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Host Immune Status and Response to Hepatitis E Virus Infection

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SUMMARY

Hepatitis E virus (HEV), identified over 30 years ago, remains a serious threat to life, health, and productivity in developing countries where access to clean water is limited. Recognition that HEV also circulates as a zoonotic and food-borne pathogen in developed countries is more recent. Even without treatment, most cases of HEV-related acute viral hepatitis (with or without jaundice) resolve within 1 to 2 months. However, HEV sometimes leads to acute liver failure, chronic infection, or extrahepatic symptoms. The mechanisms of pathogenesis appear to be substantially immune mediated. This review covers the epidemiology of HEV infection worldwide, the humoral and cellular immune responses to HEV, and the persistence and protection of antibodies produced in response to both natural infection and vaccines. We focus on the contributions of altered immune states (associated with pregnancy, human immunodeficiency virus [HIV], and immunosup-

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pressive agents used in cancer and transplant medicine) to the elevated risks of chronic infection (in immunosuppressed/immunocompromised patients) and acute liver failure and mortality (among pregnant women). We conclude by discussing outstanding questions about the immune response to HEV and interactions with hormones and comorbid conditions. These questions take on heightened importance now that a vaccine is available.

INTRODUCTION

Epidemics of jaundice with severe consequences in pregnant women have been recognized for many decades (1–3). However, the virus that causes hepatitis E was not isolated until the early 1980s, when a virologist in the former Soviet Union intentionally ingested virus excreted by ill patients in Central Asia and carried the incubating infection back to his laboratory in Moscow for identification by immune electron microscopy (4). Researchers in the next decade described the genome sequences of hepatitis E virus (HEV) strains from Burma, Pakistan, and Mexico (5–11), now identified as representing HEV genotypes 1 and 2, the strains implicated in large outbreaks in developing countries. Genotypes 3 and 4, with a zoonotic reservoir, have more recently been found to cause human infection in countries throughout the world (12) (Fig. 1). The discovery, sequencing, and phylogenetic analysis of *Hepeviridae* from an ever-expanding range of places and host species (13–18) (Fig. 2) have provided important insights into the epidemiology and geographic patterns of HEV infection and disease but have raised new questions as well.

Epidemiologic Patterns of Hepatitis E Virus Infection

Clinical presentation of hepatitis E. Hepatitis E is generally an acute, self-limiting illness, with full resolution of symptoms occurring within weeks (usually) to months (less commonly) of onset. Presenting symptoms are often nonspecific and resemble those seen in acute hepatitis A (21). Clinically, patients suffering from acute hepatitis E typically present with combinations of symptoms such as fever, anorexia, nausea and/or vomiting, lassitude/weakness, dark urine, light (clay/ash-colored) stool, and jaundice (yellowing of the skin and sclera). Pruritus and/or upper right quadrant pain may also be present (22–24).

Asymptomatic and subclinical HEV infections are common in both epidemic- and sporadic-transmission settings and have been documented in diverse geographic regions (25–35). HEV infections without overt symptoms have been detected in organ donors (36) and in contacts of case patients (33) in industrialized countries.

Several case reports have noted neurological symptoms during or shortly after acute infection, such as meningitis (37), meningoencephalitis (38), acute transverse myelitis (39), Guillain-Barré syndrome (40–46), and other peripheral neuropathies (47, 48). However, these presentations appear to be relatively infrequent.

While most cases of infection with HEV are uncomplicated and self-limiting, some individuals with hepatitis E progress to acute liver failure (ALF). ALF, also called fulminant hepatic failure if onset is within 6 to 8 weeks of first symptoms, is often fatal. A disproportionate number of these severe cases occur in pregnant women, though men and women with preexisting chronic liver disease or other medical problems appear to be at increased risk as well (49–52). Rarely, HEV infections may be prolonged or chronic, though this phenomenon has been observed primarily among patients with compromised immune systems (often transplant or cancer patients receiving immunosuppressive drugs). These more complicated cases are discussed in depth later in this review.

Human-associated genotypes 1 and 2. (i) Outbreaks and sporadic cases in developing countries. Genotype 1 (HEV-1) is the primary cause of epidemic and sporadic cases of hepatitis E in developing countries in Africa and Asia, where it is transmitted primarily through fecally contaminated water supplies. Frequent HEV-1 outbreaks affecting tens of thousands of people in Central, South, and East Asia have been documented since the 1950s; the largest known HEV epidemic to date, occurring from 1986 to 1988 in the Xinjiang region of China, sickened over 119,000 people and resulted in 707 documented fatalities, 414 of whom were pregnant women (3). Although molecular data from Central and South America are limited, locally acquired HEV-1 infections and small-scale outbreaks have been reported in Latin America as well (53, 54).

Genotype 2 (HEV-2) was first identified from cases in outbreaks in two rural towns in Morelos, Mexico, in 1986 and 1987 (9, 55, 56). Other HEV-2 strains have appeared in Africa, where they have also been implicated in outbreaks (57, 58).

(ii) Age-specific incidence and patterns of transmission of HEV-1 and HEV-2. Although, like hepatitis A virus (HAV), HEV-1 and HEV-2 are enteric viruses commonly spread through fecally contaminated water, the age-specific incidence of hepatitis E differs markedly from that of hepatitis A in most of the world. While HAV causes near-universal childhood infection in areas of endemicity, hepatitis E cases in most of the world peak in early to mid-adulthood, with both antibody prevalence and attack rates of clinical illness highest among adults and little overt disease in children (59, 60). Intrafamilial transmission of HEV appears relatively uncommon (61), though some evidence of household transmission has been reported (62–64). Slums and refugee camps are particularly vulnerable to outbreaks, as access to clean water and sanitary waste disposal facilities is often limited (30, 65–68). In addition, transient or migrant populations may repeatedly replenish the pool of susceptible individuals and/or import new infections.

Animal-associated genotypes 3 and 4. (i) Host range. Genotypes 3 and 4 (HEV-3 and HEV-4) have been found in other mammalian hosts, most notably wild and domestic swine, which serve as reservoirs for human infection (69, 70) (Fig. 2). HEV-3 is prevalent among swine worldwide (71–86) as well as in other mammals, including deer and mongooses (83, 87–89), though little is known about the sylvatic circulation of HEV.

The known animal reservoirs of HEV continue to multiply; novel members of the *Hepeviridae* have been detected in wild and farmed rabbits, wild rats, birds, bats, and trout (13, 15, 88–106). Of these, only rabbit HEV strains have been shown to share a close phylogenetic relationship and possess antigenic similarity to human- and swine-associated HEV strains. Newly identified rabbit HEV strains appear to share a common ancestor with HEV-3 based on whole-genome and open reading frame 2 (ORF2) sequence comparisons (88, 93). However, rabbit strains contain an ~90-nucleotide insertion in ORF1 and cluster separately from most human and swine HEV-3 strains (88, 95, 100).

Genotype 4 is indigenous to South and East Asia (18), where it has been detected in both wild and domesticated swine (84, 98, 107–110). Short HEV sequence fragments obtained from sheep and cattle fecal samples, clustering with genotype 4, have been

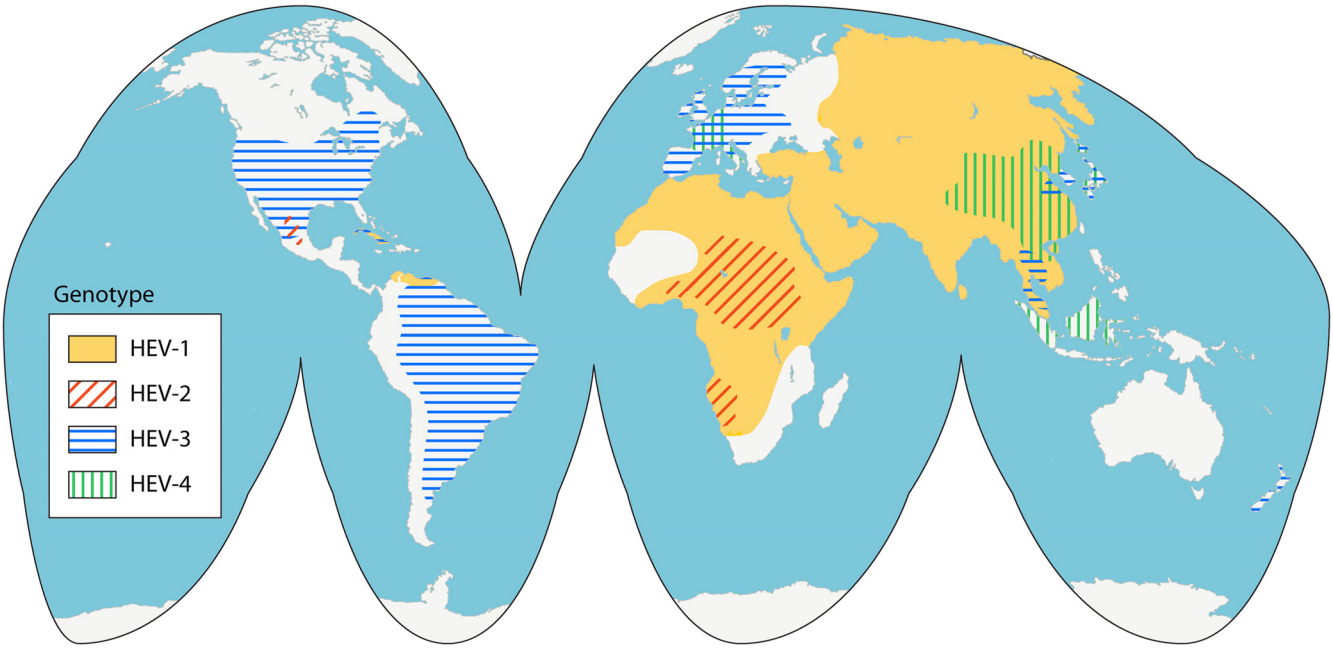

FIG 1 Global distribution of hepatitis E virus (HEV) genotypes 1 to 4 in humans. Genotypes 1 and 2 circulate in human populations and are transmitted primarily through fecally contaminated water supplies. Genotype 2 was first identified in Mexico but has subsequently been found across Africa. Genotypes 3 and 4, with reservoirs in swine and other species, are the dominant genotypes affecting human populations in industrialized countries. (Basemap of Earth adapted and simplified from "Blue Marble" imagery [NASA Earth Observatory, http://visibleearth.nasa.gov/view_cat.php?categoryID=1484], projected using G.Projector v.1.5 [NASA Goddard Institute for Space Studies, http://www.giss.nasa.gov/tools/gprojector/].)

reported in the Chinese-language literature (111, 112), but evidence for this expanded host range requires replication (70). Serologic evidence of HEV infection obtained from a variety of mammals around the world, including dogs, goats, camels, cows, and buffalo, has yet to be followed by successful isolation and sequencing of HEV strains from these species (14, 16, 17, 113, 114).

Studies in eastern China have recently documented a shift in the HEV strains causing human illness; over the past decade or so, HEV-4 strains of zoonotic origin have overtaken HEV-1 strains as the major cause of hepatitis E in this region (115–117). More recently, both imported and locally acquired HEV-4 strains have been detected in Europe and the Americas (118–124).

In the relatively wealthy nations of Europe, North America, and East Asia, human infections with HEV-3 and HEV-4 are often asymptomatic (33, 125), though more virulent strains appear to exist (126, 127). In these settings, autochthonous HEV-3 appears to pose the greatest threat to people with chronic medical conditions that require immunosuppressive therapy or that directly compromise the immune system and/or liver (128–130).

(ii) Routes of exposure to animal-associated HEV. Identified human exposures to HEV-3 and HEV-4 have occurred via consumption of undercooked pork or game meats, especially liver sausages or other organ meats, which are frequently contaminated with HEV (70, 131–138). HEV-3 has also been detected in bivalves in sewage-contaminated waters (139–141), and shellfish consumption has been identified as a possible risk factor for infection (142, 143).

However, cases without obvious food-linked exposures have been reported frequently, suggesting that other environmental exposures may play a role (144). Occupational exposures to farm animals, especially swine, have been associated with HEV infection in some studies in Africa, Europe, and the United States (73, 133, 145, 146), but a recent study in Thailand found no difference between the seroprevalence among swine workers and that among others in the local population (147). Inadequately treated manure from swine farms represents another potential source of environmental contamination (148–150).

A cross-sectional study of the U.S. population found that the anti-HEV seroprevalence was elevated among those with pets at home (35). In 2003, the pet cat of a Japanese man who developed hepatitis E was found to have anti-HEV antibodies (151); subsequent to this case, a substantial proportion of sampled Japanese pet cats were found to be seropositive (152). These findings suggest that some pet-related exposures—perhaps contaminated animal food, indirect contact with wild or domesticated animal reservoirs, or outdoor activity—could mediate some of the risk of human infection with zoonotic strains.

Regional variations in occurrence and severity of hepatitis E in pregnancy. Although severe liver disease among pregnant women, with high mortality, is the hallmark of epidemics of HEV-1 in Asia and Africa, there have been reports of severe hepatitis among pregnant women infected with HEV-3 in countries where locally acquired genotype 1 infections do not occur. Clinical hepatitis E attributed to HEV-3 was recently reported in a pregnant woman in France (153). HEV-3-linked acute liver failure also occurred in a nonpregnant Spanish woman whose medical history was devoid of known risk factors for severe hepatitis E (154). The woman reported long-term use of hormonal contraceptives (norgestrel/ethinyl estradiol) and was found to have hepatic adenomas upon examination, which the authors speculated may reflect elevated estrogen levels, mimicking pregnancy, prior to the onset of hepatitis E (154).

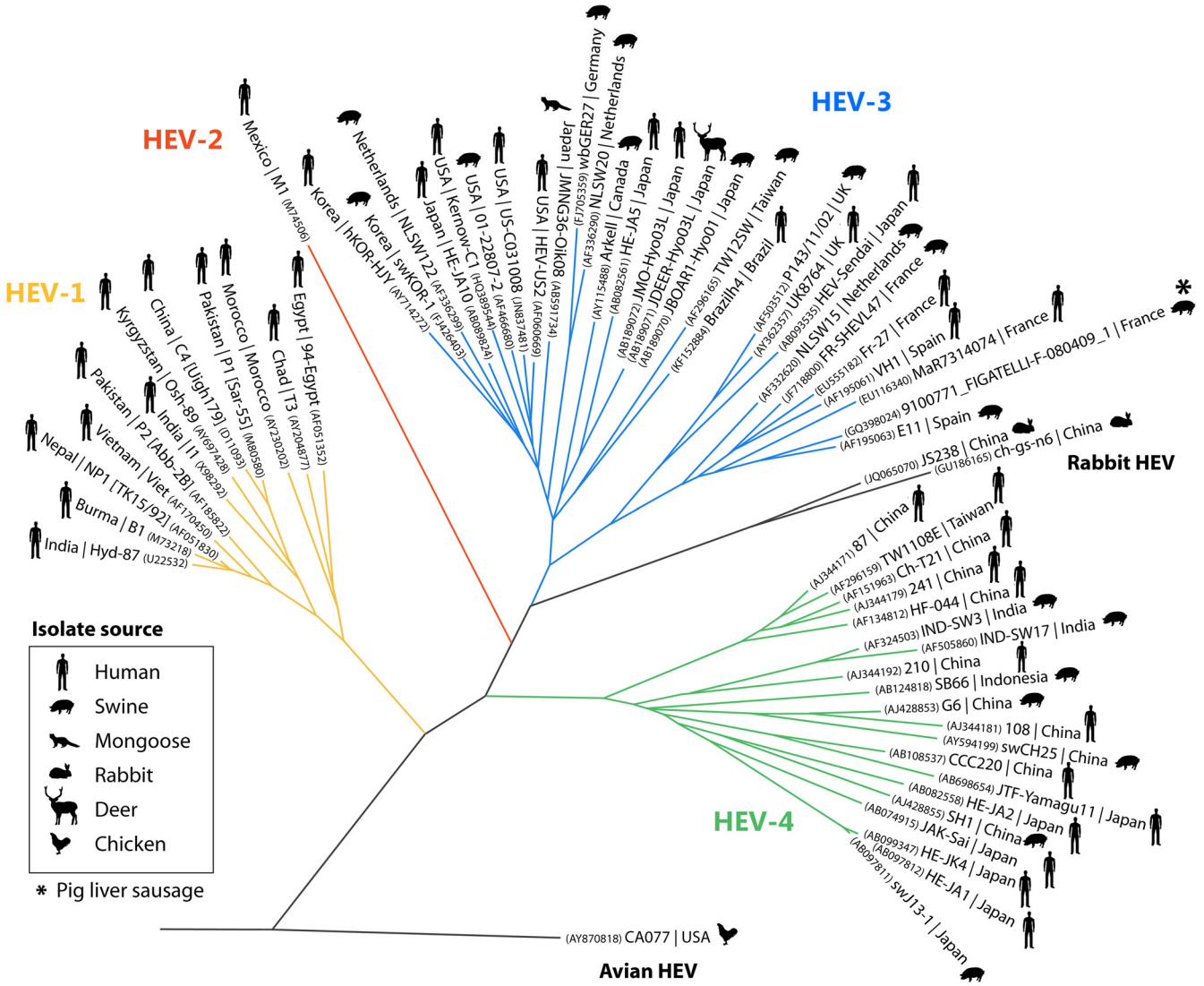

FIG 2 Phylogenetic tree of global hepatitis E virus (HEV) isolates, based on a portion of the nucleotide sequence encoding the capsid protein. Genotypes 1 and 2 (HEV-1 and HEV-2) circulate among humans, primarily in Africa and Asia, while genotypes 3 and 4 (HEV-3 and HEV-4) have animal reservoirs, and zoonotic, often food-borne, transmission has often been implicated where a source of infection can be identified. Recently discovered rabbit strains appear to form a closely related clade. Sequences from open reading frame 2 (ORF2), homologous to the 350-bp segment of the Burma B1 strain used by Lu et al. (12), were identified from within the GenBank database (accession numbers are in parentheses). Alignments were performed using the Basic Local Alignment Search Tool (BLAST) (19), and the tree was modified with MEGA5.2 (20).

Whether these reports suggest that pregnancy or pregnancy-like states may represent a risk factor for more severe clinical disease even in high-income countries where HEV-3 and HEV-4 circulate, or whether the paucity of such reports in the face of 10 to 20% population seroprevalence supports the increased virulence of genotype 1 viruses for pregnant women, is not certain. Severe infections during pregnancy in developing countries may be primarily a result of greater virulence of the human-adapted HEV-1 and HEV-2 genotypes, increased susceptibility of pregnant women in developing countries where these genotypes are endemic, or the epidemiologic conditions of exposure to these viruses (155, 156). Also, in many developed-country settings, awareness of hepatitis E as a plausible diagnosis may be low, leading to missed cases and underdiagnosis of this infection.

Also unexplained is the contrast between the apparently infrequent and unremarkable occurrence of hepatitis E in women in Egypt (157) and the disproportionately severe hepatitis E observed in pregnant women in sub-Saharan Africa and in South and Southeast Asia, despite the fact that HEV-1 predominates in all of these regions (158). The different patterns of illness seen among pregnant women, paralleling regional differences in age-specific attack rates and seroprevalence (34, 159, 160), remain perplexing (Table 1). The study of this range of possible outcomes of HEV infection is challenging, given that most HEV research occurs either in acute-outbreak settings or in clinical contexts where only severely ill patients are typically referred. The prospective identification of HEV seroconverters and the study of subsequent disease outcomes require the longitudinal surveillance and follow-up of large pregnancy cohorts, an expensive prospect for a

TABLE 1 Seroprevalence of IgG antibodies to HEV among asymptomatic pregnant women recruited from community-based cohorts or antenatal clinics[b]

Study location; yr (reference)	Anti-HEV IgG assay used (reference)	Seroprevalence		Risk factor(s) for seropositivity
		No. positive/ total	% Positive	
Egypt, Nile Delta; 1997–2003 (157)	NIH in-house EIA	2046/2428	84.3	Older age, eating unwashed produce, >4 siblings, no prior miscarriages, more cat contact, village of residence
Egypt, Alexandria; 1995 (361)	Abbott Labs ELISA	8/18	44.4	
India, New Delhi; 2006–2007 (26)	Genelabs ELISA	101/300	33.7	Less education, lower socioeconomic status
Indonesia, Bali; 2003 (362)	Recombinant genotype 4 capsid protein-based ELISA (363)	151/819	18.4	District of residence, Hindu (higher risk) vs Muslim (lower risk)
Gabon; 2005 (364)	Genelabs ELISA	119/840	14.1	Urban (higher risk) vs rural (lower risk)
Turkey, Afyon; 2000–2002 (365)	Virotech GmbH microELISA	31/245	12.6	Older age
Tunisia, Sousse; 2006 (366)	Globe Diagnostics EIA	49/404	12.1	Older age, higher parity, larger household size
Burkina Faso, Ouagadougou[a]; 2010–2012 (367)	DIA.PRO or Wantai HEV IgG ELISA	22/189	11.6	
China, Yunnan; dates not stated (368)	ELISA, manufacturer not stated	30/293	10.2	
Turkey, Aydin; dates not stated (369)	Globe Diagnostics ELISA	27/386	7.0	Less education

[a] The seroprevalence of antibodies to HAV was also very low (15 to 30%, increasing with age) in this population.
[b] IgG, immunoglobulin G; HAV, hepatitis A virus; HEV, hepatitis E virus; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; NIH, U.S. National Institutes of Health.

pathogen that has yet to achieve standing even as a "neglected" disease.

Hypotheses Regarding Regional Differences in the Nature and Impact of HEV

Ecologic influences on HEV epidemiology across regions. Limited exposures, typically low doses of virus, and better overall health may protect most otherwise-healthy people in industrialized nations from clinically apparent hepatitis caused by HEV-3 (35). In developing countries in Asia and Africa, where HEV-1 predominates, human infections with HEV-3 and HEV-4 are rarely reported, and no large outbreaks have been attributed to these strains. However, HEV-3 and HEV-4 have been confirmed sporadically in local populations, in travelers to these regions (119, 144), and in resident animal populations and locally obtained meat (107, 108, 114, 161, 162).

Broad environmental, dietary, and overall health differences across settings and limited information on the distribution of viral subgenotypes in many parts of the world make it difficult to discern whether HEV-1 and HEV-2 are inherently more virulent in humans than HEV-3 and HEV-4 or whether the occurrence of epidemics and the incidence of illness and death reflect primarily exposure- and host-related risk factors. Similarly, it remains unclear to what extent subtle subgenotypic differences in HEV-1 strains may contribute to the variability in patterns of illness in areas of endemicity and what can instead be explained by host vulnerabilities (e.g., genotype, nutritional status, coinfections, and immunocompetence) or by environmental determinants of timing and dose of exposures (e.g., seasonal rainfall patterns, sanitation systems, and animal exposures).

Genotypic and subgenotypic variation and virulence. Despite the challenge of confounding by ecologic factors, there is some evidence to suggest that differences in circulating virus strains may influence patterns and severity of illness. Studies of circulating subgenotypes and strains within geographic regions have identified several variants with increased or decreased virulence.

Renou et al. have suggested that HEV-3 (subtype 3c), which is common in Europe, may be less likely to produce symptomatic illness than genotype 1 (33); however, the better overall health status and typically nonwaterborne exposures of individuals in industrialized countries may at least partly explain the relative lack of symptomatic cases in these settings. Cordoba and colleagues identified an attenuated swine HEV-3 strain from the United States with mutations in the sequences encoding the capsid protein that appeared to be associated with reduced viral replication (163).

On the other hand, successful *in vitro* cultivation of HEV-3 and HEV-4 strains with nucleotide substitutions associated with more severe illness was reported by Inoue and colleagues in Japan in 2009 (127). In a comparison of isolates from patients with milder and more severe hepatitis E, several substitutions in the RNA helicase and capsid protein-encoding domains, in particular, were found to be associated with severe hepatitis E leading to liver failure (127). Mutations identified in HEV-3 isolates collected from several severe hepatitis E cases across Japan, including another substitution affecting the helicase domain, also suggest that these mutations may affect the pathogenetic potential of HEV strains (126). A series of cases in France, with patients who presented with more severe disease than typical HEV-3 patients from the same area, were attributed to HEV-4 strains closely related to a Belgian swine isolate; however, specific mutations related to virulence in these strains were not identified (123).

A recent report by Shukla and colleagues described the integration of a nucleotide sequence from human host S17 rRNA into the HEV-3 genome in a patient with chronic HEV infection who had both neurologic and hepatic symptoms (164). In contrast to other tested HEV strains, this recombinant virus (the Kernow-C1 strain) replicated in cell culture and also may have grown in extrahepatic sites in the patient (164, 165). Similarly, Nguyen et al. isolated an HEV-3 strain from a chronically infected U.S. liver transplant patient that contained an insertion derived from the human ribosomal S19 sequence, and this strain, too, predominated in cell culture compared with isolates lacking the insertion

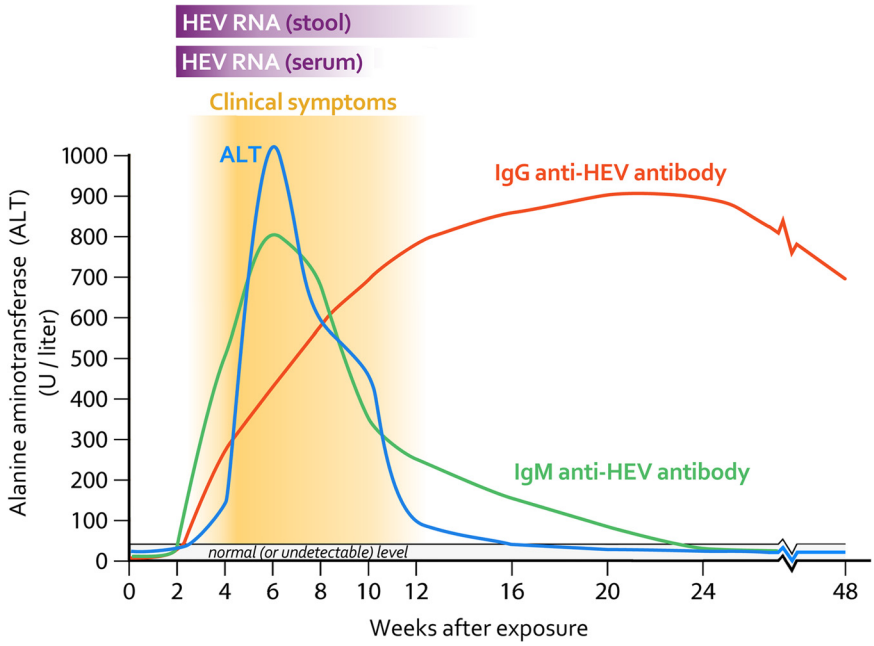

FIG 3 Course of acute hepatitis E virus (HEV) infection. Acute hepatitis E is characterized by symptoms such as fever, anorexia, vomiting, and jaundice, with onset several weeks after initial exposure. The onset of clinical symptoms coincides with a sharp rise in serum alanine transaminase (ALT) levels. Symptoms may persist for a few weeks to a month or more. ALT levels return to normal during convalescence. HEV RNA may be detected in both serum and stool early in the course of infection, but serum viremia may be difficult to detect by the time cases come to clinical attention. Anti-HEV IgM titers increase rapidly and then wane over the weeks following infection, while anti-HEV IgG antibody titers continue to rise more gradually during the convalescent period, and detectable anti-HEV IgG may persist for months to years. (Adapted from Fig. 2 of reference 170, with permission of the publisher [copyright 2012 Massachusetts Medical Society].)

(166). These observations suggest another source of genomic variation that may be important in the pathogenesis and epidemiology of HEV.

TYPICAL IMMUNE RESPONSES TO HEPATITIS E VIRUS

Natural History of Acute HEV Infections

Course of infection and immune response in acute, uncomplicated hepatitis E. Studies of human volunteers (4, 167) and experimentally infected nonhuman primates (168) suggest that the incubation period of HEV usually lasts roughly 4 to 6 weeks from infection to onset of symptoms, though incubation periods from as short as 9 days (in a pregnant macaque experimentally inoculated with an HEV-1 strain from India) (168) to upwards of 2 months (169) have been reported. Figure 3 summarizes the time sequence of clinical symptoms and biomarkers of infection and immune response in typical clinical hepatitis E in humans (170).

Viremia in acute hepatitis E generally persists for less than a month following symptom onset in otherwise-healthy individuals, and HEV RNA may be undetectable in serum or stool by the time patients come to clinical attention. Chandra et al. (171) followed 60 patients with acute hepatitis E who presented at a tertiary care facility in Rajasthan, India. They detected HEV RNA in the stools of 42/60 hepatitis E patients in the first week following onset of illness and in 12/60 up to 28 days later but in none beyond 28 days (171). In the sera of these patients, HEV RNA was detectable in 51/60 in the first week, dropping to 4/60 at 5 to 6 weeks after symptom onset and to none after 6 weeks. Only 48/60 patients had detectable anti-HEV immunoglobulin (Ig) M even in the first week following symptom onset, and the proportion of IgM-positive cases declined monotonically over the next 6 weeks; among the initially IgM-negative patients, 13 nonetheless had detectable HEV RNA in feces or serum (171), suggesting that low antibody titers may not be informative about viral load. Aggarwal et al. (172) detected HEV RNA in stool and serum samples for up to 1 month following symptom onset in 20 patients who presented with acute hepatitis E during an outbreak in Lucknow, India (172). In one patient only, HEV RNA was detected in serum at 45 days after symptom onset, after alanine aminotransferase (ALT) levels had returned to normal, but no RNA was detected in the patient's stool (172). A study of sporadic viral hepatitis infections in Egypt, mostly among children, found HEV RNA in the stools of only two of 56 patients and in no serum samples from patients testing positive for anti-HEV IgM, with a median ALT level of 94 U/liter and a median aspartate aminotransferase (AST) level of 89 U/liter in the total patient sample (173).

Evidence for Immunopathogenesis in Hepatitis E

Both human and animal studies have suggested that the immune response, rather than viral damage to hepatocytes, may drive clinical manifestations of hepatitis E, including both self-limiting acute viral hepatitis (AVH) and also acute liver failure (ALF). One indication that pathogenesis may be mediated in large part by the immune system rather than by the virus itself is that the onset of icteric symptoms typically coincides with a rise in antibodies and a decline in viral load (174) (Fig. 3).

Elevated antibody titers, proinflammatory cytokines, and limited viral RNA in HEV-associated liver failure versus acute hepatitis E. In a study of Indian patients with HEV-induced acute hepatitis or acute liver failure and healthy controls, Saravanabalaji et al. (175) found higher anti-HEV IgM and IgG titers, as well as

higher gamma interferon (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin-2 (IL-2), and IL-10 levels, in the patients with liver failure than in patients with self-limiting acute hepatitis. HEV RNA, on the other hand, was detected in the self-limited acute hepatitis cases but not in the patients with liver failure. As the majority of patients with ALF developed encephalopathy and were tested within 2 weeks of symptom onset and AVH patients were also sampled an average of ~14 days after symptom onset, it is unlikely that the time that elapsed from disease onset to sampling could explain the absence of HEV RNA among liver failure patients. The authors interpreted these findings as suggesting that stimulation of both Th1- and Th2-type immune responses may play a role in liver failure among patients with symptomatic hepatitis E (175). However, apparently contradictory results from other studies of HEV-induced liver failure, such as the finding of increased viral load in pregnant women with ALF versus those with milder hepatitis E, suggest that the picture may be more complicated (176).

Polymorphisms in cytokine-related genes and proinflammatory responses in severe hepatitis E. Mishra and Arankalle (177) examined single nucleotide polymorphisms (SNPs) and haplotypes related to genes for TNF-α and IFN-γ in cases and controls from rural Maharashtra State, India. Most cases were detected during HEV genotype 1 outbreaks from 2005 to 2010, but some sporadic hepatitis E cases were included as well ($n = 25$ cases of acute liver failure, 353 AVH cases, 136 subclinical infections, and 374 controls negative for both HEV antibodies and hepatitis symptoms) (177). In this study, the TNF-α −308AA genotype (versus GA or GG), which is associated with increased TNF-α production, was more common among all infected individuals (including those without symptoms) than among uninfected controls. The A allele was enriched in patients with fatal acute liver failure compared with surviving patients. TNF-α −1031CC and IFN-γ +874TT were associated with increased odds of severe hepatitis E (177). These authors also noted overrepresentation of the T (versus A) allele at IFN-γ +874, which is linked to higher IFN-γ production, among symptomatic cases. Patients with acute liver failure had elevated IFN-γ concentrations relative to those of patients with milder acute hepatitis, and a continued increase in IFN-γ was seen in both groups as they recovered, while patients who died had much lower IFN-γ concentrations (177).

Cellular Immune Response

NK cell and T-cell activity. Natural killer (NK) cells may play an important role in mediating the immune response to HEV infection. Srivastava et al. (178) examined the cytokine and T-cell profiles of 31 acute hepatitis E patients and 18 healthy controls in Lucknow, India, with both groups consisting mostly of males. They found that the HEV patients had significantly lower proportions of $CD3^+/CD69^+/IFN\text{-}\gamma^+$ and $CD3^+/CD69^+/TNF\text{-}\alpha^+$ staining peripheral blood mononuclear cells (PBMCs) following stimulation and increased proportions of $CD4^+$ cells, but similar levels of $CD3^+/CD69^+/IL\text{-}4^+$ cells and $CD8^+$ cells, compared to healthy controls (178). Cells from patients and controls exposed to HEV ORF 2 proteins did not differ in production of IFN-γ, TNF-α, or IL-4; however, IFN-γ was elevated in the supernatants of cultures from ORF2-stimulated PBMCs from patients compared with controls, and upregulation of IFN-γ mRNA transcription was detected only among hepatitis E patients (178). The authors speculated that increases in $CD4^+$ cells among patients may reflect increases in the natural killer cell population, which may in turn produce the elevated levels of IFN-γ seen in patients and contribute to hepatocyte death in hepatitis E (178).

Subsequently, the same research group measured NK ($CD3^-/CD56^+$) and NKT ($CD3^+/CD56^+$) cell populations in PBMCs from a larger sample of acute hepatitis E patients ($n = 41$) and healthy controls ($n = 61$), mostly men (179). In this population, they also evaluated lysis of target cells by NK cells using a lactate dehydrogenase release assay. Among hepatitis E patients, NK and NKT cells were reduced as a fraction of PBMCs compared with controls; however, the proportion of the NK cells that were activated was markedly higher among patients. Despite this, there was no apparent difference in cytotoxicity in target cells (179). The authors suggest that depletion of total NK and NKT cells among PBMCs may be due to the preferential accumulation and/or apoptosis of NK and NKT cells in the livers of infected individuals, though direct measurement of this phenomenon in living patients would be ethically challenging. They also suggest that a reduced NK cell prevalence among pregnant women may help explain their greater susceptibility to severe hepatitis E because it would reduce their ability to clear the virus from the liver (179). Consistent with this hypothesis, Majumdar et al. (180) found reduced lymphocyte reactivity to HEV ORF2 proteins in PBMCs taken from patients with HEV-induced acute liver failure compared with samples from less severe acute hepatitis E cases (180).

Circumventing ethical issues in studying living patients, Prabhu et al. (181) examined lymphocytes from liver biopsy specimens of recently deceased patients who had suffered from HEV-related acute liver failure ($n = 37$) and compared these with archived normal biopsy specimens from portal hypertension patients ($n = 10$) and patients with acute liver failure from other hepatotropic viruses ($n = 9$). Higher $CD56^+$ cell counts were present in HEV patients than in patients who were infected with HAV, HBV, or HCV (181).

Unlike Srivastava et al., this group found increased $CD8^+$ cell proportions among cases of liver failure caused both by HEV and by other viruses, compared with those in healthy controls (181). This discrepancy may be explained by the fact that these cell populations were taken directly from lymphocytic infiltrates in the liver, rather than from the blood, as suggested by Srivastava et al. (179), though Prabhu et al. intimate that the greater presence of $CD8^+$ cells in lymphocytic infiltrates from HEV patients may indicate that these cells may be more prominent in the pathogenesis of HEV, as they are in other hepatitides, than are NK cells (181). However, convergent findings pointing to an important role for NK cells suggest that their importance should not be minimized.

Alterations in function of NF-κB. The activity of nuclear factor kappa B (NF-κB), which has broad transcription regulation functions during response to infection, appears to be altered by HEV. Prusty et al. (182) examined the DNA binding activities of the p50 and p65 subunits of NF-κB in pregnant women with HEV-associated AVH ($n = 5$) or ALF ($n = 5$) and healthy pregnant controls ($n = 10$). Among women with (mostly fatal) ALF, compared with both milder acute hepatitis cases and healthy controls, NF-κB DNA binding in hepatocytes and PBMCs was high, but the p65 subunit was virtually absent. To further the mechanistic understanding of this anomaly, Surjit and colleagues (183) worked with human hepatoma cells transfected with HEV ORF2 and ORF3 proteins. They found that cells producing ORF2, but not ORF3, interrupted the signaling cascades that induce NF-κB activity. By

interacting with the F-box protein, the ORF2 protein disrupted ubiquitination of cellular IκBα, increasing its persistence and selectively inhibiting the IκBα degradation-induced migration of p65 to the nucleus (183). Anti-p65 antibody, applied to nuclear and cytoplasmic fractions of ORF2-transfected cells, revealed accumulation of p65 in the cytoplasm, whereas mock-transfected cells had an abundance of p65 in the nucleus. The authors observed downstream effects, including decreased binding of NF-κB to the heavy chain of major histocompatibility complex (MHC) I in ORF2-transfected cells and a decrease in transcription of IL-6 and IL-8 (183). Although these results suggest mechanisms by which HEV may alter and evade the body's immune response and perhaps set the stage for clinical illness, Surjit et al. cautioned that studies in living organisms infected with circulating viruses are necessary to replicate and refine their *in vitro* findings (183).

Scope and Duration of Protective Immunity to HEV following Infection

Until recently, there were few laboratory-confirmed reports of reinfection with HEV among immunocompetent persons, which suggested the possibility of broad, enduring protection following resolution of natural infection (184–186). However, follow-up studies of both naturally infected and vaccinated individuals, as well as of experimentally inoculated animals, have demonstrated loss of antibodies and waning protection against reinfection.

Serologic evidence and animal studies suggest that infection with one strain of HEV confers cross-protection to other strains, even across genotypes 1 to 4, owing to the existence of a common serotype (7, 187–192). However, serologic studies in animals have suggested that protective immunity may not always be complete. Likewise, follow-up studies in human populations have yielded disparate findings regarding the persistence of IgG antibodies and of protection from subsequent illness over time, with uncertain implications for lifelong immunity. The extent to which the timing, dose, and nature of exposures influence the development and maintenance of protective immunity across populations remains to be determined.

Marked variability in the sensitivity and specificity of HEV assays complicates the interpretation and comparison of serologic studies (193–199), and this fact should be borne in mind when considering the serologic data presented in this section and elsewhere. Studies with early anti-HEV IgM and IgG commercial assays often failed to detect seropositive individuals, undercounting the seroprevalence (200). Case reports and clinical studies from Europe have also raised suspicions about serologic cross-reactivity in the presence of other viral infections, such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV) (201, 202). Several recent serologic assays and other diagnostic methods have been found to have improved performance in a wide range of settings (194, 198, 203–207).

Antibody persistence and cross-protection in animals. Early experimental studies demonstrated broad cross-reactivity and neutralization activity of sera containing anti-HEV antibodies to genotypically diverse HEV strains (196). Ten cynomolgus macaques experimentally infected with any of four Indian HEV strains isolated from human cases showed no evidence of viral replication upon challenge with different HEV strains 1.5 to 2.75 years later (188). Meng et al. (190) found that convalescent-phase sera from macaques inoculated with strains from Burma, Mexico, and Pakistan, as well as sera from naturally infected human cases in India, China, Nepal, and Somalia, effectively neutralized infectious challenges with the Burmese, Mexican, Pakistani, and Moroccan HEV strains. However, sera from rabbits and guinea pigs experimentally inoculated with recombinant HEV ORF2 proteins did not elicit similarly robust responses (190). Purcell et al. (208) examined initial responses to different HEV strains among a variety of nonhuman primates, as well as in swine. They found that swine were more susceptible to infection with a (porcine) genotype 3 HEV strain than rhesus monkeys. Swine were not susceptible to genotype 1 HEV; however, several primates could be infected with HEV-1 viral strains. In response to inoculation with genotype 1 HEV, cynomolgus and rhesus macaques showed greater elevations in alanine aminotransferase (ALT) levels than chimpanzees (208).

Other animal studies have largely (but not universally) reaffirmed that natural infection confers cross-protection but have raised questions about the completeness and duration of immunity. Huang et al. (209) inoculated 11 macaques with fecal suspensions containing HEV genotypes 1 (from humans) and 4 (from humans and swine) and demonstrated protection against acute hepatitis (i.e., elevation of liver enzymes) upon later cross-challenge. However, about half of these monkeys (6/11 in total) showed evidence of fecal shedding, transient IgM seropositivity, or increased IgG production following repeat inoculation (209). Similarly, follow-up of the macaques experimentally infected by Arankalle et al. (188) documented a decline in anti-HEV IgG titers over the course of 5 to 7 years at a rate that "was not a function of the number of exposures to HEV, and probably represented biological variations among individual monkeys" (191). HEV RNA was detected in the feces of one of nine previously infected monkeys cross-challenged 5 years after primary inoculation, though ALT levels in all nine monkeys remained normal. An anti-HEV IgG booster effect was seen following reinoculation in some, but not all, animals (191).

Recently, Sanford et al. demonstrated that specific-pathogen-free pigs challenged with either genotype 3 or 4 HEV strains from humans at 12 weeks after inoculation with a swine-origin genotype 3 HEV strain showed no replication of the challenge viruses (no detectable HEV RNA in serum or feces) and no booster effect on IgG titers (192). Sows infected naturally in a farm environment in Spain, however, showed detectable anti-HEV IgG at the prefarrowing stage, but 5 of these sows later showed HEV viremia at the breeding stage (210). An additional pig from one of these farms showed evidence of infection with two genotypically distinct strains at 13 and 25 weeks (210), a phenomenon that these authors had observed in an earlier study as well (72), suggesting that some swine in settings of endemicity may be susceptible to reinfection or superinfections by multiple genotypes of HEV.

Rabbits are susceptible to infection with at least some strains of HEV-3 and HEV-4 but appear to be resistant to infection with HEV-1 (211, 212). Conversely, rabbit HEV strains can infect pigs and macaques (213, 214), and they can replicate in two human cancer cell lines (96), suggesting the ability to adapt to other mammalian hosts. A study in China found no evidence of natural cross-species infection with rabbit HEV (93). However, a strain isolated from a human in France shared a 93-nucleotide insertion found in French rabbit strains, and it was more closely related to the rabbit strains (>80% identity) than to HEV genotypes 1 to 4 (95). Rabbit HEV shares the same serotype as HEV-1 to -4, and infection in rabbits confers some cross-protection; rabbits experimentally in-

fected with either a rabbit strain of HEV or a human HEV-4 strain had a shorter duration of fecal shedding upon challenge with the other strain than did HEV-naive rabbits (99).

Antibody persistence in humans. Longitudinal follow-up studies of both epidemic and sporadic cases in humans have provided inconsistent seroepidemiologic results. Some, but not all, of the inconsistency may be explained by variations in the performance characteristics of the serologic tests used in these studies.

Early evidence for the persistence of anti-HEV IgG and its ability to prevent overt disease in humans was provided by Bryan et al. (184). They developed a new enzyme-linked immunoassay (ELISA) by cloning the ORF2 segment of an HEV strain (SAR-55) implicated in a school outbreak in Sargodha, Pakistan, in 1987. Twenty months after the outbreak, they still detected anti-HEV IgG in all 33 patients who were initially hospitalized with acute hepatitis E. Furthermore, all 30 contacts of these patients who had anti-HEV IgG at the time of the outbreak remained free of acute hepatitis, while 8/24 contacts who were seronegative prior to the outbreak became ill and were hospitalized as the outbreak progressed (184).

Chadha et al. (185) followed children and adults with sporadic and outbreak-associated hepatitis E contracted in 1988 and 1989 in Maharashtra State, India. Although they documented waning IgG titers over a period of 5 years, all cases remained seropositive. Antibody titer trajectories did not differ by age. None of the cases had a recurrence of hepatitis symptoms from 6 months through the end of the follow-up period (185). Myint et al. found a similar pattern in 62 Nepali adults, with a decline in total Ig initially and over the course of 14 months following acute illness but persistently detectable antibodies in all patients (215).

In Barcelona, Spain, three confirmed (IgM- and RNA-positive) hepatitis E patients, including two autochthonous cases of HEV-3, developed and retained anti-HEV IgG for 9 months following hospital admission (216). In contrast, in a small cohort from Singapore, only 6 of 10 hepatitis E patients with anti-HEV IgM (but without detectable serum viremia) during the acute phase of illness developed detectable anti-HEV IgG, five of them within the first week (217). All six who did develop anti-HEV IgG antibodies, however, remained seropositive for 18 months. Coinfection with other hepatotropic viruses (acute HAV and chronic HBV infection) was common in this cohort (217).

Seroreversion and susceptibility to clinical disease following natural infection. In contrast to the observations of Bryan et al. (184), but as seen in the experimental animal studies, seroreversion has been documented repeatedly in human follow-up studies, though without clear geographic or demographic patterns. A follow-up study of sporadic HEV hepatitis cases among rural Egyptian children found that of six children (ages 3 to 8) with detectable IgM and IgG anti-HEV antibodies upon admission to Benha Fever Hospital, four were seronegative for IgG 9 months later by a four-antigen ELISA (218). This led Goldsmith et al. to suggest that rapid loss of IgG antibodies might be a typical feature of HEV infection (218).

In response to that study in Egypt, Khuroo et al. (219) noted that fewer than half (21/45) of sampled adult patients affected by the 1978 Kashmir outbreak remained seropositive 14 years later. Although serosampling was not done in the interim, the authors pointed to the lack of subsequent clinical hepatitis among the original 1978 epidemic cases, as well as the low prevalence of anti-HEV IgG among controls, as evidence that seropositivity had likely persisted in those 21 individuals over the 14-year span (219). A 30-year follow-up in one village showed only a 7.3% prevalence of IgG among individuals alive during the 1978 epidemic (versus 29.4% population seroprevalence shortly after the initial epidemic), suggesting a further decline over time in the absence of additional outbreaks (220).

Loss of IgG within 2 years of infection was also seen in a sizeable fraction of cases (17/60) in Borneo following a 1991 outbreak (221). Here, in contrast to the suggestion by Chadha et al. of age independence in India (185), Corwin et al. noted greater persistence of antibodies among those below 30 years of age than among those older than 30 (221). Among South Asian expatriate workers in Kuwait, 90 to 100% of patients retained IgG antibodies over the course of 1 year (sampled at 3-month intervals), though loss to follow-up was high and only eight initially seropositive cases (who all remained seropositive) were followed for a full 12 months (186).

In a long-term follow-up study of hepatitis patients seen at a hospital in Kunming, China, 28 patients seropositive for anti-HEV IgG at 6 months into follow-up were all seronegative by 60 months, with the majority seroreverting within 2 years (222).

In San Marino, a country where HEV is not endemic, follow-up of anti-HEV IgG-seropositive residents identified by population-based sampling showed that only a minority (37%) retained anti-HEV IgG after 5 years; the prevalence of antibodies was higher among those who had initially had anti-HEV IgG plus strongly positive Western blot (WB) results than among those with weakly positive WB values and those who were WB negative (223). One of two initially seropositive Chilean children (of 168 low-socioeconomic-status children tested) remained anti-HEV IgG seropositive for a year following initial detection, while the other reverted to seronegative (224).

The literature on anti-HEV seroprevalence over time suggests wide population variation in the extent and timing of anti-HEV antibody decline. However, much of this variability is likely attributable to differences in methodology and, in particular, to the use of assays with different sensitivities. The associations of antibody persistence and loss with dose, timing, frequency, and route of exposure, as well as viral strain- and host-specific factors, require further elucidation.

Protective Immunity following Vaccination

Results from both animal and human studies have suggested that repeated exposures to virus or viral antigens result in more robust immunogenicity and confer greater protection from overt disease upon subsequent viral challenge. However, subclinical HEV infection subsequent to vaccination has been demonstrated in monkeys in several preclinical trials (225–230) and more recently confirmed in follow-up of humans participating in the large recombinant vaccine trial in Jiangsu, China (231). The duration of protection from clinical disease remains unknown, and optimal dosing and booster schedules remain to be determined.

Results from animal studies. Kamili et al. (227) developed a DNA vaccine consisting of a transfected plasmid encoding an HEV-1 ORF2 capsid protein. HEV-seronegative female cynomolgus macaques that received this vaccine via Helios gene gun (Bio-Rad) ($n = 3$) developed increased titers of anti-HEV IgG following serial vaccinations and developed no evidence of infection upon inoculation with an HEV-2 strain 16 weeks after the initial vaccine dose. Interestingly, although serial doses of vaccine given monthly

prior to the challenge had each resulted in increases in antibody titer followed by a gradual decline, inoculation with live virus 3 weeks after the last vaccine dose did not have a booster effect (227). In contrast, macaques that received either a placebo via the gene gun ($n = 2$) or an intradermal administration of the ORF2 vaccine ($n = 2$) all became infected, with HEV RNA present in stool within several days and in serum within 2 weeks, though only one (in the placebo gene gun group) had elevated liver enzymes. All of these monkeys seroconverted within 1 month, and at 15 weeks postchallenge, they had higher anti-HEV titers than the macaques that had received the active gene gun vaccine and were protected from infection (227).

A team at the U.S. National Institutes of Health (NIH) evaluated a recombinant vaccine that they developed from the 55-kDa protein encoded by HEV-1 ORF2 of the Pakistani SAR-55 reference strain and expressed in baculovirus-infected insect cells (229). They found that two doses of this vaccine in amounts ranging from 0.4 μg to 50 μg, administered 1 month apart, were sufficient to protect 32 rhesus macaques from acute hepatitis but not infection by HEV-1. There was no apparent association between vaccine dose and titer of HEV RNA in serum or feces among vaccinated monkeys (229). The 50-μg dose also protected against hepatitis when monkeys were challenged by the (HEV-2) Mexican reference strain a month after the second vaccine dose. All monkeys receiving a placebo vaccine (alum only) developed clinical hepatitis, as did monkeys vaccinated only after exposure to HEV (229). A follow-up study by this team tested the 56-kDa capsid protein-based vaccine in doses of 1 μg and 10 μg administered twice and 10 μg administered once, all with alum adjuvant. Eight weeks following vaccination or placebo, each of the rhesus monkeys was challenged with 10^4 genome equivalents of either the Pakistan or Mexico HEV strain. By 8 weeks of follow-up, the two-administration regimen, regardless of dose, achieved immunogenicity and protection against hepatitis that were superior to those of the single 10-μg dose (228).

Another recombinant vaccine was developed by Huang et al. (226) from the 56-kDa capsid antigen of a Chinese HEV-4 strain isolated from a human case. This vaccine was administered intramuscularly with adjuvant to 6 seronegative macaques, while a saline placebo was administered to 6 seronegative controls. Researchers examined the influence of the challenge inoculation dose (5×10^4 genome equivalents, 5×10^5 genome equivalents, or no virus) and genotype (HEV-1 or HEV-4) on vaccine efficacy. They found that the vaccinated monkeys resisted infection with 5×10^4 genome equivalents of both HEV genotypes 1 and 4 but showed elevations in liver enzymes and fecal shedding of viral RNA upon challenge with 5×10^5 genome equivalents of HEV-4; the corresponding dose of HEV-1 was not tested. Compared with that in control monkeys, the duration of fecal shedding in vaccinated monkeys was abbreviated (226).

Results from human vaccine trials. The largest randomized, controlled, phase III vaccine trial to date was conducted in Jiangsu Province, China, and enrolled 112,604 healthy adult participants, using the recombinant vaccine HEV239 (232, 233). Approximately 14,000 of the original participants, 12,409 of them with prior anti-HEV serology results, were followed for 2 years after receipt of 3 doses of vaccine ($n = 6,176$) or placebo ($n = 6,233$) (231). The research team identified asymptomatic infections through serosurveillance, defining a case as an individual with a 4-fold increase in anti-HEV IgG level in serial samples. Clinical cases were detected through an algorithm of symptom surveillance plus laboratory confirmation, testing those with fatigue or loss of appetite for elevated ALT and then demonstrating the presence of HEV RNA, anti-HEV IgM, or a 4-fold increase in anti-HEV IgG titer (231). Three clinical cases and 112 subclinical infections were detected in the placebo group during the extended follow-up period using this combination of surveillance strategies, while 24 asymptomatic infections were recorded in the vaccinated group. No clinical illness was observed among vaccinated individuals who developed infections. These results suggest a vaccine efficacy of approximately 79.2% (95% confidence interval [CI], 67.7% to 86.6%) in preventing infection, with the possibility of greater protection against clinical illness (231). Lower antibody titers were associated with an increased risk of infection among both the vaccine and placebo groups, though in general, those who received the vaccine had higher antibody titers at the beginning of follow-up than those who had been infected naturally in the past (231). A 2-year follow-up study was recently published, comparing antibody response in vaccinated adults with and without hepatitis B virus surface antigen (234). The results revealed no differences in response between these populations, with elevated anti-HEV IgG persisting in both groups at 31 months after the first dose of vaccine. Titers among participants who were seropositive at baseline for anti-HEV IgG, regardless of hepatitis B virus serostatus, were higher than titers among participants who were seronegative for anti-HEV IgG at the time of vaccination (234). The HEV239 vaccine has been approved for use in China, and it is now commercially available there (235, 236).

The only other large phase III vaccine trial in human subjects was conducted in Nepal and became the subject of political and ethical debate, in part because, despite good efficacy, the vaccine was never produced commercially after the trial was completed (237–246). This vaccine, also a recombinant vaccine, was based on an HEV ORF2-encoded capsid protein expressed in baculovirus-infected insect cells (230, 247, 248). In this trial, 1,794 subjects, mostly male army conscripts, were randomized to three doses of vaccine ($n = 898$) or placebo ($n = 896$) (247). The second and third doses were given at 1 and 6 months following the first dose, and subjects were followed for just over 2 years. During the follow-up period, 66/896 and 3/898 subjects in the placebo and vaccine groups, respectively, developed hepatitis E, as defined by jaundice or a combination of other symptoms plus elevated ALT or bilirubin levels. This yielded a vaccine efficacy against clinical illness of 88.5% (95% CI, 77.1% to 94.2%), which was even higher when the analysis was restricted to hepatitis E cases occurring after the full 3-dose regimen had been completed (247).

Booster effects. Stoszek et al. (34) proposed that repeated lifetime contact with a dominant, less virulent, possibly zoonotic strain of HEV (e.g., of genotype 3) would create a booster effect and might explain the pattern of high background anti-HEV IgG prevalence (~2/3 in two rural villages) coupled with asymptomatic seroconversion in rural Egypt (34). Khuroo, similarly, suggested that a natural decline in antibody titers over time, in the absence of repeated exposures to HEV, might both explain the observed variability in population seroprevalence estimates in India and also underlie the occurrence of repeated epidemics as the proportion of the population susceptible to infection increases as a function of time since the last epidemic (220).

Stimulation of memory cells might also result in rapid boosting of a protective antibody response following an initial infection.

Shata et al. (249) developed an HEV ORF2-specific IFN-γ enzyme-linked immunoassay to detect persistent cellular immune responses in the peripheral blood mononuclear cells (PBMCs) of experimentally infected and control chimpanzees, as well as of naturally infected and control humans. Among IgG-positive chimpanzees that had been acutely infected with the SAR-55 Pakistani HEV strain 3 to 4 years earlier, the number of IFN-secreting cells (ISC) detected in PBMCs was significantly higher (median = 205.6 ISC/10^6 cells) than that among control chimpanzees (median = 12 ISC/10^6 cells). Among human volunteers, 12 anti-HEV IgG-positive individuals from Egypt and the United States and 19 seronegative participants from the United States also had markedly different concentrations of IFN-secreting cells among PBMCs. When stimulated with pooled ORF2 peptides, PBMCs from the convalescent patients had a median of 373 ISC/10^6 cells detected by enzyme-linked immunosorbent spot (ELISPOT) assay, while control participants had a median of 1 ISC/10^6 cells. The authors suggested that the robust IgG antibody and cell-mediated responses detected in one well-studied U.S. patient who had traveled to Egypt 2 months prior to the study were likely due to (re)exposure in adulthood rather than to persistent cellular immunity from childhood (249).

More recently, Husain et al. (250) developed another enzyme-linked immunospot assay to detect HEV pORF2- and pORF3-specific IgG-secreting B cells, as well as HEV pORF2-specific IFN-γ-secreting cells. They found that, on average, levels of anti-HEV IgG-secreting B cells were similar in both anti-HEV IgG-seropositive ($n = 12$) and seronegative ($n = 13$) healthy residents in India (where HEV-1 is endemic). Regardless of serostatus, these Indian participants generally possessed higher levels of HEV pORF2-specific IFN-γ-secreting lymphocytes than healthy U.S. residents serving as controls ($n = 8$), among whom no such cells were detected, although the differences were not statistically significant in the small sample. The authors suggested that their methods may be more sensitive to prior HEV infection than typical serologic methods but noted that their results require replication in larger samples and more diverse geographic regions (250).

It now appears likely that seroepidemiologic studies have underestimated the cumulative lifetime occurrence of HEV infection in regions of endemicity, due to both limitations and inconsistencies in detection methods and also natural waning of anti-HEV antibodies over time. Additional work is needed to establish the extent to which cell-mediated mechanisms may provide protection to previously infected individuals who lack detectable circulating antibodies. The phenomenon of seroreversion suggests that caution is warranted in drawing serosurvey-based inferences about population susceptibility, long-term protection, recurrence of epidemics, and geographic and demographic patterns of hepatitis E. Rigorous studies using improved diagnostic methods will allow for more accurate and more nuanced assessment of population incidence, seroprevalence, and antibody persistence.

COMPLICATED INFECTIONS, IMMUNE RESPONSES, AND OUTCOMES

Coinfection with Multiple HEV Strains

In the past decade, cases of simultaneous coinfection with multiple HEV strains have been reported in humans. The first observation, in 2002, documented two different swine-associated genotypes of HEV (HEV-3 and HEV-4) in an otherwise-healthy Japanese sushi chef who presented with acute viral hepatitis (251, 252). More recently, a chronic coinfection was reported, with two distinct variants of genotype 3 (3c and 3e) repeatedly detected in serum from a French kidney transplant recipient who had consumed figatellu, an often-undercooked pig liver sausage known to be a frequent vehicle for HEV transmission in the region (253). An additional genotype 3 coinfection was detected in an immunocompetent man in Scotland who developed severe icteric hepatitis. The coinfection was identified by the presence of 18 nucleotide substitutions within the ORF1 hypervariable region and fewer substitutions within ORF2 and ORF3, which resulted in clustering of his coinfecting strains into two phylogenetically distinct populations within genotype 3 (254).

HEV coinfections have likewise been reported in swine, the presumed source of many human infections in regions where HEV-3 and HEV-4 are predominant. In the Amazon Basin, possible 3c/3f coinfections or recombinant strains were identified in two slaughtered pigs by amplification of ORF1 and ORF2 (74).

A natural recombinant HEV-3 strain was recently isolated from a fecal sample obtained from a chronic HEV (HIV-positive) patient in the United Kingdom (164). This strain, Kernow-C1, contained an ~170-nucleotide insertion in the hypervariable region with close identity to a human ribosomal S17 gene, and the authors speculated that such recombination events, previously unknown, may underlie the divergence and epidemiologic diversity of HEV genotypes (164).

There are limited data on coinfections involving genotypes 1 and 2. However, genotype 1a/1c coinfections were documented in 2 people hospitalized in Kathmandu, Nepal (255, 256). While HEV-4 has been amplified from serum, liver, and stool samples from swine in India (107, 114, 161, 162, 257), there have been no reports of human coinfection with both HEV-1 and -4. Differences in primary exposure routes (contaminated water for HEV-1 and -2 versus direct contact with infected animals or undercooked meat for HEV-3 and -4) may explain why no such coinfections have been reported. Another contributing factor is the infrequent detection of human HEV-4 infections in India (144, 257), despite evidence of human HEV-4 infections elsewhere in Asia (258) and experimental evidence that HEV-4 strains found in India can infect other primates (259). Vivek and Kang (108), for example, failed to detect HEV genotype 4 RNA in sera from 34 swine handlers exposed to pigs (some of which were viremic), yet using a modern immunoassay, they found an exceptionally high (~94.1%) prevalence of anti-HEV IgG in this occupationally exposed population, which the authors interpreted as possibly suggestive of zoonotic transmission (108).

The relative lack of cross-species infections in settings where HEV-1 and HEV-2 are dominant, despite human contact with pigs and other susceptible animals, also raises questions about host specificity and adaptation, exposure patterns and infective doses, strain predominance, and prevalence. However, it is also likely that limited molecular surveillance in these settings helps to explain the paucity of reports of both intragenotypic coinfections and cross-species infections. In both developing and industrialized countries, HEV surveillance is in its infancy, and most coinfections are likely missed because they are not characterized in detail—if they are even correctly diagnosed as HEV.

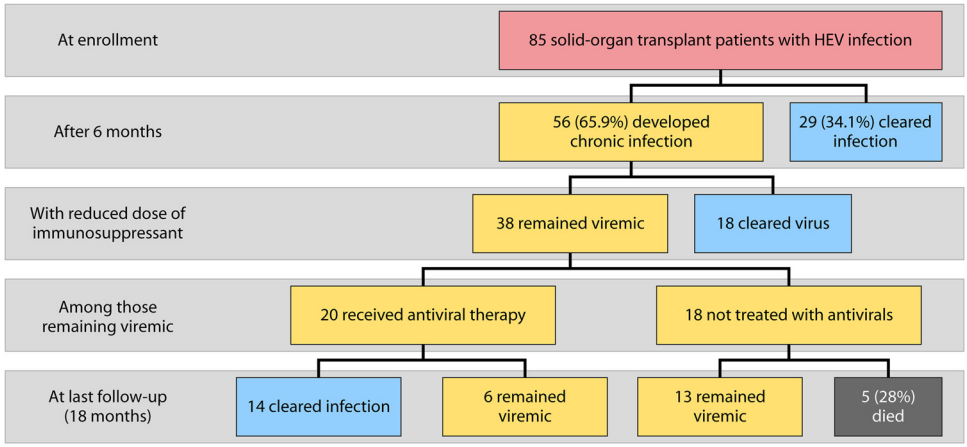

FIG 4 Chronic hepatitis E in solid-organ transplant recipients (results of a 17-center study). (Data are from reference 275; the figure was created by the authors after a slide presented by Norah Terrault [from "Hepatitis E Virus in Organ-Transplant Recipients" at IDWeek 2012, San Diego, California, 19 October 2012 {http://idsa.confex.com/idsa/2012/webprogram/Paper33770.html}].)

Immunosuppression and Impaired Viral Clearance

Chronic HEV infections, which are rarely seen in otherwise-healthy individuals, are increasingly being recognized in patients with impaired immune function. Most immunosuppressed and immunocompromised patients acquire HEV infections through fecal-oral or food-borne routes of exposure, though cases of transplant (36)-, transfusion (31, 135, 260–264)-, and nosocomially (265) transmitted HEV infections have all been documented. Patients receiving immunosuppressive therapies due to organ transplantation or cancers, in particular, appear to be susceptible to a chronic course of HEV. It is less clear to what extent other comorbid diseases, including coinfection with HIV, may impair viral clearance and affect the course of the illness, though chronic HEV infections have been documented in a number of HIV-positive patients (266–274).

Chronic HEV infections tend to complicate medical management of both the hepatitis and the comorbid condition and are associated with poorer outcomes, including both hepatic and extrahepatic morbidity. For example, seven patients with chronic HEV infection who had predominantly neurologic symptoms were reported by Kamar and colleagues, and HEV RNA was detected in cerebrospinal fluid samples from 4 of these patients (48).

HEV in transplant recipients. Individuals receiving solid-organ transplants require lifelong immunosuppressive therapy to prevent rejection of the transplanted organ(s), which, as a consequence, hinders the ability of the immune system to clear viral infections. The underlying disease processes (including other hepatotropic infections) that necessitated the transplantation may also play a role in susceptibility and response to HEV infection.

It has been recognized recently that patients who have had solid-organ or bone marrow transplants are at risk of developing chronic HEV infection if they are infected after their transplant while being treated with immunosuppressive drugs to prevent rejection of the allograft (76, 254–257). Kamar and colleagues evaluated the factors associated with chronic hepatitis in 85 patients with HEV infection from 17 transplant centers in Europe and North America (275) (Fig. 4). Overall, 56 patients (65.9%) developed chronic hepatitis, with infection persisting for 6 months or more. In multivariate analysis, the independent factors associated with chronic hepatitis were the use of tacrolimus rather than cyclosporine and a low platelet count at the time of HEV diagnosis. Among patients with chronic hepatitis E, 18 (32.1%) achieved viral clearance after the immunosuppressive therapy was reduced (275).

Halac et al. (276) recently documented serial, discrete viremic episodes in a young liver transplant recipient on immunosuppressive therapy, apparently caused by two distinct strains of HEV subgenotype 3a that were both known from local swine populations, suggesting (possibly zoonotic) reinfection despite the presence of both anti-HEV IgG and IgM in the patient's serum from even before the first identified episode of viremia (276).

Although the underlying illnesses necessitating organ transplantation may be associated with increased likelihood of transfusions, poor hepatic function, and/or generalized immune abnormalities, any of which could plausibly increase the risk of hepatitis E, empirical evidence for these hypothesized associations has not materialized. Studies of hemodialysis patients, for example, have not consistently found an increased prevalence of anti-HEV antibodies or an increased incidence of hepatitis E prior to kidney transplantation. In the mid-1990s, French kidney transplant patients were found to have a higher seroprevalence of anti-HEV IgG than the general population, suggesting possible exposure to the pathogen through transfusion and/or hemodialysis (277). A longitudinal study of Indian hemodialysis patients documented seroconversion in 5/64 patients over 18 months, but the authors indicated that these seroconversions were without evidence of clinical illness (278). A cross-sectional study of Turkish dialysis patients and controls found an increased prevalence of anti-HEV IgG in the patients versus controls (9/43 [17%] versus 4/42 [8.6%]) (279), as did a similar matched case-control study in Saudi Arabia comparing dialysis patients with clinical and hospital controls (4.8% versus 0.3%) (280). In Tabriz, Iran, the prevalence of anti-HEV IgG in dialysis patients was 7.4%, which was actually lower than in the authors' study of the general population, and neither duration of dialysis nor demographic factors appeared to be associated with seropositivity (281). Likewise, in Urmia, Iran, Khameneh et al. (282) found no association between seropositivity for anti-HEV IgG and dialysis history or transfusion among kidney

transplant recipients, though the prevalence of antibodies in these patients (30.8%) was quite high. Two studies in Greece in the late 1990s, one in a semirural area in the northwest and the other in Athens, documented a higher seroprevalence of anti-HEV IgG in hemodialysis patients than among healthy controls. The Athens study showed no association of HEV serostatus with dialysis after adjustment for age and sex (283), while the study in semirural Epirus and Agrinion found age and sex to be unrelated to HEV serostatus (284). Fabrizi et al. (285) found a low seroprevalence (6/204 [3%]) among Italian dialysis patients in Lecco, northern Italy, but this study lacked a comparison group. Sylvan et al. found no increased anti-HEV seroprevalence among dialysis patients in Sweden (11/182 [6.0%] versus 18/349 [5.2%]) (286). A 67-year-old Japanese man beginning hemodialysis had a prolonged course of infection, with fecal shedding of HEV in serial samples from day 22 to day 79 and an isolated detection of HEV RNA in stool on day 121 after symptom onset (287).

Cancer patients. Patients with cancers, especially those with hematologic malignancies such as acute lymphoblastic leukemia (ALL), often receive radiation and/or immunosuppressive drugs in conjunction with autologous or allogeneic stem cell transplants. In this patient population, both acute and chronic HEV infections have been detected, frequently complicating treatment decisions.

Several recent studies have suggested that active HEV infections in patients on immunosuppressive therapy regimens are typically acquired *de novo* and do not represent reactivation of latent HEV in individuals who have previously cleared an infection (288–290). One possible exception was a report of reactivation in a man who had become anti-HEV IgM seronegative but later, concurrent with a relapse of ALL, became viremic again (291).

Most information on HEV in patients with cancer comes from case reports or small case series. No clear associations have been found between any particular immunosuppressive regimen and HEV infection or chronicity; cases of HEV have been reported in patients taking cyclosporine (288, 290–292), corticosteroids (289, 290), methotrexate (288, 290, 291), and rituximab (291, 293, 294), for example, as well as other drugs, often in combination. However, Kamar and colleagues documented a greater likelihood of chronicity in patients taking tacrolimus than in those taking cyclosporine and a corresponding increase in viral clearance in patients with lower tacrolimus trough levels than in patients with higher trough levels (128).

Outcomes have varied among cancer patients who develop HEV infections. Antiviral therapy (289) and temporary cessation of immunosuppressive treatment have been reported to result in resolution of infection in some individuals, though others have recovered without changes to their therapy, and others have had a chronic or fatal course of infection. The underlying health of these patients at the time of infection may help explain the differences in outcomes.

Persons with HIV coinfections. Despite the immunocompromised status of most HIV-positive individuals and their increased vulnerability to numerous infections, there have been conflicting reports as to whether HEV infections are unusually common, eventful, or likely to become chronic in HIV-positive populations. Immunodeficiency may predispose individuals to HEV infections yet obscure their detection by hindering seroconversion. However, to the extent that clinical symptoms of hepatitis E may be mediated by immunopathogenic mechanisms, lower $CD4^+$ cell counts and a weaker immune response may moderate the effects of limited infection-fighting ability and reduce the likelihood of symptomatic or severe hepatitis E.

Early studies of HEV in patients with HIV and AIDS yielded mixed results. Several studies found HIV-positive and AIDS patients to have an increased seroprevalence of anti-HEV IgG compared to those without HIV infection (295–297). Montella et al.—controversially—interpreted their finding of higher HEV seroprevalence in Italian HIV-positive homosexual men than in HIV-negative homosexual men and injection drug users as "[confirmation of] the role of transmission through the fecal-oral route facilitated by sexual practices" (297). Several letter writers quickly offered alternative explanations, suggesting that differences in seropositivity could be attributable to greater infection susceptibility and/or nonspecific enzyme immunoassay (EIA) reactivity among HIV-positive patients (298, 299). Christensen et al. found no association of anti-HEV antibodies with sexual or drug use practices among HIV-negative prisoners in Denmark, but there was an association with anti-HAV antibodies, pointing to exposures to typical fecal-oral routes of transmission (300).

Meanwhile, other studies did not find notable differences in seroprevalence between HIV-positive and HIV-negative populations (285, 301, 302). Bissuel and his colleagues in France wrote in *The Lancet* that "HEV serologic testing is not of interest in [the HIV-positive] population" in the absence of information about incidence (301). However, the poor sensitivity of some early assays could also have resulted in biases in case ascertainment in the context of weaker immune responses.

More recent studies focusing on detection of anti-HEV IgM, IgG, or RNA have identified both acute (266, 303–313) and chronic (266, 268–274) HEV infections in HIV-positive patients, though it remains unclear whether or not seroprevalence is any greater in people with HIV (272, 273, 300, 309, 310, 314–318). Chronic HEV infections in HIV-positive individuals have been associated with quick progression to cirrhosis (269–271), though it is not clear whether HEV-linked cryptogenic cirrhosis is more common in HIV-infected individuals than in the general population (310, 311, 315, 319).

Among people with HIV, viral load and $CD4^+$ cell count may be related to seropositivity or chronicity of infection. A serologic study of samples from U.S. military personnel and their families found that HEV seropositivity in HIV-positive persons was associated with a lower $CD4^+$ cell count and higher HIV viral load, independent of antiretroviral drug use (303). A cohort of Swiss HIV patients were more likely to have chronic HEV infections if their $CD4^+$ cell counts were low (273), but a study in France, which also detected a chronic HEV case with low $CD4^+$ levels, suggested that overall anti-HEV IgG seropositivity was unrelated to $CD4^+$ cell count (272). Despite remaining inconsistencies regarding seroprevalence differences, it is apparent that individuals with HIV, particularly those with low $CD4^+$ cell counts, may be at risk for chronic HEV infection. As a result, a number of researchers have called for targeted HEV screening of people with HIV who have elevated liver enzymes with unknown cause (156, 270, 272, 273, 307, 309–311, 313, 314, 316, 319–321).

Understanding the influence of HIV on the course, severity, and diagnosis of HEV infections, as well as the role of antiretroviral therapy (ART), is especially critical in the areas of sub-Saharan Africa where HEV-1 and HEV-2 are endemic. Early studies in

Burundi and Central African Republic did not detect differences in HEV seropositivity related to HIV status (302, 322). A small 1995 study in Gabon found no HEV-seropositive persons among 35 adults, though the sample size and relatively low assay sensitivity likely limited the ability to detect cases (323). Other studies, however, have described aspects of the HEV-HIV nexus that are of concern for already-strained health systems.

A large, retrospective analysis of serum samples from HIV-positive adults and children in Cameroon and Ghana ($n = 1,544$ total) detected high anti-HEV IgG seroprevalence, especially in Ghanaian adults (45.3%), with lower prevalence in Cameroonian adults (14.2%) and children (2.0%) (324). Although no HEV RNA was detected in any of the samples, the high seroprevalence indicates substantial exposure to the virus in this population.

Andersson et al. (325) report a case of chronic hepatitis E in a South African man with HIV whose ALT levels rose markedly upon initiation of antiretroviral therapy (ART). Using stored serum samples, they demonstrated that the man had circulating HEV RNA but was seronegative for anti-HEV IgM or IgG for nearly a year prior to ART initiation, and he did not seroconvert until HIV treatment began. They suggest that this course of infection, which the patient ultimately cleared after his $CD4^+$ cell counts had risen and HIV viremia was undetectable, represents an immune reconstitution syndrome (325).

Pregnant women with HIV, who are already at increased risk of mortality, are also susceptible to HEV infections. Caron et al. found an association between HEV seropositivity and HIV viral load in a group of 183 pregnant women in Gabon (306). This study was cross-sectional, however, and little is known about the effects of HIV infection in pregnancy on HEV susceptibility, pathogenesis, and natural history. Additional work is required to understand the intersection of HIV and HEV epidemics in Africa.

Hepatitis E in Pregnancy: Maternal and Neonatal Health

Epidemiology of hepatitis E in pregnant women. Severe hepatitis E disproportionately affects pregnant women, with a high incidence of acute liver failure and reported case-fatality rates of ~15 to 30% (240, 326, 327). This perplexing and grave feature, which is distinctive of hepatitis E epidemics, has been noted for decades (perhaps centuries) but remains poorly explained (3). Recent work in Bangladesh suggests that acute hepatitis, with HEV the probable etiologic agent in a majority of cases, may underlie an astonishing ~10 to 25% of pregnancy-related deaths (65, 237, 328). In addition to the effects on maternal health, fetal and newborn health may also be compromised, with elevated risk of miscarriage, stillbirth, premature delivery, and neonatal jaundice (176, 328–335). Vertical transmission appears to be common among mothers with symptomatic hepatitis E, with deleterious effects on fetal and neonatal health (334, 336, 337). Because few studies have addressed the issue, it is unclear to what extent the fetuses and neonates of women with subclinical or asymptomatic infection are at risk (370). There are not yet any reliable data on whether HEV is transmissible via breast milk. Geographic discrepancies in the frequency and severity of clinical hepatitis E in pregnant and postpartum women persist.

Immune function and susceptibility to viral infection during pregnancy. Pregnancy is associated with changes in sex hormone levels and immune system function (Fig. 5) that serve primarily to protect the fetus from attack by the maternal immune system but also exert strong effects on the immune response to pathogens. In addition to maternally mediated changes in the biochemical milieu, fetal hormones may also affect susceptibility to infection. Pregnancy-related changes in body chemistry and fetal and placental influences have been variously linked to increases in the severity of certain infections, including *Plasmodium falciparum* malaria, leprosy, influenza, varicella, viral hemorrhagic fevers, and measles (338) and decreases in the severity of some autoimmune diseases, e.g., rheumatoid arthritis (339), during pregnancy.

During pregnancy, a shift from T helper cell type 1 (Th1)-dominated to T helper cell type 2 (Th2)-dominated immune responses, or "Th2 bias," has been hypothesized to help protect the fetus by suppressing macrophage activation (340). Th1-type responses are marked by increases in IFN-γ synthesis, and this type of response appears to help protect against parasitic infections (341). Th2 responses, on the other hand, are tipped toward anti-inflammatory cytokines, such as IL-4, IL-6, and IL-10, and increases in antibody production (342, 343).

These changes in the immunologic environment are not instantaneous but vary with increasing estradiol and progesterone levels (342), becoming most apparent as the pregnancy approaches term. Extrapolation from serial measurements of IFN-γ and IL-6 (as biomarkers of Th1- and Th2-type responses, respectively) in 35 healthy pregnant women in Quebec suggested that Th1-type responses prevail until the mid-second trimester, with IFN-γ decreasing and IL-6 increasing from the 10th to 40th weeks of gestation (344). Serial serum samples from a cohort of 50 healthy pregnant and postpartum women in New York City showed elevated levels of TNF-α throughout pregnancy compared with 6 months postpartum (345). These women also experienced increases in levels of α-defensins and IP10 and decreases in IFN-γ during gestation (345, 346).

A study of 111 pregnant, 126 postpartum, and 86 nonpregnant healthy women in Japan indicated that natural killer (NK) cell activity was markedly reduced by the third trimester of pregnancy but relatively high during the first trimester and the first month postpartum (347). Similarly, the Viral Immunity in Pregnancy study in New York City suggested a nadir in NK cell activity in the third trimester (346).

Caution is warranted, however, in generalizing biomarker findings from healthy pregnant women in industrialized countries to women in resource-limited settings.

Hypotheses regarding mediation of HEV severity in pregnant women. The interplay of these factors in hepatitis E during pregnancy is complex and not yet well understood. Pal et al. (349) measured cytokine responses in cells from pregnant and nonpregnant women with HEV in India, as well as from healthy pregnant and nonpregnant controls. They found a Th2 bias among pregnant women with HEV, as well as an increased lymphoproliferative response to stimulation relative to that in healthy pregnant women. However, as their study was cross-sectional, infection-induced changes in cytokine and lymphoproliferative responses, as opposed to preexisting differences that predispose to disease, cannot be excluded.

In addition to mediating shifts in the immune system, pregnancy-associated hormones may also directly influence viral replication (350). Poorer outcomes in HEV-infected pregnant patients have been associated with higher viral load (176, 351), but not consistently (175). Elevated sex steroid hormones in women with HEV-associated acute liver failure, relative to those with milder illness, may suggest that higher estradiol and progesterone

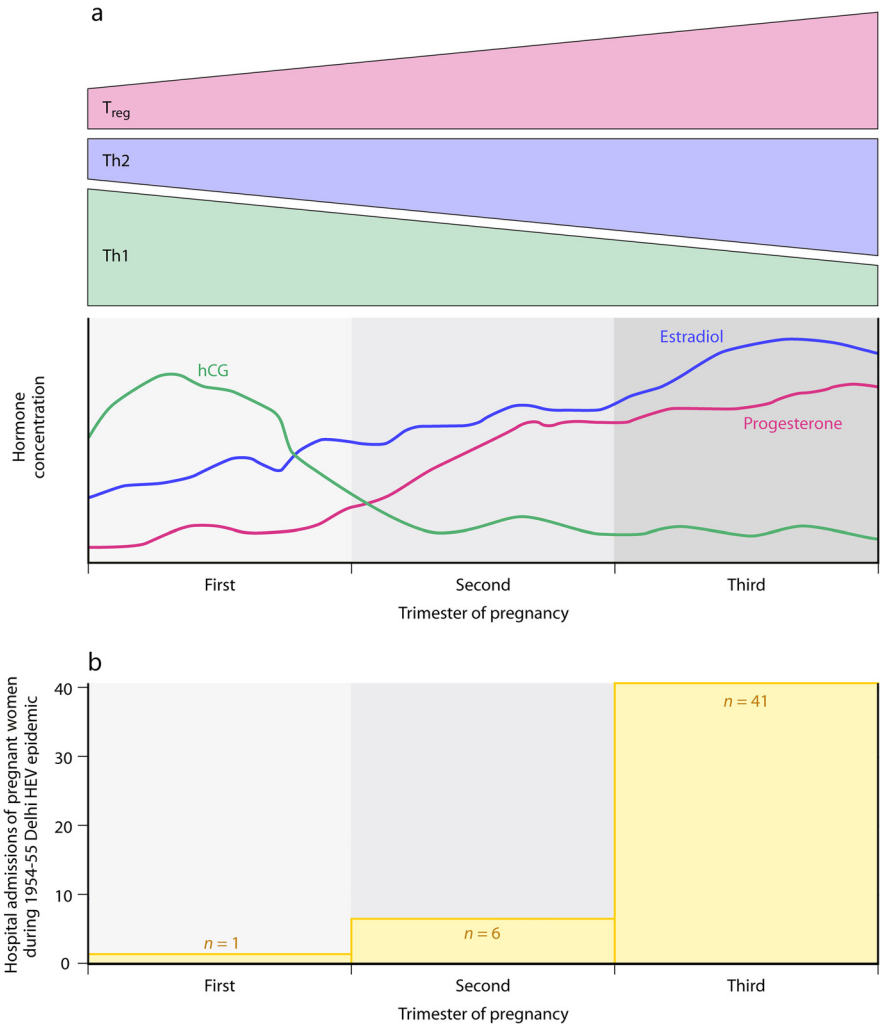

FIG 5 Changes in hormone levels and immune function are associated with an increased risk of severe hepatitis E in late pregnancy. (a) Changes in hormone levels and immune function over the course of pregnancy. Pregnancy is characterized by marked changes in hormone levels and corresponding shifts in immune status, which vary over the course of gestation. Levels of estradiol and progesterone are at their lowest early in pregnancy, while an increase in human chorionic gonadotropin (hCG) levels occurs and then begins to wane during the first trimester. As estradiol and progesterone levels continue to rise over the course of pregnancy, the dominant T helper 1 (Th1) immune regimen, associated with proinflammatory activity, is gradually superseded by T helper 2 (Th2)-biased responses associated with anti-inflammatory activity. Regulatory T-cell (Treg) activity also increases over the course of pregnancy. (Adapted from Fig. 2 of reference 348 with permission from Elsevier.) (b) Distribution by trimester of hospital admissions of pregnant women with acute hepatitis during the historic Delhi hepatitis E virus (HEV) epidemic of 1954 to 1955. An association of greater hepatitis E severity with more advanced pregnancy is a frequent observation during outbreaks and among sporadic cases. Alterations in both hormone levels and immune function during pregnancy appear to contribute to these outcomes. Data are from reference 335.

levels are a risk factor predisposing women to poorer outcomes; however, the elevated hormone levels may also be triggered by the infection state itself (350).

Host factors such as nutritional status, which may affect and be affected by pregnancy, may also contribute to the immune response to HEV infection in pregnant women. In contrast to the findings of Pal et al. (349), preliminary work in Bangladesh has suggested that the immune profiles of pregnant women who develop clinical hepatitis E may not reflect the Th1-Th2 shift observed in other cohorts of pregnant women, and it is possible that this is related to micronutrient deficiencies (352). Pregnant women elsewhere in South Asia are often deficient in several micronutrients, and seasonal food availability may exert a major influence on maternal micronutrient status (353). A proteome analysis conducted in a cohort of pregnant women in southern Nepal identified changes from the first to third trimesters in the expression of proteins, some of which had not previously been reported in studies of healthy pregnant women (354). Several proteins whose expression differed significantly between the first and third trimesters were associated with immune function and inflammation, including gelsolin, pregnancy zone, plasma protease C1 inhibitor, and various complement-related subcomponents, as well as other proteins whose functions remain uncertain (354). Environmentally and genetically mediated differences in immune system modulation over the course of pregnancy could help explain regional differences in the observed hepatitis E incidence and severity during pregnancy.

Hepatitis E as a catalyst for coagulopathy may also contribute

to maternal morbidity and mortality. Hemorrhage, often postpartum hemorrhage (PPH), is the leading proximal cause of maternal death in developing countries (355, 356). If HEV infection disrupts clotting, this may further increase the likelihood of uncontrolled bleeding during the peripartum period. As PPH remains one of the major causes of maternal mortality globally, especially in areas of endemicity, it may be that some proportion of peripartum hepatitis E is misclassified as delivery-associated PPH; this and other manifestations of HEV infections in pregnancy may explain the underrecognition of HEV etiologies in emergency obstetric complications.

Women admitted to a tertiary care hospital in New Delhi, India, with acute HEV ($n = 132$) had significantly elevated prothrombin times relative to those of women admitted for other acute viral hepatitides ($n = 88$) (330). The HEV-infected women had a greater incidence of antepartum (but not postpartum) hemorrhage, including gastrointestinal bleeding, and elevated maternal mortality. In marked contrast to other studies, the women with acute HEV in this study were admitted with a lower average gestational age than women with other acute viral hepatitis (330). Puri et al. (357), working in the same hospital in New Delhi in subsequent years, conducted a case-control study of third-trimester pregnant women with acute HEV and coagulopathy, comparing those who did ($n = 13$) and did not ($n = 25$) suffer postpartum bleeding. Women with postpartum hemorrhage had approximately five times the odds of having experienced hepatic encephalopathy as women without PPH and had 20 times the odds of a gastrointestinal bleed, though only gastrointestinal bleeding remained a significant clinical predictor of PPH after controlling for other factors. Fully a third of women admitted to the hospital with acute HEV infections experienced postpartum hemorrhage (357).

Work by Geng et al. (358) suggests possible mechanisms by which HEV infection may contribute to dysregulation of coagulation, which may pose a particular hazard to maternal health. Their study of HEV-1, HEV-4, and rabbit HEV ORF3 protein interactions with human liver cell proteins found that HEV ORF3 may interact with several clotting-related pathways. Specifically, they propose that downregulation of fibrinogen production may precipitate hemostasis, eventually depleting clotting factors, and that several other protein pathways may also be disturbed (358). Poliakova et al. (359) also observed dysregulated coagulation among HEV patients with acute liver failure, although their study did not focus specifically on pregnant women.

Despite emerging evidence explaining the role(s) of hepatitis E in maternal and neonatal morbidity and mortality, HEV-related deaths in pregnant women, especially if unaccompanied by frank jaundice, may be not be identified or recorded as such. Careful examination of the proximal and distal causes of maternal death, in clinical studies and, importantly, in community-based studies, may help elucidate the contribution of HEV infection and associated risk factors to maternal death. Maternal verbal autopsy methods used in both rural and urban Bangladesh have revealed a higher-than-anticipated prevalence (9.8 to 25%) of jaundice and/or acute viral hepatitis-like illnesses among women who died from all pregnancy-related causes during the maternal period (65, 237, 328). Similar investigations, especially if supported by serologic and/or molecular confirmation of etiology, could help clarify the role of HEV in maternal death in other settings and suggest new avenues for prevention of maternal mortality.

The long-awaited release of a commercial vaccine against hepatitis E in China (236) is a hopeful sign for prevention of HEV-associated morbidity and mortality among pregnant and postpartum women. However, the vaccine has not yet been tested for safety and efficacy in large populations of pregnant women or in places where HEV genotype 1 is the primary cause of human infection (237). Although a *post hoc* study of 34 pregnant women inadvertently included in the Chinese vaccine trial revealed no obvious differences in immunogenicity or safety (360), the "hormonal and immunological milieu of pregnant women is strikingly different from that of women who are not pregnant" (348), and thus dedicated studies are needed to establish more clearly the risks, benefits, and optimal timing of vaccination in the context of pregnancy, for both the mother and her fetus (348).

CONCLUSIONS

The global medical and public health communities have finally begun to appreciate the importance of HEV infections, but there remain important scientific, economic, cultural, and administrative obstacles to controlling the impact of HEV on morbidity and mortality worldwide. Despite the established and well-documented global burden of HEV, over many decades, this pathogen remains relatively neglected on the global public health stage.

Robust, credible surveillance is hindered by lack of medical and laboratory infrastructure and by lack of awareness of HEV. Diagnostic assays with good sensitivity and specificity have only recently become commercially available, and it is important to facilitate global access to the tools necessary to identify and respond to HEV infections, whether sporadic cases or nascent outbreaks. Clinical and field surveillance, coupled with laboratory investigations of viral strains isolated from human cases, will help advance our understanding of the relative virulence of HEV genotypes, intragenotypic variation, and other features of HEV's global epidemiology. Even in the areas where HEV is most endemic and in emergency situations where the risk of HEV infection is high, this virus has not been routinely sought after, largely due to these limitations.

Vaccines to combat HEV have been developed and tested, and one highly efficacious vaccine is now available to consumers in China. In light of this, understanding the determinants of susceptibility and resistance to repeat infection and clinical disease is imperative. Identifying environmental factors, such as regional climatic patterns, water and sanitation practices, and farming and food processing practices, that affect lifetime exposures to HEV may help both to explain regional differences in the age-specific incidence and severity of HEV that cannot be explained solely by genotypic variability and also to provide risk-based strategies for intervention. Meanwhile, deciphering the nuances of individual risk and host-related factors may lead to better identification, preventive precautions, and secondary or tertiary management of highly vulnerable individuals.

Both laboratory-based mechanistic and experimental studies and clinical and epidemiologic studies of HEV-infected human patients have yielded exciting insights into the pathogenesis of HEV. Still, more work is needed to understand chronic and extrahepatic HEV infections and to refine promising treatment approaches. Likewise, additional research to increase our understanding of the spectrum of responses to HEV infection, both in pregnant women and in nonpregnant adults and children, may help us more effectively address the global impact of HEV.

What is clear is that the many perplexing facets of this virus are

likely to be the result of complex interactions between host, environment, and agent characteristics, combining in different ways across regions where this virus persists. Global human movement, complex international food systems, and unpredictable humanitarian emergencies will likely continue to challenge our grasp of HEV in the coming decades. Still, the advent of promising vaccines and insights into the appropriate management of HEV infections lends a hopeful outlook for the future.

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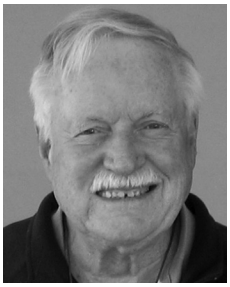

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