

Erasmus MC



Viroscience lab

WHERE SKILLS MEET TO STUDY & PROTECT

A microscopic view of several spherical, blue, textured virus particles against a dark blue background with a grid pattern.

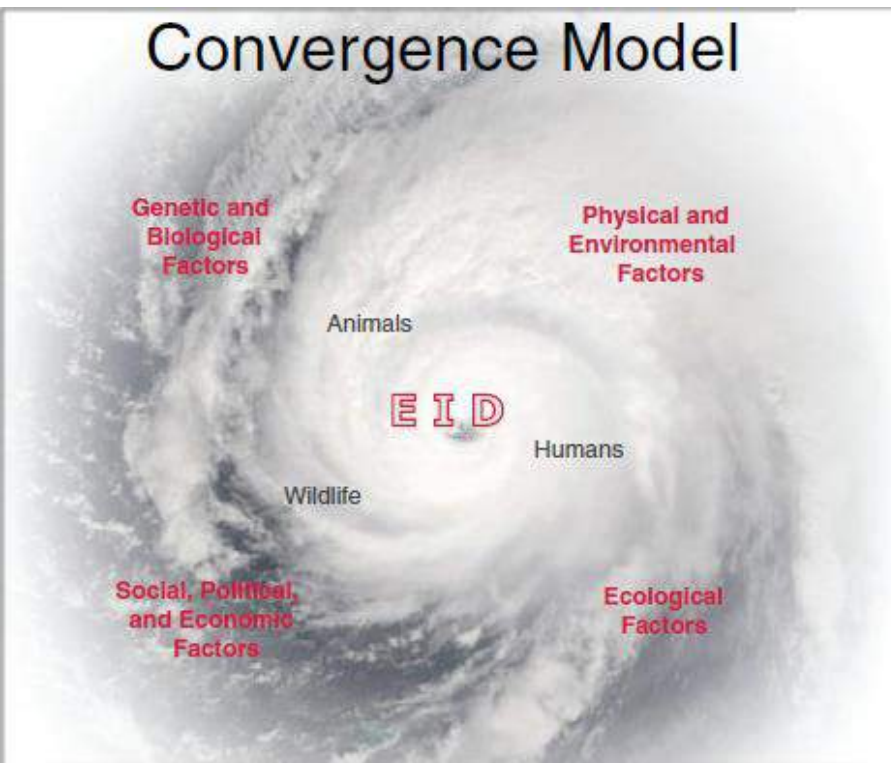
Virale Reisgenoten: Het Ongeziene Gevaar van Hepatitis E en Andere Infecties

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Interactions among host, pathogen, and environment can lead to the (re)emergence of infectious diseases



- Intensive agricultural practices
- Increased interactions between humans, domestic animals and wildlife
- Environmental “commons” such as water: contamination

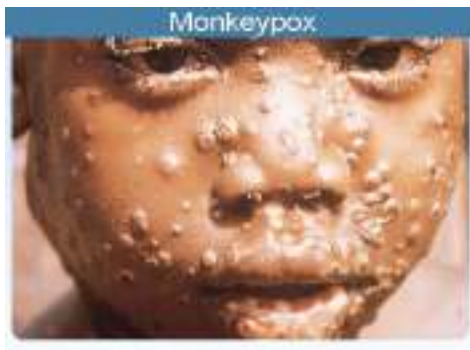
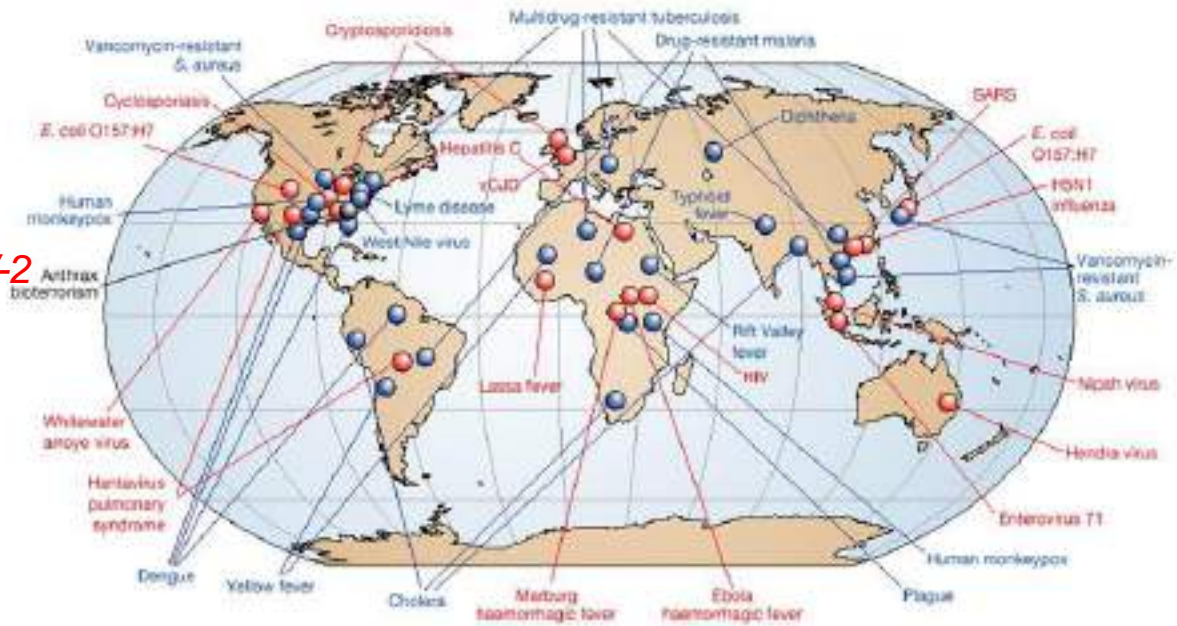
One world > any infectious disease can spread globally in a single flight > this is a joint concern and responsibility



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Zikavirus
 MERS
 SARS-CoV-2



Rioolwater in de zee: Stranden op Tenerife gesloten voor zwemmers

gearchiveerd: 10/04/2022 Gepubliceerd: 10/04/2022 Laatst gewijzigd: 10/10/2022



Tenerife heeft een telling van 195 lozingspunten. Hiervan hebben 128 geen autorisatie

Afvalwater van nieuw ziekenhuis Curaçao gaat in zee



Foto: De uitlozing van afvalwater van het nieuwe ziekenhuis in zee toest Kim Hendriks



Transmission routes foodborne viruses



Fecal oral transmission

Food handler
High incidence
Human pathogens
End of chain
Local, endemic

*Norovirus, Sapovirus,
Hepatitis A*

Berries, ready to eat food



Fecal oral transmission

Food production phase
High incidence
Human and animal pathogens
Globalisation
Mixed infections > risk
Early in chain
Diffuse widespread

*Norovirus, sapovirus,
rotavirus, Hepatitis A
hepatitis E, enterovirus*

Shellfish, irrigated products



Oral transmission and food handling

Zoonotic
Early in chain
Rare
Globalisation
Emerging infections

*Avian influenza, SARS,
SARS-CoV-2?, Nipah,
Ebola*

Meat, animal products

Norovirus

- The most common viral cause of diarrhea
- Each year 1 in 20 people gets infected
- Contaminated seafood, crops, outbreaks in health care settings
- Large amounts of virus is shedded through the gastrointestinal tract
- Not effectively removed from sewage treatment systems



Imported frozen berries suspected in hepatitis A outbreak

Modes of hepatitis A virus transmission*

Person-to-person contact
Transmission within households
Sexual transmission
Residential institution transmission
Daycare center transmission
Transmission among military personnel
Contact with contaminated food or water
Consumption of raw or undercooked shellfish, vegetables, or other foods
Consumption of foods contaminated by infected food handlers
Blood transfusion
Illicit drug use

* Hepatitis A virus is usually transmitted via the fecal-oral route, either via person-to-person contact or consumption of contaminated food or water.

UpToDate®



Outbreak Investigation of Hepatitis A Virus: Strawberries (May 2022)



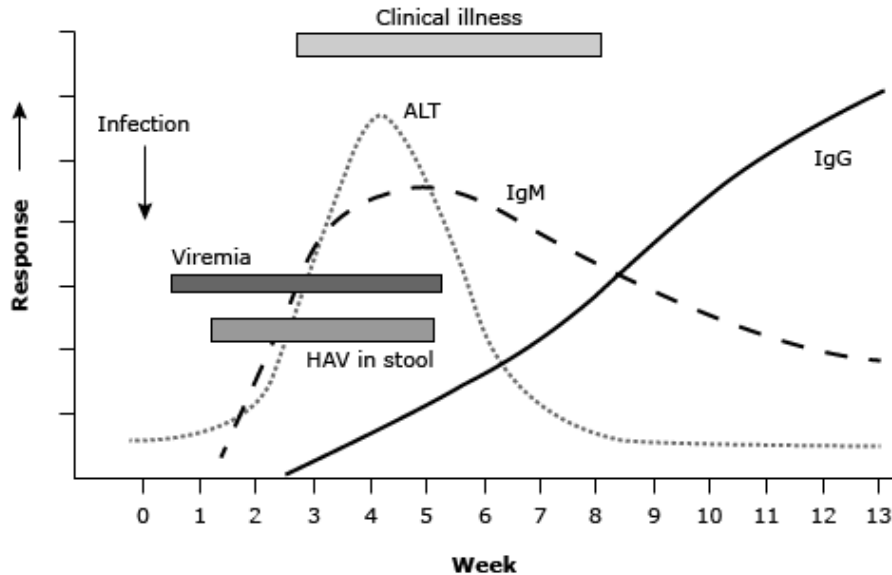
Sun-dried tomatoes



Clinical course Hepatitis A and diagnostics



Course of hepatitis A



Timeline for hepatitis A manifestations.

ALT: alanine transaminase; HAV: hepatitis A virus; Ig: immunoglobulin.

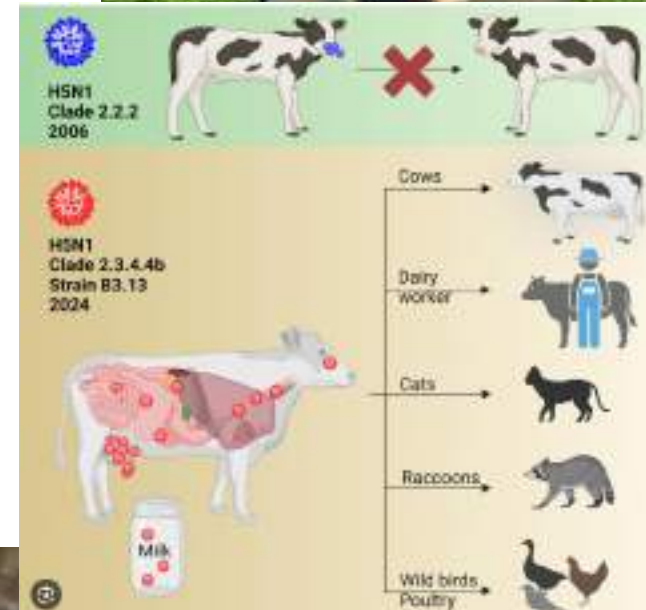
- Symptomatic illness due to HAV occurs in more than 70 percent of adults. Symptoms are uncommon in children <6 years of age.
- Fecal-oral route
- Incubation period: 30 days (15-50)
- Nausea, vomiting, anorexia, fever, malaise, abdominal pain, jaundice, pruritis.
- Hepatomegalie 80% of cases
- <1% acute liver injury
- Vaccine is available

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Emerging viruses and the food chain

- SARS – wild animals
- Nipah – palm sap, fruits>pigs>people
- Avian influenza- food handlers, blood
- Filoviruses – hunters, food handlers
- Monkeypox – hunters
- Rift valley fever – animal products, slaughter
- International food contamination events occur frequently
- Can be vehicle for dissemination of infections, even if not primary mode of transmission





Nipah outbreaks

- Paramyxoviridae, henipah viruses
- General malaise, encephalitis
- Nipah outbreaks Bangladesh, India, Malaysia, Singapore
- Contaminated fruit/palm sap
- Malaysia: Sept 1998-May 1999:
Pigs infected: 283 human cases of acute encephalitis: 109 deaths (CFR 39%)



Hepatitis E Virus

- Non-enveloped RNA virus belonging to Hepeviridae family
- 27-34 nm in diameter, 7.2 kb + sense ssRNA
- Transmission feco-oral, contaminated water/food
- Four genotypes
- gt 1-2 outbreaks in resource limited countries
- gt 3-4 zoonotic, in humans/pigs/game, in industrialised countries

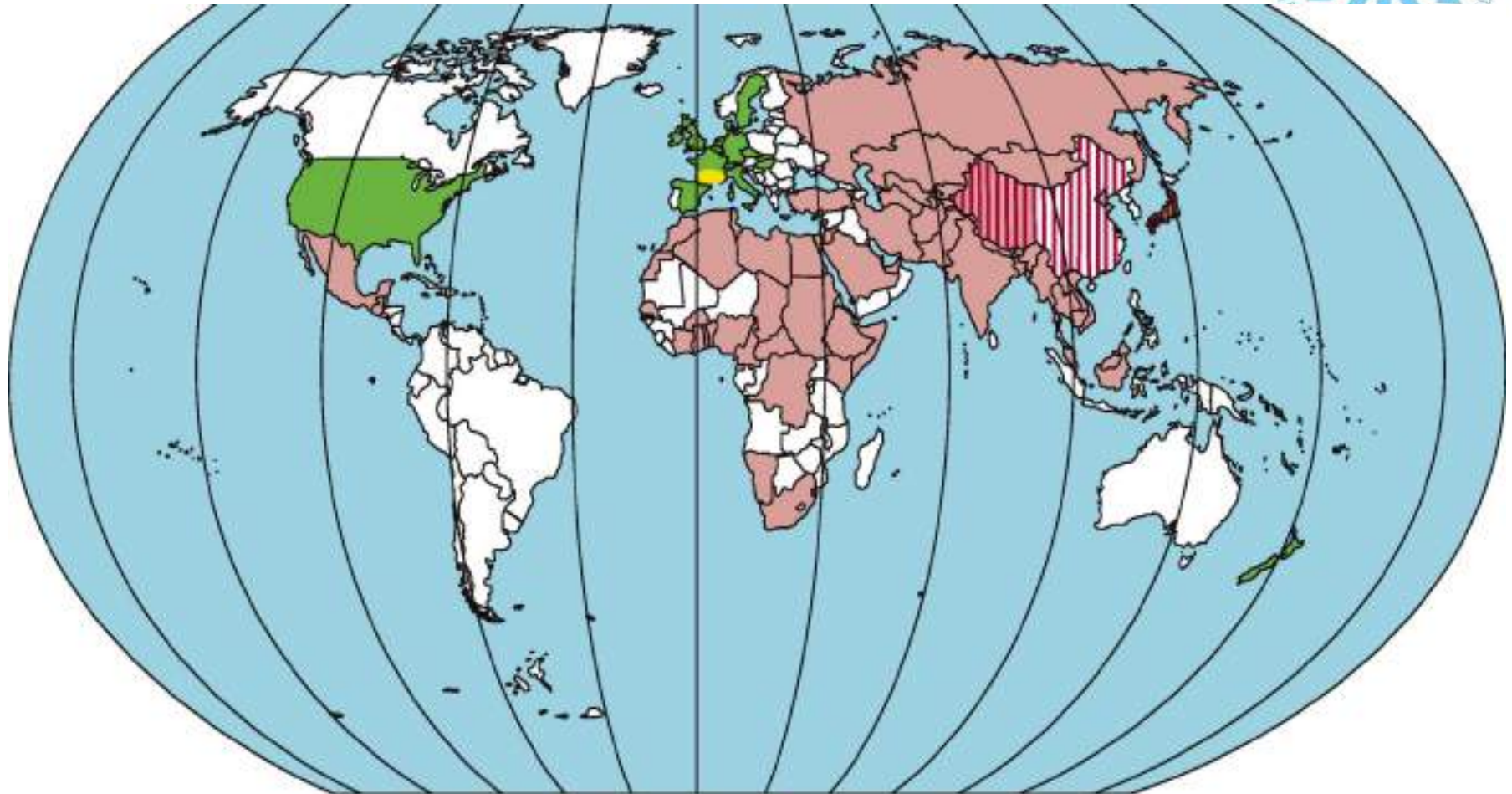






NIGERIA

"People are dying of hepatitis E because they don't have soap or clean water"



Global distribution of HEV genotypes



- | | | | |
|--|--|---|--|
|  Genotype 1 and 2 |  Genotype 3 |  Genotype 3 |  Genotype 4 |
| • Endemic | • Sporadic | • Hyperendemic | • Sporadic |
| • Waterborne | • Zoonotic | • area | • Zoonotic |

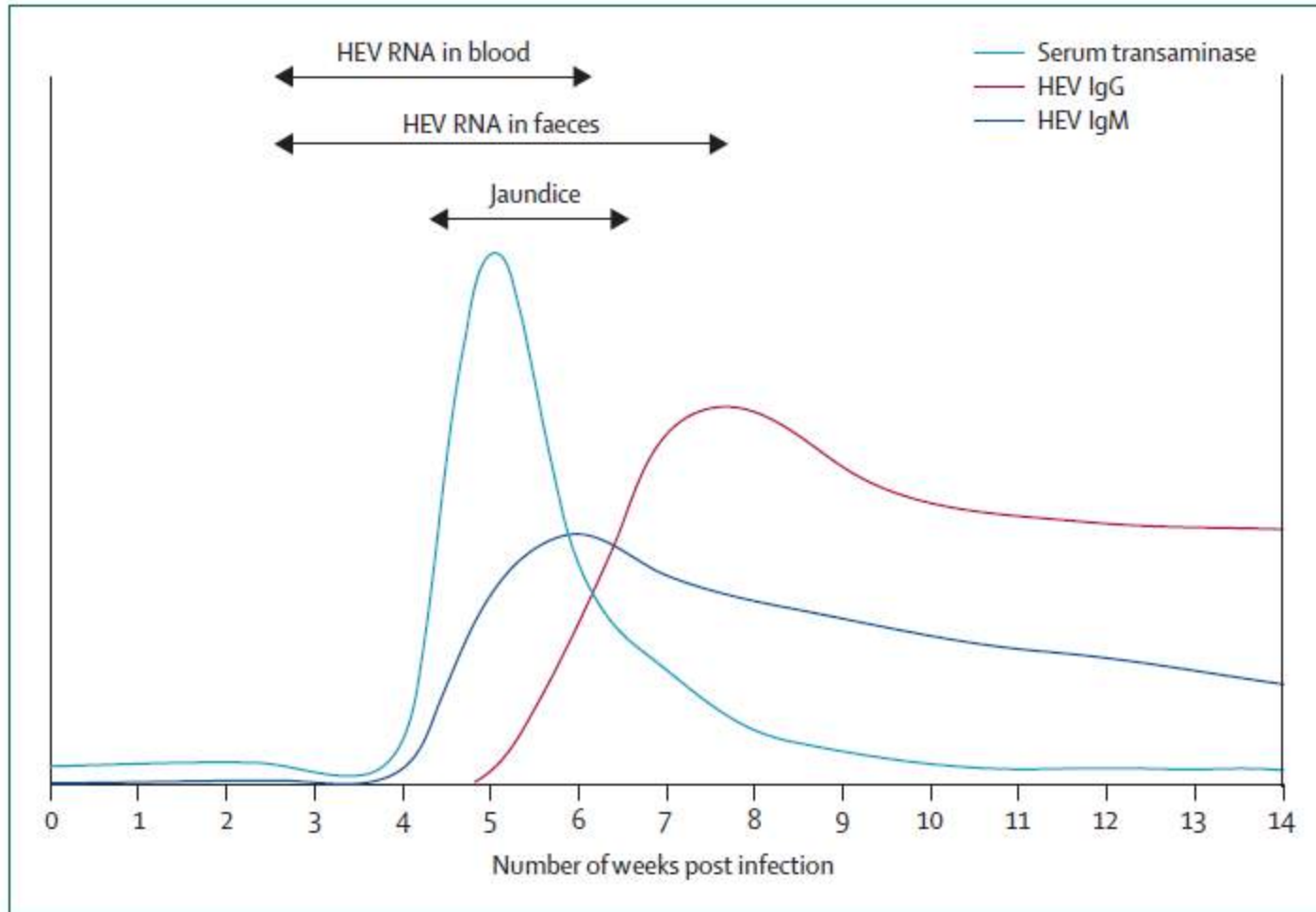
Clinical presentation of hepatitis E virus



- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Jaundice
- Dark urine
- Clay-colored stool
- Reported range S:AS infection from 1:2 to 1:13.
- Mortality gt1: overall 1-4%, pregnant women 15-25%
- Neurological symptoms



HEV infection in the immunocompetent



HEV in the news



Wild kan besmet zijn met hepatitis E

Vara vroege vogels



30 november 2010 12:30

Wilde zwijnen en edelherten kunnen besmet zijn met het hepatitis E virus (HEV). Dat zei een Rijksinstituut voor Volksgezondheid en Milieu (RIVM) dinsdag naar aanleiding van een onderzoek in Splits. Door het eten van rauw vlees van besmette dieren kunnen mensen ziek worden.



One in ten sausages may carry the hepatitis virus: Cases of rare deadly strain have risen 40% in a year

17 januari 2014

Artsennet.nl

Hepatitis E kan verlammingen veroorzaken

Het hepatitis E-virus kan niet alleen ernstige leverontsteking veroorzaken, maar ook twee acute zenuwaandoeningen, die gepaard kunnen gaan met verlammingen.

Dit blijkt uit onderzoek van het Erasmus MC gepubliceerd in *Neurology*. Het gaat om het syndroom van Guillain-Barré en de chronische inflammatoire demyeliniserende neuropathie, ook wel het syndroom van Parsonage Turner. Beide ziektes kunnen de ledematen ernstig verlammen.

Complicatie

In beide neurologische aandoeningen was al bekend dat ze kunnen optreden als ernstige complicatie na een milde infectie. De oorzaak ligt bij een verkeerde reactie van het immuunsysteem op deze infectie, waarbij ook het zenuwweefsel wordt beschadigd.

Very rare, cases have risen by nearly 40 per cent in a year. Pregnant women are at greatest risk of dying, rising to one in five pregnant women who eat a dangerous pork product - they contain liver meat.

Daily mail 15-09-13

September 2013 | UPDATED: 21:35 GMT, 15 September 2013

...al mensen gevonden, maar waarschijnlijk zijn er veel meer mensen die het virus hebben, verloopt net als hepatitis A en geneest na verloop van tijd.

Het varkensvirus'

g 28 juni 2011 | 07:52

Tekstgrootte



Kerstine

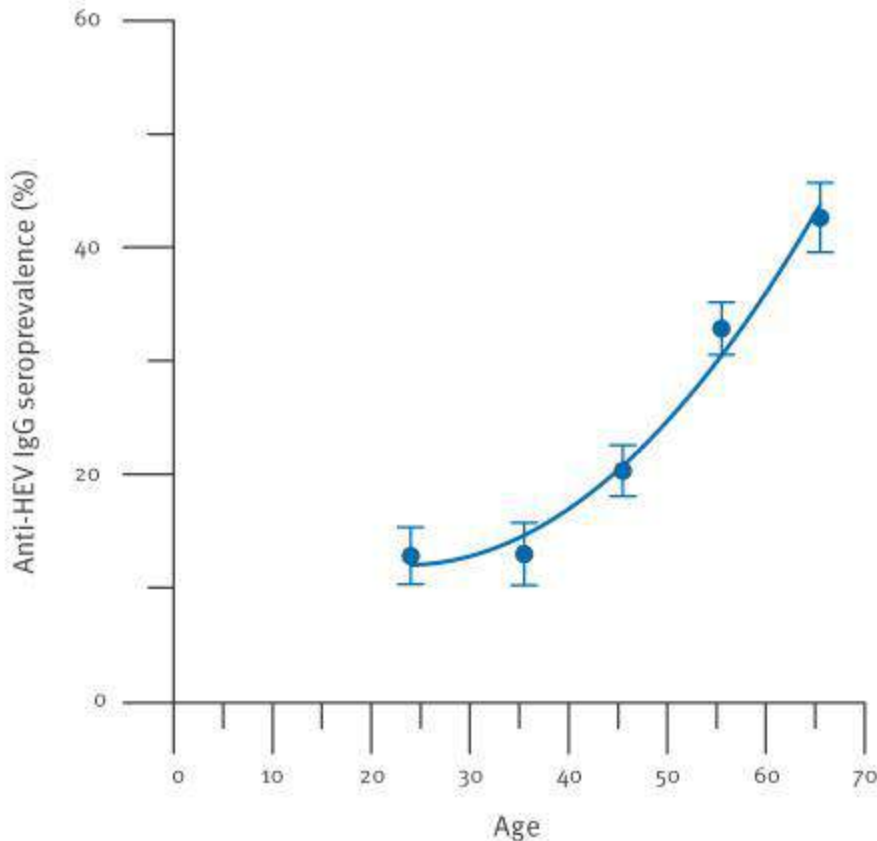


BN-de Stem 28 juni 2011



FIGURE 2

Anti-hepatitis E virus IgG seroprevalence in 10-year age groups of blood donors, the Netherlands, 2011–2012 (n=5,239)



HEV IgG seroprevalence ranged from 13% among donors younger than 30 years to 43% in donors older than 60 years

The first group represents donors between 18 and 29 years rather than a 10-year group. Error bars indicate the 95% confidence interval for each age group.

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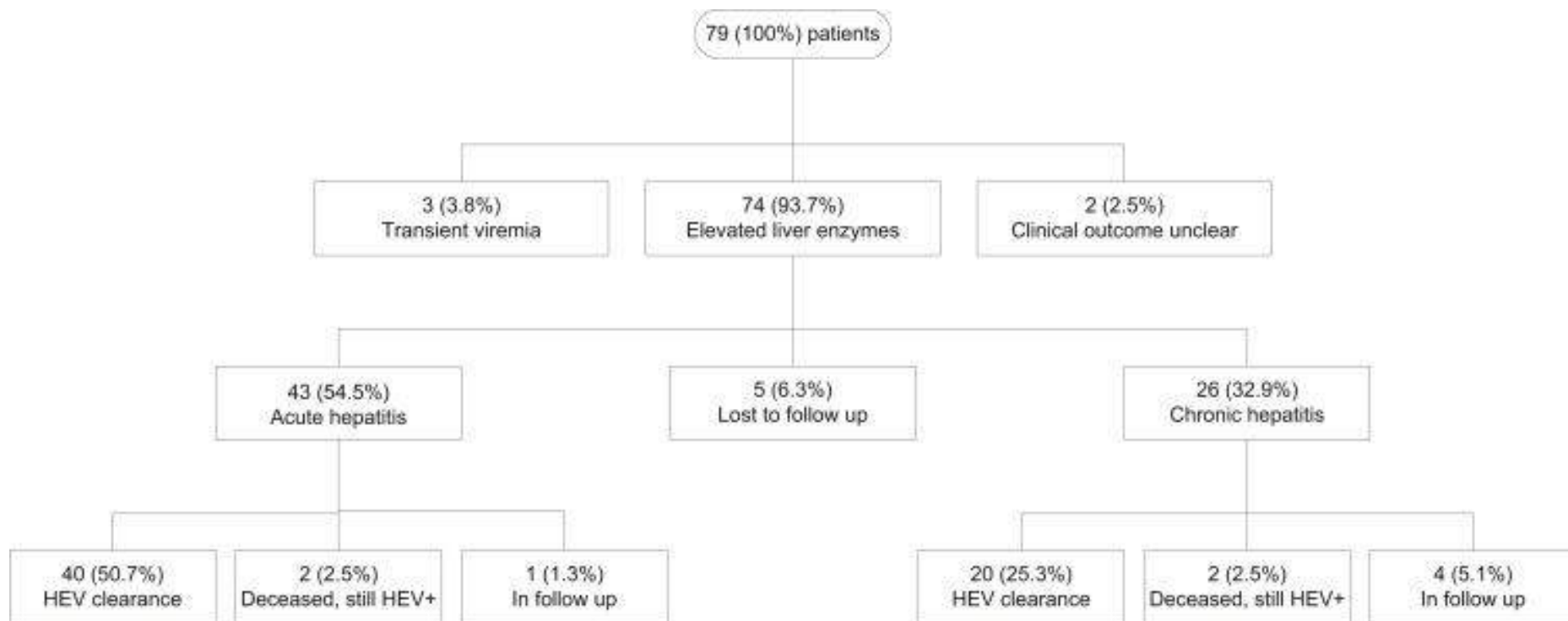




HEV in the Erasmus MC

- 79 patients
 - 61 immunocompromised
 - 35 solid organ recipients
 - 18 hematological patients
 - 2 both SOT/haematological malignancy
 - 6 other
 - 18 “immune competent”
 - 15 patients received no immunosuppressants
 - 2 patients received prednisolone and 1 patient received methotrexate

Flowchart of the clinical course in HEV-infected patients of the cohort





HEV infection

- Chronic HEV infection is reported in the transplant setting (both SOT and hematological patients)
 - Persistent viraemia
 - Persistently raised transaminase activity
 - Histological features associated with chronic hepatitis
 - Evidence of rapid development of cirrhosis
- PCR is superior to serology to detect infection in immunocompromised patients
- Drug induced liver injury: be aware of hepatitis E virus

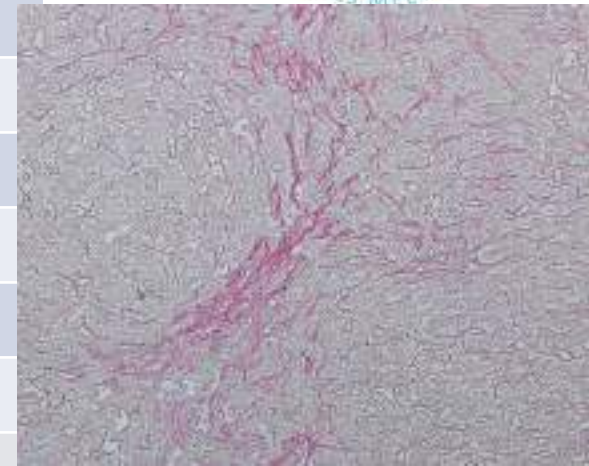
Parameters of HEV confirmed cases of SOT and AlloHSCT group



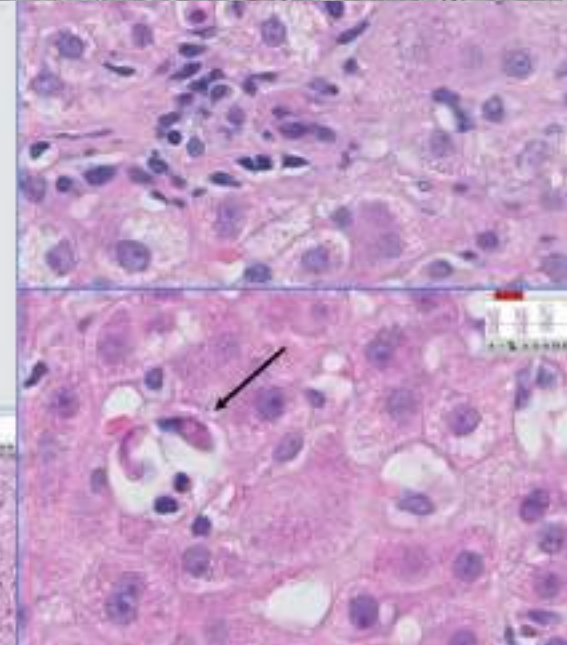
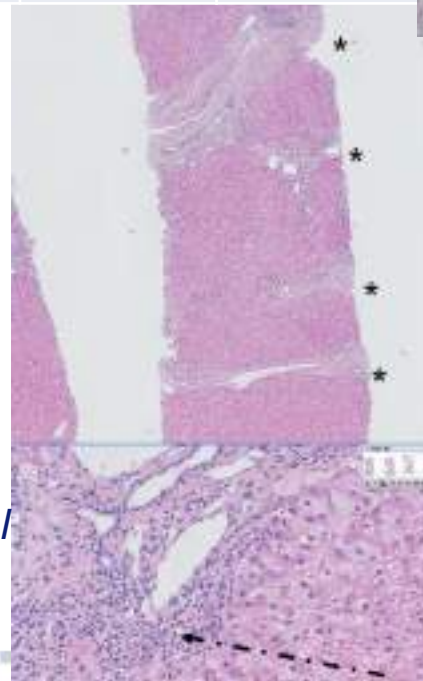
	SOT - recipients Median (range)	Allo-HSCT recipients Median (range)	ULN (F/M)
Peak ALAT (U/L)	329 (70-909)	430 (213 – 1507)	33/44
Peak HEV RNA (log IU/ml)	7.21 (6.15 – 8.30)	7.26 (5.34-8.49)	NA
period of HEV RNA positivity (mos)	10.8 (6.3 -55.1)	6.4 (1.6 – 42.4)	NA
time between the Tx and first HEV-RNA positive (mos)	23.9 (-3.6 – 240)	4.6 (-2.1 – 18.3)	NA
Lag time PCR pos prior to HEV IgM (days)	64 (-35 – 842)	65 (0 -245)	NA
Lag time PCR pos prior to HEV IgG (days)	129 (0- 842)	126 (-594 – 351)	NA



Infection time (months)	Periportal necrosis	Intralobular Inflammation	Portal inflammation	Fibrosis	Total HAI score
9	1	3	2	3	9
5	1	2	1	3	7
7	3	3	3	3	12
5	0	1	0	0	1
22	3	3	3	3	12
8	1	1	1	1	4

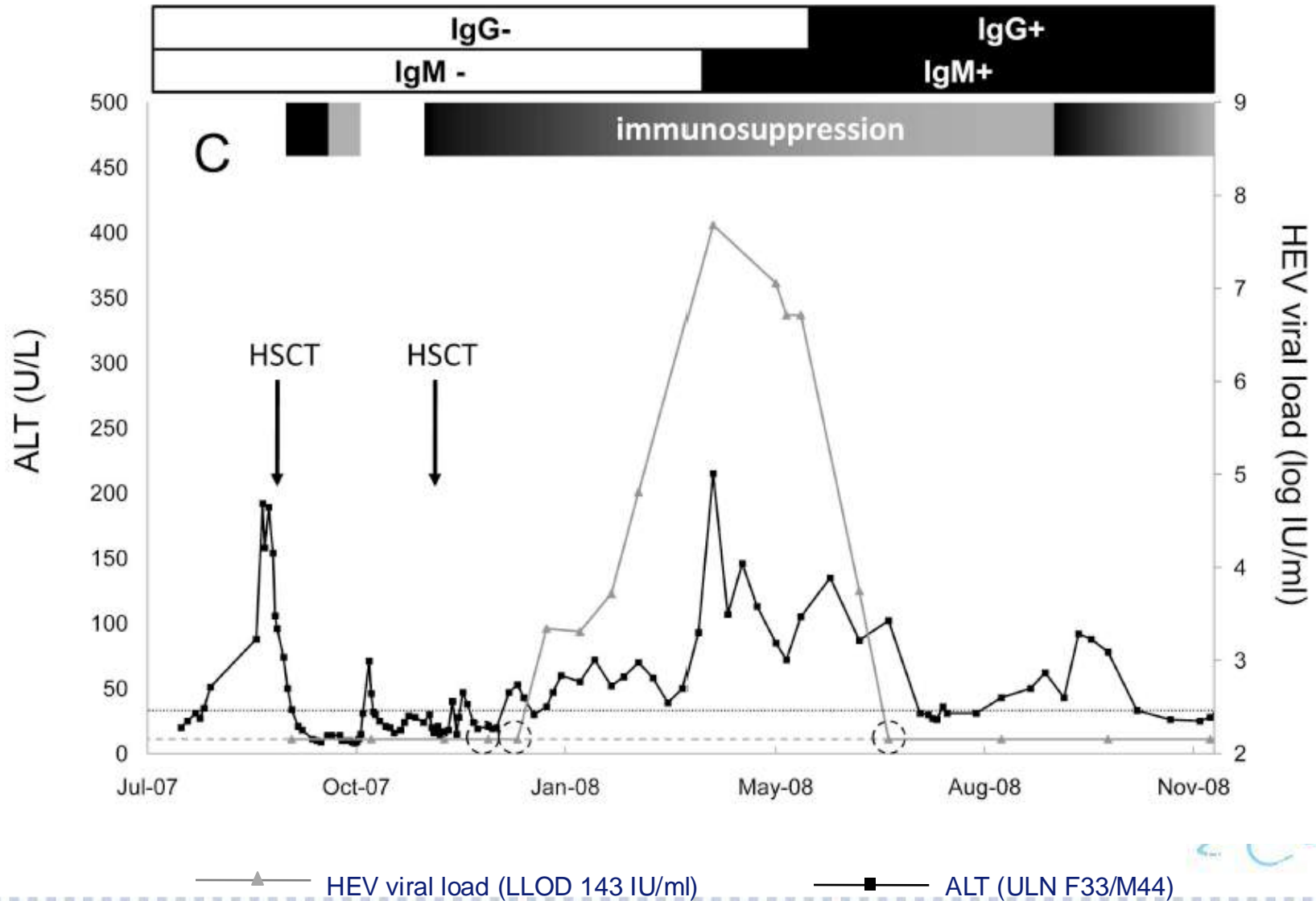


Individual Knodell score (HAI) of liver biopsy specimens heart transplant recipients



Versluis J and Pas SD et al, Blood 2013
Koning L, Pas SD et al J Heart and Lung Transpl

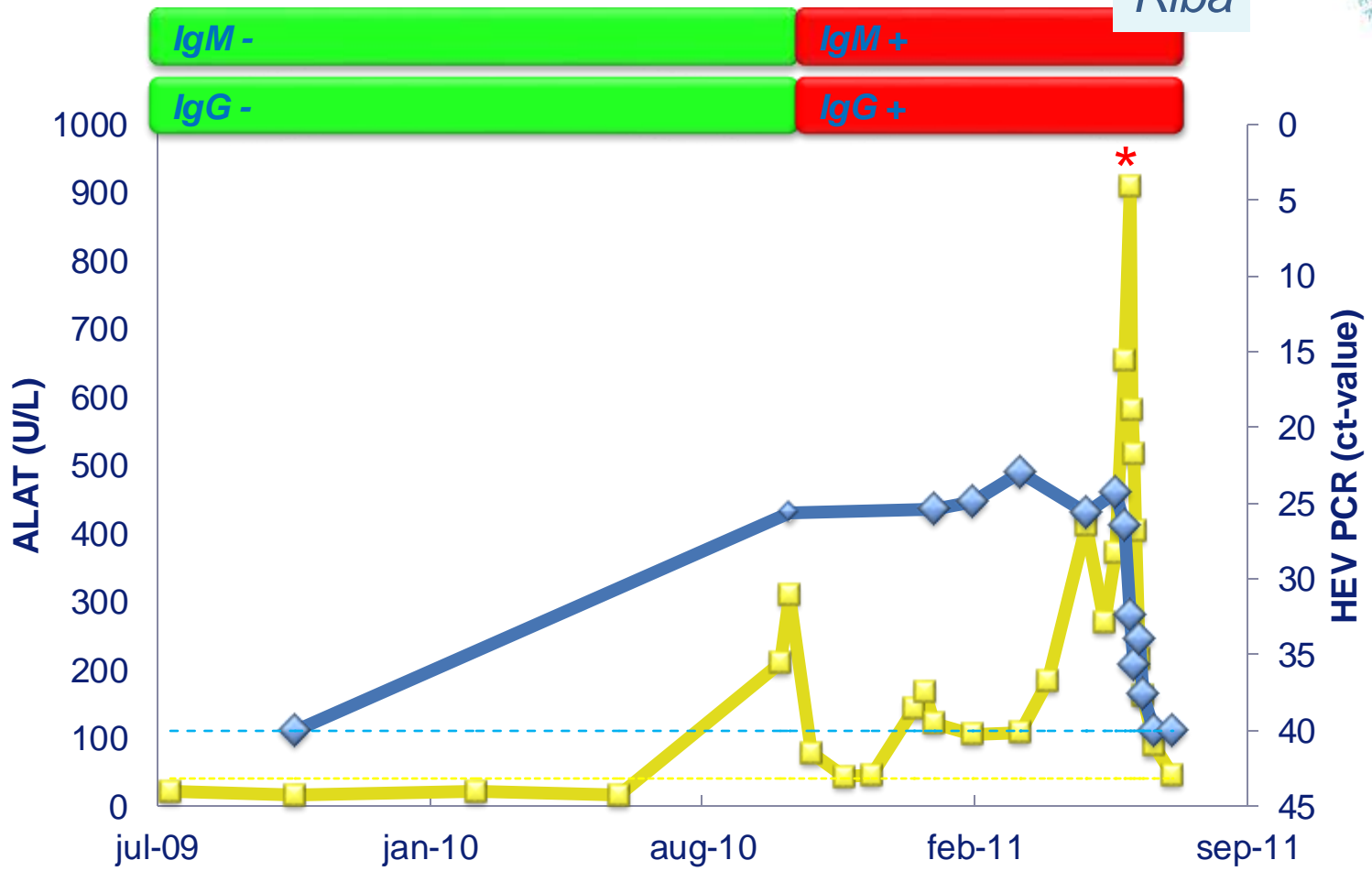
Course of infection in AlloHST recipient





Course of chronic HEV infection in LTX patient

Riba



■ ALAT
 - - - ULN ALAT
 ◆ PCR hepatitis E
 - - - LOD HEV PCR

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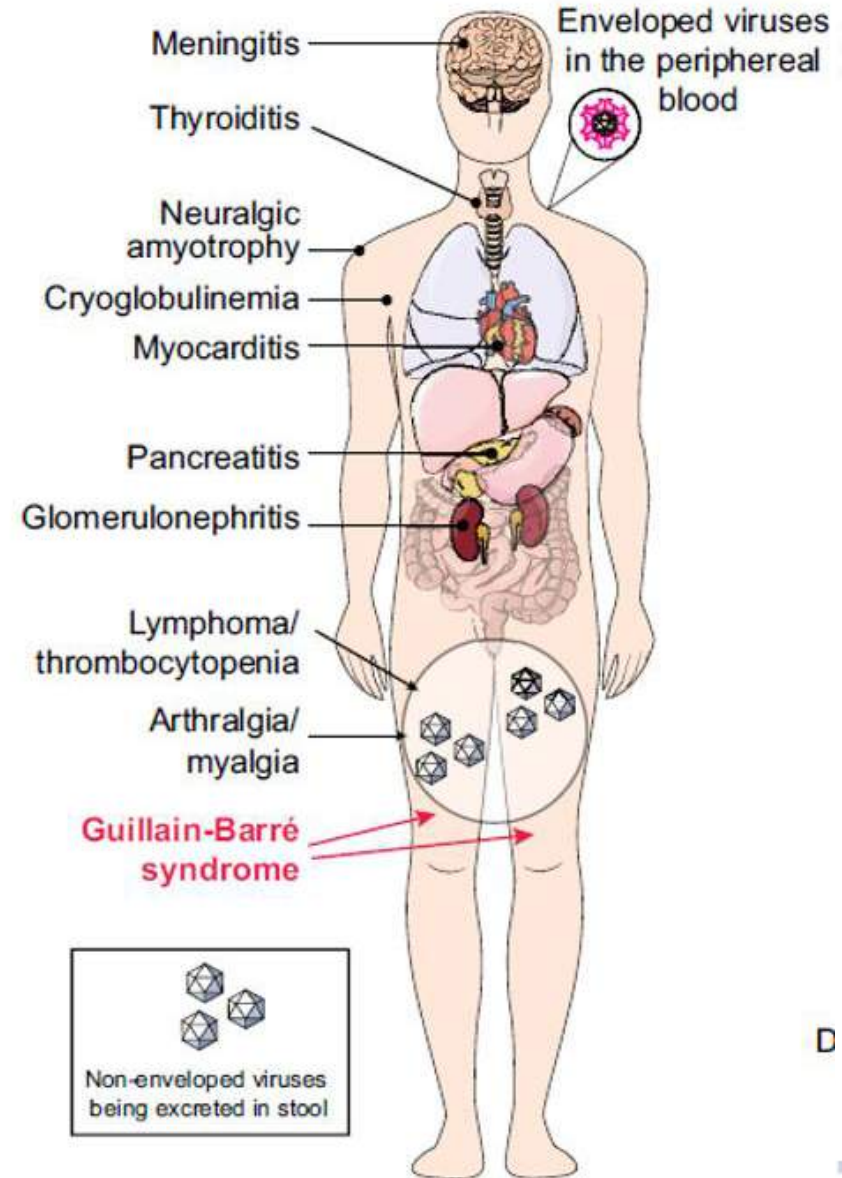
Extrahepatic manifestations of

Neurological

- Guillan Barre Syndrome
- Neuralgic amyotrophy
- Encephalitis/myelitis

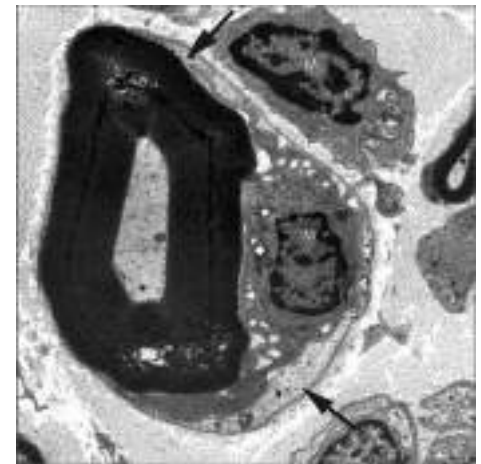


A Reported extrahepatic organ manifestations in the context of hepatitis E virus infection



Guillain-Barré syndrome (GBS)

- Post-infectious immune-mediated polyradiculoneuropathy
- Incidence 1-2/100.000/year (life-time risk of 1:1000)
- Clinical features:
 - rapidly progressive weakness in legs and arms
 - proportion with involvement cranial and/or sensory nerves
 - respiratory failure requiring ventilation at ICU (25%)
- Pathology:
 - Demyelination and macrophage infiltration:
 - (axonal degeneration)
- Clinical course:
 - acute onset and monophasic
 - frequent residual disability (15% wheelchair bound)



Neuralgic amyotrophy: syndrome of Parsonage-Turner (Neurology 2014;82:498-503)

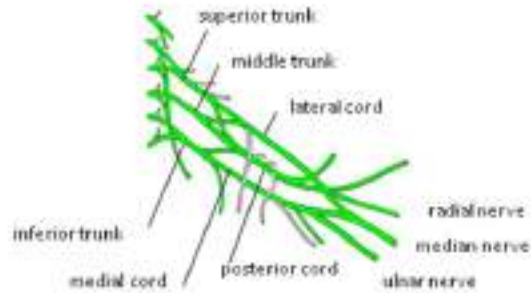


- Immune- mediated post-infectious peripheral nervous system disorder
- At presentation a minority of NA patients have mildly deranged liver function tests of unknown cause
- HEV testing was conducted in a retrospective cohort of 28 Cornish NA-patients (2011-2013) and a well-defined prospective cohort of 38 consecutive Dutch NA-patients (2004-2007).
- Acute phase, pretreatment serum samples were analyzed for the presence of anti-HEV IgM and IgG and HEV RNA (quantative real-time PCR).

Brachial plexograms of anti-HEV IgM associated neuralgic amyotrophy patients



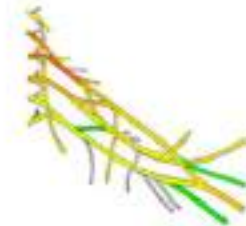
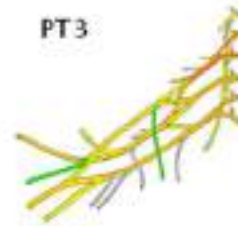
normal left brachial plexus



right

left

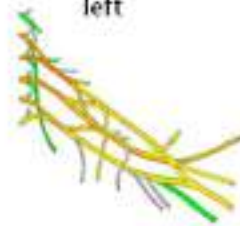
PT3



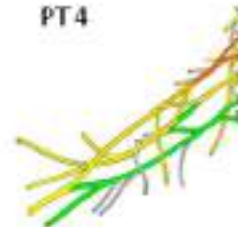
PT1 right



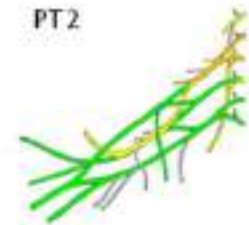
left



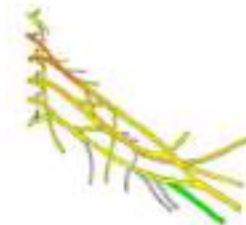
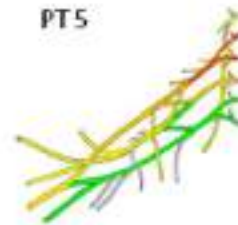
PT4

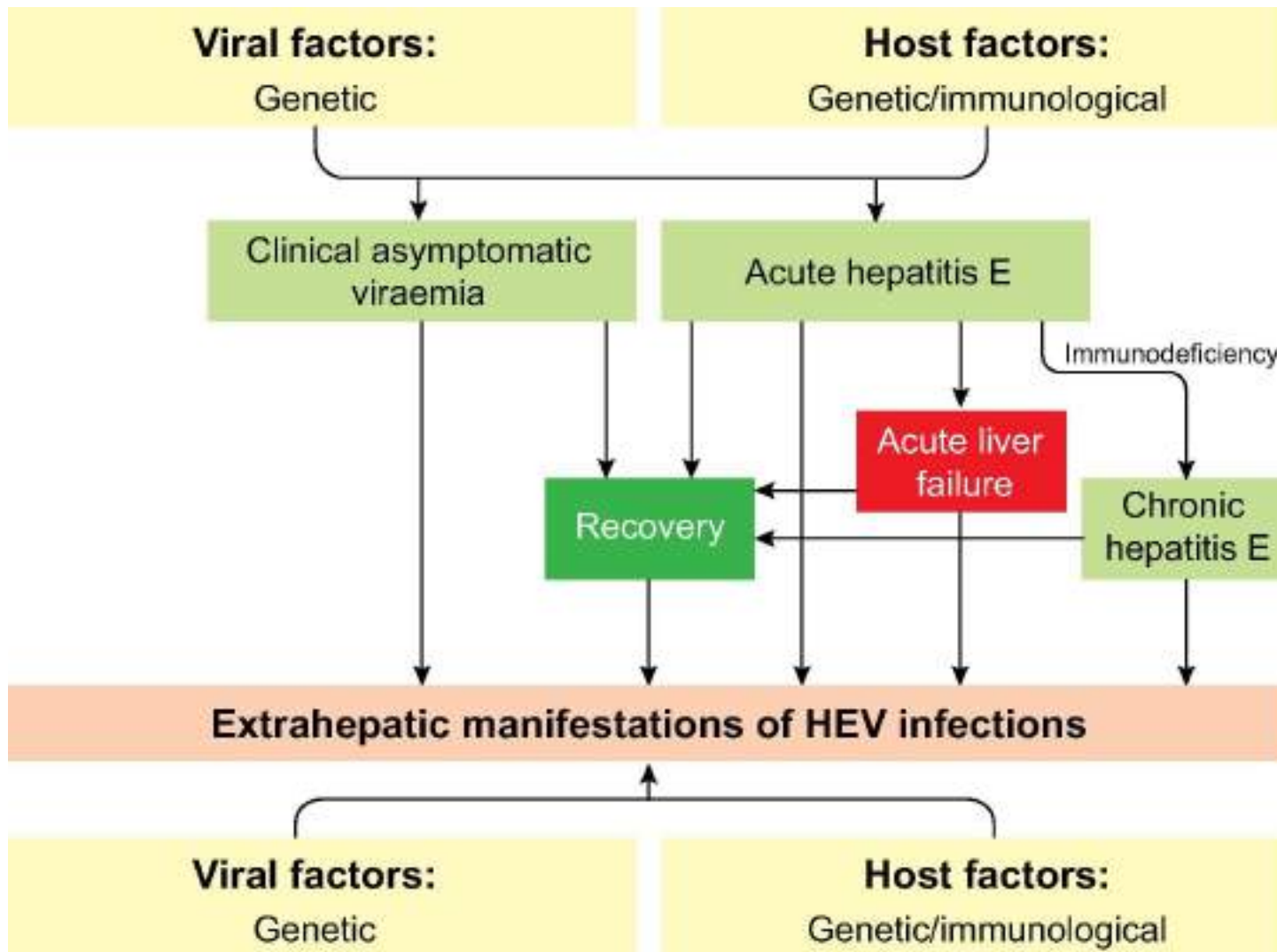


PT2



PT5







Conclusions

- Chronic HEV infection is reported in the transplant setting (both SOT and hematological patients)
 - Persistent viraemia
 - Persistently raised transaminase activity
 - Histological features associated with chronic hepatitis
 - Evidence of rapid development of cirrhosis
- PCR is superior to serology to detect infection in immunocompromised patients
- Therapeutic options for chronic HEV includes tapering immunosuppressiva and secondly ribavirine,
- Extrahepatic manifestations have been associated with HEV