Epidemiology of Genotype 1 and 2 Hepatitis E Virus Infections

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Hepatitis E virus (HEV) genotypes 1 and 2 are responsible for the majority of acute viral hepatitis infections in endemic areas in South Asia and sub-Saharan Africa. In addition to frequent sporadic illnesses throughout the year, these viruses often cause large epidemics in association with monsoon rains in Asia or during humanitarian crises in Africa. Clinical hepatitis commonly involves adults more often than young children, with an overall mortality of ~1%. However, the mortality among pregnant women is often 30% or higher. HEV infection in pregnant women frequently leads to infant mortality or premature delivery. Hepatitis E is an important, yet largely neglected, global public health problem.

Epidemics of jaundice have been recognized for several centuries. They have often occurred during military campaigns or after environmental disasters, such as monsoon rains, floods, or earthquakes. In the early 20th century, it was hypothesized that these outbreaks might be the result of a virus, which was transmitted directly from person-to-person or by contaminated water (McDonald 1908; Findlay and Dunlop 1931). Many of these outbreaks, particularly the smaller ones, may have been the result of hepatitis A. However, a large waterborne outbreak occurred in Delhi, India, in December 1955, which resulted in more than 29,000 reported cases of hepatitis (Viswanathan 1957). Several epidemiologic features of this outbreak

differed from those common in sporadic hepatitis cases. First, this large epidemic declined abruptly without evidence that secondary person-to-person spread of infections among household contacts was common. Second, there were 266 deaths, resulting in an overall mortality of ~1%, but 102 deaths occurred in pregnant women who had a mortality rate of >20% (Naidu and Viswanathan 1957). These unusual epidemiologic features of the India outbreak led some infectious disease experts to postulate that the infectious agent responsible for the epidemic was different from that causing sporadic cases of hepatitis. Another similar outbreak occurred in Kashmir in 1978, leading the investigators to question whether the epidemic might

K.E. Nelson et al.

be caused by a novel hepatitis virus (Khuroo et al. 1983). Additionally, a liver specialist in California described up to four separate attacks of acute hepatitis in several hospitalized patients, further confirming the probable existence of multiple human hepatitis viruses (Mosley et al. 1977).

After hepatitis A virus (HAV) was identified by immune electron microscopy in 1973 (Feinstone et al. 1973), researchers tested stored sera collected from convalescent patients involved in the 1955 outbreak in Delhi and found no evidence of HAV infection (Wong et al. 1980). The novel syndrome was called enterically transmitted non-A/non-B (ET-NANB) hepatitis. Subsequently, while investigating an outbreak with similar epidemiologic features in Afghanistan, Mikhail Balayan, using immune electron microscopy, detected 27–30 nm viral particles in his own stool 4 weeks after ingesting filtered feces from nine patients with ET-NANB characteristics (Balayan et al. 1983). The virus was shown to be distinct from HAV and infectious for cynomolgus monkeys, in which it recapitulated the disease. A similar ET-NANB isolate from Burma was molecularly cloned and sequenced, and found to be a single-stranded, positive-sense RNA virus with a genomic organization resembling that of caliciviruses (Tam et al. 1991). However, the nucleotide sequence of the virus is sufficiently different to warrant its classification within a separate virus family, the *Hepeviridae* (Smith et al. 2014).

GEOGRAPHIC DISTRIBUTION OF HEPATITIS E VIRUS (HEV) GENOTYPES

Thus far, five genotypes that are pathogenic for humans have been identified. Genotype (gt)1 and gt2 are pathogenic only for humans, whereas gt3 and gt4 have animal reservoirs in swine, deer, wild boars, and rabbits. gt7 is the most recently identified human pathogenic genotype and has a reservoir in camels (Lee et al. 2016). It was found to be responsible for a single human infection in a camel owner who had received a liver transplant and lived in the United Arab Emirates. gt1 strains are present in the Indian subcontinent, China, Bangladesh, Nepal, Paki-

stan, Afghanistan, and most countries in sub-Saharan Africa. gt2 strains are present in Mexico, Nigeria, Chad, Sudan, and the Central African Republic, whereas gt3 strains are present in Europe, the United States, and other North American countries, Central and Southern Japan, New Zealand, and Australia. gt4 HEV is found in China, northern Japan, and India (Fig. 1). gt7 has only been identified in the United Arab Emirates but little research into the geographic distribution of this genotype has been completed.

CLINICAL FEATURES OF HEV INFECTIONS

Acute hepatitis E has an incubation period of 3–8 weeks (Labrique et al. 2010a). There is a short prodromal period, followed by jaundice and abdominal discomfort lasting for a few days to several weeks. The majority of infected individuals are asymptomatic but have elevated serum liver enzyme activities. A prospective study in rural Bangladesh found that only 20% of infections identified prospectively were symptomatic (Labrique et al. 2010b). The proportion of infections that are subclinical may be even higher in persons infected with gt3 or gt4 viruses. In addition to acute infection, subjects who are significantly immunocompromised, such as solid-organ transplant recipients receiving immunosuppressive drugs to prevent rejection of the transplant, may develop chronic infection. Chronic gt1 or gt2 HEV infections have not been reported to date, however.

Fulminant hepatitis among pregnant women has been a common feature of epidemics of hepatitis because of gt1 HEV. Although severe or fulminant hepatitis in pregnancy has not been reported with gt3 or gt4 infections, a recently published review reported two cases of fulminant hepatitis among nine pregnant women with autochthonous HEV infections in developed countries (Lachish et al. 2015). Fulminant hepatitis has been commonly seen in pregnant women who acquired the infection in countries endemic for gt1 HEV and then immigrated to developed countries (Zaaijer et al. 1993; Lachish et al. 2015).

Rarely, patients with acute HEV infection may develop extrahepatic manifestations such

Figure 1. Geographic variation in levels of endemicity for hepatitis E virus (HEV). (Modified figure is taken from the U.S. Centers for Disease Control and Prevention; see wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-e.)

as neuritis, Guillain-Barré syndrome, glomerulonephritis, or aplastic anemia (Mishra et al. 1999; Aggarwal 2011; Haffar et al. 2015). Such extrahepatic disease, especially neurological involvement, may be less frequent with gt1 or gt2 HEV than with gt3 infections (Dalton et al. 2016). Three case-control studies have shown a significant association between HEV infection and Guillain-Barré syndrome. These were performed in Holland (van den Berg et al. 2014), Bangladesh (Geurtsvankessel et al. 2013), and Japan (Fukae et al. 2016).

THE GLOBAL BURDEN OF GENOTYPE 1 AND 2 HEV

A study was published in 2012, which estimated the global burden of infections with HEV gt1 and gt2 in 2005 (Rein et al. 2012). These investigators estimated that 20.1 million incident infections (95% confidence interval [CI]: 2.8–37.0) occurred in the nine regions of the world in which gt1 and gt2 are endemic, resulting in

3.4 (95% CI: 0.5–6.5) million symptomatic cases, 70,000 (95% CI: 12,400–132,732) deaths, and 3000 (95% CI: 1892–4424) stillbirths. An independent analysis of the global burden of viral hepatitis from 1990 to 2013 was published in 2016 (Stanaway et al. 2016). This study estimated there had been a 63% increase in mortality attributable to viral hepatitis between 1990 and 2012, primarily as a result of increasing population size. The mortality attributed to HEV was estimated to have declined during the period related to improvements in sanitation in several low-income endemic countries. The incidence of HEV gt1 and gt2 infection was estimated to peak between ages 15 and 30 (Fig. 2) (Rein et al. 2012).

HEV GENOTYPE 1

Outbreaks of disease caused by HEV gt1 strains are almost always a result of waterborne transmission of the virus. Large outbreaks have been commonly reported in India, Pakistan, Nepal,

K.E. Nelson et al.

Figure 2. Estimated incidence of hepatitis E virus (HEV) by age and global burden of disease region in 2005. (From Rein et al. 2012; reprinted, with permission, from John Wiley and Sons © 2012.)

Bangladesh, and other South Asian countries (Table 1). However, the largest recorded outbreak occurred between 1986 and 1988, with 120,000 reported cases and 765 deaths, of which 51 were in pregnant women (Wang 1989). Following the outbreak in Delhi in 1955, India experienced frequent outbreaks affecting hundreds or thousands of people, particularly between 1975 and 1994. The largest outbreak in India occurred in Kanpur from December 1990 to April 1991 and involved 79,000 cases of clinical hepatitis (Naik et al. 1992). An outbreak in Kashmir, India, in 1978–1979 involved 20,000 people and resulted in 600 deaths, of which 436 were pregnant women (Khuroo 1980). Other Asian countries have also reported

outbreaks of HEV, including Pakistan, Indonesia, Myanmar, Vietnam, Japan, China, Bangladesh, Nepal, Iraq, Uzbekistan, and Turkmenistan (Hakim et al. 2017).

HEV outbreaks also have been reported from 14 countries in Africa, including Egypt, Kenya, Sudan, South Sudan, Central African Republic, Uganda, Chad, Republic of Djibouti, Algeria, Namibia, Morocco, Somalia, Ethiopia, South Africa, and Cameroon (Kim et al. 2014). In contrast to the epidemics in Asia, the African epidemics did not occur during monsoon rains but were often linked to contaminated water and humanitarian crises, occurring in refugee camps, during wars, or civil conflicts. Two small gt1 outbreaks were reported from Cuba (de la

Table 1. Morbidity and mortality from selected waterborne hepatitis E virus epidemics

Site	Years	Cases	Total deaths	Deaths of pregnant women
Delhi, India	1954–1955	29,300	266	102
Bosnia, Yugoslavia	1964	4984	98	82
Kathmandu, Nepal	1973	10,000	118	30
Kashmir, India	1978–1979	20,000	600	436
Xinjiang, China	1986–1988	119,280	705	51
Shebeli, Somalia	1988–1989	11,413	346	48
Maharashtra, India	1989–1990	3580	50	32
Kanpur, India	1991	70,000	48	13
Islamabad, Pakistan	1993–1994	3458	8	4
Darfur, Sudan	2004	2621	45	19
Kitgum, Uganda	2007–2009	4789	72	13
Nellore, Andhra Pradesh, India	2008–2009	23,915	315	Unknown
Dhaka, Bangladesh	2008–2009	4751	18	4
Rajshahi, Bangladesh	2010	2162	12	3
Ichalkaranji/Kolhapur, Maharashtra, India	2012	5165	36	5
Refugee Camps, Upper Nile, South Sudan	2012–2013	10,055	214	22
Biratnagar, Morang, Nepal	2014	7000	17	2
Raipur, Chhattisgarh, India	2014	5000	31	12
Napak, Karamoja, Uganda	2013–2014	1498	32	18
Sambalpur, Odisha, India	2014–2015	3000	50	2
Refugee Camps, Gambella, Ethiopia	2014–2015	1117	21	2
Shimla/Solan, Himachal Pradesh, India	2015–2016	5000–10,000	22	3
Beria, South Sudan	2015–2016	2475	21	Unknown

Data from Teo 2012; reprinted, with permission, from Cambridge University Press © 2018, and Nelson et al. 2016; reprinted, with permission, from Wolters Kluwer Health © 2016, respectively.

Caridad Montalvo Villalba et al. 2008). Although no outbreaks of HEV have occurred in the United States or Western Europe in the 20th or 21st centuries, many outbreaks of acute jaundice with high mortality in pregnant women were reported in the 19th century (Teo 2012). Apparently, improved sanitation and water treatment has eliminated HEV gt1 waterborne outbreaks in the United States and Europe during the 20th century.

During most of these outbreaks, there was no evidence of frequent person-to-person transmission. Often, only single cases were reported in a household, or multiple cases occurred simultaneously. However, in an outbreak in Uganda between October 2007 and August 2009, 2531 (78.6%) of 3218 cases lived in a household with more than one case (Teshale et al. 2010). In the households with multiple cases, 616 secondary cases (24.9%) occurred more than 8 weeks after the index case in the

household. Because the investigators were unable to identify HEV RNA in water supplies from households with multiple cases, they believed secondary cases were likely to have been transmitted from the index case. The epidemic persisted for >18 months, and the researchers concluded there was significant secondary person-to-person spread. Nonetheless, although the evidence supports the probability of some person-to-person spread of infection in this outbreak, the majority of infections appear to have been waterborne (Aggarwal and Gandhi 2010).

Although large epidemics of waterborne HEV have been reported frequently, endemic transmission during the dry season is also common in countries with recurring epidemics, when the levels of water contamination can increase. Many of the outbreaks in India, Nepal, and Bangladesh occurred during or immediately following monsoon rains. However, outbreaks are also associated with broken water pipelines,

K.E. Nelson et al.

use of untreated water from rivers or shallow wells for drinking, failure of water treatment plants, and inadequate chlorination of the water supply (Hakim et al. 2017). A large commercial laboratory in Dhaka, Bangladesh has found HEV infection to be the most frequent etiology of clinical hepatitis throughout the year (Sazzad et al. 2017). Surveillance of patients with acute jaundice in Northern Uganda has found most cases to be from HEV infection throughout the year (Gerbi et al. 2015). Persistent continuous transmission may be necessary to maintain a human reservoir of gt1 HEV between large outbreaks in endemic countries.

HEV GENOTYPE 2

The first outbreaks of HEV gt2 infection were recognized in Huitzililla and Telixtac, Mexico, in late 1986 (Velazquez et al. 1990). The first outbreak began in June, 1 month after the start of the rainy season. It resulted in 94 icteric cases and two deaths in women. This outbreak lasted 3 months. The second outbreak of 129 cases among 2194 inhabitants in Telixtac began in August 1986, about 3 months after the rainy season. One death occurred in a nonpregnant woman; another pregnant woman was ill but recovered. However, her 3-month-old infant died of unknown causes. The investigators studying this outbreak identified 32–34 nm viral particles in samples of stool from cases using immune electron microscopy. The genome of the Mexican virus was molecularly cloned and sequenced; it was found to have 76% nucleic acid identity overall with the Burma isolate and was therefore classified in a distinct genotype, HEV gt2 (Huang et al. 1992).

A waterborne outbreak of hepatitis E affecting >600 people was reported in 1995 in Namibia (Maila et al. 2004). This strain was virtually identical to the HEV gt2 virus from Mexico. Another outbreak occurred in 2004 in several refugee camps in Sudan and Chad. HEV isolates from this outbreak were genetically heterogeneous; 23 isolates from Sudan and five viruses from Chad clustered with gt1 strains, but four isolates were similar to gt2 strains from Mexico (Nicand et al. 2005). The epidemiology and clin-

ical features of gt1 and two viruses appeared to be quite similar. Other gt2 strains have been isolated from patients in Nigeria (Buisson et al. 2000) and the Central African Republic (Escriba et al. 2008). A reference sequence derived from the HEV gt2 isolate (Mex-14) from Mexico has been published recently (Genbank KX578717) (Kaiser et al. 2017).

RISK FACTORS FOR HEV GENOTYPE 1 AND 2 INFECTIONS

During community-wide outbreaks of HEV, the incidence is highest in adolescents and adults in the second through the fourth decades of life. Young children under age 10 have lower rates of infection and clinical illness (Figs. 2 and 3) (Rein et al. 2012). The reasons for the sparing of young children are not understood. However, it is possible that children consume less contaminated water, and thus may be exposed to HEV below the infectious dose. Recent evidence from Bangladesh suggests that children infected with HEV may lose detectable antibodies more quickly than adults, complicating the interpretation of cross-sectional studies of antibody prevalence (Kmush et al. 2016).

Most epidemiological studies of HEV have been performed during or following outbreaks, therefore risk factors for sporadic infection have not been well studied. To better understand the epidemiology and risk factors for HEV during various seasons and climatic conditions, a prospective study was performed involving a cohort of 1134 randomly selected subjects in a population of 23,500 persons in rural Bangladesh (Labrique et al. 2009, 2010b). At baseline, the HEV seroprevalence was 22.5%. During the first 12 months of follow-up, there were 49 seroconversions indicating an overall incidence density of 60.3 (95% CI: 44.6–79.7) per 1000 person-years. Of the seroconverters, 33 subjects reported at least one symptom of a hepatitis-like illness and six reported that they were jaundiced. There were no significant differences between seroconverters and controls in household size, location of primary employment, or socioeconomic status. The incidence was lower in individuals under age 10, with an incidence of 28.9 per 1000

Epidemiology of Genotype 1 and 2 HEV Infections

Figure 3. Estimated seroprevalence of hepatitis E virus (HEV) by age and global burden of disease region in 2005. (From Rein et al. 2012; reprinted, with permission, from John Wiley and Sons © 2012.)

person-years. The incidence was similar among males and females. The subjects were followed for another 6 months for observation during a monsoon season. During this follow-up, another 26 seroconverters were detected for 359 person-years, for an incidence of 72.4 (95% CI: 47.3, 106.1) per 1000 person-years.

A second prospective study was performed in which a clinical algorithm screening for signs or symptoms of hepatitis, such as abdominal pain, dark urine, jaundice, and clay-colored stools, was used to detect possible HEV infections among a population of 23,500 people who had routine household visits from a trained health worker every 30 days (Labrique et al.

2013). All subjects in the community over the age of 1 year were included in this study. Sera from subjects with symptoms possibly as a result of HEV infection were tested serologically. If HEV infection was confirmed, four age-matched controls were selected. Both cases and controls were interviewed to assess risk factors for infection. This study found several risk factors to be significant in a multivariate analysis, including recent exposure to a jaundiced person, travel to a town or city in the last 3 months, unsanitary toilet use, working outside the home, injections in the last 3 months, larger household size, and low household construction score (Table 2). This study suggests there may be multiple

K.E. Nelson et al.

Table 2. Multivariate conditional logistic regression model of risk factors for HEV disease^a

Characteristic	Manual (forced) model ^b			Stepwise selected model ^c		
	OR	95% CI	p Value	OR	95% CI	p Value
Gender (0 = male, 1 = female) ^d	0.30	0.07–1.20	0.088	-	-	-
Recent exposure to “jaundice” patient	63.50	8.07–499.50	<0.000	82.50	8.77–776.39	<0.000
Travel to town/city in the past 3 months	2.80	0.78–10.08	0.114	4.25	1.06–17.10	0.041
Unsanitary toilet use	4.39	1.02–18.98	0.048	5.14	1.20–22.01	0.027
Work outside the home	19.36	1.39–269.75	0.027	19.80	1.89–207.96	0.013
Outdoor work (farming/fishing/labor)	4.17	0.73–23.78	0.108	8.63	1.33–56.09	0.024
Injection in the last 3 months	18.44	2.10–162.05	0.009	15.50	1.97–121.76	0.009
Household size (≤ 4 , 5–6, ≥ 7 members)	0.49	0.29–0.84	0.009	0.17	0.05–0.56	0.004
Household construction score (1–6)	-	-	-	0.35	0.13–0.98	0.045

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^aOnly the models constructed using the liberal case definition are shown as the conservative case definition was extremely restricted by a low sample size.^bModel reflects explanatory variables of interest significant at the 25% level ($p < 0.25$) in univariate conditional logistic regression and retained at least 15% ($p < 0.15$) significance in the multiple, adjusted model.^cModel selected by forward and reverse stepwise conditional logistic regression, including variables significant at the 25% level ($p < 0.25$) in univariate analysis and retained in the final model if significant at the 10% ($p < 0.10$) level.^dGender was left out of the stepwise model as female gender was strongly inversely correlated with work outside the home or with performing outdoor work. Stratified analysis was not possible or appropriate because of extremely small numbers in each cell.

sources of person-to-person transmission in a low-resource rural community in a country with frequent, large rainy season epidemics.

A prospective study of 757 healthy army soldiers and police officers was performed in the Kathmandu Valley of Nepal in March to September 1992 and September 1993 (Clayson et al. 1997). At baseline, 186 (24.6%) of the subjects were anti-HEV immunoglobulin (Ig)G-positive. During the 6 months between March and September 1992, 19 persons seroconverted. Four of the 19 were jaundiced. During the 12 months between September 1992 and September 1993 another 35 people were infected. The incidence was highest in younger subjects, aged 12–19 years. The overall incidence of infection was 64 per 1000 person-years. The incidence of disease was 20 per 1000 person-years.

Another prospective study was performed in two villages in Egypt. The baseline prevalence of anti-HEV antibody was 67.7%. The study enrolled 919 villagers who were seronegative for HEV. Thirty-four seroconverters were identified indicating an incidence of HEV infection of 41.6 per 1000 person-years. All seroconverters were asymptomatic. There was no association

between seroconversion and socioeconomic factors, source of water, sanitation, hand and vegetable washing, or other environmental variables (Stoszek et al. 2006b). Both gt1 and gt3 HEV have been identified in Egypt, but gt1 strains are more frequent.

The reasons for the differences evident in the clinical and epidemiologic characteristics of acute HEV infections in Egyptian versus South Asian populations are not known. Young children have high seroprevalence of antibodies to HEV in Egypt (Kamel et al. 1995; Darwish et al. 1996; Fix et al. 2000), and asymptomatic HEV infections are common among adults, including pregnant women (Stoszek et al. 2006a), in contrast to South Asian populations. Monsoon rains with flooding do not occur in Egypt. However, exposure to water that is highly contaminated with HEV may be common in early life. It has been theorized that most adult infections in Egypt occur in people who had a primary infection in childhood and in whom antibodies are no longer detectable, and who clear a second infection later in life without developing symptoms by activating an immune memory response (Stoszek et al. 2006b).

RACE AND SUSCEPTIBILITY TO HEV INFECTION

Within the United States, blacks appear to have lower rates of HEV infection. The prevalence of anti-HEV IgG (caused presumably by previous gt3 or gt4 infection) in the National Health and Nutrition Study (NHANES) was 15.3% in non-Hispanic blacks, 22.3% in non-Hispanic whites, and 21.8% in Mexican-Americans (Kuniholm et al. 2009). Among non-Hispanic blacks, the anti-HEV IgG seroprevalence was lower in people with certain polymorphisms in the gene encoding apolipoprotein E gene (*APOE*), a protein that mediates lipoprotein metabolism. HEV seropositivity was significantly lower in subjects carrying the *APOE* ϵ 4 allele (odds ratio 0.5, 95% CI: 0.4–0.7) compared with those with the *APOE* ϵ 2 allele (Zhang et al. 2015). Also, in South Africa, where gt1 virus has been endemic, the prevalence of anti-HEV IgG was lower in black blood donors in South Africa than in white or mixed-race donors (Lopes et al. 2017).

HEPATITIS E IN PREGNANCY

High maternal and fetal morbidity and mortality are characteristic epidemiologic features of HEV gt1 infections in pregnant women. The pathogenesis of these more severe infections in pregnant women is not well understood. Severe or fatal infections are more common in late pregnancy, during the second or third trimesters.

One explanation that has been proposed for the more severe disease in pregnant women is the shift that occurs in the predominant immune response from a T-helper cell type 1 (Th1) to a Th2-dominated response in late pregnancy to protect the fetus by suppressing macrophage activation (Romagnani 1997). Changes in immunologic responses develop gradually throughout pregnancy and vary with increased estradiol and progesterone levels as the pregnancy progresses toward term (Robinson and Klein 2012; Krain et al. 2014). The somewhat immunocompromised status of women in late pregnancy could inhibit the development of an immune response capable of controlling an acute HEV infection (Krain et al. 2014).

However, other factors may contribute to the increased severity of HEV among pregnant women and their infants. Nutritional deficiencies exacerbated by increased nutritional requirements to sustain a pregnancy could contribute to more severe disease in late pregnancy (Kumar et al. 2017). A study of 144 pregnant women with HEV hepatitis found lower levels of pre-albumin, folate, and lower body mass index, and upper arm skinfold thickness than healthy controls (Kumar et al. 2017). Deficiencies in zinc, vitamin D, and anemia have been associated with an increased incidence of HEV infections in populations in rural Bangladesh (Kmush et al. 2016). Also, HEV infections have been associated with elevated levels of arsenic among pregnant women in Bangladesh (Heaney et al. 2015).

Pregnant women commonly develop hepatic cholestasis (“fatty liver”) as a complication of their pregnancy (Wong et al. 2008). This could result in a type of “acute on chronic” liver disease with more severe outcomes, when women are infected from waterborne HEV during late pregnancy. The status of pregnant women who develop fulminant HEV in comparison with those who control an HEV infection has not been well characterized prospectively, although a Th2 immune response to HEV infection has been well documented among pregnant women, as alluded to above (Pal et al. 2005; Krain et al. 2014).

Severe or fatal cases of HEV among pregnant women may present with fulminant hepatic failure (FHF), bleeding, eclampsia, or disseminated intravascular coagulation (Khuroo and Kamili 2003; Jilani et al. 2007; Patra et al. 2007). It has been hypothesized that pregnant women may have an increased viral load related to replication of HEV in the infant or the placenta (Khuroo and Kamili 2003; Bose et al. 2014). Pregnant women with FHF have been found to have higher viral loads than those with uncomplicated acute hepatitis (Kar et al. 2008). However, another study in India found higher serum viral loads in patients with acute hepatitis who survived than in those with fulminant hepatitis (Saravanabalaji et al. 2009). The interpretation of these reports is made difficult by the fact that the viral load could be reduced if

K.E. Nelson et al.

measured after severe liver disease has resulted in hepatic necrosis with declines in the production of virus. As a contributing factor, the HEV ORF3 protein has been suggested to interfere with the normal coagulation process, leading to hemorrhage during pregnancy (Geng et al. 2013).

Additional research to understand the immunopathogenesis of fulminant hepatitis in pregnant women infected with HEV should be a high priority. Two studies indicated that 9%–20% of maternal mortality in Bangladesh was accompanied by jaundice, likely reflecting HEV infection (Labrique et al. 2012; Shah et al. 2016) and further emphasizing the public health importance of gt1 and gt2 HEV. There is also a need to understand risk factors for severe disease. One study found activation of both Th1 and Th2 cytokines before HEV infection in pregnant women. However, none of the women studied developed fulminant hepatitis (Kmush et al. 2016).

PREVENTION AND TREATMENT

Prevention of gt1 and gt2 HEV infections is very difficult because of constraints on resources in which HEV is endemic. Water from rivers or surface water often contains high levels of microbial contamination. Deep tube wells can provide access to water that is free of contamination. However, tube wells often contain dangerous levels of arsenic, especially in Northern India and Bangladesh (Smith et al. 2000). Boiling water before drinking will inactivate HEV and other pathogens but is often impractical for daily use in low-resource countries. Chlorination also inactivates HEV and is often effective at slowing outbreaks (Girones et al. 2014; Guerrero-Latorre et al. 2016). However, a program to add chlorine to drinking water during an outbreak in Darfur, Sudan, in 2004 failed to prevent new HEV infections (Guthmann et al. 2006).

The use of an HEV vaccine to prevent HEV in high-risk populations is a more promising strategy. Two subunit vaccines have undergone phase 3 trials and been found to be effective (Shrestha et al. 2007; Zhu et al. 2010). However, only one vaccine has been licensed for use and it is only available in China (see Innis and Lynch

2018). This subunit vaccine is given in three doses at 0, 1, and 6 months and was found to be 86.8% (95% CI: 71% to 94%) effective in preventing infection 4.5 years after vaccination (Zhang et al. 2015). Additional research is needed to determine the efficacy of this vaccine in high-risk populations, especially pregnant women, using accelerated vaccine schedules suitable for outbreak situations (Nelson et al. 2014).

Ribavirin treatment of chronic HEV infections in transplant patients has been effective (Kamar et al. 2015). However, ribavirin treatment of pregnant women or other patients with fulminant hepatitis has not been reported. Although ribavirin is generally contraindicated in pregnant women because of the risk of teratogenicity, it might be relatively safe in pregnancies in the third trimester because the infant's organs have already developed. However, a risk-benefit analysis of ribavirin treatment in the third trimester of pregnancy is needed. Additionally, ribavirin is not likely to be as effective in controlling the immunopathology associated with HEV in pregnancy with severe or fulminant hepatitis as it has been in treating chronic infections in transplant patients. Better methods are needed to prevent and treat gt1 and gt2 HEV infections, especially in low-resource settings.

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K.E. Nelson et al.

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