

REVIEW
ARTICLE

Epidemiology of Hepatitis E in Iran and Pakistan

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Introduction

Hepatitis E virus (HEV) is a spherical, non-enveloped, single-stranded RNA virus ⁽¹⁻⁴⁾. It has five genotypes: genotype I (Asia-Africa), genotype II (United States), genotype III (Mexico), genotype IV (Beijing, China), and genotype V (Europe) ⁽⁵⁻⁷⁾. HEV is excreted in feces and is transmitted predominantly by the fecal-oral route, usually through contaminated water. Most of the HEV outbreaks have been observed during the rainy seasons or after floods ⁽⁸⁾. The reservoir of the virus during the inter-epidemic periods in endemic countries probably resides in the environment, in sub-clinically HEV-infected humans, and/or animals infected with an HEV-like virus. HEV infection can occur either in large epidemics in endemic regions, e.g., Southeast Asia, India, Central Asia, Africa, Mexico, Republics of the former Soviet Union, Afghanistan, Bangladesh, Borneo, Burma, China, Mongolia, Nepal, Pakistan, Thailand, Vietnam, and

some parts of the Middle East or in sporadic forms in developed or developing countries ⁽⁸⁻¹²⁾. Until 1997, hepatitis E was thought to occur only in developing countries but there are many sporadic reports from developed nations ^(13, 14). In countries where the virus is endemic, HEV is associated with more than 50% of sporadic cases of acute hepatitis. The disease

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is self-limited and clinical illness due to HEV infection is similar to other forms of viral hepatitis except in pregnant women in whom the illness is particularly severe with a mortality rate as high as 25% (4, 15).

Transmission of HEV infection during outbreaks primarily occurs through contaminated water (16). Evidence also exists that some animals can be reservoirs of HEV; for example, HEV infection has been demonstrated in swine (17). Swine and human HEV strains from a particular geographic region often appear to be genetically close (18, 19). HEV is a zoonotic pathogen and pigs are reservoirs. The data demonstrated the presence of HEV RNA in commercial pig livers sold in local grocery stores in the USA, thus raising a public-health concern for food-borne HEV infection (20). There are controversies about parenteral transmission of HEV infection. Some studies revealed that unlike other enterically transmitted infections, person-to-person transmission of HEV occurs infrequently (21). In hemodialysis patients the HEV infection may be transmitted from person to person in the hemodialysis unit as a nosocomial infection (22).

In Pakistan, HEV remains highly endemic, mainly affecting the adult population (23). Iran is a country with few suspected outbreaks of HEV (24). In this manuscript, we reviewed the literature of HEV infection in the populations of Iran and Pakistan to determine the seroprevalence and routes of transmission of the infection.

Materials and Methods

The researchers conducted a literature search using the *MedLine* (1966 to July 2008), *EMBASE/Excerpta Medica* (1980 to July 2008), *OVID* (1966 to July 2008), Google Scholar (for Local websites and medical journals), *SID*, *EMRMedex*, websites of Iranian universities and *IranMedex*. We did a manual search using citations in the previous publications of Pakistanian articles and tried to find the full text or abstract of them by another search in Google and sending letters to addresses of authors and ask for full text of the articles. We searched the *PakMediNet* and found 58 journals and searched them. The following keywords were used: "Hepatitis E," "Epidemiology," "Iran," and "Pakistan," and "Non-A Non-B." We used the data about the seroepidemiology, risk factors and transmission routes in the studies. In addition our research was restricted to English- and Persian-language articles. We excluded the similar articles retrieved through different search engines.

Geographic characteristics

Pakistan is located in southern Asia, bordering the Arabian Sea, between India on the East and Iran and Afghanistan on the West and China in the North. Pakistan have an old history and the Indus valley civilization, one of the oldest in the world which dates back to at least 5000 years before, spread over much of what is presently named Pakistan. Pakistan with a population of 164,741,924 is an under-developed country. The burden of HEV-related active viral hepatitis has been shown in various studies. Iran with a population of 65,397,521 is a developing country. Iran is located in the Middle East and acts as a bridge between the Indian subcontinent, Arab peninsula, Middle Asia, and Europe. This particular geographic situation, along with the mass immigration from Afghanistan and Iraq, have all affected epidemiology of HEV in this country. The accessibility to safe water, passage of sewage and using the healthy toilets are important in epidemiology of HEV infection. These indices are better in Iran than Pakistan (WHO report).

Epidemiology of Hepatitis E

Iran is a country with few suspected outbreaks of HEV (24). The first report of epidemic of HEV infection was reported by Hatami in 1991 from Kermanshah that had some mortality in pregnant women (25). At the same time, there was another report from Fereidoon-Shahr, Isfahan, with more than 100 cases. In 1992, about 154 cases were reported from Lordegan (Southwest of Iran) with a mortality of two pregnant women (24, 25). Studies in blood donors in Iran has shown that the prevalence of HEV infection is 7.8% in Tehran (the Capital of Iran) (26), 7.8% in Tabriz (27), and 11.5% in Khuzestan (28). The seroprevalence has increased significantly with age (27-30). These data have shown that the prevalence rate in Iranian blood donors are generally higher than figures reported from developed countries (0.4%-3.9%) (31, 32); although lower than those from other countries of the Eastern Mediterranean Region where reports of anti-HEV have been observed (27, 33). The prevalence of more than 5% correlates with the prevalence of endemic areas. The obtained value is higher than that obtained in Israel (Jews: 2.8% and Arabs: 1.8%) (34) and Ankara, Turkey (3.8%) (35), but less than rates reported for the Iraqi-Kurdish refugees (16.4%) (36) and general population in Pakistan (17.5%) (37).

A report from general population in Mazendaran (North of Iran) showed that 1.1% of children younger than 10 years and 7.2% of population between 20 and 25 years old were positive for anti-HEV IgG antibody. The prevalence was more common in rural areas, more dense families, and those with lower educational level ⁽³⁸⁾. A study in Nahavand, a city in Hamadan province, has shown the prevalence rate of 9.3% in general population ⁽³⁹⁾. A recent report from Isfahan revealed that the overall anti-HEV seroprevalence was 3.8% in general population ⁽²⁹⁾. The prevalence is even different in various cities in a certain province ⁽²⁹⁾. Another study on hemodialysis patients in Tabriz has revealed a prevalence rate of 7.4% ⁽³⁰⁾; another study from East Azerbaijan showed that 27.5% of patients with chronic liver disease and 19.7% of controls were positive for anti-HEV IgG antibody that showed the high variance in the epidemiology of infection in the country ⁽⁴⁰⁾. A population-based study in Nahavand indicated that the prevalence rate of anti-HEV IgG among healthy population was 9.6% ⁽⁴¹⁾.

In Iranian soldiers, the prevalence of HEV infection was 1.1% which was much lower than other reports. We believe that the reasons are improvement in sanitation and water supply which is supported by the fact that we have witnessed a decrease in the prevalence of HAV and HEV infections in young people in Iran ⁽⁴²⁾ (Table 1).

In Pakistan, HEV remains highly endemic, mainly affecting the adult population ⁽²³⁾ and sporadic cases of hepatitis E occur throughout the year. However, small outbreaks and epidemics of hepatitis E have been reported from the cities of Peshawar, Mardan, Abbottabad, Rawalpindi-Islamabad, Sargodha, Multan, Hyderabad, Quetta and Karachi. A large epidemic of hepatitis E occurred in one of the army garrisons at Lahore in

early 1995, when more than 600 cases were treated as inpatients ⁽²³⁾. In 1972, an outbreak of acute viral hepatitis was observed in an army battalion on field exercises. Within three weeks, about 250 cases of acute viral hepatitis were reported, and all of the infected persons had had a common source of drinking water (untreated river water) ⁽⁴³⁾. Hepatitis E outbreaks have been documented in military populations in Chad ⁽⁴⁴⁾, Djibouti ⁽⁴⁵⁾, Nepal ⁽⁴⁶⁾, Ethiopia ⁽⁴⁷⁾, and among Bangladeshi soldiers serving with the UN Forces in Haiti ⁽⁴⁸⁾, but apparently not American or Belgian Forces serving in Somalia ⁽⁴⁴⁾. This alarm the western military personals when they have a trip to an endemic region. Fortunately, there is not any outbreaks in military personals in Iran before, during and after the imposed war between Iran and Iraq (1981-1987).

During December 1993 and in the first three months of 1994, an explosive water-borne epidemic of HEV infection occurred in two sectors of Islamabad, Pakistan. In a survey of a population of 36,705 individuals, a total of 3,827 cases with acute icteric hepatitis were recorded with an overall attack rate of 10.4%. The water-borne nature of the epidemic was suggested by a study of the case distribution according to water supply. All the four reported adult deaths occurred among women in their third trimester of pregnancy with a case fatality rate of 11.4%, while the other four fatal cases were newborn infants of mothers with acute icteric hepatitis. Although the aggregation of cases within households was significantly related to the family size, the temporal relationship between cases in households with two or more cases revealed that 83.7% of 1,463 presumed secondary cases occurred within one month of the first case in the same household, which is not suggestive of a person-to-person transmission pattern of the disease ⁽⁴⁹⁾. A

study was conducted in two tertiary care teaching hospitals, *i.e.*, Khyber Teaching Hospital and PGMI Lady Reading Hospital, Peshawar, Pakistan in 2002. Amongst the total number of 148 with acute hepatitis, 21 (14.1%) suffered from hepatitis E. Most of the patients had a benign self-limiting illness ⁽⁵⁰⁾.

The prevalence of hepatitis E antibody in pregnant women was determined in 65 pregnant women. We found that the prevalence of HEV was 57% in

Table 1. Seroepidemiology of Hepatitis E in Iran.

Authors (Ref)	Province name	year	Group study	Anti-HEV Ab+
Aminiafshar, <i>et al.</i> ⁽²⁶⁾	Tehran	2004	Blood donor	7.8% (7/90)
Taremi, <i>et al.</i> ⁽²⁷⁾	Tabriz	2007	Blood donor	7.8% (31/ 399)
Assarehzadegan, <i>et al.</i> ⁽²⁸⁾	Khuzestan	2008	Blood donor	11.5% (46/400)
Saffar, <i>et al.</i> ⁽⁵⁸⁾	Mazandaran	2005	General population	1.1% in those aged <10 yrs 7.2% in 20-25 yrs
Ataci, <i>et al.</i> ⁽²⁹⁾	Isfahan	2008	General population	Overall, 3.8%
Taremi, <i>et al.</i> ⁽⁴⁰⁾	Hamadan	2008	General Population	Overall 9.3%
Somi, <i>et al.</i> ⁽⁴²⁾	Tabriz	2007	Chronic liver disease	27.5% in CLD 19.7% in Controls
Taremi, <i>et al.</i> ⁽⁴¹⁾	Tabriz	2005	Hemodialysis	7.4%
Ghorbani, <i>et al.</i> ⁽⁵⁹⁾	Tehran	2007	Military personnel	1.1%

pregnant women with jaundice, that HEV is endemic in Karachi, and that it occurs in pregnant women more frequently in the last trimester⁽⁵¹⁾.

An outbreak of hepatitis caused by HEV in Abbottabad, Pakistan was traced to fecal contamination of a water system. Of 109 men hospitalized with hepatitis, 104 (95%) had serologic evidence of acute hepatitis E. The prevalence of anti-HEV in this population before the outbreak was estimated to be 30%. The presence of anti-HEV IgG appeared to protect against clinical hepatitis or development of serologic evidence of new infection with HEV. This was apparently caused by an isolate of HEV that is genetically distinct from the HEV strain that caused the Sargodha outbreak. Genetic analysis of a fecal isolate of HEV from an outbreak in Sargodha indicated that it was closely related to isolates from China which passed across the Hindu Kush Mountains from Pakistan. In contrast, an isolate from the present outbreak that occurred in 1988 in Abbottabad was genetically related to South Asian isolates from India, Burma, and Nepal⁽⁵²⁾ (Table 2).

Table 2. Outbreaks of Hepatitis E in Pakistan.

Authors (Ref)	Name of city	Year	Group study	Anti-HEV +
Akram, <i>et al.</i> ⁽⁴⁶⁾	CENTO region	1972	Army battalion	250 cases
Rab, <i>et al.</i> ⁽⁵²⁾	Islamabad	1993	General population	3,827 pts with acute hepatitis
Malik, <i>et al.</i> ⁽²³⁾	Lahore	1995	Military personnel	600 pts admitted
Shams, <i>et al.</i> ⁽⁵⁴⁾	Karachi	2001	Pregnant with Jaundice	57% (37/65)
Saeedi, <i>et al.</i> ⁽⁵³⁾	Peshawar	2002	Admitted to hospital	14.1% (21/148)
Bryan, <i>et al.</i> ⁽⁵⁵⁾	Abbottabad	2002	Hospitalized Military personnel	95% (104/109)

military conflicts in the border of Pakistan and Afghanistan. Sporadic cases of symptomatic HEV infection have been reported in United States travelers and UK visitors to developing countries including Pakistan⁽⁵⁴⁾. The western people should be aware of the infection and take care of themselves. Attention to water supply is very important. However, primary prevention of HEV infection is the cornerstone of HEV control in our region and solely depends upon the improvement of the sanitary conditions of the society, provision of sanitary water, proper disposal of wastes, and avoidance of contamination of food. Contaminated water is a potential source for the spread of this transmissible enteric disease. Pigs and animals have a minor role in HEV infection in our region. Preparing sanitary water for agriculture, especially vegetables, avoiding contamination of water pipelines with sources of infection, improving the knowledge and culture to preserve the hygiene of water, and suspicious of HEV infection in patients with hepatitis are all necessary. Genetic and immunologic studies of cases of sporadic and outbreak infections help in detecting the port of entry, transmission control and prepare of an effective vaccine in the future.

Conclusions

On two borders of Iran, it is a war-like situation. Due to the damage to water supply infrastructures and its contamination with sewage, report of cases of HEV infection in general population and military personnel is a serious health problem. Traveling to Iraq, Pakistan, and Afghanistan should be asked in approach cases with clinical symptoms of acute viral hepatitis. Helping these countries by funding and donating materials for health education campaign and providing water and sanitation measures are good strategies for controlling the infection⁽⁵³⁾. The number of outbreaks in Iran is less than Pakistan which is attributed to a better level of sanitation and water supplies especially in rural areas of Iran. Outbreaks in military personals in Pakistan have gained more attention for an ongoing unrecognized

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