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THE STATE UNIVERSITY
OF NEW JERSEY

Chronic Hepatitis E and Others

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Disclosure

None

Case presentation

35-year-old Nigerian man with a history of chronic HBV (inactive carrier), not on any antiviral therapy, have been admitted for new onset jaundice and generalized malaise. He had recent travel to Africa in last 1 month and had gastroenteritis during his travel to Africa treated with Pepto-Bismol. No history of new medication use

On Exam: He has scleral icterus. Otherwise unremarkable exam

Diagnostic work-up:

US liver with doppler: Normal examination.

Tbili	6.4
AST	892
ALT	1620
ALP	137
INR	1.0
HBV DNA	21 IU/mL
HCV RNA	Not detected
HEV IGG/IGM	Positive
HDV IGM/IGG	Negative
Hep A IGM/IGG	Negative
ANA/ASMA/IGG	WNL

Case presentation

Which of the following statement is true ?

a. Most likely cause of acute hepatitis is HBV flare
b. Most likely cause of acute hepatitis is HDV infection
c. Most likely cause of acute hepatitis is Hep A infection
d. Most likely cause of acute hepatitis is HEV infection

- **Acute infection**
- **Chronic infection**
- **Extrahepatic manifestations**
- **Diagnosis**
- **Treatment**

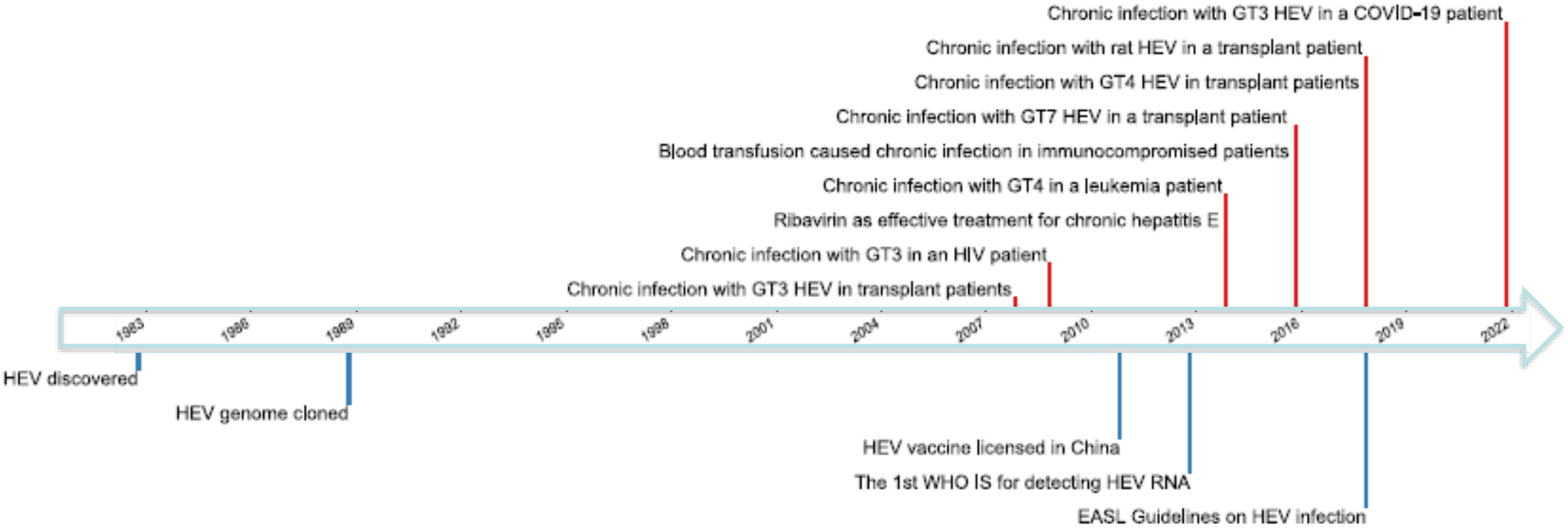
Epidemiology

- HEV was thought to be limited to certain developing countries BUT
  - HEV is endemic
  - Largely a zoonotic infection
  - Leading cause of acute viral hepatitis in developing countries

- WHO, estimates 20 million HEV infections/year worldwide
  - 3.3 million symptomatic cases of HEV
  - 44 000 deaths in 2015

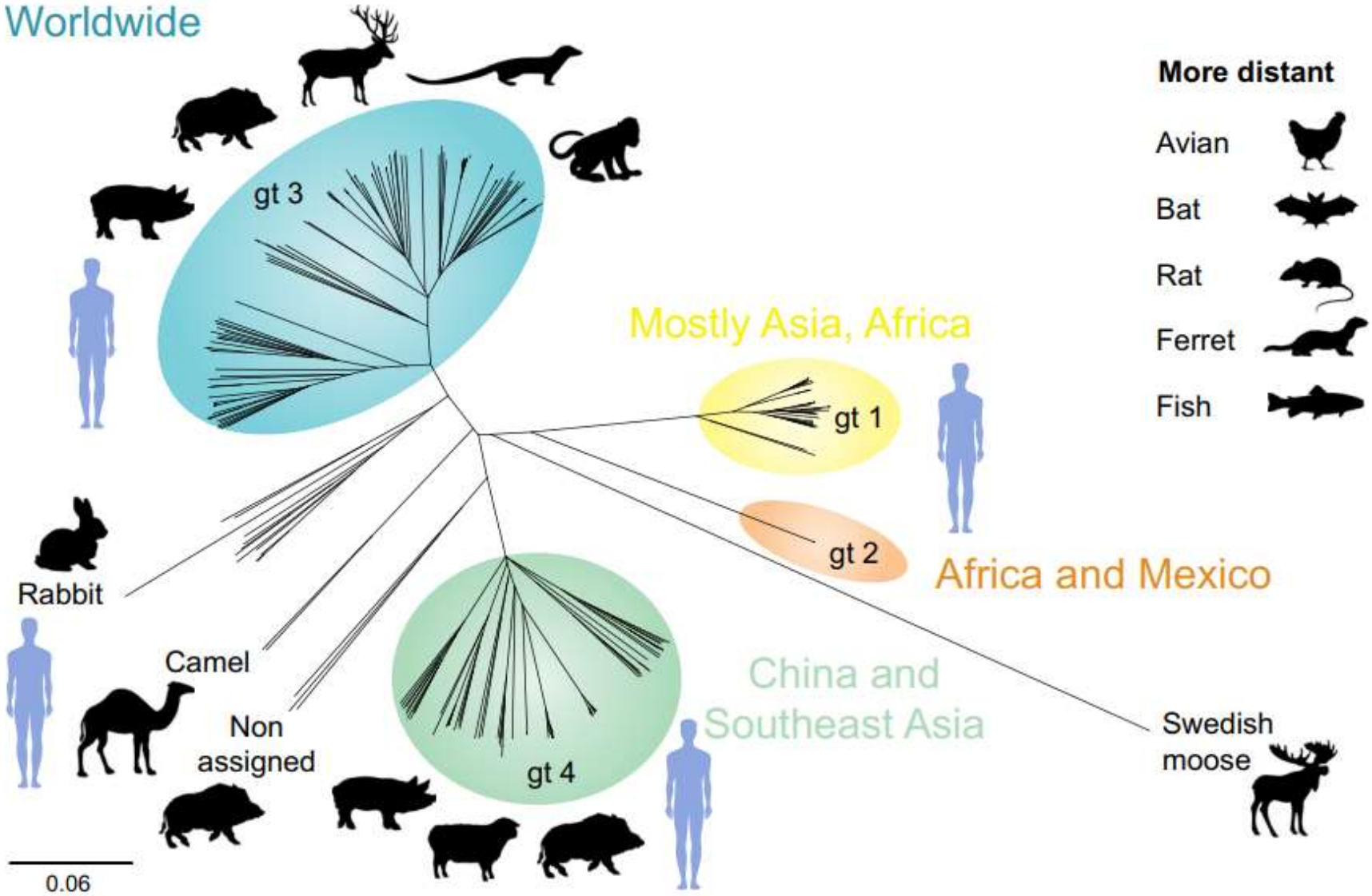
https://www.who.int/news-room/fact-sheets/detail/hepatitis-e

A brief timeline of major developments in the field of HEV



Modified form Ma Z, et al. J Hepatol. 2022 Oct;77(4):1109-1123

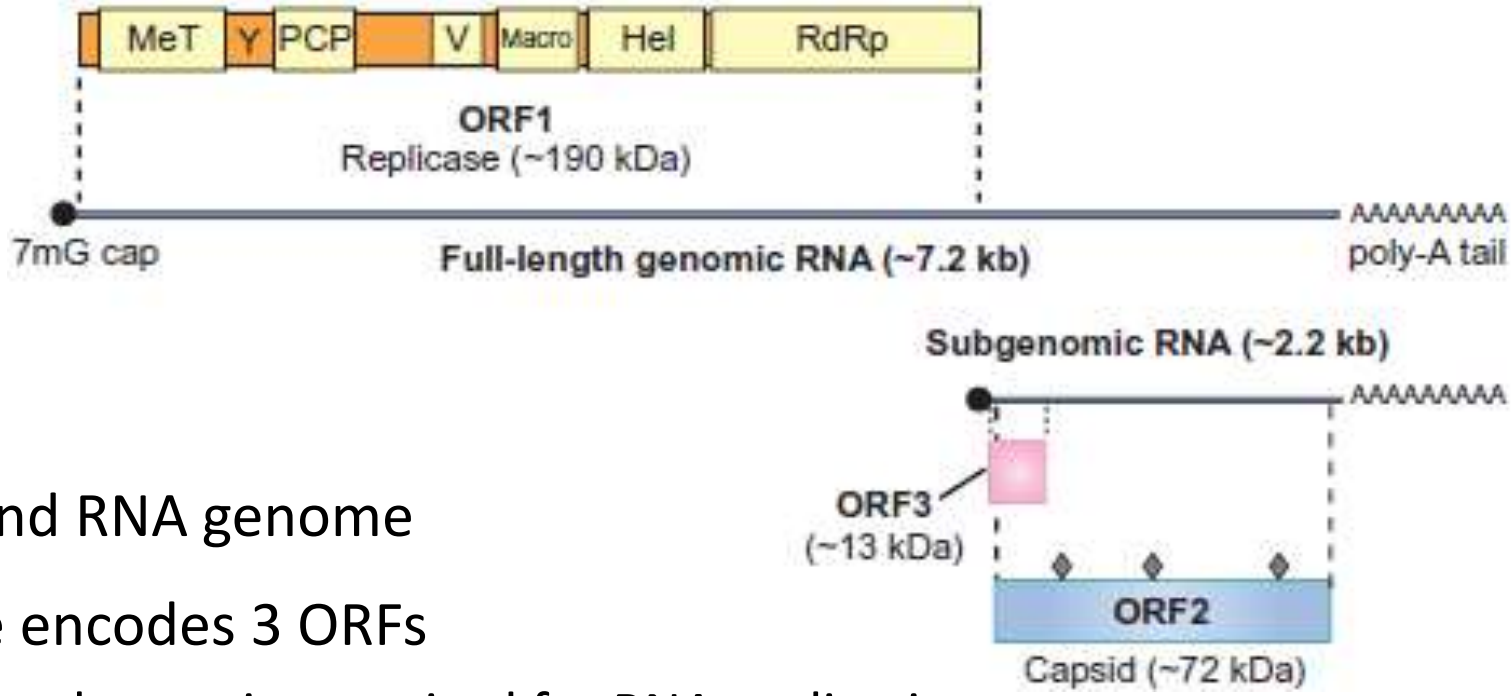
Phylogenetic relationship of hepeviruses



- The advancement in sequencing technology allowed the identification of novel HEV related viruses in variety of animals

Debing Y, et al. J Hepatol 2016;65:200–12

Virology ~ Genetic organization of the HEV



- Positive single-strand RNA genome
- The 7.2 kb genome encodes 3 ORFs
  - ORF1 encodes a polyprotein, required for RNA replication
  - ORF2 encodes the capsid protein
  - ORF3 protein involve in releasing new virions
- Two viral RNA species are generated during HEV genome replication
  - The full-length RNA of 7.2 Kb and a subgenomic RNA 2.2 kb

*Open reading frames (ORFs)
*kb: kilo base *kDa: kilodalton

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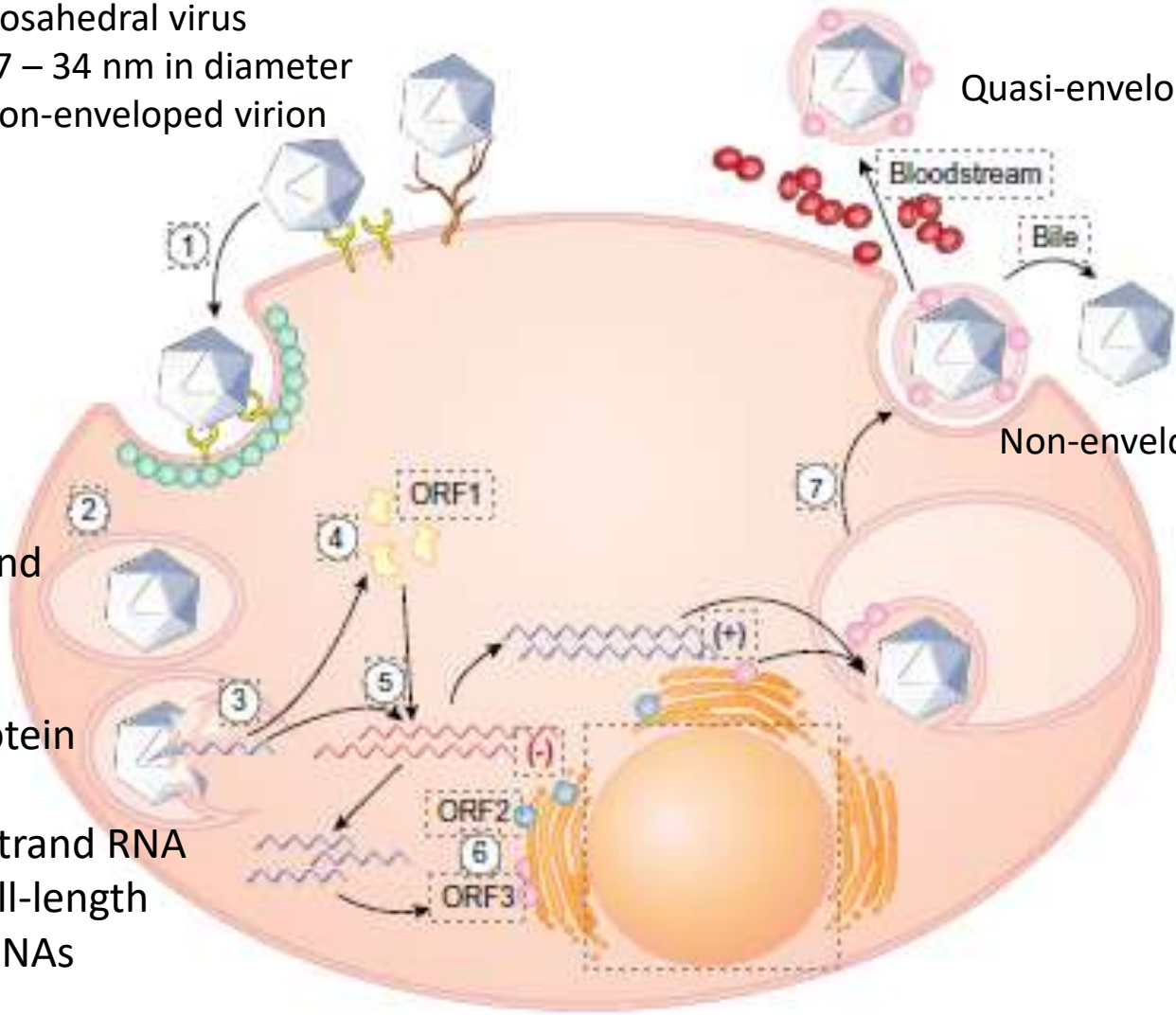
Virology ~ A life cycle of HEV

Icosahedral virus
27 – 34 nm in diameter
Non-enveloped virion



1. Viral attachment to heparin sulfate proteoglycans and entry through unidentified receptor(s)
2. Clathrin mediated endocytosis
3. Release of the viral positive-strand RNA genome into the cytosol
4. Translation to yield the ORF1 protein
5. Replication through a negative-strand RNA intermediate and synthesis of full-length as well as a 2.2 kb subgenomic RNAs
6. Translation of the subgenomic RNA to yield ORF2 and ORF3 proteins
7. Packaging, assembly and release of newly formed virus.

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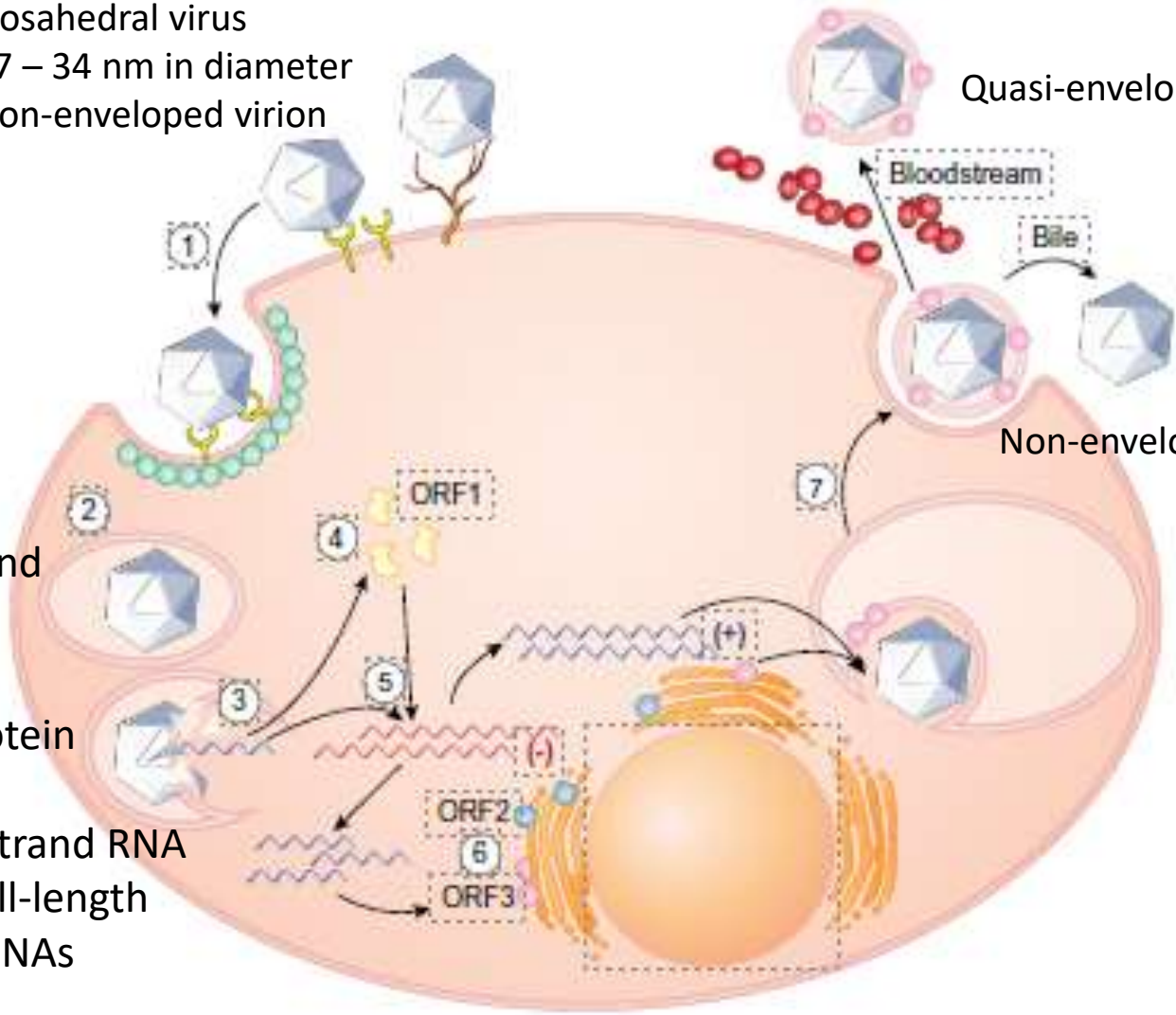

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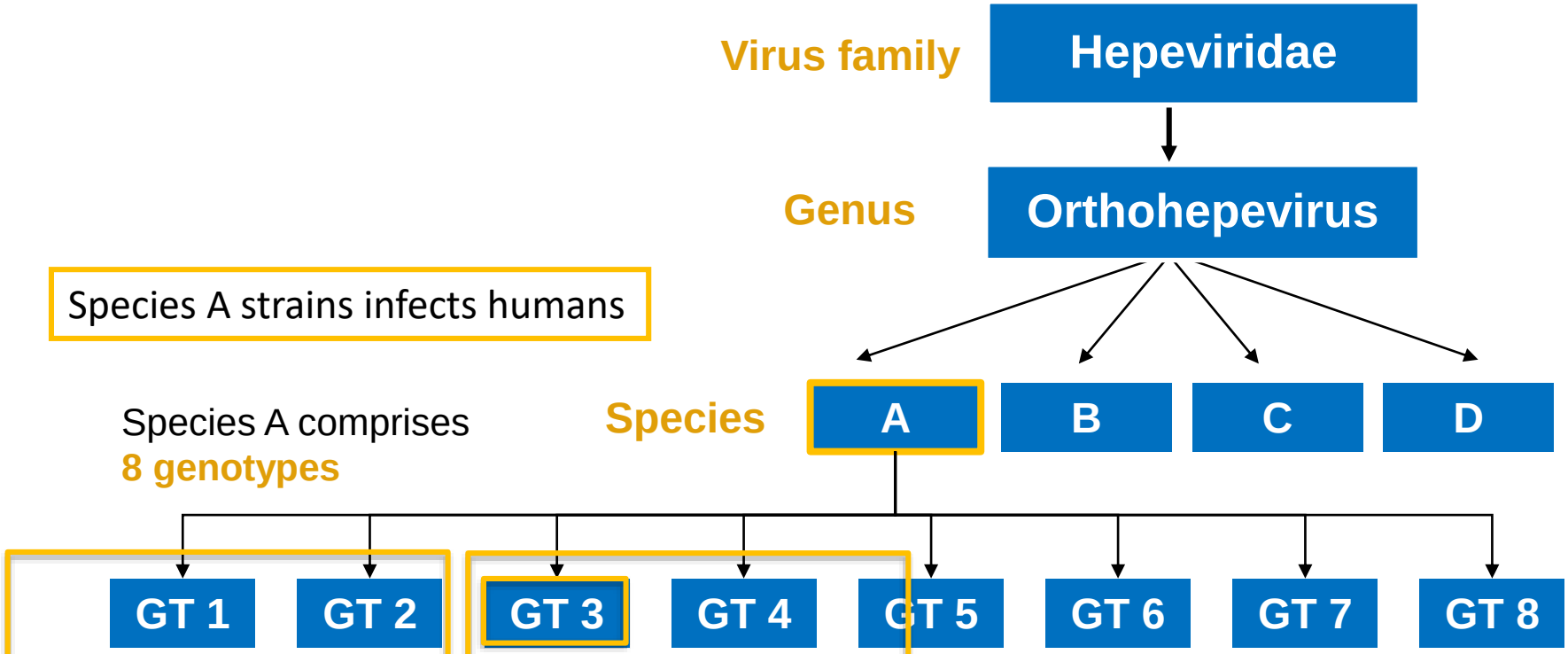
Virology of HEV



EASL Clinical Practice Guidelines J Hepatol. 2018 Jun;68(6):1256-1271
https://www.cdc.gov/hepatitis/hev/hevfaq.htm#section1

HEV Genotype 1 and 2

- ~20 million infections worldwide
  - 3 million symptomatic cases and 70,000 deaths/year*
  - Geographic location
    - GT-1: Africa and Asia
    - GT-2: Mexico and West Africa
- Brief, self-limiting, usually in young adults
- Never chronic
  - Acute-on-chronic liver failure possible
- High mortality in pregnancy (25%)

Travellers with hepatitis returning from areas endemic for HEV GT 1 or 2 should be tested for HEV

**Data from 2005*

Debing Y, et al. J Hepatol 2016;65:200–12
EASL Clinical Practice Guidelines J Hepatol. 2018 Jun;68(6):1256-1271

HEV Genotype 3 and 4

- Endemic in some developing countries, as well as most high-income countries
- Geographic Location
  - GT-3: Developed Countries
  - GT-4: China, Taiwan, Japan
- Transmission route
  - Food borne
- Most common cause of acute viral hepatitis in many European countries
- Estimated that ≥2 million locally acquired HEV infections/year
  - Most as a result of zoonotic infection
    - Primary hosts are pigs
- HEV GT 3 and 4 tend to affect older males
  - In one study, M:F ratio was 3:1; median age, 63 years[1]

1. Dalton HR, et al. Eur J Gastroenterol Hepatol 2008;20:784–90;
EASL Clinical Practice Guidelines J Hepatol. 2018 Jun;68(6):1256-1271

HEV GT 3 ~ Acute infection

- Acute HEV GT 3 infection is clinically silent in most patients
  - <5% may develop symptoms of acute hepatitis
    - Elevated liver enzymes, jaundice and non-specific symptoms
- Immunocompetent patients clear the infection spontaneously
  - Progression to ALF is rare with HEV GT 3
  - ACLF occurs occasionally
- Non-sterilizing immunity develops after infection has cleared
  - Re-infection possible, but with lower risk of symptomatic hepatitis

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HEV Chronic infection

- Definition: Persistence of HEV replication for 6 months
- Immunosuppressed patients may fail to clear HEV infection
  - Progression to chronic hepatitis
  - Only with GT 3 &4 infection
- Solid organ transplant recipients
  - ~50–66% of HEV-infected organ transplant recipients develop chronic hepatitis
- Most patients are asymptomatic and present with mild and persistent LFT abnormalities

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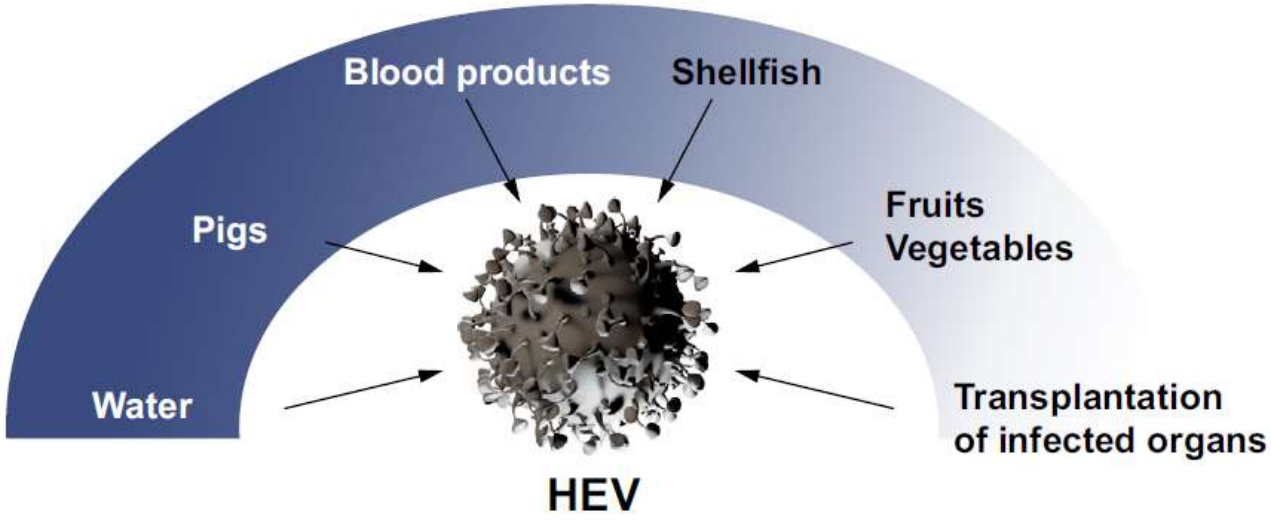
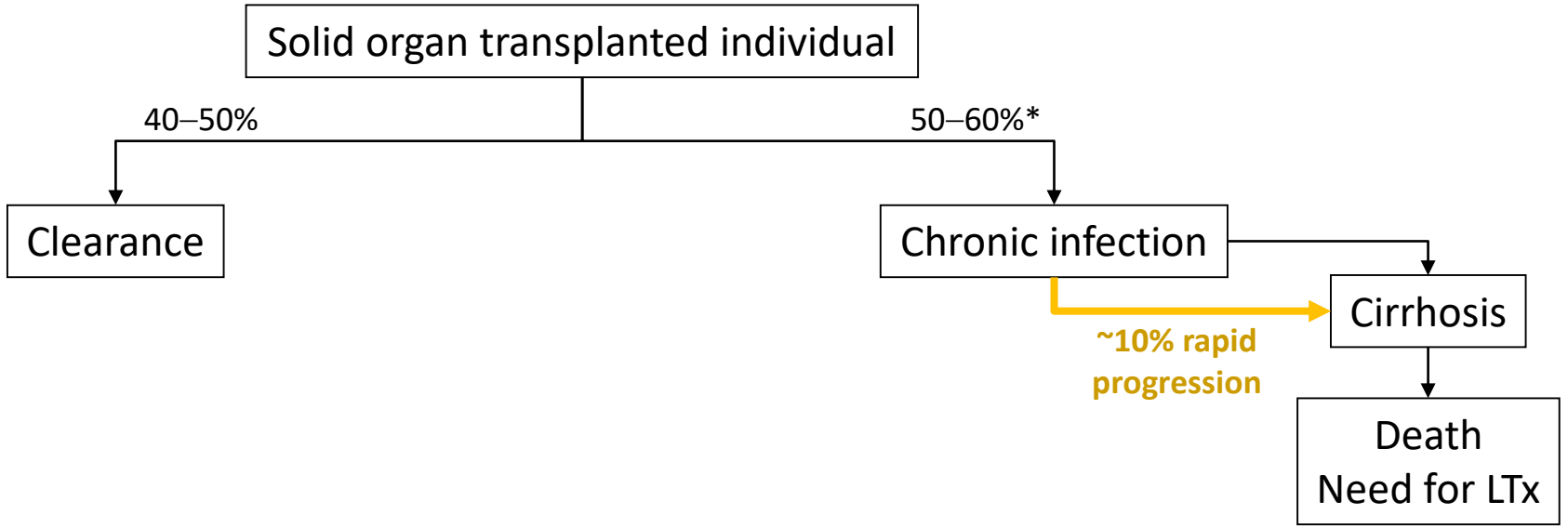
Disease progression in transplanted individuals





*Possible increased likelihood for LTx recipients, only GT 3

Behrendt P, et al. J Hepatol 2014;61:1418–29
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Extrahepatic manifestations

Organ system	Clinical syndrome	Notes
Neurological	• Neuralgic amyotrophy • Guillain–Barré syndrome • Meningoencephalitis • Mononeuritis multiplex • Myositis • Bell's palsy, vestibular neuritis, and peripheral neuropathy	• ~150 cases of neurological injury (in HEV GT 3); mainly Europe • HEV GT 1 in Asia • Most (>90%) cases in the immunocompetent
Renal	• Membranoproliferative and membranous glomerulonephritis • IgA nephropathy	• Mainly immunosuppressed GT 3-infected patients • Renal function improves and proteinuria levels decrease following HEV clearance
Haematological	• Cryoglobulinaemia • Thrombocytopenia • Monoclonal immunoglobulin • Aplastic anaemia • Haemolytic anaemia	• Occurs mainly in association with renal disease • Mild thrombocytopenia is common; rarely severe • Reported in 25% of cases of acute HEV in UK study
Other	• Acute pancreatitis • Arthritis • Myocarditis • Autoimmune thyroiditis	• 55 cases worldwide. HEV GT 1 only; usually mild

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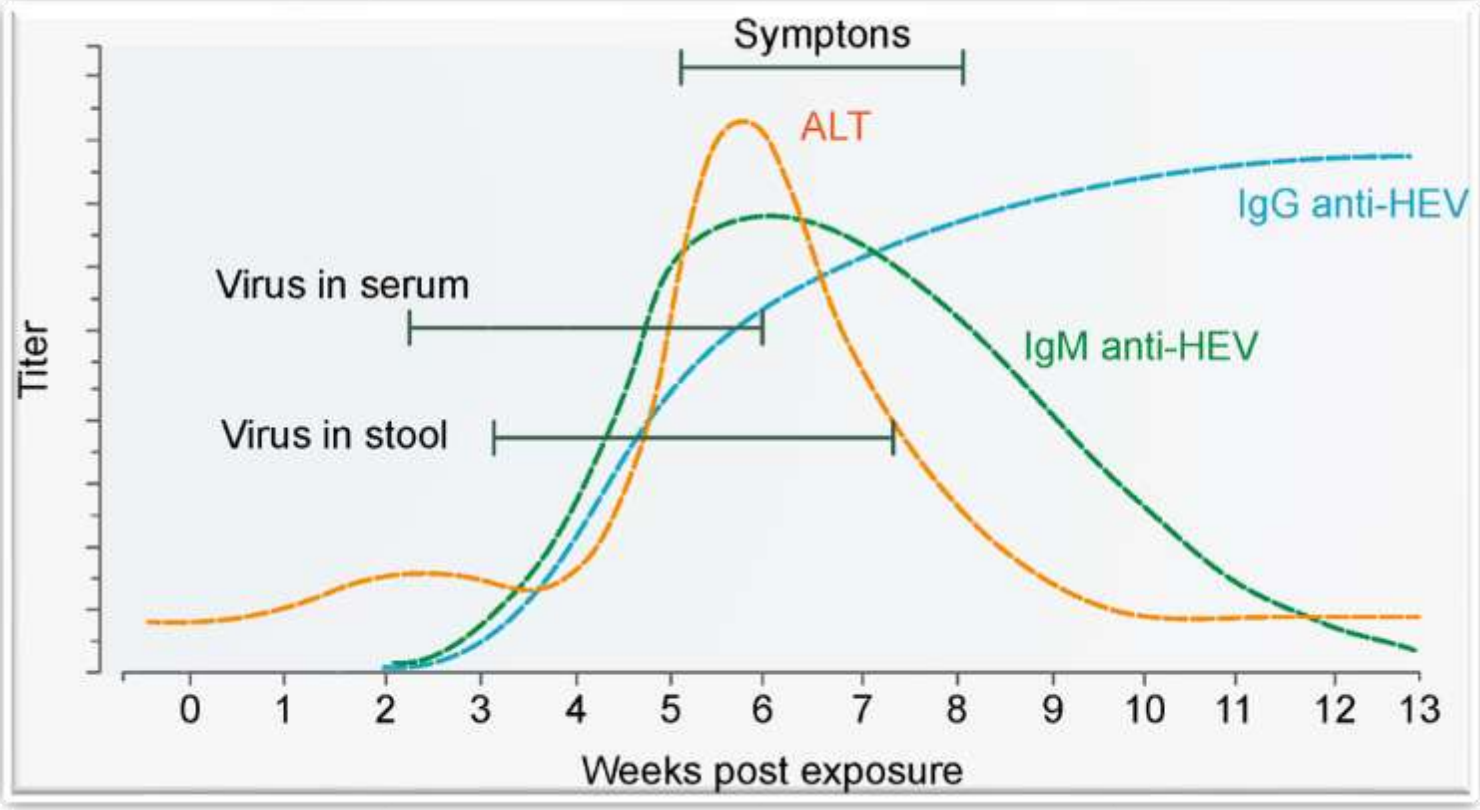
Laboratory diagnosis of HEV infection

- Incubation period for HEV is ~15–60 days
- HEV RNA is detected ~3 weeks post-infection in blood and stool
  - Shortly before onset of symptoms
- Biochemical markers are elevated at the onset of symptoms
  - HEV IgM followed by HEV IgG



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Laboratory diagnosis of HEV infection

- HEV infection can be diagnosed by detection of anti-HEV antibodies
  - IgM, IgG or both in combination with HEV NAT

Infection status	Positive markers
Current infection – acute	• HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen
Current infection – chronic	• HEV RNA (± anti-HEV) ≥3 months • HEV antigen
Past infection	• Anti-HEV IgG

*Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive

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Molecular analysis of HEV ~ Role of HEV Viral Load

- Detection of HEV RNA in blood or stool is indicative of HEV infection

- In immunosuppressed patients with chronic HEV, anti-HEV antibodies are often undetectable
  - HEV RNA is the only reliable means of diagnosis

- In chronic cases, viral load testing should be used
  - To evaluate patient response to treatment
  - To identify relapsing infections

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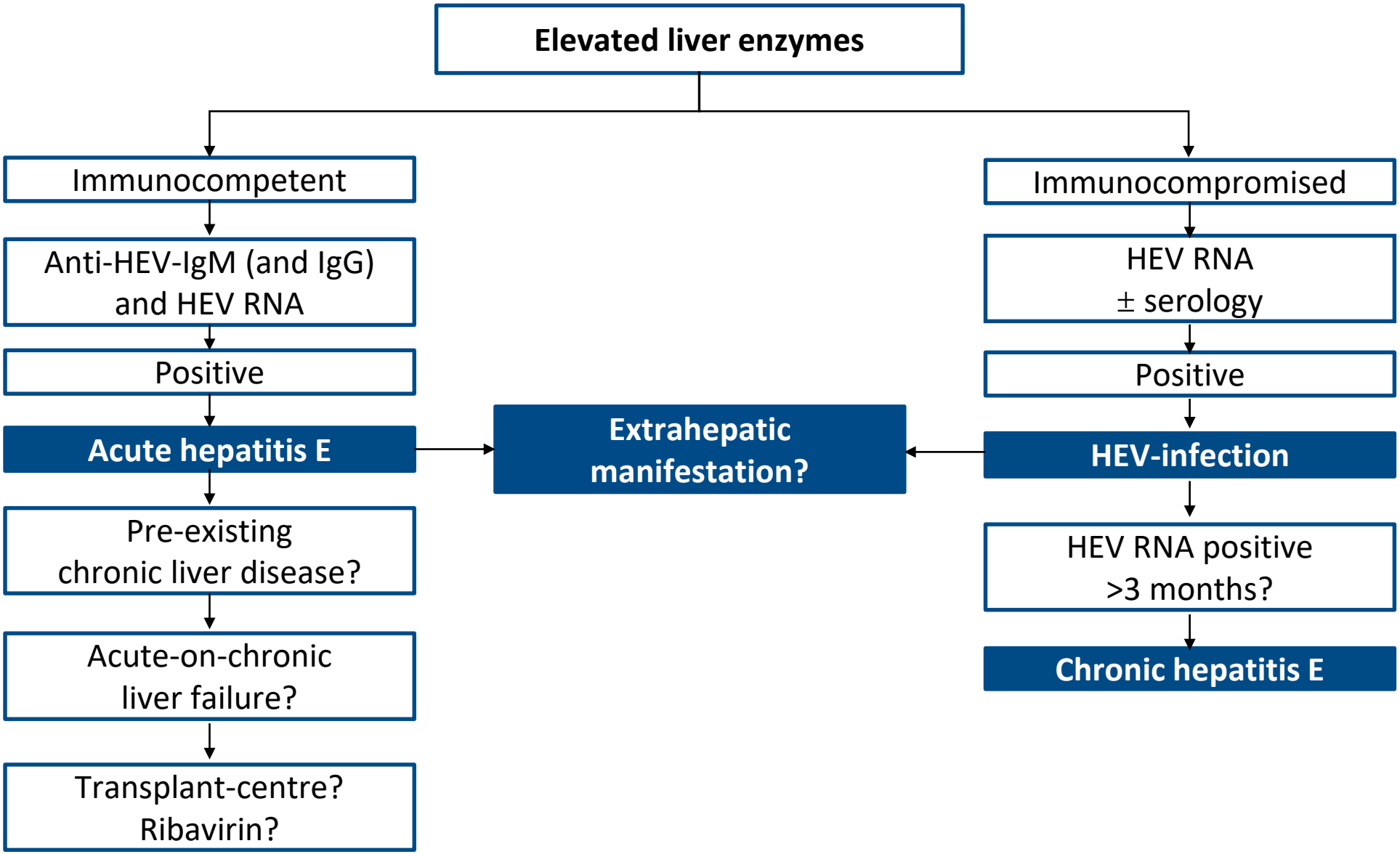
Diagnostic algorithm for HEV infection



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Differential diagnosis

Infection status	Differential diagnosis
Acute infection	• Drug-induced liver injury (DILI) • Autoimmune hepatitis (AIH) • Seronegative hepatitis • EBV hepatitis • Acute hepatitis B • Acute hepatitis A • Acute hepatitis C • CMV hepatitis
Chronic infection in immunosuppressed individuals	• Graft rejection • Drug-induced liver injury • Recurrence of primary liver pathology in LTx recipients • Graft vs. host disease • Intercurrent infections; e.g. sepsis • EBV and CMV reactivation

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Prevention of HEV infection

- Consumption of undercooked meat from pigs, wild boar, and deer is a clear risk factor for HEV infection
  - Immunocompromised individuals and those with chronic liver diseases should avoid consumption of undercooked meat (pork, wild boar) and shellfish

- Risk of patient-to-patient transmission is poorly defined
  - Sexual transmission has been described in MSM
  - Stool contains high amounts of infectious HEV particles
    - Strict hygiene is required

- A vaccine has been developed but is only licensed in China

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Prevention of HEV infection

- HEV can also be transmitted iatrogenically
  - Through infected blood and blood products
- NAT is screening methodology of choice
- Universal screening for HEV in blood donors:
  - Several countries, Ireland, UK, France, Netherlands, Germany, Spain, Austria and Japan
- In US, screening in under consideration

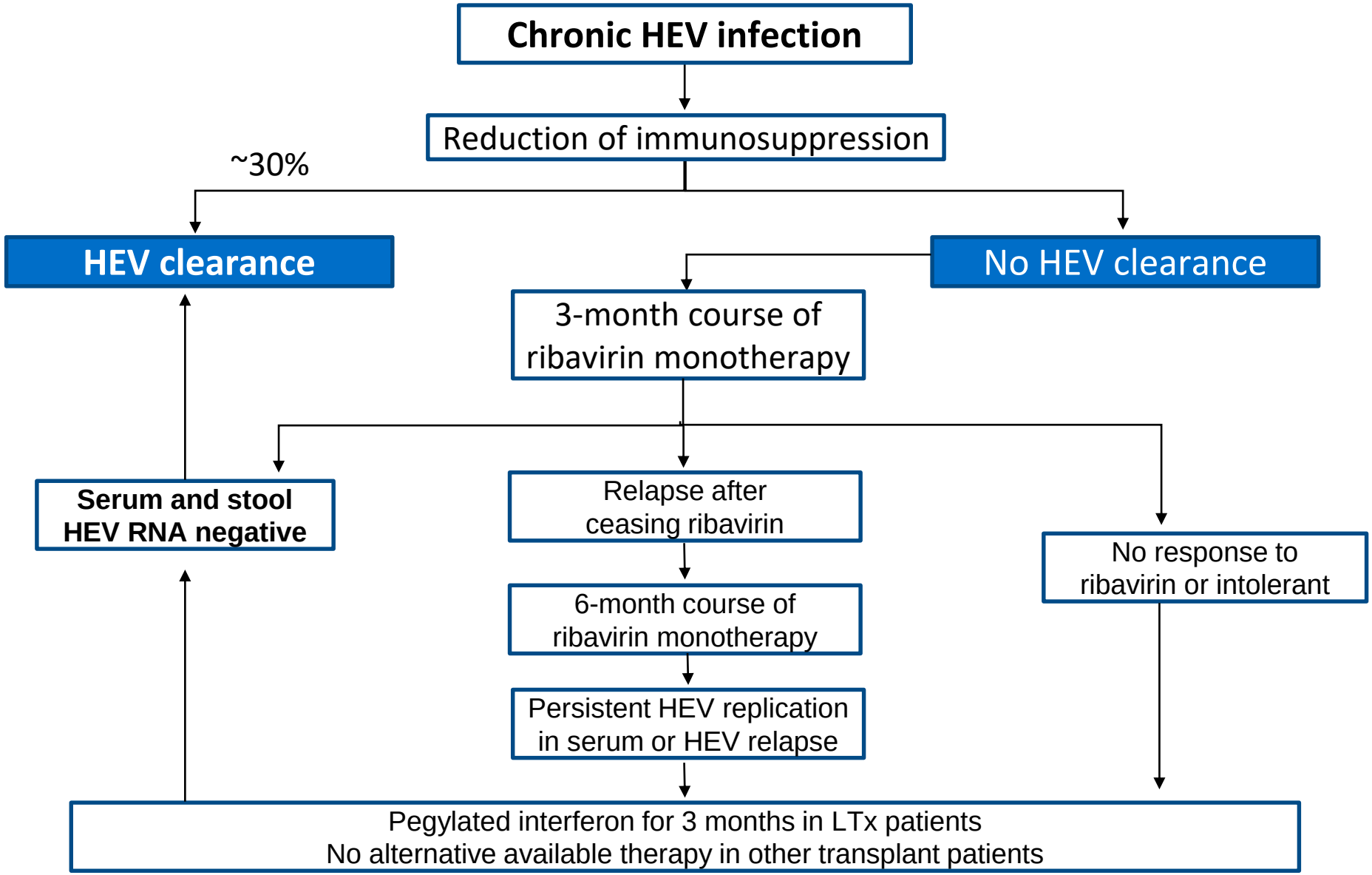
EASL J Hepatol. 2018 Jun;68(6):1256-1271
Ma Z, et al. J Hepatol. 2022 Oct;77(4):1109-1123

Treatment of acute HEV infection

- Acute HEV infection does not usually require antiviral therapy
  - Majority of the HEV infection resolves spontaneously
  - Some patients may progress to liver failure
- Ribavirin
  - Early therapy of acute HEV may shorten course of disease and reduce overall morbidity
  - May be considered in cases of severe acute hepatitis or acute-on-chronic liver failure
- Corticosteroids
  - Were used in some case of ALF and retrospectively identified as HEV infection with improved liver function [(1)]
  - Insufficient data to support the corticosteroids for HEV induced ALF

Manka P, et al. Clin Gastroenterol Hepatol 2015;13:1836–1842.
EASL J Hepatol. 2018 Jun;68(6):1256-1271

Treatment of HEV infection in Solid Organ Transplant



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Summary

- HEV infection represents an important global public health problem and is a cause of significant morbidity and mortality worldwide
- Travellers with evidence of hepatitis returning from areas endemic for HEV GT 1 or 2 should be tested for HEV
- HEV testing should be considered in patient with neuralgic amyotrophy and Guillain–Barré syndrome
- All immunosuppressed patients with unexplained abnormal LFTs should be tested for HEV infection
- HEV infection can be diagnosed by detection of anti-HEV antibodies (IgM, IgG or both in combination with HEV NAT)
- Decrease immunosuppression at diagnosis of chronic HEV infection in solid organ transplant recipients, if possible
- Ribavirin therapy for 12 weeks in patients with chronic HEV infection

Unanswered questions

- Why do only specific HEV genotype causes chronic infections ?
- Does person to person spread occur with HEV GT 3 and 4 ?
- HEV virions can be detected in seminal fluids, can HEV be sexually transmitted ?
- Should transplant recipient living in endemic areas be screened for HEV infection ?
- Should organ donors be screened for HEV ?
- Should blood donation screening for HEV RNA be done universally ?
- What is optimal dose and duration of Ribavirin therapy ?

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~ Thank you