Hepatitis E in children: A position paper by the ESPGHAN Hepatology Committee

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Author contributions

All 11 co-authors fulfilled the following requirements:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Two authors, i.e. Björn Fischler and Dominique Debray performed the literature search and prepared the first draft for discussion and further revision with all other co-authors, as described in Methods.

Abstract

Background: Hepatitis E virus (HEV) is endemic in large parts of the developing world. Waterborne transmission of genotypes 1 or 2 commonly causes acute hepatitis, which is usually self limited in healthy individuals. In addition, acute HEV infections also occur outside endemic areas, mostly related to foodborne transmission of HEV genotype 3. A growing number of publications in the last decade have reported chronic infection progressing to cirrhosis in immunosuppressed patients. It has also been suggested that HEV transmission may occur via contaminated blood products. This publication aims to provide recommendations for diagnosis, prevention and treatment of HEV infection, particularly in children after solid organ transplantation (SOT).

Methods: A systematic PubMed literature search on HEV infection from 1990 to January 2016 was performed focusing on paediatric studies. The existing body of evidence was reviewed and recommendations were agreed upon following discussion and unanimous agreement by all members of the ESPGHAN Hepatology Committee during a consensus
meeting in January 2016. In the absence of randomized controlled studies these recommendations were considered to be expert opinions.

Key recommendations are:

Immunocompetent children with increased transaminases and/or extrahepatic manifestations should be considered for testing for evidence of HEV infection. Immunocompromised children with increased aminotransferases should be repeatedly tested for HEV and may require therapeutic intervention.

**Keywords:** hepatitis E virus, epidemiology, diagnosis, chronic infection, immunosuppressed patients, treatment

**Introduction**

Hepatitis E virus (HEV) is a single-stranded, non-enveloped RNA virus and is the only virus within the genus *Hepevirus* and the family *Hepeviridae*. Four different genotypes (1-4) have been reported to infect humans (Table 1)\(^1\). Genotype 1 is associated with both endemic and epidemic cases in Asia and Africa, whereas genotype 2 is most prevalent in Africa and Central America. There are no known animal reservoirs for genotype 2, while genotype 1 infection of pigs was recently reported. Genotype 3, which is prevalent in Europe and North America, can infect several animal species and at present is considered to be a zoonotic infection\(^1,2\). HEV genotype 4 has also been detected in animals bot in South East Asia and Europe\(^3,4\).

During the first two decades after its discovery in the late 1980’s, HEV was associated only with acute infections transmitted via the fecal-oral route. The infection was considered to be self-limited in most patients. A surprising 25% mortality in pregnant women remained unexplained \(^5\). More recent data show that acute infections occur also outside endemic areas, attributable to zoonotic spread of the virus. Furthermore, the virus may lead to chronic
infection, as demonstrated in several cohorts of immunosuppressed patients \(^1\). Although most of this data were initially presented in adult studies, recent publications underline some of the specific paediatric issues \(^6\)-\(^9\). At present there are no guidelines with regard to HEV infection and its relevance to paediatric liver disease. The aim of this paper was therefore to review the available data and recommend appropriate steps for diagnosis, prevention, and treatment in children.

**Methods**

Members of the ESPGHAN hepatology committee formulated clinical questions relevant for the diagnosis, prevention and treatment of HEV infection in children, particularly in patients with a history of solid organ transplantation (SOT). Two members (BF, DD) reviewed the literature to answer the questions.

Available literature was screened by a PubMed search for publications written in English or other languages if clinically relevant from 1990 until January 2016 using the following search terms: Hepatitis E, children, epidemiology, diagnosis, acute liver failure, prevention, vaccine, transmission, treatment. Because no randomized controlled trials were available, and the pediatric literature on HEV infection remains scarce, answers to questions and subsequent recommendations were largely based on expert opinions. Grading of recommendations was therefore not feasible.

A first draft was sent to all of the committee members for discussion in October 2015. The committee members were asked to review and give their opinions separately. The committee agreed unanimously on all recommendations at a meeting in a consensus meeting in January 2016.
Epidemiology

Epidemiological patterns of HEV infection differ between tropical and subtropical developing countries with poor hygiene conditions (including large parts of Asia, Africa and central America) where the disease is highly endemic, and industrialized countries in Europe, North America, New Zealand and Japan where the disease occurs mainly as sporadic autochthonous (locally acquired) cases. Of the four major genotypes, HEV genotypes 1 and 2 are responsible for waterborne endemic and sporadic cases occurring in developing countries, with a high mortality rate among pregnant women and subjects with preexisting liver cirrhosis. Genotype 1 infections have also been diagnosed in developed countries following travel to endemic regions, but the scale of imported HEV infection in developed countries is unknown. A recent study from the Netherlands showed that autochthonous HEV both in children and adults is generally predominant over imported travel-related cases, while in Italy, most cases were travel related caused by genotype 1. By contrast, HEV genotype 3 is responsible for the majority of autochthonous cases of acute hepatitis E in Europe and the United States while HEV genotype 4 disease is prevalent in China and Taiwan. HEV genotypes 3 and 4 are believed to be zoonotically transmitted by consumption of contaminated food.

Epidemiological studies from most developing countries show that HEV seroprevalence increases with age from less than 10% in children aged <10 years to up to 76% in adolescents and 84% in adults in Egypt. In one study, HEV seroprevalence in blood donors ranged from 5.4% among Tunisians to over 50% among Egyptians. This suggests that blood transfusion could be a common route of HEV transmission in these countries.

The incidence of hepatitis E in developed countries is not known, but recent studies have shown that locally acquired hepatitis E has become more common than hepatitis A in the UK and Japan. HEV seroprevalence in blood donors using different immunoassays to test for
HEV IgG varies from <1% to above 20% with a wide regional differences even within the same country. Analysis of the National Health and Nutrition Evaluation Survey data (NHANES) in the United States, showed that in 2010 the overall HEV seroprevalence in the general population aged 6 years and older was estimated to be about 6.0% - much higher than the prevalence hepatitis C virus antibodies (1.3%) and hepatitis B surface antigen (0.4%), but lower than hepatitis A IgG seroprevalence (34.8%). On multivariate analysis, increasing age significantly correlated with HEV seroprevalence. The prevalence of anti-HEV antibodies in children aged 6 to 19 years was 0.8% among males and 1.1% among females. Available data among children in other developed countries are limited to 3 studies from Spain, Germany and Japan reporting a prevalence of anti-HEV antibodies between 1 and 7.5%. The largest pediatric study recently conducted in Germany (1646 children aged 0-17 yrs) revealed an increasing prevalence of HEV antibodies with age: from 0.4% in infants below 2 yrs of age up to 1.5% in the 15 to 17-year old group.

1. How and when should children be tested for evidence of HEV infection?

Available diagnostic tools in routine clinical practice include detection of viral RNA by PCR and IgM and IgG antibodies using different serological methods. However, studies comparing commercial and in-house assays for serological detection showed disturbing differences in diagnostic yield. In particular, sensitivity varied between as low as 20% to over 90% depending on method used. At present, there is no universally accepted assay for HEV IgM and IgG detection.

In acute symptomatic infection, HEV RNA is detectable in feces from 1 week before to as many as 52 days after the onset of clinical signs. HEV RNA, HEV IgM and HEV IgG can be detected in serum within 3 days of symptom onset in at least two thirds of patients and in 90% by day 7 of the infection. At 6 weeks after the onset of symptoms, HEV RNA is no longer
detected in serum, while HEV IgM is still measured in about one third and HEV IgG in almost all patients. For immunocompetent patients with suspected acute infection, initial testing for HEV IgM and HEV IgG is often sufficient. If both tests are negative but the suspicion of hepatitis E remains, HEV RNA should be quantified in serum. On the other hand, a negative HEV RNA test in a symptomatic immunocompetent patient should prompt analysis of HEV IgM and HEV IgG, since the viraemic period is rather short.

In immunocompromised patients - for example after SOT or stem cell transplantation or in HIV-infected individuals - testing for HEV RNA in serum is clearly preferrable since these patients often may not mount an antibody response. In immunosuppressed patients, HEV fecal shedding may persist for up to 2 years or more after the diagnosis, and therefore testing for HEV RNA in feces is useful to screen for asymptomatic HEV chronic carriers.

The clinical presentation of HEV acute infection resembles hepatitis A virus (HAV) infection, with most cases being asymptomatic. The incidence of acute hepatitis with jaundice increases with age. The incubation period ranges from 15–60 days, with a mean of 40 days. The clinical features include jaundice, fever, flu-like symptoms, abdominal pain, vomiting, anorexia, and hepatomegaly. A minority of children may develop acute liver failure (ALF), especially those with pre-existing chronic liver disease. Two large pediatric series from India, where genotype 1 is highly endemic, reported HEV or HAV and HEV coinfection as the main causes of ALF or acute decompensation of underlying chronic liver disease. Locally acquired HEV genotype 3 infection was also recognized as a cause of ALF in developed countries both in adults and in children in one case series from Argentina. However, the frequency of pediatric ALF related to HEV infection in Europe remains unknown, as children with ALF are not routinely tested for evidence of infection with HEV.

It is only recently that chronic HEV infection has been documented in small case series of immunosuppressed children following SOT with mild aminotransferase elevation lasting >6
months 6, 8, 9. This finding, which was associated with chronic viremia, was also reported in children with HIV infection and haematological malignancies 7. In one series from Germany, 4 of 124 (3.2%) children following SOT (2 post–liver transplant and 2 post–renal transplant) were found to be anti-HEV IgG positive, but only one renal transplant recipient developed chronic hepatitis with persistently elevated liver enzymes and HEV fecal shedding 24 months after diagnosis 8. In a report from France, 8 of 96 (8.3%) children with liver or combined liver-kidney transplants were found to be anti-HEV IgG positive, but none developed chronic hepatitis with HEV RNA detected in serum 42. In a series from Canada, 12 out of 14 children with abnormal aminotransferases and evidence of chronic hepatitis following liver transplant, tested anti-HEV IgG positive. It is important to highlight that only 1 of the 14 patients had measurable IgM and IgG 2 years following diagnosis while HEV RNA was found in annual samples from 10 to 16 years post transplant, which coincided with the development of cirrhosis 6. In another series from Germany, the cause of chronic graft hepatitis was assigned to HEV infection in only 1 of 22 liver transplanted children with chronic graft dysfunction 9.

Chronic HEV infection has also been documented following stem cell transplantation in an adolescent who later developed cirrhosis and portal hypertension 7. Similar presentations have been described in genotype 3 infections and in one child with genotype 4 infection 43. Chronic infections due to genotypes 1 or 2 have not been reported.

Children receiving immunosuppressive treatments for any other indication than SOT, such as autoimmune disease, nephrotic syndrome, inflammatory bowel disease, are also at risk for HEV chronic hepatitis. The overall prevalence of HEV acute infection and chronicity rates in immunocompromised children are not known, given that HEV is rarely sought in this population in case of abnormal liver enzymes. In most cases of infected SOT patients, HEV infection was acquired after transplantation, most likely through foodborne transmission. Blood transmission of HEV has rarely been reported in this setting 44, 45. To date, only one case of occult HEV infection in an adult, transmitted via transplanted liver was reported from
Germany. HEV reactivation after SOT or stem cell transplantation in anti-HEV IgG positive recipients is unlikely to occur but reinfection in those with low IgG titers may occur. If liver transplantation is required once chronic infection is established, it is likely that chronic hepatitis E will recur in the liver graft. Risk factors independently associated with chronic infection include heavy immunosuppression, reflected by a shorter time from transplantation to infection, lower CD2, CD3, CD4 and total lymphocyte counts as well as use of tacrolimus-based rather than cyclosporin-based regimen.

Unless HEV screening is routine, the diagnosis can easily be missed because the clinical features of acute and chronic HEV infection are often non-specific. Most patients have no symptoms, subtle biological abnormalities, and very few present with jaundice. Liver histology shows portal hepatitis with dense lymphocytic infiltrate, piecemeal necrosis, and fibrosis that may mimic acute liver graft rejection or de novo autoimmune hepatitis. Finally, several extrahepatic manifestations such as neurological disorders, acute pancreatitis, severe thrombocytopenia, haemolytic anemia, and haemophagocytic syndrome have been associated with locally acquired acute and chronic HEV genotype 3 infection both in adults and children. There are a few case reports of HEV-related membranoproliferative glomerulonephritis, membranous glomerulonephritis or nephrotic syndrome in kidney or liver transplant patients with chronic HEV genotype 3 infection. Of note, proteinuria decreased or disappeared in these patients after HEV clearance. The pathological mechanisms responsible for the extrahepatic manifestations remain unclear.

Although neurologic manifestations or kidney disease have not yet been reported in immunosuppressed children, it seems reasonable to assume that they may occur. Something to keep in mind is that these extra-hepatic manifestations can overshadow the liver injury and HEV may not be suspected.
The committee recommends that:

- Immunocompetent children with increased transaminases and/or extrahepatic manifestations such as neurological symptoms, acute pancreatitis, thrombocytopenia, haemolytic anemia of unknown cause should be considered for testing for evidence of HEV infection. Serological methods detecting IgM and IgG can be used for primary testing. If they are negative but the suspicion of HEV infection remains, the use of PCR methods to detect HEV RNA in serum is recommended.

- Immunocompromised children with increased aminotransferases, including paediatric solid organ and stem cell transplant recipients, and other children receiving immunosuppressants with no identifiable cause of elevated aminotransferases should be repeatedly tested for HEV. HEV chronic infection needs to be considered in the differential diagnosis of graft dysfunction i.e. acute and late cellular rejection and de novo autoimmune hepatitis after liver transplantation.

2. Which are the transmission routes of HEV infection relevant to children and what preventive measures should be considered?

Fecal-oral transmission

Hepatitis E is generally transmitted by the fecal-oral route through the consumption of contaminated drinking water or food. In developing countries, drinking of water contaminated with genotype 1 or 2 HEV is responsible for most sporadic cases and large outbreaks, while in developed countries most cases of autochthonous hepatitis E are related to genotype 3 infection, likely due to consumption of undercooked infected pork or game (wild boar and deer) meat, rabbits and seafood. HEV genotype 3 can infect several animal species with potential transmission to humans. HEV RNA was found in 11% of pig livers obtained from grocery stores in the United States, and in 10% of pork sausages in the UK. Outbreaks of
hepatitis E in southern France have been linked to consumption of raw figatelli pig liver sausages through the identification of HEV strains ⁵⁸. Zoonotic transmission of HEV genotype 4 has also been reported in France and Asia ⁶³-⁶⁶.

Cooking foods at temperatures greater than 70°C for at least 20 minutes is required to inactivate the virus and decrease the risk of foodborne infection ⁶⁷.

In contrast to what is reported for hepatitis A and other enteric viruses, person-to-person transmission of HEV seems rare. However, since HEV RNA is detectable in feces from infected individuals, strict hygiene measures must be in place to avoid the spread of the disease among household and nursery contacts, and infected patients in the hospital ⁶⁸, ⁶⁹.

**Vertical transmission**

Acute infection during pregnancy is associated with an increased risk of liver failure in the mother, especially in certain geographical areas in India, where the mortality rate has been reported to be as high as 25% ⁵. The excessive mortality rates in pregnancy with HEV genotypes 1 and 2 are puzzling. They are not seen with genotypes 3 and 4, although there have been a few documented cases in pregnant women ¹-⁷¹. Recently, impaired macrophages phagocytic activity and reduced Toll-like receptor signaling were suggested to contribute to the development and severity of ALF in pregnant women ⁷⁰.

In endemic regions, fetuses or newborns born to mothers with acute third trimester infections have a 50 and 100% risk of infection ⁷²-⁷⁴. The placenta may act as a viral reservoir ⁷⁵. Khuroo et al. described 26 infected pregnant women, of whom 15 had ALF and 11 had acute hepatitis without liver failure ⁷². Five of those with ALF died before delivery. Of the remaining 21, 15 (71%) transmitted the infection to their offspring, and 5 of the 15 infants died resulting in 40% mortality. The remaining 9 infants who survived cleared the virus and normalized their liver function ⁷². A recent study suggests that HEV may be responsible for more than 3,000 stillbirths annually in developing countries, including fetal deaths linked to
antenatal maternal mortality. Data on vertical transmission of HEV outside endemic areas are scarce. Reports from South West Europe on a limited number of patients suggest this risk to be very low.

In one study HEV RNA and antibodies were detected in breast milk (colostrum) of infected mothers, but at lower levels than in the corresponding serum samples. Breast fed babies of infected mothers did not seem to be at higher risk than those who were bottle-fed. The authors concluded that further studies are warranted to determine whether breast feeding can be recommended.

**Transmission from blood products**

Several case reports have described transmission of HEV infection by blood transfusions. Using pooled plasma to analyze HEV RNA by PCR in a very large number of donors (165,000), Baylis et al. detected HEV RNA in German (1 in 4,500) and Swedish (1 in 8,000) plasma donors, but not in any of 51,000 donors from the United States. In a Chinese study HEV RNA/antigen was detected in approximately six of 10,000 blood donations, while in an Austrian study HEV RNA was identified in seven out of 58,000 blood donors. HEV transmission was also documented in 4 of 17 patients treated with pooled solvent detergent-treated plasma in Canada.

To date, the most comprehensive study on this subject was performed in South East England, analyzing samples from 225,000 donors. HEV RNA was detected in approximately one in 2,800 blood donations and the majority of these donors were antibody negative. The blood product recipients were identified and a large proportion of them subsequently tested. Overall, 18 of 43 were positive for HEV RNA. Viraemia persisted in recipients who were on immune suppression for their underlying disease. Only one infected recipient developed clinical hepatitis, whereas another four had elevated transaminases without clinical symptoms. The authors concluded that the detection rate of HEV RNA was higher than expected and that the
number of infected immune suppressed recipients with persistent viraemia was concerning. While they stopped short of recommending universal HEV RNA testing of blood donors, this was suggested in the accompanying editorial 86.

Given the endemic spread of HEV infection in certain parts of the world, the development of a prophylactic vaccine has been a priority. To date, two different recombinant vaccines against HEV have been developed and investigated in placebo-controlled studies. A baculovirus-expressed hepatitis E viral protein vaccine was compared to placebo in 1,800 adult healthy men and non-pregnant women recruited from the Nepalese army. A significant antibody response was noted in 81% of vaccinees one month after the second dose and in 100% one month after the third dose. Moreover, after the full three doses, hepatitis E developed in only 3 subjects in the vaccinated group compared with 66 subjects in the placebo group 87. No major side effects were described.

An E. Coli expressed hepatitis E viral protein vaccine has been developed and licensed in China. A large placebo-controlled trial of more than 100,000 healthy men and non-pregnant women aged 16-65 years showed a very good antibody response in the vaccinated ones. Follow-up one year after the third dose showed 15 infected subjects in placebo group and none in the vaccinated group 88. No major side effects were noted. Follow-up after 4.5 years revealed a persistently satisfactory immune response to the vaccine 89.

While the results from the studies mentioned above are very promising, further studies are needed to assess the efficacy and safety of these vaccines in specific populations such as infants/children, pregnant women and immunocompromised patients.

The committee recommends that

- Immunocompromised individuals should be advised to avoid eating uncooked pork
and game meat or raw seafood to prevent zoonotic infection with HEV genotype 3.

- Because chronic HEV carriers are potentially infectious, prevention of HEV transmission by implementing strict hygienic measures has to be considered both during inpatient and outpatient management.

- Given that ribavirin is contraindicated in pregnancy, non teratogenic antiviral compounds are required in an attempt to improve the course of ALF in pregnant women and prevent HEV transmission to the offspring. In the meantime, in patients with acute HEV infection due to genotype 1 or 2, it would be reasonable to consider ribavirin treatment during the third trimester of pregnancy due to the high mortality of untreated HEV in the mothers and vertically infected infants.

- Universal and effective HEV screening of plasma derived medicinal products should be implemented.

- The development and implementation of a pangenotypic HEV vaccine for at risk groups should be encouraged.

3. How should pediatricians treat acute or chronic HEV infection?

In the majority of acute HEV infections, no treatment will be required as these infections will clear uneventfully. Treatment of ALF caused by HEV infection is mainly supportive, and may indicate liver transplantation. However, in cases of fulminant HEV infections, a short course of ribavirin has been shown to lead to complete recovery, avoiding the need for liver transplantation. Data from the transplant setting have shown that a reduction in the levels of immunosuppression led to viral clearance in more than 30% of cases. However, no spontaneous clearance was observed between months 3 and 6 after infection in SOT-recipients if HEV RNA persisted for more than three months despite immunosuppression reduction. Treatment with pegylated interferon (peg-IFN-α2a) or ribavirin has been
attempted in adult SOT recipients in whom it is not possible to reduce immunosuppression or in the absence of HEV clearance within 3 months after immunosuppression reduction, \(^{92,95}\). Because peg-IFN-α2a is not as effective as ribavirin and increases the risk of acute graft rejection \(^{95}\), ribavirin is currently the medication of choice used in adult transplant recipients with a high rate of sustained virologic response \(^{92,93}\). To date, the largest study on the efficacy and safety of ribavirin therapy in adult SOT recipients reported on fifty-nine patients treated with ribavirin [median dose of 8.1 mg/kg bw/day (range, 0.6 to 16.3)] for a median duration of 3 months (range, 1 to 18) after the diagnosis of HEV infection \(^{92}\). At the end of therapy, HEV clearance was observed in 95% of patients. Only 10 patients experienced a recurrence of HEV replication within 1 and 3 months after discontinuing ribavirin. A sustained virological response (SVR), defined as an undetectable serum HEV RNA for at least 6 months after cessation of ribavirin treatment, occurred in 46 of the 59 patients (78%). There was no significant difference between the 39 patients who had received ribavirin therapy for 3 months or less and the 20 patients who had received it for more than 3 months (74% and 85%, respectively). A SVR was also observed in 4 of the patients who had a recurrence and were re-treated for a longer period up to 15 months. Interestingly, protracted fecal HEV shedding during treatment may predict relapse \(^{96}\). Anaemia was the main side effect, requiring reduction in ribavirin dose in 29% of the patients, use of erythropoietin in 54%, and blood transfusions in 12%; no episodes of acute rejection were observed during ribavirin therapy \(^{92}\).

In a more recent study of 61 immunocompromised patients, 27 were not treated, 4 of whom developed chronic infection while 2 were lost to follow up and 5 died while HEV RNA positive \(^{93}\). Eight patients (including 5 SOT-recipients) were treated solely by immunosuppression reduction and all successfully cleared the virus, within a median of 207 days (27–1306). Twenty-six patients (including 19 SOT) were treated with ribavirin at a median dose of 10.4 mg/kg (1.96–25.04), starting at a median of 97 days (0–1825) after the diagnosis of HEV infection and for a median duration of treatment was 94 days (10–560). In
21 (81%) patients, a sustained viral response was documented. Median treatment duration for HEV clearance was two months demonstrating a rapid response to treatment. Only one patient had recurrence but achieved viral clearance after re-treatment with ribavirin. Although three month duration of ribavirin monotherapy seems appropriate, a longer therapy may be needed in those who remain viraemic one month after the initiation of therapy. In SOT patients given ribavirin for 3 months, decreased viral concentration within the first week post-ribavirin therapy has been shown to be an independent predictive factor for SVR, and a decreased HEV concentration of 0.5 log copies/mL or greater had an 88% positive predictive value for SVR. Monitoring HEV fecal excretion might be used to determine the optimal duration of ribavirin therapy. It is, however, still uncertain whether ribavirin for more than 3 months can improve the virological response given that viral isolates with ribavirin resistance have been identified. Recent in vitro studies have shown that sofosbuvir inhibits the replication of hepatitis E virus genotype 3, and that the combination of sofosbuvir and ribavirin results in an additive antiviral effect, something auspicious of new therapeutic alternatives in immunocompromised patients.

Data on the use of ribavirin in SOT children with chronic hepatitis E remain scarce. Ribavirin was used effectively to treat chronic graft hepatitis after liver transplantation in one 10 year-old child at a dose of 15 mg/kg body weight per day for 6 months. Clearance of HEV RNA occurred within 42 days after initiation of therapy and lasted over 3 months after discontinuing ribavirin treatment. Anaemia requiring blood transfusion was the main adverse effect.

The committee recommends that:

- No treatment is indicated for self limited acute hepatitis E in otherwise healthy children.

- Ribavirin treatment can be considered for acute hepatitis E in children with underlying chronic liver disease given the high mortality rate.
- At the time of acute HEV infection in immunocompromised children:

  - When feasible, immunosuppression should be reduced.
  - If this is not possible or in the absence of HEV RNA clearance within 3 months, ribavirin should be considered (15 mg/kg/d) for three months with close monitoring for anaemia and renal function.
  - HEV clearance should be monitored by PCR on a monthly basis during the treatment and for three months after its discontinuation. Longer duration of therapy may be necessary if HEV clearance in serum or in the stools is not achieved after 3 months.
References


Table 1. Main characteristics and clinical features of the 4 Hepatitis E virus genotypes

<table>
<thead>
<tr>
<th>HEV genotypes</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Geographic distribution</td>
<td>Developing countries Asia/Africa</td>
<td>Sub-Saharan Africa, Mexico</td>
<td>Developed countries USA, Europe, New Zealand, Argentina</td>
<td>India, Eastern Asia (China, Taiwan, Japan, Vietnam)</td>
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<td>Hosts</td>
<td>Human, pig</td>
<td>Human</td>
<td>Human, pig, other mammalian species, shellfish</td>
<td>Human, pig, other mammalian species</td>
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<td>Pattern of infection</td>
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<td>Route of transmission</td>
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<td></td>
<td>Waterborne, Fecal-oral</td>
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<td></td>
<td>Foodborne</td>
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<td>Blood transfusion</td>
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<td></td>
<td>Vertical (mother to child)</td>
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<td>Clinical features</td>
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<td>Highest attack rate</td>
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<td>Asymptomatic</td>
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<td>yes / elderly, chronic liver disease</td>
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<td>Acute liver failure / risk factor</td>
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