



## Hot Topic Commentary

# Acute Severe Hepatitis of Unknown Origin in Children Across the World: A 2022 Source of Concern

Lampros Chrysavgis<sup>1</sup> and Evangelos Cholongitas<sup>1\*</sup>

First Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", Athens, Greece

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At the beginning of April 2022, the World Health Organization (WHO) identified 10 cases of acute severe hepatitis in children younger than 10 years of age, across central Scotland.<sup>1</sup> None of the typical hepatitis viruses (A–E) that are known to cause acute viral hepatitis were isolated from any of those cases, and no common environmental exposures were found. Based on the latest data (up to 26 May 2022), approximately 152 cases of acute severe hepatitis were reported in the European Union and 222 cases in the UK.<sup>2</sup> Moreover, more than 38 of the cases received a liver transplant and at least 14 deaths were reported (Table 1).<sup>2,3</sup> The WHO, European Centre for Disease Prevention and Control, and UK Health Security Agency have posted reports trying to inform about the recent cases of acute hepatitis of unknown origin. Concerning the case definition by WHO, a description of a confirmed case is not available at present, while a probable case is considered a person presenting with acute hepatitis that cannot be attributed to the hepatitis viruses A–E, with serum aminotransferase levels >500 IU/L (aspartate aminotransferase or alanine aminotransferase), who is 16 years or younger, since October 2021 (Table 2).<sup>2–4</sup> As for the clinical presentation, most of the cases presented with gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain, while a proportion of them presented jaundice and acute liver failure.<sup>5</sup> More precisely, a technical briefing derived from England involved 144 cases with a median age of 3 years and equally distributed among both sexes (50% were female).<sup>4</sup> The most common symptom was jaundice (68.8%), followed by vomiting (57.6%), diarrhea (43.1%), pale stools (42.7%), and abdominal pain (36.1%).<sup>4</sup> Noteworthy, a previous review of all available liver specimens ( $n=14$ ) was undertaken and demonstrated a relatively wide spectrum of disease severity, ranging from mild hepatocellular injury to massive necrosis of the hepatic parenchyma.<sup>6</sup> A non-specific pattern of the hepatic injury

was identified, whilst no causal factor was observed in histological specimens.<sup>6</sup>

### Potential pathogen investigations

As we initially outlined, the common viruses responsible for acute hepatitis (hepatitis viruses A–E) have not been detected in any of the cases worldwide. Among 181 cases that have been tested for human adenovirus (HAdVs) and were reported to WHO, 110 (60.8%) were HAdVs-positive.<sup>2</sup> Of a small sample size that has been typed so far in the UK, 77% (27 out of 35 cases) have been identified as HAdV F type 41.<sup>4</sup> Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was PCR-detected in 23 out of the 188 (12.2%) cases, while a fewer number of patients were detected with a SARS-CoV-2 and adenovirus co-infection.<sup>2</sup> However, it should be noted that a detection of a specific adenovirus in blood was not accompanied by the detection of the same virus in other non-blood samples, raising a concern for potential mixed infection.<sup>6</sup>

HAdVs are non-enveloped double-stranded DNA viruses, common pathogens that usually cause a self-limited infection transmitted from person-to-person. Among 50 distinct adenoviruses accounting for mostly respiratory diseases, the adenovirus F type 41 commonly presents as diarrhea, vomiting and fever, whereas in some cases there is accompaniment by respiratory symptoms.<sup>7</sup> While infections by HAdV have been associated with acute hepatitis in immunocompromised children, a link between adenovirus type F 41 infection and hepatitis in immunocompetent children had not been described so far.<sup>7</sup>

### Coronavirus disease 2019 (COVID-19) and acute hepatitis

There are hypotheses concerning the potential correlation between SARS-CoV-2 infection or immunization and HAdVs infections. We shall point out that during the COVID-19 pandemic, a lower circulation of respiratory viruses, including HAdVs has been observed and consequently, the children are more susceptible to those viruses due to the delayed epidemiological exposure.<sup>8</sup> However, Brodin *et al.*<sup>9</sup> proposed that a previous SARS-CoV-2 infection could potentially reserve virus particles that over time could lead to super antigen-mediated immune cell activation. Upon a subsequent HAdV infection, that superantigen T-cell activation could lead to interferon- $\gamma$ -mediated excessive apoptosis of hepatocytes

**Abbreviations:** WHO, World Health Organization; HAdV, human adenovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

**\*Correspondence to:** Evangelos Cholongitas, First Department of Internal Medicine, "Laiko" General Hospital of Athens, National and Kapodistrian University of Athens, Agiou Thoma 17, Athens 11527, Greece. ORCID: <https://orcid.org/0000-0002-3645-582X>. Tel: +30-213-2061643, Fax: +30-213-2061795, E-mail: [cholongitas@yahoo.gr](mailto:cholongitas@yahoo.gr)

**Table 1. Number of identified cases, liver transplantations and deaths by the hepatitis of unknown origin per territory and country, as of 26 May, 2022**

Country	Cases	Liver Transplantations	Deaths
EU/UK			
Total	374	38	14
Austria	<5		
Belgium	14		
Bulgaria	<5		
Cyprus	<5		
Denmark	7		
France	<5		
Greece	<5		
Ireland	7	<5	1
Italy	27	<5	
Netherlands	14	<5	
Norway	<5		
Poland	<5		
Portugal	11		
Romania	<5	<5	
Slovakia	<5		
Slovenia	<5		
Spain	29	<5	
Sweden	9		
United Kingdom	222	11	
Outside of EU/UK			
Argentina	<5	<5	
Canada	10	<5	
Indonesia	<5		6
Israel	12	<5	
Japan	31		
Maldives	<5		
Mexico	10		1
Moldova	<5		
Palestine	<5		1
Panama	<5		
Serbia	<5	<5	
Singapore	<5		
South Korea	<5		
USA	216	15	5

and acute hepatitis.<sup>9</sup> Moreover, a possible relation between a previous SARS-CoV-2 infection by omicron (B.1.1.529) variant and a concomitant HAdV infection is also under investigation. Nonetheless, speculations related to side effects of COVID-19 immunization can be ruled out, since most of the children affected have not been vaccinated.<sup>3</sup>

### Perspectives

From our point of view, gathering additional data is of car-

dinal importance to further investigate those hypotheses and explain the recent cases of acute hepatitis. Beyond the initial cases reported in the UK, the subsequent increment in the diagnosis of new HAdV infections worldwide could potentially incorporate a bias since it could be the result of increased testing and high surveillance by Health Authorities worldwide. Meanwhile, there is also the possibility of a novel HAdV with its own characteristics that causes human infection with liver specification or a HAdV/another pathogen co-infection as well as either an environmentally or food-derived toxin that acts as a hepatotoxic agent.

**Table 2. Previous and current working case definitions of the acute severe hepatitis of unknown origin in children by the World Health Organization (WHO), European Centre for Disease Prevention and Control (ECDC) and UK Health Security Agency (UKHSA)**

Case definition	Description
Current WHO (as of 23 April, 2022) and ECDC (as of 11 May, 2022) case definition	
Confirmed	N/A at present
Probable	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) with serum aminotransferase >500 IU/L (AST or ALT), who is 16 years or younger, since 1 October, 2021.
Epi-linked	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) of any age who is a close-contact of a probable case since 1 October, 2021.
Current UKHSA definition	
Confirmed	A person presenting since 1 January, 2022 with an acute hepatitis (non-hepatitis viruses A–E) or an expected presentation of metabolic, inherited or genetic, congenital or mechanical cause with serum aminotransferase >500 IU/L (AST or ALT), who is 10 years-old and younger.
Probable	A person presenting with an acute hepatitis since 1 January, 2022 with an acute hepatitis (non-hepatitis viruses A–E) or an expected presentation of metabolic, inherited or genetic, congenital or mechanical cause with serum aminotransferase >500 IU/L (AST or ALT), who is 11 to 15 years-old.
Epi-linked	A person presenting since 1 January, 2022 with an acute hepatitis (non-hepatitis viruses A–E) who is a close-contact of a confirmed case.
Previous WHO case definition (until 22 April, 2022)	
Confirmed	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) with AST or ALT >500 U/L, who is 10 years-old or under, since 1 January, 2022.
Probable	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) with AST or ALT >500 U/L, who is 11–16 years-old, since 1 January, 2022.
Epi-linked	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) of any age, who is a close-contact of a confirmed case since 1 January, 2022.

ECDC, European Centre for Disease Control; N/A, not available; UKHSA, United Kingdom Health Security Agency.

Of importance, since a confirmed etiology for the disease as well as the pattern of transmission are still under investigation, the realistic likelihood of emergence as a pandemic cannot be fully assessed. Along this line, since few epidemiological-linked cases have been reported,<sup>4</sup> a potential human-to-human infection cannot yet be ruled out. In that case-scenario, the concern for a pandemic of acute hepatitis would be increased significantly. On the contrary, the identification of a rarer source of infection or a more complicated mode of transmission would mediate the risk of a pandemic substantially. Furthermore, as the potent relation between acute hepatitis and the COVID-19 pandemic is currently being assessed, the present and future progression of the latter may also affect the aforementioned risk of hepatitis infection. Yet, more solid ground is needed for an evidence-based assessment. Of note, there is no specific treatment for children with acute hepatitis, and the optimal case management is mainly supportive. However, upon liver failure, the affected children would ultimately need liver transplantation, which is not a realistic possibility in many countries. Based on the current data, general infection prevention measures are recommended by the WHO, including frequent hand-washing with soap and water, good ventilation of indoor places, consumption of safe water and food, implementing appropriate cooking practices, while encouraging medical attention upon presentation of suspect symptoms.<sup>2</sup> Conclusively, further work is required to identify new cases, infectious or non-infectious causes, potential risk factors, and in depth-with sequencing-virus characterization.

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## Conflict of interest

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## Author contributions

Study concept and design (LC, EC), acquisition of the data (LC), analysis and interpretation of the data (LC), drafting of the manuscript (LC), critical revision of the manuscript for important intellectual content (EC), administrative, technical, or material support (EC), and study supervision (EC). All authors have made a significant contribution to this study and have approved the final manuscript.

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