COMMENTARY
EMERGING NEWS FROM ECCMID 2022

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Pediatric Cases with Acute Severe Hepatitis of Unknown Origin: Summary of Special Session "Acute Severe Hepatitis of Unknown Etiology In Children" at the 32nd ECCMID in Lisbon, Portugal

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Following the increase in number of pediatric cases with acute severe hepatitis of unknown etiology (ASHep-UE), in collaboration with the European Center for Disease Prevention and Control (ECDC) and the UK Health Security Agency (UKHSA), a special late-breaking session "Hepatitis of unknown origin" was organized at the 32nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2022 in Lisbon on the 25th of April, between 9.00-10.00 am. There were two invited speakers, **Dr Aikaterini Mougkou** from ECDC Sweden and **Dr Meera Chand** from UKHSA.

Dr Mougkou presented an overview of the pediatric cases with ASHep-UE in the European Union (EU) and the European Economic Area (EEA) countries. As of April 23, 2022, there are 33 cases of ASHep-UE among children aged between 18 months and 16 years in nine EU/EEA countries: Spain 11, Denmark 6, Ireland 4, Netherlands 4, France 2, Norway 2, Italy 2, Romania 1 and Belgium 1. All cases were negative for hepatitis viruses A-E. In seven cases adenovirus was positive either in stool or blood specimens, while four cases were positive for SARS-CoV-2. In four cases liver transplantation was performed. Regarding data from non-EU countries, 114 cases are reported in the UK (60 cases positive for adenovirus and 18 for SARS-CoV-2), 12 cases in Israel (no adenovirus or SARS-CoV-2 reported) and nine cases in the USA (all positive for adenovirus). Altogether 12 cases have required liver transplantation. Clinical presentation included signs and symptoms of severe acute hepatitis: jaundice, abdominal pain, fatigue, diarrhea, nausea/vomiting, fever (only a few) and lethargy. Most cases were previously healthy. The majority of cases have been hospitalized and some progressed to acute liver failure re-

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quiring liver transplantation. All countries are conducting extensive epidemiological, microbiological and toxicological investigations, however, no common exposure has been identified so far. There is no link to COVID-19 vaccination and no clustering of cases. It was stressed that there are uncertainties regarding the actual number of cases as existing national surveillance systems for viral hepatitis are not designed to detect such a signal. In addition, no common case definition is finalized, yet. Issues to be clarified include the exact age range of the affected population, clinical presentation (looking at potential asymptomatic/mild cases), defining and standardizing testing strategies, exploring potential risk factors and transmission routes. ECDC is committed to sharing information with EU/EEA countries using the EpiPlus platform to share updates and investigation tools (case definitions, testing algorithms, trawling questionnaire) and to communicate directly with European Network for Hepatitis B and C Surveillance members. It is asking EU/EEA countries to report suspected cases to ECDC and is communicating with professional societies such as the European Association for the Study of the Liver (EASL), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Society for the Pediatric Infectious Diseases (ESPID). It is collecting emerging information from available sources such as EpiPlus, teh Early Warning and Response System of the European Union (EWRS) and the media and is communicating with the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). ECDC`s next steps will bepublishing of a rapid risk assesment by April 28, 2022, and giving regular updates in the Weekly Communicable Disease Threats Report (CDTR). It will establish a new system for reporting national data on cases by EU/EEA countries and other countries in the WHO EURO region to The European Surveillance System (TESSy) at ECDC.

ECDC recommends the following tests in pediatric cases with ASHep-UE:

- **In blood:** Serology for hepatitis A-E viruses, EBV, CMV and SARS-CoV-2; PCR for adenovirus, CMV, EBV, enterovirus, parechovirus, HSV, HHV-6, HHV-7, HAV, HCV and HEV.
- **In throat swab:** PCR for influenza virus, adenovirus, parainfluenza virus, rhinovirus, RSV, human bocavirus 1-3, SARS-CoV-2 and enterovirus; culture for *Streptococcus* group A.
- **In stool/rectal swab:** PCR for noroviruses, enterovirus, rotavirus, astrovirus, sapovirus, adenovirus and enteric bacterial pathogens; culture for *Campylobacter*, *Salmonella*, *Shigella*, *E. coli* O157.
- **In urine:** PCR for *Leptospira* and culture.

Dr Chand from UKHSA presented a talk on "Investigation into acute hepatitis of unknown etiology in children in England". On March 31, 2022, Public Health Scotland was alerted about reporting of five cases of ASHep-UE among children in the previous three weeks (normally four cases per year occur in Scotland). Rapid case finding confirmed a total of 13 Scottish cases.

The case definition for confirmed cases is: A person presenting with acute hepatitis (negative for hepatitis viruses A-E) with serum transaminase >500 IU/L who is 10 years old and under, since January 1, 2022. Cases between 11-16 years of age are defined as possible cases. A person of any age presenting with an acute hepatitis (negative for hepatitis viruses A-E) who is a close contact of a confirmed case, since January 1, 2022 is defined as an Epi-linked case.

As of April 21, 2022, 114 cases of ASHep-UA have been reported in the UK. Out of 81 cases reported in England, the median age is three years and the vast majority of case are 1-6 years old. Cases in England are not epidemiologically linked and are dispersed all over the country. Seven cases have required liver transplantation and none has died.

Adenovirus has been detected in 40 out of 53 cases (75%). Preliminary subtyping as identified 41F in some blood samples. Dr Chand stressed the fact that it is too early to confirm the characterization. Adenovirus sequencing from multiple cases from multiple countries is needed. SARS-CoV-2 tested positive on admission in 10 out of 62 cases [16%, two genotyped as Omicron and two as VOC- 22 Jan-01 (BA.2 or sublineage)]. Eight cases tested positive for EBV, five for enterovirus, three for CMV, six for HHV-6, three for HHV-7, and two for RSV. Acute hepatitis has not been a common feature of COVID-19 in children.

Of 8883 children in the CO-CIN study, 3171 had ALT measured; only 13 of 3171 had ALT > 500 IU/L.

UKHSA working hypotheses include:

1. A cofactor affecting young children which is rendering normal adenovirus infections more severe or causing them to trigger immunopathology. The cofactor may be:

- Susceptibility, for example due to lack of prior exposure during the pandemic,
- A prior infection with SARS-CoV-2 or another infection, including an Omicron restricted effect,
- A coinfection with SARS-CoV-2 or another infection,
- A toxin including aflatoxin, drug or environmental exposure.

2. A novel variant of adenovirus, with or without a contribution from a cofactor as listed above.

3. A drug, toxin or environmental exposure.

4. A novel pathogen either acting alone or as a coinfection.

5. A new variant of SARS-CoV-2.

Investigations which are underway or planned soon in the UK are:

- **Analytic epidemiology:** Matched case-control study to test the association of hepatitis with adenovirus infection
- **Mechanism of liver injury:** Investigations on liver tissue to include electron microscopy, expert histopathology review, and T cell subset analysis
- **Pathogen investigation:** Adenovirus whole-genome sequencing from cases and community samples, metagenomic sequencing of blood and liver tissue from cases, viral culture of adenovirus and phenotypic characterization including assessment of hepatotropism in vitro, adenovirus and SARS-CoV-2 serology of cases, SARS-CoV-2 sequencing in positive cases, retrospective wastewater analysis for adenovirus
- **Host characterization:** Harmonized clinical data collection and analysis, host genetic characterization, immunological characterization including T cell activation studies and transcriptomics.

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