Acute Hepatitis of Unknown Origin
Quick Reference for Clinical Health Care Workers

National Institute for Communicable Diseases (NICD)
24-hour hotline number: 0800 212 552

27 May 2022

Outbreak Overview

On 5th April 2022, the World Health Organization (WHO) received notification of 10 cases of severe acute hepatitis of unknown aetiology from central Scotland in the United Kingdom (UK). Since then, there has been a continuing increase in the number of reports of these cases among previously well children. As of 26 May 2022, 650 probable cases fitting the WHO case definition have been reported from 33 countries in five WHO Regions, with 99 additional cases pending classification. The majority of probable reported cases (374) are from the WHO European Region (22 countries), with 222 cases from the United Kingdom alone. Of the probable cases, at least 38 children have required transplants, and nine deaths have been reported to WHO. To date, there have been no cases reported in the African region. These cases of severe acute hepatitis are of particular concern as most cases have affected children under 6 years of age who were previously well.

Suspected Aetiology

Ongoing investigations suggest this acute hepatitis may be linked to **adenovirus infection**, however the exact aetiology remains to be determined. Adenovirus has not yet been identified in the liver tissue samples analysed, and adenovirus is ubiquitous, so the currently observed and tenuous associations may well be co-incidental. The potential role of SARS-CoV-2 is also under investigation, as it has been detected in a few cases, either in isolation or with adenoviral co-infection. There is currently no evidence of an association between COVID-19 vaccination and acute hepatitis of unknown origin. Tests for hepatitis viruses A-E have been negative in all cases. Clinicians are advised to consider adenovirus testing in paediatric patients presenting with hepatitis of unknown cause. There is currently no documented association with travel, diet or water source in any of the cases.

Signs and Symptoms of acute hepatitis

1. Jaundice
2. Nonspecific gastrointestinal symptoms (abdominal pain, diarrhoea, nausea, vomiting)
3. General symptoms of hepatitis (dark urine; pale coloured faeces; pruritus; muscle and joint pain; fatigue)

Working Case Definition for Testing

Confirmed: Not applicable at present

Probable: A child or adolescent who is 16 years and younger, presenting with acute hepatitis (non-hepatitis A, B or C) of unknown aetiology with serum transaminase >500 IU/L (AST or ALT), with no evidence of toxin ingestion, since 1 October 2021. **NICD will test these cases for adenovirus infection*

Epi-linked: A person presenting with acute hepatitis (non-hepatitis A, B or C*) of any age who is a close contact of a probable case, since 1 October 2021.

Cases with alternative diagnoses will be not be included in the dataset for evaluation.

For enquiries please call the NICD hotline on 0800 212 552 and email outbreak@nicd.ac.za. During working hours, please contact Dr Nishi Prabdial-Sing, (niship@nicd.ac.za/ 011 386 6347/084 511 7539), or Jayendrie Thaver for laboratory enquiries, and Chenoa Sankar for epidemiological enquiries.

The differential diagnosis of acute hepatitis in children

- Viral hepatitis due to hepatitis A, B+/-D, C or E
- Hepatitis secondary to a viral infection with CMV, HSV, EBV, HHV-6, HHV-7, or more rarely due to influenza or respiratory syncytial virus, and possibly adenovirus
- Hepatitis due to overwhelming systemic bacterial or fungal infection of any kind, more commonly caused by *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis,* and enteric bacteria
- Toxin ingestion should be ruled out, especially paracetamol overdose. Some traditional herbal medications have been implicated
- Current infection with SARS-CoV-2 should be ruled out.

NB: *All tests for these conditions should be submitted to usual testing laboratory (NHLS in public sector, or private laboratories in the private sector).*

The NICD will test the following sample types for adenovirus.

(Sample collection instructions may be found on the NICD website, 'Diseases A-Z, under 'Hepatitis of uncertain aetiology')

- Stool – submit a 'brown swab' or stool specimen in a sealed jar
- Blood – submit whole blood in an EDTA tube (purple top)
- Throat swab – collect a swab
- Tissue (e.g liver biopsy – please consult laboratory)

Specimen submission instructions:

1. Label all samples 'NICD/CVI laboratory - Attention Jayendrie Thaver,' (jayendriet@nicd.ac.za/ 011 386 6419/ 083 266 3323).
2. For every patient, please complete a case investigation form (CIF) and submit it along with the specimens to the NICD.
3. CIFs are available on the NICD website and also from NICD Centre for Vaccines and Immunology (CVI) (epidemiologist Chenoa Sankar (chenoas@nicd.ac.za/ 078 371 0927).