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LETTER TO THE EDITOR

Acute hepatitis of unknown etiology: a proposed diagnostic approach

Hepatitis aguda de etiología desconocida: una propuesta de abordaje diagnóstico

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Recently, acute and severe hepatitis cases in children have increased, triggering close epidemiological surveillance worldwide[1]. Between April 5 and May 26, 2022, 650 probable cases have been reported to the World Health Organization (WHO) from 33 countries, with the United Kingdom and the United States reporting most cases, followed by Japan, Spain, and Italy[2].

The WHO defines a probable case as any person presenting with acute hepatitis (not hepatitis A-E) with serum transaminase levels > 500 IU/L (aspartate aminotransferase or alanine aminotransferase) and age ≤ 16 years (Table 1)[3], mainly with gastrointestinal symptoms, such as vomiting, acholia, and jaundice, and respiratory symptoms in a lower percentage (Table 2)[2].

Table 1. Case definitions according to the World Health Organization

Case	Definition
Confirmed	No definition
Probable	Any individual aged ≤ 16 years who presents acute hepatitis (not hepatitis A-E), with serum transaminase levels > 500 IU/L (AST or ALT) since October 1, 2021
Contact	Any individual of any age who presents with acute hepatitis (not hepatitis A-E) and has been in close contact with a probable case since October 1, 2021
Cases with other explanations for clinical presentation should be excluded. Delta testing is not required, as it is only performed in HBsAg-positive individuals to establish the presence of coinfection	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B virus surface antigen.

Etiology of acute hepatitis

Cases have tested negative for A-E viruses. A UK study involving 126 children documented the presence of adenovirus in 72% (n = 91). It was also identified in 44% of stool and 29% of respiratory specimens. Twenty-four children (18%) had active SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. Epstein-Barr, enterovirus, cytomegalovirus, respiratory syncytial virus, and human herpesviruses 6 and 7 were identified less frequently[4-6].

According to the European Centre for Disease Prevention and Control (ECDC), several hypotheses have emerged based on present-day evidence. The most compelling relates to a cofactor affecting children that cause mild adenovirus infections to become more severe or trigger immune-mediated liver damage. This cofactor may be related to susceptibility due to a lack of prior exposure to adenovirus during the pandemic, a previous SARS-CoV-2 infection, or a toxin, drug, or environmental exposure[1,7].

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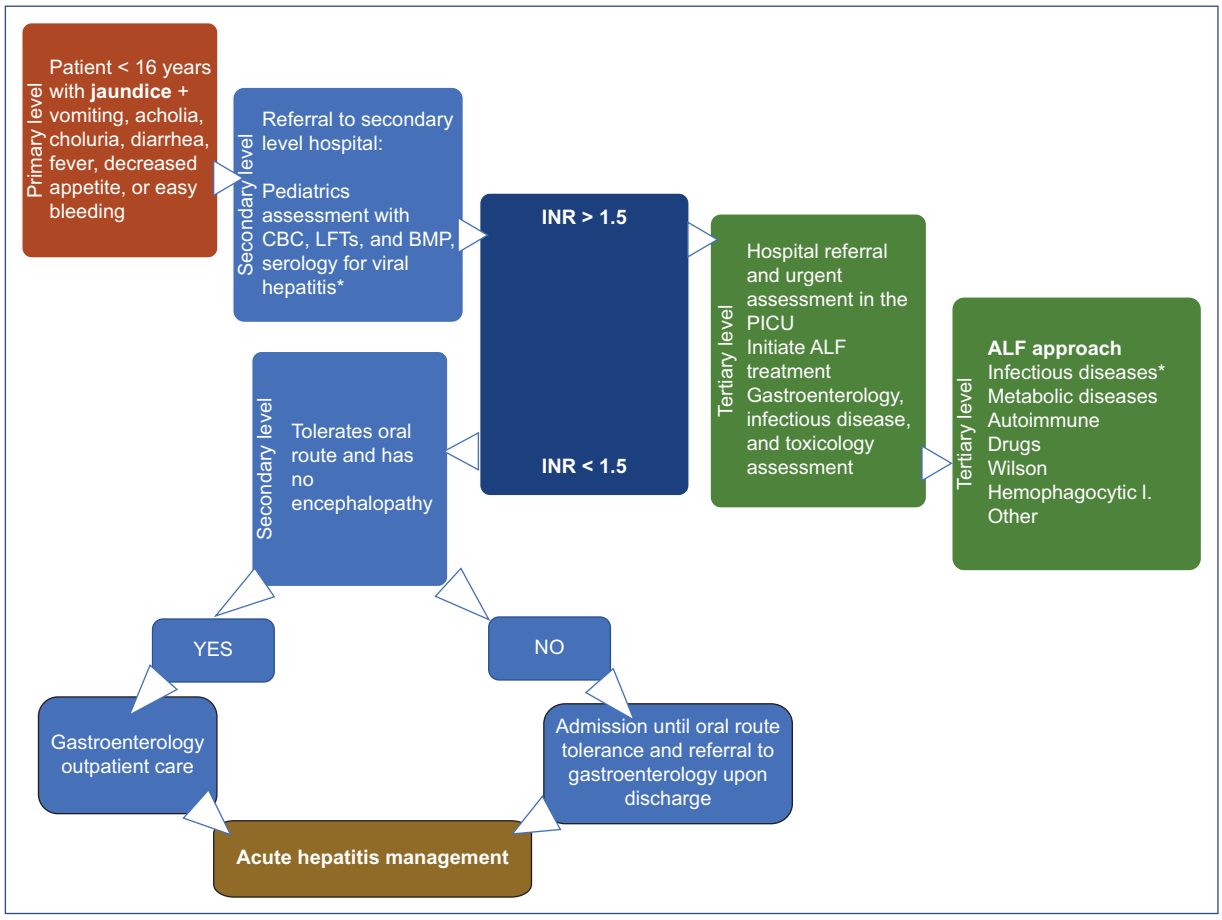

Figure 1. Diagnostic approach to suspected acute hepatitis.
ALF: acute liver failure; BMP: basic metabolic panel; CBC: complete blood count; INR: international normalized ratio; LFTs: liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, albumin, total bilirubin, direct bilirubin, and coagulation tests); PICU: Pediatric Intensive Care Unit.
*Consider hepatitis A, B, C, and E, Epstein-Barr virus, cytomegalovirus, leptospirosis, human parvovirus B19, adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpesvirus.

Proposed diagnostic approach

Upon identification of a probable case of hepatitis, the conventional care process should be conducted, allowing for differential diagnosis since acute hepatitis is not a new disease. Throughout history, cases of unknown or idiopathic causes have been documented after searching for the most common causes. For this reason, it is necessary to adopt a systematic evaluation, tiered by the level of care and age group, to manage cases with symptoms consistent with acute hepatitis (Figure 1).

This evaluation is intended to determine the etiology of the liver injury and not ignore other known causes of hepatitis, such as autoimmune, toxic, and other infectious diseases caused by hepatotropic and non-hepatotropic viruses, including hemophagocytic lymphohistiocytosis,

Table 2. Clinical presentation in children with acute hepatitis of unknown etiology

Signs or symptoms	Percentage
Jaundice	71%
Vomiting	63%
Acholia	50%
Diarrhea	45%
Fever	31%
Respiratory symptoms	19%

in which patients present with hepatic inflammation and may develop acute liver failure[8].

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Cevik M, Rasmussen AL, Bogoch II, Kindrachuk J. Acute hepatitis of unknown origin in children. BMJ. 2022;377:o1197.
2. World Health Organization. Acute hepatitis of unknown aetiology in children—Multi-country. Geneva: World Health Organization; 2022. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/DON-389
3. World Health Organization. Disease outbreak news: Severe acute hepatitis of unknown aetiology in children–Multi-country. Geneva: World Health Organization; 2022. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376.
4. Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, et al. Acute hepatitis and adenovirus infection among children—Alabama, October 2021-February 2022. MMWR Morb Mortal Wkly Rep. 2022;71:638-40.
5. Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. Euro Surveill. 2022;27:2200318.
6. UK Health Security Agency. Baillie K, Baldevarona J, Bindra R, Bradshaw D, Breuer J, Blomquiste P, et al. Investigation into acute hepatitis of unknown aetiology in children in England—technical briefing. London: UK Health Security Agency; 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1073704/acute-hepatitis-technical-briefing-2.pdf.
7. European Centre for Disease Prevention and Control. Increase in severe acute hepatitis cases of unknown aetiology in children. Stockholm: European Centre for Disease Prevention and Control; 2022. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-20220420-218-erratum.pdf.
8. Squires JE, Alonso EM, Ibrahim SH, Kasper V, Kehar M, Martinez M, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the diagnosis and management of pediatric acute liver failure. J Pediatr Gastroenterol Nutr. 2022;74:138-58.