



May 13, 2022

Re: Updated Recommendations for Adenovirus Testing and Reporting of Children with Acute Hepatitis

Summary:

The Centers for Disease Control and Prevention (CDC) on April 21, 2022, issued a Health Alert Network (HAN) Health Update to provide clinicians and public health authorities with updated information about an epidemiologic investigation of pediatric cases of hepatitis of unknown etiology in the United States. This investigation focuses on collecting information to describe the epidemiology, etiology, clinical presentation, severity, and risk factors related to illness and to identify any relationship between adenovirus infection or other factors and hepatitis.

As of May 5, 2022, CDC and state partners are investigating 109 children with hepatitis of unknown origin across 25 states and territories, more than half of whom have tested positive for adenovirus with more than 90% hospitalized, 14% with liver transplants, and five deaths under investigation. Because this investigation is ongoing and includes reviewing cases of hepatitis of unknown cause with onset since October 2021, patients under investigation are not limited to current or newly diagnosed pediatric hepatitis illnesses.

Recommendations for Clinicians:

- 1. Clinicians should continue to follow standard practice for evaluating and managing patients with hepatitis of unknown etiology.**
2. Clinicians should consider adenovirus testing in pediatric patients with hepatitis of unknown etiology.
3. Notify Pima County Health Department at 520-724-7749 of children <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 patients are still under medical care or have residual specimens available, please contact Pima County Health Department at 520-724-7797 for assistance.

Because the potential relationship between adenovirus infection and hepatitis is still under investigation, clinicians should consider collecting the following specimen types from pediatric patients with hepatitis of unknown cause for adenovirus detection:

- Blood specimen collected in Ethylenediaminetetraacetic Acid (EDTA) (whole blood, plasma, or serum); whole blood is preferred to plasma and serum)
- Respiratory specimen (nasopharyngeal swab, sputum, or bronchioalveolar lavage [BAL])
- Stool specimen or rectal swab; a stool specimen is preferred to a rectal swab

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- Liver tissue, if a biopsy was clinically indicated, or if tissue from native liver explant or autopsy is available:
 - 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 $\leq -70^{\circ}\text{C}$

Nucleic acid amplification testing (NAAT), such as polymerase chain reaction (PCR), is preferred for adenovirus detection (currently not available for FFPE liver biopsy or native liver explant). Testing whole blood by PCR is more sensitive to and is preferred over testing plasma by PCR.

Background:

Hepatitis is inflammation of the liver that can be caused by viral infections, alcohol use, toxins, medications, and certain other medical conditions. In the United States, the most common causes of viral hepatitis are hepatitis A, hepatitis B, and hepatitis C viruses [2]. Signs and symptoms of hepatitis include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, light-colored stools, joint pain, and jaundice [2]. Treatment of hepatitis depends on the underlying etiology.

Adenoviruses are double-stranded DNA viruses that spread by close personal contact, respiratory droplets, and fomites [3]. There are more than 50 types of immunologically distinct adenoviruses that can cause infections in humans. Adenovirus symptoms differ depending on the adenovirus type, most commonly causing respiratory illness, but also gastroenteritis, conjunctivitis, cystitis, and, less commonly, neurological disease [3]. There is no specific treatment for adenovirus infections; treatment is mainly supportive.

Adenovirus type 41 commonly causes pediatric acute gastroenteritis, which typically presents as diarrhea, vomiting, and fever; it can often be accompanied by respiratory symptoms [4]. While there have been case reports of hepatitis in immunocompromised children with adenovirus type 41 infection, adenovirus type 41 is not known to be a cause of hepatitis in otherwise healthy children [5, 6].

References:

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[2] Hepatitis Webpage. Centers for Disease Control and Prevention. Available from: <https://www.cdc.gov/hepatitis/abc/index.htm>

[3] Adenoviruses Webpage. Centers for Disease Control and Prevention. Available from: <http://www.cdc.gov/adenovirus/index.html>

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Thank you,
Pima County Health Department

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