Hepatitis E: When to think about? How to treat?

Heiner Wedemeyer
EUROPE’S NEW HEPATITIS PROBLEM
Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

By Kai Kupferschmidt
Is hepatitis E really a problem?

Numbers

The Disease

Pathogenesis

Treatment
Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983

- HEV: spherical, positive-stranded RNA virus
The Hepatitis E Virus

Study of hepatitis E virus infection of genotype 1 and 3 in mice with humanised liver.


- HEV from stool is more infectious than plasma HEV
- HEV GT3 leads to lower viral load than HEV GT1
Hepatitis E Virus Lifecycle and Identification of 3 Forms of the ORF2 Capsid Protein.

Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983

- HEV: spherical, positive-stranded RNA virus

- 7 Different genotypes, but only one serotype
  (only genotypes 1-4 (and 7?) infect humans)

*Lee et al. Camelid HEV in a liver transplanted patient consuming camel milk and meat.*
*Gastroenterology Feb 2016*
Hepatitis E Genotypes
Increasing Seroprevalence with age (USA)

Kuniholm et al. JID 2009
... but a decline over time (1996 vs. 2011) (Germany)
Regional differences in HEV seroprevalence rates (France)
Hepatitis E Genotype 3 Infection

A Zoonosis!
HEV has been detected in

- Pigs  
  Goens, *Anim Health Res Rev* 2004
- Deer  
- Wild Boars  
  Kaci et al., *Vet Microbiol* 2008
- Mongeese  
  Meng et al., *J Viral Hepati* 2009
- Shellfish (Outbreak on a cruise ship!)  
  Said et al., *Emerg Infect Dis* 2009
- Rodents incl. Rats  
  Easterbrook et al., *Epidemiol Infect* 2007

HEV RNA has frequently been detected in meat of commercial pigs!

Increased seroprevalence in individuals with contacts to pigs!
Hepatitis E: A Zoonosis!

HEV genotype 4 in cows which was excreted into milk in China (mixed farming)

Bächlein et al. Hepatology 2017
No detection of HEV RNA in milk collected in Germany
Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983

- HEV: spherical, positive-stranded RNA virus

- 5 Different genotypes, but only one serotype

- Self-limiting mild to moderate disease in immunocompetent patients (mortality rate of 0.4-4.0%)
  Wedemeyer et al., Gastroenterology 2012; Kamar et al., Lancet 2012

Rein et al., Hepatology 2011

70.000 deaths per year!
Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983

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- Self-limiting mild to moderate disease in immunocompetent patients (mortality rate of 0.4-4.0%)
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- more frequent fulminant courses in patients with underlying chronic liver disease and pregnant women
Is HEV testing of relevance for transfusion of blood products?
Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

Summary

Background The prevalence of hepatitis E virus (HEV) genotype 3 infections in the English population (including blood donors) is unknown, but is probably widespread, and the virus has been detected in pooled plasma products.
Post-Transfusion hepatitis in immunocompromised patients despite serological immunity

Course of alanine aminotransferase (ALT) levels, hepatitis E virus (HEV) viral load (VL), and anti-HEV immunoglobulin G (IgG) status in a stem cell transplant recipient (A) and a heart transplant recipient (B) chronically infected by 1 HEV-positive blood donation.
Chronic Hepatitis E
Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

Nassim Kamar, M.D., Ph.D., Janick Selves, M.D., Jean-Michel Mansuy, M.D., Leila Ouezzani, M.D., Jean-Marie Péron, M.D., Ph.D., Joëlle Guitard, M.D., Olivier Cointault, M.D., Laure Esposito, M.D., Florence Abravanel, Pharm.D., Marie Danjoux, M.D., Dominique Durand, M.D., Jean-Pierre Vinel, M.D., Jacques Izopet, Pharm.D., Ph.D., and Lionel Rostaing, M.D., Ph.D.
Chronic Hepatitis E in Organ Transplant Recipients

Liver Transplantation
Haagsma et al., Liver Transplantation 2009
Pischke et al., Liver Transplantation 2010
Kamar et al., Gastroenterology 2011

Kidney Transplantation
Kamar et al., Gastroenterology 2011
Pas et al., Emerg Infect Diseases 2012
Moal et al., J Med Virol 2013

Heart Transplantation
Pischke et al., Am J Transplantation 2012
Koning et al., J Heart Lung Transplant 2013

Lung Transplantation
Riezbeos-Brilman et al. J Heart & Lung Transpl 2012
Pischke et al., Transpl Infectious Diseases 2014
Chronic Hepatitis E in Organ Transplant Recipients

- Prevalence of chronic infection 1-4%
- Chronicity of acute infection 40-80%
  - maybe higher after liver transplantation
- More rapid disease progression
  - cirrhosis with 1-2 years of infection!
- RNA-positivity associated with increased ALT levels
  - testing of patients with increased ALT levels only?
- HCV RNA testing required
- HEV antigen testing discriminates acute vs. chronic hepatitis E
HEV-Ag levels differentiate acute and chronic hepatitis E
HEV Ag may persist even after HEV RNA clearance

**BEHRENDT et al., J Infect Diseases 2016**

OD 450/630

HAV infected
acutely HEV infected
chronically HEV infected

patient #6

OD 450/630 (S/CO)

0.01 0.1 1 10 100

0 100 200

days
Immunsuppression und HEV Replikation

- possibly higher for tacrolimus vs. cyclosporine
  maybe higher after liver than after kidney transplantation
  Kamar et al., Gastroenterology 2011

- In vitro effects of immunosuppressive drugs on HEV infection & replication

  tacrolimus: HEV infection ↑↑
  cyclosporine: HEV replication ↑
  mTOR inhibitors: HEV replication ↑↑
  mycophenolate: HEV replication ↓↓
  corticosteroids: HEV replication ↔

Chronic Hepatitis E
Beyond Transplantation?

- Cases of immunodeficiency or other types of immunosuppression
  
  Grewal et al., Hepatology 2013
  Höner zu Siederdissen, Hepatology 2014
Persistent HEV infection in a HIV+ patient with low CD4+ counts
HEV Infection: More than a liver disease?

Wedemeyer & Cornberg; Liver International April 2016

The hepatitis E virus: a likely cause of extrahepatic diseases!
Hepatitis E and Autoimmune-Hepatitis

Higher Prevalence of anti-HEV antibodies in AIH patients

... associated with HEV-specific T cell responses
HEV infection and Guillain-Barre Syndrome

van den Berg et al., Neurology 2014; 82: 491-497

- 201 GBS patients vs. 201 controls
- Anti-HEV IgM 10 (5%) vs. 1 (0.5%)
- 4 patients HEV RNA-positive
- No HEV RNA- detection in CSF
HEV-associated cryoglobulinaemia and extrahepatic manifestations of hepatitis E

Figure 1: Course of creatinine and creatinine kinase

Figure 2: Rash in a patient with mixed-cryoglobulinaemia after clearance of chronic hepatitis E virus infection
Role of HEV in acute non-traumatic neurological injury

Webb, Dalton et al., Journal of Hepatology 2017 epub
- Prospective HEV screening of patients with neurological injury (non-traumatic)

- 2.4% of acute neurology patients have evidence for HEV infection

Jones et al., EASL ILC 2017 PS-104:
- HEV-associated neuralgic amyotrophy has a different phenotype than HEV-neg. NA:
  - bilateral;
  - more neurol. Damage
  - involvement outside brachial plexus

<table>
<thead>
<tr>
<th>Acute neurological event</th>
<th>Number tested (n=)</th>
<th>Number tested</th>
<th>HEV infection n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuralgic amyotrophy</td>
<td>5</td>
<td>3</td>
<td>(60%)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>11</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>7</td>
<td>1</td>
<td>(14%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>7</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Cranial Nerve palsies</td>
<td>31</td>
<td>1</td>
<td>(3%)</td>
</tr>
<tr>
<td>Seizure(s)</td>
<td>44</td>
<td>3*</td>
<td>(7%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>170</td>
<td>4</td>
<td>(2%)</td>
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<tr>
<td>Transient ischaemic attack</td>
<td>68</td>
<td>0</td>
<td>(0%)</td>
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<tr>
<td>Migraine/headaches</td>
<td>51</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>12</td>
<td>0</td>
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<tr>
<td>Myelitis</td>
<td>14</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>25</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>0</td>
<td>(0%)</td>
</tr>
</tbody>
</table>
HEV can replicate in various extrahepatic cell lines including neuronal-derived cells
Immunity against HEV
HEV-specific CD4+ and CD8+ T-cell responses
Cross-Genotype-specific CD4+ and CD8 + HEV T Cells in Acute Hepatitis E
HEV-specific T cell responses are targeted against structural and non-structural proteins

ORF-1

ORF-2/3

CD8+

CD4+
Treatment of Hepatitis E
Ribavirin is effective against HEV

*Kamar et al., NEJM March 2014*

59 patients treated for a median of 3 months
46 patients with SVR (78%)
Selection of an HEV-variant with increased replication fitness
Ribavirin induces HEV mutagenesis

![Graph showing the number of sites exhibiting non-synonymous substitutions with and without Ribavirin (RBV). The graph indicates a significant increase in substitutions with RBV.](image)

**Patient #1**

- **Synonymous substitution**
- **Non-synonymous substitution**
- **Transition**
- **Transversion**

**Graph showing the number of sites exhibiting substitutions over time (months) with Ribavirin (RBV).**
Sofosbuvir to treat chronic Hepatitis E?

Van der Valk et al; J Hepatol  2016
Hepatitis E – Future Directions

- Better define the animal and environmental reservoir
  
  *Food safety, sewage, water, ...*

- Should all blood products be screened for HEV RNA?

- Immunity against HEV
  
  *A vaccine against HEV is licensed only in China*

- Factors explaining severe acute and chronic liver disease
  
  *pregnancy, immunosuppression, etc.*

- Extrahepatic manifestations

- Pathogenesis of HEV
  
  *virology and immunology!*

- We need alternative antiviral drugs!
  
  *Ribavirin has side effects and treatment failure occurs*