# Hepatitis E: a UK perspective

***Hepatitis E is increasingly recognized as a cause of viral hepatitis within the UK and should be considered in any patient presenting with acute hepatitis. Mortality rates of around 4% have been described, but are even higher during pregnancy.***

Hepatitis E has previously been considered to only affect people who have travelled to endemic regions. However, in recent years there have been an increasing number of cases reported within the UK. Awareness of this form of viral hepatitis is important, considering its high mortality rates in certain patient groups. This article aims to provide a clinical perspective of hepatitis E virus infection in the UK.

Although unnamed, hepatitis E virus was first described as a distinct entity in 1980 following the study of a waterborne epidemic of viral hepatitis in the Kashmir valley, India (Khuroo, 1980). In 1983 Balayan et al identified the viral agent by analysing stool specimens from a human volunteer using immune electron microscopy. Cloning of part of the hepatitis E virus genome by Reyes et al in 1990 eventually lead to the development of enzyme-linked immunosorbent assays (ELISA) and detection of hepatitis E virus RNA by reverse transcriptase polymerase chain reaction (rt-PCR). At this time the name 'hepatitis E' was proposed, having previously been called enterically transmitted non-A, non-B hepatitis (Reyes et al, 1990).

Hepatitis E is a positive sense, single-stranded, non-enveloped RNA virus. Virus particles are 27–34 nm in diameter (Krawczynski, 1993). It is presently the only identified member of the Hepeviridae family (genus Hepevirus), having been reclassified from the Caliciviridae family. Only one virus serotype is recognized, with four main genotypes (Lu et al, 2006).

Hepatitis E virus has been increasingly acknowledged in recent years as a cause of acute viral hepatitis within our indigenous population. This has resulted in an increasing number of requests for hepatitis E virus serology and number of cases diagnosed – Lewis et al (2008) reported diagnosis of 125 cases in 2003, 150 cases in 2004 and 329 cases of acute hepatitis E in 2005.

## Seroprevalence

Hepatitis E virus has traditionally been associated with endemic infection occurring in parts of Asia, Africa and India. While the majority of cases identified in the UK still relate to foreign travel (69%), there has been an increasing awareness of autochthonous (locally acquired) infection (Ijaz et al, 2005).

There remains limited data available on seroprevalence rates in the UK. Immunoglobulin G (IgG) seropositivity rates in inner-city London have been reported at 3.9–8.8%, highest in non-UK-born residents (Bernal et al, 1996). A more recent study performed in south-west England demonstrated 17% of blood donors to be anti-hepatitis E virus IgG positive. Higher rates occurred in individuals >60 years old (25.5%) and males (Dalton et al, 2007a). Patient age and sex are consistent risk factors for hepatitis E virus identified in studies of our indigenous population (Ijaz et al, 2005).

Seroprevalence rates in other developed countries have been reported at 16.6% of blood donors from the south west of France and 21.3% of blood donors from Baltimore, USA (Thomas et al, 1997; Mansuy et al, 2008).

## Presentation

Hepatitis E virus can result in subclinical infection as indicated by the high seroprevalence rates in asymptomatic individuals. It may also present as a self-limiting hepatitis with symptoms similar to other forms of acute viral hepatitis including jaundice, abdominal pain, fever, nausea, vomiting and reduced appetite. Symptoms of cholestasis (e.g. pruritis) occur in approximately 25% of patients with hepatitis E virus infection (Khuroo et al, 1994). In developed countries, a small proportion of patients may develop a fulminant hepatitis (Ijaz et al, 2005).

The incubation period ranges from 2–10 weeks after exposure, with the clinical illness usually lasting around 1–4 weeks (Aggarwal and Krawczynski, 2000). Liver function tests initially indicate hepatitis with elevated aspartate transaminase and alanine transaminase levels. Some patients later develop a cholestatic picture to their liver function with a rise in their alkaline phosphatase and gamma-glutamyl transpeptidase levels.

## Diagnosis

The diagnosis of hepatitis E virus infection is most commonly made using ELISA. Acute infection is confirmed in patients with biochemical evidence of hepatitis and either reactive serology for anti-hepatitis E virus IgM, a rising titre of anti-hepatitis E virus IgG or detection of hepatitis E virus RNA by rt-PCR. PCR may be performed on serum, faecal or liver specimens. Isolated RNA may then be sequenced to identify a viral geno-

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type. Within the UK the two main genotypes detected are: genotype 1 – seen with travel-associated hepatitis E virus; and genotype 3 – seen with non-travel associated hepatitis E virus (Ijaz et al, 2005).

Anti-hepatitis E virus IgM levels rise soon after onset of the clinical illness shortly followed by a rise in anti-hepatitis E virus IgG. Anti-hepatitis E virus IgM disappears over several months. Anti-hepatitis E virus IgG may persist for over 14 years, but whether lifelong immunity is conferred after acute infection remains uncertain (Aggarwal and Krawczynski, 2000).

False positive anti-hepatitis E virus IgM results are unusual but have been observed by Worm et al (2002) in cases of autoimmune hepatitis and some rheumatological conditions.

## Transmission

The transmission of hepatitis E virus is thought to occur predominantly through the faecal oral route. This was demonstrated in a historical human volunteer study where one volunteer (the study author) ingested faecal particles from patients with 'enterically transmitted non-A, non-B hepatitis' – the previous name for hepatitis E virus. He developed acute hepatitis with evidence of virus particles in his stool, detected by immune electron microscopy. Serology was negative for acute hepatitis A. These virus particles were inoculated intravenously into two cynomolgus monkeys who also developed hepatitis, with an antibody response to these particles (Balayan et al, 1983).

Epidemics of hepatitis E virus are thought to occur secondary to contaminated drinking water. Person to person transmission does not appear to be a major factor in either sporadic or epidemic cases (Khuroo, 2003; Somani et al, 2003).

Available evidence also suggests zoonotic spread, with undercooked foods acting as a further mode of transmission. Cases have been reported after ingestion of raw or undercooked shellfish, pork, venison and boar meat (Lu et al, 2006; Dalton et al, 2007b). Hepatitis E virus appears to survive at some lower temperatures used to cook these meats (Emerson et al, 2005). Analysis of specimens of pig liver from grocery stores in Hokkaido, Japan revealed 1.9% had detectable hepatitis E virus RNA belonging to genotypes 3 and 4. One isolate was identical to that found in a patient presenting with acute hepatitis E virus infection (Yazaki et al, 2003). These reports have relevance as hepatitis E virus seroprevalence in UK pig herds may be as high as 85.5%, containing clusters of genotype 3 (Banks et al, 2004). Ijaz et al (2005) have shown that genotype 3 sequences identified in autochthonous hepatitis E virus are closely related to those from British pigs. High IgG seroprevalence rates of hepatitis E virus in pigs from endemic and non-endemic countries have been reported worldwide (Meng et al, 1999). The prevalence of hepatitis E virus antibodies in people handling pigs is around 1.5 times higher than blood donors from the same regions (Meng et al, 2002). Some sequences of swine hepatitis E virus are closely related to strains of human hepatitis E virus isolated in the USA. Experimental transmission of hepatitis E virus has been successful from swine to rhesus monkeys and from humans to pathogen-free swine (Meng et al, 1998).

A further animal reservoir for hepatitis E virus includes rats. Seroprevalence rates of up to 90% have been identified in some regions of the USA, from both rural and urban areas. As in humans, seroprevalence increased with the rats' estimated age (Kabrane-Lazizi et al, 1999).

There have been case reports of transfusion-transmitted cases, although these appear to be rare. In one case a patient developed acute hepatitis after receiving blood products to treat anaemia during lymphoma treatment. The hepatitis E virus sequences of the blood donor and recipient were confirmed to be identical (Boxall et al, 2006).

## Seasonality

There is evidence of seasonal variability of cases within the UK. The majority of patients present during spring (43%) or summer (33%) months, although the reasons for this are unclear (Dalton et al, 2007b).

## At risk groups

The case fatality rates in epidemic areas are reported at 0.5–4% (Aggarwal and Krawczynski, 2000). This is similar to rates recently reported during a retrospective national survey in France (4.2%), a non-endemic country (Renou et al, 2008). Several studies have shown an unexpectedly high mortality in pregnancy, with mortality rates of 20% reported in the third trimester of pregnancy (Krawczynski, 1993). Vertical transmission occurs in a third of cases and is associated with high infant mortality rates. Infant deaths are reported to occur as a result of hypoglycaemia and massive hepatic necrosis. Preterm deliveries occur in around two thirds of pregnancies (Kumar et al, 2004).

Patients with chronic liver disease are another at risk group, with hepatitis E virus IgG seroprevalence rates reported at 13.4% in south west England (Dalton et al, 2007a). Hepatitis E virus infection may act as a precipitating factor for the decompensation of these patients and should always be considered if no alternative cause is identified. It is associated with high mortality rates in this group of patients (Ramachandran et al (2004) reported that six out of nine patients died of advanced liver failure).

## Treatment

As with other forms of acute viral hepatitis, the mainstay of treatment remains supportive. Fulminant hepatic failure as a result acute hepatitis E virus is a rare indication for liver transplantation (Nicoluzzi et al, 2001; Ijaz et al, 2005). This virus is not associated with cirrhosis or hepatocellular carcinoma.

## Prevention and immunization

Epidemics of hepatitis E virus abroad have been associated with poor water supply and sanitation. Advice should therefore be given to travellers to endemic areas to ensure a clean basic water supply. Owing to the associations with rare and undercooked shellfish and meats these should be avoided both in the UK and abroad. These risks should be particularly highlighted to pregnant travellers, in whom infection is associated with significantly increased mortality rates.

Passive immunization using immunoglobulins has not been shown to be effective in preventing clinical disease (Aggarwal and Krawczynski, 2000).

A commercially available vaccine for hepatitis E virus is not presently available. However, a phase II, randomized, placebo-controlled trial performed in volunteers from the Nepalese army compared the use of a hepatitis E virus recombinant protein vaccine with placebo. All volunteers received intramuscular injections of either placebo or vaccine at 0, 1 and 6 months. The vaccine appeared effective, with vaccine efficacy reported at 95.5% after three doses, falling to 85.7% after two doses. The symptom profile was similar in both groups apart from an increase in injection site pain in the vaccine group (Shrestha et al, 2007).

The indications for this vaccine are likely to be similar to those for the hepatitis A vaccine. It may be offered to military personnel, business people and travellers to endemic regions. Depending upon safety data it may also be offered to higher risk groups including pregnant women in endemic areas and who are travelling, and patients with chronic liver disease.

## Conclusions

Hepatitis E virus is increasingly recognized as a cause of viral hepatitis in our indigenous population and should be considered in any patient presenting with acute hepatitis. Transmission is thought to occur through several routes and appropriate advice should be offered to travellers to endemic regions. **BJHM**

*Conflict of interest: none.*


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## KEY POINTS

- Hepatitis E virus is an important cause of autochthonous (locally acquired) infection and should be considered in all patients presenting with acute hepatitis.
- Transmission is usually faecal oral, but may also be via zoonotic or transfusion-transmitted spread.
- Hepatitis E virus has significant mortality rates in the third trimester of pregnancy and in patients with chronic liver disease.
- Treatment remains predominantly supportive.
- Vaccines are undergoing clinical trials and if successful may be commercially available in the near future.