

FREQUENCY OF HEPATITIS B SURFACE ANTIGEN AND ANTI-HEPATITIS C VIRUS ANTIBODIES IN HEALTH WORKERS OF A TERTIARY CARE HOSPITAL, PESHAWAR

Farhad Ali¹, Abdul Khaliq², Sultan Zeb Khan³, Sabreen Hassan⁴, Irfan Ullah⁵, Shahid Ali⁶

¹ Research cell, Khyber College of Dentistry, Peshawar.

² THQ Hospital Dir Lower, KPK.

³ Department of Oral Pathology Khyber College of Dentistry Peshawar.

⁴ Department of Oral Pathology Khyber College of Dentistry Peshawar.

⁵ DHQ Teaching Hospital, KDA Kohat.

⁶ IPMS, Khyber Medical University, Peshawar.

Abstract

Objectives: To determine the Frequency of HBV and HCV among apparently healthy health workers of Hayatabad medical complex (HMC Peshawar)

Materials & Methods: This was a cross-sectional using convenient sampling conducted at Pathology Department, HMC Peshawar from December 2016 to May 2017. Six hundred fifty blood samples from the Medical Staff of HMC Peshawar were screened for HBs Ag and Anti HCV Antibodies by ELISA method.

Results: The results of the study show that out of 650 samples taken from different staff Members (Doctors, Nurses, Paramedical Staff and Other Health supporting staff) 33 were positive. From overall positive samples, 16 were HBV positive, and 17 were HCV positive. Class IV Staff is represented with a higher number of total screened persons with HBV and HCV. From overall screened persons, 2.46% are Class IV /Health Supporting Staff, and 0.92% were Paramedics, 0.76% Staff Nurses while 0.61% of Student Nurses and only 0.3% are Doctors. In Hayatabad Medical Complex there are about 1500 Medical staf and other Supporting staf work and deal with Patients in different ways, 650 staff were screened for HBs Ag and HCV. The prevalence of hepatitis B surface antigen is 2.4%, and Anti HCV Antibodies is 2.6%. Class IV Staf is represented with a higher number of total screened persons with HBV and HCV.

Conclusion: Chronic Hepatitis B and C infection are common in the asymptotic healthy population of a Tertiary Care Hospital Hayatabad Medical Complex Peshawar like elsewhere in Pakistan. These are possible candidates for chronic liver disease and potential sources of spread of infection both horizontally and vertically.

Key Words:

Introduction

Hepatitis “B” virus (HBV) and Hepatitis C virus (HCV) are important causes of chronic liver disease

and hepatocellular carcinoma¹. Pakistan is categorised in the intermediate zone for the prevalence of HBV infection (2.7%). According to an estimate, there are about 4.5 million HBV carriers in Pakistan. Accurate epidemiological information of HCV infection is still scanty from Pakistan¹.

Prevalence of HBV infection is variable in different parts of the world and different in the same

Correspondence:

Farhad Ali

Assistant Professor, Biostatistics

Khyber College of Dentistry, Peshawar. KP, Pakistan.

Cell # +92-332-5925549

E-mail: fktkcdc@gmail.com

country, for example, HBV prevalence in Calicut India is 0.52 % and 6.1 % in Korean Americans. Overall Prevalence of HBV infection in Pakistan is 4.4 %².

A safe and effective vaccine against HBV is available for nearly 25 years. In 2001-2002, Pakistan included this vaccine in (EPI) with a grant of Global Alliance for Vaccines and Immunization (GAVIO). Unfortunately, the vaccination coverage is low in Pakistani adult population because of the lack of funding and infrastructure to purchase and deliver the vaccine. Reported HBV vaccination coverage in general population is 10 %³.

Acute hepatitis C refers to the first six months after infection. Between 60 % to 70% of infected people, develop no symptoms during the acute phase. Symptoms of acute hepatitis C include low appetite, fatigue, abdominal pain, jaundice, and flu-like symptoms⁴. The hepatitis C virus is usually detectable in the blood by PCR within 1 to 3 weeks after infection, and antibodies to the virus are generally detectable within 3 to 15 weeks. Spontaneous viral clearance rates are highly variable between 10 % to 60% as shown by normalization of the SGPT and SGOT, and plasma HCV-RNA clearance. However, persistent infections are common, and most patients develop chronic hepatitis C. Previous practice was not to treat acute infections to see if the person would spontaneously clear; recent studies have shown that treatment during the acute phase of genotype one infections has a greater than 90% success rate. The hepatitis C virus is transmitted by blood-to-blood contact. In developed countries, it is estimated that 90% of persons with chronic HCV infection were infected through transfusion of unscreened blood products or via injecting drug use⁴.

In developing countries, the primary sources of HCV infection are unsterilized injection equipment and infusion of inadequately screened blood products, needles or syringes, hemodialysis equipment, oral hygiene instruments etc. Chronic hepatitis C is defined as infection with HCV persisting for more than six months. Clinically, it is often asymptomatic, and it is mostly discovered accidentally. Generalized signs and symptoms associated with chronic hepatitis C include fatigue, flu-like symptoms, joint pains, itching, sleep disturbances, appetite changes, nausea, and depression^{5,6,9}.

Tattooing dyes, ink pots, stylish and piercing

implements can transmit the virus. HCV is not spread through casual contacts, such as hugging, kissing, or sharing eating or cooking utensils. Vertical transmission refers to the transmission of a communicable disease from an infected mother to her child during the birth process⁶.

The diagnosis of hepatitis C is rarely made during the acute phase of the disease, individuals infected with HCV tested for using polymerase chain reaction PCR; transcription mediated amplification TMA, or branched DNA b-DNA. All HCV nucleic acid molecular tests have the capacity to detect not only whether the virus is present, but also to measure the amount of virus present in the blood, the HCV viral load⁷. According to CDC, hepatitis C virus is spread by exposure to large quantities of blood, either through the skin or by injection: No vaccine protects against contracting hepatitis. Vaccines are under development, and some have shown encouraging results⁸.

In Pakistan, many regions have an alarmingly high rate of uncontrolled outbreaks that has infected approximately 6% of the population⁹. The virus affects not only the liver, but other tissues organs, and systems as well. 3 Persistent infection of Hepatitis "C" appears to be due to weak CD4+ and CD8+ T-cell responses during acute infection, which fails to control viral replication¹⁰.

Sexual transmission of HCV is considered to be rare¹¹. The fact that, old-age at the time of infection is also observed to increase the risk of infection⁵. However, females are more likely to experience spontaneous clearance of infection than males¹². In such situations, the HCV-RNA molecular-detection by polymerase chain reaction (RT-PCR) is highly sensitive and is a reliable test for the early diagnosis of HCV infection¹⁰.

Keeping in view the above circumstances the project has been designed to study and analysed the prevalence of HBs Ag, and HCV infected individuals from a tertiary care hospital (Post Graduate Medical Institute Hayatabad Medical Complex Peshawar Khyber Pakhtoon Khawa-Pakistan.)

Materials and Methods

This cross-sectional study was carried out at Pathology Department Hayatabad Medical Complex (HMC) Peshawar from December 2016 to May 2017.

Before the study, approval from the ethical research committee of Sarhad University of Information Technology (SUIT) was taken through convenient sampling. The purpose of the study and confidentiality were explained to the participants, and informed consent was taken from each participant. Six hundred and fifty (650) blood samples from 650 participants of the medical staff of Hayatabad Medical Complex Peshawar. All the samples were tested in the histopathology section of the Hayatabad medical complex laboratory by trained personnel of the laboratory. The reports were collected back on the same day and data were recorded in the Performa included biodata of the participant like age, sex, service duration HBV vaccination status and results of the HBs Ag and anti HCV antibodies. The data were analysed by SPSS 20.

Results

Out of 650 samples of the blood from different staff Members were Screened for HBs Ag and Anti-HCV. We found that Six hundred and seventeen (94.9%) Subjects were Negative. Thirty-three (5.1 %) Subjects were positive for Hepatitis B and Hepatitis C in overall Screened staff. From overall positive samples, sixteen 16 (2.46 %) were positive for HBs Ag, and Seventeen 17 (2.61 %) were positive for Anti HCV (Table. 4.1)

From overall six hundred and fifty screened staff persons, the combined prevalence of HBs Ag and HCV show that sixteen (2.46%)were Class IV /Health Supporting Staff, six (0.92%) were Paramedics, ive (0.76%) were Staff Nurses, four (0.61%) were Student Nurses and only four (0.3%) are Doctors.

Class IV Staff were represented with a higher number of total screened persons with prevalence of HBs Ag sixteen (4.0%) and Anti-HCV were Seventeen (5.2%), following by paramedical staff with prevalence of HBs Ag four (3.0%) and two (1.5%), in doctors HBs Ag one (2.0%) and Anti-HCV one (2.0%).In staf Nurses, HBs Ag three(1.9%) and Anti-HCV were two(1.2%).In Student Nurses, HBs Ag was only one(0.65%), and Anti-HCV were three (1.96%).

Discussion

To determine the Frequency of hepatitis B surface antigen (HBs Ag) and anti-hepatitis C virus antibodies (Anti-HCV) in Health workers of a

Table 4.1: Seroprevalence of HBs Ag and Anti- HCV, in Health workers of HMC Peshawar by type

S.No.	Job Title	Total No	HBs Ag +	HCV+
1	Doctors	49	01	01
2	Paramedical Staf	120	04	02
3	Staf Nurses	156	03	02
4	Student Nurses	153	01	03
5	Class IV Staf	172	07	09
Total Screened		650	16	17

Fig: 4.2 Graphical representation of HBs Ag/HCV positive staf

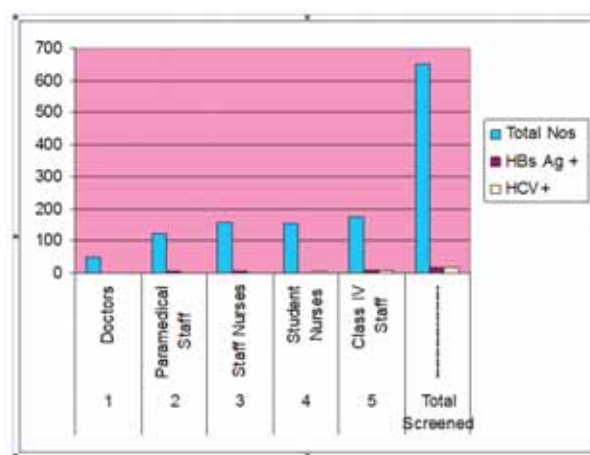


Table 4.3: Percentage of HBs Ag + positive Staf

S.No.	Job Title	N	HCV+	%age
1	Doctors	49	01	2.0
2	Paramedical Staf	120	04	3.0
3	Staf Nurses	156	03	1.9
4	Student Nurses	153	01	0.65
5	Class IV Staf	172	07	4.0
Total Screened		650	16	2.46

tertiary care Hospital, Hayatabad Medical Complex Peshawar. Out of 650 samples of the blood from different staff, Members were Screened for HBs Ag and Anti-HCV. We found that Six hundred and seventeen (94.9%) Subjects were Negative. Thirty-three (5.1 %) Subjects were positive for Hepatitis B and Hepatitis C in overall Screened staff. From overall positive samples, sixteen 16 (2.46 %) were positive for HBs Ag, and Seventeen 17 (2.61 %) were positive for Anti HCV. Conirmation of a diagnosis of hepatitis B and

Fig: 4.4 Graphical representations of HBs Ag positive staf

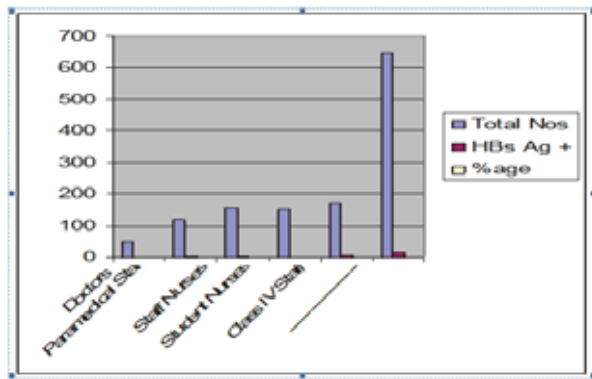
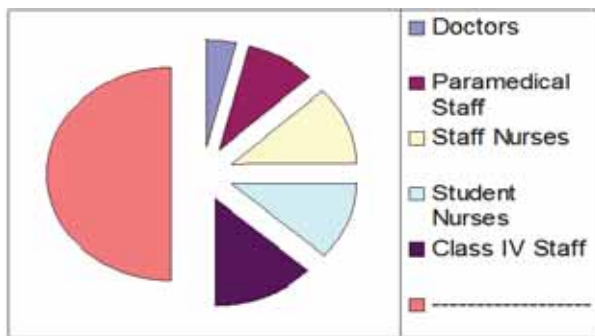


Table 4.5: Percentages of HCV positive staf

S.No.	Job Title	N	HCV+	%age
1	Doctors	49	01	2.0
2	Paramedical Staf	120	02	1.5
3	Staf Nurses	156	02	1.2
4	Student Nurses	153	03	1.96
5	Class IV Staf	172	09	5.2
Total Screened		650	17	2.61

Fig: 4.6 Graphical representation of Anti- HCV +VE positive staf



assessment of prognosis relies on examination of a liver biopsy. Most people who are chronic inactive carriers (no symptoms, HbsAg-positive, normal serum aminotransferase activity) generally have little or no inflammation on biopsy. An important feature in such patients is the presence of “ground glass cells” in liver biopsy, i.e. liver cells producing large amounts of HBsAg.

Substantial inflammation and the presence of fibrosis or cirrhosis correlate with a worse prognosis. A major problem estimating the prognosis of patients with chronic hepatitis C is that it is difficult to predict who will have a relatively benign course and who will go on to develop cirrhosis or cancer.

One clear factor for progression to cirrhosis is concurrent alcohol abuse. Viral genotype may also play a role. There is a wide variation in the prevalence of anti-HCV antibodies and HBsAg worldwide. The global prevalence of HCV is 3%. The prevalence of HCV is high in Africa, especially in some Egyptian cities where more than 15% of the population is infected³⁸. The carrier rate of HBs Ag varies from 0.1% to 0.2% in Britain and USA, more than 3% in Greece and southern Italy, and up to 15% in Africa and the Far East³⁹. Pakistan is highly endemic with hepatitis B and hepatitis C⁴⁰. Studies are too limited to give a clear picture of the prevalence of hepatitis B and hepatitis C at the national level, especially among healthy individuals. Most previous studies targeted different small groups of individuals with some clinical indications, so they do not accurately reflect the overall prevalence in Pakistan.

Hepatitis B and C are global health problems mostly in developing countries. Besides other modes of infection, occupational exposure of health care workers to infected blood remains one of the major modes of infection and risk factor. Some of the studies conducted in Pakistan have revealed varying rates of HBV and HCV prevalence in different patients groups as well as the general population. Nasir et al. described prevalence of (2.56%) for HBV and (5.31%) for HCV in health looking general population. Khattak et al. found that HBV was seen in (3.3%) and HCV in(4.0%) blood donors. The Present study has revealed an overall 8.0% prevalence of HBV, HCV and hepatitis B+C mixed infection in health care workers. Hepatitis B and hepatitis C each alone was seen in 5.6% individuals. Hepatitis B and hepatitis C mixed infection were seen in 3.2% individuals.

Regarding vaccination against HBV, 98% of individuals were vaccinated, and the remaining 52% were not. Among 5 out of 10 individuals having HBV, none had been vaccinated against HBV. Nilofer et al. reported different figures regarding the vaccination of health care workers²². Risk factors for HBV and HCV transmission in the present study included dental procedures, needle prick and surgical procedures.

On the other hand, needle prick injuries were found to be the main risk factor for HBV, and HCV transmission amongst health care workers studied

previously. There have been numerous studies from all over Pakistan on the prevalence of chronic Hepatitis B and C infection. Over 350 reports, papers and presentations estimate the combined prevalence of hepatitis B and C in various parts of Pakistan at 8-10%. These studies have looked into specific risk groups such as blood recipients, paid blood donors, patients suffering from liver disorders, haemodialysis patients, health care workers and voluntary blood donors. While our study shows that from 650 Blood samples from different Health workers including 49 Doctors, 156 Staff Nurses, 153 Student Nurses, 120 Paramedical Staff and 172 Other Class VI/ Health supporting staff), from A tertiary care hospital Hayatabad Medical Complex Peshawar were Screened. The combined prevalence of HBs Ag and HCV show that sixteen (2.46%) were Class IV /Health Supporting Staff, six (0.92%) were Paramedics, five (0.76%) were Staff Nurses, four (0.61%) were Student Nurses and only four (0.3%) are Doctors. A Total of thirty-three (5.1%) were positive for HBV and HCV. From overall positive samples, sixteen (2.46 %) were positive for HBs Ag, and Seventeen (2.61 %) were positive for Anti HCV.

In this study age and employment duration strongly correlated with HBV prevalence. One reason may be because seasoned staff member dealt with patients in an inadequately equipped set-up, which predisposed them to these risks even more. In addition to that, there was a lack of awareness of personal prophylaxis and probably no or little vaccination option available to them. This logic is also proposed in other literature. Most of the HBV infected HCW's in the present study had undergraduate level education. This fact alone is enough to put a rigorous emphasis on their proper education which also is most likely to serve as an effective tool in controlling professional injuries. Nurses and technicians were at high risk of HBV infection as they interact first with the patient. Prevalence of HBV might associate with their low socioeconomic status as it is the disease of poverty. Similar to Sarwar and colleagues nine none of the doctor was found positive, but not by the other studies that among HCWs, surgeons/doctors have the highest risk of HBV infection from their patients. The current study showed that excessive risk of exposures among the HCV as a whole as well as among different occupations Nurses had the highest predisposition to occupational accidents, also

reported by others^{4,6,18,20,21}. Laboratory workers and anaesthesia technicians comprised another major portion of occupational injuries, also analyzed by the others^{4,7,12}. In the current study, the percentage of reported incidents in doctors was lower than other studies. The absolute recording of professional injuries was frequent in nurses, but the percentage was greater in the physicians as this group was found more inclined to self assesses and not report such injuries²². The incidence of occupational exposure is a common feature of studies across the world²³. Factors associated with an increased risk of occupational exposure can differ from place to place depending on the standard of facilities²³⁻²⁵. Poor economic situation doesn't allow facility and personnel to achieve the proper level of sophistication and therein lies the problem^{26,27}.

It is a matter of the fact that the risk factors against the vaccination coverage would vary among different occupations and different regions of the country^{33,34}. Collection of the data of the risk factors against the vaccination provides valuable information for identification and evaluation. By eliminating these factors and providing necessary facilities, 100% vaccination coverage is well within the realm of possibility³¹. We believe our study was able to shed light on the major hurdles to vaccine coverage, including work pressure, negligence and the high cost of the vaccine. We also hope that our study can be used as a precedent to develop important guidelines which, if properly implemented, will be able to curb one of the root causes of the spread of Hepatitis B.

Conclusion

Chronic Hepatitis B and C infection are common in the asymptotic healthy population of a Tertiary Care Hospital Hayatabad Medical Complex Peshawar like elsewhere in Pakistan. These are possible candidates for chronic liver disease and potential sources of spread of infection both horizontally and vertically.

References

1. Yacoub,R.,A.R.Ali,G.Moukeh, A.Lahdo, Y.Mouhammad, M. Nasser.Hepatitis B vaccination status and needlestick injuries among healthcare workers in syria.J.GlobInfectDis.2010;2(1):28-34.
2. Ahmad N, Asgher M, Shaique M, Qureshi JA. An evidence of high prevalence of Hepatitis C virus in Faisalabad, Pakistan. Saudi Med J. 2007 Mar;28(3):390-5

3. Stefanova-Petrova, D.V., H.T.Anelia, E.J.Naumova, A.P. Mihailova, E.A. Hadjiev, R.P. Dikova, M.I. Vukov, K.G. Tehernev. Chronic HCV infection: prevalence of extrahepatic manifestations and association with cryoglobulinemia in Bulgarian patients. *World J. Gastroenterol.* 2007; 13(48): 6518-6528.
4. Souza, K.P., J.A.Luz, SA.Teles, M. A. Carneiro, L.I.A. Oliveira, A.S.Gomes, M.A.Dias S.A.Gomes, CF.Yoshida, RM Martins. *Mem Inst Oswaldo Cruz Jul* 2003;.98(5):599-603.
5. Sobesky, R., P. Lebray, B.Nalpas, A.Vallet-Pichard, H.Fontaine, J.L.Lagneau and S. Pol. Pathological evolution of Hepatitis C Virus-healthy carriers. *World J. Gastroenterol.*2008; 14(24): 3861-3865
6. M.Torres, P.Lardelli, S.Blotner, S.Zeuzem.May. "Chronic hepatitis C in patients with persistently normal alanine transaminase levels". *Clinical Gastroenterology and Hepatology.* 2006;4 (5): 645-52.
7. Sharma, G.K., M.M.Gilson, H.Nathan, M.A.Makary. Needlestick injuries among medical students: incidence and implications. *Academic Medicine.* .2009: 84(12):1815-1821.
8. Shah, SW., S.Sha, M.Younus, S.Adil, SH.Jafri, and F.Hassan. Hepatitis C virus infection in asymptomatic male volunteer blood donors in Karachi, Pakistan. *J.Med* 2004: 2(5)190-2.
9. Sallie, R., Replicative, Homeostasis. A fundamental mechanism mediating selective viral replication and escape mutation. *Virol J.* 2005;2:10-23.
10. Reddy, A.K., K.V.Dakshinamurty, and.Lakshmi. The utility of HCV core antigen ELISA in the screening for HCV infection in patients on hemodialysis. *Ind. J. Med. Microbiol.* 2006: 24(1): 55-57.
11. Wicker, S., J.Cinatl, A.Berger, H.W.Doerr, R.Gottschalk, H.F.Rabenau. Determination of Risk of Infection with Blood-borne Pathogens Following a Needlestick Injury in Hospital Workers. *Ann Occup Hyg.* 2008.
12. Raja, N.S., and K.A. Janjua. Epidemiology of Hepatitis C Virus infection in Pakistan. *J. Microbial Immunol. Infect.* 2008; 41: 4-8.
13. Park, N.H., Y.H.Chung, H.S.Lee. Impacts of vaccination on hepatitis B viral infections in Korea over a 25-year period. *Intervirolgy.* 2010: 53(1+):20-28.
14. Nagao, Y., H.Matsuoka, T Kawaguchi, T.Ide, M. Sata. HBV and HCV infection in Japanese dental care workers. *Int J Mol Med.* 2008; 21(6):791-799.
15. Nadeem, S.R., and A.J.Khalid. Epidemiology of hepatitis C virus infection in Pakistan. *J Microbiol Immunol Infect.* 2008; 41:4-8.
16. Micallef, J.M., J.M. Kaldor, and G.J. Dore. Spontaneous viral clearance following acute Hepatitis C infection: a systematic review of longitudinal studies. *J. Viral Hepat.* 2006. 13: 34-41.
17. Mengal, H.U., N.Howteeraku, N.Suwannapong, T.Rajatanun. Factors relating to acceptance of hepatitis B virus vaccination by nursing students in a tertiary hospital, Pakistan. *J Health Popul Nutr.* .2008: 26(1):46-53.
18. Mehta, A., C.Rodrigues, T.Singhal. Interventions to reduce needlestick injuries at a tertiary care centre. *Indian J Med Microbiol.* 2010: 28(1):17-20.
19. Mathews, R.J, K., Leiss, J.T.Lyde, S.Sousa, J.M.Ratcliffe, J Jagger. Provision and use of personal protective equipment and safety devices in the National Study to Prevent Blood Exposure in Paramedics. *Am J Infect Control.* 2008: 36(10):743-749.
20. Manns, M.P., G.R.Foster, J.K.Rockstroh, S.Zeuzem, F. Zoulim, M.Houghton. "The way forward in HCV treatment—inding the right path". *Nat Rev Drug Dis - cov.*2007: 6 (12): 991-1000.
21. MacCannell, T., A.K. Laramie, A.Gomaa, JF. Perz. Occupational exposure of health care personnel to hepatitis B and hepatitis C: prevention and surveillance strategies. *Clin Liver Dis.* 2010: 14(1):23-36, vii.
22. Vescio, M.F., B.Longo, S.Babudieri. April. "Correlates of hepatitis C virus seropositivity in prison inmates: a meta-analysis". *Journal of Epidemiology and Community Health.* 2008: 62 (4): 305-13.
23. Luckhaupt S.E, G.M.Calvert. Deaths due to bloodborne infections and their sequelae among health-care workers. *Am J Ind Med* 2008; 51(11):812-824.
24. Lu, J., Y.Zhou, X.Lin. General epidemiological parameters of viral hepatitis A, B, C, and E in six regions of China: a cross-sectional study in 2007. *PLoS One.* 4(12):8467.
25. Lee, R. Occupational transmission of blood-borne diseases to healthcare workers in developing countries: meeting the challenges. *J Hosp Infect.* 2009: 72(4):285-291.
26. Lanini, S., V.Puro, F.N.Lauria, F.N.Fusco, C.Nisii, G.Ippolito. Patient to patient transmission of hepatitis B virus: a systematic review of reports on outbreaks between 1992 and 2007. *BMC Med.* 2009: 7(1):15.
27. Kurbanov, F., Y.Tanaka, F.Sugauchi, H.Kato, R.Ruzibakiev, M. Zalyalieva, Z. Yunusova, M.Mizokami. HCV molecular epidemiology in Uzbekistan. *J. Med. Virol.*2003: 69(3):367-375
28. Kamal, S.M. Acute hepatitis C: prospects and challenges. *World J. Gastroenterol.* 2007;13(48): 6455-6457.
29. Jessica, P., M.D.Hwang, M.P.H.Mahfam, M.D.Mohseni, J. Beverly.Gor, D.Ed, M.S.Sijin Wen, Heather Guerrero, M.John and MD.Vierling. Vol 100, No. Sl. *American Journal of Public Health.* 2010: S118-S124
30. Jayanth, S.T., H. Kirupakaran, KN.Brahmadathan,

- L.Gnanaraj, G Kang.Needlestick injuries in a tertiary care hospital. *Indian J Med Microbiol.* 2009; 27(1):44-47.
31. Jaeckel, E., M.Cornberg, H.Wedemeyer, T.Santantonio, J.Mayer, T Zankel, M.Pastore, M.Dietrich, M.Trautwein, MP.Manns.Treatment of acute hepatitis C with interferon alfa-2b. *New England Journal of Medicine.* .November. 2001 345 (20): 1452–1457.
 32. Hladik, W.,P.Kataaha,J.Mermin,M.Purdy,G.Otekat,E.Lackritz,M.J.Alter,R.Downing . Jun .2006.*Trop Med Int Health.*11(6):951-4.
 33. Varsou, O., J.S.Lemon, F.D.Dick.Sharps injuries among medical students. *Occup Med (Lond).* 2009.
 34. Hadiziyannis, S.J., H. Settle, T.R.Morgan, V. Balan, M.Diago, P.Marcellin, G. Ramadori, H.Bodenheimer, D.Bernstein, M.Rizzetto, S. Zeuzem, P.J.Pokros, A. Lin and A.M.Akrill.Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C a randomised study of treatment duration and ribavirin dose. *Ann. Intern. Med.* 2004: 140: 346-355.