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Hepatology

Severe hepatitis in pediatric patients: The Severe Hepatitis In Pediatric Patients (SHIPP) registry

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Abstract

Objectives: Clusters of severe acute hepatitis in children were reported worldwide beginning in October 2021. Although most children recovered, some progressed to liver failure leading to death or liver transplantation. Herein, we characterize the clinical characteristics, and outcomes of this group of children through an international collaborative effort.

Methods: Participation was solicited via a global listserv to pediatric gastroenterologists worldwide. Patients <18 years, alanine aminotransferase >500 U/L, without chronic liver disease or acetaminophen ingestion were eligible. Data were submitted by individual sites into a Research Electronic Data Capture registry created in July 2022.

Results: Two hundred and seven cases were collected, with a peak incidence of 28 in April 2022. The median age was 40 months, 52.7% were male, 63.3% were white, and 44% were Hispanic. At presentation, 80% reported gastrointestinal symptoms followed by fever (27.7%). The median duration of hospitalization was 5.5 days with 51 patients requiring intensive care. Adenovirus serum/whole blood DNA was detected in 28/133 (21%) and seven patients were treated with cidofovir. Liver biopsies, performed in 76 patients revealed portal and lobular inflammation with none identifying a viral etiology. Eleven patients underwent liver transplantation, four were adenovirus positive, all of whom survived. There were four reported deaths.

Conclusions: In this large data set of pediatric patients with severe acute hepatitis, the majority did not have a singular definitive etiology but did recover spontaneously. Continued community surveillance and close cooperation are critical toward understanding the etiology of such clusters in pediatrics.

KEYWORDS

adenovirus, liver transplant

INTRODUCTION

In October 2021, Children's of Alabama in Birmingham, Alabama, notified the Centers for Disease Control (CDC) regarding a cluster of cases of severe acute hepatitis in children; several of whom presented in acute liver failure with at least three patients progressing to liver transplantation.[1] This observation marked the advent of an unprecedented surge of similar reports from across the globe, associated with concurrent adenovirus infection,

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reaching more than 1000 cases by the end of 2022.[2] The CDC issued a Health Alert Network Health Advisory in April 2022 advising testing and reporting of severe acute hepatitis in children caused by adenovirus.[3] Severe acute hepatitis in pediatric patients is uncommon with indeterminate causes accounting for 20%–30% of cases.[4] While the definition of severe acute hepatitis varied, it was generally accepted that an alanine aminotransferase (ALT) greater than 500 U/L in a patient under 16 years of age was characteristic of severe acute hepatitis. In the United States, like other countries, federal agencies such as the CDC were involved to assess the scope and severity of this potential novel outbreak.

The CDC and World Health Organization (WHO) along with other agencies worldwide have all collected data surrounding the outbreak with accompanying findings steadily being published. As a community of pediatric gastroenterologists, we found ourselves aptly positioned in our role as first responders to investigate this phenomenon. We formed a collaborative network that fosters data collection and submission to accurately and judiciously compile these findings on children affected by severe acute hepatitis.

In this report, we surveyed pediatric gastroenterologists identified from an established electronic listserv to aggregate the clinical characteristics of pediatric patients with severe acute hepatitis with the last entry occurring in February 2023.

What Is Known?

- Clusters of severe acute hepatitis were reported worldwide over the course of 18 months from 2021 to 2023.
- Majority of patients survived, however, some underwent liver transplantation.
- No single etiologic agent was identified, although adenovirus has been implicated.

What Is New?

- The majority of patients presented with gastrointestinal symptoms.
- One-fifth had detectable Adenovirus in serum or whole blood.
- Adenovirus was not detected in any liver biopsy specimens by histopathology.

1 | METHODS

A web-based case report form was developed using Research Electronic Data Capture (REDCap) to form a global registry of patients with severe acute hepatitis due to adenovirus or other causes which was endorsed by both the American Association for the Study of Liver Diseases (AASLD) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN).[5,6] The case report form consisted of 81 multiple choice and free response questions. Respondents were asked to consider only pediatric patients under 18 years of age who developed severe acute hepatitis from September 1, 2021, onwards due to adenovirus or hepatitis of unknown etiology. Severe acute hepatitis was defined as ALT ≥ 500 U/L and total bilirubin ≥ 1.5 mg/dL in accordance with similar parameters being used worldwide. Patients with chronic hepatitis or acute hepatitis of known noninfectious etiology (e.g., Wilson disease, autoimmune hepatitis, metabolic dysfunction-associated steatohepatitis) were excluded. The case report form collected the following information: reporter institution, patient demographics (age, country/state of residence, sex, race, and ethnicity), clinical presentation (month/year of diagnosis, clinical findings, and laboratory results), testing performed (viral testing, screening for autoimmune hepatitis and Wilson's disease), and clinical outcomes (mortality, need for liver transplantation, hospitalization, and need for intensive care). No patient identifiers were collected.

A recruitment letter with the REDCap link was disseminated to pediatric gastroenterologists across the United States and internationally using a listserv (pedgi@list.uvm.edu) in July 2022. No written consent was obtained though reporters were able to "Opt Out" of being acknowledged as a contributor. Once the REDCap survey was completed, reporters were not able to access the survey again or update data. The last data entry occurred in February 2023.

1.1 | Ethics statement

This project was approved by the Vanderbilt University Medical Center Institutional Review Board.

1.2 | Statistical methods

Descriptive statistics were employed for data presentation. Percentages, medians, means, and ranges were used for continuous variables, while categorical variables were presented as counts and numeric proportions. Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp.

2 | RESULTS

Twenty-six centers from six countries (the United States, Canada, South Africa, Pakistan, Australia, and Jamaica) submitted 213 cases, seven of which

were outside North America. One entry was excluded as the patient had autoimmune hepatitis before presentation, and five entries were not considered due to inability to achieve data sharing agreements with their institution.

The median age at presentation was 40 months (interquartile range [IQR]: 17,101.50). One hundred and nine (52.7%) were male, 131 (63.3%) were White, and 91 (44%) were Hispanic. Within our cohort, the cases peaked at 28 cases per month in April 2022 (Figure 1).

At presentation, gastrointestinal symptoms were most commonly reported (80%) followed by fever (27.7%) and respiratory symptoms (22%) (Table 1). Twenty-five patients were on chronic medication, with four on immunosuppressants. Twenty-two patients (10.3%) had evidence of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the past year. Twenty-seven patients presented with encephalopathy, five of these eventually were transplanted while 22 recovered.

Nearly all (93.7%) of our cohort were hospitalized with a median hospital length of stay of 5.5 days (IQR: 3,13) and 51 (24.6%) requiring intensive care unit (ICU) level care.

2.1 | Biochemical and infectious testing

Peak biochemical values are shown in Table 2. As this was an international survey using self-report, investigative testing for severe acute hepatitis was not standardized for each case. Table S1 lists the common viruses tested and their results.

Although a minority of patients had respiratory symptoms, viral respiratory panels were performed on the majority of patients (147/207, 71%). Of these, 68 (46.3%) were positive, including some with multiple pathogens detected. Rhino/Enterovirus was the most common virus detected ($N = 38$) and 18 patients had detectable adenovirus. Of these, eight had adenovirus

TABLE 1 Symptoms on admission.

Fever	28.2%
Gastrointestinal symptoms (vomiting)	58.9%
Diarrhea	25.1%
Hepatomegaly	30.4%
Splenomegaly	9.2%
URI symptoms	22.7%
Encephalopathy	13.2%

Abbreviation: URI, upper respiratory infection.

TABLE 2 Labs collected with peak values.

Peak lab values	Median	IQR	Number of missing values (%)
AST (units/L)	2332	943–4186	6 (2.9)
ALT (units/L)	2066	985–3459	5 (2.4)
Total billirubin (mg/dL)	6	1.5–12.3	5 (2.4)
Direct billirubin (mg/dL)	5.25	1.1–8.9	31 (15)
Ammonia (mcmol/L)	63	32–105	93 (45)
INR	1.4	1.1–2	9 (4.3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range.

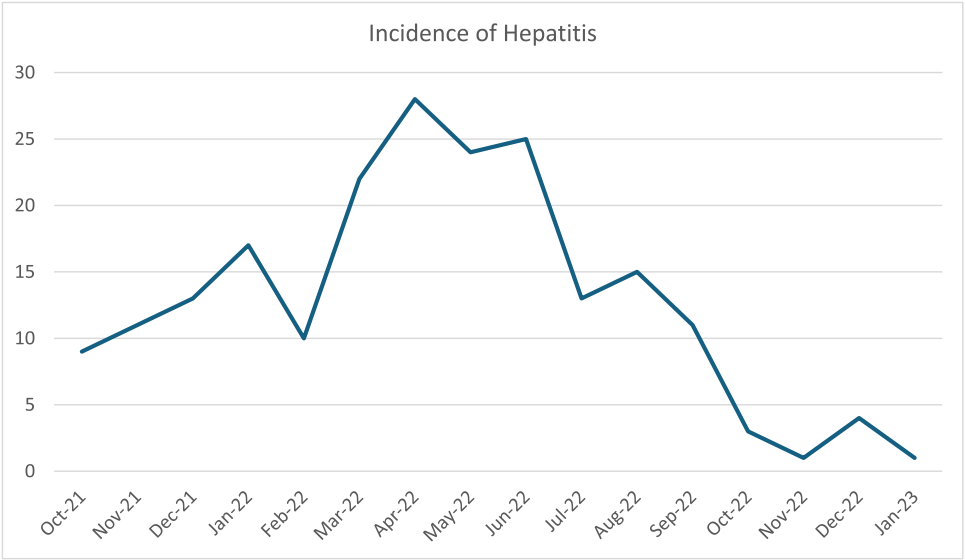

FIGURE 1 Incidence of severe acute hepatitis between October 2021 and January 2023.

solely detected while the remaining 10 had multiple viruses on their panels. Four patients tested positive for SARS-CoV-2. Adenovirus stool testing was performed in 47 patients and adenovirus was detected in seven.

2.2 | Serum adenovirus

Serum adenovirus testing was performed on 133 patients of which 28 were positive (21%). Of the positive, nine were also found to be positive for adenovirus on respiratory panel testing and 12 were negative. The remaining were not tested. Seven patients were treated with Cidofovir, one of whom was serum adenovirus negative.

2.3 | Clinical management

Forty-five (21.7%) were treated with antibiotics and 57 (27.5%) received steroids. Liver biopsies were acquired in 76 patients. Biopsy data received from different centers was inconsistent and ranged from full reports to one-sentence impressions. Median total bilirubin was significantly higher in biopsied patients $p < 0.001$ (12.4 vs. 2.6 Aspartae aminotransferase [AST], ALT, and international normalized ratio [INR]) were also higher but did not reach significance. The majority reported portal and lobular inflammation (93%) and none identified a specific viral etiology on histopathology (Figure S1).

2.4 | Outcomes

Eleven patients underwent liver transplantation; seven were male and three were female. All had adenovirus serum testing done (seven whole blood and four serum) and four were positive (three whole blood and one serum).

Transplanted patients had higher AST, ALT, INR, and total bilirubin when compared to nontransplanted patients, but no significant difference in mean age or gender (Table 3).

There were four deaths in the overall cohort. One death from cerebral herniation from intracranial hemorrhage and another from complications of their underlying seizure disorder, cause of death in two patients was not provided. All patients that were transplanted were alive at the time of data collection for this report. The remainder had no known sequalae of their illness.

3 | DISCUSSION

According to "The Principles of Quantum Mechanics" there is a principle of physics, "The observer effect," wherein the underlying idea is that the mere act of observing a system may produce disturbance in the system.[7] In our international collaborative report of more than 200 prospectively accrued cases of severe acute hepatitis our readers may suggest that we were similarly looking for these cases more keenly than ever before, and therefore describe a phenomenon that is cyclical but not unique.

We clearly do not have data (case control or otherwise) to directly answer this very valid criticism scientifically, however given the preponderance of simultaneous parallel reporting in real time of various smaller cohorts, we tend to err on the side of reporting our collective data set as the largest of those reports and hope that it will be used to better understand severe acute hepatitis in children overall.

Our study highlights the extraordinary global response and collaboration within the pediatric hepatology and gastroenterology communities. The swift mobilization of networks, the sharing of data, and the analysis of cases across multiple centers worldwide exemplify the strength and resilience of our field. This unprecedented effort enabled a rapid understanding of an emerging outbreak, demonstrating our capacity to address urgent pediatric health challenges, including this unexplained surge in hepatitis cases. Beyond these findings, our report emphasizes the need for

TABLE 3 Comparison of transplanted to nontransplanted patients and associated lab values.

		Nontransplanted ($N = 196$)	Transplanted ($N = 11$)	Mann– Whitney U
Age in months	Median (IQR)	39 (17–110)	26 (9–74)	0.34
AST (units/L)	Median (IQR)	3350 (890–4030)	4046 (4000–5432)	0.006
ALT (units/L)	Median (IQR)	1970 (945–3391)	2994 (2359–4695)	0.036
INR	Median (IQR)	1.34 (1.1–1.9)	5.8 (2.7–8.8)	<0.001
Total bilirubin (mg/dL)	Median (IQR)	5.7 (1.3–10.9)	21.2 (16.9–25.1)	<0.001
Ammonia (mcmol/L)	Median (IQR)	57 (32–90)	151 (112–226)	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range.

continued research to better comprehend the intermittent patterns of hepatitis. Investigating the potential roles of unrecognized environmental or immunological factors is crucial to unlocking the underlying mechanisms driving severe acute hepatitis and mitigating its impact on future pediatric populations.

We found the majority of patients were young, afebrile and presented with gastrointestinal symptoms (vomiting) This would hint at a gastrointestinal pathogen as the cause of illness. Stool testing was uncommon and likely not indicated in patients without significant diarrhea. As most reporters were based out of tertiary medical centers the majority of patients were hospitalized in this cohort and biases us toward more significant disease.

Despite the absence of upper respiratory symptoms, 71% had respiratory panel testing performed, almost half were positive with a multitude of viruses being detected including adenovirus. While some testing may have been driven by coronavirus disease 2019 (COVID) protocols, a recent meta-analysis has called into question the utility of such viral panels, demonstrating increased prescription of antivirals and patient satisfaction but concluded the benefit of routine testing is limited.[8]

Clinical management of patients varied as was expected in an international cohort. Patients with significant cholestasis were more likely to undergo liver biopsy which reflects our common practice to obtain a tissue specimen to aid in diagnosis of severe acute hepatitis. The absence of hallmark features of a particular disease is in itself critically valuable in the evaluation of children with severe acute hepatitis and liver failure particularly when liver transplantation is being considered.[9]

Transplanted patients had good outcomes similar to historical reports of children with acute liver failure.[10] Four deaths were reported, however, complete data were not provided for two of the cases and a determination whether it was related to infectious or hepatic etiology cannot be speculated. The Hepatitis of Unknown etiology group at the CDC has reported 23 deaths in a group of 392 cases of severe acute hepatitis collected between October 2021 and June 2023.[11] Of these, 15 were excluded for not meeting reporting criteria, leaving a total of eight patients. Four of the patients tested positive for adenovirus, however two were immunocompromised and one was less than 12 months of age. They concluded that the diversity of patients precluded the description of broad commonalities however, adenovirus remains an important consideration in the etiology of pediatric patients with severe acute hepatitis.

A National Library of Medicine (PubMed) search performed on February 14, 2024 with the search terms "severe acute hepatitis children" produced 128 peer-reviewed publications in 2022, which is more than the previous 3 years (2019–2021) combined. The increased academic interest in this potentially life-threatening illness in pediatric medicine, in of itself, is worth collating and disbursing our data set to the scientific community at large. Of note, in the 3 years since these initial reports, no subsequent large scale reports of increases in the incidence of severe acute hepatitis have emerged.

Since we started our data collection, several landmark articles have been published on severe acute hepatitis in children with varying results. Some have documented an increase in the incidence of adenovirus positivity in patients with severe acute hepatitis, others have not shown these on liver biopsy specimens while still others have proposed alternative viral agents such as adeno associated virus 2 (AAV2).[12–14] Despite these findings, the exact etiology of these cases remains unclear. Multiple hypotheses—including adenovirus, AAV2, and other viral pathogens—have been put forward, yet none provide a comprehensive explanation for the outbreak. Each hypothesis carries limitations: for instance, while adenovirus has been frequently detected, its histological findings often do not align with typical adenovirus-associated hepatitis. Similarly, AAV2 requires co-infection with a helper virus, making it difficult to pinpoint as the primary cause. These complexities highlight that no single factor appears sufficient to account for the surge in severe acute hepatitis. We have summarized the leading etiological hypotheses and their respective limitations in Table S2, which emphasizes the significant gaps in our current understanding and underscores the need for continued research to fully elucidate the underlying causes.

Our report clearly has limitations. First, it was biased toward larger academic centers that would have the resources to identify and report cases to their national authorities. Further, we were dependent on local site pathologists to read individual liver biopsies and therefore are subject to intraobserver bias of pathology readings. Participating centers submitted data prospectively to their local and national public health authorities in response to the call for monitoring however, our request to share the same data could have been misconstrued as a retrospective data collation.

4 | CONCLUSION

Despite these limitations, there is no other more comprehensive global data set available for the severe acute hepatitis outbreak witnessed across the globe over the post-pandemic period. We may speculate that a generation of children were suddenly exposed to a myriad of respiratory viral infections that triggered a spike in the case counts of hepatotropic viral infection

(adenoviral and otherwise) induced illnesses. However, that is a speculation that cannot be proven without the sustained intensive monitoring regime as was made possible through international efforts during the period these data were collated.

We therefore share these data to serve as a call to arms to continue to monitor and collate data for this critical pediatric aliment which has long remained an enigma to modern medicine. Maybe, by observing this phenomenon tenaciously, we may better understand the underlying pathophysiology of severe acute hepatitis and generate a more meaningful "disturbance" from our observations.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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