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REVIEW ARTICLE

Hepatitis C infection in Iran; A review article

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INTRODUCTION

Hepatitis C is a global health problem worldwide affecting over 170-200 million people and the virus is distributed worldwide with prevalence varying between different countries from 0.2 up to 40% (1,2). Hepatitis C virus (HCV) is spread parenterally, either through intravenous drug use or, in lesser-developed countries, through transfusion of blood products and contamination during medical procedures. Despite a declining incidence of new infections, the burden of disease, both in terms of mortality and in terms of cost, is expected to increase over the next decade and HCV infection will be a potential cause of substantial morbidity and mortality in the future (1,2). Hepatitis B is a preventable infection by vaccination and the prevalence rate has been decreased in our community, however, hepatitis C is an emerging disease. Hepatitis C as the first cause of liver disease necessitates further liver transplantation (3-6).

HCV can be easily transmitted through blood products and infected syringes, and infection rates are typically high among intravenous drug users (IDUs) (7-10). IDUs are at high risk of acquiring parenterally transmitted diseases especially HIV and HCV infections (11). Hemophilia and thallassemic patients are prone to be infected with HCV infection, too. Control of HCV infection is an important public health concern because the majority of infections do not resolve but lead to chronic infection (3,12). Epidemiology and routes of transmission of hepatitis has been changed during the past 18 years. As the sensitivity of HCV screening tests had increased, new viral infection transmittable through blood products has been virtually eliminated in developed countries and had decreased in developing countries (13).

In this manuscript studies about epidemiology, prevalence, and transmission of hepatitis C in Iran and adjacent countries are reviewed.

Methods

A variety of sources were used to access data for this review. A *MEDLINE* search (1970-2005) of published articles was performed with key words "hepatitis C", "HCV" "prevalence", "thalassemia", "hemophilia", "blood donor", "intravenous drug users", "transfusion", hemodialysis, "Iran", "Afghanistan", "Pakistan", "Iraq", and " Turkey".

Modes of transmission

The main risk factor for acquiring HCV infection before the routine anti-HCV screening of blood donors was blood transfusion (14,15). Nevertheless, now the relatively high proportion of non-transfused hepatitis C cases suggests that transfusion is not the predominant route of transmission of HCV in Iran. The development of tests for surrogate markers for HCV and screening

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of blood donors has decreased the risk of HCV transmission to 0.001% per unit of transfused blood in developed countries. Nowadays, intravenous drug abuse is the major risk factor for HCV infection (16). Injecting drug use now is responsible for at least more than 60% of new cases of HCV infection worldwide. Because of sharing contaminated needles and other equipments used in injection, use of shooting galleries, cocaine use, unsafe sexual activities, and sharing the shaving equipments, IDUs constitute one of the most important groups at risk of being infected with HCV (15,17). In deed, it has been identified as the most common viral infection affecting IDUs (11). Rates of anti-HCV prevalence among IDUs vary by region, but exceed 20% in IDUs in the world. If the prevalence would be high as in Pakistan (at least 90%) , the HCV infection will be expand from IDUs to general population and it alarms other countries to understand the risk factors for transmission of infection and to stop it as soon as possible (18). The risk of acquiring the hepatitis C with 80% of young IDUs infected is within the first year (19). Nosocomial transmission of HCV seems to occur more frequently in developing countries because optimal precautions may not be taken. Therapeutic injections by health care providers (20), shaving by barbers, tattooing and ear-piercing, known to be associated with HCV infection (21,22), are common in developing countries. The sexual transmission of HCV infection is possible, but it is relatively rare and most of studies showed nearly 5% of infected cases in heterosexual multipartners (23). Anti-HCV positivity is clearly associated with presence of anti-HIV antibodies in all studies (24). The risk of transmission of HCV infection from infected mothers to infants is very low and less than 5% (25), however, in HIV-positive mothers with high levels of HCV-RNA, this route will play a significant role.

Modes of transmission in Iran

In a study in Iranian blood donors, transfusion, undergoing endoscopy, extramarital sexual activities, non-intravenous (IV) drug abuse, IV drug abuse, and receiving wounds at war were found to be independent risk factors of being HCV-positive (Odds ratio: 17, 4, 42.2, 34.4, 52.8 and 5.2, respectively) (15). No apparent risk factor could be demonstrated in 24.5% of the positive cases (15). There are certain medical procedures, lifestyle patterns, and customs and cultural matters in Iran that predispose people to a number of HCV risk factors (15).

To clarify the possible risk factors, numerous studies have been achieved in Iran especially in prisons. In Guilan province, of 460 inmates, 209 (45.4%) were anti-HCV positive and 88.9% of intravenous drug abusers were infected. HCV-positive status was significantly associated with intravenous drug use, skin tattoos and duration of imprisonment (26). Another study in 427 drug abuser inmates in the central prison of Hamadan, showed a total number of 149 IV drug abusers (IDA) and 278 non-IV drug abusers (NIDA). The overall rate of antibody positivity among inmates was 30% for HCV. The seroprevalence of HCV infection among drug abuser prisoners in comparison with the general population in Iran is quite high (30% vs.0.2%). The results indicate the importance of policies to prevent transmission of HCV infection during and following incarceration (27). In a study in 226 gypsies of Southwest of Iran, 7 were positive for anti-HCV. Tattooing and phlebotomy are very common practices among gypsies (28).

Another study was conducted among HCV positive individuals referred to Ahwaz Jundi-Shapour University Hospitals from 1999 to 2003 (29). A total of 514 subjects were studied for HCV, among whom 254 were HCV-positive. Transfusion (52%), non-intravenous drug abuse and IV drug abuse (14.5%), hemodialysis (10%), receiving

wounds at war and extramarital sexual activities (2.4%), as well as tattooing (3.6%) were found to be independent risk factors (29).

In order to determine whether HCV infection of index cases increases intrafamilial transmission (sexual and nonsexual contacts) of HCV, 300-household contacts of 60 index cases (40 males and 20 females) of HCV infection and 360 matched controls in Ahwaz Jundi-Shapour University hospitals were enrolled. Only 4 of 300 (1.33%) cases of household contacts without percutaneous risk factors were positive for HCV-Ab while the remaining 296 family contacts were negative for anti-HCV. The mean age of the index cases was 28.4 years. The anti-HCV frequencies in parents, spouses, children of the index cases were 0.87% (1/115), 3.39% (2/59) and 0.79% (1/126), respectively. The prevalence of positive HCV Ab among household contacts (1.33%) was not significantly higher than that in the controls (1%). Intrafamilial transmission of HCV is not the significant transmission route and sexual transmission does not seem to play a role in the intrafamilial spread of HCV infection. Intrafamilial transmission of HCV is possible but occurs at a low rate (30).

Modes of transmission in the neighbors

HCV is generally transmitted by the parenteral route. Family members of infected patients and low socio-economic status also correlate with an increased risk of HCV infection. Non-sexual household contacts such as sharing tooth brushes, nail clippers and razor blades are risk factors for HCV transmission in Pakistan (31,32).

In developing countries including Pakistan, the risk of HCV transmission through blood transfusion is unknown but considered to be high due to the lack of appropriate screening of blood (33). Low educational level and/or low socio-economic status has also been associated with the prevalence of a number of infectious diseases. It seems that blood transfusion is still the major cause of HCV transmission in Pakistan (34). It can be safely assumed that testing for HCV in the rural areas of the country is even less frequent, making blood transfusions still the major cause of HCV transmission in the country. Pakistan has a larger problem in terms of hepatitis C compared to its eastern and western neighbors (India and Iran) as well as others in the region (Saudi Arabia and Turkey). Community trends like reuse of disposable and/or glass syringes, repeated use of potentially contaminated razors by barbers, improper dental practices (16) and other risk factors seem to be unchanged. Widespread practices such as unsafe injections, improper disposal of hazardous waste, recycling of used syringes without proper sterilization, sharing of needles by injecting drug users and unsafe sex are believed to facilitate the transmission of these infections, resulting in high prevalence rates in the country (16,35). I visited two cases with post-transfusion hepatitis C from south of Iraq last year. I am sure that the screening of all blood products in Iraq is not valid and it seems that transfusion has an important role in transmission of HCV infection in Iraq.

There is an enormous dependence on parenteral therapy for treatment, both in the form of injections and infusion of drips, driven by cultural beliefs in the power of parenteral therapy. The use of inadequately sterilized undisposable medical materials, e.g., needles and scalpels, has also been shown to transmit HCV (36). There are some evidence of occupational and nosocomial transmission of HCV infection. Inadvertent needle-stick injuries and lack of application of universal precautions may be contributing factors (37). In one Pakistani community, HCV seroprevalence was 6.5%, and individuals who received more therapeutic injections were found to be at a higher risk of infection (38). Pakistan has one of the highest frequencies of injections in the world. The average number of injections per person per year is

8.5 and 49% of patients receive injections at their first outpatient visit (16). In addition to the unnecessary use of injections, injection practices are not safe in the country. Another risk factor in Pakistan is excessive use of barbers for shaving (39).

There are both geographic and temporal differences in the patterns of HCV infection. For example, vastly different countries, including the Iraq, Turkey, Pakistan, belong to regions of the world with different overall average prevalences of HCV infection that is related to different status of the health, and risk factors.

HCV global magnitude in general population

In Iran, we do not have an overall estimation of HCV infection and there are scanty studies addressing HCV prevalence. Overall estimation of HCV infection can be used for health programming and promoting HCV infection programs in our country. Recently we did a meta-analysis for estimation of HCV prevalence in general population in Iran (Alavian et al, 2009, In press), and found that the prevalence in several provinces was varied from 0% in Khuzestan and Tehran provinces (40,41) to 1.3% in Guilan province (42). Reported percentages were homogenous and had statistical significance (test for heterogeneity: Q= 1607.73, df=11, p<0.001). Therefore, the overall estimation of HCV prevalence in Iran according to data of eight provinces and ELISA detecting test (for HCV-Ab) was %4.45 (95%CI: 1.29– 7.61%). In two studies from Chaharmahal-va-Bakhtiari and East Azarbaijan confirmatory tests were not applied, therefore the results were excluded from the final analysis. Prevalence of HCV in general population in Iran with Survey Data analysis according to information of 6 provinces is %0.16.

In one Pakistani community, HCV seroprevalence was 6.5%, and individuals who received more therapeutic injections were found to be at a higher risk of infection (38). In Iraq, HCV-antibody seroprevalence among pregnant women has been recorded 3.2%, a figure that may reflect seroprevalence among normal population (43).

HCV global magnitude in blood donors

The prevalence of anti-HCV antibody among blood donors varies from 0.12% in Tehran (15), 0.5% in Babol (15) and 0.38-1.1% in Kashan (44) from Iran, 3.68% (31) and 5.31% (45) in Pakistan. Although there are not any published data from Afghanistan and Iraq, the situation should be serious in these two countries because of war. Table 1 represents the prevalence of HCV infection in blood donors.

Table 1. Prevalence of HCV infection in blood donors

Country	Author(s)	Sample size	HCV seropositivity, +/total (%)	EIA generation
Iran	Alavian et al. (15)	Cross sectional-First Blood donors	(0.12%)	Second
Iran	Afzali et al. (44)	Cohort	4774/ 43731 (0.38-1.1%)	ND
Iran	Aghajanipoor et al. (46)	Cross sectional	79/16576 (0.5%)	Third
Pakistan	Sultan et al (31)	Cohort in 10 years	1529/41 498 (3.68%)	Third
Pakistan	Khokhar et al (45)	Volunteer male donors	3762/ 47 538 (5.31%)	Third

HCV global magnitude in drug abusers

Injecting drug use has been the predominant mode of transmission during the past 40 years in developed countries, and now accounts for most newly acquired infections in many other countries especially in developing countries. Although increasing infection rates among young injection drug users during the first 2-3 years of injection have been slowed in recent years, incidence among new injectors remains high. As expected, the prevalence of anti-HCV antibodies in IDUs has been extremely high.

Nowadays, intravenous drug abusers with an incidence around 50-100% of anti-HCV positive subjects all over the world not only have the highest prevalence of HCV infection but also constitute a potential reservoir of HCV in the community. In Iran, the intravenous drug users (IDUs) had HCV infection between 38% and 46.6% (27,28,30).

Hepatitis C exposure and antibody positivity rates among injection drug users have been reported to be higher than 50% compared to 10% in the same general population (47-49).

HCV global magnitude in hemophiliacs

Patients with hemophilia constitute a high-risk group for acquisition of HCV infection. Transmission of HCV via blood products has been a significant source of hepatitis C infection for patients with hemophilia. Extensive seroepidemiological studies have shown that 60–91% of patients with haemophilia have antibodies to HCV (50,51). The prevalence of HCV infection in Iranian hemophilic patients was 15.6% in Fars and 76.7% in north-west of Iran (52). Recently we did a meta-analysis and found the prevalence rate of anti-HCV Ab by Elisa among Iranian hemophilic patients to be 40.8% (31.08-50.59%) (Alavian et al. 2009, in press).

HCV global magnitude in thallassemic patients

HCV infection among Iranian thalassemic patients has a prevalence rate between 15.7 and 63.8% (53,54). In our experience on thalassemic patients in Tehran, 24.2% were anti-HCV positive. HCV seropositivity was significantly associated with longer history of transfusion, but patients who had received their first blood transfusion after implementation of compulsory blood donors screening in Iran in 1995, had a significantly lower rate of HCV infection compared to those transfused after then (55). The prevalence rate was 67.3% in Iraq (56), 40% in Saudi Arabia (57), and 14% in Turkey (58). In our recent meta-analysis the prevalence rate in 14 provinces in Iran was 15.77% (between 12.60 and 18.92%) (Alavian et al. 2009, in press). Table 2 summarizes the prevalence of HCV infection in high risk groups in Iran.

Table 2. Prevalence of HCV infection in high risk group in Iran

Author(s)	Ref. year	Risk group	HCV seropositivity, +/total (%)	EIA generation
Zali et al (59)	1995	IDUs	182/402, (45.3%)	Third
Mohamad-Alizadeh et al (27)	2002	IDUs	128/427, (30%)	Third
Alavian et al (60)	2001	Hemophilia	106/176, (60.2%)	Second
Karimi et al (52)	2001	Hemophilia	44/281, (15.65%)	Third
Alavian et al (53)	2002	thalassemia	(24.2%)	Second
Akbari et al (61)	2007	thalassemia	(25%,)	Third
Alavian et al (62)	2003	Hemodialysis patients	111/838 (13.2%)	Third
Jabbari et al (20)	2008	Hemodialysis patients	23/93 (24.7%)	Third

HCV global magnitude in patients on hemodialysis

HCV infection is an important issue in hemodialysis (HD) patients and the prevalence of anti-HCV Ab varies geographically, both inside and between countries (21,22). The reported anti-HCV sero-positivity was 71% from Kuwait (63) and 13.2% in Iran (62). The high prevalence of sero-positivity for HCV among hemodialysis patients was initially attributed to blood transfusions for treatment of uremic anemia in this population (64-68). Some investigators have suggested a decline in HCV prevalence among HD patients in recent years, mostly attributable to strict adherence to universal precautions and with (69-75) or without (47,48,76) observing isolation measures. This decrease is more significant and was reported from Iran (48,49). However, several recent reports have failed to recognize blood

transfusion as an independent risk factor in HCV spread among HD subjects (77-89). Indeed, erythropoietin prescription from the late 1980s onward reduced the HD patients' need for blood transfusion. Furthermore, introduction of sensitive tests for screening of blood donors has markedly reduced the risk of HCV transmission through blood product transfusion. Nonetheless, considering the fact that new HCV infections do still occur in patients without a history of transfusion, the duration of hemodialysis is increasingly being considered as a risk for HCV infection (90,91). Almost all recent surveys on the subject have congruently suggested the length of time on HD as a risk factor for HCV seropositivity (62,78-85,92-100).

Nosocomial patient-to-patient transmission of HCV infection among HD patients is suggested by several investigators who performed phylogenetic analysis of HCV viral isolates (80,101-107). Lack of strict adherence to universal precautions by staff and sharing of articles such as multidose drugs might be the main mode of nosocomial HCV spread among HD patients (103,105,107-109).

Discussion

There are enough evidences to support that imprisonment and more specifically syringe sharing in prison may be an important risk factor for HIV and HCV infections (17,110-113). Injecting drug use and syringe sharing in prisons are common among IDUs (110,114-116). Syringe sharing in prison is strongly and independently associated with HIV and HCV infections (17,110). This provides further evidence that prisons are places where IDUs who continue to inject are at high risk of HIV and HCV infections (17,110). In prisons, syringes tend to be used by many individuals. Thus, the risk of syringe contamination by these viruses is much higher in prisons than outside where syringes are usually shared with only one or two other subjects (114). In most prisons, it is not possible to entirely prevent the injection use of illicit drugs. The lack of access to new injecting equipment in the majority of prisons results in prisons effectively acting as an incubator for the hepatitis C epidemic. However, injection with contaminated equipment could be substantially reduced if sterile injection equipment is available. Pilot projects which provided sterile injection equipment in prisons (via syringe vending machines) showed no any adverse effects such as increased injecting drug use or offences against prison personnel (17). The good opportunities in prison to contact large number of IDUs over longer periods should not be missed. There should be specific activities to repeatedly counsel imprisoned IDUs on the risks of parenterally transmitted infections.

A range of prevention measures for IDUs has been implemented including syringe exchange programs, syringe vending machines, increased outreach efforts, and access to methadone maintenance treatment (MMT). Many studies have shown the lower levels of current syringe sharing among IDUs on MMT (117,118). Other risk factors such as tattooing in prisons are important in transmission of HIV and HCV infection (110,111,119,120). Educating prisoners about this important potential route for transmission of HIV and HCV is important. Syringe exchange and distribution is the primary HCV prevention strategy targeting IDUs, although evidence of risk reduction impact is stronger for HIV (121,122) and there are only modest evidences of impact regarding HCV (118,123,124). High efficient of transmission of HCV infection and potential for transmission via contaminated injecting equipment other than needles and syringes, such as filters and spoons are responsible for this difference (8,125,126). The emphasis by some programs on needles and syringes as disease vectors to the exclusion of other equipment may also contribute to HCV spread. Meanwhile, there is growing epidemiological evidence based on the risk factors associated with

HCV transmission. We need to develop new ways to fill the knowledge gap regarding HCV prevention.

Despite the growing evidence that hepatitis C is an urgent public health issue, few countries have developed strategic national responses to address the hepatitis C epidemics within their populations. Since people who inject or have injected illicit drugs are the main group infected in almost all local epidemics (11), hepatitis C responses, where they do exist, have largely focused on harm reduction. Although significant advances have been made in preventing HIV infection amongst IDUs with harm reduction programs, both prevalence and incidence of hepatitis C remains high amongst IDUs (127-129).

The data are from some cross-sectional studies in IDUs or as case control studies in blood donors or population-base studies would clarify the importance of IDUs as the main cause of hepatitis C in our region now. We need a surveillance system to follow the prevalence and incidence of infection in IDUs in our region. The inability of any country, even those with established national hepatitis C policies, to prevent large numbers of new infections, has led some to question the effectiveness of harm reduction in relation to hepatitis C prevention (130).

Conclusion

It is very clear that the prevalence of HCV infection in general population in Iran is much less than our adjacent countries. The epidemiology and prevalence of HCV infection has changed in many countries in the world and in Iran, too (131).

Harm reduction as the core activity of triangular clinics serves the infected ones well while other supportive services help healthy but at risk population prevent the spread of HIV, HCV and other related ailments. We hope the already-in-place program of harm reduction gets national to cover all high-risk populations including IDUs in and out of prison (132).

Continued education of the public and healthcare professionals will play an important part in control of this problem since injections in the healthcare setting that are reported as a risk factor for acquisition of hepatitis B and C in the community.

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