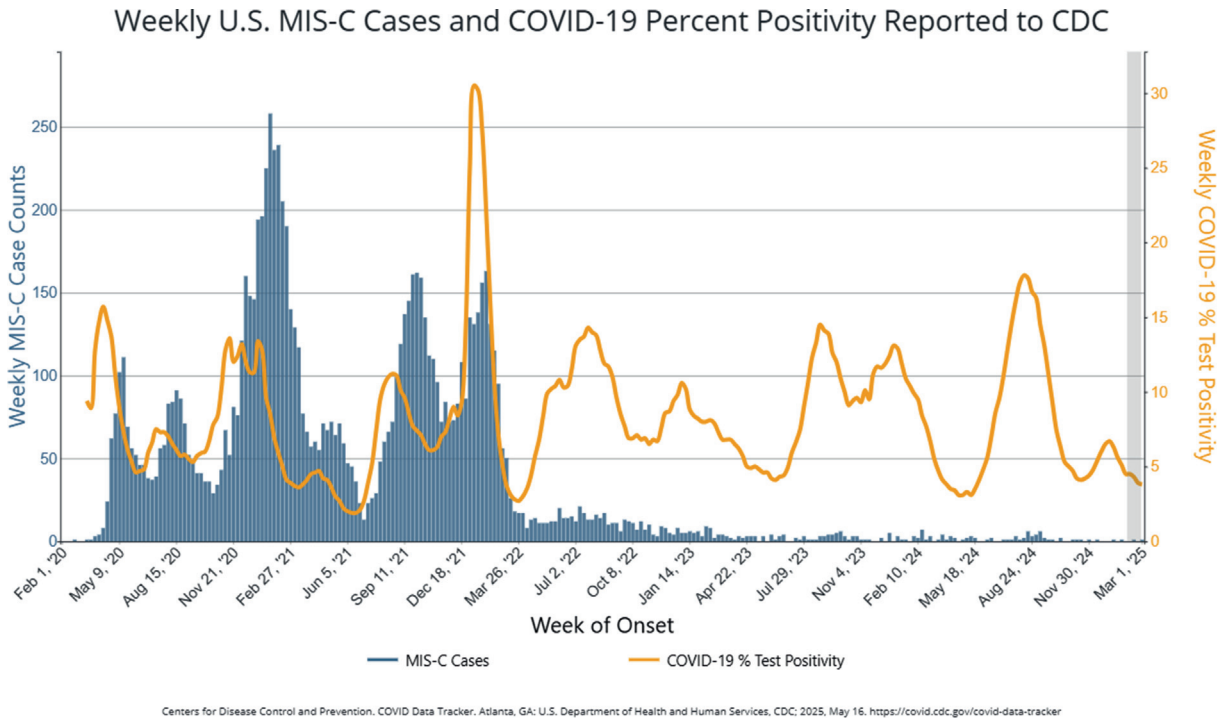

Figure 1 Live tracking data from CDC comparing confirmed COVID cases to cases meeting criteria for MIS-C until April 2025.

developed a prospective monitoring model based around the initial SAR-CoV-2 variant and adjusted following the alpha wave.[15] This model initially correlated well with observed new cases of PIMS-TS through the alpha and delta waves but showed significant divergence with the arrival of omicron (Figure 2). Their team proposed that the newer variants have a reduced risk of causing PIMS-TS than previous variants, a position that is supported by observed data in other studies.[16]

Treatment

During the initial phase of PIMS-TS cases, there were a variety of different treatments used in the management of PIMS-TS cases. These included steroids, IV immunoglobulin and biological immune modulating agents. Of these biological agents, the most commonly reported in literature were anakinra (a recombinant version of the human interlukin 1 receptor antagonist protein), tocilizumab (a monoclonal antibody that blocks the interleukin -6 receptor) and infliximab (a monoclonal antibody that blocks the effects of tumour necrosis factor alpha).

The early consensus treatment recommendations recommended the use of all three of these treatment options (steroids, IVIG and immune modulation), often in combination for children meeting criteria for PIMS-TS.[17] Some early studies had suggested limited short-term improvements in biochemical markers with these treatments compared to the usual standards of care.[18] However, larger studies including the UK RECOVERY study[19] have shown some differences.

The RECOVERY trial was a national randomized control platform trial run in the UK in 2020–2022 looking at treatment options for COVID-19 with a trial arm focused on paediatric patients with PIMS-TS. This arm randomized 214 children meeting diagnostic criteria 1:1:1 into one of three arms – usual care, usual care + methylprednisolone and usual care + IVIG. These arms matched with the consensus treatment algorithms at the time.

Children aged greater than 1 yr with ongoing fever and inflammatory response were eligible for a second randomization, comparing tocilizumab, anakinra and usual care (randomized 2:2:1). The outcome of the trial showed that compared to usual care, there was moderate evidence that methylprednisolone reduced length of hospital stay, but that there was no difference between IVIG and usual care. The study also showed that in children requiring an additional agent, tocilizumab demonstrated a reduction in length of hospital stay but with an observed increased need for inotropic support. Anakinra demonstrated no difference compared to standard care.

Though the study was relatively small in terms of numbers recruited, it remains one of the largest randomized control studies of children with PIMS-TS.

Another study of note was BATS - Best Available Treatment Study.[20] This was an international observational cohort study looking at IVIG and steroids treatment in children managed for MIS-C, with the primary outcomes being the need for inotropic or ventilation support, or death. This study compiled outcome data of 614 children divided mostly into three groups – those receiving IVIG alone, those receiving IVIG + steroids and those receiving only steroid therapy. There was a smaller group who received neither steroids nor IVIG. The overall outcome did not demonstrate any clear benefit of IVIG or steroids. However, the author team noted that when they analysed the smaller group who met the WHO criteria (similar to PIMS-TS), there was moderate evidence favouring steroids over IVIG with fewer children requiring respiratory support.

It would therefore seem prudent to suggest that children meeting criteria for PIMS-TS should be managed with methylprednisolone as a first line agent. If the child still has fevers or elevated biochemical evidence of inflammation, tocilizumab should be used as a second line agent provided the child is being managed in a PICU setting.

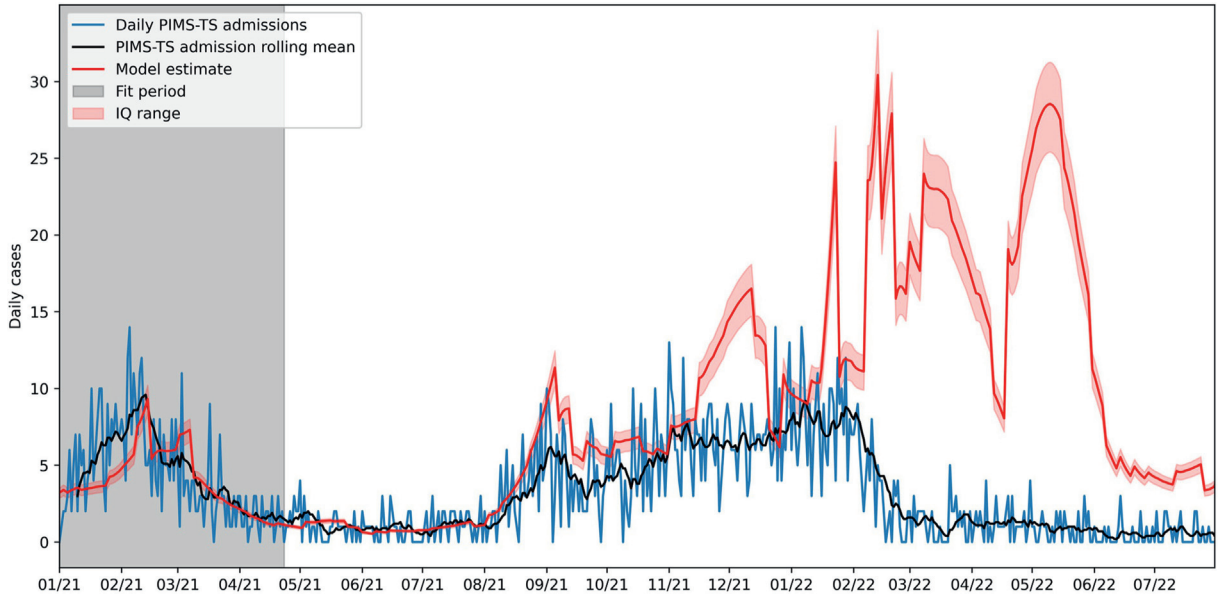

Figure 2 Forecasted PIMS-TS admissions based on a model fitted to the Alpha variant wave of COVID-19, alongside observed PIMS-TS admissions. Reproduced from reference 15 with permission from Elsevier.

The other supportive therapy used in children meeting criteria for PIMS-TS in the use of prophylactic anticoagulation, with the most common reported agents being low molecular weight heparin or IV unfractionated heparin infusion.[17,21] This seems prudent given that there is some evidence of increased risk of thrombotic microangiopathy (TMA) in children with COVID/PIMS-TS[22] similar to the increased risk seen in adults. The use of anticoagulation may be due to the perceived risk of thrombosis in children who present with myocardial dysfunction, which can often be seen in children with PIMS-TS.[1,2] However, this risk does not appear to be supported by evidence, with reported rates of thrombosis in children with PIMS-TS being low.[23,24] Given the potential risk of bleeding, the need for anticoagulation seems limited, however there may still be a role for children who are found to have evidence of coronary artery inflammation or dilatation.

Outcomes

With the early recognition of symptoms of PIMS-TS overlapping with Kawasaki Disease (KD), and with some cases of PIMS-TS developing coronary artery inflammation,[1,2,25] there was an early focus on the cardiac outcomes and follow-up of these children. Traditionally it was felt that in Kawasaki disease, up to 30% of untreated children[26] developed coronary artery aneurysms, remaining as high as 19% of children with Kawasaki Disease despite treatment with IVIG.[27] The rates seen in children with PIMS-TS were lower, with studies reporting 14–15% of cases showing coronary artery involvement.[4,28] Recent prospective studies have shown that 3–6% of children presenting with PIMS-TS were found to have persisting coronary artery abnormalities at follow-up.[29,30] This compares to approximately 4% of children with Kawasaki Disease[31] but seemingly without the risk of developing giant aneurysms that exists with KD.

Recently published data from Ireland and Germany[32,33] suggests that coronary artery involvement in PIMS-TS was more common in younger children. The German data[33] also notes a reduction in incidence of coronary involvement with each significant variant of COVID-19. They describe the incidence of coronary artery aneurysm decreasing from 9.8% during the first wave, to 2.0% during the omicron wave.

Left ventricular dysfunction was a common finding on echocardiogram in children with PIMS-TS, present in up to 34% of cases,[28] this did not result in long term complications with studies reporting full resolution of left ventricular function on follow-up.[25,29,30,34]

Overall mortality for PIMS-TS was very low, estimated at less than 1% of children presenting with PIMS-TS.[35–37] However, some studies have shown that children can experience some lasting symptoms. One UK study[38] found that 45% of children had an impaired 6-minute walk test score at 6-month follow-up, and a USA study[39] found that 20% of children continued to report fatigue at 6 months and 40% feeling below their pre-pandemic physical capability. Other studies[39–41] have demonstrated symptoms including brain fog, headache, sleep disturbance and mood change continuing for up to a year post PIMS-TS.

Though the initial focus of follow-up following PIMS-TS was based around cardiac surveillance, these studies showing a wider impact on the children affected highlight that the ongoing effects following PIMS-TS need greater thought and study.

PIMS-TS has also taught us about flexibility and international collaboration. After identification of this new disease, international webinars sharing expertise and experience were rapidly organized, using the (at the time) novel adoption of video meeting platforms. Although this had great strengths, it also tended to coalesce thoughts and treatment strategies, meaning an extremely rapid emergence of a standard: a set of blood tests (difficult to interpret as they are not standard in similar conditions), then treatment with IVIG, anticoagulants, and steroids. None of this had any evidence base, and well-meaning studies attempting to break through this dogma at time struggled to achieve clinician equipoise.

There are very many positives we can take from how well we shared this experience, but we must also be humble to understand that true progress comes from understanding how much we do not know and being open to have this challenged.

Conclusion

As we look back on the COVID-19 pandemic, PIMS-TS was a rapidly emergent, novel condition with an initial high incidence of cardiovascular compromise requiring hospitalization and often intensive care support. Inter-organizational co-operation and communication lead to rapid convergence in management of the condition, and also a rapid expansion of observational studies.

Many support strategies were utilized due to concerns derived from the experience of other similar conditions. However, as the understanding of PIMS-TS has expanded, and the evidence behind these treatments has increased, we are now able to reflect and evaluate these support strategies. The use of immunoglobulin, though commonplace, is now not supported by outcome data and considering its limited supply would no longer be recommended.

Thankfully, PIMS-TS has turned out to have a very low mortality and currently seems to have only mild ongoing comorbidity. It seems that regardless of presenting severity and treatment strategy used, almost all children made a full physical recovery. The changes seen in coronary arteries, however, will continue to need follow-up to determine if any long term increased cardiovascular risk exists, like that seen in Kawasaki Disease. It is also fortunate that the incidence of cases, and burden of disease for each case, has decreased with each major COVID-19 variant. This in some way mimics the decrease in rates of hospitalization due to COVID-19 that has been seen over the last couple of years. ◆

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