Hepatitis E: a relevant clinical problem?

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
Reported Hepatitis E Cases in Germany

- 2001: 1930 cases
- 2002: 0 cases
- 2003: 1267 cases
- 2004: 1930 cases
- 2005: 670 cases
- 2006: 2014 cases
- 2007: 2015 cases
- 2008: 2016 cases
- 2009: 2017 cases
- 2010: 2018 cases
- 2011: 2019 cases
- 2012: 2020 cases
- 2013: 2021 cases
- 2014: 2022 cases
Hepatitis E

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

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


[Diagram showing the ORFs of the Hepatitis E virus with annotations for ORF1, ORF2, ORF3, and their respective functions and locations.]
Hepatitis E


- 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)

FIG. 1. Prevalence of anti-HEV IgG and IgM: distribution in French administrative areas. A color code describes the anti-HEV IgG seroprevalence classes. Black numbers represent the seroprevalence of anti-HEV IgM in each administrative area.
Hepatitis E Genotype 3 Infection

–

A Zoonosis!
Hepatitis E Genotype 3 Infection: A Zoonosis!

HEV has been detected in

- Pigs  
  Goens, Anim Health Res Rev 2004
- Deer  
  Tei, Lancet 2003; Tomiyama, J Viral Hepatitis 2009
- Wild Boars  
  Kaci et al., Vet Microbiol 2008
- Mongeese  
  Meng et al., J Viral Hepatitis 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

70,000 deaths per year!

Rein et al., Hepatology 2011
World Hepatitis Day — July 28, 2013

Investigation of Hepatitis E Outbreak Among Refugees — Upper Nile, South Sudan, 2012-2013
Hepatitis E in Africa – Outbreaks and Genotypes

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

- more frequent fulminant courses in patients with underlying chronic liver disease and pregnant women
HEV as a cause of acute liver failure in Germany

ALF N = 80

IgG

Negative n = 67

Not clear n = 1

Positive n = 12

IgM

Negative n = 64

Positive n = 3

Negative n = 1

Positive n = 2

PCR

Negative n = 63

Positive n = 1

Positive n = 3

Negative n = 1

Negative n = 7

Positive n = 1

Negative n = 1

Positive n = 2

Fallberichte

Letal verlaufene akute Hepatitis E unter Vedolizumab
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
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
  
<table>
<thead>
<tr>
<th>Drug</th>
<th>HEV Infection/Replication</th>
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<tbody>
<tr>
<td>tacrolimus</td>
<td>↑↑</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>↑</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>↑↑</td>
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<tr>
<td>mycophenolate</td>
<td>↓↓</td>
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<tr>
<td>corticosteroids</td>
<td>↔</td>
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*Debing, Neyts et al, AAC 2014; 58: 267; Wang, Pan et al., Gastroenterology 2014; 146: 1775 ; Zhou, Pan et al., J Hepatol 2014; 61: 746; Behrendt, Wedemeyer et al. J Hepatol 2014; 61: 1418*
Chronic Hepatitis E
Beyond Transplantation?

➢ Cases of immunodeficiency or other types of immunosuppression

*Grewal et al., Hepatology 2013*

*Höner zu Siederdissen, Hepatology 2014*
HEV in HIV+ individuals

- **Lower** HEV prevalence in HIV-positive migrants from Africa (compared to German HIV+ patients)  
  *Pischke et al., Intervirology 2015*

- **Similar** HEV seroprevalence in HIV+ individuals in Europe individuals with a CD4+ T cell count >200 cells/mm³.  
  *Hartl et al., Viruses 2016*
HIV+ individuals have a similar HEV seroprevalence in Europe - with major regional differences.
HEV in HIV+ individuals

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  *Pischke et al., Intervirology 2015*

- **Similar** HEV seroprevalence in HIV+ individuals in Europe individuals with a CD4+ T cell count >200 cells/mm³.

  *Hartl et al., Viruses 2016*

- **Persistent HEV infection** in HIV+ individuals
  - *chronic courses possible (Dalton et al. NEJM 2009)*
  - *despite negative serology (Kuniholm et al., Hepatology 2016)*
Persistent HEV infection in a HIV+ patient with low CD4+ counts

Dalton et al., NEJM 2009
Persistent HEV infection in a HIV+ women despite negative serology (and low ALT levels)
HEV in HIV+ individuals

- **Lower** HEV prevalence in HIV-positive migrants from Africa (compared to German HIV+ patients)
  
  *Pischke et al., Intervirology 2015*

- **Similar** HEV seroprevalence in HIV+ individuals in Europe individuals with a CD4+ T cell count >200 cells/mm³.
  
  *Hartl et al., Viruses 2016*

- **Persistent** HEV infection in HIV+ individuals
  
  - chronic courses possible (Dalton et al. NEJM 2009)
  
  - despite negative serology (Kuniholm et al., Hepatology 2016)

  - despite CD4+ counts >200/mm³ (Ingiliz et al, Clin Res Hepatol Gastro 2016)
HEV Infection: More than a liver disease?

PRO VIEW

DOI: 10.1111/liv.13088

The hepatitis E virus: a likely cause of extrahepatic diseases!

Wedemeyer & Cornberg; Liver International April 2016
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
Possible extrahepatic manifestations of hepatitis E

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Patient cohort</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>glomerulonephritis</td>
<td>Organ transplant recipients with chronic hepatitis E</td>
<td>Kamar et al. Transplantation 2012</td>
</tr>
<tr>
<td>cryoglobulinaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy after</td>
<td>Kidney Transplant recipients</td>
<td>Taton et al., Transpl Infect Dise 2013</td>
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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
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

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 A: Number of sites exhibiting non-synonymous substitutions over time in Patient #1 with and without Ribavirin (RBV).

Graph B: Comparison of non-synonymous substitutions between -RBV and +RBV groups, with a significant difference indicated by ****.
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
  *Liver international debate April 2016*

- Pathogenesis of HEV
  *virology and immunology!*

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