Hepatitis A (Hepatitis A virus)
Laboratory case definition

The Public Health Laboratory Network (PHLN) has developed standard case definitions for the diagnosis of key diseases in Australia. This document contains the laboratory case definition for hepatitis A virus.

Authorisation: PHLN
Consensus date: 30 May 2011

1 PHLN Summary Laboratory Definition

1.1 Condition:
Hepatitis A

Definitive Criteria

1. Detection of hepatitis A virus by nucleic acid testing
2. Detection of anti-hepatitis A IgM, in the absence of recent vaccination within the last 12 weeks
3. Seroconversion from hepatitis A IgG negative to positive.

2 Introduction

Hepatitis A virus (HAV), the causative agent of hepatitis A, is a non-enveloped, single-stranded RNA virus, which is a member of the Hepatovirus genus of the family Picomaviridae. HAV displays a high degree of genetic conservation throughout its genome and there is only one serotype. There is enough genetic diversity though, to define six genotypes consisting of three that infect humans (I, II and III) and three simian strains (IV, V and VI). Former human genotype VII has now been incorporated into the genotype II clade.¹

HAV is the most common cause of infectious hepatitis worldwide with more than 1.5 million cases each year. In Australia there are approximately 300 to 500 cases of HAV infection reported annually and this has been declining since the 1990s.² HAV is transmitted via the faecal-oral route through direct contact of an infected person, or by ingestion of contaminated food or water. Risk factors for acquisition of HAV include low socioeconomic status, large household size, overcrowding, living in a rural area and having limited access to clean water sources or sanitation facilities. HAV is stable in the environment for up to 1 month and is inactivated by temperatures exceeding 85°C and by some disinfectants; including chlorine and formalin.
True chronic hepatitis attributable to HAV has not been documented. However a small proportion of patients may have persisting HAV replication and transaminitis for up to a year or longer. Relapsing illness within weeks of apparent recovery, with reappearance of HAV in the faeces has also been described.

2.1 Clinical Presentation

The clinical presentation typically has four phases;

- the first phase is an incubation period of 15-50 days where, although asymptomatic, there may be shedding of virus in the stool
- this is followed by the second, preicteric phase, which lasts for between 3-21 days and consists of nonspecific symptoms, such as nausea, vomiting, abdominal pain, anorexia, malaise and fever
- in the third phase, dark urine and raised bilirubin are followed by the onset of jaundice, usually resolving within a few weeks
- the final phase is convalescence, where liver function normalises and the patient recovers over about a 1 month period

On rare occasions fulminant hepatitis may occur, otherwise complications of HAV infection are rare and the case fatality rate is low, (<0.5%). In children, HAV usually causes either an asymptomatic infection, or a mild illness without jaundice.

2.2 Treatment

There is no specific treatment for HAV, although symptoms can be relieved with rest, a diet avoiding hepatotoxins and adequate fluid intake.

2.3 Prevention

There are currently five hepatitis A vaccines, two combined hepatitis A/hepatitis B vaccines and one combined hepatitis A/typhoid vaccine, registered for use in Australia. These vaccines are made from inactive HAV and all appear to be highly immunogenic in both children and adults. Universal seroconversion usually occurs by 4 weeks post first vaccination, although a second dose of vaccine is required for long term protection. The duration of immunity has not been defined, although probably persists for many years and there is no current evidence that any further booster doses are required. The vaccines have a high protective efficacy of greater than 95%.

Hepatitis A vaccine is currently recommended for:

- those travelling to moderately to highly endemic areas
- Aboriginal and Torres Straight Islander children residing in the Northern Territory, Queensland, South Australia and Western Australia
- those whose lifestyle may put them at risk of acquiring HAV
- people with intellectual disabilities
- people who are chronically infected with either hepatitis B or hepatitis C virus
- patients with chronic liver disease

Normal human immunoglobulin can be used for individuals exposed to the virus; where administration should be within 2 weeks of the exposure.
3 Tests

3.1 Culture

HAV grows slowly in a restricted number of cell lines and rarely produces a cytopathic effect. Due to poor sensitivity and the prolonged time to obtain a result, culture is not useful for diagnosis or epidemiological studies. Immunological assays have been used to detect HAV antigens and include radioimmunoassays and in situ hybridisation, but these are mostly used in research and reference laboratories.

3.2 Electron Microscopy

Although HAV can be detected by electron microscopy this is of limited diagnostic utility. HAV cannot be visually distinguished from other picornaviruses without recourse to more complex techniques such as immune electron microscopy (IEM) and relatively high numbers of viral particles are required for visualization. Peak shedding usually occurs before the onset of symptoms.

3.3 Serological Diagnosis

Anti-HAV IgM antibodies are detectable within 5-10 days of symptom onset and last for between 3 to 6 months. Anti-HAV IgG antibodies appear soon after the onset of symptoms and are usually detectable for life, conferring immunity. Both anti-HAV IgM and IgG antibodies are usually present at the time of sample collection.9

There are commercially available IgM and total anti-HAV antibody enzyme immunoassays (EIAs). Current or recent infection can be determined by the presence of the anti-HAV IgM antibodies. The presence of anti-HAV total antibodies in the absence of anti-HAV IgM antibodies is used to differentiate past from recent infection. There has recently been the development of anti-HAV IgG avidity tests that are able to aid in the diagnosis of acute HAV in the presence of possible false positive anti-HAV IgM results, although these tests are not yet commercially available.5

Following immunisation with hepatitis A vaccine, there may be a anti-HAV IgM transient response in some people. Anti-HAV IgM has been detected 2-3 weeks after vaccination in 8-20% of adults,10 and in some studies has persisted for periods of between 1 and 6 months.11,12 Anti-HAV IgG antibodies are made by all those immunised, although the current commercially available tests are not sensitive enough to detect the total anti-HAV antibodies in the majority of patients, especially many years after immunisation.9

3.3.1 Specimens

Standard methods for collection, transport and storage of serum or plasma are adequate for the detection of both anti-HAV IgM and IgG antibodies. IgM and IgG anti-HAV antibodies are also detectable in saliva, urine and faeces, but these are not recommended specimens for serology testing.

3.3.2 Test Sensitivity

The anti-HAV IgM and total antibody EIAs have sensitivities of greater than 95%, when tested on specimens from patients with typical symptoms. However sensitivity drops off when testing specimens from asymptomatic patients.13
3.3.3 Test Specificity

The anti-HAV IgM and total antibody EIAs have specificities of close to 100%.

3.3.4 Acceptance Criteria

Negative and positive controls should be included in all runs and fall within the reference range. These controls are usually included with the test kit.

3.3.5 Suitable Test Validation Criteria

- Adequate recording of serum and test kit storage and processing conditions
- Adequate record of QC monitoring of test kit performance

3.3.6 Suitable External QC programme

Participation in the NATA or RCPA quality control programmes.

3.3.7 Special Considerations

False positive IgMs occur in the elderly population and in the presence of other infectious agents. Therefore the test should only be performed in patients with a clinical picture of hepatitis A.

3.4 Nucleic Acid Testing

Amplification of viral RNA by reverse transcriptase-PCR is currently the most sensitive and widely used method of detection of HAV RNA, although it is available in only a few centres and rarely used for routine diagnosis. PCR may aid in cases of clinicobiological discrepancies for example demonstrating HAV shedding in relapsing hepatitis A where the presence of HAV IgM from the initial symptoms will render serology unhelpful. PCR may also be valuable in outbreak investigations and epidemiological studies to facilitate examination of relatedness between strains by nucleic acid sequencing.

HAV displays a high degree of antigenic and genetic conservation, because it does not readily accumulate mutations as in many other RNA viruses. HAV-RNA is detectable in serum by reverse transcription-PCR, 2 weeks before and 1 to 3 months after symptom onset. HAV-RNA detectability in stool lasts from a few days to up to 3 months.

3.4.1 Specimens

Standard method for collection, transport and storage of serum or plasma are adequate for detection and genotyping of strains for epidemiological studies. In addition to serum faeces are also adequate in particular circumstances such as the investigation of severe acute disease, relapsing disease, or outbreaks. Faeces is stable in solid mass or slurry for many years at -70°C, although serum is preferred.

3.4.2 Test Sensitivity

Highly sensitive; approaching 100%

3.4.3 Test Specificity

Highly specific; approaching 100%
3.4.4 Suitable External QC Programme

None available.

4 Agreed Typing And Subtyping Methods

Amplification and sequencing of viral isolates using nucleic acid based technology can help to identify cases of Hepatitis A that might be part of a common source outbreak.

The different HAV strains may be grouped by comparing a 168 nucleotide fragment of the VP1-P2A junction region and has been described using the method of Rico-Hesse and co-workers, for the genetic classification of poliovirus strains. This currently allows the differentiation of 6 genotypes (I, II, III, IV, V and VI), with genotypes I and III being further divided into subgenotypes, (IA, IB, IIIA and IIIB).

More recently molecular epidemiological studies have utilised a 390 nucleotide fragment from the VP1-P2B region, which incorporates the 2A region, one of the more variable regions of the genome. This allows the potential for greater differentiation of relatedness amongst HAV isolates. The study of other genome areas may also be useful in determining the frequency of recombination in HAV and the emergence of new genetic or antigenic variants.

4.1 SNOMED CT concepts

<table>
<thead>
<tr>
<th>SNOMED CT concept</th>
<th>SNOMED CT Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis, type A (disorder)</td>
<td>40468003</td>
</tr>
<tr>
<td>Hepatitis A virus (organism)</td>
<td>62944002</td>
</tr>
<tr>
<td>Hepatitis A antibody test (procedure)</td>
<td>313613002</td>
</tr>
<tr>
<td>Hepatitis A virus RNA assay (procedure)</td>
<td>122334007</td>
</tr>
<tr>
<td>Hepatitis A virus antibody, total measurement (procedure)</td>
<td>104374007</td>
</tr>
<tr>
<td>Hepatitis A virus antibody, IgM type (procedure)</td>
<td>88159009</td>
</tr>
</tbody>
</table>
5 References


