ORIGINAL ARTICLE

Clinical Spectrum of Children with Acute Hepatitis of Unknown Cause

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ABSTRACT

BACKGROUND

Since January 2022, there has been an increase in reports of cases of acute hepatitis of unknown cause in children. Although cases have been reported across multiple continents, most have been reported in the United Kingdom. Investigations are ongoing to identify the causative agent or agents.

METHODS

We conducted a retrospective study involving children referred to a single pediatric liver-transplantation center in the United Kingdom between January 1 and April 11, 2022. These children were 10 years of age or younger and had hepatitis that met the case definition of the U.K. Health Security Agency for confirmed acute hepatitis that was not hepatitis A through E and did not have a metabolic, inherited or genetic, congenital, or mechanical cause, in the context of a serum aminotransferase level greater than 500 IU per liter. We reviewed medical records and documented demographic characteristics, clinical features, and results of liver biochemical, serologic, and molecular tests for hepatotropic and other viruses, as well as radiologic and clinical outcomes. The outcomes were classified as an improving condition, liver transplantation, or death.

RESULTS

A total of 44 children had hepatitis that met the confirmed case definition, and most were previously healthy. The median age was 4 years (range, 1 to 7). Common presenting features were jaundice (in 93% of the children), vomiting (in 54%), and diarrhea (in 32%). Among the 30 patients who underwent molecular testing for human adenovirus, 27 (90%) were positive. Fulminant liver failure developed in 6 patients (14%), all of whom received a liver transplant. None of the patients died. All the children, including the 6 who received liver transplants, were discharged home.

CONCLUSIONS

In this series involving 44 young children with acute hepatitis of uncertain cause, human adenovirus was isolated in most of the children, but its role in the pathogenesis of this illness has not been established.

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The World Health Organization (WHO) published a disease outbreak notification on April 15, 2022, after 10 cases of acute hepatitis of unknown cause in children were reported across central Scotland between January and March 2022.[1] The WHO further reported at least 650 probable cases that were diagnosed between April 5 and May 26, 2022, across 33 countries, from the Eastern Mediterranean, European, Pan American, Southeast Asian, and Western Pacific regions.[2] Most of the additional patients (222 children [34.2%]) were from the United Kingdom.

A U.K. Health Security Agency (UKHSA) technical briefing released on May 19, 2022, provided an epidemiologic update on 197 confirmed and possible cases reported between January 1 and May 16, 2022, in the United Kingdom.[3] The children presented with jaundice (in 68.8%), vomiting (in 57.6%), pale stools (in 42.7%), and gastrointestinal symptoms, including diarrhea (in 43.1%), nausea (25.7%), and abdominal pain (36.1%). All the children had negative tests for common infective causes, including hepatitis A through E, cytomegalovirus (CMV), and Epstein–Barr virus (EBV), and no common toxin exposure or travel history was reported. A total of 11 children (5.6%) underwent liver transplantation.[3]

Public health agencies across the world are collaborating and investigations are ongoing to delineate the pathogenesis of this illness. Of the 197 children in the United Kingdom with cases reported in the UKHSA technical briefing report, 179 underwent molecular testing for human adenovirus. Of these children, 116 (64.8%) were positive, and a possible relationship between acute hepatitis and human adenovirus is being investigated.[3]

We work at one of the three specialized pediatric liver-transplantation centers in the United Kingdom, providing ongoing medical advice for the treatment of children with liver disease in regional hospitals through the National On-Call Referral System (NORSe). Children with acute liver failure and those who are likely to have progression to acute liver failure are transferred to our center for further inpatient care. In this report, we describe the clinical presentation, course of illness, and early outcomes of acute hepatitis of unknown cause in children who were referred to our center from various regions of the United Kingdom. The UKHSA was informed of all the cases, and this cohort was included in the pooled analysis reported in the UKHSA technical briefing and case update release.[3]

Methods

Patients

All the children who were 16 years of age or younger and who were referred to our unit between January 1 and April 11, 2022, underwent screening. The children who were included in this report are those who were 10 years of age or younger and had acute hepatitis that was consistent with the confirmed case definition of the UKHSA (i.e., acute hepatitis that is not due to hepatitis A through E viruses or a metabolic, inherited or genetic, congenital, or mechanical cause, with a serum aminotransferase level >500 IU per liter in a child who is ≤10 years of age presenting after January 1, 2022).[3]

Testing and Definitions

Demographic, biochemical, and radiologic data were collected from NORSe records and inpatient notes. We recorded the results of the full blood count, liver biochemical tests, and coagulation screening. We also recorded the results of tests to diagnose the cause of acute hepatitis, including viral serologic tests for hepatitis A through E viruses and molecular tests for CMV, EBV, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), parvovirus, and adenovirus infections in blood, fecal, and respiratory samples (when available). The interval from the onset of jaundice to the peak serum bilirubin and alanine aminotransferase (ALT) levels was recorded.

Some patients underwent additional testing because of elevated liver aminotransferase levels; these tests included ferritin and serum alpha$_1$-antitrypsin levels, celiac screening, and serum immunoglobulin, autoantibody, ceruloplasmin, and serum paracetamol levels; these results were recorded when available. All the children underwent abdominal ultrasonographic examination, and liver histologic findings were included if a biopsy sample was available or if the liver was explanted for transplantation. Histologic findings were analyzed after the application of hematoxylin Verhoeff–van Gieson stain, reticulin stain, orcein stain, periodic acid–Schiff stain, periodic

acid–Schiff stain with diastase digestion, Perls Prussian blue stain, and viral immunostains.

Acute liver failure was defined as coagulopathy (not corrected with vitamin K) with a prothrombin time of greater than 15 seconds and an international normalized ratio of greater than 1.5 in patients with encephalopathy, or as a prothrombin time of greater than 20 seconds and an international normalized ratio of greater than 2 in patients with or without encephalopathy.[4]

TREATMENT

Patients were treated in accordance with our acute liver failure protocol, which included intravenous broad-spectrum antibiotics, antifungal agents, a proton-pump inhibitor, vitamin K, and restriction of fluids to a 70% maintenance level with dextrose to maintain normoglycemia. Children who did not have liver failure received supportive care with oral fat-soluble vitamins (vitamins K, A, D, and E) and ursodeoxycholic acid and were monitored closely with blood tests to detect clinical deterioration.

Children with acute liver failure were listed in the super-urgent category 6 for liver transplantation under the National Health Service Blood and Transplant 195/7 U.K. policy.[5] This category prioritizes acute liver failure over other indications for liver transplantation. Cidofovir was administered after transplantation only if the whole-blood polymerase-chain-reaction (PCR) assay for human adenovirus indicated a viral load greater than 500 copies per milliliter.

STATISTICAL ANALYSIS

Clinical outcomes were recorded in three categories: improving condition (i.e., resolving liver dysfunction, as indicated by a consistent decrease in the bilirubin and aminotransferase levels with normal coagulation), liver transplantation, and death. The number of days from initial presentation to listing for liver transplantation, the time from jaundice to encephalopathy, the interval from listing for transplantation to transplantation, and the human adenovirus viral load on PCR after transplantation were reported as medians with a range. The use of antiviral treatment with cidofovir was recorded for the patients who underwent transplantation.

RESULTS

PATIENTS INCLUDED IN THE CASE SERIES

Of the 50 children with acute hepatitis referred to our center between January 1 and April 11, 2022, a total of 44 had hepatitis that met the definition of a confirmed case (Fig. 1). Of the 6 children who were excluded, 3 were positive for hepatitis A, 1 was positive for EBV, 1 had streptococcal sepsis, and 1 had an ALT level below 500 IU per liter. A total of 13 of the 44 children were transferred to our center, and the rest were cared for locally. The numbers of children who were admitted to our center and those who eventually underwent liver transplantation between January and April 2022 were substantially higher than the numbers in the previous years between 2012 and 2021. From

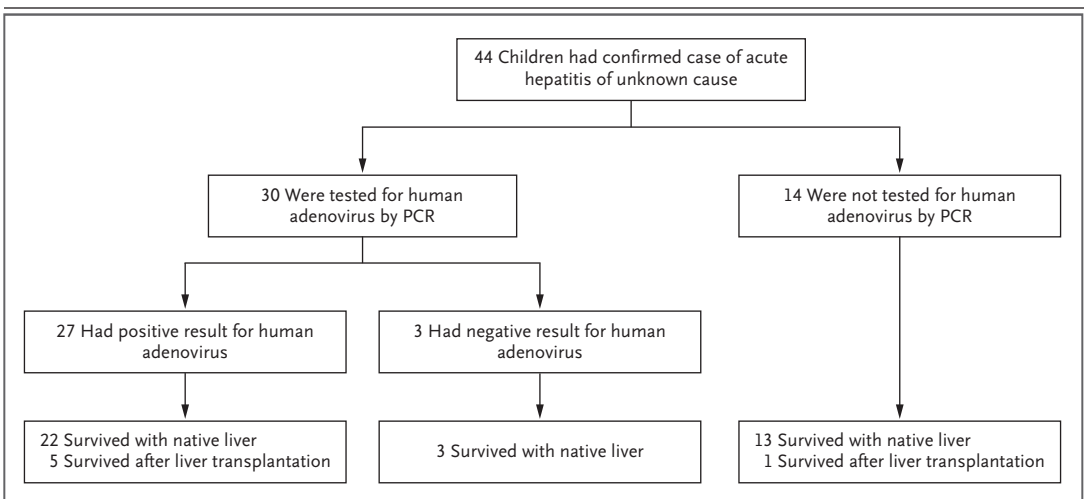

Figure 1. Confirmed Cases and Outcomes of Acute Hepatitis of Unknown Cause.

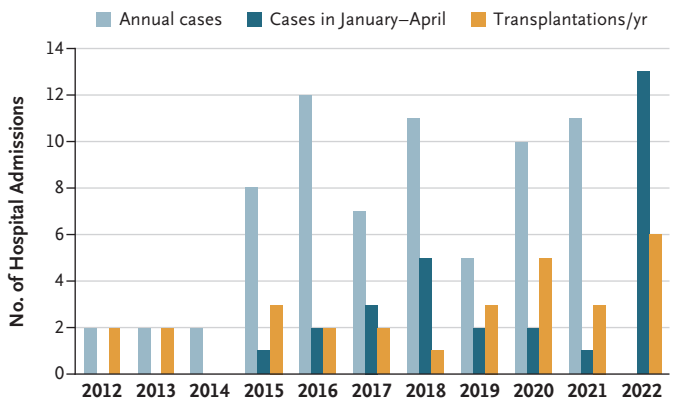

Figure 2. Hospital Admissions for Acute Hepatitis of Unknown Cause and Liver Transplantation for Acute Liver Failure of Unknown Cause.

Annual data from 2012 through 2021 and data for the months from January through April between 2012 and 2022 are shown. Data for transplantations in 2022 are for January 11 through April 11.

Table 1. Presenting Symptoms and Ultrasonographic Findings.

Symptom or Finding	All Children (N=44)
	no. (%)
Presenting features	
Jaundice	41 (93)
Vomiting	24 (54)
Diarrhea	14 (32)
Pale stools	13 (30)
Abdominal pain	12 (27)
Lethargy	10 (23)
Dark urine	6 (14)
Coryza	6 (14)
Pyrexia	4 (9)
Pruritus	1 (2)
Findings on abdominal ultrasonographic examination	
Gall bladder thickening	20 (45)
Mild hepatomegaly	12 (27)
Mild splenomegaly	8 (18)
Normal findings	6 (14)
Abdominal lymph nodes	6 (14)
Abdominal fluid	1 (2)
"Starry sky" appearance*	2 (4)

* Starry sky appearance of the liver is caused by accentuated portal venules with diminished liver parenchymal echogenicity.

January through April 2022, a total of 13 children were admitted to our center with acute hepatitis of unknown cause, as compared with 1 to 5 children during the same months in the previous years (Fig. 2).

CLINICAL PRESENTATION AND DIAGNOSTIC TESTING

Only 3 of the 44 children had chronic health conditions. Of these 3 children, 1 had an allergy to cow's milk, 1 had constipation, and 1 had autism. The patients were widely distributed geographically across the United Kingdom (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and among the children for whom records were available (80%), all were White. The children came to medical attention predominantly because of jaundice (in 93%) (Table 1). Other common presenting features included vomiting (in 54%), diarrhea (in 32%), abdominal pain (in 27%), and lethargy (in 23%), and these features were present at a median of 3 days (range, 0 to 42) before the onset of jaundice.

Clinical examination findings at presentation were documented in 34 children. These findings included icterus in 24 children, hepatomegaly in 18, a normal abdominal examination in 10, and a completely normal clinical examination in 2.

Table 2 lists the demographic characteristics of the patients and the values at presentation and the peak values of liver biochemical tests. Among the 38 children who did not undergo liver transplantation, the median interval from the identification of jaundice to the peak bilirubin level was 5 days (range, 1 to 11) and to the peak ALT level, 3 days (range, 1 to 8). After a median of 2.5 days (range, 1 to 9), a prothrombin time of greater than 15 seconds developed in 16 children.

The intervals from the onset of jaundice to the peak bilirubin level, ALT level, and prothrombin time were not analyzed in the transplantation group because the natural history of the disease is altered by transplantation. All the patients with a prothrombin time of 20 seconds or less recovered spontaneously, whereas 6 patients who had illness that progressed, with a prothrombin time of greater than 20 seconds despite the administration of vitamin K, eventually underwent transplantation. The interval from the onset of jaundice to a prothrombin time of greater than 20 seconds was recorded at a median of 7 days (range, 5 to 9) in the transplantation group.

Table 2. Demographic and Clinical Characteristics of the Patients.*

Variable	Total Cohort (N=44)	Children Who Did Not Undergo Transplantation (N=38)	Children Who Underwent Transplantation (N=6)	Normal Range
Median age (range) — yr	4 (1–7)	4 (1–7)	2 (1–4)	
Sex — no. (%)				
Female	24 (55)	21 (55)	3 (50)	
Male	20 (45)	17 (45)	3 (50)	
Median white-cell count (range) — per mm^3†	9000 (5000–15,000)	8000 (5000–15,000)	10,000 (8000–12,000)	5000–16,000
Median serum bilirubin level (range) — mg/dl				
At presentation	5.8 (0.3–10.6)	5.4 (0.3–10.6)	7.6 (6.9–9.4)	0–1
Peak	8.2 (0.3–17.1)	5.4 (0.3–14.8)	15.8 (11.4–17.1)	0–1
Median alanine aminotransferase level (range) — IU/liter				
At presentation	2558 (53–5897)	2476 (53–5086)	2978 (1798–5897)	0–41
Peak	2858 (603–6279)	2694 (603–5086)	3410 (2819–5897)	0–41
Median γ-glutamyl transferase level (range) — IU/liter‡	122 (25–348)	126 (25–348)	116 (59–165)	0–25
Median serum albumin level (range) — g/liter‡	36 (27–43)	36 (27–43)	35 (31–38)	41–52
Median prothrombin time (range) — sec				
At presentation	14.0 (12.0–28.0)	13.2 (12.0–19.2)	16.6 (15.3–28.0)	9–13
Peak	14.2 (13.0–86.0)	13.7 (15.0–19.2)	50.0 (36.0–86.0)	9–13

* Values shown are values at presentation unless otherwise specified. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.
† Data were missing for 12 patients (11 children who did not undergo transplantation and 1 child who underwent transplantation).
‡ Data were missing for 3 patients who did not undergo transplantation.

The complete blood count was available in 32 patients and was unremarkable in 31 patients. One patient had a low hemoglobin level and a low neutrophil count at presentation. They each received one blood transfusion, and 3 days later, the counts recovered to normal levels. Renal function remained normal in all the patients.

The ferritin level was available in 12 children and ranged from 31 to 5082 μg per liter (normal range, 5.3 to 99.9). The serum immunoglobulin level was available in 34 children, of whom 32 had levels in the normal range for children (5.46 to 16.05 g per liter) and 2 had higher-than-normal levels, at 18 g per liter and 20 g per liter, respectively. These 2 children did not undergo liver transplantation. They were retested at follow-up and had normal immunoglobulin levels. The autoimmune profile was available in 35 children; 28 had normal results, 7 had positive tests for antinuclear antibodies (1:80 titer in 1 patient and the rest weakly positive), and 6 had positive tests for smooth-muscle antibodies (1:40 in 1 patient and the rest weakly positive). Eight children underwent celiac screening, and the serum ceruloplasmin level was measured in 12 children, the paracetamol level in 7, and the $alpha_1$-antitrypsin level in 5; all these findings were in the normal range.

We did not have data on previous SARS-CoV-2 infection in our cohort except for 1 child who had a positive test 6 to 8 weeks before presenting with hepatitis. None of the children, to our knowledge, had received a SARS-CoV-2 vaccine. Of the 39 children who underwent molecular testing for SARS-CoV-2 during the evaluation, 11 (28%) tested positive. Of the 13 children who underwent SARS-CoV-2 antibody testing, 5 (38%) tested positive.

Of the 30 patients tested for human adenovirus,

Table 3. Pathogen Tests.*

Test	Value
	no. of patients with positive tests/no. of patients tested (%)
Human adenovirus whole-blood qPCR†	25/27 (93)
SARS-CoV-2	
Molecular test	11/39 (28)
Serologic test	5/13 (38)
Enterovirus or rhinovirus PCR	5/9 (56)
Human herpesvirus 6 blood qPCR	2/10 (20)
Influenza type A or B PCR	1/4 (25)
Respiratory syncytial virus PCR	0/2
Human herpesvirus 7 blood qPCR	1/2 (50)
Parvovirus serologic test	0/12

* PCR denotes polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Of the 30 patients who underwent quantitative PCR (qPCR) testing for adenovirus, 27 had whole-blood testing, 3 had testing of fecal samples (2 patients [67%] were positive), and 6 had testing or respiratory samples (4 patients [67%] were positive). Only 1 patient was tested and was positive in all three sites. In the blood samples used for testing, the type (whole blood, plasma, or serum) was not known.

27 (90%) were positive (Table 3). Samples were obtained from one or more sites — blood, feces, and respiratory secretions. Adenovirus detection was more common in blood (93%) than in respiratory samples (67%) or feces (67%). Two patients who had positive tests for human adenovirus in feces and respiratory secretions (1 patient each) were found to have negative results on blood testing, but a false negative result cannot be ruled out because the type of sample tested (blood or serum) was not known. The median human adenovirus viral load on PCR was 2733 copies per milliliter (range, detectable but below the level of quantification to 39,445) in the children who did not undergo transplantation (22 patients) as compared with a median of 20,772 copies per milliliter (range, 3798 to 29,594) in those who did undergo transplantation (5 patients). Tests for other viruses were conducted infrequently (Table 2). All the children had negative test results for CMV. Testing for EBV viral capsid antigen was positive in 2 children, and testing for nuclear antigen was positive in 1 child.

All 44 children underwent abdominal ultrasonographic examination. The findings are shown in Table 1.

LIVER TRANSPLANTATION

In our cohort, 38 patients (86%) had spontaneous improvement, whereas 6 patients (14%) had liver dysfunction that continued to worsen; these 6 patients had progression to acute liver failure and underwent liver transplantation. Among the 6 patients in the transplantation group, 5 patients had rapidly progressive encephalopathy, with an interval from the onset of jaundice to encephalopathy of 6 to 7 days. The median interval from listing for transplantation to transplantation was 2 days (range, 0 to 5). All the patients who underwent transplantation received a cadaveric reduced or split left-lateral-segment liver graft, and the donor-selection criteria were widened because urgent transplantation was warranted.

Four of the five children with human adenovirus viremia after transplantation received cidofovir until the adenovirus viral load on PCR was less than 500 copies per milliliter. The viral load decreased to less than 500 copies per milliliter at a median of 8 days (range, 2 to 16) after transplantation. None of the patients in this cohort received glucocorticoids or any other immunomodulating agents, and no changes were made to the usual immunosuppressive regimen (interleukin-2 receptor antagonist at induction, long-term treatment with tacrolimus, and azathioprine). One child who underwent transplantation early in the year did not receive cidofovir and had adenovirus viremia until 26 days after transplantation, according to retrospective tests of stored blood samples. All the children in our series, including the six who received liver transplants, were discharged home.

Liver histologic findings were available in nine children (from six explanted livers and three liver-biopsy specimens). Explanted livers were small, smooth, and gray with bile staining of the cut surface. Microscopy showed distorted architecture with portal tracts containing appropriately sized bile ducts with mild to diffuse inflammation consisting of lymphocytes, plasma cells, and eosinophils. Lymphocytes were predominantly CD8 T cells with few CD4 T cells and CD20 B cells. Viable parenchyma showed severe disarray with hepatocyte ballooning, canalicular cholestasis, and scattered apoptotic bodies. The histologic findings were similar in all biopsy specimens; however, panacinar necrosis was focal in children who recovered, whereas submassive necrosis with parenchyma replaced with sheets of macrophages

was seen in explants. None had viral inclusions, and immunohistochemical tests for human adenovirus were negative. One biopsy specimen was checked with an EBV-encoded small RNAs in situ hybridization assay and showed very occasional positive lymphocytes in sinusoids (1 per high-power field). There was no fibrous tissue or evidence of underlying chronic liver disease (Fig. S2). Iron, copper-associated protein, and periodic acid–Schiff stain with diastase digestion–positive globules were not seen. The results of adenovirus PCR assays targeting the hexogene were reported in three of the six explant homogenates and were positive. Nucleotide sequencing of the PCR product indicated that the sequence had close similarity to human adenovirus serotype 41F.

The liver is a vascular organ, and further analysis is warranted to elucidate whether this positivity reflects results in blood rather than in liver tissue. The UKHSA performed metagenomic analysis of blood and liver tissue, and adeno-associated virus 2 and herpesvirus, among other viruses, were detected. The importance of these findings is undergoing further evaluation.[3]

DISCUSSION

We report a case series of 44 children with acute hepatitis of unknown cause referred to a pediatric hepatology tertiary referral unit in the United Kingdom in 2022. Most of these young children were previously well. Although the hepatitis resolved in most of the patients, the high incidence of progression to hepatic failure warranting transplantation (in 14% of the patients) underscores the severity of the illness.

Although investigation for a causative agent or agents of acute hepatitis in these children is ongoing, the results of biochemical tests during the prodromal phase suggesting acute hepatitis and the ultrasonographic findings of thickening of the gall bladder wall with pericholecystic fluid, abdominal lymph nodes, and mild hepatosplenomegaly are consistent with a possible viral cause. Extensive viral testing has identified adenovirus as the most common pathogen, although other viruses have been identified infrequently. The UKHSA[3] reported the human adenovirus subtype to be 41F. This subtype is primarily known to cause gastroenteritis and differs in tissue tropism from the subtypes that cause respiratory and ocular infections.[6,7]

Positive adenovirus tests on routine clinical evaluations are recorded in a second-generation surveillance system in the United Kingdom, and reports of positive human adenovirus tests from any sampling site — blood, stool, or respiratory secretions — in children 1 to 4 years of age were reported to be more common from November 2021 through April 2022 than in the previous 5 years.[3,8] However, this comparison warrants caution because the testing and reporting procedures are variable and influenced by clinical presentation. Adenovirus infections are typically self-limiting in immunocompetent children, but they may cause serious disseminated infection in immunocompromised children. A 13-month prospective study conducted by the British Paediatric Surveillance Unit starting on January 1, 2014, showed adenovirus as a cause of acute infectious hepatitis in hospitalized children in 6% of cases (5 of 81).[9]

The cause of the current cases of acute hepatitis in children is unclear because the liver histologic findings were negative for viral inclusion bodies and viral immunostains. The working hypothesis includes an abnormal host response, possibly because of a lack of exposure as a result of the SARS-CoV-2 pandemic lockdown, an epidemic of normal human adenovirus causing complications to manifest more frequently, or increased susceptibility to human adenovirus because of drugs, environmental agents, or concomitant coinfections with other viruses, including SARS-CoV-2.[3] With the exception of 1 patient who had a positive SARS-CoV-2 test 6 to 8 weeks before presentation with acute hepatitis, there was no clear history of SARS-CoV-2 infection in our patients before presentation. However, it is difficult to be certain because we did not have documentation of symptoms or previous tests undertaken. Molecular testing for SARS-CoV-2 was positive in 11 of the 39 children (28%) tested at the time of hospital admission with acute hepatitis. Of the 13 children who underwent serologic testing for SARS-CoV-2, 5 (38%) were positive.

The pooled data in the UKHSA technical briefing include 125 children from England who were tested for SARS-CoV-2 (on PCR or lateral-flow testing). Of the 16 children with positive tests, 13 were positive on admission and 3 were positive 8 weeks before presentation at the hospital.[3] The UKHSA is undertaking retrospective serologic testing for SARS-CoV-2 to explore its

role in the pathogenesis of acute hepatitis, but interpretation and correlation of the data may be difficult given the high prevalence of SARS-CoV-2 in the general population.[3]

A similar outbreak of severe hepatitis was reported from October 2021 through February 2022 in the United States. Nine children in Alabama were identified who had presented with both acute hepatitis and human adenovirus viremia. The pattern observed was similar to that in our cohort, and the median age at presentation was 2 years 11 months. All the children were reported to be previously healthy and presented with a preceding gastrointestinal illness before the onset of jaundice. Three children in this cohort had acute liver failure. One child recovered with supportive measures; the other two children received cidofovir, intravenous immune globulin, and glucocorticoids, but their condition did not improve, and they eventually underwent liver transplantation.[10,11]

Our cohort did not have very high ferritin levels or other diagnostic features that would implicate secondary hemophagocytic lymphohistiocytosis as a contributing factor. The presenting and peak bilirubin and ALT levels, prothrombin time, and adenovirus loads on PCR were higher among the children who underwent transplantation than among those who did not undergo transplantation, but the small size of the cohort precludes meaningful statistical comparisons.

The use of antiviral therapy for human adenovirus infection in immunocompetent children is not supported by randomized, controlled trials. However, the use of cidofovir is considered to be the standard practice in immunocompromised recipients of solid organs and bone marrow.[12,13] Although its role in disseminated disease in immunocompetent children is less clear, there are reports of successful use.[14] The children in our cohort had decreasing adenoviral loads after transplantation, with or without cidofovir (in four children and one child, respectively). The time to reach a viral load of less than 500 copies per milliliter was longer in the child who did not receive cidofovir (26 days) than in the children who received cidofovir (2 to 16 days). Data are lacking on the recommended duration of treatment. Case reports have suggested ongoing treatment until the viral load is undetectable, with discontinuation if side effects are seen.[15] A consensus clinical framework is now available in the United Kingdom to guide professionals caring for these children.[16] It is possible that the human adenovirus may have an immunopathogenic mechanism of injury, and the use of glucocorticoids in conjunction with cidofovir is being explored.

No deaths were recorded in our series. Children who recovered without transplantation underwent follow-up blood tests in their regional hospitals. Not all follow-up results were available to us, but we had information on 11 patients, of whom 7 had normalization of liver biochemical tests at 4 to 8 weeks after the first hospital presentation. All the children have been advised to have ongoing monitoring for aplastic anemia in line with the consensus framework clinical guideline of the Royal College of Paediatrics and Child Health.[16]

The limitation of our study is the small cohort of patients evaluated retrospectively; in addition, some data were missing. As more data become available, an understanding of the natural history and immunopathogenesis of this illness will be helpful in planning interventions. Further studies with metagenomics and immunologic investigations of the host are being undertaken by the health authorities in the United Kingdom to understand the hepatotropism of this illness.

There is currently an increased incidence of acute hepatitis among young children, and 14% of the children in our cohort with this condition underwent liver transplantation. Although new cases continue to be identified across the United Kingdom, there is an overall decline corresponding to the declining trend in the prevalence of human adenovirus infection among children who are 1 to 4 years of age.[8] Clinicians should be vigilant about identifying children who present with prodromal illness followed by jaundice. Diagnostic testing, including molecular testing of whole blood for viruses, should be conducted as recommended by public health agencies.[17]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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