Hepatitis E Transmission in Blood Components:

New recommendations for immunocompromised patients
Overview

- Hepatitis E Virus (HEV): Transmission, incidence and presentation
- Emerging evidence regarding HEV transmission from blood components and dietary consumption
- Latest SaBTO recommendations
- Guidance regarding signs/symptoms, investigations and management of transplant patient with suspected HEV
- Implementing changes
Hepatitis E

- Hepatitis E Virus (HEV)
  - RNA virus
  - Four genotypes:
    - 1 + 2 are human viruses
    - 3 + 4 are animal viruses (transmitted zoonotically)

- Increase in the reported cases of HEV arising from infection acquired in the UK i.e. ‘non-travel associated’

- Cases of non-travel associated infection are most likely to be:
  - Caused by the genotype 3 stain (associated with pigs)
# Hepatitis E

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of confirmed cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>124</td>
</tr>
<tr>
<td>2004</td>
<td>149</td>
</tr>
<tr>
<td>2005</td>
<td>329</td>
</tr>
<tr>
<td>2006</td>
<td>289</td>
</tr>
<tr>
<td>2007</td>
<td>162</td>
</tr>
<tr>
<td>2008</td>
<td>176</td>
</tr>
<tr>
<td>2009</td>
<td>175</td>
</tr>
<tr>
<td>2010</td>
<td>274</td>
</tr>
<tr>
<td>2011</td>
<td>456</td>
</tr>
<tr>
<td>2012</td>
<td>578</td>
</tr>
<tr>
<td>2013</td>
<td>692</td>
</tr>
<tr>
<td>2014</td>
<td>869</td>
</tr>
<tr>
<td>2015</td>
<td>190 (Jan to March)</td>
</tr>
</tbody>
</table>

Hepatitis E

- HEV is passed via oral-faecal route (contaminated sewage) in developing countries
- In developed counties, transmission potentially linked to:
  - eating under-cooked pork and game, processed pork products and some shell fish
  - transmission via blood components and organ transplantation
    - HEV detected in pooled plasma products
Hepatitis E

- Usually presents as an acute but mild transient illness requiring supportive management only
- Average incubation period is approximately 40 days
- Symptoms can last on average 1-4 weeks
  - Some asymptomatic
  - Mild non-specific illness (fatigue, fever, nausea/vomiting)
  - Derangement in liver enzymes and jaundice
Hepatitis E

- Immunocompetent patients are usually able to clear the virus.
- In immunosuppressed patients, such as those undergoing transplant, HEV is more difficult to clear.
  - Lead to chronic changes including chronic inflammation and potential to develop cirrhosis.
Hepatitis E risk from blood donations

One in almost every 5,000 blood donors in England could be infected with hepatitis E, according to a new study.

Experts said that around 1,200 transfusions containing the virus are likely to be given to patients every year in England.
Lancet Paper: Hepatitis E virus in blood components: a prevalence transmission study in southeast England

• Published July 2014

• NHSBT and Public Health England

• Prospective study monitoring Hepatitis E detection in 225,000 donations between October 2012 – September 2013

• Objectives:
  – Prevalence of HEV RNA in blood donation
  – Outcomes of those exposed
Lancet Paper: Hepatitis E virus in blood components: a prevalence transmission study in southeast England

• Results:
  – 79/225 000 donations containing HEV RNA identified
    – Prevalence 1 in 2848 donations
  – 54 of 79 HEV RNA-positive samples genotyped, all genotype 3 virus
  – 129 blood components associated with HEV viraemic donation
**Lancet Paper: Hepatitis E virus in blood components: a prevalence transmission study in southeast England**

<table>
<thead>
<tr>
<th>Recipients of blood components</th>
<th>Infected recipients</th>
<th>Uninfected recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>16</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Pooled platelets</td>
<td>10</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>14</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Pooled granulocytes</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>18 (42%)</td>
</tr>
</tbody>
</table>

Table adapted from ‘Table 2: Association between transfused blood components and transmission of hepatitis E virus in 43 of 60 exposed patients in whom follow-up was possible’
**Lancet Paper:** Hepatitis E virus in blood components: a prevalence transmission study in southeast England

<table>
<thead>
<tr>
<th>Inferred immune suppression</th>
<th>Median weeks to RNA positivity</th>
<th>Median weeks to first detection of antibody</th>
<th>Median duration of infection (weeks)</th>
<th>Viral clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>5</td>
<td>7</td>
<td>10</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>11</td>
<td>18</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>37.5</td>
<td>30</td>
<td>2/4 (50%)</td>
</tr>
</tbody>
</table>

Table adapted from ‘Table 3: Outcome in 18 recipients infected by transfusion of a blood component from a viraemic donor, ranked by immunosuppression’
Lancet Paper: Hepatitis E virus in blood components: a prevalence transmission study in southeast England

• Conclusions:
  – HEV genotype 3 infections are widespread in the English population and in blood donors
  – Transfusion-transmitted infection rarely causes acute morbidity
  – In some immunocompromised patients, infection became persistent
Dietary Considerations

Hepatitis E virus in England and Wales: indigenous infection is associated with the consumption of processed pork products

- Pork pies (OR 6.33 95% CI 1.41-28.48, p=0.009)
- Sausages (OR 7.59 95% CI 1.81-31.84, p=0.004)
- Ham (OR 10.98 95% CI 1.84-65.35, p=0.003)

Prevalence of hepatitis E virus in slaughter-aged pigs in Scotland

- Overall seroprevalence (anti-HEV IgG+ and/or IgA+ and/or IgM+) 61.4%
- HEV RNA detected in 72/162 serum samples (44.4%)
- Partially sequenced 8 of the HEV-RNA-positive samples – all of genotype 3
Dietary Considerations

- Strong association between HEV genotype 3 and rise of non-travel related HEV infection in the UK
- Strong association between genotype 3 and pork/pork products
- Is the risk of transmission from food higher than that of transmission via blood component or transplant?
Advisory Committee for the Safety of Blood, Tissues and Organs

In response to the Lancet article, specific SaBTO Hepatitis E working group

Key Recommendations:

- Introduce donor blood component testing to provide hepatitis E negative components for patients undergoing solid organ or allogeneic stem cell transplants.

- Provide advice to allogeneic stem cell transplant and solid organ patients regarding risk of eating poorly-cooked pork or pork products including sausages and offal.
Date 13 August 2015

Dear Colleague

HEPATITIS E VIRUS AND ALLOGENIC STEM CELL TRANSPLANTATION

We are seeing a significant increase in the number of reports of cases of hepatitis E virus (HEV) arising from infection acquired in the UK. In most cases, the infection is mild and self-limiting but there is increasing evidence that HEV infection in the immunosuppressed patient may lead to persistent infection which may lead to chronic hepatitis and cirrhosis.

SaBTO is currently assessing the implications of transmission of HEV by blood, blood products, organs and tissues and any actions that can be taken to lower the infection risk in the context of blood and organ donation/transplantation.

The significance and impact on stem cell transplant recipients is not yet clear. In the interim, we are writing to clinicians to ensure they are aware of the possibility that HEV may be transmitted through the use of blood and blood products, through transplantation and through diet (especially inadequately cooked pork and pork products such as sausages and offal).

Clinicians concerned about possible infection should discuss diagnosis and treatment with their colleagues in Virology and Hepatology.

We attach an information leaflet which we hope is helpful. Please pass this on to your colleagues.

Diagnosis: a high index of suspicion is needed.

Blood testing:
- Liver tests may be normal or show mild hepatitis
- Liver test abnormalities may be ascribed to drug toxicity or GVHD
- Serum IgM and IgG anti-HEV may be negative
- HEV PCR is the favoured diagnostic test

HEPATITIS E VIRUS PATIENT INFORMATION LEAFLET

What is hepatitis E?
Hepatitis E is an illness of the liver caused by the Hepatitis E Virus (HEV), a virus which can infect both animals and humans. There are four genetic types (HEV-1 to HEV-4) of HEV. In most cases, HEV infection causes no symptoms but if it does, the resulting disease, hepatitis E, is usually mild. In rare cases of HEV, liver damage can be severe and fatal, particularly in pregnant women. The common hepatitis E virus in the country, HEV-3, appears to follow a different pattern. While the HEV virus infection will usually clear by itself, in individuals whose immune system is suppressed following transplantation, for example - the virus can result in an asymptomatic persistent infection which may lead to chronic inflammation of the liver.

How common is hepatitis E?
Hepatitis E due to HEV is very rare in the UK and is due to consumption of contaminated food. The disease is common in Asia, Africa and Central America. However, HEV infection is more common in the UK, and in recent years the number of confirmed cases has increased significantly. It is not known how many people in the UK may get infected each year.

How can I tell if I have been infected by Hepatitis E Virus?
Most people who get infected with Hepatitis E Virus will never know they have it, and so there will be no symptoms. However, in individuals who are immunosuppressed, symptoms may be more severe or persistent, and the infection may become chronic. Blood tests can be undertaken to confirm HEV infection.

How is Hepatitis E Virus transmitted?
In the developing world, the HEV is transmitted by the consumption of human sewage-contaminated food or water. In the developed world, HEV is transmitted through the consumption of undercooked pork and shellfish. Person to person transmission of the HEV virus is rare, although someone with hepatitis E should always wash their hands after using the toilet. There have also been cases of the virus being transmitted through blood transfusion and transplantation.

How is hepatitis E treated?
In most cases, hepatitis E infection clears by itself, with no need for any treatment. However, where in immunosuppressed patients the hepatitis E infection has become persistent and long-term (chronic), minor changes in their immunosuppressive regimen can clear the infection. Where this is not the case antiviral treatment has been used successfully.
Recommendations: Transplant patients with signs/symptoms

- High index of clinical suspicion in patients

- **Blood tests:**
  - Liver function may be normal or demonstrate a mild hepatitis picture
    - This may be assigned to another cause (e.g. drug-induced or GVHD)
  - IgG or IgM anti-HEV may be negative

  - Need to confirm with HEV PCR
Recommendations: Transplant Patients with signs/symptoms

- **Hepatic histology:**
  - Liver biopsy may demonstrate non-specific hepatitis
    - This again may be assigned to another cause such as drug-induced injury, GVHD, rejection or another cause of hepatitis
  - Need to confirm with HEV Ag immunohistochemistry
Recommendations: Results

• **Positive results:**
  – Discuss results with virology and hepatology
  – Monitor for chronicity (re-test 1 month for PCR and serology)
  – Morphology of liver and assess for fibrosis
  – Review immunosuppression and potential modulation
  – Those still present after 3 months, consider the use of Ribavirin (use off license)
  – **Positive HEV thought to be from blood component, report to NHSBT**
Neonates, pregnancy and other vulnerable patient groups

- NHSBT and the Welsh Blood Service will also be providing HEV negative blood components for neonates
- The Scottish Blood Transfusion Service currently considering this option
- No evidence at present to support the need for HEV blood components for pregnant women
- Further research required regarding patients with chronic liver disease, haemoglobinopathies and other immunocompromised patients
How long do we need to continue to provide HEV negative components for?

- There has been no official recommendation for the duration which patients who have received an allogeneic SCT or solid organ transplant required HEV negative blood.

- Should we follow similar timelines recommended for the irradiation of blood components?
Summary

- Evidence of increasing HEV genotype 3 infection in the UK
- Concern immunosuppressed patients (both allogeneic SCT and solid organ) are at risk of acquiring HEV via blood components and transplant
- Immunosuppression has been linked to delayed clearing of the virus and hence, potential for chronic liver changes
Summary

- Recommendation is for all allogeneic stem cell transplant and solid organ patients to receive hepatitis E negative blood components.
- Patients should also receive dietary advice regarding the preparation of pork and pork containing products.
- SaBTO will revisit this decision in 2018 but further clarification about the time frame for requirements in the specific patient groups is being sought.
Acknowledgement

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For producing this presentation