HEPATITIS E

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Unidad de Hepatología y Trasplante Hepático

Hospital El Cruce

AGENDA

- ✓INTRODUCCION
  - Epidemiología
  - Características del HEV
- ✓CURSO CLINICO
  - Transmisión
  - Formas Clínicas
  - Manifestaciones Extrahepáticas
- ✓DIAGNOSTICO
- ✓TRATAMIENTO

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HEPATITIS E

- Primer brote en Nueva Delhi, India en 1955
- Segundo gran brote en Kashmir en 1978
- En 1983 durante una epidemia inexplicable de hepatitis aguda en soldados rusos en Afghanistan, fue descubierto el HEV
- Un miembro del equipo de pesquisa ingirió un reservorio de extracto fecal de los soldados infectados y desarrolló un cuadro de hepatitis aguda, el virus fue estudiado en heces y se encontraron partículas virales microscópicas del HEV
- Luego de este episodio, el genoma fue clonado y secuenciado a partir de muestras de bilis de monos infectados experimentalmente

Intervirology *20:* 23–31 (1983)

0300-5526/83/0201-0023$2.75/0

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

M. S. Balayan[a], *A. G. Andjaparidze*[a], *S. S. Savinskaya*[a], *E. S. Ketiladze*[b], *D. M. Braginsky*[b], *A. P. Savinov*[a], *V. F. Poleschuk*[a]

[a] Institute of Poliomyelitis and Viral Encephalitides, and
[b] D. I. Ivanovsky Institute of Virology, USSR Academy of Medical Sciences, Moscow, USSR

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.

A large waterborne viral hepatitis E epidemic in Kanpur, India

S.R. Naik,[1] R. Aggarwal,[2] P.N. Salunke,[3] & N.N. Mehrotra[4]

In 1991 the largest epidemic of viral hepatitis E yet reported occurred in Kanpur (population, 2.1 million), India. The incidence of icteric hepatitis from December 1990 to April 1991 among the inhabitants of 420 randomly sampled houses in seven of the city's 50 wards was 3.76% (138 out of 3666 individuals), i.e., an estimated 79 091 persons in the city as a whole were affected. The attack rate was higher for males than females (5.3% versus 3.3%; P = 0.013) and for adults than children aged <10 years (4.26% versus 1.29%; P = 0.0006). The incidence of hepatitis was higher in those city wards that were supplied with drinking-water consisting of a mixture of river Ganges and tubewell water than in those wards supplied only with tubewell water (5.6% versus 1.2%; P = 10^{-6}). In the mixed-water areas, the incidence decreased as the drinking-water source changed from only tap to both tap and handpump, to only handpump (7.8%, 6.8%, and 4.3% respectively; P = 0.023). None of the sera collected from 41 hepatitis patients during the epidemic showed evidence of hepatitis virus A or B.

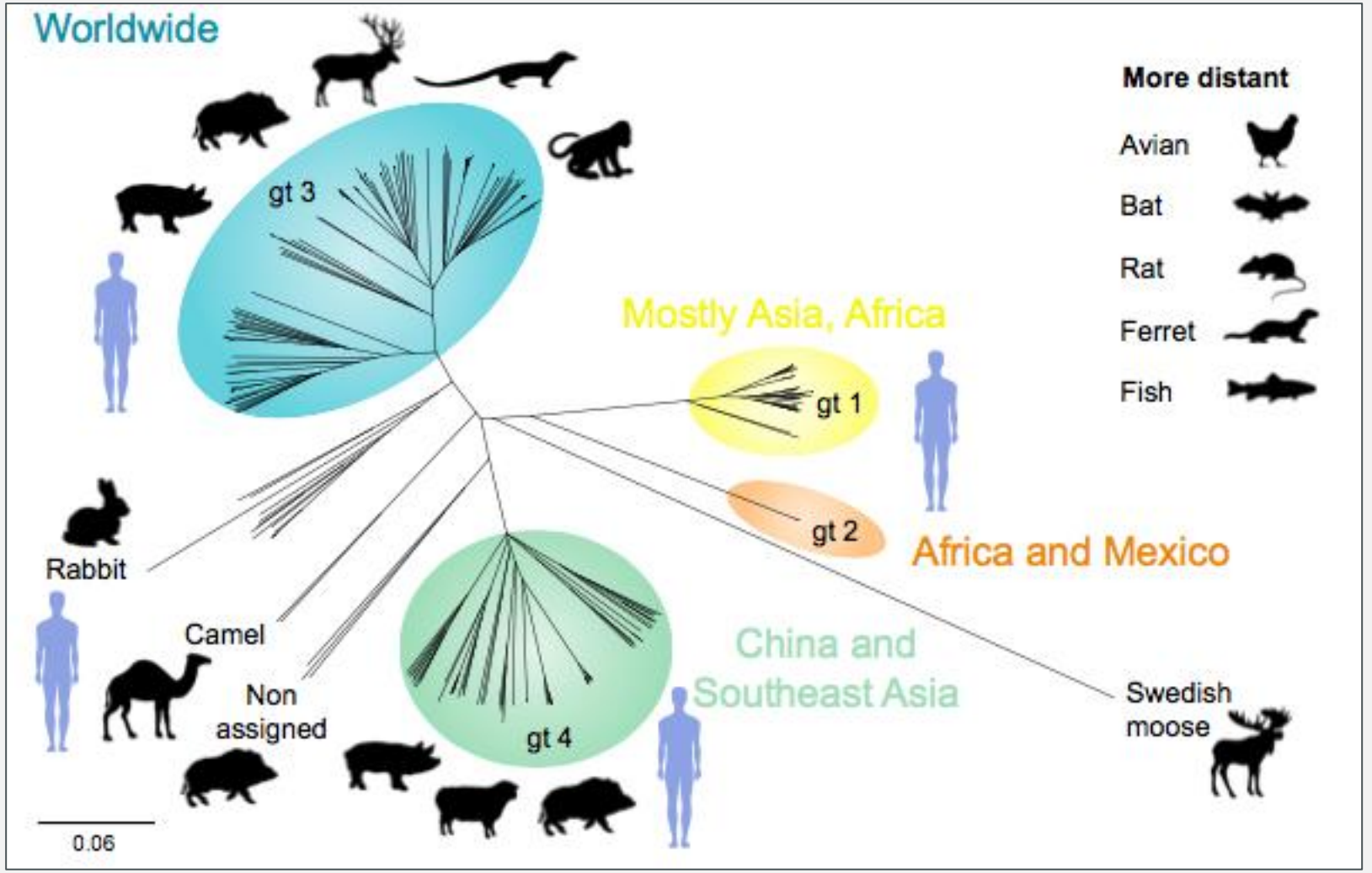
There were two peaks in the epidemic (in February and April 1991). The first peak was probably caused by faecal contamination of river water, indicated by water analysis data, and the second, by inadequate chlorination of water in a reservoir. There was no evidence of secondary intrafamilial spread.

Bulletin of the World Health Organization, **70** (5): 597–604 (1992)

HEPATITIS E

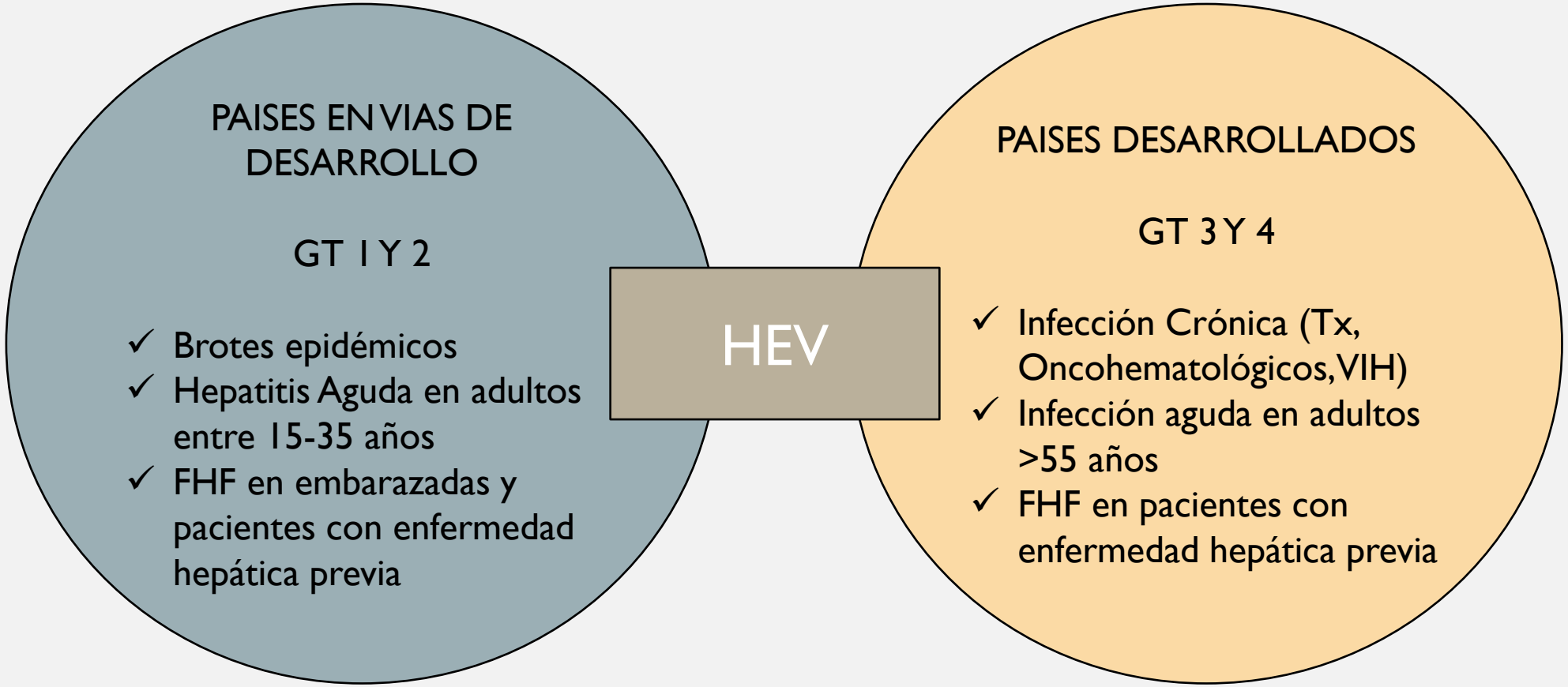
- Enfermedad infecciosa de distribución mundial causada por el virus de la hepatitis E (HEV)
- Virus RNA de la familia Hepeviridae con 1 serotipo y 8 genotipos descriptos
- Se estiman alrededor de 20 millones de nuevos casos en el mundo/año y alrededor de 70000 muertes/año
- Cambio de paradigma en las últimas décadas
- Puede manifestarse con curso agudo o crónico dependiendo del patrón de distribución del virus

ARBOL FILOGENETICO DEL HEV

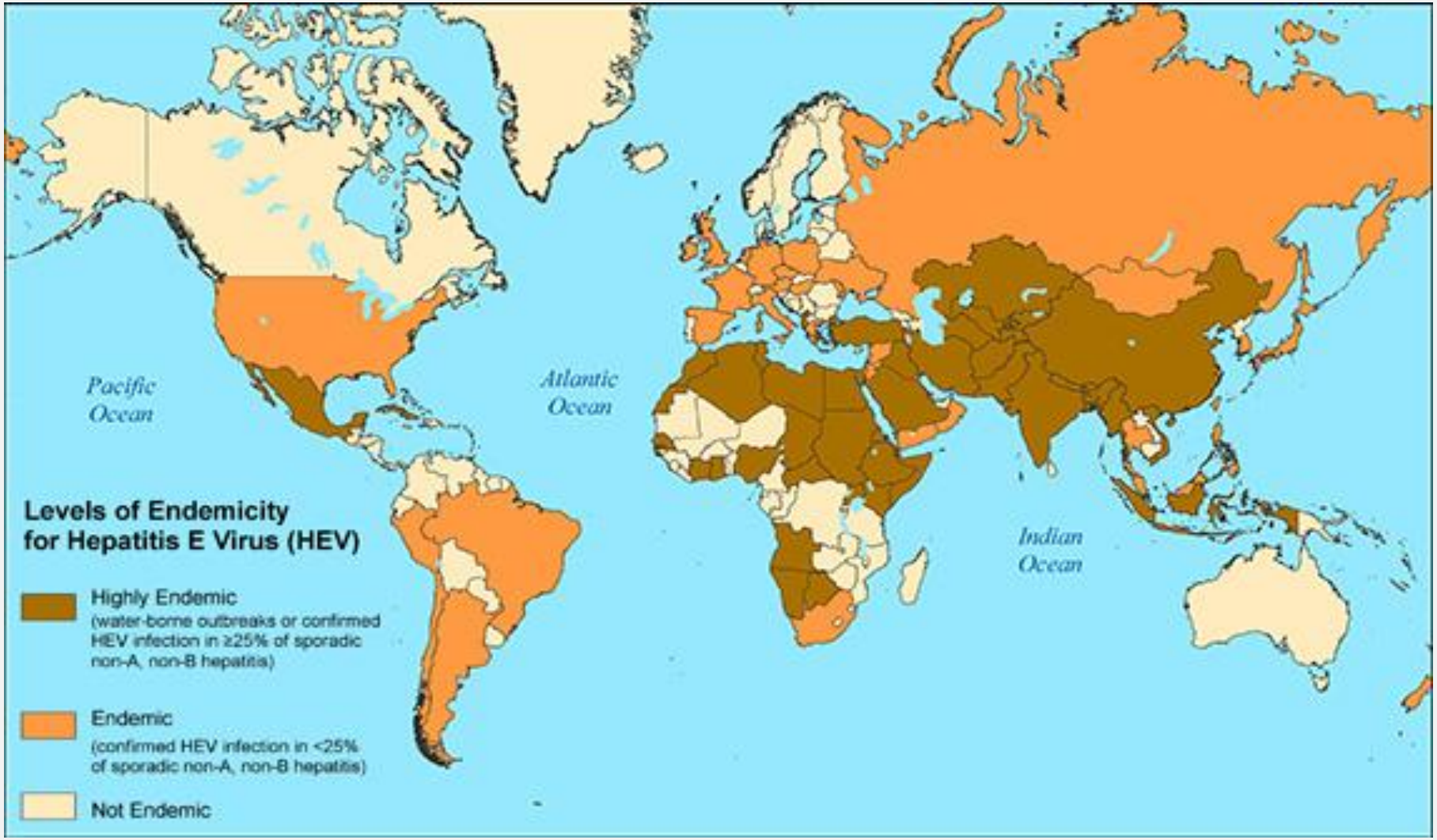


Debing et al, 2016

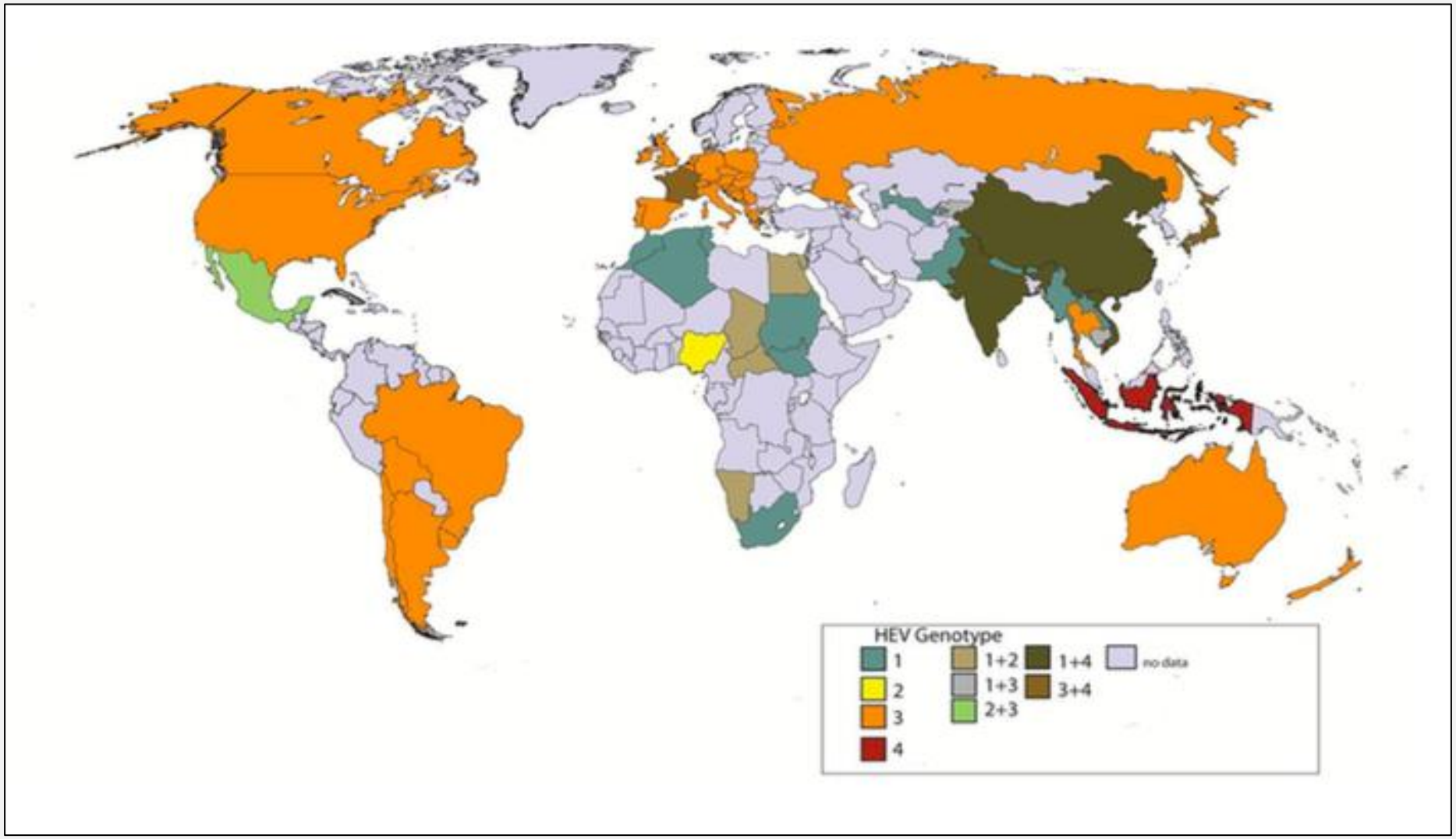
LAS DOS CARAS DE UNA MISMA INFECCION



NIVELES DE ENDEMICIDAD PARA EL HEV



DISTRIBUCION MUNDIAL POR GENOTIPO



HEPATITIS E

- GT 1 y 2: asociado a brotes epidémicos con reservorio en aguas contaminadas El mayor riesgo lo constituye el grupo embarazadas
- GT 3 y 4: se relaciona a infecciones zoonóticas no epidémicas en Europa, América del Norte y Sur y Australia. Mayor riesgo en ancianos y enfermos crónicos
- GT 5, 6, 7 y 8: se vinculan como reservorios principales jabalíes salvajes y camellos
- Existe un tipo de HEV sin genotipo, que se describió en ratas en China como reservorio que podría afectar principalmente pacientes inmunocomprometidos
- Los hemoderivados constituyen un reservorio recientemente probado

SITUACION EN ARGENTINA

PREVALENCIA DE HEV IGG EN DIFERENTES POBLACIONES

Country	Population	N° of cases	IgG anti-HEV % of positivity	Test utilized
Argentina	Pediatrics	1304	0.15	Abbot GmbH Diagnostika, Germany.
	Previous surgery	1735	3.1	Abbot GmbH Diagnostika, Germany.
	Blood donors	2157	1.8	Abbot GmbH Diagnostika, Germany.
	HIV +	484	6.6	Abbot GmbH Diagnostika, Germany.
	General population	433	4.4	Diapro, Italy
	Volunteers	95	9.5	Diapro, Italy
	Volunteers	28	14.3	Wantai, China
	Blood donors	24	16.7	Wantai, China
	Health care workers	27	14.8	Wantai, China
	HIV +	28	35.7	Wantai, China
	HIV +	204	7.3	Diapro, Italy
	Solid organ transplant recipients	120	5.8	Diapro, Italy
	Dialysis patients	88	10.2	Diapro, Italy

CASOS DE HEV DETECTADOS POR IGM HEV Y/O RNA HEV

Country	Studied patients	IgM anti-HEV	HEV RNA	HEV genotype (N)
Argentina	Not given	Nd	2	3i (2)
	35	3	3	3i (3)
	231	6	9	1a (1)[a] 3a (5) 3b (1)
	143	4	9	3a (7) 3i (2)

DETECCION AMBIENTAL DE RNA HEV

Country	Source	% of HEV detection (positive/n)	HEV genotype and subtype	Amplified genomic region	Year of detection
Argentina	River water	3.2% (1/32)	3c	ORF2*	2010
	Dam water	2.1% (1/48) 7.57% (5/66)	3	ORF2*	2013 2015
	Sewage	6.3% (3/48)	3a, 3b, 3c	ORF2*	2007, 2010, 2011

Pisano MB y col, 2018

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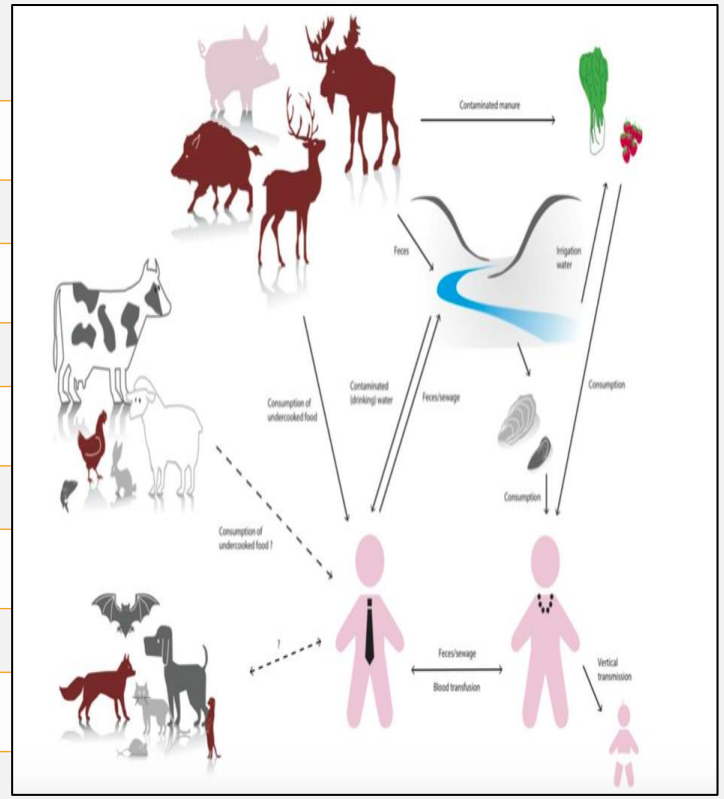
HEV

- Fecal-Oral (alimentos, agua, etc)
- Productos cárnicos: cocción > 5 min a 70°C
- Hemoderivados
- Transmisión vertical
- Transmisión ocupacional



- PERIODO DE INCUBACION: entre 2 y 6 semanas
- ELIMINACION DEL VIRUS: 1 semana antes del inicio de los síntomas y hasta 3 semanas (sangre) y 6 (materia fecal) luego de la finalización

Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

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See Comment page 1729

Transfusion Microbiology, National Health Service Blood and Transplant, London, UK (P E Hewitt FRCPath, S R Brailsford PhD, R Brett BSc, S Dicks MSc, A Kitchen PhD, P Patel MSc, K I Tettmar MBA, J Tossell RN, I Ushiro-Lumb FRCPath, Prof R S Tedder FRCPath); Blood Borne Virus Unit, Virus Reference Department, Microbiology Services (S Ijaz PhD, S Dicks, B Haywood BSc, P Patel, J Poh PhD, K I Tettmar, I Ushiro-Lumb, Prof R S Tedder) and Centre for Infectious Disease Surveillance and Control (S R Brailsford, I T R Kennedy MFPH, K Russell MFPH), Public Health England, London, UK; and University College London, Gower Street, London, UK (Prof R S Tedder)

Summary

Background The prevalence of hepatitis E virus (HEV) genotype 3 infections in the English population (including blood donors) is unknown, but is probably widespread, and the virus has been detected in pooled plasma products. HEV-infected donors have been retrospectively identified through investigation of reported cases of possible transfusion-transmitted hepatitis E. The frequency of HEV transmission by transfusion and its outcome remains unknown. We report the prevalence of HEV RNA in blood donations, the transmission of the virus through a range of blood components, and describe the resulting morbidity in the recipients.

Methods From Oct 8, 2012, to Sept 30, 2013, 225 000 blood donations that were collected in southeast England were screened retrospectively for HEV RNA. Donations containing HEV were characterised by use of serology and genomic phylogeny. Recipients, who received any blood components from these donations, were identified and the outcome of exposure was ascertained.

Findings 79 donors were viraemic with genotype 3 HEV, giving an RNA prevalence of one in 2848. Most viraemic donors were seronegative at the time of donation. The 79 donations had been used to prepare 129 blood components, 62 of which had been transfused before identification of the infected donation. Follow-up of 43 recipients showed 18 (42%) had evidence of infection. Absence of detectable antibody and high viral load in the donation rendered infection more likely. Recipient immunosuppression delayed or prevented seroconversion and extended the duration of viraemia. Three recipients cleared longstanding infection after intervention with ribavirin or alteration in immunosuppressive therapy. Ten recipients developed prolonged or persistent infection. Transaminitis was common, but short-term morbidity was rare; only one recipient developed apparent but clinically mild post-transfusion hepatitis.

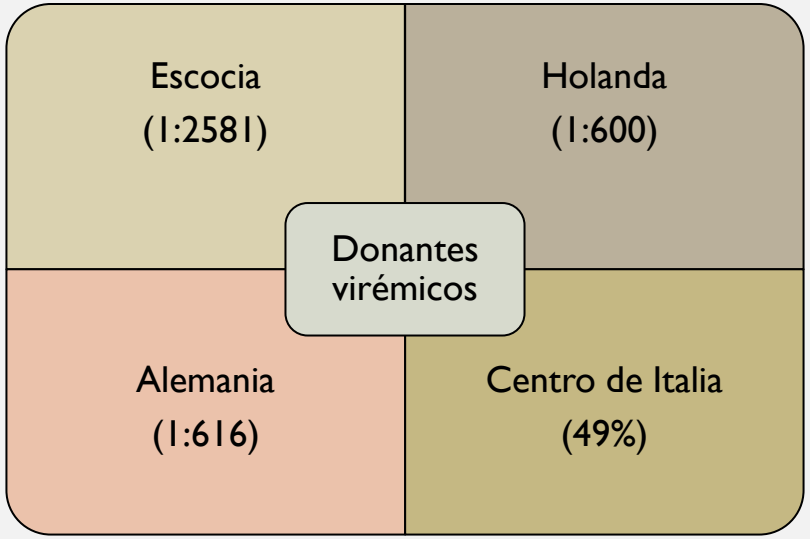
Interpretation Our findings suggest that HEV genotype 3 infections are widespread in the English population and in blood donors. Transfusion-transmitted infections rarely caused acute morbidity, but in some immunosuppressed patients became persistent. Although at present blood donations are not screened, an agreed policy is needed for the identification of patients with persistent HEV infection, irrespective of origin, so that they can be offered antiviral therapy.

METODOS

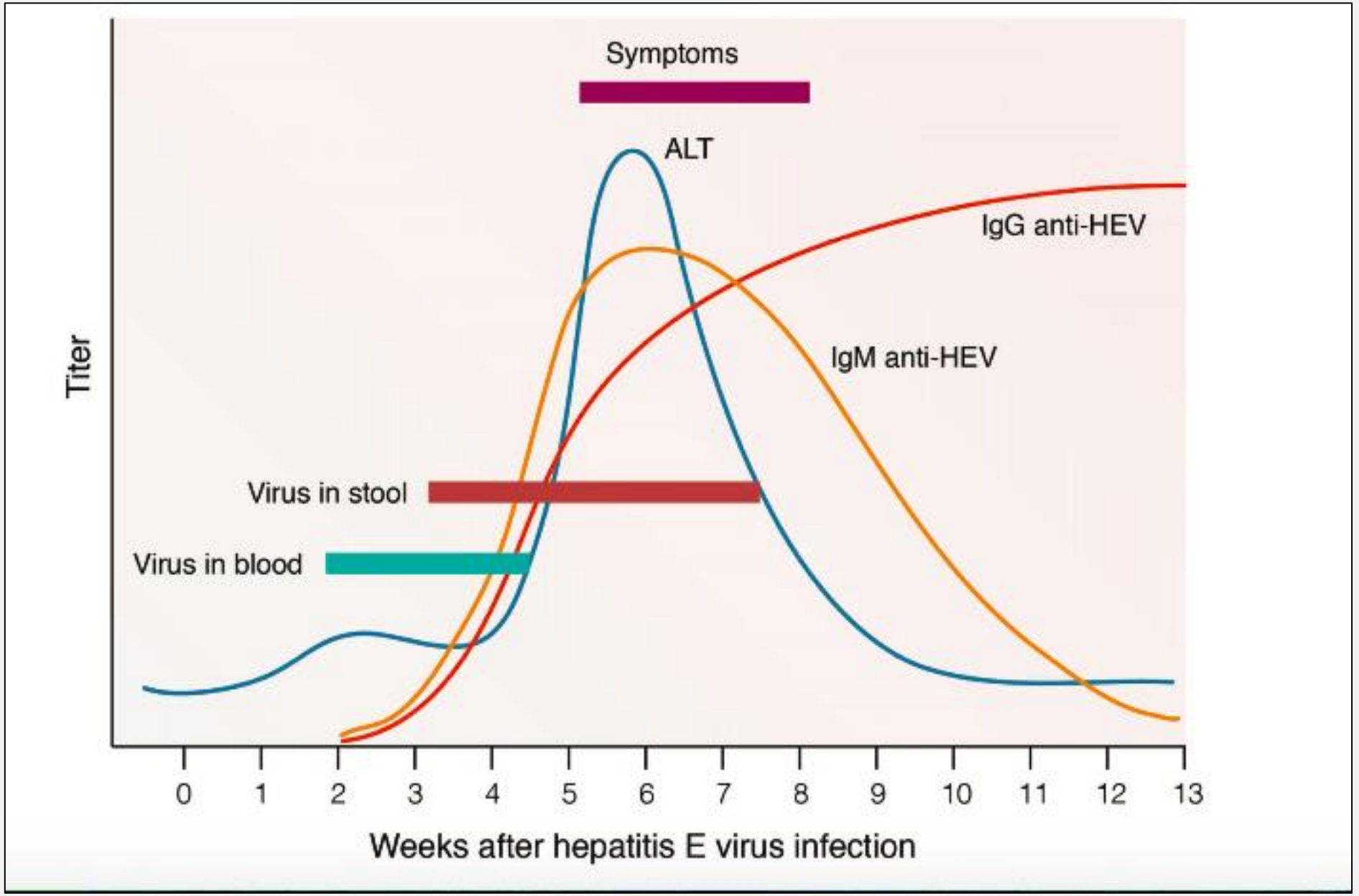
- Se analizaron 225.000 muestras para HEV
- Las positivas se genotipificaron y se identificaron a los receptores

RESULTADOS

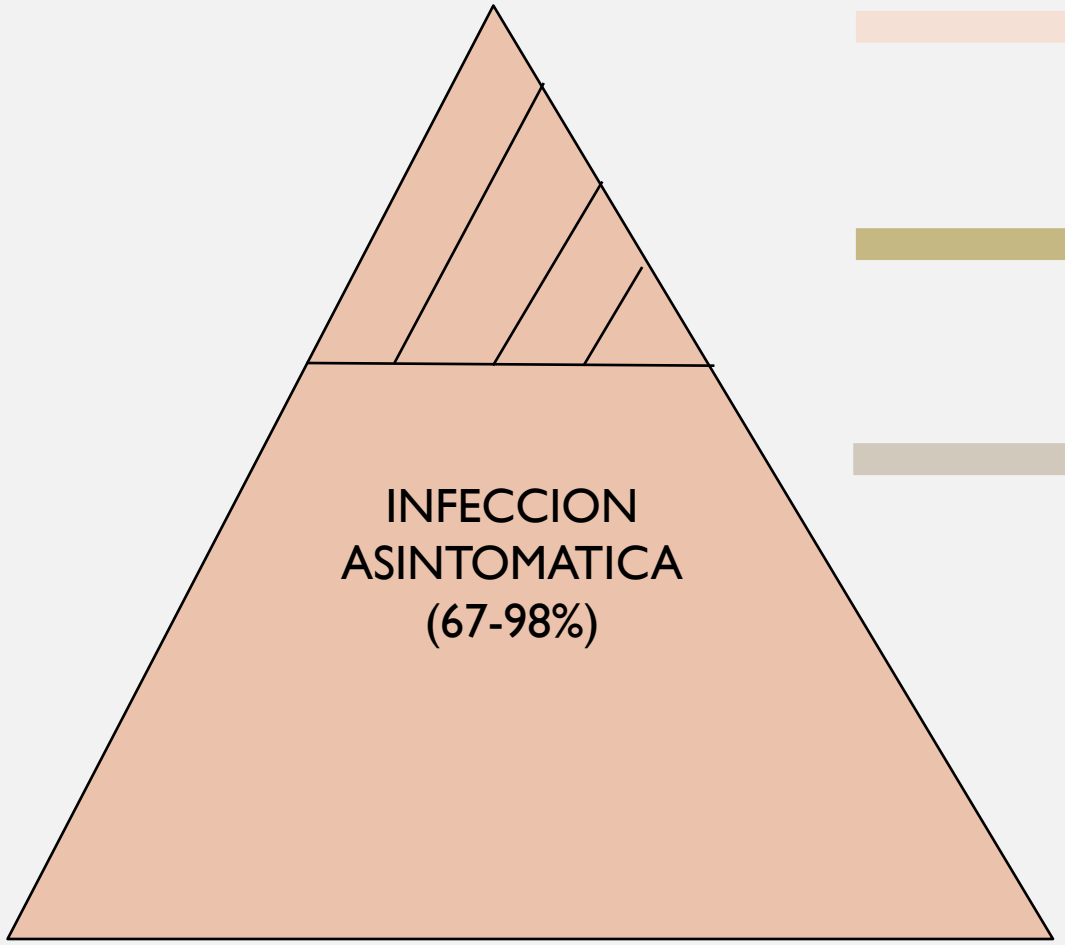
- 79 donantes virémicos (GT3) 1:2848
- Se prepararon 129 hemoderivados
- Se transfundieron 63
- En el seguimiento de 43 pacientes, 18 (42%) presentaron evidencia de infección



PERFIL SEROLOGICO Y BIOQUIMICO HEV



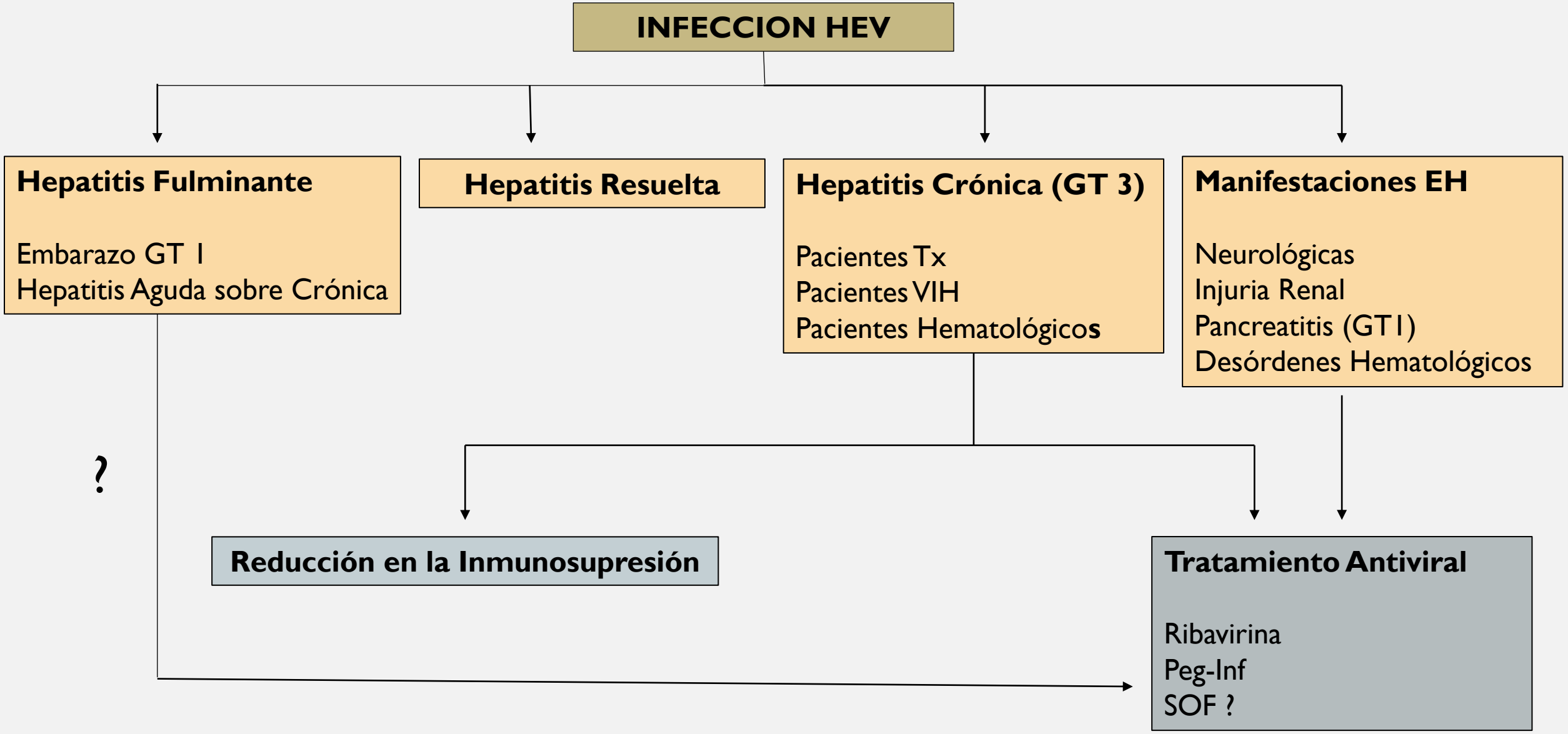
SUBDIAGNOSTICO



Infecciones Severas Agudas:
- ✓ Pacientes con enfermedad hepática previa
- ✓ Embarazadas en países en vías de desarrollo

Infecciones crónicas:
- ✓ Pacientes inmunosuprimidos

Manifestaciones extrahepáticas
- ✓ Neurológicas
- ✓ Renales
- ✓ Hematológicas



Modificado Khuroo et al, 2015

	PAISES EN DESARROLLO	PAISES DESARROLLADOS
Genotipo	HEV-1 / HEV-2	HEV-3 / HEV-4
Distribución	Asia, Africa, Latinoamérica, Oeste Africa	Mundial, China, Este de Asia, Europa Central
Patrón de la enfermedad	Epidémica/ Endémica	Autóctonos, Esporádicos
Estacional	Si	No
Reservorio	Humano	Animal (cerdos, jabalíes, ciervos)
Transmisión	Agua, interpersonal, vertical	Zoonosis, Profesional, Agua
Asoc con Transfusiones	Reportado	Frecuente
Edad	15-40	>50
Sexo	2 : 1	3:1
Curso clínico	Autolimitado	Autolimitado
Factores de riesgo	Embarazo, Cirrosis	Cirrosis, Tx, VIH
Enfermedad Extrahepática	Si	Si
Enfermedad crónica	No reportado	GT 3, Tx, VIH, Politransfundidos
Impacto	3.4 mill/año, 70000 muertes	Desconocido

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NON-COMMISSIONED REVIEW

JVH WILEY

Hepatitis E during pregnancy: Maternal and foetal case-fatality rates and adverse outcomes—A systematic review

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[2]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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Anne Bergløv, Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark.
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Abstract

Hepatitis E virus infection during pregnancy can have severe consequences for mother and child, such as vertical transmission, fulminant hepatic failure, even foetal or maternal mortality. The aim of this systematic review is to describe maternal, foetal and neonatal case-fatality rates as well as the prevalence of adverse outcomes in relation to hepatitis E virus infection during pregnancy. A systematic literature search was performed in Pubmed, Embase, Cochrane and CINAHL. Search terms included Pregnant, Women, Maternal, Infant, Foetal, Neonatal and Hepatitis E virus. Data were extracted using predefined data collection forms. All studies were quality assessed, either by the Newcastle-Ottawa Scale or by an adapted assessment scale for cross-sectional studies. We found 23 eligible studies, all observational, which were included in this systematic review with a total of 1338 cases. The median maternal, foetal and neonatal case-fatality rates were 26% (IQR 17%-41%), 33% (IQR 19%-37%) and 8% (IQR 3%-20%), respectively. Adverse outcomes such as fulminant hepatic failure, preterm labour, postpartum haemorrhage, low birth weight and vertical transmission were reported. The two studies that reported the highest prevalence of fulminant hepatic failure also reported the highest case-fatality rates. The median prevalence of fulminant hepatic failure was 45.3%. This systematic review found a high case-fatality rate among pregnant women infected with hepatitis E virus and a high rate of adverse outcomes among these women and their children. The results from this review mainly apply to hospital settings and symptomatic pregnant women from endemic countries.

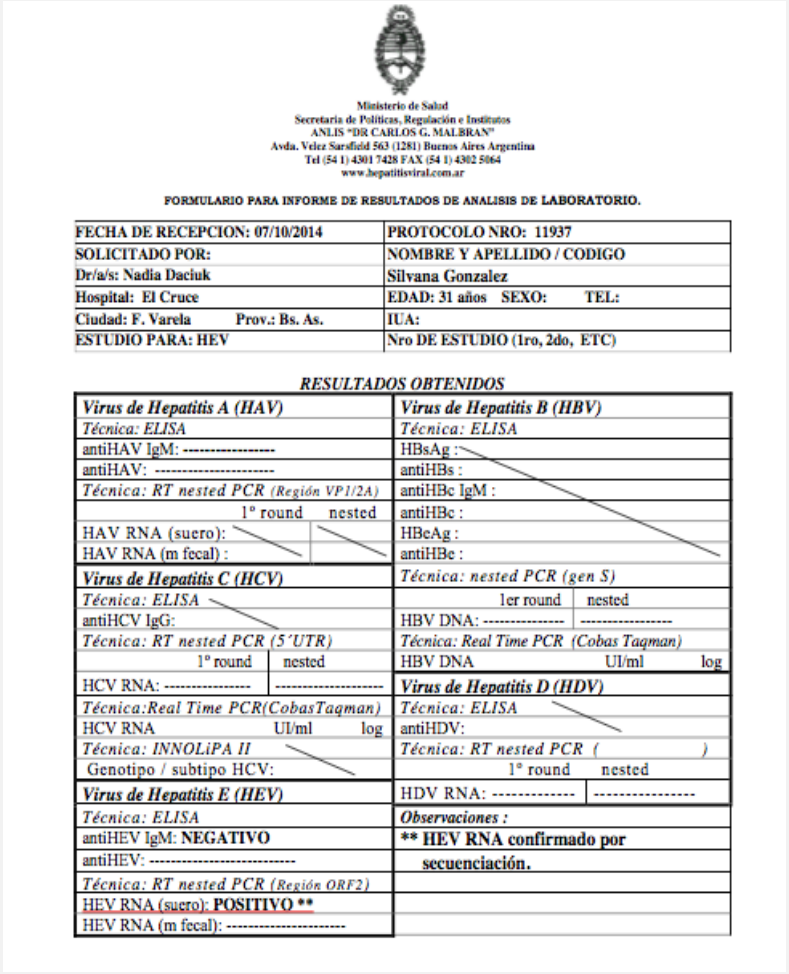
KEYWORDS
foetus, hepatitis E virus, mortality, pregnant women, systematic review

EMBARAZO

- 23 estudios, 1338 casos
- Mortalidad 26%
- Cambios inmunológicos y hormonales
- Elevado riesgo en el 3er trimestre
- GT 1 y 2, presentan peor evolución
- Madre: hemorragia, eclampsia, FHF
- Hijo: transmisión vertical y muerte

HEC, Octubre 2014

- ✓ Paciente femenina de 31 años de edad, derivada de la localidad de Henderson por cuadro de hepatitis aguda grave
- ✓ Embarazo de 14 semanas
- ✓ Evoluciona a FHA por lo que se realiza THO
- ✓ Aborto espontáneo 48 hs posteriores a la cirugía
- ✓ Resultado RNA(+) para HEV



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www.hepatitisviral.com.ar

FORMULARIO PARA INFORME DE RESULTADOS DE ANALISIS DE LABORATORIO.

FECHA DE RECEPCION: 07/10/2014	**PROTOCOLO NRO: 11937**
SOLICITADO POR:	**NOMBRE Y APELLIDO / CODIGO**
Dr/a/s: Nadia Daciuk	**Silvana Gonzalez**
Hospital: El Cruce	**EDAD: 31 años SEXO: TEL:**
Ciudad: F. Varela Prov.: Bs. As.	**IUA:**
ESTUDIO PARA: HEV	**Nro DE ESTUDIO (1ro, 2do, ETC)**

RESULTADOS OBTENIDOS

Virus de Hepatitis A (HAV)	***Virus de Hepatitis B (HBV)***
Técnica: ELISA	*Técnica: ELISA*
antiHAV IgM: ----------	HBsAg :
antiHAV: ----------	antiHBs :
Técnica: RT nested PCR (Región VP1/2A)	antiHBc IgM :
1° round nested	antiHBc :
HAV RNA (suero):	HBeAg :
HAV RNA (m fecal) :	antiHBe :
Virus de Hepatitis C (HCV)	*Técnica: nested PCR (gen S)*
Técnica: ELISA	1er round nested
antiHCV IgG:	HBV DNA: ---------- ----------
Técnica: RT nested PCR (5´UTR)	*Técnica: Real Time PCR (Cobas Taqman)*
1° round nested	HBV DNA UI/ml log
HCV RNA: ---------- ----------	***Virus de Hepatitis D (HDV)***
Técnica:Real Time PCR(CobasTaqman)	*Técnica: ELISA*
HCV RNA UI/ml log	antiHDV:
Técnica: INNOLiPA II	*Técnica: RT nested PCR ( )*
Genotipo / subtipo HCV:	1° round nested
Virus de Hepatitis E (HEV)	HDV RNA: ---------- ----------
Técnica: ELISA	***Observaciones :***
antiHEV IgM: **NEGATIVO**	** **HEV RNA confirmado por secuenciación.**
antiHEV: ----------	
Técnica: RT nested PCR (Región ORF2)	
HEV RNA (suero): **POSITIVO** **	
HEV RNA (m fecal): ----------	

ELSEVIER

Journal of Hepatology 46 (2007) 387–394

Journal of Hepatology

www.elsevier.com/locate/jhep

Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death☆

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[1]Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India
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[3]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Background/Aims: India is hyper-endemic for hepatitis E virus (HEV). HEV infection in cirrhosis may cause high mortality. Prospective study evaluating HEV infection in cirrhotics is scarce.

Methods: Consecutive patients with cirrhosis and healthy controls were included. Cirrhotics were categorized to 3 groups, (Group I – rapid decompensation, Group II – chronically decompensated, Group III – cirrhotics without decompensation). Sera from cirrhotics and controls were tested for HEV-RNA (RT-PCR). HEV-RNA positivity among cirrhotics and controls was compared. Natural course and mortality rate between HEV infected and non-infected cirrhotics were assessed during a 12-month follow-up.

Results: 107 cirrhotics and 200 controls were included. 30 (28%) cirrhotics and 9 (4.5%) controls had detectable HEV-RNA ($p < 0.001$). HEV- RNA positivity among Group I ($n = 42$), II ($n = 32$) and III ($n = 33$) cirrhotics was 21 (50%), 6 (19%) and 3 (10%), respectively ($p = 0.002$). 70% (21/30) with HEV infection and 27% (21/77) without it had rapid decompensation ($p = 0.001$). Mortality between HEV infected and non-infected cirrhotics at 4 weeks (43% vs. 22%, $p = 0.001$) and 12 month (70% vs. 30%, $p = 0.001$) was different. Multivariate analysis identified HEV infection, Child-Pugh's score, renal failure, and sepsis as independent factors for mortality.

Conclusions: In India, cirrhotics were prone to HEV infection, which was associated with rapid decompensation and death.

Keywords: HEV; Cirrhosis; Decompensation; Death

METODOS

- Se incluyeron pacientes cirróticos (n:107) y controles (n:200)
- Cirróticos: 3 grupos
  G1: Descompensación rápida (n:42)
  G2: Crónicamente descompensados (n:32)
  G3: Sin descompensación (n:33)
- Se tomaron muestras para RNA HEV
- Los positivos cirróticos se compararon con los negativos

RESULTADOS

- Cirróticos: 30 (28% total) RNA (+) / Control 9 RNA (+) (4.5%)
  G1: 21 RNA (+) (50%),G2: 6 RNA(+) (19%),
  G3: 3 RNA (+) (10%)
- 70% (21/30) cirróticos (+), tuvieron descompensación rápida vs 27% (21/77) cirróticos (-).
- Mortalidad entre cirróticos (+) y (-) a las 4 sem fue 43% vs 22% y al año 70% vs 30%

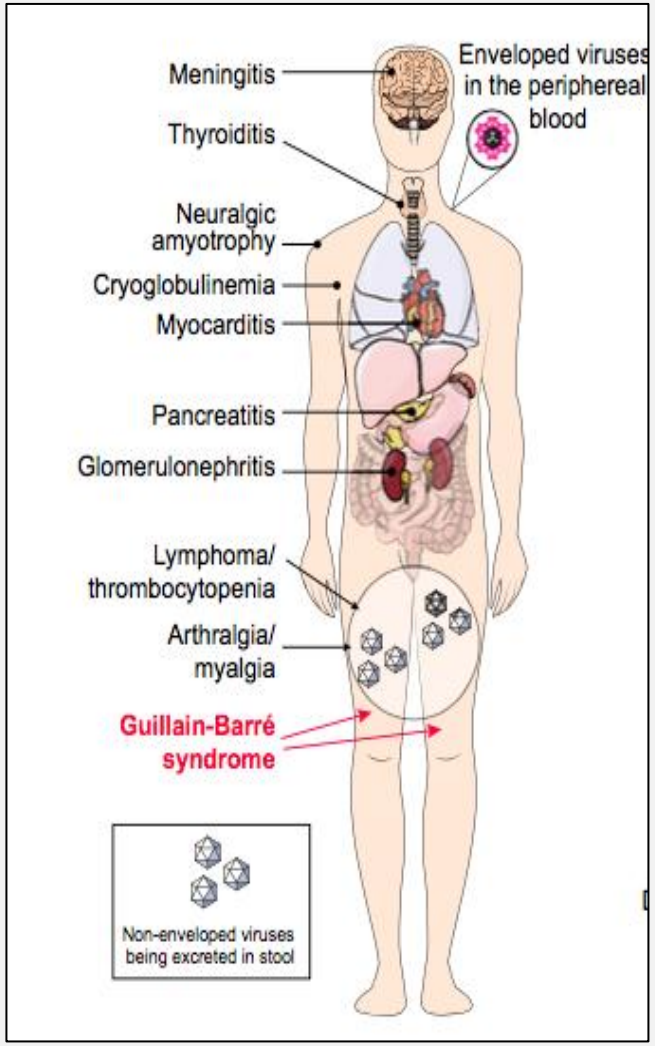
MANIFESTACIONES EXTRAHEPATICAS HEV

NEUROLOGICAS
(GT 1, 3 y 4)
- Amiotrofia Neurálgica
- Sindrome Guillain Barré
- Parálisis de Bell
- Mielitis Transversa Aguda
- Meningoencefalitis Aguda

RENALES
(GT 3)
- GMNF MP
- GMNF Membranosa

PANCREATICAS
(GT 1)

HEMATOLOGICAS
(GT 1)
- Anemia crónica
- Trombocitopenia
- Anemia Hemolítica
- Anemia aplásica
- Crioglobulinemia



Pischke et al, 2017

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TESTS DIAGNOSTICOS DISPONIBLES PARA LA DETECCION DE HEV

ANTI HEV IGM	ANTI HEV IGG	TESTS MOLECULARES
Wantai /HEV IgM Rapid Test	Wantai / HEV ELISA IgG	Altona Diag / Real Star HEV RT PCR
MP Diagnostics/Hev IgM	MP Diagnostics / HEV IgG ELISA	Mikrogen Diag / AmpliCube HEV
MP Diagnostics/ HEV IgM ELISA	Adaltis / EIAgen HEV	Eurobio / Eurobioplex HEV RNA
Mikrogen/recomWELL HEV Igm	Mikrogen / recom/WELL HEV IgG	Fast- track Diag / FTD Hepatitis E RNA
Diapro/ HEV IgM	Euroimmun/ ELISA Anti-Virus HEV IgG	ROCHE COBAS HEV / COBAS 6800
Biomerieux/ VIDAS anti-HEV IgM	Diapro / HEV IgG	
Virclia/HEV IgM	Biomerieux / VIDAS anti-HEV IgG	

EASL Congress, 2019

En el diagnóstico HEV, se recomienda la utilización de serología y NATs (Técnicas de amplificación molecular) (A1)

Para el diagnóstico de HEV crónica se recomiendan estrictamente la detección de RNA (A1)

Todos los pacientes con sospecha de hepatitis viral deberían ser testeados para HEV (A1)

Pacientes con diagnóstico de DILI, deberían ser testeados para HEV (A1)

HEV CI Practice Guideline EASL, 2018

INDICACIONES DE TESTEO PARA HEV

SITUACION INMUNOLOGICA	INDICACIONES
INMUNOCOMPETENTES	• Pacientes con evidencia de hepatitis
	• Sospecha de DILI
	• Enfermedad Hepática Descompensada
	• Manifestaciones Neurológicas: Amiotrofia Neurálgica, Sindr. GB, Encefalitis, Neuropatía Aguda y aumento de ALT
	• Donantes de órganos
INMUNOCOMPROMETIDOS	• Similares a inmunocompetentes
	• ALT persistentemente elevada

HEV CI Practice Guideline, EASL 2018

Alimentary Pharmacology & Therapeutics

The role of hepatitis E virus testing in drug-induced liver injury

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SUMMARY

Background
Locally acquired hepatitis E is an emerging infection in developed countries and can be misdiagnosed as drug-induced liver injury.

Aim
To study the role of hepatitis E virus (HEV) testing in drug-induced liver injury.

Methods
Retrospective review of a cohort of patients with suspected drug-induced liver injury ($n = 69$) and hepatitis E ($n = 45$). The standard criteria for drug-induced liver injury were applied. Patients with suspected drug-induced liver injury who met these criteria were retrospectively tested for HEV on stored sera taken at the time of presentation. The two cohorts were compared to determine variables that predicted either of the diagnoses.

Results
Forty-seven out of 69 patients had criterion-referenced drug-induced liver injury. 22/47 were HEV negative and thus had confirmed drug-induced liver injury. 19/47 were not tested for HEV, as there was no sera available from the time of presentation. 6/47 were HEV positive and thus did not have drug-induced liver injury, but had hepatitis E infection. Compared to patients with confirmed drug-induced liver injury, patients with hepatitis E were significantly more likely to be male (OR 3.09, CI 1.05–9.08); less likely to present in November and December (0.03, CI 0.01–0.52); have lower serum bilirubin ($P = 0.015$); and higher serum alanine aminotransferase ($P < 0.001$) and alanine aminotransferase/alkaline phosphatase ratio ($P < 0.001$).

Conclusion
The diagnosis of drug-induced liver injury is not secure without testing for HEV.

METODOS

- 69 pctes con diagnóstico de DILI y 45 HEV
- Todos cumplieron criterios para DILI
- Se procesaron las muestras para HEV y se analizaron variables predictoras de ambos diagnósticos

RESULTADOS

- 47/69 reunieron criterios para DILI
- 19/47 no fueron testeados
- 6/47 (+) refutando el DILI

GASTROENTEROLOGY 2011;141:1665–1672

Acute Hepatitis E Infection Accounts for Some Cases of Suspected Drug-Induced Liver Injury

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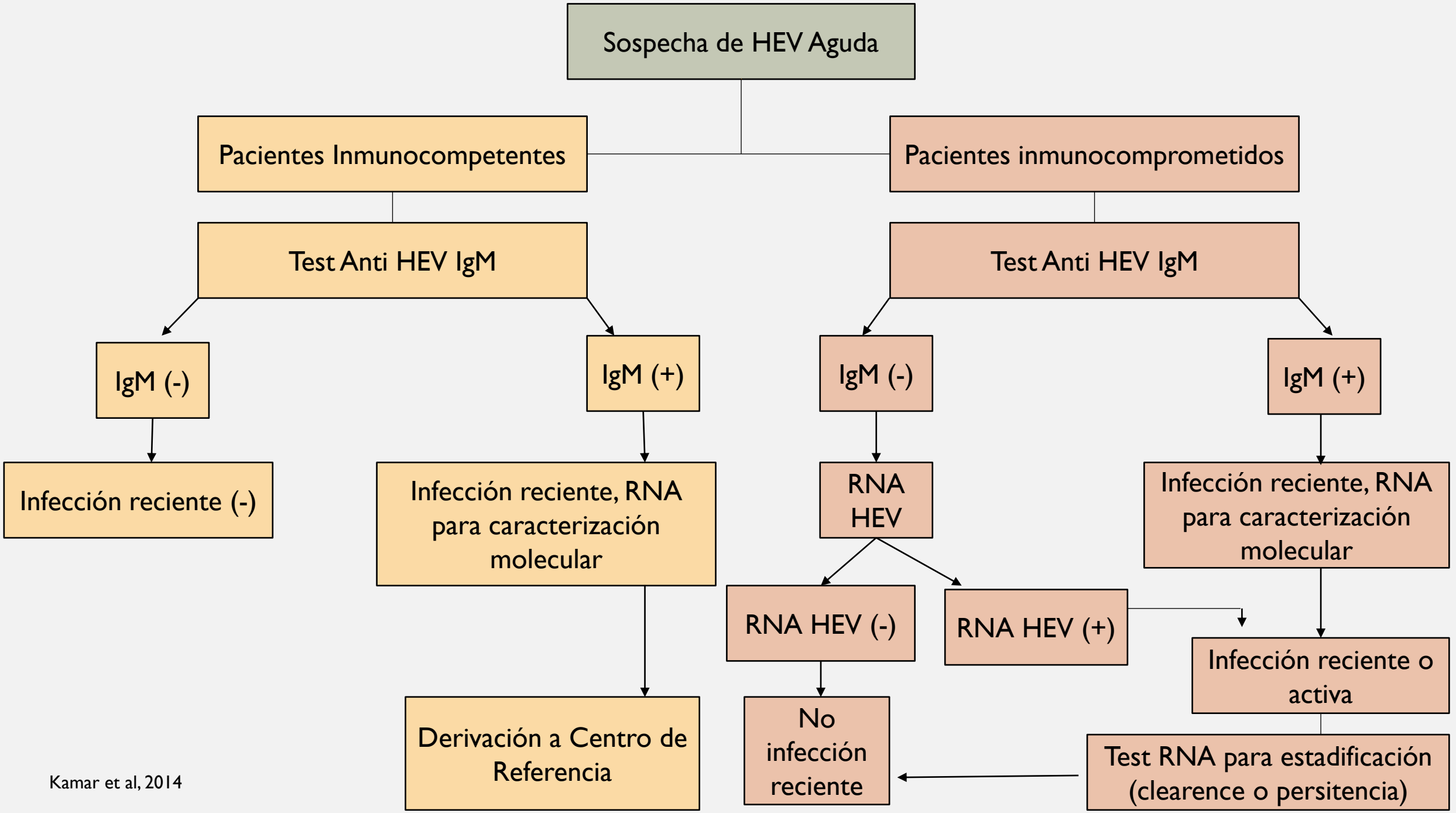
BACKGROUND & AIMS: The diagnosis of drug-induced liver injury relies on exclusion of other causes, including viral hepatitis A, B, and C. Hepatitis E virus (HEV) infection has been proposed as another cause of suspected drug-induced liver disease. We assessed the frequency of HEV infection among patients with drug-induced liver injury in the United States. **METHODS:** The Drug-Induced Liver Injury Network (DILIN) is a prospective study of patients with suspected drug-induced liver injury; clinical information and biological samples are collected to investigate pathogenesis and disease progression. We analyzed serum samples, collected from patients enrolled in DILIN, for immunoglobulin (Ig) G and IgM against HEV; selected samples were tested for HEV RNA. **RESULTS:** Among 318 patients with suspected drug-induced liver injury, 50 (16%) tested positive for anti-HEV IgG and 9 (3%) for anti-HEV IgM. The samples that contained anti-HEV IgM (collected 2 to 24 weeks after onset of symptoms) included 4 that tested positive for HEV RNA genotype 3. Samples from the 6-month follow-up visit were available from 4 patients; they were negative for anti-HEV IgM, but levels of anti-HEV IgG increased with time. Patients who had anti-HEV IgM were mostly older men (89%; mean age, 67 years), and 2 were human immunodeficiency virus positive. Clinical reassessment of the 9 patients with anti-HEV IgM indicated that acute hepatitis E was the most likely diagnosis for 7 and might be the primary diagnosis for 2. **CONCLUSIONS: HEV infection contributes to a small but important proportion of cases of acute liver injury that are suspected to be drug induced. Serologic testing for HEV infection should be performed, particularly if clinical features are compatible with acute viral hepatitis.**

METODOS

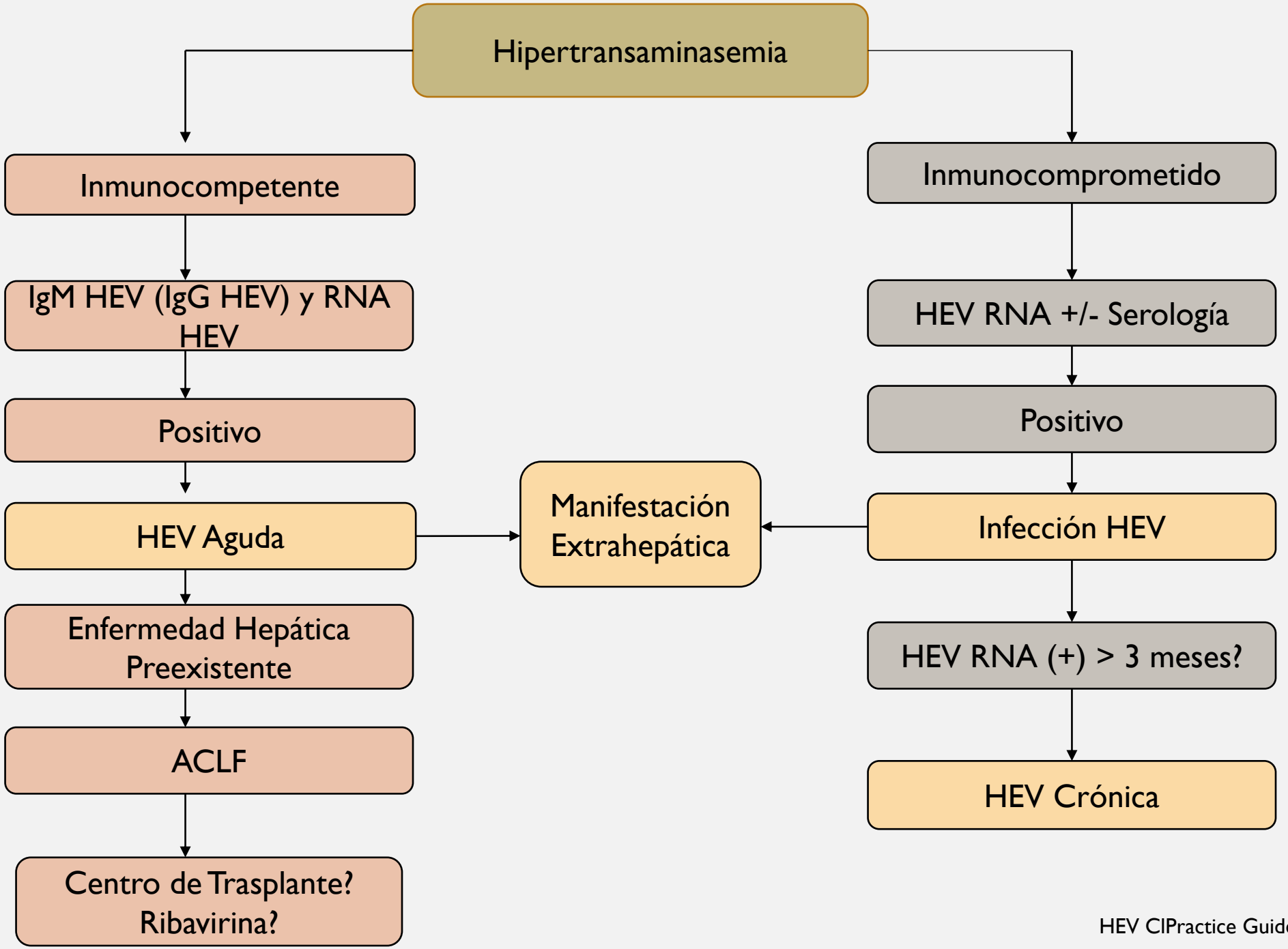
- Se testearon 318 pacientes con diagnóstico de DILI (IgG /IgM HEV), obtenidos en DILIN
- Período entre 2 y 24 semanas luego del inicio de los síntomas

RESULTADOS

- 50 (16%): IgG HEV (+)
- 9 (3%): IgM HEV (+); 4 con RNA (+) GT 3
- La reevaluación de los pacientes consideró que en 7 de ellos el HEV era el diagnóstico más probable y el definitivo en 2



Kamar et al, 2014



HEV ClPractice Guidelines, EASL, 2018

AGENDA

✓INTRODUCCION

- Epidemiología
- Características del HEV

✓CURSO CLINICO

- Transmisión
- Formas Clínicas
- Manifestaciones Extrahepáticas

✓DIAGNOSTICO

✓TRATAMIENTO

TRATAMIENTO

- ✓ Pocas veces requerido
- ✓ Cuadros autolimitados
- ✓ Mejoría en la función hepática
- ✓ No hay tratamientos estandarizados

TX OS

- ✓ Rápida progresión a la cirrosis (20-50%, 5 años)
- ✓ Primera línea, disminución de la IS
- ✓ 30% respuesta
- ✓ mTOR promueve replicación HEV
- ✓ Ribavirina (mutaciones)
- ✓ Peg-Inf
- ✓ Mayores limitaciones en riñón, corazón, pulmón

VIH

- ✓ Pueden eliminar el virus a través de la reconstitución inmune
- ✓ Ribavirina
- ✓ Peg-Inf

ONCOHEMATOLOGICOS

- ✓ Espectro más limitado
- ✓ Ribavirina

EMBARAZO

- ✓ Derivación a centro de Tx ante FHF
- ✓ Uso de Ribavirina discutido por riesgo de teratogenicidad

GASTROENTEROLOGY 2010;139:1612–1618

CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Ribavirin Therapy Inhibits Viral Replication on Patients With Chronic Hepatitis E Virus Infection

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BACKGROUND & AIMS: Hepatitis E virus (HEV) infection can evolve to chronic hepatitis in immunocompromised patients. Pegylated α-interferon can effectively treat chronic HEV infection after liver transplantation but is contraindicated for kidney transplantation. We assessed the antiviral effect of ribavirin monotherapy in patients with chronic HEV infection following kidney transplantation. **METHODS:** In a pilot study performed at Toulouse University Hospital, 6 patients that received kidney transplants who were positive for HEV RNA (infected with HEV for 36.5 months; [range, 11–46 months]) were given ribavirin monotherapy for 3 months. Ribavirin was given at 600–800 mg/day in 2 separate doses, based on the patient's ability to clear creatinine. **RESULTS:** Median serum concentration of HEV RNA at baseline was 5.77 log copies/mL (range, 4.35–7.35 log copies/mL). Three months after ribavirin therapy commenced, HEV RNA was undetectable in serum samples from all patients. A sustained virologic response was observed in 4 patients; the other 2 patients relapsed at 1 and 2 months after ribavirin therapy ended. At the end of the study, all patients had normal levels of alanine and aspartate aminotransferase. Anemia was the main side effect caused by ribavirin therapy. **CONCLUSIONS: Ribavirin monotherapy inhibits the replication of HEV in vivo and might induce a sustained virological response in patients with chronic HEV infections. Further studies are required to determine the optimal duration of ribavirin therapy.**

METODOS

- 6 pacientes tx renales, HEV (+)
- Ribavirina monoterapia por 3 meses, 600-800 mg/dia

RESULTADOS

- Al finalizar el tratamiento, todos tuvieron RNA no detectable
- RVS: 4 pacientes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients

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ABSTRACT

BACKGROUND

There is no established therapy for hepatitis E virus (HEV) infection. The aim of this retrospective, multicenter case series was to assess the effects of ribavirin as monotherapy for solid-organ transplant recipients with prolonged HEV viremia.

METHODS

We examined the records of 59 patients who had received a solid-organ transplant (37 kidney-transplant recipients, 10 liver-transplant recipients, 5 heart-transplant recipients, 5 kidney and pancreas–transplant recipients, and 2 lung-transplant recipients). Ribavirin therapy was initiated a median of 9 months (range, 1 to 82) after the diagnosis of HEV infection at a median dose of 600 mg per day (range, 29 to 1200), which was equivalent to 8.1 mg per kilogram of body weight per day (range, 0.6 to 16.3). Patients received ribavirin for a median of 3 months (range, 1 to 18); 66% of the patients received ribavirin for 3 months or less.

RESULTS

All the patients had HEV viremia when ribavirin was initiated (all 54 in whom genotyping was performed had HEV genotype 3). At the end of therapy, HEV clearance was observed in 95% of the patients. A recurrence of HEV replication occurred in 10 patients after ribavirin was stopped. A sustained virologic response, defined as an undetectable serum HEV RNA level at least 6 months after cessation of ribavirin therapy, occurred in 46 of the 59 patients (78%). A sustained virologic response was also observed in 4 patients who had a recurrence and were re-treated for a longer period. A higher lymphocyte count when ribavirin therapy was initiated was associated with a greater likelihood of a sustained virologic response. Anemia was the main identified side effect and required a reduction in ribavirin dose in 29% of the patients, the use of erythropoietin in 54%, and blood transfusions in 12%.

CONCLUSIONS

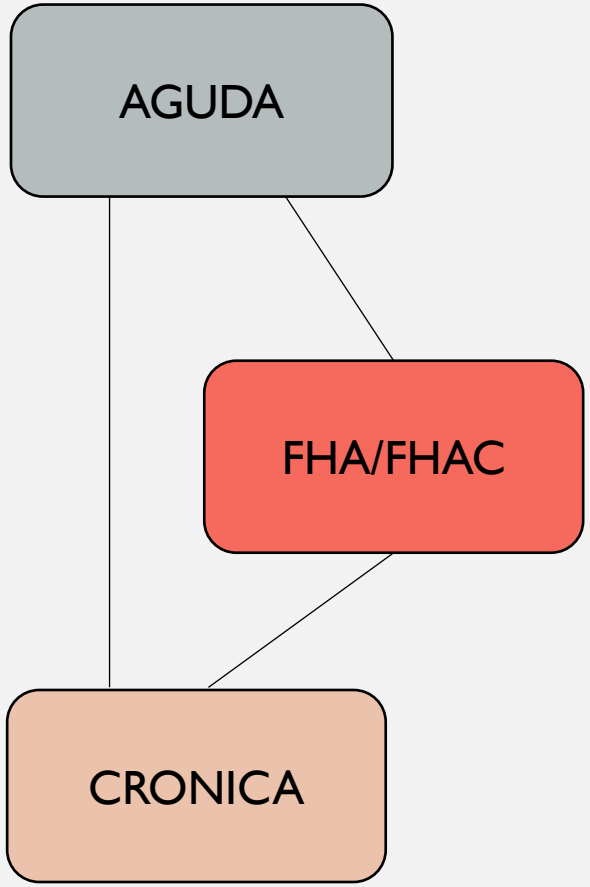
This retrospective, multicenter study showed that ribavirin as monotherapy may be effective in the treatment of chronic HEV infection; a 3-month course seemed to be an appropriate duration of therapy for most patients.

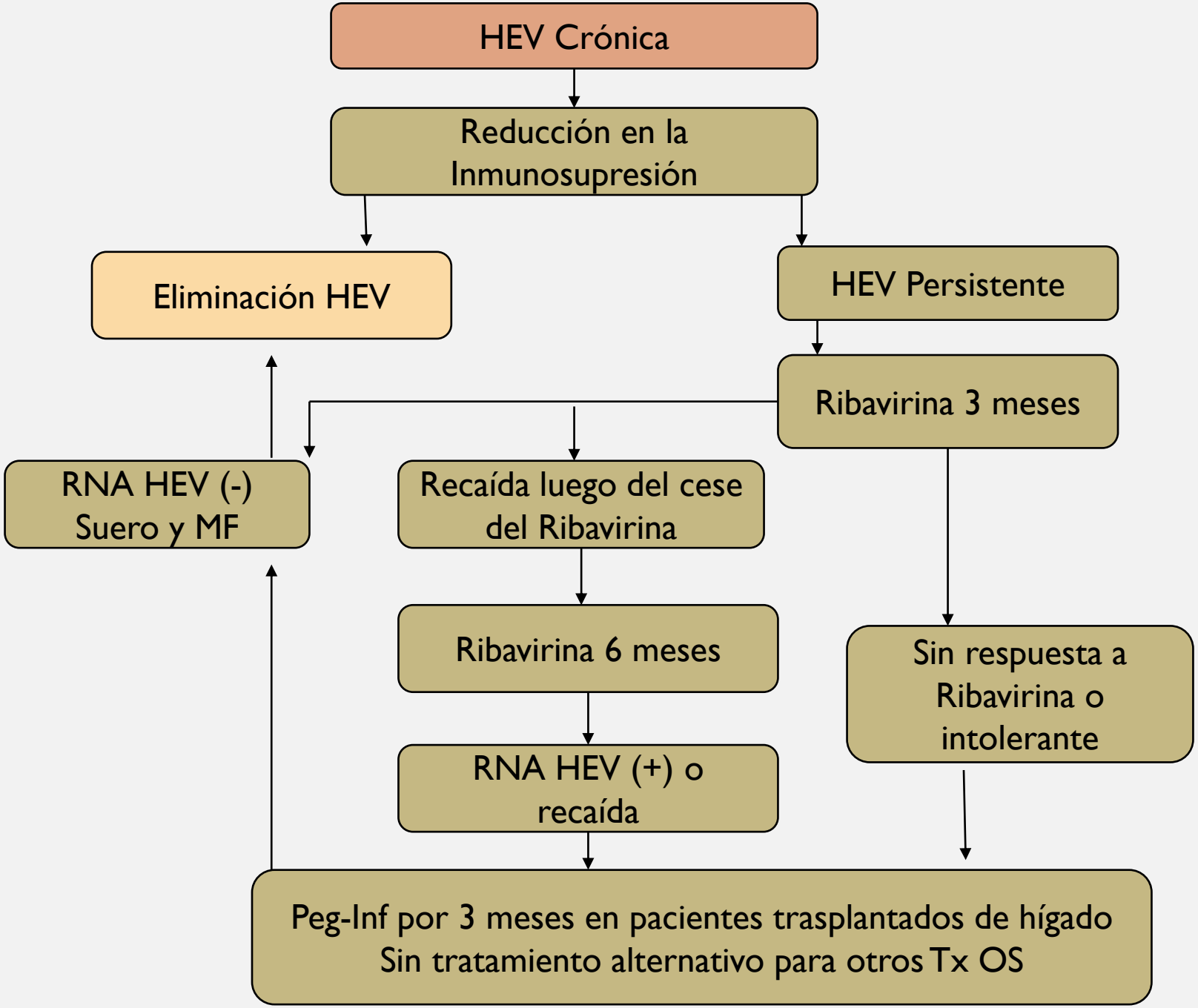
METODOS

- 59 pacientes tx (37 riñón, 10 hígado, 5 corazón, 5 reno-páncreas, 2 pulmón)
- 54 GT 3
- Se administró Ribavirina en dosis de 600 a 1200 mg por una media de 3 meses

RESULTADOS

- 95% presentaron clearence viral
- Recurrencia en 10 pacientes, 4 respondieron prolongando el tratamiento
- RVS 78% (46/79)





HEV CI Practice Guidelines EASL, 2018

RIBAVIRINA

- ✓ Fácil de administrar, buen perfil de seguridad
- ✓ Predictor de RVS: disminución de 0.5 log en CV 1ra semana
- ✓ Mejora la función hepática
- ✓ Monoterapia por 3-6 meses

INMUNIZACION

- ✓ A la fecha no existe vacuna aceptada universalmente
- ✓ En 2011 se patentó una vacuna en China (HEV239, Hecolin)
- ✓ Eficaz para GT 1 y 4, atenuando el cuadro clínico y las complicaciones
- ✓ Actuaría además como control de transmisión
- ✓ La FDA aceptó su uso en USA para ensayos clínicos
- ✓ No se utiliza rutinariamente en embarazadas

CONCLUSIONES

- Infección de ***distribución mundial***, con patrón de prevalencia variable
- En Argentina se expresa como una zoonosis, con prevalencia del ***GT 3 ,*** conformando un área de baja endemicidad
- El curso de la enfermedad en todos los genotipos es por lo general ***autolimitado***
- Los grupos de riesgo se encuentran constituídos por ***embarazadas, trasplantados e inmunosuprimidos*** donde la evolución es principalmente a la cronicidad o a la descompensación hepática en la gran mayoría de los casos

CONCLUSIONES

- El diagnóstico debe realizarse con ***técnicas de amplificación molecular***, ya que las serologías pueden no reflejar fidedignamente el período de infección
- El único fármaco recomendado a la fecha es la ***Ribavirina*** por 3 a 6 meses
- La prevención radica en políticas de salud tendientes al control y ***eliminación de los reservorios*** de manera tal de impedir la perpetuación del virus en el medioambiente