

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): the Evelina Experience

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INTRODUCTION

In the midst of lockdown, just as patient acuity and bed pressures eased, a number of teenagers were transferred to the paediatric intensive care unit (PICU) at Evelina London Children's Hospital for inotropic support in the absence of respiratory involvement or any features of acute Severe acute respiratory syndrome related coronavirus 2 (SARS CoV-2) infection.¹ All patients had features of toxic shock syndrome (TSS) but no pathogens were identified despite extensive microbiological investigation. Several new patients presented over the next few days; febrile with high inflammatory markers and multisystem involvement. The unusually high number of cases raised concerns, which were discussed with Public Health England regarding a possible infectious disease cluster with pathogen unknown.

Following several discussions with National Health Service England (NHSE) and pan-London tertiary paediatric services who had also seen cases, a consensus was reached that a new clinical phenomenon was being seen across London. It was sufficiently concerning to send out an NHSE alert at the end of April which triggered international discussion.² Numerous teleconferences later, the emerging condition had a name; paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).³ Since the alert other countries have reported similar cases (figure 1).⁴⁻⁶

PRESENTATION

Over 6 weeks more than 70 patients were admitted to Evelina London Children's

Hospital who fulfilled criteria for a diagnosis of PIMS-TS.³ The majority of patients were between 9 years and 16 years of age with the youngest presenting at only 3 months. A higher proportion of patients was male, from black, Asian and minority ethnic groups, and had a parent classed as a key worker.

All of the patients presented with a history of fever and most presented with gastrointestinal symptoms including abdominal pain, diarrhoea or vomiting. A number of patients were transferred following surgery for symptoms and signs classical of acute appendicitis but intraoperatively found to have a normal appendix. Other presenting features included conjunctivitis, rashes and lethargy.

Key laboratory findings on presentation included a very high C reactive protein (CRP), high ferritin, raised neutrophils, low lymphocytes, raised D-dimer, raised troponin I, raised N-terminal pro B-type natriuretic peptide and low vitamin D levels.

The most common cardiac manifestation was myocarditis with impaired function. Other cardiac abnormalities included arrhythmias, ischaemia and pericardial effusions. Patients were monitored closely for coronary artery dilatation which in

some patients continued to progress despite improvement in clinical symptoms and laboratory markers.

Acute kidney injury was the most common renal complication which improved with conservative management. Some patients developed thrombus formation and pulmonary emboli due to their prothrombotic state. Neurological involvement was also observed with one patient developing autoimmune encephalitis.

PATHOGENESIS

Most patients with PIMS-TS reported no preceding illness or mild symptoms consistent with COVID-19, 4–6 weeks prior to presentation. Others had a household member with previous symptoms consistent with COVID-19 infection. Most patients with PIMS-TS were SARS-CoV-2 PCR-negative but positive for IgG antibodies against SARS-CoV-2 indicating previous infection. It has been postulated that a host immune response to SARS-CoV-2 triggers an inflammatory response.

Although cases of PIMS-TS have similarities to Kawasaki disease (KD) and TSS, there are clear differences.⁷ Patients with PIMS-TS are older and present with higher inflammatory markers including CRP and ferritin plus higher troponin I suggestive of myocardial ischaemia. Like TSS a proportion of patients with PIMS-TS present in shock with poor cardiac function but none had confirmed staphylococcus or streptococcus on microbiology.

MANAGEMENT

Assessment, stabilisation and early involvement of specialist centres

The majority of the patients needed intensive care for cardiovascular instability requiring single or multiple inotropic agents. Early discussion with specialist

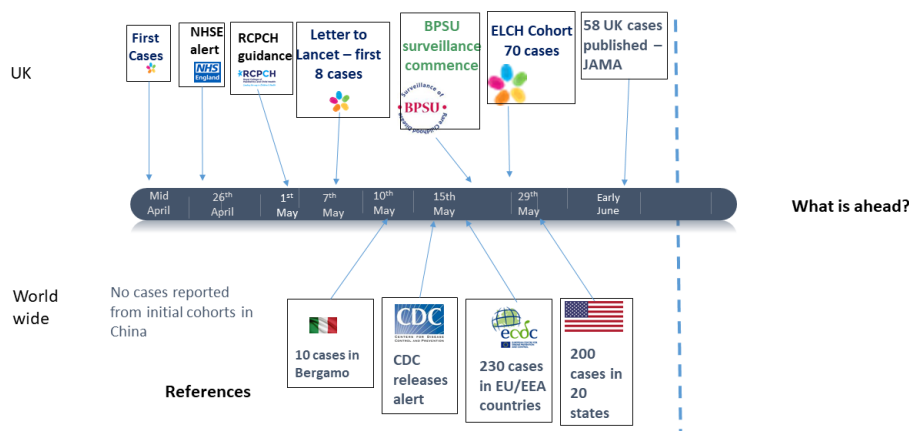


Figure 1 Timeline of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) development.¹⁻⁴⁻⁶⁻⁹ NHSE, National Health Service England.

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centres and transfer to a centre with PICU and cardiology on site is a necessity.

Management for each patient was decided within a multidisciplinary team (MDT) setting including General Paediatrics, Cardiology, Paediatric Infectious Diseases and Immunology (PIID), Rheumatology, PICU, Haematology, Renal and Pharmacy, with re-evaluation on a twice daily basis as a minimum. A General Paediatric overview was vital in coordinating the MDT and providing holistic care.

Treatment

In our cohort, as we gained experience, prompting earlier diagnosis and treatment initiation, fewer cardiac complications and reduced PICU stay were observed. Treatments included intravenous immunoglobulin, methylprednisolone and biologics including tocilizumab, infliximab and anakinra. Currently there is no evidence for this area and recruiting children to research studies such as Recovery (<https://www.recoverytrial.net/>) and the 'Best available treatment study (BATS) for inflammatory conditions associated with COVID-19' (<https://doi.org/10.1186/ISRCTN69546370>) will hopefully provide evidence on which to base our treatment decisions. All patients receiving treatment were routinely prescribed aspirin, prophylactic dalteparin, high dose cholecalciferol and omeprazole.

Psychology and support

Play therapy involvement and psychological support for this cohort was quickly escalated. Families were understandably extremely worried by the sudden clinical deterioration of their previously well child and need for intensive care. Multiple interventions including scans, cannulas and blood tests by staff masked in personal protective equipment added to the stress. Psychology support is now a routine part of the care offered.

OVERCOMING CHALLENGES

To cope with the large number of unpredictable and high acuity patients with PIMS-TS, additional staffing was required on our paediatric wards. Within days, the number of high dependency unit (HDU) beds was rapidly increased to accommodate the intense level of monitoring and treatment required. Ward rounds, handovers, MDT meetings and pathways were rapidly revised and implemented. We sought the return of our experienced paediatric nurses and doctors who had been redeployed to adult services. Additional pharmacists, psychologists and play

therapists also joined a newly created and dedicated PIMS-TS team with representation from General Paediatrics, PIID, Cardiology and Rheumatology to manage the daily care of the patients. This ensured individualised, holistic management plans could be made to provide the highest quality of care. The responsiveness by everyone involved was phenomenal.

As patients are discharged the next challenge is ensuring follow-up plans are appropriately tailored, responsive and clinically robust. In the current lockdown era, this is no small task given the numbers involved, the follow-up investigations needed, plus national pressures to reduce face-to-face appointments.

Managing a new condition with no published consensus on treatment was a huge challenge, especially given the large numbers and high acuity of the patients who were admitted. Seeking out opinions, information and advice from other centres, nationally and internationally, as well as shared learning with other paediatric specialities has been key in helping manage these children. Collaborative learning and reflection has enabled us to develop a treatment pathway and shared management pathway for our patients. We have witnessed the MDT working at its best within the hospital, united with the sole aim of combating this rare condition.

NEXT STEPS

Long-term follow-up is essential to enable us to understand the long-term implications and prognosis for these patients. Planning and vigilance is required to manage a possible influx of patients with PIMS-TS if there is another surge of SARS-CoV-2.

An ongoing coordinated effort is required to undertake paediatric research to understand PIMS-TS and establish the most effective treatment. The British Paediatric Surveillance Unit team is collecting data about all reported cases in the UK and Ireland.⁸ We eagerly await the publication of evidence which may support, or disprove an association with SARS-CoV-2. Certainly, the clinical histories taken from this cohort offer fascinating glimpses into the possibilities of an association.

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