Hyperinflammatory shock in children during COVID-19 pandemic

South Thames Retrieval Service in London, UK, provides paediatric intensive care support and retrieval to 2 million children in South East England. During a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome,[1] or toxic shock syndrome (typical number is one or two children per week). This case cluster formed the basis of a national alert.

All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. All children except one were well above the 75th centile

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	Age; weight; BMI; comorbidities	Clinical presentation		Organ support	Pharmacological treatment	Imaging results	Laboratory results	Microbiology results	PICU length of stay; outcome
		Initial	PICU referral						
Patient 1 (male, Afro-Caribbean)	14 years; 95 kg; BMI 33 kg/m²; no comorbidities	4 days >40°C; 3 days non-bloody diarrhoea; abdominal pain; headache	BP 80/40 mmHg; HR 120 beats/min; RR 40 breaths per min; work of breathing; SatO2 99% NCO2	MV, RRT, VA-ECMO	Dopamine, noradrenaline, argipressin, adrenaline milrinone, hydroxicortisone, IVIG, ceftriaxone, clindamycin	RV dysfunction/ elevate RVSP; ileitis, GB oedema and dilated biliary tree, ascites, bilateral basal lung consolidations and diffuse nodules	Ferritin 4220 µg/L; D-dimers 13·4 mg/L; troponin 675 ng/L; proBNP >35 000; CRP 556 mg/L; procalcitonin>100 µg/L; albumin 20 g/L; platelets 123×10⁹	SARS-CoV-2 positive (post mortem)	6 days; demise (right MCA and ACA ischaemic infarction)
Patient 2 (male, Afro-Caribbean)	8 years; 30 kg; BMI 18 kg/m²; no comorbidities	5 days >39°C; non-bloody diarrhoea; abdominal pain; conjunctivitis; rash	BP 81/37 mmHg; HR 165 beats/min; RR 40 breaths/ min; SVIA	MV	Noradrenaline, adrenaline, IVIG, infliximab, methylprednisolone, ceftriaxone, clindamycin	Mild biventricular dysfunction, severely dilated coronaries; ascites, pleural effusions	Ferritin 277 µg/L; D-dimers 4·8 mg/L; troponin 25 ng/L; CRP 295 mg/L; procalcitonin 8·4 µg/L; albumin 18 g/L; platelets 61×10⁹	SARS-CoV-2 negative; likely COVID-19 exposure from mother	4 days; alive
Patient 3 (male, Middle-Eastern)	4 years; 18 kg; BMI 17 kg/m²; no comorbidities	4 days >39°C; diarrhoea and vomiting; abdominal pain; rash; conjunctivitis	BP 90/30 mmHg; HR 170 beats/min; RR 35 breaths/ min; SVIA	MV	Noradrenaline, adrenaline, IVIG ceftriaxone, clindamycin	Ascites, pleural effusions	Ferritin 574 µg/L; D-dimers 11·7 mg/L; tropinin 45 ng/L; CRP 322 mg/L; procalcitonin 10·3 µg/L; albumin 22 g/L; platelets 103×10⁹	Adenovirus positive; HERV positive	4 days; alive
Patient 4 (female, Afro-Caribbean)	13 years; 64 kg; BMI 33 kg/m²; no comorbidities	5 days >39°C; non-bloody diarrhoea; abdominal pain; conjunctivitis	BP 77/41 mmHg; HR 127 beats/min; RR 24 breaths/ min; SVIA	HFNC	Noradrenaline, milrinone, IVIG, ceftriaxone, clindamycin	Moderate-severe LV dysfunction; ascites	Ferritin 631 µg/L; D-dimers 3·4 mg/L; troponin 250 ng/L; proBNP 13427 ng/L; CRP 307 mg/L; procalcitonin 12·1 µg/L; albumin 21 g/L; platelets 146×10⁹	SARS-CoV-2 negative	5 days; alive
Patient 5 (male, Asian)	6 years; 22 kg; BMI 14 kg/m²; autism, ADHD	4 days >39°C; odynophagia; rash; conjunctivitis	BP 85/43 mmHg; HR 150 beats/min; RR 50 breaths/ min; SVIA	NIV	Milrinone, IVIG, methylprednisolone, aspirin, ceftriaxone	Dilated LV, AVVR, pericoronary hyperechogenicity	Ferritin 550 µg/L; D-dimers 11·1 mg/L; troponin 47 ng/L; NT-proBNP 7004 ng/L; CRP 183 mg/L; albumin 24 g/L; platelets 165×10⁹	SARS-CoV-2 positive; likely COVID-19 exposure from father	4 days; alive
Patient 6 (female, Afro-Caribbean)	6 years; 26 kg; BMI 15 kg/m²; no comorbidities	5 days >39°C; myalgia; 3 days diarrhoea and vomiting; conjunctivitis	BP 77/46 mmHg; HR 120 beats/min; RR 40 breaths/ min; SVIA	NIV	Dopamine, noradrenaline, milrinone, IVIG, methylprednisolone, aspirin, ceftriaxone, clindamycin	Mild LV systolic impairment	Ferritin 1023 µg/L; D-dimers 9·9 mg/L; troponin 45 ng/L; NT-proBNP 9376 ng/L; CRP mg/L 169; procalcitonin 11·6 µg/L; albumin 25 g/L; platelets 158	SARS-CoV-2 negative; confirmed COVID-19 exposure from grandfather	3 days; alive
Patient 7 (male, Afro-Caribbean	12 years; 50kg; BMI 20 kg/m²; alopecia areata, hayfever	4 days >39°C; 2 days diarrhoea and vomiting; abdominal pain; rash; odynophagia; headache	BP 80/48 mmHg; HR 125 beats/min; RR 47 breaths/ min; SatO₂ 98%; HFNC FiO₂ 0.35	MV	Noradrenaline, adrenaline, milrinone, IVIG, methylprednisolone, heparin, ceftriaxone, clindamycin, metronidazole	Severe biventricular impairment; ileitis, ascites, pleural effusions	Ferritin 958 µg/L; D-dimer 24·5 mg/L; troponin 813 ng/L; NT-proBNP >35 000 ng/L; CRP 251 mg/L; procalcitonin 71·5 µg/L; albumin 24 g/L; platelets 273×10⁹	SARS-CoV-2 negative	4 days; alive
Patient 8 (female, Afro-Caribbean)	8 years; 50 kg; BMI 25 kg/m²; no comorbidities	4 days >39°C; odynophagia; 2 days diarrhoea and vomiting; abdominal pain	BP 82/41 mmHg; HR 130 beats/min; RR 35 breaths/ min; SatO₂ 97% NCO2	MV	Dopamine, noradrenaline, milrinone, IVIG, aspirin, ceftriaxone, clindamycin	Moderate LV dysfunction	Ferritin 460 µg/L; D-dimers 4·3 mg/L; troponin 120 ng/L; CRP 347 mg/L; procalcitonin 7·42 µg/L; albumin 22 g/L; platelets 296×10⁹	SARS-CoV-2 negative; likely COVID-19 exposure from parent	7 days; alive

ACA= anterior cerebral artery. ADHD=attention deficit hyperactivity disorder. AVR=atrioventricular valve regurgitation. BMI=body mass index. BP=blood pressure. COVID-19=coronavirus disease 2019. CRP=C-reactive protein. FiO_2=fraction of inspired oxygen. HERV=human endogenous retrovirus. HFNC=high-flow nasal canula. HR=heart rate. IVIG=human intravenous immunoglobulin. LV=left ventricle. MCA=middle cerebral artery. MV=mechanical ventilation via endotracheal tube. NIV=non-invasive ventilation. PICU=paediatric intensive care unit. RA=room air. RR=respiratory rate. RRT=renal replacement therapy. RV=right ventricle. RVSP=right ventricular systolic pressure. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. $SatO_2$=oxygen saturation. SVIA=self-ventilating in air. VA-ECMO=veno-arterial extracorporeal membrane oxygenation.

Table: **Demographics, clinical findings, imaging findings, treatment, and outcome from PICU**

for weight. Four children had known family exposure to coronavirus disease 2019 (COVID-19). Demographics, clinical findings, imaging findings, treatment, and outcome for this cluster of eight children are shown in the table.

Clinical presentations were similar, with unrelenting fever (38–40°C), variable rash, conjunctivitis, peripheral oedema, and generalised extremity pain with significant gastrointestinal symptoms. All progressed to warm, vasoplegic shock, refractory to volume resuscitation and eventually requiring noradrenaline and milrinone for haemodynamic support. Most of the children had no significant respiratory involvement, although seven of the children required mechanical ventilation for cardiovascular stabilisation. Other notable features (besides persistent fever and rash) included development of small pleural, pericardial, and ascitic effusions, suggestive of a diffuse inflammatory process.

All children tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on bronchoalveolar lavage or nasopharyngeal aspirates. Despite being critically unwell, with laboratory evidence of infection or inflammation[3] including elevated concentrations of C-reactive protein, procalcitonin, ferritin, triglycerides, and D-dimers, no pathological organism was identified in seven of the children. Adenovirus and enterovirus were isolated in one child.

Baseline electrocardiograms were non-specific; however, a common echocardiographic finding was echo-bright coronary vessels (appendix), which progressed to giant coronary aneurysm in one patient within a week of discharge from paediatric intensive care (appendix). One child developed arrhythmia with refractory shock, requiring extracorporeal life support, and died from a large cerebrovascular infarct. The myocardial involvement[2] in this syndrome is evidenced by very elevated cardiac enzymes during the course of illness.

See Online for appendix

All children were given intravenous immunoglobulin (2 g/kg) in the first 24 h, and antibiotic cover including ceftriaxone and clindamycin. Subsequently, six children have been given 50 mg/kg aspirin. All of the children were discharged from PICU after 4–6 days. Since discharge, two of the children have tested positive for SARS-CoV-2 (including the child who died, in whom SARS-CoV-2 was detected post mortem). All children are receiving ongoing surveillance for coronary abnormalities.

We suggest that this clinical picture represents a new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection manifesting as a hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki disease shock syndrome. The multifaceted nature of the disease course underlines the need for multispecialty input (intensive care, cardiology, infectious diseases, immunology, and rheumatology).

The intention of this Correspondence is to bring this subset of children to the attention of the wider paediatric community and to optimise early recognition and management. As this Correspondence goes to press, 1 week after the initial submission, the Evelina London Children's Hospital paediatric intensive care unit has managed more than 20 children with similar clinical presentation, the first ten of whom tested positive for antibody (including the original eight children in the cohort described above).

We declare no competing interests.

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1 Zhang M-M, Shi L, Lin Y, Liu Y. Clinical analysis of Kawasaki disease shock syndrome. *Chin Med J (Engl)* 2017; **130:** 2891–92.

2 Liu P, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020; published online April 15. DOI:10.1161/CIRCULATIONAHA.120.047549.

3 Li Y, Zou L, Wu J, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN- as biomarkers for early recognition. *Pediatr Rheumatol Online J* 2019; **17:** 1.

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