New Zealand Paediatric Surveillance Unit

ACUTE HEPATITIS PROTOCOL

CONDITION TO BE STUDIED
Acute hepatitis in children

CASE DEFINITION
An acute hepatitis, in a child aged 0–16 years (inclusive), with discrete or acute onset of symptoms (e.g. fever, jaundice, abdominal pain, fatigue, loss of appetite, dark urine, pale coloured stools, itchy skin, muscle or joint pain, nausea or vomiting); AND elevated serum transaminase (ALT) levels (>300U/L).

Please report any case of acute hepatitis irrespective of whether an infectious agent is identified.

Reported cases will be filtered to identify outbreak-specific cases meeting the WHO definition of a probable case: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021 (*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 will be discarded from the 'acute hepatitis of unknown origin' category, but included in overall acute hepatitis surveillance.

REPORTING INSTRUCTIONS
Please report any child or young person (aged 0–16 years) under your care who presents with an acute hepatitis with aspartate transaminase (AST) or alanine transaminase (ALT) over 300 U/L

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STATEMENT OF RESEARCH QUESTIONS
In New Zealand, what features are associated with acute hepatitis with aspartate transaminase (AST) or alanine transaminase (ALT) over 300 U/L in children aged under 17 years, presenting after 1 January 2021?

PROPOSED STARTING DATE May 2022
PROPOSED DURATION OF STUDY [open-ended]

BACKGROUND INFORMATION

On 5 April 2022 the United Kingdom (UK) advised the World Health Organization (WHO) of 10 cases of severe acute hepatitis in previously healthy young children (age range: 11 months to five years) across central Scotland of unknown aetiology. Most cases had symptom onset in March 2022.[1] A few days later it became clear that there had been more cases across the UK, with a total of 74 cases identified.[2] The first five cases in Scotland were described in a rapid surveillance report.[3]

The reported cases are characterised by the following clinical syndrome:[4]

- Acute hepatitis with markedly elevated liver enzymes, often with jaundice
- Sometimes preceded by gastrointestinal symptoms
- Children usually aged under 10 years
- Laboratory testing excludes hepatitis type A, B, C, and E viruses (and D where applicable)
- Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and/or adenovirus have been detected in several cases
- Some cases have required transfer to specialist children's liver units and six children have undergone liver transplantation.

Later in April confirmed or possible cases had been reported in at least 12 countries, although it remains uncertain whether there is an increase in hepatitis cases in children, or increased reporting due to raised awareness.[5] [6]

There does not seem to be any association with COVID-19 vaccination. None of the early cases had received vaccine for COVID-19; most were aged under 5 years so not eligible.[5]

Additionally, a small cluster of up to 15 cases of acute hepatitis were detected in New Zealand children between May and September 2021. These children were also young, and often reported a prodromal or concurrent viral infection. Several had viruses identified, including adenovirus, RSV, rotavirus and enterovirus. One child required liver transplantation. These diagnoses were made prior to the onset of the outbreaks of the delta and omicron variants of SARS-CoV-2 infection in New Zealand and prior to the commencement of COVID-19 vaccination in children. The transplanted child had acute respiratory syncytial virus infection (RSV) at the time of transplant but the role of this virus in the pathogenesis of acute liver failure is unknown.

In this New Zealand Paediatric Surveillance Unit study the ALT/AST levels are set at >300U/L, whereas internationally a cut off of 500IU/L is used. This is because some NZ laboratories have assays for AST/ALT where 25 is the upper limit or normal (ULN), whereas others use 60. Therefore 300 is approx. the lowest 10 x ULN we would expect.

WHY ARE THE PROPOSED RESEARCH QUESTIONS IMPORTANT?

There is genuine uncertainty about the aetiology of the rise in cases of acute hepatitis in children observed in the United Kingdom and now in some other countries.

The WHO has stated that "further work is required to identify cases both inside the United Kingdom and internationally. The priority is to determine the aetiology of these cases to guide further clinical and public health actions … Temporal and geographical information of the cases, as well as their contacts should be reviewed for potential risk factors."

WHO has encouraged Member States to identify potential cases, investigate and report results. New Zealand is in a good position to contribute to international surveillance, given a robust active surveillance programme and good engagement with the paediatric workforce.

In addition, the proposed research would allow the investigators to look more broadly at all causes of acute hepatitis in children in New Zealand which has not been studied or surveyed before. This is important because of the unique ethnic composition of the NZ population. Other non-viral diseases presenting with acute hepatitis, including Wilson disease and auto-immune liver disease have unknown prevalence and incidence in New Zealand.

RESEARCH METHODS

This will be a rapid surveillance study in response to an emerging condition. There will be a 'once off' retrospective question looking at the past year, then ongoing surveillance using the usual NZPSU monthly reporting process.

Specimens (blood, nasopharyngeal swab, urine, stool) will be collected as clinically indicated and with advice from Paediatric Infectious Diseases Specialists and Paediatric Gastroenterologists/Hepatologists.

Data will be collected as per NZPSU protocols and entered into a securely stored electronic spreadsheet. Data will be accessed only by the research team. Analysis will lead to a descriptive case series with a particular focus on identification of identified viral pathogens.

Is a follow-up study planned? If yes, please give details.

To be confirmed

REFERENCES

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