

Hepatitis E in Children: A Position Paper by the ESPGHAN Hepatology Committee

*Björn Fischler, †Ulrich Baumann, ‡Antal Dezsofi, §Nedim Hadzic, ||Loreto Hierro, ¶Jörg Jahnel, #Valérie McLin, **Valerio Nobili, ††Francoise Smets, ‡‡Henkjan Verkade, and §§Dominique Debray

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. **Methods:** A systematic PubMed literature search on HEV infection from 1990 to January 2016 was performed focusing on pediatric 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: 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.

Key Words: chronic infection, diagnosis, epidemiology, hepatitis E virus, immunosuppressed patients, treatment

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Hepatitis E virus (HEV) is a single-stranded, nonenveloped 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, whereas 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 (1,3). HEV genotype 4 has also been detected in animals both in Southeast Asia and Europe (4,5).

During the first 2 decades after its discovery in the late 1980s, 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 (6). 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 these data were initially presented in adult studies, recent publications underline some of the specific pediatric issues (7–10). At present there are no guidelines with regard to HEV infection and its relevance to pediatric liver disease. The aim of this article 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 (ALF), prevention, vaccine, transmission, and 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.

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From the *Department of Paediatrics, CLINTEC, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, the †Division of Paediatric Gastroenterology and Hepatology, Department of Paediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany, the ‡First Department of Paediatrics, Semmelweis University, Budapest, Hungary, the §Paediatric Centre for Hepatology, Gastroenterology and Nutrition, King's College Hospital, London, UK, the ||Paediatric Hepatology Service, Hospital Infantil Universitario "La Paz," Madrid, Spain, the ¶Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Austria, the #Paediatric Gastroenterology Unit, Department of Pediatrics, University Hospitals Geneva, Switzerland, the **Hepatometabolic Unit, Bambino Gesù Children's Hospital, Rome, Italy, the ††Paediatric Gastroenterology and Hepatology Unit, IREC, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, the ‡‡Department of Paediatrics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, and the §§Paediatric Hepatology Unit, Hôpital NECKER-APHP, Paris, France.

Address correspondence and reprint requests to Björn Fischer, MD, PhD, Department of Paediatrics, CLINTEC, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden SE-14186 (e-mail: bjorn.fischler@karolinska.se).

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TABLE 1. Main characteristics and clinical features of the 4 hepatitis E virus genotypes (1,2)

HEV genotypes	1	2	3	4
Year of discovery	1983	1986	1995	2003
Geographic distribution	Developing countries; Asia/Africa	Sub-Saharan Africa, Mexico	Developed countries; USA, Europe, New Zealand, Argentina	India, Eastern Asia (China, Taiwan, Japan, Vietnam)
Hosts	Human, pig	Human	Human, pig, other mammalian species, shellfish	Human, pig, other mammalian species
Pattern of infection	Endemic		Sporadic	
Route of transmission				
Waterborne, fecal-oral	Yes		Possible	
Foodborne	Possible (genotype 1)		Yes	
Zoonotic	Possible (genotype 1)		Yes	
Person to person	Possible		Possible	
Blood transfusion	Yes		Yes	
Vertical (mother to child)	Yes		Yes	
Clinical features				
Sex preponderance	No		Male	
Highest attack rate	15–30 Years		>40 Years	
Clinical presentation				
Asymptomatic	Common		Common	
Acute liver failure/risk factor	Yes (genotype 1)/pregnancy, infancy		Yes/elderly, chronic liver disease	
Chronic hepatitis/risk factor	Not reported		Yes/immune deficiency	
Extrahepatic manifestations	Not reported		Yes (genotype 3)	
Mortality rate	<3% But 20%–25% during pregnancy		<1%	

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 during 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 (1,11). Of the 4 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 (1,12). Genotype 1 infections have also been diagnosed in developed countries following travel to endemic regions (12), 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, whereas in Italy, most cases were travel related caused by genotype 1 (13,14). In contrast, HEV genotype 3 is responsible for the majority of autochthonous cases of acute hepatitis E in Europe and the United States, whereas HEV genotype 4 disease is prevalent in China and Taiwan (1,12). HEV genotypes 3 and 4 are believed to be zoonotically transmitted by consumption of contaminated food (1,12).

Epidemiological studies from most developing countries show that HEV seroprevalence increases with age from <10% in children ages <10 years to up to 76% in adolescents and 84% in

adults in Egypt (15). In one study, HEV seroprevalence in blood donors ranged from 5.4% among Tunisians to >50% among Egyptians (16). 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 (17,18). HEV seroprevalence in blood donors using different immunoassays to test for HEV immunoglobulin G (IgG) varies from <1% to >20% with a wide regional differences even within the same country (17,19–26). Analysis of the National Health and Nutrition Evaluation Survey data in the United States, showed that in 2010 the overall HEV seroprevalence in the general population ages 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%) (25). On multivariate analysis, increasing age significantly correlated with HEV seroprevalence. The prevalence of anti-HEV antibodies in children ages 6 to 19 years was 0.8% among boys and 1.1% among girls (25). Available data among children in other developed countries are limited to 3 studies from Spain (27), Germany (28), and Japan (29) reporting a prevalence of anti-HEV antibodies between 1% and 7.5%. The largest pediatric study recently conducted in Germany (1646 children ages 0–17 years) revealed an increasing prevalence of HEV antibodies with age: from 0.4% in infants younger than 2 years of age up to 1.5% in the 15- to 17-year-old group (28).

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 polymerase chain reaction (PCR) and

immunoglobulin M (IgM) and IgG antibodies using different serological methods. Studies comparing commercial and in-house assays for serological detection, however, showed disturbing differences in diagnostic yield. In particular, sensitivity varied between as low as 20% to >90% depending on method used (30–32). At present, there is no universally accepted assay for HEV IgM and IgG detection (33).

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 (15). At 6 weeks after the onset of symptoms, HEV RNA is no longer detected in serum, whereas 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 (34). In contrast, a negative HEV RNA test in a symptomatic immunocompetent patient should prompt analysis of HEV IgM and HEV IgG, because the viremic period is rather short.

In immunocompromised patients—for example, after SOT or stem cell transplantation or in HIV-infected individuals (35)—testing for HEV RNA in serum is clearly preferable because these patients often may not mount an antibody response (3). In immunosuppressed patients, HEV fecal shedding may persist for up to 2 years or more after the diagnosis (9), 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 infection, with most cases being asymptomatic (1,15,17). The incidence of acute hepatitis with jaundice increases with age. The incubation period ranges from 15 to 60 days, with a mean of 40 days. The clinical features include jaundice, fever, flu-like symptoms, abdominal pain, vomiting, anorexia, and hepatomegaly (1,15,17). A minority of children may develop ALF, especially those with pre-existing chronic liver disease (36–39). Two large pediatric series from India, in which genotype 1 is highly endemic, reported HEV or hepatitis A virus and HEV coinfection as the main causes of ALF or acute decompensation of underlying chronic liver disease (36,37). Locally acquired HEV genotype 3 infection was also recognized as a cause of ALF in developed countries both in adults and in children in 1 case series from Argentina (1,39–42). The frequency of pediatric ALF related to HEV infection in Europe, however, 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 (7,9,10). This finding, which was associated with chronic viremia, was also reported in children with HIV infection and hematological malignancies (8). In 1 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 1 renal transplant recipient developed chronic hepatitis with persistently elevated liver enzymes and HEV fecal shedding 24 months after diagnosis (9). 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 (43). In a series from Canada, 12 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 after diagnosis, whereas HEV RNA was found in annual samples from 10 to 16 years after transplant, which coincided with the development of cirrhosis (7). 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 (10). Chronic HEV infection has also been documented after stem cell transplantation in an adolescent who later developed cirrhosis and portal hypertension (8). Similar presentations have been described in genotype 3 infections and in 1 child with genotype 4 infection (44). 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, and 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 patients who underwent SOT, HEV infection was acquired after transplantation, most likely through foodborne transmission. Blood transmission of HEV has rarely been reported in this setting (45,46). To date, only 1 case of occult HEV infection in an adult, transmitted via transplanted liver was reported from Germany (47). HEV reactivation after SOT or stem cell transplantation in anti-HEV IgG positive recipients is unlikely to occur (45,48,49), but reinfection in those with low IgG titers may occur (50). If liver transplantation is required once chronic infection is established, it is likely that chronic hepatitis E will recur in the liver graft (51). 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 and use of tacrolimus-based rather than cyclosporin-based regimen (52).

Unless HEV screening is routine, the diagnosis can easily be missed because the clinical features of acute and chronic HEV infection are often nonspecific (53). 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 (10,54,55).

Finally, several extrahepatic manifestations such as neurological disorders, acute pancreatitis, severe thrombocytopenia, hemolytic anemia, and hemophagocytic syndrome have been associated with locally acquired acute and chronic HEV genotype 3 infection both in adults and children (56,57). 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 (58). 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 has not yet been reported in immunosuppressed children, it seems reasonable to assume that they may occur. Something to keep in mind is that these extrahepatic 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, and hemolytic 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 pediatric 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, that is, acute and late cellular rejection and de novo autoimmune hepatitis after liver transplantation.

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, whereas 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 (11,59–61). 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 (62), and in 10% of pork sausages in the UK (63). Outbreaks of hepatitis E in southern France have been linked to consumption of raw figatelli pig liver sausages through the identification of HEV strains (59). Zoonotic transmission of HEV genotype 4 has also been reported in France and Asia (64–67).

Cooking foods at temperatures $>70^{\circ}\text{C}$ for at least 20 minutes is required to inactivate the virus and decrease the risk of foodborne infection (68).

In contrast to what is reported for hepatitis A and other enteric viruses, person-to-person transmission of HEV seems rare. Because HEV RNA is detectable in feces from infected individuals, strict hygiene measures must, however, be in place to avoid the spread of the disease among household and nursery contacts, and infected patients in the hospital (69,70).

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% (6). 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 (72).

In endemic regions, fetuses or newborns born to mothers with acute third trimester infections have a 50% and 100% risk of infection (73–75). The placenta may act as a viral reservoir (76). Khuroo et al (73) described 26 infected pregnant women, of whom 15 had ALF and 11 had acute hepatitis without liver failure. 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 (73). A recent study suggests that HEV may be responsible for >3000 stillbirths annually in developing countries, including fetal deaths linked to antenatal maternal mortality (77).

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 low (78–80).

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. Breastfed babies of infected mothers did not seem to be at higher risk than those who were bottle fed (81). The authors concluded that further studies are warranted to determine whether breastfeeding can be recommended.

Transmission From Blood Products

Several case reports have described transmission of HEV infection by blood transfusions (46,82). Using pooled plasma to analyze HEV RNA by PCR in a large number of donors (165,000), Baylis et al (83) detected HEV RNA in German (1 in 4500) and Swedish (1 in 8000) 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 6 of 10,000 blood donations (84), whereas in an Austrian study HEV RNA was identified in 7 of 58,000 blood donors (26). HEV transmission was also documented in 4 of 17 patients treated with pooled solvent detergent-treated plasma in Canada (85).

To date, the most comprehensive study on this subject was performed in South East England, analyzing samples from 225,000 donors (86). HEV RNA was detected in approximately 1 in 2800 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. Viremia persisted in recipients who were on immune suppression for their underlying disease. Only 1 infected recipient developed clinical hepatitis, whereas another 4 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 viremia was concerning. Although they stopped short of recommending universal HEV RNA testing of blood donors, this was suggested in the accompanying editorial (87).

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, 2 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 1800 adult healthy men and nonpregnant women recruited from the Nepal army. A significant antibody response was noted in 81% of vaccinees 1 month after the second dose and in 100% 1 month after the third dose. Moreover, after the full 3 doses, hepatitis E developed in only 3 subjects in the vaccinated group compared with 66 subjects in the placebo group (88). No major side effects were described.

An *Escherichia 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 nonpregnant women ages 16 to 65 years showed a good antibody response in the vaccinated ones. Follow-up 1 year after the third dose showed 15 infected subjects in placebo group and none in the vaccinated group (89). No major side effects were noted. Follow-up after 4.5 years revealed a persistently satisfactory immune response to the vaccine (90).

Although the results from the studies mentioned above are 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, nonteratogenic 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 pangentotypic HEV vaccine for at risk groups should be encouraged.

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. In cases of fulminant HEV infections, a short course of ribavirin has, however, been shown to lead to complete recovery, avoiding the need for liver transplantation (91,92).

Data from the transplant setting have shown that a reduction in the levels of immunosuppression led to viral clearance in >30% of cases (52,93,94). No spontaneous clearance was, however, observed between months 3 and 6 after infection in SOT recipients if HEV RNA persisted for more than 3 months despite immunosuppression reduction (94,95). Treatment with pegylated interferon (peg-IFN- α 2a) 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 (93,96). Because peg-IFN- α 2a is not as effective as ribavirin and increases the risk of acute graft rejection (96), ribavirin is currently the medication of choice used in adult transplant recipients with a high rate of sustained virologic response (93,94). To date, the largest study on the efficacy and safety of ribavirin therapy in adult SOT recipients reported on 59 patients treated with ribavirin (median dose of 8.1 mg/kg body weight per day [range, 0.6–16.3]) for a median duration of 3 months (range, 1–18) after the diagnosis of HEV infection (93). 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 \leq 3 months and the 20 patients who had received it for >3 months (74% and 85%, respectively). An 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 (97). Anemia 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 (93). In a more recent study of 61 immunocompromised patients, 27 were not treated, 4 of whom developed chronic infection, whereas 2 were lost to follow-up and 5 died while HEV RNA positive (94).

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 of 94 days (10–560). In 21 (81%) patients, a sustained viral response was documented. Median treatment duration for HEV clearance was 2 months demonstrating a rapid response to treatment. Only 1 patient had recurrence but achieved viral clearance after re-treatment with ribavirin (94). Although 3-month duration of ribavirin monotherapy seems appropriate, a longer therapy may be needed in those who remain viremic 1 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 \geq 0.5 log copies/mL had an 88% positive predictive value for SVR (98). Monitoring HEV fecal excretion may be used to determine the optimal duration of ribavirin therapy (97). 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 (99). Recent *in vitro* studies have shown that sofosbuvir inhibits the replication of HEV 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 (100).

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 (10). Clearance of HEV RNA occurred within 42 days after initiation of therapy and lasted for 3 months after discontinuing ribavirin treatment. Anemia 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/day) for 3 months with close monitoring for anemia and renal function.
 - HEV clearance should be monitored by PCR on a monthly basis during the treatment and for 3 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.

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