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Original article

An urgent need to review the approach to a febrile child in the COVID-19 era?

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Abstract

Background: There have been reports of a new hyperinflammatory syndrome in children defined as the Paediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19 (PIMS-TS). Our hospital has experienced a great proportion of children attending an Emergency Department (ED) with possible PIMS-TS so far reported in the UK.

Objectives: We describe the clinical and biochemical findings in children with possible PIMS-TS in the context of a local ED.

Settings: Queen Elizabeth Hospital (QEH), Woolwich, a District General Hospital (DGH) in South London.

Participants: From 14th March to 18th May 2020, children presenting to QEH and transferred to tertiary care for possible PIMS-TS, with a history of fever and hyperinflammatory symptoms, raised inflammatory markers and without a clear clinical or microbial cause were identified. Demographic data, clinical and laboratory data were recorded as median [range].

Results: 17 children (12 male) were identified aged 11 [1-16] years. 17/17 had a fever; other common symptoms were conjunctival injection, rash and gastrointestinal symptoms. Lymphopenia and raised inflammatory markers were evident. 15/17 were tested with nasopharyngeal and oropharyngeal SARS-CoV-2 PCR swabs and 15/15 were negative. Before transfer, one child required intubation and four required inotropes. All children were transferred to a tertiary unit, 10 within the first 24 hours. After transfer, 2/17 had microbial causes evident on urine/stool culture.

Conclusions: PIMS-TS is proving challenging to diagnose in a DGH ED because of heterogeneity of symptoms and laboratory markers, overlapping with other diseases, and cardiac complications despite deceptively benign presentations. There is an urgent need to review the approach to a febrile child in this setting, to optimise identification of PIMS-TS. Prognostic markers and risk stratification methods would help paediatricians working in the ED and general paediatric wards.

Keywords

Inflammatory syndrome, COVID-19, paediatric, fever, pandemic, multisystemic.

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Background

There have been reports of a new hyper-inflammatory syndrome in children, coinciding with the COVID-19 pandemic. The Royal College of Paediatrics and Child Health (RCPCH), UK, followed by the World Health Organisation, have recently released guidance on a Paediatric Inflammatory Multisystemic Syndrome temporally associated with COVID-19 (PIMS-TS) on 1st May and 15th May 2020, respectively [1, 2], with a case definition of a persistent fever and inflammation, evidence of organ dysfunction and exclusion of any other microbial cause, with a negative or positive SARS-CoV-2 PCR result (**Fig. 1**).

Children presenting with this new constellation of symptoms have been reported in the UK [3], in Italy [4] and also in the media from France and the US [5]. Five of the children described in this report were included in the Paediatric Intensive Care Unit (PICU) series by Riphagen et al. [3]. Possible complications described include cardiovascular compromise requiring ventilatory support or extra-corporeal membrane oxygenation (ECMO) and cardiac effects such as myocarditis and coronary aneurysms.

Queen Elizabeth Hospital (QEH), Woolwich, is a District General Hospital (DGH) in South London covering a local population of 66,043 children, with 62% being from a Black and Minority Ethnic group [6].

We summarise here the clinical and biochemical picture of 17 children presenting to QEH with symptoms meeting the RCPCH case definition of PIMS-TS (**Fig. 1**) and, discuss some of the challenges in diagnosis and management in the context of a local Emergency Department (ED).

Methods

From 14th March to 18th May 2020, children presenting to QEH and transferred to a tertiary Paediatric Unit, meeting the case definition, were

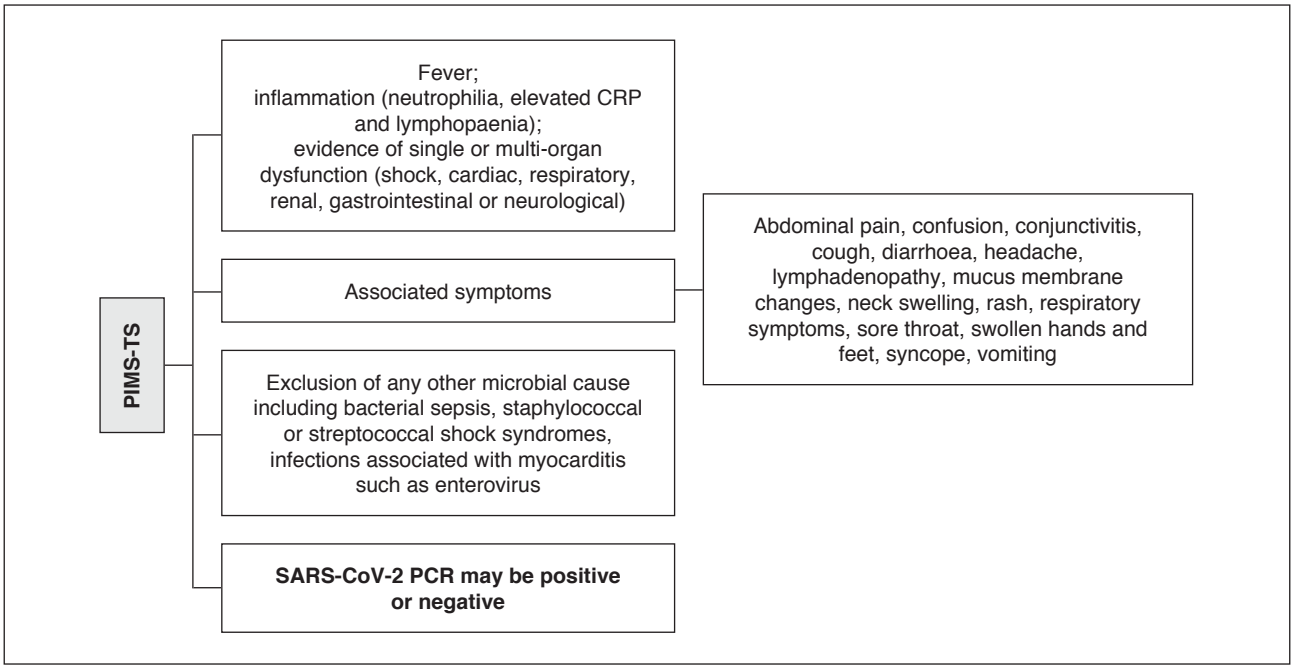

Figure 1. RCPCH definition of PIMS-TS [1].
CRP: C-reactive protein; PIMS-TS: Paediatric Inflammatory Multisystemic Syndrome temporally associated with COVID-19; RCPCH: Royal College of Paediatrics and Child Health.

identified. Demographic data, symptom type and duration, clinical findings and observations were retrospectively recorded.

Baseline blood tests included full blood count, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine kinase (CK), erythrocyte sedimentation rate (ESR), coagulation function, fibrinogen, D-dimer, liver function, renal function, vitamin D, and blood and urine cultures. Other investigations recorded where available included urine dipstick results, electrocardiographs (ECG) and chest radiographs. Nasopharyngeal and oropharyngeal SARS-CoV-2 PCR swabs are routinely taken from all children who attend ED with infectious symptoms and are likely to require admission – results are recorded where available.

Emergency treatment including antibiotics, fluid resuscitation and use of ventilatory and inotropic support before transfer were also recorded. All results are reported as median [range, number with data available, normal range].

Results

17 children (12 male) were identified. Age at presentation was 11 [1-16, n = 17] years. Seven were of Black African ethnicity, three Caucasian, three Eastern European, two Afro-Caribbean, one Asian Indian and one Hispanic. 15/17 were previously fit and well – one had a history of lupus and was on immunosuppressive therapy and one had epilepsy and took antiepileptic medication. 16/17 were up to date with immunisations and only one had a travel history of note – having recently come to the UK from Eastern Europe. One child reported recent contact with a person unwell with respiratory symptoms; a further four children had family members who were key workers during the COVID-19 pandemic. There was no history of previous infection, respiratory symptoms or fever in the preceding six weeks for any of the 17 children.

All 17 children had a fever with a duration of 4 [1-21, n = 17] days at presentation, following that, the most common presenting symptoms were vomiting without bile or blood, abdominal pain, diarrhoea, bilateral conjunctival injection without discharge, and polymorphic blanching rash. Other symptoms included hand changes including swelling and palmar desquamation bilaterally, cracked lips, chest pain and breathlessness (**Tab. 1**).

Table 1. Description of symptoms of 17 children presenting to QEH, who were transferred to tertiary care for possible PIMS-TS.

Symptom	No. of children
Fever	17/17 (100%)
Vomiting	13/17 (76.5%)
Abdominal pain	12/17 (70.6%)
Diarrhoea	11/17 (64.7%)
Non-purulent conjunctival injection	9/17 (52.9%)
Polymorphic rash	7/17 (41.2%)
Oedematous extremities	3/17 (17.6%)
Epistaxis	3/17 (17.6%)
Respiratory distress	2/17 (11.8%)
Chest pain	2/17 (11.8%)
Cracked lips	2/17 (11.8%)
Cough	1/17 (5.9%)

PIMS-TS: Paediatric Inflammatory Multisystemic Syndrome temporally associated with COVID-19; QEH: Queen Elizabeth Hospital (Woolwich, London, UK).

At presentation, all 17 children were febrile with a median temperature of 39.1°C [38.3-40.6, n = 17], 10 were tachycardic and nine were hypotensive for their age group, four were tachypnoeic but all children had normal oxygen saturations breathing unsupported. Venous blood gas recordings were largely normal with a lactate of 2.2 mmol/L [0.8-5.9, n = 15, normal < 1.9] and glucose of 6.3 mmol/L [4.8-8.7, n = 15].

Laboratory blood tests showed a lymphopenia of 0.6 x 10^9/L [0.2-6.1, n = 17, normal: 1.0-3.0 x 10^9/L] and raised inflammatory markers with a CRP of 146 mg/L [1-462, n = 17, normal: < 5], ferritin of 322 ug/L [73-1,142, n = 15, normal: 30-400], LDH 328 U/L [220-965, n = 12, normal: 0-190], with 3/12 children having a raised troponin T level (20, 73 and 347 ng/L, normal < 14) and 2/6 with raised BNP (806 and 69 pmol/L, normal 0-47). 8/8 children who had fibrinogen levels recorded were raised [median 4.35; 3.83-> 5 g/L; normal 1.8-3.6] and 8/8 D-dimer levels were raised [median 924 ng/mL; 242-14,764; n = 8, normal 0-230].

8/17 children had abnormal renal function (creatinine 57 umol/L [19-158, n = 17]), with a sodium of 135 mmol/L [125-140, n = 17, normal 135-145]. Median alanine transaminase was 36 U/L [9-72, n = 17, normal 0-41] and INR was 1.3 [1.1-1.5, n = 16, normal 0.9-1.2]. 10/13 children had a low vitamin D level (median 34 nmol/L [< 13 - 89, n = 13, normal 50-120]).

15/15 blood cultures and 9/11 urine cultures available were sterile at 48 hours with one urine culture positive for *E. coli* at 48 hours, with 50-

1,000 white cells on microscopy. Of the six stool cultures sent, one grew *Salmonella spp.* at five days and five had no growth. 2/17 children were transferred to tertiary care directly from the ED and did not have SARS-CoV-2 swabs sent at QEH. 15/15 nasopharyngeal and oropharyngeal SARS-CoV-2 swab results available were negative (**Tab. 2**).

12/17 were treated with ceftriaxone (50-80 mg/kg OD) and clindamycin (10 mg/kg QDS) – one additionally received acyclovir and gentamicin; three were treated with ceftriaxone only; one was treated with piperacillin-tazobactam, gentamicin and clindamycin; and one with ceftriaxone, clindamycin, metronidazole and gentamicin. One child also received intravenous immunoglobulin following tertiary advice and another child received both vitamin K for abnormal coagulative function and, following tertiary advice, aspirin while awaiting transfer for possible PIMS-TS.

Before transfer, 11/17 children required a fluid bolus with a total bolus volume ranging between 15-60 ml/kg of normal saline, 1/17 required intubation and mechanical ventilation for cardiovascular stabilisation and 4/17 required peripheral inotropes. All 17 children were transferred to a tertiary care unit with an on-site PICU and paediatric infectious disease specialists – 10/17 children were transferred within the first 24 hours of admission.

Discussion

Over two months, 17 children and young people presented with features of PIMS-TS to our DGH ED. Consistent features were a persistent fever associated predominantly with gastrointestinal symptoms and rash, accompanied by raised inflammatory markers and lymphopenia, in keeping with the recent case definition for PIMS-TS [1]. This report details 17 children who required transfer to a tertiary unit for ongoing management, with over half being haemodynamically unstable before transfer. Five of these 17 children were previously reported by Riphagen et al. in a case series of eight children with PIMS-TS at Evelina PICU. The authors found that 7/8 had abnormal echocardiograms, with a spectrum of ventricular impairment, dysfunction and dilated coronary arteries and one child died following a cerebral infarct after starting ECMO [3].

2/17 children described here, who were transferred directly from QEH ED, later had positive microbiology samples which identified a

Table 2. Description of laboratory markers in 17 children presenting to QEH, who were transferred to tertiary care for work up of possible PIMS-TS.

Marker	Normal range	Median [range; n]
White cell count, x 10^9/L	3.7-9.5	8.4 [2.7-21.4; 17]
Lymphocytes, x 10^9/L	1.0-3.0	0.6 [0.2-6.1; 17]
Neutrophils, x 10^9/L	2.0-7.0	7.0 [2.4-16.2; 17]
Platelet count, x 10^9/L	150-410	206 [88-437; 17]
Haemoglobin, g/L	130-170	113 [85-156; 17]
CRP, mg/L	< 5	146 [1-462; 17]
Ferritin, ug/L	30-400	322 [73-1,142; 15]
LDH, U/L	0-190	328 [220-965; 12]
CK, U/L	< 190	120 [34-249; 11]
ESR, mm/h	1.0-12.0	40 [5-118; 14]
INR	0.9-1.2	1.3 [1.1-1.5; 16]
D-dimer, ng/mL	0-230	924 [242-14,764; 8]
Fibrinogen, g/L	1.8-3.6	4.35 [3.83- > 5; 8]
High sensitivity troponin T, ng/L	< 14	< 13 [< 13-347; 12]
NT-Pro-BNP, pmol/L	0-47	20 [< 5-806; 6]
Sodium, mmol/L	135-145	135 [125-140; 17]
Potassium, mmol/L	3.5-5.1	4.0 [3.5-4.9; 17]
Creatinine, umol/L	Age-dependent	57 [19-158; 17]
Alanine transaminase, U/L	0-41	36 [9-72; 17]
Vitamin D, nmol/L	50-120	34 [< 13-89; 13]
Blood culture	Sterile 15/15	
Urine culture	Sterile 9/11	
	E. coli 1/11	
	No result available 1/11	
Stool culture	*Salmonella spp.* 1/6	
	No growth 5/6	
SARS-CoV-2 swab	Negative 15/15	

CK: creatine kinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; PIMS-TS: Paediatric Inflammatory Multisystemic Syndrome temporally associated with COVID-19; QEH: Queen Elizabeth Hospital, (Woolwich, London, UK).

source for symptoms (sepsis secondary to *E. coli* urinary tract infection in one child and *Salmonella spp.* in the stool culture in another). However, at the time of the initial presentation, PIMS-TS could not be ruled out and the clinical picture warranted urgent transfer to a tertiary unit without awaiting culture results, to ensure timely cardiac imaging and multidisciplinary review. Therefore, in the interest of accurately describing our experience from the perspective of a DGH ED with the results available at time of transfer, we have included these children in our analysis.

In the limited literature available describing this phenomenon, 2/10 children tested positive using SARS-CoV-2 PCR nasopharyngeal and oropharyngeal swabs in an Italian study [4] and 2/8 children tested positive in the South London PICU cohort [3]. Data show the sensitivity of testing for SARS-CoV-2 on a single upper respiratory tract sample is around 86% in symptomatic patients if conducted appropriately [7]. It is not possible to infer an association or causality to COVID-19, and not in the remit of this report to hypothesise pathophysiology for an emerging hyperinflammatory syndrome. In view of the RCPCH guidance [1], the febrile symptoms and the contemporaneous presentation, we have managed these children as suspected COVID-19 cases during their admission.

We have seen a large number of children presenting to a DGH and requiring transfer for management of possible PIMS-TS. There is no obvious explanation for a higher incidence to occur in this specific area in South London, and apart from their geographical distribution, no apparent association between our cases. There appears to be a minority of Caucasian children in our cohort, which appears reflective of the local population [6].

PIMS-TS is proving challenging to diagnose in the ED, firstly because of the heterogeneity of clinical presentation and laboratory markers. Secondly, some children appear haemodynamically unstable at presentation and others are admitted to the ward for monitoring before a clinical deterioration and retrieval. Additionally, the symptoms have substantial overlap with common serious and mild paediatric presentations including Kawasaki Disease, Toxic Shock Syndrome, Haemophagocytic Lymphohistiocytosis, Macrophage Activation Syndrome, gastroenteritis, streptococcal infections, urinary tract infections and viral illnesses [8]. One of our children was reviewed by the surgical team and suspected to have appendicitis, with an inflamed appendix visualised on abdominal ultrasound; however, the laboratory picture showed a normal neutrophil count and lymphopenia associated with raised CRP, ferritin and D-dimer. A recent correspondence by the paediatric surgical team at Great Ormond Street Hospital has also highlighted the risk of mistaking symptoms of PIMS-TS for appendicitis [9].

Of the 17 children who have been transferred to tertiary care for management of possible PIMS-TS, two subsequently had other microbial causes revealed making PIMS-TS less likely. In contrast, a 16-year-old boy later was found to have a left ventricular thrombus on echocardiogram, had an initial CRP of 85 mg/L at presentation, associated with a D-dimer of 14,764 ng/mL. This boy's mother had requested a medical appointment three times before attending our ED with a 9-day history of fever. There have been a range of CRP values in reported cases of possible PIMS-TS, including cases without raised inflammatory markers [10]. As the CRP trend is still unknown in this condition, basing management on a single result may be misleading, risking a possibility of 'missed cases'.

Therefore, there is an urgent need to review the approach to a febrile child in the ED, in order to optimise identification of PIMS-TS. This includes the threshold to send blood tests, decision for admission, discussion and transfer to tertiary care.

Following our DGH experience of 17 children who have been transferred with possible PIMS-TS, we have adapted our departmental approach to include a risk stratification for admission according to clinical presentation, haemodynamic status and inflammatory markers, with a low threshold for sending blood tests for any child presenting with a persistent fever without a clear cause (**Fig. 2**) [1, 11, 12]. Additionally, there is a significant prevalence of abnormal cardiac function and coronary aneurysms reported even in children who did not require mechanical ventilation or inotropes [4] and children can deteriorate after an initial normal echocardiograms and ECG [13]. Therefore, we have a low threshold for discussion and referral to tertiary care for serial echocardiograms and ongoing cardiology review.

The consequences of a lower threshold for investigations, including the PIMS-TS panel [1] in children who present equivocally, include difficulty in interpreting abnormal results in the context of a well child – the distributions of D-dimer, LDH,

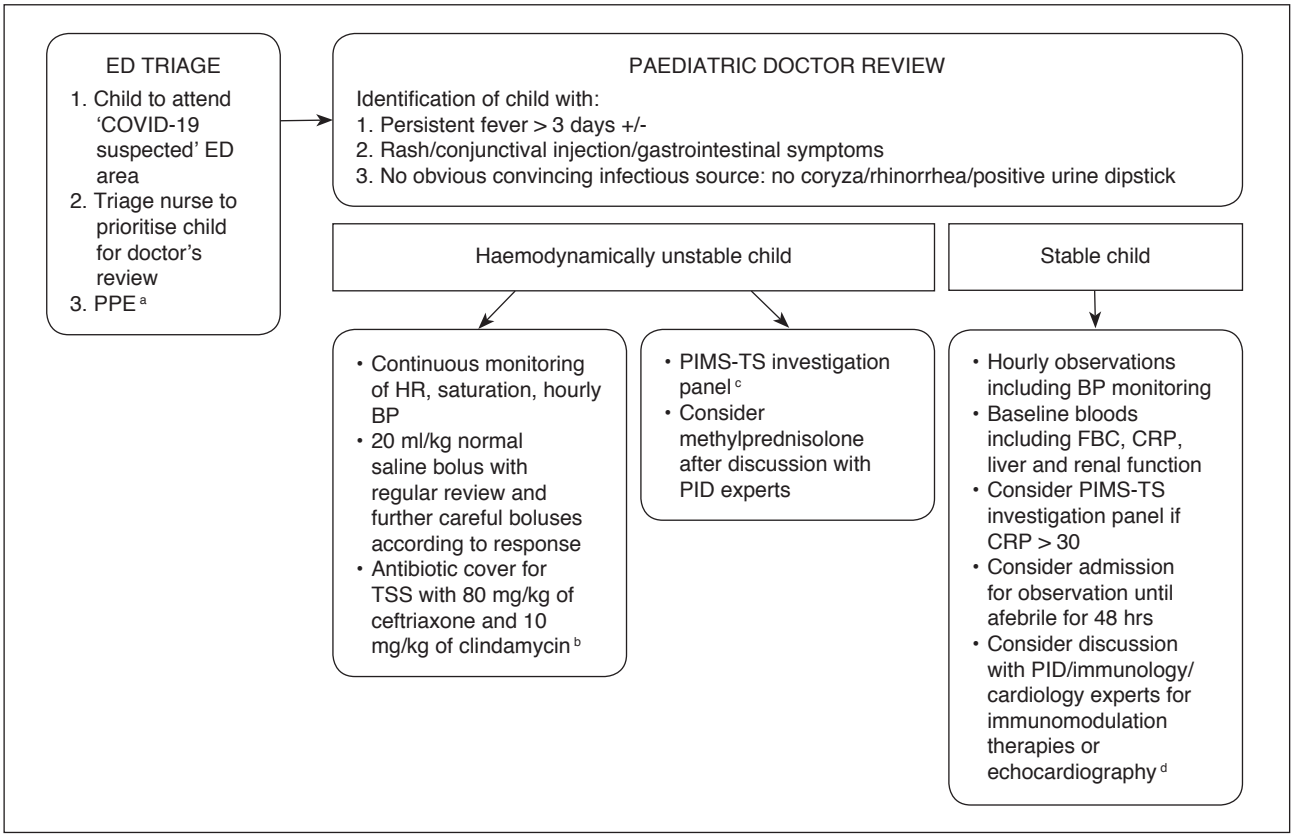

Figure 2. ED management of children with suspected PIMS-TS [1].
[a] According to PHE guidelines [11]; [b] dosing according to BNFc; [c] according to RCPCH guidelines [1]; [d] according to PICU guidelines [12]. BNFc: British National Formulary for Children; BP: blood pressure; CRP: C-reactive protein; ED: Emergency Department; FBC: full blood count; HR: heart rate; PHE: Public Health England; PICU: Paediatric Intensive Care Unit; PID: paediatric infection disease; PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with COVID-19; PPE: personal protection equipments; RCPCH: Royal College of Paediatrics and Child Health; TSS: toxic shock syndrome.

CK, ESR, and many other inflammatory markers in common upper respiratory tract or urinary tract infections are not widely understood. While currently there is capacity to refer equivocal cases and stable children to tertiary care for inpatient echocardiography, if we consider the rate of children who will present with a persistent fever and no obvious cause, ward capacity and tertiary care referral services may reach capacity and the commissioners need to be aware. However, missing a cardiac complication such as an aneurysm, however rare, could have significant implications in later life [14], therefore, we may have to review service pathways in the short and medium term.

Finally, we must consider the effect of coping with admission during the COVID-19 pandemic on children and families, including the anxiety induced by the possibility of PIMS-TS, and the challenges for doctors conducting these conversations because of the paucity of data.

As more data are published, the identification of prognostic markers and development of risk scores will help paediatricians working in the ED and general paediatric wards to identify and prioritise children at risk of PIMS-TS. Until then, it should be included in the differential diagnoses of a febrile child, although rare, in view of possible life-threatening complications.

Conclusion

As a General Paediatric Department in South London, we have experienced a new clinical picture of a hyperinflammatory syndrome emerging in the COVID-19 era, which fulfils the PIMS-TS case definition [1]. Following our DGH experience of 17 children requiring transfer to tertiary care, we have identified a need to review our threshold for blood tests, admission for observation, and discussion with tertiary multidisciplinary care. We hope to raise awareness of this condition and generate discussion of practice among the general paediatricians, emergency doctors and general practitioners to whom these children will present.

Abbreviations

BNFc: British National Formulary for Children
BP: blood pressure
CK: creatine kinase
CRP: C-reactive protein
DGH: District General Hospital
ECG: electrocardiographs
ECMO: extra-corporeal membrane oxygenation
ED: Emergency Department
ESR: erythrocyte sedimentation rate
FBC: full blood count
HR: heart rate
LDH: lactate dehydrogenase
OD: once daily
PHE: Public Health England
PICU: Paediatric Intensive Care Unit
PID: paediatric infection disease
PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with COVID-19
PPE: personal protection equipments
QDS: *quater die sumendum* (to be taken four times daily)
QEH: Queen Elizabeth Hospital
RCPCH: Royal College of Paediatrics and Child Health
TSS: toxic shock syndrome

Consent

Parents were informed and consented for collection of clinical and laboratory data and publication of non-identifiable patient information.

Declaration of interest

The Authors declare that there is no conflict of interest. Funding: nil.

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