



Guidance for diagnostic testing of cases with severe acute hepatitis of unknown aetiology in children

25 May 2022

Key points

- Collect multiple specimen types as close as possible to the onset of symptoms, including whole blood, plasma, oro-/naso-pharyngeal, stool, and urine (and if possible, liver biopsy) from the cases under investigation. Ensure that a sufficient quantity is collected for all testing and for potential storage for future testing.
- Preliminary data indicate that whole blood is an important sample matrix to test for viruses, particularly adenovirus.
- ECDC suggests that sequential sampling for detection, quantification and metagenomic purposes are performed at defined and documented timepoints. Suggested timepoints include at hospital admission, by patient deterioration, before and after any interventions, including therapeutic ones, and by patient recovery.
- It is important to ensure that tests are carried out for both adenovirus and SARS-CoV-2 (PCR and serology), in addition to other infectious agents.
- Simultaneously start investigations for non-infectious causes of hepatitis.
- If diagnostics are not available locally, specimens should be promptly referred to national laboratories for aetiological investigations, typing, and pathogen characterisation. Transport media for each type of specimen, storage, and shipping conditions (e.g. temperature) should be discussed with the reference laboratory to assure the quality of specimens.
- Any samples that have tested positive for adenovirus and/or SARS-CoV-2 should ideally be sent for typing as soon as possible or be shipped to a reference laboratory capable of performing the typing and/or virus sequencing.
- Laboratories with metagenomic capacities have been identified to support countries seeking metagenomic analysis of specimens from probable cases.

Scope of this document

This document provides guidance on diagnostic testing, molecular characterisation and metagenomic analysis for suspect cases of severe acute hepatitis of unknown aetiology.

Target audience

This document is intended to support public health authorities, clinicians, and laboratories in European Union/European Economic Area (EU/EEA) countries in planning a testing strategy for the investigation of suspected cases of severe acute hepatitis.

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Background

An increase in severe acute hepatitis cases of unknown aetiology among children with no underlying conditions was first reported by the United Kingdom (UK) on 5 April 2022. Testing excluded viral hepatitis types A, B, C, D and E and other known common and uncommon infectious and non-infectious causes of acute hepatitis. Following this alert, the United States and several EU/EEA and other countries have reported suspected cases.

As of [19 May 2022](#), 303 cases have been reported in the EU/EEA and the wider WHO European region.

The UK Health Security Agency (UK-HSA) published a technical briefing on 19 May 2022, and findings from their investigations have informed this technical guideline [1-3]. The clinical presentation in most of the cases is that of severe acute hepatitis requiring hospitalisation, with jaundice and markedly elevated liver transaminases.

Countries in the EU/EEA and wider WHO European region report cases to The European Surveillance System (TESSy). As of 18 May 2022, 276 cases were reported (including 144 cases from the UK). Of 156 cases with information, 22 (14.1%) were admitted to an intensive care unit. Of the 117 cases for which this information was available, 14 (12%) have received a liver transplant. One death has been associated with this disease.

Epidemiological and laboratory investigations, including toxicological analysis, of suspected cases are still ongoing to help determine the underlying aetiology and the actual increased incidence of hepatitis in different countries.

ECDC has published a [rapid risk assessment](#) [4] on this incident outlining the current knowledge and working hypotheses. Based on the findings from the UK-HSA technical briefing, adenovirus infection represents an important element of the aetiological pathway. Of note, adenovirus detection has been superior in whole blood compared to serum or plasma [3].

Of the cases submitted to TESSy, 81 cases were tested for adenovirus by any specimen type, of which 110 (60.8%) tested positive. The positivity rate was the highest in whole blood specimens (69.5%). The UK-HSA reports that typing by partial hexon gene sequencing most commonly shows that the adenovirus present in blood is type 41F (27 of 35 cases with an available result, 77%) [3]. Of five cases with hepatitis and adenovirus infection in Alabama, the United States, all had type 41F [3,5]. Data on typing in TESSy are still incomplete. Whole genome sequencing (WGS) has been attempted in the UK but it has not yet been possible to obtain a good quality full adenovirus genome from a case. However, this is essential to progress the investigations. Recent metagenomics findings have identified Adeno-Associated Virus 2 (AAV-2) in a number of samples tested from cases. ECDC and UK's investigations are still underway to clarify the importance of this finding [1,6].

Another hypothesis is that current or previous infection with SARS-CoV-2 may be causing or contributing to the clinical presentation, either through a post-infectious syndrome or together with a secondary infection with another virus [3,7].

Testing

ECDC recommends that all possible cases of hepatitis of unknown origin undergo a standardised set of diagnostic procedures to identify possible infectious and non-infectious aetiologies. Specialist patient care should not be delayed by the diagnostic processes proposed in this document but should be promptly provided according to clinical best practices.

Suggested investigation process

In addition to the routine diagnostic process for paediatric cases of acute hepatitis, ECDC advise Member States to implement the following investigation procedure:

- Collect multiple specimen types as close as possible to the onset of symptoms, including whole blood, plasma/serum, oro-/naso-pharyngeal, stool and urine. Preliminary data indicate that whole blood is an important sample matrix to test for adenovirus.
- Collect a sufficient quantity of each type of specimen to perform the tests described in Table 1 below.
- Consider collecting an extra amount of each specimen type for future testing, and ensure that it is stored under appropriate conditions (see text box below).

Storage of specimens for future testing:

The following types of specimens could be stored for future testing, preferentially at -80°C, as soon as a suspect case is identified:

- serum and EDTA samples
- nasal and throat swabs (bacterial and viral)
- faecal sample for further testing as required
- urine sample for further testing as required
- any available biopsy material.

- Store residual tissue from liver biopsies and from explanted livers for future testing, if such procedures are undertaken as part of the diagnostic and clinical management of cases.
- Sequential sampling should be performed for detection, quantification and metagenomic purposes at defined and documented timepoints. Suggested timepoints include:
 - at hospital admission/first visit to healthcare;
 - when clinical conditions start to deteriorate;
 - pre- and post any interventions including therapeutic ones;
 - at patient recovery.
- Ensure that tests are carried out for both adenovirus and SARS-CoV-2, in addition to other infectious agents and that serology for SARS-CoV-2 is also performed.
 - Any samples that have tested positive for adenovirus and/or SARS-CoV-2 should ideally be sent for typing as soon as possible or be shipped to a reference laboratory capable of performing the typing.
- Investigations for non-infectious causes of hepatitis (see Table 2) should be conducted simultaneously with the investigations for infectious causes.
- If any diagnostics are not available locally, specimens should be promptly referred to national laboratories for aetiological investigations, typing and pathogen characterisation. Transport media for each type of specimen, storage and shipping conditions (e.g. temperature) should be discussed with the reference laboratory to assure the quality of specimens.

Table 1. Recommendations for testing of infectious aetiologies in suspected cases of acute hepatitis

Sample type	Test type	Pathogen
Blood (whole and plasma)	Serology	A, B, C, D ¹ , E hepatitis viruses, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella, HIV, SARS-CoV-2 serology ²
	Serology	Anti-streptolysin O titre (if relevant clinical history) ³
	Culture	If clinically indicated, e.g. fever, as per routine procedures for bacteria/fungi
	Culture ⁴	Adenovirus, CMV, EBV, HSV, influenza
	PCR	Adenovirus ⁵ , enteroviruses, CMV, EBV, HSV, HHV6 and 7, parechovirus, parvovirus B19, hepatitis A, C, E, leptospira (if relevant clinical history)
Oro/Nasopharyngeal swab	PCR	Respiratory virus screening (including but not limited to influenza, adenovirus, parainfluenza, rhinovirus, respiratory syncytial virus (RSV), human bocavirus 1-3, SARS-CoV-2, enteroviruses, human metapneumovirus (hMPV), parechovirus, human coronaviruses)
	Culture	Streptococcus group A
Stool or rectal swab	PCR	Enteric viruses screening (including but not limited to adenovirus, norovirus, enteroviruses, rotavirus, astrovirus, sapovirus, SARS-CoV-2)
	PCR	Enteric bacterial pathogens (incl. <i>Salmonella spp</i> , if a screening panel is used)
	Culture	<i>Campylobacter</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E. coli</i> 0157
	Culture ⁴	Adenovirus, enteroviruses, rotavirus
Urine	PCR	Leptospira (if relevant clinical history), adenovirus
	Culture	If clinically indicated, as per routine procedures for bacterial pathogens

If liver specimens of suspected cases are available from biopsies or transplants, immunohistochemistry and PCR alongside the histological analysis should be performed in specialised centres.

¹ Hepatitis D should only be tested if HBV is present.

² If possible anti-S, and anti N / IgG and IgM.

³ Serology for *Brucella spp*, *Bartonella henselae*, *Borrelia burgdorferi* (if epidemiologically appropriate), leptospira (if relevant clinical history) can also be considered.

⁴ Only to be performed in laboratories experienced in cell culturing.

⁵ Please provide cycle threshold (Ct) values from PCR in whole blood samples when reporting probable cases in TESSy, as a proxy of nucleic acid quantification when available.

Non-infectious causes of hepatitis

Hepatitis in children can also be caused by non-infectious causes. Table 2 outlines some of the most common non-infectious causes of hepatitis in children. Laboratory screening tests for metabolic and autoimmune diseases are recommended to exclude non-infectious causes of acute hepatitis in children. Such tests often require a longer time than microbiological investigations, and it is therefore necessary to run them in parallel. Early consultation with a paediatric liver specialist is advised to guide the diagnostic work-up according to the age and clinical and biochemical characteristics of the patient. In children with acute hepatitis and acute liver failure, early referral to a liver transplant centre is indicated.

Table 2. Non-infectious causes of hepatitis* [8]

Groups of non-infectious causes of hepatitis	Diseases and syndromes affecting children with severe hepatitis
Auto-immune disorders	Autoimmune hepatitis Autoimmune sclerosing cholangitis Celiac disease
Inherited Disorders	Inherited disorders of carbohydrate metabolism Inherited disorders of protein metabolism Inherited defects of lipid metabolism Lysosomal storage disorders Mitochondrial disorders
Toxic exposure	Direct hepatic injury (e.g. solvents, nitrosamines) Indirect hepatic injury through immune mechanism (e.g. heavy metals) Drug-induced liver injury (DILI) Herbal supplement-induced liver injury (HILI)
Other causes	Metabolic (associated) fatty liver disease Hemophagocytic lymphohistiocytosis Budd-Chiari syndrome Gestational alloimmune liver disease

*Refer to a liver specialist for the appropriate investigation

Toxicological investigations

As the disease aetiology remains unknown, possible exposure to drugs or toxins should still be considered. A number of case-control studies are ongoing in the UK looking into potential exposures to toxic agents, including drugs [1]. ECDC is collaborating with toxicologists from the European Food Safety Authority (EFSA) to identify suitable testing methodologies and available testing centres in the EU/EEA that are specialised in liver toxicity.

Drug-induced liver injury is also under consideration. Due to the young age of the current patient group, potential candidates include acetaminophen (paracetamol), valproic acid, antimicrobials (e.g. amoxicillin-clavulanate), nonsteroidal anti-inflammatory drugs and aspirin [9]. UK-HSA's initial epidemiological investigations identified recent acetaminophen use among probable cases, but the use appears to have been for therapeutic purposes and below toxic levels [3,7].

ECDC currently advises undertaking a detailed history of exposure for all suspected cases, including drugs and herbal dietary supplements. Acetaminophen levels in blood should be measured in cases with a history of recent use, especially if overdosing is suspected. It would also be prudent to store frozen blood, plasma, and urine samples from suspected cases for potential future testing.

Adenovirus testing

Detection

Laboratory diagnostics of adenovirus infections are usually performed using antigen detection tests, PCR, and virus culturing on respiratory and/or stool samples. PCR-based assays are the standard testing tools due to their high sensitivity and specificity, short turnaround time, and ability to effectively detect adenovirus in most specimen types [10-16].

A variety of in-house and commercial PCR assays for detection of adenovirus are used across EU/EEA countries. The primers used are usually pan-adenovirus primers detecting most of adenovirus types. However, specific 40/41 PCR assays also exist and laboratories should ensure the assays they use are able to detect a variety of types including 41.

Where quantitative assays are not available, quantification of adenovirus or other positive PCR findings in samples including whole blood should be conducted with cycle threshold (Ct) values as a proxy of viral load, and if possible, using sequential sampling over time.

Whole blood is recommended over plasma [6]. Detection of adenovirus in peripheral blood has been shown to be indicative, and in some cases correlated, with disseminated disease in immunocompromised patients [17,18].

Typing

Sequence-based typing is fundamental for confirmation and epidemiological investigations of the dynamics and evolution of adenovirus infections. Published methods of typing adenovirus based on amplification and sequencing of the hexon gene rely on targeting conserved regions that flank variable regions capable of distinguishing between known adenovirus types [19-21].

To date, type confirmation in the UK and USA has been based on a combination of positive diagnostic PCRs combined with typing PCRs or sequencing regions of the hexon gene [1,5,22-24].

No agreed upon protocol for adenovirus sequence-based typing exists, however, ECDC is working closely with international partners to identify a standardised protocol that can be shared with EU/EEA countries to support their investigations.

Viroscience at the Erasmus Medical Centre, use the primers described by Sarantis *et al.* (Forward: CTGATGTACTACAACAGCACTGGCAACATGGG and Reverse: GCGTTGCGGTGGTGGTTAAATGGGTTTACGTTGTCCAT) for PCR amplification of the hexon gene, followed by Sanger sequencing, when typing adenovirus [21].

Whole genome sequencing

Whole genome sequencing (WGS) is essential to characterise the virus. In the current outbreak low viral loads of adenovirus in the blood have resulted in low quality sequencing data [1].

A protocol for WGS of adenovirus in blood has not yet been agreed upon, but ECDC is working closely with international partners to identify standardised protocols to facilitate adenovirus WGS efforts. ECDC encourages countries to pursue WGS and share consensus genomes with ECDC via TESSy and upload to public databases (e.g. [ENA](#), [GenBank](#)) as soon as the sequences become available.

Reporting of laboratory results

Results from laboratory testing should be reported to local and national public health authorities. The nominated national authorities should then report relevant data to TESSy, including positive and negative findings as per the most recent ECDC reporting protocol [25].

ECDC recommends sharing genome sequence data in the public domain ([ENA](#), [GenBank](#)) to allow easy access for all international stakeholders and sharing with ECDC for inclusion in multi-country analysis. A data field has been created in TESSy. ECDC encourages countries to upload available hexon gene sequences in a timely manner to facilitate joint investigations.

An EpiPulse event has also been created in which nominated users at national public health authorities can upload any additional relevant microbiological or clinical findings in a free text format to share data with other countries in a timely and confidential manner.

Metagenomic analysis

Traditional molecular diagnostic techniques target known/suspected pathogens and are likely to miss rare or previously unknown pathogens. Metagenomics allows for the detection of known pathogens but also unexpected or previously unknown pathogens by sequencing the total genetic material (DNA and RNA) in a sample. In scenarios where the aetiology is unknown, metagenomic analysis is an important approach towards identifying underlying microbial agents [26]. Institutes with metagenomic capacities should consider analysing samples of probable and epidemiologically linked cases. Samples for analysis include plasma, whole blood and/or available liver biopsies, but can be extended to any relevant samples.

Countries undertaking metagenomic analysis are encouraged to collect and report the following information to ECDC: Sample information (Laboratory key, sample type, time of sampling in relation to hospital admission and disease onset), treatments administered that may affect results (e.g. blood transfusions), a description of the sequencing technology used (sample preparation, library preparation method and type of sequencer), total number of library reads (DNA/RNA), number of target reads (DNA/RNA) per finding, description of species similarity and mapping methods, species confirmed by specific PCR (Yes/No), and a description of bioinformatic tools used (for published pipelines provide references and for in-house pipelines the Github code).

For institutes lacking metagenomic capacity and seeking support, services are available at no cost for the analysis of relevant samples with two institutes based in Sweden and the Netherlands (See section on Support services for EU/EEA countries below).

Countries are encouraged to follow up observations made by metagenomic testing using pathogen-specific laboratory methods. This includes setting up specific real-time PCR assays for confirming and quantifying findings in broader groups of cases and controls. The relevance of the UK detection of Adeno-Associated Virus 2 (AAV-2) is one observation that can require follow-up testing using specific laboratory assays.

Support services for EU/EEA countries

- Countries seeking support in adenovirus typing can contact
 - Department of Viroscience of the Erasmus Medical Centre in the Netherlands directly via Janko van Beek (j.h.g.vanbeek@erasmusmc.nl).
- Countries seeking metagenomic support can contact the following centres:
 - Department of Viroscience of the Erasmus Medical Centre in the Netherlands via Janko van Beek (j.h.g.vanbeek@erasmusmc.nl) or
 - Department of Clinical Microbiology at Karolinska University Hospital, Sweden, via Tobias Allander (tobias.allander@regionstockholm.se).
- When contacting laboratories for laboratory support, please keep ECDC typing@ecdc.europa.eu in copy.
- A Material Transfer Agreement template to facilitate sample sharing is available from ECDC upon request. Please contact typing@ecdc.europa.eu for further information.
- Institutes seeking typing and/or metagenomic analysis will need to cover associated shipping costs.
- Once WGS protocols are available, support can be provided via ECDC-outsourced sequencing services. EU/EEA countries seeking WGS support are welcome to contact typing@ecdc.europa.eu.
- Additional laboratories that can offer metagenomic services to other EU/EEA countries or other alternative approaches are encouraged to contact ECDC at typing@ecdc.europa.eu.

Limitations

This guidance document was undertaken based on evidence available to ECDC at the time of publication.

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

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