Hepatitis E virus infection

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INTRODUCTION

Hepatitis E virus (HEV) is one of the most common causes, yet least diagnosed etiologies, of acute viral hepatitis [1]. HEV infection has a global distribution, with distinct differences in transmission and disease outcomes in resource-rich versus resource-limited areas.

This topic will review the epidemiology, clinical manifestations, diagnosis, and treatment of HEV infection in adults. Other causes of viral hepatitis are discussed in detail separately. (See "Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis" and "Hepatitis B virus: Clinical manifestations and natural history" and "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

VIROLOGY

Composition and structure — HEV is a small, icosahedral, nonenveloped single-stranded RNA virus that is approximately 27 to 34 nm in diameter [2-6]. It has been classified as the single member of the genus *Hepevirus* in the family *Hepeviridae* [7]. The Orthohepevirae include hepatitis E viruses affecting vertebrates and can be further divided into groups A through D. Group A includes viruses primarily infecting humans, pigs, deer, and rabbits, while group C includes a unique rat HEV that can be transmitted to humans [8]. Groups B and D cause disease in avian species and bats, respectively [9].

Three large open reading frames (ORFs) of the positive-sense RNA of HEV have been described [10]:

- The largest ORF consists of 1693 codons; it codes for nonstructural proteins that are responsible for the processing and replication of the virus, including a methyltransferase, an RNA helicase, a cysteine protease, and an RNA polymerase [11].
- The second ORF is composed of 660 codons and codes for viral capsid structural proteins.
- The third ORF consists of 123 codons; data suggest that it acts as a viroporin, which may facilitate release of infectious virions from infected cells [12].

Genotypes — There are a wide range of HEV genotypes that demonstrate varying degrees of host specificity [13]. Among group A hepatitis E viruses, genotypes 1 and 2 appear to be confined to humans, while genotypes 3 and 4 infect humans and animals (including but not limited to swine, deer, dolphins, cows, nonhuman primates, and bears) [14]. There is increasing interest in rodent-associated HEV (group C), which may infect humans as a secondary host and can lead to severe acute and/or chronic hepatitis [15]. HEV genotypes differ in their prevalence by geographic region and in their route of transmission (eg, waterborne versus zoonotic) as discussed below. (See 'Epidemiology' below and 'Transmission' below.)

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that HEV causes 20 million new infections annually, with more than 3 million cases of acute hepatitis and over 55,000 deaths [16]. HEV infection has a global distribution [2,17-30]. Specific genotypes result in infection in different geographic areas.

- Genotypes 1 and 2 have been reported mainly in Asia, India, and North Africa.
- Genotype 2 has been identified in Mexico and West Africa.
- Genotype 3 is prevalent in Western countries, as well as in Asia and North America.
- Genotype 4 has been detected in Asian and European countries.

The prevalence rates of hepatitis E antibody are higher in resource-limited countries as compared with developed countries (10 to 70 versus 1 to 21 percent) [31-33]. The highest prevalence is in Asia and Africa where outbreaks of HEV have been related to consumption of contaminated drinking water [1,34-37]. (See 'Transmission' below.)

An outbreak of HEV in the Lake Chad region of Africa was reported in 2017 [38]. The outbreak was first noted in Niger, where an increase in cases of jaundice was observed among pregnant

women in January 2017. As of May 3, 2017, the WHO reported 282 suspected cases, including 27 deaths among pregnant women [39]. In July of 2017, the WHO reported an outbreak in nearby Nigeria, where 146 confirmed and suspected cases were reported. (See 'Pregnant women' below.)

Although rates of HEV are higher in resource-limited countries, HEV is widespread in parts of Europe, particularly in Germany, France, the Netherlands, and Switzerland [40,41]. In a 2017 surveillance analysis, the European Centre for Disease Prevention reported an increase in the number of confirmed HEV cases in Europe: from 514 cases in 2005 to 5617 cases in 2015 [42]. However, it is unclear if this represents a true rise in HEV incidence or an increase in detection of cases due to growing awareness and testing for HEV [43]. (See 'Transmission' below.)

In the United States, the overall seroprevalence of HEV was estimated to be 21 percent between 1988 through 1994 [20]. The prevalence was highest in non-Hispanic White persons and those living in the Midwest and/or metropolitan areas. The risk was also greater in those who had a pet at home or consumed liver or other organ meats more than once per month. High rates of HEV seroprevalence have been seen in those with chronic hepatitis C infection [44].

However, rates of HEV exposure in the United States appear to be declining. As an example, in a study that analyzed data from the National Health and Nutrition Examination Survey, antibody levels among those aged ≥6 years were only 6 percent from 2009 to 2010 [45]. In a cross-sectional study of 18,829 blood donations over a six-month period in 2013, two samples had HEV RNA [46]. Samples were taken from six geographic regions, and both positive samples were from the Midwest, where the overall prevalence appears to be higher.

TRANSMISSION

Transmission of HEV can occur through contaminated food and water, blood transfusions, and through mother-to-child transmission. Although person-to-person transmission is uncommon, patients are infectious during fecal shedding. Specific genotypes differ in their route of transmission. Additional information on the different HEV genotypes is presented above. (See 'Genotypes' above.)

- **Contaminated food and water**
  - **Waterborne infection** – HEV genotype 1 and 2 infections are spread by fecally contaminated water in endemic areas [3,47]. Thus, in resource-limited countries where sanitation and water purification services are limited, there is a high rate of lifetime exposure to HEV associated with HEV genotype 1 and 2 (and possibly 4) infection. Acute

hepatitis due to waterborne infection may appear as an endemic process with a high cumulative lifetime risk of exposure. This pattern is seen in the Nile River valley and is thought to be associated with contaminated ground water obtained from shallow wells [48]. In other parts of the world (eg, Africa, India, Bangladesh), endemic waterborne disease occurs at a baseline rate, but is punctuated by explosive epidemics of acute HEV-associated hepatitis [39,49,50].

- **Zoonotic transmission** – HEV genotypes 3 and 4 usually cause infections due to consumption of contaminated food. Most cases are sporadic and unidentified as an acute viral hepatitis, although isolated outbreaks have occurred, including an HEV outbreak associated with consumption of shellfish that affected passengers on a cruise ship [51]. Zoonotic transmission of HEV is also supported by the observation of high anti-HEV seroprevalence among individuals with occupational exposure to animals [18,27,52].

  Swine are most frequently implicated in transmission, followed by consumption of filter feeder shellfish [53-56]. However, many animal species (including rodents in some regions), have been identified as part of the viral reservoir of disease [57]. HEV transmission has been reported from consumption of undercooked deer meat, wild boar meat, pig liver sausage, and internal organs of animals in Japan and in parts of Europe (eg, Germany and France) [41,58-61]. One study strongly implicated cow milk as a potential source of HEV genotype 4 in China [62]. In addition, transmission of HEV to rhesus macaques was reported following administration of both raw and pasteurized milk [62].

  There are limited data regarding food preparation to reduce/eliminate HEV transmission. In one study, cooking liver at 191°F for five minutes or boiling liver for five minutes reduced the risk of transmission by inactivating HEV [63]. It has been speculated that the lower rates of transmission of genotype 3 HEV observed in the United States versus in Europe may be due to greater consumption of preprocessed/cooked commercial pork products, which are less utilized in Western Europe [64].

- **Blood transfusion** – HEV can be transmitted by blood transfusions, particularly in endemic areas [65-68]. In one study that evaluated the prevalence and transmission of HEV in 225,000 blood donations, 79 HEV genotype 3 RNA-positive donations were detected [68]. These donations were used to prepare 129 blood components and 62 were transfused. On follow-up testing of 43 recipients, 18 (42 percent) HEV infections were detected. A subsequent analysis of samples from North American blood donors (United States and

Canada) found that HEV RNA was present in 1 in 16,908 donation samples from US donors, with higher levels seen in Canadian samples [69].

- **Perinatal transmission** – There are limited data regarding vertical transmission of HEV from infected mothers to their infants. Case series suggest that HEV infection can be transmitted from mother to newborn with substantial perinatal morbidity and mortality; however, its contribution to the overall disease burden appears to be small [70-72].

- **Transmission in breast milk** – It is unclear if breastfeeding is a potential route of HEV transmission. However, there is sufficient concern to discourage breastfeeding among confirmed HEV-infected mothers until further data are available. In one case report, HEV was isolated in breast milk during the acute phase of HEV infection [73]. Milk and serum HEV titers were comparable.

ACUTE HEPATITIS E

HEV generally causes a self-limited acute infection, although acute hepatic failure can develop in a small proportion of patients.

Clinical features — The incubation period of HEV infection ranges from 15 to 60 days [2,17,74,75]. The vast majority of patients with acute HEV are asymptomatic or mildly symptomatic [76]. The proportion of people who develop clinical features following acute infection varies based upon age and prior HEV exposure [48].

In symptomatic patients, jaundice is usually accompanied by malaise, anorexia, nausea, vomiting, abdominal pain, fever, and hepatomegaly [77]. Other less common features include diarrhea, arthralgia, pruritus, and urticarial rash [78-81].

In addition, patients occasionally have extrahepatic findings. These include [82]:

- Hematologic abnormalities including thrombocytopenia, hemolysis, and aplastic anaemia
- Acute thyroiditis
- Membranous glomerulonephritis
- Acute pancreatitis
- Neurologic diseases including:
    - Acute transverse myelitis
    - Acute meningoencephalitis
    - Aseptic meningitis
    - Neuralgic amyotrophy

- Pseudotumor cerebri
- Bilateral pyramidal syndrome
- Guillain–Barré syndrome
- Cranial nerve palsies
- Peripheral neuropathy

Laboratory findings — Laboratory findings include elevated serum concentrations of bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase [78,83]. Symptoms coincide with a sharp rise in serum ALT levels, which may rise up into the thousands and return to normal during convalescence [84]. Resolution of the abnormal biochemical tests generally occurs within one to six weeks after the onset of the illness (figure 1).

Liver histology — Morphological features of HEV include those noted with cholestatic and classic types of acute viral hepatitis. Cholestatic forms are characterized by bile stasis in canaliculi and gland-like transformation of hepatocytes. Other histologic findings include focal necrosis, ballooned hepatocytes, and acidophilic degeneration of hepatocytes [1,85]. In fatal cases, submassive or massive hepatic necrosis is present [17,79].

In immunosuppressed patients, development of chronic hepatitis leads to inflammation and progressive fibrosis, which can lead to cirrhosis. In patients who have undergone organ transplantation, this process may be mistaken for rejection [86]. (See 'Chronic hepatitis E' below.)

Complications — The majority of patients who acquire HEV spontaneously clear the virus. However, patients may develop complications such as acute hepatic failure, cholestatic hepatitis, or chronic HEV.

Acute hepatic failure — A small proportion (0.5 to 4 percent) of HEV-infected persons develop acute hepatic failure [87]. As an example, in the United States Acute Liver Failure Study, only 3 of 681 adults demonstrated anti-HEV IgM antibodies, but none were HEV RNA positive, indicating that acute HEV is not a common cause of acute hepatic failure in the United States [88]. When it does occur, acute hepatic failure is more likely in those who are pregnant and in those who are malnourished or have pre-existing liver disease. (See 'Special populations' below.)

Acute hepatic failure is characterized by hepatic encephalopathy, elevated aminotransferases (often with abnormal bilirubin and alkaline phosphatase levels), and impaired synthetic function (international normalized ratio ≥1.5). Acute hepatic failure carries a high mortality if intensive care support and liver transplantation are not available, resulting in an overall case fatality rate of 0.5 to 3 percent [89]. (See "Acute liver failure in adults: Etiology, clinical manifestations, and

diagnosis" and "Acute liver failure in adults: Management and prognosis" and 'Special populations' below.)

Cholestatic hepatitis — Prolonged cholestasis, characterized by a protracted period of jaundice (lasting >3 months), has been described in up to 60 percent of patients with acute HEV [90]. Patients may be asymptomatic or have symptoms of pruritus due to cholestasis. In general, cholestatic hepatitis resolves spontaneously within weeks to months with no sequelae [91]. Recovery is marked by viral clearance, an increase in IgG anti-HEV titers, and a decrease in IgM anti-HEV levels [92].

Chronic hepatitis E — Chronic HEV infection is defined empirically as detection of HEV RNA in serum or stool for longer than six months. Chronic HEV almost exclusively occurs in immunosuppressed patients (eg, those with HIV infection, following solid organ or bone marrow transplantation) [93-96]. Chronic infection is typically with HEV genotype 3 infection, although chronic infection with genotype 4 and 7 has been documented in transplant recipients [97-99]. Chronic HEV infection with genotypes 1 and 2 have not been reported. (See 'Solid organ transplant recipients' below and 'HIV and other immunosuppressed hosts' below and 'Genotypes' above.)

As with most chronic viral hepatitis patients, symptoms are minimal and include fatigue and nonspecific findings until progression to decompensated cirrhosis occurs. Patients with chronic HEV have persistently elevated aminotransferase levels, detectable serum HEV RNA, and histologic findings compatible with chronic viral hepatitis. (See 'Liver histology' above.)

SPECIAL POPULATIONS

Pregnant women — In regions where HEV infection is endemic, acute hepatic failure occurs more frequently when HEV occurs during pregnancy. In one study in India, hepatic failure was more common during the third trimester [100]. Acute HEV infection during pregnancy has been associated with a mortality rate of 15 to 25 percent [3,39,50,85,101,102]. However, exposure to HEV early in life may reduce the risk of acute liver failure in pregnant women who become reinfected later in life (eg, pregnant women in Egypt) [103]. While the mechanism of HEV-induced hepatic failure is unknown, reduced Toll-like receptor (TLR) expression (eg, TLR3 and LR7) may contribute to disease severity [104,105]. Poor outcomes in pregnancy may also be due in part to poor nutritional status [106] and lack of access to supportive medical care [107].

Pre-existing liver disease or malnutrition — Infection with HEV can lead to hepatic decompensation in patients with pre-existing liver disease (ie, acute on chronic liver disease)

and in those who are malnourished [108,109]. In a case-control study that evaluated the impact of HEV in patients with hepatitis C virus-associated advanced liver fibrosis/cirrhosis, there was a higher HEV seroconversion rate among the 89 cases who developed hepatic decompensation compared with the 267 controls patients without decompensation (4.5 versus 2.2 percent) [110], although this failed to reach statistical significance.

Solid organ transplant recipients — A subset of patients who undergo solid organ transplantation (eg, kidney, liver, and kidney-pancreas) appear to develop chronic HEV infection [111-118]. In a retrospective multicenter study that included 85 recipients of solid organ transplants, the rate of chronic infection among those who were acutely infected with HEV after transplant was approximately 70 percent [119]. In a prospective cohort of 700 solid organ transplant recipients, 34 (5 percent) acquired HEV infection, of whom 47 percent developed chronic infection [118].

Chronic infection appears to be related to impaired HEV-specific T-cell responses [120]. Chronic hepatitis has been associated with lower counts of lymphocytes and of CD2, CD3, and CD4 T cells; use of tacrolimus; a low platelet count at the time of diagnosis with HEV infection; younger age; and liver transplantation [111,118,119]. An important risk factor for acute HEV infection in solid organ transplant recipients appears to be consumption of insufficiently cooked game meat or pork products [121]. (See 'Transmission' above.)

The natural history of chronic HEV infection in transplant recipients is incompletely understood, but rapid progression of liver disease to cirrhosis has been reported [112,116]. Chronically infected patients may also be at risk for HEV reactivation [122]. However, studies have been conflicting and the risk, if present, appears to be small [118].

HIV and other immunosuppressed hosts — Case reports have described chronic infection with HEV in patients with HIV infection and in patients with non-Hodgkin lymphoma receiving rituximab, suggesting that immunosuppression predisposes patients to chronic infection outside of the transplant setting [93,94].

Among HIV-infected patients, there appears to be a higher rate of HEV exposure as compared with the general population; however, overall rates of chronic HEV infection appear to be relatively low [123,124]. As an example, one study reported a cross-section analysis of 448 HIV-infected patients, where anti-HEV IgG was present in 10.4 percent, but HEV RNA was identified in only 1 of 45 patients tested [125]. (See 'Chronic hepatitis E' above.)

DIAGNOSIS

General approach — The diagnosis of HEV should be considered in patients who present with acute or chronic hepatitis that cannot be explained by other causes. This includes putative cases of drug-induced liver injury which have been misclassified because HEV testing was not performed [126]. It is particularly important that the diagnosis of HEV infection be considered in groups that are at risk for developing rapidly progressive liver disease, such as pregnant women, patients with underlying liver disease, solid organ transplant recipients, and those with hematologic malignancies [127]. (See 'Special populations' above.)

- **Acute HEV** –The diagnosis of acute HEV is complicated by the lack of a standardized assay. Multiple commercial enzyme immunoassay (EIA) kits have been developed and have high variability in terms of test performance; both false positives and negatives are common with available assays.

  - In general, the initial test method is an anti-HEV IgM assay. The presence of IgM anti-HEV antibodies is suggestive of recent HEV infection. (See 'Antibody testing' below.)

  - If the initial test is positive, confirmatory testing should be performed when available since no single EIA method achieves high specificity. Confirmatory testing may include an alternate anti-HEV IgM, evidence of rising anti-HEV IgG titers (greater than fivefold change over two weeks), or detection of HEV RNA in serum or stool [128].

  - If initial EIA testing is negative, and there is still a high suspicion for HEV infection, repeat testing should be performed, preferably with an HEV RNA assay. The use of RNA testing is particularly important in immunocompromised hosts with suspected HEV due to a high rate of false-negative antibody testing [84,129,130]. (See 'HEV RNA assay' below.)

- **Chronic HEV** – In patients with suspected chronic HEV infection, detection of HEV RNA in serum is the mainstay of diagnosis. Chronic HEV infection is defined as detection of HEV RNA in serum or stool for longer than six months.

  Testing for IgG anti-HEV antibodies is of limited utility in the diagnosis of chronic HEV infection. The presence of IgG (or total) anti-HEV antibodies is a marker of exposure to HEV, which can be either recent or remote. In addition, the decline in IgG anti-HEV titers with time might adversely affect its sensitivity for detecting remote infection (figure 1).

Diagnostic tests — There are no commercial tests for HEV licensed in the United States; however, there are research laboratories that can test for anti-HEV by EIA or Western blot of serum and for HEV genomes by polymerase chain reaction of blood or feces [131]. In the United

States, these tests can be located through the Centers for Disease Control and Prevention (CDC; 1-800-CDC-INFO).

Antibody testing — The timing of appearance of HEV markers is important for interpreting results of serologic testing in the setting of acute hepatitis (figure 1).

- IgM anti-HEV appears during the early phase of clinical illness and disappears rapidly over four to five months (figure 1) [83]. Although IgM anti-HEV has been detected in the serum by EIA in more than 90 percent of patients in some outbreak settings when samples were obtained within one week to two months after the onset of illness, serology may be negative in a substantial proportion of patients with acute infection [132]. As an example, in a series of 44 children with acute HEV (defined as acute hepatitis with HEV viremia in serum and stool by cell culture and polymerase chain reaction), only 35 percent of patients tested positive for IgM anti-HEV in serum and only 3 percent were positive for IgG anti-HEV [133]. In another report, the sensitivity and specificity for IgM anti-HEV were 27 and 92 percent, respectively. HEV RNA was detected in 23 percent of patients followed by detection of specific IgM in 17 percent and IgG in 13 percent of patients [134].

- The IgG response appears shortly after the IgM response, and its titer increases throughout the acute phase into the convalescent phase. It is unclear how long IgG anti-HEV antibodies persist. In one report, antibodies were detected as long as 14 years after the acute phase of illness; however, a booster effect due to reinfection could not be excluded [74,83,135-137]. In other follow-up studies, IgG antibody titers showed a rapid decline but were detectable 14 to 20 months after an acute HEV infection. Discordance between assays of IgG anti-HEV antibody is even higher as compared with assays for IgM anti-HEV antibody [138].

HEV RNA assay — HEV can be detected in stool approximately one week before the onset of illness and can persist for as long as two weeks thereafter [2,139-141]. In serum, HEV may be detected two to six weeks after infection and can persist for two to four weeks in those who resolve acute infection. Although HEV viremia is short-lived in most patients with acute infection, it can persist for years in those who develop chronic infection (figure 1) [142,143]. (See 'Chronic hepatitis E' above.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients presenting with an elevation in aminotransferases, with or without symptoms of hepatitis, is broad and can include infectious and noninfectious causes.

Liver disease caused by infectious causes includes:

- Hepatitis A virus infection
- Acute or chronic hepatitis B virus infection
- Chronic hepatitis C infection
- Acute or chronic hepatitis D infection (in the setting of concurrent or pre-existing HBV infection)
- Hepatitis due to herpes simplex virus infection
- Hepatitis due to Epstein-Barr virus infection
- Hepatitis due to cytomegalovirus infection

Liver disease caused by toxins:

- Alcoholic hepatitis
- Acetaminophen toxicity
- Drug-induced liver injury/idiosyncratic drug reactions (including herbal supplements and illicit drugs)
- Toxin-induced hepatitis (eg, mushroom poisoning, carbon tetrachloride)

Liver disease by metabolic disorders:

- Nonalcoholic steatohepatitis
- Autoimmune hepatitis
- Wilson disease
- Hereditary hemochromatosis
- Alpha-1 antitrypsin deficiency

Liver disease by other causes:

- Ischemic hepatitis
- Budd-Chiari syndrome
- HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome
- Acute fatty liver of pregnancy

Elevated aminotransferases may also be seen in patients with systemic disease, such as:

- Muscle diseases
- Thyroid disease
- Celiac disease
- Adrenal insufficiency
- Anorexia nervosa

Differentiating among these entities requires a thorough history to identify risk factors for and symptoms of the various disorders, as well as laboratory tests. The approach to the evaluation of a patient with abnormal liver tests is discussed in detail elsewhere. (See "Approach to the patient with abnormal liver biochemical and function tests".)

MANAGEMENT

Management of HEV depends upon the immune status of the patient and the stage of disease (eg, acute versus chronic).

Acute hepatitis E — For most patients, the management of acute HEV infection is supportive, as the disease appears to be mild and self-limited in immunocompetent patients. However, patients with acute HEV infection who develop fulminant hepatic failure may require liver transplantation [144]. The management of acute liver failure is discussed in detail separately. (See "Acute liver failure in adults: Management and prognosis", section on 'General management'.)

The role of antiviral therapy in immunocompromised patients with acute HEV has not been established [145]. Ribavirin should not be used in pregnant women as it is a potent teratogen. In addition, although small retrospective studies have suggested that patients with chronic liver disease and those receiving immunosuppressive therapy may benefit from ribavirin monotherapy [92,146-152], it is unclear if improvement was spontaneous or due to ribavirin in the absence of controls. As an example, in a retrospective study in France, 21 patients with acute HEV due to genotype 3 or 4 disease were treated with ribavirin monotherapy for a median of 26 days; in addition, immunosuppressive therapy was suspended during treatment in six patients [152]. All patients cleared HEV within six weeks, with a median time to viral clearance of 29 days; however, two patients died from liver failure, both of whom had underlying chronic liver disease.

Chronic hepatitis E — Chronic HEV occurs almost exclusively in immunocompromised patients. (See 'Chronic hepatitis E' above.)

The management of chronic infection involves reduction of immunosuppressive therapy and/or antiviral therapy (algorithm 1). The goal of treatment is to eradicate HEV RNA, which is predicted by achieving a sustained virologic response (SVR). An SVR is defined as the absence of HEV RNA by polymerase chain reaction 12 weeks after cessation of treatment. Patients with an SVR are considered cured since there is no viral reservoir, similar to hepatitis C virus; however, they remain at risk for reinfection. (See 'Transmission' above.)

Reduction of immunosuppression — A reduction in immunosuppressive therapy is the first step in the treatment of chronic HEV infection. There are no clear data to guide how immunosuppressive therapy should be reduced; however, for solid organ transplant recipients, we typically reduce tacrolimus first, if possible, since there is an association of chronic infection with tacrolimus. (See 'Solid organ transplant recipients' above.)

Clearance of chronic HEV infection has been reported after reducing or withdrawing immunosuppressive therapy [119,153]. As an example, in a retrospective series that evaluated 85 solid organ transplant recipients with chronic HEV, reduction of immunosuppressive therapy resulted in viral clearance in approximately 30 percent of patients [119].

Antiviral therapy — Antiviral therapy is directed against genotype 3, since chronic infection is typically observed in patients with this genotype [154]. (See 'Chronic hepatitis E' above and 'Genotypes' above.)

Whom to treat — We suggest a 12-week course of ribavirin monotherapy to certain nonpregnant patients with chronic HEV infection [84].

- In solid organ transplant recipients, we administer ribavirin in conjunction with reducing immunosuppressive therapy.
- For others, we administer antiviral therapy if immunosuppressive therapy cannot be reduced, or if the patient has persistent HEV RNA despite a reduction in immunosuppressive therapy for 12 weeks [144,154]. (See 'Reduction of immunosuppression' above.)

The dose of ribavirin is 600 to 1000 mg daily (administered in two divided doses). Monitoring for toxicity and assessing the response to therapy are discussed below. (See 'Monitoring for toxicity' below and 'Assessing response to antiviral therapy' below.)

Although no randomized trials have evaluated the use of ribavirin for the treatment of chronic HEV, case series have suggested a benefit [155-160]. As an example, in a multicenter retrospective study that evaluated 59 solid organ transplant recipients with chronic HEV infection who received ribavirin (median dose 600 mg daily) for a median of three months, HEV clearance was observed in 56 (95 percent) patients, and an SVR was observed in 46 patients (78 percent) [155]. Anemia was the most common side effect and required a reduction in ribavirin dose, use of erythropoietin, and blood transfusions in 29, 54, and 12 percent of individuals, respectively.

Monitoring for toxicity — Intermittent laboratory monitoring is warranted during and after treatment of HEV to monitor for drug toxicity. In the absence of data to suggest otherwise, we check basic laboratory tests (complete blood count, creatinine with estimated glomerular filtration rate calculation, liver enzymes, and bilirubin levels) at week 4 of treatment, with more frequent monitoring for concerning results or trends.

We then check the complete blood count at weeks 8 and 12 to evaluate for anemia associated with ribavirin. For those who develop anemia, the dose of ribavirin can be adjusted based on the severity and comorbidities. (See "Overview of the management of chronic hepatitis C virus infection".)

Ribavirin should not be used in pregnant women as it is a potent teratogen. Thus, for women of childbearing age taking ribavirin, assessment of contraception use and pregnancy testing should be performed during and for six months after treatment. Men taking a ribavirin-containing regimen should be counseled on contraceptive use for sex with a woman of childbearing age during and for six months after treatment.

Assessing response to antiviral therapy — To assess the response to antiviral therapy, we typically check both stool and serum HEV RNA at week 12 (algorithm 1). We check both sera and stool since persistence of HEV RNA in the stools at the end of therapy is associated with HEV relapse after ribavirin cessation, even if serum HEV RNA is absent [159].

The subsequent approach to treatment depends upon the virologic response:

- **Undetectable HEV RNA after initial treatment** – Ribavirin can be stopped if the HEV RNA is negative in the sera and stool at week 12. We then repeat HEV RNA testing in blood and stool 12 weeks following the cessation of therapy to determine if the virologic response is sustained.

  If the patient has detectable HEV RNA in blood or stool after responding to the initial 12-week course of therapy, a 24-week course of ribavirin should be initiated. HEV RNA testing should be performed at the end of treatment and, if negative, again 12 weeks later. The approach to treatment failure is described below. (See 'Treatment failure' below.)

  In the multicenter study that evaluated 59 solid-organ transplant recipients described above, 6 of the 10 patients with a recurrence of HEV following initial ribavirin treatment were retreated for a longer duration, and four had an SVR [155].

- **Detectable HEV RNA after initial treatment** – If HEV is detectable in serum and/or stools at week 12, ribavirin therapy should be extended for an additional 12 weeks. Follow-up

testing of serum and stool should be performed at the end of treatment, and if the HEV RNA is negative, testing should be repeated 12 weeks after that. The management of patients with persistent viremia or relapse is described below. (See 'Treatment failure' below.)

One study suggested that a decrease in HEV RNA of more than 0.5 log copies/mL within the first week after initiating ribavirin therapy may be predictive of an SVR. However, additional studies are needed to determine if an early response should be used to guide the duration of therapy [161].

Treatment failure — Patients who fail to achieve an SVR should continue to be followed for signs of progression of liver disease. There is no established alternative antiviral therapy with evidence of efficacy in this setting.

Therapies that have been considered for the management of treatment failure include pegylated interferon-alfa and sofosbuvir. However, concerns regarding toxicity and efficacy prevent these agents from being used in routine care. As examples:

- Pegylated interferon-alpha – There are limited data to support the use of pegylated interferon-alpha for liver transplant patients with persistent infection who fail ribavirin [84,146]. In one series of three liver transplant recipients, viral clearance was observed after three months of treatment with pegylated interferon [162]. However, interferon has an immunostimulatory effect that can increase the risk of acute rejection in all organ transplant settings [84].

- Sofosbuvir – Sofosbuvir appears to control HEV in a cell culture model treatment [163]. However, in contrast with in vitro observations, an HEV/hepatitis C virus coinfected patient who received treatment with a 12-week course of sofosbuvir and daclatasvir failed to clear HEV RNA [164].

PREVENTION

- **General measures** – Travelers to regions where HEV is endemic (eg, Asia, Africa, the Middle East, and Central America) should follow the general precautions used for the prevention of travelers' diarrhea [165]. This includes avoidance of water of unknown purity, food from street vendors, raw or undercooked seafood, meat or pork products, and raw vegetables. Travelers to Europe should also avoid uncooked and undercooked pork/boar sausage or other wild animal meats (eg, rabbit) that have not been properly

heated. (See 'Epidemiology' above and 'Transmission' above and "Travel advice", section on 'Food and water'.)

- **Vaccines** – Recombinant vaccines have demonstrated efficacy against HEV [76,166-169]. In one randomized trial in China, 112,604 healthy adults were assigned to three doses of HEV recombinant vaccine or a hepatitis B vaccine as control. The protective efficacy of the vaccine against HEV over a 12-month period after vaccination was 96 percent [76,170]. Vaccine efficacy 4.5 years after the first vaccination was 87 percent [171]. This vaccine is licensed in China but is not available elsewhere. It is unclear whether this vaccine will protect against all common genotypes, though in vitro activity against nonhomologous genotypes (2 through 4) has been described [172].

- Immune globulin – The efficacy of pre- or postexposure immune globulin prophylaxis for the prevention of HEV has not been established [173,174].

SUMMARY AND RECOMMENDATIONS

- **Virology and transmission** – Hepatitis E virus (HEV) is a single-stranded RNA virus that causes a self-limited, acute viral hepatitis. HEV infection has a global distribution, but the prevalence rates are higher in resource-limited countries as compared with developed countries. There are four genotypes of HEV that can infect humans. Genotype prevalence varies across geographic regions. (See 'Virology' above and 'Epidemiology' above.)

  Transmission of HEV can occur through contaminated food and water, blood transfusions, and through mother-to-child transmission. Distinct genotypes differ in their route of transmission. HEV genotype 1 and 2 typically cause sporadic hepatitis and outbreaks of HEV in areas such as Asia and Africa, which are related to consumption of contaminated drinking water. By contrast, zoonotic transmission, which occurs from ingestion of undercooked meat or through close contact with animals, usually occurs in Europe, North America, and Far East Asia, and results from genotype 3 and, less frequently, genotype 4. (See 'Transmission' above and 'Genotypes' above.)

- **Clinical features of hepatitis E virus infection** – The clinical signs and symptoms in patients with typical HEV infection are similar to those seen with other forms of acute viral hepatitis. Jaundice is usually accompanied by malaise, anorexia, nausea, vomiting, abdominal pain, fever, and hepatomegaly. Other less common features include diarrhea, arthralgia, pruritus, and urticarial rash. (See 'Acute hepatitis E' above.)

Most patients who acquire HEV spontaneously clear the virus, although up to 60 percent of patients may have prolonged cholestasis. Acute hepatic failure is more likely in those who are pregnant and in those who are malnourished or have pre-existing liver disease. Chronic HEV has been described almost exclusively in immunocompromised patients (eg, solid organ transplant recipients). (See 'Complications' above and 'Special populations' above.)

- **Diagnosis** – The diagnosis of acute HEV is typically based upon the detection of IgM antibodies to HEV, but both false positives and negative are common with available assays. Thus, additional serologic testing or HEV RNA testing should be performed to confirm the diagnosis. (See 'General approach' above and 'Antibody testing' above.)

  In patients with suspected chronic HEV infection, detection of HEV RNA in serum is the mainstay of diagnosis. Chronic HEV infection is defined as detection of HEV RNA in serum or stool for longer than six months. (See 'General approach' above and 'HEV RNA assay' above.)

- **Management** – The management of acute HEV infection is usually supportive, as the disease appears to be mild and self-limited in immunocompetent patients. (See 'Acute hepatitis E' above.)

  The management of chronic infection involves a reduction of immunosuppressive therapy and/or the use of antiviral therapy (algorithm 1). We suggest a 12-week course of antiviral therapy for certain nonpregnant patients (eg, for solid organ transplant recipients, if immunosuppressive therapy cannot be reduced, if the patient has persistent HEV RNA despite a reduction in immunosuppressive therapy) (**Grade 2C**). Most experience has been with ribavirin monotherapy. The subsequent approach to treatment depends upon the virologic response. (See 'Chronic hepatitis E' above.)

- **Prevention** – To prevent HEV infection, travelers to endemic areas (ie, Asia, Africa, Middle East, and Central America) should engage in practices that may prevent infection, such as avoiding drinking water of unknown purity, uncooked shellfish, and uncooked fruits or vegetables. In addition, travelers to Europe should avoid uncooked and undercooked pork/boar sausage or other wild animal meats (eg, rabbit) that have not been properly heated. A vaccine against HEV has been developed but is not widely available. (See 'Prevention' above.)

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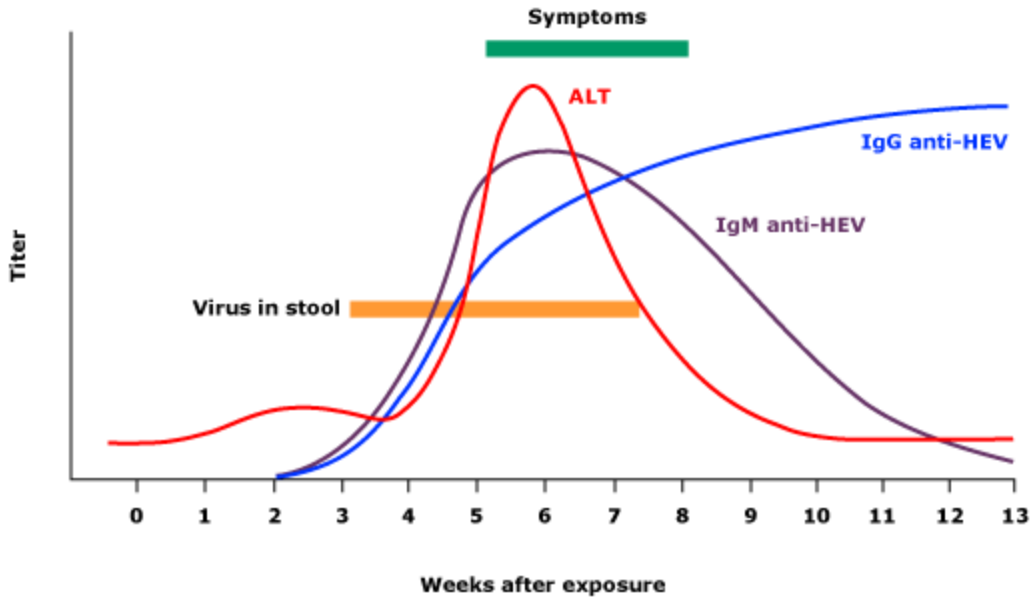
Topic 3677 Version 34.0

GRAPHICS

Hepatitis E virus (HEV) infection typical serologic course



ALT: alanine aminotransferase; IgG: immunoglobulin G.

Reproduced from: Centers for Disease Control and Prevention. www.cdc.gov/hepatitis/index.htm

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Graphic 81261 Version 2.0

Antiviral treatment for chronic hepatitis E virus in treatment-naïve nonpregna

HEV: hepatitis E virus.

* In solid organ transplant recipients, we typically reduce tacrolimus first if possible. In addition, for such pa administer antiviral therapy in conjunction with reducing immunosuppressive therapy.

¶ HEV RNA assay should be performed in both stool and serum.

Δ HEV RNA should not detected in both stool and serum.

◇ HEV RNA detected in either stool or serum.

Graphic 114389 Version 1.0

Contributor Disclosures

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