Acute hepatitis A to E, diagnosis and management

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Acute hepatitis A to E: Topics

• Frequency and epidemiological aspects

• Natural course
  • Predictors of severe hepatitis or acute liver failure

• Diagnostic challenges

• Treatment options (new perspectives)
Hepatitis A

Hepatitis A virus (HAV) genotypes and sub-genotypes are shown in a phylogenetic tree. The tree illustrates the nucleotide variation among different genotypes, with a scale indicating a 3% variation. The viral life cycle is depicted with an emphasis on the role of the ESCRT (Endosomal Sorting Complex Required for Transport) machinery in the formation of multivesicular bodies and infected liver vacuoles (ILV). The process involves the release of eHAV (encephalomyocarditis virus-like particles) into the plasma membrane.

Lemon S et al. J Hepatol 2018; 68:167
HAV susceptibility profiles in the EU (2000-2014)

Carrillo-Santistev e et al. Lancet Infect Dis. 2017; 17:306
HAV Epidemiology

• Large food-borne hepatitis A outbreaks may affect the increasingly susceptible European general population

• With the growing international food trade, frozen berries are a potential high-risk food
Hepatitis A outbreak in Europe: Associated with consumption of frozen berries

Severi E et al. Euro Surveill 2015;20:21192
Hepatitis A outbreak in Europe: Associated with consumption of frozen berries
Hepatitis A outbreak in Europe: Associated with consumption of frozen berries

- From January 2013 to August 2014, 1,589 hepatitis A cases were reported associated with the multistate outbreak
- 70% of cases were treated in-hospital for a median time of 6 days
  - 2 HAV-associated deaths
HAV a sexually transmitted disease

• Hepatitis A outbreaks among the men who have sex with men (MSM) community in European metropolitan cities
Hepatitis A outbreak in men who have sex with men (MSM) in Berlin

- Since November 14\textsuperscript{th} 2016, 37 acute hepatitis A cases in Berlin
  - 37 male patients (median age 31 years)
  - 30 MSM

[Graph showing distribution of cases by week and year]
Phylogentic analyses of HAV strains obtained from hepatitis A outbreaks in MSM in European cities


Rodríguez-Tajes S et al. Liver Int 2018;38:588
Clinical course of HAV infection

• Ultimately, hepatitis A resolves completely in >99% of the cases

• A relapse of symptoms has been reported in 3%-20% of clinical cases
  • The person who just recovered falls sick again with another acute episode, which appears several weeks after the first bout and is associated with re-elevation of ALT and viraemia manifested by re-detection of HAV RNA in blood and shedding of HAV in stools. Recovery is usually complete within 24 weeks
Trends in disease and complications of hepatitis A virus infection in the United States, 1999–2011: A new concern for adults?

HAV-related hospitalizations increased from 7.3% in 1999 to 24.5% in 2011

Age group-related hepatitis A death rate

## Acute hepatitis A-related mortality in Taiwan – Age matters

*Chen et al. Journal of Viral Hepatitis. 2016*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>≤19</th>
<th>20–39</th>
<th>40–59</th>
<th>≥60</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>257</td>
<td>1099</td>
<td>608</td>
<td>503</td>
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</tr>
<tr>
<td>Death, no. (%)</td>
<td>1 (0.4)</td>
<td>6 (0.5)</td>
<td>20 (3.3)</td>
<td>24 (4.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>6.6 ± 4.3</td>
<td>9.1 ± 42.7</td>
<td>9.8 ± 17.1</td>
<td>11.4 ± 17.1</td>
<td>.042</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>175</td>
<td>598</td>
<td>389</td>
<td>361</td>
<td></td>
</tr>
<tr>
<td>Death, no. (%)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>2 (0.5)</td>
<td>13 (3.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>7.0 ± 7.8</td>
<td>7.4 ± 4.9</td>
<td>8.2 ± 7.9</td>
<td>10.9 ± 11.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

LOS, length-of-stay in hospital.
Diagnostic challenges in acute HAV infection
Window phase of anti-HAV IgM antibodies

Window phase of anti-HAV IgM antibodies

Patients with acute hepatitis
N=684

Serology for acute viral hepatitis

Acute hepatitis of other etiologies (n=27)

Anti-HAV IgM(+) Retest of anti-HAV IgM

81%

Acute hepatitis A (group 1, n=553)

10%

Acute hepatitis A (group 2, n=67)

Acute hepatitis of other etiologies (group 3, n=37)

False-positive IgM antibodies to HAV in autoimmune events

- False-positive HAV IgM antibodies are well recognized
  - Only ~10% of seropositive patients may meet the clinical criteria for a diagnosis of acute HAV infection
- False-positive HAV IgM may represent a polyclonal B-cell autoimmune-mediated response
- Just as false positive antibodies can be produced during true infection with viral hepatitis, antibodies to viral hepatitis antigens can be produced in response to autoimmune clinical phenomena

Clinicians must recognize that false positive antibodies can result in diagnostic errors and delay in appropriate patient care

Severe acute hepatitis A – treatment options?
Hepatitis A: Milk thistle – A new treatment option?

Esser-Nobis K et al. Hepatology 2015;62:397-408
Steroids in severe/fulminant acute hepatitis A?
Zakaria HM *et al.* J Viral Hepat. 2018; Feb 3.

Steroid therapy in living and dead patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Living (n = 19)</th>
<th>Dead (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid therapy</td>
<td>15 (78.9)</td>
<td>3 (21.4)</td>
<td>.001</td>
</tr>
</tbody>
</table>

N=33 children with severe or fulminant acute hepatitis A
HAV post-exposure prophylaxis (PEP)
Effectiveness of hepatitis A vaccination among HIV-positive individuals during a large HAV outbreak in Taipei

![Graph showing cumulative HAV infections over duration of follow-up (months). The graph compares unvaccinated and vaccinated groups.]

**Number at risk**

<table>
<thead>
<tr>
<th>Duration of follow-up (Months)</th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1515</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>527</td>
<td>848</td>
</tr>
<tr>
<td>10</td>
<td>247</td>
<td>954</td>
</tr>
<tr>
<td>15</td>
<td>102</td>
<td>886</td>
</tr>
<tr>
<td>20</td>
<td>33</td>
<td>387</td>
</tr>
<tr>
<td>25</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Lin KY et al. Hepatology 2018; Jan 12
Hepatitis E Virus (HEV)-Infektion
Epidemiology of hepatitis E virus infection

Number of reported laboratory-confirmed cases of Hepatitis E virus (HEV) by country, 2006–2015*

*2015 data not complete

Acute hepatitis E and the risk of liver failure?

- Differences between EU/US and Asian countries?
Acute HEV infection is very rare in adult Americans with ALF (i.e., 0.4%) and could not be implicated in any indeterminate, autoimmune, or pregnancy-related ALF cases
The global burden of HEV outbreaks: Case fatality rate in the overall population and pregnant women

Hakim MS et al. Liver Int 2016 (epub)
Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy?

### Differences in mean HEV RNA concentrations

<table>
<thead>
<tr>
<th>Group</th>
<th>Status</th>
<th>Mean viral load (copies/mL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVH (N = 120)</td>
<td>Pregnant</td>
<td>769</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AVH (N = 50)</td>
<td>Non-pregnant women and girls</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>ALF (N = 52)</td>
<td>Pregnant</td>
<td>129.984</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALF (N = 28)</td>
<td>Non-pregnant women and girls</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>AVH (N = 20)</td>
<td>Men and boys</td>
<td>15</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>ALF (N = 5)</td>
<td>Men and boys</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Genetic variability of HEV and clinical implications

• Association of HEV genotypes with clinical course of symptomatic infection:
  • HEV-1 and HEV-2: mainly contribute to severe acute hepatitis
  • HEV-3, HEV-4 and HEV-7: can lead to chronic hepatitis in immunocompromised patients

• HEV-4 associated with more severe outcomes than HEV-3

• HEV-1 but not HEV-3 or HEV-4 associated with severe forms of liver disease and complications in pregnant women

van Tong H et al. EBioMedicine 2016; 11: 31-42
Genetic variability of HEV and clinical implications

van Tong H et al. EBioMedicine 2016; 11: 31-42
Underlying chronic liver disease – a risk factor for disease severity in acute HEV infections

512 studied cases

301 acute-on-CLDs (58.8%)

211 acute without underlying CLDs (41.2%)

107 Cirrhotic (35.3%)

194 Non-cirrhotic (64.7%)

86 severe (80.4%)

20 fatal cases (18.7%)

10 icteric (9.4%)

7 anicteric (6.6%)

4 asymptomatic (3.8%)

62 severe (32.0%)

14 fatal cases (7.2%)

100 icteric (51.5%)

21 anicteric (10.8%)

11 asymptomatic (5.8%)

67 severe (31.8%)

11 fatal cases (5.2%)

101 icteric hepatitis (47.9%)

28 anicteric hepatitis (13.3%)

15 asymptomatic (7.1%)

Zhang et al. Aliment Pharmacol Ther 2017;45:701
Diagnostic challenges in hepatitis E virus infection
Laboratory diagnosis of HEV infection

- Incubation period for HEV is ~15–60 days
  - HEV RNA is detected ~3 weeks post-infection in blood and stool (shortly before onset of symptoms)
- At clinical onset biochemical markers become elevated - First IgM followed by IgG
Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive.

**Acute HEV infection can be diagnosed by detection of anti-HEV antibodies**
- IgM, IgG or both by enzyme immunoassays in combination with HEV NAT
- Serological testing relies upon detection of anti-IgM and (rising) IgG

**Laboratory diagnosis of HEV infection**

<table>
<thead>
<tr>
<th>Infection status</th>
<th>Positive markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current infection – acute</strong></td>
<td>• HEV RNA +</td>
</tr>
<tr>
<td></td>
<td>• HEV RNA + anti-HEV IgM</td>
</tr>
<tr>
<td></td>
<td>• HEV RNA + anti-HEV IgG*</td>
</tr>
<tr>
<td></td>
<td>• HEV RNA + anti-HEV IgM + anti-HEV IgG</td>
</tr>
<tr>
<td></td>
<td>• Anti-HEV IgM + anti-HEV IgG (rising)</td>
</tr>
<tr>
<td></td>
<td>• HEV antigen</td>
</tr>
<tr>
<td><strong>Past infection</strong></td>
<td>• Anti-HEV IgG</td>
</tr>
</tbody>
</table>

*Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive.

EASL CPG HEV. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]
## Diagnostic Performance of Five Assays for Anti-Hepatitis E Virus IgG and IgM

<table>
<thead>
<tr>
<th>Reference reagent or patient sample</th>
<th>Detection limit for assay:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mikrogen</td>
</tr>
<tr>
<td><strong>Anti-HEV IgM</strong></td>
<td></td>
</tr>
<tr>
<td>WHO 95/584 100 IU/mL (IU/mL)</td>
<td>16</td>
</tr>
<tr>
<td>Sample 17176/13</td>
<td>1/53</td>
</tr>
<tr>
<td>Sample 4290/14</td>
<td>1/43</td>
</tr>
<tr>
<td><strong>Anti-HEV IgG</strong></td>
<td></td>
</tr>
<tr>
<td>WHO 95/584 100 IU/mL (IU/mL)</td>
<td>0.9</td>
</tr>
<tr>
<td>Sample 17176/13</td>
<td>1/86</td>
</tr>
<tr>
<td>Sample 4290/14</td>
<td>1/230</td>
</tr>
</tbody>
</table>
Summary

• The range of sensitivity for anti-HEV detection is broad (42% to 96%) – no gold standard available!

• The detection limit varied up to 19-fold for IgM and 17-fold for IgG between assays

• Axiom-Test, followed by DiaPro-Test and DSI with highest sensitivity for anti-HEV IgM

• Mikrogen- and DSI assay showed more frequently unspecified anti-HEV IgM reactions

• HEV RNA detection in 13 anti-HEV IgM negative samples
  • Issue of sensitivity of the assays or acute HEV infection not leading to anti-HEV-IgM production
  • HEV RNA may be warranted as a complement in the laboratory diagnosis of ongoing HEV infection
Treatment of severe acute hepatitis E
Treatment of severe acute hepatitis E with ribavirin

Treatment of autochthonous acute HEV infection with short-term ribavirin: a retrospective multicenter study

- Effectiveness a short-term RBV (600–1200 mg / day) in patients with acute HEV infection (N=21)
- Therapy stopped when HEV RNA undetectable
- 9 patients had a severe HEV infection
  - PT index decline, liver failure
- 6/9 patients were over 70 years old
- 4/9 patients received immunosuppressive therapy
- Average therapy duration: 26 days
- HEV RNA became undetectable and ALT levels normalised in all patients
- 2 patients died (RBV initiated late during the course when hepatic encephalopathy already existed)

Péron JM et al. Liver Int 2015
Treatment of acute HEV infection

• Acute HEV infection does not usually require antiviral therapy*
• Most cases of HEV infection are spontaneously cleared
  • Some patients may progress to liver failure
  • Ribavirin
    • Early therapy of acute HEV may shorten course of disease and reduce overall morbidity

Recommendation

• Ribavirin treatment may be considered in cases of severe acute hepatitis or acute-on-chronic liver failure

*Grade of evidence A
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]
Steroid therapy for severe acute HEV infections?

- **AST (UI)**
- **INR**

Sebode M. et al. BMC Gastroenterol 2014;14:191
Steroid therapy for severe acute HEV infections?

- HEV RNA by PCR out of peripheral blood
- HEV RNA by PCR out of liver tissue

Sebode M. et al. BMC Gastroenterol 2014;14:191
Extrahepatic manifestations of HEV infection

- Meningitis
- Thyroiditis
- Neuralgic amyotrophy
- Cryoglobulinemia
- Myocarditis
- Pancreatitis
- Glomerulonephritis
- Lymphoma/thrombocytopenia
- Arthralgia/myalgia
- Guillain-Barré syndrome

Non-enveloped viruses being excreted in stool

Pischke et al., Journal of Hepatology 2017;66(5):1082-1095
Acute hepatitis B
Treatment indication for patients with acute hepatitis B

Recommendations:

• More than 95% of adults with acute HBV hepatitis do not require specific treatment, because they will fully recover spontaneously (Evidence level II-2, grade of recommendation 1)

• Only patients with severe acute hepatitis B, characterized by coagulopathy or protracted course, should be treated with NA and considered for liver transplantation (Evidence level II-2, grade of recommendation 1)
NUC treatment for severe acute hepatitis B?

• Definition of severe?

INR > 1.5 or Prothrombin index ≤ 40%?

• Lower rate of anti-HBs seroconversion due to NUC treatment?
**Early nucleoside analog therapy for acute hepatitis B**

**Survival**

- **LAM vs. control**
- **Age >45 vs. <45 years**
- **HBV DNA decline** Fast vs. slow*

Randomisation: Placebo (n=40) or Lamivudine 100 mg (n=40)

*Fast HBV DNA decline: ≥ 2 log within 2 weeks*
Early nucleoside analog therapy for acute hepatitis B

Early initiation of therapy with lamivudine was associated with a reduction in the rate of liver failure (9% vs. 35%)

Randomisation: Placebo (n=40) or Lamivudine 100 mg (n=40)

*Fast HBV DNA decline: ≥ 2 log within 2 weeks
Risk factors for long-term persistence of serum HBsAg following acute HBV infection in Japanese adults

Importance of timing of NUC treatment (before/after Week 8)

- Onset of NA treatment over 8 weeks
- Onset of NA treatment within 8 weeks

Log-rank test, P<0.0001

 Patients at risk:
- Onset over 8 weeks: 17, 15, 12, 9, 4, 2
- Onset within 8 weeks: 86, 66, 15, 0, 0

Ito K et al. Hepatology 2014;59: 89-97
Acute hepatitis C
Acute hepatitis C – whom to treat?

• How to predict a chronic course?
Dynamics of HCV RNA levels during acute hepatitis C

## Prediction of spontaneous HCV clearance

### (A) Score 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-off</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>IL28B</em> rs12979860</td>
<td>C/C</td>
<td>1</td>
</tr>
<tr>
<td>Age at infection</td>
<td>≤35</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>≥6</td>
<td>1</td>
</tr>
</tbody>
</table>

**HCV-RNA log drop from diagnosis until week 4**

- Increase or log drop <1.0: 0
- Log drop ≥1.0-<2.5: 1
- Log drop ≥2.5: 2

**Maximum**: 5
DAA treatment of acute hepatitis C

Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study

Lancet Infect Dis 2017; 17: 215-22
Treatment of acute hepatitis C with SOF/LDV

Deterding K et al. Lance Infect Dis 2017; 17: 2115
Treatment of acute hepatitis C
A cost-effectiveness approach

Bethea ED et al. Hepatology 2018; 67: 837
Considerations when treating severe acute hepatitis – timing matters

TIME

Variable time interval to hepatitis flare

Leading cause (virus, drugs, immune mechanisms)

Viral load

ALT

Hepatic Failure

Chronic Hepatitis

Acute Hepatitis (transient)

“silent”


FCH = fibrosing cholestatic hepatitis
Considerations when treating severe acute hepatitis – timing matters


FCH = fibrosing cholestatic hepatitis