

# Updated information regarding acute severe hepatitis of unknown origin in children: Viewpoints of and insights from pediatricians

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**SUMMARY** Recently, the morbidity of acute severe hepatitis of unknown origin in children (SHIC) has tended to decrease, but this condition should not be ignored because of its uncertain but severe nature. The current study briefly summarizes updated information regarding the epidemiological, clinical, and etiological aspects of SHIC based on the newest information available. Opinions from pediatricians are also presented. In light of the *status quo* of SHIC and COVID-19 globally, several suggestions are proposed to improve future studies, which could help to further explore the underlying mechanisms of SHIC in the context of COVID-19.

**Keywords** acute severe hepatitis of unknown origin in children, COVID-19, adenovirus, SARS-CoV-2, immune reaction

Acute severe hepatitis of unknown origin in children (SHIC) was first reported on March 31, 2022 in Scotland (1). The World Health Organization (WHO) subsequently reported ten cases of analogous severe hepatitis in children on April 15, 2022, mainly occurring in the United Kingdom (UK) (2). Later, a total of 746 cases of SHIC were reported in 36 countries and regions other than the UK (3). There were no subsequent reports indicative of a SHIC pandemic, and only 44 new cases were reported in 10 countries according to data as of August 26, 2022 (Figure 1) (4). Nonetheless, this condition has garnered considerable attention because of its "uncertain but severe" nature as well as the fact that it "only" affects children. A number of studies have attempted to elucidate the pathophysiology of this hepatitis in terms of its epidemiology (5), immunology (3), and clinical manifestations (6). A viral infection seems to be the leading hypothesis among many researchers (5,7-9), but there is limited evidence to identify a definitive pathology. Previous studies by the current authors presented primary information regarding SHIC in June (10) and August (11) of 2022. The current study offers comments and insights on SHIC from the perspective of pediatricians based on updated information. These opinions might help to explore the etiology and improve the diagnosis and treatment of this hepatitis.

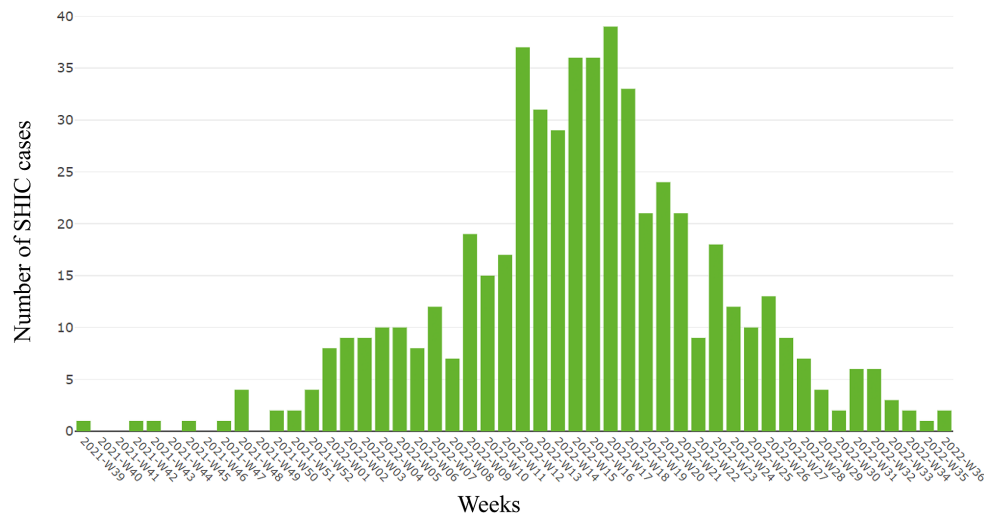
## 1. A summary of what is known

### *The status quo of SHIC globally*

From April 5, 2022 to September 30, 2022, a total of 555 cases of SHIC were reported in 22 countries (4), but only 44 new cases were reported from July 29, 2022 to August 26, 2022 (Figure 1). Hence, SHIC does not represent a global pandemic, and its incidence is decreasing.

### *Hypotheses regarding its etiology*

According to a report from the WHO, 231 (53.1%) of 435 patients tested positive for adenovirus, and whole blood specimens exhibited the highest positivity. Approximately 11% tested positive for SARS-CoV-2 according to a PCR assay, while 62.2% tested positive according to serology (4). These findings strongly imply a close association between viral infection and SHIC, a contention that is supported by most researchers (5,7-9). Abnormal susceptibility or an aberrant host response due to an infection (particularly a viral one), toxin, drug, or environmental exposure might play a role in the pathophysiology of SHIC. Thus far, conventional hepatitis A-E virus and COVID-19 vaccines have been eliminated from its etiology (12). Conversely, several potential pathogens were considered: 1) Adenovirus:



**Figure 1. Number of SHIC cases per week (Updated on September 29, 2022).** All data (Figure) are publicly available information from the Joint ECDC-WHO Regional Office. <https://www.ecdc.europa.eu/en/hepatitis/joint-hepatitis-unknown-origin-children-surveillance-bulletin>

Early in 2008, Ozbay *et al.* found that an adenovirus infection might cause acute liver failure in healthy children (13). Adenovirus, and particularly the 41F strain, is regarded as the most likely pathogen causing SHIC (2) since 53.1% cases were reported to test positive according to whole blood specimens (4). A report from the UK Health Security Agency speculated that infection with the adenovirus may alter immunity in healthy children, thus leading to SHIC (14). Vidal *et al.* found that positivity for adenovirus was closely associated with indicators of disease severity, such as ICU admission and liver transplantation (5). Kelly *et al.* also discussed whether a mutation of the adenovirus triggers an abnormal immune response and potentially causes SHIC (15). Thus far, however, there is insufficient conclusive or direct evidence regarding the role of adenovirus. Perez-Gracia *et al.* found that approximately half of patients tested positive for adenovirus according to whole blood specimens. However, none tested positive according to liver and plasma samples (7). These findings lessen adenovirus as a potential etiology of SHIC. 2) SARS-CoV-2: SARS-CoV-2 is the second pathogen that is considered relevant to SHIC. Sacco *et al.* contended that SARS-CoV-2 living in the gastrointestinal tract can act as a superantigen, receiving continuous and repeated activating stimuli from the adenovirus (or co-infection) and eventually causing SHIC (16). This hypothesis regards SHIC as part of a multi-system inflammatory syndrome.

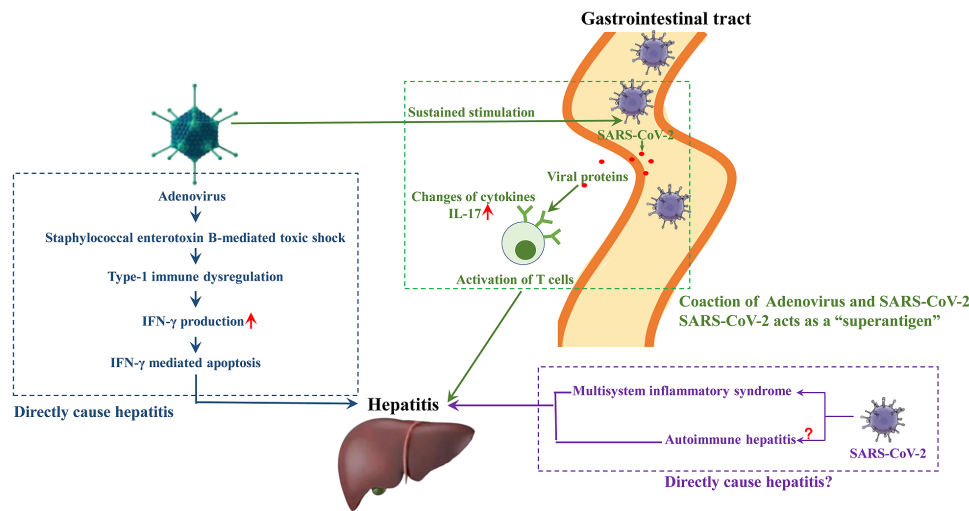
#### Clinical characteristics of reported cases

All of the reported cases of SHIC involve children under 16 years of age; most involved children ages 0-5, a few involved those ages 6-10, and very few involved those ages 11-15 (in the study by Vidal *et al.*, the respective proportions were 77.3%, 14.8%, and 8.0%) (5). In the report by the WHO, children

ages 0-5 accounted for 75.9% of cases (4). All of the children presented with manifestations of acute hepatitis, i.e., significantly elevated (over 500 U/L) serum levels of aspartate transaminase (AST) and/or alanine transaminase (ALT) (6). The symptoms were nonspecific and included jaundice, vomiting, pale stools, fever, and gastrointestinal symptoms. Hepatomegaly and hepatic encephalopathy were also reported (17). Of 344 children, 252 (73.3%) recovered, but 89 (25.8%) required intensive care, and 22 (6.4%) of the latter required liver transplantation (4). Vidal *et al.* found that patients of a young age and with an adenovirus infection were more likely to develop severe hepatitis and thus need to be admitted to the ICU or undergo a liver transplantation (5).

#### Diagnosis and treatment

The etiology of SHIC remains unclear, so all the available diagnostic protocols seem to be oriented toward an "exclusionary" or "exploratory" diagnosis (6). A diagnosis of exclusion means two steps: 1) Confirmation of hepatitis: usually using indices like ALT and/or AST and 2) Exclusion of hepatitis with known causes, such as an infection with hepatitis virus A, B, C, D, or E; medication/vaccine or toxin-related hepatitis; autoimmune-related hepatitis; and secondary hepatitis related to a disease in some other system. An exploratory diagnosis means a spectrum of laboratory tests/examinations and imaging studies including 1) hepatitis-related indices to confirm hepatitis and assess its severity; 2) virus-related indices to eliminate known viruses and to identify potential pathogens; and 3) imaging studies to confirm hepatitis and its complications (such as hepatic encephalopathy). Samples including whole blood, plasma, nasopharyngeal swabs, stool, and urine should be collected. If possible, a liver biopsy is also suggested.



**Figure 2** Potential mechanisms of SHIC on the basis of the interactions among adenovirus, SARS-CoV-2, and immune reactions. Three potential pathways of SHIC: Adenovirus-related (blue), SARS-CoV-2-related (purple), and interaction-related (green).

Thus far, there is no specific treatment for SHIC. Reported therapeutic strategies including 1) supportive therapy, 2) symptomatic therapy, and 3) antiviral therapy is only recommended for patients who are positive for a viral infection, such as administration of ribavirin to treat an adenovirus infection (18). Strategies also include 4) treatment of complications and 5) liver transplantation as the option of last resort for patients with severe hepatic damage. These strategies are not specific in comparison to those used to treat severe hepatitis with a known etiology.

## 2. Opinions regarding SHIC

### *Is SHIC an emerging infectious disease (EID)?*

Evidence of a source of infection, a route of transmission, and susceptible hosts is essential to identifying an EID. Thus far, however, there is insufficient evidence regarding the source of infection. The available reports have noted a close association among adenovirus, SARS-CoV-2, and SHIC, but there is no evidence that these viruses cause SHIC. In addition, no novel hepatitis viruses have been found. Hence, the source of infection is unknown. All of the cases seem to be sporadic, though they did resemble an "outbreak" in the middle of 2022. None of the reports have documented evidence of human-to-human transmission. An important finding is the lack of any specific antibody related to this "outbreak." Hence, there are insufficient grounds to classify SHIC as an EID based on currently available information.

### *Are children susceptible hosts?*

In an era of COVID-19, measures to prevent COVID-19 (wearing a mask, social distancing, *etc.*) might limit children's exposure to pathogens (including adenovirus),

and particularly childhood viruses. This might cause an abnormal immune response, particularly among children with insufficient acquired immunity. This is considered an "immune gap" (19) and might be a potential explanation for why most of the cases involved young children.

Another potential problem is "reporting bias." An "outbreak among children in a short period of time" is an eye-catching description. However, whether acute severe hepatitis of unknown etiology also develops in adults is unknown, and this fact cannot be ignored.

### *The potential pathophysiological interpretation of SHIC*

On the basis of the available information, the potential pathophysiological interpretation of the pathogenesis of SHIC might lie in the interactions/crosstalk among adenovirus, SARS-CoV-2, and the immune system. Common pathogens like adenovirus can cause hepatitis in children (13) and adults (20) with compromised immunity. Moreover, the role of SARS-CoV-2 cannot be ignored. Several studies have reported that SARS-CoV-2 acts as a "superantigen" in the gastrointestinal tract (3,16,21), and this may play a role in the pathogenesis of SHIC. In addition, acquired immunity in children might be insufficient in the context of COVID-19. The complex interactions among the adenovirus, gastrointestinal SARS-CoV-2, and abnormal immune reactions might explain the incidence of SHIC during the COVID-19 pandemic (Figure 2). This hypothesis warrants further investigation. However, some researchers have also pointed out that SHIC developed during the COVID-19 pandemic, hence the presence of COVID-19 in SHIC might be a coincidence (3) that may be related to vaccination or the virus itself.

## 3. Concluding remarks: Challenges and prospects for the future

At this moment, the morbidity of SHIC is tending to decrease, but SHIC should not be ignored. As a disease with an etiology and pathogenesis that remain unclear, no one knows when and where an "outbreak" of SHIC will occur again in the future. The following suggestions have been offered from the viewpoint of pediatricians:

**Epidemiology:** Creating and enhancing a global surveillance/reporting system for hepatitis of unknown origin is an urgent task. This system should include not only the cases in children but also in adults. This would help to collect detailed information and provide a comprehensive understanding regarding this indeterminate form of hepatitis.

**Pathology:** A liver biopsy is the gold standard for identification of pathological changes as well as pathogens and immune reactions in local lesions. A liver biopsy should be performed in all patients with this indeterminate form of hepatitis.

**Mechanisms:** Interactions/crosstalk among adenovirus, SARS-CoV-2, and immune reactions should be further investigated. Additional mainstream technologies like high-throughput sequencing and -omic analyses should be used to help with these investigations.

**Prevention:** Common preventive measures, such as prevention of fecal-oral transmission, should be enhanced particularly in young children. Likewise, preventive measures by family members, medical personnel, and caregivers should also be emphasized due to the uncertain nature of this disease.

Thus far, there is limited available information with which to obtain a comprehensive understanding of and insights into SHIC. More efforts should be made to investigate this hepatitis of unknown etiology by pediatricians and also by all researchers working in the field of infectious diseases.

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