Hepatitis E virus

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THE MICROORGANISM AND ITS CLINICAL PRESENTATION

Hepatitis E virus (HEV) is a single-stranded RNA virus, classified in the family of Hepeviruses. HEV comprises of multiple genotypes (gt). Gt 1 - gt4 and gt7 are found in humans. Gt 1 and gt2 seem to be restricted to humans. The others have been detected in animals, including pigs (gt 3, gt 4) and camelids (gt 7, gt 8). Gt 3 is the only genotype that is prevalent worldwide, whereas the others are limited to specific regions.

Transmission is mainly human-to-human and zoonotic.

The incubation time is 2-8 (average 4) weeks. Most cases are asymptomatic. Clinical symptoms range from mild to severe acute hepatitis leading to liver failure in a minority of patients, predominantly middle aged men. In children, the disease is mostly asymptomatic or mild [Al-Sadeq 2018, Kamar 2014, LCI 2019]; symptoms increase with age. A vaccine against HEV infection is licensed only in China.

COMPLICATIONS

HEV infections in immunocompromised patients may lead to chronic HEV infection, defined as persistence of HEV RNA in blood for a least six months. Rare complications are liver failure and neurological diseases (Guillain-Barré syndrome or neuralgic amyotrophy). Pregnant women may have an increased risk of severe disease and death when infected by gt 1 and gt 2 [Kamar 2014].

EPIDEMIOLOGY

Gt 1 and gt 2 are mainly present in India, Pakistan and Bangladesh, and infection with these genotypes is considered to be travel-associated (human to human: faeco-oral) in other countries. Gt 3 and to a lesser extent gt 4 are found as a cause of food-borne infection (faecally contaminated and inadequately heated) in many high-income countries. Symptomatic gt 3 patients are predominantly males >50 years, with pre-existing liver disease or persons with an impaired immune system.

Transmission by contaminated blood products and vertical transmission has been documented [LCI 2019, Zaaijer 2015, Bi 2020].

The seroprevalence of HEV depends heavily on the selected serological assay to detect IgG antibodies (see pitfalls). Although the seroprevalence in industrialised countries ranges from <1% (Norway) to >20% (France), there are regional differences observed within these countries. The average seroprevalence ranges from 1-10% in high-income countries, to 20% in sub-Saharan Africa to 2-70% in Asia. There is a potential birth cohort effect resulting in higher seroprevalence rates in older patients. Chronic infection occurs in immunocompromised patients and can be difficult to treat. Reinfection seems possible based on vaccination studies, cohort studies and case reports but is rare [Abravanel 2014, Baylis 2015].

DIAGNOSTIC TESTING

The clinical, viral and serological course are depicted in figure 1.

Techniques

- Molecular: HEV-PCR on blood, faeces and body fluids (prolonged secretion of HEV RNA in immunocompromised patients >3 months).
- Serological: EIAs IgM and IgG to test for anti-HEV antibodies. Tests use recombinant genotype 1 antigen which reacts with all genotypes and does not show cross-reactions with other pathogens. There is a WHO standard reference test for IgG to evaluate analytical sensitivity [Ferguson 2001]. As in most tests, IgM is subject to false positivity by EBV and CMV (see general chapter pitfalls) [Hyams 2014]. Other tests are not used in the Netherlands* **.
- Immunoblot: used for confirmation of specificity [Herremans 2007] if PCR is not available and in cases with positive IgM and negative PCR.
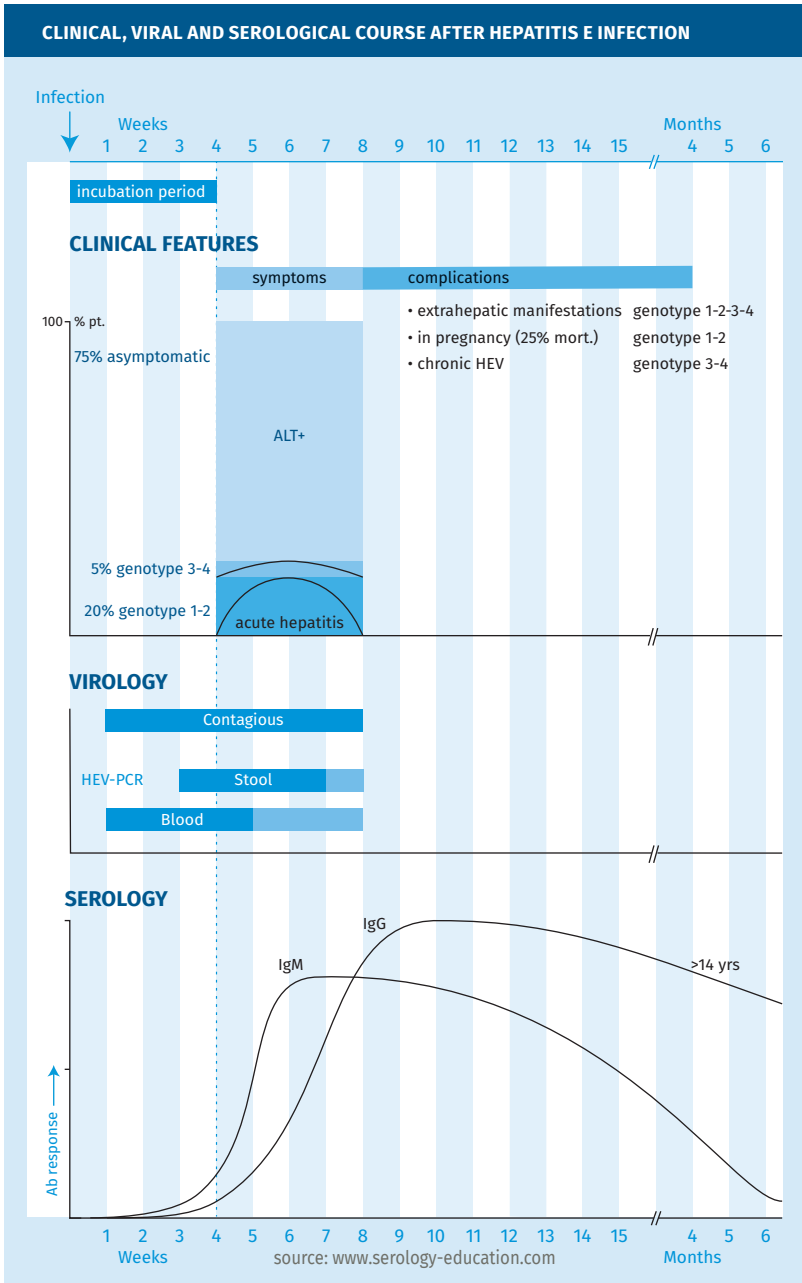
PRACTICAL USE OF SEROLOGY

Screening

Testing for past infection and vaccination: IgG anti-HEV with WHO reference [Bendall 2010]. Screening is not generally recommended because the presence of IgG does not indicate immunity against a new infection.

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* IgG tests also used for avidity testing to estimate the onset of infection [Bigaillon 2010].

** Antigen tests: to detect HEV capsid positive 2 weeks after exposure, remaining positive for 4-5 weeks.

FIGURE 1.

CLINICAL, VIRAL AND SEROLOGICAL COURSE AFTER HEPATITIS E INFECTION

Infection

Weeks
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Months
4 5 6

incubation period

CLINICAL FEATURES

symptoms   complications

• extrahepatic manifestations   genotype 1-2-3-4
• in pregnancy (25% mort.)   genotype 1-2
• chronic HEV   genotype 3-4

100 ─ % pt.

75% asymptomatic

ALT+

5% genotype 3-4
20% genotype 1-2

acute hepatitis

VIROLOGY

Contagious

HEV-PCR   Stool

Blood

SEROLOGY

IgG

IgM

>14 yrs

Ab response

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15   4 5 6
Weeks   source: www.serology-education.com   Months

[Aggarwal 2000, Al-Sadeq 2018, Huang 2010, Kamar 2014, Zhang 2020].

Suspected infection in immunocompetent child or adult
First choice is anti-HEV-IgM positive 4 weeks after exposure. Confirmation is carried out with HEV PCR. IgM and IgG anti-HEV can be performed on serum. HEV PCR on faeces or plasma is used to confirm results. Suspicious are laboratory confirmed hepatitis.

Suspected infection in immunocompromised child or adult
Perform HEV PCR on faeces or plasma because of delayed or absent IgM and IgG response.

INTERPRETATION OF SEROLOGY

TABLE 1.

IgM	IgG/total Ig	Interpretation
Negative	Negative	No infection
Negative	Positive	Past infection (or vaccination)
Positive	Positive	Recent infection*
Positive	Negative	Recent infection*, **

  * When in doubt, confirm with PCR on plasma or faeces.

** Low level IgM with a negative IgG: beware of false positive IgM (see chapter "Pitfalls of serological testing").

SENSITIVITY AND SPECIFICITY

TABLE 2.

	Sensitivity	Specificity
Anti-HEV IgM	65-97%	74-100%

In immunocompetent patients, IgM can most often be detected once clinical manifestations are present. Upon diagnostic testing, IgG is already detectable in most patients. IgM peaks around 6 weeks and gradually declines. IgG levels remain elevated over years and possibly lifelong.

The sensitivity and specificity of serological assays for HEV varies widely. In addition, the relative sensitivity for the different genotypes differs and manufacturers should evaluate their assay for suitability in detecting immune responses against emerging genotypes (such as gt 3) [Zhang 2020, Al-Sadeq 2018, Kar 2020].

In general, the sensitivity of IgM tests for detection of a recent infection

with HEV ranges between 65-97%. The specificity ranges between 74100%. There is a WHO standard as reference only for IgG. Comparing results is not possible.

Another aspect of variation between different manufacturers is the long term IgG response. Some assays (e.g. Wantai) detect long-term antibody responses in much larger proportion of subjects than others (e.g. MP). The exact explanation for this phenomenon is not known, because the exact antigens and method of preparation are not disclosed for all assays and different cut-offs are used. When performing seroprevalence studies, this inter-test variation needs to be taken into account as it may lead to a significant bias between studies [Bendall 2010].

PITFALLS

- A specific pitfall for HEV infections is the lack or delay of antibody responses in immunocompromised patients. In this group, PCR is the method of choice for detecting a recent or chronic HEV infection.
- Despite the fact that HEV is a known cause of acute hepatitis, testing for HEV is not always included in so-called Hepatitis panels when ordering tests. Doctors should check whether HEV testing is included in the algorithms for viral hepatitis.
- See general chapter "Pitfalls" for cross-reactions [Hyams 2014].

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KEYWORDS

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