Hepatitis E : what is the issue?

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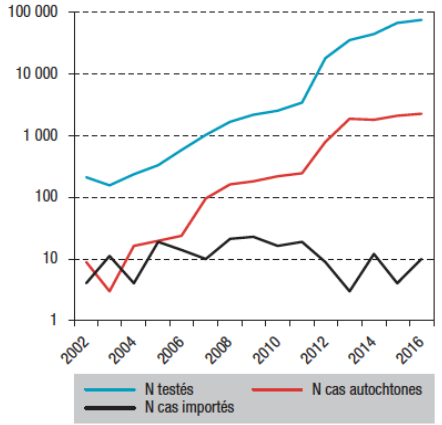
Figure 1
Évolution du nombre de personnes testées et du nombre de cas d'hépatite E diagnostiqués par an, France métropolitaine, 2002-2016



Source : Centre national de référence des virus des hépatites à transmission entérique (CNR).

Hepatitis E in 2020

- Incidence is high and rising
- Subtype counts
- Risk of transmission by transfusion
- Neurological disorders are frequent
- Treatment of acute hepatitis E with ribavirin in immunocompetent patients
- Second line treatment of chronically infected patients

Epidemiology

- 1st cause of acute hepatitis
  - Worldwide, in Europe, in France
- 20 million cases/year
  - 70 000 deaths/year
  - > 3 million symptomatic patients
- In Europe: 2 million cases/year
- In France: 2302 cases in 2016: 99% autochthonous

WHO. Viral hepatitis. Jul, 2015
EASL guidelines 2018 vol 68 1256

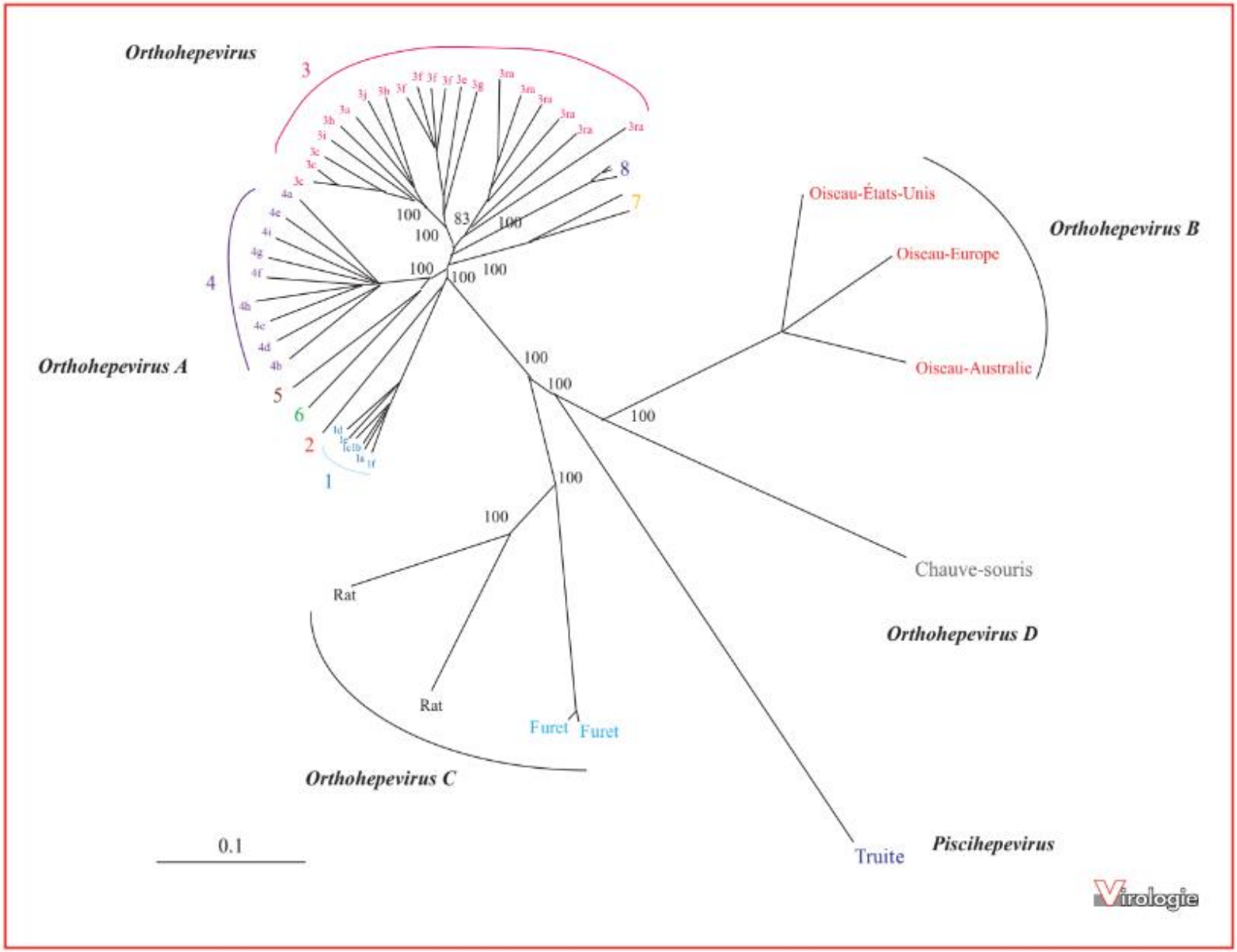
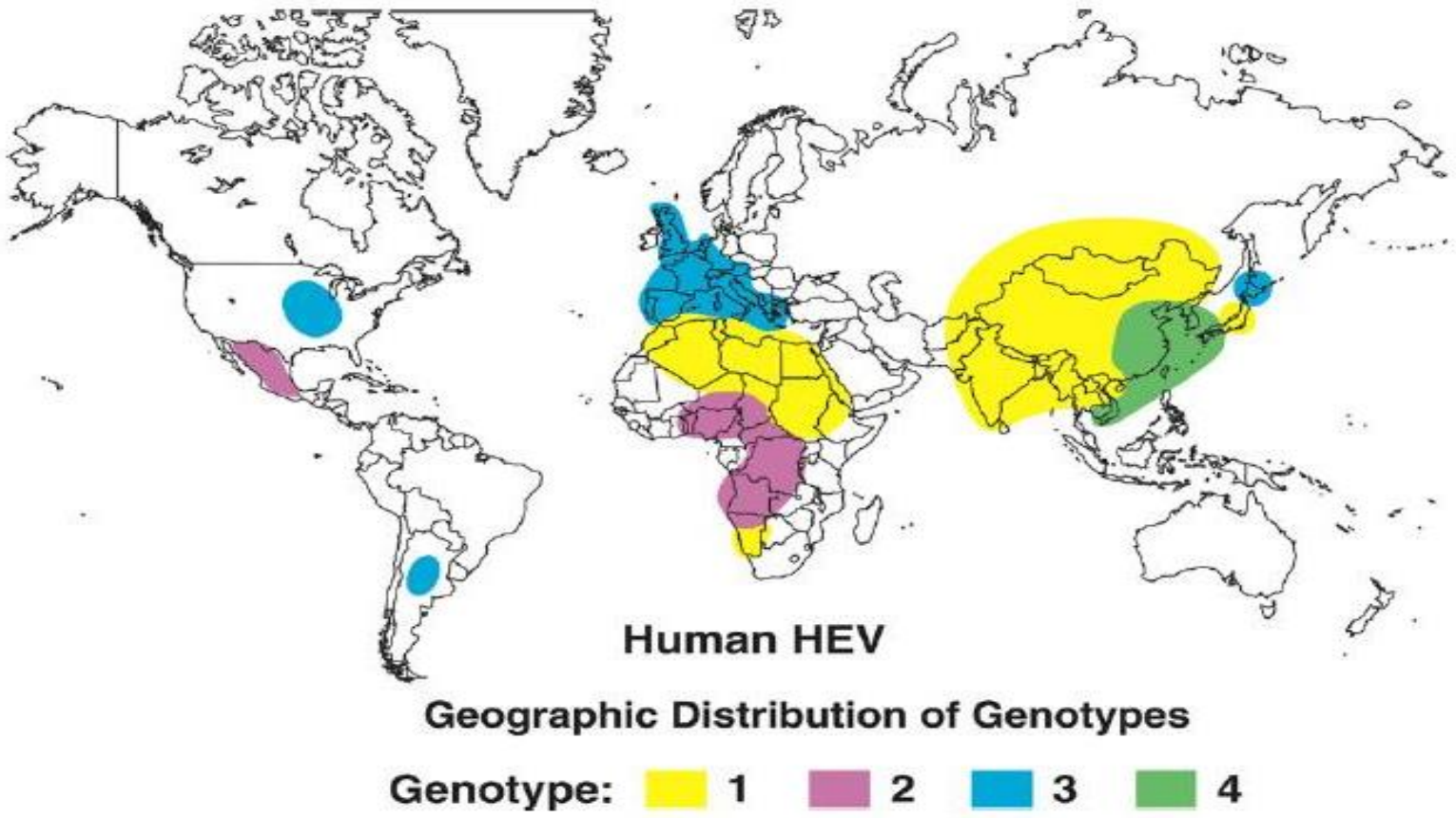


Figure 1. Arbre phylogénétique basé sur les séquences de génomes complets disponibles du virus de l'hépatite E (VHE). Les séquences ont été alignées en utilisant le logiciel ClustalW. L'arbre phylogénétique a été obtenu avec la méthode de Neighbor-Joining (correction de Kimura à deux paramètres). L'espèce *Orthohepevirus* A est divisée en huit génotypes : les génotypes 1 et 2 sont strictement humains tandis que les génotypes 3 à 8 possèdent un réservoir animal. Plusieurs sous-génotypes (désignés par une lettre) ont été décrits pour les génotypes 1 à 4.

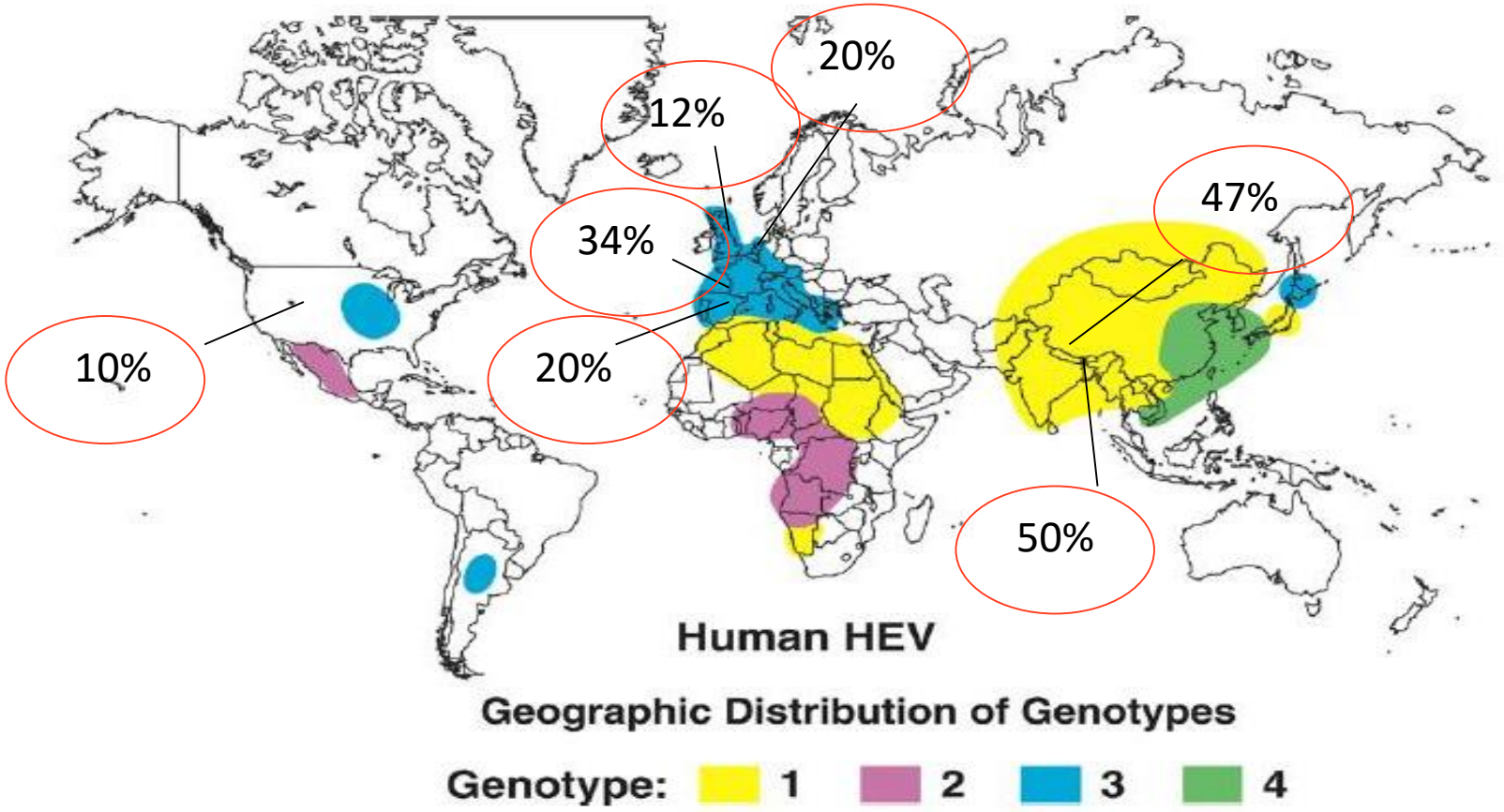
Worlwide distribution



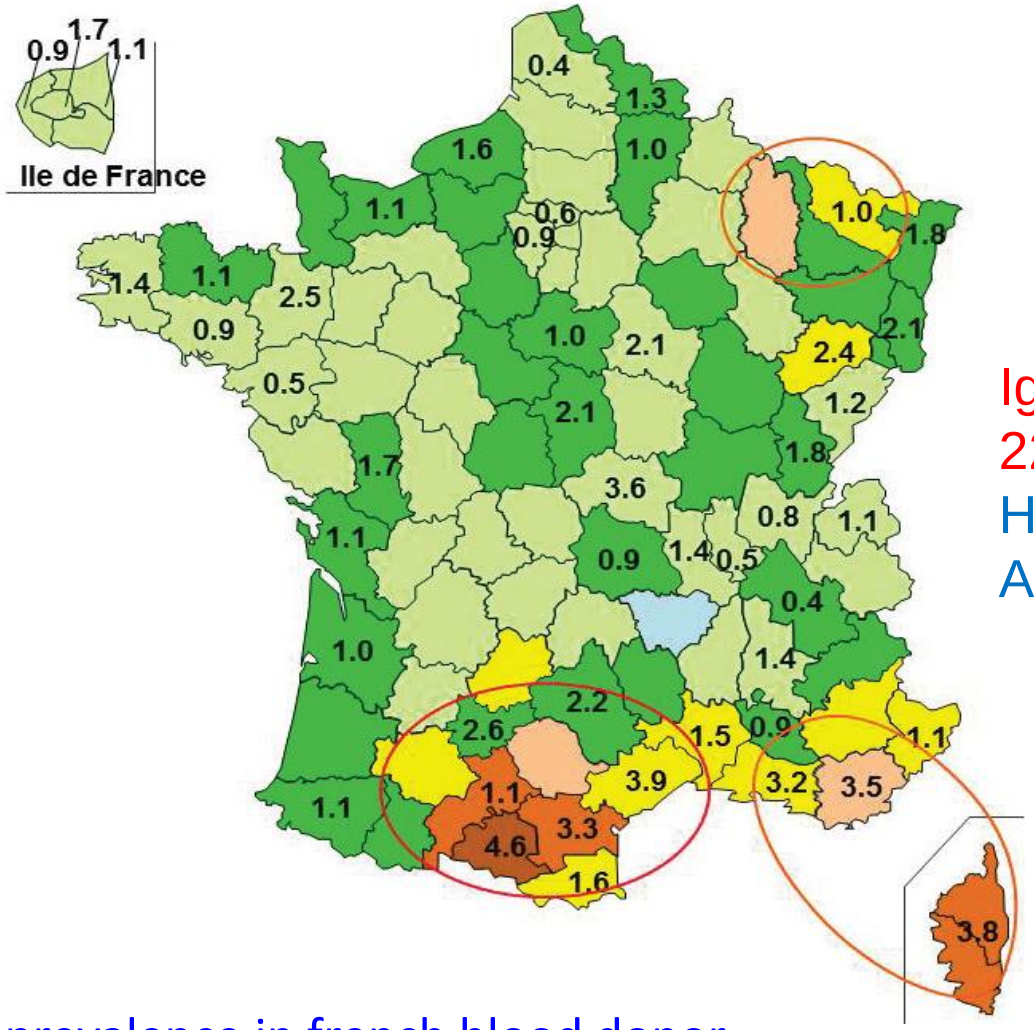
Comparison of HEV genotypes

Characteristics	HEV 1 and 2	HEV3 and 4
Source of infection	Obligate human pathogen	Zoonotic Blood supply
Route of infection	Faecal-oral via infected water	Consumption of infected pork Blood supply
Outbreaks	Yes	No
Clinical attack rate	1:5	< 1:10
Demographics	Mainly affects young adults	Mainly affects older men Male:female ratio 3:1
Chronic infection	No	Yes in immunosuppressed individuals
Occurrence of second HEV infection	Yes	Yes
Neurological sequelae	Yes	Yes

Seroprevalence



Stramer SLTransfusion 2015
Izopet J Clin Virol 2015
Dalton H Curr Infect Dis Rep 2014



IgG seroprevalence :
22,4 % in France
Haute Loire : 8%
Ariège : 86,4%

IgG and IgM seroprevalence in french blood donor

Blue < 10%, green 20-30%, yellow 30-40%, pink 40-50 %
Orange 60-70%, brown > 70%

Mansuy et al Hepatology 2016

Figure 1

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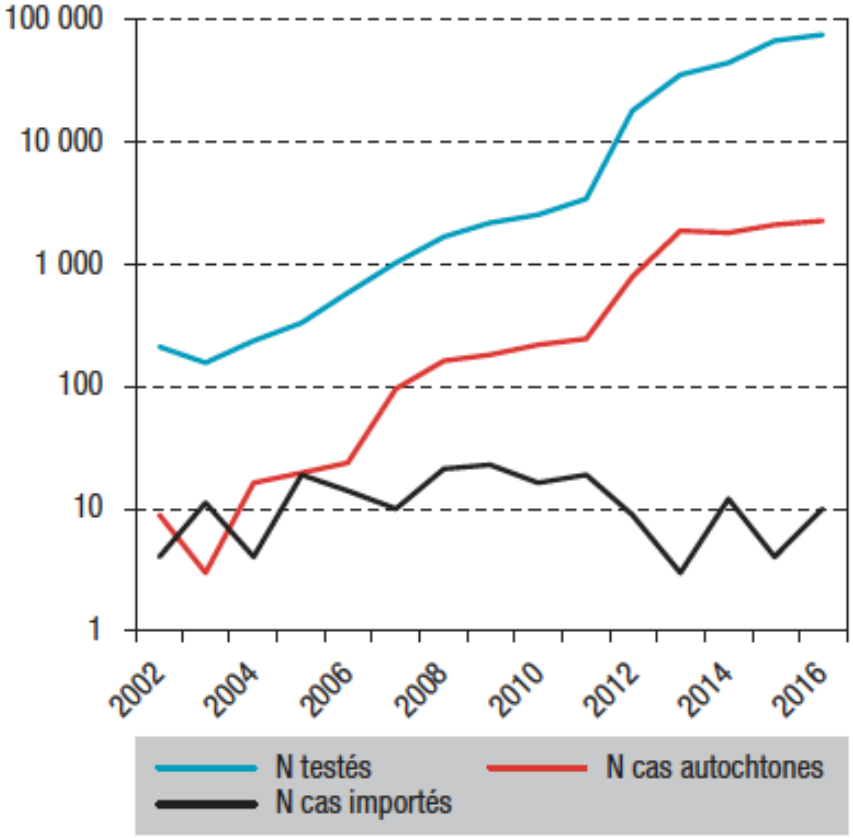


Source : Centre national de référence des virus des hépatites à transmission entérique (CNR).

2302 cases in 2016
10 imported

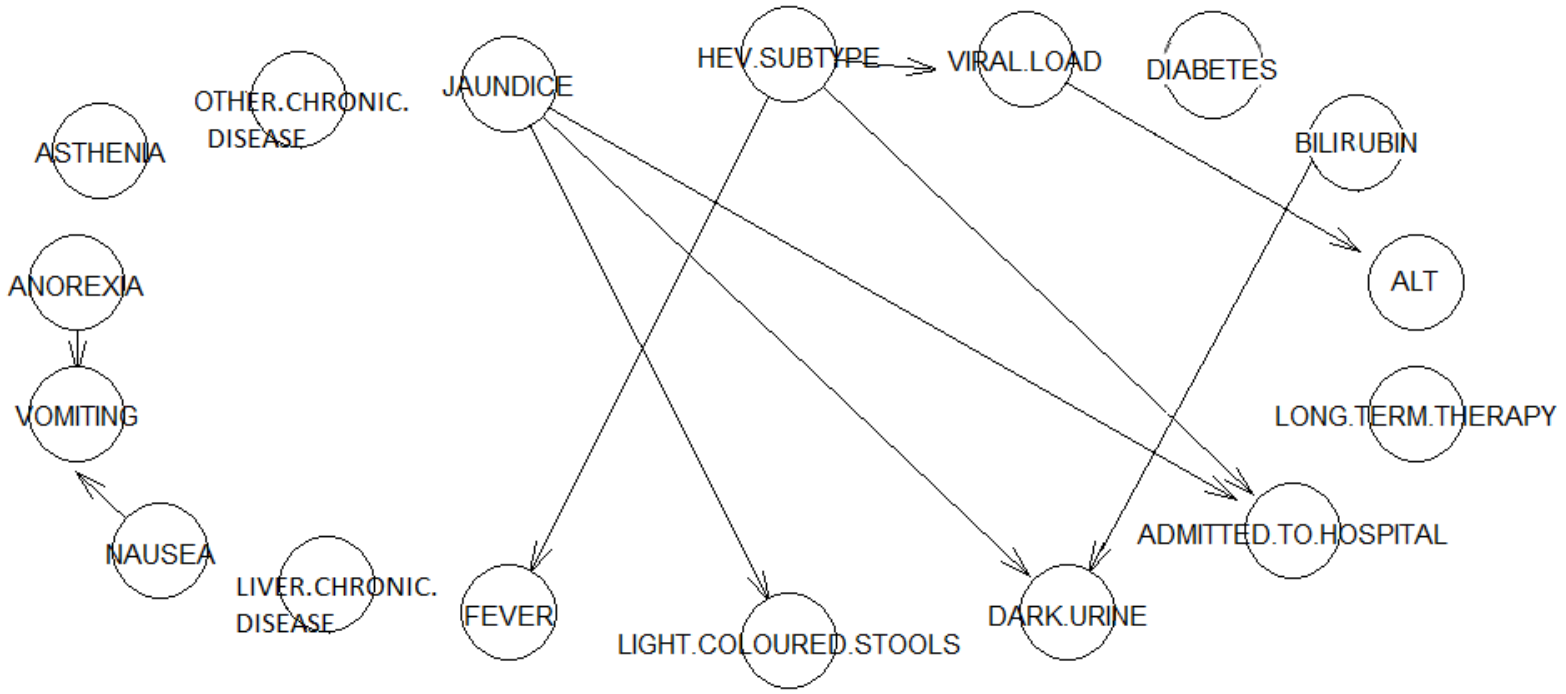
Couturier et al BEH 28 11 sept 2018

- Seroprevalence is high (very high in some regions)
- Incidence is rising
- Most cases go unnoticed
- Role of subtype ?

Do genotypes and sub-types matter ?

- HEV-1 and HEV-4 may be associated with a higher morbidity but patients are different

- More hospitalisations with HEV-3f
  - Subissi J Epidemiol Infec 2017
  - Abravanel Liver Int 2019
    - Fever : OR 6.1; 95% CI: 1.4-26.1
    - Greater viral load : OR 7.4; 95% CI: 1.3-42.2
    - More hospitalizations : OR 7.6; 95% CI: 1.1-51.4



- Directed acyclic graph describing the relationships between HEV subtype and clinical and biological varaiables

- Incidence is high and rising
- Subtype counts
- Risk of transmission by transfusion
- Neurological disorders are frequent
- Treatment of acute hepatitis E with ribavirin in immunocompetent patients
- Second line treatment of chronically infected patients

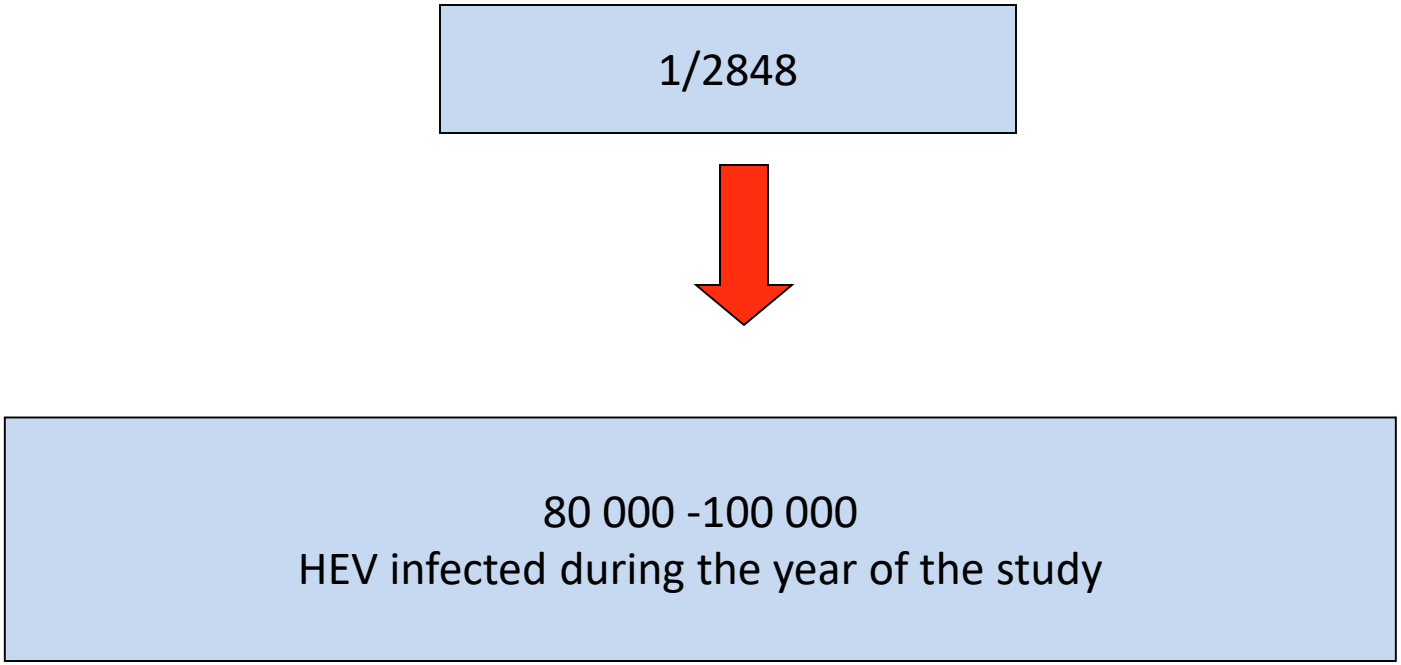
Transmission (Developed countries genotype 3)

- Transfusion
  - England
    - Oct 2012 to sept 2013
    - 225 000 blood donations , southeast England
    - Mini pools of 24 donors
    - 1/2848 viremic donors, 71% seronegative
    - Transfusion of 62 contaminated blood components
      - 42% HEV infection, 1 apparent clinically mild hepatitis, 10 developped prolonged infection
    - Risk factors for HEV transmission:
      - Volume transfused (PFC, platelets)
      - Absence of donor detectable Ab
      - High viral load

Hewitt PA Lancet 2014

Transmission (Developed countries genotypes 3)

- Transfusion
  - England



Hewitt PA Lancet 2014

Transmission (Developped countries genotypes 3)

- Transfusion : viremic donors
  - HEV viremia 1/600 to 1/2500 in European countries with high endimicity (1/800 in France)
  - HEV viremia 1/2300 to 1/14500 in European countries with intermediate to low endemicity

Gallian P Transfusion 2017
Izopet J J clin virol 2019

  - US 1/9500
    - 18,829 donations
    - 6 US geographic regions,
    - 2 pos donors from Midwest
    - 9% IgG prevalence (MP Biochemicals)

Stramer SL Transfusion 2015

- There is a risk of transmission with blood transfusion
- Blood donations are already screened in Ireland, the UK, the Netherlands and Switzerland.
- In France, HEV is detected in plasma donations used in the preparation of fresh frozen plasma

- Incidence is high and rising
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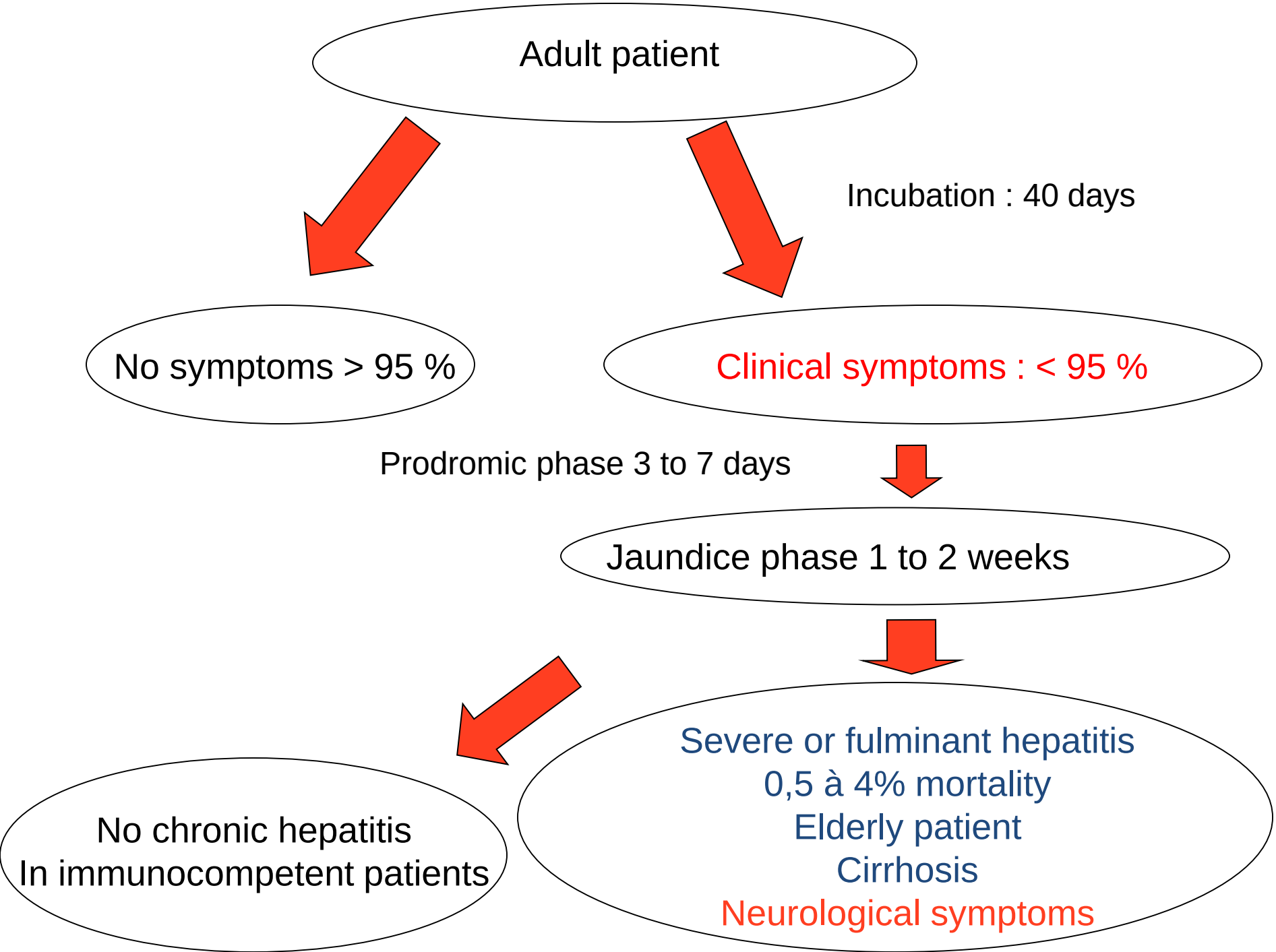
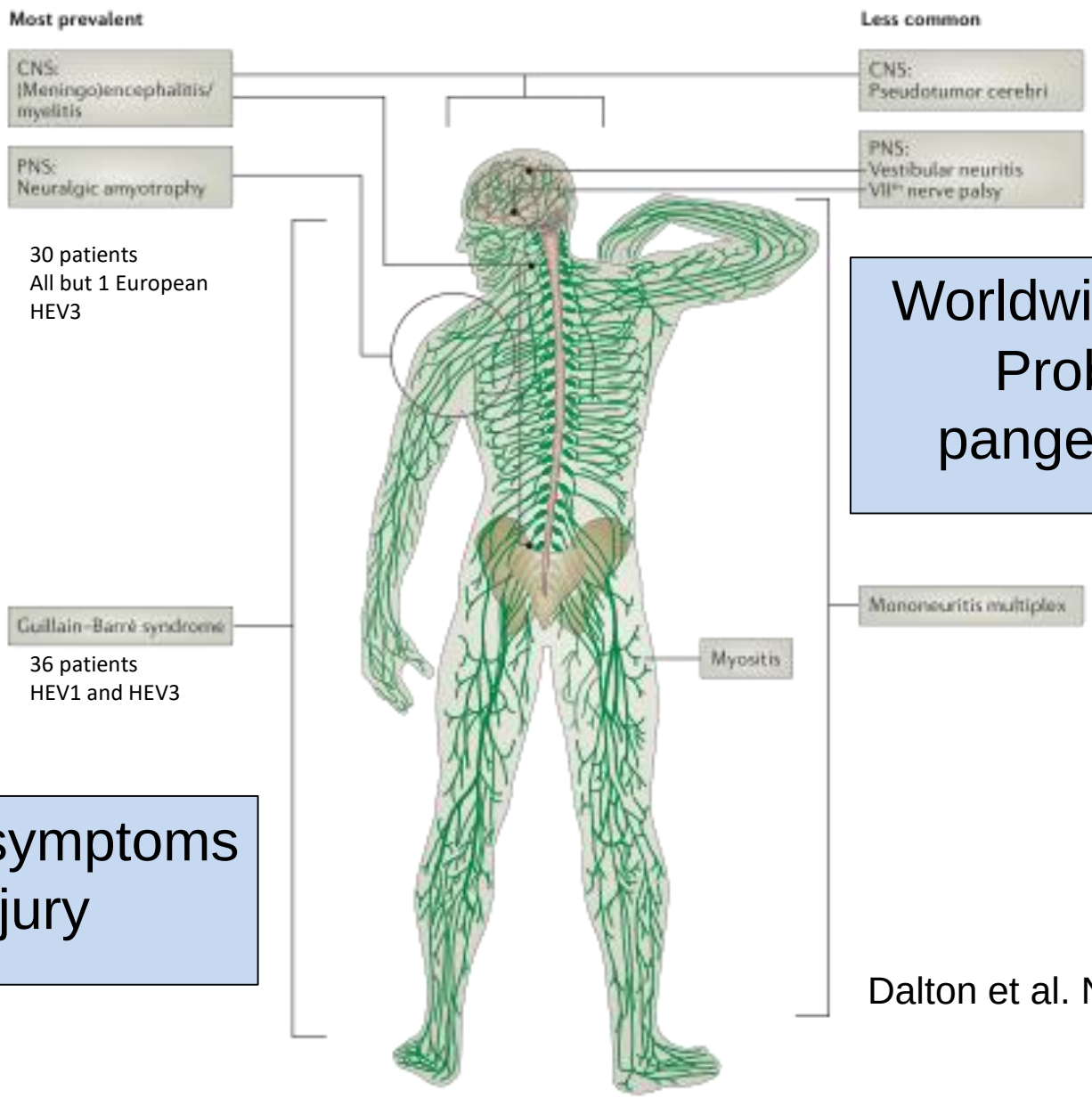

Adult patient
Incubation : 40 days
No symptoms > 95 %
Clinical symptoms : < 95 %
Prodromic phase 3 to 7 days
Jaundice phase 1 to 2 weeks
No chronic hepatitis
In immunocompetent patients
Severe or fulminant hepatitis
0,5 à 4% mortality
Elderly patient
Cirrhosis
Neurological symptoms

Neurological disorders during HEV infection



Worldwide cases
Probably pangenotypic

Mild liver symptoms or injury

Dalton et al. Nature Rev 2016

Clinical caracteristics
Jan 2015-dec 2015

Symptoms	N = 137
Age	53 ± 14
Male	66 %
Hospitalisation	74,5 %
Asthenia	85,4 %
Jaundice	43 %
Neurologic disorders	16.5 %

Abravanel et al J Infection 2018

Prevalence of HEV infection in patients with neurological symptoms : Guillain Barré syndrome

- Guillain Barré syndrome
  - Royal Cornwall hospital UK, Radboud University Nijmegen MC, Netherlands
  - 201 patients with GBS, 201 healthy controls
  - 5% : 10/201 patients (Pos PCR in 4 patients), mildly increased liver tests in 70 %
  - (1/201 in the healthy controls, OR 10.5, 95 % confidence interval 1.3-82.6, p = 0.026))

Van den Berg B Neurology 2014

Prevalence of HEV infection in patients with neurological symptoms : neuralgic amyotrophy

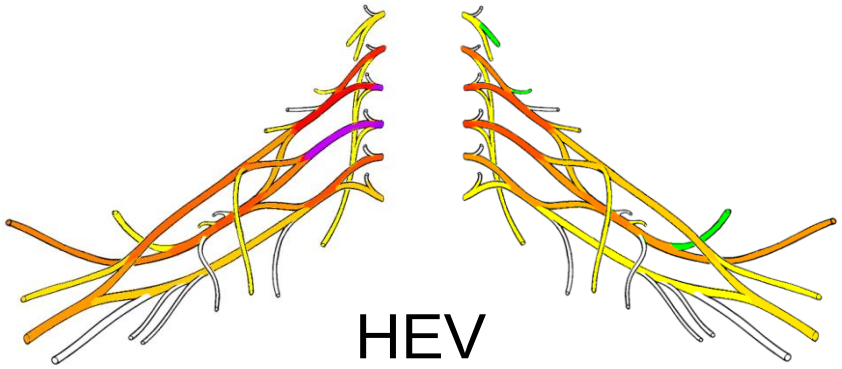
- Neuralgic amyotrophy (Parsonage Turner syndrome)
  - Royal Cornwall hospital UK, Radboud University Nijmegen MC, Netherlands
  - Retrospective and prospective cohorts

  - 10 % : 5/47 patients (4 HEV PCR pos)
  - Bilateral brachial involvement (1/2 in non HEV cases)
  - Significant residual neurologic impairment at 6 months

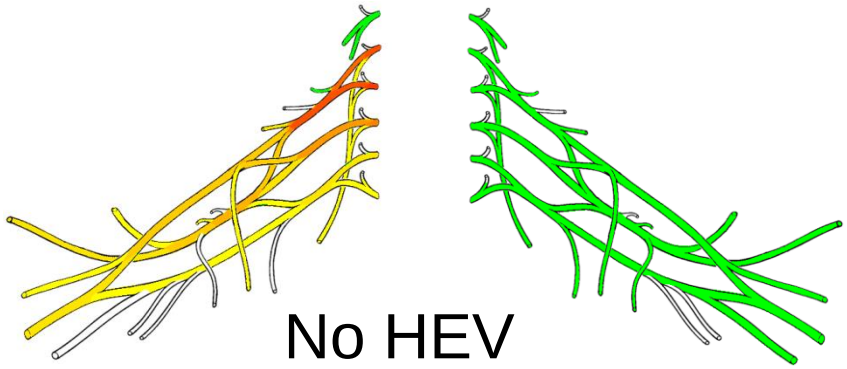
Van Eijk JJ Neurology 2014

Neuralgic amyotrophy (Parsonage Turner syndrome)

- European multicentric study, 11 centers, 7 countries
- 57 cases of NA associated to HEV infection vs 61 not associated
  - Normal enzymes in 6 cases, 51/57 anicteric
  - Asymmetrical, bilateral involvement (80% vs 8.6%)
  - Damage outside the brachial plexus (58.5 % vs 10.5%)
    - Phrenic nerve, lumboscral plexus injury
  - More sensory symptoms



HEV



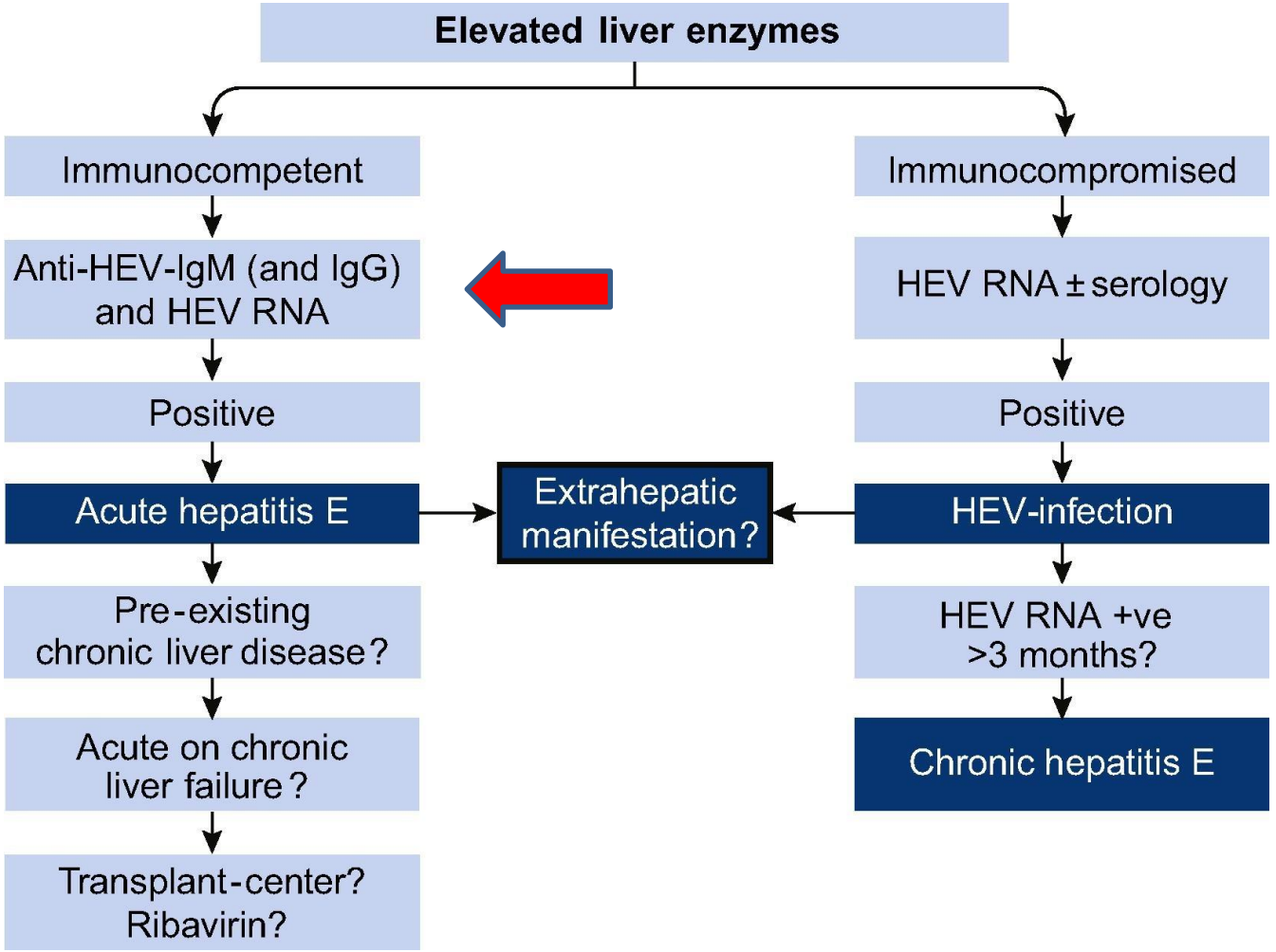
No HEV

Dalton H et al Neurology 2017

When should you look for HEV?
EASL guidelines

- Acute viral hepatitis (first line workup) (A1)
- Suspected drug induced liver injury (A1)
- Decompensated cirrhosis
- Guillain Barré syndrome, neuralgic amyotrophy(B1), encephalitis ou myelitis (C2)
- Acute neurological symptoms associated with elevated transaminases
- Elevated transaminases following transfusion (A1)

HEV diagnosis
EASL guidelines



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- Incidence is high and rising
- Subtype counts
- Risk of transmission by transfusion
- Neurological disorders are frequent
- Treatment of acute hepatitis E with ribavirin in immunocompetent patients
- Second line treatment of chronically infected patients

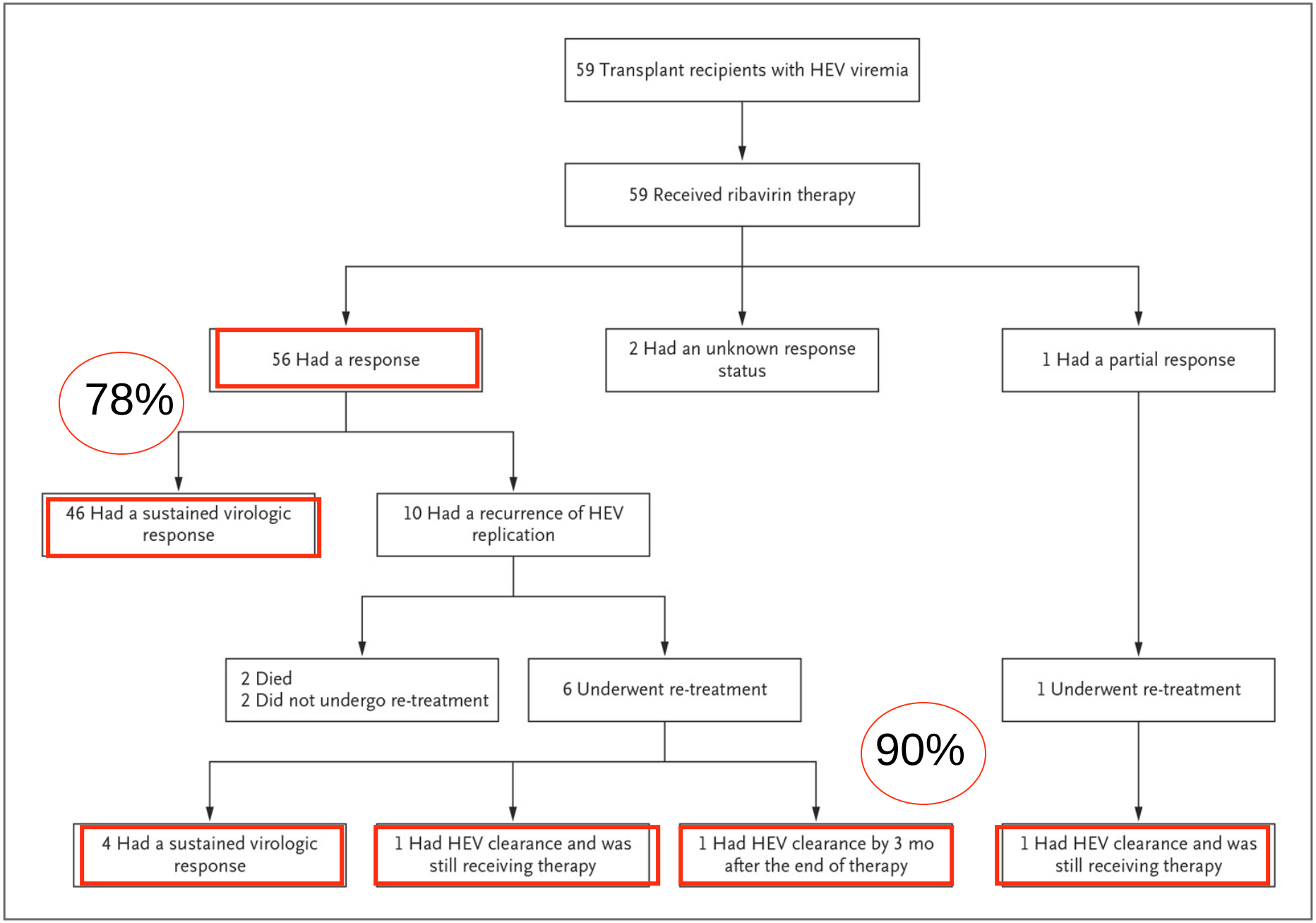
Original Article

Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients

Nassim Kamar, M.D., Ph.D., Jacques Izopet, Pharm.D., Ph.D., Simona Tripon, M.D., Michael Bismuth, M.D., Sophie Hillaire, M.D., Jérôme Dumortier, M.D., Ph.D., Sylvie Radenne, M.D., Audrey Coilly, M.D., Valérie Garrigue, M.D., Louis D'Alteroche, M.D., Matthias Buchler, M.D., Ph.D., Lionel Couzi, M.D., Ph.D., Pascal Lebray, M.D., Sebastien Dharancy, M.D., Ph.D., Anne Minello, M.D., Maryvonne Hourmant, M.D., Ph.D., Anne-Marie Roque-Afonso, M.D., Ph.D., Florence Abravanel, Pharm.D., Ph.D., Stanislas Pol, M.D., Ph.D., Lionel Rostaing, M.D., Ph.D., and Vincent Mallet, M.D., Ph.D.

N Engl J Med
Volume 370(12):1111-1120
March 20, 2014

The NEW ENGLAND JOURNAL of MEDICINE


59 Transplant recipients with HEV viremia
59 Received ribavirin therapy
56 Had a response
2 Had an unknown response status
1 Had a partial response
78%
46 Had a sustained virologic response
10 Had a recurrence of HEV replication
2 Died
2 Did not undergo re-treatment
6 Underwent re-treatment
1 Underwent re-treatment
90%
4 Had a sustained virologic response
1 Had HEV clearance and was still receiving therapy
1 Had HEV clearance by 3 mo after the end of therapy
1 Had HEV clearance and was still receiving therapy

Risk factors for viral relapse

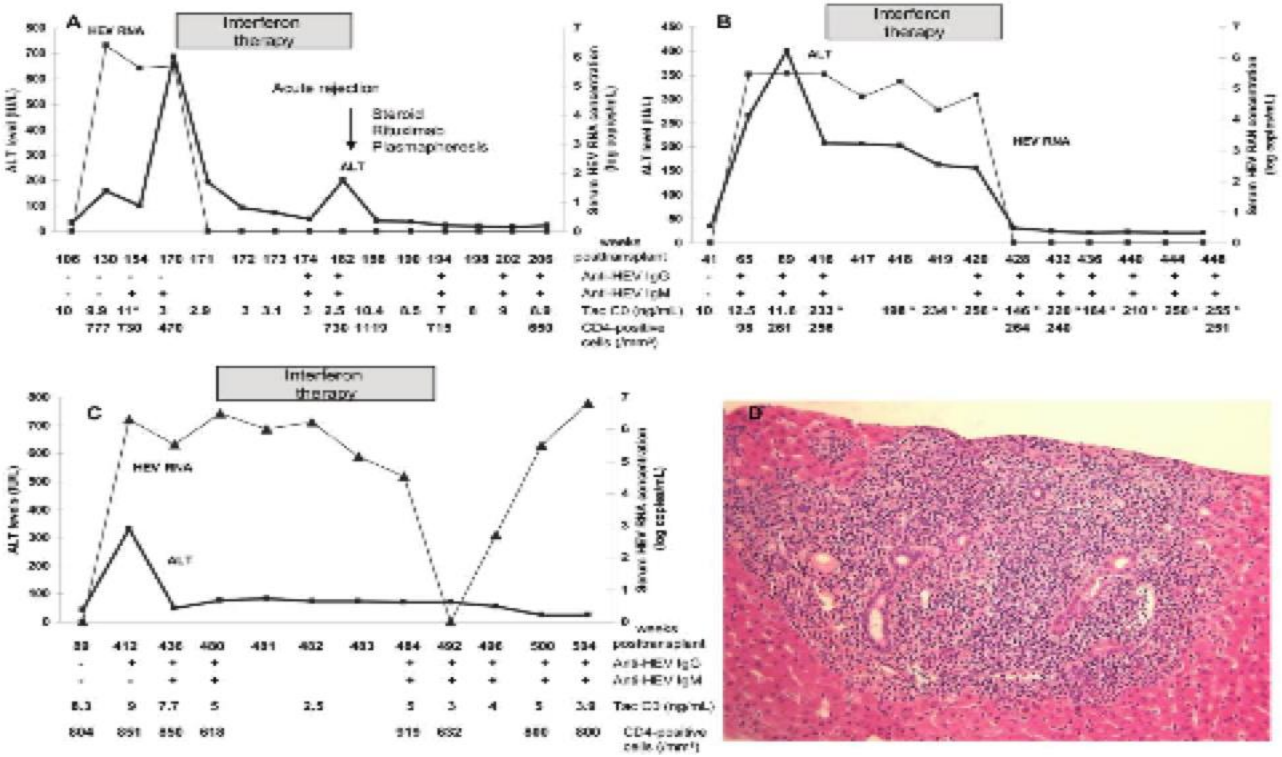
- Lymphocyte count at the start of ribavirin
- Serum HEV RNA detectable at 1 month
- Poor tolerance of ribavirin requiring dose reduction and blood transfusion
- Stool HEV RNA at the end of treatment+++

Kamar N NEJM 2014
Abravanel CID 2014
Kamar Clin Inf Dis 2019

- Mutation of G1634R viral polymerase : enhances replication
  - Does not affect viral clearance

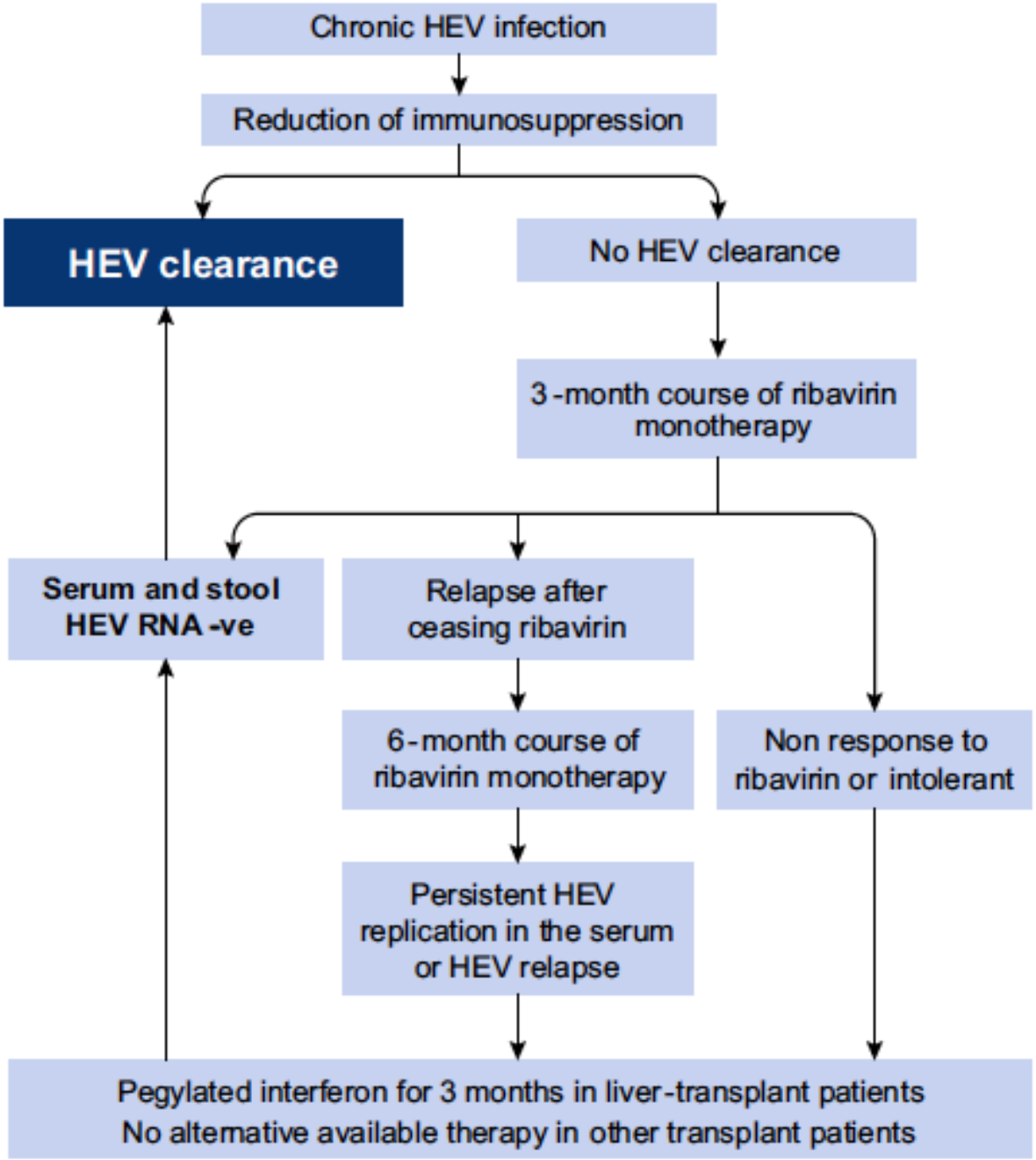
Debing Y Gastroenterology 2014
Kamar Clin Inf Dis 2019

Treatment of chronic hepatitis E in transplant patients : interferon-α



Peg-interféron-α 2a 135 ug/week, 3 months

Kamar CID 2010


Chronic HEV infection
Reduction of immunosuppression
HEV clearance
No HEV clearance
3-month course of ribavirin monotherapy
Serum and stool HEV RNA -ve
Relapse after ceasing ribavirin
Non response to ribavirin or intolerant
6-month course of ribavirin monotherapy
Persistent HEV replication in the serum or HEV relapse
Pegylated interferon for 3 months in liver-transplant patients
No alternative available therapy in other transplant patients

- Incidence is high and rising
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Should we treat acute HEV infection ?

- Multicentric french study
- 21 patients treated with ribavirin during an acute infection
  - 9 patients for a severe hepatitis (PT < 50%)
  - 6 patients > 70 years
  - 4 patients treated with immunosuppressive drugs for auto-immune disease
  - 2 patients undergoing chemotherapy for solid tumor cancer
- « A la carte treatment » : ribavirin for the duration of viremia, stopped when HEV became undetectable in the serum (median 26 days)
- Good tolerance
- HEV undetectable in a median 29 days

Péron JM Liver Int 2015

Should we treat acute HEV infection ?
EASL guidelines

- Ribavirin treatment may be considered in cases of severe acute hepatitis E or acute-on-chronic liver failure (C2)

- Speaker's opinion
  - Elderly patients (> 70 years old)
  - Patients undergoing chemotherapy
  - Neurological symptoms

In all cases HEV must be detectable in the serum

Conclusion 1

- HEV infection diagnosis is rising
- Subtype 3f may be more severe
- Neurological symptoms are frequent (Neuralgic amyotrophy +++)

Conclusion 2

- Ribavirin treatment may be considered in cases of severe acute hepatitis E (including neurological symptoms ?) or acute-on-chronic liver failure

- Chronic hepatitis E is treated with 3 months ribavirin and 3 more months if M3 stool PCR is positive.
- In case of relapse a 6 months regimen of ribavirin is indicated
- Interferon therapy can be added in case of ribavirin failure in selected patients (liver transplant, hematological mailgnancies, AIDS)

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