Current concepts in hepatitis E. Does it exist in Greece?

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Lab of Internal Medicine
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Thessaly University
Discovery of Hepatitis E

• 1955-56: Large epidemic of viral hepatitis in Delhi ($\approx$30000 cases of jaundice)

• Initially thought to be classic example of epidemic acute hepatitis A: "waterborne, acute & self-limited"

• Subsequent serologic testing of samples from the Delhi and other outbreaks in India determined that they could not be attributed to hepatitis A = > "Epidemic non-A, non-B hepatitis"

Discovery of Hepatitis E

• Human volunteer given pooled stool extract -> prospectively collected stool & serum
  – **Day 37**: nausea, fever and abdominal pain
  – **Day 43**: jaundice, ↑↑↑AST, ALT
  – Symptomatic for 25 days

• **Electron microscopy** on acute phase stool samples: 34 nm virus like particles

Balayan, Intervirology 1983.
Molecular virology

- small icosahedral, nonenveloped, single-stranded, positive-sense RNA virus
- 27-34 nm
- genome 7.2 kb
- 3 overlapping reading frames (ORF1, ORF2, ORF3)

Molecular virology

- 5 different genotypes, but only one serotype
- **Genotype 1-4**: immunopathogenic

HEV

Geographical Distribution & Genotypes

- **Genotype 1 and 2**: common cause of epidemic hepatitis E
- **Genotype 3 and 4**: zoonoses found mostly in swine

Aggarwal, Hepatology 2011
## World-Wide Burden of Hepatitis E

Global prevalence of anti-HEV IgG in different populations

<table>
<thead>
<tr>
<th>Regions</th>
<th>Prevalence (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-to-medium income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kashmir region</td>
<td>49.6</td>
<td>Khuroo et al[35]</td>
</tr>
<tr>
<td>India</td>
<td>23.8-28.7</td>
<td>Mathur et al[76]</td>
</tr>
<tr>
<td>Myanmar</td>
<td>32.0</td>
<td>Nakai et al[77]</td>
</tr>
<tr>
<td>Egypt</td>
<td>67.7</td>
<td>Stoszek et al[71]</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>22.5</td>
<td>Labrique et al[78]</td>
</tr>
<tr>
<td>China</td>
<td>19.7</td>
<td>Dong et al[79]</td>
</tr>
<tr>
<td>Mexico</td>
<td>36.6</td>
<td>Alvarado-Esquível et al[80]</td>
</tr>
<tr>
<td>Thailand</td>
<td>14.0</td>
<td>Gonwong et al[75]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>42.7</td>
<td>Junaid et al[81]</td>
</tr>
<tr>
<td>Industrialized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>17.0</td>
<td>Wenzel et al[82]</td>
</tr>
<tr>
<td>United States</td>
<td>6.0</td>
<td>Teshale et al[83]</td>
</tr>
</tbody>
</table>
Hepatitis E Seroprevalence in Europe: A meta-analysis

Hartl, Viruses 2016.
Hepatitis E
Does it exist in Greece?

Risk factors:
- transfusion
- occupation
- hospitalization
- anti-HCV (+)
- anti-HBc (+)

Psichogiou, J Hepatol 1995.
Hepatitis E
Does it exist in Greece?

Table 1. Characteristics of the individuals tested for anti-HEV and the seroprevalence of IgG anti-HEV by EIA and Western blot assay

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Males</th>
<th>Females</th>
<th>Age Range</th>
<th>Median</th>
<th>IgG Anti-HEV positivity by EIA (%)</th>
<th>Confirmation by Western blot (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents of the Epirus region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy blood donors</td>
<td>2636</td>
<td>2223</td>
<td>413</td>
<td>18-60</td>
<td>42</td>
<td>6 (0.23)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Refugees</td>
<td>350</td>
<td>229</td>
<td>121</td>
<td>17-57</td>
<td>39</td>
<td>17 (4.85)</td>
<td>5/8 (62.5)</td>
</tr>
<tr>
<td>Children</td>
<td>165</td>
<td>82</td>
<td>83</td>
<td>0-14</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IDUs*</td>
<td>65</td>
<td>47</td>
<td>18</td>
<td>21-40</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multiply transfused patients†</td>
<td>62</td>
<td>36</td>
<td>26</td>
<td>15-73</td>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with chronic viral hepatitis‡</td>
<td>75</td>
<td>41</td>
<td>34</td>
<td>22-68</td>
<td>45</td>
<td>4 (5.30)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Chronic hemodialysis patients</td>
<td>149</td>
<td>99</td>
<td>50</td>
<td>12-80</td>
<td>48</td>
<td>2 (1.34)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Residents of Agrinio area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy blood donors</td>
<td>380</td>
<td>250</td>
<td>130</td>
<td>20-60</td>
<td>41</td>
<td>2 (0.53)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Chronic hemodialysis patients</td>
<td>62</td>
<td>41</td>
<td>21</td>
<td>18-79</td>
<td>50</td>
<td>6 (9.70)</td>
<td>6/6 (100)</td>
</tr>
</tbody>
</table>

* The addicts were residents of Athens, Greece.
† Patients with hematologic malignancies or hemolytic hemoglobinopathies.
Hepatitis E
Does it exist in Greece?

351 patients (5 hemodialysis units in Thessaly)

- 5.7% HBsAg +
- 23.6% HCV +
- 17 (4.8%) HEV +

9.8% Karditsa

Hemodialysis patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>20 (5.5)</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>245 (66.9)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>175 (47.8)</td>
</tr>
<tr>
<td>HBeAg</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>73 (19.9)</td>
</tr>
<tr>
<td>HBV-DNA</td>
<td>15 (4.1)</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>88 (24)</td>
</tr>
<tr>
<td>Anti-HEV</td>
<td>15 (4.1)</td>
</tr>
</tbody>
</table>


Mina & Dalekos, WJG 2010.
Hepatitis E
Does it exist in Greece?

Implication for an alternative parenteral spread of HEV infection

<table>
<thead>
<tr>
<th>Prevalence (%) of viral hepatitides and HTLV-I/II infection markers in patients and in healthy control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n=204)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Anti-HTLV-I/II (%)</td>
</tr>
<tr>
<td>HBsAg (%)/95% CI</td>
</tr>
<tr>
<td>Anti-HBs (%)/95% CI</td>
</tr>
<tr>
<td>Anti-HBc (%)/95% CI</td>
</tr>
<tr>
<td>Anti-HBe (%)/95% CI</td>
</tr>
<tr>
<td>Anti-HDV (%)</td>
</tr>
<tr>
<td>Anti-HCV (%)/95% CI</td>
</tr>
<tr>
<td>Anti-HEV (%)/95% CI</td>
</tr>
</tbody>
</table>

Epidemiological and demographic factors in anti-HEV positive and negative patients

<table>
<thead>
<tr>
<th></th>
<th>HEV pos</th>
<th>HEV neg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.1±5.3</td>
<td>61.4±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/1</td>
<td>163/29</td>
<td>NS</td>
</tr>
<tr>
<td>Time from operation (months)</td>
<td>91.3±65.0</td>
<td>58.65±52.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Location of operation (Greece/Abroad)</td>
<td>9/2</td>
<td>150/42</td>
<td>NS</td>
</tr>
<tr>
<td>Time of operation (before/after 1991)</td>
<td>7/4</td>
<td>78/114</td>
<td>NS</td>
</tr>
</tbody>
</table>

Hepatitis E
Does it exist in Greece?

HEV RNA detection: 3%

Occurrence of human enteric viruses in commercial mussels at retail level in three European countries.

HEV RNA detection: 3.42%

Harmonised investigation of the occurrence of human enteric viruses in the leafy green vegetable supply chain in three European countries.
Hepatitis E
Does it exist in Greece?

Seroprevalence of hepatitis E virus in blood donors in Greece

- 265 blood donors (Athens)
- anti-HEV IgG (EIAgen; Adaltis Inc, Milan, Italy)
- all positive donors resided in urban areas
- none reported an occupation related to swineherds handling
- none of them had a recent history (past year) of travel in endemic areas
- 6/23 anti-HEV IgG (+) abnormal AST

Pittaras, Vox Sang 2014
Increased awareness for HEV infections

Proportion of reported cases of acute viral hepatitis in Germany

Robert-Koch-Institute data.
Routes of HEV transmission

proven modes (solid arrows)
potential modes (dashed arrows)

Sayed, Hepatology 2015
Avoid eating uncooked meat!
The best way to prevent foodborne transmitted hepatitis E

- HEV can be inactivated by temperatures >70°C

- Cooking meat for 1 minute at 70°C => 0.48 log reduction in concentration of infectious HEV particles

- Heating at 95°C reduced the concentration another 3.67 log

Schielke, Virol J 2011
HEV can also be transmitted by blood transfusion...

- 225,000 blood donations tested in UK
- 1/2848 donations HEV RNA (+)
- all genotype 3
- transmission rate: **42%**
- 2/3 of patients cleared infection spontaneously
- recipient immunosuppression delayed or prevented seroconversion & extended the duration of viremia

Hewitt, Lancet 2014
HEV can also be transmitted by blood transfusion.

<table>
<thead>
<tr>
<th>Country</th>
<th>Blood Donors HEV RNA Positive</th>
<th>HEV IgG Seroprevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midi-Pyrénées, Southwest France *</td>
<td>1:1438 (1:2200) **</td>
<td>52.5%</td>
<td>Gallian et al., 2014 [15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mansuy et al., 2011 [18]</td>
</tr>
<tr>
<td>Germany</td>
<td>1:1200</td>
<td>29.5%</td>
<td>Vollmer et al., 2012 [16]</td>
</tr>
<tr>
<td></td>
<td>1:4525</td>
<td></td>
<td>Baylis et al., 2012 [36]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1:2671</td>
<td>27.0%</td>
<td>Slot et al., 2013 [37]</td>
</tr>
<tr>
<td></td>
<td>1:7000</td>
<td></td>
<td>Ijaz et al., 2012 [38]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beale et al., 2011 [39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dalton et al., 2008 [4]</td>
</tr>
<tr>
<td>Sweden</td>
<td>1:7986</td>
<td>NA</td>
<td>Baylis et al., 2012 [36]</td>
</tr>
<tr>
<td>Austria</td>
<td>1:8416</td>
<td>13.5%</td>
<td>Fischer et al., 2015 [40]</td>
</tr>
<tr>
<td>Scotland</td>
<td>1:14,520</td>
<td>4.7%</td>
<td>Cleland et al., 2013 [35]</td>
</tr>
</tbody>
</table>

Seroprevalence studies have been restricted to those employing the highly-sensitive and partially-validated Wantai anti-HEV IgG assay. HEV RNA was genotype 3 in all cases. * deconstructed solvent-detergent treated mini-pools. NA: not available. ** Midi-Pyrénées/Méditerranées: 1:1438, France: 1:2200.

Hartl, Viruses 2016.
HEV can also be transmitted by blood transfusion...

- Plasma donations tested positive for HEV RNA:
  - **Sweden**, 1 of 7986
  - **Germany**, 1 of 4525
  - **10% of plasma pools** tested positive for HEV RNA in Germany

- This high number of HEV-contaminated blood donations indicates that most HEV infections take a subclinical course.

### Table 1  Analysis of plasma fractionation pools for the presence of HEV RNA

<table>
<thead>
<tr>
<th>Source of pools</th>
<th>No. positive/no. analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>3/34</td>
</tr>
<tr>
<td>Europe/North America</td>
<td>0/3</td>
</tr>
<tr>
<td>North America</td>
<td>1/4</td>
</tr>
<tr>
<td>Middle East</td>
<td>0/11</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>4/23</td>
</tr>
<tr>
<td>Overall</td>
<td>8/75</td>
</tr>
</tbody>
</table>

Baylis, Vox Sang 2012.
Diagnosis

Antibody isotypes and time course

- **IgM anti-HEV:**
  - appear within 3-4 days of the onset of jaundice
  - persist for a few months (average 5 months)

- **IgG anti-HEV:**
  - appear shortly after the IgM antibody response
  - persist from 14 months to 14 years

Performance of assays for anti-HEV antibodies varies: Wantai® kit seems to be superior.
Performance of assays for anti-HEV antibodies varies: Wantai® kit seems to be superior

E2S domain of HEV capsid is bacterially expressed Peptide contains all identified neutralizing epitopes

HEV RNA Assays: Target Region of Primers

The available amplification-based assays vary in their performance characteristics.

Wedemeyer, Gastroenterology 2012.
Standardization of Hepatitis E Virus (HEV) Nucleic Acid Amplification Technique-Based Assays: an Initial Study To Evaluate a Panel of HEV Strains and Investigate Laboratory Performance

Sally A. Baylis,* Kay-Martin Hanschmann, Johannes Blümel, and C. Micha Nübling on behalf of the HEV Collaborative Study Group‡

FIG. 2. Analysis of viral loads (log_{10} copies/ml) by laboratory and sample. (a) HRC-HE104 genotype 3a. (b) JRC-HE3 genotype 3b. (c) RKI genotype 3f. (d) HRC-HE15 genotype 4c.

100- to 1,000-fold difference in sensitivity between the majority of assays, independent of the virus strain.
Undetectable HEV RNA does not rule out infection

- Sensitivity depends on:
  - how early the patient presents
  - timely collection of specimens
  - rapid transport
  - processing
  - viral genotype inclusivity

Comparison of HEV RT-PCR Assays
(Mokhtari et al., J Clin Virol Sept 2013)

- 5 Assays
- 47 samples with acute hepatitis E
- Detection Rates: 100%, 100%, 97%, 97% & 83%

Clinical course of HEV infection

Wedemeyer, Gastroenterology 2012.
Clinical presentation
Acute Hepatitis

• Asymptomatic carriers to fulminant hepatitis

• Incubation period: 3-8 weeks

• Symptomatic phase: days to weeks (mean 4-6 weeks)

• ↑ risk of acute liver failure:
  – pregnant women
  – preexisting liver disease
  – immunosuppression

HEV infection during pregnancy: Why is the disease stormy? Not really known!

- malnutrition superimposed on the normal demands of pregnancy
- "Th2 bias" $\rightarrow$ ↓ macrophage activation
- ↑ steroid hormones:
  - promote viral replication
  - immunosuppressive
- ↓ expression of the progesterone receptor
- ↑ nutritional demands $\rightarrow$ ↑ ATP/ADP-sensitive kinase AMP $\rightarrow$ ↑ mTOR

Clinical presentation

Hepatitis E virus infection beyond the liver?

Pische, J Hepatol (in press).
Clinical presentation
Chronic hepatitis

- **Definition:**
  - ↑AST/ALT
  - HEV RNA +
  - >3-6 months

- **Genotype 3**

- **Risk factors:**
  - immunosuppression, solid organ transplantation, HIV infection, hemodialysis, hematological malignancies

- **Rapidly progresses** to cirrhosis (10% in 2 years) and end-stage liver disease

Infections in organ transplant recipients

- retrospective analysis of data of 17 centres
- 85 cases of autochthonous HEV infection in solid organ transplant recipients
- 56/85 (65.9%) developed chronic hepatitis E
- **predictive factors** associated with chronicity:
  - use of tacrolimus rather than cyclosporine
  - low platelet count at diagnosis of HEV infection
- 18/56 (32.1%) achieved sustained HEV clearance following a **reduction in the dose of immunosuppression**

Kamar, Gastroenterology 2011
Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient

Schlosser, J Hepatol 2012.
Acute hepatitis E on other Chronic Liver Disease

• 228 pts with acute HEV with underlying chronic HBV

• more severe in cirrhotic than in non-cirrhotic
  – complications 77.7% vs. 28.4%
  – mortality 21.3% vs 7.5%

• risk factors in non-cirrhotic patients
  – intermediate HBV DNA levels
  – alcohol consumption
  – diabetes
  – kidney diseases

Chen, WJG 2016
Acute Hepatitis E
Often Misdiagnosed

- Drug or herbal-induced liver disease
- Atypical viral hepatitis (CMV, EBV, adenovirus)
- Acute decompensation of chronic liver disease
- Acute cholecystitis
- Nonalcoholic steatohepatitis
- Acute liver injury of indeterminate cause
- Other???
The diagnosis of DILI is not secure in without testing for HEV

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>300 pts DILIN network</td>
<td>681 pts ALF</td>
<td>47 pts DILI suspected</td>
<td>80 pts ALF, acute hepatitis</td>
<td>80 pts acute severe liver injury</td>
</tr>
<tr>
<td>anti-HEV IgG</td>
<td>16%</td>
<td>43%</td>
<td></td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>anti-HEV IgM</td>
<td>3%</td>
<td>0.4%</td>
<td></td>
<td>21.4%</td>
<td>6.2%</td>
</tr>
<tr>
<td>HEV RNA</td>
<td>1.3%</td>
<td>0%</td>
<td></td>
<td>10%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
Severe and/or acute non-A, non-B, non-C hepatitis with autoimmune features:
Consider acute HEV hepatitis, not just AIH!

- 4 acute HEV among 13 acute non-A, non-B, non-C hepatitis cases (30.7%, during 2 years period)
- 3/4 misdiagnosed as acute AIH
- 1/4 misdiagnosed as AIH relapse in AIH patient under immunosuppression

Zachou, Gatselis, Dalekos (data in preparation)
<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>50</td>
<td>65</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>sex</td>
<td>♀</td>
<td>♂</td>
<td>♂</td>
<td>♂</td>
</tr>
<tr>
<td>medical Hx</td>
<td>none</td>
<td>alcohol</td>
<td>NHL</td>
<td>AIH, ITP</td>
</tr>
<tr>
<td>AST/ALT (U/L)</td>
<td>&gt;1000</td>
<td>893/960</td>
<td>455/1163</td>
<td>589/475</td>
</tr>
<tr>
<td>bilirubin (mg/dL)</td>
<td>14.7</td>
<td>8.77</td>
<td>4.81</td>
<td>1.3</td>
</tr>
<tr>
<td>INR</td>
<td>1.25</td>
<td>1.42</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>1770</td>
<td>2400</td>
<td>1800</td>
<td>712</td>
</tr>
<tr>
<td>SMA</td>
<td>&gt;1/320</td>
<td>&gt;1/320</td>
<td>&gt;1/320</td>
<td>&gt;1/320</td>
</tr>
<tr>
<td>animal contact</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>travel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>liver biopsy</td>
<td>interface hepatitis, emperipolesis, rosetting</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>simplified score AIH</td>
<td>definite</td>
<td>probable</td>
<td>probable</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
Severe and/or acute non-A, non-B, non-C hepatitis with autoimmune features: Consider acute HEV hepatitis, not just AIH!

- Treatment: Pre + MMF
- AEs:
  - hepatic encephalopathy
- Treatment discontinuation at month 1

Patient B

Acute Hepatitis E

Zachou, Gatselis, Dalekos (data in preparation)
Hepatitis E - Histology

- no HEV-typical characteristics
- differential diagnosis AIH may be difficult
HEV infection & Autoimmune Hepatitis

Hypotheses:

a) triggering factor?
b) risk factors for acquiring HEV?
c) cross reactivity?
d) false AIH diagnosis?

anti-HEV IgG prevalence

Pischke, PLoS ONE 2014
HEV infection & Autoimmune Hepatitis

anti-HEV IgG prevalence

<table>
<thead>
<tr>
<th></th>
<th>AIH n=354</th>
<th>Blood donors n=5926</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>26.7%</td>
<td>29.9%</td>
</tr>
</tbody>
</table>

P > 0.05

Fig. 1. Anti-HEV IgG seroprevalence in the 10-year age groups of AIH patients and the general population in the Netherlands.

Treatment

• acute hepatitis E does not require treatment in immune-competent individuals

• data on treatment of HEV immunocompromised, frequently chronic hepatitis is sparse, and, therefore, patient tailored therapy is the best option
Treatment:
The most important step that should be considered is whether immunosuppression can be reduced.

“A double-edged sword”

- 25% HEV clearance by this strategy
- ↑ risk of transplant organ rejection

- pegylated interferon: side effects
- ribavirin is an option

Kamar, Transplantation 2010.
• 59 patients treated with ribavirin
• median dose: 8.1 mg/kg/day
• median duration: 3 months (1-18)
• Results:
  – HEV clearance (eot): 95%
  – SVR: 46/59 (78%)
  – 10 patients experienced a recurrence of HEV replication
  – 6/10 underwent re-treatment: 4 SVR24, 1 responder on treatment, 1 SVR12
  – no difference between duration ≤3 months vs >3 months
Treatment:
Modifications/Reduction in immunosuppression

- **Steroids**: did not affect viral replication
- **Calcineurin inhibitors** (CsA and tacrolimus) & **Rapamycin and Everolimus**: stimulate HEV replication
- **Mycophenolate**: inhibits HEV replication
- Beneficial effect of combining ribavirin with MMF

Treatment: Sofosbuvir inhibits HEV replication in vitro and results in an additive effect when combined with Ribavirin

Sofosbuvir inhibits the replication of HEV (GT-3) both in subgenomic replicon systems as well as a full-length infectious clone.

Dao Thi, Gastroenterology 2016.
Treatment: Sofosbuvir shows antiviral activity in a patient with chronic hepatitis E virus infection

van der Valk, J Hepatol 2017.
Vaccination

- HEV 239 – genotype 1 and 4 (Hecolin®)
- HEV 239 (n=56,032) vs placebo (n=56,302)
- Endpoint: prevention of hepatitis E during 12 months
- 15 participants in the placebo group developed hepatitis E vs 0 in vaccine group
- Efficacy 100%
- No serious adverse events

Approved in China in 2012.
Still unclear if it is protective against HEV-GT3.
Its value for use in industrialized nations has yet to be determined.

Take home messages
“Hepatitis E: The Dogma should be revised”
“Time to change the textbooks”

- common in the developing world but **also may occur in the West as autochthonous infection (a zoonosis)**
- **parenteral transmission** is indisputable
- causes: acute self-limited disease, acute liver failure, **acute-on-chronic liver injury and chronic hepatitis with complications**
- may be **misdiagnosed** as DILI, AIH etc.
- **testing for hepatitis E should be part of the diagnostic analysis** of all patients with acute or chronic hepatitis that cannot be explained by other causes
- **accurate diagnostic assays, preventive measures, vaccines and therapy** are definitely needed
Thank you for your attention!