Hepatitis E

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Purpose of review
Hepatitis E has been regarded as a disease of the developing world, where it causes large waterborne outbreaks and sporadic cases of hepatitis. Recent research has shown this received wisdom to be mistaken.

Recent findings
Recent studies have shown that authochtonous (locally acquired) hepatitis E does occur in developed countries, is caused by hepatitis E virus (HEV) genotypes 3 and 4, and is zoonotic with pigs as the primary host. Most infections are clinically inapparent. However, acute symptomatic hepatitis E has a predilection for middle-aged and elderly men, with an excess mortality in patients with underlying chronic liver disease. Chronic infection occurs in the immunosuppressed with rapidly progressive cirrhosis if untreated, the treatment of choice being ribavirin monotherapy for 3 months. Hepatitis E has a range of extra-hepatic manifestations, including a spectrum of neurological syndromes. HEV can be transmitted by blood transfusion and has recently been found in donated blood in a number of countries.

Summary
The diagnosis should be considered in any patient with a raised alanine aminotranferase, irrespective of age or travel history. The safety of blood products needs to be fully assessed, as a matter of priority, as blood donors are not currently screened for HEV.

Keywords
blood products, cirrhosis, epidemiology, hepatitis E, zoonosis

INTRODUCTION

Hepatitis E virus (HEV) was discovered nearly 30 years ago, and has since been identified as the cause of major outbreaks of waterborne hepatitis in Asia and Africa, which may involve tens of thousands of cases [1▪▪,2]. These continue to occur in locations with poor sanitary infrastructure, and are commonplace in refugee camps, such as the January 2013 outbreak in southern Sudan. Although these outbreaks of hepatitis E are associated with significant morbidity and mortality, they have received scant scientific attention or research funding. Hepatitis E has truly been a 'neglected infectious disease'. So neglected, in fact, that it was omitted from the WHO list of 'neglected infectious diseases' [3▪▪].

The research field in HEV is changing rapidly. In recent years, studies have shown that HEV causes acute and chronic infection in Europe, North America and Japan. In these geographical locations, in contrast to resource-poor countries, hepatitis E is a zoonosis, with farmed and wild pigs as the primary host. Hepatitis E in developed countries is much more common than previously appreciated and is commonly asymptomatic. As a result, and of concern, HEV has found its way into the blood supply in Europe and Japan [1▪▪,2]. HEV is now the focus of greater attention worldwide, and the number of HEV-related publications has more than doubled in the last 7 years.

HEPATITIS E VIRUS: BASIC VIROLOGY

HEV is a small nonenveloped virus of 27–34 nm, with a positive-sense, single-stranded RNA 7.2-kilobases-long genome. HEV belongs to the genus *Hepevirus* in the *Hepeviridae* family, which contains HEV found in a number of mammals, but also avian HEV and cutthroat trout virus. The two latter groups share approximately 50% nucleotide

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KEY POINTS

- Hepatitis E is a global health problem, as in developed countries it is caused by zoonotic infection with HEV genotypes 3 and 4, with pigs as the primary host.
- In developed countries, acute HEV has a predilection for middle-aged/elderly men, with an excess mortality in patients with underlying chronic liver disease.
- Chronic infection occurs in the immunosuppressed with rapidly progressive cirrhosis (10% in 2 years) if untreated.
- The diagnosis of hepatitis E should be considered in any patient with a serum transaminitis, irrespective of age or travel history, and especially so in patients with neurological symptoms or who are immunosuppressed.
- Hepatitis E is frequently asymptomatic, and HEV has been found in donated blood in a number of countries, the risks of which require urgent assessment.

sequence identity with mammalian HEV strains and have not been associated with human cases. Four HEV genotypes infect humans. Genotypes 1 and 2 are only found in humans; genotypes 3 and 4 are found in animals and also cause human disease [1▪▪]. Other novel HEV genotypes have so far only been detected in animals.

HEPATITIS E VIRUS IN DEVELOPING COUNTRIES

In southeast Asia and many parts of Africa, hepatitis E is caused by HEV genotype 1. HEV genotype 2 occurs in Mexico and parts of Africa. These HEV genotypes are spread by the oro-faecal route via infected water in areas with poor sanitation. Infections occur either sporadically or, more dramatically, in huge outbreaks. The largest documented outbreak took place in northwest China in 1986–1988 involving approximately 120 000 cases. Typically, hepatitis E causes a brief self-limiting hepatitis in young adults. Most cases recover within a few weeks, but there is significant, unexplained mortality (~25%) in pregnant women [1▪▪,2,3▪▪]. Hepatitis E also carries a poor prognosis in individuals with preexisting chronic liver disease, with a 12-month mortality from 'acute-on-chronic' liver failure of 70% [4,5]. Unlike HEV genotype 3 (see later), HEV genotypes 1 and 2 have not been shown to cause chronic infection.

A recent study has estimated that in nine of 21 Global Burden of Disease regions, there are 3.4 million symptomatic cases of hepatitis E each year, with 70 000 deaths and 3000 stillbirths [6▪]. This is almost certainly an underestimate of the Global Burden of Disease associated with hepatitis E, as another study estimates there are 1000 HEV-related maternal deaths per annum in Bangladesh alone [3▪▪]. In most parts of the world, there are insufficient data to make an assessment of the impact of HEV on human health. This includes many of the poorest countries of the world (genotypes 1 and 2) and some of the wealthiest (genotypes 3 and 4). Until recently, for example, little was known about HEV in South America. Recent studies indicate its presence there, mostly causing sporadic cases. Although HEV genotype 1 has been detected, the majority of cases are caused by HEV genotype 3, which is also present in local pig populations. These initial data suggest that the epidemiology of hepatitis E in South America is similar to that in developed countries [7–11].

HEPATITIS E VIRUS IN DEVELOPED COUNTRIES

Hepatitis E in developed countries has been described as an 'emerging disease'. It would be more accurate to say that hepatitis E is a disease that is emerging in human consciousness, as HEV has almost certainly caused unrecognized disease in humans for centuries.

Historical context

Biological time-clock studies suggest that HEV diverged into four genotypes about 500 years ago. Although HEV was only discovered recently, it has probably caused disease in humans for centuries. Historical descriptions of outbreaks of jaundice and deaths in pregnant women suggest that in the 19th and early 20th centuries, hepatitis E was present in Germany, France, Italy and the Balkans [12▪▪]. It is likely that these were caused by HEV genotypes 1 or 2, because maternal mortality is a 'signature' of these genotypes. After the Second World War, outbreaks of jaundice associated with deaths in pregnant women ceased to be reported in Europe and started to appear in Asia and Africa. One explanation for these observations is that improvement in water sanitation in Europe asserted negative ecological pressure on genotype 1 and 2, which migrated south and east, leaving genotype 3 in its primary host, the pig.

Animal hosts

HEV genotype 3 is found in pigs and wild boar worldwide, and in addition genotype 4 is found in pigs in China and Japan. Infected pigs are

asymptomatic, but excrete very large quantities of HEV in their faeces. The pig is considered to be a primary host, and there is very close sequence homology between HEV strains recovered from pigs and humans. A recent study of HEV transmission in pigs showed that it is highly contagious. R_0 (the basic reproductive rate of the virus) lies in the range 5–8, a value similar to that for smallpox or measles in a naive human population. Consequently, following the introduction of HEV into a pig herd infection is near universal [13▪▪]. In the same study, 73% of fattening pigs studied in the Netherlands were excreting HEV in their stool.

HEV has also been found in deer, which are a proven source of human infection. However, compared with pigs they are a less important reservoir, as the prevalence of HEV in deer herds is lower, and deer meat is less commonly consumed in most countries [2]. HEV has been documented in a diverse range of mammals, including bats, ferrets, rats and rabbits. It is uncertain if most of these animal reservoirs pose a threat to human health [14], with the exception of rabbit HEV, which has been linked to human disease [15▪].

Source and route of infection

In most human cases of hepatitis E, it is not possible to determine the source or route of infection. However, consumption of infected pork/wild game is strongly suspected. HEV has been found in pork products at point of sale to the public in a number of countries in Europe, Japan and the United States. Recently, HEV genotype 3 was found throughout the human food chain in the United Kingdom and was found to contaminate 10% of retail sausages that were tested [16▪▪]. HEV is relatively heat resistant; cooking temperatures of 71°C for 20 min are required to inactivate it [17]. HEV has also been found in foods that are served uncooked, such as a traditional French air-dried pig-liver sausage [18▪▪].

Waterborne transmission may also be important (Fig. 1). HEV has been found in watercourses and seawater [19]. Human infection with HEV might occur through recreational use of such water, or consumption of foodstuffs contaminated with infected water, as HEV has recently been found in shellfish [20▪,21] and strawberries [22▪]. In southwest England, 50% of cases of hepatitis E were found to live within 2 km of the coast. It is suspected that this could relate to recreational contact with contaminated water [23▪▪].

Seroprevalence and incidence

Early studies showed that the prevalence of anti-HEV immunoglobulin G (IgG) in many developed countries was low, ranging from 1–2%. These studies are flawed, because they used IgG assays of poor sensitivity. More recent studies, using more sensitive assays, have produced higher estimates of seroprevalence, with rates of 16% in southwest England, 29% in Germany [24▪▪] and 52% in southwest France [18▪▪]. The latter result has provoked debate. Sceptics argue that this result cannot be accurate, and must reflect nonspecific positivity in the assay. However, the seroprevalence in children aged 2–4 years is only 2%, suggesting that the assay does not suffer from high rates of false positivity. Furthermore, this prevalence is consistent with the elevated incidence of HEV infection among organ transplant recipients in Toulouse (3.2% of these patients have new HEV viraemia detected yearly). These data suggest that HEV is hyperendemic in the Toulouse area. The reason for this is uncertain.

Other estimates of incidence rely on changes in seroprevalence over time. In the United States, the annual incidence is thought to be 0.7% [25], in the United Kingdom it is 0.2% [26]. These data imply that HEV infection is common, with up to 120 000 cases per year in the United Kingdom. In 2012, there were 566 laboratory confirmed cases of hepatitis E reported in England and Wales [27]. This suggests that most cases of hepatitis E either have no symptoms, that symptomatic cases are not being diagnosed or that diagnosed cases are not reported.

Acute hepatitis E

Autochthonous (locally acquired) zoonotic hepatitis E has been found in many developed countries in Europe, New Zealand, North America (all genotype 3) [28▪] and Japan (genotype 3 and 4). Cases have a uniform and striking demography as, in contrast to the developing world, hepatitis E has a predilection for middle-aged/elderly men (median age 60 years, male:female ratio 3 : 1). The reason why hepatitis E appears more commonly in older men is uncertain. It is unlikely to be because of increased exposure to HEV, as exposure is unrelated to age or sex. One plausible hypothesis is that clinical disease expression reflects subclinical hepatic steatosis/fibrosis, because hepatitis E is more common in individuals who drink excessive amounts of alcohol [29].

After an incubation period of 2–6 weeks, most cases of acute hepatitis E present with symptoms indistinguishable from other forms of viral hepatitis. Typical laboratory parameters and the differential diagnosis [30,31▪,32▪] are shown in Table 1. In most cases, the patients recover within 4–6 weeks, but patients with underlying chronic liver disease

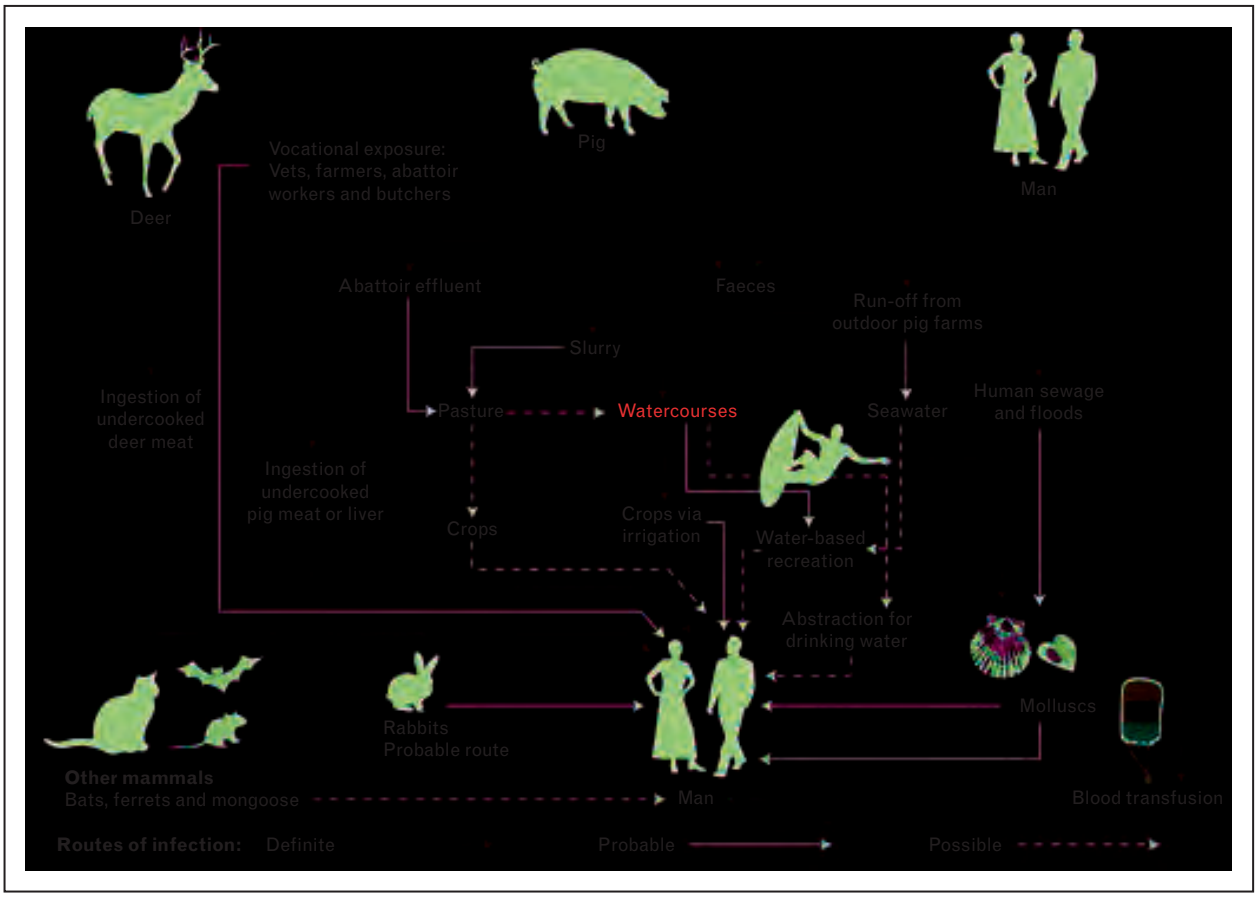

FIGURE 1. Zoonotic hepatitis E virus: sources and routes of infection.

have a poor prognosis with excess mortality from subacute liver failure [1▪▪].

Most cases of hepatitis E in Europe are caused by HEV genotype 3. Recently, HEV genotype 4 has been documented in European pigs, and there have been two clusters of human infection caused by genotype 4 in France and Italy [33▪,34▪]. The clinical features of hepatitis caused by genotype 4 are the same as genotype 3. Excess mortality in pregnant women is not seen with either genotype [35].

Chronic hepatitis E

Chronic infection has been found in the immunosuppressed including transplant recipients, patients with haematological malignancies and individuals with HIV. Approximately 60% of solid organ transplant recipients exposed to HEV develop chronic infection, and within 2 years 10% are cirrhotic [36]. This has caused alarm in transplant centres worldwide, and several recent studies indicate that chronic infection occurs in all types of solid organ transplant recipients and in children as well as adults. The prevalence in transplant populations is 1.0–2.3% [37▪▪,38▪–42▪,43▪▪]. Chronic infection is usually asymptomatic with modestly elevated liver function tests, and has only been observed with HEV genotype 3 so far (Table 2) [44▪▪].

EXTRA-HEPATIC MANIFESTATIONS OF HEPATITIS E

Hepatitis E has been shown to produce a range of extra-hepatic manifestations, including acute pancreatitis, thrombocytopenia, aplastic anaemia [45], acute thyroiditis [46] and glomerulonephritis [47▪▪]. Of most interest, 5% of cases present with a neurological illness [48]. The spectrum of neurological injury is wide and includes Bell's palsy, encephalitis, brachial neuropathy, peripheral neuropathy and Guillain–Barré syndrome [49▪▪]. HEV-associated neurological illness occurs worldwide, in acute and chronic cases, and the long-term outcome is variable. The pathophysiological mechanisms are uncertain, but neurotrophic quasispecies may be directly neuropathogenic [48]. The incidence of neurological injury associated with HEV is unknown. Neurological features dominate the clinical picture, patients are anicteric and have a modest

Table 1. Differential diagnosis of a patient with a serum transaminitis

	Male:female ratio	Age (years)	ALT (IU/l)	ALKP (IU/l)	Bilirubin (μmol/l)	Notes
Drug-induced hepatitis	1.0	65 (17–83)	398 (48–1456)	367 (129–1088)	199 (20–651)	The diagnosis of drug-induced hepatitis is not secure without excluding HEV infection*
Autoimmune hepatitis	0.3	64 (15–91)	748 (22–2519)	231 (104–948)	122 (32–634)	Most common in women more than 60 years; LFTs may have been abnormal for some time
Acute HEV	3.0	62 (38–86)	1460 (159–6357)	236 (90–464)	46 (6–352)	The commonest cause of viral hepatitis; may present with neurological signs
EBV	1.4	40 (18–68)	395 (87–1362)	345 (160–756)	74 (13–165)	Occurs at any age; 95% have lymphocytosis and splenomegaly; symptoms of infectious mononucleosis occur in a small minority
HBV	1.2	39 (20–60)	1727 (505–3218)	230 (66–406)	122 (36–315)	
HAV	0.7	44 (22–60)	1056 (88–4122)	211 (91–342)	144 (42–214)	Becoming more uncommon; age of presentation is increasing
Acute HCV	**	40 (32–48)	1544 (901–2092)	255 (122–353)	117 (33–217)	Rare

Notes: ALT, alanine aminotransferase; normal adult range = 3–35 IU/l. ALKP = alkaline phosphatase; normal adult range = 10–105 IU/l. Bilirubin normal adult range = 3–17 μmol/l. The data are expressed as median values with ranges in parentheses, and are derived from more than 2000 consecutive patients with jaundice presenting to the Jaundice Hotline Clinic, Truro, Cornwall, United Kingdom (1998–2012). The diagnoses are placed in order of frequency in which these occur in this group of patients. HEV, hepatitis E virus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HAV, hepatitis A virus; HCV, hepatitis C virus; LFTs, liver function tests [30,31▪,32▪].

*A UK study found that 13% of patients with 'criterion-referenced' drug-induced liver had been misdiagnosed: they had HEV genotype 3 infection [30].

**Too few cases to give a meaningful sex ratio.

Table 2. Hepatitis E virus infection in the immunocompetent and immunosuppressed

	Immunocompetent	Immunosuppressed
Presentation	Often symptomatic	Rarely symptomatic
ALT	200–3000 IU/l	200–300 IU/l
Genotype	Genotype 1,2,3,4	Only genotype 3 [44▪▪]
HEV diagnostics	Increase in IgG and IgM. PCR is positive in 75%	Serological testing is unreliable. The diagnosis should be established by PCR
Outcome	Resolving hepatitis	Chronic infection occurs in 60% of patients; 10% develop cirrhosis within 2 years
Therapy	Most patients require no treatment. Ribavirin has been used successfully in a small number of patients with severe hepatitis and underlying chronic liver disease	A 3-month course of ribavirin therapy is recommended for patients with chronic infection

ALT, alanine aminotransferase; HEV, hepatits E virus.

transaminitis, and so the diagnosis is easily overlooked [1▪▪,48].

HEPATITIS E VIRUS AND THE BLOOD SUPPLY

Posttransfusion hepatitis caused by HEV has been documented in a number of countries. HEV has been found in asymptomatic donors in Germany, United Kingdom, Sweden and Japan [50▪,51▪▪,52▪▪]. The incidence of viraemic donations is high (range 1 in 1200–1 in 8000), the alanine aminotransferase is often normal, and HEV serology may be negative. The clinical consequences of using infected blood products are uncertain. Immunocompetent recipients are likely to have an asymptomatic infection. However, recipients who have chronic liver disease or who are immunosuppressed (two significant populations of blood product recipients) are much more likely to have an adverse outcome. The impact of HEV on blood transfusion services is the subject of on-going research and debate.

DIAGNOSIS

The diagnosis of hepatitis E should be considered in any patient with a transaminitis, with or without neurological symptoms, irrespective of age or travel history. The diagnosis is established by a combination of serological and molecular (polymerase chain reaction) techniques. Although there are four genotypes of HEV, there is only one serotype. The serological response follows the conventional pattern with a brief immunoglobulin M (IgM) response followed by more durable IgG antibodies. In acute infection, viraemia peaks during the incubation period and early symptomatic phase of disease. Viral RNA can be detected just prior to the clinical symptoms in both serum and stool. HEV RNA levels are transient and become undetectable in the blood within 21 days of symptom onset [1▪▪,2].

The serological diagnosis of acute HEV infection relies on detecting IgM antibodies directed against recombinant viral antigens. Positive IgM results suggest an acute infection, which may be confirmed by detection of rising reactivity in a HEV IgG assay or by the detection of viral RNA by molecular techniques. Establishing a diagnosis is not always straightforward, as there are considerable differences in sensitivity and specificity of commercially available serological assays, and the period of viraemia may be brief: a negative PCR result does not exclude the diagnosis. In addition, second infections with HEV can occur. Typically, such patients are IgM negative, are more likely to be women and have a milder illness. In chronic infection, serology is unreliable, and the diagnosis should be established by molecular techniques [1▪▪].

TREATMENT

Most cases of acute hepatitis E require no treatment, as the illness is self-limiting. Patients with severe hepatitis and underlying chronic liver disease have a poor prognosis. A number of such patients have been treated successfully with ribavirin [53▪,54].

Immunosuppressed patients with chronic infection should be treated, as without treatment they may develop rapidly progressive cirrhosis. In transplant recipients, the first step is to reduce the dose of immunosuppressive therapy, if possible. This will achieve viral clearance in up to 30%. If this is ineffective, or is not possible because of organ rejection, then a 3-month course of ribavirin will clear HEV in the majority of patients [1▪▪,43▪▪,55▪▪]. Chronic HEV/HIV coinfection is uncommon, but antiviral therapy has been used successfully in a

small number of patients [56▪]. All cases of chronic HEV infection in patients with HIV occurred at CD4 cell counts less than 250/mm^3. A case report from South Africa has shown that HEV clearance may be associated with immune reconstitution hepatitis, following initiation of antiretroviral therapy [57▪].

PREVENTION

A well tolerated and effective vaccine for HEV has been developed [58], and was licensed for use in China in 2012. It is uncertain whether it will be available in other countries. Without vaccination, the most important method of prevention in developing countries is the provision of safe drinking water. In developed countries, prevention is more problematic as there are several possible routes of infection and a large animal reservoir.

CONCLUSION

Many unanswered questions remain regarding HEV [1▪▪]. What is beyond doubt is that hepatitis E is no longer confined to developing countries and has become a global health issue. In developed countries, it causes acute and chronic infection and has a range of extra-hepatic manifestations, including a spectrum of neurological syndromes. The diagnosis should be considered in any patient with a serum transaminitis, irrespective of age or travel history, and especially so in patients with neurological symptoms.

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Conflicts of interest

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J.G.H. has no conflicts of interest.

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