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HEALTH ALERT NETWORK | HEALTH ADVISORY | May 9, 2022

UPDATE: Guidance for Adenovirus Testing and Typing of Patients Under Investigation – Pediatric Acute Hepatitis of Unknown Etiology

NDDoH HAN Archive | Call for Case Reports –Pediatric Acute Hepatitis of Unknown Etiology

On Thursday, April 21, 2022, CDC issued the Health Alert Network (HAN) Health Advisory to notify clinicians and public health authorities of children identified with hepatitis and adenovirus infection. A cluster of pediatric cases with significant liver injury with positive adenovirus infection have been identified and reported to CDC since November 2021. A possible association between pediatric hepatitis and adenovirus infection is currently under investigation after subsequent laboratory testing identified adenovirus type 41 infection in several cases. Clinicians should consider adenovirus testing in addition to the usual hepatitis diagnostic work-up.

Clinicians should report patients <10 years of age with elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (>500 U/L) who have an unknown etiology for their hepatitis (with or without any adenovirus testing results, independent of the results) since October 1, 2021. If you are currently caring for patients or have residual specimens, please Contact NDDoH for guidance on submitting these specimens.

Any patient meeting these criteria should be reported to the North Dakota Department of Health by calling 701-328-2378 or 1-800-472-2180. Reports made to the North Dakota Department of Health will be forwarded to the CDC. Assistance with laboratory testing can be obtained by calling the Laboratory Services Section at 701-328-6272.

A standard diagnostic workup for children with acute hepatitis should be done locally by treating clinicians.

CDC recommends including adenovirus testing in children with acute hepatitis

Because the potential relationship between adenovirus and acute hepatitis is still under a national epidemiologic investigation, and not limited to individual patient care, please consider collection and submission of the following specimen types (if available) for adenovirus detection.

- Blood specimen collected in purple top EDTA tube (whole blood, plasma) or serum; whole blood is preferred to plasma

- Respiratory specimen (nasopharyngeal swab in VTM/UTM, sputum, or bronchioalveolar lavage [BAL])
- Stool specimen (or rectal swab in VTM/UTM); whenever possible, a stool specimen is preferred to a rectal swab
- If a liver biopsy has already been performed as clinically indicated, or from native liver explant or autopsy:
    - Formalin-fixed, paraffin embedded (FFPE) liver tissue
    - Fresh liver tissue, frozen on dry ice or liquid nitrogen immediately or as soon as possible, and stored at ≤ -70°C

Nucleic acid amplification testing (NAAT, e.g. PCR) is preferred for adenovirus detection (currently not available for FFPE liver biopsy or native liver explant). Testing whole blood by PCR may be more sensitive than testing plasma by PCR and is preferred.

Instructions for **Diagnostic** adenovirus testing of clinical specimens

Any clinical specimens that can be tested locally, should be, to ensure the timeliest results for patient care.

- Volume permitting, prepare one aliquot for diagnostic testing and one aliquot for adenovirus typing.
    - Aliquot for the diagnostic test according to the instructions in the applicable test order
    - Aliquot for adenovirus typing (minimum volume = 0.5 mL) and store frozen (use ≤ -20°C if available).
- Any residual clinical specimens or aliquots that were positive for adenovirus and collected from pediatric cases with acute hepatitis should be kept frozen (use ≤ -20°C if available) until adenovirus typing can be completed.

For any diagnostic testing needs beyond the local capacity see below for the following recommendations by testing type

Reference laboratory submission:

NDDoH, Laboratory Services Section is able to perform the following tests:

- Respiratory Panel PCR
    - Specimen Type: Nasopharyngeal swab in viral transport media or saline
    - Stability: Ambient: 4 hours; Refrigerated: 3 days; Frozen 30 days

- Gastrointestinal Panel which includes results for Adenovirus F40/41
    - Specimen Type: 1mL stool in Cary-Blair medium
    - Stability: Ambient: 4 days; refrigerated: 4 days; Frozen: Unacceptable

Adenovirus PCR testing capacity for whole blood is less common than testing of respiratory or stool specimens and may require submission to a reference laboratory.

- Reference Laboratories confirmed to do whole blood (in EDTA) adenovirus PCR include ARUP Laboratories and Quest Diagnostics (San Juan Capistrano Location) and the Minnesota Department of Public Health
    - Specimen containers should be sealed with Parafilm® and must be securely packed with absorbent material to prevent breakage and spillage.
    - Transport and ship at 4C° (refrigerated with cold packs).
    - DO NOT freeze the whole blood for diagnostic PCR testing.

- **Quest Diagnostics:** 0.35 mL minimum volume, specimen stability (48 hours room temperature; 7 days refrigerated); Adenovirus DNA, Quantitative Real-Time PCR | Test Detail | Quest Diagnostics
- **ARUP Laboratories:** 0.50 mL minimum volume, specimen stability (24 hours room temperature; 5 days refrigerated); (Adenovirus, Quantitative PCR | ARUP Laboratories Test Directory), TAT 1-4 days.
- **Minnesota Department of Health:** EDTA whole blood or plasma; whole blood specimens are preferred over plasma. Refrigerate (2-8°C) EDTA and ship on ice packs and do not freeze. To utilize MDH, all specimens must be sent through NDDoH. For further guidance, contact NDDoH prior to submitting a specimen.

Instructions for **Adenovirus typing** submissions for **positive** clinical specimens

Any clinical specimens that test positive for adenovirus via PCR may be submitted to NDDoH, Laboratory Services for further typing and/or whole genome sequencing. Specimens must also include two primary patient identifiers on the specimen container, in compliance with CLIA regulations, in case additional diagnostic tests are needed. Acceptable primary patient identifiers include:

- Full patient name (First and last name)
- Date of birth
- A unique ID from the time of specimen collection (secondary unique identifiers do not qualify, such as a state public health lab ID)

Any residual clinical specimens or aliquots that were positive for adenovirus and collected from pediatric cases with acute hepatitis should be stored frozen (use ≤ -70° if available) for adenovirus typing. The minimum volume requirement for adenovirus typing is 0.5 mL

Submit specimens on dry ice to NDDoH, Laboratory Services, including any local test results and a notification that these specimens are associated with the "Adenovirus/Hepatitis Investigation in Children."

Instructions for submission of virus isolates

If any virus isolates are obtained through the culturing of clinical specimens related to the pediatric hepatitis cases, please notify NDDoH, Laboratory Services for further instruction.

Instructions for submission **fixed** tissues for pathology testing

Fixed liver tissue samples (liver biopsy, explants, or autopsy) will receive routine histopathological examination and may be tested by immunohistochemistry for adenovirus and other pathogens at the clinical institution. When these samples are collected as clinically indicated, FFPE liver tissue can be submitted to CDC for additional pathologic characterization and infectious disease testing.

Notify NDDoH, Laboratory Services regarding potential submissions; all submissions will require pre-approval. Do not send specimens to CDC until pre-approval and submission instructions are provided by the state public health department or CDC.

Fixed liver tissue from patients who meet the following criteria can be submitted to CDC:

- Pediatric patients with hepatitis of unknown etiology meeting the current case definition

  AND, for which

- Formalin-fixed, paraffin embedded liver tissue specimens are available that a) demonstrate histopathologic evidence of hepatitis AND b) have been submerged in formalin for ≤ 2 weeks prior to embedding in paraffin.

Categories of Health Alert Network messages:

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HAN Info Service Does not require immediate action; provides general public health information

##This message was distributed to state and local health officers, state and local epidemiologists, state and local laboratory directors, public information officers, HAN coordinators, and clinician organizations##

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