

**Supplementary information**

---

**Sudden onset hepatitis in children**

---

In the format provided by the  
authors and unedited

## Supplementary Box 1 | Sudden onset hepatitis of unknown cause

### Existing reports and case studies

- UK Health Security Agency (UKHSA) investigation into acute hepatitis of unknown aetiology in children in England<sup>S1</sup>
- World Health Organization (WHO) update on acute hepatitis of unknown aetiology in children<sup>S2</sup>
- European Centre for Disease Prevention and Control (ECDC) report on hepatitis of unknown aetiology in children<sup>S3</sup>
- Report on paediatric acute liver failure<sup>S4</sup>
- ECDC guidance for diagnostic testing of cases with severe acute hepatitis of unknown aetiology in children<sup>S5</sup>
- Preprint reports on liver manifestations and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children<sup>S6,S7</sup>
- European Association of the Study of the Liver (EASL) Studio special edition webinar on unexplained acute hepatitis in children<sup>S8</sup>
- UKHSA report on substantial reduction of childhood infections in 2020-2021<sup>S9</sup>
- UKHSA report on norovirus and rotavirus infections<sup>S10</sup>
- UKHSA report on adenovirus and other childhood respiratory infections<sup>S11</sup>
- British Society of Gastroenterology (BSG) resource on drug-induced liver injury, outlining distinction between autoimmune manifestations and check-point inhibitor hepatitis<sup>S12</sup>
- World Hepatitis Alliance and WHO latest update on unexplained hepatitis in children<sup>S13</sup>
- Case reports in Israel<sup>S14</sup>
- ISARIC CCP–UK activities in response to outbreak of unexplained hepatitis in children; ISARIC 4C<sup>S15</sup>

### WHO working case definition

- Confirmed: N/A at present
- Probable: A person presenting with an acute hepatitis (non-hepatitis A-E<sup>a</sup>) with serum transaminase levels >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021
- Epidemiologically linked: A person presenting with an acute hepatitis (non-hepatitis A-E<sup>a</sup>) of any age who is a close contact of a probable case, since 1 October 2021

<sup>a</sup>If 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. Delta testing is not required, as it is only undertaken in persons who are positive for hepatitis B surface antigen to establish presence of co-infection. ALT, alanine transaminase; AST, aspartate transaminase; N/A, not applicable.

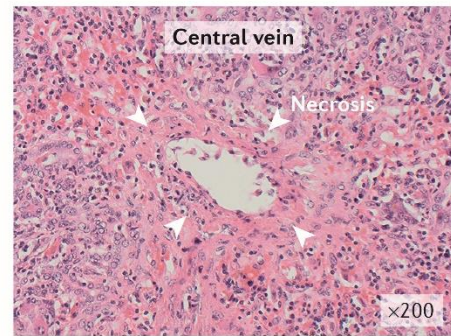
## Supplementary Figure 1 | Unexplained sudden onset hepatitis in children in the UK – current clinical investigations in the UK.

### Clinical investigations in the UK

- Pathogens tested positive in some children — adenovirus (77/97 cases of blood tested, 27/35 were type 41F), SARS-CoV-2 (16/125), 7 children were coinfecting with adenovirus and SARS-CoV-2. Fewer children positive for CMV, EBV, enterovirus, HHV6, HHV7 and RSV
- Paracetamol — administered within permitted doses in three-quarters of the children tested
- Fluconazole and mycotoxins — under investigation, no causative link to these cases to date

### Non-specific hepatitis and necrosis

- Ranging from mild hepatocellular injury to massive hepatic necrosis
- Immune infiltrates
- Mainly CD8<sup>+</sup> T cells
- No viral inclusion bodies



Published in UKHSA technical briefing 3 (Supplementary Box 1), and example histological image showing non-specific hepatitis and necrosis in a case of unexplained sudden onset hepatitis in a child. Image courtesy of R.M. Brown, University Hospitals Birmingham, UK. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpes virus; RSV, respiratory syncytial virus; UKHSA, UK Health Security Agency.

### Supplementary reference list

- S1. UK Health Security Agency (UKHSA). Investigation into acute hepatitis of unknown aetiology in children in England Technical briefing 3, 19 May 2022. *UK Government* [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1077027/acute-hepatitis-technical-briefing\\_3.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077027/acute-hepatitis-technical-briefing_3.pdf) (2022).
- S2. World Health Organisation (WHO). Acute hepatitis of unknown aetiology in children - Multi-country, 27 May 2022. *WHO* <https://www.who.int/emergencies/disease-outbreak-news/item/DON-389> (2022).
- S3. European Centre for Disease Prevention and Control (ECDC). Epidemiological update: Hepatitis of unknown aetiology in children. 11 May 2022. *ECDC* <https://www.ecdc.europa.eu/en/news-events/epidemiological-update-hepatitis-unknown-aetiology-children#:~:text=Worldwide%20update,have%20received%20a%20liver%20transplant> (2022).
- S4. Zellos A. et al. Proceedings of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Monothematic Conference, 2020: “Acute Liver Failure in Children”: Treatment and Directions for Future Research. *J. Pediatr. Gastroenterol. Nutr.* **74**, 338-347 (2022).
- S5. European Centre for Disease Prevention and Control (ECDC). Guidance for diagnostic testing of cases with severe acute hepatitis of unknown aetiology in children: 25 May 2022. *ECDC* <https://www.ecdc.europa.eu/en/publications-data/guidance-diagnostic-testing-cases-severe-acute-hepatitis-unknown-aetiology> (2022).
- S6. Rawat SK, Asati AA, Jain A, Mishra N, Ratho RK. Covid-19 associated hepatitis in children (CAH-C) during the second wave of SARS-CoV-2 infections in Central India: is it a complication or transient phenomenon? [preprint] *medRxiv* <https://doi.org/10.1101/2021.07.23.21260716> (2022).
- S7. Kendall, E.K. et al. Elevated liver enzymes and bilirubin following SARS-CoV-2 infection in children under 10. *Medrxiv* <https://doi.org/10.1101/2022.05.10.22274866> (2022).

- S8. EASL. European Association for the Study of the Liver Studio Special Edition: Unexplained acute hepatitis in children, 24 May 2022 [webinar]. *EASL* <https://easlcampus.eu/videos/easl-studio-special-edition-unexplained-acute-hepatitis-children> (2022).
- S9. UK HSA Blog on increase in unexplained hepatitis in children. <https://ukhsa.blog.gov.uk/2022/05/09/an-increase-in-hepatitis-cases-in-children/> (2022).
- S10. Increase in norovirus and rotavirus cases in children in 2021-2022. [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1073141/UKHSA-norovirus-bulletin-2021-to-2022-week-18.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1073141/UKHSA-norovirus-bulletin-2021-to-2022-week-18.pdf) (2022)
- S11. Increase in adenovirus and other respiratory virus cases in children in 2021-2022. <https://www.gov.uk/government/publications/respiratory-infections-laboratory-reports-2022/reports-of-respiratory-infections-made-to-ukhsa-from-ukhsa-and-nhs-laboratories-in-england-and-wales-weeks-49-to-2-2021-to-2022> (2022).
- S12. British Society for Gastroenterology on checkpoint inhibitor hepatitis. <https://www.bsg.org.uk/web-education-articles-list/drug-induced-liver-injury/> (2022).
- S13. World Hepatitis Alliance and WHO joint news release from the World Hepatitis Summit 2022. <https://www.who.int/news/item/07-06-2022-world-hepatitis-summit-2022-urges-action-to-eliminate-viral-hepatitis-as-unexplained-hepatitis-cases-in-children-rise-globally> (2022).
- S14. Efrati, I. Israel examining 12 cases of kids' hepatitis after WHO warning. HAARETZ <https://www.haaretz.com/israel-news/2022-04-21/ty-article/israel-examining-12-cases-of-kids-hepatitis-after-who-warning/00000180-6567-d5ca-a986-7f6f8a990000> (2022).
- S15. ISARIC4C on unexplained hepatitis in children. <https://isaric4c.net/hepatitis/> (2022).