Clinical Practice Guidelines

HEV

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About these slides

- These slides give a comprehensive overview of the EASL clinical practice guidelines on the management of hepatitis E infection
- The guidelines were first presented at the International Liver Congress 2018 and will be published soon in the Journal of Hepatology
  - The full publication will be downloadable from the Clinical Practice Guidelines section of the EASL website once available
- Please feel free to use, adapt, and share these slides for your own personal use; however, please acknowledge EASL as the source

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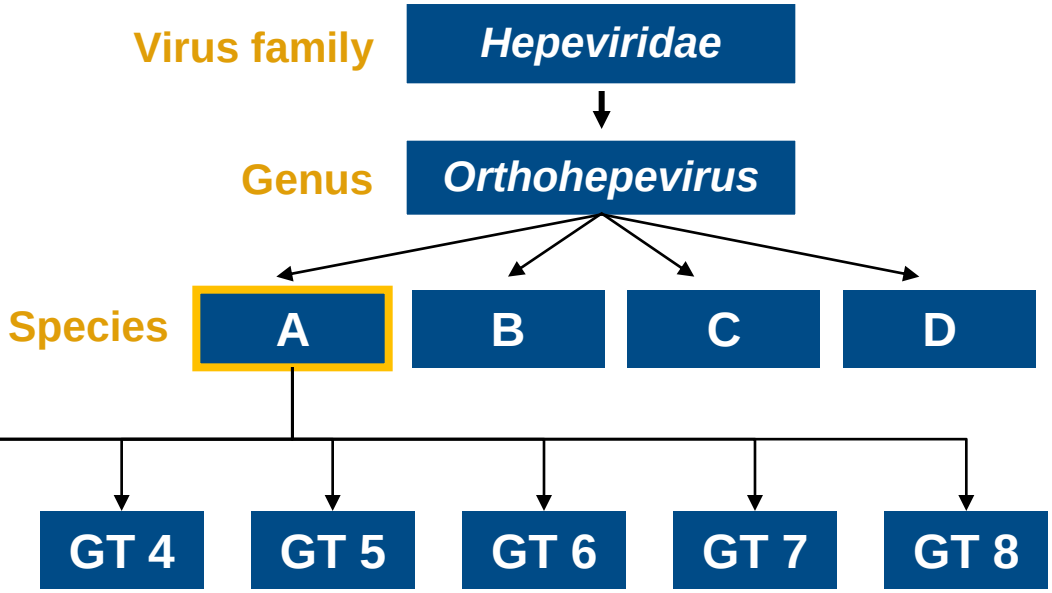
Virology of HEV

Hepeviridae viruses infect mammals, birds and fish

Strains infecting humans belong to the *Orthohepevirus* genus, species A

Species A comprises **8 genotypes**



- Only infect humans
- **Faecal–oral spread** via contaminated water
- Large **outbreaks**
- Brief, **self-limiting**
- Never chronic
- High mortality in **pregnancy** (25%)

- **Endemic** in animal species; eg, pigs and wild boar
- **Zoonotic** infections in humans
- **High-income countries**
- China: GT 4 most common
- S. America: GT 3 only

- Have only been reported in wild boar

- GT 7 identified in patient regularly consuming camel meat and milk
- Have since been identified in camels

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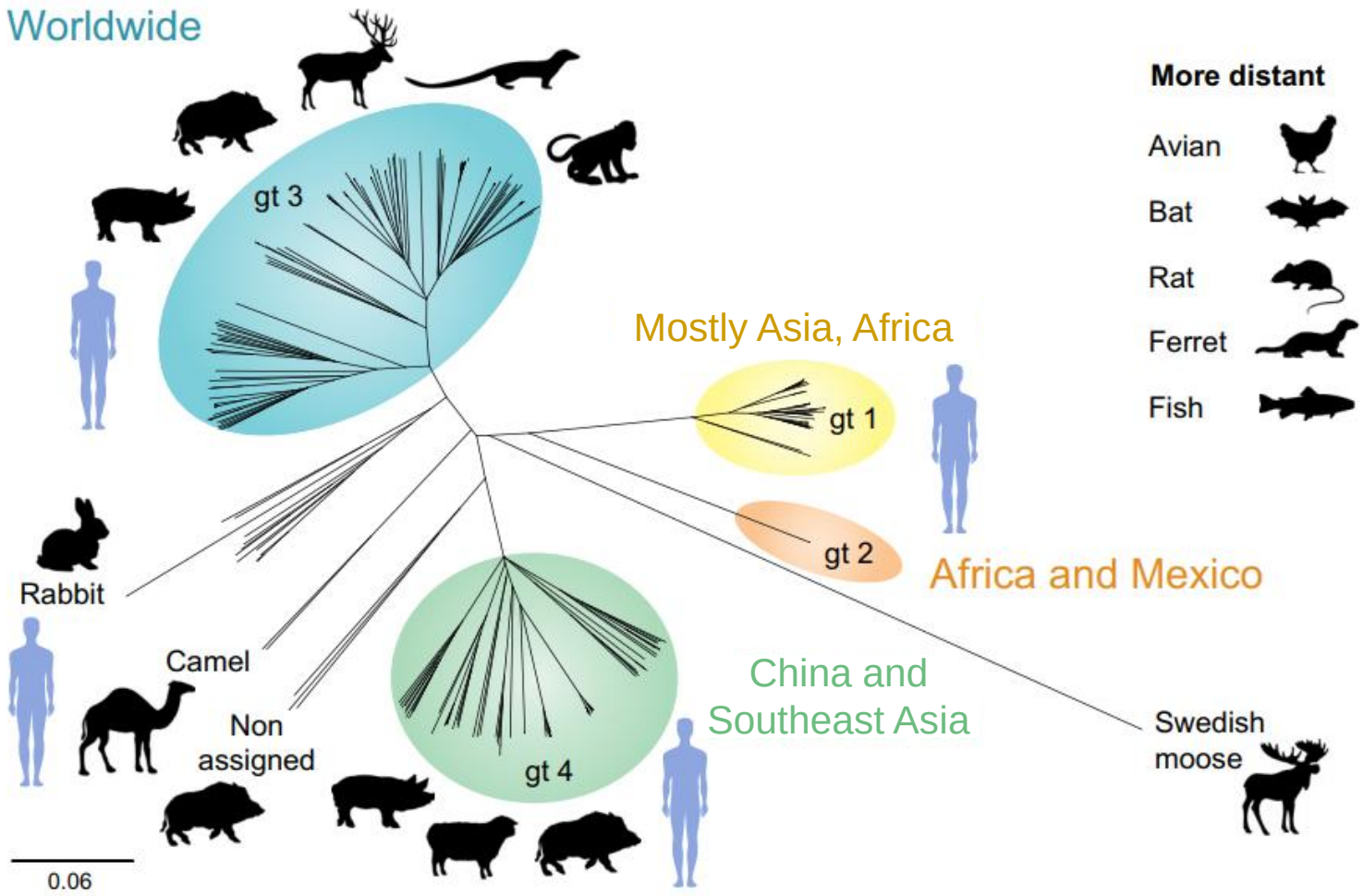
Phylogenetic relationship of hepeviruses identified in various hosts



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

HEV GT 1 and 2 in brief

- ~20 million infections worldwide
  - 3 million symptomatic cases and 70,000 deaths/year*
  - WHO guidelines should be consulted for management of outbreaks of acute HEV in resource-limited settings
- Brief, self-limiting, usually in young adults
- Never chronic
  - Acute-on-chronic liver failure possible
- High mortality in pregnancy (25%)

Recommendations	Level of evidence	Grade of recommendation
• **Travellers** with hepatitis returning **from areas endemic** for HEV GT 1 or 2 **should be tested** for HEV	A	1
• **Pregnant women** with HEV GT 1 or 2 **should be cared for in a high-dependency setting**, and transferred to a liver transplant unit if liver failure occurs	A	1

*Data from 2005

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HEV GT 3 and 4: epidemiology

- Endemic in some developing countries, as well as most high-income countries
- 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 an English study, male:female ratio was 3:1; median age, 63 years[1]
- Incidence varies between and within countries, and over time
  - Multiple ‘hotspots’ of HEV infection in Europe

1. Dalton HR, et al. Eur J Gastroenterol Hepatol 2008;20:784–90;
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Clinical aspects: 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

Recommendations	Level of evidence	Grade of recommendation
Should test for HEV in: • All patients with symptoms consistent with acute hepatitis	A	1
Suggest testing for HEV in: • Patients with unexplained flares of chronic liver disease	C	2

*Fatigue, itching and nausea

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Clinical aspects: chronic infection

- Immunosuppressed patients can fail to clear HEV infection
  - Progression to chronic hepatitis*
- Immunosuppressed groups include:
  - Solid organ transplant recipients
    - ~50–66% of HEV-infected organ transplant recipients develop chronic hepatitis
  - Patients with haematological disorders
  - Individuals living with HIV
  - Patients with rheumatic disorders receiving heavy immunosuppression
- Most patients are asymptomatic and present with mild and persistent LFT abnormalities

Chronic HEV has mainly been described in the solid organ transplant setting

Recommendations	Grade of evidence	Grade of recommendation
Should test for HEV in: • All immunosuppressed patients with unexplained abnormal LFTs	A	1

*Persistence of HEV replication for 3 months. In rare cases, spontaneous clearance has been observed between 3 and 6 months

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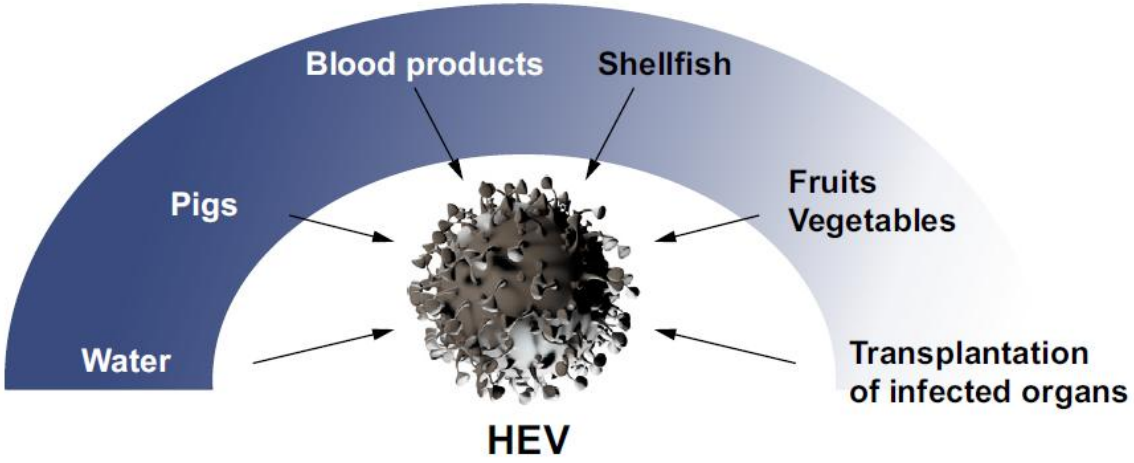
Transmission and disease progression in transplanted individuals



Solid organ transplanted individual

40–50%

Clearance

50–60%*

Chronic infection

~10% rapid progression

Cirrhosis

Death
Need for LTx

*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

- Extrahepatic manifestations of HEV are increasingly recognized

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 • Most (>90%) cases in the immunocompetent **Most important**
Renal*	• Membranoproliferative and membranous glomerulonephritis • IgA nephropathy	• Mainly immunosuppressed GT 3-infected patients • Renal function improves and proteinuria levels decrease following HEV clearance
Haematological	• Thrombocytopenia • Monoclonal immunoglobulin • Cryoglobulinaemia • Aplastic anaemia† • Haemolytic anaemia†	• Mild thrombocytopenia is common; occasionally severe • Reported in 25% of cases of acute HEV in UK study • Occurs mainly in association with renal disease
Other	• Acute pancreatitis • Arthritis† • Myocarditis† • Autoimmune thyroiditis†	• 55 cases worldwide. HEV GT 1 only; usually mild

*There is good evidence to support a causal role for HEV and these associated conditions. For the other extrahepatic manifestations, causality remains to be established; †Case reports only

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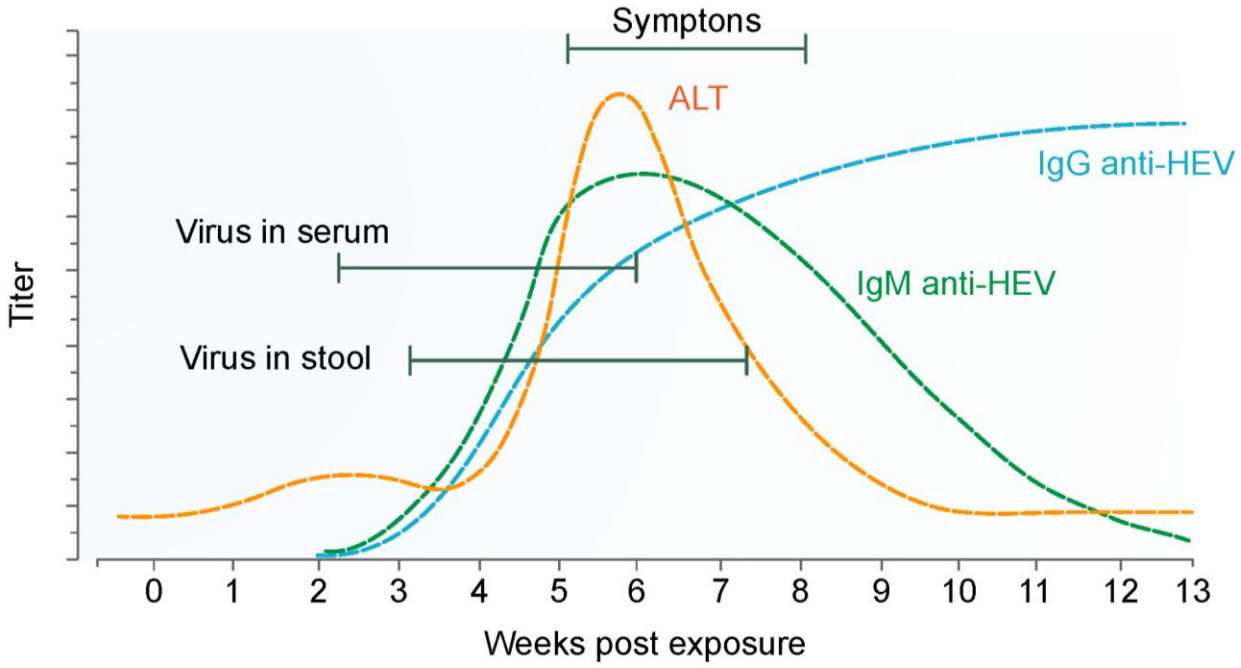
Laboratory diagnosis of HEV infection

- 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
- At clinical onset biochemical markers become elevated
  - First IgM followed by IgG



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Laboratory diagnosis of HEV infection

- Acute HEV infection can be diagnosed by detection of anti-HEV antibodies
  - IgM, IgG or both by enzyme immunoassays in combination with HEV NAT
- Serological testing relies upon detection of anti-IgM and (rising) IgG

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

- 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
  - NATs are 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

Recommendations	Grade of evidence	Grade of recommendation
• **A combination of serology and NAT testing** should be used to diagnose HEV infection	A	1
• NAT testing should be used to diagnose chronic HEV infection	A	1

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Treatment of acute HEV infection

- Acute HEV infection does not usually require antiviral therapy*
- Most cases of HEV infection are spontaneously cleared
  - Some patients may progress to liver failure
  - Ribavirin
    - Early therapy of acute HEV may shorten course of disease and reduce overall morbidity

Recommendation	Grade of evidence	Grade of recommendation
• Ribavirin treatment may be considered in cases of severe acute hepatitis or acute-on-chronic liver failure	C	2

*Grade of evidence A

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Management of HEV infection

- Optimal treatment duration in patients who test HEV RNA positive after 4 or 8 weeks of therapy and who are HEV RNA negative after 12 weeks of therapy is unknown*
- Optimal therapeutic approach unknown in patients who show no response to ribavirin and/or who relapse after retreatment*

Recommendation	Grade of evidence	Grade of recommendation
• If HEV RNA is still detectable in serum and/or stool after 12 weeks, ribavirin monotherapy may be continued for an additional 3 months (6 months therapy overall)	C	2
• Liver transplant recipients who show no response to ribavirin can be considered for treatment with pegylated interferon-α	C	2

*Grade of evidence C

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