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The recent outbreak of acute severe hepatitis in children of unknown origin

To the Editor:

Recently, acute hepatitis of unknown aetiology among young children appeared in many countries, causing global concern. We read with great interest Marcus *et al.*'s manuscript that reviews the available information concerning this recent outbreak and introduces some of the discussed hypotheses for its development.¹ Herein, we add a few noteworthy points.

First, it must be determined whether this hepatitis of unknown cause in multiple countries is actually the same hepatitis, which requires a global sharing of information and academic collaboration. Second, in addition to a throat swab test to confirm SARS-CoV-2 infection, blood tests for antibodies should also be used to rule out a history of infection. Lately, a study by Ratho *et al.*, published on the preprint platform medRxiv, showed that of 475 children with a history of SARS-CoV-2 infection, 37 children developed COVID-19-associated hepatitis.² These cases presented symptoms including nausea, vomiting, loss of appetite, fatigue, and low fever of less than 38°C, but lacked significantly elevated inflammatory markers. Similarly, in the cases of children in Scotland reported by Marsh *et al.*, almost all reported gastrointestinal symptoms including diarrhoea or vomiting and lethargy, but no fever, in the weeks prior to admission.³ In the study by Ratho *et al.*, the majority of these children with COVID-19-associated hepatitis were asymptomatic or had mild COVID-19 before sud-

denly developing hepatitis 2–6 weeks later. Surprisingly, 35 children tested negative for SARS-CoV-2 by PCR at the time of admission. Therefore, we recommend that previous studies confirm a history of SARS-CoV-2 infection in children with hepatitis of unknown aetiology by blood antibody testing.

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Authors' contributions

Jing Huang and Guangting Zeng initiated and conceptualised the idea. Guangting Zeng wrote the letter, and Jing Huang revised the letter.

Supplementary data

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The recent outbreak of acute severe hepatitis in children of unknown origin – what is known so far

To the Editor:

We have read with great interest the manuscript by Mücke and Zeuzem accepted for publication in the *Journal of Hepatology* in May 2022. The authors discuss the current concern over an increasing number of children presenting with a so-called severe non-A-E hepatitis, a finding initially reported from the United Kingdom across central Scotland (World Health Organization [WHO] Disease Outbreak News 15th Apr 2022) and subsequently from 15 other countries.¹ The authors discuss different potential epidemiologic reasons for the occurrence, as well as one particular concern, also raised by the authorities, which is the potential association of human adenovirus (hADV) infection with these cases, more precisely an infection with a specific hADV serotype F41.²

More recently, on May 11th, the Centers for Disease Control and Prevention (CDC) updated the North American experience, where 109 children were reported having unknown hepatitis, out of whom more than half tested positive for adenovirus, 14% required liver transplantation (LT) and 5 died.³ On May 12th, a group of representatives for the European reference network (ERN) RARE-LIVER published the data of a short survey which was sent to all ERN members with a specialized service in pediatric hepatology, summarizing a total of 64 cases of acute hepatitis recorded since January 2022 from 34 centers and 22 countries throughout Europe and Israel. In 38 (60%) of these cases a plausible cause for the acute hepatitis was identified. Four might have been related to a SARS-CoV-2 infection (3 had active COVID-19) and in 9, different viruses including adenovirus (n = 4), were detected. Four of the children required LT and 4 (3 before LT, 1 after LT) died.⁴

Since devastating courses of severe acute hepatitis, with death or the need for LT, are indeed highly worrying, and demand further precise work up, a group of German pediatric hepatologists and representatives of the German pediatric LT centers discussed these reports at the annual meeting of the German speaking Association (Germany, Austria, Swiss) of pediatric Gastroenterology, Hepatology and Nutrition (GPGE) on May 13th in Rostock, Germany. The expert

consensus concluded that it is currently too early to describe a new 'wave' of severe cases with non-A-E hepatitis. The current cluster resembles the expected amount and distribution of children presenting with acute severe hepatitis or acute liver failure.⁴ Discussion regarding an hADV infection causing the presented cases was particularly highly debated, as thus far no case of ADV infiltration of the liver has been reported. It is expected that a change in societal behavior, and less exposure to pathogens due to various measures during the SARS-CoV-2 pandemic, might cause changes in established transmission patterns of viral infections as well as individual immune responses. This hypothesis is supported by the current decrease of influenza A infections,⁵ or by a timely shift of respiratory syncytial virus (RSV) infections in the last few years.⁶ An overall higher current incidence of classic hADV infections in children presenting with respiratory symptoms was also reported. For comparison, the elevated number of cases of severe hepatitis and gastrointestinal symptoms after the 1918 flu pandemic was discussed.⁷

Of concern is a potential association of the reported cases with a previous SARS-CoV-2 infection which might have caused hepatitis leading to i) a higher susceptibility of the liver and ii) an overwhelming inflammation in the setting of any other viral infection, which can also be seen in so-called seronegative autoimmune hepatitis or hepatitis-associated aplastic anemia.

We endorse the conclusion of Mücke and Zeuzem, and support activities by health agencies such as the WHO, the European Centre for Disease Prevention and Control, and local authorities, to collect more and precise data in a timely fashion.^{1–4,8–10} However, we advise caution in making early and/or premature conclusions concerning this sensitive matter, since to date, and to the best of our knowledge (at least in Germany and within the ERN community), there has been no substantial increase in severe pediatric acute hepatitis and/or acute liver failure of unknown origin.

To put these cases within the correct clinical context, we therefore strongly suggest using established pediatric infrastructures provided by, for example, the ERN RARE-LIVER and other expert bodies, such as national and international associations of pediatric hepatologists (GPGE, the European and North