International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 19-04-2019; Accepted: 22-05-2019
www.medicalsciencejournal.com
Volume 5; Issue 6; June 2019; Page No. 92-98

Seroprevalence of hepatitis e in patients with chronic liver disease: A study in Dhaka Shishu (children) hospital, Dhaka, Bangladesh

Dr. Ahmed Rashidul Hasan[1], Dr. Salahuddin Mahmud[2], Kamrun Nahar[3], Dr. Emdadul Haque[4], Dr. AKM Khairul Islam[5]

[1] RMO, Paediatric Gastroenterology, Dept. of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital Dhaka, Bangladesh.
[2] Assistant Professor, Paediatric Gastroenterology, Dept. of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
[3] Classified Specialist in Paedatrics Oncology, Combined Military Hospital, Dhaka, Bangladesh.
[4] Registrar, Paediatric Gastroenterology, Dept. of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
[5] RMO, Emergency, Observation and Referral Unit, Dhaka Shishu (children) hospital, Dhaka, Bangladesh

Abstract
Introduction: Super infection with HEV in patients with chronic liver disease (CLD) can cause severe hepatic decompensation leading to increased morbidity and mortality. This study aimed to determine seroprevalence of HEV infection among CLD patients compared to blood donors from Bangladesh.
Methods: CLD patients and a bunch ancient matched blood donors with traditional liver perform tests were evaluated for the presence of anti-HEV immune gamma globulin protein in their sera for proof of liver disease E. The risk factors were estimated.
Results: The mean age of CLD patients was 18 years (range: 1-18). 27.5% of patients were HEV IgG-positive. Among the controls 19.7% were positive for anti-HEV IgG. By multivariate analysis, there was no association between positive anti-HEV IgG and etiology of chronic liver disease, gender, literacy, accommodation, and number of family members in patients or controls. Mean age of patients infected with HEV in both groups was significantly more than the seronegative ones.
Conclusions: We found high seroprevalence of HEV-antibody among blood donors and CLD patients in our study, so we recommend more attention to hygiene of food and water. In addition, such patients should be informed about the potential risks and simple ways to prevent the disease in their regular life and travels. This issue must be concerned in cases of "acute on chronic" hepatitis in CLD patients.

Keywords: Hepatitis E, seroprevalence, chronic liver disease, Bangladesh

1. Introduction
Hepatitis E virus (HEV) has been concerned in most epidemics and sporadic cases of viral hepatitis in endemic regions [1] and is an important public health disquiet in many developing countries of southeast and Central Asia, the Middle East, northern and western parts of Africa, and Mexico, where outbreaks have been reported [2, 3]. HEV infection is generally a self-limiting illness with low mortality but may predispose chronic liver disease (CLD) patients to severe liver decompensation [4]. HEV is the causative agent of both water-borne epidemics and sporadic cases of viral hepatitis in regions with inadequate sanitation. Bangladesh with few suspected outbreaks of HEV [5] is expected to have a high chance of hepatitis E occurrence. However, there are few documented studies to explain the statistical characteristics of this infection in the general population, and specific groups of people like CLD patients. We studied the anti-HEV seropositivity in a group of CLD patients in Tabriz, and compared it to a group of healthy blood donors of the same region.

2. Materials and Methods
This study was 200 patients from Hepatitis Clinical Hepatology & Nutrition Dept. Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from 2016 to 2017, diagnosed to have CLD were evaluated for the presence of anti-HEV IgG antibody (DIA-PRO, Bangladersh) in their sera for evidence of hepatitis E. Age-matched subjects attended the center due to other diseases with normal liver function tests (LFT) and negative markers for viral hepatitis were also studied as controls (n=110). 5 ml venous blood samples were taken after interview and physical examination. Data were collected on patients' age, gender, marital status, number of children, literacy, place of birth, place of living, etiology of liver disease, anti-HEV IgG, viral hepatitis serum markers, and serum protein electrophoresis. Data were analyzed using "SPSS" Windows 10. Continuous variables were compared using the student's *t-test*. Correlations between nominal variables were analyzed using chi-square test (Fisher's exact where necessary). Potential predictor variables used in the logistic regression

analysis included race, etiology of liver disease, age and risk factors for viral hepatitis transmission. P<0.05 was considered significant.

3. Results

The mean age of CLD patients was 2.26±6.19 years (range: 1-16). More than 50% of these patients were aged between 1 to 10 years (M/F: 125/75). Mean age of controls was 4.54±8.73 years (range: 11-18). The male proportion of controls was 47.9%. No patients had a history of fulminant hepatitis. One hundred and fifty-eight patients had evidence of cirrhosis (79%), based on either a liver biopsy or clinical, laboratory, and radiologic findings. Seroprevalence and etiology of CLD is shown in Table 1. Fifty-five (27.5%) patients were HEV IgG-positive. Figure 1 shows seroprevalence of HEV in study population according to age groups. Mean level of serum albumin, SGOT and SGPT in cirrhotic patients was 3.7, 69.3 and 54.6 U/L, respectively which was not related to HEV seropositivity. Among the controls, 37 (19.7%) were positive for anti-HEV IgG. The higher prevalence of seropositivity for HEV infection in CLD patients in comparison with that of healthy donors didn't reach the statistical significance. Mean age of the patients infected with HEV in both groups was significantly more than seronegative subjects (P<0.005). There was a trend toward a higher incidence of HAV in rural inhabitants which didn't reach statistical significance. The mean age and number of family members in seronegative and seropositive patients were almost equal. By multivariate logistic regression, we didn't find any association between positive anti-HEV IgG and etiology of CLD, gender, literacy, accommodation (rural/urban), and number of family members in either patients or controls.

Table 1: HEV seroprevalence in the patients' subtypes of chronic liver disease, sex and accommodation (N=200).

Male gender	**N 121**	**HEV seroprevalence 29.6%**
Cause of chronic liver disease		
Cirrhosis		
Hepatitis B	61	31.1%
Hepatitis C	7	28.6%
Autoimmune	33	18.2%
Cryptogenic	52	30.8%
Primary biliary	4	50.0%
Alcohol	1	100%
Chronic hepatitis		
Hepatitis B	22	18.2%
Hepatitis C	10	30.0%
Autoimmune	6	16.7%
Wilson's disease	4	0%
Accommodation		
Rural	64	39.1%
Urban	136	18.4%

.

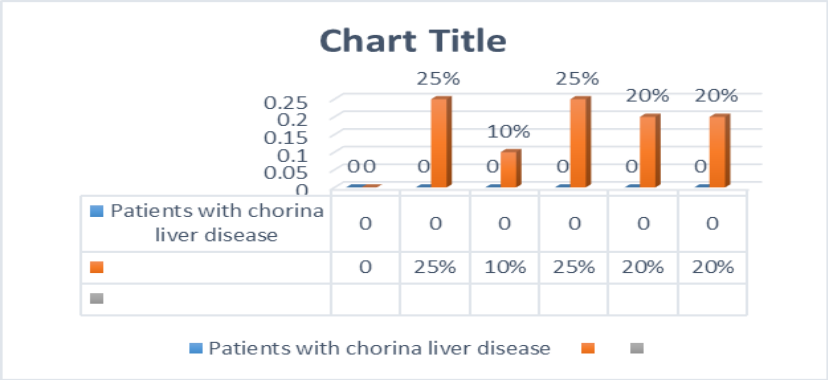

Fig 1: Age distribution of HEV seroprevalence (%) in patients with chronic liver disease compared with controls.

Table 2: Studies that evaluated the impact of hepatitis E virus (HEV) infection on chronic liver disease (CLD) or acute-on-chronic liver failure (ACLF) patients.

Co untry	**Region/City**	**Population**	**Number of patients**	**Cases of decompensation due to HEV infection, n (%)**	**Reference**
India	New Delhi	Cirrhotic patients with liver	CHD = 1	CHD = 6 (1. %)	[12]
		decompensation	ACLF = 2	ACLF = 21 (0%)	
India	Lucknow	ACLF patients	121	80 (66.1%)	[1]
India	New Delhi	CHBV patients with acute hepatitis		8 (18.6%)[1]	[16]
India	New Delhi	Cirrhotic patients with liver	10	10 (100%)	[1]

		decompensation			
India	Vellore	ACLF patients		(100%)	[18]
Bangladesh	Dhaka	ACLF patients	6	1 (21. %)	[28]
Bangladesh	Dhaka	Cirrh decompensation otic children with liver	2	1 (. %)	[2]
Nepal	Kathmandu	Cirrhotic patients with liver decompensation	12	12 (100%)	[1]
Nepal	Kathmandu	ACLF patients		(100%)	[2]
Pakistan	Karachi	ACLF patients		(100%)	[10]
		EUROPE			
UK	London	Acute HEV infected patients	0	(. %)	[8– 0]
Egypt	Mansoura	ACLF patients	100	1 (1 %)	[8]
Gambia	Banjul	ACLF patients	0	0	[ ]
USA	Houston	AMERICA HCV cirrhotic patients with cancer		0	[0]
USA	Ann Arbor, Bethesda, Maywood, Philadelphia, Pittsburgh, Charleston, Dallas	ACLF patients	681	(0. %)	[1]

Number of cases (n); hepatitis E virus (HEV); chronic hepatic decompensation (CHD); acute-on-chronic liver failure (ACLF); hepatitis A virus (HAV); chronic hepatitis B virus (CHBV); United Kingdom (UK); human immunode ciency virus (HIV) [1]. Two cases were superinfected with both HAV and HEV.

Impact of Acute HEV Infection on CLD in Asia. Asia is associate degree HEV-endemic space and several other outbreaks are rumored. The four major HEV genotypes have been reported in this area [46]. Nevertheless, the majority of cases in India and China are due to HEV genotype, whereas the majority of cases in Japan are due to genotypes and [46]. The rest report linking HEV infection to liver decompensation was in Pakistan [10]. In that study, 2 CLD patients were tested for hepatitis A (HAV) and HEV antibodies. Interestingly, the cause of sudden liver decompensation in all patients with ACLF included in the study (100%) was HEV superinfection. Seroprevalence of HAV was considerably higher than the seroprevalence of HEV (.8% and 1. %), probably because % to 100% of patients with CLD in this highly endemic area have been immunized against HAV infection (the HAV vaccine has been available since 1) [48]. Accordingly, HEV infection could be an important trigger of liver decompensation in CLD patients in this area. An increasing number of studies in this setting have evaluated this association in HEV-endemic areas in Asia (summarized in Table 2).

Hepatitis B

Bangladesh is in the intermediate prevalence zone of hepatitis B virus (HBV), with a 40% lifetime risk of acquiring the virus by its residents. Hepatitis B has been extensively studied in Bangladesh. The prevalence of HBV in Bangladesh is 5.4% with neonatal, perinatal, and preschool transmission, injection, treatment from quack, mass vaccination against chickenpox and cholera, haircut and shaving at barber shop have been identified as the principal modes of transmission of the virus in the country [21]. In a local study, liver biopsy was done in 141 inactive HBV carriers with no liver-related complains in order to evaluate the extent of hepatic inflammation and fibrosis. Although the patients were inactive HBV carriers, mild to moderate levels of necroinflammation (HAI-NI>7) was seen in 26% patients. Seventeen had severe hepatic fibrosis (HAI-F>3). A total of 10 patients had both moderate hepatic inflammation (HAI-NI>7) and sever hepatic fibrosis (HAI-F>3) [2]. Subsequently a much larger study evaluated 702 chronic HBV carriers detected incidentally. This later study exhibited low HBV DNA levels (>10^5 copies/ml) in 49.3% and normal about 50% (ULN; >42 U/l). In spite of having low HBV DNA and normal ALT, significant levels of patients had moderate hepatic inflammation (HAI-NI≥7) and severe hepatic fibrosis (HAI-F≥3).[23]Characteristics of chronic hepatitis B (CHB) have also been evaluated. Initially, the predominant genotype of HBV in Bangladesh was shown to be D (50%) followed by C (39%). Recently, we are analyzing about 500 randomly collected sera for genotyping and it appears that HBV genotype C is the prominent genotype of HBV in Bangladesh. As expected, genotype C is more frequently associated with raised ALT (94 *vs*50%) and more extensive hepatic necroinflammation (64.7 *vs* 36.4%) in Bangladesh [24]. Another study was conducted with 155 CHB patients to compare between HBeAg positive and negative infection. It was seen that although there was no significant difference in hepatic necroinflammation between these two groups, HBeAg negative CHB was associated with more advanced hepatic fibrosis (28.3 *vs* 19.6%) [25]. On the other hand, another study involving 159 CHB patients failed to reveal any correlation between severity of hepatic histo-pathological changes and HBV DNA level in both HBeAg positive and negative CHB [26]. In a more recent study, the utility of ALT levels in predicting liver disease severity has been assessed. This study of 255 CHB patients clearly demonstrated that the levels of ALT is not indicative of liver damage in many cases [27]. Economic burden of HBV on our economy has also been studied. It was calculated that if only 1°% of our HBV infected population receives treatment, it translates into US$ 16-1440 million per-annum [28]. Several clinical trials have been conducted in Bangladesh, like combination therapy with lamivudine and vaccine in CHB [29] and interferon and lamivudine in pediatric patients with CHB [30], which showed limited success and the more recent study of combination therapy with half dose and shorter duration pegylated interferon in combination with entecavir in CHB, which was very promising [31]. However, the study currently

ongoing in Bangladesh, that deserves special mention, is the phase III clinical trial involving a therapeutic vaccine (NASVAC) head to head with pegylated interferon in 160 CHB patients. Data emerging from the already completed phase I/II as well as this ongoing study suggests that NASVAC is likely to be as effective, but with much superior safety profile compared to the only other immune-modulator against HBV currently in the market, i.e. pegylated interferon [32, 33].

Hepatitis C

Several studies have been carried out in Bangladesh to assess the prevalence of HCV in different population. However, data vary considerably among regions and groups. In fact, in the absence of a properly designed population based study the exact HCV prevalence in Bangladesh remains a matter of debate. In one of the earliest publications in the 1990s, Khan *et al* reported zero prevalence of HCV in the country! [34] This was, however, contradicted by Akbar *et al* who found more than 5% prevalence of HCV in apparently healthy Bangladeshis [35]. Two decades later, in 2011, Mahtab *et al* reported 0.88% prevalence of the virus in adult residents of a locality adjacent to the capital city Dhaka [36]. However, at around the same time, a study by Ashraf *et al*. revealed a much lower prevalence of HCV at only 0.2% among the residents of an urban slum in Dhaka [37]. Outside Dhaka city, Rudra *et al*. found 6.25% prevalence of HCV in Mymensingh city of the country in 2011 [38]. and a year earlier the same author found the prevalence of HCV to be 0.04% in Khulna city. Both these studies were carried out among blood donors in the transfusion medicine departments of two different public medical colleges in these two cities respectively. The prevalence of HCV in Bangladeshi immigrants to Europe is also found in the published literature. Aliberch *et al* reports 0.09% prevalence of the virus among young Bangladeshi immigrants to Spain [39], while in a study by Uddin *et al*, the figure is higher at 0.6% among Bangladeshi immigrants to UK, which has the largest Bangladeshi immigrant population in Europe [40]. As expected high-risk population have a much higher prevalence of HCV in Bangladesh as elsewhere in the world. Shirin *et al* found the prevalence of HCV to be 24.8 and 5.8% respectively among intravenous and non-intravenous drug abusers.[21]Interestingly, this figure has been shown to be only 2% among patients with beta thalassemia major [41]. In the work by Mahtab *et al* the major risk factors identified for HCV infection in Bangladesh were treatment by unqualified and traditional practitioners, history of mass vaccination against smallpox, hair cutting and shaving by barbers and body piercing [46]. Chakrabarty *et al* identified lack of people's knowledge about transfusion transmitted infections as a risk factor for HCV transmission [42]. The prevalence of HCV infection was significantly higher among the intravenous drug abusers in a study by Shirin *et al*, but the study did not find any association between transmission of HCV and sexual promiscuity [21]. Waheed *et al* has observed that in developing countries like Bangladesh, nonimplementation of international standards regarding blood transfusion, shaving from barbers, reuse of needles for ear and nose piercing, reuse of injections, injecting drug users, tattooing, unsterilized dental and surgical instruments are important sources of HCV transmission [43]. In fact, road side barber shaving has been reported to be very high (34-49%) in Bangladesh [44]. According to a study by Mahtab *et al* genotype 3 is the predominant genotype of HCV in the country [45]. The study revealed that 41% had genotype 3, 31°% had mixed genotypes 3 + 4 and 21%% had genotype 1. Patients also had genotypes 2, 4, 5 and mixed genotypes 5 + 6, the figure being 1.6% in each case. The same group, in another publication, also reported higher prevalence of genotype 3 (89.2%) in Bangladeshi HCV infected patients. In this paper, they also found 8.1% genotype 1 and 2.7% mixed genotypes 5 + 6 [46]. There are several papers reporting treatment response in HCV infected Bangladeshis with standard combination regimen of pegylated interferon and ribavirin. In a recent study Rahman *et al*, it is observed that genotype 3 (a, b) patients attained 47.05% sustained virological response (SVR) as opposed to 100% SVR attained in genotypes 1 (a, b), 3 and 4 mixed, 2b and 4 HCV infections [47]. The same group observed late relapse of HCV in 4 of 52 patients with initial SVR over a 5 years follow-up period. Relapse was more common in patients with cirrhosis of liver (50%) against (2.17%) without cirrhosis [48]. Study reported that end of treatment response (ETR) achieved in 80% patients with genotype 3 [28]. This figure was 100% for genotype 1 and 100% for mixed genotypes 5 + 6. In 2.7% patients, treatment had to be discontinued due to side effects of medication and 5.4% patients were lost on follow-up.

Hepatitis E

Acute hepatitis due to hepatitis E virus (HEV) is endemic in Bangladesh. Although acute HEV is seen sporadically round the year and outbreaks are common in the monsoon and after floods which this allows sewerage contamination of supply and ground water. However, sporadic outbreaks are also reported [49]. Genotype 1 HEV is common in Bangladesh [49]. It has been shown that 58.33% acute viral hepatitis in Bangladesh is due to HEV. The virus is also responsible for 56.52% cases of fulminant hepatic failure (FHF) and 21.7% cases of decompensation of liver cirrhosis [50]. While HEV is associated with 80% mortality in 3rd trimester of pregnancy, it also remains the leading cause (21.7%) acute insult in patients with another potentially fatal liver disease, acute on chronic liver failure (ACLF) [51].

Distribution of liver diseases

In a recent retrospective study, data of 59,227 patients, aged from 1 to 18 years patients from the seven different administrative divisions of Bangladesh between January 2015 and 2016 were analyzed. Although all patients presented at the department of hepatology, 13.2% were diagnosed with liver diseases. Patients with liver diseases were largely laid low with chronic liver diseases (CLD) (37-69%). Complication of CLD, like viscus brain disorder, was less frequent in regions with higher aid system. Nonviral infections, like liver symptom and biliary ascarisis, weren't uncommon. Acute hepatitis was another very common entity and contributed to approximately 20% cases [52].

Hepatocellular carcinoma

Hepatitis B virus remains the leading cause of HCC in Bangladesh. Different studies estimate that in this country, 46.9 to 61% HCC is due to HBV. A recent study showed that HBV is responsible for 41% cases of HCC while HCV accounts for 5% and approximately 20.5% likely to be associated with fatty liver diseases. Mean age of HCC patients in Bangladesh is 18 years [53].

4. Discussion

Hepatitis E is one of the important hygienic harms in developing countries. There is no previous published epidemiologic data about hepatitis E from north-west of Bangladesh. Here, we studied the anti-HEV seropositivity in a group of healthy blood donors in our region and observed a higher prevalence of HEV seropositivity comparing to other reports from Bangladesh [6]. Even though the seroprevalence of HEV was higher among CLD patients, it was not statistically different from that of donors with normal LFT. Seroprevalence of HEV infection varies between 1-7% in countries like Australia [8], Germany [9], France [10] and The Netherlands [11]. In contrast, the seroprevalence rates in Asia [12-14], Africa [15] and South America [16] are higher and reported to be 5.5% to 71% in various studies. The socio-economic status and sanitary conditions prevailing in the community may explain the major differences in the prevalence patterns seen across the regions. HEV antibody has been reported as 3.8% in Turkey [17], 16.4% in Saudi Arabia blood donors [18] and 17.5% in general population of Pakistan [7]; neighbors of Bangladesh. The present study obtained a high prevalence of positive anti-HEV (27.5%) which is close to reports from local countries. Besides, higher prevalence of positive anti-HEV antibody in the third to fifth decennials when the person is more in touch with the community may be a result of recent increase in this enterically transmitted virus spread. The contemporary high prevalence of anti-HEV in CLD patients requires more attention to this group. It is not completely known how long the anti-HEV antibody persists after exposure. Reported cases of recurrent acute HEV infections (19) suggest that, at least in some patients, the anti-HEV antibody may not persist for a long time. Thus adult population remains vulnerable to acute HEV infection, which, in CLD patients can cause a severe illness. This group of patients, together with women of childbearing age will benefit from a protective HEV vaccine if this becomes available. In conclusion, seroprevalence of anti-HEV antibody among blood donors and CLD patients in our study in north-west of Bangladesh is high, especially when compared to a recent study from Tehran, Bangladesh which showed a prevalence of anti-HEV antibody to be 6% in CLD patients and 5% in controls [20]. We recommend more attention to hygienic status of food and water. In addition, such patients should be informed about the potential risks and simple ways to prevent the disease in their regular life and travels. This issue must be concerned in cases of "acute on chronic" hepatitis in CLD patients especially in regions with high prevalence.

5. Conclusion

We found high seroprevalence of HEV-antibody among blood donors and CLD patients in our study, so we recommend more attention to hygiene of food and water. In addition, such patients should be informed about the potential risks and simple ways to prevent the disease in their regular life and travels. This issue must be concerned in cases of "acute on chronic" hepatitis in CLD patients. Hepatitis E is one of the important hygienic harms in developing countries. There is no previous published epidemiologic data about hepatitis E from north-west of Bangladesh. Here, we studied the anti-HEV seropositivity in a group of healthy blood donors in our region and observed a higher prevalence of HEV seropositivity comparing to other reports from Bangladesh. In short, Bangladesh, like our neighbors harbor massive HBV and HCV-infected population. Being the third leading reason behind deaths of patients admitted in tertiary hospitals of the country. Liver diseases pose significant burden to the country's economy and healthcare delivery system. Moreover, HBV infection in Bangladesh is relatively unusual, nontreatment friendly and rather aggressive. Studies further demonstrate that considerable numbers of apparently healthy subjects in Bangladesh are unaware of the fact that they are chronically infected by HBV and many of them have already developed progressive liver damage. Local and regional strategies are, therefore, needed for containment and management of HBV infection in our region and our hepatologists, with their limited resources, are currently trying hard to address these issues. This will be further strengthened when organizations, like Miyakawa Memorial Research Foundation (MMRF), will come forward.

6. References

1. Panda SK, Datta R, Kaur J, Zuckerman AJ, Nayak NC. Enterically transmitted non-A, non-B hepatitis: recovery of virus-like particles from an epidemic in south Delhi and transmission studies in rhesus monkeys. Hepatology 1989; 10: 466-72.
2. Viswanathan R. A review of the literature on the epidemiology of infectious hepatitis. Indian J Med Res 1957; 45 (Suppl): 145-55.
3. Velazquez O, Stetler HC, Avila C, Ornelas G, Alvarez C, Hadler SC, *et al*. Epidemic transmission of enterically transmitted non-A, non-B hepatitis in Mexico, 1986-1987. JAMA 1990; 263: 3281-5.
4. Ramachandran J, Eapen CE, Kang G, Abraham P, Hubert DD, Kurian G, *et al*. Hepatitis E superinfection produces severe decompensation in patients with chronic liver disease. J Gastroenterol Hepatol 2004; 19: 134-8.
5. Ariyegan M, Amini S. Hepatitis E epidemic in Bangladesh. J Med Council Bangladesh 1998; 15: 139-43.
6. Aminiafshar S, Alimagham M, Gachkar L, Yousefi F, Attarchi Z. Anti-Hepatitis E Virus Seropositivity in a Group of Blood Donors. Bangladesh J Public Health 2004; 33: 53-6.
7. Hamid SS, Atiq M, Shehzad F, Yasmeen A, Nissa T, Salam A, *et al*. Hepatitis E virus superinfection in patients with chronic liver disease. Hepatology 2002; 36: 474-8.
8. Moaven L, Van Asten M, Crofts N, Locarnini SA. Seroepidemiology of hepatitis E in selected Australian populations. J Med Virol 1995; 45: 326-30.
9. Trautwein C, Kiral G, Tillmann HL, Witteler H, Michel G, Manns MP. Risk factors and prevalence of hepatitis E in German immigrants from the former Soviet Union. J Med Virol 1995; 45: 429-34.
10. Coursaget P, Depril N, Buisson Y, Molinie C, Roue R. Hepatitis type E in a French population: detection of anti-HEV by a synthetic peptide-based enzyme-linked immunosorbent assay. Res Virol 1994; 145: 51-7.
11. Zaaijer HL, Kok M, Lelie PN, Timmerman RJ, Chau K, van der Pal HJ. Hepatitis E in The Netherlands: imported and endemic. Lancet 1993; 341: 826.
12. Arankalle VA, Tsarev SA, Chadha MS, Alling DW,

Emerson SU, Banerjee K, *et al*. Age-specific prevalence of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. J Infect Dis 1995; 171: 447-50.
13. Koshy A, Richards AL, al-Mufti S, Grover S, Shabrawy MA, Pacsa A, *et al*. Acute sporadic hepatitis E in Kuwait. J Med Virol 1994; 42: 405-8.
14. Tan D, Im SW, Yao JL, Ng MH. Acute sporadic hepatitis E virus infection in southern China. J Hepatol 1995; 23: 239-45.
15. Grabow WO, Favorov MO, Khudyakova NS, Taylor MB, Fields HA. Hepatitis E seroprevalence in selected individuals in South Africa. J Med Virol 1994; 44: 384-8.
16. Pujol FH, Favorov MO, Marcano T, Este JA, Magris M, Liprandi F, *et al*. Prevalence of antibodies against hepatitis E virus among urban and rural populations in Venezuela. J Med Virol 1994; 42: 234-6.
17. Cesur S, Akin K, Dogaroglu I, Birengel S, Balik I. Hepatitis A and hepatitis E seroprevalence in adults in the Ankara area. Mikrobiyol Bul 2002; 36: 79-83.
18. Abdelaal M, Zawawi TH, al Sobhi E, Jeje O, Gilpin C, Kinsara A, *et al*. Epidemiology of hepatitis E virus in male blood donors in Jeddah, Saudi Arabia. Ir J Med Sci 1998; 167: 94-6.
19. Ke WM, Tan D, Li JG, Izumi S, Shinji Y, Hotta H, *et al*. Consecutive evaluation of immunoglobulin M and G antibodies against hepatitis E virus. J Gastroenterol 1996; 31: 818-22.
20. Shavakhi A, Esteghamat F, Sharifian A, Mohamad Alizade A, Khodadostan M, Somi M, *et al*. Evaluation of hepatitis E in cirrhotic patients, a case control study. Govaresh 2007; 12: 27-9.
21. Mahtab MA, Rahman S, Akbar SM, Khan SI, Uddin H, Karim MF, Ahmed F. Combination therapy of lamivudine and interferon alpha in pediatric patients with chronic hepatitis B at Bangladesh: a safe and effective therapeutic approach for pediatric CHB patients of developing countries. Int J Immunopathol Pharmacol. 2010; 23(2):659–664. [PubMed] [Google Scholar]
22. . Mahtab MA, Akbar SF, Rahman S. Response to combination therapy with ‘shorter duration’ and ‘half dose’ pegylated interferon and entecavir in chronic hepatitis B in Bangladesh. J Hepatol. 2012; 2(56(issue)):65. [Google Scholar]
23. 12. Akbar SMF, Mahtab MA, Aguilar JC, Onji M, Mishiro M. Therapeutic potential of a novel therapeutic vaccine containing both hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) administered through mucosal and parental route in patients with chronic hepatitis B. Hepato-logy. 2010; 52(Suppl 4):538–539. [Google Scholar]
24. 13. Mahtab MA, Akbar SMF, Rubido JCA, Uddin H, Khan SI, Rahman S. Therapeutic potential of a combined hepatitis B virus surface and core antigen vaccine in patients with chronic hepatitis B. Hepatol Int. 2013;7(4):981–989. [PubMed] [Google Scholar]
25. 14. Khan M, Husain M, Yano M *et al*. Comparison of seroepide-miology of hepatitis C in blood donors between Bangladesh and Japan. Gastroenterol Jpn. 1993; 28(Suppl 5):28–31. [PubMed] [Google Scholar]
26. 15. Akbar SMF, Hossain M, Hossain MF *et al*. Seroepidemiology of hepatitis viruses of chronic liver diseases in Bangladesh: high prevalence of HCV among blood donors and healthy persons. Hepatol Res. 1997; 7(2):113–120. [Google Scholar]
27. Mahtab MA, Karim F, Foster G, Akbar SMF, Rahman S. Prevalence and risk factors of asymptomatic HCV infection in Bangladesh. J Clin Experiment Hepatol. 2011; 1(1):13–16. [PMC free article] [PubMed] [Google Scholar]
28. Ashraf H, Alam NH, Rothermundt C *et al*. Prevalence and risk factors of hepatitis B and C virus infections in an impoverished urban community in Dhaka, Bangladesh. MC Infect Dis. 2010;10(1):208.[PMC free article] [PubMed] [Google Scholar]
29. 18. Rudra S, Chakrabarty P, Hossain MA, Akhter H, Bhuiyan MR. Seroprevalence of Hepatitis B, Hepatitis C HIV Infections in blood donors of Khulna, Bangladesh. Mymensingh Med J. 2010;19(4):515–519.[PubMed] [Google Scholar]
30. Aliberch MRM, Buxo AE, Gil BM *et al*. Indication of determination of antibodies against hepatitis C and A viruses in the protocol for the care of young immigrants. Gac Sanit. 2010; 24(4):288–292. [PubMed] [Google Scholar]
31. Uddin G, Shoeb D, Solaiman S *et al*. Prevalence of chronic viral hepatitis in people of south Asian ethnicity living in England: the prevalence cannot necessarily be predicted from the prevalence in the country of origin. J Viral Hepat. 2010; 17(5):327–335. [PubMed] [Google Scholar]
32. Shirin T, Ahmed T, Iqbal A, Islam M, Islam MN. Prevalence and risk factors of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus infections among drug addicts in Bangladesh. J Health Popul Nutr. 2000; 18(3):145–150. [PubMed] [Google Scholar]
33. Chakrabarty P, Rudra S, Hossain MA. Prevalence of HBV and HCV among the multi-transfused beta thalassemic major patients in a day care centre of blood transfusion department of Mymensingh Medical College Hospital. Mymensingh Med J. 2014; 23(2):235–241. [PubMed] [Google Scholar]
34. Waheed Y, Shafi T, Safi SZ, Qadri I. HCV in Pakistani: a systematic review of prevalence genotypes and risk factors. World J Gastroenterol. 2009; 15(45):5647–5653. [PMC free article] [PubMed] [Google Scholar]
35. Waheed Y, Safi SZ, Qadri I. Role of potash alum in hepatitis C virus transmission at barber’s shop.Virol J. 2011 May 9; 8:211. [PMC free article] [PubMed] [Google Scholar]
36. Mahtab MA, Rahman S, Khan M, Karim F, Sharif NM, Shrestha A. Genotypes of HCV in Bangladesh: Experience from a tertiary centre. Hungarian Med J. 2008; 2(4):577–581. [Google Scholar]
37. Mahtab MA, Rahman S, Karim MF, Khan M. Genotypes of HCV in Bangladesh: experience from a tertiary centre. J Gastroenterol Hepatol. 2008; 23(Suppl):27–28. [Google Scholar]
38. Rahman MZ, Perveen S, Mahmuduzzaman M *et al*. Peginterferon α-2a and rivabirin in the treatment of chronic Hepatitis C. Mymensingh Med J. 2014 Apr;23(2):335–340. [PubMed] [Google Scholar]
39. Rahman MZ, Ahmed DS, Masud H *et al*. Sustained virological response after treatment in patients with

chronic hepatitis C infection—a 5-year follow-up. Bangladesh Med Res Counc Bull. 2013;39(1):11–13.[PubMed] [Google Scholar]
40. Rashid MH, Akbar SMF, Takahashi K, Mahtab MA, Khan MSI, Alim MA, Ekram ARMS, Khan MMR, Arai M, Mishiro S. Epidemiological and molecular analyses of a non-seasonal outbreak of acute icteric hepatitis E in Bangladesh. J Med Virol. 2013; 85(8):1369–1376. [PubMed] [Google Scholar]
41. Mahtab MA, Rahman S, Khan M, Karim MF. HEV infection as an etiologic factor for acute hepatitis: experience from a tertiary hospital in bangladesh. J Health Popul Nutri. 2009;27(1):14–19.[PMC free article] [PubMed] [Google Scholar]
42. Mahtab MA, Rahman S, Khan M, Karim MF. Hepatitis E virus is the leading cause of acute-on-chronic liver disease: Experience from a tertiary centre in Bangladesh. Hepat Bil Pancreat Dis Int. 2009; 8(1):50–52. [PubMed] [Google Scholar]
43. Rahman S, Ahmed MF, Alam MJ, Debnath CR, Hoque MI, Hussain MM, Kabir AKMS, Karim MF, Khondokar FA, Mahtab MA *et al*. Distribution of liver disease in Bangladesh: a cross country study.Euroasian J Hepato-Gastroenterol. 2014; 4(1):25–30. [PMC free article] [PubMed] [Google Scholar]
44. Karim MF, Mahtab MA, Rahman S, Ahmed F. Hepatitis B virus related hepatocellular carcinoma is the predominant cause of liver cancer in Bangladesh. J Acute Dis. 2013; 1(1):35–37. [Google Scholar]
45. Abedin MF, Hoque MM, Islam ASMSM, Chowdhury MFI, Das DC, Begum SA, Mamun AA, Mahtab MA, Rahman S, Saha AK. Chronic liver disease is one of the leading causes of death in Bangladesh: experience by death audit from a tertiary hospital. Euroasian J Hepato-Gastroenterol. 2014; 4(1):17–20. [PMC free article] [PubMed] [Google Scholar]
46. Hoofnagle JH, Nelson KE, Purcell RH, Hepatitis E. Te New England Journal of Medicine. 2012; 6(1):12-12.
47. Kamar N, Bendall R, Legrand-Abravanel F, *et al*. Hepatitis E, Te Lancet. 2012; 8(2):88.
48. Hamid SS, Atiq M, Shehzad F, *et al*. Hepatitis E virus super-infection in patients with chronic liver disease, Hepatology. 2002; 6(2):8. lts of a serological study," Te National Medical Journal of India, vol. 1 , pp. 26 -268