

May 2, 2022

## Recommendations for Adenovirus Testing and Reporting of Children with Acute Hepatitis of Unknown Etiology

### Summary

The Delaware Public Health District (DPHD) is issuing this Health Advisory to notify clinicians of a cluster of children identified with hepatitis and adenovirus infection. In November 2021, clinicians at a large children's hospital in Alabama notified CDC of five pediatric patients with significant liver injury, including three with acute liver failure, who also tested positive for adenovirus. All children were previously healthy. None had COVID-19. Case-finding efforts at this hospital identified four additional pediatric patients with hepatitis and adenovirus infection for a total of nine patients admitted from October 2021 through February 2022. In two patients, plasma samples were negative for adenovirus by quantitative polymerase chain reaction (qPCR), but both patients were positive when retested using whole blood. Two patients required liver transplants; no patients died. A possible association between pediatric hepatitis and adenovirus infection is currently under investigation. Cases of pediatric hepatitis in children who tested negative for hepatitis viruses A, B, C, D, and E were reported earlier this month in the United Kingdom, including some with adenovirus infection [1].

This Health Advisory serves to notify US clinicians who may encounter pediatric patients with hepatitis of unknown etiology to consider adenovirus testing and to elicit reporting of such cases to public health authorities. Nucleic acid amplification testing (NAAT, e.g. PCR) is preferred for adenovirus detection and may be performed on respiratory specimens, stool or rectal swabs, or blood.

### 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. Adenoviruses most commonly cause respiratory illness but depending on the adenovirus type they can cause other illnesses such as gastroenteritis, conjunctivitis, cystitis, and, less commonly, neurological disease [3]. There is no specific treatment for adenovirus infections.

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].

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## Recommendations

1. Clinicians should consider adenovirus testing in pediatric patients with hepatitis of unknown etiology. NAAT (e.g. PCR) is preferable and may be done on respiratory specimens, stool or rectal swabs, or blood.
2. 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.

## Reporting

Hepatitis is a class B reportable disease. Healthcare providers should report cases or suspected cases to DPHD by the end of the next business day by calling (740) 368-1700, or faxing the information to 740-203-2040.

DPHD is requesting notification from clinicians 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 save and freeze them for possible additional testing and contact DPHD for additional instructions.

Please contact DPHD at 740-368-1700 and ask for a member of the Disease Control and Response Unit to notify of any cases meeting the above criteria or with any related questions.

## For More Information

<https://www.cdc.gov/hepatitis/index.htm>

<https://www.cdc.gov/adenovirus/index.html>

## References

[1] World Health Organization. Acute hepatitis of unknown aetiology - the United Kingdom of Great Britain and Northern Ireland. Disease Outbreak News [Internet]. 2022 Apr 15; Available from: <https://www.who.int/emergencies/disease-outbreak-news/item/acute-hepatitis-of-unknown-aetiology---theunited-kingdom-of-great-britain-and-northern-ireland>

[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>

[4] Kang G. Viral Diarrhea. International Encyclopedia of Public Health [Internet]. Elsevier; 2017. P. 260-7. Available from <https://www.sciencedirect.com/referencework/9780128037089/international-encyclopediaof-public-health>

[5] Munoz FM, Piedra PA, Demmler GJ. Disseminated Adenovirus Disease in Immunocompromised and Immunocompetent Children. CLIN INFECT DIS. 1998. Nov;27(5):1194-200. <https://doi.org/10.1086/514978>

[6] Peled N, Nakar C, Huberman H, Scherf E, Samra Z, Finkelstein Y, et al. Adenovirus Infection in Hospitalized Immunocompetent Children. Clin Pediatr (Phila). 2004 Apr;43(3):223-9. <https://doi.org/10.1177/000992280404300303>