Hepatitis E Virus in Transfusion and Transplantation: UK situation

Lorna Williamson
UK Advisory Committee for Safety of Blood Tissues and Organs (SaBTO):
HEV Working Group 2014-16

To establish HEV incidence/prevalence in donors of blood, stem cells, tissues, organs and gametes

To understand the clinical risks of HEV in transfusion and transplant recipients

To determine the optimal strategy to mitigate any clinical risks identified.
Reported HEV infections to Public Health England

- **Total**
- **Indigenous**
- **Travel**

Year:
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013

Number:
- 0
- 100
- 200
- 300
- 400
- 500
- 600
- 700
- 800
HEV infection in UK

- Clinical cases increasing (Public Health England enhanced surveillance):
  - England: 600/yr in 2012 to 800/yr in 2014
- Attack rate: 0.1-0.2%/yr = 1 in 500/yr.
- Prevalence of immune antibody:
  - 13% England
  - Increases with age
  - May have fallen over last 20 years
HEV natural history

- Increasing in W Europe, genotypes 3 and 4; linked to pork, wild boar, venison
- Incubation period 40 days; virus in blood for 3 weeks; then IgM and IgG with viral clearance.
- Asymptomatic or mild symptoms; jaundice rare
- ?extra-hepatic features.
- BUT ? fulminant/chronic if immunosuppressed/underlying liver disease
UK pigs all carry HEV but it’s different to UK humans
HEV in UK people matches that in pigs from Denmark and Netherlands ----
Prevention and treatment

- Thorough cooking of pork products
- Hand hygiene in food handlers
- No vaccine licenced in Europe
- Most cases need no specific treatment
- In immunosuppressed, ribavirin for 3 months effective
HEV in immunosuppressed

- Small case series reporting progression to chronic carriage/liver disease in up to 60% of infected solid organ transplants
  - Could be confused with liver rejection
- Chronic liver disease also reported in allogeneic stem cell transplant recipients (case reports)
  - Could be confused with GvHD
- Chronic carriage in some HIV positive people
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma Discovered via donor lookback</td>
<td>Stem cell transplant recipient</td>
<td>Ca. bladder Ca. prostate (129 donor exposures)</td>
<td>Liver disease Encephalopathy</td>
</tr>
<tr>
<td>Red cells</td>
<td>FFP</td>
<td>FFP</td>
<td>FFP</td>
</tr>
<tr>
<td>Cleared virus</td>
<td>Died other causes</td>
<td>Cleared virus</td>
<td>Cleared virus</td>
</tr>
</tbody>
</table>
Risks in specific transfusion recipients

No clinical cases reported via transfusion:

– Pregnancy
– Neonates & infants
– Haemoglobinopathy patients
– HIV positive people (though HEV is described)

BUT low awareness of HEV amongst clinicians
Viraemia rates from blood donor surveys

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>RNA positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>2012-13</td>
<td>1 in 2218</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2013</td>
<td>1 in 1761</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2011-12</td>
<td>1 in 2671</td>
</tr>
<tr>
<td>Germany</td>
<td>2011</td>
<td>1 in 1240</td>
</tr>
<tr>
<td>[Scotland]</td>
<td>2004-08</td>
<td>1 in 14,520</td>
</tr>
<tr>
<td>England</td>
<td>2012-13</td>
<td>1 in 2848</td>
</tr>
</tbody>
</table>
NHSBT/PHE

donor/recipient study
(Hewitt et al Lancet 2014)

• Only donor/recipient study so far
• Donors 1 in 2848 virus positive
• 18/43 recipients had evidence of HEV transmission (40%)- 6 had antibody and 12 RNA
• Transmission from red cells, FFP, platelets, granulocytes
• Transmission rates higher if high viral load/large plasma volumes (small nos)
Effect of immune suppression on recipient outcome
(Hewitt et al Lancet 2014)

<table>
<thead>
<tr>
<th></th>
<th>NONE/MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>10 weeks of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HEV in</td>
<td>in 8</td>
<td>in 5</td>
<td>in 2/3</td>
</tr>
<tr>
<td>Viral clearance</td>
<td>in 8</td>
<td>in 3/4</td>
<td>in 2/3</td>
</tr>
<tr>
<td>Clinical hepatitis:</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Organ and stem cell transplant recipients appear to be at highest risk of serious clinical sequelae

They might acquire HEV from blood, from diet, and from the transplant - how best to protect?
## Infection risk from transfusion

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Probability of Clinically significant HEV Infection</th>
<th>Transplant Activity 2013-14 UK</th>
<th>Number of years before HEV infection via transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Estimate</td>
<td>Upper Estimate</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.122%</td>
<td>0.140%</td>
<td>900</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.006%</td>
<td>0.007%</td>
<td>3,055</td>
</tr>
<tr>
<td>Lung</td>
<td>0.098%</td>
<td>0.112%</td>
<td>210</td>
</tr>
<tr>
<td>Heart</td>
<td>0.061%</td>
<td>0.070%</td>
<td>197</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.027%</td>
<td>0.031%</td>
<td>261</td>
</tr>
<tr>
<td>Intestinal</td>
<td>0.061%</td>
<td>0.070%</td>
<td>26</td>
</tr>
<tr>
<td>Multivisceral</td>
<td>0.851%</td>
<td>0.978%</td>
<td>13</td>
</tr>
<tr>
<td>Heart/Lung</td>
<td>0.147%</td>
<td>0.168%</td>
<td>8</td>
</tr>
<tr>
<td>Kidney &amp; Pancreas</td>
<td>0.033%</td>
<td>0.038%</td>
<td>188</td>
</tr>
<tr>
<td>Kidney &amp; Heart</td>
<td>0.067%</td>
<td>0.077%</td>
<td>1</td>
</tr>
<tr>
<td>Kidney &amp; Liver</td>
<td>0.128%</td>
<td>0.147%</td>
<td>12</td>
</tr>
<tr>
<td>Allogeneic Stem Cell</td>
<td>0.232%</td>
<td>0.267%</td>
<td>1,615</td>
</tr>
</tbody>
</table>
## Strategies to provide ‘HEV-safe’ blood components

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor selection by occupation or diet</td>
<td>No (vegetarians only 7%)</td>
</tr>
<tr>
<td>Test donors for HEV RNA</td>
<td>Yes</td>
</tr>
<tr>
<td>Create donor panel with immune anti-HEV</td>
<td>No</td>
</tr>
<tr>
<td>Pathogen inactivation of FFP or platelets</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>
RNA HEV testing of blood donors

- 2 CE marked suppliers- Roche & Grifols
- Can be done in 16-24 pools
- In-house confirmatory assay available
- Manageable impact on supply
  - Donors would be deferred for 6 months
  - Need to retest before return to donation
  - No lookback if previous donations < 4 months
International situation re blood donor screening

• Netherlands - next speaker!
• France: testing for Octaplas manufacture and some FFP
• Ireland: universal testing for 5 years from Jan 2016 - individual NAT
• EBA survey ongoing
• Surveys in N America, Australia, Japan
Pathogen inactivation

- No licensed systems for red cells
- Platelets
  - Mirasol- no information, little routine use
  - Intercept- no information, transmissions from FFP
- FFP
  - Intercept - 2 transmissions
  - Methylene blue - no information
  - Solvent detergent – previous transmissions from N American product; Octaplas now tested for RNA/antibody
Policy considerations

• Product liability lies with Blood Services
• Precautionary principle if uncertainty
• Penrose Inquiry – HIV/HCV in Scotland
• Not enough outcome data to calculate cost-effectiveness
• Proportionate response for high-risk recipients
• Universal vs selective testing
  – Can hospital staff/computers manage it?
  – Do hospitals/Blood Services know what blood is used for when not testing?
HEV is evolving, evidence is limited, so the situation needs to be kept under review.

A. There is no pressing case for screening of the entire blood supply at this time.

B. Transplant recipients and patients with chronic liver disease are at particular risk of serious sequelae. Therefore UK Blood Services should, without delay, prepare costed plans to provide HEV tested components for such patients.

C. Organ/stem cell donors should be tested if liver function is abnormal

D. HEV testing should be performed in transplant patients if liver function becomes abnormal
SaBTO Recommendations (2)  
April 2015

E. Awareness of HEV needs to be increased amongst clinicians treating transplant patients, pregnant women, neonates and transfusion-dependent patients.

F. No specific mitigation steps are needed for recipients of tissues*, gametes or embryos.

*consider pancreatic islets and hepatocytes as organs.
SaBTO special meeting July 2015: Recommendations

• Provide tested components for stem cell and solid organ transplant recipients

• Testing in pools of 24, 6 month donor deferral
  – To be implemented early 2016

• Information and dietary advice sent to transplant clinicians for patients
1. Provide HEV-negative components for **allogeneic** stem cell transplant patients

   - start 3 months before transplant and at diagnosis for acute leukaemia if potentially transplantable
   - continue until 6 months after transplant, or off immunosuppression
   - NOT autologous stem cell transplant recipients
SaBTO/
British Transplantation Society
Jan 2016 – detailed policy for organ recipients

2. Provide HEV-tested components for solid organ transplant recipients
   - from time of listing for transplant
   - continue while on immunosuppression
   - also for extra-corporeal perfusion
UK Blood Services position

Selective screening starts March/April 2016 as per recommendations

ALSO HEV-neg components for neonates

- highly transfused and long-lived
- clinical picture unknown
- by-product of testing for transplants
- modest extra cost.
Transmissions from organs and stem cells

• One reported transmission from a transplanted liver (not in UK)

• Approx one organ donor/year calculated to be virus positive

• One stem cell donor with acute HEV
Ongoing policy issues

• Easy to test living donors
• Strategy for testing deceased organ donors - results not available until after transplants done
• Strategy for transplant recipients
Infections in Transplant Recipients from Diet

- **Annual Dietary Attack Risk: 0.2% = 1 in 500/yr**

- **Liver transplant - 1 person/yr predicted to have HEV infection via blood, but 16 infections/yr predicted through diet in all recipients.**

<table>
<thead>
<tr>
<th>Transplant</th>
<th>Number of years before HEV infection via transfusion</th>
<th>Number of transplants functioning at 31 March 2014</th>
<th>Yearly HEV infections via diet for all living transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1-2</td>
<td>8,300</td>
<td>16-17</td>
</tr>
<tr>
<td>Kidney</td>
<td>4-5</td>
<td>31,000</td>
<td>62-63</td>
</tr>
<tr>
<td>Lung</td>
<td>4-5</td>
<td>3,600</td>
<td>7-8</td>
</tr>
<tr>
<td>Heart</td>
<td>7-8</td>
<td>3,600</td>
<td>7-8</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12-14</td>
<td>1,800</td>
<td>3-4</td>
</tr>
<tr>
<td>Intestinal</td>
<td>54-62</td>
<td>100</td>
<td>0-0.5</td>
</tr>
</tbody>
</table>
Prevalence of HEV infection in organ and allogeneic stem cell transplant recipients

• Audit Objectives:

1. Determine the prevalence of HEV viraemia in organ and stem cell recipients on immunosuppressive agents (cyclosporin or tacrolimus)
   - Biochemistry samples tested for HEV RNA in 16 pools

2. Follow up identified HEV-infected recipients in order to monitor outcome.

3. Understand factors associated with outcome of HEV infection.
Prevalence of HEV infection in organ and allogeneic stem cell transplant recipients (in progress)

- 784 tested in 49 pools of 16
  - 6/49 positive pools resolved
  - Resolution
    - 4 confirmed RNA positive = 0.51% = 1 in 200
    - 3/4 IgM/IgG positive, ¼ IgM/IgG negative
    - Confirmation ongoing outside of audit. Clinical data capture separate.
National register of chronic HEV cases

• **Aims:**
  1. Monitor numbers to assess scale of issue,
  2. Collate data on liver biochemistry to inform testing strategies,
  3. Identify risk factors for persistence to help identify at-risk groups
Chronic HEV cases: snapshot

- **Sex**
  - Male
  - Female

- **Age**
  - 0-17
  - 18-24
  - 35-59
  - 60+

- **Underlying disease**
  - SOT
  - HSCT
  - HIV+
  - Haematological malignancy (without HSCT)
  - Chemotherapy/other
  - Unknown (insufficient data)

- **Treatment**
  - Treated
  - Not treated/No data/considered for treatment

- **Outcome**
  - Viral clearance
  - Ongoing viraemia (no intervention)
  - Death with ongoing viraemia
  - Unknown/insufficient follow up time/currently on treatment
Chronic HEV in a non-immunocompromised patient----an interesting case....

• 64 ♂
  – PMH: Hypertension/Previous TIA
  – Acute HEV Sept 2014 – hepatology- pos serology
    • Travelled to Southern France Aug 2014 – duck liver
  – Discharged to GP as liver function tests had near normalised
  – re-referred to hospital in Jan 2015 with ‘grumbling LFTs’
An interesting case….

ALT over time
An interesting case....

- **64 ♂**
  - HEV RNA positive Jan 2015
  - Liver biopsy – mild fibrosis
  - Fibroscan 10.1kPa (intermediate fibrosis)
  - Jan 16- still HEV RNA pos (>53 weeks)
  - **No immunocompromise identified**
    - HIV negative/Normal total WCC/No immunosuppression
Acknowledgements

• Pat Hewitt, Richard Tedder, Samreen Ijaz, Steven Dicks, PHE/NHSBT Bloodborne virus lab
• Su Brailsford & NHSBT/PHE epidemiology team
• James Neuberger & NHSBT organ donation & transplant team
• Michael Ankcorn, clinical research fellow
BACKUP
Solvent-detergent FFP

• Pooled product, licensed medicinal (Octaplas)
• Two transmissions reported from Vitex product Canada
• Octapharma now requesting tested plasma and will set safe levels for pools
• **UPDATE**
• Could become safe option for high risk patients
Clinical features other than hepatitis

- Mainly studied by Dalton et al in Exeter; SW England
- Neurological: Guillain-Barré, neuropathies
- Renal, pancreas, thyroid
- Low platelets, high lymphocytes
- Remain to be confirmed in other series
Collection of Donor Samples

Manchester - Blood Donors Collected

Filton - Blood Donors Collected

(data correct as of 3rd February 2016)

(in progress, as at 3rd Feb 2016)

Aiming to test 14,500 samples

- Donor plasma screened using Fortress HEV IgG ELISA Assay

<table>
<thead>
<tr>
<th>Collection Site</th>
<th>Racks Tested</th>
<th>Donors Screened</th>
<th>IgG Reactive Donors</th>
<th>HEV Seroprevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester</td>
<td>55</td>
<td>4840</td>
<td>422</td>
<td>8.72%</td>
</tr>
<tr>
<td>Filton</td>
<td>50</td>
<td>4400</td>
<td>717</td>
<td>16.30%</td>
</tr>
<tr>
<td>Combined Totals</td>
<td>105</td>
<td>9240</td>
<td>1139</td>
<td>12.33%</td>
</tr>
</tbody>
</table>
HEV Seroprevalence – Age & Gender

HEV Seroprevalence (Percentages derived from 9,240 Blood Donors)

(data correct as of 3rd February 2016)
National register of chronic HEV cases

• Background
  – Recognition of Chronic HEV (G3) in immunocompromised patients in Europe
  – Not really recognised as a problem in UK
    • Most data from hyperendemic areas of France
    • ~62 cases known to PHE across England/Wales since 2007
  – But
    • No testing strategy – risk factors not defined
    • Clinical outcome data including response to treatment largely unknown
    • HEV RNA testing at local centres impact ability to monitor these infections
Prevalence of HEV infection in SOT recipients & HSCT

• **Background:**
  - Chronic HEV occurs in immunocompromised patients
  - PHE are aware of ~62 patients since 2007

• However we do **not** know:
  - Prevalence of viraemia in UK cohorts
  - Optimal testing strategy
    - screening annually/3m vs with deranged LFTs
  - Risk factors for chronic infection and outcomes in such patients
National register of chronic HEV cases

• Concept:
  – Central register hosted by PHE
  – Unlinked clinical data:
    • Underlying disease/immunosuppression
    • Clinical symptoms and liver dysfunction
    • Treatment outcomes
    • Adverse events of treatment
SaBTO recommendations: further information needed

- The changing epidemiology in blood donors
- HEV acquisition, chronicity and clinical sequelae in transplant recipients
- HEV acquisition in transfusion-dependent patients and transfused neonates/children
- Effectiveness of pathogen inactivation methods for platelets and FFP
Should transplant recipients be tested?

• Close to 50,000 living recipients
• Ongoing infection risk through diet- ?80-100/yr
• Number with chronic carriage unknown; treatable with ribavirin
• Severe liver disease a risk
• Costs of testing all recipients once ~£0.5M
Prevalence of HEV infection in SOT recipients & HSCT

• Audit Methods:

• SOT & HSCT recipients undergoing therapeutic drug monitoring (TDM)
  – De-duplicated in Birmingham
  – Separate aliquot to Colindale

• Tested for HEV RNA in Minipools of 16

• Positive pools are resolved
  – tested individually for RNA & serology
QE, Birmingham - sampling
- TDM samples - separated plasma
- After de-duplication 200 samples/week batched and sent every 2 weeks
- Total ~5000 patients

Colindale - testing
- Minipools of 16 (100ul)
- Extract on Qiasymphony (1.6ml in - 1ml extract)
- HEV Taqman with standards $10^4$, $10^3$, $10^2$ and IC

Resolution of minipools
- Extracted from original tube on NP96 (200ul)
- HEV Taqman with standards $10^7$, $10^6$, $10^5$, $10^4$, $10^3$, $10^2$ and IC

Positive results
- Serology performed
- Lead clinician informed

Outside of audit
- 2nd sample to confirm
- Monthly monitoring
- Clinical data capture for steering committee