



## Hepatitis E: Still Waters Run Deep

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### Abstract

Hepatitis E is an infectious inflammatory disease of the liver caused by the hepatitis E virus (HEV), a single-stranded RNA virus. Today, it is estimated that there are more than 20 million HEV infections every year, leading to 3.3 million symptomatic cases and more than 56,000 deaths. For a long time it was believed that HEV was a travel-associated disease, endemic in developing countries with poor hygienic standards and unsafe water supply. However, over the past years, publications have demonstrated that autochthonous HEV infections in industrialized countries are far more common than previously thought. Awareness for HEV amongst health care practitioners in industrialized countries is still limited. This relatively rare disease is of great importance, especially in immunocompromised patients where it can cause chronic liver disease. This article comprehensively reviews current literature to give an overview on clinically important topics. It will focus on epidemiological aspects, acute and chronic HEV infection as well as extra-hepatic manifestations, diagnostic approach and treatment options. Furthermore, the article is concluded with a brief outlook on perspectives and urgent problems to be addressed in the future.

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### Introduction

Hepatitis E is an infectious disease causing acute and – under specific conditions – chronic inflammation of the liver. The disease is caused by the hepatitis E virus (HEV), which is a small, single-stranded RNA virus. It is the sole member of the genus *Hepevirus*, in the family of *Hepeviridae*.<sup>1</sup> The existence of the virus was first hypothesized following an outbreak in the Kashmir valley of India in 1978, causing 52,000 icteric patients and 1,700 deaths.<sup>2</sup> However, it took another decade to sequence the full genome of the virus.

The taxonomy of HEV genotypes (GTs) and strains is undergoing a permanent evolution.<sup>3</sup> Traditionally, it was

grouped into four different GTs (HEV GT 1–4). Recently, it was demonstrated that there are actually eight different GTs, based on the reference sequences.<sup>1,3</sup> However, clinical and epidemiological characteristics of the “new” GTs need further clarification. GT 1–4 are the classical humanopathogenic GTs and show a specific geographical distribution. GT 1 and 2 are endemic in a number of tropical countries with frequent water contaminations and are transmitted via the fecal-oral route.<sup>4</sup> In European industrialized countries, GT 3 is most common while GT 4 is common in industrialized Asian nations. Recently, HEV GT 4 has been described to be present in Europe in single cases and is not limited to Asia.<sup>5</sup> GT 3 and 4 are known zoonoses and transmitted via consumption of undercooked or raw meat. Domestic swine, wild boar and deer are classic examples as sources of HEV infection (Table 1). In addition, camels, rabbits, chicken, rats, bats and other animals have been identified as reservoirs of the virus.<sup>6–9</sup> Furthermore, it can also be transmitted by viremic blood products<sup>10</sup> and by such vegetables and fruits as spinach, rocket, mixed salads or strawberries.<sup>11,12</sup>

Today it is estimated that there are more than 20 million tropical HEV infections every year, leading to 3.3 million symptomatic cases and more than 56,000 deaths, while symptomatic hepatitis E in industrialized countries is a rare disease.<sup>4,13</sup> Most cases of HEV infection are asymptomatic. Following an incubation period of 2–10 weeks, usually unspecific symptoms (e.g., mild fever, reduced appetite, abdominal pain, joint pain, rash, dark urine, pale stools, jaundice, enlarged and tender liver) last for 1–6 weeks.<sup>9</sup> These symptoms are indistinguishable from those of other liver diseases. The related acute liver failure most often occurs in pregnant women, who are also at risk of fetal loss.<sup>14</sup>

Usually, HEV is an acute self-limiting disease.<sup>4</sup> However, in immunosuppressed individuals, such as solid organ recipients, GT 3 and 4 can cause chronic hepatitis leading to cirrhosis and its complications.<sup>4</sup> This has not been reported for GT 1 or 2. There are also some extra-hepatic manifestations associated with HEV, including Guillain-Barre syndrome and cryoglobulinemia, amongst others.<sup>15</sup>

There are different treatment options for chronic hepatitis E, including reduction of immunosuppression, administration of pegylated-interferon  $\alpha$  or use of ribavirin. However, no drug has yet been approved for the treatment of HEV infections. Randomized studies are needed to validate the value of ribavirin for the treatment of acute or chronic HEV infections.

### History of hepatitis E

In 1978, the first described outbreak of hepatitis E took place in the Kashmir valley, a very rural and poor part of India.<sup>2</sup> While many believed that this was a hepatitis A or B epidemic,

**Keywords:** Hepatitis E; Hepatitis E virus (HEV); Ribavirin; Transplantation; Extrahepatic.

**Abbreviations:** ALT, alanine aminotransferase; FDA, Food and Drug Administration; GT, genotype; HEV, hepatitis E virus; HIV, human immunodeficiency virus; NAT, nucleic acid testing.

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**Table 1. HEV genotypes and sources of infection**

HEV genotype	Area	Sources of infection	Comment
GT 1	Tropical developing countries of Asia and Africa	Contaminated drinking water	No zoonotic relevance No chronic infections described
GT 2	Tropical countries of Africa or Mexico/ Central America	Contaminated drinking water	No zoonotic relevance No chronic infections described
GT 3	Industrialized nations, worldwide distribution, autochthonous in Europe, North and South America, Australia and large parts of Asia	Foodborne zoonosis → Swine → Deer → Cats → Rats → Rabbits → Mongooses → Cows → Cow's milk → Sheep → Strawberries → Vegetables → Blood products	Chronic HEV infections described in several cohorts of immunosuppressed patients
GT 4	Mainly in Asia, recently single cases in Europe	Foodborne zoonosis → Swine	Chronic HEV infections described in single immunosuppressed patients
GT 5	Japan	Wild boar	Relevance for humans still unclear
GT 6	Japan	Wild boar	Relevance for humans still unclear
GT 7	Middle East	Dromedary camels (one-humped camels)	Chronic infection in a liver transplant recipient who regularly consumed camel meat and milk
GT 8	Middle East	Bactrian camels (two-humped camels)	Relevance for humans still unclear

the epidemiological and clinical features did not quite fit hepatitis A or B; those features being predominantly young adults affected and pregnant women having shown very high mortality rates. The course of disease was self-limited. Ultimately, sera were lacking serological markers of hepatitis A and B. It was then hypothesized that there must be another virus distinct from hepatitis A and B as well as from the post-transfusion non-A, non-B hepatitis (hepatitis C), due to the mode of infection. Further studies revealed that this still unknown virus was endemic in India and the major cause of acute sporadic viral hepatitis.<sup>2</sup>

In 1981, another outbreak of hepatitis E amongst Russian military personnel stationed in Afghanistan occurred. This epidemic resembled features similar to the outbreak in Kashmir. In a self-experimentation, Balayan ingested pooled stools of nine infected soldiers.<sup>16</sup> He subsequently developed jaundice and elevated liver tests. Later, his team discovered virus-like particles, which were visualized by immune electron

microscopy. These particles reacted in the immune electron microscopy test with sera from individuals who had experienced two non-B hepatitis episodes but did not react with sera from routine anti-HAV IgM-positive hepatitis patients. Later, primates were experimentally infected with virus-containing stool extract which resulted in histopathologically confirmed hepatitis and abnormal liver tests.

It took another 10 years before the full genome of the virus was sequenced in 1991 and diagnostic assays were developed.<sup>2</sup> In the past few years, the perception of hepatitis E in industrialized countries has shifted from a mere travel-associated disease to a disease with autochthonous infections.<sup>4</sup> In 2010, a detailed phylogenetic analysis of the HEV GTs 1, 3 and 4 studied the descent of modern HEV GTs and revealed that the most recent common ancestor existed between the 7<sup>th</sup> and 15<sup>th</sup> century.<sup>17</sup> Furthermore, a substantial temporal variation in the rate of transmission among HEV GTs in different geographic regions late in the 20th century has been suggested.<sup>17</sup>

### Enveloped or non-enveloped virus?

HEV is an enterically transmitted hepatotropic virus. For decades this virus has been assumed to be non-enveloped only.<sup>18</sup> In contrast, recent studies have demonstrated that HEV is completely cloaked in host membranes and resistant to neutralizing antibodies while circulating in the patient's blood. In summary, there are two variants, one enveloped and one non-enveloped.<sup>18</sup> The clinical and pathophysiological features of these variants still need to be studied in more detail, especially to identify the differences regarding organ tropism and infectivity. Furthermore, the receptor which enables cellular entry of HEV still needs to be determined.

### Epidemiology

It is estimated that there are more than 20 million HEV infections every year in the tropics, leading to 3.3 million symptomatic cases and more than 56,000 deaths.<sup>13</sup> However, robust data on seroprevalence rates of anti-HEV IgG in tropical countries is largely lacking. In industrialized countries, far less symptomatic cases of HEV infection are reported.

Recently, a large meta-analysis revealed that the seroprevalence rates primarily depend on the seroassay used, followed by the geographical region and the cohort of individuals studied.<sup>19</sup> Seroprevalence is higher in individuals exposed to swine and/or wild animals, and increases with age.<sup>19</sup> Various European countries, such as France or the Netherlands, have anti-HEV rates of more than 30%.<sup>19</sup>

Testing for HEV antibodies is, to date, a field of controversy. It is still under debate which assay to use, and the Food and Drug Administration (FDA) has not yet approved a single assay in the United States to test for HEV. Due to limited sensitivity of several assays, older epidemiological studies on seroprevalence of anti-HEV IgG in Europe largely underestimated the burden of the disease.<sup>19</sup> On the contrary, various studies have shown a decline of the seroprevalence in several industrialized countries over time.<sup>19</sup> However, while seroprevalence rates have seemed to decrease, the rate of reported HEV infections and symptomatic cases is increasing in Europe.<sup>20</sup> This apparent contradiction can be explained by a raised awareness for HEV amongst health care practitioners.

There is a specific geographic distribution of the GTs 1–4 (Table 1). While GT 1 is responsible for most cases of endemic and epidemic HEV in Asia, GT 2 is the main source of infection in Africa and Central America.<sup>9</sup> GTs 1 and 2 are obligate human pathogens and are transmitted via the fecal-oral route.<sup>9</sup>

Areas with poor hygiene standards, high population density and unsafe water supply are most often affected.<sup>9</sup> Refugee camps are also prone to outbreaks.<sup>21,22</sup> Sporadic cases in the tropics as well as large outbreaks typically affect young adults (15–30 years-old). It is unclear why children are less often infected, since infections via the fecal-oral route are often infections of the first decade of life, such as is seen for hepatitis A. Incidence of symptomatic disease and mortality rates are much higher in pregnant women as compared to other groups of patients.<sup>14</sup>

In contrast to GTs 1 and 2, GTs 3 and 4 are found in humans and various animals (e.g., domestic swine, wild boar, deer, camels, chicken, rabbits, rats, bats and others) in Europe, the United States and Asia.<sup>9</sup> Furthermore, HEV-specific antibodies could be found in sheep and cows.<sup>23</sup> Especially for the European HEV GT 3, several different sources of infection have been described (Table 1). The main source of infection in

industrialized countries is the consumption of raw or undercooked meat of domestic pig.<sup>9</sup> The role of contact with other animals as source of infection is less clear and needs further investigation. There are also reports on direct transmission between humans, infection via transplanted organs and also consumption of salads and strawberries.<sup>11,12,24</sup> Furthermore, there is a report from China suggesting milk products as potential source of HEV GT 4.<sup>25</sup> However, the virus becomes inactivated upon heating over 70° C.

Another source of infection with GTs 3 and 4 are blood products, including blood plasma. In Europe, 1:1.000 to 1:10.000 blood donors are HEV viremic (Table 2). Recent unpublished data from our own group suggested an even higher HEV RNA prevalence among blood donors in some European regions. One of the largest studies was conducted in Southeast England, in which 225,000 blood donations were tested retrospectively.<sup>10</sup> Seventy-nine of these donations had detectable HEV RNA (1:2850). Follow-up of 43 recipients revealed 18 (43%) developed signs of HEV infection. Ten recipients developed prolonged viremia. Three immunocompromised recipients needed ribavirin treatment to clear the infection, and only one patient developed apparent post-transfusion hepatitis. Two cases of transfusion-transmitted HEV infections by erythrocyte and platelet concentrates from one asymptomatic donor were reported from Germany;<sup>26</sup> both recipients were immunocompromised, presented with elevated alanine aminotransferase (ALT) and developed a chronic course of the infection. Other cases of transfusion-associated hepatitis E were reported from Australia, France, the United Kingdom, Spain and Japan (Table 3).<sup>27–37</sup>

The aforementioned studies demonstrated that HEV viremic donors were mostly asymptomatic and showed no elevated ALT at time of donation. Thus, blood donor interviews are not effective to identify viremic donors. Also, studies on feasible procedures to safely inactivate the HEV are missing. Recently, the general HEV RNA screening of blood donations is discussed controversially. On the one hand, rapid progression to liver cirrhosis in chronically HEV-infected immunosuppressed patients has been documented. On the other hand, robust data are lacking on whether HEV RNA screening of blood products can effectively reduce HEV infections in immunocompromised patients, as dietary exposure still affects them.

**Table 2. Extra-hepatic manifestations (modified from Pischke *et al*. *J Hepatol* 2017<sup>15</sup>)**

Extra-hepatic manifestation	Likelihood of causal relationship
Neuralgic amyotrophy	Likely (associated with GT 3)
Guillain-Barre syndrome	Likely (associated with GT 3)
Pancreatitis	Likely (associated with GT 1)
Glomerulonephritis	Likely (associated with GT 3)
Cryoglobulinemia	Possible (associated with GT 3)
Hematological diseases	Possible (associated with GTs 1 and 3)
Meningitis	Possible (associated with GT 3)
Autoimmune hepatitis	Still unclear (associated with GT 3)
Thyroiditis	Doubtful (associated with GT 3)
Myocarditis	Doubtful (associated with GT 3)

**Table 3. HEV viremia among blood donors**

Country	Method	Samples	Results	Author, <i>Journal</i> Year <sup>Ref</sup>
Canada	Pools of 48/100	13.993	0 in 13.993	Fearon <i>et al.</i> , <i>Transfusion</i> 2017 <sup>78</sup>
France	Pools of 96	53.234	1:2218	Gallian <i>et al.</i> , <i>Emerg Infect Dis</i> 2014 <sup>79</sup>
Germany	Pools of 48	16.000	1:1250	Vollmer <i>et al.</i> , <i>J Clin Microbiol</i> 2012 <sup>80</sup>
	Pools of 96	18.100	1:4525	Baylis <i>et al.</i> , <i>Vox Sang</i> 2012 <sup>81</sup>
Spain	Pools of	9.998	1:3333	Sauleda <i>et al.</i> , <i>Transfusion</i> 2015 <sup>82</sup>
The Netherlands	Pools of 96/192	59.474	1:1440	Hogema <i>et al.</i> , <i>Transfusion</i> 2016 <sup>83</sup>
United States	Singly	18.829	1:9500	Stramer <i>et al.</i> , <i>ISBT Sci Ser</i> 2014 <sup>84</sup>
United Kingdom	Pools of 24	225.000	1:2850	Hewitt <i>et al.</i> , <i>Lancet</i> 2014 <sup>10</sup>

A cost-effectiveness study from the Netherlands using a simulation model concluded that HEV RNA screening of blood products is not excessively expensive compared to other screening tests.<sup>38</sup> In that study, the authors estimated only 1 in 700 HEV infections to be transfusion-associated in the Netherlands.<sup>38</sup>

All in all, uncertainties about the epidemiology of HEV remain. So far, only the United Kingdom has implemented an HEV screening of blood products intended for patients at risk of chronic HEV infection. The European Pharmacopoeia introduced a general HEV RNA screening of plasma pools for the production of solvent/detergent plasma. In healthy subjects, less than 5% of HEV infections become symptomatic.<sup>9</sup> The reasons for this low manifestation rate are unclear and it can only be speculated that factors like viral load exposure, pathogenicity of HEV strain, genetic and immunological features play a role.<sup>9</sup>

### Acute hepatitis E

In immunocompetent individuals HEV infection is usually asymptomatic, especially during childhood.<sup>9</sup> Most cases of symptomatic, acute hepatitis E worldwide occur in the tropics and are caused by GTs 1 and 2.<sup>9</sup> Some differences between GTs and course of acute HEV infection have been observed. HEV GT 1 or 2 infection is usually a disease of young adults, while GT 3 infection in higher income countries usually affect older males.<sup>39,40</sup> Furthermore, HEV GT 1 and 2 infections seem to be associated with a more severe disease and a higher manifestation rate.<sup>41,42</sup> While manifestation rates in industrialized countries are relatively clear (1–2%), there is a lack of robust data on seroprevalence and manifestation rates in developing countries.<sup>9</sup>

Typical symptoms of HEV include unspecific symptoms, such as mild fever, reduced appetite, abdominal pain, joint pain and rash. Some patients may develop dark urine, pale stools, jaundice, itching and an enlarged, tender liver.<sup>9</sup> This is usually accompanied by abnormal liver tests. Symptoms occur after an incubation period of 2–6 weeks.<sup>9</sup> Patients very rarely develop acute liver failure. In the tropics, most cases of severe liver disease and acute liver failure occur in pregnant women.<sup>14,43</sup> It is speculated that this is due to hormonal and immunological changes during pregnancy.<sup>14,44</sup> An association between reduced expression of the progesterone receptor and fatal outcome of hepatitis E in pregnant women has been reported.<sup>45</sup> A German study comparing imported and autochthonous HEV infections ( $n = 27$ ) demonstrated that imported HEV infections are associated with higher

transaminases, international normalized ratio and bilirubin levels compared to autochthonous cases.<sup>42</sup> That study demonstrated an association between the HEV GTs and severity of the hepatitis disease.

Another study investigated if there is an association between variability and pathogenicity of various HEV GT 3 subtypes.<sup>46</sup> However, despite that study containing more than 600 patients from four countries, no association between severity of hepatitis E and HEV GT 3 subtypes was found.<sup>46</sup> Thus, the clinical relevance of GT 3 subtypes still needs to be determined, while the relevance of the main GTs has been suggested. The most relevant group of patients at risk for a more severe course of HEV GT 3 infection are patients with underlying chronic liver disease, such as alcohol abuse, chronic viral hepatitis, non-alcoholic steatohepatitis, autoimmune liver disease or hereditary liver diseases.<sup>9</sup> Acute-on-chronic liver failure due to acute HEV infection is a potentially life-threatening complication.

In industrialized countries, there are some case reports on prolonged viremia in immunocompetent individuals.<sup>47</sup> However, prolonged viremia in “healthy” individuals should always raise suspicion for an undiagnosed disturbance of the immune system.<sup>48</sup> To date, no case of HEV-associated cirrhosis or complications of cirrhosis in immunocompetent individuals has been published and no case of development of hepatocellular carcinoma has been observed in patients with chronic hepatitis E and cirrhosis.

### Chronic hepatitis E

In 2008, Kamar *et al.*<sup>49</sup> and Gerolami *et al.*<sup>50</sup> described chronic hepatitis E in liver and kidney transplant recipients. Systematic studies revealed that the prevalence of HEV infection in cohorts of liver or kidney transplant recipients was approximately 1% in a Dutch and a German cohort.<sup>51,52</sup> In addition to liver or kidney transplant recipients, chronic hepatitis E has also been observed in heart or lung transplant recipients as well as patients infected with the human immunodeficiency virus (HIV) and stem cell transplant recipients.<sup>53–55</sup> Interestingly, heart transplant recipients have a much higher anti-HEV seroprevalence than liver or kidney transplant recipients, healthy controls or cardiac patients without transplantation.<sup>54</sup> This increased seroprevalence has been confirmed by two independent serological assays.<sup>56</sup> Perhaps this phenomenon is caused by the high rate of blood products that heart transplant recipients receive.

Chronic hepatitis E can lead to fibrosis, cirrhosis and chronic liver failure. However, reduction of immunosuppression or

treatment with ribavirin are possible therapeutic strategies.<sup>57</sup> Even in patients who failed to achieve clearance of the virus (i.e. sustained virological response), it could be demonstrated that regression of liver fibrosis might occur.<sup>58</sup> Furthermore, it has been demonstrated that established HEV infection in immunosuppressed individuals, such as HIV-patients, might persist despite recovery of the immune system.<sup>59</sup>

It is still under debate if HEV GT 1 or 2 can also induce chronic hepatitis E. However, a study from India did not observe any case of chronic hepatitis E in a cohort of 205 kidney transplant recipients.<sup>60</sup> Despite 7% (n = 14) of studied patients having had detectable anti-HEV IgM — indicating recent contact with HEV — no patient developed chronic infection (0/14). In contrast, 47% (16/34) of French kidney transplant recipients with HEV infection after transplantation developed chronic hepatitis E in a large study.<sup>61</sup> Thus, Indian kidney transplant recipients with HEV GT 1 infections either do not develop chronic HEV infections or do so far more rarely than French kidney transplant recipients ( $p < 0.001$ , chi-square test).

However, in another Asian country, in Japan, GTs 3 and 4 are prevalent. In a large Japanese multicentric cohort study of liver transplant recipients only 0.12% of patients (2/1651) suffered from chronic HEV infection.<sup>62</sup> This low rate of HEV infections in transplant recipients was significantly lower than in seven European cohorts of transplant recipients, in which a prevalence of chronic HEV infection was found at rates of 0.7% to 3.2% (median: 1.4%).<sup>63</sup> In summary, neither in GT 1 nor in GT 3 endemic regions in Asia does chronic HEV have the same importance as in Europe. Data about chronic hepatitis E in the United States are scarce due to no FDA-approved test being available.<sup>64,65</sup>

### Extra-hepatic manifestations

Several extra-hepatic symptoms and diseases have been associated with acute or previous HEV infection (Table 2).<sup>15</sup> Some of these diseases might be caused by direct effects of the virus to tissue of organs other than the liver, and some might be caused by an overwhelming immune response stimulated by HEV. Still others of these phenomena might not be associated with HEV but might only have occurred accidentally and occasionally in the context of hepatitis E. A proven pathophysiological link has still not been established for any of these assumed “extra-hepatic manifestations of HEV infection”.

While pancreatitis has frequently been observed in the context of tropical HEV infections, glomerulonephritis or such neurological symptoms as neurologic amyotrophy or Guillain-Barre syndrome have frequently been associated with HEV GT 3 infections in industrialized countries.<sup>15</sup> However, it still needs to be determined if a tropism of the various GTs is causative for this phenomenon.

### Diagnosis of HEV

The laboratory diagnosis of HEV infection is based on the detection of antibodies against HEV (IgM and IgG), detection of HEV antigen or detection of HEV RNA in plasma, serum or stool through quantitative PCR. Anti-IgM-antibodies are markers of acute HEV infection. They are detectable within 2–4 weeks after infection and persist for 3–5 months afterwards. Also, anti-HEV IgA has been shown to be a marker of acute infection, but is not established in routine diagnostics.<sup>66</sup> Anti-IgG antibodies last for many years, represent a previous

exposure to HEV and are detectable in 95% of patients at initial clinical presentation.<sup>67</sup>

Viral nucleic acid testing (NAT) in plasma, serum and stool is a highly sensitive method to detect HEV infection and might be essential in diagnosing HEV infection in the immunocompromised, as some patients remain antibody-negative. Hence, NAT is the preferred diagnostic method. Non-standardized assays used in laboratories worldwide have differences in sensitivity and specificity for HEV RNA and antibody testing. In 2013, international standards for HEV PCR techniques were introduced in a World Health Organization initiative to improve comparability of HEV prevalence data.<sup>68</sup>

### Treatment

There is little literature on the treatment of hepatitis E, especially for acute hepatitis E, and so far no drug has been approved for the treatment of acute or chronic hepatitis E. However, it should be kept in mind that most infections with HEV are self-limited and therefore do not need to be treated.

In the setting of acute hepatitis E, the knowledge on treatment options is very limited. However, there are reports that ribavirin is a possible treatment option to prevent fatal cases of acute and acute-on-chronic liver failures.<sup>69–72</sup> To date, no case-controlled studies have been conducted on the efficacy of ribavirin in acute hepatitis E. Thus, whether patients with acute hepatitis E should be treated in centers with experience and whether ribavirin therapy should be initiated needs to be decided on a case-by-case basis.

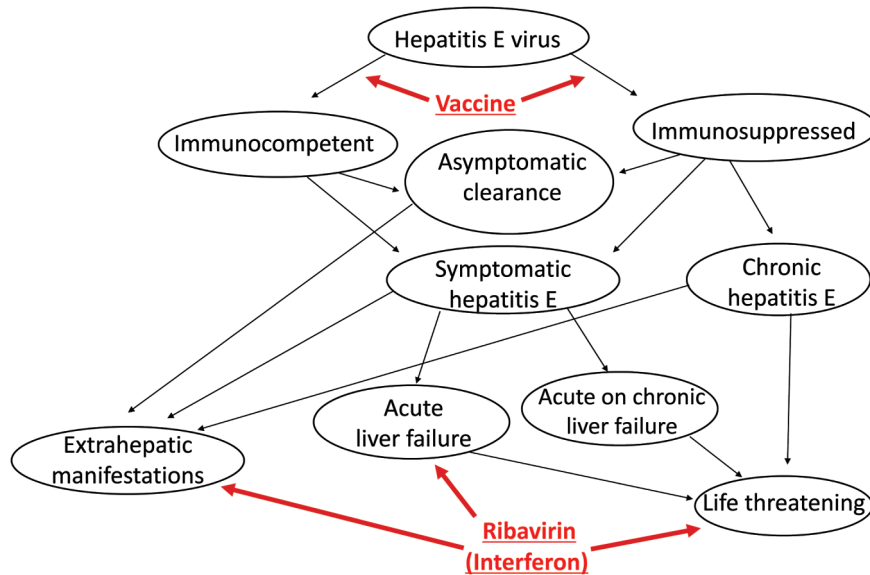
Treatment options for chronic hepatitis E include the use of ribavirin administration of pegylated-interferon and reduction of immunosuppression. The first step in this setting should be the evaluation of the possibility to reduce immunosuppression.<sup>57</sup> Approximately 50% of HEV infections in transplant recipients lead to chronic hepatitis E.<sup>54,61</sup> Thus, treating each immunosuppressed patient with diagnosed hepatitis E will result in unnecessary treatment of half of the patients. Ribavirin use for treatment of hepatitis E presents an off-label medication with possible side effects, mainly anemia. To avoid unnecessary ribavirin courses in patients who will clear the infection spontaneously, only patients chronically infected with HEV, patients who develop liver failure caused by HEV or patients with assumed HEV-associated severe extra-hepatic manifestations should be treated with ribavirin (Fig. 1). This leads to elimination of the virus in the vast majority of cases.

### Vaccination

Initially, a promising vaccine was evaluated in 2006 within a large trial containing 2000 Nepalese soldiers and showed effective prevention of hepatitis E.<sup>73</sup> However, further development and distribution of this vaccine has been stopped. A further vaccine has been studied within a large trial (n > 11.000 individuals) and has shown safety and efficacy to prevent hepatitis E.<sup>74</sup> This vaccine (Hecolin) has been approved for the use in China, where it has been available since 2012.

There are still no data on the use of the Hecolin vaccine in transplant recipients and/or patients with HEV GT 3 infections. A topic of special relevance is the use of this vaccine in pregnant women, as 10% of maternal deaths in rural Bangladesh are caused by HEV, and this indicates that more than 10,000 cases of maternal deaths in Southern Asia could be





**Fig. 1. Possible courses of HEV infection and optional interventions.**

prevented by this vaccine.<sup>75</sup> This topic has been under intensive debate within the World Health Organization.<sup>76</sup> Within the successful phase 3 study of the Hecolin vaccine there were inadvertently 37 pregnant women in the vaccine group and 31 in the placebo group.<sup>77</sup> However, there were no severe adverse events reported in these women, indicating safety of the vaccine during pregnancy. While 19 women in the vaccine group and 14 in the placebo group underwent elective abortion there were 18 and 17 live births in the vaccine and the placebo group, respectively. However, these data represented a small subgroup and further larger studies are necessary to determine the value of the vaccine in pregnant women.

### Perspectives

There is an urgent need for treatment options for acute hepatitis E in pregnant women in the tropics. Due to potential fetotoxicity of ribavirin, it is contra-indicated in these patients. However, pregnant women have the highest mortality rates of all hepatitis E patients. This raises the question if ribavirin could be beneficial in this setting. However, to date there is no study to evaluate this. Furthermore, use of the vaccine for pregnant women needs to be clarified.

Despite several diseases having been suspected as the cause, the trigger of or as being promoted by HEV infection, the pathophysiological link between any of these diseases and HEV has still not been established and needs further investigation.

Optimal treatment strategies for patients with HEV-induced acute liver failure or for immunosuppressed patients with chronic hepatitis E need to be established. There are several reports about the use of ribavirin for the treatment of HEV infections. However, the optimal dosage and treatment duration still needs to be determined. Furthermore, the role of HEV mutations and their prognostic value for prediction of non-response should be clarified.

The relevance of blood-borne HEV transmission and the risk for various subgroups of recipients of blood products

requires further investigation. Furthermore, the responsible governments worldwide need to discuss the question of whether blood products should be tested for HEV.

### Conflict of interest

The authors have no conflict of interests related to this publication.

### Author contributions

Conception of study objectives and/or design, interpretation of findings, drafting the article (MW, ML, SP), interpretation of findings, revising the article for important intellectual content (DW), revising the article for important intellectual content (ML, SP).

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