ALBERTA PRECISION LABORATORIES
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Laboratory Bulletin

DATE:	2022 May 9
TO:	Health Care Providers
FROM:	Public Health Laboratory (ProvLab), Alberta Precision Laboratories (APL)
RE:	**Emerging issue – acute, severe hepatitis of unknown aetiology in children**

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Key Messages

- Acute, severe hepatitis of unknown origin in children (aged 0-16 years) is a recently described syndrome deemed to be an emerging international health issue.
- The Virologist-on-call (VOC) at the Public Health Laboratory (ProvLab, Alberta Precision Laboratories) is available daily to provide consultation on further investigation for this emerging health issue from a microbiology perspective. VOC consultation for all suspect cases is advised.
- The recommended testing for evaluation of potential aetiologies of this syndrome are advised here in a phased approach.
- Any microbiology investigations for probable cases of this newly emerging syndrome should be clearly identified on paper/electronic requisitions so that further detailed work-up can be undertaken by the Public Health Laboratory, if deemed appropriate.
- Acute, severe hepatitis of unknown origin in children is a reportable condition to public health (https://www.alberta.ca/notifiable-disease-guidelines.aspx).
- Further details of this syndrome and reporting information is available from CMOH Letter to Medical Officers of Health Re: Acute Hepatitis non A-E (alberta.ca).

Background

- On April 23, 2022 the World Health Organisation (WHO) published on their website a summary of cases of acute, severe hepatitis of unknown origin in children (aged 0-16 years of age).
- At the date of writing of this bulletin, cases have been identified in the United States, Europe, and Israel.
- The exact cause of this syndrome at present remains unclear and is actively being investigated worldwide.
- Outcomes of this condition can be serious.

Recommended testing

- Evaluation for potential aetiologies of this condition is advised in a phased approach.
- The information attached to this bulletin outlines the testing that is available from the ProvLab and details on how to collect the specimens.
- Orders must be entered individually for each test.

Actions required

- Clinicians in Alberta should monitor for and help identify any cases of unexplained acute, sever hepatitis in the paediatric age group (0-16 years) of patients as per the case definition above.
- These cases require intensive investigations to help ensure appropriate reporting and evaluation of these patients, which can be complicated to order and collect specimens for.

- The Virologist-on-call (VOC) at the Public Health Laboratory (Alberta Precision Laboratories) is available on a daily bases to help clinicians with microbiology-related investigations for this syndrome. This includes helping to outline which investigations are recommended, types of specimens to collect, testing to order, and help ensure the correct testing is carried out from a Public Health testing perspective.
- The VOC at the Public Health Laboratory (ProvLab) can be contacted by requesting they be paged via (780) 407-8822 (Edmonton) or (403) 944-1200 (Calgary).

Inquiries and feedback may be directed to

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Approved by

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Acute, Severe Hepatitis of Unknown Aetiology in Children Public Health Related Testing Guidance
Public Health Laboratory (ProvLab), Alberta Precision Laboratories

Document date: May 6, 2022

!! PLEASE READ FIRST !!

- Initial testing for aetiologies of hepatitis should be carried out taking patient presentation, history, and risk factors into consideration. This includes any relevant travel history.
- Early consultation (i.e. upon hospital admission) with paediatric hepatology/gastroenterology and/or infectious diseases is strongly advised.
- While the below represents a microbiology-related work-up, toxicological, vascular, immunological, metabolic, and genetic causes of hepatitis should be considered. All laboratory results should be correlated with patient presentation.
- The Virologist-on-call (VOC) at the Public Health Lab (ProvLab, Alberta Precision Labs) should be consulted for **all** children and adolescents presenting with hepatitis without a readily apparent cause. The VOC is on-call and available daily.
    - Edmonton: Page Virologist-on-call via (780) 407-8822
    - Calgary: Page Virologist-on-call via (403) 944-1200
- Indicate on the paper/electronic requisition that you are investigating a patient with severe acute paediatric hepatitis. Failure to do so may result in delays in testing.
- Serologies should be drawn **PRIOR** to infusion of any blood products (e.g. packed red cells, platelets, IVIG, fresh frozen plasma, etc.) if at all possible.

Working case definition:

Confirmed	N/A at present
Probable	A person presenting with an acute hepatitis (**non hepatitis A-E* and without another definitive cause**) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021
Epi-linked	A person presenting with an acute hepatitis **(non hepatitis A-E* and without another definitive cause)** of any age who is a close contact of a probable case, since 1 October 2021.

**If hepatitis A-E serology results are pending, but other criteria met, these can be reported to public health and the case will be classified as "pending classification".*

Reference: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376.

Microbiology Work Up Notes

NOTES:

- Work-up is advised in 3 phases.
    - Phase 1 – Initial viral hepatitis serology and hepatitis virus testing. Includes testing as indicated based on clinical presentation and history.
    - Phase 2 – Other causes of hepatitis (including non-viral).
    - Phase 3 – Liver biopsy (*as guided by sub-specialist consultation*).
- If the patient has a compatible diagnosis with their presentation with testing from Phase 1, then further investigation may not be required. Please consult with gastroenterology/hepatology/infectious diseases.
- A positive SARS-CoV-2 (COVID-19) PCR/NAT result should **not** stop progression to Phase 2 testing given active circulation of SARS-CoV-2 infection in the community.
- If Phase 2 work-up is conducted, it is advised you order **all** tests listed at once to minimise phlebotomy attempts on the patient.

Phase 1 of work-up

Agent	*Test*	*Specimen*
Hepatitis A virus (HAV)[a]	Hepatitis A IgM Hepatitis A IgG	• One 4-5 mL SST (gold top) tube.
Hepatitis B virus (HBV)[a, b]	• Hepatitis B surface antigen (HBsAg) • Hepatitis B core antibody (total) (anti-HBc total) • Hepatitis B core antibody IgM (anti-HBc IgM) • Hepatitis B surface antibody (anti-HBs)	
Hepatitis C virus (HCV)[a]	Anti-HCV antibody	
Hepatitis E virus (HEV)[c]	Anti-HEV IgM Anti-HEV IgG HEV PCR/NAT	• One 3 mL SST (gold top) tube (dedicated)
SARS-CoV-2 (COVID-19)	SARS-CoV-2 PCR/NAT	One or more of: • NP swab • NP aspirate • Bronchoalveolar lavage fluid • Endotracheal aspirate

- Routine microbiology cultures (e.g. blood, urine, CSF) as per clinical assessment.
- Any other tests as indicated based on patient history and clinical assessment.
- Any testing indicated as per travel or exposure history (if any).

[a]PCR/NAT testing for hepatitis A, B, or C should only be done in cases of abnormal serological testing. Severe/urgent clinical worsening of the patient may be an exception. To request PCR testing (in addition to serology tests) please consult with the Virologist-on-call at ProvLab.

[b]Hepatitis D should only be tested for once a patient is confirmed to have active hepatitis B infection. An individual cannot have Hepatitis D without having active hepatitis B.

[c]HDV and HEV testing is conducted at the National Microbiology Laboratory (Winnipeg, MB). HEV IgM/IgG will be run first, with HEV PCR/NAT done automatically if one of these are positive. Thus, the turn-around time for results can be prolonged. Please notify the VOC you are ordering these tests so we can help expedite testing. You should not await results for HEV to move onto Phase 2 of the work-up.

Phase 2 of work-up

NOTE: It is advised that **all** the phase 2 testing is ordered at once if Phase 2 work-up is conducted.

Agent	*Test*	*Specimen*
Serology testing		
CMV (serology)	CMV IgM CMV IgG	Two 3-mL SST (gold top) tubes.
EBV (serology)	EBV Serology Panel - EBV VCA IgM - EBV VCA IgG - EBV NA IgG	
Parvovirus B19 (serology)	Parvovirus B19 IgM Parvovirus B19 IgG	
SARS-CoV-2 (serology)	SARS-CoV-2 Serology ***must notify VOC to ask for nucleocapsid IgG**	
Blood molecular testing		
HSV-1, HSV-2, VZV[c]	HSV-1, HSV-2, and VZV blood PCR/NAT	Two 4-mL EDTA (lavender top) tubes.
EBV	EBV PCR/NAT	
Adenovirus (blood)	Adenovirus blood PCR/NAT	
HHV-6	HHV6 blood PCR/NAT	
Other molecular testing		
Respiratory viruses (including adenovirus)	Respiratory pathogen panel (RPP)[d]	One or more of: • NP swab • NP aspirate • Bronchoalveolar lavage fluid • Endotracheal aspirate
Enteric viruses (including adenovirus)	Gastrointestinal viral panel[e]	Stool in a **sterile container.** (do NOT place stool in fixative).

[d] RPP tests for adenovirus, influenza A/B, parainfluenza, respiratory syncytial virus, human metapneumoviruses, endemic human coronavirus (NL63, HKU1, 229E, OC43), and enterovirus/rhinovirus.

[e] GI viral panel tests for norovirus, sapovirus, adenovirus, and rotavirus.

Phase 3 of work-up
(as guided by sub-specialist consultation)

In the instance that liver biopsy is conducted, the following testing is advised. This information can be provided to interventional radiology or the clinician conducting the liver biopsy for diagnosis.

NOTE:

- It is **very important** that attention is paid to the container in which sample is placed for the test request.
- Inform the Virologist-on-call that a liver biopsy is being conducted.

Test	***Where conducted***	***Container***
Adenovirus PCR/NAT	Public Health Lab (ProvLab)	Place specimen for these tests into a sterile container on gauze that is moistened with sterile saline. ***Do NOT place samples for viral PCR/NAT testing into formalin.***
HSV-1, HSV-2, VZV PCR/NAT	Public Health Lab (ProvLab)	
Histopathology	Pathology services	Submit as per routine specimens to pathology. Be sure to request for viral staining.