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 anomalies may be ascribed to drug toxicity or GVHD
- Serum IgM and IgG anti-HEV may be negative
- HEV PCR is the favoured diagnostic test

**Liver histology:**
- Non-specific hepatitis
- May be attributed to rejection, graft-versus-host disease (in the setting of transplantation), drug-induced liver injury or other causes of hepatitis
- Immunohistochemistry for HEV Ag is informative
Management in the transplant patient:
Confirm persistence by resampling for PCR and serology at one month
Assess liver morphology and fibrosis
Review immunosuppression for possibility of modulation
If no clearance within three months, consider a three month course of Ribavirin (note this use is off licence).

If you suspect stem cell or blood/blood product transmission, please report this to your blood service:

England and North Wales
NHS Blood and Transplant via the Consultant Haematologist with responsibility for blood transfusion or by visiting

Northern Ireland
NIBTS Regulatory Affairs and Compliance Department. Clinical advice will be provided by Dr K Maguire, extension 4687 or Dr K Morris, extension 4644.

Scotland
SNBTS via the Haematology Registrar.

Wales
Welsh Blood Services Medical Director on 01443 622016.

Advice on screening, viral load monitoring and confirming viral clearance is available:

England
Virus Reference Department, Public Health England, Colindale, (telephone 020 8327 6014) or from an expert virologist.

Northern Ireland
Regional Virology Laboratory, Belfast Health and Social Care Trust (Duty virologist Tel 07889086946)

Scotland
From any expert microbiologist

Wales
Welsh Specialist Virology Unit, University Hospital Wales on 029 2074 2178 (in hours) or the microbiologist on call, contactable via UHW switchboard on 029 2074 7747 (out of hours).

Please share this information with your colleagues.

Finally, we have also attached a patient information sheet. Please pass this information on to your stem cell transplant patients through all available means, and update your dietary advice for such patients with immediate effect.

Thank you.

Yours sincerely

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SaBTO HEV SCT Clinician Letter draft v0.3i
Information on Hepatitis E

HEPATITIS E VIRUS AND STEM CELL TRANSPLANTATION

Incidence: uncertain but is increasing in NW Europe. HEV RNA found in about 1 in 2-3000 blood donors\(^1\). Infection is transmitted by red cells, platelets, granulocytes, Octaplas and FFP, with a transmission rate of ~40%. Donor exposure via platelets is likely to increase as production of apheresis platelets decreases from 80% to 40%.

Source of infection: G3 is acquired through the diet, mainly inadequately cooked pork, wild boar and venison, but may also be transmitted by blood, blood products and organs. Based on current data, it seems that there is a much greater risk of infection from diet than from blood or organ transmission.

Natural history: incubation period around 40 days, the viraemic period is about 3 weeks but virus is excreted in stool for a further two weeks. Infection is usually mild and may be anicteric. Chronicity may be seen in immunosuppressed patients, particularly in the solid organ transplant recipient in whom immunosuppression is long-term. The persistent liver infection may progress to chronic hepatitis and cirrhosis.

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 1-4 (G1-G4) of HEV. HEV infection usually causes no symptoms but if it does, it produces only a mild disease, hepatitis E. In rare cases of G1, G2 and G4 infections, however, it can prove fatal, particularly in pregnant women. The common virus in this country and Europe, G3 does not do so. Normally the G3 virus infection will clear by itself. However, it has been shown that in individuals whose immune system is suppressed following transplantation the virus can result in an asymptomatic persistent infection which may lead to chronic inflammation of the liver.

How can I tell if I have been infected by HEV?
Symptoms of hepatitis E include yellowing of the skin and eyes (jaundice), darkening of the urine and pale stools preceded by tiredness, fever, nausea, vomiting, abdominal pain and loss of appetite and usually resolve within four weeks. Immunosuppression makes it unlikely to develop symptoms but blood tests can be undertaken to confirm HEV infection.

How common is hepatitis E?
Hepatitis E due to G1, G2 and G4 occurs in regions of the world where sanitation may be poor including parts of Asia, Africa and Central America. However HEV infection caught in this country is caused by G3. This was first recognised in 2003 and the numbers of confirmed G3 hepatitis E cases and infections have increased significantly over the past few years. It is now likely that as many as 100,000 persons may suffer acute infections each year and that less than 1 in 100 will have any illness at all.

How is hepatitis E virus transmitted?
Throughout the developing world, the virus is transmitted by the consumption of human sewage-contaminated food or water. In the developed world the virus is believed to transmit from animals to humans through the consumption of undercooked or raw pig and game meat, processed pork, and shellfish. Person to person transmission of the G3 virus is very rare though the virus has been transmitted through blood transfusion and transplantation. Someone with hepatitis E should always wash their hands after using the toilet.

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How is chronic hepatitis E treated?
Patients with chronic infection may cure themselves of the infection either spontaneously or by minor changes in the immunosuppressive regimens. Where this is not the case antiviral treatment has been used successfully.

Can hepatitis E infection be prevented?
Currently, there is no licensed vaccine for hepatitis E. In the UK it is important to make sure that food containing pig meat until steaming hot throughout, the meat is no longer pink and the juices run clear (especially sausages) is thoroughly cooked. When travelling to countries with poor sanitation, it is advisable to boil all drinking water, including water used for brushing teeth. Avoid the consumption of raw or undercooked meat and shellfish. Following this guidance will help to reduce the risk from other hazards which may be associated with food (e.g. *Listeria*).

Where can I get further help?
Further information and advice is available from:
NHS Direct (tel: 0845 46 47 or www.nhsdirect.nhs.uk/) or NHS Inform in Scotland (www.nhsinform.co.uk or 0800 22 44 88) or your own GP
(www.food.gov.uk/science/microbiology/hepatitis-e)