

Hepatitis E: What's hot in 2018?

Heiner Wedemeyer



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August 26 2016

Science
AAAS

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

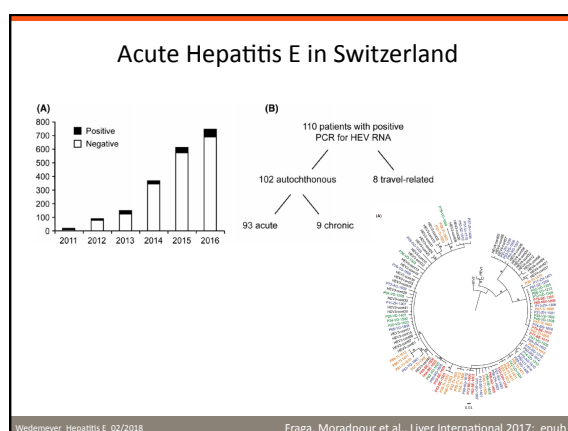
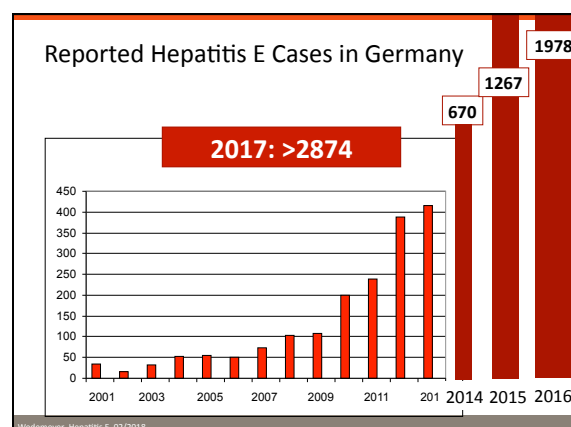


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Is hepatitis E really a problem?

- Numbers
- The Disease
- Pathogenesis
- Treatment

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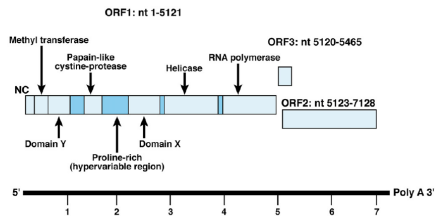
Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983
Balayan et al., 1983, 20: 23-31.
- HEV: spherical, positive-stranded RNA virus

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The Hepatitis E Virus

A novel ORF-4 ? Nair et al. PlosPathogens April 1st 2016



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Wedemeyer, Pischke & Manns, Gastroenterology 2012

What's new in HEV virology?

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Human liver chimeric mice as a new model of chronic hepatitis E virus infection and preclinical drug evaluation.

Allweiss L, Gass S, Giersch K, Groth A, Kah J, Volz T, Rapp G, Schöbel A, Lohse AW, Polywka S, Pischke S, Herker E, Dandri M, Lütgehetmann M. J Hepatol. 2016 May;64(5):1033-1040.

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

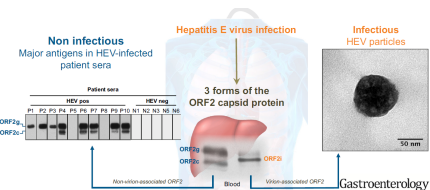
Sayed IM, Verhoye L, Cocquerel L, Abravanel F, Faquet L, Montpellier C, Debing Y, Farhoudi A, Wychowski C, Dubuisson J, Leroux-Roels G, Neyts J, Izopet J, Michiels T, Meuleman P. Gut. 2017 May;66(5):920-929.

- HEV from stool is more infectious than plasma HEV
- HEV GT3 leads to lower viral load than HEV GT1

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Hepatitis E Virus Lifecycle and Identification of 3 Forms of the ORF2 Capsid Protein.

Montpellier C, Wychowski C, Sayed IM, Meunier JC, Saliou JM, Ankavay M, Bull A, Pillez A, Abravanel F, Helle F, Brochat E, Drobacq H, Farhat R, Aliouat-Denis CM, Haddad JG, Izopet J, Meuleman P, Goffard A, Dubuisson J, Cocquerel L. Gastroenterology. 2017 Sep 25.

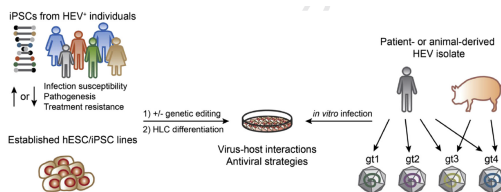


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Pan-Genotype Hepatitis E Virus Replication in Stem Cell-derived Hepatocellular Systems

Xianfang Wu,^{1,2} Viet Loan Dao Thi,^{1,2} Peng Liu,^{1,2} Constantin N. Takacs,^{1,2,3} Kuanhui Xiang,^{1,2} Linda Andrus,¹ Jérôme Gouttenoire,¹ Darius Moradpour,² and Charles M. Rice¹

Gastroenterology. epub Dec 2017

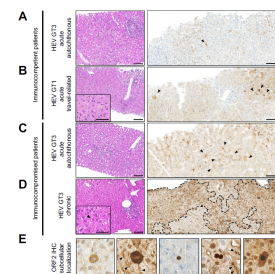


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Visualization of hepatitis E virus RNA and proteins in the human liver

Daniela Lenggenhager¹, Jérôme Gouttenoire^{1,2}, Mohsen Malehmir¹, Marion Bawohl¹, Hanna Honcharova-Biletska¹, Susanne Kreuter¹, David Senécal¹, Jörg Neuweier¹, Sandra Hürlimann¹, Patrick Aepli¹, Montserrat Fraga¹, Roland Sahli¹, Luigi Terracciano³, Laura Rubbia-Brandi¹, Beat Mühlhaupt^{1,2}, Christine Sempoux¹, Darius Moradpour¹, Achim Weber^{1,2}

J Hepatol 2017; 67: 471-79



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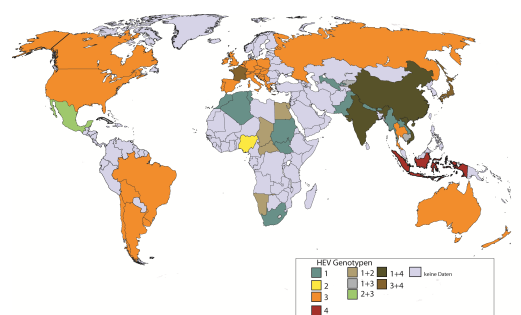
Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983
Balayan et al., 1983. 20: 23-31.
- 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

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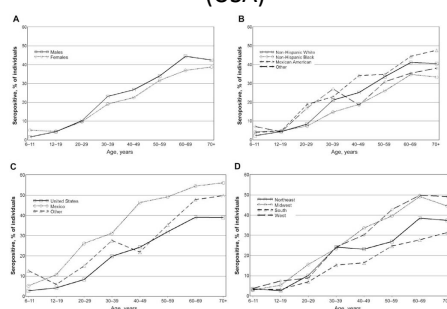
Hepatitis E Genotypes



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Pischke et al. Deutsches Ärzteblatt 2014

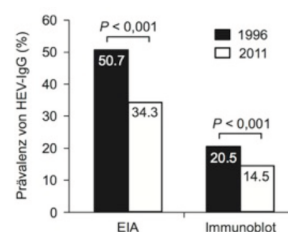
Increasing Seroprevalence with age (USA)



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Kuniholm et al. JID 2009

... but a decline over time (1996 vs. 2011) (Germany)



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Wenzel et al. Hepatology 2014

Hepatitis E Genotype 3 Infection

A Zoonosis!



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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 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!

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Hepatitis E: A Zoonosis!



Wang et al. Hepatology Aug 2016

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

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Hepatitis E

- Waterborne hepatitis, first described in 1980, HEV: 1983
Balayan et al., 1983. 20: 23-31.
- 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!

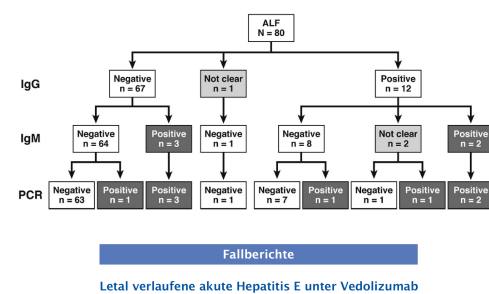
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Hepatitis E

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Balayan et al., 1983. 20: 23-31.
- HEV: spherical, positive-stranded RNA virus
Mushawar IK, J Med Virol 2008. 80: 646-58
- 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
Bhatia, et al. Hepatology 2008. 48: 1577-85; Jin et al., Epidemiol & Infect 2016

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HEV as a cause of acute liver failure in Germany



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Manka, ... Canbay, Clin Gastroenterol Hepatol 2015;13:1840

Hepatitis E virus as a cause of acute hepatitis acquired in Switzerland

Montserrat Fraga¹ | Christopher Doering¹ | Hervé Moulin² | Florian Bihl³ | Felix Brunner⁴ | Beat Mühlhaupt⁵ | Paolo Ripellino⁶ | David Semela⁷ | Felix Sticker⁸ | Benedetta Terzoli Beretta-Piccoli⁹ | Vincent Aubert⁸ | Amalia Telenti² | Gilbert Greub² | Roland Sahli² | Darius Moradpour¹

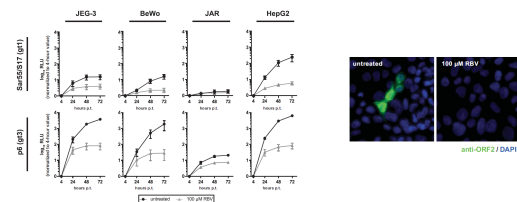
93 cases

2 fatal outcomes in patients with underlying chronic liver disease

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Hepatitis E Virus Replication and Interferon Responses in Human Placental Cells

Leonard Knegedorf¹, Sergio A. Davis¹, Viet Loan Dao Thi², Yaminik Dehing³, Richard J. P. Brown¹, Florian W. R. Vondrusch^{4,5}, Kathrin Reuter¹, Martina Friedland¹, Tami Khori¹, Michael Engelmann¹, Brigitte Renner⁶, Heiner Wedemeyer^{1,8}, Patrick Behndt^{1,9}, Johan Neyns², Thomas Putschmann^{1,2}, Daniel Todt¹⁰, and Elke Steinmann⁷



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Knegedorf et al., Hepatology Communications 2018 epub

Is HEV testing of relevance for transfusion of blood products?

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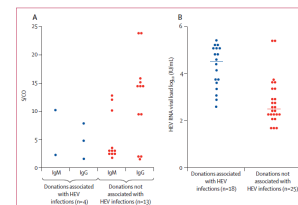
Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

Patricia E Hewitt, Samreen Ijaz, Su R Braithford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poth, Katherine Russell, Kate I Tetmar, 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.

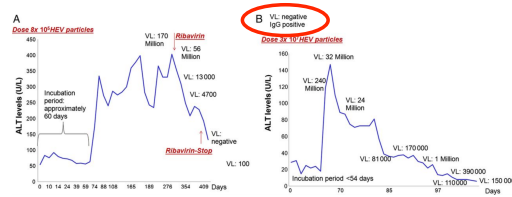
Published Online
July 28, 2014



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Lancet July 2014

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.

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Pischke et al., Clin Infect Dis. 2016;63(4):569-570. doi:10.1093/cid/ciw309

Chronic Hepatitis E

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The NEW ENGLAND JOURNAL of MEDICINE

February 2008

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 Ouezani, 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 Danjou, M.D., Dominique Durand, M.D., Jean-Pierre Vinel, M.D., Jacques Izopet, Pharm.D., Ph.D., and Lionel Rostaing, M.D., Ph.D.

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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

Riezbees-Brilman et al., J Heart & Lung Transpl 2012
Pischke et al., Transpl Infectious Diseases 2014

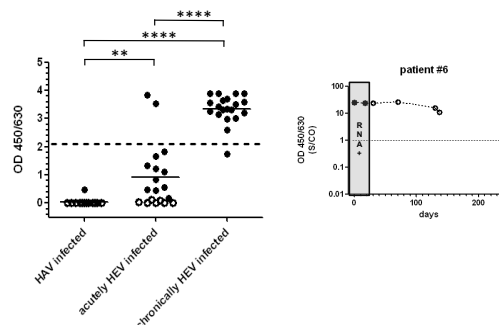
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Chronic Hepatitis E in Organ Transplant Recipients

- 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

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HEV-Ag levels differentiate acute and chronic hepatitis E HEV Ag may persist even after HEV RNA clearance



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Behrendt et al., J Infect Diseases 2016

Immunosuppression 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 ↔

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

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HEV Infection: More than a liver disease?



PRO VIEW

DOI:10.1111/liv.13088
Liver Int. 2016; 36: 473-476.

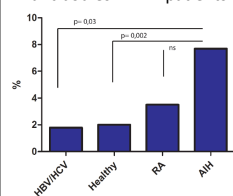
The hepatitis E virus: a likely cause of extrahepatic diseases!

Wedemeyer & Cornberg; Liver International April 2016

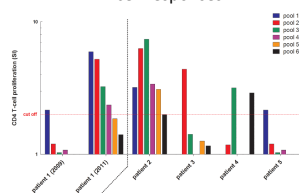
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Hepatitis E and Autoimmune-Hepatitis

Higher Prevalence of anti-HEV antibodies in AIH patients



... associated with HEV-specific T cell responses



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Pischke et al., PlosOne 2014

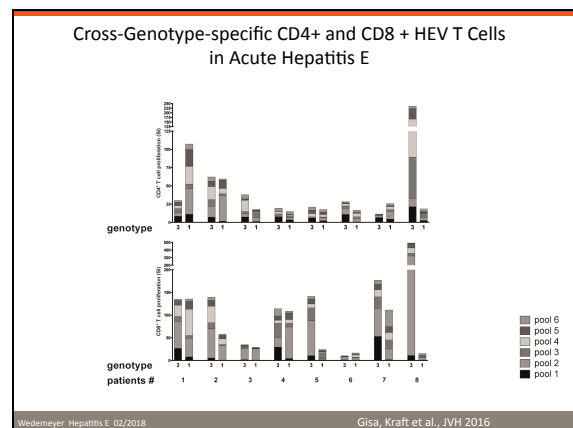
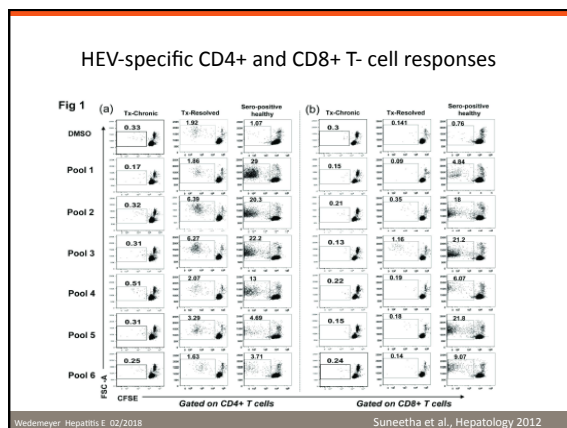
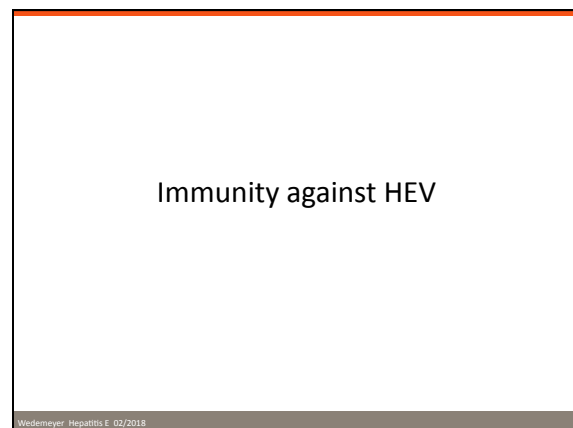
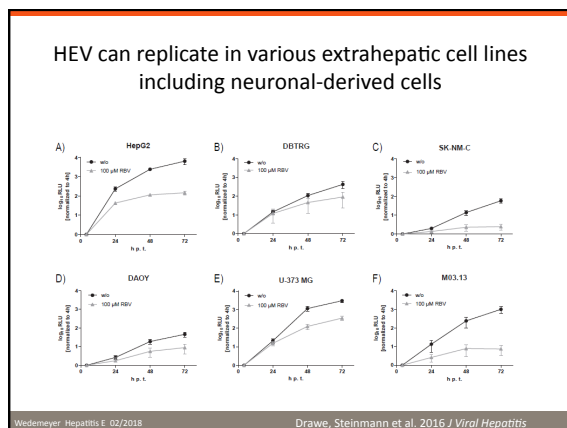
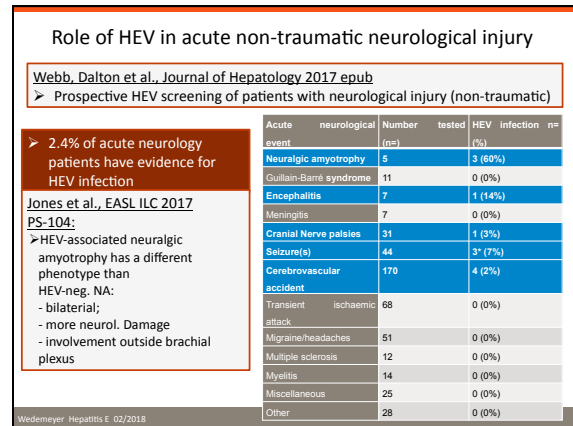
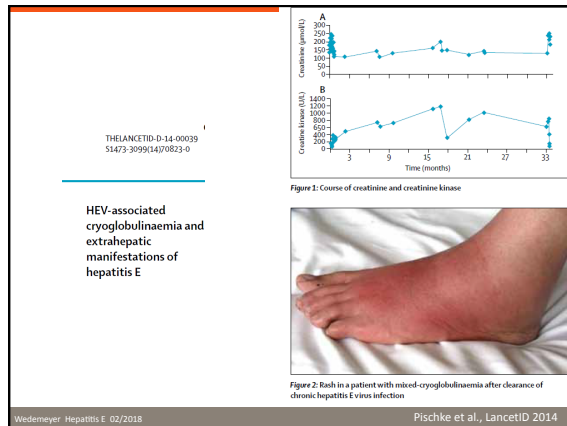
HEV infection and Guillain-Barre Syndrome

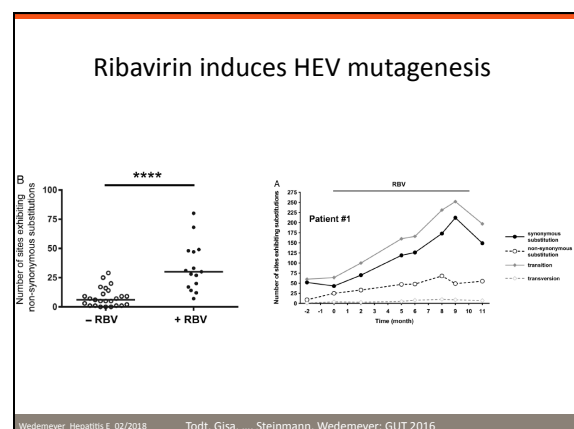
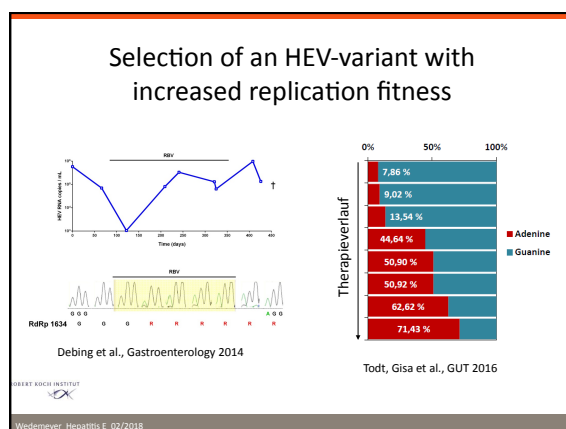
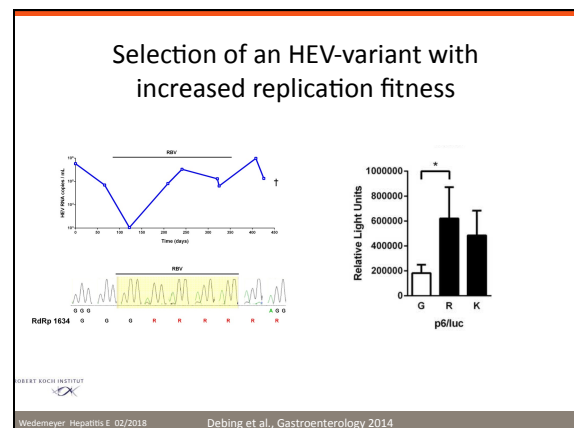
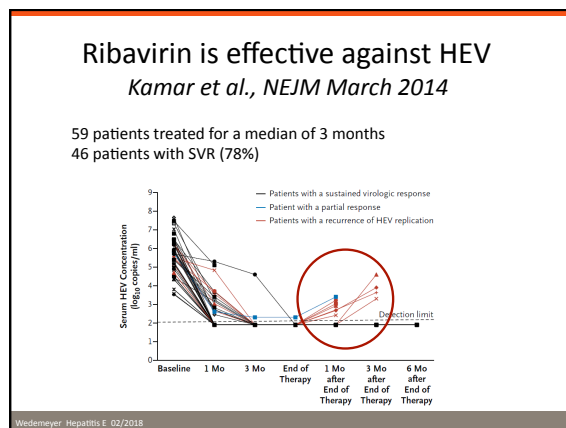
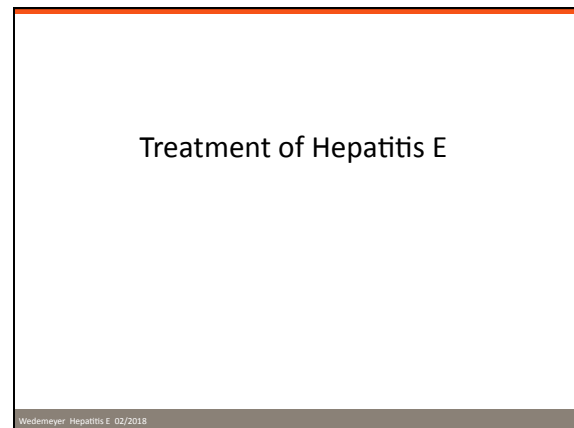
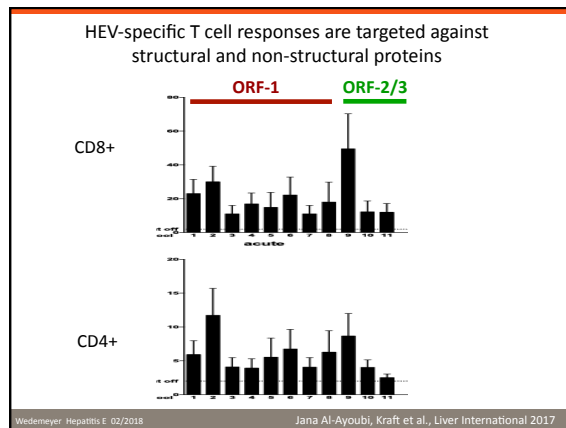
van den Berg et al., Neurology 2014; 82: 491-497

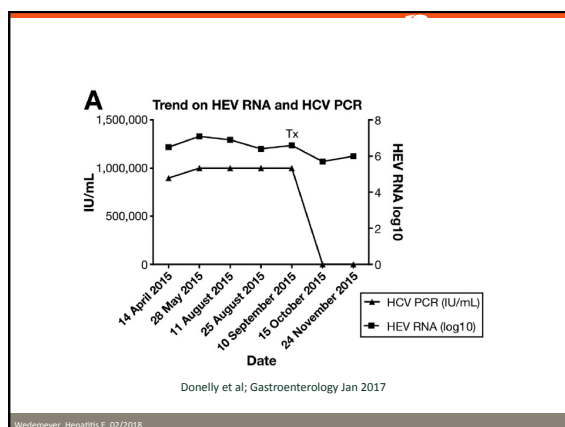
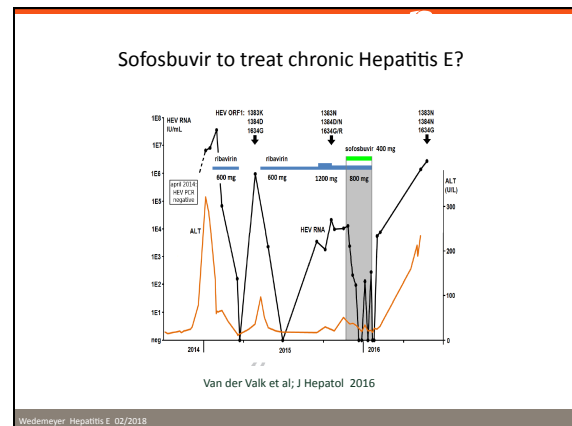
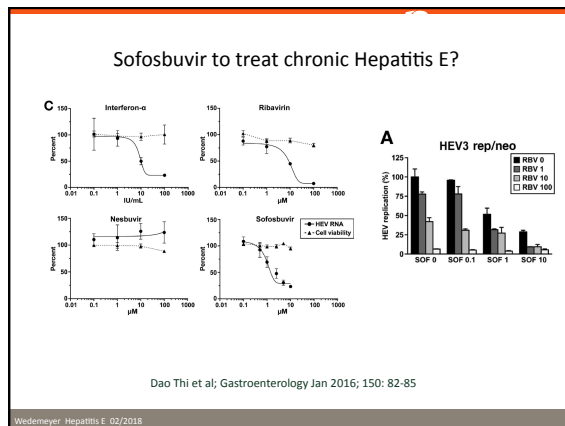
- 201 GBS patients vs. 201 controls
- Anti-HEV IgM 10 (5%) vs. 1 (0.5%)
- 4 patients HEV RNA-positive
- No HEV RNA- detection in CSF

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- ### 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
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