Hepatitis E virus \textit{genotype 3}: what we know so far

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HEV gt 3: the issues

- sources and routes of infection
- incidence and course of infection in blood donors
- infectivity, inactivation and removal of HEV gt3
- course of gt3 hepatitis E in patients
- consequences for blood safety
sources and routes of infection

- pooled feces from 97 Dutch pig farms:
  51/97 (53%) HEV RNA positive.
  Rutjes ea, Em.Inf.Dis. 2009

- pork products in France:
  figatelli 30%; liver sausages 29%; quenelles 25%;
  dried salted liver 3% HEV RNA positive.
  Pavio ea, Em.Inf.Dis. 2014

- pork products in UK:
  consumption of pork pie, ham and sausages from major UK
  supermarket chain signif. associated with indigenous infection.
  Said ea, Epid.Inf. 2013

- leafy green vegetables in Serbia, Greece, Poland:
  5/146 (3.4%) samples HEV RNA positive.
  Kokkinos ea, Food Env.Vir. 2012
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HEV RNA positive blood donors

a) Baylis, Vox 2012; b) Vollmer, JCM 2012; c) Slot, EuroSurv.2013; d) Cleland, Vox 2013;
e) Hewitt, Lancet 2014; f) Gallian, EID 2014; g) Sauleda, Transfusion 2014; h) Fischer, PlosOne 2015;
Course of infection in 41 NL blood donors

presentation by dr. Hogema:
- duration of viremia.
- 2/3 seroneg. : seroconverted

- serial viremic donations:
  donors apparently not affected

- normal or slightly elevated ALT
  (several reports)

- does viremic re-infection occur?
anti-HEV seroprevalence: age cohort effect

Ijaz ea (UK), JCV 2009

Wenzel ea (SE.Germany), Hepatol. 2014

Christensen ea (Denmark), CID 2008

Hogema ea (NL), Transfusion 2014
anti-HEV seroprevalence: age cohort effect

and recent increase of incidence:

Hogema ea, Transfusion 2014
Monthly donorscreening for HEV RNA in NL

~2000 donations/month; in pools of 96; for SD-plasma production

Overall: 57 / 73341 (1:1287) donations HEV+ (all asymptomatic, ‘acute’: seroconverting)
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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 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 Ushiroyumokra, Richard S Tedder

Serological and molecular evidence of a plausible transmission of hepatitis E virus through pooled plasma

A. Andonov, G. Rock, L. Lin, J. Borlang, J. Hooper, E. Grudeski, J. Wu & Members of the Canadian Apheresis Group

Hepatitis E transmission by transfusion of Intercept blood system-treated plasma

Hauser ea (France)

TRANSFUSION-TRANSMITTED HEPATITIS E IN GERMANY, 2013

D Huzly, M Umhau, D Bettinger, T Cathomen, F Emmerich, P Hasselblatt, H Hengel, R Herzog, O Kappert, S Maassen, E Schorb, C Schulz-Huotari, R Thimme, R Unmüssig, J J Wenzel, M Panning

Transfusion-transmitted hepatitis E in a patient with myelodysplastic syndromes

Yukihiro Kimura, Akihiko Gotoh, Seiichiro Katagiri, Yuji Hoshi, Shigebaru Uchida, Atsushi Yamashita, Yoko Takahashi, Tatsuyuki Fukutake, Toru Kiguchi, Kazuma Ohyashiki
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2012-2013: 79 / 225,000 donations (1:2848) HEV+ (all gt3):
- 18/43 (42%) of recipients infected
- transmission associated with: viral load, seronegative donor.

> Not all viremic donors transmit HEV.

Cave pseudo transmission:
11 cases of “post-transfusion hep E” notified to Sanquin:
10 : all implicated donations HEV PCR negative.
1 : 1 implicated donor HEV RNA positive.
HEV: inactivation and removal

ad interim interpretation at Sanquin:

Effective removal or inactivation:
- Planova15N of Planova20N filtration
- Pasteurisation at 60 °C
- Immunoaffinity chromatography purification

Limited or no inactivation:
- SD treatment
- Low-pH treatment
- Alcohol fractionation
- Neutralisation by anti-HEV antibodies
  (due to a protective lipid layer covering HEV virions in blood: only neutralisation in serum or cell cultures after SD- or protease treatment)

See:
Summary of workshop presentations in Appendix to reflection paper, of the “EMA Workshop on viral safety of plasma-derived medicinal products with respect to hepatitis E virus” (London, Oct. 28th/29th, 2014); aimed to be released for public consultation in July 2015.
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course of HEV gt3 infection in patients

1. the good news about HEV gt3: apparently no morbidity in pregnant women, newborns, children and majority of adults

2. acute, mild hepatitis in middle aged (wo)men:
81 Dutch hep. E patients: risk factors

2009-2014: 4067 samples submitted for 'hep.seroology': 144 HEV-IgM and PCR pos. > questionnaire > 81 responses

subset: 52 Dutch hep E patients, no travel and no immune sup./def.
course of HEV gt3 infection in patients

1. the good news:
   apparently no morbidity in pregnant women, newborns, children and majority of adults

2. acute, mild hepatitis in middle aged (wo)men

3. acute and/or chronic hepatitis in transplant, chemo, etc. patients:
   - mimicking drug induced liver injury
   - mimicking graft versus host disease of the liver
   - rapid cirrhosis
case 1: Mr. A, 51 yrs

[Graph showing HEV RNA levels and ALAT activity over time with markers for dialysis, kidney transplantation, etanercept, and ribavirin treatment.]
case 2: girl B, 11 yrs  kidney failure e.c.i.

A. Bouts, Pediatrics 2015, vol 135, nr 4
case 3: mrs. C, 55 yrs
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HEV gt3 and blood banking

General considerations:
- HEV gt3 poses a threat to immunosuppressed patients, but timely diagnosis and treatment are possible.
- Vulnerable patients must be screened for HEV, irrespective of blood transfusion/products. (Based on ALT elevation, or once a year?)

Options for donor screening:
- none / for at-risk recipients / universal.
- If donor screening is indicated: above which incidence?
- pooled or individual HEV NAT? Or are HEV IgG+ donors safe (NL: 27%)?
- Sanquin: “Make food and water safe, in stead of blood supply”.

Policy and decision making:
UK: SaBTO HEV Blood Services Sub Group is studying options.
NL: Ministry of health has to answer 20+ HEV related questions posed by members of parliament.
France, Germany, Spain, Japan, Ireland:
HEV team at Sanquin:

Boris Hogema
Michel Molier
Ed Slot
Hidde Koot
Hans Zaatier

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