Hepatitis E

in humans

Alfredo Pérez (Hospital 12 de Octubre, Madrid. Spain)
**VIRAL HEPATITIS**

Those caused by different viruses with primary tropism for the liver tissue

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genome</strong></td>
<td>RNA (7,5 kb)</td>
<td>DNA (3,2kb)</td>
<td>RNA (10 kb)</td>
<td>RNA (1,7 kb)</td>
<td>RNA (7,6 kb)</td>
</tr>
<tr>
<td><strong>Incubation</strong></td>
<td>14-50 days</td>
<td>30-180 days</td>
<td>14-160 days</td>
<td>21-42 days</td>
<td>15-63 days</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>Fecal-oral</td>
<td>Parenteral, sexual, vertical</td>
<td>Parenteral(UDI)</td>
<td>Parenteral</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes (HBV)</td>
<td>Yes (China)</td>
</tr>
<tr>
<td><strong>Chronic Infection</strong></td>
<td>No</td>
<td>Yes &gt;80% in Nb. &lt;5% in adults</td>
<td>Yes 70%-85%</td>
<td>Yes Coinfection: 5% Superinf.: &gt;80%</td>
<td>Rare (Immunocompromissed 50% en TOS)</td>
</tr>
</tbody>
</table>
HEV Genotypes responsible for most infections in humans: HEV1, HEV2, HEV3 and HEV4 (a single serotype)

Taxonomy
Family Hepeviridae
- Genre Orthohepevirus:
  A: includes genotypes 1-7
  B: chicken virus
  C: rat, ferret virus
  D: bat virus
- Genre Piscihepevirus

Debing Y. et al. 2016. J Hepatol
**Hepatitis E, until recently (early years of this century) thought to be limited to certain developing countries...**

<table>
<thead>
<tr>
<th><strong>HEV</strong> (Developing region)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPIDEMIOLOGY</strong></td>
</tr>
<tr>
<td>Reservoir</td>
</tr>
<tr>
<td>Transmission</td>
</tr>
<tr>
<td>Seroprevalence</td>
</tr>
<tr>
<td>Outbreaks</td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
</tr>
<tr>
<td>Age of infection</td>
</tr>
<tr>
<td>Syntomatic cases</td>
</tr>
<tr>
<td>Evolution</td>
</tr>
<tr>
<td>Chronic infection</td>
</tr>
<tr>
<td>Severe in pregnancy</td>
</tr>
</tbody>
</table>

The Two Faces of Hepatitis E Virus

Eyasu H. Teshale, Dale J. Hu, and Scott D. Holmberg
Division of Viral Hepatitis, National Center for HIV, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Hepatitis E is a puzzling double-faced disease, with contrasting epidemiological and disease patterns in developing and industrialized countries.
### HEV: two different epidemiological and clinical scenarios

<table>
<thead>
<tr>
<th></th>
<th>DEVELOPING REGIONS (High-endemicity areas)</th>
<th>DEVELOPED REGIONS (Low-endemicity areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td>Genotypes 1 y 2</td>
<td>Genotypes 3 y 4</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reservoir</td>
<td>Humans</td>
<td>Animals (mainly swines)</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral (water)</td>
<td>Contaminated meat/direct contact</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Seroprevalence</td>
<td>Elevated</td>
<td>Variable</td>
</tr>
<tr>
<td>Outbreaks</td>
<td>Yes</td>
<td>No (sporadic)</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of infection</td>
<td>15-30 y.</td>
<td>&gt;50 y.</td>
</tr>
<tr>
<td>Symptomatic cases</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Evolution</td>
<td>Autolimited</td>
<td>Autolimited</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>No</td>
<td>Yes (immunocompromised)</td>
</tr>
<tr>
<td>Severe in pregnancy</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Reservoir: only humans
Source: water supplies contaminated
Reservoir: animals (mainly swines)

Van der Poel WH. Curr Opin Virol 2014; Pavio N. Curr Opin Virol 2015
Transmission person to person?
### Hepatitis E and blood donation safety in selected European countries: a shift to screening?

<table>
<thead>
<tr>
<th>Country</th>
<th>HEV RNA positive donations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>1:2,331</td>
<td>Harritshøj LH. (2016)</td>
</tr>
<tr>
<td>France</td>
<td>1:2,218</td>
<td>Gallian P. (2012-3)</td>
</tr>
<tr>
<td>Ireland</td>
<td>1:2,778</td>
<td>O’Riordan J. (2016)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1:726</td>
<td>Hogema BM (2016)</td>
</tr>
</tbody>
</table>

0.02–0.14% of blood donations are positive for HEV RNA.

Transmission mechanism, to be taken into account in transplants.
Epidemiology of HEV infection

Seroprevalence studies

Serological data suggest that HEV infection occurs in most parts of the world.
All European HEV-seroprevalence studies from 2003 to 2015 were reviewed. The results of these studies have produced high variability of seroprevalence rates, making interpretation increasingly problematic.

The observed heterogeneity was attributed to:

- **Geographical region studied** (between and within countries)
- **Assay employed** (significant differences in sensitivity)
- **Study cohort** (general population, swine contact, HIV, ...)

Hartl J, et al. Viruses 2016, 8, 211
Variability of seroprevalence

Heterogeneity explained by geographical location
Hepatitis E seroprevalence in Europe. Heterogeneity explained by geographical location

Range: 0.6% - 52.5%
Regional variations in seroprevalence

Studied population and method:
- 10,569 donors (18-70 y)
- Sept 2011 to May 2012
- Assay: Wantai HEV IgG

Overall seroprevalence:
HEV IgG: 22.4% (8%-86.4%)
Variability of seroprevalence

Heterogeneity explained by used seroassay

Different prevalence rates using different assays
Hepatitis E seroprevalence in the general European population

Heterogeneity explained by used seroassay

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>Wantai</th>
<th>Mikrogen</th>
<th>MP</th>
<th>Abbott</th>
<th>Adaltis</th>
<th>Dia.Pro</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population (%)</td>
<td>16.90</td>
<td>10.11</td>
<td>6.50</td>
<td>2.29</td>
<td>8.72</td>
<td>4.35</td>
<td>12.48</td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>88,204</td>
<td>1777</td>
<td>14,385</td>
<td>1077</td>
<td>nd *</td>
<td>5,176</td>
<td>3667</td>
</tr>
</tbody>
</table>

Different prevalence rates using different assays in general European population

Commercial assays vary considerably in sensitivity

Hartl J, et al. Viruses 2016, 8, 211
Seroprevalence in a given population when different anti HEV-IgG assays are used.

High Prevalence of Anti-Hepatitis E Virus Antibodies in Blood Donors From South West France

IgG-HEV EIA
Genelabs Diagnostics
Seroprevalence 16.6%

n: 512 (18-64 y.)
Same samples taken:
2003-2004

IgG-HEV EIA
Wantai Biologic
Seroprevalence 52.5%

Emerging Infectious Diseases • Vol. 17, No. 12, Dec 2011
Seroprevalence in a given population by different anti HEV-IgG assays

Seroprevalence of hepatitis E virus (HEV) and detection of HEV RNA with a transcription-mediated amplification assay in blood donors from Catalonia (Spain)

Silvia Sauleda,1,2 Edgar Ong,3 Marta Bes,1,2 Alanna Janssen,3 Robin Cory,3 Maria Babizki,3 Tim Shin,3 Andre Lindquist,7 Anh Hoang,3 Lee Vang,3 Maria Piron,1,2 Natàlia Casamitjana,1 Marco Koppelman,1 Lisa Danzig,5 and Jeffrey M. Linnen3

IgG-HEV EIA Mikrogen

IgG-HEV EIA Wantai Biologic

Seroprevalence 10,7%

Seroprevalence 19,9%

n: 1,082 (18-64 y.)
Same samples taken:
2003-2004
Variability of seroprevalence

Heterogeneity explained by study cohort
Hepatitis E seroprevalence in Europe.
Heterogeneity explained by study cohort

Relationship between anti-HEV IgG seroprevalence rates and the assay employed.

Individuals with close contact to swine/wild animals had higher seroprevalence

Hartl J, et al. Viruses 2016, 8, 211
Epidemiology of HEV infection

Is exposure to HEV a recent phenomenon in developed countries?

Is it an infection that was not diagnosed in the past?
The seroprevalence during the period of time studied, has decreased somewhat more than twice.
Time Trend of the Prevalence of Hepatitis E Antibodies among Farmers and Blood Donors: A Potential Zoonosis in Denmark

Peer B. Christensen,1 Ronald E. Engle,2 Charlotte Hjort,3 Keld M. Homburg,4 Werner Vach,1 Jørgen Georgsen,4 and Robert H. Purcell6

Departments of Infectious Diseases and Clinical Immunology, Odense University Hospital, and Department of Statistics, University of Southern Denmark, Odense, *Department of Environmental and Occupational Medicine, Institute of Public Health, University of Aarhus, Aarhus, and 
Department of Clinical Immunology, Region Zealand, Hospital South, Næstved, Denmark; and 4Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Same assay: IgG-HEV EIA “in house” NIH

Seroprevalence blood donors

1983

n: 169

32,9%

1983

n: 461

2003

20,6%

n: 504

2013

10,7%

Anti-HEV prevalence had decreased by 3 times among Danish blood donors over 30 years.
Is exposure to HEV a recent phenomenon in developed countries? Is it an infection that was not diagnosed in the past?

It seems that HEV infection already occurred in the past, even more prevalent than now.
Clinical aspects

Clinical manifestations
Clinical manifestations

Similar to other viral hepatitis:
- **Pre-icteric phase**
  - Fatigue
  - Abdominal pain
  - Loss of appetite
  - Nausea
  - Diarrhea
  - Fever
- **Icteric phase**
  - Jaundice
  - Dark urine

Usually a self-limiting illness that lasts 4–6 weeks, without the need for antiviral therapies.

Elevation of ALT (alanine aminotransferase) is the best indicator of acute liver injury.
A small proportion (0.5–2%) of individuals infected with HEV develop acute liver failure. Presence of pre-existing chronic liver diseases increases the risk of liver failure (high mortality, of up to 67%).

### Severe clinical manifestations depending on genotype

<table>
<thead>
<tr>
<th>Genotypes 1 y 2 (Developing regions)</th>
<th>Genotypes 3 y 4 (Developed regions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of <strong>fulminant disease</strong> among pregnant women (particularly in 2nd and 3rd trimesters)</td>
<td><strong>Chronic infection</strong> among <strong>immunosuppressed</strong> persons, primarily organ transplant recipients (rapid progression to liver cirrhosis)</td>
</tr>
<tr>
<td>Vertical transmission: premature births and prenatal mortality</td>
<td></td>
</tr>
</tbody>
</table>

Clinical aspects

Acute infection
Noticeable increase in reported cases of HEV in recent years (From 514 in 2005 to 5,617 cases in 2015, with overall more than 21,000 cases reported)

*Data available for Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the UK.

SURVEILLANCE REPORT. Hepatitis E in the EU/EEA, 2005–2015. ECDC 2017
The number of confirmed HEV cases have been increasing: more than three-fold between 2011 and 2015

- Infections were mainly:
  - Locally-acquired (HEV3)
  - Man older than 50 years

- More than 75% of all HEV cases reported in: Germany, France and the UK.

...and in other countries?
Objective: Before incorporating the HEV diagnostic tests in the routine serological profile for viral hepatitis, a pilot study was carried out to evaluate the relative importance of the different hepatotropic viruses (A, B, C, D and E) in the etiology of acute hepatitis.

Materials and methods:
Design: retrospective study during 2013 and 2014.
Population: patients attending emergencies H. 12 de Octubre (Madrid)
Inclusion criteria: ALT>10x higher NUL with a requested serological profile for viral hepatitis.
Samples: serum bank
Serology testing: markers for acute viral hepatitis (A, B, C, D and E)

More details of the study are presented in the poster session of this workshop.
Changeable etiology of acute viral hepatitis: current role of Hepatitis E Virus

569 patients
ALT ≥ 10x

In 298 patients, requested serology

25 patients Insufic. sample

Studied patients: 273

Acute viral hepatitis: 46

14 Hepatitis A (30%)
10 Hepatitis B (22%)
7 Hepatitis C (15%)
15 Hepatitis E (33%)

12 IgM (+) /RNA-HEV(+)*
3 IgM (+) Index > 3

*In 4 samples the genotype was determined, they were HEV3
Results

- HEV is a frequent cause of episodes of acute hepatitis in our setting (33%)
- All the cases of acute hepatitis E were patients older than 40
- 73% were men
- 93% were autochthonous cases
- 53% had liver disease (cirrhosis or hepatic steatosis) prior to HEV infection
- 1 case was a hepatic transplant recipient.

More details of the study are presented in the poster session of this workshop.
Clinical aspects

Chronic infection
HEV genotypes 3 and 4
(Viremia persistence (HEV RNA) > 3 - 6 months)
Immunosuppressed patients can fail to clear HEV infection (Chronic courses may be more frequent after liver transplantation)

The overall frequency of HEV infection in European and North American transplant cohorts is low: 2%-6%

The absolute frequency of chronic hepatitis E after liver transplantation is low: 1-3% in most studies.

Chronic hepatitis E is often associated with rapid progression to liver cirrhosis.
Clinical aspects

Extrahepatic manifestations
HEV tropism may not be restricted to the liver, possibly explaining some extrahepatic manifestations.

Reported sites of HEV replication:

Animal models:
- Pig: intestine, kidney, lymph nodes
- Rabbit: stomach, intestine, kidney, spleen
- Monkeys: kidney

Pischke S. Journal of Hepatology 2017 vol. 66 j 1082–1095
Debing et al. Journal of Hepatology 2016 vol. 65 j 200–212
**Extrahepatic manifestations associated to HEV infection**

(pathophysiological proof of this causal relationship is still pending)

**Neurological complications**

- Neurologic amyotrophy (brachial neuritis)
- Guillain-Barré syndrome
  - (In CSF: HEV-RNA and intrathecal ab production)

**Renal disorders**

- Glomerulonephritis (HEV-RNA in the urine)

**Other complications**

- Acute pancreatitis (HEV 1)
- Hematological manifestations

These manifestations appear associated with both chronic and acute infections.

Debing Y. *Journal of Hepatology* 2016 vol. 65 j 200–212
Pischke S. *Journal of Hepatology* 2017 vol. 66 j 1082–1095
Hepatitis E: Natural History

HEV infection

- Asymptomatic (70%-90%)
  - Resolving acute hepatitis
  - Fulminant hepatitis (HEV-I): 15-20%
    - Pregnancy (HEV-I)
    - Acute-on chronic hepatitis

- Symptomatic clinically recognised (5%-20%)
  - Chronic hepatitis (HEV-3)
    - Transplant patients
    - HIV patients
    - Hematological patients

- Symptomatic clinically not recognised
  - Extrahepatic manifestations
    - Neurological symptoms
    - Kidney injury
    - Pancreatitis (HEV-I)
    - Hematological disorders

? Reduction in immunosuppression

? Anti-viral therapy
  - Ribavirin monotherapy
  - Pegylated-interferon

Summary

• Serological data suggest that HEV infection occurs in most parts of the world.

• The seroprevalence studies in Europe should be interpreted with caution: Technical standardization of serologic methods may be needed to harmonize results to compare prevalence in different geographical regions.

• Acute hepatitis E is usually self-limiting and risk factors for severity are:
  – Pregnancy (HEV1)
  – Pre-existing chronic liver disease

• HEV 3 and 4, can take chronic courses in immunocompromised individuals (specially liver transplantation)
In August 1981, he ingests a stool extract of hepatitis patients and describes the etiological agent (HEV).