

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Epidemiologic Concerns and Advances in Knowledge on Hepatitis E



Rakesh Aggarwal, MD, DM
Professor
Department of Gastroenterology
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow, India

G&H What is the potential epidemiologic impact of hepatitis E in developed countries in light of ease of travel?

RA Hepatitis E, a disease caused by infection with the hepatitis E virus (HEV), is highly endemic in several developing countries in Asia and Africa where contamination of water supplies and lack of adequate sanitation are frequent. In these areas, a large proportion of cases of acute viral hepatitis are due to genotype 1 or 2 HEV infection. In contrast, the disease is quite infrequent in developed countries. Most of the cases of hepatitis E in these areas are related to travel to disease-endemic areas; however, some cases with locally acquired HEV (usually belonging to genotype 3 and occasionally genotype 4) infection do occur.

With the global trend of increasing travel and migration, an increased frequency of travel-associated hepatitis E may be expected. However, the number of cases of travel-associated HEV in developed countries has remained small. This is possibly because most short-term business travellers take precautions to avoid consumption of potentially contaminated food or water. Also, in several endemic areas (eg, China), the frequency of hepatitis E has fallen in recent years with economic development and consequent improvement in water quality and sanitation.

In fact, travel-associated hepatitis E is seen more often among immigrants residing in developed countries who visit their home countries where the disease is endemic. This is possibly because visits of such travellers to disease-endemic areas are longer in duration and their likelihood of exposure to contaminated food or drink may be higher.

G&H What have been the common sources of hepatitis E in nonendemic areas?

RA As mentioned, most cases of hepatitis E that are recognized in nonendemic countries (mainly North America, Europe, Australia, and parts of Asia such as Japan) are related to travel to disease-endemic areas.

The exact source of HEV infection acquired in nonendemic areas remains somewhat uncertain. In separate studies from several developed countries, HEV RNA has been detected in meat products made from pigs (often pig liver), and observational studies have shown an association between consumption of such meat products, usually without adequate cooking, and the occurrence of hepatitis E. In addition, nucleic acid sequences of HEV isolates from these meats and from human cases have been found to be closely related to each other. These pieces of evidence suggest that at least a proportion of cases with locally acquired HEV infection in developed countries are related to consumption of undercooked meat from HEV-infected animals.

G&H What symptoms should elicit clinical suspicion, particularly when hepatitis E occurs outside of endemic areas?

RA Hepatitis E does not have any specific symptoms to distinguish it from other forms of acute viral hepatitis. Thus, patients who are infected with HEV usually present with evidence of liver injury, such as jaundice. Other patients may present with nonspecific symptoms or deranged liver function test results.

G&H What are the differential diagnoses of hepatitis E?

RA Clinical differential diagnoses of hepatitis E in nonendemic areas include other infectious (hepatitis A or B and occasionally acute infection with hepatitis C virus, Epstein-Barr virus, or cytomegalovirus) and noninfectious causes of liver injury (autoimmune liver disease, alcohol, or drugs and toxins). The distinction between these conditions depends on clinical history (eg, alcohol or drug use and other autoimmune phenomena) or specific serologic markers, such as for other viral infections or autoantibodies.

The lack of clinical distinction between hepatitis E and other forms of liver disease is best exemplified by recent reports that a proportion of patients who had previously been thought to have had drug-induced liver injury turned out to have serologic evidence of recent HEV infection, and, thus, the diagnosis was reclassified as hepatitis E.

G&H Does hepatitis E have a different presentation or clinical course in nonendemic areas compared with endemic areas?

RA Patients infected with HEV in both endemic and nonendemic countries may present with symptoms that are typical of liver disease (ie, jaundice), nonspecific symptoms (such as general ill health, malaise, loss of appetite, nausea, vomiting, joint pains, fever, and abdominal pain), or with deranged liver function tests, most often in the form of elevated alanine transaminase levels. The enzyme elevation can vary widely in degree and may, in fact, be absent in some patients. The disease in nonendemic areas is generally self-limiting, as it is also in disease-endemic areas.

Some patients in either area may have acute liver injury superimposed on preexisting chronic liver disease. Such patients are more likely to have severe illness and may have a poorer outcome.

G&H Are different populations at risk for acute disease in relation to geographic locale?

RA In nonendemic, developed countries, the disease usually affects middle-aged or elderly individuals; this is in contrast to disease-endemic areas, where most of the cases occur among young adults. Also, patients in nonendemic areas often have other coexisting illnesses or history of alcohol consumption.

G&H Why might pregnant women who become infected with HEV be at particular risk for severe disease and poor prognosis?

RA During outbreaks in disease-endemic regions, hepatitis E occurs more often in pregnant women than

nonpregnant women or men. In addition, the disease more often progresses to acute hepatic failure in pregnant women compared with nonpregnant women.

Pregnant women with hepatitis E in disease-endemic areas have a high mortality rate (10–25%) and often have poor obstetric outcomes, such as premature labor or stillbirth. In contrast, the data from developed countries on hepatitis E during pregnancy are limited to a few case reports. In these cases, the disease was not particularly severe. However, this seemingly contradictory finding may be related to the occurrence of hepatitis E at an older age (after the years of fertility have passed) in the developed parts of the world.

The reason for more frequent and more severe disease among pregnant women with hepatitis E remains unclear. Various hypotheses have included a somewhat weaker immune response in pregnant women, an altered balance of T-helper type 1 and type 2 responses (Th1/Th2 bias), or changes in expression of some genes in the presence of hormonal changes associated with pregnancy (progesterone/estrogen excess).

G&H What explains the relatively high rate of the presence of anti-HEV antibodies in individuals from developed countries?

RA In a study of sera from the National Health and Nutrition Examination Survey III cohort, anti-HEV antibodies were detected in 21% of subjects, indicating a high rate of exposure to HEV infection. In contrast, clinical HEV infection is quite infrequent, with only a few isolated cases.

The high antibody positivity rate among persons living in nonendemic areas may reflect one or more of the following: (1) failure to recognize symptomatic HEV infections due to nonavailability of or failure to perform tests for HEV infection; (2) asymptomatic infection with HEV, which results in antibody development but does not result in development of disease; (3) false-positive test results due to cross-reactivity with another infective agent; or (4) nonspecificity of the assay(s) used. The contribution of each of these components to the HEV seropositivity rate remains unclear.

G&H Should US physicians give more attention than is customary to hepatitis E when considering differential diagnoses?

RA Although cases of acute hepatitis E have been reported in the United States, these have been quite infrequent. Because of this and because no specific treatment is needed in uncomplicated cases of acute hepatitis E, paying too much attention or spending a lot

of resources on the diagnosis of hepatitis E in individual cases of viral hepatitis may not be worthwhile. An added complication is the nonavailability of an approved antibody test for the diagnosis of acute HEV infection in the United States. Furthermore, in a nonendemic setting with low pretest probability of HEV infection, the positive predictive value of a positive immunoglobulin test result is likely to be low, and it would be essential to confirm such a result using nucleic acid testing.

However, testing for HEV infection may have a role in cases of complicated illnesses, such as acute liver failure, in which the etiology is unknown; cases in which there is an epidemiologic reason to suspect hepatitis E (eg, in a pig handler); or in selected cases with liver disease for epidemiologic surveillance.

Testing for HEV infection may have a greater role in immunosuppressed persons with unexplained liver injury because, if such an infection is detected, specific treatment may be possible.

G&H How is hepatitis E best managed?

RA Because the disease is usually self-limiting, no treatment may really be needed in most of the cases. Occasional case reports of treatment of acute severe hepatitis E with ribavirin in persons with or without underlying chronic liver disease have been published. However, the published data on the need and efficacy of such therapy are inconclusive.

In patients with chronic HEV infection (among immunosuppressed persons, often organ transplant recipients who are receiving immunosuppressive drugs), reduction of immunosuppression, if possible, leads to the disappearance of viremia in about one third of patients. In organ transplant recipients, treatment with oral ribavirin for 3 months, under close supervision for adverse events, is often successful in eradicating chronic HEV infection. In other immunosuppressed patients with chronic hepatitis E, interferon-alpha, ribavirin, or a combination of these drugs have shown good results in individual cases or short case series. In the absence of comparative studies, the relative efficacy of these treatment options remains unclear.

G&H What is the outlook for the introduction of a hepatitis E vaccine?

RA Two different subunit vaccines have been tested successfully in clinical trials. The first of these contains a 56-kDa recombinant viral capsid protein, which is expressed in insect cells as virus-like particles. The other vaccine contains a 26-kDa recombinant protein expressed in *Escherichia coli*, which also forms virus-like particles. In separate trials conducted in disease-endemic areas (Nepal and China, respectively), both vaccines were found to be safe and highly immunogenic, and they showed good efficacy in preventing clinical hepatitis E. However, data on the duration of protection following immunization are lacking. Also, no data are available on the vaccines' efficacy in high-risk groups, such as pregnant women, patients with chronic liver disease, or immunosuppressed groups. No head-to-head comparison of the 2 vaccines is available.

G&H What are the obstacles to the licensing and availability of such a vaccine?

RA One of these vaccines, produced by a Chinese company (Xiamen Innovax), has been approved for sale within China. Although this vaccine should be useful in travellers to disease-endemic areas, it is not yet available outside of China.

Besides the limitations already noted above, obstacles to the widespread use of hepatitis E vaccines include the high cost, lack of clarity on optimal strategies for deployment of hepatitis E vaccines in endemic areas (ie, selective vaccination of high-risk groups versus universal use), and lack of data on duration of protection provided by the available vaccines.

Suggested Reading

Aggarwal R, Jameel S. Hepatitis E. *Hepatology*. 2011;54:2218-2226.

Aggarwal R. Diagnosis of hepatitis E. *Nat Rev Gastroenterol Hepatol*. 2013;10:24-33.

Aggarwal R. Clinical presentation of hepatitis E. *Virus Res*. 2011;161:15-22.

Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis*. 2008;8:698-709.

Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. *N Engl J Med*. 2012;67:1237-1244.