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Hepatitis E Virus Infection

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SUMMARY

Hepatitis E virus (HEV) infection is a worldwide disease. An improved understanding of the natural history of HEV infection has been achieved within the last decade. Several reservoirs and transmission modes have been identified. Hepatitis E is an underdiagnosed disease, in part due to the use of serological assays with low sensitivity. However, diagnostic tools, including nucleic acid-based tests, have been improved. The epidemiology and clinical features of hepatitis E differ between developing and developed countries. HEV infection is usually an acute self-limiting disease, but in developed countries it causes chronic infection with rapidly progressive cirrhosis in organ transplant recipients, patients with hematological malignancy requiring chemotherapy, and individuals with HIV. HEV also causes extrahepatic manifestations, including a number of neurological syndromes and renal injury. Acute infection usually requires no treatment, but chronic infection should be treated by reducing immunosuppression in transplant patients and/or the use of antiviral therapy. In this comprehensive review, we summarize the current knowledge about the virus itself, as well as the epidemiology, diagnostics, natural history, and management of HEV infection in developing and developed countries.

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INTRODUCTION

Retrospective studies in India of large waterborne epidemics of hepatitis, originally attributed to hepatitis A virus, suggested the existence of a new form of enterically transmitted viral hepatitis, which was later named hepatitis E (1, 2). The hepatitis E virus (HEV) was discovered in 1983 by investigators of an outbreak of unexplained hepatitis in Soviet soldiers in Afghanistan (3). After a member of the research team ingested a pooled fecal extract from affected military personnel, he developed acute hepatitis, and small viral particles were detected in his stool by immune electron microscopy. The viral genome was subsequently cloned and sequenced using samples of bile obtained from experimentally infected macaques (4, 5). An enzyme immunoassay was also developed for detection of antibodies to HEV (6). The first animal strain of HEV, swine HEV, was identified and characterized from pigs in the United States (7). Phylogenetic analyses of many HEV strains based on complete virus genomes and a range of subgenomic regions led to the recognition of 4 major genotypes (genotypes 1 to 4 [HEV1, HEV2, HEV3, and HEV4]) (8).

Human infection with HEV has two distinct epidemiological patterns (9–12). In areas of poor sanitation, HEV1 and HEV2 are transmitted between humans by the fecal-oral route, usually via contaminated water. This results in frequent sporadic cases and occasional large outbreaks. In developed countries, HEV3 and HEV4 are transmitted zoonotically from animal reservoirs, with sporadic cases that have increasingly been reported in the past few years due to improvements of diagnostic tools and screening strategies. HEV is probably the most common cause of acute viral hepatitis in the world (9–11). In addition, chronic HEV infections leading to chronic hepatitis and cirrhosis have been described for immunocompromised patients with HEV3 (13).

CLINICAL COURSE

Developing Countries

Detailed information on the clinical course of HEV infection can be found in Table 1. In most patients, hepatitis E causes a self-limiting illness which lasts a few weeks. Following an incubation period of 2 to 6 weeks, symptoms of hepatitis develop, with fever and nausea followed by abdominal pain, vomiting, anorexia, malaise, and hepatomegaly. Jaundice occurs in about 40% of patients (14). Excess mortality is seen in pregnant females and individuals with underlying chronic liver disease. Chronic infection with genotypes 1 and 2 has not been documented, although only limited studies have been performed to date. In a recent study of 205 renal transplant recipients in India, Naik and colleagues found no evidence of chronic infection with HEV in an area of genotype 1 hyperendemicity (15).

Developed Countries

Acute infection. The clinical features of acute autochthonous hepatitis E caused by HEV genotypes 3 and 4 are indistinguishable from those of hepatitis E in developing countries, except that patients are usually middle-aged/elderly males (16). Most cases are sporadic, and large outbreaks do not occur, although there have been a number of well-documented small clusters of cases from a point-source food outbreak (17). However, in most cases, the source of infection remains uncertain (18).

Jaundice occurs in about 75% of patients. Other common symptoms include nausea, fever, malaise, arthralgia, vomiting, diarrhea, and abdominal pain. The alanine aminotransferase (ALT) level is usually 1,000 to 3,000 IU/liter, but the range is wide. Some patients have a much more modest transaminitis, and, rarely, the ALT level is normal in blood samples taken at the time of viremia (19). In the majority of patients, the disease is self-limiting, with symptomatic and biochemical recovery within 4 to 6 weeks. In two groups of patients, the natural history and prognosis are different: patients who have underlying chronic liver disease have a poor prognosis, and individuals who are immunosuppressed often develop chronic infection (see below) (20). A minority of patients present with neurological symptoms, and when this occurs, the diagnosis may easily be overlooked because the neurological illness dominates the clinical picture (see below) (21).

There are few studies that have addressed the issue of differences in pathogenicity between HEV3 and HEV4. In a Japanese study, patients with HEV4 had significantly higher peak alanine aminotransferase levels than those of patients with HEV3 (22). In a French study, the clinical presentation was more severe in a small group of patients with HEV4 infections, representing a unique cluster, than in patients with HEV3 infections (23). Further studies are needed to clarify the association between HEV genotype and outcomes of HEV infection.

HEV infection may be misdiagnosed as DILI. Drug-induced liver injury (DILI) occurs more frequently in the elderly (in whom polypharmacy is common), as does autochthonous hepatitis E, and the clinical features may be indistinguishable. The diagnosis of DILI is based on a number of criteria. These include a temporal relationship between starting a drug and developing hepatitis (usually 5 to 30 days), a temporal relationship between stopping the offending drug and the resolution of hepatitis, and the exclusion of all other causes of hepatocellular injury. In a study of a group of patients with criterion-referenced DILI from Southwest England, it was found that the diagnosis of DILI had been made in error in some patients, as 13% of patients with "DILI" who were tested retrospectively had HEV genotype 3 infection (24). In a more recent study from the United States, 3% of patients with "DILI" had been diagnosed erroneously, as they had hepatitis E on subsequent testing (25). These studies illustrate the importance of excluding other causes of hepatocellular injury before making a diagnosis of DILI and suggest that the diagnosis of DILI should not be made without excluding HEV infection, particularly in individuals with high serum alanine aminotransferase levels.

Extrahepatic Manifestations of HEV

In addition to the classical hepatic manifestations, HEV is responsible for extrahepatic disorders. These include a range of neurological syndromes, renal injury, pancreatitis, and hematological problems.

Neurological disorders. Neurological symptoms have been described for HEV1 and acute and chronic HEV3 infections (26). The neurological manifestations observed in HEV patients are Guillain-Barré syndrome (27–35), Bell's palsy (36), neuralgic amyotrophy (37, 38), acute transverse myelitis (39), and acute meningoencephalitis (29, 40). In a retrospective analysis of 126 patients with HEV infection, neurological symptoms were observed in 7 patients (5.5%), including 3 immunocompetent patients with acute HEV3 infection, 3 solid organ transplant (SOT) recipients, and 1 HIV-positive individual with chronic infection (21). Recently, Guillain-Barré syndrome associated with necrotizing myositis was described for a liver transplant recipient (41). It is

TABLE 1 Epidemiology and clinical features of HEV infection in developing and developed countries

Feature	Description or value	
	HEV in developing countries	HEV in developed countries
Epidemiology		
Genotypes	1 and 2	3 and 4
Source of infection	Human	Zoonotic; pigs are primary host[a]
Route of infection	Fecal-oral via infected water	Fecal-oral via infected pig meat, direct exposure, infected water
Transfusion-related infection	Yes	Yes
Seroprevalence	Low in children of <15 yr, increases rapidly from ages 15 to 30 yr	Steady increase throughout age groups
Incidence	Variable: 64/1,000 patient-yr, Bangladesh	Variable: 3/100 patient-yr, South of France; 7/1,000 patient-yr, USA
Outbreaks	Yes; can involve thousands of cases	No; occasional small case clusters from a food point source
Attack rate	~1 in 2	67–98% of those infected are asymptomatic
Person-to-person spread	Very limited	No
Seasonality	Yes; outbreaks occur at times of flooding/monsoon	No
Disease in travelers returning from areas of endemicity	Well described	Is beginning to emerge as high-risk areas become defined
Clinical features		
Age at infection (yr)	15–30	>50
Sex (male/female ratio)	2:1	>3:1
Clinical course	Self-limiting hepatitis in most	Self-limiting hepatitis in most
Neurological complications	Yes	Yes
Deaths in pregnant females	Yes; 20–25% in final trimester[b]	No
Outcome in patients with underlying chronic liver disease	Poor	Poor
Chronic infection	No	Yes; genotype 3 only
Burden of disease	3.4 million cases/yr, 70,000 deaths, 3,000 stillbirths[c]	Unknown

[a] HEV genotypes 3 and 4 have also been transmitted from human to human via infected blood products.
[b] The epidemiology and clinical course of HEV genotype 1 in Egypt are significantly different from those in other developing countries. In Egypt, the seroprevalence is similar to that of HAV, with nearly universal exposure in childhood, and the risks to pregnant females may be less. The reason for these observations is unknown.
[c] Data are for 9 of 21 regions defined for the Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study), which represent 71% of the world's population.

interesting that HEV RNA in the cerebrospinal fluid (CSF) was documented for all patients with chronic HEV infection presenting with neurological syndromes (21). Clonal sequences in the CSF and serum of a kidney transplant recipient with chronic HEV and neurological symptoms demonstrated quasispecies compartmentalization. This suggests that HEV-associated neurological injury might be linked to the emergence of neurotropic variants (42). More recently, cases of anti-ganglioside GM1-positive and anti-GM2-positive Guillain-Barré syndrome associated with HEV infection have been described (28, 33).

Kidney injury. Impaired renal function has been noted in both acute and chronic HEV infections (43, 44). As with other hepatotropic viruses, HEV1 and -3 infections can cause glomerular disease. Two different histological patterns of glomerular disease have been observed: membrano-proliferative and membranous glomerulonephritis (44). These kidney injuries were observed in immunocompetent patients (45) as well as kidney and liver transplant patients (44). The pathophysiological mechanisms of HEV-associated renal injury are uncertain, but cryoglobulinemia may have an important role, as cryoglobulinemia has been documented for patients with chronic infection (44).

Pancreatitis. Acute pancreatitis has been associated with HEV1 infection (46–49). However, no cases of pancreatitis have been reported with any of the other genotypes.

Hematological disorders. Thrombocytopenia and aplastic anemia have been reported for acute HEV infection (50–52).

HEV Infection and Pregnancy

A recent study estimated that in 2005, in 9/21 Global Burden of Disease regions (exclusively developing countries), there were 3.4 million symptomatic cases of hepatitis E, with 70,000 deaths and 3,000 stillbirths (53). A significant proportion of the deaths were in pregnant women. This estimate of the disease burden may well be an underestimate of the global burden of disease associated with hepatitis E, as another recent study suggests that there may be approximately 1,000 maternal deaths per annum in Bangladesh alone (54).

Numerous studies from developing countries have shown excess mortality in pregnant females who develop hepatitis E virus infection. The mortality is 20 to 25% and usually occurs in the third trimester (14). Pregnant women die of obstetric problems, including hemorrhage or eclampsia, or develop fulminant hepatic failure. Stillbirths are common, as is vertical transmission to infants who survive, who have an increased neonatal morbidity and mortality (55). The excess mortality in pregnancy with HEV genotypes 1 and 2 is unique. It is not seen with genotypes 3 and 4, although there have been a few documented cases in pregnant females (56–58), nor is it seen with other hepatotropic viruses.

The cause of excess maternal mortality in patients with hepatitis E virus infection is uncertain and has been the subject of many studies and much debate. Pregnancy is characterized by a state of maternal immune tolerance toward the fetus. T-cell activity is

TABLE 2 Immunological and hormonal changes in pregnant females with hepatitis E virus infection and fulminant hepatic failure

Study	Country	Findings[a]
Salam et al., 2013 (60)	India	Increased TNF-α
Prabhu et al., 2011 (61)	India	Increased cytotoxic T cells in liver biopsy specimens
Bose et al., 2011 (62)	India	HEV load increased in patients with FHF, increased incidence of FHF and child mortality in patients with progesterone receptor gene mutations, reduced progesterone receptor and progesterone blocking factor in patients with FHF, reduced IL-12/IL-10 ratio
Prusty et al., 2007 (63)	India	Suppression of NF-κBp65 in PBMCs and liver biopsy samples
Jilani et al., 2007 (64)	India	Reduced CD4 cells, increased CD8 cells, increased estrogen, progesterone, and β-HCG levels
Pal et al., 2005 (65)	India	Shift to Th2 immunological profile, reduced lymphocyte response to PHA

[a] TNF-α, tumor necrosis factor alpha; FHF, fulminant hepatic failure; PBMCs, peripheral blood mononuclear cells; β-HCG, human chorionic gonadotropin beta; PHA, phytohemagglutinin.

reduced, there is a reduction in cytokine production in the first 20 weeks, Th2 responses predominate, and immunological changes in the placenta downregulate antigen presentation. The changes in maternal immunological responses are driven, at least in part, by significant changes in hormone profiles, with increased levels of progesterone, estrogen, and human chorionic gonadotropin (59). Studies have shown significant differences in immunological and hormonal responses in pregnant women with fulminant hepatic failure caused by hepatitis E (60–65). These are summarized in Table 2. Finally, recent studies showed that among women infected with HEV, higher viral loads were observed in pregnant women than in women who were not pregnant (66, 67).

In some geographical locations in developing countries, there appears to be no excess mortality in pregnancy with hepatitis E virus infection. For example, in Egypt, hepatitis E appears to follow a benign course in pregnancy, although it is caused by HEV genotype 1 (59). The explanation for this observation is not known. It could relate to differences in maternal major histocompatibility complex (MHC) phenotypes in such locations. Another possibility is that the predominant quasispecies of HEV genotype 1 in these locations is less virulent, as HEV amino acid mutations have been observed in cases of fulminant hepatic failure in India (68). Finally, it could be that such populations have had high levels of early childhood exposure to HEV, resulting in attenuated disease on reexposure. The latter hypothesis is supported by the finding of an anti-HEV IgG seroprevalence of up to 78% in a study of pregnant Egyptian females (69).

HEV Infection in Patients with Preexisting Liver Disease

Patients with underlying chronic liver disease who develop hepatitis E have a poor prognosis, as they frequently develop acute or subacute liver failure. In a study of a large cohort of patients in India with decompensated chronic liver disease, patients who had decompensation because of acute hepatitis E virus infection had a significantly worse prognosis than patients who had decompensation due to another cause (70). The 12-month mortality in the cohort with hepatitis E virus infection was 70%. In developed countries, smaller studies have also shown a poor prognosis for patients with underlying chronic liver disease (71, 72), but it is not clear how frequently this occurs, as such patients are currently not routinely tested for evidence of infection with HEV. However, two studies show that there is a strong relationship between deaths from decompensated chronic liver disease and pork consumption in developed countries (73, 74). The reason for this observation is uncertain, but it might be explained by unrecognized infection with HEV. Studies to address this hypothesis are ongoing, and the results are awaited with interest.

VIRUS BIOLOGY, RESERVOIR, AND TRANSMISSION

HEV is a nonenveloped virus with an icosahedral capsid and a size of 27 to 34 nm. The virus has a positive-sense, single-stranded, 7.2-kb RNA genome which is capped and polyadenylated at the 5′ and 3′ termini, respectively (4, 5). The HEV genome contains three open reading frames (ORFs). ORF1 encodes a protein of 1,693 amino acids containing functional domains present in the nonstructural proteins of other positive-strand RNA viruses (75). These functional domains include methyltransferase, cysteine protease, RNA helicase, and RNA-dependent RNA polymerase domains. ORF2 encodes the viral capsid protein of 660 amino acids that is responsible for virion assembly (76), interaction with target cells (77, 78), and immunogenicity (79). The ORF2 protein consists of three linear domains: the shell domain (S) (amino acids 129 to 319), the middle domain (M) (amino acids 320 to 455), and the protruding domain (P) (amino acids 456 to 606), harboring the neutralizing epitope(s) (80–84). ORF3, which overlaps ORF2, encodes a small protein of 113 or 114 amino acids that is involved in virion morphogenesis and release (85–87).

HEV replicates in the cytoplasm, with a subgenomic RNA producing the ORF2 and ORF3 proteins and the full genomic RNA encoding nonstructural proteins and serving as a template for replication (Fig. 1). Current data suggest that the ORF1 protein is not subjected to proteolytic processing (88). HEV replicates in hepatocytes but also in the small intestine, colon, and lymph nodes, as demonstrated by detection of negative-sense RNA intermediates (89).

Until recently, there was no reliable cell culture system for HEV, and this produced significant difficulties in terms of detailed analysis of the basic biology of HEV. The first efficient cell culture systems were developed for HEV3 and HEV4 by using PLC/PRF/5 cells, derived from human hepatocarcinoma, and A549 cells, derived from human lung cancer (90–92). These cell lines permitted the propagation of HEV from fecal samples as well as from serum samples. HepG2/C3A cells, derived from human hepatocarcinoma, were also able to adapt a HEV3 strain from the feces of a chronically infected patient (93). Interestingly, a human-sequence insert identified in the ORF1 region of HEV RNA could have facilitated cell culture adaptation (93, 94). Other *in vitro* models that have morphological and functional properties similar to those of primary hepatocytes have been described recently (95). Sucrose density gradient fractionation revealed that cell culture-

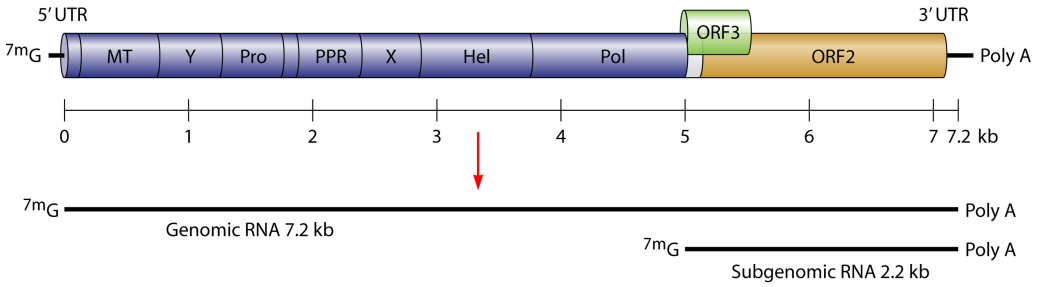

FIG 1 Hepatitis E virus genome.

generated HEV particles and those in circulating blood have a lower density (1.15 to 1.16 g/ml) than that of HEV particles in feces (1.27 to 1.28 g/ml), reflecting the fact that cell culture-generated HEV and blood HEV are associated with lipids (90).

The infectivity titer of a standard stock of a prototype strain of HEV genotype 1 (SAR-55) was determined in cynomolgus macaques (96). However, comparative information on infective doses of different HEV strains is not available. Besides viral factors (genotype, size of the dose, and type of preparation), host factors and the transmission route (fecal-oral versus intravenous inoculation) are key parameters. Nonhuman primates such as rhesus and cynomolgus macaques and chimpanzees have been used as experimental models for all four main genotypes of HEV. Pigs and rabbits are used for infectivity studies of HEV genotypes 3 and 4. Only one serotype has been recognized for HEV.

Experimental cross-species infections demonstrated that the same viral doses inoculated into cynomolgus macaques induced variations in the overall course of disease (97, 98). The recent availability of efficient cell culture systems for HEV will be useful for determining the infectivity titers of inocula in future studies. These data are essential for risk assessment studies.

In developing countries, where HEV1 and HEV2 are transmitted via contaminated water, fecal shedding of HEV by humans with clinical or subclinical infection maintains a circulating pool of infectious individuals who contaminate water supplies, thus maintaining the disease in endemic populations (99, 100). HEV1 and HEV2 mainly infect humans, and detection of HEV in sewage indicates an important role for an environmental reservoir (101).

In developed countries, where most cases of HEV infection are autochthonous (locally acquired), the importance of animal reservoirs has become clear. HEV strains infecting mammals such as domestic pigs, wild boar, deer, and rabbits are causative agents of zoonotic infection in humans (7, 17, 102, 103). The major animal reservoir is domestic pigs, with a very high prevalence in many countries and asymptomatic infection in the animal host (104). HEV3 has a worldwide distribution (18). In contrast, HEV4 is found largely in China and Japan (8) but was recently detected in Europe, both in pigs (105) and in humans (106–108). HEV3 and HEV4 are also detected in wild boar and deer, but the prevalence is low compared to that in domestic pigs (104).

The complete range of mammalian species that may act as reservoirs for HEV is unknown. However, HEV variants infecting rats (109), ferrets (110), mongoose (111), and bats (112) have not been found in humans. Zoonotic transmission of HEV may be mainly via the consumption of uncooked or undercooked infected pork or game (wild boar, deer, or rabbit) meat (17, 113–116). In a case-control study in Germany, HEV seroprevalence was associated with consumption of offal and wild boar (117). In another case-control study, in France, HEV infection was associated with consumption of game meat (118). The thermal stability of HEV has been investigated. HEV remains viable after heating to 56°C for 1 h (119), and cooking temperatures of 71°C for 20 min are required to fully inactivate the virus (120).

Direct contact with HEV-infected animals is another possible route of transmission of HEV (121–123). Seroprevalence studies show that veterinarians and swine handlers are more likely than the general population to be anti-HEV IgG positive (124).

The waterborne route of infection may also be important for HEV3 and HEV4. HEV3 has been detected in untreated wastewater, swine manure, swine slurry storage facilities, and river water (125–129). HEV3 has also been detected in mussels and oysters (130, 131). A case-control study of an outbreak of HEV3 on a cruise ship suggested that the route of infection may have been via the consumption of shellfish (132). The relative importance of environmental transmission of HEV3 and HEV4 remains unknown.

Finally, transfusion-transmitted HEV infection has been documented in a number of countries (133–138). HEV has also been detected in blood products (139–142). A total of 0.7% of plasma minipools from donors in England were found to contain HEV RNA (141), and a prevalence of 10% was found for donors in Germany (140). Current estimations of positive HEV RNA in blood donations are as follows: 1 in 7,040 in the United Kingdom (141), 1 in 4,525 and 1 in 3,179 in Germany (142, 143), 1 in 3,090 in the Netherlands (144), and 1 in 1,430 in China (145). Regarding the safety of biopharmaceutical materials, such as plasma-derived medicinal products, it is important to guarantee the efficacy of manufacturing process steps in inactivating/eliminating HEV. HEV infectivity assays could be useful for validation studies of viral safety in this setting (146).

MOLECULAR EPIDEMIOLOGY

HEV is classified in the genus *Hepevirus* in the *Hepeviridae* family (147). This family contains viruses that infect mammals, including humans, as well as birds and fish. Avian HEV (148) and cutthroat trout virus (149) share about 50% of the nucleotide sequence of mammalian HEV strains and have not been associated with human cases. While the most common classification system identifies 4 major mammalian HEV genotypes (HEV1 to -4) and several subgenotypes within each genotype (8), recent data based on complete genome sequences from human and animal strains and ORF1/ORF2 amino acid sequences indicate the existence of 3 groups of mammalian HEV (150). The first group corresponds to viruses infecting humans, pigs, wild boar, deer, and rabbit. This

group contains the four major HEV genotypes and new genotypes from wild boar (151) and rabbit (152). The second group corresponds to viruses infecting rats and ferrets (109, 110), and the third group corresponds to viruses infecting bats (112). Therefore, a new nomenclature of HEV will probably be used in the future. Four tentative genera were recently proposed (153): *Orthohepevirus*, including mammalian strains except bat HEV; *Chiropteranhepevirus*, including bat strains; *Avihepevirus*, including avian strains; and *Piscihepevirus*, including cutthroat trout virus.

Recent genetic variability studies indicate that no consistent criteria can be defined for the assignment of subgenotypes within each genotype (150, 154). However, several studies based on full-length genome sequences and the classification system dividing the four major HEV genotypes into 24 subgenotypes (5 for HEV1, 2 for HEV2, 10 for HEV3, and 7 for HEV4) have provided interesting molecular epidemiological data (8, 155). In developing countries, subgenotypes 1a, 1b, and 1c are prevalent in Asia, while subgenotypes 1d and 1e are found in Africa (8). Subgenotypes 3a and 3b, circulating in the United States and Japan, are clearly distinct from subgenotypes 3f, 3c, and 3e, circulating in Europe (102, 156, 157). Phylogenetic and coalescence analyses based on numerous full-length sequences of HEV3 from acute hepatitis patients, domestic swine, and wild boars provide evidence that subgenotype 3e strains were introduced from Europe into Japan through the importation of pigs in the 1960s (158). This study also suggests the direction of gene flow of HEV subgenotype 3e in Japan from swine to wild boars.

In many geographic areas, phylogenetic studies have shown that HEV strains circulating in pigs and human beings are very closely related, which supports the notion of autochthonous zoonotic transmission (159, 160). The same proportions of subgenotype 3f, 3c, and 3e strains in human and pig populations have been reported in France (157). Thus, there is considerable evidence that HEV strains circulating among swine and humans are closely genetically related, which supports the hypothesis of zoonotic transmission of HEV through consumption of raw or undercooked pig products. Nevertheless, HEV infection may also be acquired from environmental exposure.

In certain geographic areas, genetic dissociation between local human and swine strains has been observed. For example, in central China, analysis of HEV strains from humans and commercially reared pigs showed that human and swine HEV strains belonged to differing HEV4 subgenotypes (161). This is different from the case in eastern and western China, where HEV transmission from swine to humans is frequent. In India, there is a wide separation between HEV strains circulating in animal and human populations, as swine HEV strains belong to genotype 4 and human HEV strains belong to genotype 1 (162, 163). In Bolivia, a study showed that swine sequences belonged to subgenotype 3i and human sequences belonged to subgenotype 3e (164). The mechanisms of the dissociation of HEV strains between animal hosts and humans are unknown.

Rabbit HEV strains have been characterized in farmed and wild rabbits in China (152), the United States (165), and Europe (102). Interestingly, a human strain closely related to rabbit HEV was identified, supporting zoonotic transmission (102). Full-length genomic sequence analysis indicates that all rabbit strains belong to the same clade, with nucleotide sequences 72.2 to 78.2% identical to those of HEV genotypes 1 to 4. The genomes of rabbit HEV and the TLS-18516 human strain harbor a molecular signature in the X domain of ORF1 that is not present in any known strains of HEV genotypes 1 to 4 or in the new genotypes from rat, wild boar, and bats (166). A phylogenetic tree based on full-length sequences of HEV strains is shown in Fig. 2.

Evolutionary history and population dynamic studies show that HEV has evolved through a number of steps, in which the ancestors of HEV adapted to a succession of animal hosts, including humans (167). A common ancestor that existed between 500 and 1,300 years ago has been suggested based on molecular clock analysis. Genotypes 1, 3, and 4 expanded during the 20th century, with different population dynamics. Genotype 1 increased in population size about 30 to 35 years ago. In contrast, genotypes 3 and 4 underwent an increase in population size starting in the late 19th century. However, a recent study in Nanjing, China, suggested that genotype 4 underwent a relatively recent expansion, in the late 20th century, with no change in the dominant subgenotype 4a over the past decade (168). This is in line with other studies that observed within China a decrease in the prevalence of HEV1 accompanied by an increase in the prevalence of HEV4 (169, 170).

DIAGNOSTICS

HEV infection can be diagnosed either indirectly by detecting serum anti-HEV antibodies or directly by detecting the HEV genome in blood or other bodily fluids.

Following an incubation period of 2 to 6 weeks, an initial short-lived IgM response is followed by longer-lasting IgG antibodies. Commercial enzyme immunoassays and rapid immunochromatographic kits based on ORF2/ORF3 peptides or recombinant antigens from HEV1 can detect the presence of IgM or IgG antibodies induced by the four major genotypes of HEV, representing a single serotype (171, 172). There is no genotype-specific serologic testing. No cross-reactivity of HEV antigen with another pathogen has been reported. A previous study determined the kinetics of anti-HEV antibodies after HEV infection (173). At clinical presentation, anti-HEV IgM levels had already reached the peak level, but they remained at relatively high levels for 8 weeks. IgM antibodies declined rapidly thereafter, falling below the cutoff level among most patients after 32 weeks. HEV IgG levels were rising when patients presented. The antibody reached peak levels about 4 weeks after the onset of symptoms and was maintained at high levels for more than 1 year (173). The exact duration of the anti-HEV IgG antibody response remains uncertain. In one study, anti-HEV IgG antibody was detectable in nearly half of patients who had hepatitis E 14 years previously (174).

The presence of anti-HEV IgM is a marker of acute infection. Six IgM anti-HEV enzyme immunoassays have been compared using sera from immunocompetent individuals infected with all four genotypes of HEV (175). This study showed that the sensitivities of the tests were between 72% and 98% and the specificities were between 78.2% and 95.6%. Another study evaluated the performances of two microplate assays and one rapid test (176). The sensitivities ranged from 80% to 90%, and the specificities were >99.5%. Good sensitivity of the two IgM assays frequently employed in Europe, the Adaltis test and the Wantai test, was recently demonstrated by testing samples from 44 immunocompetent patients and 40 immunocompromised patients with acute HEV infection. Using a validated PCR assay as a reference, the sensitivity was 97.7% for immunocompetent patients and 85 to 87% for immunocompromised patients; no sample collected during acute infection was anti-HEV IgM negative and anti-HEV IgG positive,

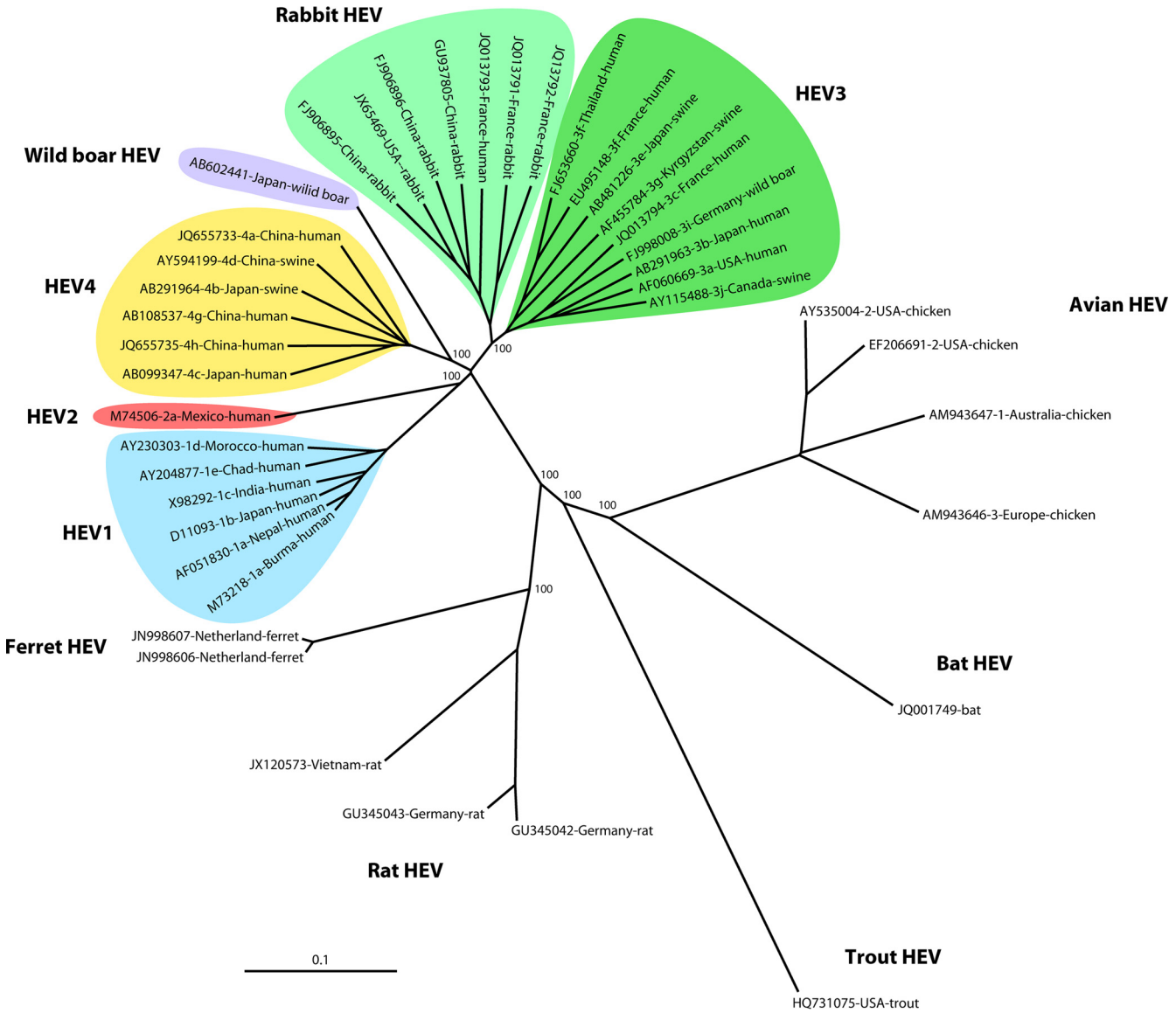

FIG 2 Phylogenetic tree based on full-length sequences of HEV strains. Sequences were aligned by using ClustalW (MEGA5 [www.megasoftware.net] and BioEdit, version 7.0 [www.mbio.ncsu.edu/bioedit/bioedit]). The phylogenetic tree was created by the neighbor-joining (Kimura two-parameter) method, with a bootstrap of 1,000 replicates. GenBank accession numbers are shown for each HEV strain used in the phylogenetic analysis. The scale bar indicates the number of nucleotide substitutions per site.

and both IgM tests were highly specific (>99.5%) (177). "Point-of-care" assays have also been developed to test for anti-HEV IgM antibodies (178). These immunochromatographic assays are easy to use, give a result within a few minutes, and are ideally suited to resource-limited settings. One such commercially available assay showed a sensitivity and specificity of 93% and 99.7%, respectively, with sera from patients from Southeast Asia, where HEV1 is prevalent (179), and of 82% and 100%, respectively, for HEV3 in France (176).

The presence of anti-HEV IgG alone is a marker of past infection. The current WHO reference reagent for hepatitis E serum IgG was established in 2002 from a U.S. citizen infected in India (National Institute for Biological Standards and Control [NIBSC] code 95/584) (180). This material is essential for evaluating the analytical sensitivity of anti-HEV IgG assays. Available assays vary considerably in their performance (181–183). Most of the currently available anti-HEV IgG assays have been validated against sera obtained from patients with recent infection, and their ability to detect distant infection is unknown. The limits of detection of these assays vary between 0.25 WHO unit/ml and 2.5 WHO units/ml (184). Anti-HEV IgG is sometimes undetectable in some assays after HEV infection (185, 186). This variability must be taken into account when interpreting data regarding HEV seroprevalence that are currently available in the literature. The use of more sensitive IgG assays has led to increases in seroprevalence estimates, by a factor of 3 to 4 (184, 187). For example, in a study using an insensitive "first-generation" IgG assay, the seroprevalence in southwestern England was 3.6%, but it rose to 16% when a more sensitive, partially validated assay was employed (184). By using the same sensitive IgG assay, i.e., the Wantai test, with a limit

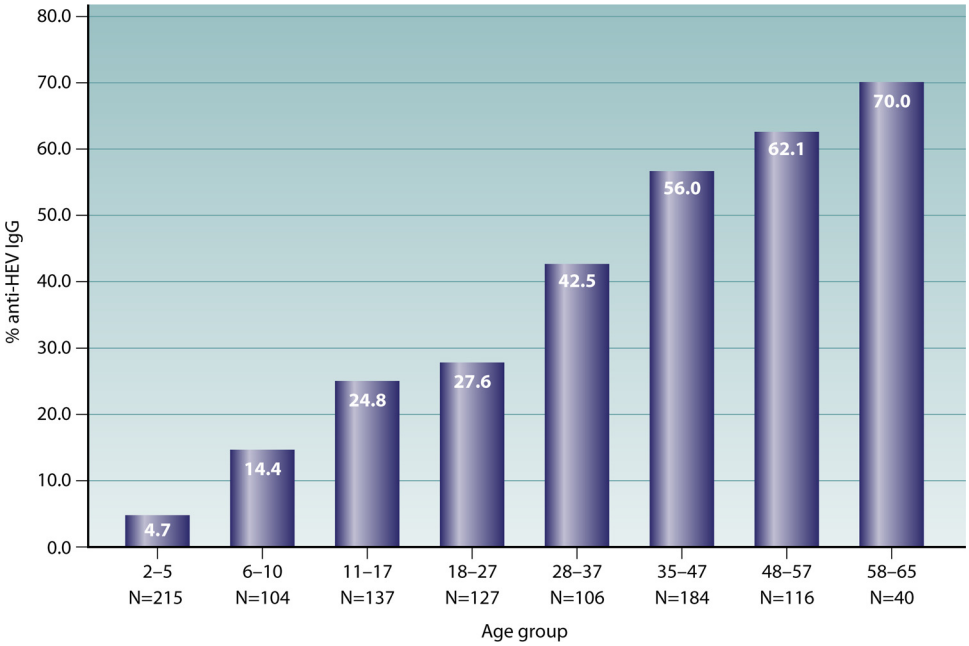

FIG 3 Anti-hepatitis E virus IgG distribution in Midi-Pyrenees area of France, according to age.

of detection of 0.25 WHO unit/ml and excellent specificity, direct comparisons of seroprevalence between populations in distinct geographic areas can now be made. IgG seroprevalence in blood donors is 52% in southwestern France (187), 29% in Germany (183), 27% in the Netherlands (144), and 16% in southwestern England (20). This suggests that HEV is hyperendemic in the Toulouse area of France, which is congruent with the large number of cases documented in the Midi-Pyrenees area and the high incidence (3.2%) of infection documented by molecular techniques in local transplant recipients (188). A clearer picture of HEV epidemiology is now emerging which shows significant variations in seroprevalence both between and within countries and a gradual increase of IgG seroprevalence with the age of individuals, as illustrated in Fig. 3.

Determination of the anti-HEV IgG concentration (185, 189) could be useful for determining the level of anti-HEV IgG that reliably prevents infection after natural infection or vaccine administration in clinical trials. A vaccine study suggested that an antibody concentration of 2.5 U/ml was protective (190). IgG protection is not type specific. In a recombinant genotype 1 HEV vaccine, both genotype 1 and 4 infections were prevented, indicating cross-protection against different HEV genotypes (191). More studies are needed to evaluate the clinical value of IgG immunoblot assays (192) and avidity tests (185).

In patients with acute HEV infection, viremia peaks during the incubation period and during the early symptomatic phase (99, 173). HEV RNA becomes undetectable in blood about 3 weeks after the onset of symptoms but can be detected in feces for another 2 weeks. Thus, if patients are sampled late in the symptomatic phase of illness, a negative HEV RNA result does not exclude recent infection. Serum HEV RNA concentrations in the acute phase range from 2.1 to 8.3 log copies/ml in immunocompetent patients (177). There is no relationship between the HEV RNA concentration in serum and clinical symptoms. In solid organ transplant recipients with acute hepatitis E, the HEV RNA concentration ranged from 2.7 to 7.8 log copies/ml (118) and was not associated with the evolution to chronic infection. Detection and quantification of HEV RNA in blood and other compartments are based on real-time PCR with primers targeting conserved regions between HEV genotypes. A study demonstrated the influence of HEV3 diversity on HEV quantification and revealed an optimal performance for assays based on primers targeting the ORF3 region (193). In a multicenter international study, large variations in performance of in-house PCR methods were observed, with interlaboratory differences of 2 to 3 log copies/ml for sensitivity and 0.4 to 1 log copy/ml for reproducibility (194). Although most PCR assays, including commercial assays (195, 196), target ORF3, there is no specific target with particularly poor performance. Another nucleic acid amplification technique, the loop-mediated isothermal amplification (LAMP) assay, has been developed for the detection of HEV RNA (197). This technique, based on a set of six primers that recognize eight distinct regions on the target sequence, enables a one-step, single-tube, isothermal amplification of HEV RNA. The LAMP assay is quicker than real-time PCR and does not need special equipment, making it suitable in resource-limited areas. Recently, a WHO international standard (genotype 3a) was established (196), which is an important step in both standardization of HEV RNA detection and accurate quantification. This also provides control material for comparing the analytical sensitivities of nucleic acid-based methods. Finally, the first commercial HEV RNA assays have now been evaluated against the international standard and generally showed good performance (143, 195).

Considering the performance of anti-HEV IgM assays, we suggest that they can be used as first-line diagnostic assays (Fig. 4). In immunocompromised patients, HEV RNA testing is also needed due to impaired immune responses and poorer performance of IgM assays for this population. In the immunocompromised,

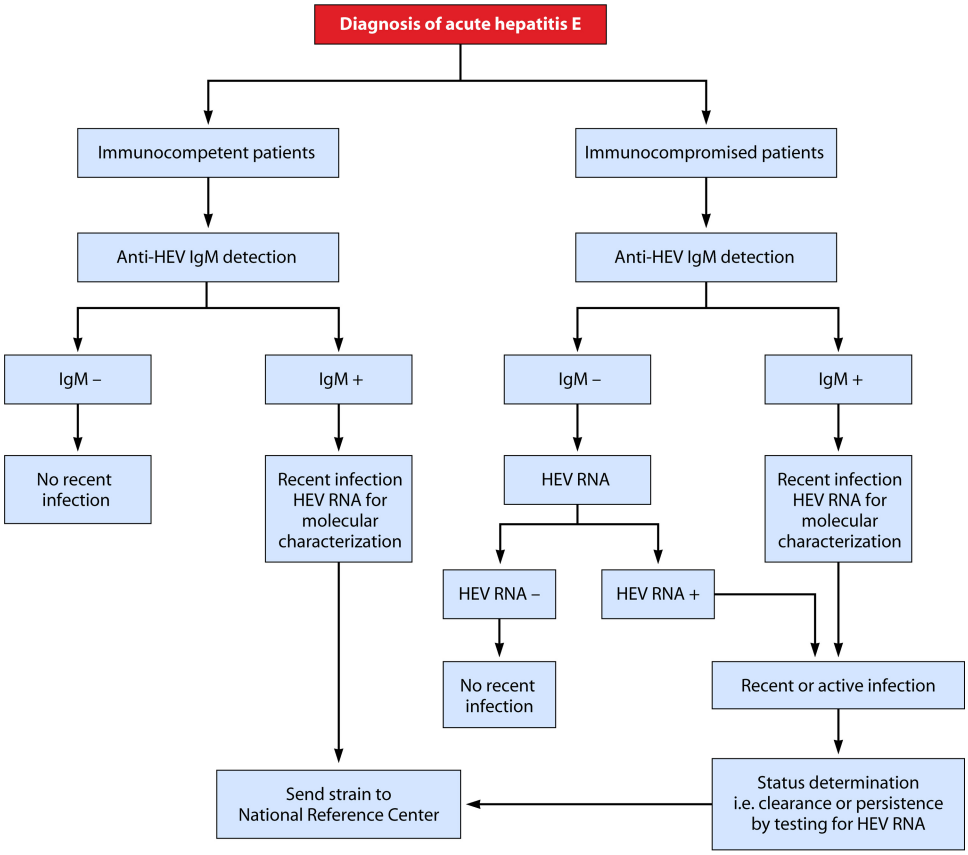

FIG 4 Flow diagram for diagnosis of acute hepatitis E virus infection.

HEV RNA testing is useful for molecular characterization and is essential to delineate chronic infection: if HEV RNA persists for 3 months, then the patient is very unlikely to achieve spontaneous viral clearance without therapeutic intervention (198). Monitoring of HEV RNA is also crucial for the management of chronic HEV infection after reduction of immunosuppression or after initiation of antiviral therapy. Sensitive anti-HEV IgG assays with a low limit of detection are essential for detecting previous exposure to HEV.

GENERAL EPIDEMIOLOGY

HEV Infection in Developing Countries

Detailed information on the epidemiology of HEV infection can be found in Table 1. In developing countries, hepatitis E is a waterborne infection caused by HEV genotype 1 or 2, which is spread between humans when there is a breakdown in clean water supplies. Sporadic cases occur throughout the year, punctuated by occasional dramatic outbreaks involving thousands or tens of thousands of cases (10). Outbreaks of hepatitis E are often seasonal, and in countries such as Nepal, they are more likely to occur at the time of the monsoon (14). The clinical attack rate in an outbreak is about 1 in 2, and in some studies, males are more likely to be affected (male/female ratio = 2:1). Person-to-person spread has been thought not to be an important mode of disease transmission. However, a study from Uganda provides some evidence that household factors could be important in disease transmission (199), and person-to-person spread may have been a factor in the recent extended outbreak in South Sudan (200).

In many developing countries, anti-HEV IgG seroprevalence studies show that most children under the age of 10 years have not been exposed to HEV (201). The seroprevalence increases dramatically between the ages of 15 and 30 years, and it plateaus at around 30% (14). These findings are curious, consistent, and unexplained and contrast with hepatitis A virus (HAV) seroprevalence, which in most developing countries shows nearly universal exposure to HAV by the age of 10 years. One exception to these observations is found in Egypt. In Egypt, the seroprevalence rates are generally higher (up to 80%), and in some studies, children aged less than 10 years of age have high levels of previous exposure to HEV (202, 203). In South America, seroprevalence studies show a wide range of results, ranging from <1% to 20% (204). The seroprevalence varies between and within countries and may reflect, in part, the populations studied and the sensitivity of the assay employed. In some countries, such as Brazil and Argentina, hepatitis E has been studied more extensively. The epidemiology resembles that found in developed countries, with HEV genotype 3 found in both porcine and human populations (164, 204–208).

The incidence of infection varies between and within countries and over time. Hepatitis E is particularly common in some Southeast Asian countries (Nepal, Bangladesh, India, and Pakistan), and there have been numerous large outbreaks in African refugee camps in the last 20 years (199), such as the recent one in South

Sudan, in 2012 to 2013 (200). Sporadic cases of hepatitis E caused by genotypes 1 and 2 occur in travelers/workers returning to developed countries from areas of hyperendemicity and are well documented in the literature (209).

HEV Infection in Developed Countries

Over the last 15 years, it has become evident that hepatitis E is not a disease confined to developing countries or travelers returning from such locations. Numerous studies show that autochthonous (locally acquired) hepatitis E is a problem across Europe, North America, New Zealand, and Japan (19, 20, 210–212). In contrast to the case in developing countries, autochthonous hepatitis E is a zoonotic infection caused by HEV genotypes 3 and 4, and an important route of infection is by consumption of uncooked or poorly cooked pork or game meat (10).

In developed countries, anti-HEV IgG seroprevalence studies are problematic (see above). Many of the earlier studies showed very low seroprevalences, in the 1 to 2% range (184). Most of these studies used anti-HEV assays of poor sensitivity and almost certainly significantly underestimated the true seroprevalence (144, 184, 185, 213).

There is considerable geographic variation in seroprevalence and incidence in developed countries. For example, the seroprevalence in the south of France is four times higher than that found in the north of France (214). In the United Kingdom, there is also a significant north-south difference, with seroprevalences of 16% in southwestern England (20), 12% in the rest of England (215), and 4.6% in Edinburgh, Scotland (216). The reasons why seroprevalence varies in this way are not understood. The data regarding the incidence of hepatitis E in developed countries are limited, but estimates are high: 0.2% in the United Kingdom (215) and 0.7% in the United States (217). The latter figure suggests that each year, in the United States, there are over 2 million infections with HEV. This mind-boggling figure is at odds with the very small number of autochthonous cases that have been documented in the United States (210). One reason for the discrepancy is that currently in the United States, there are no diagnostic assays that are approved by the FDA for use in humans, so many cases will simply be "missed." In addition, the evidence suggests that most infections with HEV genotypes 3 and 4 are asymptomatic (132).

Perhaps the most striking aspect of the epidemiology of autochthonous hepatitis E in developed countries is the demography of those affected. In sharp contrast to the case in developing countries, in developed countries autochthonous infection has a predilection for middle-aged elderly males (mean age, ~60 years; male/female ratio, >3:1) (19, 20, 210–212). This is a consistent and intriguing finding but is largely unexplained. It seems unlikely that older men are exposed to HEV more often, as exposure appears to be unrelated to age or sex. This implies that host factors could be important, and two case-control studies have shown that hepatitis E is more common in excessive consumers of ethanol. One hypothesis that might explain these observations is that individuals who consume excessive amounts of alcohol are prone to subclinical hepatic steatosis and scarring, which may, in turn, lead to clinical disease expression on exposure to HEV (132, 218).

Two studies from the United Kingdom have shown that cases of hepatitis E cluster around the coast (219, 220). Provisional data from a case-control study in Cornwall show that, compared to controls, patients with hepatitis E are more likely to reside within 2.5 km of the sea. The reason for this finding is unknown. It might be that individuals who live in coastal locations are more likely to consume shellfish, as HEV genotype 3 has been found in shellfish in several locations, including around the coast of the United Kingdom. Another possible explanation is that people who live near the coast may have become infected via recreational use of seawater, as HEV was recently found in seawater in Japan (221).

CHRONIC HEV INFECTION

Chronic HEV Infection in Solid Organ Transplant Patients

An increasing number of recent studies have shown that HEV can cause chronic infection that can rapidly result in cirrhosis (13). Although the majority of chronic HEV cases are diagnosed in the transplant population (13, 222–228), several chronic cases have also been observed in patients coinfected by HIV (229) and in hematological patients treated with anticancer chemotherapy (230). All chronic HEV cases were observed in patients infected by HEV genotype 3. No case of chronic HEV genotype 1, 2, or 4 infection has been described. All chronic cases have been autochthonous and have not been associated with travel. A diagnosis of chronic hepatitis used to be considered when persisting HEV replication lasted for at least 6 months. However, very recently, in the setting of organ transplantation, it was observed that no spontaneous clearance of HEV occurs between 3 and 6 months after an acute infection. This suggests that chronic HEV infection should be considered when HEV replication persists for more than 3 months (198).

Adult SOT patients. (i) HEV transmission in SOT patients. The route of HEV transmission in SOT recipients appears to be similar to that seen in the general population, i.e., consumption of pork, game meats, and shellfish (10). Although blood transfusion is a recognized route of HEV transmission (231–233) and is quite common after transplantation, cases of transfusion-induced HEV transmission have rarely been reported in this setting (188, 234). HEV transmission by the grafted organ has been reported but is uncommon. In the region of HEV hyperendemicity of southwestern France, no case of HEV transmission in an allograft has been reported (188). To date, only one case of occult HEV transmission in a liver allograft has been described from Germany (235).

(ii) Prevalence and incidence. As mentioned above, the considerable variability in performance of serological tests (175, 184) and accuracy of in-house PCR assays (194, 196) makes it difficult to clearly define the seroprevalence and incidence of HEV infection in the SOT population. Consequently, the following results should be considered with caution. The prevalence of HEV infection in SOT recipients ranges from 2.3% to 43.9%, depending on the serological test employed (Table 3) (188, 227, 236–241). Overall, the incidence of HEV infection, based on the detection of HEV RNA, varies from 0.9 to 3.5% (Table 3) (188, 227, 237–241). However, when looking for HEV RNA only among transplant patients with increased liver enzyme levels, incidences have been found to range between 4.3 and 6.5% (13, 242).

(iii) Natural history. A multicenter retrospective analysis of 85 SOT recipients from 17 transplant centers provided interesting data regarding the natural history of HEV infection in this cohort of immunosuppressed patients (225). Thirty-four percent of the patients had spontaneous clearance of HEV within the first 6 months after HEV was diagnosed and no HEV reactivation later on, whereas 66% developed chronic hepatitis (225). Nine of 85 patients (9.4%) developed cirrhosis (225). Of these, a number of

TABLE 3 Prevalence of anti-HEV IgG and HEV RNA among transplant patients

Study	No. of patients	Transplanted organ(s)[a]	Serology test	Prevalence (%)	
				Anti-HEV IgG	HEV RNA
Abravanel et al. (286)	88	SCT	Wantai	36	
Buti et al. (236)	108	KT, LT	Biokits	2.3	
Haagsma et al. (237)	285	LT	Genelabs	3.5	1.75
Kamar et al. (13)	217[b]	KT, LT, SPK	Abbott		6.5
Knoenecke et al. (285)	52	SCT	Abbott	5.3	0
Legrand-Abravanel et al. (188)	700	KT, LT, SPK	Adaltis	12.7	3.2
Moal et al. (238)	1,350	KT	Adaltis		1.2
Moal et al. (242)	160[b]	KT	Adaltis	14	4.3
Pas et al. (239)	1,200	SOT	Wantai		1
Pischke et al. (227)	274	HT	Genelabs	11.3	1.5
Pischke et al. (240)	226	LT	Abbott	4.4	0.9
Riezebos-Brilman et al. (241)	468	Lung transplantation			2.1

[a] SCT, stem cell transplantation; KT, kidney transplantation; LT, liver transplantation; SPK, simultaneous kidney-pancreas transplantation; SOT, solid organ transplantation; HT, heart transplantation.
[b] Transplant patients with increased liver enzyme levels.

patients died from decompensated cirrhosis. Several other cases of HEV-induced cirrhosis have been reported (223–225, 227, 235, 243–245). Chronic infection with HEV sometimes necessitates retransplantation in liver transplant recipients. Such individuals who do not achieve viral clearance before retransplantation may get recurrent infection with HEV after retransplantation, with associated progressive chronic hepatitis (224). In contrast, renal transplant patients with chronic HEV infection who achieve sustained viral clearance do not relapse after retransplantation (246).

Among SOT patients, only 32% of patients are symptomatic (225). Fatigue is the main symptom, and clinically apparent jaundice is very uncommon. Liver enzyme levels are increased (~300 IU/liter) but are much lower than those usually observed in immunocompetent patients (~1,000 to 3,000 IU/liter). HEV seroconversion may be delayed, and in some patients, it may not occur at all. It has been observed that liver fibrosis progresses strikingly rapidly in SOT patients with chronic HEV infection (223, 225, 244). This rapid progression is observed in liver and nonliver transplant patients. The liver fibrosis progression seems to be faster than that observed in hepatitis C virus (HCV)-infected SOT patients, and it can lead to cirrhosis only 2 or 3 years after infection (244). No correlation has been observed between HEV load and liver fibrosis progression (118). However, slow HEV quasispecies diversification (intersample variability within the same individual) during the first year after infection has been associated with rapidly developing liver fibrosis (247). At the acute phase, the dominant histological lesions in transplant patients consisted of lobular inflammation without ballooning, but with spotty necrosis with associated acidophilic bodies. The portal tract was mildly or moderately expanded and included an inflammatory infiltrate composed mainly of lymphocytes. Mild piecemeal necrosis was also observed (13). In established chronic HEV infection, liver biopsy specimens showed features of chronic viral hepatitis. Typical features included scarring/fibrosis, portal hepatitis (lymphocytic infiltrates and piecemeal necrosis), and mild/moderate lobular hepatitis (13).

(iv) Predictive factors for developing chronic hepatitis. Several studies have attempted to determine predictive factors associated with the development of chronic infection in SOT patients exposed to HEV. Two studies have shown that chronic infection is more likely to develop in profoundly immunosuppressed patients. Indeed, CD2, CD3, and CD4 T-cell subsets are significantly lower, and evolve in a shorter time after transplantation, in patients who develop chronic hepatitis than in those with spontaneous clearance of HEV (13, 225). The use of tacrolimus, a more potent immunosuppressant than cyclosporine, has also been associated with chronic HEV infection (225). In addition, HEV-specific T-cell proliferative responses are decreased in transplant patients, particularly in those with chronic infection (248, 249). Compared to patients with resolving hepatitis, individuals who develop chronic HEV infection have lower serum concentrations of interleukin-1 (IL-1) receptor antagonist and IL-2 receptor during the acute phase of HEV infection (247). Increased serum concentrations of chemokines implicated in leukocyte recruitment to the liver, such as RANTES, MIP-1β, MCP-1, and CXCL8, have been associated with persistent infection (247).

In a large multicenter study, the use of tacrolimus (compared to cyclosporine) and a low platelet count were the only two independent predictive factors for chronic hepatitis in SOT patients exposed to HEV (225). Pischke et al. found that the use of mycophenolate mofetil was associated with HEV clearance in heart transplant patients (227), although the data need to be confirmed. In addition, SOT recipients who develop chronic infection have greater heterogeneity of HEV quasispecies at the start of the infection than individuals with resolving hepatitis (247, 250). In renal transplant recipients with chronic HEV infection, interferon-stimulated genes are upregulated (251). However, HEV appears to downregulate alpha interferon (IFN-α)-induced gene expression *in vitro* (252).

Pediatric SOT patients. Very few studies have assessed the prevalence and incidence of HEV infection among pediatric solid organ transplant patients. Among a group of Canadian pediatric liver transplant patients with increased liver enzyme levels and features of chronic hepatitis ($n = 14$), Halac et al. reported a seroconversion rate after transplantation of 50% (243). One of these patients developed chronic HEV3 infection. Very recently, Hoerning et al. assessed the seroprevalence of anti-HEV IgG among 124 German pediatric solid organ transplant patients (41 kidney

transplant and 83 liver transplant patients). Overall, the HEV seroprevalence was 3.2%. One of the four anti-HEV-seropositive patients developed chronic HEV3 infection (253). In addition, one case of chronic HEV infection was detected among 22 liver-transplanted children with chronic graft hepatitis (254). A case of resolving HEV infection has also been reported from southeastern France (255). Hence, HEV infection should be considered a cause of hepatitis in pediatric SOT patients.

Chronic HEV Infection in HIV Patients

Chronic infection with HEV infection has also been described for immunocompromised individuals with HIV infection. As with the SOT population, because of the variable quality of virological assays, the data on seroprevalence and incidence of HEV RNA should be approached with caution. The seroprevalence of anti-HEV IgG in HIV-positive cohorts ranges from 1.5% to 11.2% (256–265). The incidence of HEV infection, defined by detection of HEV RNA in the serum, is low, ranging from 0 to 1.3% (256–260, 262–266). Around 20 cases of HEV coinfection proven by the detection of HEV RNA have been documented worldwide (58, 229, 256–258, 260, 263, 267–274). Five cases of chronic coinfection with HEV and two cases of documented HEV-related cirrhosis have been described, all of which were HEV3 infections in individuals with low CD4 counts ($<250/mm^3$) (229, 257, 258, 260, 271, 274). An analysis of the HEV genotype 3 strain recovered from the stools of an HIV-positive patient with HEV-induced cirrhosis showed that the virus contained an insertion of 58 amino acids encoded by a human ribosomal protein gene (93), confirming that a human/hepatitis E recombinant virus exists (275). The clinical and biological presentation is quite similar to that observed in SOT patients. The modes of HEV acquisition are probably similar to those in SOT patients and the general population. The possibility of sexual transmission is controversial (259, 276). In a recent study, it was shown that men having sex with men might be at risk for HEV acquisition (276). Intravenous drug use may be a risk factor for autochthonous HEV infection (277). However, in a more recent study, the HEV IgG seroprevalence among HIV- and hepatitis C virus-coinfected patients was 5.3% (2/38 patients), which was much lower than that in blood donors and not related to intravenous drug use (278).

Chronic HEV Infection in Hematological Patients

No studies have systematically assessed the prevalence or incidence of chronic HEV infection among hematological patients receiving chemotherapy, and only a small number of patients have been found to have chronic HEV infection in this situation. These cases include a patient with untreated hairy cell leukemia, a patient with idiopathic CD4 T lymphopenia, and patients treated for lymphoma, chronic myelomonocytic leukemia, and B-cell chronic lymphocytic leukemia (230, 233, 279–284). The clinical and biological presentation is quite similar to that observed in SOT patients.

The incidence of HEV infection and HEV seroprevalence among stem cell transplant patients have been assessed in two studies using differing serological tests. The anti-HEV seroprevalence was 5.8% in a German study (285) and 36% in a French one (286). In both studies, ongoing HEV infection was absent. Prior to allogeneic stem cell transplantation, Versluis et al. recently reported an anti-HEV IgG prevalence of 13% (287). HEV RNA was found in 8 of 328 stem cell transplant patients (2.4%) (287), and 5 patients developed chronic hepatitis (287). Case reports of chronic HEV infection in hematological patients include a patient with myeloma who required a stem cell transplant (284), a child with HEV-associated cirrhosis following bone marrow transplantation (288), and a case of HEV reactivation in a patient with acute lymphoblastic leukemia after allogeneic stem cell transplantation (289). Very recently, another case of HEV reactivation was suspected in a hematological patient (287), but no HEV reactivation was seen in a study from France (286). There are still some unresolved questions in the setting of stem cell transplantation, i.e., should all patients undergoing stem cell transplantation be screened for HEV RNA, especially if liver enzyme levels are increased? How should a viremic patient requiring a stem cell transplantation be managed? Recently, an acute infection with HEV3 was documented for a patient with chronic leukemia following infusion of donor lymphocytes. The patient developed acute liver failure and died 6 weeks later (290). This case report has prompted clinicians to screen such patients with abnormal liver function tests for HEV RNA before stem cell transplantation.

TREATMENT OF HEV INFECTION

Treatment of HEV Infection in SOT Patients

The management of chronic HEV infection has been studied mainly in SOT patients. Chronic HEV infection is usually observed in deeply immunosuppressed patients. Reduction of immunosuppressive therapy in SOT patients, especially of agents that target T cells (225, 244), results in viral clearance in nearly one-third of patients (225, 244). In the remaining SOT recipients, antiviral therapy has been used. All published data are based on small series and case reports, as no large randomized trials have been conducted. A 3-month course of pegylated interferon therapy (135 μg/week) has been used in three liver transplant patients (291) and one hemodialysis patient who was previously a recipient of a kidney allograft (292). A sustained virological response was obtained in three of the four patients (291, 292). A 12-month course of pegylated interferon therapy was also effective for treating chronic HEV infection after liver transplantation (293). However, interferon cannot be used after kidney, heart, or lung transplantation, because it increases the risk of acute rejection (294). Hence, short courses of ribavirin monotherapy have been used, producing promising and very interesting results, in both adults and pediatric organ transplant patients (Table 4) (41, 222, 226, 227, 241, 254, 282, 295–297). Further large studies are needed to confirm these preliminary observations. The mechanism by which ribavirin achieves HEV clearance is still unknown. It could be due to a direct inhibition of viral replication or to an immunomodulatory effect (298). In summary, in SOT patients with chronic HEV infection, the reduction of immunosuppressive therapy, especially of agents that target T-cell function, is first-line therapy, followed by ribavirin monotherapy in patients who fail to clear HEV (299).

Treatment of HEV Infection in HIV Patients

Few coinfected HIV-HEV patients have been given antiviral therapy. Overall, five patients have been given antiviral therapy: pegylated interferon alone for 6 months ($n = 1$) (274), ribavirin alone for 3 months ($n = 1$) (273) or 6 months ($n = 2$) (300), and pegylated interferon for 6 months followed by combination therapy with pegylated interferon and ribavirin for 3 months ($n = 1$)

TABLE 4 Ribavirin therapy in nonimmunocompetent patients

Study	No. of patients	Immunosuppressed patient group[a]	Duration of treatment (mo)	No. of patients with:	
				Virological response	Sustained virological response
Alric et al. (279)	1	Hematological patient	3	1	1
Chaillon et al. (295)	1	HT	3	1	1
Dalton et al. (301)	1[b]	HIV	3	1	1
de Niet et al. (222)	1	KT	3	1	1
Del Bello et al. (41)	1	LT	3	1	1
Hajji et al. (273)	1	HIV	3	1	1
Junge et al. (254)	1	LT	6	1	1
Kamar et al. (296)	8	KT/SPK	3	8	4 of 6[c]
Koning et al. (226)	4	HT	3–12	3	3
Mallet et al. (282)	2	SPK, hematological patient	3	2	2
Neukam et al. (300)	1	HIV	6	2	1
Pischke et al. (297)	11	KT, HT, lung transplantation	5	9	9
Pischke et al. (227)	4	HT	5	3	3
Riezebos-Brilman et al. (241)	2	Lung transplantation	4	2	2

[a] HT, heart transplantation; HIV, human immunodeficiency virus; KT, kidney transplantation; LT, liver transplantation; SPK, simultaneous kidney-pancreas transplantation.
[b] The patient received combined therapy with pegylated interferon and ribavirin.
[c] Six of the eight patients had a 6-month follow-up after ribavirin cessation.

(301). A sustained virological response was observed in all except one patient, who was treated with a 6-month course of ribavirin monotherapy (300).

Treatment of HEV Infection in Hematological Patients

Both pegylated interferon alone and ribavirin alone for 3 months have been used, resulting in a sustained virological response in 3 hematological patients with chronic HEV infection (279, 280, 282, 287).

Treatment of HEV Infection in Patients with Severe Acute HEV Infection

A small number of patients with acute HEV1 or HEV3 infection have been treated with antiviral therapy. These were patients who were considered to be at high risk, with either preexisting chronic liver disease or severe or fulminant hepatitis (302–304). Such patients were treated with ribavirin monotherapy, producing rapid clearance of HEV and the avoidance of liver transplantation in some patients.

PREVENTION OF HEV INFECTION

HEV1 infection can be prevented by providing clean drinking water and improving the sanitary infrastructure in developing countries. HEV3 infection may be prevented by avoiding eating undercooked meat, especially pork products. Note that it has been shown that HEV is completely inactivated when heated above 70°C (119).

Two candidate HEV vaccines have been developed and have been found to be safe and immunogenic (190, 191). The first vaccine is a 56-kDa protein encoded by ORF2 of a HEV1 strain, expressed in insect cells. In a phase II trial conducted in Nepal on male army recruits, participants with undetectable anti-HEV were

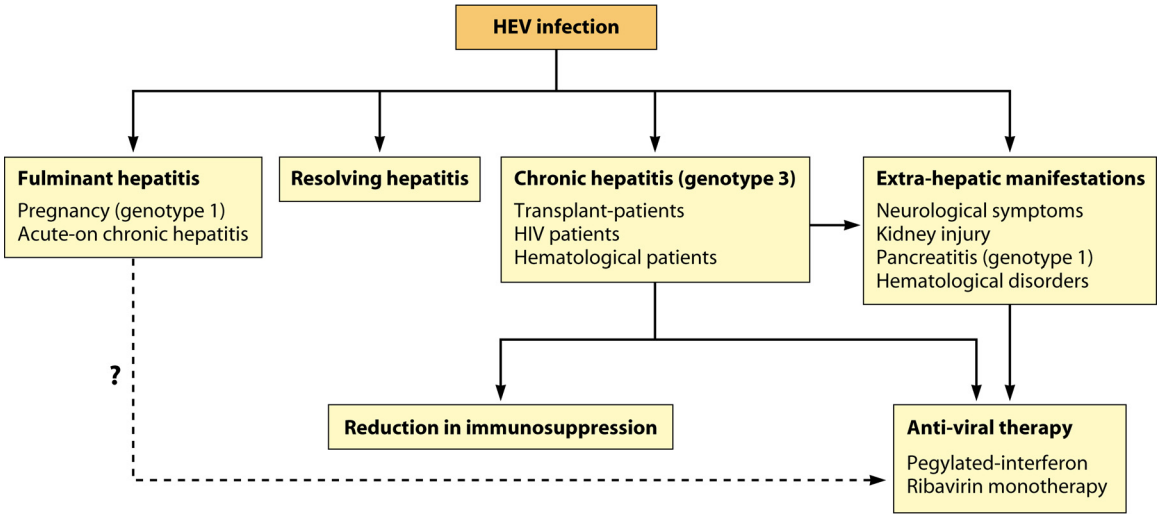

FIG 5 Different patterns of hepatitis E virus infection.

randomized to receive 3 doses of either 20 μg of the 56-kDa vaccine ($n = 898$) or placebo ($n = 896$), at 0, 1, and 6 months, and were followed up for an average of 804 days (190). The vaccine was well tolerated and highly immunogenic, with efficacy against hepatitis E virus infection of 95.5% (95% confidence interval [CI], 85.6 to 98.6%). The second vaccine, HEV 239, is a 26-kDa protein encoded by ORF2 of HEV1 (305). The vaccine is expressed in *Escherichia coli* and occurs as virus-like particles of 23 nm in diameter. In a phase II study conducted among seronegative adults, the vaccine was found to be safe and immunogenic and conferred protection against HEV infection, with an efficacy of 83% (306). In a phase III trial in 11 townships in eastern China, participants were randomly assigned to receive either three intramuscular injections of HEV 239, at 0, 1, and 6 months ($n = 56{,}302$), or hepatitis B vaccine as a placebo ($n = 56{,}302$) and were followed up for occurrence of acute hepatitis to month 19 (191). The vaccine was well tolerated and protected against hepatitis E, with an efficacy of 100% (95% CI, 72.1 to 100.0%). This vaccine has been licensed for use in the People's Republic of China, but it is not certain if and when this vaccine will be licensed for use in humans in other countries.

CONCLUSIONS

HEV infection is an underdiagnosed disease that has diverse clinical features (Fig. 5). Further studies are required to more clearly determine its prevalence and incidence, as well as to improve the understanding of its natural history and management.

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