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

Clinician Outreach and Communication Activity (COCA) Call

Thursday, May 19, 2022

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- CDC did not accept financial or in-kind support from ineligible companies for this continuing education activity.

Objectives

At the conclusion of today's session, the participant will be able to accomplish the following:

1. Describe the current investigation of cases in Alabama and other U.S. states.

2. Discuss the unknown etiology of cases as it relates to hepatitis and adenovirus type 41.

3. Explain how clinicians can best support the investigation through testing and reporting cases in their states.

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov

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Pediatric Hepatitis in Alabama

L. Amanda Ingram, MPH

Epidemiologist Supervisor

Alabama Department of Public Health

Infectious Diseases & Outbreaks

ALABAMA PUBLIC HEALTH

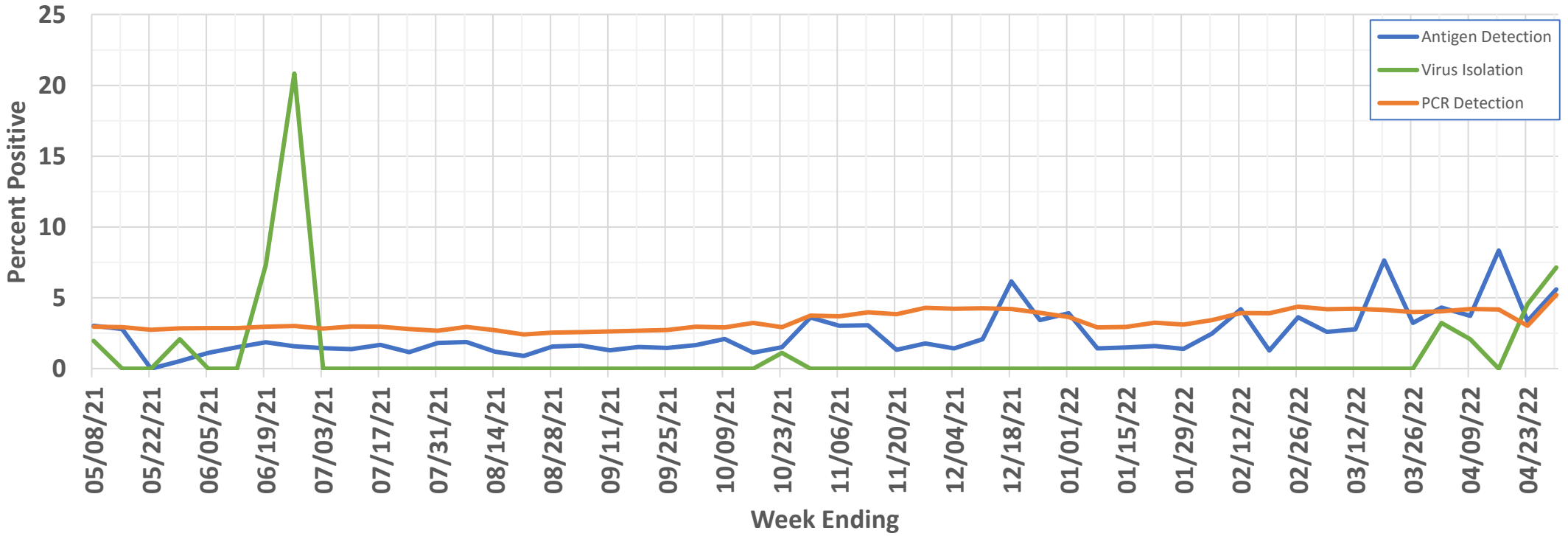
And so, it began…

- October 12 – November 1, 2021
  - 4 children under the age of 6 years presented to the Emergency Department at a large pediatric hospital in Alabama
  - Symptoms of varying degrees of acute liver injury/failure
  - All positive for Adenovirus, with 3 (75%) Type 41
- No significant underlying health conditions reported
- Only one reported taking medications at home
- Each resided in geographically different areas of the state

By November 4…

- Public health authorities were alerted by the clinicians
- Initial conference call was held with local, state, and federal partners to discuss observations and next steps
- Requested specimens to be sent to Wadsworth Center (New York) for genomic typing and, if possible, sequencing

Respiratory adenoviruses do not demonstrate discernible seasonal patterns in the U.S.



Source: National Respiratory and Enteric Virus Surveillance System (NREVSS)

Rank	Adenovirus Type	Number (Percent)
1	Type 3	341 (22.8%)
2	Type 2	293 (19.6%)
3	Type 1	248 (16.6%)
4	Type 4	185 (12.4%)
5	Type 7	127 (8.5%)
6	Type 14	89 (5.9%)
14	Type 41	5 (0.3%)
--	All Others	209 (14.0%)

Respiratory

Gastrointestinal

Source: Binder AM, Biggs HM, Haynes AK, et al. Human Adenovirus Surveillance — United States, 2003–2016. MMWR Morb Mortal Wkly Rep 2017;66:1039–1042.

Adenovirus Type 41 is not even ranked in the top 10

National Adenovirus Type Reporting System 2003-2016

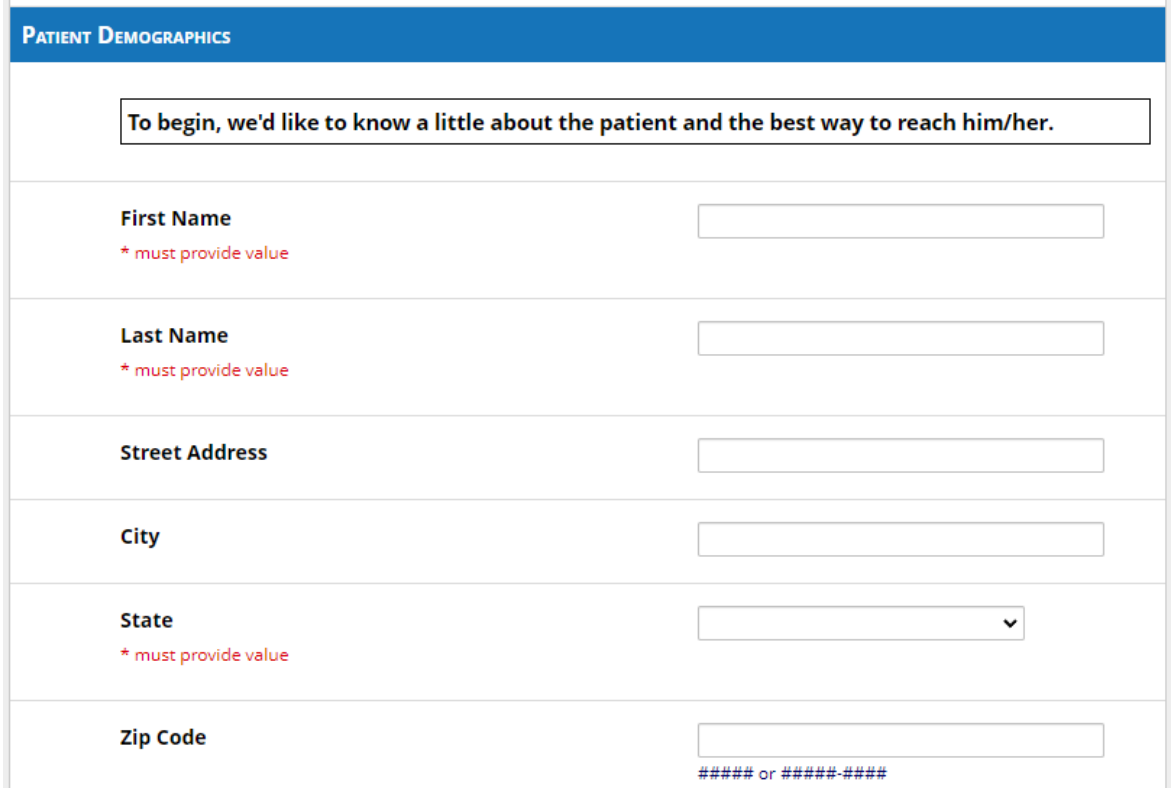
Two calls for additional cases issued

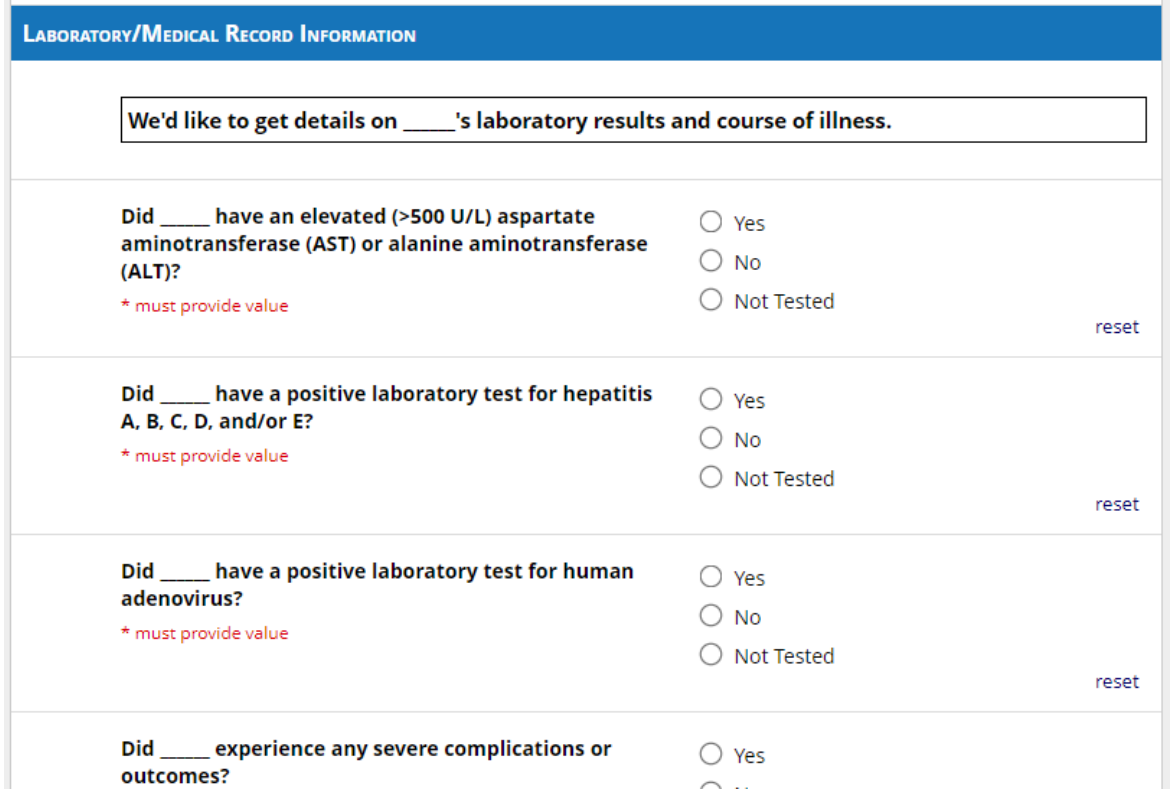
February 2022

April 2022

Comparison of the Call for Cases

February 2022	April 2022
• Adenoviral gastroenteritis among otherwise healthy individuals	• Individuals with elevated liver enzymes (ALT or AST >500 U/L)
• Unusual presentations (e.g., jaundice, acute liver injury/failure, hemophagocytic lymphohistiocytosis, etc.)	• Unknown etiology for their hepatitis
• Adult and pediatric	• Since October 1, 2021
	• Children less than 10 years old

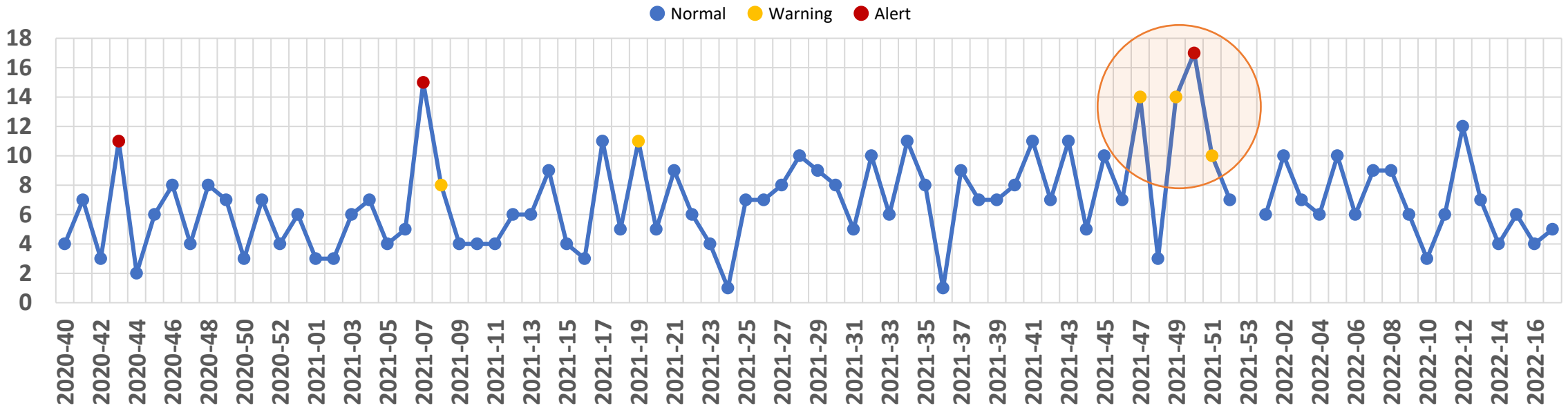




REDCap Survey

Of the 9 submissions, only 3 met the case definition

Weekly Emergency Department (ED) Visits in Alabama among Children (<10 years old) with Hepatitis, Jaundice, or Liver Failure (October 2020 – April 2022)



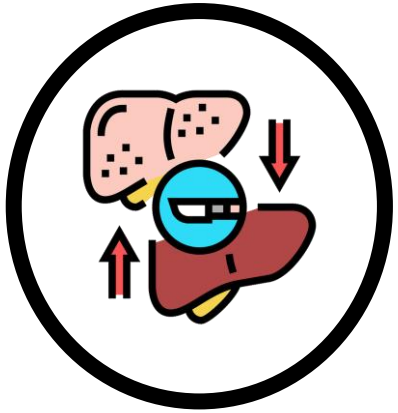
An increase in ED visits statewide was observed among children (<10 years old) presenting with hepatitis, jaundice, and liver failure between November 21 and December 25, 2021.

Alabama's Syndromic Surveillance (AlaSyS) Program

Pediatric Hepatitis Case Characteristics

12

Hospitalizations



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Deaths

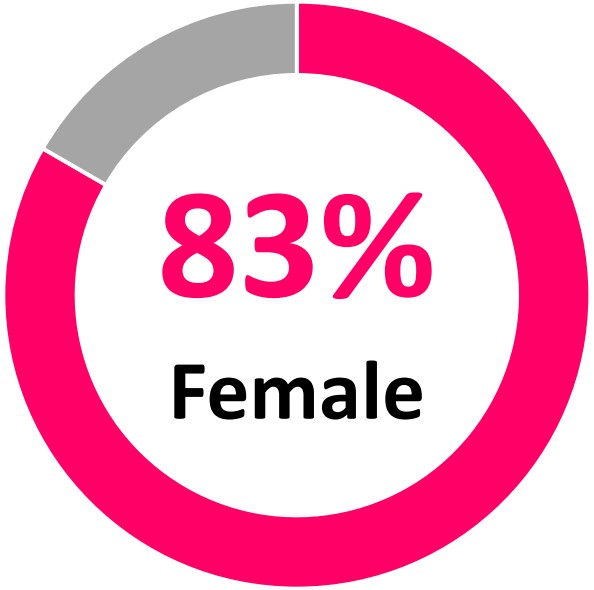
12

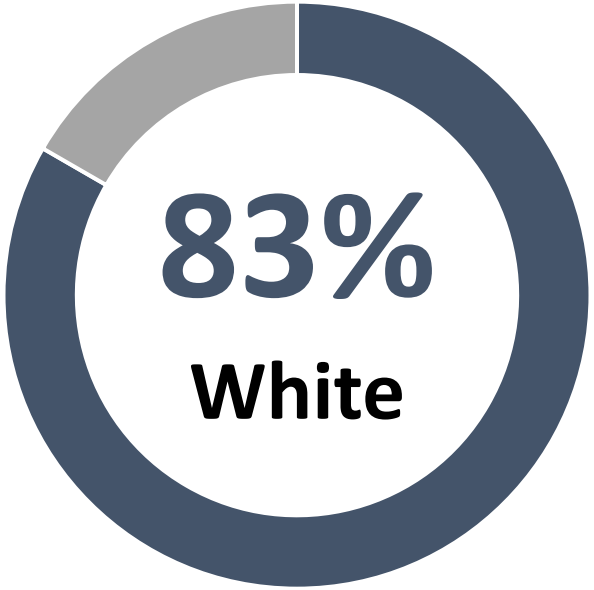
Cases

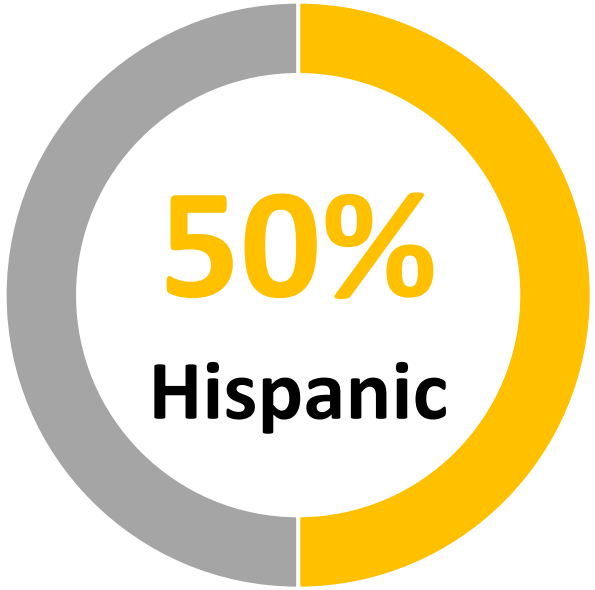
2

Transplants

Pediatric Hepatitis Case Demographics



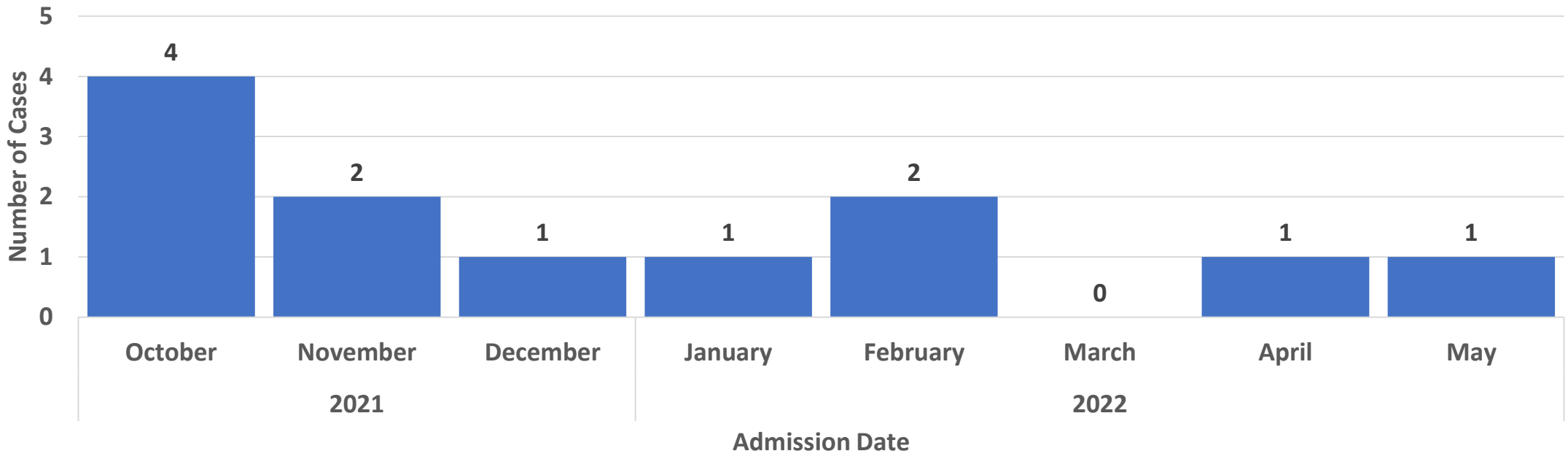




2 years (0-6)

Median Age (Range)

All but 2 (83%) cases reported were admitted within a 5-month span



Laboratory Findings

- Adenovirus detected in 12 (100%) cases
  - 10 (91%) detected in whole blood
  - 5 (45%) Type[a] 41
  - 2 (17%) Type[b] 40/41
- None (0%) met the criteria for whole genome sequencing
- Multiple viral pathogens were detected at time of illness for 9 (75%) cases
  - None (0%) were positive for SARS-CoV-2

[a]Genomic typing via Sangar method
[b]Gastrointestinal panel targets are unable to distinguish between Type 40 and 41


Of the 3 patients eligible for COVID-19 vaccination,
none received the vaccine prior to illness

Review AlaSyS Details

Chart Abstraction

Exposure Interview

Self-knowledge Check

Which virus was NOT detected in any of the cases in Alabama?

A. Adenovirus
B. Human coronavirus OC43
C. Rotavirus A
D. SARS-CoV-2
E. All of the Above

Self-knowledge Check

The correct answer is: D. SARS-CoV-2.

Adenovirus was detected in all cases reported in Alabama. There were six other viral pathogens detected including rhinovirus/enterovirus, respiratory syncytial virus, human coronavirus OC43, human metapneumovirus, and rotavirus A, but at a lesser frequency. SARS-CoV-2 was not detected in any of the cases.

Acute Hepatitis of Unknown etiology – Alabama Experience

Helena Gutierrez, MD

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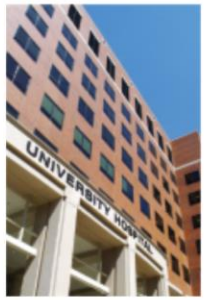
The University of Alabama at Birmingham

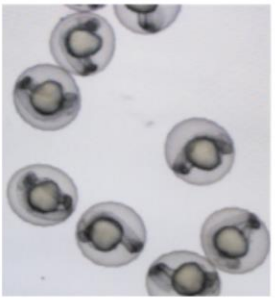
UAB MEDICINE

Children's of Alabama










Acute Hepatitis and Pediatric Acute Liver Failure

Acute Hepatitis

Hepatitis is defined as inflammation of the liver regardless of etiology.

- Elevations of liver enzymes reflect damage to the liver.
- Abnormal albumin or INR may be seen in the setting of impaired liver synthetic function.

Clinical presentation:

- Asymptomatic
- Mild-to-moderate symptoms of hepatic damage (jaundice, abdominal pain, malaise, etc.)
- Signs and symptoms of cirrhosis (ascites, coagulopathy, hepatic encephalopathy, gastrointestinal bleeding)
- liver failure (compromised synthetic function including hyperammonemia, coagulopathy, hepatic encephalopathy)

Acute Hepatitis

Differential Diagnosis of Hepatitis in Children*	
Hepatotrophic Viruses	**Other Viral Infections**
Hepatitis A	Adenovirus
Hepatitis B	Arbovirus
Hepatitis C	Coxsackievirus
Hepatitis D	Cytomegalovirus
Hepatitis E	Enterovirus
Nonviral infections	Epstein-Barr virus
Abscess	Herpes simplex virus
Amebiasis	HIV
Bacterial sepsis	Paramyxovirus
Brucellosis	Rubella
Fitz-Hugh-Curtis syndrome	Varicella zoster
Histoplasmosis	
Leptospirosis	
Tuberculosis	

Acute Hepatitis

Differential Diagnosis of Hepatitis in Children*	
Autoimmune	**Metabolic**
Chronic autoimmune hepatitis	Alpha 1 antitrypsin deficiency
Systemic lupus erythematosus	Glycogen storage disease
Juvenile rheumatoid arthritis	Tyrosenemia
Anatomic	Wilson disease
Choledocal Cyst	Other
Biliary atresia	**Toxic**
Other	Iatrogenic/drug induced
Hemodynamic	Environmental (pesticides)
Shock	**Others**
Congestive-heart failure	Nonalcoholic fatty liver disease
Budd-Chiari syndrome	Sclerosing Cholangitis
Other	Reye's syndrome

Pediatric Acute Liver Failure (PALF)

Acute onset of liver disease without evidence of chronic liver disease

- Biochemical evidence of severe liver injury
- Coagulopathy not corrected by vitamin K
  - Prothrombin time (PT) ≥ 15 s or INR ≥ 1.5 with evidence of hepatic encephalopathy or PT >20 s or INR >2 with or without encephalopathy

The overall incidence is unknown

- Population-wide rates are estimated at 500–600 cases per year*

Approx. 31% of cases are of indeterminate etiology**

In 2020, 502 pediatric liver transplants were performed in the United States***

- other/unknown diagnosis (21.6%)***

*Kulkarni S, et al. Use of pediatric health information system database to study the trends in the incidence, management, etiology, and outcomes due to pediatric acute liver failure in the United States from 2008 to 2013. Pediatr Transplant 2015;19:888–95

**Narkewicz MR, et al. A learning collaborative approach increases specificity of diagnosis of acute liver failure in pediatric patients. Clin Gastroenterol Hepatol 2018;16:1801.e3– 10.e3.

*** Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2020 Annual Data Report.

Children with hepatitis and adenovirus viremia – Alabama, October 2021 – February 2022

Clinical Demographics (N=9)

Age range: 1.1 – 6.5 years old

- 0-2 years: 5 (55%)
- 3-4 years: 1 (11.1%)
- 5-6 years: 3 (33.3%)

Gender

- Female: 7 (77.8%)

Race

- White: 9 (100%)

Ethnicity

- Hispanic: 6 (66.7%)
- Non- Hispanic: 3 (33.3%)
- All patients (n=9) reside in Alabama—

though no geographical linkage has been determined

Presenting Symptoms

Symptoms	N=9	%
Emesis	7	77.8
Diarrhea	6	66.7
Fever	5	55.6
Fatigue	4	44.4
Upper respiratory symptoms	3	33.3
Poor appetite	3	33.3
Dark urine	2	22.2

Initial Physical Exam

Initial PE findings	N=9	%
Scleral Icterus	8	88.9%
Jaundice	6	66.7%
Hepatomegaly	7	77.8%
Splenomegaly	1	11.1%
Hepatic encephalopathy	1	11.1%
Ascites	0	0%

Initial Labs on Presentation

Initial labs	Median	Range
ALT (U/L)	1724.4	602.9 – 4695.8
AST (U/L)	1963	447 – 4000
Total bilirubin (mg/dL)	7.0	0.23 – 13.5
Direct bilirubin (mg/dL)	5.5	0.14 – 10
INR	1.2	1 – 7.3
Ammonia (umol/L) [n=6]	73.4	49.9 – 85.0

In children, median ALT levels range from 14 to 21 U/L (boys) and 14 to 20 U/L (girls); and median AST 23.1 to 46.1 U/L (girls) and 25.7 to 47.6 U/L (boys)*

Clinical Work-up

Infectious work-up

- All (100%) tested positive for HAdV per whole blood qPCR
  - Median initial HAdV: 11,060 copies/mL (range 991 – 70,680 copies/mL)

- Six (66.7%) tested positive for EBV per whole blood qPCR
  - Median initial EBV: 1,680 copies/mL (range 80-1680 copies/mL)
  - 5 of 5 tested negative for EBV IgM, 4 of 5 EBNA positive

- All (100%) tested negative for SARS-CoV-2 by NAAT

- All (100%) tested negative for viral hepatitis A-C

- A variety of viruses were detected on respiratory PCR panel (n=8)
  - 4 of 8 tested positive for enterovirus/rhinovirus, 1 of 8 positive for metapneumovirus, 1 of 8 positive for RSV, 1 of 8 positive for coronavirus OC43
  - 1 of 8 tested positive for HAdV

- HAdV detected in stool of one patient (11.1%)
  - 3 had stool pathogen GI PCR panel

Clinical Work-up

Autoimmune

- Five (55.6%) with elevated IgG (range 1315 – 2198)
- Four (44.%) with positive auto-antibody (ANA or SMA, range 1:40-1:80)
- None met probable or definite criteria for Dx of AIH*

Metabolic

- Serum amino acids (n=5), 3/5 nonspecific abnormalities & 2/5 normal
- Urine organic acids (n= 5), 4/5 nonspecific abnormalities & 1/5 normal
- Acyl-carnitine profile (n=4), 1/4 nonspecific abnormalities & 3/4 normal
- A1AT phenotypes (n=5), PiMM 5/5.
- Ceruloplasmin (n=6), normal 6/6.

Other

- Acetaminophen level (n=7), normal 7/7

Clinical Work-up

Pathology – liver biopsy obtained in six patients (66.7%)

- All with variable degrees of acute hepatitis (lobular, interface, portal), cannalicular cholestasis, spotty hepatocyte necrosis and fibrosis
- None demonstrated confluent necrosis typically seen in HAdV hepatitis
- HAdV was not detected on IHC and viral inclusions were not identified on EM for all patients
- EBER staining was negative on all patients
- HAdV qualitative PCR done in fresh liver tissue, 2 of 3 positive (66.6%).

Clinical Course

Six patients did not progress to PALF

- Non-PALF children had statistically lower ALT and AST upon presentation
  - ALT (911.9 vs. 3854.3 U/L; P<0.01) and AST (1626 vs. 4000 U/L, p<0.01)
- Median viral load was lower in non-PALF vs PALF children (9,262.5 vs 55,340 copies/mL; p=0.051)
- At clinic follow-up (median 38 days), 3 of 5 children had HAdV viremia (median 2,062 copies/mL)
- All are doing well with their native livers

Three (33.3%) patients presented with or progressed into PALF

- Median peak INR 8.8
- Median peak ammonia 169.6 umol/L
- One recovered spontaneously and is doing well with a native liver

Clinical Course

Two initially presented with INR <2.0 but then progressed to PALF

- Median viral load at presentation was higher in these two children (transplanted) vs non-transplanted children (63,010 copies/ml vs 7,465 copies/ml, P= 0.0001)
- Cidofovir provided to both children
- Despite treatment, HAdV viral load remained persistently elevated (Median peak: 103,400 copies/mL)
- Both developed HE and ascites; one required Continuous Renal Replacement Therapy (CRRT)
- One required total plasma exchange secondary to bleeding and coagulopathy
- One met criteria for secondary hemophagocytic lymphohistiocytosis (HLH) and was started on etoposide/dexamethasone
- Both transferred to another quaternary hospital for possible extracorporeal liver support to serve as medical bridge to liver transplant (in the setting of HAdV viremia as a probable contraindication)
- Both underwent successful LT and doing well

Self-knowledge Check

A measurement for liver dysfunction includes:

A. Alanine transaminase (ALT) and Aspartate aminotransferase (AST)

B. International Normalized Ratio (INR)

C. Serum Albumin

D. B and C only

E. All of the Above

Self-knowledge Check

The correct answer is: D

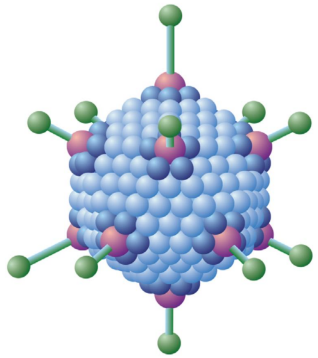
The coagulation proteins needed in the blood clotting cascade are primarily produced in the liver. Severe liver injury leads to a reduction of the liver synthetic function and therefore decreased synthesis of clotting factors.

Albumin is produced by the liver. Serum albumin is low in liver failure.









Texas Children's Hospital®

Baylor College of Medicine

Adenovirus & Acute Hepatitis of Unknown Etiology

Elizabeth A. Moulton, MD, PhD

Pediatric Infectious Diseases

May 19, 2022

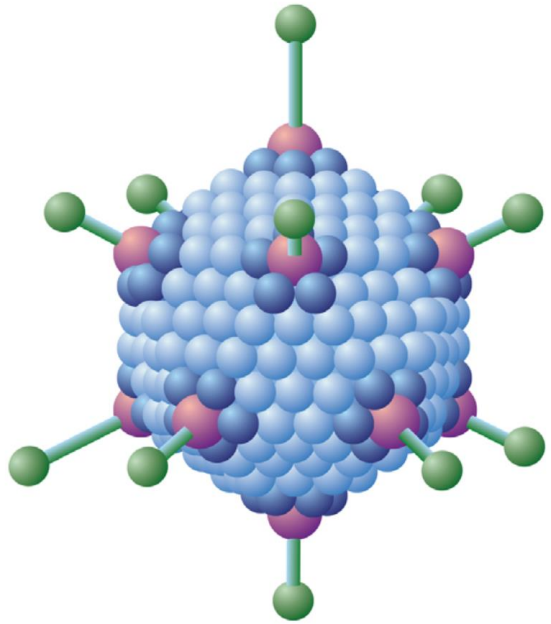
Pediatrics

Adenovirus Types

Species	Serotypes	Clinical syndromes
A	31	Infantile gastroenteritis*
B	3, 7, 21	Upper respiratory disease, pneumonia, pharyngoconjunctival fever
	11, 34, 35	Hemorrhagic cystitis, interstitial nephritis
	14	Pneumonia
C	1, 2, 5	Upper respiratory disease, pneumonia, hepatitis
D	8, 19, 37	Epidemic keratoconjunctivitis
E	4	Upper respiratory disease, pneumonia
F	40, 41	Infantile gastroenteritis

Remaining serotypes are infrequently isolated or not clearly associated with disease.

* Association with gastroenteritis not as firmly established as with types 40 and 41.



Pathogenesis, epidemiology, and clinical manifestations of adenovirus infection UpToDate

Rafie K, *et al*. The structure of enteric human adenovirus 41—A leading cause of diarrhea in children. Sci Adv 2021;7(2):eabe0974.

Fulminant Adenovirus Hepatitis

Table 1 Characteristics of 89 patients with HAdV hepatitis

Characteristic	Number of patients (%)
Age	
Pediatric (0–17)	57 (64)
Adult (18 and older)	32 (36)
Gender	
Male	32 (53)
Female	28 (47)
Underlying condition	98%
Liver transplant	43 (48)
Bone marrow transplant	19 (21)
Chemotherapy	11 (12)
SCID	5 (6)
HIV infection	4 (4)
Renal transplant	2 (2)
Heart transplant	2 (2)
Neonates (no known comorbidity)	2 (2)
CLL	1 (1)

	Number of patients (%)
Presenting symptoms ($N = 74$)	
Fever	68 (92)
Lethargy/malaise	15 (20)
Diarrhea	9 (12)
Jaundice	7 (10)
CT imaging findings ($N = 9$)	
Multiple hypodense lesions	7 (78)
Single hypodense lesion	1 (11)
Normal	1 (11)
Liver histopathology ($N = 64$)	
Necrosis	60 (94)
Intranuclear inclusions	46 (72)
Smudge cells	13 (21)
Method of adenovirus detection in the liver ($N = 89$)	
Culture	58 (65)
Immunohistochemistry	53 (60)
Electron microscopy	48 (54)
Polymerase chain reaction	5 (6)
In-situ hybridization	4 (5)
Outcome ($N = 89$)	
Survival	24 (27)
Death	65 (73)

Ronan BA, Agrwal N, Carey EJ, et al. Fulminant hepatitis due to human adenovirus. Infection 2014;42(1):105–11.

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Table 3 Management-based outcomes of patients with HAdV hepatitis. ($N = 47$)

Treatment	Number of cases	Survival
Reduced immunosuppression	25	14 (59 %)
Reduced immunosuppression + antiviral	1 cidofovir	1
	1 ribavirin	1
Liver re-transplantation	12	6 (50 %)
Cidofovir + IVIG	2	2
IVIG alone	4	0
Cidofovir alone	2	0

Ronan BA, Agrwal N, Carey EJ, et al. Fulminant hepatitis due to human adenovirus. Infection 2014;42(1):105–11.

Adenovirus Hepatitis Histopathology

TABLE 2. Histopathologic Characteristics of Adenovirus Hepatitis Cases

Case	Specimen Type	Necrosis Extent	Necrosis (%)	Neutrophils	Lymphocytes	Granulomas	Inclusions	IHC
1	B	Submassive	60	0	0	0	1	+
2	B	Massive	95	0	0	0	1	+
	B	None	0	0	1	1	0	–
3	B	Spotty	10	0	1	0	1	+
4	B	Submassive	40	0	0	0	1	+
5	B	Spotty	10	0	1	0	1	+
	A	Massive	70	0	1	0	1	+
6	B	Submassive	30	0	0	0	1	+
	A	Massive	70	0	1	0	1	+
7	A	Submassive	60	0	0	0	1	–
8	B	Spotty	10	0	0	0	1	+
	A	Massive	40	0	0	0	1	+
9	B	Submassive	50	0	0	0	1	+
	A	Massive	70	0	0	0	1	+
10	B	Spotty	10	0	1	0	1	+
11	B	Spotty	10	0	0	0	1	NP
12	B	Spotty	5	0	0	0	1	+

0 indicates absent; 1, present; A, autopsy; B, biopsy; NP, not performed.

Schaberg KB, Kambham N, Sibley RK, Higgins JPT. Adenovirus Hepatitis. Am J Surg Pathology 2017;41(6):810–9.

Histopathology of Adenovirus Inclusions

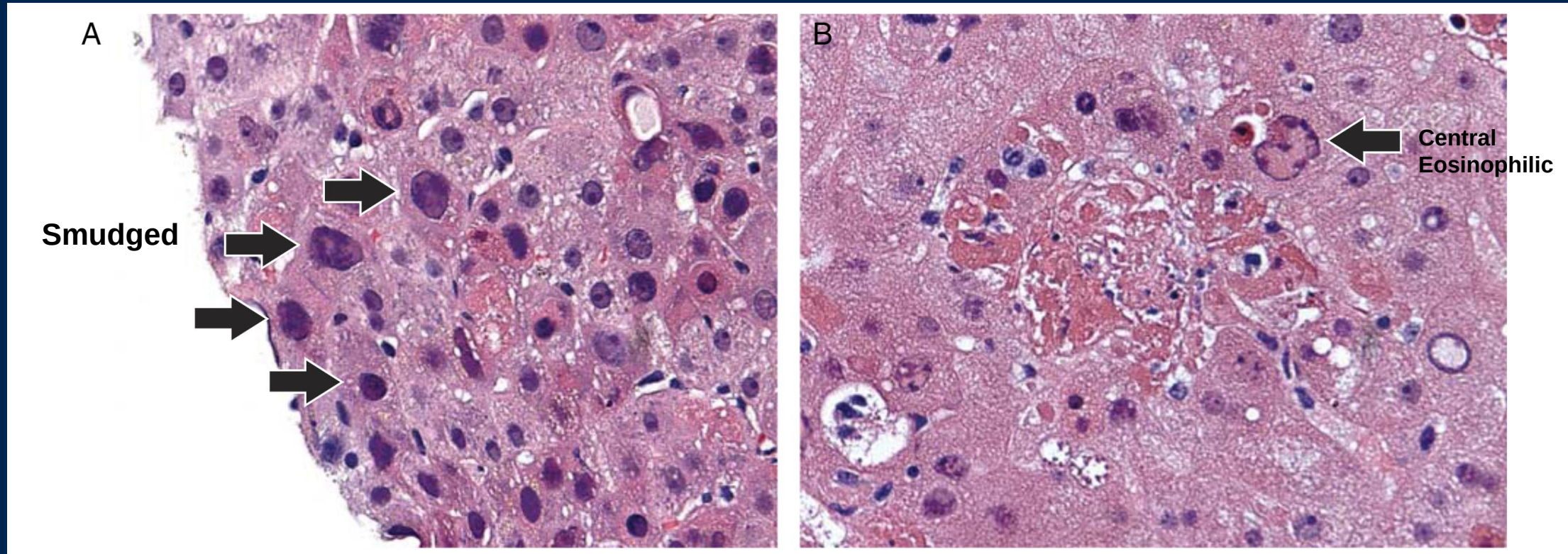


FIGURE 2. Hepatocyte intranuclear viral inclusions. The majority of viral inclusions are basophilic and have a smudged or glassy appearance (A; case 4). Select inclusions are demarcated by arrows. Large, well-developed inclusions may have a central eosinophilic appearance (B; case 6). Although the majority of inclusions are located at the periphery of areas of necrosis (B), inclusions may also be located scattered throughout the lobule (A).

Schaberg KB, Kambham N, Sibley RK, Higgins JPT. Adenovirus Hepatitis. Am J Surg Pathology 2017;41(6):810–9.

Histopathology of Adenovirus Hepatitis

Focal Necrosis

Massive Necrosis

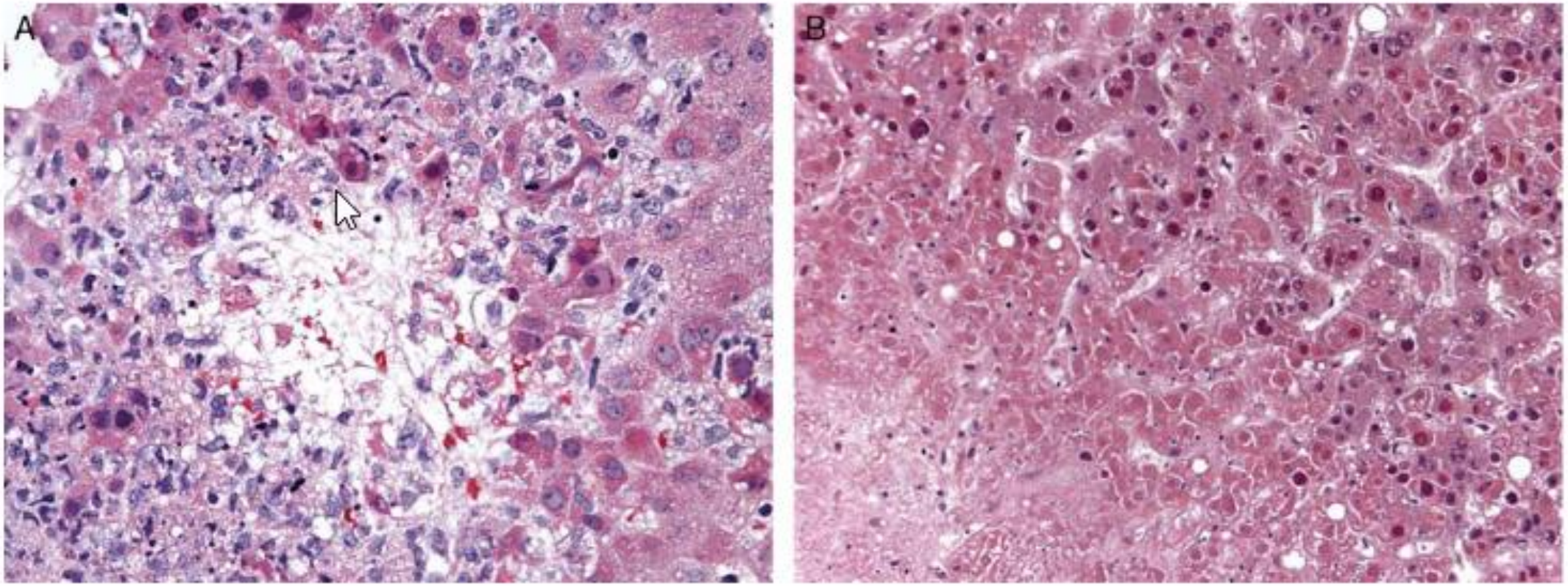


FIGURE 1. Coagulative necrosis. Although all cases showed coagulative necrosis, necrosis can vary from focal, and spotty (A; case 3) to massive (B; case 9). While the majority of cases showed no associated inflammation (B), several cases showed focal, lymphohistiocytic inflammation (A).

Schaberg KB, Kambham N, Sibley RK, Higgins JPT. Adenovirus Hepatitis. Am J Surg Pathology 2017;41(6):810–9.

Adenovirus species F (40/41) Viremia Occurs During Acute Gastroenteritis

- Evaluated children in Brazil hospitalized for acute gastroenteritis 2012-2015
- Of the 110 Adenovirus-positive feces samples, 80 paired sera were tested for this virus, of which 51 (64%) showed positive results
- 26 (70.3%) pairs (feces plus sera) presented concordant results after sequencing being classified as: **species F (21/26; 80.8%),** A (1/26; 3.8%), B (1/26; 3.8%), and C (3/26; 11.5%).

Portal TM, Reymão TKA, Neto GAQ, et al. Detection and genotyping of enteric viruses in hospitalized children with acute gastroenteritis in Belém, Brazil: Occurrence of adenovirus viremia by species F, types 40/41. J Med Virol 2019;91(3):378–84.

CDC Recommended Adenovirus Testing for Acute Hepatitis

- Nucleic acid amplification testing (NAAT, e.g., PCR) is preferred.
- **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, nasal wash, 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

https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/laboratories-testing-typing.html

Whole Blood Quantitative Adenovirus PCR

- ARUP Laboratories: Adenovirus, **Quantitative** PCR, Test Code 2007192, 0.5 mL minimum volume, specimen stability (5 days refrigerated), turn around time 1-4 days.
  - Quantitative range of this assay is 3.0- 7.0 log copies/mL (1,000-10,000,000 copies/mL).
  - Changes < 0.5 log can reflect variability in test as opposed to clinical change
- Quest Diagnostics: Adenovirus DNA, **Quantitative** Real-Time PCR, Test code 19726, 0.35 mL minimum volume, specimen stability (48 hours room temperature; 7 days refrigerated)
- **DO NOT freeze** the whole blood for diagnostic PCR testing

Respiratory Adenovirus PCR

- Eurofins-Viracor:
  - **Qualitative**, NP Swab Test Code 7525, Nasal Swab Test Code 7530
  - **Quantitative**, Nasal Aspirate Test Code 7531, NP wash Test Code 7547, NP aspirate Test Code 7524, Nasal wash Test Code 7513, Trach aspirate Test Code 7519, BAL Test Code 7509
- ARUP Laboratories:
  - Adenovirus by **Qualitative** PCR; BAL, NP swab, sputum; Test Code 2007473, store frozen, ship on dry ice, turn around time 1-4 days.
- Quest Diagnostics:
  - Adenovirus DNA, **Qualitative** Real-Time PCR; bronchial lavage/wash, sputum, nasopharyngeal lavage/wash, tracheal lavage/wash; Test Code 16046.

Stool Adenovirus PCR

- Eurofins-Viracor:
  - **Qualitative**, Fecal, Test Code 7508, Size of pea or 2 mL liquid stool, store frozen, ship on dry ice, results 8-12 hours after receipt of specimen.
  - Detects all known adenovirus serotypes

- Adenovirus 40/41 testing is on some gastrointestinal pathogen multiplex PCR panels

- Adenovirus 41 does not grow in routine viral culture

Tissue Adenovirus PCR

- Eurofins-Viracor:
  - **Qualitative (needle core biopsy)**, Test Code 7506
  - **Quantitative (explanted liver)**, Test Code 7505, 5 mg fresh tissue (approximately ½ of a pencil eraser size), store frozen, ship on dry ice, results 8-12 hours after receipt of specimen
- ARUP Laboratories:
  - Adenovirus by **Qualitative** PCR, Test Code 2007473, store frozen, ship on dry ice, turn around time 1-4 days.
- Quest Diagnostics:
  - Adenovirus DNA, **Qualitative** Real-Time PCR, Test Code 16046, 3 cubic mm tissue, store frozen, ship on dry ice.

Adenovirus Typing

- Volume permitting, prepare one aliquot for diagnostic testing and one for adenovirus typing.
  - Aliquot for the diagnostic test and store the specimens at an appropriate temperature according to the instructions
  - Aliquot for adenovirus typing (**minimum volume = 0.5 mL**) and store frozen (use ≤ -70° C if available)
- Any residual clinical specimens or aliquots that were positive for adenovirus from pediatric cases with acute hepatitis should be kept frozen (use ≤ -70° C if available) until adenovirus typing can be completed through State Public Health Laboratories.

https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/laboratories-testing-typing.html

Self-knowledge Check

3 year-old previously healthy boy developed vomiting and diarrhea 6 days ago. Vomiting improved but he has a poor appetite, and the diarrhea continues. Parents noticed last night that his eyes appeared slightly yellow, and this morning he is jaundiced prompting presentation. His ALT is 2000, AST 2500, and total bilirubin is 8. Testing for hepatitis A, B, and C is negative. What would be the **best** test of the following to evaluate for adenovirus in this patient?

A. Adenovirus QUANTitative PCR on plasma
B. Adenovirus QUANTtitative PCR on whole blood
C. Adenovirus QUALitiative PCR on whole blood
D. B and C only
E. All of the Above

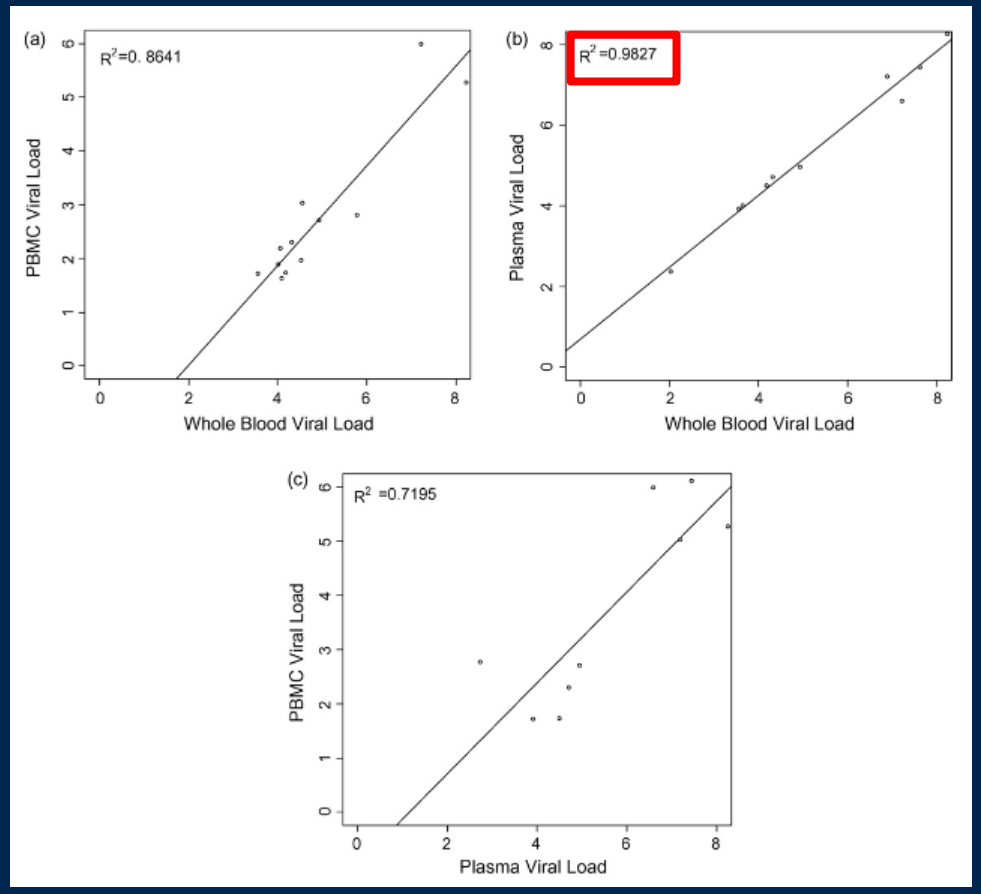
Self-knowledge Check

The correct answer is: **B**

The reason for this is because adenovirus whole blood PCR has anecdotally been more sensitive than adenovirus plasma PCR in patients with acute hepatitis associated with adenovirus viremia.

Quantitative PCR measures the level of adenovirus in the whole blood. In general for adenovirus, higher levels of viremia correlate with more severe disease. The trajectory of the adenovirus viremia can be monitored over time using the same laboratory and specimen type (whole blood), which is especially useful in patients with severe hepatitis or acute liver failure.

Rarely Whole Blood is Positive when Plasma is Negative for Adenovirus



- 61 samples with both Whole Blood and Plasma viral loads
- 10 samples both positive
- R^2 = 0.98

- **1 positive in whole blood only**
  - **33,693 copies/ml**

- 2 positive in plasma only
  - 543 & 750 copies/ml

Perlman J *et al.* Journal of Clinical Virology 40 (2007) 295–300

Infection Control and Prevention

- **Wash hands with soap and water**
- Adenovirus are non-enveloped, so are difficult to inactivate with alcohol-based hand sanitizer
- May remain viable on skin, fomites, and environmental surfaces for extended periods
- Consider contact and droplet precautions for children with acute hepatitis for the duration of the illness unless an alternative etiology is identified.

RedBook Adenovirus

Financial Disclosure

- Co-investigator for Pfizer SARS-CoV-2 pediatric vaccine trials

Overview of Nationwide Investigation of Pediatric Hepatitis of Unknown Etiology

Jacqueline Tate, PhD

Division of Viral Diseases

19 May 2022

Health Alert Network (HAN): Health Advisory April 21, 2022

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

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
Thursday, April 21, 2022, 11:00 AM ET
CDCHAN-00462

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to notify clinicians and public health authorities 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; all five that were sequenced had adenovirus type 41 infection identified. 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 transplant; 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 state public health authorities and to CDC. 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.

Available: https://emergency.cdc.gov/han/2022/han00462.asp#:~:text=Signs%20and%20symptoms%20of%20hepatitis,depends%20on%20the%20underlying%20etiology

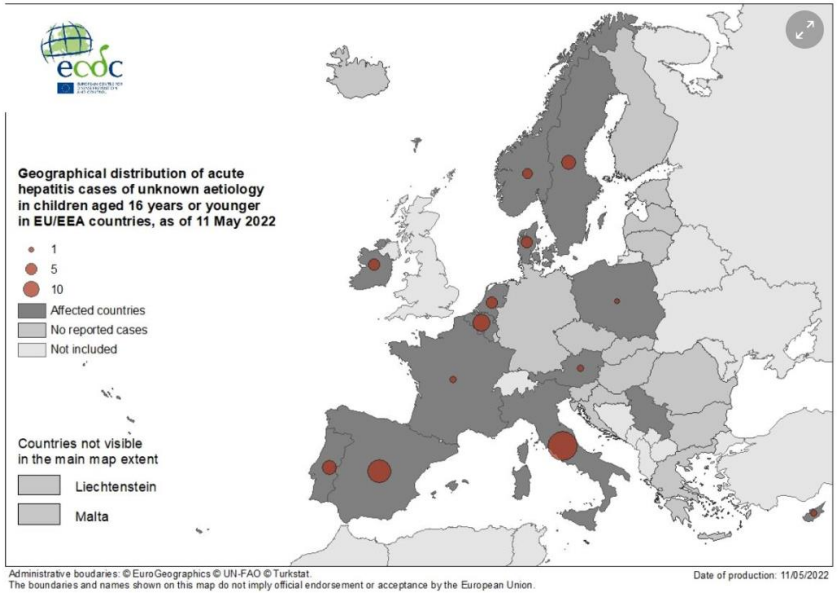
UK Health Security Agency Brief: 6 May 2022

- January 1–May 3, 163 cases of non-A-E hepatitis identified in children <16 years of age with transaminases >500 iu/l
  - Most cases <5 years of age
  - Gastroenteritis-type prodrome followed by onset of jaundice
  - Adenovirus detected in 91 (72%) of 126 cases tested; Of 18 cases successfully subtyped, all were serotype 41f
    - Community transmission rates of adenovirus increasing in the UK since end of 2021
    - Most common additional pathogen detected: SARS-CoV-2 24 (18%) of 132 tested
    - Additional testing for HHV, EBV, CMV, RSV, HSV, and others identified a smaller number of cases
- Leading hypothesis: A cofactor affecting young children is rendering normal adenovirus infections more severe or causing them to trigger immunopathology
  - Continue to investigate the role of SARS-CoV-2 and to work on ruling out any toxicology component

Reference: Acute hepatitis of unknown aetiology technical briefing 2 (publishing.service.gov.uk)

Global Reporting: Severe Hepatitis of Unknown Origin in Children – 1 October – 13 May 2022

- 232 cases reported from 14 countries in WHO EURO region
  - 1 month to 16 years old; 76% <5 years of age
  - 13 (6%) required transplantation
  - 1 death reported
  - 151 tested for adenovirus, 90 (60%) were positive
    - Highest positivity in whole blood specimens (69%)
  - 20 (12%) of 173 positive for SARS-CoV-2 by PCR
    - 14 (74%) of 19 tested had positive serology results
  - Majority of cases reported from UK (131; 56%)
- 72 cases have been reported by 12 additional countries globally



References:Joint ECDC-WHO Regional Office for Europe Hepatitis of Unknown Origin in Children Surveillance Bulletin (europa.eu) and Epidemiological update: Hepatitis of unknown aetiology in children (europa.eu)

Patients under investigation in the United States

- Received preliminary reports of 180 patients under investigation through 18 May 2022
  - Reported from 36 jurisdictions – geographically distributed
  - Not concentrated in time – cases reported October 2021 – May 2022
  - Most (>90%) were hospitalized
  - 8% required liver transplant
  - 5 deaths under investigation
  - >50% with confirmed adenovirus

Approach to the nationwide investigation

- Adenovirus ***may*** be the cause for these reported cases
  - Also exploring other potential exposures (medications, other infections, toxins, food, water, etc.)

- Keeping an open mind and focusing on hypothesis generation

- Will share information as we learn more and focus the investigation based on our findings

Working Hypotheses

- Adenovirus (type 41) infection, with or without other cofactors
  - Unusually large season, unmasking a phenomenon that always occurred
    - Lack of exposure during COVID-19 pandemic
  - Altered susceptibility or host response to adenovirus
    - Lack of exposure during COVID-19 pandemic
    - Co-infection with another pathogen, including SARS-CoV-2
    - Prior exposure to SARS-CoV-2
    - Toxin, drug, or environmental exposure
  - Novel variant of adenovirus
- Other causes alone without adenovirus
  - Long COVID
  - Toxin, drug, or environmental exposure
  - New pathogen

What evidence support the role adenovirus?

Supporting role of adenovirus
Infection (viremia) seen in more than two-thirds of patients, across many countries
Limited data show greater viral load in children who required transplant
Age group typical for adenovirus, and this age group that may have increased susceptibility from lack of exposure during pandemic
Preceding gastrointestinal illness reported in some patients
No clear alternate hypothesis so far

What evidence questions the role of adenovirus?

Questioning role of adenovirus
Adenovirus not a well recognized cause of hepatitis in healthy children
Pathology not consistent with typical adenovirus hepatitis (immunocompromised children)
Evidence of viral infection not detected in liver (yet)
Metagenomic studies from UK did not find adenovirus infection (role of AAV2?)
Limited sequencing data indicate multiple strains

Patients Under Investigation (PUIs)

- 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

- Notify your state health department of any cases meeting the above criteria or with any related questions.

What will we want for PUIs?

- Detailed medical chart abstraction to collect information on clinical course of illness and testing results
- Questionnaire collecting information on wide variety of potential exposures
- Additional lab testing (next slide)

General Guidance for Diagnostic Testing in Pediatric Hepatitis Cases

- Standard diagnostic workup for acute hepatitis should be done locally per treating clinician(s).
  - Pursue diagnostic workup for all likely causes of acute pediatric hepatitis (comprehensive infectious workup, immunologic workup, etc.)
- CDC recommends including adenovirus testing in children with acute hepatitis.
- Because we are still investigating the potential relationship between adenovirus infection and acute hepatitis, consider ordering a clinical PCR adenovirus test for all of the following (if available):
  - Respiratory specimen
  - Stool specimen (or rectal swab)
  - Blood specimen (whole blood, plasma, or serum)

Three Types of Laboratory Testing for Epidemiologic Investigation

- Adenovirus detection (diagnostic)
  - Obtain diagnostic PCR testing on all specimens (respiratory/enteric/blood/tissue); if you do not have local access to PCR testing, reach out to your state public health department for instructions
- Adenovirus typing
  - Save all adenovirus positive specimens for adenovirus genotyping; state public health department will provide shipping instructions
- Tissue pathology
  - Save any liver tissues (liver biopsy or native liver explant or autopsy) following local clinical diagnostic review; state public health department will provide shipping instructions

Health Alert Network (HAN): Updated Health Advisory - May 11, 2022

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

Distributed via the CDC Health Alert Network
May 11, 2022, 12:15 PM ET
CDCHAN-00465

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this 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.

Available:[HAN Archive - 00465 | Health Alert Network (HAN) (cdc.gov)]

Self-knowledge Check

For patients under investigation, clinicians should consider ordering a clinical PCR adenovirus test for which of the following specimens (if available)?

A. Respiratory specimen
B. Stool specimen (or rectal swab)
C. Blood specimen (whole blood, plasma, or serum)
D. All of the above

Self-knowledge Check

The answer is **D: All of the above**

Because we are still investigating the potential relationship between adenovirus infection and acute hepatitis, clinicians should consider ordering a clinical PCR adenovirus test for all of the following (if available):

- Respiratory specimen
- Stool specimen (or rectal swab)
- Blood specimen (whole blood, plasma, or serum)

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov

Continuing Education

- All continuing education for COCA Calls is issued online through the CDC Training & Continuing Education Online system at https://tceols.cdc.gov/.

- Those who participate in today's COCA Call and wish to receive continuing education please complete the online evaluation by **June 20, 2022,** with the course code **WC4520-051922**. The access code is **COCA051922.**

- Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between **June 21, 2022,** and **June 21, 2024,** and use course code **WD4520-051922**. The access code is **COCA051922.**

- Continuing education certificates can be printed immediately upon completion of your online evaluation. A cumulative transcript of all CDC/ATSDR CEs obtained through the CDC Training & Continuing Education Online System will be maintained for each user.

Today's COCA Call Will Be Available to View On-Demand

- **When:** A few hours after the live call ends*
- **What:** Video recording
- **Where:** On the COCA Call webpage https://emergency.cdc.gov/coca/calls/2022/callinfo_051922.asp

**A transcript and closed-captioned video will be available shortly after the original video recording posts at the above link.*

Upcoming COCA Calls & Additional COVID-19 Resources

- Continue to visit https://emergency.cdc.gov/coca/ to get more details about upcoming COCA Calls, as COCA intends to host more COCA Calls to keep you informed of the latest guidance and updates on COVID-19.

- Subscribe to receive notifications about upcoming COCA calls and other COCA products and services at emergency.cdc.gov/coca/subscribe.asp.

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