Epidemiology of hepatitis C virus infection

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Abstract

Hepatitis C is a major cause of chronic liver disease worldwide. There is a significant variation in the prevalence of hepatitis C virus (HCV) infection, according to the geographic region investigated. These discrepancies reflect not only distinct epidemiological characteristics among populations, but also differences in methodologies. Although data are scarce, estimates indicate that, in Brazil, the prevalence of HCV infection is intermediate, ranging from 1% to 2%. The most important risk factors for HCV infection include intravenous drug use, blood product transfusion, organ transplantation, hemodialysis, occupational exposure, sexual transmission, and vertical transmission. Due to lack of vaccine or effective post-exposure prophylaxis, the main focus of prevention is to recognize and control these risk factors. In this article, we review the literature on the prevalence of HCV infection, particularly in Brazil. In addition, we discuss the pattern of HCV infection according to the age groups and risk factors.

Keywords: Hepatitis C; epidemiology; infectious disease transmission; prevalence; risk factors.

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Introduction

Since the isolation of complementary DNA of hepatitis C virus (HCV) by Choo *et al.*[1], in 1989,hepatitis C has been recognized as one of the main causes of chronic liver disease worldwide.

Prevention and control of hepatitis C depend on a complex evaluation of global distribution of HCV infection, determination of its risk factors, and assessment of factors that accelerate disease progression. Moreover, due to the lack of a vaccine or some form of post-exposure prophylaxis, an accurate epidemiological assessment to plan primary prevention actions in any given population is essential[2].

Search criteria

An exhaustive review of the literature on the epidemiology of hepatitis C was carried out. The Medline and Scielo databank were searched using the following combination of words: hepatitis C; epidemiology; prevalence; risk factors; and transmission. Studies or case reports, correspondences, commentaries, or non-published studies were not included.

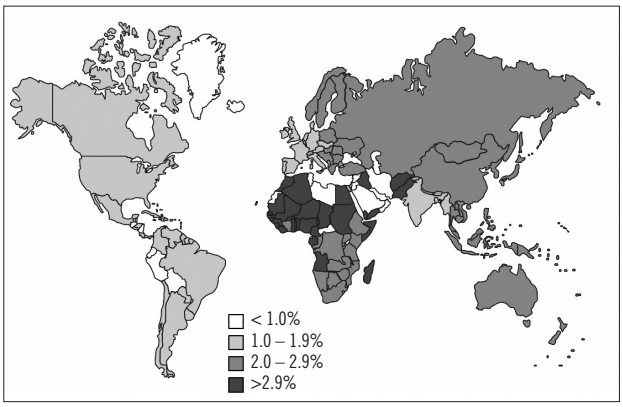
Global prevalence

One of the ways of estimating the prevalence of hepatitis C is through seroprevalence studies performed in blood donors. However, since this is a population with specific characteristics, such studies may not accurately represent the real prevalence of disease. This discrepancy has been demonstrated in the North American population, which in the 1990s had an estimated prevalence of HCV infection of 0.6% in studies of blood donors and 1.8% in general population[3]. Other investigations, such as those in patients with chronic liver disease, should also be carefully interpreted, since those individuals do not adequately represent the total population of a specific area. Although populational studies with representative samples of one or more communities are more appropriate, they are more complex and expensive and may not be accomplished in most regions of the world. Even with these considerations, estimates indicate a global prevalence around 2% to 3%, i.e., between 123 million and 170 million people with HCV infection worldwide[2,4-7].

Although hepatitis C is considered endemic worldwide, there is a high degree of geographical variation in its distribution[2,4-7]. In many countries data are missing, and estimates are based on adjusted means for a specific region. Figure 1 shows the estimated prevalence of HCV infection according to geographic region.

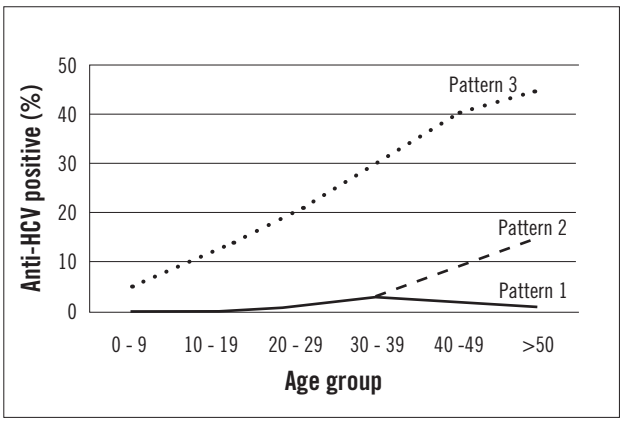
The prevalence of HCV infection is low, in the United Kingdom, Scandinavia (0.01% to 0.1%), Americas, Western Europe, Australia, and South Africa (0.2% to 0.5%)[8]. Intermediate prevalence is seen in Eastern Europe, Mediterranean, Middle East, and India[8]. Other countries with intermediate prevalence include Brazil, Eastern Europe, parts of Africa, and Asia[4,8]. Egypt has a high prevalence of HCV infection (17% to 26%). besides Hubei, Mongolia, and Pakistan[4,6].

Figure 1 – Estimated prevalence of HCV infection according to geographic area (adapted from Perz et al.[8]).



There is only a limited number of studies relating the prevalence of HCV infection at different ages, and they show not only regional but temporal variations that reflect times of HCV transmission increased risk in each region[6]. In these works, at least three distinct epidemiological patterns are observed (Figure 2). The first pattern occurs in countries like USA and Australia with the highest prevalence of HCV in the population between 30 and 39 years of age and lower prevalence in those aged below 20 and above 50 years[4]. In this case, it has been hypothesized that higher rates of transmission had, in the recent past, affected the 10 to 30 years age group[4]. The second pattern, seen in Turkey, Spain, Italy, Japan, and China, the majority of those infected are over the age of 50, which might indicate a greater risk of infection in the distant past, roughly between 40 and 60 years[4]. The third pattern, seen in Egypt, in which an increase in the number of cases with age and, at the same time, a large number of cases in all age groups,

Figure 2 – Prevalence of anti-HCV positivity per age group (see text) (adapted from Wasley & Alter[4]).



indicates an increased risk of transmission in the distant past, which is continuously maintained[2,7]. Identification of those prevalence patterns of HCV infection in different age groups probably shows the epidemiologic characteristics specific to each region. Knowledge of the prevalence pattern in different countries and places might allow greater effectiveness of HCV infection detection and control.

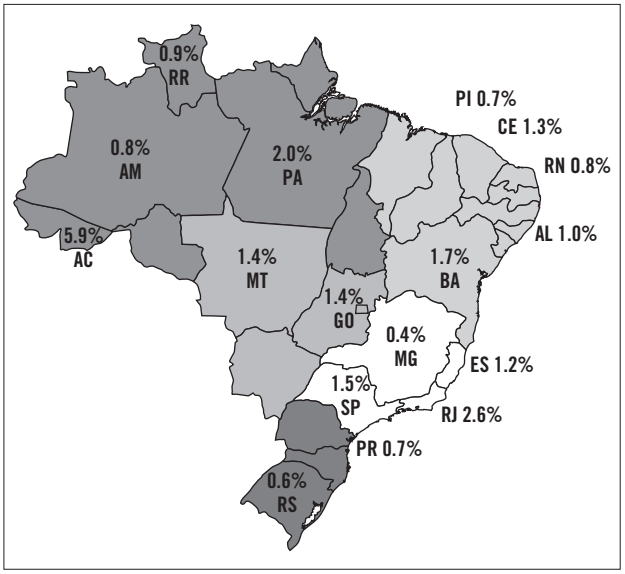
Prevalence in Brazil

Brazil is a continental country and, therefore, with large demographic, social, and cultural variations among its different regions. For this reason, studies evaluating the prevalence of HCV in Brazil are scarce and not precise, usually encompassing restrict geographic areas or specific populations, such as blood donors[9]. Reports of several studies have contradictory information, suggesting the need for studies with more appropriate methodology.

A survey by the Brazilian Society of Hepatology showed that out of 1,173,406 blood donors evaluated, 14,527 (1.23%) were positive for anti-HCV. Figure 3 shows the spatial distribution of anti-HCV positivity per state[10]. The higher prevalence rates were observed in Northern states (2.12%)[10]. On the other hand, the Southern region showed low prevalence of anti-HCV positivity (0.65%). Midwestern, Northeast, and Southeast regions showed intermediate rates (1.04%, 1.19%, and 1.43%, respectively)[10]. However, as discussed earlier, the use of a specific group, such as blood donors, limits extrapolation of these estimates for general population.

In 1998, a populational study by Focaccia *et al.*[11], reported a prevalence of anti-HCV positivity of 1.42% in 1049 residents of São Paulo county.[11] Higher prevalence was observed in individuals over 30 years of age, with the peak of 3.8% seen in the 50 to 59-year age group[11]. As mentioned before, the greater prevalence of hepatitis C observed after the age of 50 suggests infection in the distant past and a gradual dislocation among age groups, with a tendency to concentrate most cases among the elderly.

Figure 3 – Prevalence of anti-HCV positivity in blood donors in different Brazilian states[10].



Risk and transmission factors

The investigation of the risk factors for HCV infection can be done by prospective or retrospective studies, and several studies indicate as main risk factors: transfusion of blood and blood products from non-tested blood donors; organ transplantation from infected donors; IV drug use; therapy with injected drugs with contaminated (or not safe) equipment; hemodialysis; occupational exposure to blood; perinatal infection; and sexual transmission[12-16]. Moreover, due to the great variety of human activities with potential exposure to blood, several possible biologic transmission models exist, such as tattoo, piercing, barber shop, scarification rituals, circumcision, and acupuncture.

Among the different risk factors, the ones described most often in literature include blood transfusion, IV drug use, and invasive therapies with contaminated (or unsafe) equipment[12,13]. However, a significant variation on the importance of each of those factors in disease transmission was observed over time in each region[7].

Transfusion of blood products

Transfusion of blood and blood products from non-tested donors is considered the most important type of transmission. However, after randomization of predonation screening processes, a significant reduction in HCV transmission through blood products transfusion was observed[17]. It has been estimated that, between 1960 and 1991, 5% to 15% of blood product receptors were infected with HCV and that, currently, after adoption of screening tests, the risk of infection from blood transfusion is around 0.001% per unit of blood transfused[18]. Despite this significant reduction observed in the last years, a study performed in the largest blood bank in Santa Catarina demonstrated that the possibility of contamination by HCV is still in the other of one to 13.721 units of blood transfused[19], which is at least 10 times higher than that observed in developed countries[19].

Intravenous drug use

After reduction in HCV transmission by blood products transfusion, sharing contaminated material by IV drug users became the greatest risk factor for transmission of disease. Intravenous drug use was one of the main types of HCV transmission in the last 40 years in countries like the United States and Australia[12,20], being currently the main risk factor in developed countries[12,20]. In these countries, IV drug use is responsible for approximately 70% to 80% of HCV contaminations in the last 30 years[12,20].

A study by Thorpe *et al*. demonstrated that the prevalence of HCV infection among IV drug users has varied from 70% to 90%[21], and it seems to increase with the time of use[22,23]. However, some studies have demonstrated that even the recent users (less than six months) can present rates higher than 75%[21]. In Brazil, statistics are scarce. However, in a study that evaluated the prevalence of anti-HCV in IV drug users in the city of Santos, showed a rate of 75%, comparable to rates reported by most countries.

Medical procedures and nosocomial exposure

Injectable therapies with contaminated (or unsafe) equipment represent another possible form of HCV transmission[25]. Despite the scarcity of reliable data, it has been estimated that approximately two million individuals are infected annually by this route[25]. In developing countries, the supply of sterilized material can be inadequate or nonexistent. Moreover, outside of medical centers, injectable therapies might be performed by untrained individuals; therefore, throughout life, a person can received several injections with contaminated material, increasing significantly the accumulate risk of HCV infection[25]. In Egypt, the country with the higher prevalence of hepatitis C in the world, most individuals were contaminated by reusing glass syringes during national campaigns to treat schistosomiasis between 1960 and 1987[26]. Similarly, in India, the prevalence of HCV among patients who received several injectable treatments for kala-azar is 31.1%, which is significantly higher than the prevalence observed in general population[27].

Patients on hemodialysis have higher prevalence of HCV infection[5], ranging from 19% to 47.2%[10]. Among the factors associated with higher HCV infection rates in hemodialysis patients are the time of dialysis and demographic region[6], Hepatitis C virus transmission among hemodialysis patients is mainly nosocomial. Possible risk factors include sharing hemodialysis equipment and instruments and the lack of adhesion to standard precaution measures and equipment sterilization[28].

Solid organ transplantation

The estimated prevalence of HCV infection in organ transplant recipients is complicated by the influence of immunosuppression on the accuracy of serological tests commonly used. The prevalence of anti-HCV in organ donors, according to studies in cadavers, ranges from 4.2% to 5.1%, depending on the test used[29]. Recipients from anti-HCV positive donors seem to have elevated seroconversion rates; in a study with patients who received kidney grafts, 35% of recipients from anti-HCV positive donors developed post-transplantation liver disease, and 74% showed evidence of viremia[30]. Despite these data, evidence is still limited and there is a clear need for further studies to evaluate the impact of organ transplantation in the prevalence of HCV.

Occupational exposure

Needle sticks accidents with percutaneous inoculation is a well-documented HCV transmission, with seroconversion rates after a single percutaneous exposure to known infected material ranging from 3% to 10%[31,32]. For this reason, several authors have evaluated the prevalence of HCV in health care professionals. Studies in the early 1990 indicated that the prevalence of HCV infection was three times higher in health care workers than among other professionals[31]. However, other studies indicated a prevalence of 0.7% to 2% among health care workers, which is similar to that of general population. The prevalence of HCV among dentists was 0.7% to 1.7%, and, among oral surgeons, the prevalence was 2% to 9.3%[38,39]. A study with orthopedic surgeons who denied the presence of non-occupational risk factors showed a prevalence of less than 1%[40]. Despite these conflicting data, occupational exposure remains a potential risk factor for HCV infection, especially due to the absence of effective post-exposure prophylactic measures in this context.

Vertical transmission

Rates of vertical HCV transmission range from 0% to 20%, with a mean of approximately 5% in most studies[41-43]. Risk factors for vertical transmission include elevated maternal viral load, prolonged labor, internal fetal monitoring, and HIV-HCV coinfection[15,44]. Coinfected mothers were 3.8 times more prone to transmit HCV to the fetus[42]. Breast feeding did not contribute significantly to HCV transmission[43].

Sexual transmission

The risk associated with sexually transmitted HCV is not yet fully understood[5], and this risk factor is one of the most controversial in the epidemiology of hepatitis C among different results in different studies[45,46]. A higher prevalence of HCV infection has been observed among patients treated in clinics specialized in sexually transmitted diseases, among prostitutes and their partners and among patients with HIV-HCV coinfection[47-52,54].

Other risk factors related to sexual behavior seem to contribute for the higher transmission rate of HCV, including: higher number of sexual partners[46], presence of other sexually transmitted diseases, such as trichomoniasis, HIV/AIDS, syphilis, and Chlamydia,[47,48] low use of condoms[46,53], traumatic sexual experience[46,50,53], and male homosexuality[46,47,53-55]. Additionally, male-female transmission seem to be easier than female-male transmission[56].

Despite this evidence, studies with monogamous couples demonstrated low risk of sexual transmission[55]. Moreover, the possibility of intrafamilial transmission by sharing personal hygiene material or occasional exposure to contaminated blood hinders interpretation of studies assessing sexual transmission of HCV[57,58].

Conclusion

Currently, hepatitis C is one of the most common causes of chronic liver disease worldwide. Evidence suggests that most of the cases in Brazil affect individuals over 50 years of age. However, with the significant reduction in blood products transfusion-related transmission, the role of sharing contaminated material by IV drug users has been increasing and it can be responsible for a significant number of cases, especially among youngsters. Studies with proper methodology in order to establish the prevalence of hepatitis C as well as the risk factors for contracting the disease in the Brazilian population are needed to correctly implement control measures and resource allocation against HCV infection.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244:359-62.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5:558-67.
3. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, *et al*. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341:556-62.
4. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis 2000; 20:1-16.
5. Sy T, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. Int J Med Sci 2006; 3:41-6.
6. Yen T, Keeffe EB, Ahmed A. The epidemiology of hepatitis C virus infection. J Clin Gastroenterol 2003; 36:47-53.
7. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007; 13:2436-41.
8. Perz JF, Farrington LA, Pecoraro C, Hutin YJF, Armstrong GL. Estimated global prevalence of hepatitis C virus infection. In: 42nd Annual Meeting of the Infectious Diseases Society of America. Boston; Sept 30-Oct 3, 2004. Abstract.
9. Ferreira CT, Silveira TR. Hepatites virais: aspectos da epidemiologia e da prevenção. Rev Bras Epidemiol 2004; 7:473-87.
10. SBH. Relatório do Grupo de Estudo da Sociedade Brasileira de Hepatologia. Epidemiologia da infecção pelo vírus da hepatite C no Brasil. GED 1999; 18:53-58.
11. Focaccia R, da Conceicao OJ, Sette H Jr, Sabino E, Bassit L, Nitrini DR, *et al*. Estimated prevalence of viral hepatitis in the general population of the Municipality of Sao Paulo, Measured by a Serologic Survey of a Stratified, Randomized and Residence-Based Population. Braz J Infect Dis 1998; 2:269-84.
12. Alter MJ. Prevention of spread of hepatitis C. Hepatology 2002; 36:93-8.
13. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep 1998; 47:1-39.
14. Puro V, Petrosillo N, Ippolito G. Risk of hepatitis C seroconversion after occupational exposures in health care workers. Italian Study Group on Occupational Risk of HIV and Other Bloodborne Infections. Am J Infect Control 1995; 23:273-7.
15. Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. Hepatology 2002; 36:106-13.
16. Terrault N. Sexual activity as a risk factor for hepatitis C. Hepatology 2002; 36:99-105.
17. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. JAMA 2003; 289:959-62.
18. Donahue JG, Munoz A, Ness PM *et al*. The declining risk of post-transfusion hepatitis C virus infection. N Engl J Med 1992; 327:369-73.
19. Kupek E. Transfusion risk for hepatitis B, hepatitis C and HIV in the state of Santa Catarina, Brazil, 1991-2001. Braz J Infect Dis 2004; 8:236-40.
20. Dore GJ, Law M, MacDonald M, Kaldor JM. Epidemiology of hepatitis C virus infection in Australia. J Clin Virol 2003; 26:171-84.
21. Thorpe LE, Ouellet LJ, Levy JR, Williams IT, Monterroso ER. Hepatitis C virus infection: prevalence, risk factors, and prevention opportunities among young injection drug users in Chicago, 1997-1999. J Infect Dis 2000; 182:1588-94.
22. Diaz T, Des Jarlais DC, Vlahov D, Perlis TE, Edwards V, Friedman SR, *et al*. Factors associated with prevalent hepatitis C: differences among young adult injection drug users in lower and upper Manhattan, New York City. Am J Public Health 2001; 91:23-30.
23. Thomas DL, Vlahov D, Solomon L, Cohn S, Taylor E, Garfein R, *et al*. Correlates of hepatitis C virus infections among injection drug users. Medicine 1995; 74:212-20.
24. de Carvalho HB, Mesquita F, Massad E, Bueno RC, Lopes GT, Ruiz MA, *et al*. HIV and infections of similar transmission patterns in a drug injectors community of Santos, Brazil. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 12:84-92.
25. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J Std Aids 2004; 15:7-16.
26. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, MAgder LS, *et al*. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000; 355:887-91.
27. Singh S, Dwivedi SN, Sood R, Wali JP. Hepatitis B, C and human immunodeficiency virus infections in multiply-injected kala-azar patients in Delhi. Scand J Infect Dis 2000; 32:3-6.
28. Zampieron A, Jayasekera H, Elseviers M *et al*. European study on epidemiology and the management of HCV in the haemodialysis population--Part 1: centre policy. EDTNA ERCA J 2004; 30:84-90.
29. Pereira BJ, Milford EL, Kirkman RL, Quan S, Sayre KR, Johnson PJ, *et al*. Prevalence of hepatitis C virus RNA in organ donors positive for hepatitis C antibody and in the recipients of their organs. N Engl J Med 1992; 327:910-5.
30. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal transplantation. Kidney Int 1997; 51:981-99.
31. Lanphear BP, Linnemann CC, Cannon CG, DeRonde MM, Pendy L, Kerley LM. *et al*. Hepatitis C virus infection in healthcare workers: risk of exposure and infection. Infect Control Hosp Epidemiol 1994; 15:745-50.
32. Mitsui T, Iwano K, Masuko K, Yamazaki C, Okamoto H, Tsuda F, *et al*. Hepatitis C virus infection in medical personnel after needlestick accident. Hepatology 1992; 16:1109-14.
33. Thomas DL, Factor SH, Kelen GD, Washington AS, Taylor E, JR., Quinn TC. *et al*. Viral hepatitis in health care personnel at The Johns Hopkins Hospital. The seroprevalence of and risk factors for hepatitis B virus and hepatitis C virus infection. Arch Intern Med 1993; 153:1705-12.
34. Polish LB, Tong MJ, Co RL, Coleman PJ, Alter MJ. Risk factors for hepatitis C virus infection among health care personnel in a community hospital. Am J Infect Control 1993; 21:196-200.
35. Cooper BW, Krusell A, Tilton RC, Goodwin R, Levitz RE. Seroprevalence of antibodies to hepatitis C virus in high-risk hospital personnel. Infect Control Hosp Epidemiol 1992; 13:82-5.
36. Hofmann H, Kunz C. Low risk of health care workers for infection with hepatitis C virus. Infection 1990; 18:286-8.
37. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection. Clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. Medicine 2001; 80:134-51.
38. Thomas DL, Gruninger SE, Siew C, Joy ED, Quinn TC. Occupational risk of hepatitis C infections among general dentists and oral surgeons in North America. Am J Med 1996; 100:41-5.
39. Klein RS, Freeman K, Taylor PE, Stevens CE. Occupational risk for hepatitis C virus infection among New York City dentists. Lancet 1991; 338:1539-42.
40. Shapiro CN, Tokars JI, Chamberland ME. Use of the hepatitis-B vaccine and infection with hepatitis B and C among orthopaedic surgeons. The American Academy of Orthopaedic Surgeons Serosurvey Study Committee. J Bone Joint Surg Am 1996; 78:1791-800.
41. Tajiri H, Miyoshi Y, Funada S, Etani Y, Abe J, Onodera T, *et al*. Prospective study of mother-to-infant transmission of hepatitis C virus. Pediatr Infect Dis J 2001; 20:10-4.

42. Gibb DM, Goodall RL, Dunn DT, Healy M, Neave P, Cafferkey M, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet 2000; 356:904-7.
43. Thaler MM, Park CK, Landers DV, Wara DW, Houghton M, Veereman-Wauters G, et al. Vertical transmission of hepatitis C virus. Lancet 1991; 338:17-8.
44. Mast EE, Hwang LY, Seto DS, Nolte FS, Naitan OV, Wurtzel H, *et al*. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis 2005; 192:1880-9.
45. Alter MJ, Gerety RJ, Smallwood LA, Sampliner RE, Tabor E, Deinhardt F, *et al*. Sporadic non-A, non-B hepatitis: frequency and epidemiology in an urban U.S. population. J Infect Dis 1982; 145:886-93.
46. Alter MJ, Coleman PJ, Alexander WJ, Kramer E, Miller JK, Mandel E, *et al*. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. JAMA 1989; 262:1201-5.
47. Tedder RS, Gilson RJ, Briggs M, Loveday C, Cameron CH, Garson JA, *et al*. Hepatitis C virus: evidence for sexual transmission. BMJ 1991; 302:1299-302.
48. Petersen EE, Clemens R, Bock HL, Friese K, Hess G. Hepatitis B and C in heterosexual patients with various sexually transmitted diseases. Infection 1992; 20:128-31.
49. Wu JC, Wang YJ, Hwang SJ, Chen TZ, Wang YS, Lin HC, *et al*. Hepatitis D virus infection among prostitutes in Taiwan. J Gastroenterol Hepatol 1993; 8:334-7.
50. Sanchez-Quijano A, Rey C, Aguado I *et al*. Hepatitis C virus infection in sexually promiscuous groups. Eur J Clin Microbiol Infect Dis 1990; 9:610-2.
51. Filippini P, Coppola N, Scolastico C, Rossi G, Onofrio M, Sagnelli E, *et al*. Does HIV infection favor the sexual transmission of hepatitis C? Sex Transm Dis 2001; 28:725-9.
52. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Ann Intern Med 1991; 115:764-8.
53. Stevens CE. Perinatal and sexual transmission of hepatitis C virus: a preliminary report. In: Hollinger FB, Lemon SM, Margolis HS, editors. Viral hepatitis and liver disease. Philadelphia: Williams & Wilkins 1991; p.407-10.
54. Thomas DL, Zenilman JM, Alter HJ, Shih JW, Galai N, Carella AV, et al. **Sexual transmission of hepatitis C virus among patients attending** sexually transmitted diseases clinics in Baltimore--an analysis of 309 sex partnerships. J Infect Dis 1995; 171:768-75.
55. Zylberberg H, Thiers V, Lagorce D, Squadrito G, Leone F, Berthelot P, *et al*. Epidemiological and virological analysis of couples infected with hepatitis C virus. Gut 1999; 45:112-6.
56. Magder LS, Fix AD, Mikhail NN *et al*. Estimation of the risk of transmission of hepatitis C between spouses in Egypt based on seroprevalence data. Int J Epidemiol 2005; 34:160-5.
57. Cavalheiro NP, De La Rosa A, Elagin S, Tengan FM, Araújo ES, Barone AA. **Hepatitis C: sexual or intrafamilial transmission? Epi**demiological and phylogenetic analysis of hepatitis C virus in 24 infected couples. Rev Soc Bras Med Trop 2009; 42:239-44.
58. Waure C, Cefalo C, Chiaradia G, Sferazza A, Miele L, Gasbarrini G, *et al*. Intrafamilial transmission of hepatitis C virus in Italy: a systematic review. J Epidemiol Community Health 2010; 64:843-8.