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Occult Hepatitis B Infection and Its Role in Blood Safety: a Review

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Abstract

Background: Blood transfusion plays a great role in public health and the blood safety still has remained a main concern. HBV has been considered as one of the most prevalent blood borne infections. It is estimated that chronic HBV affects 350-400 million people worldwide. Comprehensive knowledge about HBV has high importance in Iran due to high number of blood dependent patients.

Material and methods: The data used in this research are derived from articles obtained by searching keywords like occult hepatitis B infection, thalassemia, hemophilia, hemodialysis, co-infection and blood transfusion in databases including PubMed, Google Scholar and Scopus. The prevalence, genotypes, HBV-HCV co-infection, HIV-HBV co-infection and their role in blood transfusion and blood safety are discussed in this review article.

Results: Iran is in intermediate endemicity region and studies have reported that between 10–60% of the Iranian population has the evidence of HBV infection, with 2-7% being chronic carriers. In blood donors the rate of infection is lower than general population. The occult hepatitis B infection is the main concern in blood safety due to transmission of the HBV via seronegative blood components. Iranian researches have reported a 1-2% prevalence of occult hepatitis B infection among Iranian blood donors.

Conclusion: Based on our review findings the prevalence of HBV and occult hepatitis B infection in Iran is moderate, which shows the importance of taking necessary steps to reduce the transfer of infection via blood and its components.

Keywords: Hepatitis B virus, prevalence, blood donor, safety.

Introduction

Hepatitis B virus is a noncytopathic DNA virus causing acute and chronic infection in patients. This virus is the tenth cause of mortality around the world. Currently, over 400 million individuals (5% of world population) are infected with the virus [1]. Although, blood transfusion has been considered as a lifesaving treatment in many cases such as patients with anemia, trauma and obstetric problems, it can also be dangerous because of post transfusion infections including viral and bacterial pathogens [2]. HBV has been considered as one of the most prevalent blood borne infection agents [3]. Precise control of donor selection process and checking all donors for blood transfusion transmissible pathogens can reduce the risk of infectious agents, but the window period is still inevitable [4, 5]. Hence, blood transfusion should be recommended only if there is no replacing remedy. The risk of hepatitis B transmission through blood transfusion has obviously been reduced via HBsAg screening in recent years [6]. The screening of drawn blood for HBsAg began in 1970s, so the incidence of hepatitis B through blood transfusion was greatly reduced. However, many reports published around the world still emphasize on the transmission of this virus through blood transfusion [7, 8].

Although, HBsAg screening using ELISA (Enzyme-Linked Immunosorbent Assay) technique

is used to reduce transmission of HBV through blood and blood products, many reports indicate HBV transmission through HBsAg negative bloods[7, 9] showing that the study of blood products only by means of detecting HBsAg is not enough to recognize sample HBV infectivity [9, 10] since HBV infection may exist without detectable HBsAg, as occult hepatitis B infection (OBI) [11].

OBI is characterized by a low level of virus replication and absence of HBsAg in screening tests [12] . OBI is defined by detection of HBV DNA in serum and/or liver of patients and the absence of HBsAg, with presence or absence of anti-HBc or anti-HBs [9, 11-18]. Despite the worldwide HBV vaccination program, hepatitis B is still problematic in blood products [19]. Based on the fact that, OBI can be considered as an important risk factor for HBV transmission in the blood recipients, many researchers have studied the prevalence of OBI in blood donors, and the risk of OBI transmission by means of blood and blood products. The main aim of this review article was to collect recent data regarding OBI prevalence among blood donors with emphasizes on Iranian blood donors.

HBV Prevalence

It is estimated that chronic HBV affects 350-400 million people worldwide, with a mortality rate of 500,000 to 1.2 million deaths per year caused by acute or chronic hepatitis B infection, cirrhosis and hepatocellular carcinoma (HCC) [20]. For the year 2000, the model estimated that 620,000 patients died worldwide from HBV-related causes: 580,000 (94%) from chronic infection-related cirrhosis and HCC and 40,000 (6%) from acute hepatitis B [21]. The model of surviving birth cohort, for the year 2000, estimated that without vaccination, 64.8 million would become HBV-infected and 1.4 million would die from HBV-related disease [21, 22]. Infections acquired during the prenatal period, in early childhood (<5 years old), and in 5 years old children account for 21%, 48%, and 31% of deaths, respectively [21]. Furthermore, 4.5 million new HBV infections occur worldwide each year, of which a quarter progress to liver disease [23]. HBeAg-negative chronic hepatitis B and OBI are two special clinical entities, of which the prevalence and clinical implications remain to be explored [9].

Interestingly, the predominant transmission routes of diseases are different according to the endemicity of HBV infection [24]. In areas of high HBV endemicity, prenatal transmission is the main route of transmission, whereas in areas with low HBV endemicity, sexual contact amongst high-risk adults is the predominant route [25]. The prevalence of HBV infection varies markedly throughout the world [26]. In a study by Arababadi et al. to identify the status of OBI among blood donors in Rafsanjan-Iran, it

Table1: HBV prevalence in different groups of Iranian population.

Type of sample	HBsAg/HBcAb/ HBsAb	Location	sample number	Duration	Reference
Healthy Iranian	62 (1.5%) seropositive: $HBsAb^+$ 15%, $HBcAb^+$ 6.3 %, 12.5% were positive for both.	Hormozgan	4087	2008-2009	(51)
Blood donors	352 (9.5%) $HBcAb^+$	Rafsanjan	3700	2009	(52)
kidney transplant recipients and donors	HBV S $gene^+$ in 102	Fars	273	2005-2008	(53)
Male injection drug abusers	$HBsAg^+$ (5.8%)	Tehran	499	2006	(54)
Injection drug abusers	$HBsAg^+$ (4.7%)	Hormozgan	249	2002	(55)
Homeless men	87 HBV positive: 8$HBsAg^+$ and 86 HBc Ab^+	Tehran	202	2007	(56)
Hemodialysis patients	$HBsAg^+$ (5.1%)	Khuzestan	214	2005-2006	(57)
Beta-thalassemia patients	$HBsAg^+$ (1.5%)	Multicenter	732	2006	(58)

was observed that 16.1% of HBsAg negative and anti-hepatitis B core (anti-HBc) positive (HBsAg-/anti-HBC+) blood donors (57/352) were HBV DNA positive, which is 1.54% (57/3700) of the total collected samples. In other words, 1.54% of blood donors were infected by OBI [27]. Also, in another study done by Arababadi et al. which also evaluated two different populations regarding the prevalence of OBI among blood donors, they have reported that of 545 (0.92%) donors from Isfahan and 270 (1.45%) from Rafsanjan were infected by OBI, respectively [28]. In a study by Behbahani et al., from 2000 blood donors referred to a blood transfusion center in Fars province, Iran, 0.8% were infected by the clinical form of OBI [29]. Amini et al. also evaluated 2000 donors from Tehran, and found that 0.15% of blood donors carried OBI [30]. Collectively, studies on Iranian population have indicated 1-2% prevalence of OBI among Iranian blood donors [27].

García-Montalvo et al. from Mexico showed the prevalence of OBI to be 0.7% among blood donors[31]. OBI has also been detected in patients without hepatic disease including blood donors with normal hepatic enzymes and in general population [16]. OBI has been reported in 0.1- 2.4% of HBsAg negative and anti-HBc positive donors in Western countries like United States [32, 33]. The incidence of OBI in the Asian population with normal liver enzymes has been reported to be 7.5-16% [34-36]. OBI has also been observed in 45-50% of intravenous drug users or hemophilia patients [37], in up to 36% of the hemodialysis patients [38, 39], and in 8-51% of HIV positive patients [40, 41].

High endemicity

Hepatitis B is highly endemic in populated developing regions such as Southeast Asia, China, Sub-Saharan Africa and the Amazon Basin, where at least 8% of the population are chronic carriers of HBV. In these areas,70–95% of the population show past or present serological evidence of HBV infection. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high [42].

Table2: Common HBV genotypes in Asia, Middle East and Iran.

Country	Genotype	Sample	Location	Year	Reference
Iran	D	Asymptomatic HBV infected patients	Rafsanjan	2009	(66)
		Patients with HBV-associated HCC	Iran	2000-2007	(67)
		HBV-infected patients	Iran	2004-2007	(68)
		HBV-infected patients	Southwest Iran	2007	(69)
		HBV-infected patients	Tehran	2002 - 2006	(70)
		HBV-infected patients	Tehran	2004	(71)
		HBV infected Blood donors	Southwest Iran	2008	(29) (72)
Pakistan	D (70%) and (A 20%) and AD (10%)	HBsAg positive patient	Karachi	2006 - 2007	(73)
Philippine	A (28%) and C (26%)	Chronic HBV-infected patients	Cebu	2008	(74)
Egypt	C	HBV infected patients	Ismailia	2000-2003	(75)
Korea	C	HBV-infected patients	Several cities and harbors throughout the Korean peninsula	2008	(76)
Hong Kong	B (49%) and C (51%)	Chronic hepatitis B patients	Hong Kong	2008	(77)

Intermediate Endemicity

Hepatitis B is moderately endemic in parts of eastern and Southern Europe, the Middle east, Japan, and parts of South America, between 10–60% of the population have evidences of infection and 2-7% are chronic carriers [9]. There is also intermediate prevalence of HBV with a 2.14% infection rate in Iran [43]. HBV related disease is common in these areas because of infection in adolescents and adults; however, the high rates of chronic infection are mostly due to infections occurring in infants and children [43, 44] (Table 1).

Low Endemicity

The endemicity of HBV is low in most developed areas like in North America, Northern and Western Europe and Australia. In these regions, HBV infects 5-7% of the population, and only 0.5-2% of the population are chronic carriers [9].

Incidence and risk of OBI in recipients of blood products

The risk of OBI through transfusion is significantly higher than HIV-1 or HCV [45]. HBV transmission from OBI positive donors with a low level of HBV DNA has been reported [19]. HBV transmission is also dependent upon viral load in blood components [45]. In a study, it was demonstrated that four out of five OBI donors who carried the D genotype and another one with A2 genotype were capable of transmitting hepatitis to blood recipients [19]. Therefore, it seems that HBV genotype can be considered as important risk factor in HBV transmission via OBI infected patients.

OBI incidence in hemophiliacs

Hemophiliacs who receive high quantities of blood and its components are at high risks of infection by blood transfusion [46]. Previous reports from Pakistan [47] and Japan [48] have demonstrated that the prevalence of OBI among hemophiliacs is 1.73% and 2.51%, respectively.

Incidence of OBI in thalassemia patients

Thalassemia patients, like hemophiliacs who receive great quantities of blood and blood components, are at risks of OBI transmission [49]. In a report from India, it was reported that OBI prevalence was 31.4% among thalassemia patients[50], while our previous study on 60 thalassemic patients identified that none of patients were infected by OBI [49].

Table3: HBV-HCV co-infection prevalence from different studies in Iran.

Target population	Location	Number of patients under study	Comments	Year	Reference
First time blood donors	Bushehr	51884	HBV-HCV co-infection 0.013 %(7 persons).	2010	105
Chronic hepatitis C virus	Tehran	103	20 Patients affected with OBV.	2009	106
Pregnant women	Malekan	680	3(0.49%) pregnant women were HBV/ HCV co-infection.	2007	107
HBsAg-positive subjects	Golestan	138	Anti-HCV antibody was positive in 17(12.3%) of the 138 subjects.	2006	108
Chronic liver disease (CLD) patients	Tehran	35	77.1 percent of 35 patients were HCV positive and 8(22%) of these were occult HBV infection.	2005	109
Chronic HBV patients	Tehran	264	12 patients (4.54%) were positive for anti-HCV antibody.	2011	110
Injection drug users (IDUs)	Tehran	899	HBV/HCV co-infections were 21.0%.	2010	111
HIV positive patients	Tehran	201	HBV and HCV coinfection was observed in 73 of 201(36.3%) respectively.	2009	112

Genotype

There are 8 HBV genotypes (A-H), which were identified based on an intergroup divergence of 8% or 4% in the S nucleotide sequence of the gene[10]. HBV genotypes are known to be geographically segregated [59]. Genotype A is pandemic and most prevalent in northern Europe, North America, and central Africa. Genotypes B and C have been observed in Southeast Asia and the Far East. Genotype D is distributed worldwide and is most prevalent in the Mediterranean region. Genotypes E and F are prevalent in West Africa and in Amerindian population, respectively [60]. A few cases of HBV/E in the Americas suggest a relatively recent HBV/E expansion in the population in America, because of the high HBV/E prevalence in Africa coupled with the high volume of the African American slave trade that took place between the 17th and the 19th century [30, 61-63]. Recently, genotype G was identified in the USA and France [64]. Genotype H is found in Central America [65]. Table 2 illustrates common HBV genotypes in Asia, Middle East and Iran.

Complications

Hepatocellular carcinoma

As early as 1970, chronic infection with the HBV was noted to be associated with the development of HCC [78]. It has been estimated that 80% of HCC worldwide is etiologically associated with HBV [79], and hepatitis C virus is the second etiology of HCC[16]. It is estimated that 550,000-600,000 of new HCC incidence happened in year 2010 [80]. HBV belongs to a group of oncogenic viruses known as hepadnavirus and can integrate its DNA into the genome of the infected hepatocytes. It has been established that HBV DNA integration to the hepatocytes genome can lead to HCC. Interestingly, the integration has been observed in about 80% of human HBV infected patients [81]. The hepatitis B x gene (HBx) product has been implicated in HCC, because it is a transcriptional activator of various cellular genes associated with growth control[82]. A recent longitudinal study of 3,653 HBsAg-positive subjects in Taiwan revealed that elevated serum levels of HBV DNA (>10,000 copies/mL; ~ 2000 IU/mL) at baseline was a strong predictor of subsequent development of HCC, independent of serum hepatitis B e antigen (HBeAg) status, serum aminotransferases levels or the presence of cirrhosis [83]. Genotype B is more inclined to HCC development, whereas, genotypes A and C cause hepatitis and cirrhosis more than HCC [84]. In patients with HCC, 14-100% are positive for anti-HBc and 8–87% of patients are not positive for any markers which are considered to be OBI [16].

Table4: HBV- HIV co-infection in different populations, Iran.

Target population	Location	Number of patients under study	Comments	Year	Reference
hronic HBV patients	Tehran	264	1 patient (0.37%) was positive for anti-HIV antibody	2011	110
IV Drug abusers (IDU) patients	Tehran	899	HIV/HBV, co-infections were seen in 7.8% of patients	2010	111
HIV positive patients	Tehran	201	The maximum prevalence of HBV-HIV co-infection was seen in intravenous drug abusers; 61.2%	2009	112
HIV infected Patients	Isfahan	130	15 subjects (11.5%) were HBsAg positive, 100 (77%) were anti-HCV positive and 12 subjects (9.2%) were positive for both.	2010	115
IV Drug abusers (IDU) patients	Ahwaz	154	104 patients (67.53%) were HIV positive. Among HIV infected, HBsAg were positive in 44.23% of patients.	2007	116

Hepatitis-associated Aplastic anemia (HAAA)

HAAA is an uncommon but distinct variant of Aplastic anemia in which pancytopenia appears two to three months after an acute attack of hepatitis. HAAA occurs most frequently in young males and is lethal if left untreated. The etiology of this syndrome is proposed to be attributed to various hepatitis viruses such as hepatitis A [85], B [86, 87], C [88] and G [89]. It has also been documented that HAAA is not related to age, sex and the severity of hepatitis [90]. It has been predominantly found in children [91], adolescent boys and young men [92, 93].

Co-infection with other transfusion transmitted infections

HCV-HBV co-infection

HBV and HCV infections can occur simultaneously. These viruses are responsible for multiple liver damages ranging from minor histological disorders to liver cirrhosis and HCC 9[4, 95]. HBV and HCV co-infections can lead to more aggravated pathologic changes of liver and lower response rates to anti-HCV therapy [96].

HBV and HCV co-infection is frequently found in intravenous (IV) drug abusers (IDU, 42.5%)[94], patients on hemodialysis (3.7%)[95], patients undergoing organ transplantation (8%) [97], and beta-thalassemic patients (10%)[98], which means they are the high risk population for concurrent HBV and HCV infections. Combined HBV/HCV infection also is possible because of common mode of viral transmission [99]. It is particularly frequent in areas where the two viruses are endemic, and in subjects with high risk of infection through parenteral routes. Depending on the geographic region, less than 1% to 48% of patients with HCV infection have been reported to be also positive for hepatitis B surface antigen (HBsAg) [100, 101], while, 3 to 30% of those with HBV infection are anti-HCV positive [102, 103]. In a study, the prevalence of occult HBV in HCV patients was from 0 to 52.3% [104]. The

Table5: HBV prevalence among different regions among blood donors (Iran).

HBsAg/ HBcAb	Location	Sample number	Year	Reference
11 (2.1%) HBcAb	Arak	531	2008	(144)
(2.07%) HBcAb	Iran/Tehran	531	2008	(145)
(1.08 %) HBsAg	Ghazvin	39598	2000-2002	(146)
(8%) HBcAb	Isfahan	545	2005	(147)
0.4% HBsAg	Jahrom	3000	2001-2003	(148)
(9.51%) HBcAb	Rafsanjan	3700	2008	(149)
(0.68%) HBsAg	Arak	11615	2004	(150)
(0.8%) HBsAg	Hamadan	18306	2004-2005	(151)
0.23% HBsAg	Boushehr	20294	2006	(152)
(0.57%, 0.52%, 0.53%, 0.53%) HBsAg	Shiraz	507531	2000-2005	(153)
0.45% HBsAg	Gilan	221508	1997–2002	(154)
1.79% in 1998 to 0.41% in 2007	Iranian Blood Transfusion Organization (IBTO)	14599783	1998-2007	(155)
0.56% for HBV	Tehran	6,499,851	2004-2007	(156)
1.78% HBsAg	Shahrekord	11,200	2009	(157)
HBcAb (4.7%) and HBsAb (5.3%)	Khorramabad and Borujerd	1000	2008	(158)
0.47% HBsAg	Hamadan	8468	2008	(159)
0.6 % HbsAg	Ahwaz	25772	2005	(160)
0.8 % HbsAg	Ahwaz	39032	2007	(161)

results of some recent studies about HBV/HCV co-infection in Iran are presented in table3.

HIV-HBV co- infection

HBV and HIV share common, mainly sexual, routes of transmission. Therefore, the prevalence of serological markers of HBV is higher among HIV infected patients than in non-HIV infected individuals [104, 113]. It is estimated that 10% of HIV infected patients in the United States and Europe are chronically co-infected with hepatitis B virus (HBV). HIV-HBV co-infected patients have higher rates of liver-related morbidity and mortality compared to patients infected with either virus alone [114]. Table 4 summarizes the recent studies about HBV/HIV co-infection in Iran.

Immunological response

HBsAg seroclearance may result in a decreased risk for HCC in the hepatitis B infected patients[40]. It will be worthwhile identifying any immune mechanisms that might contribute to HBsAg seroclearance, as they may provide targets for immunotherapy. The contributing mechanisms include acquired CD4+ and CD8+ T cell responses[117], innate immune responses [118] and mutations in the HBsAg arising from genetic drift [119]. The possibility of HBsAg seroclearance resulting from an acquired immune response to antigens within the envelope proteins is of particular interest [120]. In a study by Liang et al. [120] it was observed that the frequency and magnitude of antigen-specific T cell responses was also higher in the HBsAg seroclearance group than in subjects with immune tolerance. However, the T cell responses in the seroclearance group were almost exclusively against core antigens and only a small number of low level responses to envelope antigens were detected [120]. Recovery from acute hepatitis B is the result of a combination of cellular and humoral immune responses, whereas neutralizing antibodies (Abs) against HBsAg appear after recovery. Cellular immune responses are generally detectable before the synthesis of neutralizing Abs [121] and precede the rise of serum alanine aminotransferase (ALT) levels [122]. The clearance of HBeAg and HBsAg are mediated by cells of the innate immune response, especially NK cells [123, 124] and by CD4+ and CD8+ T cells that clear HBV by cytolytic [125], noncytolytic and cytokine-mediated mechanisms [123, 126].

Interestingly, our previous studies revealed that some features of immune responses of chronic and occult HBV infected patients are disrupted. For instance, we have previously shown that CCR5 (the receptor for CCL5, CCL4 and CCL3) has decreased on the NK cells of occult [127], chronic (unpublished data) and also T cytotoxic lymphocytes of occult[128] and chronic [129] HBV infected patients. We have also shown that serum levels of inflammatory cytokines are decreased, while, anti-inflammatory cytokines increased in the occult and chronic HBV infected patients in comparison to healthy controls [27, 130-132].

Additionally, Vitamin D3 receptor (VDR3) appears to be involved in antiviral immune responses. The polymorphisms in the T/T allele of exon 9 of VDR is possibly associated with OBI, thus it can be concluded that VDR and its functional polymorphisms are likely to be related to sensitivity and resistance of the immune system to HBV in OBI patients [133]. Therefore, it seems that the long term infected patients suffer from impaired immune responses against HBV and future studies can be considered to clear the responsible mechanisms [134].

HBV and blood banking

Blood transfusion is still one of the most important therapeutic approaches all over the world[135]. Therefore, paying attention to complications among recipients such as post transfusion infection is necessary [136]. Indeed, supplying safe blood and blood products is the main purpose of any blood transfusion service [137]. This can be achieved by providing the screening protocols of the safe blood donation. Supplying safe blood has been considered as a great concern in some less-developed and developing countries where donors are paid for whole blood collection. Paid donors are mostly from poor economic and social groups selling blood to earn money. This payment system can increase the transmission risk of blood-borne viruses [2].

As most OBI infections are asymptomatic, we can detect them only through screening of large populations. Current tests for this purpose include: 1) Liver biopsy: although diagnosis of HBV DNA in liver is the best method to detect OBI, it is not always possible to perform, and liver biopsy for routine testing of patients has not been approved by FDA [138]. 2) HBsAg detection method; the detection should be performed based on the current WHO

International Standard for HBsAg [139]. 3) Anti-HBc detection method; Infected donors may have no detectable HBsAg because of the low sensitivity of the assay. Whereas anti-HBc introduces acute, chronic or resolved HBV infections, if donors have negative serologic HBsAg with positive anti-HBc, they rarely have infectious blood products [140]. In fact, anti-HBc test can detect those donors who have a high anti-HBs titer to mimic non-infection conditions [140]. Anti-HBc-positive donors with at least 100 IU/L anti-HBs can donate blood if they have had negative HBV NAT (Nucleic acid Amplification Testing) results [141]. Diagnosis of HBV DNA in anti-HBc individuals significantly helps to identify OBI patients [138]. However, this method has two drawbacks that cannot be ignored: first it cannot detect the seronegative WP infections, and second it is not practical in regions where anti-HBc incidence is higher than 10% [142]. 4) Viral genome detection method: this method is the gold standard of identifying people with OBI [143]. Currently, real-time and nested polymerase chain reactions (PCR) are used to perform this test [139]. HBV NAT has been used for detecting the presence of HBV nucleic acid with high sensitivity and specificity (see table 5). This PCR-based technique increases the safety of blood and blood products when simultaneously performed with serologic tests mentioned, but is still unable to completely close serologic window period [7]. In some countries, including the USA and Japan, parallel screening for HBsAg and HBc-Ab is performed in all donor samples; in contrast, in India and Iran, HBc-Ab is not in the screening program for blood donors [8]. The molecular diagnostic tests such as NAT are not performed routinely in our country yet.

Conclusion

Based on our review findings, the rate of HBV prevalence and OBI in Iran is moderate. Although the blood transfer safety has improved, the use of HBsAg as the only marker to detect HBV infection in Iran does not perfectly meet blood safety goals. Considering the risk of transmission of OBI through blood products to recipients, and the fact that the available methods to identify people with OBI are not currently used by Iranian Blood Transfusion Organization, to prevent the spread of this infection in our country in addition to HBsAg detection method, Anti-HBc and viral genome detection should be applied for detection and identification of OBI contaminated blood products. This indicates the importance of taking necessary steps to reduce the transfer of infection via blood products.

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References

1. Mizukoshi E, Sidney J, Livingston B, Ghany M, Hoofnagle JH, Sette A, et al. Cellular immune responses to the hepatitis B virus polymerase. J Immunol. 2004;173(9):5863-71.
2. Luby S, Khanani R, Zia M, Vellani Z, Ali M, Qureshi AH, et al. Evaluation of blood bank practices in Karachi, Pakistan, and the government's response. Health policy and planning. 2000;15(2):217-22.
3. Ghafouri Z, Hajibaygi M, AssariSh B, Alavian S. Donor deferral and blood-borne infections in blood donors of Tehran. Sci J Iran Blood Transfus Organ. 2006;2(7):353-64.
4. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood. 2009;113(15):3406-17.
5. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. Blood. 2009;113(15):3406-17.
6. Ghafouri M. Ameli MR. Comparing prevalence of transfusion transmitted viral infections in various population groups of South Khorasan. Sci J Iran Blood Transfus Organ. 2011;7(4):242-8.
7. Ruiz-Aragon J, Marquez-Pelaez S. Assessment of nucleic acid testing (NAT) for screening hepatitis B in blood donors. Systematic review. Invest Clin. 2010;51(3):341-9. (Abstract)
8. Arababadi MK, Hassanshahi G, Pourfathollah AA, Zarandi ER, Kennedy D. Post-transfusion occult hepatitis B (OBI): a global challenge for blood recipients and health authorities. Hepat Mon. 2011;11(9):714-8.

9. Hou J, Liu Z, Gu F. Epidemiology and Prevention of Hepatitis B Virus Infection. Int J Med Sci. 2005;2(1):50-7.
10. Okamoto H, Tsuda F, Sakugawa H, Sastrosoewignjo RI, Imai M, Miyakawa Y, et al. Typing hepatitis B virus by homology in nucleotide sequence: comparison of surface antigen subtypes. The Journal of general virology. 1988;69 (Pt 10):2575-83.
11. van Ballegooijen WM, van Houdt R, Bruisten SM, Boot HJ, Coutinho RA, Wallinga J. Molecular sequence data of hepatitis B virus and genetic diversity after vaccination. Am J Epidemiol. 2009;170(12):1455-63.
12. Alvarado Mora MV, Romano CM, Gomes-Gouvea MS, Gutierrez MF, Carrilho FJ, Pinho JR. Molecular epidemiology and genetic diversity of hepatitis B virus genotype E in an isolated Afro-Colombian community. J Gen Virol. 2010;91(Pt 2):501-8.
13. Delwart E, Slikas E, Stramer SL, Kamel H, Kessler D, Krysztof D, et al. Genetic diversity of recently acquired and prevalent HIV, hepatitis B virus, and hepatitis C virus infections in US blood donors. J Infect Dis. 2012;205(6):875-85.
14. Kato N, Abe K, Mori K, Ariumi Y, Dansako H, Ikeda M. Genetic variability and diversity of intracellular genome-length hepatitis C virus RNA in long-term cell culture. Arch Virol. 2009;154(1):77-85.
15. Yu JN, Kim MY, Kim DG, Kim SE, Lee JB, Park SY, et al. Prevalence of hepatitis E virus and sapovirus in post-weaning pigs and identification of their genetic diversity. Arch Virol. 2008;153(4):739-42.
16. Makuwa M, Caron M, Souquiere S, Malonga-Mouelet G, Mahe A, Kazanji M. Prevalence and genetic diversity of hepatitis B and delta viruses in pregnant women in Gabon: molecular evidence that hepatitis delta virus clade 8 originates from and is endemic in central Africa. J Clin Microbiol. 2008;46(2):754-6.
17. Hollinger FB. Hepatitis B virus genetic diversity and its impact on diagnostic assays. J Viral Hepat. 2007;14 Suppl 1:11-5.
18. Lu L, Li C, Fu Y, Thaikruea L, Thongswat S, Maneekarn N, et al. Complete genomes for hepatitis C virus subtypes 6f, 6i, 6j and 6m: viral genetic diversity among Thai blood donors and infected spouses. J Gen Virol. 2007;88(Pt 5):1505-18.
19. Gerlich WH, Wagner FF, Chudy M, Harrishoj LH, LattermennA , Wienzek S, et al. HBsAg non-reactive HBV infection in blood donors: transmission and pathogenicity. J Med Virol. 2007;79:S32-S36..
20. Mahboobi N, Agha-Hosseini F, Safari S, Lavanchy D, Alavian SM. Hepatitis B virus infection in dentistry: a forgotten topic. Journal of viral hepatitis. 2010 ;17(5):307-16.
21. Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol. 2005;34(6):1329-39.
22. Zamani F, Fallahian F, Hashemi F, Shamsaei Z, Alavian SM. Immune response to hepatitis B vaccine in health-care workers. Saudi J Kidney Dis Transpl. 2011;22(1):179-84.
23. Zanetti AR VDP, Shouval D. The global impact of vaccination againsthepatitis B: a historical overview. Vaccine. 2008;26(49):6266-73.
24. Franco E, Bagnato B, Marino MG, Meleleo C, Serino L, Zaratti L. Hepatitis B: Epidemiology and prevention in developing countries. World J Hepatol. 2012;4(3):74-80.
25. Maddrey WC. Hepatitis B: an important public health issue. J Med Virol. 2000;61(3):362-6.
26. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. Semin Liver Dis. 1991;11(2):84-92.
27. Arababadi MK, Pourfathollah AA, Jafarzadeh AA, Hassanshahi G. Serum levels of Interleukin (IL)-10 and IL-17A in occult HBV infected South-East Iranian patients. Hepat Mon. 2010;10(1):31-5.
28. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi G, Shamizadeh A, Ahmadabadi BN, et al. The status of humoral immunity in occult HBV infection in South-Eastern Iranian patients. Clin Res Hepatol Gastroenterol. 2011;35(4):309-14.
29. Behzad-Behbahani A, Mojiri A, Saberifirozi M, Ardabili M, Beheshti M, Rahsaz M, et al. Hepatitis B virus genotypes in southwest Iran: molecular, serological and clinical outcomes. World J Gastroenterol. 2008;14(10):1510-3.
30. Amini Kafi-abad S, Talebian A, Moghtadaie M, Ranjbar Kermani F, Ferdowsian F, Samie S, et al . Detection of hepatitis B virus DNA (PCR) in HBsAg negative, anti-HBc positive blood donors in Tehran province. Sci J Blood Transfus Organ. 2007;3(5):379-87.
31. García-Montalvo BM, Ventura-Zapata LP. Molecular and serological characterization of occult hepatitis B infection in blood donors from Mexico. Annals of hepatology. 2011;10(2):133-41.
32. Dong C, Dai X, Shao JS, Hu K, Meng JH. Identification of genetic diversity of hepatitis E virus (HEV) and determination of the seroprevalence of HEV in eastern China. Arch Virol. 2007;152(4):739-46.

33. Echevarria JM, Avellon A. Hepatitis B virus genetic diversity. J Med Virol. 2006;78 Suppl 1:S36-42.
34. Norder H, Courouce AM, Coursaget P, Echevarria JM, Lee SD, Mushahwar IK, et al. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. Intervirology. 2004;47(6):289-309.
35. Mulders MN, Venard V, Njayou M, Edorh AP, Bola Oyefolu AO, Kehinde MO, et al. Low genetic diversity despite hyperendemicity of hepatitis B virus genotype E throughout West Africa. J Infect Dis. 2004;190(2):400-8.
36. Mishiro S. Genetic diversity and mutation of hepatitis E virus. Nihon Rinsho. 2004;62 Suppl 8:514-9. (Abstract)
37. 37. Holland-Staley CA, Kovari LC, Golenberg EM, Pobursky KJ, Mayers DL. Genetic diversity and response to IFN of the NS3 protease gene from clinical strains of the hepatitis C virus. Arch Virol. 2002;147(7):1385-406.
38. Lampe E, Saback FL, Viazov S, Roggendorf M, Niel C. Age-specific prevalence and genetic diversity of GBV-C/hepatitis G virus in Brazil. J Med Virol. 1998;56(1):39-43.
39. Navas S, Martin J, Quiroga JA, Castillo I, Carreno V. Genetic diversity and tissue compartmentalization of the hepatitis C virus genome in blood mononuclear cells, liver, and serum from chronic hepatitis C patients. J Virol. 1998;72(2):1640-6.
40. Kwon SY, Lee CH. Epidemiology and prevention of hepatitis B virus infection. Korean J Hepatol. 2011;17(2):87-95.
41. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol. 2006;44(1 Suppl):S6-9. Epub 2005 Nov 21.
42. Alter MJ. Epidemiology of hepatitis B in Europe and worldwide. J Hepatol. . 2003;39 Suppl 1:S64-9.
43. Alavian S, Hajarizadeh B, Ahmadzad-Asl M, Kabir A, Bagheri-Lankarani K. Hepatitis B virus infection in Iran: a systematic review. Hepat Mon. 2008;8(4):281-94.
44. Toukan A. Strategy for the control of hepatitis B virus infection in the Middle East and North Africa. The Middle East Regional Study Group. Vaccine. 1990;8 Suppl:S117-21; discussion S34-8.
45. Candotti D, Allain JP. Transfusion-transmitted hepatitis B virus infection. J Hepatol. 2009;51(4):798-809.
46. Arababadi MK, Nasiri Ahmadabadi B, Yousefi Daredor H, Kennedy D. Epidemiology of occult hepatitis B infection among thalassemic, hemophilia, and hemodialysis patients. Hepat Mon. 2012;12(5):315-9.
47. Borhany M, Shamsi T, Boota S, Ali H, Tahir N, Naz A, et al. Transfusion transmitted infections in patients with hemophilia of Karachi, Pakistan. Clin Appl Thromb Hemost. 2011;17(6):651-5.
48. Toyoda H, Hayashi K, Murakami Y, Honda T, Katano Y, Nakano I, et al. Prevalence and clinical implications of occult hepatitis B viral infection in hemophilia patients in Japan. J Med Virol. 2004;73(2):195-9.
49. Arababadi M, Hassanshahi G, Yousefi H, Zarandi E, Moradi M, Mahmoodi M. No detected hepatitis B virus-DNA in thalassemic patients infected by hepatitis C virus in Kerman province of Iran. Pak J Biol Sci. 2008;11(13):1738-41.
50. Singh H, Pradhan M, Singh RL, Phadke S, Naik SR, Aggarwal R, et al. High frequency of hepatitis B virus infection in patients with beta-thalassemia receiving multiple transfusions. Vox Sang. 2003;84(4):292-9.
51. Abedi F, Madani H, Asadi A, Nejatizadeh A. Significance of blood-related high-risk behaviors and horizontal transmission of hepatitis B virus in Iran. Arch Virol. 2011;156(4):629-35.
52. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi G, Rezvani ME. Association of exon 9 but not intron 8 VDR polymorphisms with occult HBV infection in South-Eastern Iranian patients. J Gastroenterol Hepatol. 2010;25(1):90-3.
53. Arjmandi K, Yaghobi R, Ravanshad M, Hosseini SY, Roozbeh J, Pakfetrat M. Laboratory effect of HBV infection in kidney transplant recipients and donors. Transplant Proc. 2011;43(2):554-6.
54. SeyedAlinaghi SA, Kheirandish P, Karami N, Salem S, Shirzad H, Jahani MR, et al. High prevalence of chronic hepatitis B infection among injection drug users in Iran: the need to increase vaccination of adults at risk. Acta Med Iran. 2010;48(1):58-60.
55. Davoodian P, Dadvand H, Mahoori K, Amoozandeh A, Salavati A. Prevalence of selected sexually and blood-borne infections in Injecting drug abuser inmates of bandar abbas and roodan correction facilities, Iran, 2002. Braz J Infect Dis. 2009;13(5):356-8.
56. Vahdani P, Hosseini-Moghaddam SM, Family A, Moheb-Dezfouli R. Prevalence of HBV, HCV, HIV and syphilis among homeless subjects older than fifteen years in Tehran. Arch Iran Med. 2009;12(5):483-7.
57. Assarehzadegan MA, Shakerinejad G, Noroozkohnejad R, Amini A, Rahim Rezaee SA. Prevalence of hepatitis C and B infection and HC V genotypes among hemodialysis patients in Khuzestan province, southwest Iran. Saudi J Kidney

Dis Transpl.. 2009;20(4):681-4.
58. Mirmomen S, Alavian SM, Hajarizadeh B, Kafaee J, Yektaparast B, Zahedi MJ, et al. Epidemiology of hepatitis B, hepatitis C, and human immunodeficiency virus infecions in patients with beta-thalassemia in Iran: a multicenter study. Arch Iran Med. 2006t;9(4):319-23.
59. Norder H HB, Löfdahl S, Couroucé AM, Magnius LO. Comparison of theamino acid sequences of nine different serotypes of hepatitis B surface antigenand genomic classification of the corresponding hepatitis B virus strains. J Gen Virol. 1992;73(Pt 5):1201-8.
60. Magnius LO, Norder H. Subtypes, genotypes and molecular epidemiology of the hepatitis B virus as reflected by sequence variability of the S-gene. Intervirology. 1995;38(1-2):24-34.
61. Andernach IE HJ, Muller CP. Hepatitis B virus: the genotype Epuzzle. Rev Med Virol 2009;19(4):231-40.
62. Andernach IE NC, Pape JW, Muller CP. Slave trade and hepatitis B virusgenotypes and subgenotypes in Haiti and Africa. Emerg Infect Dis. 2009;15(8):1222-8.
63. Odemuyiwa SO, Mulders MN, Oyedele OI, Ola SO, Odaibo GN, Olaleye DO, et al. Phylogenetic analysis of new hepatitis B virus isolates from Nigeria supports endemicity of genotype E in West Africa. Journal of medical virology. 2001;65(3):463-9.
64. Stuyver L, De Gendt S, Van Geyt C, Zoulim F, Fried M, Schinazi RF, et al. A new genotype of hepatitis B virus: complete genome and phylogenetic relatedness. The Journal of general virology. 2000;81(Pt 1):67-74.
65. Arauz-Ruiz P NH, Robertson BH, Magnius LO. Genotype H: a new Amerindiangenotype of hepatitis B virus revealed in Central America. J Gen Virol. 2002;83(Pt 8):2059-73.
66. Eftekhari Y, Kazemi Arababadi M, Hakimi H, Rezazadeh Zarandi E. Common HBV genotype in southeastern Iranian patients. Arch Iran Med. 2010;13(2):147-9.
67. Aghakhani A, Hamkar R, Zamani N, Eslamifar A, Banifazl M, Saadat A, et al. Hepatitis B virus genotype in Iranian patients with hepatocellular carcinoma. Int J Infect Dis. 2009;13(6):685-9.
68. Mohebbi SR, Amini-Bavil-Olyaee S, Zali N, Noorinayer B, Derakhshan F, Chiani M, et al. Molecular epidemiology of hepatitis B virus in Iran. Clin Microbiol Infect. 2008;14(9):858-66.
69. Mojiri A, Behzad-Behbahani A, Saberifirozi M, Ardabili M, Beheshti M, Rahsaz M, et al. Hepatitis B virus genotypes in southwest Iran: molecular, serological and clinical outcomes. World J Gastroenterol. 2008;14(10):1510-3.
70. Amini-Bavil-Olyaee S, Hosseini SY, Sabahi F, Alavian SM. Hepatitis B virus (HBV) genotype and YMDD motif mutation profile among patients infected with HBV and untreated with lamivudine. Int J Infect Dis. 2008;12(1):83-7.
71. Alavian SM, Keyvani H, Rezai M, Ashayeri N, Sadeghi HM. Preliminary report of hepatitis B virus genotype prevalence in Iran. World J Gastroenterol. 2006;12(32):5211-3.
72. Oraki Kohshour M, Galehdari H, Foroughmand AM, Andashti B, Jalalifar MA, Bidmeshkipour A. HBV Genotyping in HBsAg-Positive Blood Donors from Southwestern Iran. Hepat Mon. 2010;10(2):147-8.
73. Baig S, Siddiqui AA, Ahmed WU, Qureshi H, Arif A. Frequency of hepatitis C and D super infection in patients with hepatitis B related complex liver disorders. J Coll Physicians Surg Pak. 2009;19(11):699-703.
74. Batoctoy KS, Tseng TC, Kao JH, Quiza FE, Garcia LH, Sr., Lao-Tan J. HBV/A and HBV/C genotype predominance among patients with chronic hepatitis B virus infection in Cebu City, Philippines. Hepatol Int. 2011;5(3):774-81.
75. El-ghandour S, El-sayed H, Abel-hamid A, Gad S. Effectiveness of Hepatitis B Vaccination in Egyptian Infants in Ismailia governorate. Suez Canal Univ Med J. 1998;1(2):123-30.
76. Cho JH, Yoon KH, Lee KE, Park DS, Lee YJ, Moon HB, et al. Distribution of hepatitis B virus genotypes in Korea. Korean J Hepatol. 2009;15(2):140-7.
77. Chan HL, Wong GL, Tse CH, Chim AM, Yiu KK, Chan HY, et al. Hepatitis B virus genotype C is associated with more severe liver fibrosis than genotype B. Clin Gastroenterol Hepatol. 2009;7(12):1361-6.
78. Sherlock S FR, Niazi SP, Scheuer PJ. Chronic liver disease and primaryliver-cell cancer with hepatitis-associated (Australia) antigen in serum. Lancet. 1970;1(7659):1243-7.
79. Yu MC YJ, Govindarajan S, Ross RK. Epidemiology of hepatocellularcarcinoma. Can J Gastroenterol 2000;14(8):703-9.
80. Liu Y, Wu F. Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment. Environ Health Perspect. 2010;118(6):818-24.
81. Brechot C PC, Louise A, Rain B, Tiollais P. Presence of integratedhepatitis B virus DNA sequences in cellular DNA of human hepatocellularcarcinoma. Nature. 1980;286(5772):533-5.
82. Muroyama R, Kato N, Yoshida H, Otsuka M,

Moriyama M, Wang Y, et al. Nucleotide change of codon 38 in the X gene of hepatitis B virus genotype C is associated with an increased risk of hepatocellular carcinoma. Journal of hepatology. 2006;45(6):805-12.

83. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65-73.
84. Enomoto M, Tamori A, Nishiguchi S. Hepatitis B virus genotypes and response to antiviral therapy. Clin Lab. 2006;52(1-2):43-7.
85. Kagan WA, Ascensao JA, Pahwa RN, Hansen JA, Goldstein G, Valera EB, et al. Aplastic anemia: presence in human bone marrow of cells that suppress myelopoiesis. Proc Natl Acad Sci U S A. 1976;73(8):2890-4. 1976;73(8):2890-4.
86. Bozkaya H, Yurdaydin C, Toruner M, Arat M, Bozdayi AM, Erekul S, et al. Remission of severe aplastic anemia associated with hepatitis B virus infection after viral clearance: potential role of lamivudine. Digestive diseases and sciences. Dig Dis Sci. 2002;47(8):1782-5. 87. M c S w e e n e y PA CJ, Green GJ, Romeril KR. . Fatal aplastic anemiaassociated with hepatitis B viral infection. Am J Med 1988;85(2):255-6.
87. Pol S DF, Devergie A, Brechot C, Berthelot P, Gluckman E. Is hepatitis Cvirus involved in hepatitis-associated aplastic anemia? Ann Intern Med. 1990;113(6):435-7.
88. Crespo J dlB, Rivero M, Lozano JL, Fábrega E, Pons-Romero F. Hepatitis G virus infection as a possible causative agent of community-acquiredhepatitis and associated aplastic anaemia. Postgrad Med J. 1999;75(881):159-60.
89. Safadi R, Or R, Ilan Y, Naparstek E, Nagler A, Klein A, et al. Lack of known hepatitis virus inhepatitis-associated aplastic anemia and outcome after bone marrowtransplantation. Bone Marrow Transplant. 2001;27(2):183-90.
90. Savage WJ, DeRusso PA, Resar LM, Chen AR, Higman MA, Loeb DM, et al. Treatment of hepatitis-associated aplastic anemia with high-dose cyclophosphamide. Pediatr Blood Cancer. 2007;49(7):947-51.
91. Cengiz C TN, Yolcu OF, Yilmaz S. Hepatitis associated with aplasticanemia: do CD8(+) kupffer cells have a role in the pathogenesis? Dig Dis Sci. 2007;52(9):2438-43.
92. Hagler L PR, Bergin JJ, Wrensch MR. Aplastic anemia following viralhepatitis: report of two fatal cases and literature review. Medicine (Baltimore). 1975;54(2):139-64.
93. Pallas JR, Farinas-Alvarez C, Prieto D, Delgado-Rodriguez M. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. European journal of epidemiology. 1999;15(8):699-704.
94. Reddy GA, Dakshinamurthy KV, Neelaprasad P, Gangadhar T, Lakshmi V. Prevalence of HBV and HCV dual infection in patients on haemodialysis. Indian journal of medical microbiology. 2005;23(1):41-3.
95. Hollinger FB, Habibollahi P, Daneshmand AA, AlavianSM. Occult Hepatitis B Infection in Chronic Hemodialysis Patients:
96. Current Concepts and Strategy. Hepatitis Monthly. 2010;10(3):199-204.
97. Aroldi A, Lampertico P, Montagnino G, Passerini P, Villa M, Campise MR, et al. Natural history of hepatitis B and C in renal allograft recipients. Transplantation. 2005;79(9):1132-6.
98. Irshad M, Peter S. Spectrum of viral hepatitis in thalassemic children receiving multiple blood transfusions. Indian J Gastroenterol. 2002;21(5):183-4.
99. Habibollahi P, Safari S, Daryani NE, Alavian SM. Occult hepatitis B infection and its possible impact on chronic hepatitis C virus infection. Saudi J Gastroenterol. 2009;15(4):220-4.
100. Fukuda R, Ishimura N, Hamamoto S, Moritani M, Uchida Y, Ishihara S, et al. Co-infection by serologically-silent hepatitis B virus may contribute to poor interferon response in patients with chronic hepatitis C by down-regulation of type-I interferon receptor gene expression in the liver. Journal of medical virology. 2001;63(3):220-7.
101. Atanasova MV, Haydouchka IA, Zlatev SP, Stoilova YD, Iliev YT, Mateva NG. Prevalence of antibodies against hepatitis C virus and hepatitis B coinfection in healthy population in Bulgaria. A seroepidemiological study. Minerva gastroenterologica e dietologica. 2004;50(1):89-96.
102. Crespo J, Lozano JL, de la Cruz F, Rodrigo L, Rodriguez M, San Miguel G, et al. Prevalence and significance of hepatitis C viremia in chronic active hepatitis B. The American journal of gastroenterology. 1994;89(8):1147-51.
103. Guptan RC, Thakur V, Raina V, Sarin SK. Alpha-interferon therapy in chronic hepatitis due to active dual infection with hepatitis B and C viruses. J Gastroenterol Hepatol. 1999;14(9):893-8.
104. Saillour F, Dabis F, Dupon M, Lacoste D, Trimoulet P, Rispal P, et al. Prevalence and determinants of

antibodies to hepatitis C virus and markers for hepatitis B virus infection in patients with HIV infection in Aquitaine. BMJ. 1996;313(7055):461-4.
105. Maneshi HO, Zare S, Karimi M, Hajiani GR, editors. HBV and HCV viral markers seroperevalence in first-time healthy blood donors refered to transfusion centers of bushehr province, South of Iran (April 2004 to March 2008). Retrovirology. 2010; 7(Suppl 1): P151.
106. Alavian SM, Ahmadzad-Asl M, Bagheri-Lankarani K, Shahbabaie MA, Bahrami-Ahmadi A, Kabir A. Hepatitis C Infection in the General Population of Iran: A Systematic Review. Hepatitis Monthly. 2009; 9(3):211-23.
107. Sahaf F, Tanomand A, Montazam H, Sany AA. Seroprevalence of Hepatitis C, Hepatitis B and HIV and Co-Infections among Pregnant Women: A Retrospective Study in 2006 at Malekan City, Iran. Research Journal of Medical Sciences. 2007;1(2):138-41.
108. Semnani S, Roshandel G, Abdolahi N, Besharat S, Keshtkar AA, Joshaghani H, et al. Hepatitis B/C virus co-infection in Iran: a seroepidemiological study. Turk J Gastroenterol. 2007;18(1):20-1.
109. Honarkar Z, Alavian SM, Samiei S, Saeedfar K, Baladast M, Aghazadeh R, et al. Occult Hepatitis B as a Cause of Cryptogenic Cirrhosis. Hepatitis Monthly. 2004;4(8):155-60.
110. Tahaei SME, Mohebi SR, Azimzadeh P, Vahedi M, Almasi S, Romani S, et al. Frequency of HIV and HCV Co-Infections in Chronic HBV patients Referred to Taleghani Hospital, Tehran, Iran from 2006 to 2010. Hepat Mon. 2011;11(12):993-6.
111. Rahimi-Movaghar A, Razaghi E, Sahimi-Izadian E, Amin-Esmaeili M. HIV, hepatitis C virus, and hepatitis B virus co-infections among injecting drug users in Tehran, Iran. Int J Infect Dis. 2010;14(1):28-33.
112. SeyedAlinaghi S, Valiollahi P, Paydary K, Emamzadeh-Fard S, Mohraz1 M. Prevalence of hepatitis B (HBV) and C (HCV) viruses coinfections among HIV infected people in Iran. AIDS and HIV Research. 2012;4(6):181-6.
113. Enzensberger R, Braun W, July C, Helm EB, Doerr HW. Prevalence of antibodies to human herpesviruses and hepatitis B virus in patients at different stages of human immunodeficiency virus (HIV) infection. Infection. 1991;19(3):140-5.
114. Liu JY, Lin HH, Liu YC, Lee SS, Chen YL, Hung CC, et al. Extremely high prevalence and genetic diversity of hepatitis C virus infection among HIV-infected injection drug users in Taiwan. Clin Infect Dis. 2008;46(11):1761-8.
115. Ataei B, Tayeri K, Kassaian N, Farajzadegan Z, Babak A. Hepatitis B and C among Patients Infected with Human Immunodeficiency Virus in Isfahan, Iran: Seroprevalence and Associated Factors. Hepat Mon. 2010;10(3):188-92.
116. Alavi SM, Nadimi M, Shokri S, Zamani G. Seroepidemiology of Human Immunodeficiency Virus in Illicit Substance Users in Ahvaz, Iran: 2005-2006. Jundishapur Journal of Microbiology.2012;5(3):474-8.
117. Lau GK, Suri D, Liang R, Rigopoulou EI, Thomas MG, Mullerova I, et al. Resolution of chronic hepatitis B and anti-HBs seroconversion in humans by adoptive transfer of immunity to hepatitis B core antigen. Gastroenterology. 2002;122(3):614-24.
118. Fisicaro P, Valdatta C, Boni C, Massari M, Mori C, Zerbini A, et al. Early kinetics of innate and adaptive immune responses during hepatitis B virus infection. Gut. 2009;58(7):974-82.
119. Hou J, Karayiannis P, Waters J, Luo K, Liang C, Thomas HC. A unique insertion in the S gene of surface antigen negative hepatitis B virus Chinese carriers. Hepatology. 1995;21(2):273-8.
120. Liang M, Ma S, Hu X, Zhou B, Zhang J, Chen J, et al. Cellular immune responses in patients with hepatitis B surface antigen seroclearance induced by antiviral therapy. Virol J. 2011;8:69.
121. Rehermann B, Fowler P, Sidney J, Person J, Redeker A, Brown M, et al. The cytotoxic T lymphocyte response to multiple hepatitis B virus polymerase epitopes during and after acute viral hepatitis. J Exp Med. 1995;181(3):1047-58.
122. Maini MK, Boni C, Ogg GS, King AS, Reignat S, Lee CK, et al. Direct ex vivo analysis of hepatitis B virus-specific CD8(+) T cells associated with the control of infection. Gastroenterology. 1999;117(6):1386-96.
123. Guidotti LG CF. Noncytolytic control of viral infections by theinnate and adaptive immune response. Annu Rev Immunol. 2001;19:65-91.
124. 124.Kakimi K LT, Chisari FV, Guidotti LG. Inhibition ofhepatitis B virus replication by activated NK T cells does not requireinflammatory cell recruitment to the liver. J Immunol. 2001;167(12):6701-5.
125. Moriyama T, Guilhot S, Klopchin K, Moss B, Pinkert CA, Palmiter RD, et al. Immunobiology and pathogenesis of hepatocellular injury in hepatitis B virus transgenic mice. Science. 1990;248(4953):361-4.
126. Guidotti LG RR, Chung J, Shapiro M, Purcell R, Chisari FV.Science. Viralclearance without destruction of infected cells during acute HBV infection. 1999;284(5415):825-9.

127. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi G. Decreased expression of CCR5 on the NK cells in occult HBV infected patients. Lab Medicine. 2010;41(12):735-8.
128. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi G, Mohit M, Hajghani M, et al. Peripheral blood CD8+ T cells CCR5 expression and its D 32 mutation in Iranian patients with occult hepatitis B infection. Lab Medicine. 2010;41:226-30.
129. Ahmadabadi BN, Hassanshahi G, Khoramdelazad H, Mirzaei V, Sajadi SM, Hajghani M, et al. Downregulation of CCR5 Expression on the Peripheral Blood CD8(+) T Cells of Southeastern Iranian Patients with Chronic Hepatitis B Infection. Inflammation. 2013;36(1):136-40.
130. Khoramdelazad H, Hassanshahi G, Ahmadabadi BN, Arababadi MK. High serum levels of TGF-β in Iranians with chronic HBV infection. 2012;12(11):e7581. Epub 2012 Nov 5.
131. Hassanshahi G, Arababadi MK, Khoramdelazad H, Yaghini N, Zarandi ER. Assessment of CXCL12 (SDF-1alpha) Polymorphisms and Its Serum Level in Posttransfusion Occult HBV-infected Patients in Southeastern Iran. Arch Med Res. 2010;41(5):338-42.
132. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi G, Daneshmandi S, Shamsizadeh A, et al. Non-association of IL-12 +1188 and IFN-gamma +874 polymorphisms with cytokines serum level in occult HBV infected patients. Saudi J Gastroenterol. 2011;17(1):30-5.
133. Arababadi MK PA, Jafarzadeh A, Hassanshahi G, RezvaniME. Association of exon 9 but not intron 8 VDR polymorphisms with occult HBVinfection in south-eastern Iranian patients. J Gastroenterol Hepatol. 2010;25(1):90-3.
134. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi G, Mohit M, Hajghani M, et al. Evaluation of expression rate of chemokines receptor CCR5 on peripheral blood CD8+ T cells of occult hepatitis B infected patients. Journal of Mazandaran University of Medical Sciences. 2009;18(68):11-8.
135. Walker RH. Special report: transfusion risks. Am J Clin Pathol. 1987;88(3):374-8.
136. Candotti D, Allain JP. Transfusion-transmitted hepatitis B virus infection. Journal of hepatology. 2009;51(4):798-809.
137. Johnson VV, Swiatkowski SA. Scientific aspects of supplying blood to distant military theaters. Current opinion in hematology.2007;14(6):694-9.
138. Hollinger FB, Sood G. Occult hepatitis B virus infection: a covert operation. J Viral Hepat. 2010;17(1):1-15.
139. Gerlich W, Glebe D, Schuttler C. Deficiencies in the standardization and sensitivity of diagnostic tests for hepatitis B virus. J Viral Hepat. 2007;14(1):16-21.
140. Altunay H, Kosan E, Birinci I, Aksoy A, Kirali K, Saribas S, et al. Are isolated anti-HBc blood donors in high risk group? The detection of HBV DNA in isolated anti-HBc cases with nucleic acid amplification test (NAT) based on transcription-mediated amplification (TMA) and HBV discrimination. Transfus Apher Sci. 2010;43(3):265-8.
141. Burger R, Offergeld R. Testing plasma donations for hepatitis B core antigen (anti-HBc) in order to improve safety of cellular blood components and of quarantined fresh frozen plasma. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2005;48(6):698-9. [Article in German]
142. Devesa M, Pujol FH. Hepatitis B virus genetic diversity in Latin America. Virus Res. 2007;127(2):177-84.
143. Urbani S, Fagnoni F, Missale G, Franchini M. The role of anti-core antibody response in the detection of occult hepatitis B virus infection. Clin Chem Lab Med. 2010;48(1):23-9.
144. Sofian M, Aghakhani A, Izadi N, Banifazl M, Kalantar E, Eslamifar A, et al. Lack of occult hepatitis B virus infection among blood donors with isolated hepatitis B core antibody living in an HBV low prevalence region of Iran. Int J Infect Dis. 2010;14(4):e308-10.
145. Ramezani A, Banifazl M, Eslamifar A, Aghakhani A. Serological pattern of anti-HBc alone infers occult hepatitis B virus infection in high-risk individuals in Iran. J Infect Dev Ctries. 2010 Oct 28;4(10):658-61.
146. Vahid T, Alavian SM, kabir A, kafaee J, yektaparast. Hepatitis B Prevalence and Risk Factors in Blood Donors in Ghazvin, IR.Iran. Hepat. Mon. 2005;5:117-22.
147. Pourazar A, Salehi M, Oreyzi F, Jafarzadeh A, Arababadi MK, Oreizi F, Shariatinezhad K. Detection of HBV DNA in HBsAg Negative Normal Blood Donors. IJI. 2005;2(3):172-176.
148. Emamghorashi F, Fathi GH, Mohtashami A. Evaluation of demographic characteristics and hepatitis B,C and HIV prevalence among blood donors in Jahrom. Sci J Blood Transfus Organ. 2006;2(7):373-8.
149. Arababadi MK, Pourfathollah AA, Jafarzadeh A, Hassanshahi GH, Afrooz MR, Hadadian M. Occult HBV infection in Rafsanjanese blood donors. Modares Journal of Medical Sciences 2009;11:81-6.

150. Mahdaviani F, Saremi S, Maghsoudlu M, Pourfathollah AA. Prevalence of blood transmitted viral infections in regular and non-regular donors of Arak Blood Center. Sci J Blood Transfus Organ. 2006;2(7):343-51.
151. Rezazadeh M, Mani kashani K, Mohammadi A, Zandvakili H, Lotfi A, Bahrami H, et al. Prevalence of human immunodeficiency, Hepatitis B and Hepatitis C viruses in the first time, repeat and regular donors in blood transfusion center, Hamadan, 2004-2005. Iranian Journal of Infectious Diseases and Tropical Medicine. 2006;11(33):55-60.
152. Esmaeili H, Hajiani GR, Monkhian AA, Pourmahdi boroujeni M. Seroepidemiological survey of Hepatitis B, C, HIV and Syphilis among blood donors in Bushehr-IRAN. ISMJ. 2009;11(2):183-90.
153. Kasraian L, TorabJahromi SA. Prevalence of major transfusion transmitted viral infections (HCV, HBV, HIV) in Shiraz blood donors from 2000 to 2005. Sci J Blood Transfus Organ. 2007;3(5):373-8.
154. Mansour Ghanaei F, Fallah MS, Jafarshad R, Joukar F, Salari A, Tavafzadeh R, et al. Prevalence of hepatitis B and hepatitis C, and their risk factors among Guilan blood donors. Sci J Blood Transfus Organ. 2008;4(5):331-6.
155. Kafi-abad SA, Rezvan H, Abolghasemi H. Trends in prevalence of hepatitis B virus infection among Iranian blood donors, 1998-2007. Transfus Med. 2009;19(4):189-94.
156. Kafi-abad SA, Rezvan H, Abolghasemi H, Talebian A. Prevalence and trends of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus among blood donors in Iran, 2004 through 2007. Transfusion. 2009;49(10):2214-20.
157. Doosti A, Amini-Bavil-Olyaee S, Tajbakhsh E, Adeli A, Mahboudi F. Prevalence of viral hepatitis and molecular analysis of HBV among voluntary blood donors in west Iran. New Microbiol. 2009;32(2):193-8.
158. Abdi J, Moazami Goodarzi HR. Prevalence of HBcAb among the HBsAg negative first-time blood donors in Khorramabad and Borujerd blood centers. Sci J Blood Transfus Organ. 2008;4(5):323-9.
159. Ranjbarian P. Comparison of positive HBsAg prevalence in first-time, repeat, and regular blood donors for the purpose of selecting donors in Hamedan. Blood Transfusion Center Sci J Blood Transfus Organ. 2008;4(5):359-63.
160. Torabi Zadeh Maatoghi J, Jalali Far M, Kiani B, Keykhaei B, Mirzaii L, Aiobzadeh N, et al. P. 493 Significant reduction of hepatitis B virus prevalence in blood donors referred to Ahwaz blood transfusion service in 2005 (Iran). Journal of Clinical Virology. 2006;36 Suppl 2:S213.
161. Jalali Far M, Torabi Zadeh Maatoghi J, Sajadi S, Paridar M, Ghasem Zadeh A, Nasimian A. R2307 Significant reduce in hepatitis B prevalence among blood donors admitted to an Ahwaz blood transfusion service due to educational and vaccination programmes. International Journal of Antimicrobial Agents. 2007;29 Suppl 2:S669.