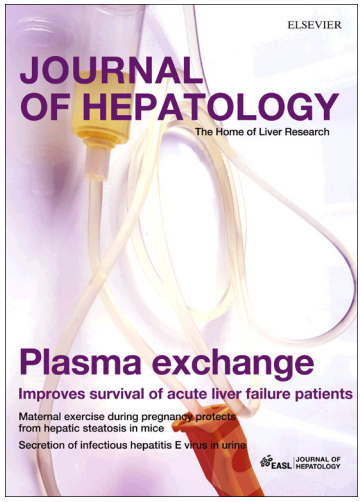

Review

Hepatitis E virus infection beyond the liver?

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PII: S0168-8278(16)30692-4
DOI: http://dx.doi.org/10.1016/j.jhep.2016.11.016
Reference: JHEPAT 6339

To appear in: *Journal of Hepatology*

Received Date: 7 July 2016
Revised Date: 13 November 2016
Accepted Date: 20 November 2016

Please cite this article as: Pischke, S., Hartl, J., Pas, S., Lohse, A., Jacobs, B., van der Eijk, A., Hepatitis E virus infection beyond the liver?, *Journal of Hepatology* (2016), doi: http://dx.doi.org/10.1016/j.jhep.2016.11.016

Hepatitis E virus infection beyond the liver?

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ALL FIGURES ARE PRELIMINARY FIGURES, FINAL LAYOUT WILL BE MADE BY THE JOURNAL OF HEPATOLOGY GRAPHICAL TEAM AFTER ACCEPTANCE

Conflict of interest:
No conflict of interest for this review paper.

Financial support:
No financial support for this review paper

Author contribution:
S. Pischke: Writing of the paper, design of tables and figures
J. Hartl: Writing of the paper
S. Pas: Writing of the paper
A.W. Lohse: Writing of the paper
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Abstract:

Hepatitis E virus (HEV) infections are not limited to the liver but may also affect other organs. Several diseases, including Guillain-Barré syndrome, neuralgic amyotrophy, glomerulonephritis, cryoglobulinemia, pancreatitis, lymphoma, thrombopenia, meningitis, thyreoiditis and myocarditis have been observed in the context of hepatitis E. To date the definite pathophysiological links between HEV and extrahepatic manifestations are not yet established. However, it is suggested that HEV-infection might be causative based on serological studies, case series, *in vitro* data and animal models . In particular neuronal and renal diseases as well as pancreatitis seem to be caused by HEV, while a causative relationship between HEV and other diseases is more doubtful.

Either direct cytopathic tissue damage by extrahepatic replication or immunological processes induced by an overwhelming host immune response are possible origins of HEV-associated extrahepatic manifestations.

Hepatologists should be aware of the possibility of acute or chronically HEV-infected patients to develop extrahepatic manifestations while neurologists, nephrologists, rheumatologists and other groups of physicians should consider HEV-infection as a potential differential diagnosis when observing one of the hereby described diseases. Ribavirin and steroids have been used in small groups of patients with extrahepatic manifestations, but the efficacy of these drugs still needs to be verified by large, multicenter studies.

This article comprehensively reviews the published literature regarding HEV and extrahepatic manifestations and discusses the probability of specific extrahepatic diseases to be caused by previous or ongoing HEV-infection and summarizes the published knowledge about antiviral treatment in extrahepatic disorders.

Introduction

Hepatitis E is an infectious inflammation of the liver caused by hepatitis E virus (HEV) and one of the most common causes of acute hepatitis and jaundice in the world (1). The four human pathogenic HEV-genotypes (GT 1-4) show a specific geographical distribution (1).

HEV GT1 and GT2 are endemic in many tropical countries and are mainly water-borne in regions with low sanitation standards. Occasionally, the infection may lead to acute liver failure, especially GT1-infection in pregnant women (1, 2). It is estimated that HEV-GT1 and GT2-infections are responsible for more than 3 million symptomatic cases of acute hepatitis causing 70.000 deaths, annually (1).

The perception of HEV-infection in the Western world has undergone a fundamental change within the last decade. While hepatitis E was mainly interpreted as a travel-associated liver disease since the 1970ties, studies published over the last decade clearly demonstrate that autochthonous HEV-infection in industrialized countries is far more common than previously suspected. In Europe and North America the most prevalent genotype is HEV-GT3, which is mainly transmitted by consumption of swine meat. Furthermore, blood products seem to be a relevant source of infection (3). In addition, an epidemiological study from France hypothesized that waterborne transmission may also play a role (4). While most contacts with HEV-GT3 induce clinically silent seroconversion, some patients, mostly older males, develop symptomatic acute hepatitis (5, 6). In particular, patients with underlying chronic liver disease are at risk to develop hepatic decompensation (5).

In 2008, Kamar et al. demonstrated that HEV-infection can evolve to chronic hepatitis and subsequently to the development of liver cirrhosis in immunosuppressed patients (5, 7-12). In immunocompromised individuals antibody production is often delayed (13, 14), HEV-viremia can be prolonged and thus measurement of HEV-RNA is essential to detect ongoing HEV-infection in this patient group. Of note, chronic HEV-infection has only been observed in HEV GT3 and GT4 infection but not in other genotypes.

Treatment with ribavirin is a therapeutic option for patients with chronic hepatitis E and has been evaluated in various studies (15, 16), while treatment with interferon is possible but can cause several side effects and is not recommended in transplant recipients (17).

In addition, several extra-hepatic manifestations in association with HEV-infection

have been reported, which adds a further aspect to the rapidly emerging field of HEV-infection. Sub-acute and monophasic neurological disorders which involve predominantly the peripheral nervous system, acute pancreatitis, glomerulonephritis, mixed cryoglobulinemia, severe thrombocytopenia and hemolytic anemia due to G6PD deficiency are frequently reported (figure 1). These manifestations may develop during or after acute or chronic HEV-infection (figure 2). However, definitive causative links between most of the described extra-hepatic conditions and HEV-infection remain to be established and the axiom "association is not causation" should be kept in mind.

The following review aims to (i) give an overview of suspected HEV-associated extra-hepatic manifestations, (ii) interpret current evidence of a causal association between HEV-infection and those syndromes, (iii) address the potential underlying pathophysiological mechanisms and (iv) summarize treatment recommendations.

Association or causation?

When new associations are defined, causality is a very easy thing to claim but very difficult to define. In 1965, the British medical statistician and physician Austin Bradford Hill published "Hill´s criteria", nine viewpoints to consider when assessing the causal nature of an observed association (18). These criteria quickly became a mainstay of modern epidemiology. We applied an adopted version of these criteria to decide for which extra-hepatic conditions current data provide sufficient evidence to assume a causal relationship to HEV-infection (table 1):

i. Strength: A strong association is more likely to have causal component than is modest association
ii. Consistency: An association is observed repeatedly by different observers
iii. Temporality: Potential extra-hepatic manifestations are increasingly observed shortly after or during HEV-infection
iv. Plausibility and analogy: Comparable or similar extra-hepatic manifestations and its underlying pathophysiological mechanisms are already established for other viral infections, e.g. hepatitis C virus-infection.
v. Experimental data support a causal relationship

Potential pathogenesis of HEV-induced extrahepatic manifestations

The mechanisms by which HEV can induce extrahepatic manifestations are largely unknown, but may be caused by either direct viral effects due to HEV-replication in affected tissues, or indirectly by various immune-mediated mechanisms (figure 1).

Various features of HEV might facilitate a broad host cell range. Cloaking of HEV in host cell membranes may result in non-specific binding and uptake by different cell types (19, 20). The virus´ ability to insert human genome sequences into the hypervariable region of the HEV-genome was shown to promote in vitro replication and might result in an altered cell tropism (21, 22). Furthermore, it was suggested that similarities between the membrane-encased HEV virion and exosomes (small vesicles involved in intercellular signalling) might permit the penetration of immunologically privileged sites such as the central nervous system (23). However, whether these mechanisms actually result in extrahepatic replication, and if so, whether extrahepatic replication is a main driver of extrahepatic tissue damage in certain conditions remains unproven (Table 1, figure 1). Nevertheless, it is noteworthy that extrahepatic HEV-replication has been demonstrated, and HEV has been detected in various tissues (Table 2) (24-30). Furthermore, swine-HEV could be detected in intestine, lymph nodes, tonsils, spleen, and kidney (31).

In line with other infections, it is most likely that immune-mediated mechanisms may induce extrahepatic manifestation. Cross-reactivity between viral epitopes and self-antigens (molecular mimicry) might induce autoimmunity, as has been shown for many viruses (32). However, molecular mimicry for HEV has thus far not been demonstrated. Deposition of HEV-antigens/antibody-immune-complexes could also contribute to the development of extrahepatic manifestations.

The potential direct and indirect mechanisms causing extrahepatic manifestations will be discussed further in the context of the respective disorders.

Neurological manifestations of HEV

Since Sood *et al.* reported the first case of Guillain-Barré syndrome (GBS) in an HEV-infected patient in India, knowledge about the spectrum and magnitude of neurological diseases associated with HEV is rapidly expanding (33).

From 2004 to 2009, more than 5% of 126 patients at 2 hospitals in the United Kingdom and France developed neurologic complications following infection with locally acquired HEV genotype 3 (34). HEV-associated neurological injury has been documented in both acute and chronic HEV-infection, with detectable HEV-RNA in the cerebrospinal fluid in some cases (35).

In general, HEV has been associated with various subacute disorders of the peripheral nervous system including Bell's palsy (facial of seventh cranial nerve), polyradiculopathy, Guillain-Barré syndrome (GBS) (peripheral nerves and nerve roots) and neuralgic amyotrophy (NA) (nerve plexus) (Table 3). Case reports on GBS and HEV come from both developed and developing countries, suggesting that this condition is not genotype specific.

Guillain-Barré syndrome (GBS):

GBS is a typical post-infectious disorder, in which severe damage to the peripheral nerves and nerve roots results in rapidly progressive weakness and sensory deficits. Molecular mimicry and a cross-reactive response play a crucial part in the pathogenesis as demonstrated by antibodies to gangliosides following infection with *Campylobacter jejuni* (36). Approximately two-third of GBS-patients report symptoms of a recent respiratory or gastro-intestinal tract infection in the 3 weeks prior to onset. Other mechanisms may also play a role in HEV, which has been demonstrated to have the ability to infect neuronal cells in vitro (24).

Infectious agents like *Campylobacter jejuni,* cytomegalovirus, Epstein-Barr virus and *Mycoplasma pneumoniae* have been associated with GBS (37). Interestingly, one-third of GBS-patients show mild liver function disturbances without an obvious cause. There are 41 GBS-cases reported in the literature in association with HEV in 18 case reports and 3 case-controlled studies (Table 3). Twenty-one patients were male, 9 females and of 11 patients sex is unknown. The mean age at presentation was 53 years; range 20-73 years. ALT-levels showed a wide range: 26-2858 IU/L (mean 918 IU/L, median 752 IU/L; data available from 28 patients).

In a case-control cohort study by van den Berg *et al.*, 10/201 (5%) patients with GBS in the Netherlands had an associated acute hepatitis E virus infection just before, or at the start of their illness (37). The frequency of a recent HEV-infection (all GT3) based on the presence of anti-HEV IgM was ten times higher than in a similar group of age- and sex matched healthy controls. HEV-RNA was found in the serum of 3/10

of the IgM positive patients, supporting the association with acute HEV-infection. In all ten cases of HEV-associated GBS the neurological illness dominated the clinical picture: all were anicteric and bilirubin levels were< 17 µmol/L in six of the cases (data biluribin levels available of 7 out of 10 patients).

The clinical features and outcome in these patients were similar to those found in other GBS-cases. The majority of HEV-associated GBS-cases in this large and clinically well-defined cohort had a sensory-motor and demyelinating form, the predominant subtype of GBS in the Netherlands.

In a recent hospital-based survey from Japan, 3/63 (4.8%) patients with GBS and Miller Fisher syndrome (MFS) were positive for HEV IgM serology compared to none of 60 control subjects (38). Of these three positive patients, two had a sensory-motor and demyelinating form of GBS, similar to the Dutch patients with HEV-associated GBS, and one patient had MFS. The other patient had a GBS-variant with paralysis of eye movement muscles (ophthalmoplegia), ataxia and reduced limb tendon reflexes. One of the patients with HEV-related GBS had serum IgM-antibodies against GM1 and the patients with HEV-related MFS had IgG-antibodies against to GQ1b. None of the 10 Dutch patients with HEV-related GBS had serum antibodies against the gangliosides GM1 or GM2.

A case-control study among GBS-patients in Bangladesh documented that 11/100 (11%) had an associated acute HEV-infection. IgM seropositive individuals were tested for HEV-RNA, yielding one positive serum sample classified as HEV-GT1 (39). Serum antibodies against gangliosides were not reported.

Since GBS is a typical post-infectious disorder of the peripheral nerve system, a causal relationship between HEV-infection and the development of GBS appears plausible. Two well-described study cohorts and a large number of case reports provide consistent data that there is a strong and temporal association between HEV-infection and GBS suggesting a causal relationship.

Neuralgic amyotrophy (NA):

NA, also known as Parsonage-Turner syndrome or brachial neuritis, is a post-infectious disorder of the brachial plexus, which is clinically dominated by severe shoulder and arm pain of acute onset followed by weakness and atrophy.

Involvement of nerves from regions other than the brachial plexus is seen in 23% of cases (40). The pathogenesis of NA is unknown, but NA may, at least partially, share its pathogenesis with GBS (40). Liver enzymes are also (mildly) raised in 25% of cases.

Thirty-seven cases describing HEV-associated NA have been reported (Table 3). In 28 of them (76%) NA was bilateral. The mean and median age of the patients was 46 and 50 years (range 28-65) and 29/36 patients (80%) were male. ALT-levels ranged widely from 27-2457 IU/L (mean 884 IU/L, median 1007 U/L). All HEV-RNA positive patients displayed GT3.

A recent study of 47 NA-patients from Cornwall (UK) and the Netherlands showed that 5/47 (11%) cases had an acute HEV-GT3 infection (40). All these HEV-associated NA-cases had bilateral involvement, compared to 15/35 (43%) of the Dutch cohort without evidence of HEV-infection. The age of the HEV-associated cases ranged from 34-40 years (median 36). All patients were anicteric with normal bilirubin levels and normal or only mildly raised ALT, only some were viremic at presentation. Anti-HEV-IgM positivity was neither related to age, gender, disease severity nor outcome.

In one well-described case-control study, a high incidence (11%) of acute HEV-GT3 infection was found. Recently, data collection of a large multi-center study on HEV-related NA was completed. The presentation of this study results is eagerly awaited and will further substantiate a causal relationship.

Other neurological manifestations

Twelve cases have been reported of neurological manifestations in association with the presence of HEV-RNA in the cerebrospinal fluid (CSF); in six patients paired serum samples also had detectable HEV-RNA levels (Table 3) (34, 41-49). Five patients were immunocompromised and chronically HEV-infected. In an HIV-positive patient with HEV in the cerebrospinal fluid and a sensory neuropathy, treatment with pegylated interferon and ribavirin resulted in a clearance of HEV and a clinical improvement of the neuropathy (48). In a chronically HEV-infected kidney transplant patient HEV-RNA was detected both in serum and CSF, but HEV-RNA sequences in CSF clearly differed from those in serum (49). In both cases quasispecies compartmentalization was suggested as a reason for this observation, but in the first case has not been demonstrated by sequencing. In 5/12 patients with HEV-RNA in

CSF, peripheral nerve involvement such as GBS or other forms of peripheral neuropathy were described. The question remains, if the presence of HEV-RNA in the CSF truly reflects CNS-infection, is the result of HEV-infection of peripheral nervous cells, as the nerve roots of the peripheral nerves are also situated within the CSF, is due to leakage of the blood-brain barrier, or is due to blood contamination of the CSF as a result of a traumatic puncture.

Recently HEV-replication in brain, myelum and CSF of experimentally infected gerbils could be demonstrated (50). Interestingly, these effects were demonstrated for a genotype 4 HEV strain suggesting potential neurological injury in humans, although so far this genotype has not been identified in patients with HEV related neurological disorders.

Mononeuritis multiplex, defined by asymmetric, asynchronous involvement of the noncontiguous nerve trunks was seen in 6 patients (41). All patients had experienced neuropathic pain and paresthesia in $\geq$1 nerve segments with hyporeflexia or areflexia. HEV-RNA was detected in serum in 4/6 and sequencing showed genotype 3 infections in all cases.

Other HEV-associated neurological disorders have also been reported, including Bell's palsy, myositis, paresthesia, pseudotumor cerebri and small fiber neuropathy, however, but a causal relationship with HEV has not been proven yet (Table 3).

The pathophysiological mechanisms of HEV-associated neurological injury require further study. The finding that hepatitis E is associated with both GBS and NA may suggest that these syndromes reflect different parts of the same spectrum of neurological immune-mediated disease. Drave *et al.* investigated whether HEV is capable of completing the viral life cycle in human neuronal cell lines and demonstrated that HEV-tropism is not restricted to the human liver as HEV could complete the full viral life cycle in M03.13 oligodendrocytes (24). Future research must clarify, if direct HEV-replication in human neuronal cells or if immune mechanisms are primarily responsible for HEV-associated neurological injury.

Association of psychiatric syndromes and hepatitis E

Some epidemiological studies from Taiwan, China and Germany demonstrated high anti-HEV-IgG seroprevalence rates in psychiatric patients (51-53). It still needs to be determined, if psychiatric patients are at higher risk of acquiring HEV-infection, or if

previous HEV-infection might trigger psychiatric diseases. Thus, this observation needs further investigations.

Hematological manifestations of hepatitis E virus

Thrombocytopenia

HEV-infection has been associated with thrombocytopenia. Woolson *et al.* found that a proportion (12/106 patients) of HEV-infected patients present with low platelets (42). In three patients the platelet count was $<100x10^9$/L, the lowest platelet count recorded at presentation was $40x10^9$/L. However, no clinical problems were observed in these cases (42).

However, nine cases of severe thrombocytopenia in HEV-infected patients have been observed: 7 men and 2 women (54-60). The mean age of the patients was 40 years; median age 38 (range 8-72). All patients presented with elevated ALT levels (mean 1213 IU/L, median 1045 IU/L, range: 461-2958 IU/L). Mean patients' platelets count was $12x10^9$ /L, median platelets count was $10x10^9$/L, range: $1x10^9$/L-$21x10^9$/L. In 2 patients platelet-associated antibodies could be detected.
The mechanism by which HEV induces thrombocytopenia is unknown. It has been speculated that the low platelet count may be immune-mediated as in other viral infections (61). Development of fibrosis with splenomegaly is another possible explanation for the observed association.

Monoclonal gammopathy of uncertain significance (MGUS)

MGUS is a clinically asymptomatic premalignant clonal lymphoplasmacytic proliferative disorder that occurs in over three percent of the general Caucasian population over the age of 50 and is typically detected as an incidental finding (62). One study described an unusually high incidence of MGUS in a patient cohort of 65 cases of acute HEV-infection in whom an electrophoresis was performed at diagnosis (42). A monoclonal paraprotein was found in 17/65 (26.2%) patients. The average age of these patients was 67 (range 51-79, median 67 years). None of the patients demonstrated any clinical or laboratory findings suggestive of myeloma or lymphoma, and no patients developed progression to lymphoid malignancy. Increased serum

immunoglobulin concentrations can be seen in patients with any chronic infection. Thus, the nature of the relationship between HEV and MGUS is not clear from the data presented; none of the patients had been tested for MGUS prior to presentation of acute HEV-infection. It is uncertain, if an immune deficit associated with MGUS raises the susceptibility for HEV leading to clinical overt symptomatic hepatitis, or if HEV has a causal role in MGUS (42).

Hemolytic anemia

Glucose 6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder, is the most common enzymatic disorder of red blood cells in humans, affecting 400 million people worldwide. Patients are most often asymptomatic, but many have episodic anemia, following exposure to infections, drugs, or chemicals, while a few have chronic hemolysis (63).

There are various case reports and case series from Southern Asia, where HEV-GT1 is circulating, describing hemolytic anemia in patients with acute hepatitis E and G6PD-deficiency. Patients presented with fever, chills, leucocytosis, hyperbilirubinemia and impaired renal function (64-68). Sometimes the decreased renal function requires dialysis, and rarely this disease took a fatal course due to cerebral bleeding, sepsis or liver failure (69, 70).

Acute renal failure is a serious potential complication of viral hepatitis and concomitant G6PD-deficiency; pathogenetic factors include acute tubular necrosis due to renal ischaemia and tubular obstruction by haemoglobin casts. Some patients with haemolysis require haemodialysis (63).

Hepatitis-associated aplastic anemia (HAAA) is an uncommon, but distinct variant of aplastic anemia, in which pancytopenia appears two to three months after an acute viral hepatitis (71). The marrow failure can be severe and is typically fatal, if untreated. Shah *et al.* reported the case of a 32-year-old Pakistani male, who developed severe aplastic anemia after a severe attack of acute hepatitis E (71). The patient presented with fever, pallor and bleeding diathesis with petechiae, bruises and mucosal bleeds. The patient failed to respond to immunosuppressive therapy.

The causative relationship between HEV-infection and anemia is difficult to establish and it is possible that less severe cases remained unnoticed and are thus underreported. Other haematological manifestations (like hemophagocytic

lymphohistiocytosis) are uncommonly reported and the role of HEV in these cases is not clear yet and should be evaluated (72).

Acute pancreatitis and HEV

Acute pancreatitis (AP) associated with viral hepatitis is a well-known phenomenon and has frequently been described for hepatitis A, B and C virus infections. AP usually occurs in the setting of fulminant viral hepatitis and patient outcome depends primarily on the severity of hepatitis. This seems to be different in HEV-related AP. Mishra *et al.* reported the first case of AP associated with non-fulminant acute hepatitis E in 1999 (73). Since then, more than 50 additional cases have been reported, whereby all patients were from southern Asia (India and Nepal) or had recently travelled to this region (73-80). Therefore HEV-GT1 infections can be presumed in all described cases, albeit HEV-genotyping was only performed in a single patient (80).

The typical clinical picture of HEV-associated AP is a young man from the Indian peninsula in his mid-twenties developing abdominal pain within 2 weeks after the occurrence of jaundice. The mean hospital stay was 9 days (74) and the vast majority of patients experienced only a mild or moderately severe pancreatitis, which usually resolved with supportive treatment (74). So far, only two fatal cases have been reported, suggesting a mortality rate of 3.8%, very similar to the mortality rate observed in AP of other causes (74).

Case-control studies on HEV-infections and AP are lacking, hence it is not possible to estimate the strength of the association. However, based on the consistency of reports, analogy to other hepatic virus infections and temporal occurrence shortly after HEV-infection a causal relationship must be assumed. Therefore, AP should be considered in patients with acute hepatitis E who develop severe abdominal pain, just as HEV-infection should be considered as possible etiology of AP in areas endemic for HEV-GT 1 infection. It remains doubtful, if there is also an association between HEV-GT3 and AP, as no case of acute pancreatitis in an HEV-infected patient from genotype 3 areas has been reported.

Renal manifestation

Except for a single case report of thrombocytopenia and membranous glomerulonephritis in acute HEV-GT1 infection (81), glomerular disease has only

been reported in HEV-GT3 infection (Table 4). One study by Kamar *et al.* provides evidence for a causal link between HEV-GT3 infection and renal injury (82). This study assessed kidney function and histology in a French cohort of 51 solid-organ transplants before, during and after HEV-infection. Glomerular filtration rate (GFR) significantly decreased both in kidney and liver transplant recipients during the acute and chronic phases of HEV-infection. This decrease seemed to be related to HEV-infection, since other causes were ruled out. Renal biopsies were performed in 5 patients, which revealed histological features of membranoproliferative glomerulonephritis (MPGN) (n=2), relapses in IgA-nephropathy (IgA-GN, n=2) and nephroangiosclerosis (n=1).

In total, at least 8 patients with HEV-GT3-associated GN have been described (83-85). Types of renal injury included MPGN (n=3), IgA-GN (n=2), membranous nephropathy (n=1), membranoproliferative GN (n=1) and nephroangiosclerosis (n=1). Most recently, a case of autochthonous HEV-induced MPGN in an immunocompetent individual has been reported (85), all other autochthonous cases occurred in immunosuppressed patients.

It has been known for almost 20 years that anti-HEV-seroprevalence is significantly increased in haemodialysis patients (86, 87). This observation is in line with the high anti-HEV-seroprevalence rate of approximately 40% in French kidney transplant candidates tested before kidney transplantation (88). The cause for this high seroprevalence is still unclear. However, hypothetically HEV-induced GN might have led to end-stage renal disease in some of these haemodialysis patients.

The underlying mechanism by which HEV-infection may induce glomerular disease remains to be established. Immune-mediated mechanisms are likely, similar to HCV-induced glomerular disease in which deposits of immune-complexes consisting of HCV-antigen, anti-HCV-IgG antibodies and a rheumatoid factor are found (89). Cryoglobulinemia associated glomerulonephritis is likely caused by an overwhelming immune response to viral antigens, similar to HBV- or HCV-associated glomerulonephritis. However, a further direct effect of HEV on the kidney cannot be ruled out.

Recently, HEV-RNA and HEV-antigens were detected in the urine of patients as well as in the urine of monkeys and rabbits chronically infected with HEV (27, 28). Renal biopsies from infected monkeys showed protein casts in the cavities of renal tubules

and severe inflammatory infiltrates in the renal interstitium (28). The detection of HEV-negative-strand-RNA suggested that these renal lesions were caused by ongoing HEV-replication in the kidney (27). Thus HEV might also be directly nephrotoxic. In line with this observation HEV-antigen of swine-HEV could be detected in experimentally infected gerbils (25).

Taneja *et al.* used two-dimensional differential imaging gel electrophoresis (DIGE) and mass spectrometry to identify biomarkers in sera and urine of acute hepatitis E patients (90). Decreased plasma transthyretin levels ($p < 0.005$) and increased urine alpha-1-microglobulin levels ($p < 0.001$) were found in acute hepatitis E patients, compared to healthy controls (90). Transthyretin is a transport protein, synthesized in the liver and involved in the transport of thyroid hormones. Mutations in the gene for transthyretin can lead to amyloidosis type 1 or 7.

Alpha-1-microglobulin is synthesized in the liver. This protein is a well known marker for a tubular kidney disease and an elevated concentration of this protein usually indicates nephritis, pylonephritis or toxic kidney injury (91). In summary, a renal tubular interstitial involvement in HEV-infected patients has been demonstrated.

Furthermore it has been demonstrated that HEV-infection affects the amino acid metabolism leading to increased levels of plasma and urinary l-proline and decreased levels of other metabolites (92). This may cause a higher risk for lactic acidosis and ketosis in hepatitis E infected patients(92). If this observation is associated with decreased kidney function in the context of hepatitis E remains to be determined.

Hence, there is evidence derived from experimental data and several possible explanations how HEV-infection could cause renal impairment. Although large studies are lacking, the study by Kamar et al. indicated a strong association between HEV infection and renal impairment. Of 51 immunosuppressed and HEV infected patients 8 developed renal impairment with no other possible causes. Therefore, HEV-infection should be considered as potential aetiology of GN and consequently, HEV should be screened for in cases of GN, especially if it is associated with elevated transaminases or occurs in immunosuppressed individuals. It is noteworthy that 7/9 cases of glomerulonephritis were published by the Toulouse group (82), which suggests underreporting or underdiagnosis of this clinical presentation of HEV-infection in other studies.

Cryoglobulinemia and HEV-infection

Mixed cryoglobulinemia is a medical condition, which can cause various symptoms by immunoglobulins that become insoluble at reduced temperatures and cause vascular damage affecting diverse tissues. Frequently, cryoglobulinemia is associated with kidney diseases, in particular glomerulonephritis, but it is not limited to renal dysfunction. HCV-infection is recognized as the major cause of mixed cryoglobulinemia (93).

In total only 10 cases of mixed cryoglobulinemia in relation to HEV-infection have been published. Reported cases shared several similar features (82, 83, 85, 94): all cases occurred in HEV-GT3 areas and all patients had type II or III mixed cryoglobulinemia. While 9 of 10 cases occurred during HEV-infection, one patient developed cryoglobulinemia after viral clearance (83). Like other viral infections, HEV might have triggered autoimmunity inducing late onset cryoglobulinemia in this patient. Furthermore, Pischke *et al.* found a considerably higher anti-HEV-IgG seroprevalence in patients with essential cryoglobulinemia compared to patients with cryoglobulinemia of a defined cause (46% vs. 23%, p=0.04) (95).

Further studies are required to substantiate the association between HEV and cryoglobulinemia, in particular the presence of HEV-RNA in the cryoprecipitate has to be demonstrated.

HEV-infection and autoimmune hepatitis (AIH)

A German (96) and a Dutch (97) study explored anti-HEV-IgG seroprevalence in AIH-patients. While the German study observed a significantly increased anti-HEV seroprevalence rate in AIH-patients, the seroprevalence rate in the Dutch cohort was also increased but failed to reach significance. It still remains controversial whether HEV-infection might be a trigger of AIH in susceptible individuals. As AIH is associated with elevated IgG-levels, false positive anti-HEV ELISA results might just as well explain the increased seroprevalence results.

Rare extrahepatic diseases observed in the context of HEV-infection

Thyroiditis:

A few cases of other, possibly immune mediated extrahepatic manifestations have been reported including six cases of thyroiditis (98-100). It was hypothesized that acute HEV-infection might have triggered the onset of autoimmune thyroiditis (46).

Myocarditis:

Three cases of symptomatic myocarditis in the context of acute HEV-infection have been published: Two men from the Indian peninsula and one patient from the USA developed myocarditis during hepatitis E (101, 102). Full recovery was observed in all cases. To test the possible association of myocarditis and hepatitis E, 18 patients with myocarditis from Southern France, an area with high endemicity for HEV, were tested for HEV by PCR in sera and stool (103). None of them tested positive. Due to the small size this study does not exclude an association of myocarditis and HEV.

Myositis:

Two cases of HEV-associated severe myositis have been described (104, 105). One of these patients was a liver transplant recipient with acute hepatitis E, associated with Guillain-Barre syndrome (104). He developed severe muscle weakness and his condition worsened. Creatine kinase (CK) level increased to 191,603 IU/L (normal <170 IU/L). HEV-viraemia could be proven by PCR, but HEV-RNA was undetectable in CSF. A biopsy of the left biceps showed myopathic changes, with a significant percentage of necrotic muscle fibers (10%) and signs of inflammation. He developed acute respiratory failure requiring mechanical ventilation (Table 5).

Henoch-Schonlein Purpura :

A single case of Henoch-Schonlein Purpura associated with acute hepatitis E in a six year old girl from India has been described. The disease resolved spontaneously after clearance of the virus (106). A causal link is thus questionable.

Treatment options of chronic hepatitis E infection

No drug has been approved for the treatment of hepatitis E, but there are several reports demonstrating good antiviral efficacy of ribavirin in patients with acute or chronic HEV-infection (15, 16). Viral clearance is usually achieved with a 3-month course of ribavirin monotherapy.

There are only single case reports about anti-viral treatment in the context of HEV-associated extra-hepatic manifestations (Table 5). A kidney transplant patient with de novo membranoproliferative glomerulonephritis (MPGN) and chronic HEV-GT3-infection was successfully treated with ribavirin, and renal function improved after viral clearance (83). A patient with GBS and severe myositis was treated with ribavirin, as was an HIV-infected patient with chronic HEV-infection and associated

peripheral neuropathy (107). Neurological symptoms improved in both cases soon after HEV-clearance. In a case series of 15 immunocompetent patients with acute HEV-infection and neurological disorders, 3 patients (PTS or mononeuritis multiplex) were treated with ribavirin or ribavirin and intravenous immunoglobulin (108). The only patient without any neurological impairment during follow-up had received ribavirin treatment. Early intervention with ribavirin in HEV-PCR positive patients with extra hepatic manifestations might improve the natural course.

In addition to ribavirin, steroids have been shown to be effective in patients with extrahepatic manifestations (Table 5). Especially patients with immunologically mediated extrahepatic manifestations after clearance of HEV-viraemia might benefit from steroid therapy (94).

Conclusions and recommendations

Despite the emerging evidence of HEV causing extrahepatic manifestations, a causal link between these diseases and HEV remains to be proven. Larger case-controlled studies are required to demonstrate a causal link between HEV-infection and extra-hepatic manifestations. Such a study-design would not only allow detecting the incidence of extrahepatic manifestations in HEV-infection, but could also identify potential host factors associated with the development of extrahepatic disorders. In addition, the effect of ribavirin treatment on extrahepatic manifestations should be clarified by prospective studies.

Diagnosis of hepatitis E can easily be missed since clinical and biochemical features of hepatitis are often mild or even absent, raising the question as to who should be tested for HEV-infection? Current data strongly indicate a causal relationship between HEV-infection and specific neurological syndromes, namely GBS and NA; the same holds true for GN with or without cryoglobulinemia (Table 1, figure 1). In these conditions HEV-PCR and HEV serology is recommended.

As far as the pathogenesis is concerned, studying cross-reactive HEV-antibodies and HEV-specific T-cell responses should give further insights. Furthermore the potential of HEV-replication in cells others than hepatocytes deserves further attention. Future research should identify potential entry mechanisms and provide unequivocal evidence for HEV-replication (i.e. negative strand viral RNA as indication for ongoing

replication) as well as its relation to the occurrence of extrahepatic tissue damage.

Undoubtedly the best way to prevent extra-hepaic HEV-associated infections is to prevent acquiring HEV infection. Thus, consumption of raw swine meat and consumption of unboiled water in tropical countries should be avoided.

Furthermore testing of blood products for HEV would avoid blood-borne HEV-transmission. However, this cost-intensive proceeding is still under debate.

In summary, HEV-infection has been observed in a broad spectrum of extrahepatic conditions. Future research is needed (i) to prove a causal link between HEV and these diseases, (ii) to study underlying pathogenic mechanisms, (iii) to identify the actual burden of disease and (iv) to evaluate potential treatment options.

Key point box:

● Various extrahepatic diseases have been observed in the context of HEV infections and have been assumed to be extrahepatic manifestations, but a pathophysiological proof of this causal relationship is still pending.

●Either direct cytopathic tissue damage by extrahepatic replication, or immunological processes induced by a cross-reactive host immune response to HEV are possible pathogenic mechanisms.

● Neurological and renal diseases are very likely causally related to HEV infection.

●Hepatologists should be aware of the possibility of acute or chronically HEV-infected patients to develop extrahepatic manifestations, and neurologists, nephrologists and rheumatologists should consider HEV-infection as a potential differential diagnosis when observing one of the hereby described diseases.

●Ribavirin and steroids have been used in some patients with extrahepatic manifestations with apparent success, but the efficacy of these drugs still needs to be verified by larger studies.

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Table 1: Likelihood of causal relationship between HEV-infection and assumed extrahepatic manifestation

Assumed extrahepatic manifestation	**Current data**	**Hill´s criteria**	**Estimated likelihood of causal relationship**
Neuralgic amyotrophy	-Acute HEV-infection in 11% of NA patients -HEV replication in neuronal cells proven (in vitro)	--> Strong association, temporality --> Experimental	Very probable
Guillain-Barré syndrome	Acute HEV-infection in 10% of GBS patients from India and 5% from the Netherlands -HEV replication in neuronal cells proven (in vitro) - Typical post-infectious condition	--> Strong association, temporality, consistency (consistent findings in 2 independent cohorts) --> Experimental --> Plausibility	Very probable
Cryoglobulinemia	- 9/10 during HEV-infection -Elevated anti-HEV seroprevalence rate in patients with idiopathic cryoglobulinemia -Similar mechanisms described for HCV	--> Temporality --> Plausibility	Possible
Glomerulonephritis	- 9/51 patients with renal	--> Strong	Very

	impairment during chronic HEV-infection -Similar mechanisms described for HCV - Evidence from various experimental data	association, --> Plausibility --> Experimental	probable
Acute pancreatitis	-Large number of reports from HEV-GT1 region describing AP shortly after the diagnosis of acute HEV-infection - Known for other viral infections, e.g. HAV/HBV/HCV-infection	--> Temporality, consistency --> Plausibility	Very probable
Haematological diseases	- Several cases observed. - High incidence of MGUS during HEV-infection in a single studiy (However, it is possible that underlying haematological disease made patients susceptible for HEV-infection)	--> Strong association	Possible
Meningitis	-HEV detection in CSF -HEV replication in neuronal cells proven	- Temporality, plausibility - Experimental	Possible
Autoimmune hepatitis	-Elevated anti-HEV seroprevalence rate in AIH patients	-	Under debate
Thyreoiditis	-Only single case reports	-	Doubtful
Myocarditis	Single cases	-	Doubtful

	-Only one single small study, which did not observe an association		

Table 2: Extrahepatic sites of HEV RNA

Tissue or body fluid with HEV detection	Relevance of study	Reference
Human neuronal cells	HEV-replication in neurons proved by In-vitro infection of neuronal derived cells	Drave et al. (24)
Human cerebrospinal fluid	Detection of HEV in cerebrospinal fluid	Comont et al. (29)
Human cerebrospinal fluid	Detection of HEV in cerebrospinal fluid	Dalton et al. (107)
Kidney of gerbils	HEV could be detected in the kidneys of gerbils experimentally infected with swine HEV.	Soomro et al. (25)
Kidney of rabbits	Kidney injury in experimaentally HEV-infected rabbits	Wang et al. (27)
Kidney and urine of monkeys	Detection of HEV in urine and kidneys of artificial infected monkeys	Geng et al. (28)
Human urine	Detection of HEV in human urine	Geng et al. (28)
Human placenta	HEV replication in placenta could be proven by a negative-strand-specific reverse transcriptase PCR.	Bose et al. (26)
Human brest milk	HEV detection in human breast milk	Rivero-Juarez et al. (30)
Milk of cattle	Sero-epidemiological association between consumption of unpasteurized milk and anti-HEV positivity in rural Mexico	Alvarado-Esquivel et a (109)
Milk of cattle	Excretion of HEV in milk of cattle	Huang et al. (110)
Milk and muscle of camels	Chronic HEV-infection in a transplant recipient acquired by consumption of camelid milk and meat	Lee et al. (111)
Intestine of swine	Proof of extraheptic HEV-replication in swine by in situ hybridization	Choi et al. (31)
Lymph nodes of swine	Proof of extraheptic HEV-replication in swine by in situ hybridization	Choi et al. (31)

Tonsils of swine	Proof of extraheptic HEV-replication in swine by in situ hybridization	Choi et al. (31)
Spleen of swine	Proof of extraheptic HEV-replication in swine by in situ hybridization	Choi et al. (31)
Kidney of swine	Proof of extraheptic HEV-replication in swine by in situ hybridization	Choi et al. (31)

Table 3: Neurological manifestations associated with HEV infection

Neurological Disorder	No. of cases	References
Peripheral nervous system diseases:		
Guillain-Barré syndrome*	n=41	(33, 34, 37-39, 44, 74, 104, 112-124)
Miller Fisher syndrome	n=2	(41)
Neuralgic amyothrophy*	n=37	(34, 40-43, 49, 125-137)
Polyradiculoneuropathy	n=2	(47)
Bell's Palsy	n=3	(138-140)
Mononeuritis multiplex	n=6	(41)
Vestibular neuritis	n=1	(42)
Oculomotor palsy	n=1	(141)
Small fiber neuropathy	n=1	(42)
Neuromyopathy	n=1	(42)
Paresthesia	n=1	(142)
Central nervous system diseases:		
Meningoencephalitis*	n=9	(34, 48, 143, 144), (43, 45-47, 122)
Transverse myelitis	n=1	(145)
Meningoradiculitis	n=2	(41)
Pseudotumor cerebri	n=1	(146)

Pyramidal syndrome	n=1	(49)

Table 4: Renal manifestations associated with HEV-infection.

Renal manifestations	No of cases / Age / sex	Country / HEV-genotype	Transplants	Author, year
Renal failure, inconspicouous biopsy	1 / 34ys / female	Netherlands / NA	None	Verschuuren, 1997 (147)
Membranoproliferative glomerulonephritis	1 / 38ys / male	India	None	Ali, 2001 (81)
No renal biopsy, liver failure	1 / 28ys / male	France/ NA	Kidney transplant	Kamar, 2005 (148)
Membranoproliferative glomerulonephritis (2x) IGA nephropathy (2x), Nephroangiosclerosis and Mixed cryoglobulinemia III	5 / 24-58ys / male	France/ 3f, 3c	Kidney transplant (n=4) Liver transplant (n=1)	Kamar, 2012 (82)
No renal biopsy, Renal failure and hyperbilirbinemia	1 / 56 / male	India / NA	None	Vikrant, 2013 (149)
Membranous nephropathy, Nephrotic syndrome	1 / 60ys / male	France / 3c	Kidney transplant	Taton, 2013 (84)
Membranoproliferative glomerulonephritis, Mixed	1 / 46 / male	France / 3f	Kidney transplant	Kamar, 2015 (150)

cryoglobulinemia II				
Membranoproliferative glomerulonephritis	1 / 46 / male	France / 3f	Kidney transplant	Del Bello, 2015 (83)
Membranoproliferative glomerulonephritis, Mixed cryoglobulinemia II in an immunocompetent patient	1 / NA / male	France / 3	No immunosuppression	Guinault, 2016 (85)

Table 5: Treatment experiences in patients with extrahepatic manifestations during HEV infection

Disease	Treatment and outcome	Reference
Myositis in an immunocompetent man with acute hepatitis E	Ribavirin: 400mg each 72hours (glomerular filtration rate <15 ml/min). Treatment for 3 months. Patient recovered partially within 3 weeks and recovered fully within 6 months.	Mengel *et al.* (105)
Myositis and Guillain-Barre in a liver transplant recipient with acute hepatitis E	Reduction of immunosuppression, intravenous immoglobulins (1 g/kg/d for 2 days) and ribavirin therapy (400 mg/d adapted to his glomerular filtration rate of 40ml/min). Ribavirin for 3 months. Weakness and neurological symptoms improved under therapy.	Del Bello *et al.* (104)
15 patients with neurological symptoms	2 patients were treated with ribavirin and intravenous immunoglobulin, 1 was treated with ribavirin only, 1 received corticosteroids, 3 were treated with immunoglobulins only and 8 were not treated. In 6 patients (40%) neurological symptoms lasted at last follow-up (range 4-126 weeks): 1 treated with ribavirin and immunoglobulins, 2 with immunoglobulins only and 3 were not treated.	Perrin *et al.* (108)
De novo membranoproliferative glomerulonephritis in a kidney transplant patient with chronic HEV gt 3f infection.	Ribavirin treatment (until month 3) (1200 mg/ day; 14 mg/kg/day) and treatment with angiotensin-converting enzyme inhibitors (irbesartan 150 mg/day).	Del Bello *et al.* (83)

	Improvement of the laboratory signs of kidney function and reduction of glomeruli hypercellularity and vasculitis lesions within a follow-up kidney biopsy.	
Membranous nephropathy in a kidney transplant recipient with HEV infection	Ribavirin treatment for 3 months led to a sustained viral response rapidly followed by complete remission of the nephrotic syndrome.	Taton *et al.* (84)
Hepatitis E with thrombocytopenia and membranous glomerulonepbritis in a patient in India.	Steroid treatment (prednisolone 80 mg/day) stopped blleding and improved kidney function. Steroids were tapered off slowly and stopped within three months.	Ali *et al.* (81)
Chronic HEV gt 3a infection with painful sensory neuropathy in the lower limbs in an HIV-infected patient	Combination of pegylated α-interferon (135 µg/week for 6 months) followed by 6 weeks of pegylated α-interferon with ribavirin (1000 mg/d). Additional 6 weeks of reduced ribavirin dose (500 mg/d)	Dalton *.et al.* (48)
Symptomatic cryoglobulinemia type 3 interpreted as overwhelming immune response in a liver transplant recipient after clearance of HEV infection	Symptoms and elevated levels of creatinine and creatinine kinase responded to steroid treatment. The patient developed fatal mucositis during the further course, after reduction of immunosuppression.	Pischke *et al.* (94)

ALL FIGURES ARE PRELIMINARY. THE GRAPHICAL DEPARTMENT OF THE JOURNAL OF HEPATOLOGY WILL CONSTRUCT THE FIGURES AFTER ACCEPTANCE OF THE PAPER

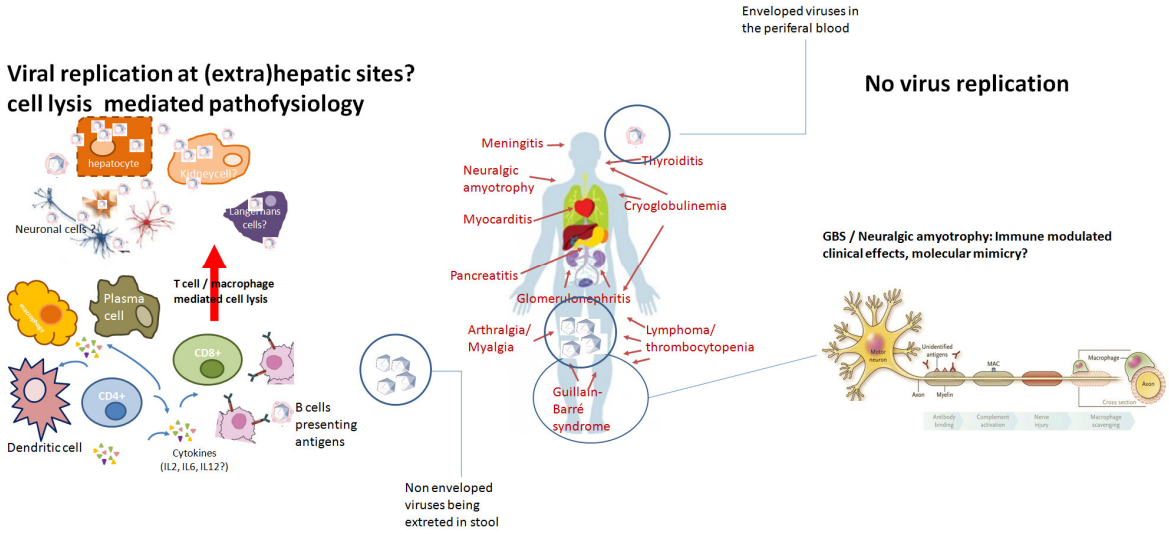

Figure 1: Reported extrahepatic manifestations of HEV infection. The pathogenesis of these manifestations is unknown but we hypothesize mechanisms with (left) or without (right) virus replication at these extrahepatic sites. Local viral replication may damage the infected cells and tissues directly or may trigger an immune response that damages these cells and tissues.

Without extrahepatic viral replication, HEV infection may induce an immune response that damages the extrahepatic sites. For example, in GBS molecular mimicry between infectious agents and peripheral nerve self-antigens may result in nerve injury, although it is unknown if such mechanisms play a role in HEV-related GBS. Other mechanisms by which an immune response to HEV may trigger extrahepatic damage is via induction of other antibodies, T-cells, deposition of HEV-antigens/antibody-immune-complexes or other mediators of inflammation.

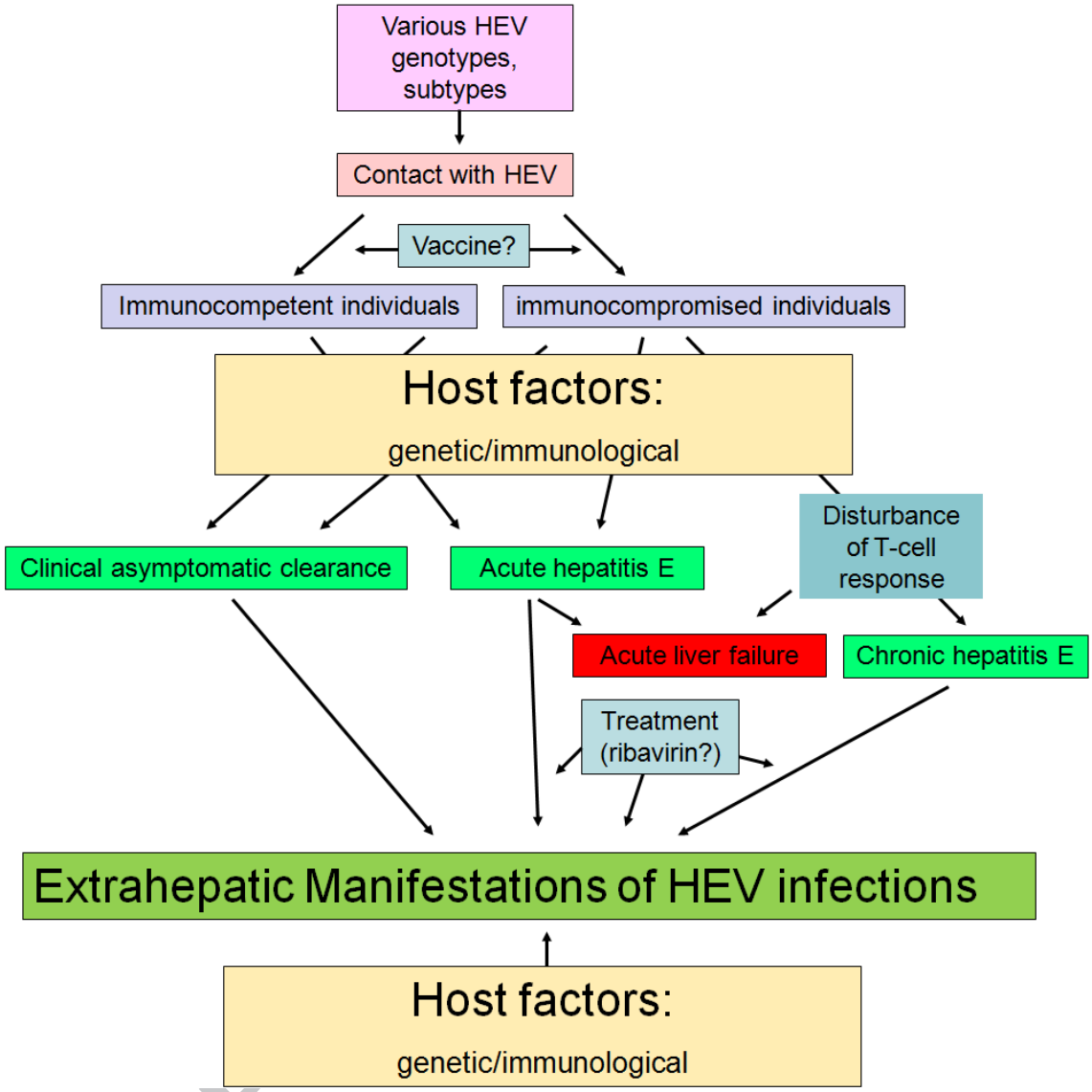

Figure 2: In immunocompetent patients, HEV-3 rarely causes a symptomatic hepatitis but can result in acute fulminant hepatitis with decompensation in patients with underlying chronic liver disease. HEV-3 and HEV-4 may lead to chronic infection in patients with an impaired immune response due to illness or medication. Both acute and chronic HEV infections have been associated with extrahepatic manifestations. Currently no vaccine is available in other countries than China, there are no data if such a vaccine would protect against HEV (re)infection in immunocompromised.