



## Red Book Online Outbreaks: Hepatitis Cases Possibly Associated with Adenoviral Infection

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As of November 9, 2022, 44 states and jurisdictions have reported 380 pediatric patients under investigation over the past 13 months, which is an increase of 270 from the 109 publicly reported on May 5. The recent increase in cases under investigation were identified retrospectively since October 1, 2021 and may not ultimately be linked to this investigation. There have been no additional deaths reported since February, and the proportion of patients requiring liver transplants has gone down from 15 percent to 9 percent since May 5. Additional testing details were updated by the CDC on May 11.

CDC continues to investigate the cause and any contributing factors (eg immune response to adenovirus, coinfections, environmental exposures, medications) related to these acute cases of hepatitis in young children.

Of the previously reported 109 cases in the US:

- The majority of cases were in young children, with a median age of 2 years
- More than half had a confirmed adenovirus infection, most commonly F type 41
- Ninety percent were hospitalized
- Fourteen percent required liver transplants
- While the majority fully recovered, five have died
- Within the last 7 months, pediatric hepatitis cases of unknown cause have been reported in the following states: Alabama, Arizona, California, Colorado, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Louisiana, Michigan, Minnesota, Missouri, North Carolina, North Dakota, Nebraska, New York, Ohio, Pennsylvania, Puerto Rico, Tennessee, Texas, Washington, and Wisconsin

In addition, as of April 23, 2022, [169 cases](#) of acute hepatitis of unknown cause have been reported by the World Health Organization (WHO) from 11 countries in Europe and in the Americas. The cases included children aged 1 month to 16 years, seventeen children (10%) had liver transplants, and one child died. Adenovirus was detected in at least 74 cases, and 18 cases were identified as F type 41. Hepatitis viruses A, B, C, D, and E were not detected; SARS-CoV-2 was identified in 20 cases of those that were tested, and 19 cases were detected with a SARS-CoV-2 and adenovirus co-infection. CDC continues to work with other public health officials around the world to learn more about these cases of acute hepatitis in children to determine the cause, manage the disease, and improve prevention.

The following summary recommends adenovirus testing in children with acute hepatitis of unknown etiology and reporting all cases to state public health authorities and the Centers for Disease Control and Prevention (CDC).

# Clinical Guidance

## Presentation

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 viruses A, B, and C. Signs and symptoms of hepatitis include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, light-colored stools, joint pain, and jaundice. Treatment of hepatitis depends on the underlying etiology.

## Diagnosis

Pediatricians and other pediatric clinicians who encounter patients with hepatitis of unknown etiology should consider adenovirus testing and reporting of such cases to state public health authorities and to the CDC. Nucleic acid amplification testing (NAAT/PCR test) is preferred for adenovirus detection and may be performed on respiratory specimens, stool or rectal swabs, or whole blood.

## Complications

Adenovirus type 41 commonly causes pediatric acute gastroenteritis, which typically presents as diarrhea, vomiting, and fever; it can often be accompanied by respiratory symptoms. Adenovirus type 41 infection is not known to be a cause of hepatitis in otherwise healthy children, but has been reported in immunocompromised children.

## Precautions

In addition to standard precautions for young children with respiratory tract infections, contact and droplet precautions are indicated for the duration of hospitalization. In immunocompromised patients, contact and droplet precautions should be extended because of possible prolonged shedding of the virus. For patients with conjunctivitis and for diapered and incontinent children with identified adenoviral gastroenteritis, contact precautions are indicated for the duration of illness. See the *Red Book Adenovirus Infections* chapter

## Prevention/Risk Mitigation

Appropriate hand hygiene, respiratory hygiene, and cough etiquette should be followed. Assiduous adherence to hand hygiene and use of disposable gloves when caring for infected patients are recommended.

## Treatment

There is no specific treatment for adenovirus infections. See the *Red Book Adenovirus Infections* chapter to learn more about supportive care.

# Reporting

## Investigation of hepatitis cases of unknown etiology

CDC is requesting notification from clinicians or state public health authorities of any children <10 years of age with elevated (>500 U/L) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels who have an unknown etiology for their clinical hepatitis presentation (irrespective of whether any adenovirus testing was performed) since October 1, 2021.

The CDC recommends the following laboratory assessment:

Clinicians should consider adenovirus testing in pediatric patients with hepatitis of unknown etiology.

- 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
- 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 and preferred over testing plasma by PCR.
- A positive whole blood PCR test would provide the strongest correlation that the adenovirus may be the cause of the patient's hepatitis.

Where possible, clinical specimens should be tested locally to ensure timely results for patient care. For any diagnostic testing needs beyond the local capacity, CDC recommends that clinicians contact their state public health laboratory.

Please email CDC at [ncirddvdgast@cdc.gov](mailto:ncirddvdgast@cdc.gov) to notify of any cases meeting the above criteria or with any related questions.

If patients are still under medical care or have residual specimens available, please save and freeze them for possible additional testing and contact CDC at [ncirddvdgast@cdc.gov](mailto:ncirddvdgast@cdc.gov) for additional instructions.

## Resources

CDC Health Advisory on Recommendations for Adenovirus Testing and Reporting of Children with Acute Hepatitis of Unknown Etiology. [HAN Archive - 00462 | Health Alert Network \(HAN\) \(cdc.gov\)](#)

Centers for Disease Control and Prevention. [Acute Hepatitis and Adenovirus Infection Among Children — Alabama, October 2021–February 2022](#). *MMWR Morb Mortal Wkly Rep.* 2022;71(18):638–640

World Health Organization (23 April 2022). Disease Outbreak News: Multi-Country – Acute, severe hepatitis of unknown origin in children. Available at: <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376>. Accessed on April 23, 2022

CDC investigating 109 pediatric hepatitis cases; link to adenovirus unclear. *AAP News*. <https://publications.aap.org/aapnews/news/20212/CDC-investigating-109-pediatric-hepatitis-cases>. Accessed on May 6, 2022

CDC Health Advisory Updated Recommendations for Adenovirus Testing and Reporting of Children with Acute Hepatitis of Unknown Etiology. [HAN Archive - 00465 | Health Alert Network \(HAN\) \(cdc.gov\)](#). Accessed on May 11, 2022

### Pediatric Practice Tools and Information

AAP Red Book: [Adenovirus Infections](#)

### Public Health Resources

CDC information: [Adenoviruses](#)

### **Infection Prevention and Control Resources**

CDC: [Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings](#)

CDC course: [Transmission-based Precautions](#)

### **Information for Patients and Caregivers**

AAP HealthyChildren.org:

- [Adenovirus Infections in Infants and Children](#)
- [Is there a hepatitis outbreak in children?](#)