26ème Journée Multidisciplinaire en
Hépatologie et Transplantation Hépatique, Lyon

Hépatite E
Actualités en 2021

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2022
Gastro-entérologie
Centre hospitalier universitaire vaudois

CHUV

Outline

- Epidemiology
- Virology
- Diagnostic tools
- Clinical presentations
- Treatment options for chronic HEV
- Prévention
- Future perspectives in clinical & translationnal research

Clinical case

- ♂ 72 ans
- Healthy, BMI 30 kg/m²
- Hospitalized in December 2018:

Jaundice

UQs abdominal pain

Fever, 38°

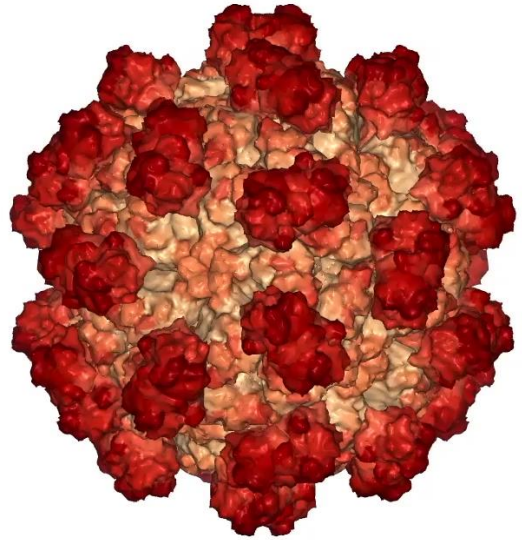
Clinical case

	13.12.2017
AST (U/l)	895
ALT (U/l)	1290
ALP (U/l)	181
Gamma-GT (U/l)	355
TB/DB(µmol/l)	210/179
Leucocytes (G/l)	6.1
CRP (mg/l)	20

Clinical case

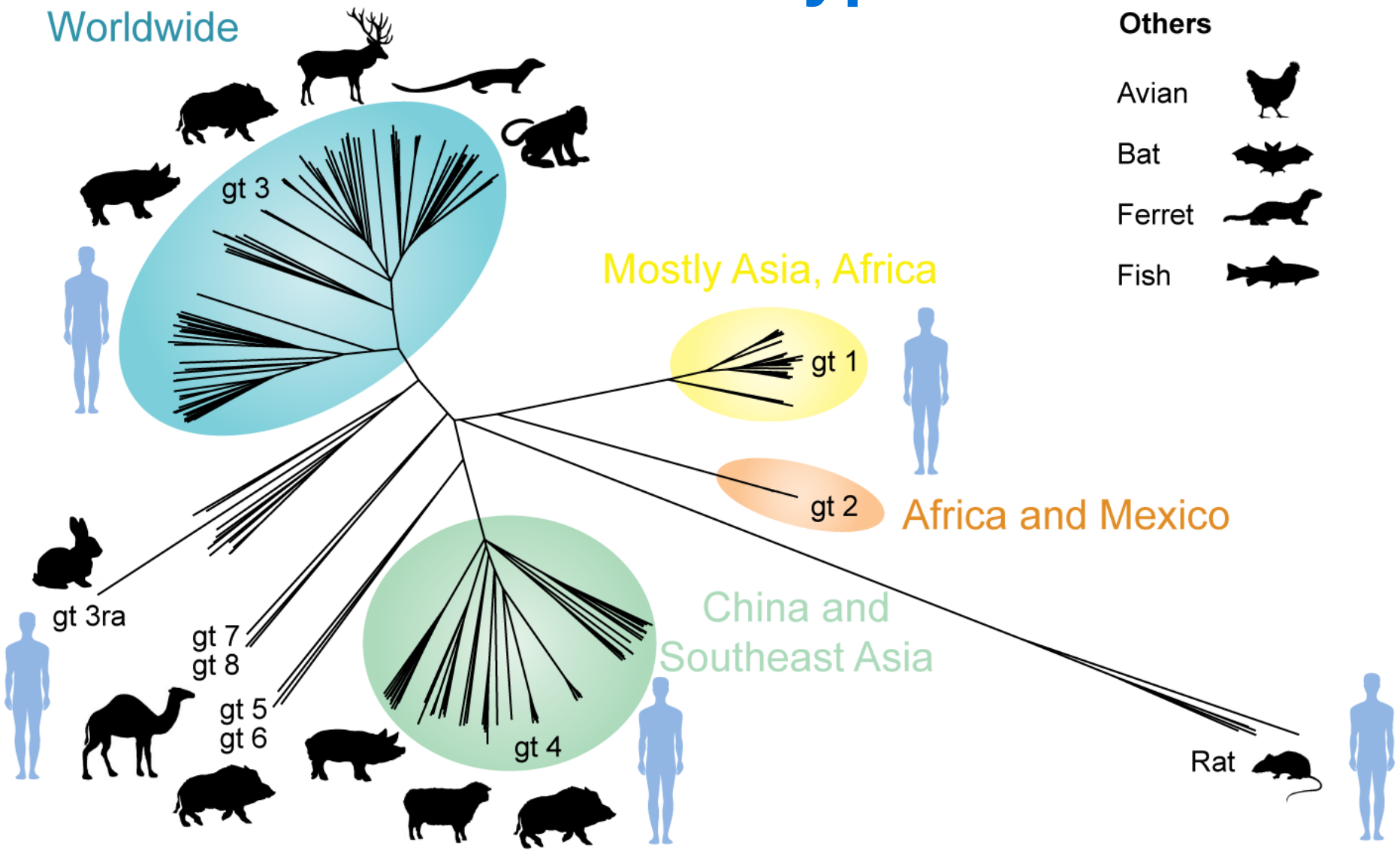
The Challenge of Hepatitis E

- **Most common cause of acute hepatitis and jaundice in the world**



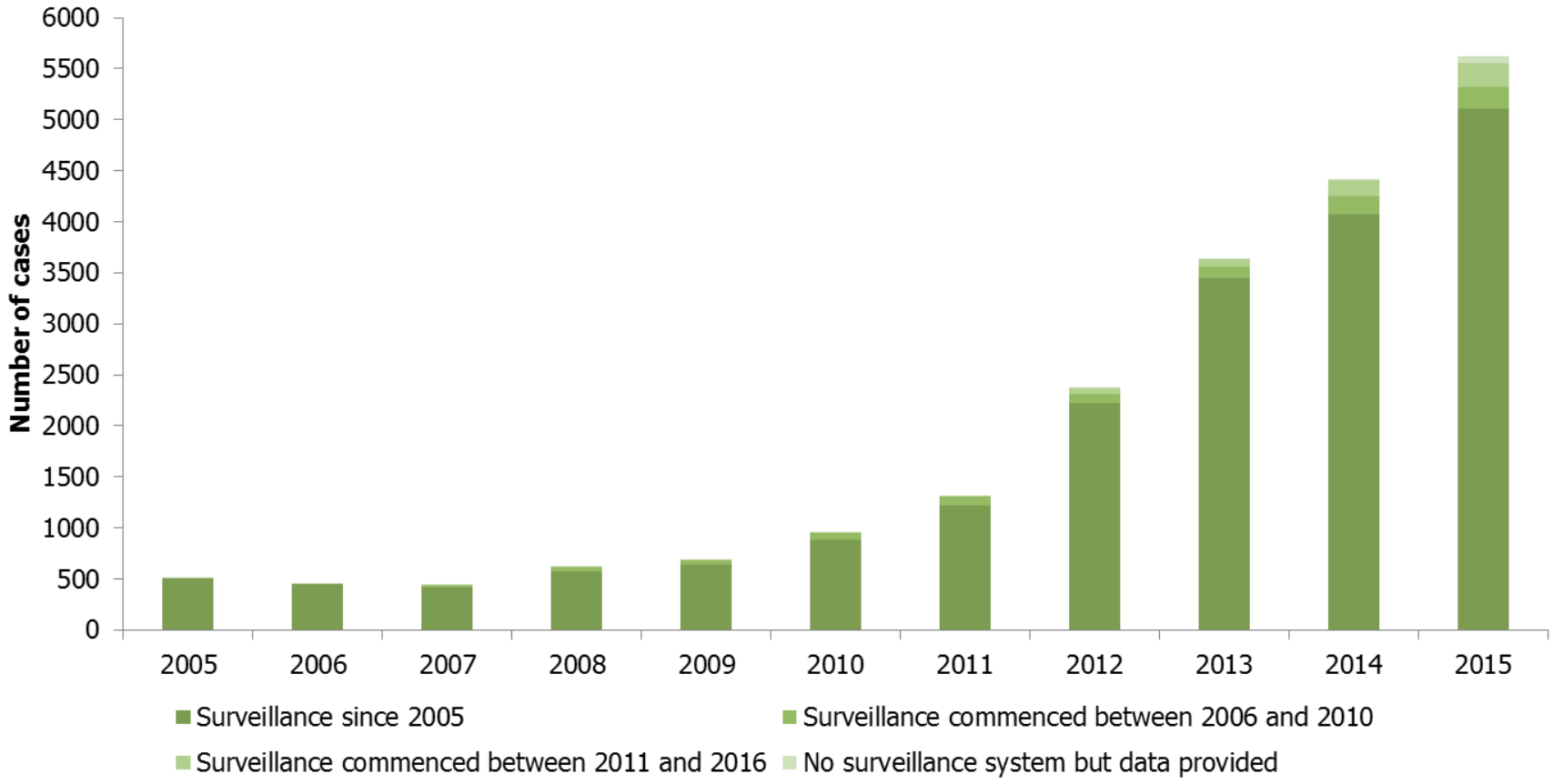
Reviewed in Hoofnagle JH *et al*. NEJM 2012;367:1237-44 and Kamar N *et al.* Nat Rev Dis Primers 2017;3:17086.
EASL Clinical Practice Guidelines on HEV infection. J Hepatol 2018;68:1256-71.
Animation based on Yamashita T et al. PNAS 2009;106:12986-91 prepared by Noémi Oechslin and Jérôme Gouttenoire.

HEV Genotypes



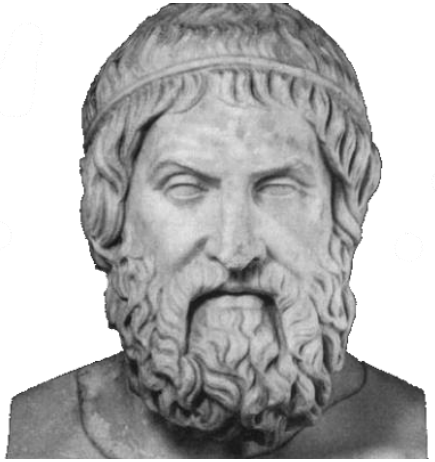
Updated from Debing Y *et al*. J Hepatol 2016;65:200-212.
See also Sahli R *et al*. J Hepatol 2019;70:1023-1025 and Sridhar S *et al*. Clin Infect Dis, in press.

HEV European surveillance program 2005–2015



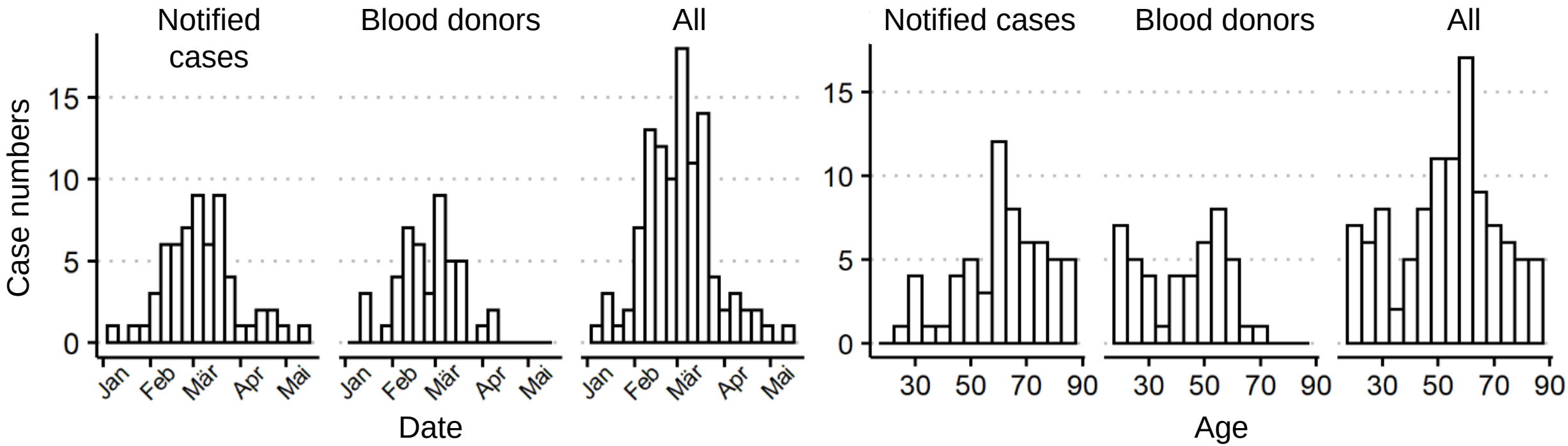
10-fold increase 2005–2015 due locally acquired infections
78% of cases reported from France, Germany and UK

Look and you will find it – what is unsought will go undetected.



Sophocles, 496-406 BC

Hepatitis E in Switzerland



- **February-March 2021** (weeks 5-12, peak week 9)
- ♂ : ♀ **≈ 2 : 1, all age groups** (peak 60 years) **and all Switzerland affected**

Courtesy of Michelle Raess, Swiss Federal Office of Public Health

Hepatitis E in Switzerland

Control of raw pork liver sausage production can reduce the incidence of HEV infection

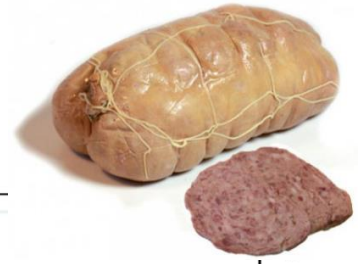
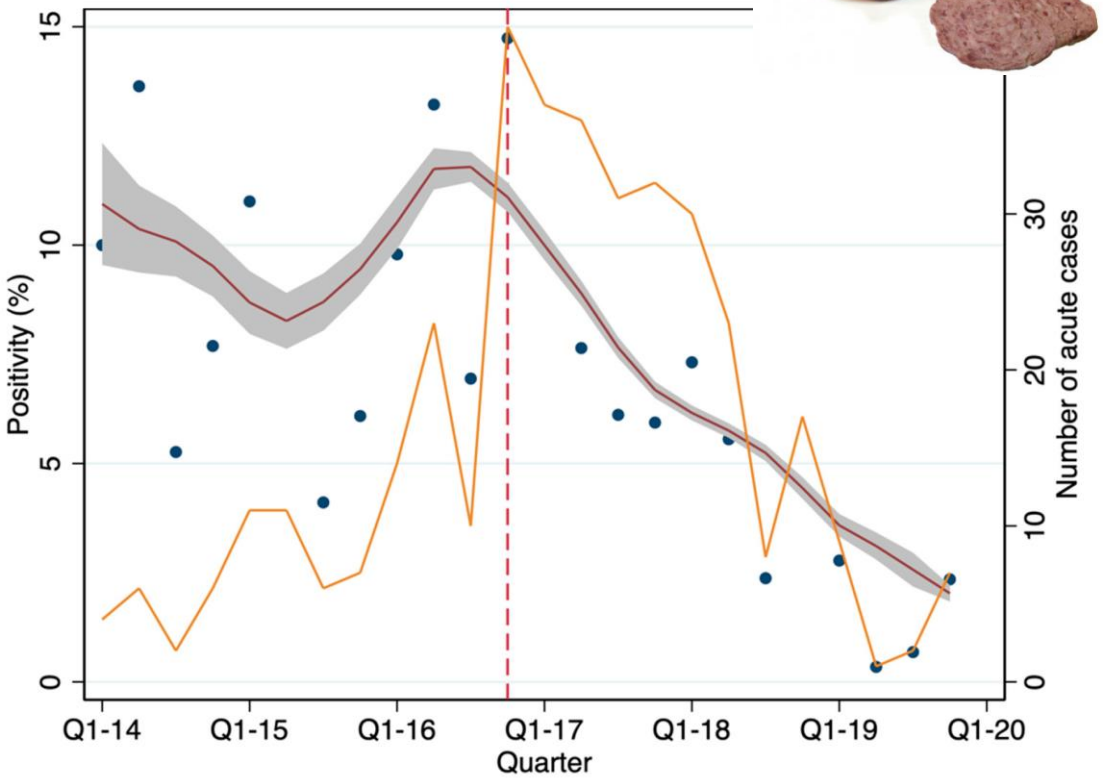


Table 1. Public intervention to control food chain supply and inform the population.

Date	Intervention	Expected Aim
November 2016	Meeting of representatives of the Cantonal Health Service, the Cantonal Veterinary Office, and the Cantonal Food Control Agency	Develop a One Health action plan to reduce human HEV exposure in the food chain at Cantonal (sub-regional) level
December 2016	Involvement of the Federal Food Safety and Veterinary Office (FSVO)	Establish effective measures to protect consumers' health and agree on appropriate risk communication strategies for local authorities
January–April 2017	Start of the active program with the involvement of the Swiss Meat Associations	Include HEV as a hazard in the HACCP * system and provide effective control measures
April 2017	Press release with recommendations by the local authorities to: (a) all meat producers: detailed description of the mandatory changes in the production of sausages containing raw pork liver (b) all medical doctors active in Southern Switzerland: explanation of the modality of HEV infection and its possible hepatic and extra-hepatic clinical manifestations	Inform the local population in order to prevent HEV infections. In particularly, protect YOPI ** people
1 May 2017	Publication of an information letter from FSVO to inform the population and the local authorities of other regions of Switzerland on the risk of HEV infection after consumption of "high risk products"	Inform the population and the local authorities of other regions of Switzerland
May 2018–May 2021	Research project: HEV along the human food chain: investigations into spread, genetic diversity and molecular tracing.	Achieve a better HEV risk assessment.

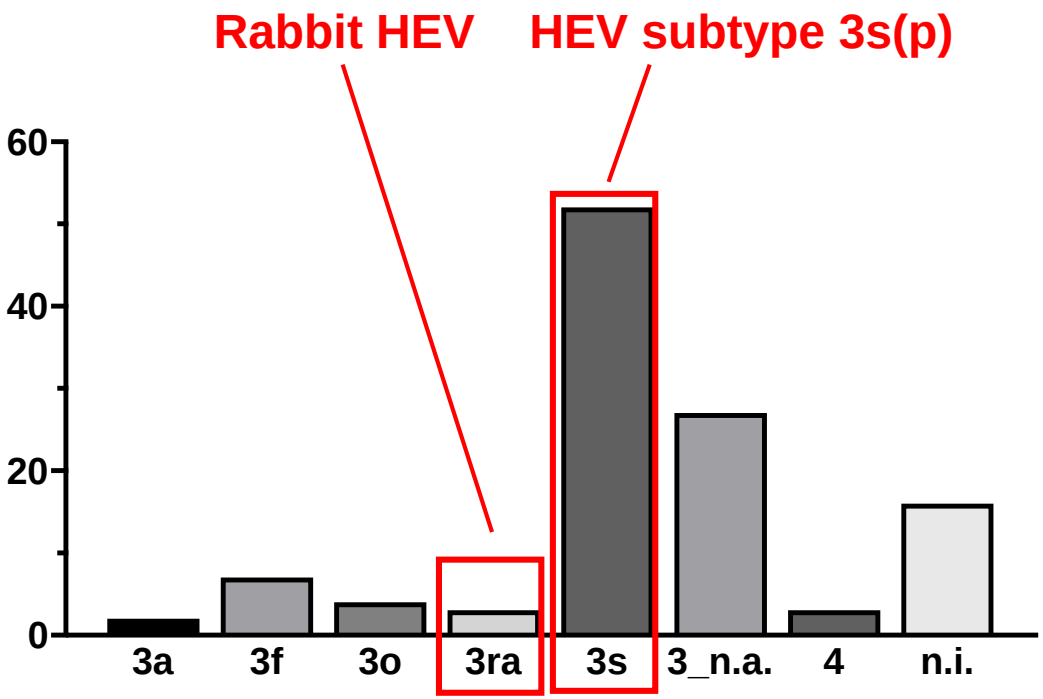
* HACCP = Hazard Analysis and Critical Control Point system; ** YOPI = young, old, pregnant, and immunosuppressed.



Ripellino P *et al*. Pathogens 2021;10:107.

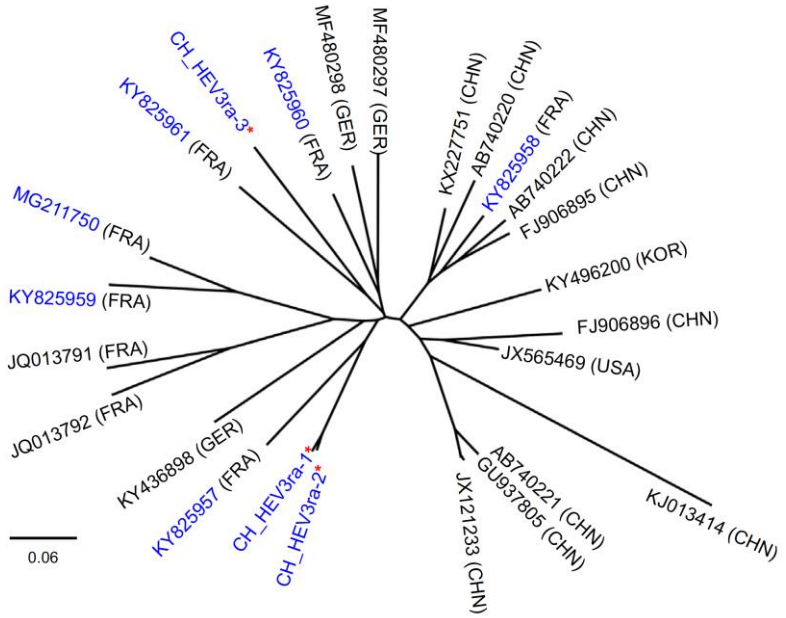
Hepatitis E in Switzerland

Analysis of 114 autochthonous cases diagnosed at the CHUV (n = 104 acute, n = 10 chronic)



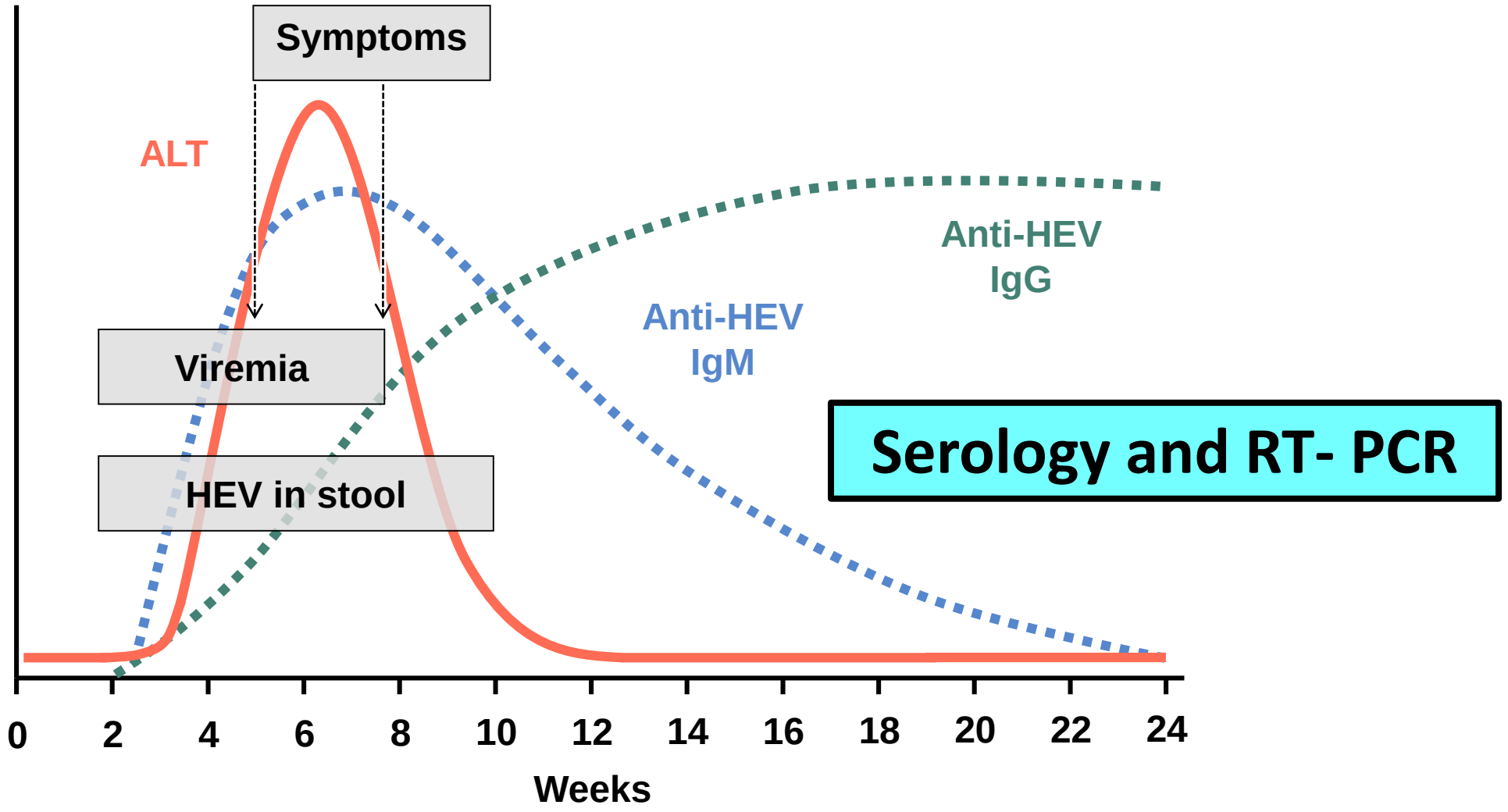
Un virus d'hépatite E particulier en Suisse

Publié le 25.02.2019 09:00 par Amelie Kittel



Sahli R *et al*. J Hepatol 2019;70:1023-1025.

Diagnostic tools



Béguelin C, Fraga M *et al*. Swiss Med Forum 2016;16:510-514.

Testing for HEV Infection

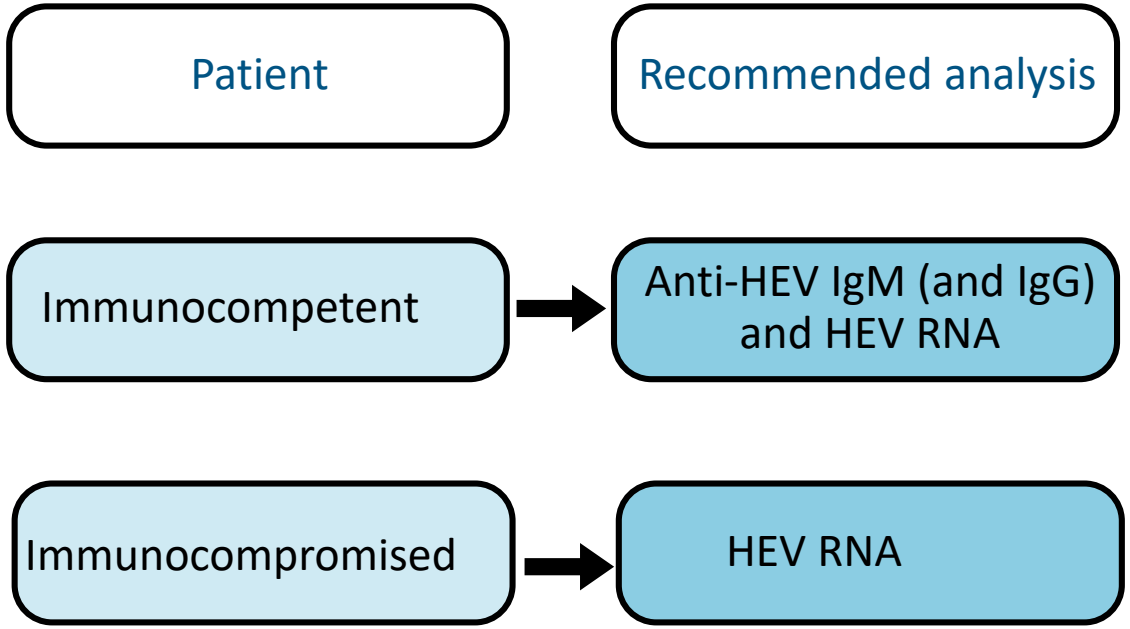


Table 5. Suggested testing for HEV.

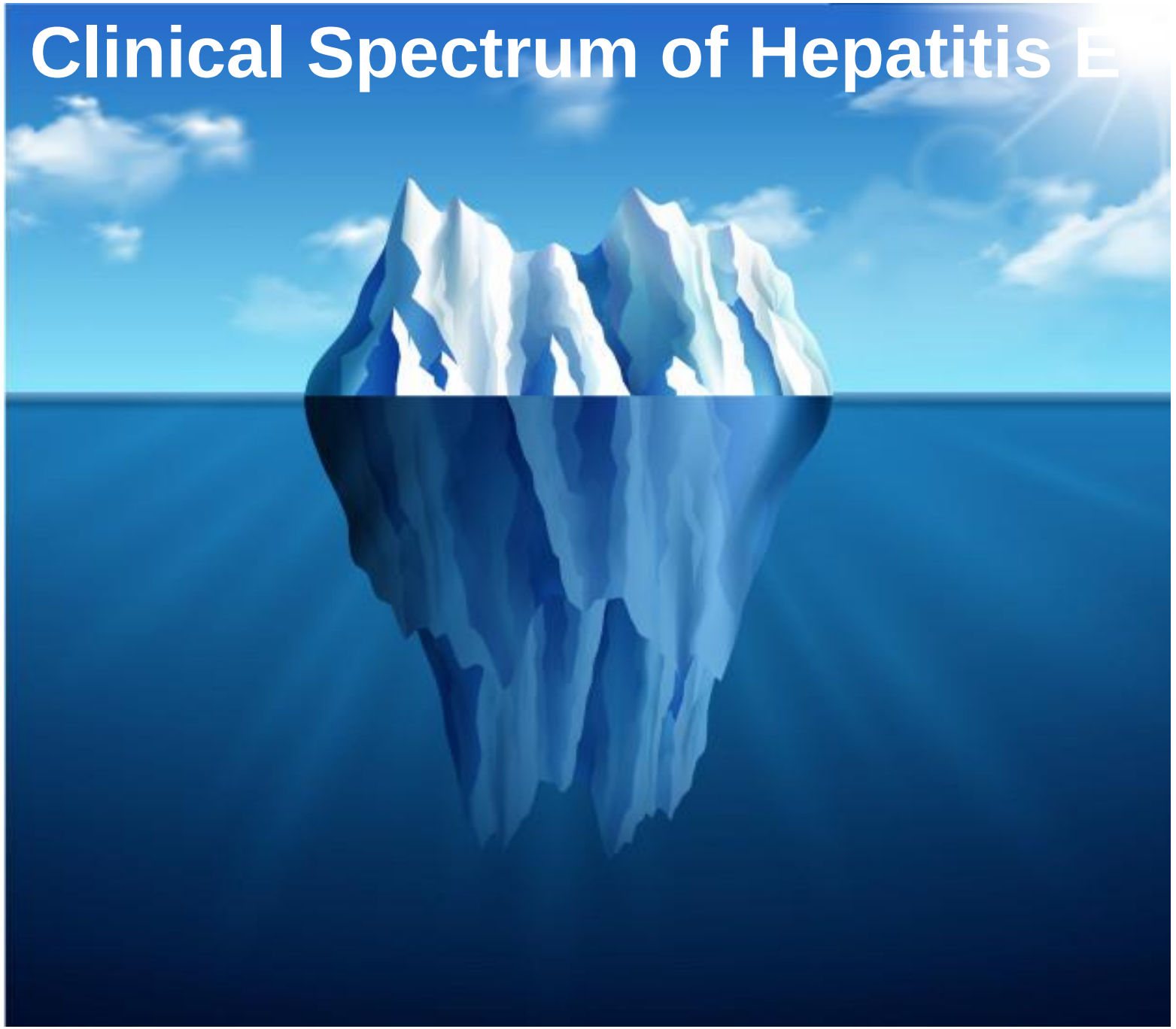
Immunological status	Patients who should be tested for HEV
Immunocompetent	• Any patient with biochemical evidence of hepatitis • Suspected drug-induced liver injury • Decompensated chronic liver disease* • Neuralgic amyotrophy* • Guillain-Barré syndrome* • Encephalitis* • Patients with unexplained acute neurology and a raised ALT**
Immunocompromised (developed countries)	• As above • Persistently abnormal ALT***

* 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 more than one occasion. ALT, alanine aminotransferase; HEV, hepatitis E virus.

Definitive diagosis: HEV RNA!

EASL CPG on HEV Infection. J Hepatol 2018;68:1256-1271 (www.easl.eu).

Clinical Spectrum of Hepatitis E



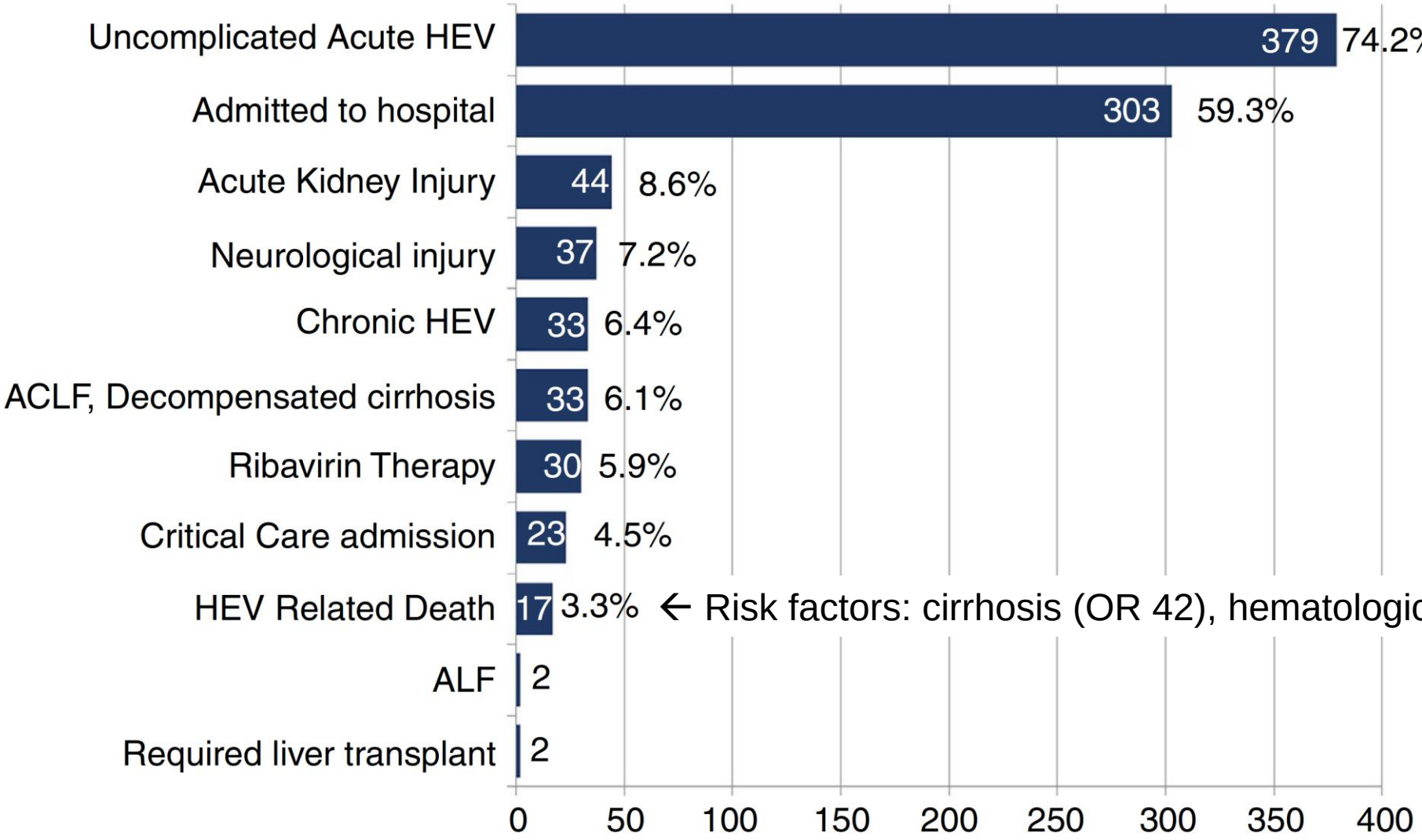
Clinical Spectrum of Hepatitis E

- **Broad spectrum of liver disease severity: asymptomatic - mild hepatitis - liver failure[1]**
- **Extrahepatic manifestations[2,3]**
- **High fatality rate in pregnant women (gt 1)[4] and patients with underlying liver disease**
- **Autochthonous acute hepatitis E "hides" in drug-induced[5] and other liver injuries**
- **Chronic hepatitis and cirrhosis in immunocompromised patients (gt 3 as well as 3ra, 4 and 7)[6]**

[1]Manka P *et al*. CGH 2015;13:1836-1842 | [2]Dalton HR *et al*. Nat Rev Neurol 2016;12:77-85 | [3]Pischke S *et al*. J Hepatol 2017;66:1082-1095 | [4]Krain LJ *et al*. Am J Trop Med Hyg 2014;90:365 | [5]Davern TJ *et al*. Gastroenterology 2011;141:1665-1672 | [6]Kamar N *et al*. NEJM 2008;358:811-817.

Morbidity and Mortality of Autochthonous Hepatitis E

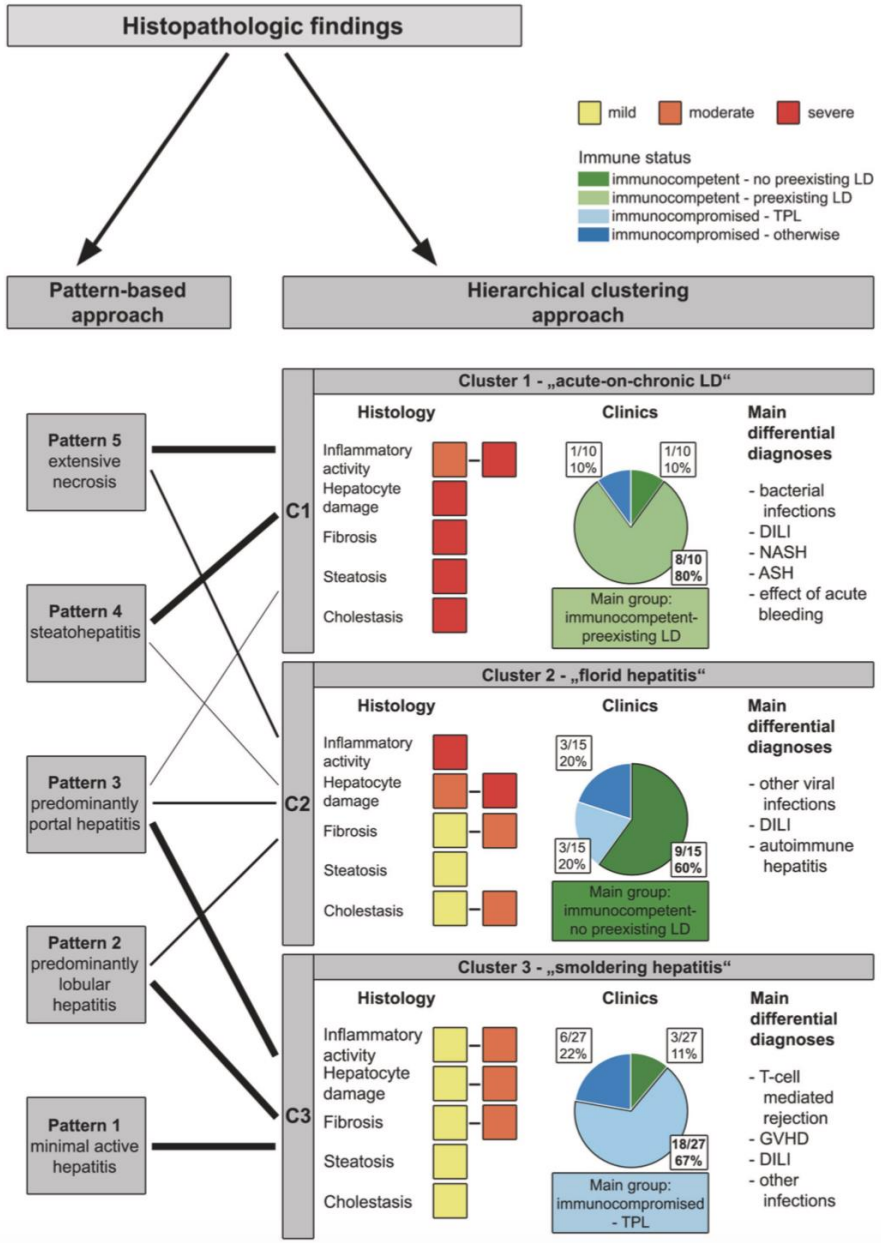
Scottland, 2013-2017 N = 511 (21% immunosuppressed, 21% diabetes, 11% cirrhosis)

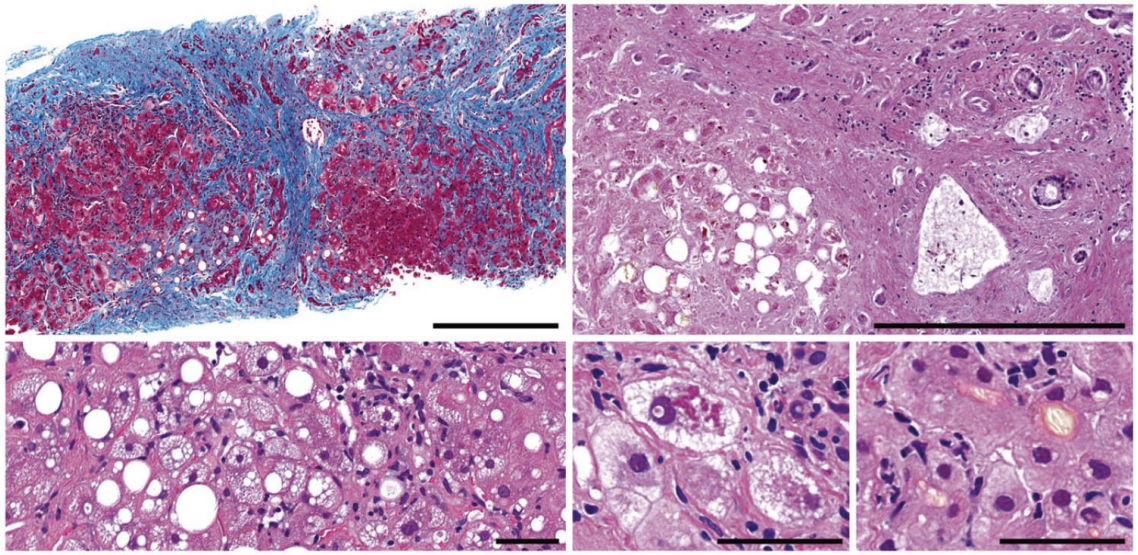


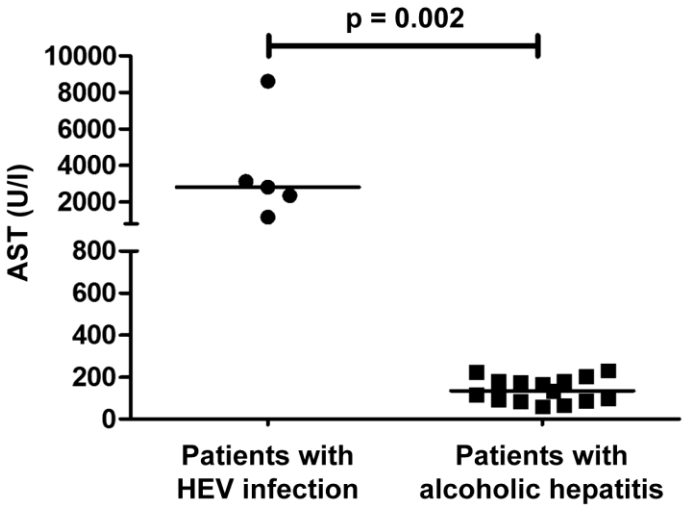
← Risk factors: cirrhosis (OR 42), hematological malignancy (OR 52)

Wallace SJ *et al*. Aliment Pharmacol Ther 2020;51:974-986.

HEV as a Trigger of Acute-on-Chronic Liver Failure

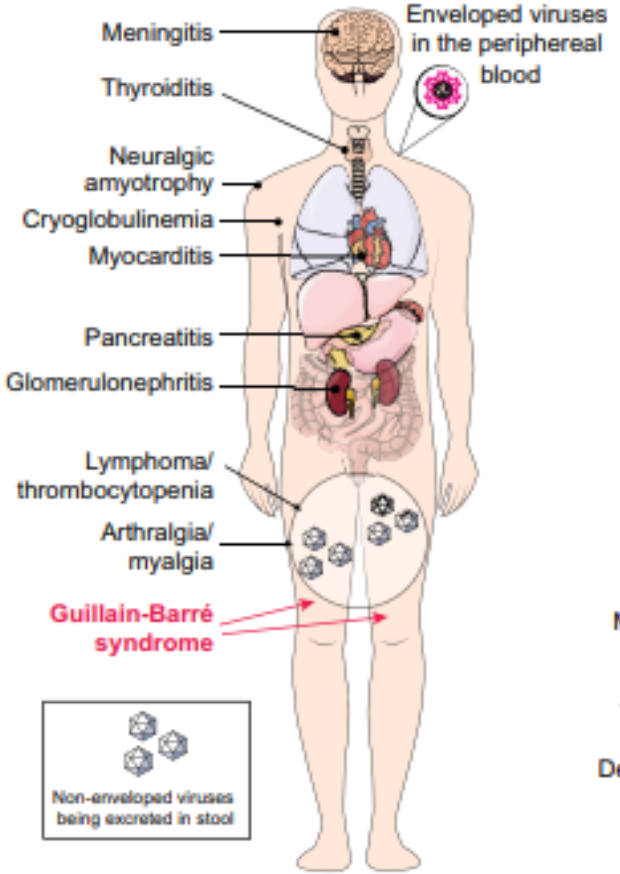




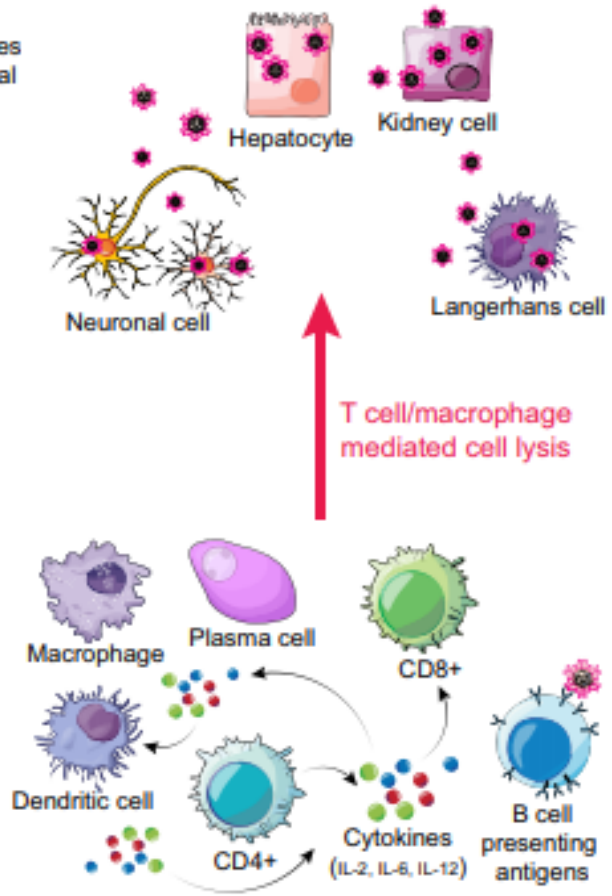


Lenggenhager D *et al*. Mod Pathol 2020.
Vieira Barbosa J *et al*. Swiss Med Wkly 2021 .

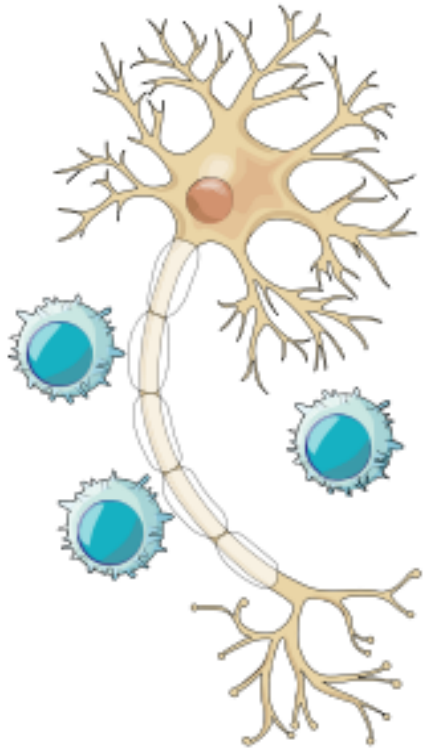
Extra-hepatic manifestations



Reported extrahepatic organ manifestations in the context of hepatitis E virus infection



Possible mechanisms of extrahepatic symptoms in the context of HEV replication



Possible mechanisms of neurological manifestations in the absence of HEV replication

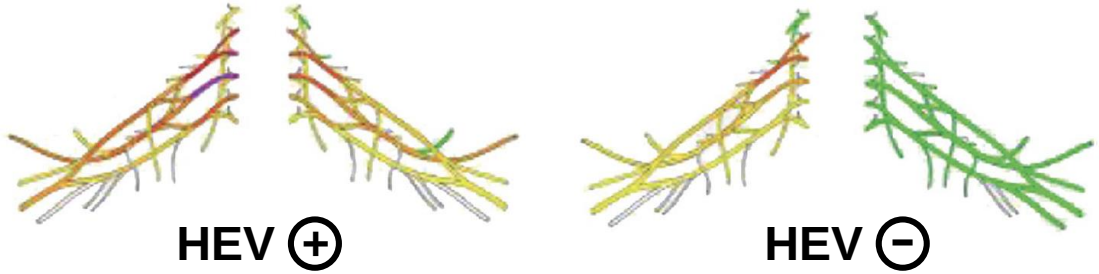
Pischke S, et al. J Hepatol 2017;66:1082–95

Neurological Complications of Hepatitis E

- **Develop in ~5% of autochthonous cases**
- **Hepatitis usually mild → include HEV early in the DD!**

<u>HEV-associated neuralgic amyotrophy</u>

- **57 HEV ⊕ compared to 61 HEV ⊖ cases**
- **Bilateral involvement 80.0 *vs*. 8.6%** (p < 0.001)
- **Damage outside brachial plexus 58.5 *vs*. 10.5%** (p < 0.01)

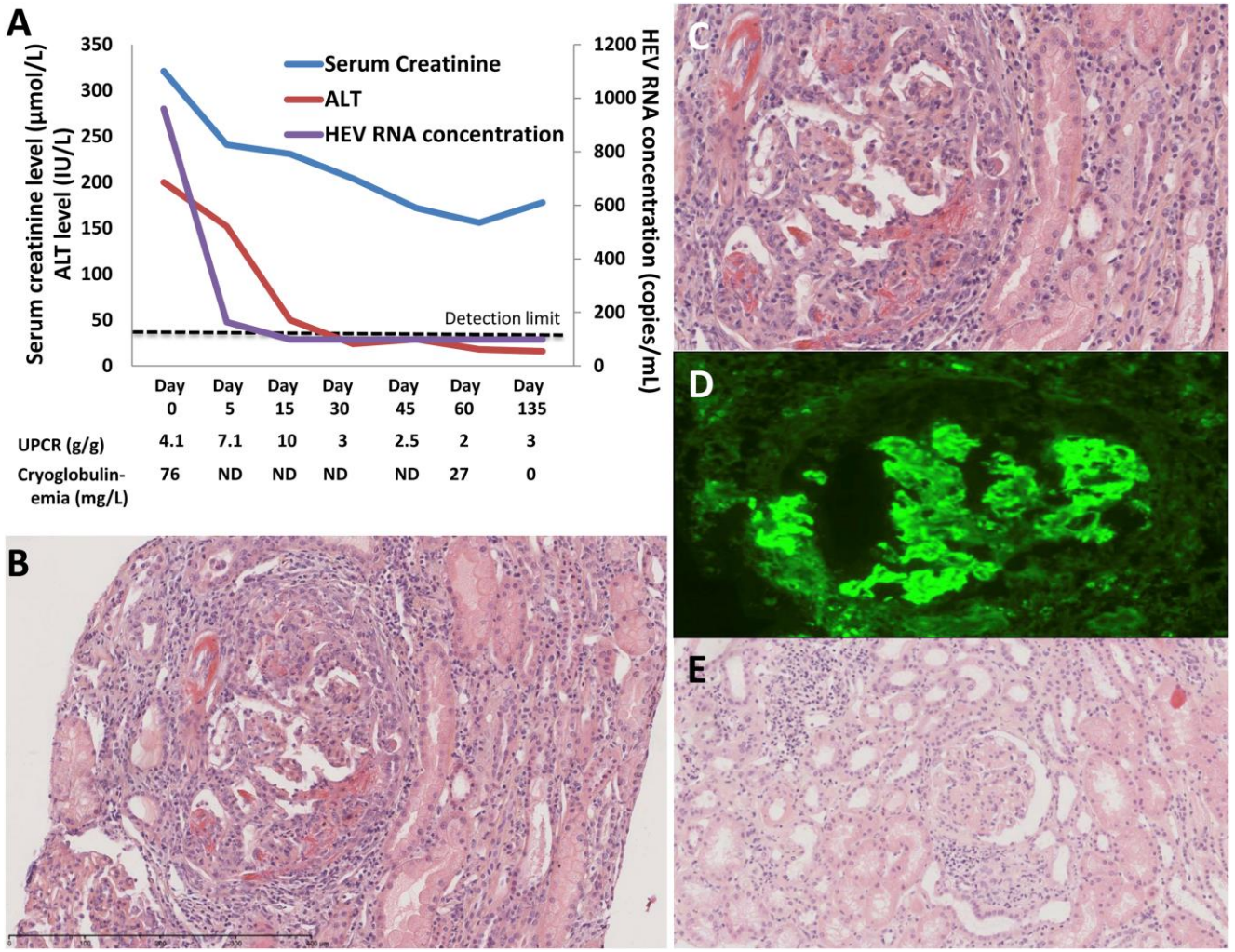


Photograph courtesy of Paolo Ripellino and Claudio Gobbi

van Eijk JJ, Dalton HR, Ripellino P *et al*. Neurology 2017;89:909-917.
Reviewed in Dalton HR *et al*. Nat Rev Neurol 2016;12:77-85.

Renal manifestations associated with HEV

Renal manifestations	No. of cases, age, sex	Country/HEV genotype	Transplants	References
Renal failure, inconspicuous biopsy	1, 34 yr, female	Netherlands/n.a.	None	Verschuuren, 1997 [147]
Membranoproliferative glomerulonephritis	1, 38 yr, male	India	None	Ali, 2001 [81]
No renal biopsy, liver failure	1, 28 yr, male	France/n.a.	Kidney transplant	Kamar, 2005 [148]
Membranoproliferative glomerulonephritis (2x) IgA nephropathy (2x), nephroangiosclerosis and mixed cryoglobulinemia III	5, 24 –58 yr, male	France/3f, 3c	Kidney transplant (n = 4) Liver transplant (n = 1)	Kamar, 2012 [82]
No renal biopsy, renal failure and hyperbilirbinemia	1, 56 yr, male	India/n.a.	None	Vikrant, 2013 [149]
Membranous nephropathy, nephrotic syndrome	1, 60 yr, male	France/3c	Kidney transplant	Taton, 2013 [84]
Membranoproliferative glomerulonephritis, mixed cryoglobulinemia II	1, 46 yr, male	France/3f	Kidney transplant	Kamar, 2015 [150]
Membranoproliferative glomerulonephritis	1, 46 yr, male	France/3f	Kidney transplant	Del Bello, 2015 [83]
Membranoproliferative glomerulonephritis, mixed cryoglobulinemia II in an immunocompetent patient	1, n.a., male	France/3	No immunosuppression	Guinault, 2016 [85]



Pischke S, et al. J Hepatol 2017;66:1082–95

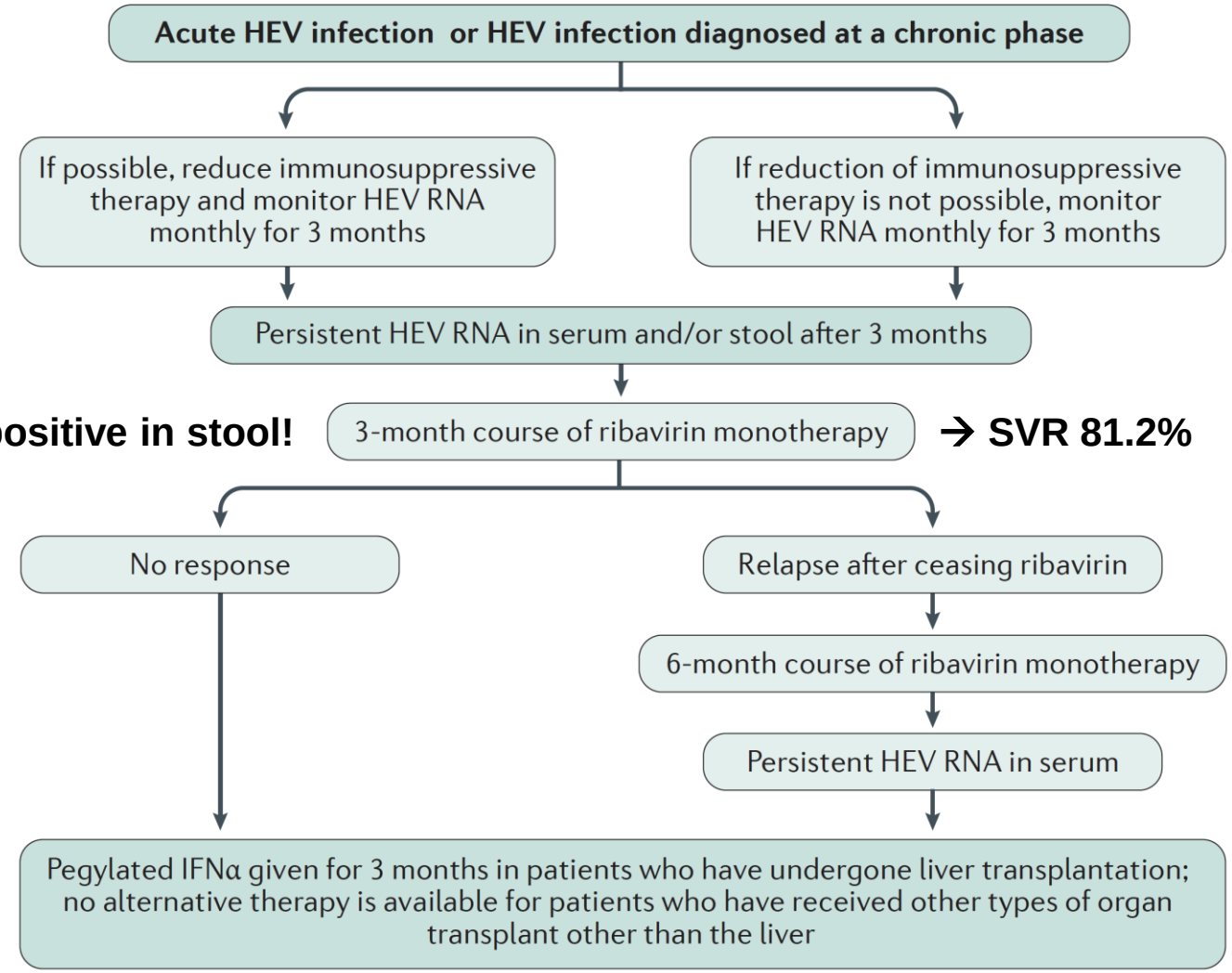
Guinault D *et al*. Am J Kidney Dis.2016

Chronic Hepatitis E

- **Immunosuppressed patients** (transplant recipients, hemato-logic cancer, HIV, ...)
- **HEV genotype 3** (as well as genotypes 3ra, 4, 7, possibly 1 and rat HEV in Hong Kong)
- **May rapidly progress to liver cirrhosis**
- **Serology often negative → HEV RNA**
- **Reduction of immunosuppression → ribavirin**
- **Ribavirin resistance emerges as a challenge → need for new therapeutic options**

Kamar N *et al*. NEJM 2008;358:811-817 and Clin Infect Dis 2020;71:1204-1211;
Marion O *et al*. J Hepatol 2019;70:206-9 | Gorris M *et al*. J Viral Hepat 2021;28:454-463.
Debing Y *et al*. J Hepatol 2016;65:499-508; Todt D, Gisa A *et al*. Gut 2016;65:1733-1743.
Reviewed in Kamar N *et al.* Nat Rev Dis Primers 2017;3:17086 and EASL CPG. J Hepatol 2018;68:1256-71.

Chronic Hepatitis E management



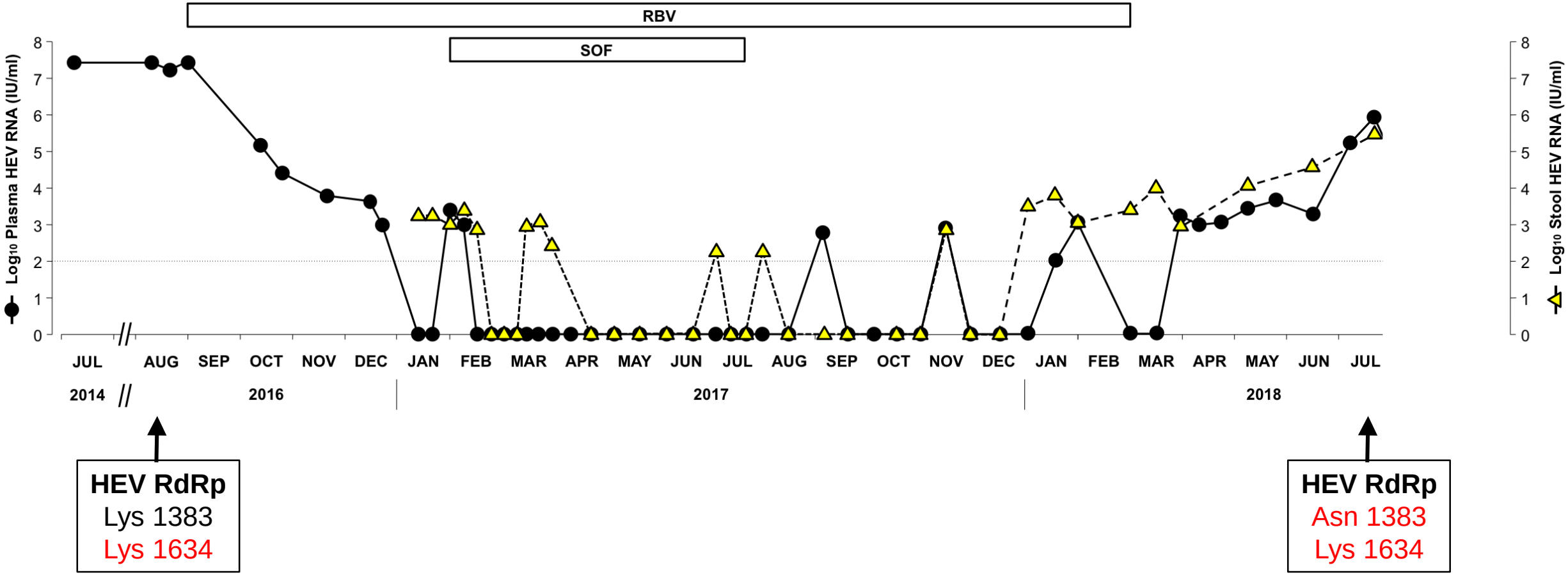
Start earlier?

Prolong if HEV RNA still positive in stool!

→ SVR 81.2%

→ SVR 89.8%

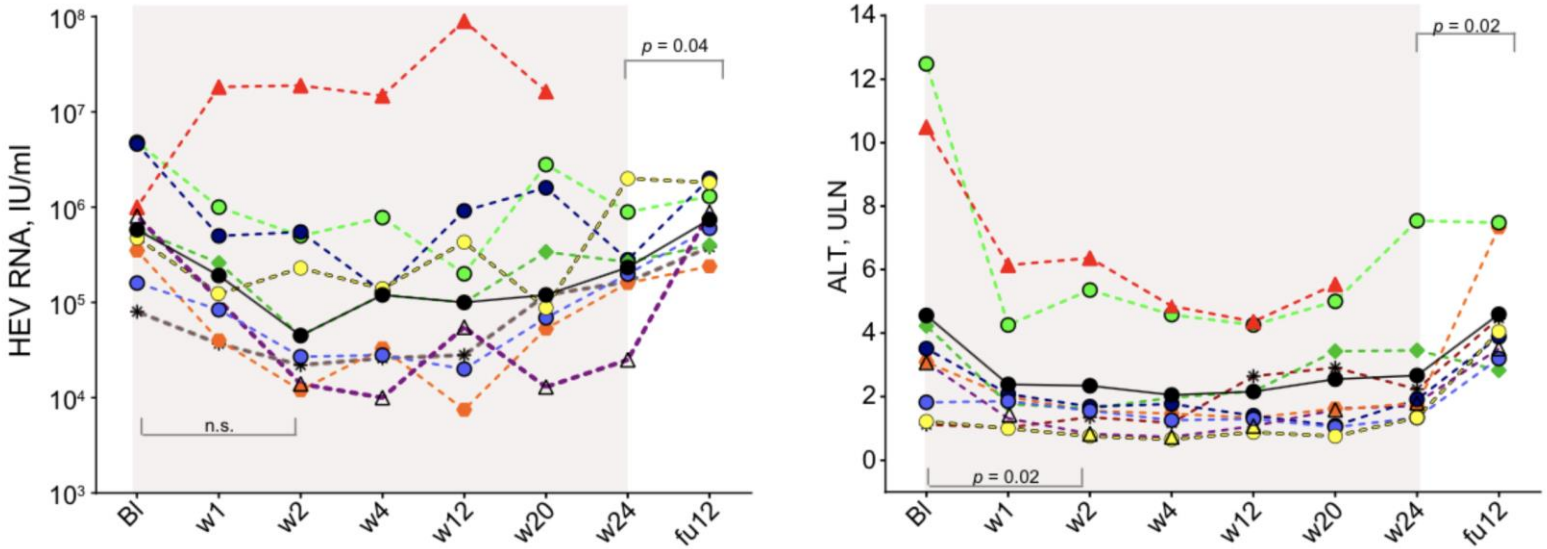
Kamar N *et al.* Nat Rev Dis Primers 2017;3:17086 and EASL CPG on HEV infection. J Hepatol 2018;68:1256-1271.
See also Marion O *et al*. J Hepatol 2019;70:206-209; van Felden J *et al*. J Hepatol 2019;71:465-472 and Kamar N *et al*. Clin Infect Dis 2020;71:1204-1211.



Fraga M *et al*. BMC Gastroenterol 2019;19:76.
Lhomme S *et al*. AAC 2015;60:1608-1614, Debing Y *et al*. J Hepatol 2016;65:499-508 and
Todt D, Gisa A *et al*. Gut 2016;65:1733-1743; reviewed in Todt D *et al*. Curr Opin Virol 2018;32:80-87.
See also Oechslin N, Da Silva N *et al*. Hepatology, in press (epub Aug 13, 2021).

Sofosbuvir for Chronic Hepatitis E

- **Sofosbuvir inhibits HEV RNA replication *in vitro* and results in an additive effect when combined with RBV[1]**
- **At least 12 case reports with mixed results (HEV clearance in 2, some antiviral effect w/o clearance in 8, no antiviral effect in 2)[2]**
- **Monotherapy with SOF yields 1-log HEV RNA decline in patients with RBV-refractory chronic hepatitis E but not viral clearance[3]**



[1]Dao Thi VL *et al*. Gastroenterology 2016;150:82-85 | [2]Fraga M *et al*. BMC Gastroenterol 2019;19:76, Schulz M *et al*. J Hepatol 2019;71:225-227, van Wezel EM *et al*. OFID 2019;6:ofz346 | [3]Cornberg M *et al*. J Hepatol, 2020;73:696-699.

Preventive efforts

- **Public health: improve food chain control**
- **Systematic blood products screening (CH since 2018)**
- **Individual: advice patients at risk against raw porc and game consumption**
- **Vaccine? Two recombinant capsid-based vaccines have proven high (96-100%) efficacy in large-scale clinical trials**

Shrestha MP *et al*. N Engl J Med 2007;356:895-903.
Zhu F-C *et al*. Lancet 2010;376:895-902.

Hepatitis E – Challenges in 2021

- Deeper understanding of the epidemiology and transmission
- Viral and host determinants of clinical outcomes
- New therapies for chronic hepatitis E
- Enhanced preventive efforts