



# Hepatitis of Unknown Origin in Children

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## ABSTRACT

During the last year, severe acute hepatitis of unknown origin has presented the maximum peak of appearance in previously healthy children under 16 years of age, exceeding 800 reported cases. The frequent clinical manifestations are of gastrointestinal origin, with jaundice and elevated liver enzymes being the main findings discussed. Routine paraclinical tests show negative results for infection with common hepatotropic viruses such as hepatitis AE, therefore, currently, the main etiological suspicion is redirected to the presence of human adenovirus serotype 41 or to the activation of immune cells mediated by SARS superantigens -CoV-2.

**KEYWORDS:** Hepatitis; Jaundice; Adenovirus; SARS-CoV-2; Complication; Fatality

**ABBREVIATIONS:** ECDC: European Center for Disease Prevention and Control; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HSV: Human Herpes Virus; RSV: Respiratory Syncytial Virus; CAT: Computed Axial Tomography; MRI: Magnetic Resonance Imaging; WHO: World Health Organization; HAdV: Human Adenovirus; ANA: Antinuclear Antibodies; ASMA: Anti-Smooth Muscle Antibodies; ALT: Alanine Aminotransferase; AAA: Antiactin Antibodies; AST: Aspartate Aminotransferase; NMR: Nuclear Magnetic Resonance; ASO: Anti-Streptolysin O; INR: International Standardized Ratio

## INTRODUCTION

On March 31, 2022, the first case of severe acute hepatitis of unknown origin in previously healthy children was reported in Scotland [1]. Since then, the significant increase in the incidence of the pathology has been clearly evidenced, reaching approximately

813 cases confirmed by the WHO in more than 40 countries belonging to regions of Europe, America and Asia by May 2022, of which the 38% required liver transplantation with 21 reported deaths [2-4]. According to current statistics, the main affected have been children between the ages of the first month of life and 16

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years with a maximum incidence peak at 5 years, it is important to mention that the presence of links has not been accurately established. epidemiological factors related to travel, family structure, parental occupation, diet, water source or overdose of hepatotoxic drugs such as paracetamol [5,6].

The etiology of hepatitis can be multifactorial and varied, and it is necessary to highlight the infectious, autoimmune, pharmacological, and metabolic-genetic origin, however, the cause of the acute development of these cases is currently still being investigated since it has not been detected in any way. The presence of hepatotropic viruses commonly related to the disease (hepatitis A, B, C, D and E) (3) is routine, so for epidemiological purposes it has been called “non-HepA-E acute hepatitis” [7,8]. According to reports established by the European Centers for Disease Control and Prevention (ECDC) in partnership with the UK Health Security Agency and the US Centers for Disease Control and Prevention (CDC), the origin can be developed from different hypotheses that include cofactors that transform a common infection into the most severe form, the role of a known agent that undergoes critical genetic changes that modify its pathogenicity, the coinfection between two or more viruses, the appearance of a new infectious agent, unexplored immunological alterations and finally, the role of

toxic or environmental agents [9]. It is important to mention that adenovirus and SARS-CoV-2 infection have recently aroused interest as a possible main focus due to findings related to reported cases. the appearance of a new infectious agent, unexplored immunological alterations and finally, the role of toxic or environmental agents. It is important to mention that adenovirus and SARS-CoV-2 infection have recently aroused interest as a possible main focus due to findings related to reported cases. General clinical manifestations are associated with abdominal pain, nausea, temperature rises, repeated emetic and/or diarrheal episodes, and finally, severe acute hepatitis evidenced by increased liver enzymes (alanine aminotransferase and aspartate aminotransferase >500 IU/L) and jaundice (2.6). The WHO, together with the ECDC and the United Kingdom Health Security Agency, have established the case definition in order to guarantee timely epidemiological notification of the situation [10], however, due to the variability of the condition and the absence of a clear definition of the underlying cause, the section established as “confirmed” is not available (Figure 1); [7].

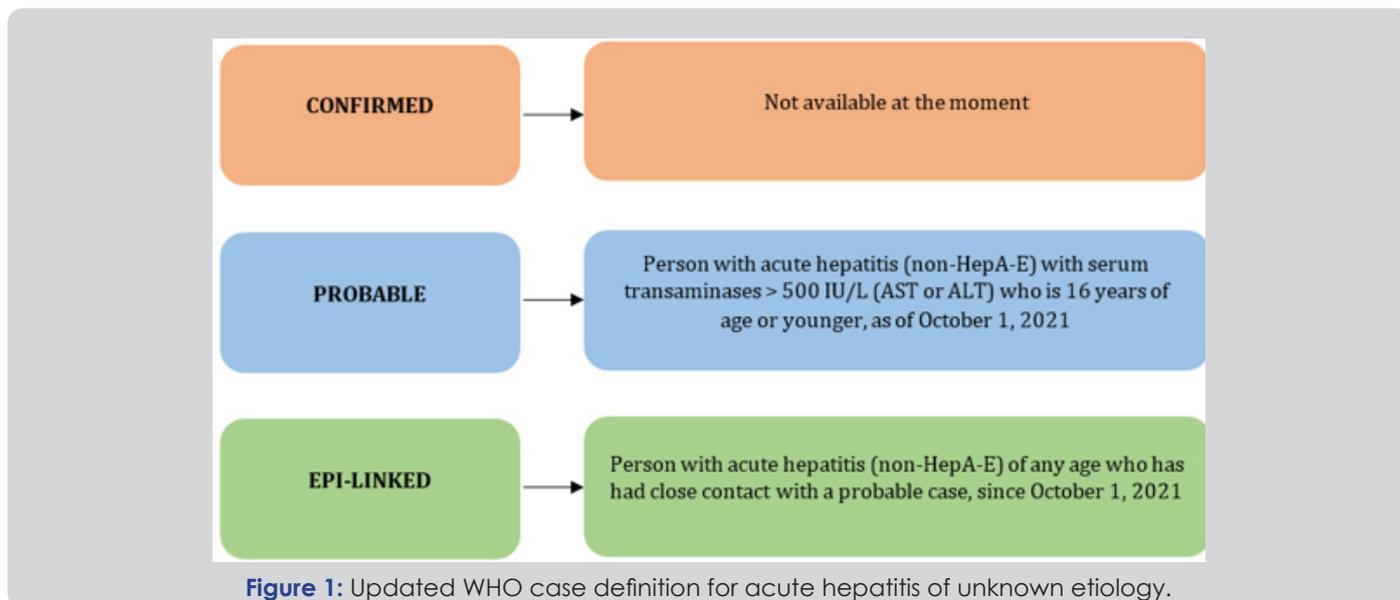


Figure 1: Updated WHO case definition for acute hepatitis of unknown etiology.

The diagnosis continues to be a challenge for the clinician who must be supported under the structure of a complete clinical history associated with a comprehensive physical examination and the taking of extension paraclinical tests, including liver function tests as well as serology, panels or cultures related to differential conditions taking into account pharynx, urine and fecal samples for Hepatitis A, B, C, D and E, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus (HSV), SARS-CoV-2, HIV, adenovirus, respiratory syncytial virus (RSV), among others [11]. According to medical criteria, imaging aids such as ultrasound, computed axial tomography (CAT) and abdominal magnetic resonance imaging (MRI) where the integrity of the liver and the structure of the bile duct will be established. Finally, in a limited number of cases, the histopathological study of the liver has been carried out; however, it has not been possible to report detailed information on the condition since, contrary to the findings evidenced in common acute viral hepatitis, there is no routine degeneration. liver disease,

necrosis, cholestasis or biliary embolism [3,10]. Finally, for the treatment it is important to mention that a complete relationship of the current literature combined with the reported experiences must be established, taking into account the requirement of symptomatic therapy, the initial etiological control and the prevention of associated complications.

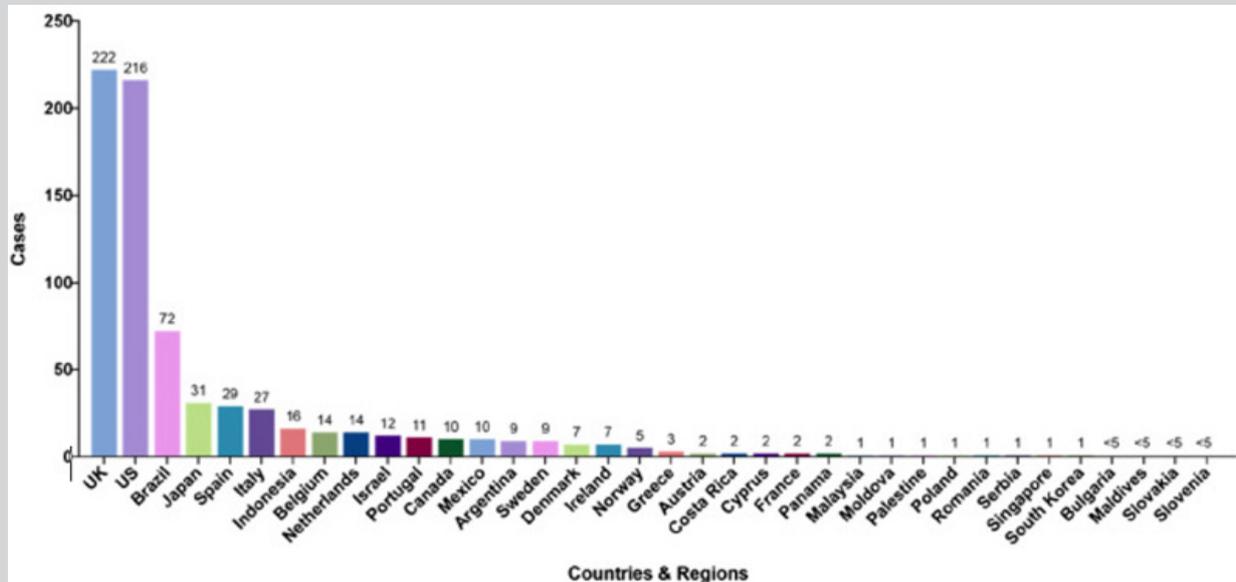
### METHODOLOGY

A systematic search of original articles, case reports and bibliographic reviews is carried out in specialized databases on the exposed subject such as ScienceDirect, Pubmed, Elsevier, Scielo and Medline. Search keywords such as: “Hepatitis”, “Unknown”, “Pediatrics”, “Outbreak”, “Etiology” and “Manifestation” are used, carefully selecting a total of 18 bibliographic references in the Spanish and English languages that were relevant. for the development of this review article.

## RESULTS AND DISCUSSION

Severe acute hepatitis of unknown origin in children has been characterized by being found as sporadic cases located in different regions or countries of the world without clear evidence of associated epidemiological correlation [11]. The most affected are children between the first month of life and 16 years of age; however, it has been estimated that close to 76% of all cases have

been reported in children under 5 years of age [9,12]. According to the information provided by different control centers such as the World Health Organization (WHO) and the European Center for Disease Prevention and Control (ECDC), until May 31, 2022 at least 813 cases had been reported with an incidence approximately 3.30 per million in the United Kingdom and 0.66 per million in the United States (Figure 2).



**Figure 2:** Distribution of reported cases of non-HepA-E hepatitis by country from October 2021 to May 2022.

There are various hypotheses related to the possible etiology of non-HepA-E acute hepatitis since the typical viruses commonly associated with the disease (Hepatitis A, B, C, D or E) have not been identified. The first and most plausible to explain is the relationship with the confirmed infection by the human adenovirus (HAdV) [13]. According to Sallam et al. [7] in most of the reported cases, the presence of nucleic acids or antibodies against this pathogen has been detected in the blood, feces and respiratory exudates. This is confirmed by Chen et al. [4] who comment that, respectively, about 75.5% and 50% of the cases reported in England and Scotland were infected with the virus, having the main serotype known as F41. This idea has generated great commotion worldwide since it is generally known that this HAdV serotype is responsible for developing self-limited gastrointestinal symptoms with asymptomatic hepatitis even more so in healthy populations [14], however, from Kleine et al. [10] do not dismiss the idea that the late exposure of the agent with the host due to the restrictions created in the midst of the Covid-19 pandemic, has generated a greater susceptibility in the patient for the development of an exaggerated immune response with hepatotoxicity. associate. On the other hand, various authors including Zhang et

The second hypothesis raised comments on the possibility of the development of autoimmune hepatitis which is characterized by a high level of IgG with several types of autoantibodies, among which antiactin antibodies (AAA), antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) stand out and antimitochondrials (AMA). In addition, histopathologically, mononuclear cell infiltrations are found in the portal area or around the portal vein, forming a well-defined hepatocyte plaque. Gao et al. [6] comment that, although this presentation is considered a

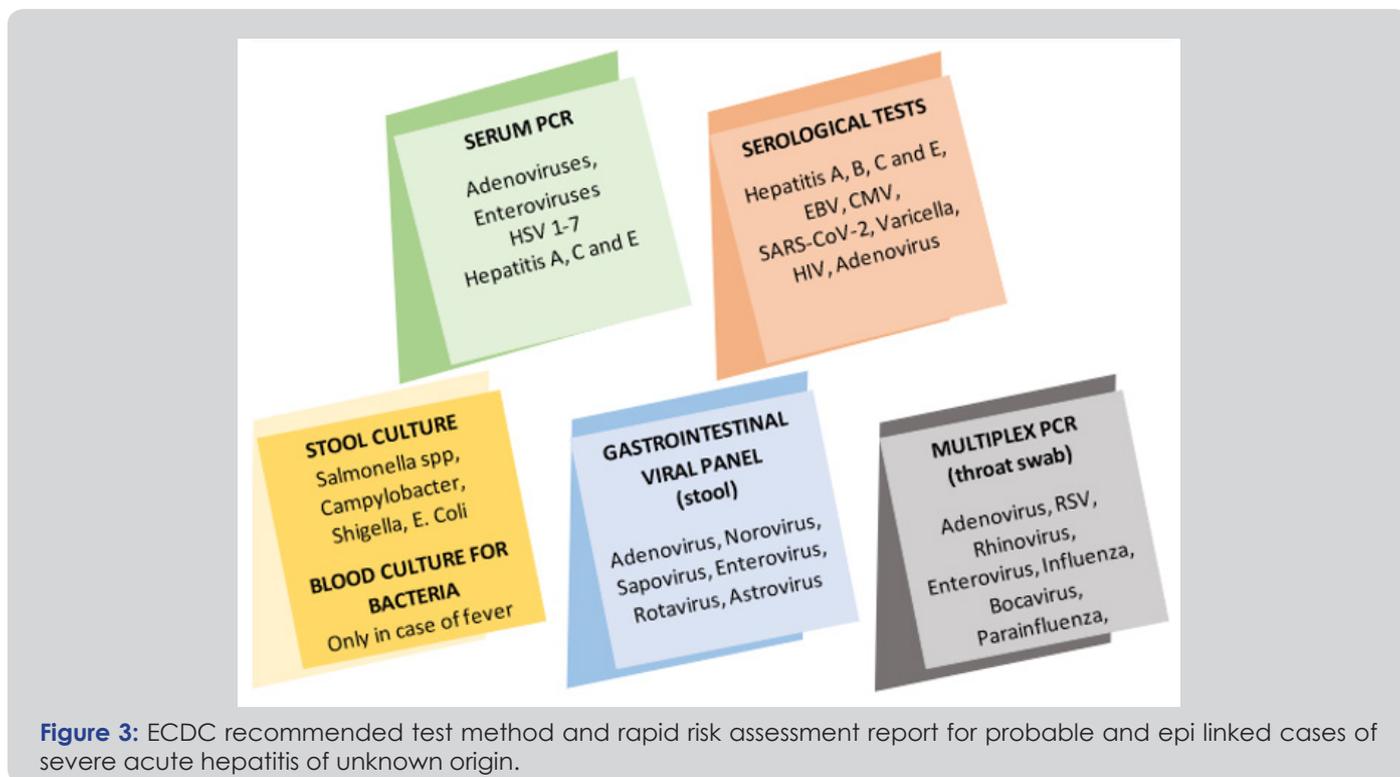
rare liver disease, it can manifest as acute hepatitis in up to 50% of pediatric cases with rapid evolution towards liver failure.

Finally, the last associated hypothesis explains the origin of the condition from the systemic inflammatory response triggered by the pediatric immune reaction against SARS-CoV-2 infection, since as mentioned by Zhang et al. [3] as of May 31, 2022, positive results were detected in 11.8% of the 204 cases tested by PCR and in 67.6% of the 34 cases tested by serology in the European Union. de Kleine et al. [10] differs from what was previously mentioned since, despite accepting that the Omicron variant presents cell tropism in the small intestine of the host, generating symptoms such as vomiting, diarrhea, abdominal pain and anorexia, acute hepatitis and jaundice have not been frequently reported. For his part, Mendez and Pal state that the evidenced relationship could only be a coincidence due to the increase in samples collected due to the contingency. It is important to highlight that the biologic designed against COVID-19 infection has not been related since most of the affected children have not been vaccinated [15].

Other detected pathogens include HSV, EBV, CMV, RSV, enterovirus, among others. Zhang et al. [3] state that this could indicate intestinal colonization or an infection secondary to liver failure. Some researchers have even speculated about the possible appearance of a new hepatotropic virus, especially one with RNA genetic material already that they have the ability to successfully transmit between species and quickly adapt to new niches. However, this information is still a matter of research. Sallam et al. [7] also mention that, although the relationship with non-infectious factors such as certain toxins, food or drugs has not been epidemiologically confirmed, it must be ruled out.

The clinical manifestations of non-HepA-E acute hepatitis are usually varied; however, jaundice was reported in approximately 68% of all patients, corresponding in turn to the main cause of medical consultation. The second most common symptom was vomiting (57%) followed by abdominal pain (36%), diarrheal stools (43%), fever (28%), nausea (25%) and finally, symptoms of respiratory origin (18%). On the other hand, Chen et al. [4] states that hypocholia or pale fecal matter has been reported in up to 50% of cases and that hepatomegaly is common but splenomegaly is

rare. The WHO comments that fever was absent in most patients [16,17]. Taking the above into account, the first step towards the possible detection of a non-HepA-E acute hepatitis case is to classify the situation using the parameters established by the WHO in 2022. Subsequently, the current guidelines established by the rapid risk assessment report are also recommended by the European Center for Disease Prevention and Control (ECDC); [1] for laboratory tests in suspected and epi linked cases (Figure 3).



**Figure 3:** ECDC recommended test method and rapid risk assessment report for probable and epi linked cases of severe acute hepatitis of unknown origin.

At this point it is important to mention that one of the main characteristics in affected patients is the presence of abnormal findings in liver function tests with a predominant hepatocellular pattern evidenced by significant elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) so its quantification together with that of total and direct bilirubin, albumin, prothrombin time, international standardized ratio (INR), fibrinogen and serum ammonia are essential for the comprehensive approach to the patient. According to Baker et al. [12] in the 9 affected children from Alabama, the ALT level ranged between 603 and 4696 IU/L while the AST range was between 447 and 4000 IU/L with reports of total bilirubin which generally range from 0.23 to 12. Some authors such as Sallam et al. [7] state that if it is clinically indicated, the initial assessment of the patient should be complemented with extension studies that allow assessing the possible etiology, as well as the associated complications. These tests include serological detection of anti-streptolysin O (ASO), throat swab culture for group A beta-hemolytic streptococci, serum or urine tests for leptospirosis, and toxicological detection with blood samples. On the other hand, Chen et al. [4] comments that imaging studies such as abdominal ultrasound and nuclear magnetic resonance (NMR) can be useful for studying the size, the structure and hepatic vascularization, taking special care with those patients who present symptoms of encephalopathy in order to achieve the effective performance of an electroencephalogram or even a computerized axial tomography (CAT) of the head to

evaluate the edema. Finally, Marsh et al. [9] comment that the histopathological changes of acute viral hepatitis are generally associated with extensive degeneration of hepatocytes, necrosis, infiltration of inflammatory cells in the lobular and portal area, as well as cholestasis and embolism. gall, but what, in the liver biopsies performed in a limited number of confirmed cases of non-HepA-E acute hepatitis, it has not been possible to demonstrate these findings in detail, highlighting the complete absence of viral inclusions or identifiable particles even by means of electron microscopy [15]. Figure 4 shows the diagnostic flowchart generated by Chen et al. [4] in the year 2022.

Medical management of non-HepA-E acute hepatitis in previously healthy children is initially based on performing symptomatic or supportive therapy which, if necessary, should be redirected after etiological control and possible complications since at present no interventions for specific management have been established. In the first section, according to Chen et al. [4], in addition to guaranteeing adequate rest and restricting protein intake by mouth, parameters related to the patient's state of consciousness, urinary volume, blood electrolytes, liver function and coagulation markers in addition to adequately intervening subsequent manifestations such as hypovolemia, hypoproteinemia, gastrointestinal bleeding, hypoglycemia or constipation as they can trigger serious complications such as hepatic encephalopathy and hepatorenal syndrome. Regarding etiological therapy, the reality

is that this has represented a challenge for the clinician, taking into account that even today the origin of the pathology is still a matter of investigation. Some authors have assessed the possibility of administering drugs such as cidofovir or ribavirin in patients

positive for adenovirus infection, however, Chen et al. [4] ensure that the former has only been effective in children receiving organ transplants solid or with severe viraemia and that only case reports support the use of the second drug [18].

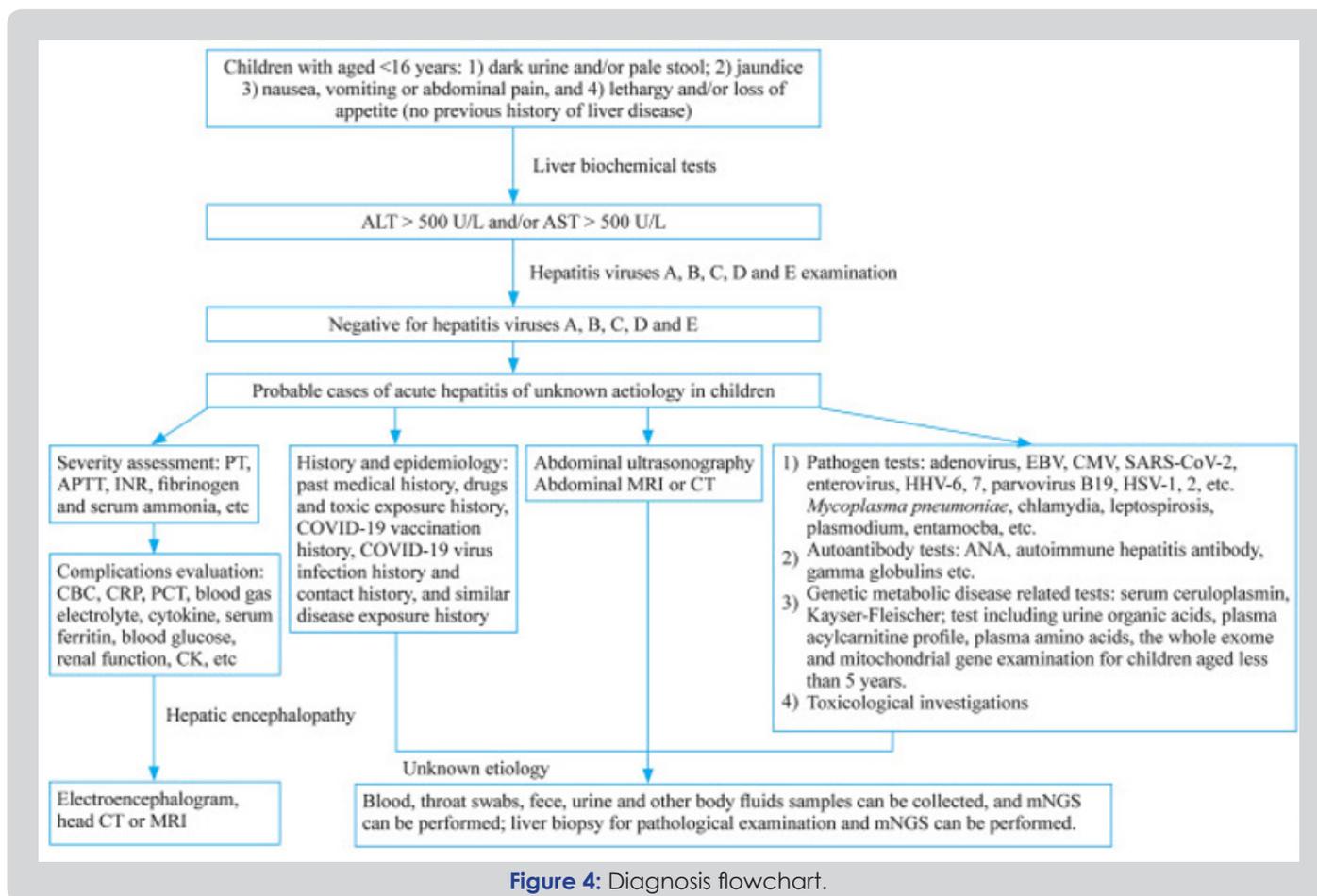


Figure 4: Diagnosis flowchart.

Table 1: Clinical and paraclinical criteria established by Nadalin et al. [13] to consider the requirement for liver transplantation.

Grade III hepatic encephalopathy
INR > 2
INR > 1.5 associated with hepatic encephalopathy
Bilirubin > 18 mg/dL
Tendency to hypoglycemia
Decreased liver size monitored by ultrasound

The care intervention of the complications will depend on the type and degree of this. In general, in hepatic encephalopathy, continuous evaluation of the grade and endotracheal intubation have been recommended for those children with levels III and IV. If necessary and given the lack of evidence, medical personnel may consider the use of hepatoprotective, vasoactive drugs or those that promote intestinal peristalsis in order to reduce the absorption of ammonia or its derivatives [7,19]. Chen et al. [4] recommend that, if possible, the use of artificial liver support should be guaranteed in those patients with liver failure complicated by severe hyperbilirubinemia, sepsis or multiple organ failure and who, finally, in cases with acute damage that do not present continuous progress

after the establishment of comprehensive medical management, liver transplantation should be considered since, according to what was reported by Sallam et al. [7], if performed at the right time, the life and functionality of the affected patient could be preserved. Nadalin et al. [13] established some criteria that could be taken into account where the degree of encephalopathy and the paraclinical report are related (Table 1), however, currently there are no well-defined or universally adapted indications for performing surgical intervention. According to Zhang et al. [3]. Finally, it is important to mention that several authors propose a strict review of the response capacity of the different health entities worldwide, as well as the current state of timely accessibility to surgical procedures

such as pediatric liver transplantation, recommending cooperation of a multidisciplinary team of health professionals specialized in comprehensive care for pediatrics, emergencies, infectious diseases, gastroenterology and intensive care, among others. This is done in order to guarantee the identification, notification and timely control of all suspected cases.

## CONCLUSION

The outbreak of severe acute hepatitis of unknown origin in children has had a trend of global appearance without evidence of clear epidemiological links, therefore, taking into account that the adenovirus has been the focus of attention as a possible etiological source, the basic preventive measures against this infection must be maintained or implemented among all communities. In the same way, it is vitally important to guarantee continuous education to families and the general public in order to promote the timely and central identification of signs or symptoms related to severity. Health personnel must maintain a high index of diagnostic suspicion accompanied by clinical surveillance, strict epidemiological and virological evaluation that allows evaluating the potential risk of the condition without neglecting the possibility of establishing surveillance or follow-up systems in the medium and long term. Finally, it is considered that the development of new investigative processes is required to accurately establish the prognosis and progression of the ongoing outbreak.

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