Acute Hepatitis of Unknown Etiology Among Young Children: Research Agenda by the ESPGHAN Hepatology Committee

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ABSTRACT

In April 2022, an increased incidence of acute hepatitis cases of unknown etiology among previously healthy children across the United Kingdom was described. Since, more than 270 cases from the United Kingdom and hundreds more from all across the world have been reported. The majority of affected children were younger than 6 years of age. The clinical presentation was nonspecific with diarrhea and vomiting usually preceding the appearance of jaundice, abdominal pain, nausea, and malaise. Approximately 5% have required liver transplantation. An infectious etiology has been considered likely given the epidemiological and clinical features of the reported cases. Between 50 and 60% of the children tested were diagnosed with adenovirus infection although a clear etiological connection has still to be demonstrated. No link with SARS-CoV-2 infection and COVID-19 vaccine was found. What is not clear to date is whether the high number of acute hepatitis cases reported is related to a true increase in incidence or heightened awareness following on from the initial reports from the United Kingdom. The Hepatology Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) developed a paper on the current outbreak of acute hepatitis of unknown etiology recognizing its importance and the need of approaching the current situation with a scientifically rigorous approach. The aims of the article are to summarize the current knowledge and to identify the most pertinent issues regarding the diagnosis and management of this condition and the research questions raised.

Key Words: acute hepatitis, children, Europe, transplantation, virus

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What Is Known

- Acute hepatitis of unknown etiology is a diagnosis of exclusion where known viruses (hepatitis A to E and nonprimary hepatotropic viruses) and other etiologies such as autoimmune, toxic, and metabolic diseases have been excluded.
- In children presenting with acute liver failure, acute hepatitis of unknown origin is responsible for 45%–50% of the cases.
- Acute hepatitis of unknown etiology can be associated with a high mortality and needs urgent referral to a specialist service with access to liver transplantation.

What Is New

- An increased incidence of acute hepatitis cases of unknown etiology in children has been reported from January to May 2022 across the United Kingdom with the majority of the patients described or reported being younger than 6 years of age.
- According to World Health Organization data, approximately 5% of the children affected in Europe and the United States have required liver transplantation and more than 20 deaths have been reported.

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An increased incidence of acute hepatitis cases of unknown etiology among previously healthy children across the United Kingdom was first reported in early April 2022 (1). Since, ongoing investigations have led to the identification of additional cases in the United Kingdom as well as across Europe and the United States (2,3). The current information available is based on a few research articles (4–8), on an early *Morbidity and Mortality Weekly Report* release by the Centers for Disease Control and Prevention (CDC) (9), on the updates provided by the UK Health Security Agency (1,10), the disease outbreak news from the World Health Organization (WHO) (2,11), the European Centre for Disease Prevention and Control news stories (12,13) and the CDC Health Advisory Alert Network and surveillance bulletin (14–15). While national and international bodies and scientific societies attempt to investigate the true epidemiology of the condition, inaccurate and misleading information in the media is causing anxiety and uncertainty. The Hepatology Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recognizing the importance of the current outbreak of acute hepatitis of unknown etiology among young children in United Kingdom, Europe, and the United States aims to summarize the current knowledge, to identify the most pertinent issues regarding diagnosis, prevention, treatment of the condition and, finally, explore potential areas of further research in a scientifically rigorous approach. It is important to highlight that acute hepatitis and acute liver failure of unknown origin are not new diseases. This document is therefore aimed at providing clinicians and potentially both national and international medical agencies with an update on the current state of affairs regarding the current outbreak of acute hepatitis of unknown origin and with a detailed research agenda.

THE CASES

In October 2021, 5 previously healthy children with significant liver injury, including three with acute liver failure, were admitted to a large children's hospital in Alabama (USA) (14). The cases were reported to the CDC in November 2021. Four additional pediatric patients were admitted in the same hospital, for a total of 9 from October 2021 through February 2022 (9,14).

On April 5, 2022, the WHO was notified by the International Health Regulations National Focal Point for the United Kingdom of 10 cases of severe acute hepatitis of unknown etiology in previously healthy young children across Scotland, UK. At that time point, a specific definition of severe acute hepatitis was not provided, but it can be assumed that the common definition was applied being acute hepatitis the inflammation of the liver biochemically characterized by the steep rise of hepatic serum biomarkers (aspartate aminotransferase and alanine aminotransferase) in children. Since following discussion within the UK Health Security Agency with collaboration of the three pediatric liver services in the United Kingdom, a working case definition was agreed upon (see below) including the presence of high levels (>500 IU/L) of aminotransferases with or without acute liver failure (international normalized ratio ≥ 1.5 in encephalopathic patients or ≥ 2.0 in nonencephalopathic patients with no known evidence of chronic liver disease not improving on parenteral administration with vitamin K) (17,18).

On April 6, the UK Health Security Agency reported on the ongoing investigation into the higher than usual incidence of hepatitis in children across the United Kingdom with identification of 60 cases since January 2022 with further increase in numbers up to more than 270 following the most recent update July 2022 (1,19). As of the end of July 2022, the joint European Centre for Disease Prevention and Control/WHO Regional Office for Europe surveillance bulletin reported 508 probable cases of acute hepatitis of unknown etiology in children aged 16 years and below from the European region (20). On July 8, according to WHO, more than 1000 cases of acute hepatitis of unknown origin have been reported from 35 countries in 5 WHO regions. It is unclear whether the high number of children reported corresponds to the usual but previously unquantified the number of acute hepatitis cases across the world, or it is the signal of a real epidemiological event. Overlaps between the different reporting systems are possible.

In April 2022, the ESPGHAN joined forces with the European Society for Paediatric Infectious Diseases, the Pediatric European Network for Treatment of AIDS Foundation, the European Clinical Research Alliance on Infectious Diseases and the International Severe Acute Respiratory and emerging Infection Consortium and initiated a multidisciplinary survey among a broad (>3000) number of hospitals to rapidly assess the extent, geographical distribution, and potential etiology of the outbreak in Europe comparing the current figures with those of the previous 5 years. Case numbers since the start of January 2022 were compared with those of the previous 5 years. An elevation in probable and severe cases of unexplained acute hepatitis was reported in 6 hospitals (Italy, Spain, Sweden, the United Kingdom, Ukraine, and Israel) and in 5 hospitals (Italy, Poland, Spain, Sweden, and the United Kingdom) in 2022 compared with the previous years, respectively (5). A similar survey conducted by European Reference Network on Hepatological Diseases (ERN RARE-LIVER) reported a suspicion of an increase, but no rise among 12 of 34 centers involved in the treatment of children with hepatitis (6).

Age Range

The median age of the Scottish children and of those treated in Alabama (USA) was 3.9 years (range 3.6–4.6 years) (4) and 2 years, 11 months (interquartile range 1 year, 8 months to 5 years, 9 months), respectively (7,9,14). Over 75% of hepatitis cases in Europe were younger than 5 years of age (20). Investigations by the national authorities are focusing on children younger than 10 years of age. According to the WHO, cases across Europe ranged between the ages of 1 month and 16 years (2).

Working Case Definition

The first working case definitions provided in the original article describing the Scottish children (4) have been changed to align with that used in England, Wales, and Northern Ireland. Table 1 summarizes the definitions currently used by the UK Health Security Agency and the European Centre for Disease Prevention and Control/WHO.

The Clinical Presentation

The awareness from the UK Health Security Agency (1) and the CDC recommendations (14) pointed out the nonspecific signs and symptoms (abdominal pain, anorexia, and myalgia) and those more typical and specific of cholestatic hepatitis including jaundice, dark urine, hypocholic stools, and pruritus.

Details on the clinical presentation were provided in the article describing the first 13 Scottish cases (4). Data were available for 9 of 13 children. Jaundice (reported in 8 of 9 cases) was accompanied by abdominal pain (7/9 cases) and nausea and malaise (6/9 cases). The clinical syndrome was preceded by gastrointestinal symptoms including diarrhea and vomiting in the weeks before admission (4/4 cases). Fever was not reported. Most of the children first described in Scotland presented with transaminases greater than 2000 IU/L (4). Among the 9 patients admitted in Alabama, 7 presented with vomiting, 6 with diarrhea, and 3 with upper respiratory symptoms. At admission, 8 patients had scleral icterus, 7 had hepatomegaly, 6 had jaundice, and 1 had encephalopathy (9). Elevated transaminases were detected among all patients (alanine aminotransferase range 603–4696 U/L; aspartate aminotransferase range 447–4000 U/L). The total bilirubin values were normal in one and elevated in 8 patients (range 0.23–13.5 mg/dL) (9). Liver biopsies from 6 patients demonstrated various degrees of hepatitis

TABLE 1. Working case definitions of acute hepatitis of unknown etiology

United Kingdom Health Security Agency	World Health Organization/European Centre for Disease Prevention and Control
Confirmed case* • Period starting January 1, 2022 • Acute hepatitis with serum transaminase AST/ALT > 500 IU/L • Hepatitis A–E, metabolic, inherited or genetic, congenital or mechanical cause excluded • <10 years of age	Confirmed case Not defined
Possible case* • Period starting January 1, 2022 • jaundice without any known cause • 11 to 15 years old	Probable case* • Period starting 1/October/2021 • Acute hepatitis with serum transaminase AST/ALT > 500 IU/L • Hepatitis A–E excluded • <16 years
Epi-linked • Period starting January 1, 2022 • Acute hepatitis (non A–E) • Close contact of a confirmed case	Epi-linked* • Period starting October 1, 2021 • Acute hepatitis (non A–E) • Any age • Close contact of a probable case

AST = aspartate transaminase, ALT = alanine transaminase. *If for the case definition hepatitis A–E serology results are awaited, but other criteria met, these can be reported and will be classified as "pending classification." Cases with other explanations for their clinical presentation are discarded.

(9). Common presenting features in the cohort recently described from Birmingham (UK) were jaundice (in 93% of the children), vomiting (in 54%), and diarrhea (in 32%) (8).

Outcome

The severity of disease of the children reported from the Scottish Cohort upon presentation to hospital was remarkable and all 13 children required hospitalization. Three were referred to a liver transplant center and one child was transplanted (4). Since then, overall, 5% of the affected children in United Kingdom (1,19), 2 of 9 children in Alabama (14), 8% of those reported by the European Centre for Disease Prevention and Control (20) and 5% of those reported by the WHO have received a liver transplant (3). At least 22 deaths have been reported by the WHO without further details provided (3).

Etiology: Facts

An infectious etiology of the hepatitis has been considered likely given the epidemiological and clinical features. Cases clustered temporally in the United Kingdom (1) and 2 pairs of the Scottish children were epidemiologically linked having had a close contact in a household (4). The temporal and geographical clustering was even more evident in the United States where all cases were diagnosed and presented at the same children's hospital in Alabama although no known epidemiological link or common exposures were found among these children (14). On the clinical ground, the presentation with prodromal symptoms and the self-resolving natural history of the disease in the majority of the children affected were suggestive of a viral infection. No common exposures to food or drinks have been identified through investigation questionnaire and toxicology analyses.

By definition of case (hepatitis of unknown origin) even if details are missing in the reports available, we assume that hepatitis viruses (A, B, C, E, and D where applicable) have been excluded in all of the cases. There is uncertainty on which laboratory tests have been used to rule out these infections. At the same time, the history of possible exposure should have been investigated and toxicologic testing, as well as, all the tests routinely performed in children with acute hepatitis and/or acute liver failure should have been performed to meet the inclusion criteria for the case definition.

Adenoviruses were first described as possible cause of the acute hepatitis on April 12 in the report by the UK Health Security Agency (1). Adenovirus was identified by real-time polymerase chain reaction (PCR) in all the 9 children in Alabama (initial viral load range 991–70,680 copies/mL). In 5, sequencing of the viral DNA led to the identification of Adenovirus type 41 (14,15).

In the article describing the initial investigation into the first Scottish cases published on 14 April, 5 of the 11 children tested were Adenovirus positive by PCR. More than 60% of the children of the UK cohort and around 55% of the cases reported by the European Centre for Disease Prevention and Control tested positive for adenovirus (20), as of the last updates. Typing by partial hexon gene sequencing shows that the adenovirus present in blood of the 52 English cases tested was type 41F in 48 cases (92%). Interestingly, on histology, no viral inclusions, immunohistochemical evidence of adenovirus or viral particles was identified by electron microscopy in the liver biopsies of 6 children diagnosed with adenovirus type 41 infection in the Alabama cohort (9). Immunohistochemistry for adenovirus showed immunoreactivity in the intrasinusoidal lumen but not in residual hepatocytes for 9 of the 14 samples UK samples tested (19).

The initial experience from the United States suggests that whole blood is more sensitive than serum for detection of adenovirus. No details are available on the type of test used for the diagnosis of the infection.

Other possible causes have been actively investigated. None of the children admitted in Alabama were SARS-CoV-2 positive. Four of the 13 Scottish cases had a recent positive SARS-CoV-2 test (2 of them 3 months before admission, 2 within 11 days of admission). In one case, the point-of-care test was positive upon admission, which was not confirmed by PCR (4). Overall, SARS-CoV-2 was identified in about 10% of those that were tested in the United Kingdom and in about 10% of those reported by the European Centre for Disease Prevention and Control (20). Furthermore, a SARS-CoV-2 and adenovirus coinfection was detected in a minority of cases (19).

In the Scottish cohort, additional nonroutine viral testing was performed in some patients and included tests for enterovirus, parechovirus, human herpesvirus 6 and 7, varicella zoster, and adenovirus (4). Seven of the nine patients of the Alabama cohort were coinfected with other viral pathogens (6 Epstein-Barr virus interpreted as a low-level reactivation of previous infections, 4 enterovirus/rhinovirus, 1 each metapneumovirus, respiratory syncytial virus, and human coronavirus OC43) (9).

No link to the COVID-19 vaccine was found in the UK cohort as none of the cases aged under 5 confirmed in the United Kingdom was vaccinated. Fewer than 5 older case-patients have been reported as having had a COVID-19 vaccination before hepatitis onset (19). Of the 134 cases with data on the COVID-19 vaccination reported by the European Centre for Disease Prevention and Control, 116 (86.6%) were unvaccinated (20). It should be noted that similar cases have not been so far reported in adults.

Adeno-associated virus 2 was detected using metagenomics in the blood and liver tissue of affected cases from the United Kingdom (19). Adeno-associated viruses are small viruses that infect humans and some other primate species not currently known to cause disease. It is unclear whether this may represent a normal reactivation of adeno-associated virus 2 during an acute viral infection or during liver injury of another cause or it has clinical significance. Recent preliminary data from case-control studies strongly support a pathogenic role of adeno-associated virus 2 and adenovirus or human herpes virus 5 coinfection.

According to the UKHSA report, 75% of children have been treated with therapeutic doses of paracetamol (19).

Histopathology findings are hard to interpret during fulminant hepatic failure because of necrosis in the liver biopsy sample. However, the pattern of necrosis among 6 explanted livers and 8 biopsies from a combination of English and Scottish cases was highly variable in severity ranging from mild hepatocellular injury to massive hepatic necrosis, and it was not consistent with known causes of viral hepatitis (21).

Etiology: Hypotheses

At the time of publication, the leading hypotheses center around viruses and host response (Table 2).

Adenovirus type 41 was isolated and sequenced in a number of cases in the United Kingdom and the United States (14). However, simply pathogen detection does not always correlate with the causative agent of the diseases (22). Adenoviruses are well-known doubled-stranded DNA viruses that spread by close personal contact, respiratory droplets, and fomites and usually cause self-limited infections. Adenoviruses most commonly cause respiratory illness and basing on the type can cause gastroenteritis, conjunctivitis, and cystitis. Adenovirus infection has been described as a cause of hepatitis and acute liver failure in immunocompetent and immunocompromised children (22–29). There are more than 50 types of immunologically distinct adenoviruses that can cause infections in humans. Adenovirus type 41 commonly causes acute gastroenteritis presenting as vomiting, diarrhea, and fever often accompanied by respiratory symptoms. A comprehensive literature review of published studies between 1960 and May 2012 recorded 57 immunosuppressed children with adenovirus hepatitis. Adenovirus types 5 and 2 (22%) were the most frequently identified. Liver histopathology showed necrosis, intranuclear inclusions, smudge cells, mild canalicular and cytoplasmic cholestasis, and steatosis (30). Hepatitis by adenovirus type 41 infection has been reported in immunocompromised children, but it is not usual to see such a severe pattern of liver disease in young and healthy children (23,24). During the current upsurge of acute hepatitis, the United Kingdom and the Netherlands reported a significant increase in community circulation of adenovirus. It is difficult to explain why acute hepatitis cases are geographically and numerically limited despite the high spreading capacity of adenovirus infections. It has been hypothesized that the severe clinical picture could result from either a new adenovirus variant or a wild variant in children with dysregulated immune response. As the result of preventive strategies during the COVID-19 pandemic, including the different gradations of social distancing, use of masks and face coverings, school closure, adenoviruses such as other viruses circulated at a lower level and children could be immunologically naive and more susceptible. Thus far, no cases or similar alert have been reported in adults. If this is confirmed, it would reinforce the hypothesis of an infection in an immunologically naive patient.

TABLE 2. Acute hepatitis of unknown etiology among young children: working hypotheses

Abnormal susceptibility to a virus and/or host response due to: - Lack of previous exposure - Priming by previous infection, including superantigen-mediated post-SARS-CoV2 immune-cell activation - Co-infection with SARS-CoV-2 or other pathogens - Toxin, drug, or environmental exposure
Increased community prevalence of adenovirus causing the emergence of a very rare or underrecognized complication
New variant of adenovirus
New variant of SARS-CoV-2
Noninfectious causes
Novel pathogen (alone or as a coinfection)

In children with acute liver failure, abnormal innate immunity, resulting in failure to limit or contract inflammatory responses leading to propagation of liver injury, has been hypothesized to play a major role in hepatocyte damage (31). Alternatively, possible contributing factors are being investigated such as other concomitant (including adeno-associated virus) or previous infection (including SARS-CoV-2 Omicron BA.2 variant or an uncharacterized SARS-CoV-2 variant) or an environmental cause. A novel virus also cannot be ruled out.

Recently, a superantigen-mediated immune-cell activation consequent to adenovirus infection with intestinal trophism in children previously infected by SARS-CoV-2 and carrying viral reservoirs has been proposed as a causal mechanism for severe acute hepatitis. SARS-CoV-2 infection can result in viral reservoir formation and persistence in the gastrointestinal tract that can lead to repeated release of viral proteins across the intestinal epithelium, giving rise to immune activation mediated by a superantigen motif within the SARS-CoV-2 spike protein that bears resemblance to Staphylococcal enterotoxin B, triggering broad and nonspecific T-cell activation. This superantigen-mediated immune-cell activation has already been proposed as the causal mechanism of multisystem inflammatory syndrome in children (32).

Finally, in children with hepatitis of unknown origin, autoantibody-negative (seronegative) autoimmune hepatitis responsive to steroid treatment has been reported in retrospective studies, at times associated with the development of aplastic anemia (33). The liver biopsy displaying interface hepatitis (34), the typical histological feature of autoimmune hepatitis, is essential in order to make the diagnosis but often precluded due to coagulopathy in cases with acute liver failure.

Antiviral Treatment

Two out of the 9 patients in the cohort from Alabama were treated with cidofovir (off-label use) and steroids and underwent liver transplantation (8,9,35).

Research Priorities

Epidemiology

Despite the multiple reports of cases of acute hepatitis of unknown origin across Europe, it is not yet clear if there has been an increase in cases or an increase in awareness leading to greater

reporting. Enhanced surveillance activities had started in European countries, but the simple count of the cases, unless exceptionally high numbers occur, could lead to misinterpretation or unjustified alarm. The rapid identification of additional cases fitting the WHO case definition (2) highlights the need of running prospective, multicenter studies with the aim of collecting data on the incidence of this cluster of acute hepatitis and acute hepatitis in general. On the clinical ground, additional information could help to both timely start supportive treatment, isolation and determine the cause of these cases to further address control and prevention actions. In the absence of comparative figures on the incidence of acute hepatitis and of acute liver failure of unknown etiology from either COVID-19 or pre-COVID-19 eras, numbers of transplants for acute liver failure could be used as a surrogate marker. It would be important, as well, to report the outcome of self-resolving cases.

At the institutional level, the European Centre for Disease Prevention and Control launched on 29 April a reporting protocol intended for reporting national case-based data for surveillance of hepatitis of unknown origin from all the countries and areas of the WHO European Region (36). This initiative should be parallel to investigator-driven studies starting from and focusing on the clinical aspects.

Etiology

More detailed investigations including clinical histories, infectious and noninfectious causes, epidemiological links, among the cases and temporal and geographical clustering are recommended. It is paramount to ascertain whether the cases described so far represent a new phenomenon or should be included in the well-known diagnosis of acute liver failure of indeterminate cause. Advanced virological including metagenomic (from blood, serum, urine, stool, respiratory, and liver samples) and toxicology (including environmental and food toxicity) testing should be undertaken. Ideally, DNA, blood samples, nasal and throat swabs, and fecal samples are stored for future centralized testing. On 6 April, the UK Health Security Agency released indications for comprehensive investigations that should be performed in all cases of acute hepatitis in which hepatitis A–E have been excluded. The suggested investigations match the common work-up for infectious diseases of children with acute hepatitis and are summarized in Table 3. A complete differential diagnosis for acute hepatitis and acute liver failure is at the same time mandatory for all children (Table 4) (17,19). It is, indeed, important not to forget the noninfectious etiologies including autoimmune, metabolic, and drug-related causes of acute severe hepatitis which must be appropriately excluded. Histopathology results from a larger patient cohort would provide additional insights on the possible viral origin. Finally, there is need to investigate underlying susceptibility of a dysregulated immune response.

Clinical Management

Children with acute, severe hepatitis and with acute liver failure should be referred and managed by pediatric hepatologists and in centers with liver transplantation facilities. A multidisciplinary approach is warranted including infectious disease specialists, virologists, and pediatric immunologists.

Adenovirus

As adenovirus has been indicated as possibly associated with pediatric hepatitis clinicians should always consider adenovirus testing in children with hepatitis of unknown etiology. Although adenovirus has been identified in a significant number of patients, it is still unclear whether it is an (almost) innocent bystander in children presenting with acute hepatitis and acute liver failure or has a pathogenic role for the clinical presentation. Nucleic acid amplification techniques (eg, PCR) is preferable over antibody testing. Anecdotal reports suggest that testing whole blood by PCR for adenovirus may be more sensitive than testing plasma by PCR (15); therefore, testing of whole blood could be considered in those without an etiology who tested negative for adenovirus in plasma samples.

There are no antivirals approved by the European Medicines Agency and the US Food and Drug Administration for the treatment of adenovirus infections. All probable and epi-linked cases should be referred to tertiary care pediatric centers with liver transplant facilities. Immunoglobulin administration, cidofovir, brincidofovir, and adenovirus-specific T lymphocytes are treatment options that are not generally indicated in immunocompetent children with hepatitis. Its use should be explored only in highly specialized centers.

TABLE 3. Infectious disease investigations suggested for children with acute hepatitis

Sample type	Test	Pathogen
Blood	PCR	Adenovirus, Enterovirus, CMV, EBV, HSV, Hepatitis A, Hepatitis C, Hepatitis E, HHV6 and 7
Blood	Serology	Hepatitis A, B, C, E, CMV, EBV, SARS-CoV-2 anti-S, SARS-CoV-2 anti-N (only if locally available)
Blood	Culture	Standard culture for bacteria/fungi
Nasal/throat swab	PCR	Respiratory virus panel (including adenovirus/enterovirus/influenza, SARS-CoV-2)
Stool	PCR	Adenovirus, sapovirus, norovirus, enterovirus Stool culture

PCR = polymerase chain reaction.

TABLE 4. Noninfectious investigations suggested for children with acute hepatitis

Type
Antinuclear antibody, antismooth muscle antibody, antiliver kidney microsomal type 1 antibody, antiliver cytosol type 1 antibody, immunoglobulin G
Ceruloplasmin, 24 hours urinary copper excretion
Celiac disease screening
Metabolic work-up
Toxicology investigations including exposure to drugs

Other Treatments

Children and adults with acute hepatitis and acute liver failure of unknown origin, including those with seronegative autoimmune hepatitis, have been treated with immunosuppressive therapy (37,38). The risks and benefits of this therapy have not been rigorously tested. The use of steroids and of other immunosuppressive treatments should be very cautiously considered outside the context of a clinical trial (39).

CONCLUSIONS

The ESPGHAN has taken steps to ensure and has made itself available to contribute to the careful monitoring of the European epidemiological situation, confirming the necessary attention in the absence, at the moment, of unjustified and potentially harmful alarmism.

Given the current lack of data regarding the annual incidence of acute severe hepatitis of unknown etiology, there is a rationale for prospectively collecting these data internationally moving forward. Investigating the host–virus response and in particular a dysregulated immune response to a supposed viral trigger is of importance in understanding the pathophysiology of this condition. This is likely also to help prognosticate outcomes in those affected.

In the meantime, children with severe acute hepatitis (transaminases > 500 IU/L) or fulfilling the diagnostic criteria for acute liver failure especially if diagnosed with adenovirus infection should be discussed with a liver transplant center and/or should be reported to the local infectious disease specialists. Pediatric hepatologists should not lose this opportunity to study and increase the knowledge on acute hepatitis and acute liver failure of unknown etiology.

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