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REVIEW

Hepatitis E: Discovery, global impact, control and cure

Mohammad S Khuroo, Mehnaaz S Khuroo, Naira S Khuroo

Mohammad S Khuroo, Naira S Khuroo, Digestive Diseases Centre, Dr. Khuroo's medical Clinic, Srinagar, Kashmir 190010, India

Mohammad S Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Kashmir 190010, India

Mehnaaz S Khuroo, Department of Pathology, Govt. Medical College, Srinagar, Kashmir 190001, India

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Correspondence to: Mohammad S Khuroo, Director, Digestive Diseases Centre, Dr. Khuroo's medical Clinic, Sector 1, SK Colony, Qamarwari, Srinagar, Kashmir 190010, India. khuroo@yahoo.com
Telephone: +91-194-2492398
Fax: +91-194-2491190

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Abstract

Hepatitis E was identified as an epidemic of non-A, non-B hepatitis from Kashmir, India in 1978. Hepatitis E virus (HEV), the etiological agent is the sole member of family Hepeviridae. The virus has marked heterogeneity and infects many animals like bats, camel, chicken, deer, boar, mongoose, pigs, rats, rabbit and cutthroat trout. Hepatitis E is a disease with a major global impact and has two distinct epidemiological patterns. Hepatitis E is an imperative health issue in developing nations, transmitted through sullied water and happens most every now in young adults. The disease is particularly severe during pregnancy and in people with underlying liver cirrhosis. Autochthonous hepatitis E is increasingly recognized in developed countries. The virus infects domestic pigs, wild boar and Sika deer in these countries. HEV infections in humans occur by eating the undercooked game flesh, raw liver from supermarkets and Figatelli sausages. Blood transfusion-associated HEV infections occur in many countries and screening of donors for HEV RNA is under consideration. Hepatitis E causes a number of extrahepatic diseases, including a wide spectrum of neurological syndromes. HEV genotype 3 causes prolonged viremia, chronic hepatitis, liver fibrosis and cirrhosis in organ transplant patients. The virus is amenable to ribavirin monotherapy and most patients clear the virus in a few weeks. Hepatitis E vaccine -239, marketed in China, has shown high efficacy with sustained protection for over four years.

Key words: Communicable diseases; Discovery; Hepatitis E; Hepatitis E virus; Vaccine; Zoonosis

Core tip: Discovery of hepatitis E came to lime light when 1978-Kashmir epidemic of hepatitis was investigated. Hepatitis E is being recognized as a clinical entity of reemerging importance. Hepatitis E virus has marked heterogeneity and infects many animals like

bats, camel, chicken, deer, boar, mongoose, pigs, rats, rabbit and cutthroat trout. Originally reported as a major health problem in poor-resource countries, hepatitis E is now recognized as an important clinical problem in the developed world. Zoonotic foodborne transmission of hepatitis E virus infections has relevance in solid organ transplant population. Major advances have been made in managing chronic hepatitis E. Hepatitis E causes a number of extrahepatic diseases, including a wide spectrum of neurological syndromes. Hepatitis E vaccine -239, marketed in China, has shown high efficacy with sustained protection for over four years.

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INTRODUCTION

Hepatitis E was identified as an epidemic of non-A, non-B hepatitis (NANBH) from Kashmir, India in 1978[1]. In the last 36 years since the discovery of the disease, major advances have occurred in relation to its causative agent, the host range in the animal kingdom, epidemiology and modes of spread[2]. Hepatitis E virus (HEV) infections are ubiquitous in developing countries as a cause of epidemic and endemic acute hepatitis[3]. However, the disease is now encountered in developed countries as well[4]. Zoonotic foodborne transmission of HEV infection has a particular relevance to the organ transplant population[5]. HEV infections cause a number of non-hepatic manifestations, which include a wide spectrum of neurological syndromes[6,7]. Transfusion-associated HEV infections are reported with increasing frequencies and screening of donors for HEV RNA is being considered[8-10]. Major advances have been made in understanding chronic hepatitis E[11] and the commercial availability of hepatitis E vaccine (HEV-239) in China promises control of epidemic and sporadic hepatitis E[12]. This article shall review the knowledge about the discovery, global impact, control and cure of hepatitis E.

DISCOVERY

Discovery of hepatitis E came to lime light when 1978-Kashmir epidemic of hepatitis was investigated[1]. This region where the disease occurred did suffer very hard weather conditions, lacked basic health care delivery system and the region was devoid of high tech cutting edge investigative facilities. Events leading to the discovery unravel a remarkable story of human interest, with its complexities, missteps, successes and failures (www.drkhuroo.in)[13]. In November 1978, Dr. Mohammad S Khuroo investigated an epidemic of jaundice in and around a town 50 km from Srinagar, Kashmir, India. The epidemic had hit two hundred villages with a population of 600000, caused around 52000 patients with icteric disease and 1700 fatalities[3]. Pregnant women were more affected and many had been reported dead. An ingenious house-to-house investigation of this and subsequent epidemics and sporadic disease was performed over a 14-year period. This led us to the discovery of an enterically transmitted NANBH, which had triggered repeated epidemics in Kashmir[2,14]. The disease affected young adults within the age group of 15 to 45 years. One remarkable discovery during this study was the relationship of this disease with pregnancy[15-17]. The agent was transmitted vertically with high fetal and perinatal mortality[18,19]. The disease was a self-limiting and did not cause chronic viremia, chronic hepatitis and cirrhosis[20]. The loss of IgG antibodies occurred in over half of the population in a period of over 14 years[21]. It was postulated that the disease was caused by yet unrecognized human hepatitis virus[1]. Simultaneously, a sporadic disease identical in epidemiology and clinical features to epidemic disease and causing around half of acute hepatitis in the population was recognized[16,22].

An outbreak of NANBH was reported in Russian military personal posted in Afghanistan[23]. The epidemic had similar epidemiological features as seen in the 1978-Kashmir epidemic. Dr. Mikhail S Balayan, in a self-experimentation, ingested pooled stool extracts from 9 such patients[23]. On 36th d after ingestion of the stool extracts, he developed severe acute hepatitis with jaundice and elevated liver tests. Stool samples of 28th d, 43th d and 45th d showed virus-like-particles (VLP) on immune electron microscopy. A number of primates were experimentally infected with the putative agent and the physicochemical properties of the agent were studied[24].

The virus could not be cloned for a number of years due to low yield of VLP in the infectious material. This was overcome by the basic perception that expansive amounts of VLP's were gotten from bile collected from infected primates. A partial cloning of the virus was done by Reyes *et al*[25] (1990). Subsequent to this, Tam *et al*[26] (1991) sequenced the full-length HEV genome of 7.2 kb and a diagnostic assay based on enzyme immunoassay was established.

HEV

Taxonomy and classification

HEV was originally thought to resemble HAV and included in *Picornaviridae* family[27]. Once morphological features and genome organization of HEV were available, it is surmised that HEV is similar to noroviruses and placed in family *Caliciviridae*, under hepevirus genus. Before long it was built up that HEV has a significant sequence difference from caliciviruses

and was removed from *Caliciviridae* and included in the "Hepatitis E-like viruses"[28]. Subsequently, based on molecular analysis, all 4 recognized genotypes HEV-1 to HEV-4 were classified as sole agents of genus Hepevirus in the *Hepeviridae* family[29]. Avian HEV was included in the unassigned genus. This classification received a setback as a number of HEV closely related to human HEV infecting rabbit and wild boar and those more divergent HEV infecting rats, ferrets, bats and cutthroat trout were identified. Recently, based on phylogenetical features and HEV hosts, the ICTV Hepeviridae study group gave a new classification for the family *Hepeviridae*[30,31]. All HEV's have been placed under Hepeviridae family and further classified under 2 genera namely Orthohepevirus, which included isolates from mammals and chicken and Piscihepevirus which included Cutthroat trout isolates. Orthohepevirus includes species A, B, C and D, while Piscihepevirus include species A only. Orthohepevirus A species included isolates from man, pigs, wild boar, rabbit, deer, mongoose and camel. This species encompassed several HEV genotypes infecting man alone (genotype HEV-1 and HEV-2); pigs and humans (genotype HEV-3 and HEV-4), wild boar (genotype HEV-5 and HEV-6) and dromedaries (genotype HEV-7). Orthohepevirus B contain viruses found in chickens and includes all three genotypes: avian HEV-1 (isolates from chicken in Australia), avian HEV-2 (isolates from chicken in United States and Canada) and avian HEV-3 (isolates from chicken in Europe and China). Orthohepevirus C includes 2 sequences namely HEV-C1 infecting rats and HEV-C2 infecting ferrets. Orthohepevirus D includes a single sequence infecting bat. Recently, partial sequences of other potential members of Hepeviridae family have been described[32-34]. The moose virus has been assigned to Orthohepevirus A, mink HEV to HEV-C2 and rat HEV to HEV-C1. All known cutthroat trout virus isolates have been included in Piscihepevirus A species within the genus Piscihepevirus. As sequences studied from the vast majority of the cutthroat trout infection isolates are just 262 nucleotides long, there are insufficient data as of now to portray outline criteria for species inside this genus.

Physico-chemical properties

The virion is a naked particle, spherical in shape and has icosahedral symmetry. The virus shows surface spikes and indentations. The particle has diameter of 27-30 nm on immune electron microscopy, 32-34 nm after sucrose gradient centrifugation and 38.5-42 nm on cryo-EM analysis[23,35]. Buoyant density of the particles in cesium chloride is around 1.35 g/cm^3[36]. The virus is relatively stable in acid and mild alkaline conditions and unaffected by chloroform and ether treatment. HEV-infected pig liver homogenates maintain infectivity if incubated at 56° for 1 h, however boiling or frying for 5 min completely inactivates the virus. Treatment of liver suspensions with Tween-20 (0.05%) and formalin (0.05%) reduced infectivity by 1000-fold. HEV is susceptible to chlorine disinfection and chlorine disinfection of water supplies is recommended during epidemics of disease[37-39].

GENETIC ORGANIZATION

HEV genome consists of single-stranded RNA, has a molecular weight of approximately 7.2 kb with positive-sense polarity and is capped with 7-methylguanine at its 5'-end and poly (A) at its 3'-end (Figure 1). The genome has UTR's at the 5' end (27 nucleotides) and at the 3' end (65 nucleotides) and a conserved stretch (58-nucleotides) near its 5' end region within open reading frame 1 (ORF1), which fold in to stem-loop and hairpin structures. HEV RNA replicates in to a genomic RNA of 7.2 kb and a bicistronic subgenomic RNA of 2.2 kb. There are 3 ORFs in the genome namely *ORF1*, *ORF2* and *ORF3*[40,41].

ORF1 of the well-characterized Burmese strain begins after 27 nucleotides of the 5' end and extends across the 58 nucleotides of the conserved region for 5079 nucleotides before terminating at nucleotide position 5109[42]. ORF1 translates in to a non-structural protein (pORF1) having 1693 amino acids (aa). ORF1 domains along with their aa boundaries based on Burmese isolate are methyltransferase from aa 56-240, a Y domain from aa 216-442, papain-like cysteine protease from aa 433-592, a proline-rich hinge domain V from aa 712-778, a X macrodomain from aa 785-942, an RNA helicase from aa 960-1204 and RNA-dependent RNA polymerase from aa 1207-1693. HEV methyltransferase catalyzes the capping of viral RNA. HEV papain till now has not been associated with any functional activity of the virus. ORF1 contains a functional protease, which may be involved in the polyprotein processing. HEV helicase and RNA-dependent RNA polymerase are needed to replicate the genomic RNA. Recombinant HEV polymerase bind to the genomic RNA at 3' end. The virion binding is facilitated by stem-loop structures and poly (A) stretch.

ORF2 starts at nucleotide 5147 (38 nucleotides 3' at the end of ORF1) and develops roughly 1980 nucleotides till nucleotide 7127[43]. ORF2 encodes pORF2, a polyprotein of 660 amino acids, which is involved in the virus assembly and binding and eliciting immune response to produce neutralizing antibodies. The pORF2 has three glycosylation sites at 137, 310 and 562 conserved asparaginase residues. HEV full-length and truncated ORF2 gene expression in baculovirus vectors generate capsid proteins with different molecular weights. Of these, two HEV capsid proteins (VLP/T=1 and VLP-T=3) form virus-like particles (VLP). While VLP/T=1 show no encapsulated RNA, VLP/T=3 contained about 2-kb RNA derived from the *ORF2* gene. The buoyant densities of VLP/T=1 and VLP/T=3 are 1.285 g/cm^3 and 1.31 g/cm^3 in CsCl

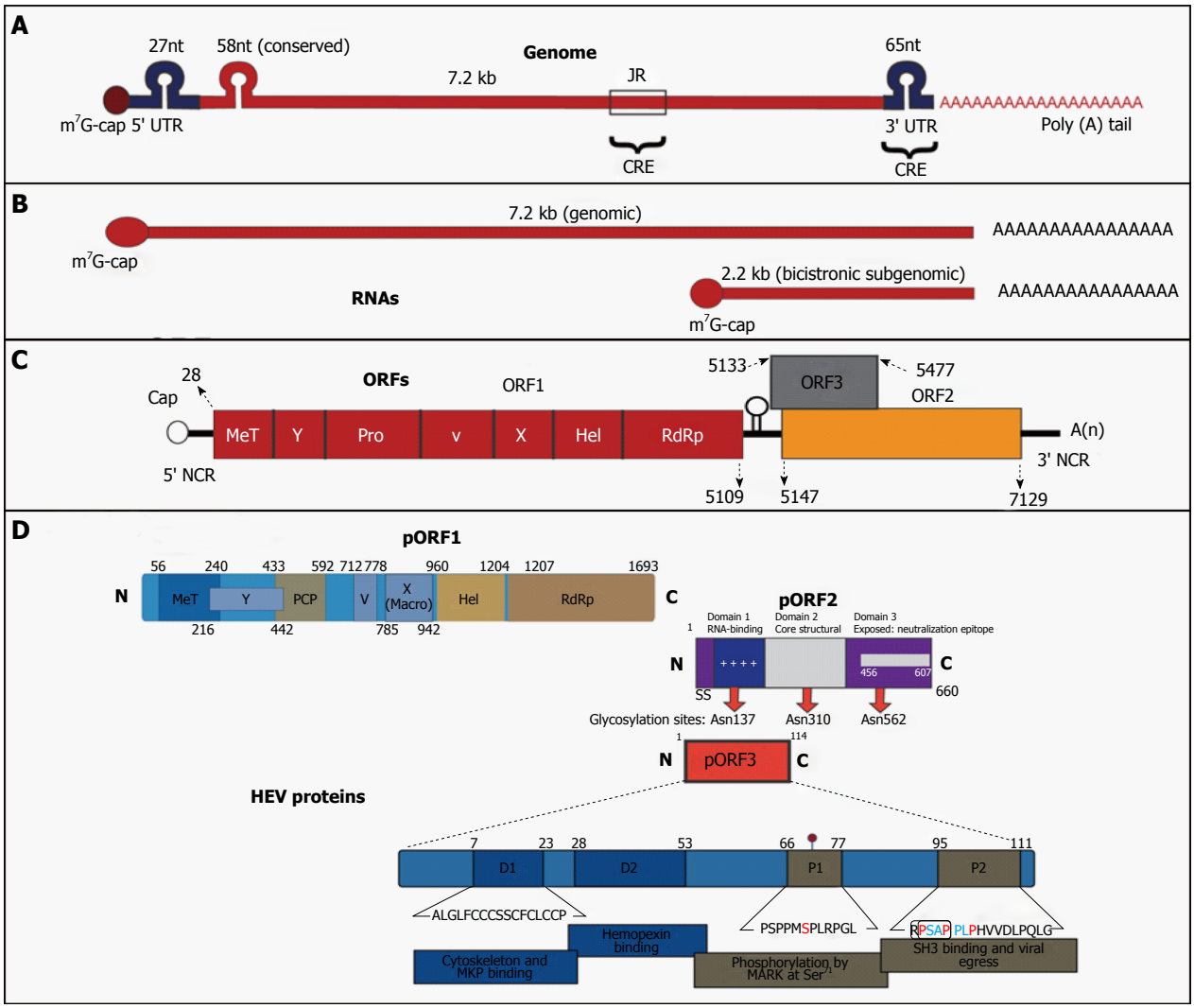

Figure 1 Hepatitis E virus. Genomic organization. A: The hepatitis E virus genome; B: Genomic RNA and bicistronic subgenomic RNA; C: Open reading frames (ORFs) and (D) 3 encoded proteins (pORF1, pORF2 and pORF3). For details, see text about hepatitis E virus. Adopted from Khuroo *et al*[143], 2016.

gradient, respectively, both smaller than the buoyant density of native HEV particles. ORF2 expression in *Escherichia coli* (*E. coli*) leads to the formation of three HEV capsid proteins, which are homodimers and include dominant antigenic sites of HEV. HEV p239 self-assemble to empty virus-like particle of 23 nm. Baculovirus/ and *E. coli* expressed VLP's are strongly immunogenic and resemble the native virus in their three-dimensional structure. Two VLP's namely p239 and recombinant Sar 56 kDa have been successfully tried as HEV vaccines. The p239 vaccine is marketed in China as Hecolin[12].

ORF3 is 345 nucleotides in length, begins 23 nucleotides 3' of the termination of ORF1[40,41]. ORF3 begins after nucleotide 5133 and terminates at nucleotide 5477 and translates in to a phosphoprotein (pORF3) of 114 aa. It has been suggested that pORF3 associates with the cytoskeleton and more specifically with microtubules. It is also implicated in HEV egress from hepatocytes[44]. ORF3 overlaps ORF2 by 328 nucleotides at the 3' end but does not overlap with ORF1.

HEV REPLICATION

HEV lacks both a proper *in vitro* culture system and animal model[45] and the life cycle of HEV remains poorly studied (Figure 2). It is assumed that HEV reaches the host through gut epithelial cells; attach to the surface of hepatocytes through heparin sulfate proteoglycans, binds to a receptor and enter the hepatocytes[46]. Once internalized, the virus is uncoated, releases RNA and nonstructural proteins of the virus are translated. Positive sense viral RNA is replicated in to negative sense RNA with help of RNA-dependent RNA polymerase. Negative sense RNA become templates for 7.2 kb positive-sense RNA and 2.2 kb subgenocmic RNA. Subsequent to this, pORF2 and pORF3 are formed with the help of subgenocmic RNA as template. pORF2 protein along with genomic RNA assemble into the new virion while the pORF3 optimizes viral replication. The virion egressed from hepatocytes are coated with pORF3 and lipid layer. Both pORF3 and lipid layer are separated from virion after egress from hepatocytes[47].

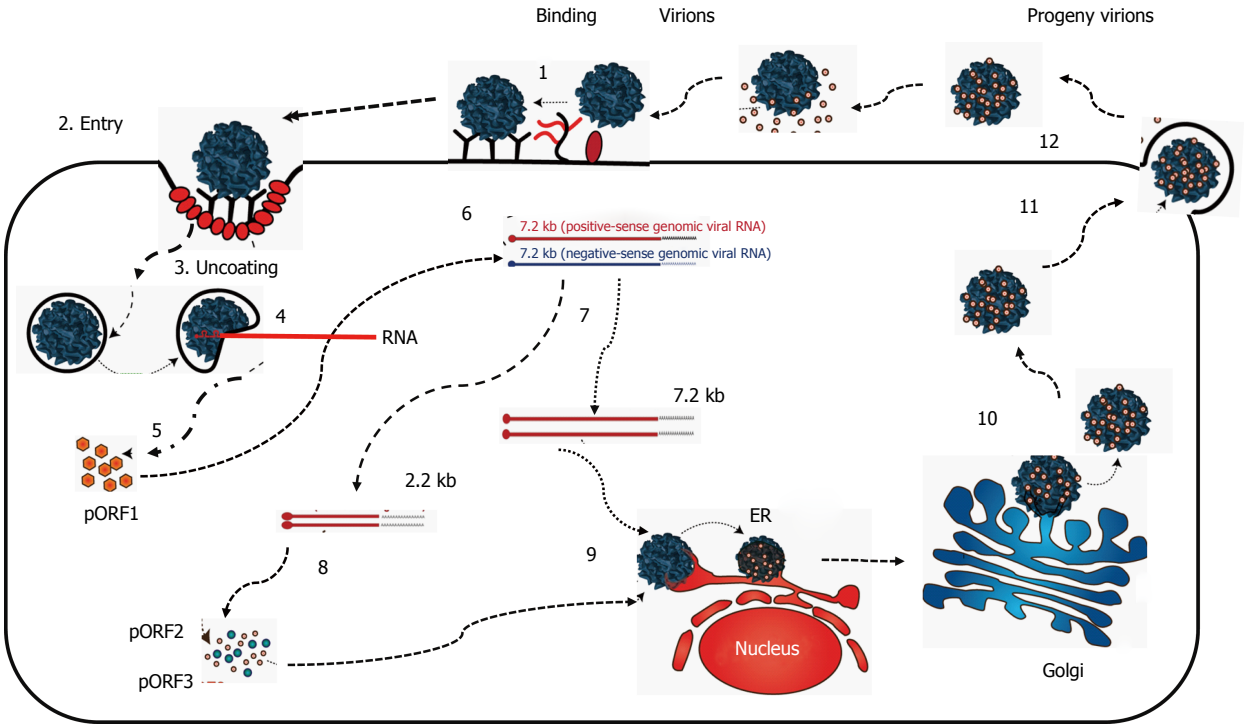

Figure 2 Proposed replication of hepatitis E virus. For details, see text about hepatitis E replication. Adopted from Khuroo *et al*[143], 2016.

HEV EVOLUTION

Hepatitis E is an ancient ailment. Epidemics of jaundice have been mentioned in medieval writing and in writings generated around 19th century. Till late it was surmised that these epidemics were caused by hepatitis A. Now we know that the disease in reality closely resembled hepatitis E[48]. However, these have not been tested serologically because of non-availability of sera. The most recent epidemic confirmed to be caused by HEV, though retrospectively, was the Delhi epidemic 1955-1956[49]. Recently, the HEV evolutionary history was studied (Figure 3)[50]. It was estimated that the tMRCAs (times-to the most-recent-common-ancestors) for mammalian HEV existed 536 to 1344 years ago. This progenitor develops in to two variants namely anthropotropic varaints, evloving in to HEV-1 and HEV-2 and enzootic variants evolving in to HEV-3 and HEV-4 respectively. The anthropotropic variant is around 367-656 years old and enzootic variant around 417 -656 years old. HEV genotypes existed at various periods namely HEV-1 (87-199 years), HEV-3 (256-342 years) and HEV-4 (131-266 years). HEV from chicken had existed for long in the evolutionary history.

ANIMAL RESERVOIRS

HEV was identified from pigs in the Unites States in 1997[51] and presently known to exist in all the countries of the world[52,53]. HEV infection develops very early and is ubiquitous in pigs from commercial farms. The infection is clinically silent, however, animals do show microscopic evidence of hepatitis. Pigs are infected by either genotype HEV-3 or HEV-4. Both have zoonotic potential and infect humans. HEV-3 has been detected in wild boar from Japan and many European countries[54-56]. HEV prevalence in wild boar was between 12.0% to 42.7% (Ig anti-HEV) and 2.5% to 25% (HEV RNA). HEV-4 and two new HEV genotypes HEV-5 and HEV-6 have been recovered from wild boar. HEV-3 has also been found in the sika/Yezo deer (Cervus nippon) from Japan and red deer (Cervus elaphus) from the Netherlands[57-59]. Mongoose has been observed to be infected with HEV and the full-length genomic arrangement of these confines have been shown to assemble with genotype HEV-3. HEV strains have been identified from rabbits from the United States and China[60,61], included as a distinct isolate of genotype HEV-3 and may be zoonotic. HEV has been discovered from dromedaries from the Middle East and the virus is named DcHEV[33]. About 1.5% of the adult dromedary fecal samples showed presence of DcHEV RNA. A comparative genomic and phylogenetic analyses showed that DcHEV represents a previously unrecognized HEV genotype and designated as HEV-7. Recently, the zoonotic potential of DcHEV has been confirmed in a liver transplant patient from Middle East, who often eat camel meat and drank camel milk[62]. Thus camel-derived food products may be a risk factor for post-transplant hepatitis E. Avian HEV causing BLSD (big liver and spleen disease) was identified in Australia in 1999[63]. Subsequently, avian HEV was identified from chicken in the United States and Canada with HSS (hepatitis-splenomegaly syndrome)[64]. Avian HEV shares approximately 50% to 60% nucleotide sequences with HEV from human and

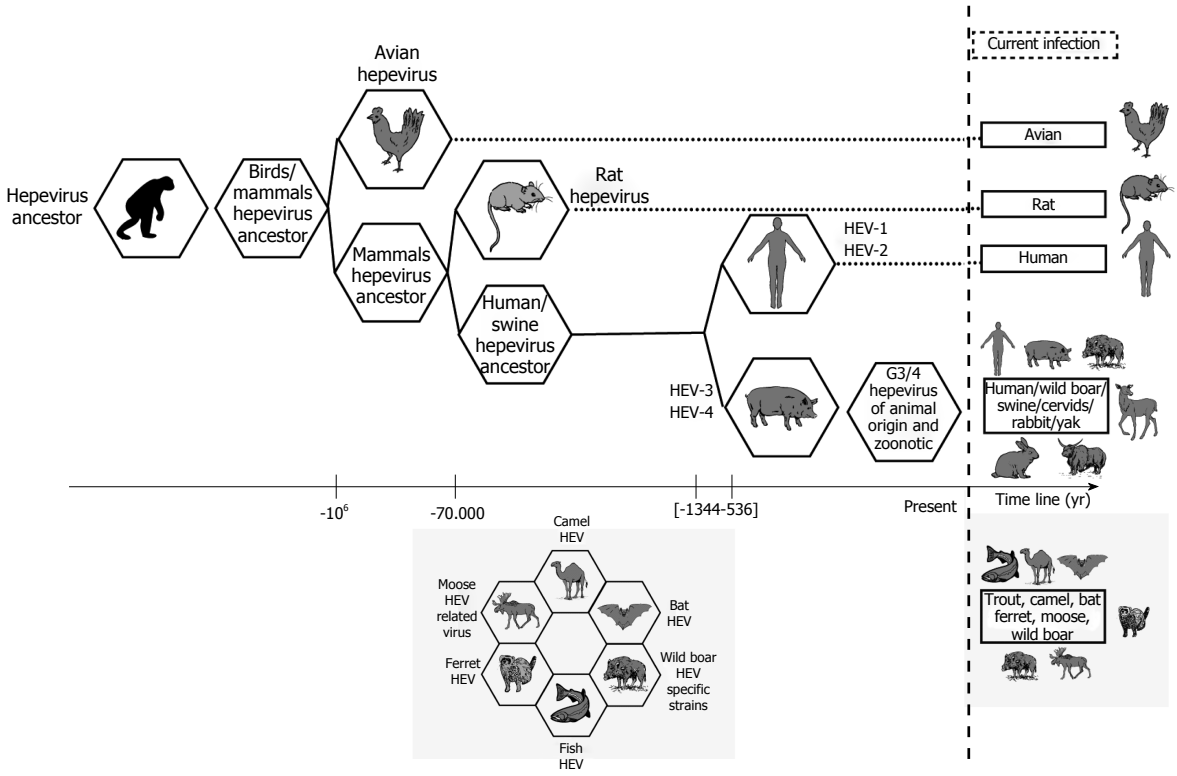

Figure 3 Evolutionary history of hepatitis E virus. The times to the most recent common ancestors (tMRCAs) for all four genotypes of HEV were calculated using BEAST to conduct a Bayesian analysis of HEV. The population dynamics for genotypes 1, 3 and 4 were analyzed using skyline plots. For details see text on HEV evolution. Source of data Purdy *et al*[50] 2010. HEV: Hepatitis E virus.

pigs. At present, avian HEV has three isolates namely from the United States, Europe and Australia[53]. HEV infects rats (Rattus norvegicus, Rattus rattus and Sigmodon hispidus*)* and bandicoots[65,66]. The rat HEV belongs to a separate species under Orthohepevirus C. Ferrets from a number of countries are infected with the virus[67] and shared 72.3% identity with rodent HEV. The ferret HEV genome organization was found to be slightly different from other HEVs and included a putative ORF (ORF4) of 552 nucleotides that overlapped with ORF1. HEV has been detected in bats from Africa, Central America, and Europe[68] and constitute a distinct genus. HEV from cutthroat trout (CTV) has sequence identity of 13% to 27% to human HEV and are classified in genus Piscihepevirus and species Piscihepevirus A in the Hepeviridae family[34].

GLOBAL DISTRIBUTION

Hepatitis E epidemiology is divided in to four distinct zones (Figures 4 and 5).

Hyperendemic zone

Hepatitis E is hyperendemic in many countries located in southern Asia (India, Bangladesh, Bhutan, Nepal, Pakistan and Sri Lanka) , southeast Asia (Burma, Cambodia, Indonesia, Thailand, Vietnam and Laos), central Asia (Kazakhstan, Tajikistan and Uzbekistan); north Africa (Algeria, Morocco, Sudan and Tunisia), east Africa (Kenya, Uganda and Burundi), west Africa (Ivory Coast, Liberia, Nigeria and Mali) and some countries in North America (Mexico)[2]. In these countries, HEV infections present as epidemic and endemic disease. Hyperendemic disease is generally brought about by HEV-1. Be that as it may, the disease is brought on by HEV-2 in Mexico and some African countries.

Endemic zone

Hepatitis E is endemic in many countries of Middle East (Turkey, Saudi Arabia, Yemen, Libya, Oman, Bahrain, Iran, Kuwait and the United Arab Emeritus), some regions of Southeast Asia (Singapore) and South America (Brazil, Argentina, Ecuador and Uruguay). Hepatitis E is responsible for more than one-fourth of all cases of acute sporadic hepatitis and fulminant hepatitis. However, epidemics of jaundice caused by HEV infections do not occur in these countries[69].

Distinctive pattern zone

Hepatitis E epidemiology in Egypt is distinctive and different from other regions of the World[70,71]. Disease occurs at young age and seroprevalence in this community resembles that of HAV. HEV infection in pregnant ladies is either asymptomatic or present as mild disease. HEV infecting Egyptian population is genotype HEV-1, with subtypes not seen in the Asian population.

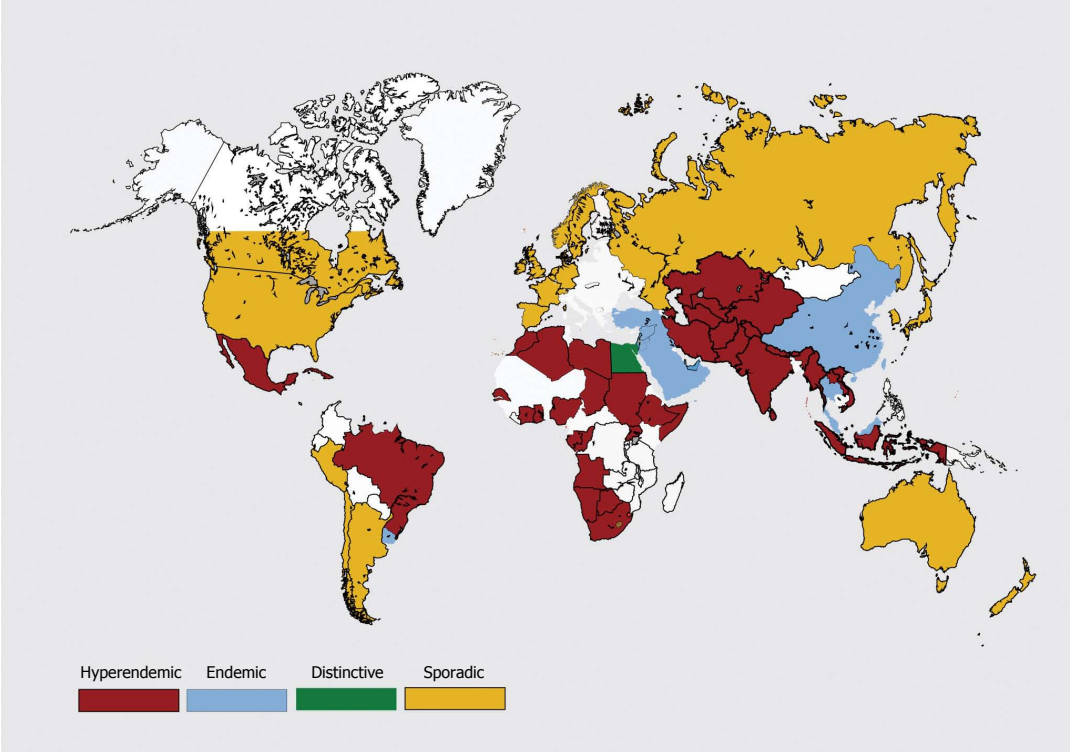

Figure 4 Global distribution of hepatitis E disease. See text under "global distribution" for explanation.

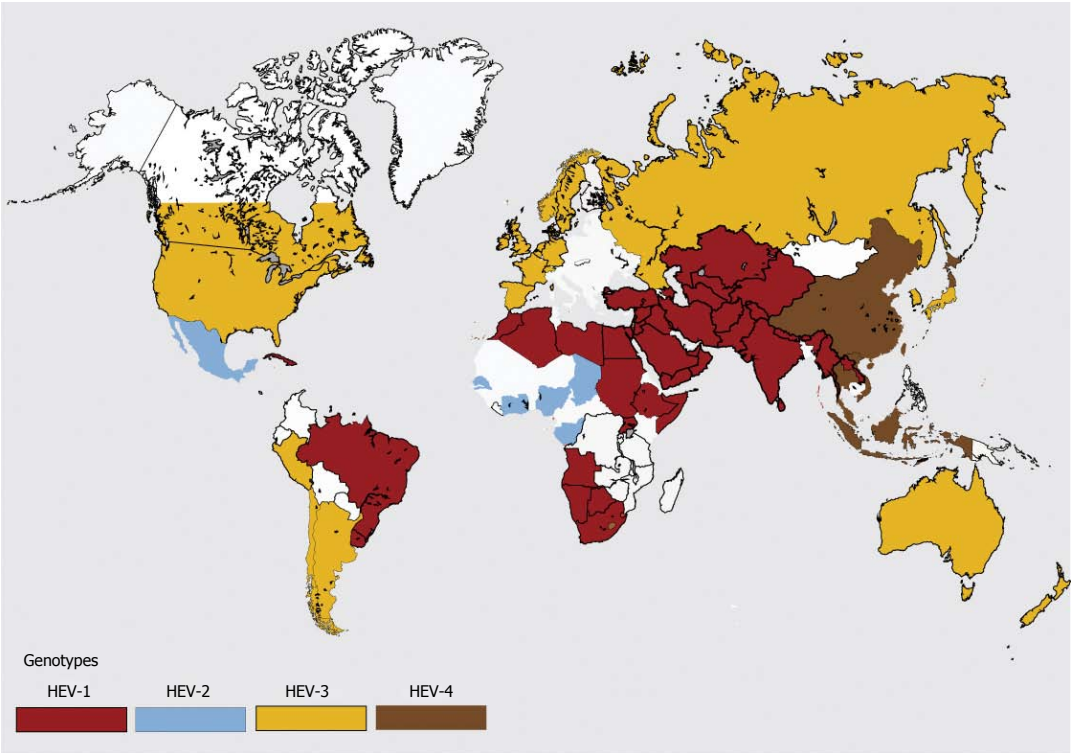

Figure 5 Global distribution of hepatitis E virus genotypes. See text under "global distribution" for explanation.

Sporadic zone

Autochthonous hepatitis E is increasingly being recognized in developed countries[72]. These infections are caused by HEV-3 and HEV-4[73-77]. Around 50 to 100 cases of hepatitis E are reported each from France, Germany, UK and many other European countries per year. Seroprevalence data show that these reported numbers are grossly lower than the actual disease load. Most HEV infections are unrecognized as these may not be tested or may be asymptomatic or

Table 1 Hepatitis E: Global epidemiology and clinical profile

	Developing countries		Developed countries	
Genotypes	HEV-1	HEV-2	HEV-3	HEV-4
Distribution	Asia, Africa, Latin America	Mexico, West Africa	Worldwide	China, East Asia, Central Europe
Disease pattern	Epidemic, Endemic		Autochthonous, sporadic, case-clusters	
Attack rate	About 1 in 2		67%-98% asymptomatic	
Seasonality	Yes		No	
Reservoir	Human		Animals (pig, boar, deer)	
Transmission	Water, person-to-person, vertical		Zoonotic-food-borne, vocational, infected water	
Transfusion-associated	Reported		Yes (well-studied)	
Seroprevalence	Low (< 15 yr), rapid increase (15-30 yr), plateau at 30%-40%		Steady increase throughout age groups; varies 7% to 21%	
Seroincidence	64/1000-yr		30 (South France), 2 (United Kingdom) 7 (United States)/1000-yr	
Age (yr)	15-40		> 50	
Sex	2:1		> 3:1	
Clinical outcome	Self-limiting in most		Self-limiting in most	
Risk factors	Pregnancy, Cirrhosis		Cirrhosis, LTx, HIV	
Deaths in pregnancy	High (25%)		Not reported	
HEV superinfections	Common, poor outcome		Reported, poor outcome	
Extra-hepatic disease	Yes		Yes	
Chronic infection	Not reported		HEV-3; SOT, HIV, hem NP	
Burden	3.4 million cases/yr, 70000 deaths, 3000 still births		Unknown	

Adopted from Khuroo *et al*[143] 2016. HEV: Hepatitis E virus; HIV: Human immunodeficiency virus.

misdiagnosed as drug-induced liver injury (DILI)[78,79].

Disease spectrum

Hepatitis E is a major global health problem and has infected one-third of the world population. Hepatitis E is a puzzling double-faced disease, with contrasting epidemiological and disease patterns in developing and industrialized countries (Table 1)[80,81].

Developing countries

In 2005, HEV-1 and HEV-2 worldwide disease burden were computed in 9 of the 21 GBD regions of 2010, representing 71% world population. It was estimated that 20 million incident infections, 3.4 million cases, 70000 deaths and 3000 stillbirths had occurred in 2005[82]. Several factors need to be considered while evaluating these numbers. Hepatitis E causes repeated epidemics. The disease frequency in these regions is in the range of 6%. The HEV antibodies show a dynamic response, with the loss of antibodies after some time in a sizeable proportion of the population. Recently, the HEV reinfections with altered immune response have been reported[14,21,83]. Thus, these calculated numbers may grossly underestimate the disease load in such countries.

Hepatitis E in resource poor countries causes massive epidemics of jaundice[2,3,84]. These regions have poor socio-economic conditions with drinking water sources which are polluted from sewage[85]. HEV infections cause a huge number of cases and is the reason for significant number of deaths, and represents a health issue in endemic regions. Of major concern is the occurrence of these epidemics on repeated occasions[2]. Over a 4-year period (1978-1982), four epidemics of hepatitis E were encountered in Kashmir, India[3]. The disease affected 52000 people and caused 1700 fatalities. Hepatitis E constitutes around 30% to 70% of sporadic viral hepatitis in endemic areas[16,22]. The disease incidence has been calculated to be around 45/1000 person per year[83] and infects around 2.2 million people per year in India[2]. HEV-related fulminant hepatic failure is a frequent occurrence and constitutes around 43% of all cases of fulminant hepatic failure[17,86]. The mortality in HEV-related liver failure has been reported as 51.9%. One of the most distinctive features of the epidemic and endemic hepatitis E is higher occurrence and mortality of disease in pregnancy[15,16]. Thus, the disease incidence was 8 times higher and acute liver failure occurred 13 times more often in pregnant women than age-matched men and non-pregnant women. The acute liver failure occurred in 44.4% in late pregnancy. Acute liver failure during pregnancy has limited pre-encephalopathy interval, rapid progression, high occurrence of brain edema and coning of the cerebellar tonsils. However, frequent occurrence of disseminated intravascular coagulation (DIC) was distinct feature of this disease. Considering the association of DIC with HEV in pregnant women, it resembles a "Schwartzman-like Phenomenon". HEV in pregnant women causes substantial fetal and perinatal mortality. There are several studies reporting intrauterine transmission of HEV with high fetal and perinatal mortality[18,19,87]. HEV infection in cirrhotic patients causes rapid deterioration of liver functions and results in high mortality[88-90]. It is estimated that around 21% of cirrhotic patients in India contract HEV superinfection, develop rapidly progressive liver failure,

with a 30-d mortality of around 34%[88,89].

Industrialized countries

Hepatitis E of indigenous origin in industrialized regions of the World is misdiagnosed as drug induced liver injury (DILI)[91]. This has been because of the absence of attention to the disease by clinicians. Most autochthonous HEV disease occurs in older individuals. Such patients have more severe liver disease, with higher hepatic or non-hepatic complications (15%) and acute liver failure (8%-11%)[92]. HEV superinfection in chronic alcoholics and alcoholic chronic liver disease has been reported, culminating in hepatic decompensation, progression of liver disease and death rate approaching to 70%[89,90,93]. Autochthonous HEV infections in industrialized countries does not cause severe disease in pregnant women.

HEV-3 causes prolonged viremia, chronic hepatitis, liver fibrosis and cirrhosis in a subgroup of immunocompromised patients. These include people with solid organ transplant (SOT), subjects who are human immunodeficiency virus (HIV) positive and in those with hematological neoplasms[94,95]. Viremia up to and beyond 3 mo suggests chronic hepatitis E. Patients with SOT in Europe have HEV RNA prevalence of 0.9% to 3.5%. Most of such patients are asymptomatic or have mild liver tests abnormalities and minimal constitutional symptoms. However, in a subgroup of patients, chronic hepatitis E leads to rapidly progressive liver fibrosis and cirrhosis over a period of 2-3 years. Of the 85 SOT patients with HEV-3 infection, 29 patients had self-limiting disease, 56 patients have chronic viremia with mild liver disease and 9 patients presented with liver fibrosis and cirrhosis. Several factors including use of tacrolimus as an immunosuppressant, thrombocytopenia, and low CD4 count as seen in HIV-infected patients were listed as high risk for progression of liver disease and development of liver fibrosis and cirrhosis[96].

Extrahepatic manifestations

Extrahepatic manifestations known to occur with hepatitis E include acute pancreatitis, thrombocytopenia, aplastic anemia, autoimmune thyroiditis, myositis, cryoglobulinemia with skin rashes and glomerulonephritis[97-99]. In addition, neurological manifestations occur in 5% of HEV infections[7,100,101]. The neurological manifestations include Bell's palsy, encephalitis, brachial neuropathy, peripheral neuropathy and Guillain-Barre syndrome. HEV related neurological disease has been reported from developing and industrialized countries and occurs in both acute and chronic HEV infections. The long-term outcome of neurological syndromes is variable. Pathogenesis of extrahepatic HEV disease is not clear and might be multifactorial. It has been proposed that immune response to HEV may play a part in neurologic disease namely by antiganglioside antibodies through molecular mimicry[102]. Although HEV is a primarily hepatotrophic virus, it has been shown to replicate in extrahepatic sites namely kidneys, small intestine, stomach, spleen, neurological tissues, and placenta[103,104].

MODE OF TRANSMISSION

There are several mechanisms of transmission of HEV infection.

Waterborne transmission

Hepatitis E in poor resource countries is spread through water contaminated by sewage[2,85]. The way water gets contaminated is different from one epidemic to another; however, it follows the similar mechanism in repeat regional epidemics. Several environmental settings contribute to contamination. These include: (1) heavy monsoon rains; (2) floods causing stagnation and reversal of flow in waterways polluting drinking water sources; (3) seeping pipes supplying drinking water laid down through or crossing across the sewage channels; (4) overcrowding with polluted water sources as in refugee dwellings and fast growing slums; and (5) raw sewage flowing in to open drinking water sources (rivers, streams, unprotected wells). It is imperative to find the mechanism of water contamination in each epidemic so that urgent measures can be taken to block contamination and control the epidemic.

Person-to-person transmission

Whether HEV infections are spread from one person to another is controversial?[105-107]. It has been proposed that this form of transmission of HEV infection does not occur as there are no secondary waves of hepatitis following the epidemic[108]. However, epidemics of hepatitis E occur due contamination of water supplies (common source infection) and whole community gets exposed to the virus at one time. In such a situation secondary waves of hepatitis cases caused by person-to-person transmission may not occur. In contrast, epidemics of hepatitis E which lack common source of infection are caused by person-to-person transmission[105]. Sporadic infections are known to spread from one person to another[106]. HEV infection occurred in 18 (29%) of the 62 household contacts to the 13 index cases of sporadic hepatitis E. However, other investigators found insignificant spread from one person to another during sporadic and epidemic hepatitis E[109].

Zoonotic transmission

HEV prevalence in several animals in India has been studied. In one such study, HEV infection was ubiquitous in several animals including domestic pig, goat, sheep and buffalo[110]. In another study, 284 domestic pigs from Maharashtra, India were studied. 122 (42.6%) and 13 (4.6%) animals were reactive for

IgG antibodies to HEV and HEV RNA respectively[111]. All isolates from domestic pigs in India were of genotype HEV-4. As human HEV infections, both epidemic and sporadic in India are caused uniformly by genotype HEV-1, it is believed that human and pig HEV infections are unrelated and zoonotic transmission plays an insignificant role in human infections in India[111].

In industrialized countries, HEV-3 and HEV-4 is spread through foodborne zoonotic transmission[112,113]. Wild boar, Sika deer and domestic pigs cross transmit HEV, and eating parboiled flesh or liver (a treat in such countries) could be responsible for the outbreaks of hepatitis E. A more common way of HEV spread is through consumption of raw livers from supermarkets or eating Corsican Figatelli sausage. Such livers and sausages are often infected with live HEV. The waste water of domestic pig dung in such countries may pollute waterways and infect those who visit sea beaches or ingest infected mollusks.

Transfusion-associated HEV

In 2004, we reported on transfusion-associated hepatitis E from Kashmir, India[8]. In a case-control study, we detected 13 HEV infections (IgM anti-HEV and HEV RNA) amongst 145 multiply transfused subjects and 2 infections amongst 250 subjects, not transfused. In another study, three post-transfusion HEV infections in 25 susceptible patients were detected and traced to 4 HEV RNA positive donor samples amongst a total of 107 samples. All the 4 donors were asymptomatic and all transfusion-associated infections in Kashmir were caused by genotype HEV-1. Subsequent to this report, a Japanese patient was found to have developed transfusion-associated HEV infection and authors reported a complete donor-patient sequence homology[114]. Several cases and case series of transfusion-associated HEV infections were reported from several countries[115,116]. In a recent study form United Kingdom, 18 (42%) of the 42 HEV-positive transfusion recipients had contracted HEV-3 infection. Of these, 3 had short lasting viremia, while 10 developed prolonged and persistent infection[117].

In developing countries, short lasting viremia often occurs in healthy donors[9,118,119]. Presently, information on HEV RNA status in potential blood donors has been reported from many countries[79,120-122]. Viremia was reported to occur in healthy donors in all countries and varied from 1 out of 672 donations (Germany) to 1 out of 8416 donations (Austria). Duration of viremia extends up to 45 d and the infectious dose of HEV is as low as its detection by RT-PCR. Based on these data, it was estimated that around 80000-100000 transfusion associated HEV infections had occurred in England in 2013. Of the 7.4 million blood products administered in Germany per year, 1600 to 5900 transfusion-associated HEV infections had occurred. Blood or blood products are often required for several clinical conditions in whom hepatitis E runs a more severe course or leads to chronic hepatitis and cirrhosis. These include pregnancy, liver disease, SOT, HIV positive and hematological neoplasm. In view of the above data there is need to conduct screening of blood donors in countries with high HEV prevalence.

Vertical transmission

HEV can be transmitted vertically to fetus and infant from the infected mothers. We studied 8 mothers who had HEV infection for evidence of vertical transmission. Six babies had contracted vertically transmitted HEV infection[18]. In another study, 26 pregnant women with HEV infection were studied for pattern of vertically-transmitted HEV infection[19]. Five mothers had died prior to delivery, 2 aborted the fetuses, 4 delivered premature babies and 15 had completed pregnancy with normal deliveries. Out of the 19 babies evaluated, 12 were reactive for IgM anti-HEV and 10 showed viremia. In all 15 (78.9%) had evidence of intrauterine HEV infection. HEV infection in babies presented as icteric hepatitis in 7, anicteric hepatitis in 5 and jaundice alone in 3. Six newborns died with liver failure and one due prematurity. Nine babies who survived had short-lasting viremia and none had evidence of chronic hepatitis or cirrhosis. Subsequent to these reports, a number of reports have documented intrauterine transmission of HEV infection with high maternal and fetal mortality[87,123]. Recently HEV replication in placenta was found to occur and correlated with fetal and maternal mortality in acute liver failure[103]. We evaluated outcome of 36 pregnant women with hepatitis E and the occurrence and severity of vertically transmitted HEV infection in fetuses/neonates and found relationship between severity of disease in fetus with severity and outcome of disease in the mother and postulated that acute liver failure in pregnant women may be an example of mirror syndrome akin to acute fatty liver of pregnancy[124].

DIAGNOSIS

Serological analysis for HEV infection has been problematic (Table 2)[125,126]. Several issues need to be addressed while evaluating these tests. Some tests have problems while applying to different genotypes. Others perform poorly in immunocompromised persons. Cross reactions with other viral infections have been reported. Several assays available have been developed and evaluated by sera from patients with recent infections. These assays often have poor performance in sensitivity and specificity. Assays developed and evaluated against WHO reference reagents give more predictable results. Assays developed on either "indirect" ELISA or class capture-ELISA technique also give better results[126]. Amongst these, 2 assays for IgM anti-HEV marketed by the Beijing Wantai Biological Pharmacy (Wantai Rapid

Table 2 Diagnosis of hepatitis E virus infection

Test	Method	Uses	Comments
IgM anti-HEV	ELISA ICT (POCT)	Acute infection	Assays vary in performance, issue of genotype applicability, poor performance in immune disorders, cross-reactive with other viral infections
IgG anti-HEV	ELISA ICT (POCT)	Seroprevalence Acute infection Natural protection Vaccine efficacy	Assays vary in performance
HEV RNA	NAT	Acute infection Confirm chronicity Anti-viral response Donor screening	Viremia short-lasting, in-house assays vary in performance, advantage immune disorders
HEV antigen	EIA	Acute infection	81% concordance with HEV RNA

Adopted from Khuroo *et al*[143], 2016. HEV: Hepatitis E virus; ICT: Immunochromatographic test; POCT: Point of care test; NAT: Nucleic acid test; EIA: Enzyme immunoassay.

test) and Genelabs Diagnostics, Singapore (Assure™) have high sensitivity and specificity. In routine clinical practice, acute HEV infection in immunocompetent patients can predictably be diagnosed by IgM anti-HEV. Around 90% patients are reactive for IgM anti-HEV at 2 wk of infection and stays so for up to 5 mo[127]. In patients with immune deficiency disease, additional testing for HEV RNA is recommended, in view of poor IgM response in this population.

IgG anti-HEV testing is useful in seroprevalence studies. Rising IgG titers may help in diagnosis of HEV infection in situations with poor IgM anti-HEV response[128]. Testing for IgG anti-HEV titers is essential for determining effectiveness of HEV vaccine. Antibody titers of 2.5 WHO units/mL following vaccination or acute HEV infection are protective.

Testing for HEV RNA is useful in several situations which include: (1) donor screening; (2) diagnosis of HEV infections in patients with poor IgM response; (3) diagnosis of chronic HEV infection; and (4) evaluating response to antiviral drug therapy[129]. In-house assays for HEV RNA detection may have limitations and needs to be standardized with WHO standard (genotype HEV-3a). Conventionally HEV RNA is detected in blood and other body fluids by RTPCR and using primers from conserved segments of HEV. Another assay, the loop-mediated isothermal amplification (LAMP) employs single-tube, one-step amplification of HEV RNA. The test is quick, reliable and needs no special equipment[130].

CONTROL AND CURE

Prevention and control of epidemics of hepatitis E in poor resource countries is a challenging task[85]. Management should be predominantly preventing and focusing on the supply of clean potable drinking water, adequate sanitation and proper sewage disposal and personal hygienic practices. During travel to countries with high prevalence of HEV infections, one should desist from use of contaminated drinks and beverages and eating of uncooked shellfish. "Clean India Campaign", a Government of India Campaign 2014 is a USD10 billion project and is meant to clean the environs, construct toilets in homes, societies and schools and execute basic hygienic practices including proper hand hygiene. It is planned that around 1.2 billion Indians shall have access to public latrines in next 5 years[85]. Numerous endemic areas lack proper healthcare amenities, disease surveillance means, health education and recognizing sick patients for referral and these activities need to be instituted[131]. Chlorination of drinking water supplies is frequently being practiced to control epidemics and does help. Administration of IgG from Indian source has not succeeded in control of epidemics[106]. Availability of hyperimmune HEV globulin and a cheap, effective and safe HEV vaccine would help to prevent and help to arrest the spread of the epidemics[132].

Acute hepatitis E in immunocompetent individuals usually only need symptomatic treatment, due short lasting viremia. Ribavirin therapy for 3 wk in patients with severe hepatitis E causes rapid improvement of liver enzymes and functions[133]. Despite the fact that ribavirin is a teratogenic drug, the dangers of untreated HEV to the mother and embryo are high, and trials of drug therapy may be advantageous in such patients. SOT patients should avoid eating uncooked game meat or domestic pig meat and liver and Figatelli sausage. In contrast, all these food items need to be heated to inactivate the virus[38].

An algorithm for treatment of HEV-3 infection in SOT patients has been developed (Table 3)[134]. Reduction in immunosuppression clears the virus in a significant proportion of patients. Calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors enhance HEV replication and may cause the increment and persistence of HEV RNA[135-138]. In contrast, mycophenolic acid (including prodrug mycophenolate mofetil) inhibits HEV replication and may help with HEV clearance in chronic hepatitis E. Ribavirin is the drug of choice for patients with persistent viremia for 3 mo[138]. PEGylated IFN can be used in patients who have had liver transplants and not in patients with other solid organ transplants[139]. Sofosbuvir, a

Table 3 Effect of drugs on hepatitis E virus replication and their use and impact on immunosuppressant therapy during chronic hepatitis E virus infection in solid organ transplant patients

Class	Drug	Effect on HEV replication	Clinical use
Calcineurin inhibitors	Cyclosporine, tacrolimus	Stimulates HEV replication with increase in HEV load and promotes HEV persistence	Reduce dose
mTOR inhibitors	Rapamycin, everolimus	Stimulates HEV replication with increase in HEV load	Reduce dose
Antimetabolite immunosuppressant	Mycophenolate mofetil	Inhibits HEV replication and helps HEV clearance	Continue the drug
Guanosine analog	Ribavirin	Inhibits HEV replication and causes HEV clearance	Primary drug for therapy
Cytokines	Pegylated interferon α	Inhibits HEV replication and causes HEV clearance	Indicated if Ribavirin therapy fails
Nucleotide analog	Sofosbuvir	Inhibits HEV replication *in vitro*	Unclear, clinical trials indicated

HEV: Hepatitis E virus.

nucleotide analog inhibitor of hepatitis C infection polymerase, additionally hinders HEV replication *in vitro* by inhibiting the viral RNA-dependent RNA polymerase[140]. The role of Sofosbuvir in acute and prolonged HEV infection needs closer examination. Some patients may develop liver fibrosis, cirrhosis and liver failure and are candidates for liver transplantation.

HEV VACCINE

HEV-239 is made of VLP, expressed in *E. coli* (368-606 aa of ORF2) from HEV-1 Chinese strain and has 2 epitopes (533 to 552 aa) and incites an incredible T cell-dependent antibody response[12,141]. The vaccine has effectively completed trials in China and is marketed (Hecolin) in 30-lg doses for 3 dose regimen (0, 1 and 6-mo). At 4.5 years, vaccine offers efficacy was 86.8%. The vaccinated patients have protective antibody levels in 87% as against 9% in the control group[142]. The vaccine has been shown to give cross-protective efficacy between genotype HEV-1 (the vaccine product) to HEV-4 (infection prevalent in area of study).

For the global launch of HEV-239 vaccine, we need safety data in children, elderly patients, patients with chronic liver disease, SOT, HIV and those with immune disorders[143]. Data regarding safety of HEV-239 in pregnant women needs to be extended. Vaccine safety when used concomitantly with other vaccine needs consideration. Post-marketing and cost-effectively studies can be conducted once a vaccine is available in other countries. HEV-239 has been found highly effective in population where HEV-4 is prevalent with low endemicity at HEV attack rate of 0.03%. It is important to determine efficacy of vaccine in the Indian subcontinent where HEV-1 infection is prevalent with very high endemicity at an attack rate of 7.36%. Also vaccine efficacy studies in regions where genotype HEV-3 is prevalent need to be done[132].

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