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Intensive Care Admissions Of Children With Paediatric Inflammatory Multi-system Syndrome Temporally Associated with SARS-CoV-2 Pandemic (PIMS-TS) In The United Kingdom

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The corresponding author confirms that he had full access to all the data in the study and has final responsibility for the decision to submit for publication

Research in context

Evidence before this study

Recent reports of a novel inflammatory syndrome in children resembling Kawasaki disease and toxic shock syndrome from many parts of the world represent an important and poorly understood aspect of the evolving pandemic. An initial case definition has been published for this syndrome, called Paediatric Inflammatory Multi-system Syndrome temporally associated with SARS-CoV-2 (PIMS-TS), in the United Kingdom.

We searched PubMed up to 18 June, 2020, without date limits or language restrictions, with different combinations of the search terms “paediatric inflammatory multi-system syndrome”, “multisystem inflammatory syndrome in children”, “atypical Kawasaki”, “inflammatory syndrome”, “intensive care units, “critical care” OR “critical illness” OR “intensive care”, “ICU” OR “PICU”.

Published reports of PIMS-TS cases so far represent single-centre case series and convenience samples, precluding a detailed analysis of clinical presentations and outcomes, especially in the sickest subset of children requiring critical care.

Added value of this study

This is the largest cohort of critically ill children with PIMS-TS reported so far, the first nationwide report, and the first to describe longitudinal data.

Coronary artery abnormalities were seen in one third of cases. Comparison with historical data indicate at least a ten-fold increase in intensive care admissions for children with an inflammatory syndrome during a six-week period in April/May 2020.

Implications of all the available evidence

There are small but important numbers of children requiring critical care admission for an unexplained multisystem inflammatory syndrome that may be associated with the COVID-19 pandemic.

Uncertainties regarding the underlying basis of this syndrome and lack of evidence regarding optimal treatments and follow up have led to considerable variation in clinical management.

Urgent efforts to recruit patients to robust clinical trials of potential treatments to reduce longer term morbidity (eg coronary artery aneurysm formation and evolution) are needed to inform clinical practice.

Abstract

Background

Clinicians observed a cluster of children with unexplained inflammation requiring admission to United Kingdom (UK) paediatric intensive care units (PICU) in April 2020. We aimed to describe the clinical characteristics, course, management and outcomes of intensive care patients with this condition, now known as Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS).

Methods

Multicentre observational study of children (<18 years), admitted to UK PICUs between 1 April and 10 May 2020, fulfilling the case definition of PIMS-TS. Routinely collected, deidentified data was analysed. PICU admission rates of PIMS-TS were compared with historical trends of PICU admissions for other inflammatory conditions.

Findings

78 children with PIMS-TS were reported by 21/23 UK PICUs. Historical data for similar inflammatory conditions showed a mean of 1 (95% CI 0·85-1·22) admissions/week, compared to a peak of 32/week for PIMS-TS. Median age was 11 (IQR 8-14) years. Males (52, 67%) and ethnic minorities (61, 78%) were over-represented. Fever (78, 100%), shock (68, 87%), abdominal pain (48, 62%), vomiting (49, 63%) and diarrhoea (50, 64%) were common. Longitudinal data over the first 4 days of admission showed serial reduction in CRP, D-Dimer, and Ferritin, while lymphocyte count increased to >1·0 x10^9/L by day 3 and troponin increased over the four days. 36 (46%) were invasively ventilated and 65 (83%) needed vasoactive infusions; 57 (73%) received steroids, 59 (76%) intravenous immunoglobulin, and 17 (22%) biologic therapies. 28 (36%) had evidence of coronary artery abnormalities (18 aneurysms, 10 echogenicity). Three children needed Extracorporeal Membrane Oxygenation, and two children died.

Interpretation

During this study period, rate of PICU admission with PIMS-TS was 11-fold higher than historical trends of similar inflammatory conditions. Clinical presentations and treatments varied. Coronary artery aneurysms are an important complication. Although immediate survival is high, the long term outcomes of PIMS-TS are unknown.

Funding

None

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been associated with nearly 4.5 million infections and over 300,000 deaths worldwide by the 15th May 2020 [1]. While approximately 3-5% of infected adults need critical care admission[2,3], children appear to be relatively spared both in frequency and severity of illness[4-7]. Data published so far indicate that the main reason for intensive care admission in children with COVID-19, similar to adults, has been respiratory disease, particularly in children with co-morbidities[8].

Over the second half of April 2020, a cluster of children presenting to Paediatric Intensive Care Units (PICUs) in the United Kingdom (UK) with an unexplained multi-system inflammatory syndrome triggered an alert by NHS England and the UK Paediatric Intensive Care Society[9]. Children with this illness appeared to have overlapping features of Kawasaki disease (KD), Toxic Shock Syndrome (TSS) and Haemophagocytic Lymphohistiocytosis (HLH)/Macrophage activation syndrome (MAS)[10]. Since then, similar cases have been reported from the United States[11] as well as Europe[12], with reports in the lay media[13]. On 1st May 2020, the Royal College of Paediatrics and Child Health (RCPCH) published a case definition and guidance related to this multi-system illness[10], defining it as a child presenting with persistent fever, inflammation, and evidence of single or multi-organ dysfunction, with exclusion of any other microbial cause, with or without polymerase chain reaction (PCR) evidence of SARS-CoV-2. In the UK this has become known as Paediatric Inflammatory Multi-system Syndrome Temporally Associated with SARS-CoV-2 Pandemic (PIMS-TS), and in the United States with a more restrictive case definition as Multisystem Inflammatory Syndrome in Children (MIS-C)[11]. Details regarding some PIMS-TS cases have been recently published from the UK and Italy. The majority of children had a negative PCR test for SARS-CoV-2 antigen, but had evidence of antibodies, indicating past infection[14,15,16]. Some of the patients reported in these cohorts were cared for in intensive care and are therefore included in this paper, although previous reports have either been from single centres or convenience samples, and have not detailed longitudinal data to assist in better understanding the trajectory and outcome of this condition..

The fact that PIMS-TS has overlapping features with KD, TSS, and HLH/MAS has triggered debate as to whether this is a new condition, or whether it is an unusual, more severe variant of these previously well-known conditions requiring critical care management[17]. Comparison with previous admission rates of inflammatory syndromes to critical care is important to ensure that this condition does not reflect an inadvertent reanalysis of the background rate of an already known pathology. Improved knowledge of the clinical course in the subset of children with PIMS-TS needing PICU admission is important to raise awareness and to identify significant areas of variation in current clinical management. In this report, we aimed to describe the clinical characteristics, treatments and outcomes of a cohort of children admitted to UK PICUs with PIMS-TS over a 40-day period in April/May 2020.

Methods

Study design and participants:

This is a multi-centre observational study of children less than 18 years of age, admitted to UK PICUs over a 40-day period (1st April 2020 to 10th May 2020), who fulfilled the case definition of PIMS-TS[10], and the first national report of these patients. The project was classified as a service evaluation by the Nottingham Research and Innovation team (Nottingham Clinical Effectiveness Team ref: 20-235C), and ethics approval was not required. The study team analysed routinely collected de-identified data submitted by clinicians from the individual PICUs as a local service evaluation. Clinicians obtained informed parental consent if required locally. Data were submitted for central analysis using a secure, web-based survey tool (Surveymonkey, USA) and included demographic details, presenting clinical features, underlying co-morbidities, laboratory markers, echocardiographic findings, interventions, treatments, and outcome (survival to PICU discharge, length of PICU stay). Serology information was collected if available.

We classified co-morbidities as minor if primary care management would ordinarily be sufficient (eg mild asthma), and major if hospital-based management would ordinarily be required (eg sickle cell disease). Ethnicity was described using UK Government standard groups and compared with reported population rates[18]. We calculated the ratio of observed weight to expected weight (based on the 50th centile weight for age and sex). Characterisation of shock into vasodilated or vasoconstricted shock was based on treating clinician's judgement. There were no interventions as part of this study. Investigations and patient management were as per the discretion of the relevant responsible medical teams. All patients had SARS-CoV-2 antigen tests performed by reverse transcriptase polymerase chain reaction (PCR). Serology for SARS-CoV-2 was performed where available.

The Paediatric Intensive Care Audit Network (PICANet) dataset contains prospectively collected patient diagnoses for patients admitted to PICUs in the UK. Anonymised summary data were provided for a five-year period (1 Jan 2015 to 31 Dec 2019) for all patients admitted to all 23 UK PICUs with a primary diagnosis of four similar inflammatory conditions (KD, TSS, HLH and MAS)[19]. The database was searched for Read(CTV3) codes Y70QV, XUauZ, G7510, A3Ay1, X70Il, X20E8, XUwry, X20E7, and XUgRm. PICANet report all incidences below 5 as "<5".

Statistical Analysis

Results are presented as numbers and proportions for categorical data and medians and inter-quartile range for continuous data. Data analyses were performed using Microsoft Excel (Microsoft Corporation, USA).

Role of the funding source:

This study was unfunded. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

During the study period, data on 78 patients admitted to PICUs and meeting case definition for PIMS-TS were submitted. Initial presenting features of 29 of these patients have been reported in a recent paper focusing on the definition of this novel condition (8 of whom had previously been reported in correspondence)[14,16]. Cardiac and renal features in 6 and 23 patients respectively have also been presented in single centre reports[20,21]. Detailed presentation, intensive care course, evolution in treatment over time, and longitudinal laboratory data in a national cohort have not been published previously. Of the 23 National Health Service (NHS) Hospital Trusts with PICUs in the UK, 15 submitted PIMS-TS patient data (median per unit 3, range 1-24), 4 reported zero patients and 2 were not admitting any children during the study period (having been converted to adult ICUs during the COVID-19 surge). The two closed units were cardiac units, and their paediatric patients were admitted to neighbouring PICUs. Two PICUs did not share data. The total number of PICU admissions of PIMS-TS cases by week (and cumulative number of admissions) are shown in Figure 1. The cumulative expected number of admissions derived from historical UK PICANet data with similar inflammatory conditions requiring PICU admission is also shown, demonstrating an increase of cases above the expected from the week beginning 20th April.

Patient characteristics are shown in Table 1. The median age was 11 (IQR 8-14) years, and two thirds of the patients (52/78, 67%) were male. Only two patients had major co-morbidities, with 61/78 (78%) having none. Afro-Caribbean and Asian ethnicities were over-represented in this cohort. The proportion of children aged 10-14 from an Asian background is 6·9%, and Afro-Caribbean 7·8% in the UK[18], in contrast to 22/78 (28%) and 37/78 (47%) of the patients in this cohort respectively. The observed percentages are well outwith the 95% confidence intervals. 3 patients had co-infections, 1 viral and two bacterial. None were judged to be clinically causative.

Shock (68/78, 87%), usually vasodilated, (55/78, 71%), abdominal pain (48/78, 62%), diarrhoea (50/78, 64%) and vomiting (49/78, 63%) were common presenting features. 70/78 (90%) of patients presented with at least one abdominal symptom. Rash (35/78, 45%), and conjunctivitis (23/78, 29%) were also seen. Of those tested for

SARS-CoV-2 IgG serology, 33/35 were positive, and one of the two negative serology patients was PCR positive. All MIS-C criteria were definitely met in 45/78 (58%), Details are shown in supplementary table 1.

Longitudinal data on the first four days of admission are presented in Table 2. Data was available for all 78 patients for day 1, and for 46 patients throughout the first four days. Only data of patients still on intensive care are displayed. Patients presented with elevated CRP (median [IQR]: 264 [192-316] mg/L) and ferritin (1042 [538-1746] µg/L), and lymphopaenia (median [IQR]: 0·70 [0·42-1·1] $x10^9$/L). Longitudinal data over the first four days of admission showed a reduction in CRP, D-Dimer, and Ferritin. Neutrophil count was static, and Creatinine and ALT remained normal. Lymphocyte count increased and the median rose above 1.0 $x10^9$ by day 3. Troponin increased over the four days.

Historical data on the incidence of PICU admission for the four similar inflammatory conditions (KD, TSS, and HLH/ MAS) between 2015 and 2019 showed that the average number of admissions to all UK PICUs combined with the four inflammatory conditions was 1 admission per week (95% confidence interval: [0·8-1·22]), with an annual total number of admissions ranging from 44 to 67. Toxic Shock Syndrome (119) and Haemophagocytic Lymphohistiocytosis/ Macrophage Activation Syndrome (114) had the highest number of total national admissions over the five years, with Kawasaki's Syndrome less common (between 30-40 in total, exact numbers not available due to small numbers as detailed above). Full details are in Supplemental table 2. During the study, the average number of weekly admissions to UK PICUs with PIMS-TS was 14 (at least 11.2 times greater than expected for similar conditions), peaking at 32 (at least a 26-fold increase).

Critical care interventions, treatments and outcomes are shown in Table 3. Overall, 36/78 (46%) children were invasively ventilated, and 3/78 (3·8%) required Extracorporeal Membrane Oxygenation (ECMO). A variety of therapies were given, with 59/78 (76%) receiving intravenous immunoglobulin and 57/78 (73%) steroids. 17/78 (22%) received biologic immunomodulation agents (8 Anakinra, 7 Infliximab, 3 Tocilizumab, 1 Rituximab). Two patients received two biologics. Only one child was treated with antiviral therapy (Remdesivir). Treatments were varied and inconsistent, however over the study period, the percentage of patients being given each therapy increased over time (Figure 2). The percentage of patient on vasoactive infusions remained constant (between 81 and 84% in weeks 3-6), however the proportion of patients invasively ventilated dropped from 5/6 (83%) (week 3) to 2/17 (12%) by week 6. Three (3·8%) patients had significant thrombi, with no pulmonary emboli. Seven (9·0%) patients received therapeutic anticoagulation, either due to thrombi or due to concerns regarding diffuse microthrombi.

One third (28/78, 36%) of patients were found to have coronary artery abnormalities on echocardiography during PICU admission. 18 had evidence of aneurysms, and 10 had coronaries which were characterised as unusually echogenic. They were no obvious differences between the demographics, presenting features, or level of invasive therapies between those with any coronary artery abnormality and those with normal coronaries, or those who were invasively ventilated or not invasively ventilated (Table 4). Similarly, no clear differences were found between those patients invasively ventilated and those not invasively ventilated.

Discussion

Our report describes the characteristics and outcomes of the largest cohort of PICU admissions to date with the newly described unexplained multi-system inflammatory syndrome named PIMS-TS in the UK. This report is the first to describe a national cohort, give full details of the presentation, clinical course on intensive care, and treatments, as well as demonstrate longitudinal laboratory results.

We found that the number of UK PICU admissions with PIMS-TS during a 40-day study period in 2020 (following the surge of COVID-19 infections in the UK) significantly exceeded the historical numbers of admissions of four inflammatory conditions with overlapping clinical features. These patients were critically unwell with multi-system disease. Although this increase in the number of patients was unexpected, it is still a small proportion of the usual expected national 250 unplanned paediatric intensive care admissions per week[19].

As of the 10th May, around 220,000 people in the UK had tested positive for SARS-CoV-2. Previous data has shown a paediatric infection rate of around 2% of the total, which would equate to 5,000 children infected. This means that PIMS-TS would have an incidence of 1.5%.

The emergence of this condition in children may have social impact also. Children have been thought of as at negligible risk from Covid-19 until now: even though the risk is still low, there are implications for health care resources and balancing the need for adult and paediatric intensive care units. Our data also has significant implications for any future peaks of PIMS-TS, especially if this coincides with a winter surge of other viral infections.

Viral sepsis with SARS-CoV-2 has been well described in adults[22]. Such patients meet clinical criteria for shock, are generally SARS CoV-2 positive on PCR from respiratory secretions and have predominantly pulmonary, renal, hepatic, and cardiac involvement. Coagulopathy is a feature in adults. In comparison, although D-Dimers are high in PIMS-TS patients, other coagulation tests were usually normal. The notable absence of severe pulmonary and renal symptoms in PIMS-TS is a further differentiation between the presentations.

In children, although the four inflammatory conditions (KD, TSS, and HLH/MAS) are well known, they cause illnesses which rarely require PICU admission[19,23]. The presenting features of these four conditions partially overlap with the presenting features of PIMS-TS; however, none of them were fully consistent with the clinical presentation and natural history seen in our report. Although the case definition for PIMS-TS is broad, there are some definitive blood markers which were largely shared by the cohort. We used the published case definition, which may include some cases which would previously have been diagnosed with one of KD, TSS, or HLH/MAS. Kawasaki disease has been known to have some seasonality[24], with peaks in presentation up to 2.5 times the background expected rate, including a known association with other coronavirus infections[25]; this is unlikely to account for the fluctuation seen in this study. Kawasaki shock syndrome shares the main features of the clinical presentations detailed in this report including shock; however, the younger age, longer duration of fever, more consistent mucosal involvement and a lack of abdominal symptoms, distinguish it from PIMS-TS[26]

A few days following our study end date, the US Centers for Disease Control and Prevention (CDC) published a more restrictive case definition for MIS-C, which required evidence of COVID-19 exposure within the 4 weeks prior to the onset of symptoms. Only one patient who met the PIMS-TS definition would definitely not have met the MIS-C criteria. It was unclear in 32/78 (41%) of our patients whether they met the stricter MIS-C definition because at the time of presentation many UK hospitals were not offering SARS-CoV-2 serology. Both criteria were met in 45/78 (58%) of patients. Emerging evidence that there are asymptomatic carriers of SARS-CoV-2 also suggests that cases may have unknowingly been in contact with SARS-CoV-2[27]. It is unclear whether the CDC definition is more sensitive or specific than the RCPCH definition in identifying true cases. Comparison between those who met the CDC criteria, and those in whom it was unclear, did not show any clear differences.

There are several clinical implications of our findings. First, the notable absence of significant respiratory involvement, the low incidence of positive SARS-CoV-2 PCR tests and the presence of SARS-CoV-2 antibodies in 24/25 (96%) patients who were tested following a negative SARS-CoV-2 PCR indicates that PIMS-TS might represent a post-COVID-19 immunological disease that is clinically distinct from acute COVID-19 infection in children. The low numbers of patients tested for antibody serology was due to unavailability of the test in those units at that time. Therefore, the value of antivirals in these cases is unclear. Only one patient was treated with Remdesivir, who was positive on PCR for SARS-CoV2. Second, the heterogeneity in clinical presentation seen with PIMS-TS, and variable overlap with previously described entities such as atypical KD, TSS or HLH/MAS, meant that there was significant variation in the range of immunomodulatory treatments were offered to these children. There is currently no evidence as to which treatments are beneficial, highlighting the need for urgent robust clinical trials, such as the RECOVERY trial, which aims to include PIMS-TS patients[28]. Third, the frequency and extent of multi-system involvement indicates that a multi-disciplinary team approach (general paediatrics, infectious diseases, cardiology, intensive care, haematology, immunology, pharmacy, and rheumatology) is very important for managing these patients. Finally, the lack of long-term follow-up data on these children means that it is difficult to anticipate and plan for

their community health care and surveillance needs following recovery. It is unknown whether these patients may have long term health problems, particularly those with echocardiographic abnormalities of their coronary arteries. We did not identify any differences in the clinical presentation or laboratory data to indicate potential prognostic factors for coronary artery abnormalities prediction.

There were higher than expected numbers of children with Asian and Afro-Caribbean ethnicities. This is consistent with the higher rates of adult patients from ethnic minority backgrounds seen with severe clinical presentations of COVID-19 disease[29], but higher than expected from previous paediatric intensive care data[30]. A link between ethnicity, incidence and outcomes is increasingly recognised in the UK[29,31]. The causes behind this are not clear, however socioeconomic factors, co-morbidities, and differences in the expression of angiotensin converting enzyme 2 have been implicated[29]. We have used UK data as our comparison denominator in our study: there are regional differences in ethnic group prevalence; however, the pandemic has affected all regions of the UK and the regional differences in PIMS-TS incidence may be linked to this.

In our study there was a higher proportion of males (67%), in contrast to a recent cross-sectional study of COVID-19 positive children admitted to 46 North American PICUs, in which 52% of patients were male[9], but similar to the experience in adult intensive care[31].

The strengths of our study include the multi-centre data coverage (data was submitted by the vast majority of PICUs in the UK) and depth of clinical detail captured. Comparison with reliable, historical data from PICANet allowed us to demonstrate a step-change in the need for PICU admission for inflammatory conditions during the COVID-19 pandemic. The main limitation is the retrospective nature of data collection; however, given the relatively short study period, the time interval between PICU admission and data collection was minimal. We are unable to offer any conclusions regarding the immunological basis behind PIMS-TS, or provide long-term data on these patients, although our study was not designed to do so. We used PICANet data as the denominator as it has a robust mechanism to obtain national critical care related information and is audited to ensure consistency. It was not possible to ensure 100% case ascertainment and therefore the numbers may be an under-estimate of PICU admissions. The selection of conditions covered by the PICANet search may not have covered all inflammatory conditions, and it is likely that a small number of patients with undiagnosed multi-system inflammatory illnesses were not included in our PICANet search. Moreover it is likely that a large population of patients affected did not need critical care admission and we may be underestimating the true incidence of PIMS-TS in the hospital population. Recently launched national initiatives (PICANet and British Paediatric Surveillance Unit[32]) to study this condition will gather ongoing data. It is unlikely that clinical practice was influenced by the RCPCH alert, as 51/78 patients predated the alert. The true incidence of coronary artery aneurysms and other complications will become clearer with longer term follow-up data. We did not capture the rationale for specific therapies used. Additional therapies that may have been provided after discharge from PICU may not have been captured.

We were unable to find clear correlations between presenting features, laboratory tests, and treatments, with the risk of having coronary artery abnormalities or being invasively ventilated. This has implications for those patients not unwell enough to need to come to the intensive care unit. We advise caution and close follow up for all PIMS-TS patients.

Conclusion

In this large cohort of children requiring critical care admission for the novel inflammatory condition known as PIMS-TS, we saw significant short-term morbidity in terms of the need for critical care interventions, but mortality was low. Nearly a third of patients had coronary artery abnormalities, although the long-term outcomes for these findings are unclear. While an increasing proportion of patients received immunomodulatory therapies, there is, as yet, no evidence to support any specific treatment, and supportive intensive care remains important. Further evidence from clinical trials and long term follow up studies is crucial to inform clinical practice.

Conflict of Interest Statement

All authors have completed the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest, and have no conflicts of interest to disclose.

Data sharing statement

Requests for data sharing to the corresponding author.

Contribution statement

1 Literature Search
2 Figures
3 Study Design
4 Data Collection
5 Data Analysis
6 Data interpretation
7 Writing

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Figure 1: PIMS-TS admissions per week to UK Paediatric Intensive Care Units 1st April to 10th May 2020, with the cumulative total, and the expected UK cumulative total of similar conditions (Kawasaki's disease, Toxic Shock Syndrome, and Haemophagocytic Lymphohistiocytosis/Macrophage activation syndrome from the previous 5 years.

Table 1: Demographics and clinical features of PICU admission for 78 PIMS-TS patients presenting to UK Paediatric Intensive Care Units.

Table 2: Laboratory results for the first 4 days of PICU admission: median [interquartile range]Table 3: Interventions on PIMS-TS patients on the intensive care unit

Figure 2: Number of patients with PIMS-TS admitted to UK Paediatric Intensive Care units, and percentage receiving individual treatments over time. Weeks with <3 patients were excluded. IVIG: Intravenous Immunoglobulins. Biologic: any of Anakinra, Infliximab, Tocilizumab, Retiximab.

Table 4: Comparison between the demographics, highest or lowest laboratory tests over the first four days of admission, presenting features, and therapies of those patients with any coronary artery abnormalities (aneurysms or echogenicity) and those with normal coronary arteries, and between those not invasively ventilated and those invasively ventilated.

Supplementary table 1: Comparison between those patients meeting US CDC MIS-C definition, and those who may not have met US CDC MIS-C definition

Supplementary table 2:

UK PICU admissions per year for inflammatory conditions 2015-2019, from submissions to PICANet.