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SARS-CoV-2 paediatric inflammatory syndrome

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Abstract

The novel post SARS-COV2 Paediatric Inflammatory Syndrome, first recognized in April 2020, took worldwide clinicians by surprise. There rapidly followed a plethora of case definitions, nomenclatures, descriptive papers, and guidelines on treatment. There has been controversy around this condition. Is it really new? Is it an atypical form of a known disease? How should we communicate and report such cases? What is the pathogenesis? Which treatments are given, and which are effective? What are the short and long-term outcomes? We are all learning fast. The clinical and immunological patterns seen are unique. There are significant differences in both presentation and pathogenesis to any known condition, including Kawasaki's disease. This implies that treatments are not necessarily transferrable: and indeed it is unknown which treatments are effective at all. Outcomes, as far as are known, are good, but long term data is lacking. The international cooperation has been an example of how today's connected medicine can be a force for good, however calm assessment of evidence remains necessary to ensure the best outcomes for our patients. This short article identifies what we have learnt from the first surge of COVID-19 cases about paediatric inflammatory syndrome and how it affects children.

Keywords COVID-19; MIS-C; multisystem inflammatory syndrome; PIMS-TS; SARS-CoV-2

Introduction

At the end of April 2020, during the Covid-19 pandemic, clinicians in the UK noted a cluster of unusual cases. Children, usually teenagers, were presenting with complex multisystem inflammatory presentations. Some were extremely sick, needing intensive care, with some deaths.

In this connected world, clinicians were able to share experiences. Local clusters of illnesses are common: anyone with hospital experience knows of weeks and indeed days where the same illnesses seem to occur. However, it rapidly became clear that this was not an isolated cluster, rather a nationwide (then worldwide) increase in these cases.

Nowadays, we are not used to new diseases in medicine. When faced with a puzzling presentation, we look at prior experience and ask more experienced colleagues. Clinicians were

suddenly faced with an illness which was totally new, and where the case definition, treatment, and outcomes were unknown. For those involved, this was simultaneously exciting, baffling, and frightening.

Case definitions

For any illness to be defined, it needs a clear definition. The first group to publish a case definition was the Royal College of Paediatrics and Child Health (RCPCH)¹ on the 1st May, closely followed by the US Centre of Disease Control (CDC)² on the 14th May, the World Health Organisation on the 15th May,³ with the British and Canadian national paediatric surveillance programmes gathering data (albeit purposefully aiming at a wider group of cases) with their own definitions.^{4,5} Each of these definitions was subtly different.⁶

There are currently three main names for this syndrome: the RCPCH's Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV2 (PIMS-TS), the CDC's Multisystem Inflammatory Syndrome in Children (MIS-C), and the WHO's Multisystem Inflammatory Disorder In Children And Adolescents (without a recognized initialism). The PIMS-TS vs MIS-C debate continues: as of the end of October 2020 PubMed listed 125 papers on searching for MIS-C and 73 for PIMS-TS. Unfortunately, this situation can only create confusion, and clinicians need to be aware that any literature searches need to use both names to ensure complete coverage of the literature. For the purposes of this review, we will use PIMS-TS, for reasons of primacy.

Most of the differences in the definitions are minor, based on interpretations of levels of the inflammatory response required. However, the main difference is whether proof, or strong suspicion, of SARS-CoV2 infection is needed. The RCPCH and British and Canadian surveillance programmes do not need such evidence, however the CDC and WHO's definitions require "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", and "Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19" respectively. The RCPCH definition, where the name of the condition includes "Temporally associated with SARS-CoV2", implies that this definition only holds during the pandemic, but does not need firm evidence of infection or contact. The interpretation of the CDC's "exposure within 4 weeks", and the WHO's "likely contact with patients with COVID-19" are open to much subjectivity. It may be argued that during a pandemic, the likelihood of exposure to SARS-CoV2 is high, therefore any case meeting the other criteria can potentially be included. Although the CDC's and WHO's definitions are more scientifically correct, it may merely move the point of in clarity. Mandating proof of past exposure is difficult when this proof is not always available, either for resource or immunological reasons.

The other "diagnostic" criteria are rather broad. They can be summarized as a child who presents with fever, laboratory evidence of inflammation, organ involvement, and no other diagnosis found. Most patients with the relatively common "culture negative sepsis" would meet this definition, and many patients with Kawasaki's syndrome, Toxic Shock syndrome, or

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Haemophagocytic Lympho- Histiocytosis would also be included. The overlap between these conditions makes true identification of this syndrome difficult.

Clinically, these patients often presented with abdominal symptoms, including vomiting, abdominal pain, and diarrhoea. Some patients underwent laparotomies for suspected appendicitis, which were all ultimately negative. Abdominal symptoms at presentation were seen in 90% of intensive care patients admitted in the UK.⁷ A rash is less common (45%), and conjunctivitis even less so (29%).

Is this syndrome really new?

The first published report of this condition described “Hyper-inflammatory shock in children during COVID-19 pandemic”.⁸ Soon after this, however, the condition was described as “severe Kawasaki-like disease”.⁹ The clinical overlap with Kawasaki’s disease, and the even less well defined “incomplete Kawasaki’s disease” has led many to diagnose, and treat this as Kawasaki’s disease.

There are, however, many differences between the presentation of Kawasaki’s disease patients and PIMS-TS patients. PIMS-TS patients are older (9 [5.7–14] vs 2.7 [1.4–4.7] years), have a higher Neutrophil count (13 [10–19] vs 7.2 [5.1–9.9] $\times 10^9/L$), have a lower lymphocyte count (0.8 [0.5–1.5] vs 2.8 [1.5–4.4] $\times 10^9/L$), have lower platelet counts (151 [104–210] vs 365 [288–462] $\times 10^9/L$), and higher C-reactive proteins (229 [156–338] vs 67 [40–150] mg/L).¹⁰ Clinically, although the presentation of PIMS-TS does share some features of Kawasaki’s disease, cervical lymphadenopathy and oral mucosal changes were not seen, with conjunctival injection and peripheral extremity changes uncommon.

The diagnosis of atypical Kawasaki’s is broad. Generally, children suspected of having KD who do not fulfil diagnostic criteria (i.e. have fever ≥ 5 days but less than four signs of mucocutaneous inflammation) can be considered to have incomplete or atypical KD.¹¹ The CDC however defines “Patients whose illness does not meet KD case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete KD”.¹² In that PIMS-TS can involve the coronary arteries, this rather broad definition would indeed fit: however, it seems biologically plausible that there may be more reasons for acquired coronary artery aneurysm than Kawasaki’s disease.

It is clear that there was a surge in cases compared to historical expectations. The UK Paediatric Intensive care experience of PIMS-TS showed a peak at over 30 times the expected admissions for similar conditions.⁷ The clinical presentations of these conditions shared features of other, known conditions, however there was no diagnosis which would fit cleanly. The significant myocardial shock seen is a distinguishing feature: this is rarely seen in the acute phase of KD, and although patients with Toxic Shock can have very severe shock, this is usually distributive rather than myocardial.

In summary, PIMS-TS is an unexpected condition which is part of a group of similar, but distinct pathologies. There is more clinical, biochemical, and symptomatic difference between PIMS-TS and Kawasaki’s disease than there is for instance between Kawasaki’s disease and Toxic Shock.

There has been discussion as to whether PIMS-TS is, in fact, just a reinterpretation of the cytokine storm seen in some adults with active SARS-CoV2 infection. Although this cytokine storm shares some features, this generally occurs in patients who are already sick with active SARS-CoV2 infection, and who presented with classical COVID-19 symptoms. PIMS-TS patients are different in that they present with the inflammation as their main feature, usually SARS-CoV2 PCR testing is negative, and the surge of cases was delayed compared to the COVID-19 pandemic. Case reports and case series have recently been published¹³ with adult patients presenting very similarly to PIMS-TS patients. This syndrome has been called Multisystem Inflammatory Syndrome in Adults, or “MIS-A”. It remains to be seen whether there will be more cases during a second wave of infections.

The CDC has performed latent class analysis on their cohort of 570 patients,¹⁴ and identifies three groups: broadly summarized as those severely affected, those with respiratory involvement (more likely to have active SARS-CoV2 infection on PCR), and a third, younger group with Kawasaki-like presentation. With ongoing evolution of the definition of this disease, it may be that only the first group are defined as “true” PIMS-TS, the second as paediatric COVID-19 disease, and the third as atypical Kawasaki’s disease.

Communication and reporting of cases

In modern medicine, such a rapid dissemination of knowledge of a new disease is unprecedented. Previously, discoveries of new diseases have necessitated careful study and peer reviewed publication. Many syndromes in medicine have dual names: not because of two collaborators sharing equally, but because the disease was discovered simultaneously by two individuals who were completely unconnected.

The United Kingdom was the first to realize that there were unusual numbers of inflammatory syndrome patients presenting. The NHS England alert published on the 26th April 2020¹⁵ gave rise to an enormous amount of publicity. A tweet detailing this alert was posted by the Paediatric Intensive Care Society (now the Paediatric Critical Care Society, @PICoSociety), which gained enormous international traction, resulted in well over one million impressions, and led to numerous conventional media articles.¹⁶

The rush to publish cases led to many papers submitted with very short turnaround times. As this is a complex, multisystem condition, there were competing papers from many different branches of medicine, including cardiology, paediatric intensive care, immunology, infectious disease teams, and rheumatology. Groups attempting careful and considered national data collection were swamped by smaller, more agile groups, who were able to publish single centre experiences very rapidly, albeit with less utility.

By the beginning and middle of May, multiple webinars^{17,18} were hosted by various groups around the world. Many attracted over 1,000 participants, explaining the clinical presentations and progression of these patients, as well as the treatments being used.

The initial publication of a letter in the Lancet was on the 7th May 2020: by the end of June, 783 cases had been published in the worldwide literature.¹⁹ This comprised 35 separate

publications, including 12 single case reports, and 20 with 10 or fewer patients. The largest group was a pan-USA study which reported 186 hospitalized patients from 26 states.²⁰

Reports followed from Italy and France.^{21–23} A selection of the earliest, and largest papers is presented in Figure 1.

Pathogenesis

The exact pathogenesis of PIMS-TS is not clear. It has been suggested that given the lag between population cases of SARS-CoV2 and PIMS-TS, and the finding that many patients are positive for antibodies rather than viral antigen, that an abnormal immune response may be a key factor. Coronaviruses are known to inhibit type I and type III interferon responses. This can lead to an immunological impasse, where the delayed interferon responses mean a longer, and more severe disease.²⁴ This does not explain, however, the timings of PIMS-TS. PIMS-TS patients are generally very well until they acutely present with their inflammatory collapse.

Some have postulated that there may be a mechanism similar to dengue fever in which the existence of antibodies contributes to an increased severity of secondary infection. Antibody dependent enhancement (ADE) causes severe Dengue infection, including Dengue shock and Dengue haemorrhagic fever. In ADE, the virus uses the phagocytotic process to enhance its own viral replication and causes the death of the immune cells. This leads to distributive shock and multi organ failure. A case report detailing a fatal presentation of PIMS-TS from heart failure showed evidence of viral presence in the myocardial tissues at the time of death suggesting a potential for “second-hit” viral mediated damage to the tissues as a factor.²⁵

A potential role for autoantibodies in the pathogenesis of KD has been described. Certain autoantibodies have been identified in PIMS-TS patients above levels seen in healthy controls, children with acute SARS-CoV2 infection or KD. The autoantibodies found to be overexpressed in PIMS-TS patients included those that are involved in lymphocyte activation, intracellular signalling pathways and heart development. In this analysis, autoantibodies to various subtypes of casein kinase were found specific to PIMS-TS. The prevalence of the potential targets for such autoantibodies across different tissues in the body could correlate with the multi system presentation in PIMS-TS.²⁶

Emerging evidence shows increased IL-18 and IL-6 profiles in PIMS-TS, with increased lymphocytic and myeloid chemotaxis and activation, and mucosal immune dysregulation.²⁷ The hyperinflammation differs from that seen in acute COVID-19, and the inflammatory profile differs from that seen in Kawasaki's disease, with IL-17A mainly involved in Kawasaki's not a feature of PIMS-TS. The PIMS-TS cytokine storm is different to that seen in adults with active COVID-19.²⁶

These differences in the immune profiles of patients with PIMS-TS further supports the status of this syndrome as a novel entity with distinctions from previously known conditions.

Treatments

Patients presenting with PIMS-TS were often critically ill, needing intensive care and on occasion even extra corporeal support. As a new condition, clinicians needed to find a way to

treat this syndrome without the usual wealth of experience and without any evidence.

Due to the similarity in presentations with Kawasaki's disease, patients were initially treated with the same cocktail of treatments which are given to patients with Kawasaki's. Anecdotes of rapid improvement, and the almost instant worldwide dissemination of this experience, ensured the rapid evolution of a “treatment orthodoxy” where IVIG, steroids and aspirin were given for all unwell patients, and biologic agents given for very unwell, or refractory cases. This treatment plan was first proposed at the end of April, disseminated through webinars and social media, and rapidly became ingrained.

However, the translation of treatments between Kawasaki's disease and PIMS-TS presumes both a shared pathophysiology (and that the treatments are indeed effective for Kawasaki's disease). The evidence base for using IVIG in Kawasaki's disease is poor, with the Cochrane review showing no significant benefit in the small number of randomized trials for medium-long term risk of developing coronary artery aneurysms.²⁸ No randomized clinical trial of long-term effects of IVIG in Kawasaki's disease has been performed since 1990. The use of steroids has greater evidential base,²⁹ and there is a complete lack of evidence for salicylates.³⁰ There is no published experience of biologic agents in Kawasaki's disease.

As PIMS-TS is an inflammatory condition, anti-inflammatory agents make biological sense. In the absence of a defined goal to treat, treating the inflammation is a sensible proxy for improvement. Neither short, nor long term data on outcomes have yet been published. It remains unknown whether the administration of neither IVIG, steroids, or biologics have any outcome on the progression of the course of the inflammation.

It is very difficult to give clear advice on treatment. On one hand, there have been no studies into how to treat this. On the other hand, expert advice from the beginning has been to treat with IVIG, steroids, and aspirin, and when this is the standard of care, backed by national consensus statements, it is very difficult to avoid these therapies. Equipoise should be maintained, and we encourage all clinicians to enrol patients into robust randomized trials, for instance the RECOVERY trial.³¹

Outcomes and follow up

In general, outcomes of PIMS-TS are good. Mortality is low: even amongst paediatric intensive care unit patients mortality is below 3%, with intensive care stays of around 5 days. Although multi organ problems are common initially, with careful supportive treatment these generally improve.³²

The major, and most worrying outcome of PIMS-TS are coronary artery aneurysms. These can be extremely dangerous and life limiting. This is an emerging field: long term follow-up data is not yet available, so we do not know the survivors' final prognosis. Some emerging data shows high levels of resolution of coronary arteries, however consequential data is yet to be published.

The UK national consensus advises close cardiology follow up, tracking the risk of coronary artery aneurysms in the medium and long term.³³ The long-term risk is undefined.

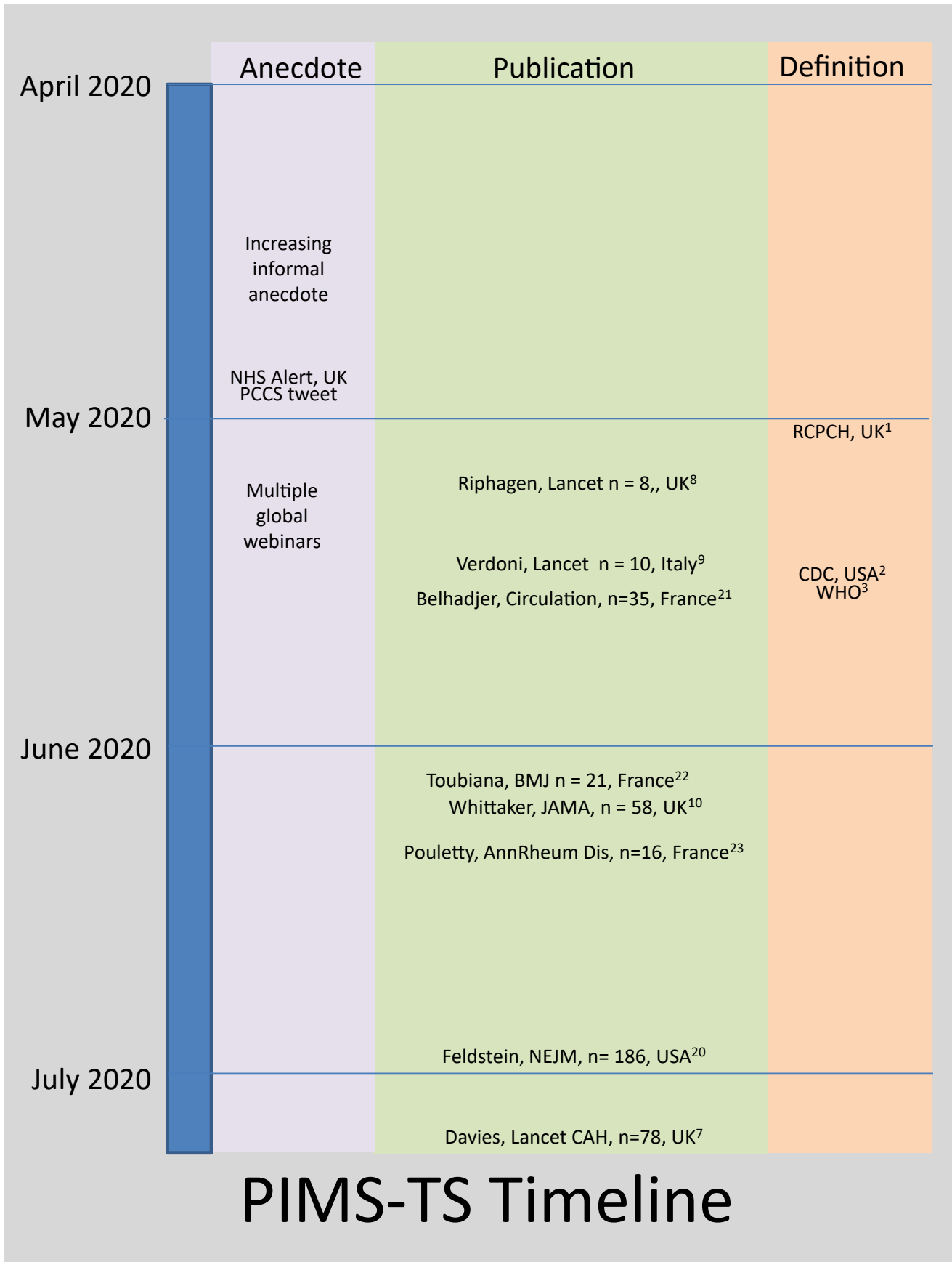


Figure 1 A timeline of the evolution of PIMS-TS.

What can we learn from this experience?

PIMS-TS, and indeed the whole SARS-CoV2 pandemic, has been an example of how the clinicians worldwide can communicate and help each other effectively and rapidly. However, rapid dissemination of experience has its risks.

All clinicians will have had experience of considering papers during journal clubs: the calm and careful dissection of methodology and outcomes is an important skill, which leads to the judicious analysis and careful decision making to the benefit of patients. Similar levels of scrutiny must be applied to both social media, and webinars.

Local, national, and international collaboration has been excellent, with much enthusiasm to share information and data. There was an inexhaustible supply of assistance and advice available.

Conclusion

PIMS-TS is a novel condition, part of the constellation of inflammatory conditions seen in children. The pathogenesis is not yet understood, neither is it known which are effective treatments. In the meantime, careful supportive care and close follow-up is important. Collaboration between specialists, as with any such complex condition, is important. ◆

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