HEPATITIS E: INFECCIÓN Y DIAGNÓSTICO DE UNA ENFERMEDAD EMERGENTE

¿UN RETO EN EL HORIZONTE?

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El conocimiento de la infección provocada por el VHE ha cambiado enormemente en los últimos diez años, hasta incluso considerarse su condición de enfermedad emergente en los países industrializados de nuestro entorno.

EUROPE'S NEW HEPATITIS PROBLEM

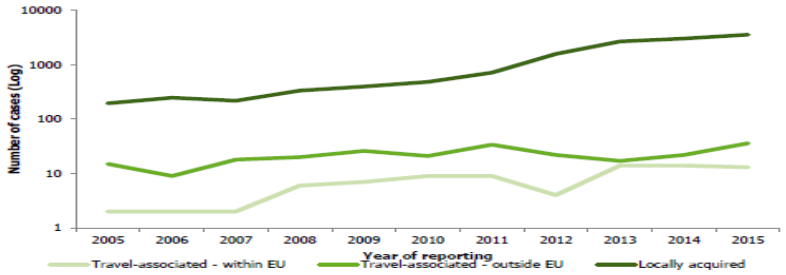
Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

By **Kai Kupferschmidt**

Science 2016; 353: 862-863

Incremento en los casos diagnosticados de HEPATITIS E en la UE durante los últimos años

Figure 3.7. Confirmed cases of hepatitis E by travel history and year, EU/EEA Member States, 2005–2015*



*Data on travel history available for: Austria, Croatia, Czech Republic, Estonia, France, Hungary, Italy, Latvia, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom (England, Wales, Northern Ireland);

Figure 3.5. Number and proportion of hospitalisations among confirmed cases of hepatitis E, EU/EEA Member States, 2005–2015*

* Data available for: Austria, Belgium, Croatia, Czech Republic, Estonia, Germany, Hungary, Italy, Latvia, Poland, Portugal, Slovakia, Slovenia, United Kingdom (Northern Ireland)

Existen datos significativos de prevalencia de la viremia por VHE y de seroprevalencia de Anti-VHE-IgG en donantes de sangre en diferentes países de la UE

TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
Transfusion Medicine | REVIEW ARTICLE

Hepatitis E: the current state of play

M. J. Ankcorn[1,2] & R. S. Tedder[1,2]

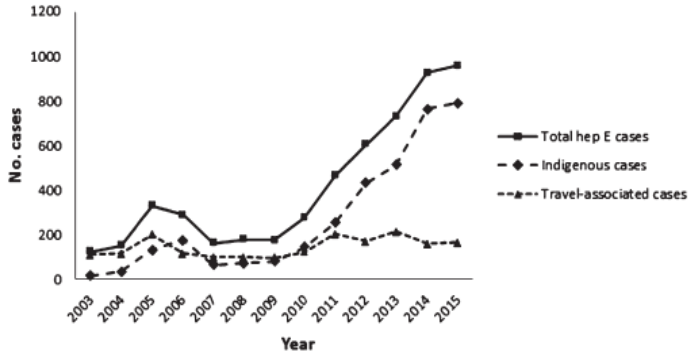


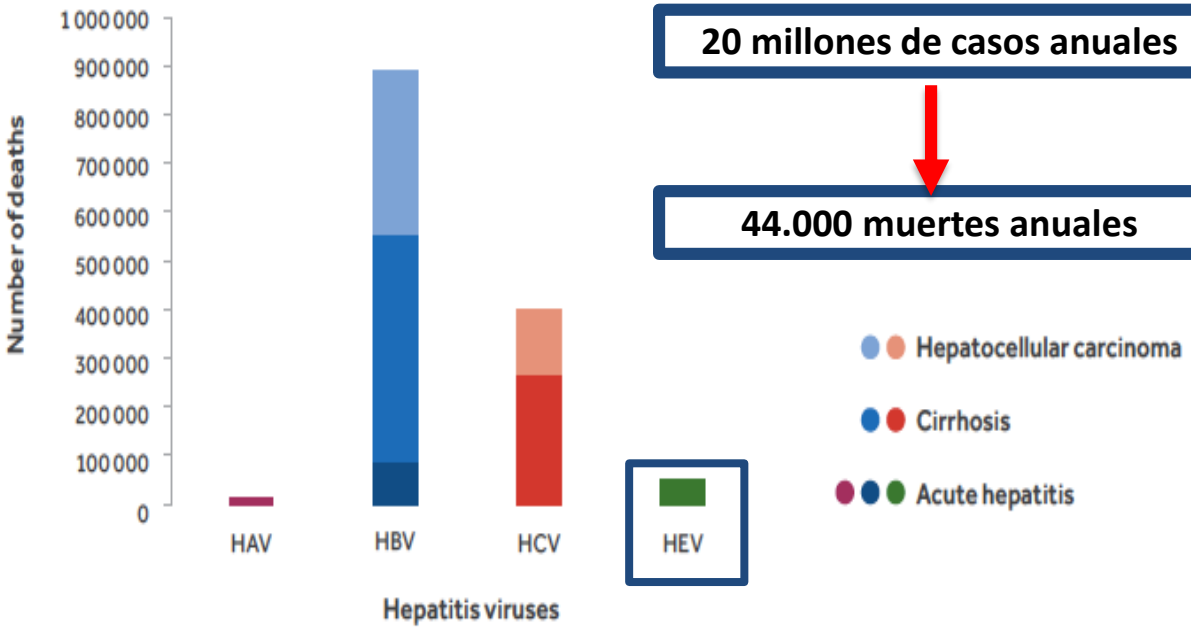
Fig. 1. Reference laboratory-confirmed HEV cases in England & Wales 2003–2015.

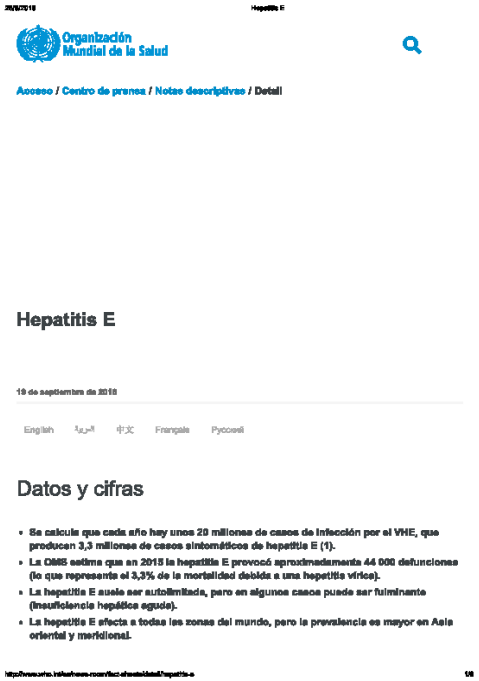
Table 2. Prevalence of HEV viraemia in blood donors and IgG seroprevalences in both blood donors and the general population from selected countries where G3 is the dominant genotype. All studies used Wantai IgG assay (Fortress Diagnostics Ltd, Antrim, Northern Ireland, UK). All percentages rounded up to whole numbers

	Country	Blood donors HEV RNA positive	Anti-HEV IgG seroprevalence (blood donors)	Anti-HEV IgG seroprevalence (general population)	Year of sampling
Europe	Austria	1:8416	14%		2013/2014, Fischer *et al.* (2015)
	England	1:2848			2012/2013, Hewitt *et al.* (2014)
			12%		2010, Beale *et al.* (2011)
	France	1:2218	25%		2012/2013, Gallian *et al.* (2014)
	SW France			34%	2010/2011, Mansuy *et al.* (2011)
			53%		2003/2004, Mansuy *et al.* (2011)
	Germany	1:1240			2011, Vollmer *et al.* (2012)
		1:4525			2011, Baylis *et al.* (2012)
				30%	2010, Wenzel *et al.* (2013)
	Netherlands	1:762			2013/2014, Hogema *et al.* (2016)
		1:2671	27%		2011/2012, Slot *et al.* (2013)
			21%		2011, Hogema *et al.* (2014)
	Spain	1:3333	20%		2013, Sauleda *et al.* (2015)
	Sweden	1:7986			2011, Baylis *et al.* (2012)
North America	USA	1:9500			2013, Stramer *et al.* (2016)
			16%		2012, Xu *et al.* (2013)
		0:1939			2011, Baylis *et al.* (2012)
	Canada	0:5000	6%		2013, Fearon *et al.* (2014)

Ankcorn MJ et al Trans Med 2017; 27: 84-95

La hepatitis E es una enfermedad infecciosa, causada por el VHE, que presenta una alta prevalencia e incidencia y que constituye una de las principales causas de hepatitis aguda en el mundo





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Hepatitis E

English | Français | Русский

Datos y cifras

- Se calcula que cada año hay unos 20 millones de casos de infección por el VHE, que producen 3,3 millones de casos sintomáticos de hepatitis E (1).
- La OMS estima que en 2015 la hepatitis E provocó aproximadamente 44 000 defunciones (lo que representa el 3,3% de la mortalidad debida a una hepatitis vírica).
- La hepatitis E suele ser autolimitada, pero en algunos casos puede ser fulminante (insuficiencia hepática aguda).
- La hepatitis E afecta a todas las zonas del mundo, pero la prevalencia es mayor en Asia oriental y meridional.

ANTECEDENTES HISTÓRICOS

El virus de la hepatitis E fue identificado por vez primera en 1980 a partir de un brote de hepatitis aguda producido en un campamento militar, durante la ocupación soviética de Afganistán.

Dr Mikhail S Balayan

Intervirology 20: 23–31 (1983)

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0300–5526/83/0201–0023$2.75/0

Evidence for a Virus in Non-A, Non-B Hepatitis Transmitted via the Fecal-Oral Route

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Key Words. Non-A, non-B hepatitis · Transmission · Virus-like particles · Immune electron microscopy · Virus serology · Cynomolgus monkeys

Summary. Typical acute hepatitis was reproduced in a human volunteer immune to hepatitis A virus (HAV) after oral administration of pooled stool extracts from presumed cases of epidemic non-A, non-B hepatitis. Markers of hepatitis B infection, anti-HAV IgM, and increase in total anti-HAV level were not detectable in the volunteer's sera during the course of infection. Spherical 27- to 30-nm virus-like particles were visualized by immune electron microscopy (IEM) in stool samples collected during preclinical and early postclinical phases. These particles banded in CsCl at a buoyant density of 1.35 g/cm³. They reacted in the IEM test with sera from individuals who had experienced two non-B hepatitis episodes but did not react with sera from routine anti-HAV IgM-positive hepatitis patients. Intravenous inoculation of cynomolgus monkeys with the virus-containing stool extract resulted in histopathologically and enzymatically confirmed hepatitis, excretion of virus-like particles, and antibody response to them.

Recent studies have led to the conclusion that there are at least two types of human non-A, non-B hepatitis which differ in their epidemiological patterns [for a review, see 1]. One type is obviously associated with the transfusion of blood or blood products, i.e., posttransfusion non-A, non-B hepatitis, and probably is caused by more than one etiological agent [2, 3]. The other type resembles type A hepatitis and seemingly has the same fecal-oral mode of transmission. This disease has been shown to occur as sporadic cases [4–6] and as waterborne epidemics [7–9]. Thus far, diagnosis of the fecal-oral non-A, non-B hepatitis has been based on the evaluation of epidemiological data and on the exclusion of viral hepatitis types A and B in serological tests, since the etiologic agent of the infection remains unidentified.

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Revised: January 7, 1983

Balayan MS et al. Intervirology 1983; 20: 23-31.

Isolation of a cDNA from the Virus Responsible for Enterically Transmitted Non-A, Non-B Hepatitis

Reyes GR et al. Science 1990; 247: 1335-39

Solid-phase enzyme-linked immunosorbent assay for hepatitis E virus IgG and IgM antibodies utilizing recombinant antigens and synthetic peptides

Dawson GJ et al. J Virol Methods 1992; 38:175-86

ASPECTOS VIROLÓGICOS

Genoma y virión: El virus de la hepatitis E es un virus ARN que pertenece al género Orthohepevirus, dentro de la familia *Hepeviridae*: Su genoma, está formado por una sola cadena de ARN de sentido positivo, de aproximadamente 7,2 kb.

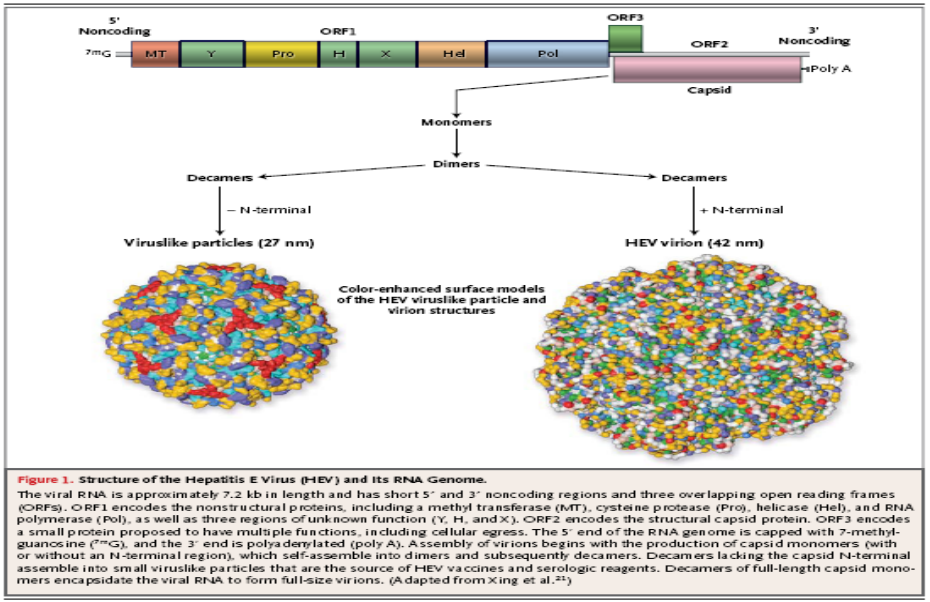

Figure 1. Structure of the Hepatitis E Virus (HEV) and Its RNA Genome.
The viral RNA is approximately 7.2 kb in length and has short 5′ and 3′ noncoding regions and three overlapping open reading frames (ORFs). ORF1 encodes the nonstructural proteins, including a methyl transferase (MT), cysteine protease (Pro), helicase (Hel), and RNA polymerase (Pol), as well as three regions of unknown function (Y, H, and X). ORF2 encodes the structural capsid protein. ORF3 encodes a small protein proposed to have multiple functions, including cellular egress. The 5′ end of the RNA genome is capped with 7-methylguanosine (^{7me}G), and the 3′ end is polyadenylated (poly A). Assembly of virions begins with the production of capsid monomers (with or without an N-terminal region), which self-assemble into dimers and subsequently decamers. Decamers lacking the capsid N-terminal assemble into small viruslike particles that are the source of HEV vaccines and serologic reagents. Decamers of full-length capsid monomers encapsidate the viral RNA to form full-size virions. (Adapted from Xing et al.[21])

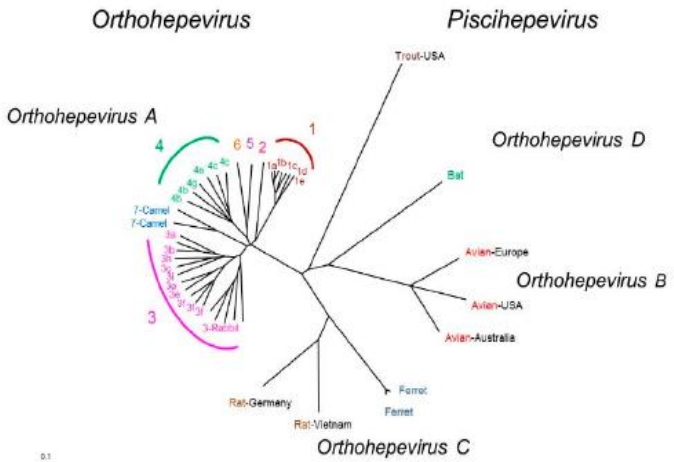

Figure 2. Phylogenetic tree based on full-length sequences of HEV strains. Sequences were aligned using ClustalW (MEGA5) and BioEdit (version 7.0). The phylogenetic tree was created by the neighbour-joining (Kimura two-parameter) method, with a bootstrap of 100 replicates. The species *Orthohepevirus A* includes 7 genotypes (HEV1–7).

Hoofnagle JH et al. N Engl J Med 2012; 367: 1237-44

Lhomme S et al. Viruses 2016; 8: E212

Ciclo replicativo: El ciclo replicativo del VHE en el hepatocito es similar al de otros virus ARN, con un ARN intermediario de sentido negativo, que por mediación de la polimerasa viral, producirá el ARN genómico y subgenómico que actuará como molde en la producción de las proteínas estructurales.

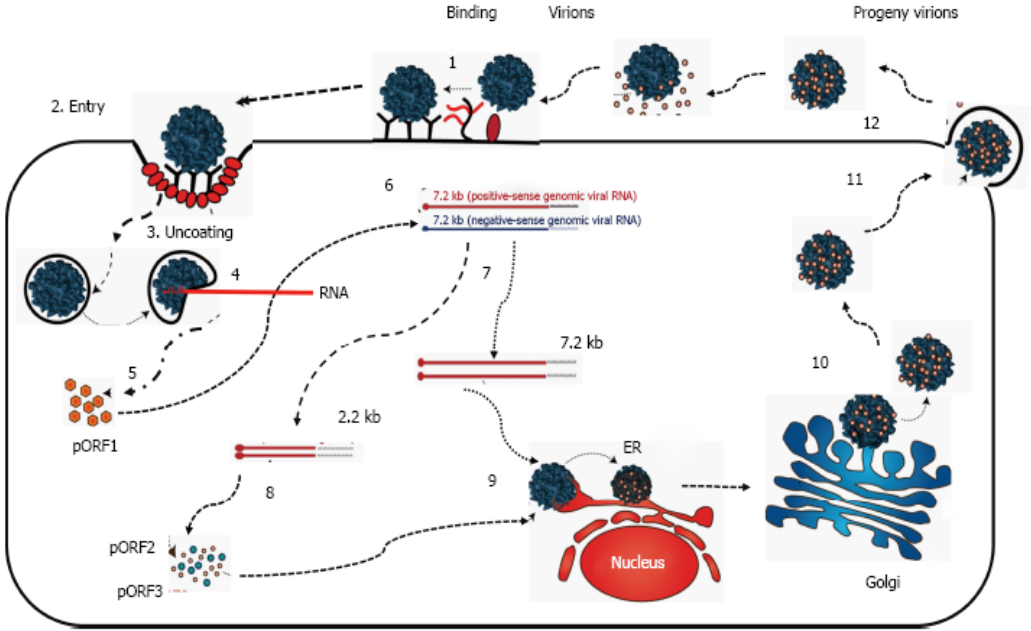

Figure 2 **Proposed replication of hepatitis E virus.** For details, see text about hepatitis E replication. Adopted from Khuroo *et al*[143], 2016.

Khuroo MS et al. World J Gastroenterol 2016; 22: 7030-45

Genotipos: La caracterización molecular de las cepas del VHE ha llevado en base a su variabilidad genética al reconocimiento de cuatro genotipos principales (GTs 1-4), con distintos subgenotipos y un solo serotipo, que afectan a humanos y están distribuidos por todo el mundo.

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.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

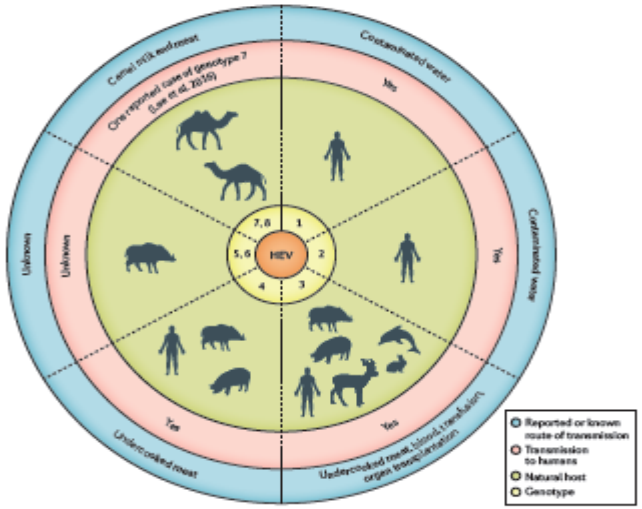

Figure 1 | Host range of hepatitis E virus. The *Orthohepevirus A* genus is classified into hepatitis E virus (HEV) genotypes 1–8. Genotypes 1 and 2 are limited to human hosts and are transmitted via the faecal–oral route, primarily through contaminated water. Genotypes 3 and 4 have multiple hosts and can be transmitted to humans through the consumption of undercooked meats, including pork. Genotypes 5 and 6 are known to infect wild boar; however, it is unknown whether these genotypes can be transmitted to humans (although there have been reports of wild boar genotype 3 HEV transmission to humans). Finally, genotypes 7 and 8 infect dromedary and Bactrian camels, respectively. There has been one case reported of genotype 7 HEV transmission to a liver transplant patient who consumed camel meat and milk[23].

Nimgaonkar I et al Nat Rev Gastroenterol Hepatol. 2018 ;15:96-110

Evolución: Los estudios de la historia evolutiva y de la dinámica poblacional del VHE muestran una serie de etapas en las que sus antecesores se habrían adaptado a una sucesión de huéspedes animales que han conducido finalmente al ser humano.

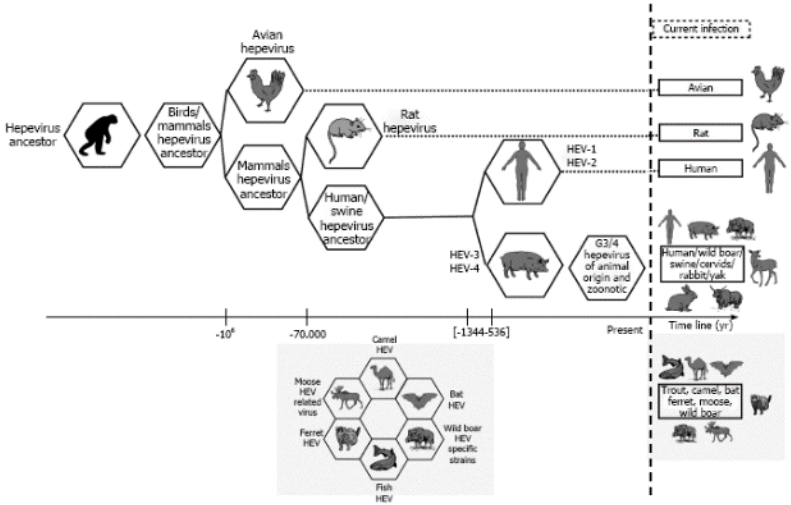

Figure 3 Evolutionary history of hepatitis E virus. The times to the most recent common ancestors (tMRCAs) for all four genotypes of HEV were calculated using BEAST to conduct a Bayesian analysis of HEV. The population dynamics for genotypes 1, 3 and 4 were analyzed using skyline plots. For details see text on HEV evolution. Source of data Purdy *et al*[93] 2010. HEV: Hepatitis E virus.

Khuroo MS et al. World J Gastroenterol 2016; 22: 7030-45

Epidemiología molecular: Los cuatro genotipos del VHE que causan patología en humanos (GT 1-4) muestran una distribución geográfica característica y presentan diferentes propiedades biológicas

Figure 1 | **Worldwide presence of HEV genotypes.** Schematic representation of the distribution of the different hepatitis E virus (HEV) genotypes. Map adapted based on data obtained from IBIS 4,215.

Table 1 | **Comparison of HEV genotypes**[1,3,104]

Characteristic	HEV 1 and 2	HEV 3 and 4
Geographical distribution	Asia (HEV1) Africa (HEV1 and HEV2) Mexico (HEV2)	Worldwide, including developed countries (HEV3) Japan, China and Europe (HEV4)
Source of infection	Obligate human pathogen	Zoonotic Blood supply
Route of infection	Faecal–oral via infected water	Oral via consumption of infected pork Parenteral, iatrogenic (blood supply)
Risk of infection from blood supply	Low	High
Outbreaks	Yes	No
Intrafamilial spread	Rare	No
Clinical attack rate	1:5 (REF. 105)	<1:10
Demographics	Mainly affects young adults	Mainly affects older men (median age 63 years, male:female ratio 3:1)
Chronic infection	No	Yes, in immunocompromised individuals Rapidly progressive liver disease if untreated: 10% of cases are cirrhotic within 2 years Viral clearance is usually achieved with a 3-month course of ribavirin monotherapy
Occurrence of second HEV infections	Yes (but poorly documented)	Yes Poorly documented for HEV3 Well documented in HEV4, more likely in women who have a milder hepatitis than is generally seen in primary infections
Clinical course	Self-limiting hepatitis in most cases	Self-limiting hepatitis in most cases
Effects during pregnancy	Mortality 25%	No evidence of increased mortality
Effects on individuals with underlying chronic liver disease	Increased mortality	Increased mortality
Neurological sequelae	Yes (but poorly documented	Yes

HEV, hepatitis E virus.

Kamar N et al. Nat Rev Dis Primers doi:10.1038/nrdp.2017.86

Dalton HR et al. Nat Rev Neurol 2016; 12: 77-85

ASPECTOS EPIDEMIOLOGICOS

Vías de transmisión: El VHE se transmite a través del agua, de productos sanguíneos, de persona a persona, verticalmente y por transmisión zoonótica. El modo de transmisión difiere en función del grado de desarrollo económico.

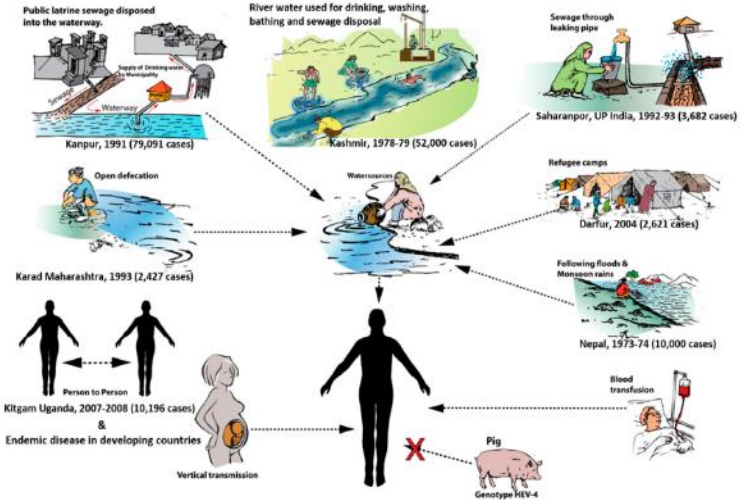

Figure 2. Modes of transmission of hepatitis E in developing countries. The settings for contamination of drinking water have been drawn in sketches, with epidemics reported in each case.

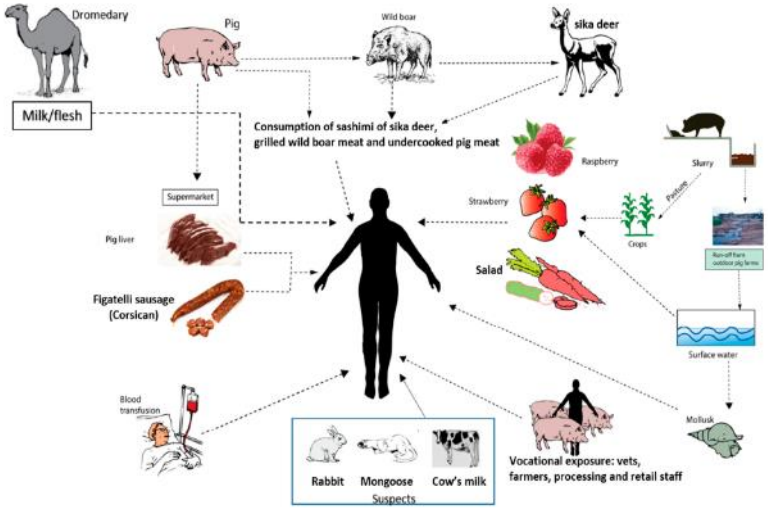

Figure 5. Zoonotic transmission of hepatitis E in developed and many developing countries.

Khuroo MS et al. Viruses 2016; 8: E253

Patrones de distribución mundial: En la actualidad y en base a la presentación de la enfermedad en la población , se reconocen 4 patrones de distribución de la infección por el VHE en el mundo: Hiperendémico, endémico, esporádico y diferente.

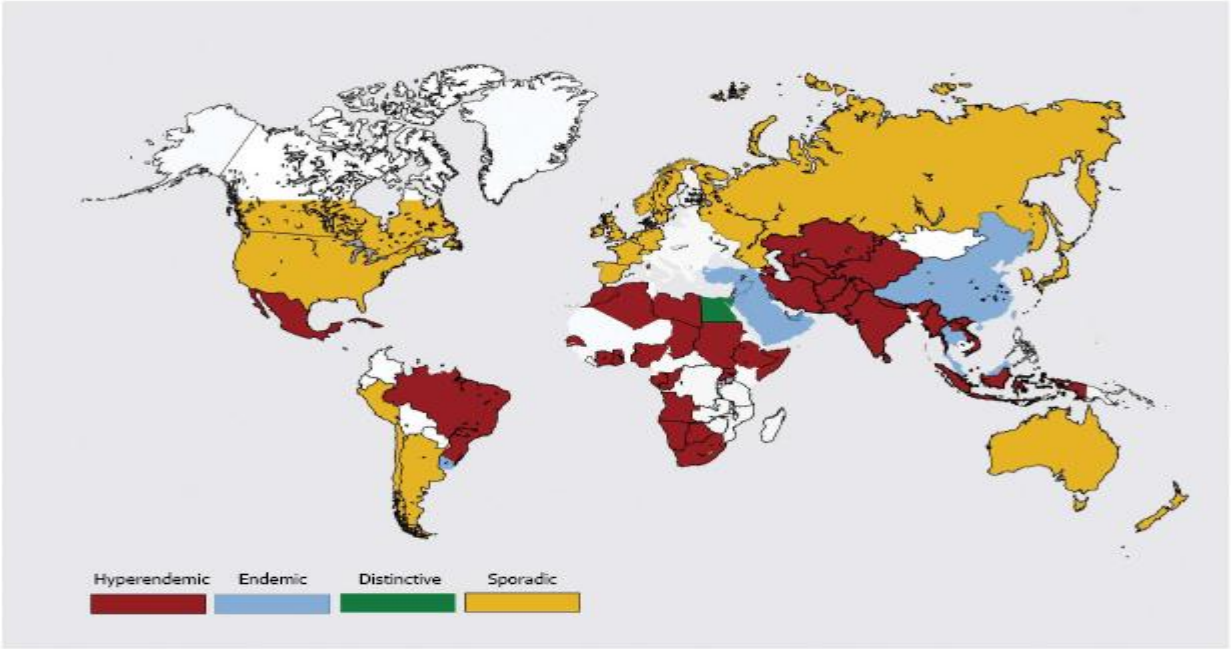

Figure 4 Global distribution of hepatitis E disease. See text under "global distribution" for explanation.

Khuroo MS et al. World J Gastroenterol 2016; 22: 7030-45

Europa: Las tasas de seroprevalencia varían significativamente entre los países y grupos de cohortes poblacionales. Por su parte la incidencia de la infección, por razones desconocidas, también varía considerablemente de un país a otro y con el tiempo, con incrementos significativos en los últimos años en algún caso.

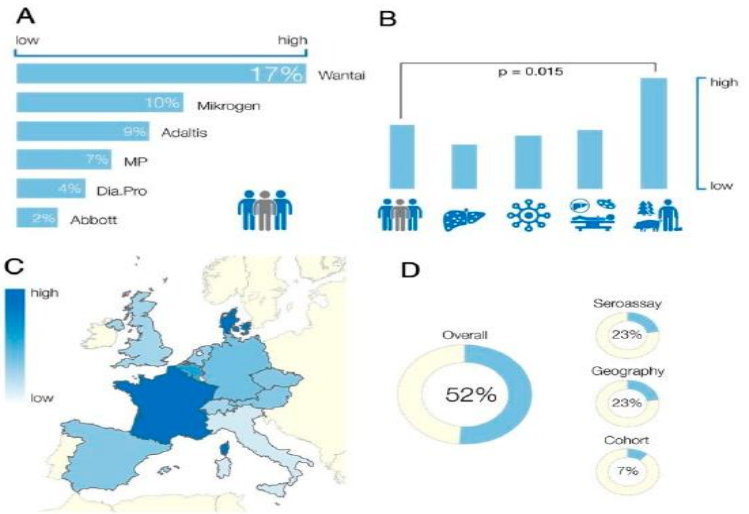

Figure 3. (**A**) Anti-HEV IgG seroprevalence rates in the general population dependent on the used seroassay; (**B**) comparison of estimated seroprevalence rates adjusted for patient cohort. Patient cohorts from left to right: general population, liver diseases, HIV infections, transplant recipients, swine/wild animal contact (farmers, veterinarians, slaughterhouse workers, forestry workers); (**C**) calculated anti-HEV seroprevalence in different European countries. Exact seroprevalence rates are displayed in Table 3; and (**D**) amount of heterogeneity explained by used seroassay, study cohort, and geographical location.

Hartl J et al. Viruses 2016; 8: E211

España: la seroprevalencia de anticuerpos frente al VHE en la población general es inferior al 10%, aumentando de manera significativa con la edad.

Enferm Infecc Microbiol Clin. 2015;33(4):281–286

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimo

Revisión

Epidemiología de la infección por el virus de la hepatitis E en España

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INFORMACIÓN DEL ARTÍCULO

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Virus de la hepatitis E
Epidemiología
Hepatitis aguda
Zoonosis virales
Seguridad alimentaria

R E S U M E N

La información generada durante los últimos 20 años permite ya describir los rasgos generales de la epidemiología y la ecología del virus de la hepatitis E en España. Las cepas del genotipo 3, y en especial las del subgenotipo 3f, circulan entre el ganado porcino y entre algunos mamíferos salvajes, y se transmitirían esporádicamente a las personas por contacto directo con los reservorios o por el consumo de alimentos procedentes de ellos. Asimismo, los mariscos bivalvos contaminados por el virus a través de las aguas residuales podrían desempeñar algún papel en dicha transmisión. Con las dificultades que aún plantea la interpretación de los datos, puede estimarse que la prevalencia de anticuerpos frente al virus de la hepatitis E en la población española sería inferior al 10%, aumentando significativamente con la edad. Entre los, aproximadamente, 150 casos de hepatitis E aguda comunicados ya en la literatura internacional, predominan los casos autóctonos observados en varones mayores de 40 años. Por otra parte, la enfermedad podría ser más frecuente en las regiones del norte de España que en otras. Aunque las hepatitis E agudas que suceden en nuestro medio no suelen presentar gran trascendencia clínica, los hallazgos puntuales de casos de hepatitis fulminante y de infecciones crónicas en pacientes inmunodeprimidos que no responden bien a la terapia con ribavirina aconsejan vigilar esta infección e incorporar su diagnóstico etiológico a la rutina de los laboratorios clínicos en mayor medida que la actual.

Epidemiology of hepatitis E virus infection in Spain

Keywords:
Hepatitis E
Hepatitis E virus
Epidemiology
Acute hepatitis
Viral zoonosis
Food safety

A B S T R A C T

The general features of the epidemiology and ecology of hepatitis E virus in Spain are already known after 20 years of investigations. Genotype 3 strains, mainly from sub-genotype 3f, circulated among swine livestock and certain wild mammals, and would be sporadically transmitted to humans through direct contact with the reservoirs or by consumption of foods derived from them. Bivalve shellfish contaminated by hepatitis E virus from sewage could also play a role in transmission. Although the interpretation of results from seroprevalence studies in low endemic settings is still controversial, antibody to hepatitis E virus displays an overall prevalence less than 10% among the population of Spain, increasing significantly with age. From the, approximately, 150 cases of acute hepatitis E recorded in the international literature, males older than 40 years, suffering a mild, locally acquired disease predominate. In addition, hepatitis E might be more frequent in the North of the country than in other regions. Although the disease does not usually have a great clinical relevance, the occasional finding of cases of fulminant hepatitis, and of ribavirin-resistant, chronic hepatitis E virus infections among the immunocompromised would recommend the surveillance of the infection by the public health authority and a better implementation of specific diagnostic procedures in clinical laboratories.

Introducción

La denominación «virus de la hepatitis E» (VHE) abarca un conjunto muy diverso de cepas virales que se ubican en 2 grupos desde el punto de vista epidemiológico. Las cepas epidémicas de transmisión fecal-oral del genotipo 1 son características del centro, sur y sureste de Asia y de África, aunque también circulan en Cuba y

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http://dx.doi.org/10.1016/j.eimc.2013.11.009

Echevarria JM et al. Enferm Infecc Microbiol Clin 2015; 33: 281-6

ASPECTOS CLÍNICOS

Patogénesis: La patogénesis de la infección por el VHE implica una interacción compleja entre el virus y el sistema inmune del huésped. El fenotipo clínico es principalmente hepatológico, pero el rango y la incidencia de los síntomas clínicos asociados al VHE se ha incrementado en los últimos años.

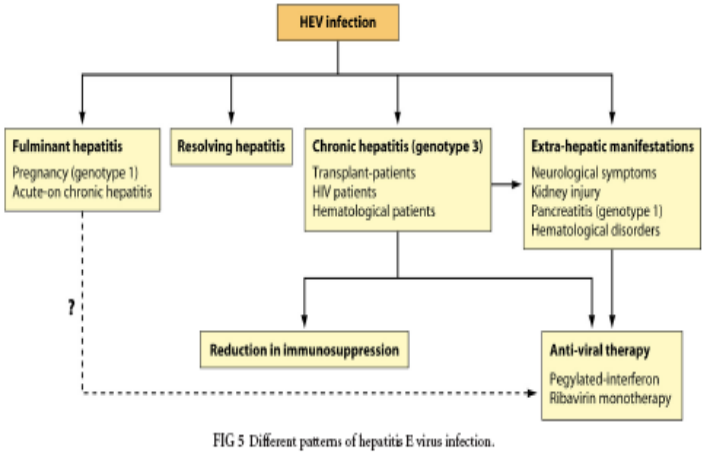

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

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.

Khuroo MS et al. World J Gastroenterol 2016; 22: 7030-45

Hepatitis aguda: Los pacientes afectados experimentan síntomas hepáticos similares a los observados en otras formas de hepatitis viral aguda. La infección es generalmente autolimitada, con recuperación clínica y bioquímica después de unas pocas semanas.

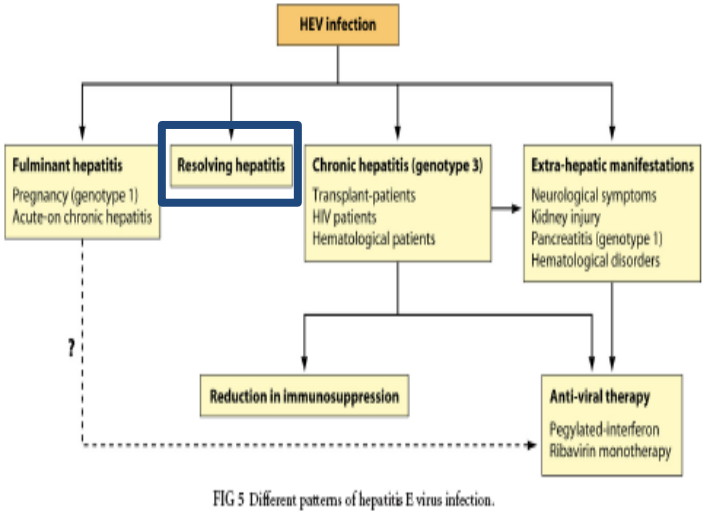

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

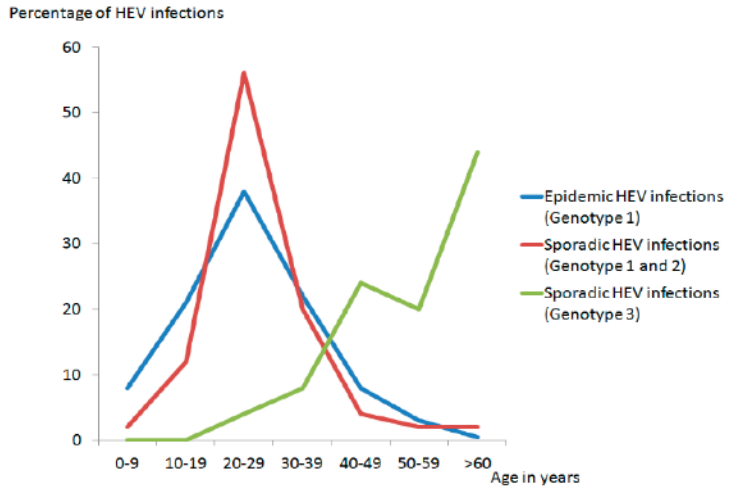

Figure 3. Distribution of HEV infections in different age groups (based on: Purcell and Emerson [61]).

Hartl J et al. Viruses 2016; 8: E299

Complicaciones: Una minoría de pacientes con hepatitis E aguda, especialmente aquellos con enfermedad hepática crónica subyacente, desarrolla complicaciones hepáticas de elevada mortalidad como descompensación hepática y fallo hepático fulminante.

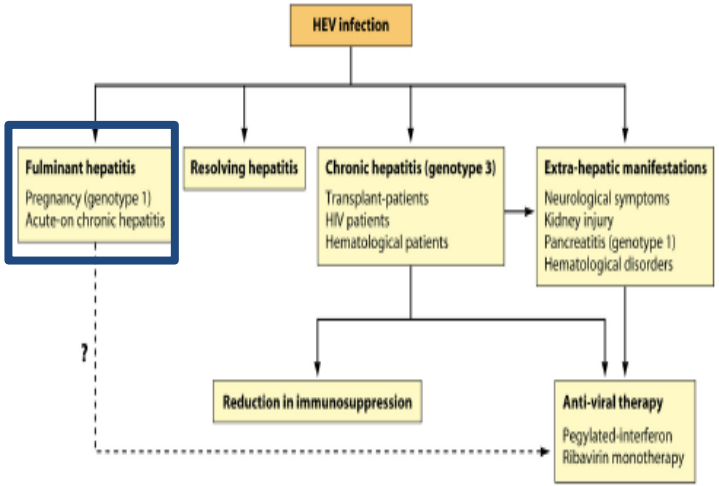

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

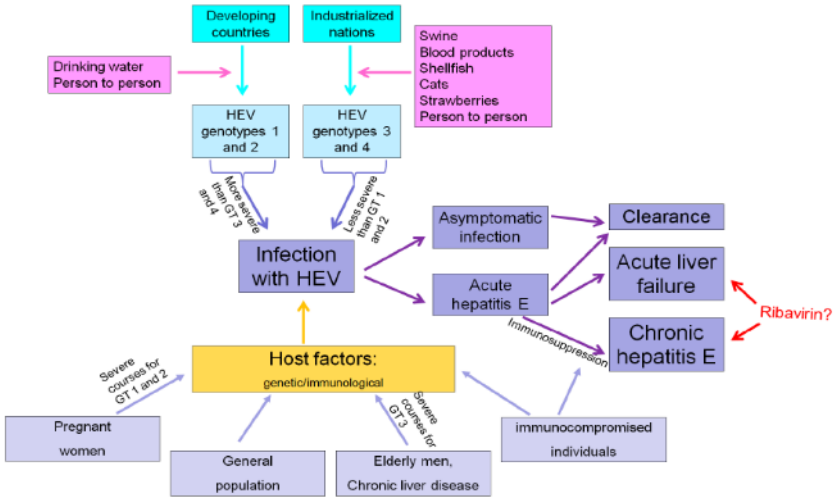

Figure 1. Possible courses of hepatitis E virus (HEV) infection. GT, genotype.

Hartl J et al. Viruses 2016; 8: E299

Hepatitis crónica: La infección crónica por el VHE se ha descrito en diferentes poblaciones de pacientes inmunodeprimidos. Los pacientes con hepatitis E crónica están generalmente asintomáticos e infectados principalmente por el GT3

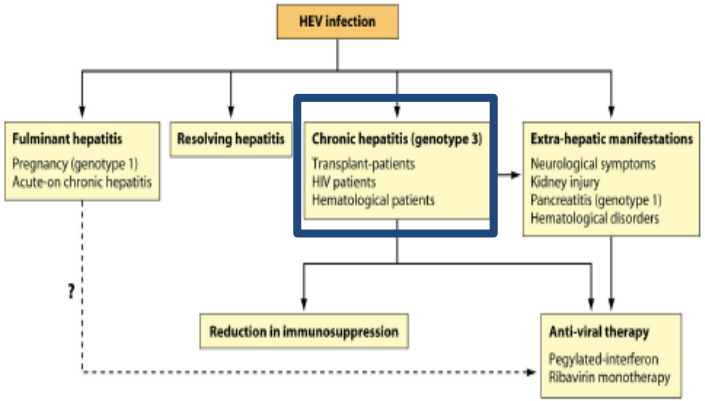

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

Nassim Kamar, M.D., Ph.D., Janick Selves, M.D., Jean-Michel Mansuy, M.D., Leila Ouezzani, M.D., Jean-Marie Péron, M.D., Ph.D., Joëlle Guitard, M.D., Olivier Cointault, M.D., Laure Esposito, M.D., Florence Abravanel, Pharm.D., Marie Danjoux, M.D., Dominique Durand, M.D., Jean-Pierre Vinel, M.D., Jacques Izopet, Pharm.D., Ph.D., and Lionel Rostaing, M.D., Ph.D.

SUMMARY

Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD8, and CD4 T cells were significantly lower in patients in whom chronic disease developed.

ACUTE HEPATITIS CAUSED BY THE HEPATITIS E VIRUS (HEV) IS ENDEMIC IN developing countries and appears to be an emerging disease in industrialized countries.[1,2] Seroprevalence studies have reported anti-HEV IgG antibodies in 6 to 16% of renal-transplant recipients.[3,4] This hepatotropic RNA virus is often not fully considered or routinely sought in cases of acute hepatitis in recipients of solid-organ transplants. Only three cases of acute HEV infection have been reported in organ-transplant recipients.[5-7] Even though two cases of persistent HEV infection have been reported,[8,9] HEV is considered an agent responsible for acute hepatitis that does not become chronic.[10]

We report here 14 cases of acute hepatitis E infection in organ-transplant recipients. We suggest that HEV infection may evolve to chronic hepatitis in immunocompromised patients.

From the Department of Nephrology, Dialysis, and Multiorgan Transplantation (N.K., L.O., J.G., O.C., L.E., D.D., L.R.) and INSERM Unité 858, IFR 31 (N.K., J.-M.P., Centre Hospitalier Universitaire, Rangueil, France; and the Departments of Histopathology (J.S., M.D.), Virology (J.-M.M., F.A., J.I.), and Hepatology (J.-M.P., J.-P.V.), and INSERM Unité 563, IFR 30 (F.A., J.I., L.R.), Centre Hospitalier Universitaire, Purpan — all in Toulouse, France. Address reprint requests to Dr. Kamar at the Department of Nephrology, Dialysis, and Multiorgan Transplantation, CHU Rangueil, TSA 50032, 31059 Toulouse CEDEX 9, France, or at kamar.n@chu-toulouse.fr.

N Engl J Med 2008;358:811-7.

PATIENTS AND METHODS

Between January 1, 2004, and December 31, 2006, all recipients of liver, kidney, or kidney and pancreas transplants attending our outpatient and inpatient clinics who presented with unexplained short-term elevations of liver-enzyme levels were screened for HEV infection by serologic and molecular tools. Patients chronically infected with hepatitis B, C, or D viruses were excluded from the study. Biliary-tract complications were ruled out by abdominal ultrasonography. Toxin- and drug-related causes of abnormal liver-function test results were ruled out by patient history. Fourteen of 217 patients (6.5%) tested positive for serum HEV RNA.

Kamar et al. N Engl J Med 2008; 358: 811-7

Complicaciones: Los pacientes inmunocomprometidos, infectados crónicamente por el VHE, pueden desarrollar enfermedad hepática progresiva con evolución a cirrosis.

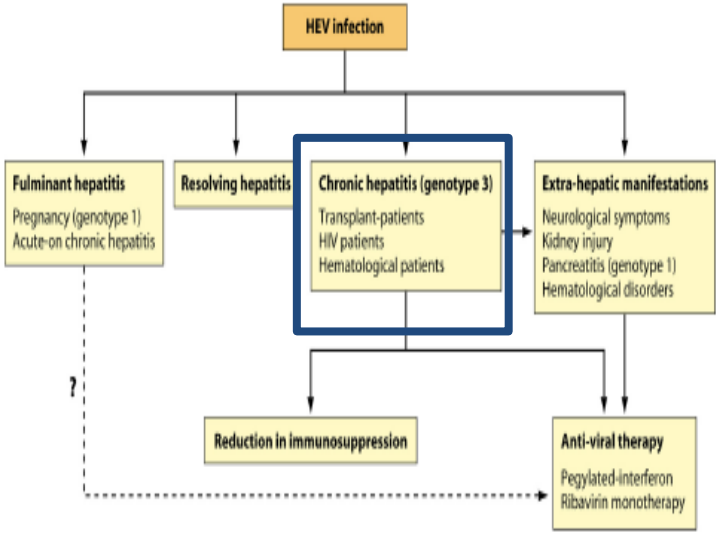

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

	Immunocompetent	Immunosuppressed
Presentation	Often symptomatic	Rarely symptomatic
ALT at diagnosis	≈1000–3000 IU/L	≈300 IU/L
HEV genotype	Genotype 1, 2, 3, or 4	Only genotype 3 HEV infection has been reported in this population
HEV diagnostics	Increase in IgG and IgM PCR is positive in 75%	Serological testing is unreliable, and seroconversion might never occur The diagnosis should be established by PCR
Outcome	Resolving hepatitis	Chronic infection occurs in 60% of patients, and 10% develop cirrhosis
Treatment	Ribavirin has been used in very few patients presenting with severe acute hepatitis	Interferon-α and ribavirin are effective treatments for treating chronic HEV infection in this population; a 3-month course of ribavirin therapy is recommended

ALT=alanine transaminase. HEV=hepatitis E virus.

Table 1: Hepatitis E virus infection in immunocompetent and immunosuppressed patients

Kamar N et al. Lancet 2012; 379: 2477-88

Manifestaciones extra-hepáticas: Varias enfermedades extra-hepáticas, principalmente neurológicas, nefrológicas y hematológicas, han sido observadas en el contexto de la hepatitis E.

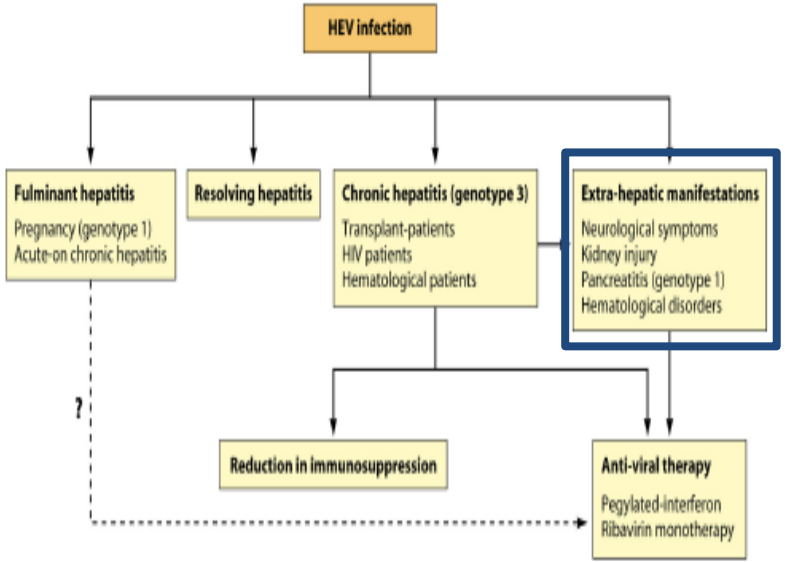

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

Box 1 | **Extrahepatic manifestations of HEV infection**

Neurological
- Guillain–Barré syndrome
- Neuralgic amyotrophy
- Encephalitis/myelitis
- Mononeuritis multiplex*
- Myositis*
- Vestibular neuritis*
- Bell palsy*

Haematological[4,98]
- Thrombocytopenia
- Lymphopenia
- Monoclonal immunoglobulin*
- Cryoglobulinaemia*[99]

Nephrological
- Glomerulonephritis[100]

Other
- Acute pancreatitis[101]
- Arthritis*[102]
- Autoimmune thyroiditis*[103]

HEV, hepatitis E virus. *Causal association not proven.

Dalton HR et al. Nat Rev Neurol 2016; 12: 77-85

Tratamiento: El tratamiento en la hepatitis E crónica y de las complicaciones de la hepatitis E aguda se fundamente principalmente en el uso de la Ribavirina, que es por ahora el tratamiento de elección.

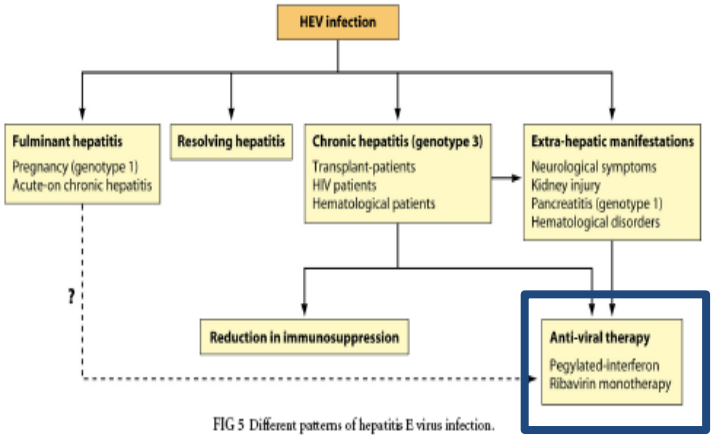

FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014; 27: 116-138

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.

Khuroo MS et al. World J Gastroenterol 2016; 22: 7030-45

PREVENCIÓN

Prevención: La prevención de la infección por el VHE en el mundo es problemática debido al elevado número, de reservorios y posibles vías de transmisión.

2015, 90, 185–200 No. 18

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

1ST MAY 2015, 90th YEAR / 1er MAI 2015, 90e ANNÉE
No. 18, 2015, 90, 185–200
http://www.who.int/wer

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Hepatitis E vaccine: WHO position paper, May 2015

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on the diseases and respective vaccines, and conclude with the current WHO position concerning their use in the global context.

The papers are reviewed by external experts and WHO staff, and reviewed and endorsed by the WHO Strategic Advisory Group of Experts on immunization (SAGE) (http://www.who.int/immunization/sage/en/). The GRADE methodology is used to systematically assess the quality of available evidence. A description of the process followed for the development of vaccine position papers is available at: http://www.who.int/immunization/position_papers/position_paper_process.pdf.

The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, the medical community, scientific media and the public.

This is the first WHO position paper on hepatitis E vaccination. It focuses primarily on the available evidence concerning the only hepatitis E vaccine that is currently licensed. Recommendations on the use of this hepatitis E vaccine were discussed by SAGE in October 2014; evidence presented at this meeting can be

Note de synthèse: position de l'OMS à propos du vaccin contre l'hépatite E, mai 2015

Introduction

Conformément à son mandat qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales utilisables contre les maladies qui ont une incidence sur la santé publique internationale. Ces notes, qui portent essentiellement sur l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations générales essentielles sur les maladies et les vaccins associés, et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins dans le contexte mondial.

Ces notes sont examinées par des experts externes et des membres du personnel de l'OMS, puis évaluées et approuvées par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE) de l'OMS (http://www.who.int/immunization/sage/fr). La méthodologie GRADE est utilisée pour évaluer de manière systématique la qualité des éléments disponibles. Une description des procédures suivies pour l'élaboration de ces notes se trouve à l'adresse: http://www.who.int/immunization/position_papers/position_paper_process.pdf.

Les notes de synthèse de l'OMS s'adressent avant tout aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination, mais elles peuvent également présenter un intérêt pour les organismes internationaux de financement, les groupes consultatifs sur la vaccination, les fabricants de vaccins, le corps médical, les médias scientifiques et le grand public.

Le présent document est la première note de synthèse de l'OMS traitant de la vaccination contre l'hépatite E. Il porte essentiellement sur les données disponibles concernant le seul vaccin actuellement homologué contre l'hépatite E. Les recommandations relatives à l'utilisation de ce vaccin ont été examinées par le SAGE en octobre 2014; les éléments présentés

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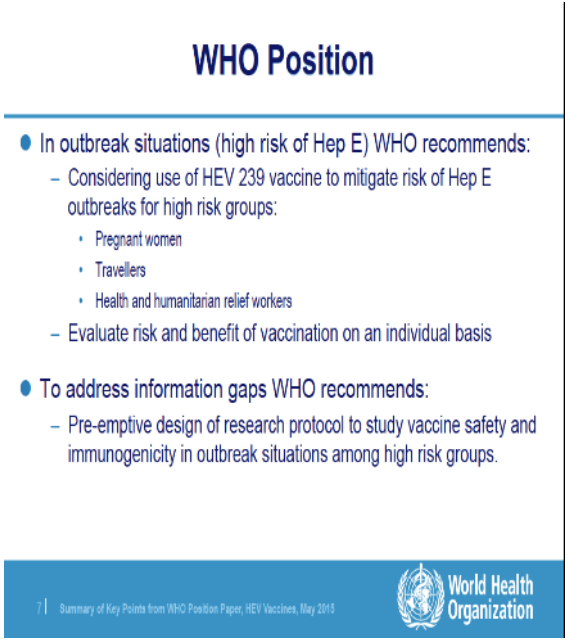


WHO Position

- In outbreak situations (high risk of Hep E) WHO recommends:
  - Considering use of HEV 239 vaccine to mitigate risk of Hep E outbreaks for high risk groups:
    - Pregnant women
    - Travellers
    - Health and humanitarian relief workers
  - Evaluate risk and benefit of vaccination on an individual basis
- To address information gaps WHO recommends:
  - Pre-emptive design of research protocol to study vaccine safety and immunogenicity in outbreak situations among high risk groups.

7 | Summary of Key Points from WHO Position Paper, HEV Vaccines, May 2015

World Health Organization

WHO. Wkly Epidemiol Rec 2014, 89, 325-35.

DIAGNÓSTICO

Diagnostico diferencial: El diagnóstico diferencial de la hepatitis E es importante en todos los casos de hepatitis aguda y crónica, en convivientes con pacientes infectados, en donantes de órganos sólidos, en pacientes con manifestaciones extra-hepáticas características y también en las hepatitis medicamentosas y autoinmunes.

Table 2. Differential diagnosis and testing algorithms for HEV

a Differential diagnosis

Causes of jaundice and a serum ALT >300 IU/l	Drug-induced liver injury Liver metastases Autoimmune hepatitis Acute HEV infection Seronegative hepatitis Epstein Barr virus hepatitis Acute HBV HAV Acute HCV Cytomegalovirus hepatitis
Causes of an ALT 100–300 IU/l in immunosuppressed transplant recipients (developed countries)	Graft rejection 'DILI' Recurrence of primary liver pathology Graft versus host disease Intercurrent infections, e.g. sepsis Chronic HEV Chronic Epstein Barr virus and Cytomegalovirus

b Suggested testing algorithm for HEV

Immunologic status	Patients who should be tested for HEV
Immunocompetent	ALT >300 IU/l 'DILI' Decompensated chronic liver disease* Guillain-Barré syndrome* Neuralgic amyotrophy* Patients with unexplained acute neurology and a raised ALT**
Immunocompromised (developed countries)	As above Persistently abnormal ALT*** Yearly PCR

ALT >300 IU/l is only a guide. Patients with lower ALT's should be tested when otherwise clinically indicated. Testing should include a combination of serological and PCR assays. In the immunocompromised PCR should always be done, as serologic assays are less reliable in this group of patients.
* Testing should be done at disease onset, irrespective of ALT results.
** Testing should be done at disease onset, if ALT is abnormal.
*** If the ALT is above the limit of normal on 2 or more occasions, the patient should be tested for HEV.

Dalton HR et al. Dig Dis 2016; 34: 308-16

Diagnóstico: microbiológico: **El diagnóstico de la infección producida por el VHE se puede hacer directamente mediante la detección del ARN viral o del AgVHE o bien indirectamente mediante la detección de los anticuerpos específicos procedentes de la respuesta inmune del huésped.**

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*[64], 2016. HEV: Hepatitis E virus; ICT: Immunochromatographic test; POCT: Point of care test; NAT: Nucleic acid test; EIA: Enzyme immunoassay.

Khuroo MS et al. World J Gastroenterol 2016; 22: 7030-45

DIAGNÓSTICO DE LA INFECCIÓN POR EL VHE:
¿ES EL VERDADERO PROBLEMA?

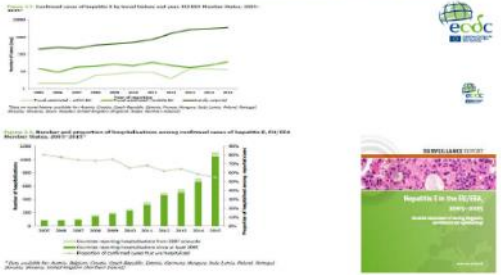
EUROPE'S NEW HEPATITIS PROBLEM

Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

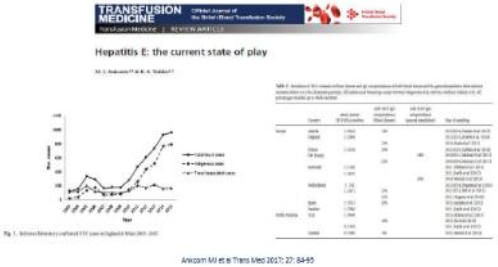
By **Kai Kupferschmidt**

Science 2016; 353: 862-863

Incremento en los casos diagnosticados de HEPATITIS E en la UE durante los últimos años



Existen datos significativos de prevalencia de la viremia por VHE y de seroprevalencia de Anti-VHE-IgG en donantes de sangre en diferentes paises de la UE



Ankcorn MJ et al Trans Med 2017; 27: 84-95

La infección por el VHE está infradiagnosticada

The Enigma of Hepatitis E Virus

Liza Bronner Murrison, PhD, MPH, and Kenneth E. Sherman, MD, PhD

Table 2. Diagnostic Opportunities and Errors

Clinical Situation	HEV Infection Misdiagnosis
Subclinical infection: patient does not seek care	No diagnosis made
Symptomatic infection; practitioner does not consider HEV infection	Non-HEV diagnosis
Indistinguishable acute HEV infection	Acute hepatitis, cause unknown Chronic liver disease (in a patient with known chronic liver disease) Flare of disease in a patient with chronic autoimmune hepatitis[27] Acute liver injury[26] Liver injury from a drug etiology[28]
Chronic HEV infection	Chronic liver disease due to HBV or HCV Chronic liver disease due to HBV/HIV or HCV/HIV coinfection[18] Autoimmune hepatitis[18] Idiopathic hepatitis[18] Acute cryptogenic hepatitis[18,21] Acute cellular rejection
HEV-induced neuralgic amyotrophy	Neuralgic amyotrophy[75]
HEV-associated Guillain-Barre syndrome	Guillain-Barre syndrome, unknown etiology

HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus.

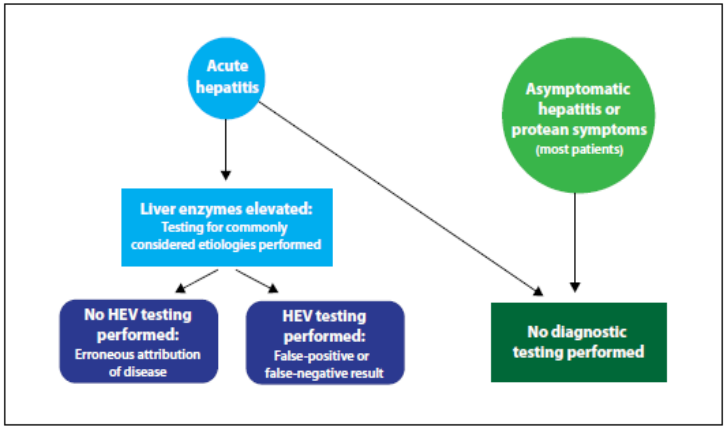


Figure. A flowchart showing the reasons clinicians may fail to diagnose HEV infection.

HEV, hepatitis E virus.

Murrison LB et al. Gastroenterol Hepatol 2017; 13: 484-91.

Causas: Presentación clínica frecuentemente asintomática, un diagnóstico diferencial erróneo y un diagnóstico microbiológico difícil y exigente.

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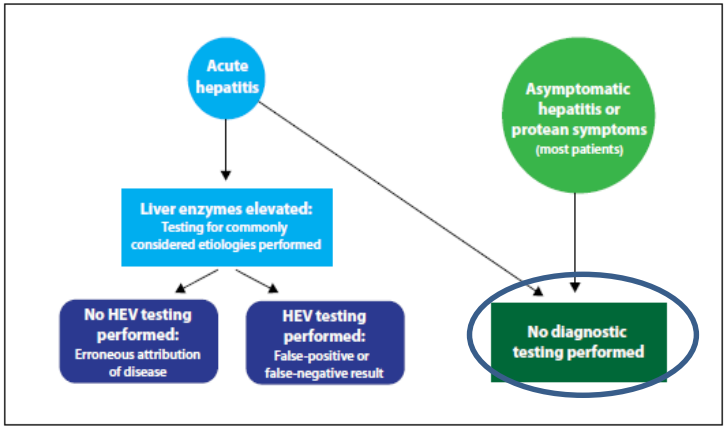

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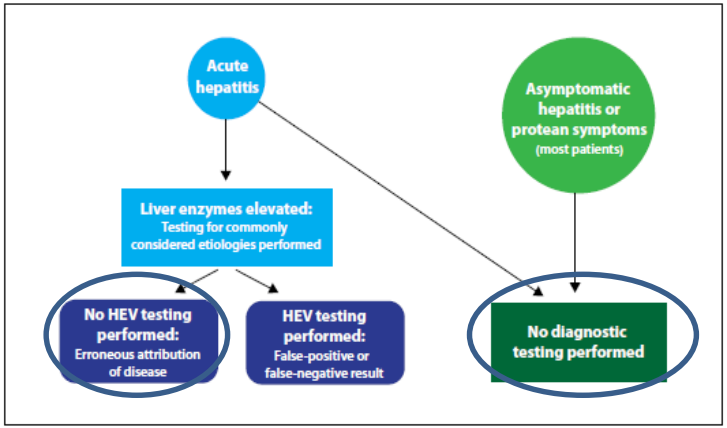

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HEV-associated Guillain-Barre syndrome	Guillain-Barre syndrome, unknown etiology

HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus.

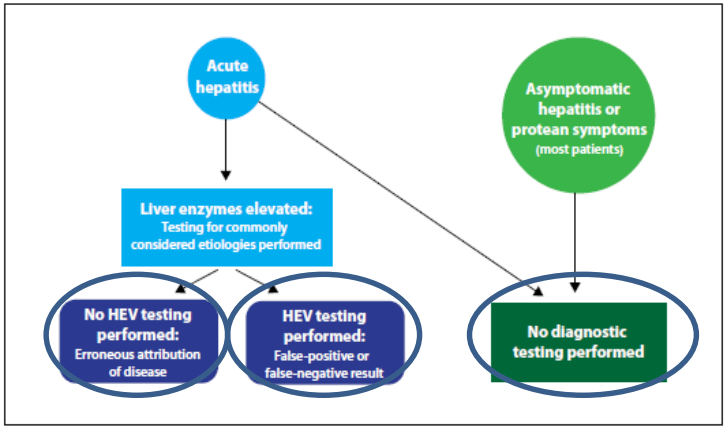

Figure. A flowchart showing the reasons clinicians may fail to diagnose HEV infection.

HEV, hepatitis E virus.

Murrison LB et al. Gastroenterol Hepatol 2017; 13: 484-91.

DIAGNÓSTICO DE LA INFECCIÓN POR EL VHE:
DIAGNÓSTICO DIFERENCIAL ERRÓNEO

GPC para el manejo de la Hepatitis E publicadas en 2018

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on hepatitis E virus infection☆

European Association for the Study of the Liver*

Summary

Infection with hepatitis E virus (HEV) is a significant cause of morbidity and mortality, representing an important global health problem. Our understanding of HEV has changed completely over the past decade. Previously, HEV was thought to be limited to certain developing countries. We now know that HEV is endemic in most high-income countries and is largely a zoonotic infection. Given the paradigm shift in our understanding of zoonotic HEV and that locally acquired HEV is now the commonest cause of acute viral hepatitis in many European countries, the focus of these Clinical Practice Guidelines will be on HEV genotype 3 (and 4).

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Introduction

As a cause of significant morbidity and mortality, infection with hepatitis E virus (HEV) represents an important global public health problem. The European Association for the Study of Liver (EASL) invited a panel of experts in the field to develop Clinical Practice Guidelines (CPGs) with a particular focus on HEV genotype (gt) 3. The objective of these CPGs was not to draft a review article on hepatitis E but rather to define specific suggestions for the management of distinct features of HEV infection, even though the supporting evidence may be weak in many cases. In order to keep the manuscript and the reference list to a reasonable length, these CPGs frequently refer to previous review articles which summarise the evidence on distinct topics in more detail. In addition, despite the increasing knowledge, areas of uncertainty exist and unanswered questions should be defined. Therefore, clinicians, patients and public health authorities must continue to make choices on the basis of the evolving evidence.

Methodology

These EASL CPGs have been prepared by a panel of experts invited by the EASL Governing Board. The recommendations were approved by the EASL Governing Board. They are based as far as possible on evidence from existing publications and presentations at international meetings as well as, if evidence was unavailable, the experts' personal experiences and opinions. Wherever possible, the level of evidence and recommendation are cited. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[1] Thus, the strength of recommendations reflects the quality of underlying evidence. The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Thus, the recommendations consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. It must be noted that only the review of literature was used to inform recommendations. Other criteria or support of recommendations (e.g. feasibility, acceptability, or cost-effectiveness were not considered (Table 1).

Background

HEV was discovered in the early 1980s. At that time, Soviet troops in Afghanistan were affected by large outbreaks of unexplained hepatitis (testing negative for hepatitis A virus [HAV] and hepatitis B virus [HBV]). A pooled sample of affected soldiers' stool was ingested by a Russian scientist. He developed a brisk hepatitis, and a new virus was found in his stool by electron microscopy.[2] Subsequently the viral genome was cloned and named HEV.[3]

Term	Definition
HEV	Hepatitis E virus
HEV infection	Infection caused by HEV which is either symptomatic or asymptomatic, including extrahepatic manifestations (e.g. neurological)
Hepatitis E	Clinical or biochemical evidence of hepatitis caused by HEV
Extrahepatic	Damage to tissues/organs outside the liver associated withcaused by HEV (see Table 2)
SVR	Sustained virologic response
R_e	The basic reproductive rate This term equates to the number of individuals infected by an index case with an infectious disease. If R_e is >1 then the infection will spread through a naïve population. The R_e of HEV in the pig population is up to 8. This means that HEV is highly infectious in the pig population, to a similar extent to measles in a measles naïve human population

* Clinical practice guidelines panel: Chair: Harry R. Dalton; Panel members: Nassim Kamar, Sally A. Baylis, Darius Moradpour, Heiner Wedemeyer; EASL Governing Board representative: Francesco Negro.

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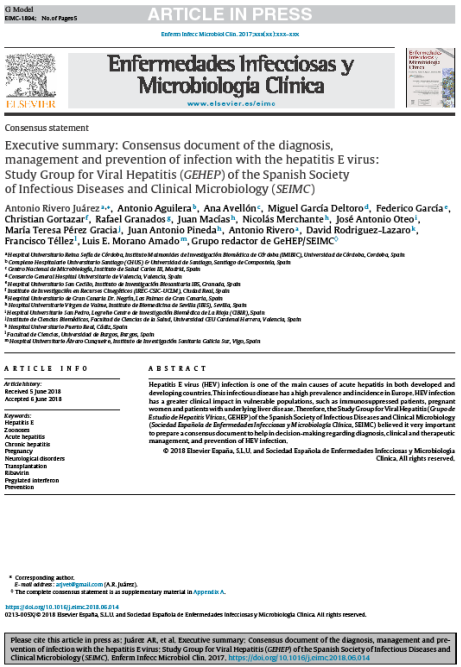
EASL. J Hepatol 2018; 68.1256-71



CJ Model
EIMC-1804; No. of Pages 5
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Enferm Infecc Microbiol Clin. 2017;xxx(xx):xxx–xxx

Enfermedades Infecciosas y Microbiología Clínica
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Consensus statement

Executive summary: Consensus document of the diagnosis, management and prevention of infection with the hepatitis E virus: Study Group for Viral Hepatitis (*GEHEP*) of the Spanish Society of Infectious Diseases and Clinical Microbiology (*SEIMC*)

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ABSTRACT

Hepatitis E virus (HEV) infection is one of the main causes of acute hepatitis in both developed and developing countries. This infectious disease has a high prevalence and incidence in Europe. HEV infection has a greater clinical impact in vulnerable populations, such as immunosuppressed patients, pregnant women and patients with underlying liver disease. Therefore, the Study Group for Viral Hepatitis (*Grupo de Estudio de Hepatitis Víricas*, GEHEP) of the Spanish Society of Infectious Diseases and Clinical Microbiology (*Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica*, SEIMC) believed it very important to prepare a consensus document to help in decision-making regarding diagnosis, clinical and therapeutic management, and prevention of HEV infection.

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† The complete consensus statement is as supplementary material in Appendix A.

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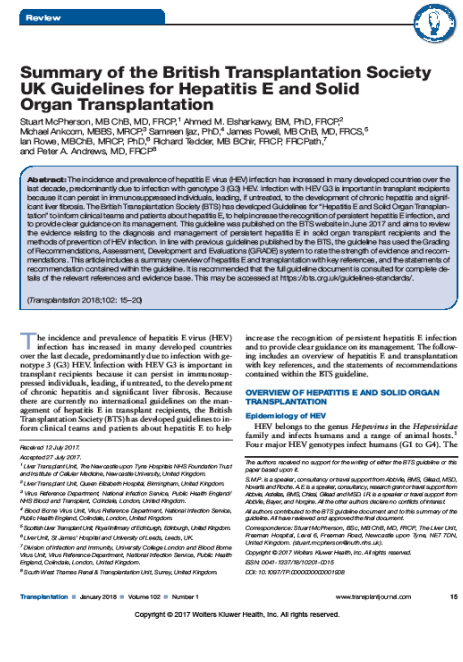
Rivero-Juárez A et al. Enferm Infecc Microbiol Clin 2018; doi: 10.1016/j.eimc.2018.06.014



Review

Summary of the British Transplantation Society UK Guidelines for Hepatitis E and Solid Organ Transplantation

Stuart McPherson, MB ChB, MD, FRCP,[1] Ahmed M. Elsharkawy, BM, PhD, FRCP,[2] Michael Ankcorn, MBBS, MRCP,[3] Samreen Ijaz, PhD,[4] James Powell, MB ChB, MD, FRCS,[5] Ian Rowe, MBChB, MRCP, PhD,[6] Richard Tedder, MB BChir, FRCP, FRCPath,[7] and Peter A. Andrews, MD, FRCP[8]

Abstract: The incidence and prevalence of hepatitis E virus (HEV) infection has increased in many developed countries over the last decade, predominantly due to infection with genotype 3 (G3). HEV infection with HEV G3 is important in transplant recipients because it can persist in immunosuppressed individuals, leading, if untreated, to the development of chronic hepatitis and significant liver fibrosis. The British Transplantation Society (BTS) has developed Guidelines for "Hepatitis E and Solid Organ Transplantation" to inform clinical teams and patients about hepatitis E, to help increase the recognition of persistent hepatitis E infection, and to provide clear guidance on its management. This guideline was published on the BTS website in June 2017 and aims to review the evidence relating to the diagnosis and management of persistent hepatitis E in solid organ transplant recipients and the methods of prevention of HEV infection. In line with previous guidelines published by the BTS, the guideline has used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system to rate the strength of evidence and recommendations. This article includes a summary overview of hepatitis E and transplantation with key references, and the statements of recommendation contained within the guideline. It is recommended that the full guideline document is consulted for complete details of the relevant references and evidence base. This may be accessed at https://bts.org.uk/guidelines-standards/.

(*Transplantation* 2018;102: 15–20)

The incidence and prevalence of hepatitis E virus (HEV) infection has increased in many developed countries over the last decade, predominantly due to infection with genotype 3 (G3) HEV. Infection with HEV G3 is important in transplant recipients because it can persist in immunosuppressed individuals, leading, if untreated, to the development of chronic hepatitis and significant liver fibrosis. Because there are currently no international guidelines on the management of hepatitis E in transplant recipients, the British Transplantation Society (BTS) has developed guidelines to inform clinical teams and patients about hepatitis E to help increase the recognition of persistent hepatitis E infection and to provide clear guidance on its management. The following includes an overview of hepatitis E and transplantation with key references, and the statements of recommendation contained within the BTS guideline.

OVERVIEW OF HEPATITIS E AND SOLID ORGAN TRANSPLANTATION

Epidemiology of HEV

HEV belongs to the genus *Hepevirus* in the *Hepeviridae* family and infects humans and a range of animal hosts.[1] Four major HEV genotypes infect humans (G1 to G4). The

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All authors contributed to the BTS guideline document and to the summary of the guideline. All have reviewed and approved the final document.
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McPherson S et al. Trasplantation 2018; 102:15-20

El documento de GEHEP/SEIMC para el manejo de la infección por el VHE se divide en cinco apartados

DOCUMENTO CONSENSO GEHEP/SEIMC MANEJO VHE	
¿QUIÉN DEBE DE SER CRIBADO FRENTE AL VHE?	1
¿CÓMO SE DIAGNOSTICA LA INFECCIÓN POR EL VHE?	2
¿A QUIÉN Y COMO TRATAR LA INFECCIÓN POR EL VHE?	3
¿CÓMO DEBEMOS HACER EL SEGUIMIENTO DE UN PACIENTE DIAGNÓSTICADO DE INFECCIÓN POR EL VHE?	4
¿QUÉ MEDIDAS DEBEMOS RECOMENDAR PARA PREVENIR LA INFECCIÓN POR EL VHE?	5

https;//www.seimc.org. Documento de Consenso VHE GeHEP:SEIMC

¿QUIÉN DEBE DE SER CRIBADO FRENTE AL VHE?		
Hepatitis aguda	*En todos los pacientes con hepatitis aguda se debe cribar la infección por VHE*	AII
	En todos los pacientes con FHA se debe se debe cribar la infección por VHE	AII
	En los pacientes con enfermedad hepática crónica conocida o de reciente diagnóstico con descompensación y/o datos sugestivos de inflamación hepática aguda, se debe hacer cribado del VHE	AII
Hepatitis crónica	*El cribado del VHE debe incluirse en la valoración de todo paciente con hepatitis crónica*	AII
	En pacientes con enfermedad hepática de origen incierto debe solicitarse el cribado del VHE	AII
Contactos o convivientes de pacientes infectados	*No se recomienda el estudio de los contactos cercanos a un caso con infección por VHE documentada, salvo que compartan exposición a la fuente de infección*	AII
Donantes de órgano sólido y donantes de sangre	*Se recomienda realizar cribaje del VHE en todos los donantes de órganos, vivos y fallecidos*	AII
	Se recomienda la realización de estudios de prevalencia de infección por VHE en donaciones de sangre en las distintas áreas de influencia de los bancos de sangre y adecuar las estrategias de cribado del VHE en cada área en función de la prevalencia de infección por VHE en las mismas	AII
Paciente con manifestaciones extrahepáticas	*En los pacientes con cualquiera de las manifestaciones clínicas extrahepáticas que se han asociado con el VHE se recomienda el cribado de infección por VHE, incluso en ausencia de alteraciones hepáticas*	BII
Paciente con sospecha de hepatitis medicamentosa	*En pacientes con sospecha de hepatitis medicamentosa, se recomienda realizar el cribado del VHE*	BII

Tabla 1. Manifestaciones extrahepáticas de la infección por el VHE [61]

Pancreatitis aguda

Manifestaciones hematológicas:

- Trombopenia, hemólisis, anemia aplásica, crioglobulinemia, gammapatía monoclonal

Fenómenos autoinmunes:

- Glomerulonefritis membranosa, púrpura Henoch-Schönlein, artralgias, rash cutáneo

Síndromes neurológicos SNC:

- Mielitis aguda transversa
- Meningoencefalitis aguda
- Meningitis aséptica
- Neuralgia amiotrófica
- Pseudotumorcerebri
- Síndrome piramidal bilateral

Síndromes neurológicos SNP:

- Síndrome de Guillain-Barré
- Parálisis de nervios craneales
- Neuropatía periférica

Rivero-Juárez A et al. Enferm Infecc Microbiol Clin 2018; doi: 10.1016/j.eimc.2018.06.014

¿A QUIÉN Y COMO TRATAR LA INFECCIÓN POR EL VHE?		
Hepatitis aguda	*Debe considerarse el tratamiento antiviral para la hepatitis aguda E en aquellos pacientes con cirrosis hepática o inmunodepresión de cualquier causa*	**BII**
	En caso de indicarse tratamiento, este consistirá en RBV ajustada a peso (1000 mg si < 75 Kg o 1200 mg si > 75 Kg) durante 3 meses	**AII**
Hepatitis crónica	*En los pacientes con inmunodepresión farmacológica y hepatitis crónica por VHE debe reducirse o suspenderse el tratamiento inmunosupresor si la situación clínica lo permite y reevaluar la persistencia de ARN-VHE en sangre y heces a las 12 semanas*	**AII**
	En caso de persistencia de ARN-VHE tras la reducción de la inmunosupresión o en aquellos casos en los que esta medida no es factible, debe iniciarse tratamiento antiviral	**AII**
	En los pacientes inmunodeprimidos de causa no farmacológica, como por ejemplo los individuos infectados por el VIH, deberá considerarse el tratamiento antiviral desde el inicio	**AII**
	El tratamiento antiviral consistirá en la administración de RBV 600 mg al día durante 12 semanas	**AII**
	A las 4 semanas debe evaluarse la presencia de ARN-VHE en suero, debiéndose prolongar el tratamiento a las 24 semanas si la carga viral es positiva	**BII**
	Si la carga viral en semana 4 es negativa debe evaluarse la presencia de ARN-VHE en heces y suero a las 12 semanas del tratamiento pudiendo suspenderse este si se ha producido aclaramiento del VHE	**BII**
	En caso de persistencia viral, debe continuarse el tratamiento hasta completar 24 semanas	**BII**
	En todos los casos deberá evaluarse la presencia de ARN-VHE en heces y suero a las 12 semanas de finalización del tratamiento	**AII**
	En caso de ausencia de RVS tras un tratamiento previo de 12 semanas debe considerarse iniciar un nuevo tratamiento con RBV durante 24 semanas	**BIII**
	En aquellos pacientes con ausencia de RVS tras un tratamiento con RBV 24 semanas, no existen opciones actuales de tratamiento alternativas que puedan recomendarse, salvo interferón pegilado en el escenario concreto del trasplante hepático	**CIII**
Manifestaciones extrahepáticas	*Ante la sospecha de manifestaciones extra-hepáticas relacionadas con infección por el VHE puede considerarse el tratamiento antiviral con RBV siguiendo las mismas pautas que para la hepatitis E crónica*	**CIII**

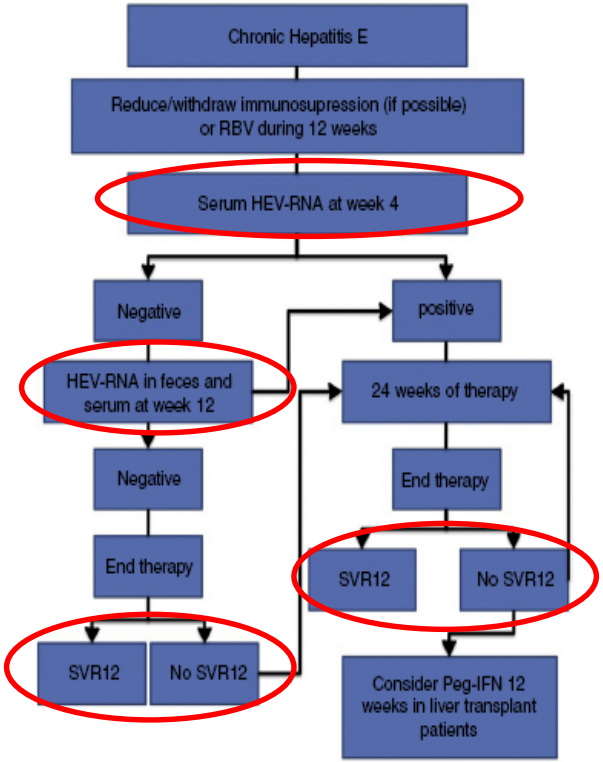


Fig. 1. Recommended management algorithm for the treatment of chronic hepatitis E.

Rivero-Juárez A et al. Enferm Infecc Microbiol Clin 2018; doi: 10.1016/j.eimc.2018.06.014

¿CÓMO DEBEMOS HACER EL SEGUIMIENTO DE UN PACIENTE DIAGNÓSTICADO DE INFECCIÓN POR EL VHE?

Infección aguda	*En pacientes inmunocompetentes con infección aguda por VHE se recomienda seguimiento durante 12 semanas y la determinación de ARN-VHE al final de este período*	AII
	En pacientes con infección aguda por VHE con evidencia clínica de insuficiencia hepática, se recomienda su ingreso en una unidad de cuidados intensivos e iniciar tratamiento frente al VHE	AIII
	En mujeres gestantes con infección aguda por VHE se recomienda la realización de controles analíticos de función hepática semanales y monitorización fetal estrecha bajo consejo ginecológico	AII
	Se debe recomendar la lactancia artificial en mujeres con infección aguda o crónica por el VHE	CIII
Infección crónica	*En pacientes con infección crónica por el VHE y RVS con inmunodepresión persistente se recomienda la realización de ARNVHE semestral durante el primer año.*	AII
	En aquellos pacientes inmunodeprimidos en los que tras alcanzar RVS se mantenga el riesgo de exposición al VHE (profesional...) se recomienda la determinación anual de ARN-VHE en sangre, dado el riesgo de reinfecciones	BII
	En pacientes con infección crónica por el VHE y con grado de fibrosis hepática F3 o F4, incluso tras alcanzar RVS, se recomienda la realización de controles ecográficos semestral de forma indefinida para despistaje de hepatocarcinoma.	CIII
Manifestaciones extrahepáticas	*En caso de manifestaciones extrahepáticas, se recomienda realizar tratamiento y seguimiento de la infección por VHE siguiendo las mismas recomendaciones citadas para la infección aguda o crónica según el caso*	CIII

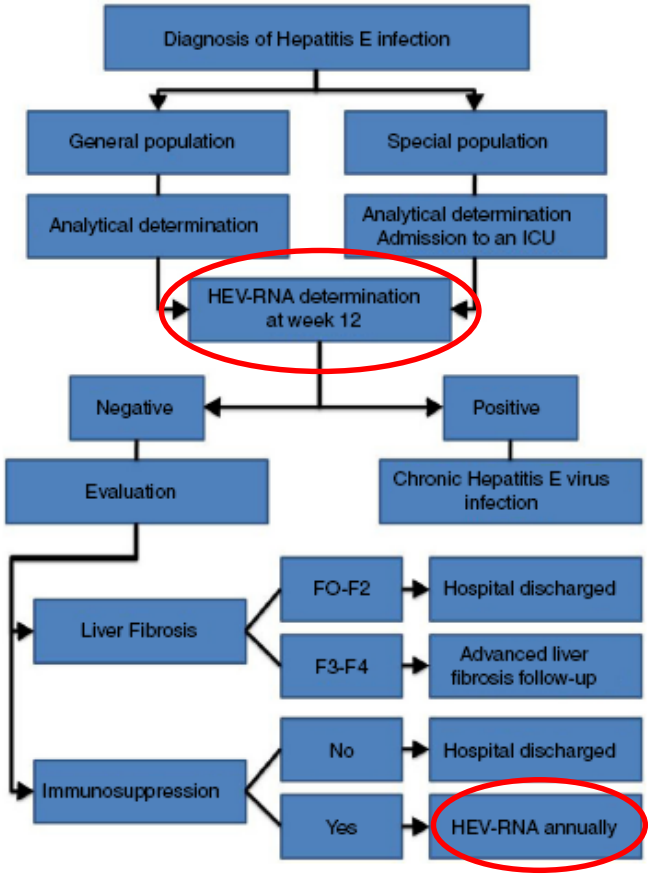


Fig. 2. Proposed algorithm for the management of HEV infection.

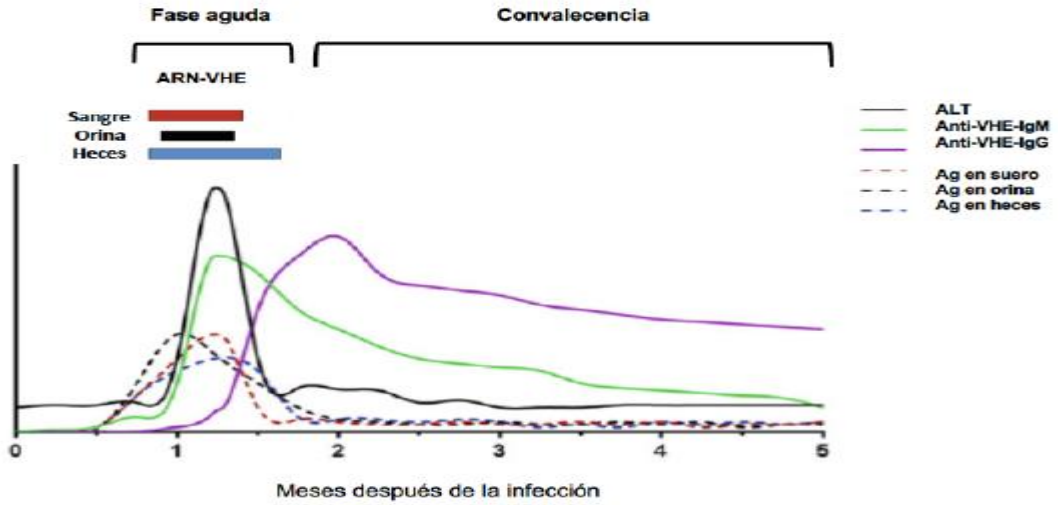
Rivero-Juárez A et al. Enferm Infecc Microbiol Clin 2018; doi: 10.1016/j.eimc.2018.06.014

DIAGNÓSTICO MICROBIOLÓGICO DE LA INFECCIÓN POR EL VHE:

DIFICIL Y EXIGENTE

Después del período de incubación, el ARN viral es detectable en sangre y heces antes de la aparición de los síntomas y durante un periodo de tiempo muy limitado. La respuesta inmune sigue el patrón típico de seroconversión con un aumento inicial y transitorio de IgM que da paso a una respuesta de IgG más sostenida.

Figura 1. Dinámica de marcadores serológicos y virológicos



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Métodos de diagnóstico directo: Los métodos más usados para el diagnostico directo de la infección por el VHE incluyen los ensayos serológicos de doble anticuerpo que detectan al Ag-VHE (pORF2) y los ensayos moleculares que detectan y/o cuantifican el ARN-VHE (ORF2 y ORF3), ambos disponibles comercialmente.

Métodos directos:

Detección del Ag-VHE (EIA doble anticuerpo)

Detección del ARN-VHE (RT-nPCR y RT-PCR tr,

Otros (IME, IHC y cultivo celular)

Khuroo MS et al. Viruses 2016; 8: E253

Métodos de diagnóstico indirecto: Los inmunoensayos enzimáticos que han sido comercializados para la detección de anticuerpos se basan en péptidos sintéticos o antígenos recombinantes de la región ORF2 y ORF3 procedentes del genotipo 1 del VHE, que pueden detectar la presencia de anticuerpos IgG e IgM inducidos por los 4 principales genotipos, ya que constituyen a su vez un sólo serotipo.

Khuroo MS et al. Viruses 2016; 8: E253

Métodos indirectos:

Detección de Anti-VHE-IgM (EIA captura, QL, IC)

Detección de Anti-VHE-IgG (EIA indirecto, QL)

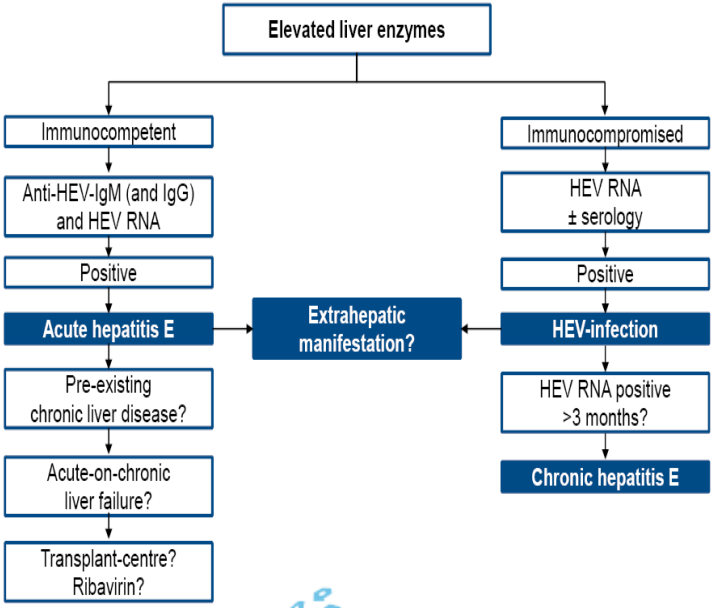
ALGORITMO DIAGNÓSTICO EN LA INFECCIÓN POR EL VHE

Cualquier algoritmo diagnóstico para la infección por el VHE se debe basar principalmente en la presencia de anticuerpos específicos Anti-VHE-IgM, y/o de los marcadores de infectividad Ag-VHE y ARN-VHE.

Table 2
Diagnostic algorithm for HEV infection.

Anti-HEV-IgM[a,c]	Positive			Negative			
HEV-RNA and/or HEV-Ag[b]	Positive	Negative		Positive		Negative	
Anti-HEV-IgG[a]		Positive	Negative	Positive	Negative	Positive	Negative
Interpretation	Acute infection Chronic infection (RNA+ >3 months)	Recent infection	Cross-reactivity[c]	Acute infection Possible reinfection	Window period Chronic infection (RNA+ >3 months)	Past infection	Absence of infection

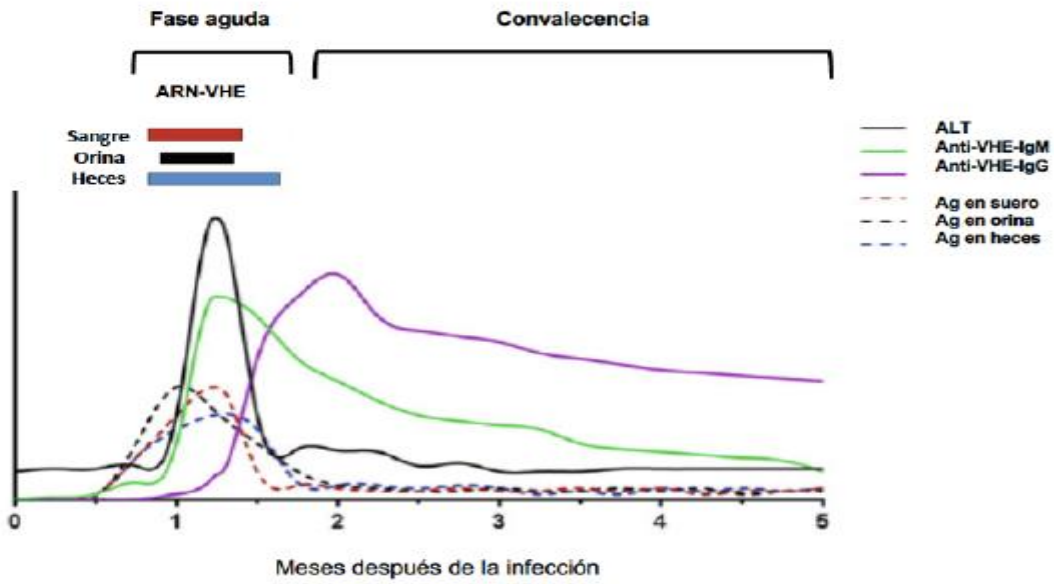
[a] Serum and/or plasma.
[b] Serum, plasma, CSF, faeces, urine, etc.
[c] Anti-HEV-IgM reactivity should be confirmed with immunoblotting and a subsequent seroconversion study.



DIFICULTADES Y EXIGENCIAS DIAGNÓSTICAS

VIREMIA DE CORTA DURACIÓN

Figura 1. Dinámica de marcadores serológicos y virológicos



https;//www.seimc.org. Documento de Consenso VHE GeHEP:SEIMC

Los ensayos moleculares para detectar y cuantificar el ARN-VHE presentan variabilidad en su rendimiento y precisan estandarización

Standardization of Hepatitis E Virus (HEV) Nucleic Acid Amplification Technique-Based Assays: an Initial Study To Evaluate a Panel of HEV Strains and Investigate Laboratory Performance▽†

Sally A. Baylis,* Kay-Martin Hanschmann, Johannes Blümel, and C. Micha Nübling on behalf of the HEV Collaborative Study Group‡

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Received 21 December 2010/Returned for modification 19 January 2011/Accepted 1 February 2011

TABLE 2. Qualitative analysis of the four HEV strains

Virus strain (genotype)	Nominal concn (log_{10} copies/ml)	% positive[a]
HRC-HE104 (3a)	6.2	96
	5.2	96
	4.2	92/88
	3.2	75/67
	2.2	38/25
	1.2	13/8
JRC-HE3 (3b)	6.4	96
	5.4	92
	4.4	92/88
	3.4	75/67
	2.4	58/33
	1.4	21/9
RKI (3f)	5.1	92
	4.1	75/71
	3.1	71/63
	2.1	33/25
	1.1	4
HRC-HE15 (4c)	5.0	92/88
	4.0	83
	3.0	50/38
	2.0	33/25
	1.0[b]	4/0

[a] For the number of positive test results, a best-case/worst-case percentage is reported for results reported as being simply positive or equivocal.

[b] Data were returned for a total number of 24 tests for each sample. However, in the case of sample 22 (genotype 4c), a false-positive result (as evidenced by the detection of an HEV genotype not represented in the panel) was reported by one laboratory and was not included during the calculation of percent positive results. A breakdown of the original data is shown in Tables S2 to S5 in the supplemental material.

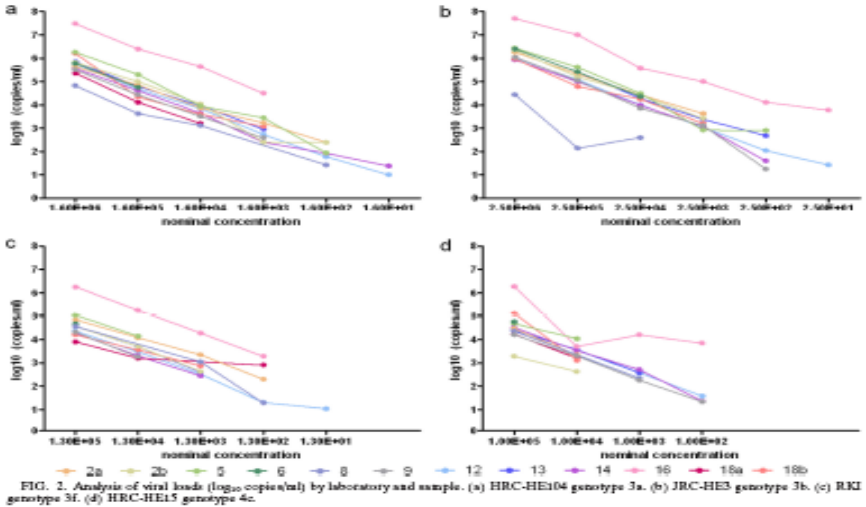


FIG. 2. Analysis of viral loads (log_{10} copies/ml) by laboratory and sample. (a) HRC-HE104 genotype 3a. (b) JRC-HE3 genotype 3b. (c) RKI genotype 3f. (d) HRC-HE15 genotype 4c.

Baylis SA et al. J Clin Microbiol 2011; 49: 1234-39.

JOURNAL OF MEDICAL MICROBIOLOGY

REVIEW
Al-Sadeq *et al.*, *Journal of Medical Microbiology* 2018;67:466–480
DOI 10.1099/jmm.0.000706

MICROBIOLOGY SOCIETY

Laboratory challenges in the diagnosis of hepatitis E virus

Duaa W. Al-Sadeq,[1]† Amin F. Majdalawieh,[2]† Areej G. Mesleh,[1] Omnya M. Abdalla[1] and Gheyath K. Nasrallah[1,3,*]

Al-Sadeq D et al . J Med Microbiol 2018; 67: 466-80

Virus Research 161 (2011) 84–92

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Review

Serological diagnostics of hepatitis E virus infection

Yury Khudyakov, Saleem Kamili *

Centers for Disease Control and Prevention, National Center for HIV/Hepatitis/STD/TB Prevention, Division of Viral Hepatitis, MS-A33/1600 Clifton Rd NE, Atlanta, GA 30333, United States

Khudiakov Y et al, Virus Res. 2011; 161: 84-92l.

En entornos de baja prevalencia, como en regiones de baja endemicidad y en pacientes con presentaciones atípicas, el VPP en los ensayos que detectan anticuerpos de tipo IgM frente al VHE sigue siendo deficiente.

Journal of Medical Virology 86:478–483 (2014)

Serological Cross Reactivity to CMV and EBV Causes Problems in the Diagnosis of Acute Hepatitis E Virus Infection

Catherine Hyams, Diana A. Mabayoje,* Ruth Copping, Desmond Maranao, Mauli Patel, Wendy Labbett, Tanzina Haque, and Daniel P. Webster
Department of Virology, Royal Free Hospital, London, United Kingdom

Hyams C et al . J Med Virol 2014; 86: 478-83

viruses

MDPI

Review

Hepatitis E Seroprevalence in Europe: A Meta-Analysis

Johannes Hartl [1,*], Benjamin Otto [1], Richie Guy Madden [2], Glynn Webb [2], Kathy Louise Woolson [2], Levente Kriston [3], Eik Vettorazzi [4], Ansgar W. Lohse [1], Harry Richard Dalton [2,†] and Sven Pischke [1,2,†]

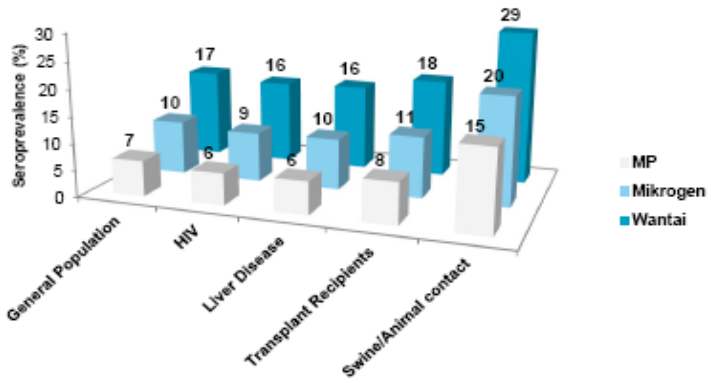


Figure 2. The relationship between anti-HEV IgG seroprevalence rates and the assay employed in different study cohorts. The difference between Wantai (WT) vs. Mikrogen (MG) and WT vs. MP was statistically significant after adjusting for study cohort (WT vs. MG: $p < 0.05$; WT vs. MP: $p < 0.001$).

Hartl J et al. Viruses 2016; 8, 211

Existe una elevada variabilidad en la sensibilidad y especificidad de los ensayos serológicos que detectan anticuerpos frente al VHE y que genera discrepancias en su interpretación

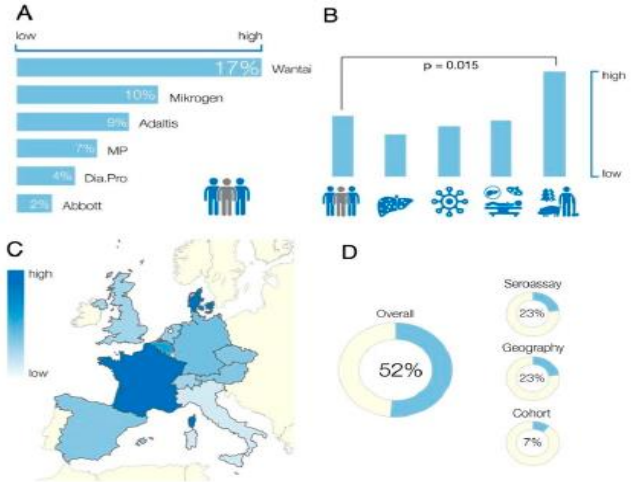


Figure 3. (A) Anti-HEV IgG seroprevalence rates in the general population dependent on the used seroassay; (B) comparison of estimated seroprevalence rates adjusted for patient cohort. Patient cohorts from left to right: general population, liver diseases, HIV infections, transplant recipients, swine/wild animal contact (farmers, veterinarians, slaughterhouse workers, forestry workers); (C) calculated anti-HEV seroprevalence in different European countries. Exact seroprevalence rates are displayed in Table 3; and (D) amount of heterogeneity explained by used seroassay, study cohort, and geographical location.

En las manifestaciones extra-hepáticas de la hepatitis E, la demostración y caracterización del ARN viral es esencial para atribuir el síndrome clínico a la infección por VHE y demostrar su grado de causalidad

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dky052

Meningitis due to autochthonous acute infection with hepatitis E virus in a chef: a case report

Emilio Rodríguez-Castro[1], Rocío Trastoy[2], Xiana Rodríguez-Osorio[1], María J. Domínguez-Santalla[3], Aida Fernández-Lebrero[1], José M. González-Alba[4] and Antonio Aguilera[2,5]*

[1]*Neurology Department, Complejo Hospitalario Universitario de Santiago de Compostela, Spain;* [2]*Microbiology Department, Complejo Hospitalario Universitario de Santiago de Compostela, Spain;* [3]*Internal Medicine Department, Complejo Hospitalario Universitario de Santiago de Compostela, Spain;* [4]*Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain;* [5]*Microbiology and Parasitology Department, Universidade de Santiago de Compostela, Spain*

*Corresponding author. Servicio de Microbiología, Complexo Hospitalario Universitario de Santiago de Compostela, Hospital de Conxo, Rua Ramon Baltar sn, 15705 Santiago de Compostela, Spain.
E-mail: antonio.aguilera.guirao@sergas.es

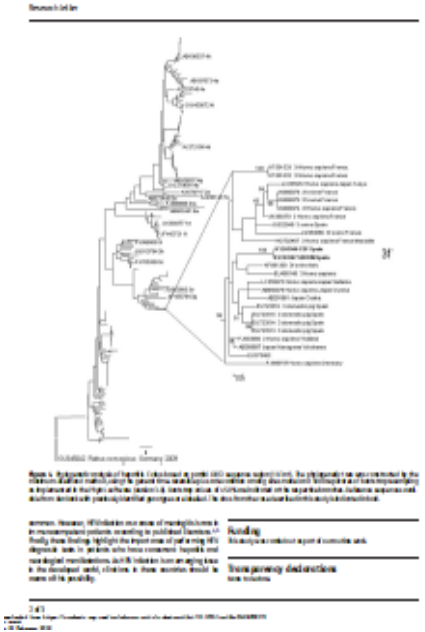
Sir,

Hepatitis E virus (HEV) is a well-known cause of acute hepatitis worldwide and a member of the genus Hepevirus in the Hepeviridae family.[1] In Western European countries, hepatitis E infection is an emerging disease, where an increasing number of autochthonous hepatitis E cases have been reported.[1] In these countries HEV infection is typically caused by genotype 3, mainly affects middle-aged or elderly males and is zoonotic with a porcine primary host.[1–3] HEV infection usually leads to acute hepatitis but it may evolve to a chronic state, especially in immunosuppressed individuals.[2] Like other viral hepatitis, several extra-hepatic manifestations have been described in association with hepatitis E, including neurological disorders such as Guillain–Barré Syndrome, neuralgic amyotrophy and encephalitis.[4–6] Herein, to our knowledge, we report for the first time in Spain a case where simultaneous acute hepatitis and meningitis occurred in a patient infected by HEV, and in whom HEV RNA was detected and characterized in serum and CSF.

A middle-aged patient, working as a chef in Galicia (in the northwest of Spain), was hospitalized due to a 3-day history of fever, arthralgia, myalgia and intense headache. He did not complain about earache, cough, expectoration, abdominal pain, nausea, vomiting, change in bowel habit or lower urinary tract symptoms. He denied recent trips abroad. Upon arrival he presented with a temperature of 37.4°C. General physical examination revealed the presence of hepatomegaly. The patient was fully conscious and oriented. Nuchal rigidity and Kernig's or Brudzinski's signs were absent. The rest of the neurological examination was also normal. At admission, blood tests detected slight neutrophilia without leucocytosis and elevation of AST (277 IU/L; reference 8–34 IU/L), ALT (441 IU/L; reference 9–38 IU/L) and GGT (344 IU/L; reference 9–38 IU/L). Coagulation tests were normal. Urinalysis showed no evidence of infection. Chest X-ray and brain computed tomography revealed no alterations. CSF examination showed a mild lymphocytic pleocytosis (34 cells/mm³; 95% lymphocytes; no red blood cells) with a slight hyperproteinorrachia (0.49 g/L, reference 0.15–0.45 g/L) and no glucose consumption.

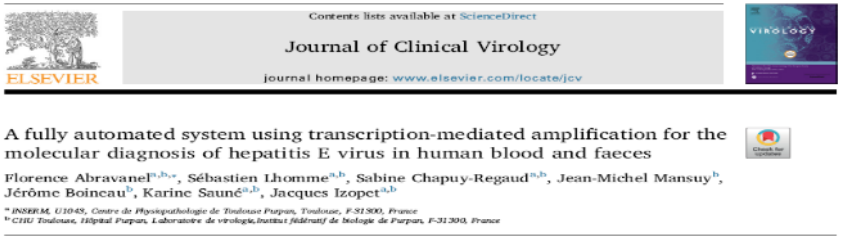
After 5 days of hospitalization significant worsening in blood tests was detected: AST 880 IU/L, ALT 2725 IU/L, GGT 607 IU/L and total bilirubin 1.3 mg/dL (reference 0.2–1.2 mg/dL). Abdominal ultrasound study showed severe hepatic steatosis and fibrosis, probably related to previous chronic and excessive alcohol consumption. Standard cultures of CSF remained negative and several infectious diseases responsible for neurological symptoms (Lyme disease, syphilis, mycoplasma, *Brucella*, *Coxiella*, *Leptospira*, HIV, herpesviruses, measles, mumps, parvovirus B19, enteroviruses) and acute hepatitides (hepatitis A, B, C) were excluded by nucleic acid and serology assays performed on serum and CSF. In contrast, HEV infection was diagnosed by detection of anti-HEV IgM [index >1.2; threshold value 1.0 in ELISA test (DIAPRO, Milan, Italy)] in serum and HEV RNA in serum and CSF. HEV RNA was recovered from CSF and serum by using in-house protocols of reverse transcription and nested PCR with a set of universal HEV PCR primers capable of detecting all four known genotypes.[7] The obtained products were confirmed by sequencing and these sequences (GenBank accession numbers KY203906 and KY203907 from CSF and serum, respectively) showed 100% nucleotide identity with each other and phylogenetic analysis identified genotype 3 subtype f (Figure 1), which is commonly found in autochthonous cases in western Spain.[8] The patient did not receive specific treatment and experienced a complete recovery without sequelae. Within 8 weeks, liver enzyme levels returned to their normal ranges and HEV RNA became undetectable both in serum and CSF.

In this case report, to our knowledge, we present the first case in Spain of an immunocompetent patient with simultaneous acute meningitis and hepatitis secondary to autochthonous HEV infection. Although the causality of HEV infection in non-hepatic manifestations might be a subject for discussion,[9] the exclusion of other possible aetiologies, the temporal association between meningitis and hepatitis and the HEV RNA detection in both serum and CSF, together support the causal relationship to HEV infection in our patient. There are several reported cases of neurological disorders secondary to HEV infection, concomitant with both acute and chronic hepatitis, and both in immunocompromised and immunocompetent patients.[4–6] The spectrum of manifestations is broad. Among them, peripheral nervous system disorders such as Guillain–Barré Syndrome and neuralgic amyotrophy are the most



Rodríguez-Castro E et al. J Antimicrob Chemother. 2018; 73:1726-28

El desarrollo de ensayos diagnósticos más fiables y estandarizados, debe de estar entre las principales prioridades en la investigación de la hepatitis E.

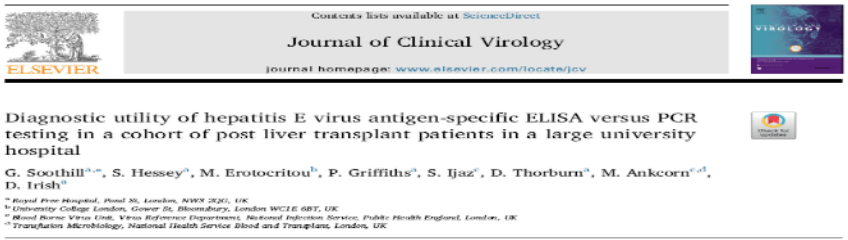

Contents lists available at ScienceDirect
Journal of Clinical Virology
journal homepage: www.elsevier.com/locate/jcv

A fully automated system using transcription-mediated amplification for the molecular diagnosis of hepatitis E virus in human blood and faeces

Florence Abravanel[a,b,*], Sébastien Lhomme[a,b], Sabine Chapuy-Regaud[a,b], Jean-Michel Mansuy[b], Jérôme Boineau[b], Karine Sauné[a,b], Jacques Izopet[a,b]

[a] INSERM, U1043, Centre de Physiopathologie de Toulouse Purpan, Toulouse, F-31300, France
[b] CHU Toulouse, Hôpital Purpan, Laboratoire de virologie, Institut fédératif de biologie de Purpan, F-31300, France

Abravanel F et al. J Clin Virol 2018; 105: 109-11


Contents lists available at ScienceDirect
Journal of Clinical Virology
journal homepage: www.elsevier.com/locate/jcv

Diagnostic utility of hepatitis E virus antigen-specific ELISA versus PCR testing in a cohort of post liver transplant patients in a large university hospital

G. Soothill[a,*], S. Hessey[a], M. Erotocritou[b], P. Griffiths[a], S. Ijaz[c], D. Thorburn[a], M. Ankcorn[c,d], D. Irish[a]

[a] Royal Free Hospital, Pond St, London, NW3 2QG, UK
[b] University College London, Gower St, Bloomsbury, London WC1E 6BT, UK
[c] Blood Borne Virus Unit, Virus Reference Department, National Infection Service, Public Health England, London, UK
[d] Transfusion Microbiology, National Health Service Blood and Transplant, London, UK

Soothill G et al. J Clin Virol 2018; 106: 44-8

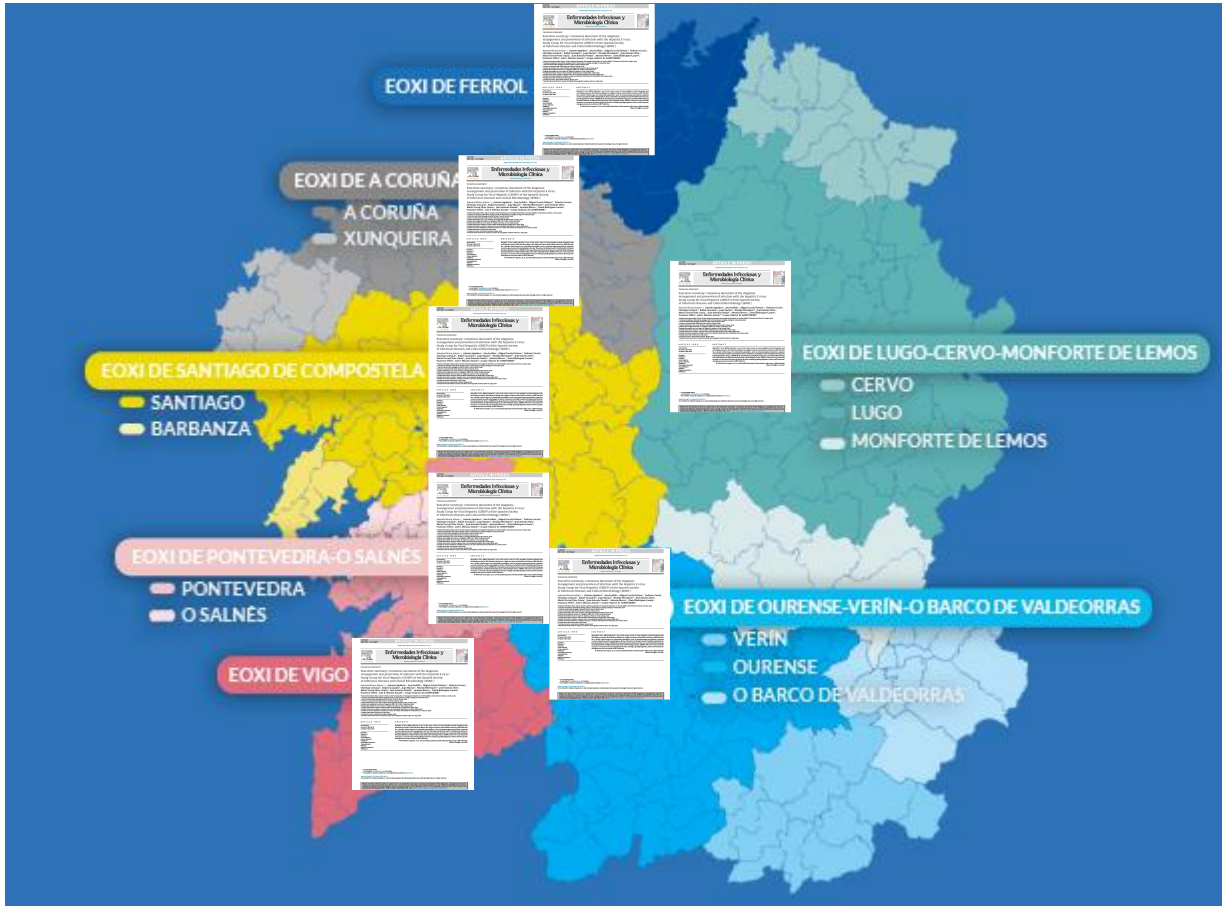
Se recomienda establecer o participar en sistemas de control de calidad basados en los estándares y reactivos de la OMS disponibles a tal efecto, para la estandarización de los diferentes resultados obtenidos en las técnicas moleculares y serológicas

Paul-Ehrlich-Institut

NIBSC
Confidence in Biological Medicines

SITUACIÓN EN GALICIA

Implementación generalizada del cribado del VHE en SNS de Galicia

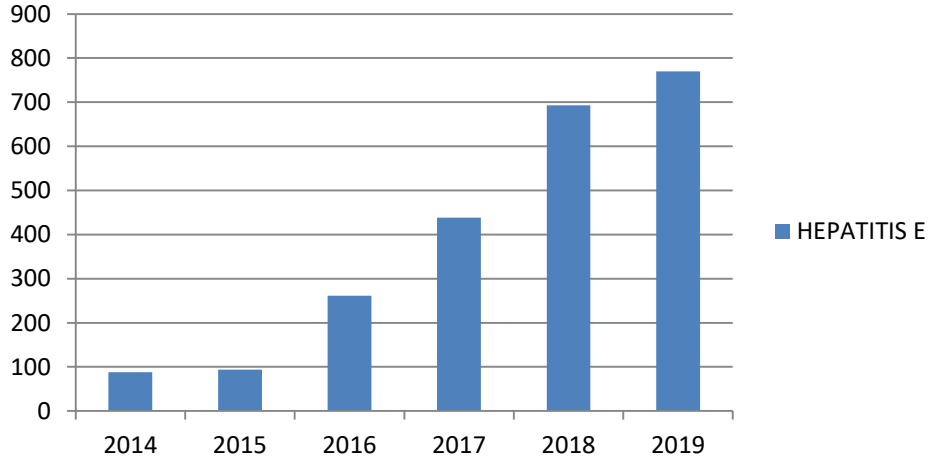


Aportación del experto

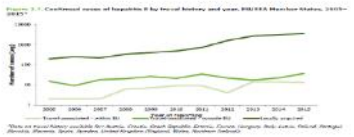
SERVIZO GALEGO de SAÚDE | Xerencia de Xestión Integrada de Santiago de Compostela
Santiago de Compostela

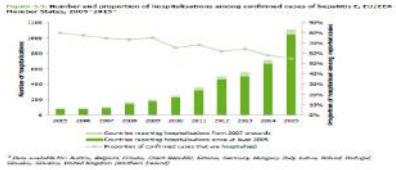
Incremento significativo del diagnóstico diferencial del VHE

DETERMINACIONES DE HEPATITIS E



Incremento en los casos diagnosticados de HEPATITIS E en la UE durante los últimos años





GPC para el manejo de la Hepatitis E publicadas en 2018

EASL J Hepatol 2018; 68:1256-71

Rivero-Juárez A et al. Enferm Infecc Microbiol Clin 2018; doi: 10.1016/j.eimc.2018.06.014

McPherson S et al. Transplantation 2018; 102:15-20

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Santiago de Compostela

Primer caso de meningitis por VHE en España

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dky052

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[1]*Neurology Department, Complejo Hospitalario Universitario de Santiago de Compostela, Spain;* [2]*Microbiology Department, Complejo Hospitalario Universitario de Santiago de Compostela, Spain;* [3]*Internal Medicine Department, Complejo Hospitalario Universitario de Santiago de Compostela, Spain;* [4]*Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain;* [5]*Microbiology and Parasitology Department, Universidade de Santiago de Compostela, Spain*

*Corresponding author. Servicio de Microbiología, Complexo Hospitalario Universitario de Santiago de Compostela, Hospital de Conxo, Rua Ramon Baltar sn, 15705 Santiago de Compostela, Spain.
E-mail: antonio.aguilera.guirao@sergas.es

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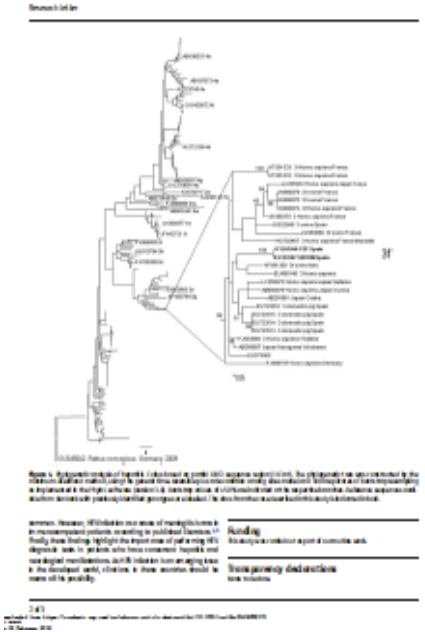


Rodríguez-Castro E et al. J Antimicrob Chemother. 2018; 73:1726-28

SERVIZO GALEGO de SAÚDE | Xerencia de Xestión Integrada de Santiago de Compostela
Santiago de Compostela

Primeros casos en España de hepatitis crónica E en trasplantados que han sido tratados

VHE

P-51. HEPATITIS E CRÓNICA EN EL TRASPLANTE DE ÓRGANO SÓLIDO: A PROPÓSITO DE UN CASO

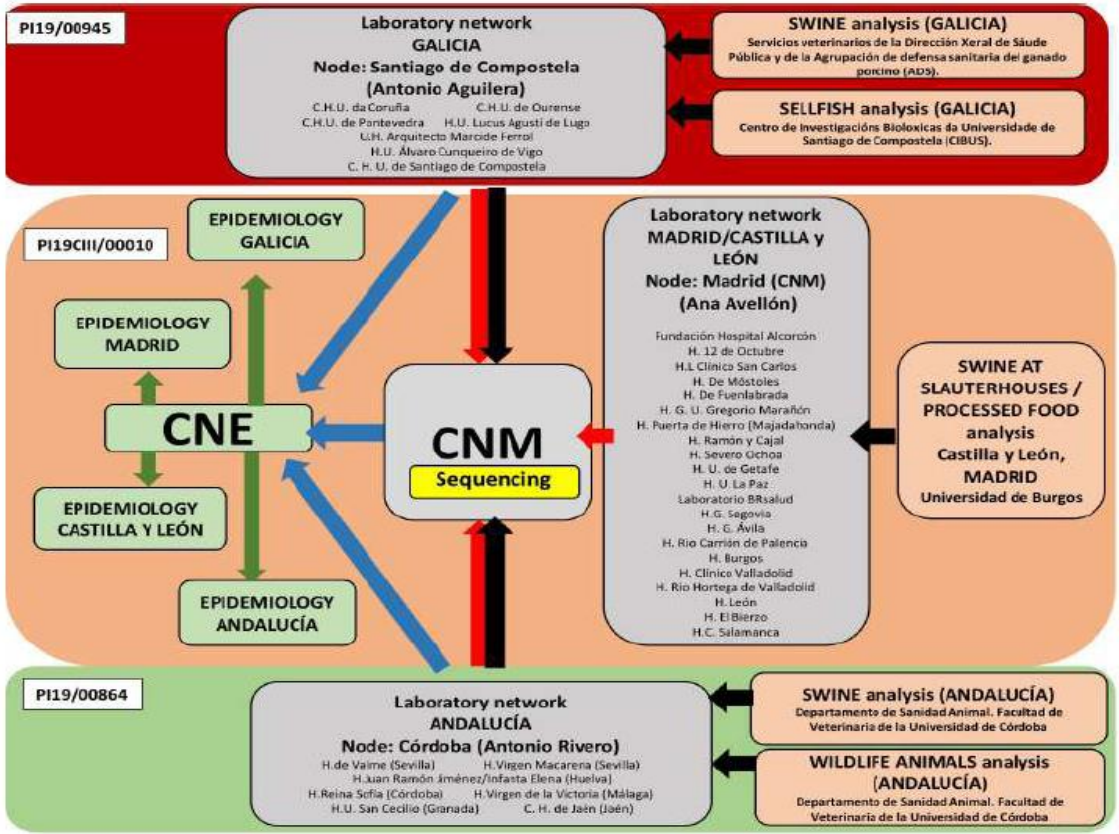
A. Aguilera[1], N. Vallejo[2], A. Vallejo[2], A.I. Díaz-Mareque[2], M. Rodríguez-Velasco[2], E. Molina[2] y A. Rivero-Juárez[3]

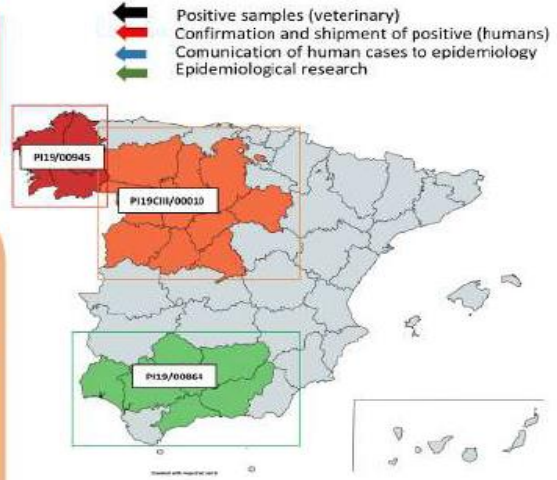
[1]Complexo Hospitalario Universitario de Santiago, Instituto de Investigación Sanitaria de Santiago, Santiago de Compostela; [2]Complexo Hospitalario Universitario de Santiago, Santiago de Compostela; [3]Hospital Universitario Reina Sofía. Instituto Maimónides de Investigación Biomédica, Córdoba.

Introducción: La infección crónica por el VHE, definida por la persistencia del ARN viral en suero o heces durante más de 6 meses, se ha descrito en pacientes inmunodeprimidos que habían recibido trasplante de órgano sólido y también en otras poblaciones de inmunodeprimidos, como pacientes oncohematológicos o infectados por el VIH. Los pacientes con hepatitis crónica E suelen estar asintomáticos e infectados principalmente por el genotipo 3.

Caso clínico: Paciente asintomático de 35 años, trasplantado renal desde hace seis, que presenta buen estado general pero con alteración de la bioquímica hepática mixta leve desde hace unos siete meses, siendo las analíticas previas normales y sin incidencias hepatobiliares, ni ictérica ni datos de coagulopatía. Desde el inicio de la alteración bioquímica se suspende la medicación que tomaba por sospecha de hepatitis medicamentosa, aunque no se observan cambios al respecto y continúa la ausencia de síntomas. La ecografía abdominal aporta datos de esteatosis hepática en hígado normofuncionante sin datos de fibrosis relevante y de etiología indeterminada, por lo que se remite a hepatología para valoración. Con los datos aportados por el laboratorio de microbiología se diagnostica de infección por el VHE con presencia de anticuerpos específicos IgG e IgM y ARN-VHE detectable, categorizada como "hepatitis crónica por VHE sin datos de

Red de investigación multidisciplinar en VHE





PROJECT TrazHE: TRACKING HEPATITIS E VIRUS INFECTION BY MEANS OF EPIDEMIOLOGICAL RESEARCH AND VIRAL WHOLE GENOME SEQUENCING.

CONSIDERACIONES FINALES

La hepatitis E ha llegado a la práctica clínica habitual para quedarse

Rat Hepatitis E Virus as Cause of Persistent Hepatitis after Liver Transplant

Siddharth Sridhar, Cyril C.Y. Yip, Shusheng Wu, Jianpiao Cai, Anna Jin-Xia Zhang, Kit-Hang Leung, Tom W.H. Chung, Jasper F.W. Chan, Wan-Mui Chan, Jade L.L. Teng, Rex K.H. Au-Yeung, Vincent C.C. Cheng, Honglin Chen, Susanna K.P. Lau, Patrick C.Y. Woo, Ning-Shao Xia, Chung-Mau Lo, Kwok-Yung Yuen

All hepatitis E virus (HEV) variants reported to infect humans belong to the species *Orthohepevirus A* (HEV-A). The zoonotic potential of the species *Orthohepevirus C* (HEV-C), which circulates in rats and is highly divergent from HEV-A, is unknown. We report a liver transplant recipient with hepatitis caused by HEV-C infection. We detected HEV-C RNA in multiple clinical samples and HEV-C antigen in the liver. The complete genome of the HEV-C isolate had 93.7% nt similarity to an HEV-C strain from Vietnam. The patient had preexisting HEV antibodies, which were not protective against HEV-C infection. Ribavirin was an effective treatment, resulting in resolution of hepatitis and clearance of HEV-C viremia. Testing for this zoonotic virus should be performed for immunocompromised and immunocompetent patients with unexplained hepatitis because routine hepatitis E diagnostic tests may miss HEV-C infection. HEV-C is also a potential threat to the blood product supply.

Hepatitis E virus (HEV) infects 20 million humans worldwide annually (*1*). HEV-infected persons usually have self-limiting acute hepatitis. However, persistent hepatitis can occur in HEV-infected immunocompromised patients who acquire infection by eating undercooked pork, rabbit, deer, camel, or boar meat (*2*–*6*). HEV transmission through blood product transfusion also has been described (*7*).

The diverse *Hepeviridae* family, which incorporates all HEV variants, includes members whose primary host species are terrestrial mammals (genus *Orthohepevirus*) and fish (genus *Piscihepevirus*) (*8*). The *Orthohepevirus* genus is classified into 4 species; HEV variants that have been reported to infect humans belong to *Orthohepevirus A* (HEV-A). Five genotypes within HEV-A (HEV-1–4 and -7) cause hepatitis in humans, and 3 genotypes (HEV-3, -4, and -7) can cause chronic hepatitis in immunocompromised patients after foodborne zoonotic transmission (*2*,*6*,*9*,*10*).

In addition to HEV-A, the *Orthohepevirus* genus includes 3 other species: *Orthohepevirus B* circulates in chickens, *Orthohepevirus C* (HEV-C) in rats and ferrets, and *Orthohepevirus D* in bats. HEV-C, also known as rat hepatitis E virus, shares only 50%–60% nt identity with HEV-A (*8*). The zoonotic potential of HEV-C is unknown; cases of clinical infection have not been reported. The substantial phylogenetic divergence between HEV-A and HEV-C, especially in critical receptor binding domains, forms a theoretical species barrier (*11*). Serologic and molecular tests for HEV are designed primarily to detect HEV-A, and they might miss HEV-C infections. Therefore, the threat to human health, including blood and organ supply safety, from HEV-C is unknown. We aimed to prove definitively that HEV-C can infect humans and describe the clinical, epidemiologic, genomic, and serologic features of this new zoonosis.

Materials and Methods

Study Population

We conducted this study in Queen Mary Hospital, a 1,700-bed tertiary care hospital in Hong Kong. We assessed 518 solid-organ transplant recipients (kidney, liver, lung, and heart transplant) who were followed up in Queen Mary Hospital for persistent biochemical hepatitis from January 1, 2014, or date of transplant (whichever date was later) through December 31, 2017. We defined persistent hepatitis as elevation of alanine aminotransferase (ALT) >1.5 times the upper limit of the reference level for a continuous period of ≥6 weeks. For patients whose ALT met this definition, we reviewed clinical records, ultrasonogram results, endoscopic retrograde cholangiopancreatography results, and laboratory results to identify the likely cause of hepatitis. We

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World's first human case of rat disease discovered

By Meera Senthilingam and Rob Picheta, CNN
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Man diagnosed with world's first human case of rat disease hepatitis E

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A 56-year-old man from Hong Kong has developed the world's first human case of rat hepatitis E, Chinese scientists announced Friday.

La correcta identificación y diagnóstico del VHE en los pacientes infectados tiene implicaciones importantes para el manejo de los mismos, para el control y prevención de la enfermedad y para la comprensión de su epidemiología

Gracias por su atención

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