

TO: Vermont Health Care Providers and Health Care Facilities
FROM: Brian Borah, MD, Epidemic Intelligence Service Officer assigned to the Vermont Department of Health

**Pediatric Hepatitis of Unknown Etiology:
Possible Association with Adenovirus-41 Infection**

BACKGROUND:

On April 21, 2022, the Centers for Disease Control and Prevention (CDC) issued a Health Advisory notifying clinicians and public health authorities of a cluster of previously healthy children, aged 1 to 6 years old, with hepatitis of unknown etiology and adenovirus infection. This report identified nine children from a large children's hospital in Alabama with adenovirus infection and severe liver injury, including three with acute liver failure, and two who required liver transplantation.

The children presented with gastroenteritis symptoms followed by onset of jaundice. None had COVID-19 and all tested negative for hepatitis virus A, B and C. Adenovirus was detected through bloodwork on all nine patients. Two of the patients initially tested negative for adenovirus by quantitative polymerase chain reaction (qPCR) in plasma samples but were later positive when retested using whole blood. Of five patients with sequenced results, all had adenovirus type 41 identified. Similar cases of pediatric hepatitis of unknown etiology have been reported from multiple European countries. Many, but not all, have had concurrent adenovirus infection.

As of May 18, 2022, the CDC and state partners are investigating 180 children with hepatitis of unknown origin across 36 states and territories. Of the 109 for whom information is available, more than half have tested positive for adenovirus, more than 90% were hospitalized, and 14% received liver transplants. There have been five deaths. There are no cases in Vermont to date.

REQUESTED ACTIONS:

- Report any child younger than 10 years of age with elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >500 IU/L who has an unknown etiology for their hepatitis since October 1, 2021, to the Vermont Department of Health at 802-863-7240. Cases should be reported irrespective of adenovirus testing or results.
- In pediatric patients with hepatitis of unknown etiology, consider adenovirus testing in respiratory specimens, stool/rectal swabs **and** blood. Nucleic acid amplification test (NAAT) (e.g., PCR) is preferable when available.

- Anecdotal reports suggest that testing whole blood by PCR may be more sensitive than testing plasma by PCR. Therefore, testing of whole blood could be considered in those without an etiology who tested negative for adenovirus in plasma samples.
- Continue to follow standard practice for evaluating and managing patients with acute hepatitis.
- For clinical or laboratory questions, please email both brian.borah@partner.vermont.gov and jill.warrington@partner.vermont.gov.

LABORATORY TESTING:

Respiratory Samples

When possible, any clinical specimens should be tested locally to ensure the timeliest results for patient care. Testing of respiratory samples is available in Vermont through:

- **University of Vermont Medical Center:** 1 ml minimum volume, specimen stability (4 days refrigerated); Respiratory Viral Panel Expanded, Test Code: RESEXP.

Whole Blood or Other Bodily Fluid or Tissue Samples

Adenovirus detection in whole blood or in other bodily fluids or tissues will require a reference laboratory submission. Specimen containers should be sealed with paraffin plastic film and securely packed with absorbent material. Containers should be shipped at 4°C. The CDC has confirmed two reference laboratories available to perform adenovirus PCR in whole blood:

- **Quest Diagnostics:** 0.35 mL minimum volume, specimen stability (48 hours room temperature, 7 days refrigerated); Adenovirus DNA, Quantitative Real-Time PCR, Test Code 19726.
- **ARUP Laboratories:** 0.50 mL minimum volume, specimen stability (24 hours room temperature, 5 days refrigerated); Adenovirus, Quantitative PCR, Test Code 2007192.

Stool and Liver Samples

Mayo Clinic Laboratories can perform testing of stool and liver samples. Volume permitting, prepare one aliquot for diagnostic testing and one aliquot for adenovirus typing.

- **Mayo Clinic Laboratories:** Stool: 0.5 g minimum volume, specimen stability (7 days refrigerated, preferred); Liver/Tissue: N/A minimum volume, specimen stability (7 days refrigerated, preferred), Adenovirus, Molecular Detection, PCR, Test Code: LADV.

Any residual specimens that were positive for adenovirus and collected from pediatric cases with acute hepatitis should be stored frozen (use $\leq -70^{\circ}\text{C}$ if available) for adenovirus typing.

If you have any additional questions, please contact the HAN Coordinator at 802-859-5900 or vthan@vermont.gov.

HAN Message Type Definitions

Health Alert: Conveys the highest level of importance; warrants immediate action or attention.

Health Advisory: Provides important information for a specific incident or situation may not require immediate action.

Health Update: Provides updated information regarding an incident or situation; unlikely to require immediate action.

Info Service Message: Provides general correspondence from VDH, which is not necessarily considered to be of an emergent nature.