Hepatitis E Seroconversion
Following plasma exchange
Hepatitis E

- A non-enveloped RNA virus, 27-34 nm diameter
- Member of Hepevirus genus/Hepeviridae family
- First documented in India in 1955
- Causes self-limited disease: L inflammation
- Chronic seen in transplants, immunosuppressed
- Transfusion transmissible 2004 Japan
Genotypes 1 & 2
affects humans only
endemic hepatitis
associated water and oral-fecal

Genotypes 3 & 4
affects pigs and humans
zoonotic transmission
GEOGRAPHIC DISTRIBUTION

Levels of Endemcity for Hepatitis E Virus (HEV)
- **Highly Endemic**: (waterborne outbreaks or confirmed HEV infection in ≥25% of sporadic non-A, non-B hepatitis)
- **Endemic**: (confirmed HEV infection in <25% of sporadic non-A, non-B hepatitis)
- **Not Endemic or Endemcity Unknown**
HEV course
CAG Trial

Study Protocol

- Diagnosis of Patient
  - Is diagnosis TIP?
    - No: Do not enroll
    - Yes: Does patient meet study criteria?
      - No: Do not enroll
      - Yes: Has patient given informed consent?
        - No: Do not enroll
        - Yes: Start anti-platelet or steroid drug therapy (optional)
          - RANDOMIZE Registration (send Consent & Form A)
            - Start plasma exchange with SDP
            - Start plasma exchange with CSP
              - 1.5 PV PE days 1, 2 & 3
                - Minimum of 4 x 0.5 PV PE over 6 days
                  - Follow-up 5 days (send Forms B & C): assess response & proceed with subsequent
          - Follow-up 1 Month (Form D)
            - Follow-up 6 Months (send Form D)
              - End of Study
A retrospective study

Samples taken at
pre, 1 and 6 months post treatment

N=38 acquired, primary TTP/HUS

Median age 49  M:F  1:2.1

1.5 PV X 3days then 1 PV
Evaluation for Hepatitis E

ANTIBODY DETECTION

1  MP Diagnostics HEV ELISA kit (Singapore)
2  Wantai HEV EIA (China)
   use recombinant antigens

HEV RNA

1  commercial
2  in house
RESULTS

N=38          19 CSP        2 FP        17  SDP

• Pre and 1 month   all –ve for HEV by ELISA

• At 1 mon          * 2/4 SDP had HEV RNA

At 6  mon          2/4 also had anti-HEV IgM
but all –ve for HEV RNA

* 1 by real-time PCR   1 by nested RT-PCR
Retest all by Wantai EIA

ONLY 2/4 previously anti IgG +ve = true

• Also had other markers for HEV infection
  anti-HEV IgM at 6 months and
  HEV RNA at 1 month

  same lot of SDP    unable to test lot

Other 2/4 evidence of prior immunity
Evidence of **passive transfer** of anti-HEV IgG

2 patients on SDP
1 patient on CSP

HEV seroprevalance in US is 21%
CONCERNS

HEV + donor may be asymptomatic with normal AST/ALT
1:2 to 1:13 developing world CDC 2012

HEV in serum not neutralized by immune sera

SDP treatment neutralizes 50% Takahashi 2010
Conclusions

No US report of HEV via transfusion

but

Data suggest high likelihood of HEV via Vitex SDP transmission in pooled plasma
Hepatitis E from blood

So it can happen, it did happen
And it will happen again

As practitioners we need to
Consider how to avoid this hazard
For Plasma Exchange

- Av TTP patient gets 40 litres of fluid
- Usually FP, CSP or a PIP

Pathogen inactivated plasma & HEV

- Intercept 2 cases France Hayser, Blood 2014
- SDP Vitex Octaplas 2001 off the market
  2 versions
- Mirasol inactivates JRC Owada
  Transfusion 2013
WHAT’S NEXT?

thank you

Gail Rock

Canadian Apheresis Group
PHAC
HEV CLINICAL FEATURES

- Incubation period: 3 to 8 weeks
- Viremia: 4-6 weeks
Figure 2: Geographic Distribution of Four Human HEV Genotypes

• The following slides are from Dr. Andonov, sent by email: May 27, 2013

• (The background graphics etc., did not copy, so we have mostly basic text.)
<table>
<thead>
<tr>
<th>HEV OUTBREAKS</th>
<th>No. of people affected</th>
<th>Type of transmission</th>
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</thead>
<tbody>
<tr>
<td>New Delhi, India (1955-56)</td>
<td>&gt;29,000</td>
<td>Waterborne (Yamuna river)</td>
</tr>
<tr>
<td>Kirgiz Republic of USSR (1955-56)</td>
<td>&gt;10,000</td>
<td>?</td>
</tr>
<tr>
<td>Myanmar (1976-77)</td>
<td>20,000</td>
<td>Waterborne</td>
</tr>
<tr>
<td>Kashmir, India (1978)</td>
<td>52,000</td>
<td>Waterborne</td>
</tr>
<tr>
<td>Somalia (1988-89)</td>
<td>11,000</td>
<td>Waterborne (Shebeli river)</td>
</tr>
<tr>
<td>Mexico (1988-89)</td>
<td>4,000</td>
<td>Waterborne</td>
</tr>
<tr>
<td>Kanpur, India (1991)</td>
<td>79,000</td>
<td>Waterborne (Ganges)</td>
</tr>
<tr>
<td>China (1991)</td>
<td>119,000</td>
<td>Waterborne</td>
</tr>
<tr>
<td>Darfur, Sudan (2004)</td>
<td>&gt;2600</td>
<td>Waterborne (0.3-06mg/l chlorine for 30’=insufficient HEV inactivation)</td>
</tr>
<tr>
<td>Uganda (2008)</td>
<td>&gt;10,000</td>
<td>Person-to-person</td>
</tr>
</tbody>
</table>
This study estimated 20.1 million incident HEV infections across the nine out of 21 GBD Regions * resulting in 70,000 deaths, and 3,000 stillbirths.

* Global Burden of Diseases, Injuries, and Risk Factors (GBD nine Regions represent 71% of the world's population).
The potential of hepatitis E virus (HEV) as a threat to blood safety

Anton Andonov

Public Health Agency of Canada, National Microbiology Laboratory, Molecular&Immunodiagnostics, Bloodborne Pathogens&Hepatitis Viruses

PDA 4th Virus & TSE Safety Forum ; June 4, 2013
HEV Discovery:

In 1983, Dr. Michael Balayan was investigating an outbreak of non-A, non-B hepatitis in a central Asian part of the Soviet Union.

Though he wanted to bring samples back to his Moscow laboratory, he lacked refrigeration. So he made a shake of yogurt and an infected patient’s stool, drank it, went back to Moscow, and waited.

When he became seriously ill a few weeks later, he started collecting and analyzing his own samples. In these he found a new virus that produced liver injury in laboratory animals and could be seen by electron microscopy. It looked a lot like hepatitis A virus, but he could show that it was not, because he already had antibodies against the hepatitis A virus and these did not react with the new virus. Balayan MS, Andjaparidze AG, Savinskaya SS, et al. (1983). "Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route". Intervirology 20 (1): 23–31.

HEPEVIRIDAE
HEPEVIRUS

ORF1 – 5kb
Met Y PCP Pr X H RdRp

Orf3

ORF2 – 2kb
Capsid

5'-utr

3'-utr

Poly (A)

5124 ...
gcggtagaatgatacatgttttgcatgcgccatgggactaccatgcgcct...

5180

Orf1 stop

Orf 3 start

Orf 2 start
Cell culture systems for propagation of HEV

- Human hepatocellular carcinoma PLC/PRF5 cell line
- Human lung cancer A549 cell line
- Human HeG2 and HuH7 cell lines (not permissive for wild-type strains of feces origin, but capable of supporting cell-culture adapted HEV strains).

HEV genotype 1, 3 and 4 from feces and serum grow in vitro.

Characterization of HEV particles in culture supernatant, circulating blood and feces

HEV in culture supernatant and serum samples: sucrose gradient density of 1.15g/ml
HEV in feces: sucrose gradient density of 1.27g/ml

Deoxycholic acid – 1.21-1.24g/ml
+trypsin – 1.27g/ml

HEV in serum cannot be neutralized by anti-HEV (+) immune sera and anti-ORF2 monoclonal antibodies!
HEV epidemiology: Hosts

Direct: virus detection

Indirect: anti-HEV detection
HEV epidemiology: mode of transmission

A. Waterborne, (faecal contamination of drinking water).

B. Zoonotic:
   B1. Foodborne
   B2. Non-foodborne through direct contact with animals

C. Bloodborne (infected blood products)

D. Person-to-person (rare?)

E. Vertical (two mother-to-child reports)

F. Nosocomial ?? (hemodialysis patients)

G. Parenteral?? (intravenous drug users)
HEV prevention and therapy

Provision of clean drinking water and improving of sanitary infrastructure.

Immunization:

1) Experimental GlaxoSmithKline Recombinant (ORF2 expression of 56kDa protein- VLPs in insect cells), highly immunogenic, with 95.5% efficacy (1800 volunteers in Nepal, followed for 804 days; HEV developed in 3 volunteers among the vaccinees compared to 66 in the placebo group).

2) Commercial; Hecolin (Xiamen Innovax Biotech, Xiamen, China). ORF2 (aa 368-660) expressed in E.Coli as VLPs. Efficacy after 1 year; 100%, down to 78.3% after two years of observation (22 asymptomatic cases among 3,567 vaccinees compared to 101 HEV cases among 3548 participants of the placebo group. Only 3 symptomatic HEV cases in total, all in the placebo group.

Ribavirin monotherapy (600–1000 mg/day) for at least 3 months seems to be the first treatment option for transplant patients with chronic hepatitis E.
The HEV “Renaissance”

there has been renewed interest in HEV due to

• Increase of HEV genotype 3 (“zoonotic type”).

• HEV and chronic liver disease in immunocompromised patients.

• HEV and blood transfusion.
HEV transmission through blood transfusion


56 transfusion recipients
19 anti-HEV IgG(+)
from 37 anti-HEV IgG(-) two seroconverted, one with ^ALT^=120IU/ml, no overt hepatitis. No HEV RNA, but samples 17 years old. HEV genotype ??


A: retrospective study
Anti-HEV IgM(+) detected in 13/145 transfused patients compared to 2/250 healthy controls (p<0.001; OR=12.21). HEV RNA(+) detected in 8/145 transfused patients compared to 2/250 healthy controls (p=0.004; OR=7.24).

B: prospective study
107 blood units transfused to 25 surgical patients; 4 units later found to be HEV RNA (+). Of the 25 patients 23 were susceptible before the transfusion. Of these laboratory evidence for HEV infection (HEV RNA(+) and anti-HEV IgM/IgG(+)) one month post transfusion found in two patients. The third transfused with HEV RNA (+) blood had no laboratory markers of HEV infection. All asymptomatic. HEV genotype ??
HEV transmission through blood transfusion cont.

(1) Hokkaido, Japan, 2004

559,545 blood donations (2000-02)
15,285 (2.7%) disqualified (ALT>60IU/l
40 had ALT>500 IU/l
18 tested for HEV RNA
6 found (+) genotype 4

<table>
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<th>46</th>
<th>51</th>
<th>66</th>
<th>78</th>
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<th>93</th>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Anti-HEV IgG</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

(2) Nagoya, Japan, 2004; hemodialysis patient after transfusion of 2 units of blood. Anti-HEV IgG but no IgM seroconversion, HEV RNA (+). Asymptomatic, ALT not increased. HEV genotype 3

(3) United Kingdom (UK), 2006; donor developed jaundice two weeks after donation, however blood products already transfused to two patients.

A) Transfusion of platelets to patient 1 (with estimated 3-4 ml of plasma) did not result in HEV infection on follow-up.
B) Transfusion of red blood cells to patient 2 (with estimated plasma of up to 30 ml) caused asymptomatic HEV Infection (seroconversion to anti-HEV IgG and HEV RNA(+), but no anti-HEV-IgM, ALT normal. HEV genotype 3
HEV transmission through blood transfusion cont.

(4) Tokyo, Japan, 2007; patient with T-cell lymphoma developed HEV infection after transfusion with 1 unit of red blood cells. ALTs = 600 IU/l. HEV genotype 3.

(5) Marseille, France, 2007; patient with rhabdoid tumor kidney developed HEV infection after transfusion with concentrated red blood cells (310 ml). ALTs = 2000 IU/l. Anti-HEV IgM weak(+), IgG remained negative. HEV genotype 3f.

(6) Hokkaido, Japan, 2008; patient with non-Hodgkin lymphoma developed HEV infection after transfusion with 200 ml of platelet concentrate. ALTs=600 IU/l, HEV RNA(+), anti-HEV IgG seroconversion, no IgMs. Symptomatic. HEV genotype 4. Donor viral load =3.1 logs copies/ml.

(7) Germany, 2013; a recipient transfused with HEV RNA(+) red blood cells remained negative for HEV RNA until day 41 posttransfusion. Insufficient infectious dose?
HEV transmission through blood transfusion cont.

Prevalence of HEV RNA among Japanese blood donors

2004 Study;
No HEV RNA(+) found among donors with normal ALT (<60 IU/l.
Three HEV RNA(+) among donors with elevated ALTs (966,62 and 61 IU/l) for a prevalence of 0.27%

2007 Study;
Donors with ALTs>61 IU/ml:
  1998; 0.3% HEV RNA(+)
  2004-06; 0.2% HEV RNA(+)
Donors with ALTs>201 IU/ml:
  1991-95: 1.3% HEV RNA(+)
  1996-99; 3.4% HEV RNA(+)
  2004-06; 3.3% HEV RNA(+)
Donors with normal ALTs; 0.067% HEV RNA (+)

2008 Study;
Hokkaido Donors with ALTs >500 IU/l -19.5%
  Donors with ALTs>200 IU/ml - 1.1%

All HEV RNA(+) samples were genotype 3 and 4.
HEV transmission through blood transfusion cont.

Prevalence of HEV RNA among blood donors

**Germany:**
Study 2012; 4/18,100 blood donors - 0.022% or 1:4525 (S.A. Baylis et al.)
Study 2012; 13/16,125 blood donors - 0.08% or 1:1240 (T. Volmer et al.)
Study 2013; 14/93,955 blood donors - 0.015% or 1:6711 (V.M. Corman et al.)

**Sweden 2012;**
12/95,835 blood donors - 0.012% or 1:7986 (S.A. Baylis et al.)

**United Kingdom 2012;** 42,000 blood donors - 0.014% or 1:7040 (S.Ijaz et al.)

**China 2010;** 46,816 blood donors - 0.067%. Note limited to only anti-HEV IgM (+) donors, therefore probably underestimated. (Q.S.Guo et al.)

Compare with residual risk of:
HBV 1:1,700,000
HCV 1:6,700,000
HIV 1:8,000,000
at Canadian Blood Services (CBS)
Thrombotic thrombocytopenic purpura (TTP) is a severe blood disorder characterised by extensive clots (platelet-rich thrombi) within the blood vessels causing thrombocytopenia, hemolytic anemia and neurological and renal impairment. Plasma exchange (1.5 volumes every day for the first 3 days) is considered the standard therapy for TTP.

**Thrombotic Thrombocytopenic Purpura treatment**

- **Cryosupernatant (CSP)**
- **Solvent-Detergent Treated Plasma (SDP)**

**Canadian blood services (CBS)**
- 220 ml/bag
- ~ 15 bags daily
- ~ 10 treatments
- 150 bags
- or total 33 litres from 150 blood donors

**U.S. Donors (VITEX)**
- Plasma pool size ~ 2500 donors
- SD treatment
- ~ 20-40 litres
Thirty-eight TTP patients received plasma exchange treatment (20-40 litres of plasma per patient); seventeen received SD-plasma, nineteen were treated with cryosupernatant plasma and two with fresh frozen plasma and Pentaspan or albumin.

None of the patients demonstrated any clinical signs of viral hepatitis during the 6-month period of observation.
<table>
<thead>
<tr>
<th>Type of plasma</th>
<th>No. patients</th>
<th>Evidence of HEV infection</th>
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</thead>
<tbody>
<tr>
<td>SDP</td>
<td>17</td>
<td>4</td>
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<tr>
<td>CSP</td>
<td>19</td>
<td>0</td>
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<tr>
<td>FFP</td>
<td>2</td>
<td>0</td>
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</table>

- **FJ705359 Germany wild boar 3i**
- **Bulgaria-749**
- **Bulgaria-698A**
- **FJ527832 China human**
- **Bulgaria-1279A**
- **Bulgaria-587**
- **AB248521 Japan swine 3e**
- **Bulgaria-77A**
- **Bulgaria-77**
- **AF455784 Kirgizia swine 3g**
- **AB073912 swine 3b**
- **AP003430 Japan human 3a**
- **AF082843 US swine**
- **AY575857 US swine 3a**
- **2026 05 Canada TTP**
  - **H5787/11 5166-5349**
  - **H4566/11 5166-5349**
  - **H4510-09**
  - **H4510/09 5067-5349(5166-6386)**
  - **H5024/10 5067-5349**
  - **H3213/11 5067-5349**
- **AF060669 US-2 human 3a**
- **H0181/12 5166-5349**
- **AY115488 Canada swine 3j**
- **NE8/12 5166-5349**
- **Bulgaria-905**
- **H-12 3375**
- **AJ271108 China HEV4**
- **M73218 Burma HEV1**
- **M74506 Mexico HEV2**

Anti-HEV IgG test performed with MP Biomedicals; former Genelabs

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Anti-HEV IgG</th>
<th>Anti-HEV IgM</th>
<th>HEV RNA</th>
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<td>0 1 6</td>
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<td>2021</td>
<td>57</td>
<td>(-) (-) (+)</td>
<td>(-) (-) (-)</td>
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<td>41</td>
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<td>28</td>
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0.02
### Anti-HEV IgG performed with WANTAI KIT

<table>
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<tr>
<th>Patient ID</th>
<th>SDP or CSP</th>
<th>Anti-HEV IgG</th>
<th>Anti-HEV IgM</th>
<th>HEV RNA</th>
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<td>(-)</td>
<td>(+)2.6</td>
<td>(+)15.1</td>
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<td>(+)1.1</td>
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<td>Patient ID</td>
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<td>Other patients receive same lot?</td>
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<tr>
<td>2007</td>
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<td>FZ10206</td>
<td>31,765ml 20,283ml 29,917ml</td>
<td>Yes (2021) No No</td>
<td>Yes 04/08/2001</td>
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<td>20,000ml 17,400ml 400ml</td>
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<td>22,600ml 6,800ml 22,800ml</td>
<td>Yes (2026, 2036) Yes (2017, 2021, 2036) Yes (2019, 2036)</td>
<td>No</td>
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</table>
Hepatitis A – reported incidence by sex, Canada 1990-2008

Rates per 100,000

Year


Male
Female
Assuming that the average incidence of HEV infection is 1.0 per 100,000 person years:

**QUESTION?**

What is the probability for HEV infection in a group of 17 TTP patients to be A) 0; B) 2 or more than 2 cases in 1 year period?

\[
\Pr(2 \text{ HEV infections}) = \frac{r(2) \cdot e^{-r}}{2!} = \frac{2 \cdot 0.00017 \cdot 0.99983}{2} = 1.44475 \times 10^{-8}
\]

Based on Poisson regression model, the probability that two or more cases of HEV infection occurred in that group during 12 months is 0.000169957.

In other word, with a P value of 0.000169957 there is only a 0.017% (or 1:5882) chance that the occurrence of two or more HEV infections would have come up in a random distribution, assuming the model is specified correctly.
Summary:

- The regularity of relatively high occurrence of transient HEV viremia among asymptomatic blood donors from different geographical areas clearly demonstrates the potential for HEV transmission from blood products. In order to mitigate the impact on blood safety HEV screening for plasma pools should be considered.

- Nucleic acid testing (NAT) is the most reliable laboratory method for screening the blood supply.

- HEV NAT selective screening of blood components intended for transplant and other immunocompromised patients should be introduced to prevent transfusion associated HEV infection depending on the endemicity of each country or region within a country.

- In Canada universal screening of the blood supply for HEV is not considered at present; however that may change as more data about the rate of viremia in asymptomatic Canadian blood donors is established as well as more information about the HEV infectious dose and related outcomes in recipients becomes available.
Acknowledgements
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