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LETTER

Outbreak of hepatitis in children: clinical course of children with acute liver failure admitted to the intensive care unit

Akash Deep[1,2*], Tassos Grammatikopoulos[2,3], Nigel Heaton[4], Anita Verma[5] and Anil Dhawan[3*]

Dear Editor,

A recent outbreak of acute non-A-E hepatitis with serum transaminases greater than 500 IU/L identified in children aged under 16 years reported in United Kingdom (UK) has become a serious cause for concern for public health authorities and paediatric liver and critical care services [1]. From 1 January to 16 May 2022, UK public health authorities have reported 197 cases with median age 3 years, male (50%), from all regions of UK with 11 children requiring liver transplantation (LT).

Paediatric liver services are centralised to 3 centres in the UK with King's College Hospital (KCH), London being the largest paediatric LT centre. Eight children were admitted to paediatric intensive care unit (PICU) at KCH from February to May 2022. In this report, we describe the ICU course of these patients (Table 1). All but one were < 5 years old; all were from White ethnic background. All children presented with abdominal symptoms (diarrhoea and vomiting) followed by jaundice and raised transaminases (alanine aminotransferase (AST) and aspartate aminotransferase (AST) > 2500 IU/L) with adenovirus DNA positivity from whole blood. All patients were screened for an extended viral panel from blood, urine, stool and respiratory samples according to UK Health Security Agency (UKHSA) recommendations [1]. Two patients had history of SARS-CoV-2 in the preceding 8 weeks. 6 out of these 8 patients had antibodies positive for SARS-CoV-2, but all were tested via polymerase chain reaction (PCR) and resulted negative for SARS-CoV-2 and none had COVID vaccine. It must be noted that according to the technical briefing of the UKHSA 25 April 2022, population cumulative seropositivity of SARS-CoV-2 was 47% in 1–4 year olds and 67% in 5–11 years old in January–February 2022 (unpublished UKHSA seroprevalence data) [2]. Official recent update on the seroprevalence in this age group is awaited.

The main reason for PICU admission was neurologic deterioration (hepatic encephalopathy) with rising ammonia, lactate and international normalized ratio (INR) (peak values—Table 1). Patients were neuro-monitored with transcranial Dopplers (TCD) and reversed jugular venous saturations. Four patients had abnormal pulsatility index on TCD and 6 showed low reversed jugular venous saturations (lowest being 25.9%) requiring intervention. They were neuro-protected with early initiation of high-volume continuous kidney replacement therapy (CKRT) (minimum CKRT dose-60 mL/kg/h initiated within 24 h of PICU admission), plasma exchange, use of hypertonic saline, noradrenaline to maintain cerebral perfusion pressure, temperature control and thiopentone infusion. All received *N*-acetylcysteine and those positive for adenovirus received at least 2 doses of cidofovir.

We used INR > 4 as the LT listing criteria. All eight children survived with six requiring LT (one was re-transplanted) and two survived without LT with one of them delisted after 6 days on the super-urgent list as his clinical and biochemical condition improved. One patient

*Correspondence: akash.deep@nhs.net; anil.dhawan@nhs.net
[1] Paediatric Intensive Care Unit, King's College Hospital NHS Foundation Trust, Denmark Hill, London, UK
[3] Paediatric Liver, GI and Nutrition Centre and Mowatlabs, King's College Hospital NHS Foundation Trust, London, UK
Full author information is available at the end of the article

Akash Deep and Anil Dhawan are joint senior and corresponding authors.

Table 1 Intensive care course of children admitted with acute liver failure due to hepatitis outbreak

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (years. months)	2.6	5	5.10	3.11	2.5	2.9	2 .11	1.8
Weight (kg)	14.2	19.8	19.4	15.1	13.6	13.7	14.8	8.2
Ethnic background	White	White	White	White	White	White	White	White
Clinical presentation at referral	Diarrhoea, vomiting for 2 weeks followed by jaundice	Vomiting, diarrhoea, abdominal pain 2 weeks, dark urine and jaundice 5 days later	Diarrhoea, nausea dark urine and jaundice, history of COVID 4 weeks back	Vomiting followed by jaundice and diarrhoea	Vomiting and diarrhoea	Diarrhoea, vomiting, and jaundice	Jaundice, drowsiness, diarrhoea	3 days of jaundice, dark urine, pale stools, loss of appetite, 6 weeks back—COVID positive
Duration of symptoms before admission to PICU (days)	20	8	16	15	20	9	7	11
Peak INR	3.4	5	4.88	9.86	7.8	4.02	5.9	3.7
Peak bilirubin (µmol/L)	249	347	389	410	294	235	368	207
Peak AST/ALT (IU/L)	5641/4518	4200/3604	3906/3789	4837/3877	4896/4854	3445/2521	6587/3770	2652/3345
Peak ammonia (µmol/L)	95	142	149	173	166	84	139	133
Peak lactate (mmol/L)	11.0	3.6	2.7	2.7	5.10	5.9	3.9	5.5
Blood virology results (maximum quantitative levels)	Adenovirus DNA positive (57,456 copies/mL)	Adenovirus DNA positive (69,561 copies/mL)	Adenovirus DNA positive (234,308 copies/mL)	Adenovirus DNA positive (236,586 copies/mL)	Adenovirus DNA positive (20,293 copies/mL) EBV positive (143,604 IU/mL)	Adenovirus DNA positive (164,732 copies/mL)	Adenovirus DNA positive (318,200 copies/mL) EBV positive-4980 IU/mL	Adenovirus at admission—negative; became positive 6 days after admission (84,737 copies/mL)
PCR for SARS-CoV-2 positive Y/N	N	N	N	N	N	N	N	N
SARS-CoV-2 antibody positive (Y/N/ID)	Y	Y	ID	Y	N	Y	Y	Y
Grade of encephalopathy	2	1	1	1	1	1	1	3
Ventilated yes/no	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peak PIP/PEEP (cm H_2O)	22/5	22/6	22/8	20/5	19/5	20/5	24/7	17/6
Peak FiO_2	0.45	0.45	0.80	0.5	0.4	0.3	1.0	0.4
Duration of mechanical ventilation (days)	4	5	25	10	5	4.5	17	10

Table 1 (continued)

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Cardiovascular								
Vasopressors	No	Noradrenaline Max dose-0.15 mcg/kg/min	Noradrenaline Max dose-0.34 mcg/kg/min	Noradrenaline Max dose-0.45 mcg/kg/min	Noradrenalin Max dose-0.35 mcg/kg/min	Noradrenaline Max dose-0.4 mcg/kg/min	Noradrenaline Max dose-0.5 mcg/kg/min	Noradrenaline Max dose-0.5 mcg/kg/min
Neuromonitoring and neuroprotection								
Neurologic monitoring	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TCD	Normal	Normal	Higher PI bilaterally	High PI bilaterally	Normal	Normal	High PI bilaterally	High PI bilaterally
Reversed jugular venous saturations yes/no	Yes Lowest-33%	Yes Lowest-47.1%	Yes Lowest-50.3%	Yes Lowest-46.8%	No	Yes 60–80%	Yes Lowest-59.4%	Yes Lowest-25.9%
Neuroprotective measures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maintain MAP > 50th centile	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Use of thiopentone	Yes	Yes	No	Yes	No	No	Yes	Yes
Hypertonic saline	Yes	Yes	Yes	Yes	No	Yes	No	No
Cooling to maintain temperature—36°	No	No	No	Yes	No	No	Yes	Yes- up to 35 °C
CRRT								
Use of CRRT	No	Yes	Yes	Yes	No	No	Yes	Yes
Initiation of CRRT from PICU admission (h)	–	50	11	7	–	–	4	24
Maximum CRRT dose (mL/kg/h)	–	60	60	80	–	–	60	80 Received plasma exchange 1.5–2 times plasma volume
Outcomes								
Outcome alive/death	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive
SNL or SLT	SNL	SLT	SLT	SLT	SLT-2 transplants Auxiliary and orthotopic transplants	SLT	SLT	SNL

Table 1 (continued)

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Median time awaiting LT (days)	Not listed	2	3	4	3	1	6	Initially listed but gradually improved clinically and biochemically and was delisted after 6 days
Cadaveric/living donor	–	DBD	DBD	Living related—LLS	Auxiliary—Whole DBD graft 1—Orthotopic LLS DBD	DBD–LLS	LLS–DBD	/
Length of stay in PICU	7 days	4 days	22 days and still in PICU	17 days	7 days—1st transplant 5 days—2nd transplant	6 days and 15 h	22 days	12 days
Explant histopathology features	Not applicable	Adenovirus immunostaining negative No significant fibrosis Portal tracts show moderate mixed inflammation, moderate lobular inflammation with areas of necrosis	Adenovirus immunostaining negative Portal and perisinusoidal fibrosis, portal areas with inflammation, fibrosis—subacute time frame	Adenovirus immunostaining negative; moderate inflammation, hepatocellular necrosis	Adenovirus immunostaining staining negative Portal and perisinusoidal fibrosis, portal areas showing mixed inflammation	Adenovirus immunostaining negative Moderate to severe lobular inflammation with patchy confluent necrosis	Adenovirus immunostaining negative Mixed inflammation at the portal areas, multiacinar confluent hepatocellular necrosis, no fibrosis	Not applicable

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CRRT* continuous renal replacement therapy, *DBD* donation after brain death, *EBV* Epstein–Barr virus, FiO_2 fraction of inspired O_2, *ID* indeterminate, *INR* international normalised ratio, *LOS* length of stay, *LSS* left lateral segment, *LT* liver transplant, *MAP* median arterial pressure, *PI* pulsatility index, *PICU* paediatric intensive care unit, *PEEP* positive end expiratory pressure, *PIP* peak inspiratory pressure, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SLT* survival with liver transplant, *SNL* survival with native liver, *TCD* transcranial doppler

received methylprednisolone for anti-nuclear antibody positivity. Five patients received LT from donors deceased after brain death diagnosis including one auxiliary graft and one received a liver graft from living donor. Median waiting time to LT from listing was 3 days (range 1–6 days). Median length of stay in PICU was 12 days (4–22 days). Longer length of stay as associated with the use of neuroprotective measures especially deep sedation pre- and post-transplant. All six explants were negative for adenovirus by immunostaining. Details of histopathology of liver explants is shown in Table 1.

Investigations as to causation in the UK-wide cases found a high occurrence of positivity for adenovirus (68% of those tested, primarily from blood), most commonly 41F type.

However, histopathology studies on the explant liver and in a few who have had biopsies have not demonstrated evidence of adenovirus in hepatocytes, though all of them revealed hepatocyte necrosis and parenchymal collapse. The lack of adenovirus demonstration in hepatocytes, but severe liver injury leading to acute liver failure may be related to an aberrant immune response from the host's immune system of liver. Detailed characterisation of immune infiltrates in the liver of children who progress to liver failure may identify a subgroup that respond to immunosuppression including steroids and avoid liver transplantation. Media speculations relating this outbreak to SARS-CoV-2 or vaccine are not yet substantiated. The presence of adenovirus in these children raises a hypothesis of SARS-CoV-2 superantigen mediated disease potentiated by a second virus [3]. The hypothesis of an aberrant immune response in those (< 10%) who required urgent transplantation is being investigated.

With a limited number of donor organs and stretched paediatric critical care capacity (at one stage, four of our patients were receiving CRRT), it is important to identify patients who should be listed for LT and others who are likely to recover with supportive therapy. The majority of children who develop hepatitis can be managed locally with expert advice from tertiary liver centres. However, good outcomes both with and without transplant can be achieved in those who progress to acute liver failure (ALF) by dedicated liver intensive care including early referral to liver transplant centres, early recognition of neurologic deterioration, early institution of high-volume extracorporeal therapies, close neuro-monitoring and neuroprotection and working in close collaboration with hepatology and transplant colleagues to decide medical treatments and timing of listing of these patients [4, 5]. As our understanding of the mechanism underpinning these cases (especially if immune-mediated) become clear, it might be possible to manage these children with intensive care therapies in conjunction with steroids and other immunomodulatory drugs.

Author details
[1] Paediatric Intensive Care Unit, King's College Hospital NHS Foundation Trust, Denmark Hill, London, UK. [2] Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK. [3] Paediatric Liver, GI and Nutrition Centre and Mowatlabs, King's College Hospital NHS Foundation Trust, London, UK. [4] Liver Transplant Surgery, Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK. [5] Department of Microbiology, King's College Hospital NHS Foundation Trust, London, UK.

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Declarations

Conflicts of interest
AkD is the Chair of Scientific Affairs of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC). AnD is a recipient of a National Institute for Health Research (NIHR) i4i grant to develop treatment for ALF with alginate microbead embedded hepatocytes and a Medical Research Council (MRC) grant for a first in human clinical trial of alginate embedded human hepatocytes as treatment for ALF (MRC *MR/V038583/1*), has been paid by Ambys and J and J for consultation, has a patent pending approval for alginate microbead manufacturing. TG is a consultant for Albireo. None of the other authors declare any conflict of interest.

Ethical approval
Since, this was already collected anonymised data, no ethics approval was required.

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