



Surto de hepatite de etiologia desconhecida, 2022

Europa e Estados Unidos

Abril/Maio de 2022

Surto de hepatite

Em 05/04/2022 o Reino Unido notificou à OMS a ocorrência de casos de hepatites de etiologia desconhecida (com resultados negativos para hepatites virais A, B, C, D e E) em crianças previamente saudáveis. Na sequência, casos em outros países da Europa e nos Estados Unidos foram notificados.

- Ao final de abril 111 casos haviam sido notificados no Reino Unido, 55 em outros 12 países da Europa, além de 12 nos Estados Unidos, 12 em Israel, e um no Japão.
- O quadro clínico é de hepatite aguda grave, com icterícia e elevação das transaminases hepáticas. Na maioria dos casos a icterícia foi precedida de sintomas gastrointestinais, como náuseas, vômitos e diarreia. Ainda não há dados disponíveis quanto ao desfecho de todos os casos, a maioria se recuperou, mas há relatos de evolução para insuficiência hepática aguda, e alguns foram submetidos a transplante hepático.
- Os casos foram testados para inúmeros agentes infecciosos. Os patógenos encontrados com maior frequência entre eles foram o SARS-CoV-2 e adenovírus.

Surto de hepatite

Na Inglaterra e Escócia, em 75,5% e 50% dos casos testaram positivo para adenovírus, respectivamente. Em 11 casos foi feita a subtipagem do adenovírus, e todos elas eram do subtipo 41F, o mesmo encontrado em alguns dos casos dos EUA (subtipo comumente associado a gastroenterites).

- Aparentemente há um aumento na detecção de adenovírus em material fecal de crianças de 1 a 4 anos no Reino Unido.
- Até o momento a investigação epidemiológica não identificou exposições em comum (incluindo a investigação de alimentos, toxinas e medicamentos). A investigação toxicológica dos casos está em andamento.
- Na Escócia observou-se a existência de vínculo epidemiológico entre dois pares de casos, mas nos demais locais não se verificou aglomeração de casos.

Surto de hepatite

Com base nas investigações realizadas até o momento, a principal hipótese seria que um co-fator afetando crianças com infecção por adenovírus, que em circunstâncias normais levaria a um quadro leve, estaria desencadeando uma infecção mais grave ou uma lesão hepática imunomediada.

- Outras hipóteses ainda estão em investigação (outros agentes infecciosos ou tóxicos).
- Ainda não se conhece a fisiopatologia da doença, nem o possível modo de transmissão.
- É uma doença rara, e ainda não há evidências de transmissão pessoa a pessoa.

Definições de caso

Epidemiological update for EU/EEA countries and the UK

EU/EEA countries

Several European countries have issued alerts through clinical and public health networks in recent days and have subsequently reported cases to ECDC.

Below is a summary of the information available in the public domain for each country as of 27 April 2022. Further case finding and investigations are ongoing. To date, the level of clinical detail available for each case is variable, but efforts are ongoing to standardise the information collected.

Table 1 shows information on cases reported to ECDC as of 27 April 2022. These are classified as confirmed and possible, according to the case definition used by the UK [2], which ECDC asked countries to use early in the outbreak. [4]

Confirmed: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 IU/l (Aspartate Transaminase-AST or Alanine Transaminase-ALT), who is 10 years and under, since 1 January 2022.

Possible: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 IU/l (AST or ALT), who is 11 to 16 years, since 1 January 2022.

Epi-linked: A person presenting with an acute hepatitis (non hep A-E*) of any age who is a close contact of a confirmed case, since 1 January 2022.

Most cases reported were aged 10 years or younger and it is possible that countries have prioritised detection in that age group; additional cases are under investigation.

In the EU/EEA, a total of approximately 55 cases have been reported. Ten tested positive for adenovirus and three cases tested positive for SARS-CoV2. Five children required liver transplantation.

Definições de caso

Joint ECDC/WHO case definition

Confirmed: Not applicable at present.

Probable: A person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D, and E*) with aspartate transaminase (AST) or alanine transaminase (ALT) over 500 IU/L, who is 16 years old or younger, since 1 October 2021.

Epidemiologically linked: A person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D, and E*) of any age who is a close contact of a probable case since 1 October 2021.

*Cases of hepatitis with known aetiology should not be reported under the [Reporting Protocol for hepatitis of unknown origin](#)

Definições de caso

Table 1. Summary of cases of severe acute hepatitis of unknown aetiology according to case definition used by the UK, with symptom onset since 1 January 2022, as of 27 April 2022 (EU/EEA countries) and as of 20 April 2022 (UK)

Country	Number of cases	Age range (years)	Adenovirus testing results*	SARS-CoV-2 test results*	Onset	Required liver transplant	N. of cases above the expected
Austria	2	<10	One negative	<i>Both had previous SARS-CoV-2 infection</i>	February 2022 – April 2022		
Belgium	2	Up to 10	Two positive	<i>Both had previous SARS-CoV-2 infection</i>	February – March 2022		
Denmark	6	Up to 16	All Negative	<i>One recent SARS-CoV-2 infection</i>	January – April 2022		Yes
France	2	<10	One positive				No
Germany	1	5	Positive	Negative	January 2022		No
Ireland	Fewer than 5	2 to 11	One positive (stool)	All Negative	Since early March		Yes
Italy	17	<16	Two positive and two negative	One positive and four negative	Since early March	1	
Netherlands	4	11 months – 8 years	Two positive	One positive	Since late February	3	Yes
Norway	2	<6 years	One positive (blood)	<i>One recent SARS-CoV-2 infection</i>	Since March	0	No
Poland	1	7	Pending	<i>Previous SARS-CoV-2 infection</i>	Late April		No
Romania	1	4	Negative	Negative	Late March		No
Spain	12 (excluding one case with symptom onset in December 2021)	18 months to 16 years	One positive	One positive and one <i>previous SARS-CoV-2 infection</i>	Early January to April 2022	1	No
United Kingdom**	111	< 16 years	40 positive	10 positive	Reported since 1 January 2022 – some had onset prior	10	Yes
EU/EEA total	Approx. 55		11	3		5	
EU/EEA and UK total	Approx. 166		51	13		15	

*Incomplete information on how many of the reported cases in each country were tested for adenovirus and SARS-CoV-2 infections.

**Data for the UK are as of 20 April 2022. Data on adenovirus and SARS-CoV-2 testing relate to the 81 cases reported in England.

Definições de caso

Table 2. Recommended testing approach for probable (and epi-linked) cases of severe acute hepatitis

Sample type	Test type	Pathogen
Blood	Serology	Hepatitis A, B, C, D*, E/ Cytomegalovirus (CMV)/Epstein-Barr virus (EBV), Varicella, HIV, SARS-CoV-2 anti-S, SARS-CoV-2 anti-N (only if locally available), Adenovirus**
	Serology	<i>Brucella</i> spp, <i>Bartonella henselae</i> , <i>Borrelia burgdorferi</i> (if epidemiologically appropriate)
	Culture	If clinically indicated i.e. fever, as per routine procedures for bacterial pathogens
	Culture	Adenovirus, CMV, EBV, HSV, influenza
	PCR***	Adenovirus**, enteroviruses, CMV, EBV, HSV, HHV6 and 7, parechovirus, hepatitis A, C, E.
	Toxicological screening	Liquid Chromatography / High Resolution Mass Spectrometry (LC/HRMS), Gas Chromatography / Mass Spectrometry (GC/MS), Inductively Coupled Plasma Mass Spectrometry (ICPMS), in a case control study
Throat swab	PCR	Respiratory virus screening by multiplex assay (including influenza, adenovirus, parainfluenza, rhinovirus, respiratory syncytial virus, human bocavirus 1-3 etc), SARS-CoV-2, enteroviruses, human metapneumovirus (hMPV)
	Culture	Streptococcus group A
Stool or rectal swab	PCR	Enteric viruses screening by multiplex assay (including, norovirus, enteroviruses, rotavirus, astrovirus, sapovirus)
	PCR	Enteric bacterial pathogens (incl. <i>Salmonella</i> , if a screening panel is used)
	Culture	<i>Campylobacter</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E.coli</i> 0157
	Culture	Adenovirus, Enteroviruses, Rotavirus
Urine	PCR	<i>Leptospira</i>
	Culture	If clinically indicated, as per routine procedures for bacterial pathogens
	Toxicological screening	Inductively Coupled Plasma Mass Spectrometry (ICPMS)

*Testing for hepatitis D only in cases positive for hepatitis B.

**Note that for adenovirus testing, detection has been found to be superior in whole blood compared to serum.

***Please provide Ct values as a proxy of nucleic acid quantification when available.

RAPID RISK ASSESSMENT

Increase in severe acute hepatitis cases of unknown aetiology in children

28 April 2022

Summary

An increase in severe acute hepatitis cases of unknown aetiology among previously healthy children was first reported by the United Kingdom (UK) to the World Health Organization's International Health Regulations (IHR) notification system on 5 April 2022 (testing had excluded viral hepatitis types A, B, C, D and E and other known causes of acute hepatitis). Following this alert, the United States and several European Union, European Economic Area (EU/EEA) and other countries have reported suspected cases.

As of 20 April 2022, 111 cases had been reported from the UK, and as of 27 April 2022 approximately 55 probable and confirmed cases have been reported from 12 EU/EEA countries. An additional 12 cases have been reported from the United States (US), 12 from Israel, and one from Japan. The clinical picture is of severe acute hepatitis requiring hospitalisation with jaundice and markedly elevated liver transaminases. In most cases to date, the onset of jaundice was preceded by a gastrointestinal illness with vomiting, diarrhoea, and nausea. Information on the outcome of the cases is still being collected. So far, most patients for whom information is available have recovered, but a number have progressed to acute liver failure and required liver transplantation.

Detailed epidemiological and laboratory investigations of the cases are still ongoing to help determine the underlying aetiology. Cases have been tested for a range of different infectious causes, and the most common pathogens found were adenovirus and SARS-CoV-2. In England and Scotland, 75.5% and 50% of cases respectively tested positive for adenovirus. Subtyping of 11 cases from the UK investigation found that these were all type 41F, which is the same subtype identified among several of the cases reported from the US. Other adenoviruses were also found in some non-blood samples among the UK cases investigated. Information on testing in the EU/EEA is incomplete, but among cases reported 11 tested positive for adenovirus. Statistical exceedance compared to positive tests in previous years in the detection of many viruses in the community has been reported by the UK, including a marked recent exceedance in adenovirus detections in faecal samples among children aged 1–4 years.

Early epidemiological investigations of cases from the UK based on trawling questionnaires have failed to identify a common exposure of note (including food, medicines, or toxins). Toxicological analysis of specimens collected from cases as part of the UK investigation is ongoing. Although epidemiological links were reported from the Scottish investigation for two pairs of cases, no other clusters have been reported. Across all reporting countries, the majority of cases to date have not had significant past medical history.

Erratum 29 April 2022: Information regarding cases in Belgium was corrected in Table 1 and on page 9.

Disclaimer: A preliminary version of this Rapid Risk Assessment was circulated through the Early Warning and Response System and was sent to national focal points in advance of publication on ECDC's website.

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Acute Hepatitis and Adenovirus Infection Among Children — Alabama, October 2021–February 2022

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During October–November 2021, clinicians at a children's hospital in Alabama identified five pediatric patients with severe hepatitis and adenovirus viremia upon admission. In November 2021, hospital clinicians, the Alabama Department of Public Health, the Jefferson County Department of Health, and CDC began an investigation. This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.*

Clinical records from the hospital were reviewed to identify patients seen on or after October 1, 2021, with hepatitis and an adenovirus infection, detected via real-time polymerase chain reaction (PCR) testing on whole blood specimens, and no other known cause for hepatitis. An additional four children were identified, for a total of nine patients with hepatitis of unknown etiology and concomitant adenovirus infection during October 2021–February 2022. On February 1, 2022, a statewide health advisory† was disseminated to aid in the identification of cases at other facilities in Alabama; no additional patients were identified.

All nine children were patients at Children's of Alabama. These patients were from geographically distinct parts of the state; no epidemiologic links among patients were identified. The median age at admission was 2 years, 11 months (IQR = 1 year, 8 months to 5 years, 9 months) and seven patients were female (Table). All patients were immunocompetent with no clinically significant medical comorbidities.

Before admission, among the nine patients, vomiting, diarrhea, and upper respiratory symptoms were reported by seven,

six, and three patients, respectively. At admission, eight patients had scleral icterus, seven had hepatomegaly, six had jaundice, and one had encephalopathy (Table). Elevated transaminases were detected among all patients§ (alanine aminotransferase [ALT] range = 603–4,696 U/L; aspartate aminotransferase [AST] range = 447–4,000 U/L); total bilirubin ranged from normal to elevated (range = 0.23–13.5 mg/dL, elevated in eight patients). All patients received negative test results for hepatitis viruses A, B, and C, and several other causes of pediatric hepatitis and infections were ruled out including autoimmune hepatitis, Wilson disease, bacteremia, urinary tract infections, and SARS-CoV-2 infection. None of the children had documented history of previous SARS-CoV-2 infection.

Adenovirus was detected in whole blood specimens from all patients by real-time PCR testing (initial viral load range = 991–70,680 copies/mL). Hexon gene hypervariable region sequencing was performed on specimens from five patients, and adenovirus type 41 was detected in all five specimens. Low viral loads precluded sequencing among three patients, and residual specimens were not available for sequencing for one patient. Seven patients were coinfecting with other viral pathogens (Table). Six received positive test results for Epstein-Barr virus (EBV) by PCR testing but negative test results for EBV immunoglobulin M (IgM) antibodies (one patient did not have IgM testing), suggesting that these were likely not acute infections but rather low-level reactivation of previous infections. Other detected viruses included enterovirus/rhinovirus, metapneumovirus, respiratory syncytial virus, and human coronavirus OC43.

* 45 C.F.R. part 46.102(f)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

† https://www.alabamapublichealth.gov/bcd/assets/adph_han_report_adenovirus_020122.pdf

§ Normal ranges are ALT = 9–25 U/L; AST = 21–44 U/L; total bilirubin = 0.1–1.0 mg/dL.



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