

## Review Article

## Acute severe hepatitis of unknown etiology in children: A mini-review

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### Abstract

The emergence of acute, severe non hepA–E hepatitis of unknown etiology (ASHUE) has attracted global concern owing to the very young age of the patients and its unknown etiology. Although this condition has been linked to several possible causes, including viral infection, drugs and/or toxin exposure, the exact cause remains unknown; this makes treatment recommendation very difficult. In this review, we summarize recent updates on the clinical manifestations, complemented with laboratory results, case numbers with the global distribution and other epidemiological characteristics, and the possible etiologies. We also provide the proposed actions that could be undertaken to control and prevent further spread of this hepatitis. Since many etiological and



pathological aspects of the acute non hepA–E hepatitis remain unclear, further research is needed to minimize the severe impact of this disease.

**Keywords:** Acute non hepA–E hepatitis, clinical manifestations, epidemiological characteristics, outbreak, prevention

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## Introduction

Several clusters of acute hepatitis in children have been reported worldwide since October 2021, mainly in the United Kingdom (UK) [1]. Due to their unique characteristics, these cases were reported as “acute severe non hepA–E hepatitis” as the test results for common viral agents (types A, B, C, D, and E) and other known etiological causes of hepatitis were all negative [1, 2]. In this article, we adopted the nomenclature “acute, severe non hepA–E hepatitis of unknown etiology” used by World Health Organization (WHO) and the UK Health Security Agency to refer to these cases of hepatitis of unknown etiology in children [5,6], referred to as ASHUE. At the end of 2021, nine cases of ASHUE were reported in the Children’s of Alabama Hospital, United States (US); identified symptoms prior to admission being vomiting (7 out of 9 cases), diarrhea (6 out of 9 cases), and jaundice (6 out of 9 cases) [3]. No patients had a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and, in a preliminary examination, all patients had negative results for hepatitis viruses A, B, and C [1].

During March and April 2022, increasing numbers of ASHUE were reported in North America, Europe, and Asia, with most cases observed in children aged between 1 month to 16 years [2,3]. As of 8 May 2022, more than 380 cases of ASHUE have been reported in 28 countries, with the largest number was recorded in the UK [4]. Even though the number of global cases are still low, their possible severity leading to deaths or liver transplants in some patients, has triggered significant concern. This is, in part, due to the simultaneous occurrence of similar cases worldwide.

ASHUE cases have been linked with several possible etiologies including adenovirus infection, coronavirus disease 2019 (COVID-19), COVID-19 vaccination, novel infectious agents, toxins, and possible foodborne-related etiology [7]. However, it remains challenging to precisely identify which of the above is a causative agent. In this mini-review, we aimed to compile the number of reported cases and distributions and to describe the clinical manifestations. In addition, we provide insights on the potential etiologies and recommend approaches to the management of the disease.

## Update of case numbers and global distribution

Of the 384 cases of ASHUE recorded to the 8<sup>th</sup> of May, 2022 (**Table 1**), 163 have been recorded in the UK, 109 cases in the US, 17 in Italy and 13 in Spain. The age range varied from one month to 16 years. In the UK, the majority (56.9%) of cases were reported in children aged between 3 and 5 years (median age 3 years) [4]. In a study from Scotland, the median age of cases was 3.9 years [5]. Several nations, including Italy, the Netherlands, Spain, UK, US, and Israel have reported that some cases went on to needing liver transplantation. In addition, eight children have died, including five Americans and three Indonesians. Despite having the highest number of reported cases, no deaths have yet been reported in the UK, perhaps due to a very efficient referral system in the country.

Currently, international travel and epidemiological ties to other countries do not appear to be the contributing factors. Adenovirus infections have been identified in numerous patients; among those for whom molecular testing results are available, they have largely been found to be due to group F serotype 41, which is a common cause of viral gastroenteritis [3, 4, 6, 7]. SARS-CoV-2 was found in a number of cases [4, 7], and co-infections of SARS-CoV-2 and adenovirus have been detected as well [5]. The global distribution of ASHUE in children as of May 8, 2022, based on data extracted from **Table 1**, is presented in **Figure 1**.

Table 1. Global case distribution of acute hepatitis of unknown etiology up to 8 May 2022

Country	Total cases	Age (years)	Gender	Adenovirus testing	SARS-CoV-2 test results	Required liver transplant	Number of deaths	References
Belgium	2	10 < 10	-	Two positive	Both had previously been infected with SARS-CoV-2.	-	-	[8-10]
Romania	5	<5 10 16 8-month 10	Girl Girl Boy -	Negative - - -	Negative - - -	-	-	[10-13]
France	2	<10	-	One positive	-	-	-	[10, 14]
Norway	2	<6	-	One positive	One recent case of SARS-CoV-2	0	-	[10, 15, 16]
Italy	17	<16	-	Two positive and two negative	One positive and four negative	1	-	[10, 17]
Netherland	4	1 to 8	-	Two positive	One positive	3	-	[10, 18]
Denmark	8	<16	-	All negative	One recent case of SARS-CoV-2	-	-	[10, 19, 20]
Austria	2	<10	-	One negative	Both had been infected with SARS-CoV-2	-	-	[10, 21, 22]
Germany	1	5	-	Positive	Negative	-	-	[10, 23]
Poland	1	7	-	-	Previously infected with SARS-CoV-2	-	-	[10, 24]
Ireland	<5	2-11	-	One positive	All negative	-	-	[10, 25]
Spain	13	1.5 to 16	Boy (3) Girl (5) No information (5)	One positive	One positive and one previously infected with SARS-CoV-2	1	-	[10, 26]
UK	163	<16	-	± 90 positive	± 20 positive	11	0	[10, 27]
US	109*	<16	-	> half cases	-	15	5	[28-30]
US	9**	<16	-	-	-	2	-	[31]
Israel	12	< 5	-	-	-	-	-	[31, 32]
Japan	7	<16	-	One positive	One positive	0	0	[33, 34]
Argentina	1	8	Boy	-	-	-	-	[35]
Costa Rica	1	2	Girl	-	-	-	-	[36]
Panama	1	2	Boy	-	-	-	-	[37]
Singapore	1	10-month	Boy	Negative	Negative	-	-	[38, 39]
Serbia	1	-	-	-	-	-	-	[40]
Palestine	1	8	Boy	-	-	-	-	[41]
Slovenia	1	-	-	-	-	-	-	[42]
Portugal	4	1 to 8	-	One positive	Negative	-	-	[43]
Indonesia	3	2, 8, and 11	-	-	Negative	-	3	[44, 45]
Malaysia	1	4	Boy	-	-	-	-	[46]
Sweden	7	-	-	-	-	-	-	[47]

- : no information; SARS-CoV-2: severe acute respiratory distress syndrome coronavirus 2; UK: United Kingdom; US: United States

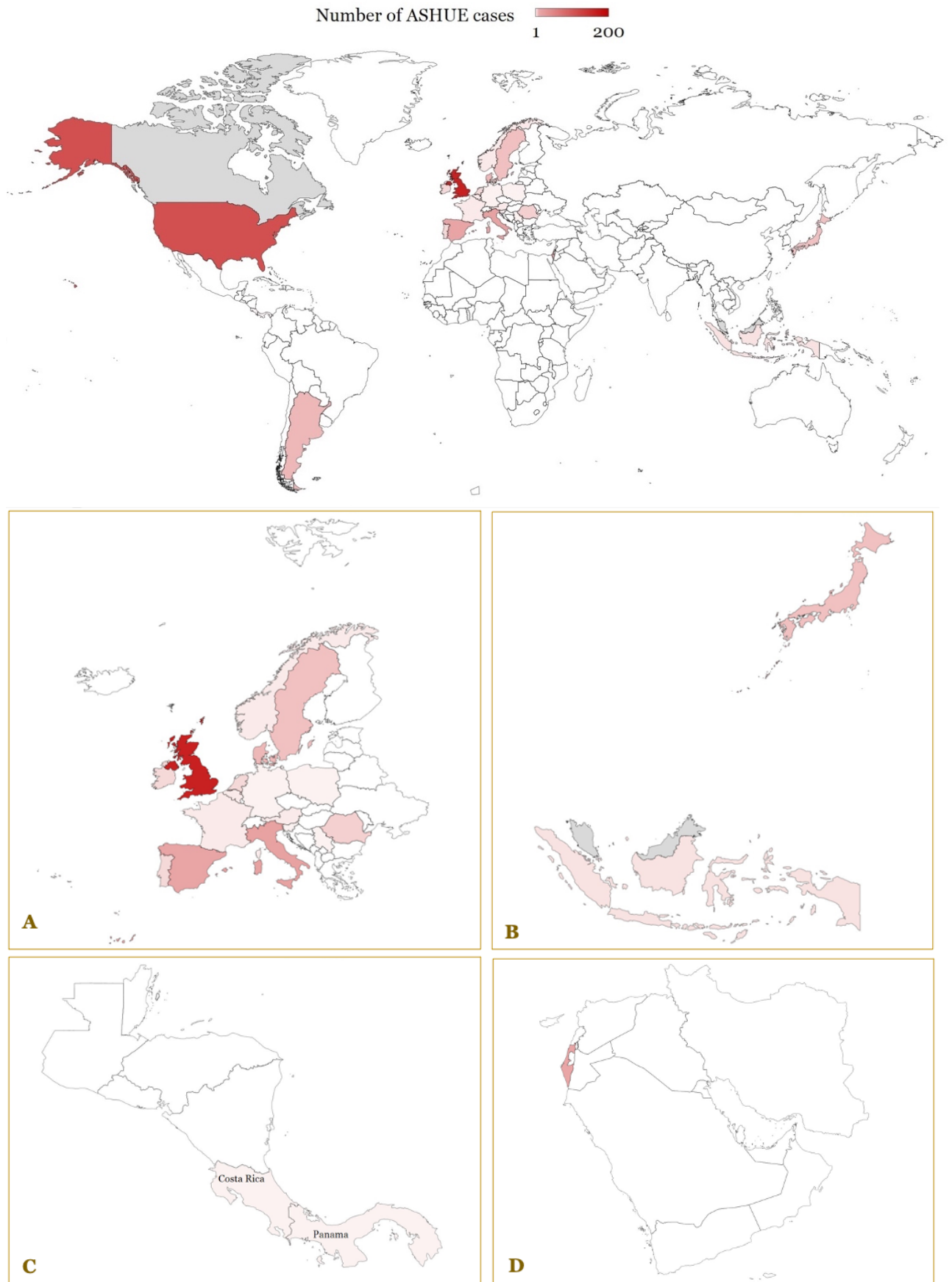


Figure 1. Global distribution of acute severe hepatitis of unknown etiology (ASHUE) in children. Countries in grey have suspected cases (unknown numbers). Specific regions of (A) Europe, (B) Asia, (C) Central America and (D) Middle East are provided separately.

## Clinical manifestations and laboratory findings

As of 8 May 2022, ASHUE cases have been reported in 28 countries. Most of the reported cases presented with hepatitis-like symptoms including jaundice, diarrhea, vomiting, abdominal pain, and nausea [5, 48]; abdominal pain and diarrhea being the most common symptoms prior to hospital admission [49]. Fever has been absent in most cases [48-50], although reported in 5 out of 9 children in Alabama [3]. Hepatomegaly was presented in 7/9 of the Alabama children, with one case had encephalopathy [3].

Laboratory examinations have shown elevated levels (more than 500 IU/L) of aspartate transaminase (AST) or alanine transaminase (ALT) [5, 50]. In the report from Alabama, ALT and AST levels among the affected children ranged between 603–4,696 IU/L and 447–4,000 IU/L, respectively [3]. Screening for hepatitis virus A, B, C, and E were negative in all reported cases, but reports of positive testing for adenovirus infection [48, 50] and SARS-CoV-2 infection [50] are increasing.

Data indicate that 91 of 126 (72%) cases tested in the UK were positive for adenovirus, and 24 of 132 tested (18%) patients were positive for SARS-CoV-2 infection [2]. Among the 55 cases reported in European Union countries, 10 (18.2%) tested positive for adenovirus and three (5.4%) for SARS-CoV-2 [2]. Among the 13 cases reported in Scotland, five were adenovirus PCR-positive [5].

In the UK, 11 out of 163 (6.7%) patients required liver transplantation [4]. Among the cases reported in Alabama, two patients recovered following transplantation while seven did not need liver transplantation [51]. Among the 55 cases reported in European Union countries, five children (9%) required transplantation [2]. Hence, a small percentage of the affected children require liver transplantation due to the rapid progression to end-stage liver failure [52-54]. Only a few deaths have been reported [55].

## Possible etiologies

Several possible etiologies of ASHUE have been proposed, including adenovirus infection, SARS-CoV-2 infection, COVID-19 vaccination, toxic agents, and a novel infectious agent [1]. The hypothetical role of adenovirus infection is currently the most plausible.

Considering the ongoing COVID-19 pandemic, it is understandable that ASHUE cases have been associated with SARS-CoV-2 infection. This suspicion is specifically derived from the finding of elevated liver transaminases and ferritin in a case report of a 10-month-old boy [56]. However, the occurrence of acute hepatitis in pediatric cases of COVID-19 is uncommon [56]. Moreover, SARS-CoV-2 results were negative in 8 out of 13 samples in Scotland [3] and in all 9 samples in Alabama [3], minimizing the hypothetical association. The link between COVID-19 vaccination and ASHUE is also unlikely as most of the patients were children under 5 years of age, who were not eligible for vaccination [31].

A UK study tested the possible role of hepatotoxins by assessing metal contents in the urine and/or organic compounds in the plasma of affected English children; an insignificant toxin content was found in the patients as compared with healthy subjects [27]. However, the investigation continues [27]. The possible role of foodborne infections/toxins, as suggested by a report from the European Society of Clinical Microbiology and Infectious Diseases needs consideration, in particular the possible role of aflatoxins [56].

Adenoviral infection has been found in three-quarters of the reported cases [3,4]. However, the presence of adenoviruses in children is not uncommon, raising the possibility of an additional cofactor, either as a direct cause of more severe disease or through the initiation of an altered immune response [27]. The emergence of a novel, more virulent variant of adenovirus is a possibility [27], but an unintended consequence of widespread social measures to protect against COVID-19 may be more likely. Widespread use of masks and social isolation has resulted in significant reduction in other airborne viral infections including influenza, respiratory syncytial virus, measles and various adenoviruses. The recent relaxation of these social measures has significantly increased the exposure to these viral agents of a population of young children whose immune system may not have been adequately challenged for two years.

It is therefore possible that sudden exposure to an adenovirus has resulted in a more vigorous immune response [8,28]. The possibility of a totally new infectious agent as the cause of ASHUE should also be considered [57].

## Treatment and preventive measures

Despite the liver has strong regenerative abilities, liver disorders can be fatal as could cause liver failure where the only effective therapy for which is liver transplantation. Unfortunately, donor shortages limit this choice, especially in low- and middle-income countries. The main treatment at present remains best supportive care.

As far as prevention is concerned, currently the only recommendation is to follow routine public health guidelines emphasizing the need for hand hygiene when unexplained cases of acute hepatitis have been identified [58].

## Conclusions and future prospects

ASHUE refers to a type of acute liver inflammation occurring in the absence of hepatitis A–E viruses. Its etiopathogenesis is still undetermined and treatment remains supportive. Although an infectious agent seems more likely, other non-infectious causes including environmental toxins, drugs and other chemical contaminants need to be considered. It may be that there is not a single etiology and that viruses, environmental contaminants or toxins are involved in different cases. Another critical point is the need for epidemiological studies to accurately record the spread and determinants of ASHUE. A strong collaboration among doctors and scientists in different countries will be instrumental to understand whether this is indeed a new disease and what the causes are.

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Not required.

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### Conflict of interest

All the authors declare that there are no conflicts of interest.

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### Underlying data

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