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Sexual transmission of hepatitis C virus

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Abstract

Background: Globally, the prevalence of HCV is estimated by the World Health Organization (2003) to be 3%, or approximately 170 million people and is anticipated to have a huge burden in future years on those infected as well as on economic costs. Hepatitis C is the leading cause of liver transplantation, cirrhosis and liver carcinoma throughout the world.

Objective: The purpose is to review literature sources to clarify the controversial subject of sexual transmission of hepatitis and provide a resource tool for health care providers.

Method: A search of electronic databases from 1991 to 2009 will be done and results summarized to display current evidence.

Findings: Of the studies summarized in the pamphlet tool the percentage of seroconversion ranged from 0% to 6% and of those that converted a number of them had other risk factors that may have attributed to their results. Studies did show that there are certain conditions that increase the risk of sexual transmission above that of the general population.

Keywords: hepatitis C, transmission, sexual transmission, intrafamilial,

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Sexual transmission of hepatitis C virus

Title: Review of literature on the sexual transmission of hepatitis C and development of a resource for health care providers.

Address the following questions: What does the current research indicate as the risk of contracting hepatitis C through sexual transmission? What does research indicate are other modes of transmission? What is the probability to contract this infection via sexual contact? What should health care providers counsel their patients about the sexual spread of hepatitis C virus (HCV) and what precautions should they take?

Purpose:

The purpose is to review literature sources to clarify the controversial subject of sexual transmission of hepatitis C. This information will be used by both health care professionals counseling their clients/patients as well as those affected by hepatitis C looking to understand the disease further. A tool will be developed that will assist health care practitioners in their counseling of clients.

Background/Rationale:

Hepatitis C is the leading cause of liver transplantation, cirrhosis and liver carcinoma throughout the world. HCV's propensity for displaying a subclinical infection (75% of those infected have a subclinical infection before progressing to a chronic illness) makes HCV difficult to study. There is no vaccine for hepatitis C so efforts to reduce the burden of disease fall on prevention methods mainly through public education.

Whether or not the hepatitis C virus is transmissible through sexual contact is not in dispute. The question is: to what extent is it transmissible? Is sexual contact a high risk or minimal? What other factors influence the sexual transmission of the virus? This information is

critical to those infected with the hepatitis C virus and their partners as it will assist them with making decisions about their lives. As sexual intercourse is common and the pool of those infected with the virus is large, any amount of sexual transmission could result in a large number of new cases.

Wong, et al (2000) used a computer cohort simulation of HCV's natural history in the US to estimate morbidity, mortality and future costs. Their study displayed staggering numbers and concluded that HCV may lead to a substantial health and economic burden over the next 10 to 20 years (Wong, et al., 2000).

Conceptual Framework:

A conceptual framework will be applied to build a foundation for the research. A conceptual framework helps to summarize existing knowledge into coherent systems, stimulate new research and explain phenomena and relationships among them (Polit, Beck & Hungler, 2001).

Mishel's "uncertainty in illness theory" fits well with the study of hepatitis C and will be used for this research. This theory's focus, as the name suggests, is uncertainty or the inability of a person to determine the meaning of illness related events. This is very applicable to the study of the effect of HCV infection on a person as the outcomes can be so variable and unpredictable. According to Mishel's theory (Smith and Liehr, 2003), uncertainty exists in illness situations that are complex and unpredicatable.

Mishel developed a revision to her theory to make it more applicable to those with chronic illness. Her reconceptualized theory of uncertainty (Smith and Liehr, 2003) is more fitting to those living with chronic illness or "illness where there is a possibility of recurrence and where self-management is the primary focus for treatment" p. 56.

The reconceptualized theory of uncertainty has a desired outcome of growth to a new value system whereas the original theory of uncertainty's goal was a return to the previous level of adaptation or functioning. Again, this is applicable to a chronic disease such as HCV where the outcomes are unpredictable and variable among those infected. One must also consider that family members also experience uncertainty and may perceive it as a significant stressor. Applying Mishel's theory to a conceptual framework will combat this uncertainty by explaining the risks, precautions and other information that those infected or living with one infected should be aware.

Literature Review:

History of discovery of the virus and major characteristics

It wasn't until 1989 that the hepatitis C virus was officially "discovered" (Gretch, 1997). Before that scientists had known of the virus's existence but hadn't identified it. Early on it was referred to as Non-A, Non-B hepatitis and scientists were aware of it due to clinical observations and tests on chimpanzees. In 1989, scientists managed to clone HCV and a breakthrough was achieved. Since that time further analysis of the virus has taken place and scientists now know that HCV is an enveloped virus of the family *Flaviviridae* and is the sole member of the genus hepacivirus (Howard, 2002). Six major genotypes have been identified along with more than 50 subtypes (Wong & Lee, 2006). Certain genotypes are predominant in some geographical areas, with genotype I being predominant in Canada.

"The hepatitis viruses have long been assumed to be highly host-specific, with infection of other nonhuman primates occurring due to inoculation with, or exposure to, human viruses" (Robertson, 2001, p. 233). Howard (2002) also identifies that individuals that recover from HCV

infection can be reinfected by noting that immune globulin given to chimpanzees fails to protect them.

The many complexities with HCV have not all been identified and there remain many unanswered questions, due in part to the failure to produce the virus *in vitro* (Howard, 2002). Hoofnagle (2002) explains that HCV RNA genomes mutate frequently and as a result, "HCV circulates in serum not as a single species but as a population of quasispecies with individual viral genomes differing by 1% to 5% in nucleotide sequence"p.22. A quasispecies is a term used at times to describe RNA virus evolution.

Epidemiology:

Globally, the prevalence of HCV infection is estimated by the World Health Organization (2003) to be 3% or approximately 170 million people worldwide and is considered endemic throughout. The distribution of HCV infection is quite variable dependant on the geographic location (see Figure 1). The industrialized nations report the lowest rates with countries in Africa and Asia reporting the highest rates (Shepard, et al., 2005).

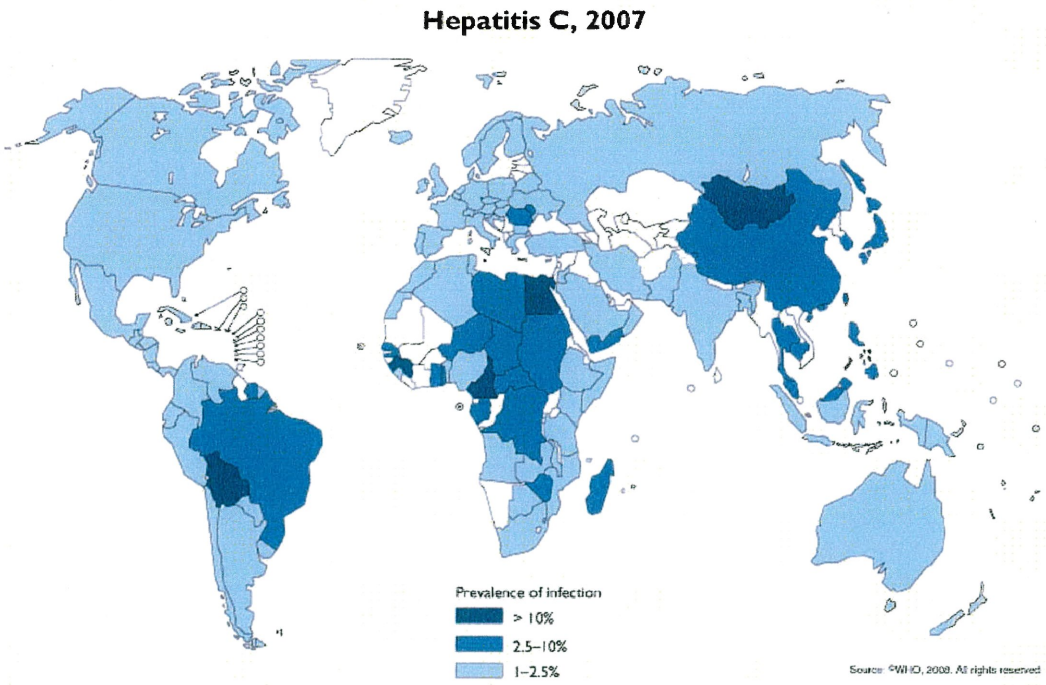

Figure 1: From "International Travel and Health", by the World Health Organization, 2009. Retrieved March 9, 2009 from http://www.who.int/ith/maps/en/index.html

Transmission patterns vary throughout the world. Current transmission of HCV in the developed world is predominantly attributable to recreational injection drug use, while in the developing world is attributable to unhygienic therapeutic injection practices and transfusions. For example, in Egypt it is estimated that the seroprevalence rate is 22% (Shepard, 2005) and it is suggested that this is attributable to contaminated glass syringes that were used in schistosomaisis treatment campaigns between 1960 and 1987. In developing countries sterile syringes are in short supply.

Also evident in the developing world is lack of adequate screening of donated blood for transfusions. "WHO's global database on blood safety estimates that 43% of donated blood in the developing world is not screened adequately for transfusion-transmitted infections including HCV" (Shepard, et al.,2005). Shepard et al (2005) state that for example, in India HCV screening of blood products is not done despite laws mandating it, primarily due to financial constraints.

In 2005 in Ontario 4,541 new cases of HCV were reported to public health making it the second most common reportable disease after Chlamydia infection (iPHIS, 2008). Remis (2006) found that an estimated 110,000 people in Ontario are HCV infected as of 2004 with an estimated 2,234 of that number in the Thunder Bay district (or a prevalence rate of 1.4%). In the Thunder Bay district there were 103 laboratory reported cases of HCV infection (newly diagnosed) in 2006, 135 in 2007 and 156 in 2008 (iPHIS, 2008). As hepatitis C is a reportable disease in Ontario certain information is collected when an individual has a confirmed positive laboratory test for the virus. This information includes not only the client's demographics but

also information on their risk factors. The most common risk factor in those newly diagnosed is a history of injection drug use.

Risk Factors:

British Columbia was the first province to start reporting hepatitis C in Canada in 1992. A conflicting report by Remis (2006), states that HCV was a reportable disease in Ontario since October of 1991. Never the less, since laboratory testing and subsequent reporting of this disease only began about that time a portion of the large increase in hepatitis C rates can be attributed to the increased testing and identification of those previously infected. The most recent data published for Canada (PHAC, 2006) indicates an incidence rate during the years 1998 and 2004 ranging between 68 per 100,000 to 45 per 100,000. These numbers indicate "newly diagnosed" cases of both acute and chronic infections. This data also indicate that there are over 8000 new infections per year making it the 2nd most often reported reportable disease. Remis (2006) conducted a modeling study to "characterize the epidemiology of hepatitis C infection in Ontario in 2004" and concluded that approximately 110,000 persons in Ontario were infected with HCV. This study also estimated that of those infected 20% were active and 33% past injection drug users, 13% had infections attributable to blood transfusions, 0.38% were hemophiliac patients and the remaining 34% were attributed to "other modes of transmission" (Remis, 2006).

The "other modes of transmission" in this research are important to determine especially with regards to counseling those infected with HCV (and those attempting not to become infected) so they can make educated choices to protect themselves and others. Unfortunately sexual transmission cannot be objectively studied. Research relies on study participants to be honest and truthful with regards to questions asked as well as to recall

information accurately. Information on the incidence of "higher risk" sexual activities among HCV positive individuals needs to be gathered. Any lack of condom use, total number of sexual partners (lifetime), anal intercourse, intercourse with tearing of mucosal lining and any co-infections with HIV are important in assessing the determination of HCV as a sexual infection (Terrault, 2005).

Current high risk factors for HCV infection (Wong & Lee, 2006) include any history of injection drug use, contaminated blood or blood products or organ transplantation before July 1990, incarceration, needlestick injuries. Injection drug use is such a major factor in the spread of HCV due in part to the ease in which the virus is spread by this route. Fewer sharing partners are required for HCV to spread than for all other types of bloodborne viruses. The virus is spread indirectly through things like cotton filters, cookers, backfilling syringes, etc. Studies have shown that the prevalence of HCV among injection drug users can be as high as 95% (Shepard, Finelli, & Alter, 2005). Wong and Lee (2006) include a sexual partner with HCV, multiple sexual partners, vaginal sex during menstruation, sexually transmitted infections and traumatic sex in their moderate risk of HCV infection category (Table 1). "Sexual transmission of HCV is uncommon and much less efficient than with hepatitis B or HIV. High HCV prevalence is found among sex workers but it is often linked to drug injection and to people who have multiple partners" (Wong & Lee, 2006, p. 650). Another view explains though that since sex is such a common behaviour and the reservoir of those infected with HCV is large, sexual transmission is a likely contributor to the numbers infected (Terrault, 2005).

Table 1: Risk Factors for HCV infection

High risk of HCV is associated with: • Any history of injection drug use • Contaminated blood or blood products or organ transplantation before July 1990 • Incarceration • Needlestick or sharp injuries • Procedures involving reusing or sharing contaminated equipment in parts of the world with high HCV prevalence • Nonsterile contaminated tattooing or body piercing equipment • Receiving hemodialysis • Sharing of personal items contaminated with blood from an infected person • Hepatitis B infection • HIV infection • Children born to a mother with HCV infection • Undiagnosed liver disease
Moderate risk of HCV infection is associated with: • A sexual partner with HCV • Multiple sex partners • Sexually transmitted infection, including lymphogranuloma venereum • Traumatic sex that involves the potential for mucosal tearing • Vaginal sex during menstruation
Transmission of HCV is NOT associated with: • Coughing • Food • Water • Sharing eating utensils • Hugging or kissing • Shaking hands • Toilet seats • Other casual contacts • Breastfeeding (unless nipples are cracked or bleeding) • Oral sex (unless there is blood exposure involved)

From "Hepatitis C: A Review for primary care physicians" by Wong, T., & Lee, S. 2006, *Canadian Medical Association Journal, 174(5)*, 649-659.

Immune Response to HCV:

To understand the differing outcomes (from spontaneous clearing of the virus to chronic infections) in people infected with HCV it is important to understand the immune response.

There are various components of the immune system that work together to fight off an array of infections. With regards to HCV there remain many unanswered questions. What is known is that the response involves both humoral (antibody production) and cellular immunity (CD4+, CD8+ and T-cells) (Gremion & Cerny, 2005).

Once HCV enters the body of a susceptible host it reaches the liver through the hepatic artery or the portal vein and begins to replicate in the hepatocytes (Mizukoshi & Rehermann, 2001). Acute hepatitis is rarely seen as the majority of cases are asymptomatic. According to Mizukoshi & Rehermann (2001), circulating HCV-specific T cells have been demonstrated as early as 3-4 weeks after infection with the HCV-specific antibody response occurring much later.

The mechanisms responsible for the persistence of HCV infection and for the liver lesions are not well understood. It is, however, believed that HCV is not directly cytopathic; the body's immune response mechanisms are the cause of the lesions. The active T-cell response to persistent HCV infection is probably the main instrument responsible (Boyer and Marcellin, 2000). The intensity of the immune response can be influenced by the dose, form, and route of infection (Mizukoshi & Rehermann, 2001). Mizukoski & Rehermann (2001) also explain that because HCV is thought to be noncytopathic it "is able to establish persistent infection without eliciting any symptoms of acute hepatitis. p. 803".

Hepatitis C virus is often described as a quasispecies due to frequent mutations that allow the virus to evade the body's immune response. As described earlier a quasispecies is a term used at times to describe the evolution of an RNA virus. It is also a model that has some controversy surrounding it.

Laboratory Testing Methods:

The initial laboratory test for identifying HCV is an enzyme immunoassay (or EIA) for the HCV antibodies. Current third generation EIA's are more sensitive than earlier tests. However, Krajden (2000) explains that their overall sensitivity is still dependent on the clinical status of the population tested. He explains that in those chronically infected the sensitivity of the EIA can reach up to 97-99% but in those acutely infected sensitivity can be as low as 50-70% at onset of symptoms (Krajden, 2000). Population prevalence also plays a part in the specificity of third generation EIA's with higher prevalence populations having a higher specificity than lower prevalence populations (Krajden, 2000).

HCV immunoblot assays were developed to be confirmatory tests for the HCV EIA tests. Since the development of the more effective third generation EIA's the usefulness of immunoblot assays has diminished. If the EIA anti-HCV test result is positive, infection can be confirmed with polymerase chain reaction (PCR)-based qualitative HCV RNA assay.

Often this confirmatory step is unnecessary, according to Wong & Lee, 2006, as clients who have elevated liver enzymes and/or any of the risk factors for hepatitis C virus infection can be diagnosed to have hepatitis C virus with a greater than 95% certainty when the EIA is positive (Figure 2). Immunocompromised clients may not have any detectable levels of HCV for months or even years. These clients are unable to produce enough antibodies necessary to have a positive EIA. When there is a low likelihood of HCV then a confirmatory test should be done to rule out a false positive test result. Neither test though can distinguish between an acute, chronic or resolved infection. Diagnosis in weakly reactive individuals typically requires nucleic acid testing (NAT) or follow-up testing to confirm seroconversion.

Nucleic acid testing or polymerase chain reaction can directly detect HCV RNA in serum, plasma or tissue and thereby confirm active infection as well as narrow the window between infection and HCV detection to as little as 1-2 weeks (Krajden, 2000). Ackerman, Ackerman & Paltiel, 2000 explain that detection of HCV RNA by polymerase chain reaction provides the 'gold standard' for the presence of new infection.

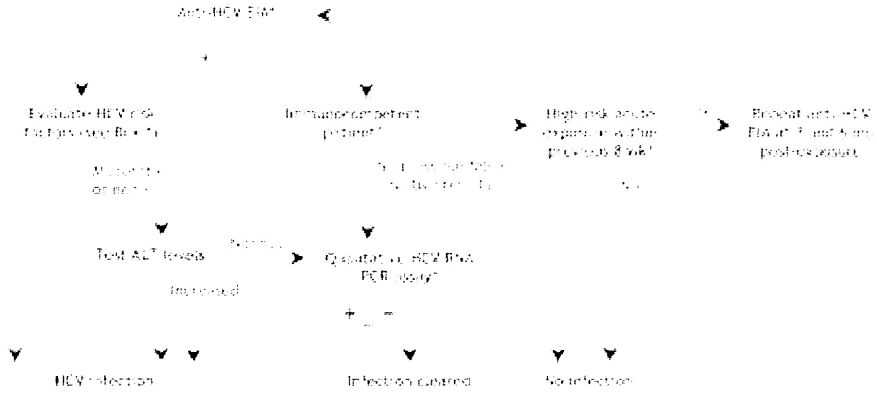

Figure 2: Algorithm for testing for hepatitis C infection.

From "Hepatitis C: A Review for primary care physicians" by Wong, T., & Lee, S. 2006, *Canadian Medical Association Journal, 174(5)*, 649-659.

Studies to detect HCV RNA in semen, vaginal secretions, cervical smears and saliva have all had mixed results. All have detected HCV in body fluids but their viral loads are low; meaning that although the virus is detectable its ability to cause transmittable infection is limited. A study of 106 homeless HCV positive men in Los Angeles found that 36 % of semen tested was positive for HCV RNA (Nyamathi, Robbins, Fahey, Wiley, Peckler, Longshore, et al, 2002).

Signs and Symptoms - Acute and Chronic:

Signs and symptoms of HCV infection can vary from one person to the next. As explained earlier, acute HCV infection is asymptomatic in most people. Data on symptoms of acute HCV infection are limited for this reason. Maheshwari, Ray and Thuluvath (2008) explain that although jaundice is often associated with a hepatitis diagnosis only 10-20% of those acutely

infected develop. However some studies have shown a higher incidence of jaundice in injection drug users. Often acutely infected HCV clients have influenza like illness, dark urine, and clay coloured stools as well as nausea and abdominal pain (Maheshwari, Ray & Thuluvath, 2008). Acute HCV infection can occur within 2-12 weeks after exposure and can last for 2- 12 weeks (Wong & Lee, 2006). Fifteen to twenty-five % of those infected will "clear" the virus meaning HCV will become undetectable in their blood and their alanine aminotransferase levels will be normal (Chen &Morgan, 2006). The other 75% to 85% will develop chronic hepatitis of which the rate of progression can be variable (see figure 3).

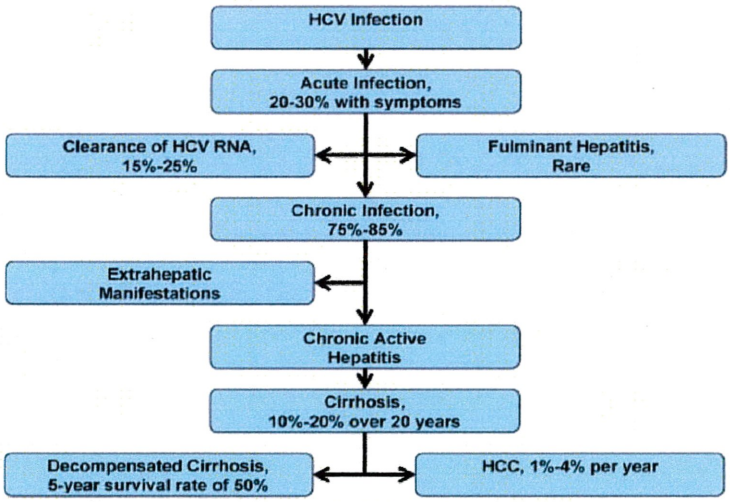

Figure 3: From "The Natural History of Hepatitis C Virus (HCV) infection" by Chen & Morgan. 2006. *International Journal of Medical Sciences, 3(2)*, 47-52.

Outcomes of chronic hepatitis C:

The natural history of HCV (as shown above in figure 3) is also an area with controversy attached. There is still incomplete knowledge on HCV infection. As Seeff (2002) explains, the ideal methods to determine the natural history of HCV (following up large groups of infected people in the acute phase and following them up without treatment until they have developed advanced liver disease or died) are for obvious reasons unethical. Given that a large percentage

of infected individuals have not reached the 20 years past infection it remains difficult to determine the outcome.

The 75% to 85% infected individuals that develop chronic infection can also have variable outcomes. The long term complications of chronic hepatitis C can be cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC), which will usually progress after many years or even decades (Hoofnagle, 2002). There are also some major extrahepatic manifestations of chronic hepatitis C. Chen and Morgan (2006) explain that these manifestations can affect many multiple organ systems including the "renal, dermatologic, hematologic and musculo-skeletal systems" p.50. Chen and Morgan (2006) also explain that cryoglobulinemia is the most common extrahepatic condition. The Mayo clinic (2009) explains that cryoglobulinemia is a presence of large amounts of cryoglobulin in the blood that clumps together under certain conditions. Cryoglubulinemia can cause symptoms such as fatigue, skin rashes, vasculitis, arthralgias, renal disease and peripheral neuropathies (Chen & Morgan, 2006).

As described in Figure 3 there remains the 10% to 20% of individuals that will develop cirrhosis with an additional 1% to 4% of patients advancing to hepatocellular carcinoma. Chronic hepatitis C infections are now believed to be the leading indication for liver transplantation in the United States and likely Canada as well (Wong, McQuillan, McHutchinson & Poynard, 2000).

Factors associated with liver disease progression:

A number of studies have identified variables that contribute to progressive liver disease. Seeff (2002) categorizes the variables into three factors: factors that are viral related, those that are host related and external factors that may modulate disease progression. Viral related factors include the viral load and genotype, but Seeff (2002) explains that there is little evidence that

viral load or genotype play a role in disease progression, although it is believed that certain genotypes respond better to treatment.

Host related factors are multiple and include age at time of infection, coinfections with HIV, HBV or schistosomaisis (primarily important in those infected in Egypt) as well as any comorbid conditions that may suppress the immune systems. Seeff (2002) reports that genetic factors of the host may also play a role; lower rates of disease progression were found in females and also among African-Americans (US).

The most commonly described extrinsic factor affecting progression of HCV is alcoholism. There is evidence that the more alcohol consumed the greater the risk and the increased speed of advancement of liver disease. Minuk (1999) found that cirrhosis was more common in infected individuals that drank more than 60g/day of alcohol over 5 years than in those that did not report drinking (56% versus 22%).

HCV-HIV Coinfection:

Injection drug use is not only the most common mode of transmission for those infected with HCV, it is also the most common way that HIV is transmitted. For this reason many injection drug users will acquire both viruses. Also, those people requiring repeated blood transfusions (either in countries with unsatisfactory testing methods or our own country before tests were made available) would be at an increased risk for contracting both viruses.

There is evidence of an increased risk of acquiring HCV if one is HIV positive. Sulkowski & Thomas (2003) explain that the rate of HCV transmission from an HIV/HCV co-infected mother to her infant (in utero) is greater than from HIV uninfected mothers to their infants. Sexual transmission of the HCV virus was found to be increased in some studies

(Myers, et al, 2009). According to Wong & Lee (2006), an HIV infection will accelerate the progression of hepatitis C, "especially if the CD4 count is below 200 cells/mL" p. 655.

Prevention Methods:

Education campaigns are the primary prevention method to decrease the spread of HCV. As the use of injection drugs is currently by far the most common mode of transmission of the virus, education campaigns need to target this group. The essential components to prevent spread of HCV in Canada and around most of the world are to institute harm reduction measures and change public policy regarding illicit drugs. Unfortunately these are measures that often meet strong resistance.

Prevention methods globally would have to look at blood screening practices and find ways to reduce costs associated so that poorer countries can ensure a safe blood supply. Injection practices globally also have a financial component that need solving with short cuts being taken in the name of saving a dollar.

New barrier precautions and safety engineered needles are minimizing known risks of occupational transmission in Canada with new legislation making the use of "safety needles" in some provinces mandatory. Again though, this is not the case in some other parts of the world.

For those infected with the virus they can minimize spread to others by not donating blood, organs, etc and never sharing any materials used to prepare or inject drugs (or inhale) (PHAC, 2009). Sharing of any type of instrument that may have blood on it (razor, clippers, and toothbrush) is not advised. Perhaps in the future a vaccine may be available to assist with prevention of HCV spread.

Methods:

A number of electronic databases from 1991 to 2009 will be searched including but not limited to PubMed, Medline, Science direct, Blackwell-Synergy, Ovid, and Embase. Search will also include a hand search of the index pages of certain relevant journals, such as Journal of Infectious Diseases, Clinical Infectious Diseases, etc. published within the past 7 years. The search to locate relevant articles, published in English, will include terms and keywords either alone or in combination such as hepatitis C transmission, sexual transmission, high risk behaviours, mode of spread, risk factors, etc. Only publications from relevant peer reviewed literature will be reviewed. Editorial and opinion fragments will be excluded from the review. Articles referenced in papers will also be searched. The lists of studies referred to in this project are by no means exhaustive of all publications with pertinent information regarding the sexual transmission of hepatitis C.

The evidence will be summarized looking at the study eligibility, the study's characteristics, methods, results and interpretations. Studies will be categorized based on study type, objectives and purpose. Results will be disseminated to health care providers by way of a counseling manual/pamphlet. This pamphlet will include basic information about HCV and include a summary of the current evidence of sexual transmission of HCV with a listing of references. Health care professionals should be able to use this information to make decisions on the counseling advice they will give their patients to assist them to make informed decisions.

Results and Discussions:

Current available recommendations and guidelines on the prevention and management of hepatitis C are on average 10 years old. Many of these recommendations indicate that the risk of sexual transmission requires further study and that it is difficult to reach a consensus on

prevention advice. The Canadian Association for Gastroenterology and the Canadian Association for the Study of the liver through a consensus conference and authored by The Laboratory Centre for Disease Control (1995) issued guidelines and recommendations with regard to the prevention and control of hepatitis C and advised that:

> "The risk of sexual transmission of HCV has not been established, but appears to be much lower than that of HIV and HBV, current knowledge does not warrant partner notification/contact tracing; however, HCV-infected persons have a personal responsibility to inform potential sexual partners that there is a risk of infection with a sexual exposure." p. 378

They go on to further separate their recommendations into two groups; those with multiple sexual partners and those in long-term monogamous sexual relationships and counsel that both groups should be provided with information that may reduce their risk of sexual transmission and also that those in long-term relationships should be offered testing by their physicians (The Laboratory Centre for Disease Control, 1995). New recommendations (Pinette, Cox, Heathcote, Moore, Adamowski, & Riehl, 2009) advise physicians that sexual activity is "safe" unless it involves trauma or high-risk sexual activity. High risk sexual activity is generally described as unprotected sex with a HCV+ partner, multiple partners, partner with a sexually transmitted infection and any sexual activity where blood may be present (i.e. during menstruation, anal intercourse, etc).

The American Centre for Disease Control, CDC, (2006) advises that HCV is not efficiently transmitted sexually and also repeats that the role of sexual activity in the transmission of HCV is unclear. They direct HCV-positive persons with one long-term, steady sex partner that there is no need to change their sexual practices (CDC, 2006). As the CDC states (2006), sexual transmission is not an efficient means of spreading the hepatitis C virus; despite the lower risk of spread (due possibly to lower titres in body fluids other than blood), the

high numbers of those infected with the virus and given that sexual activity is obviously very common, even a small risk of spread through sexual activity could theoretically play a great role in the increasing numbers.

Some research indicated that the risk of sexual transmission of the hepatitis C virus increased if the person was co-infected with HIV. Men who have sex with men (MSM) also have a higher incidence of hepatitis C transmission through sexual transmission believed to possibly be caused by a coinfection with HIV which appears to be higher in some subgroups of MSM's (van de Laar et al., 2007). Researchers also attribute some of this to higher risk sexual contact (i.e. anal intercourse), although this is not clear and there is contradictory research on this. A conflicting study found no evidence of an increased risk of HCV in MSM and felt that the divergent study results among researchers could be attributed to the low risk of transmission sexually, small study group sizes and possibly the lack of reporting of potentially important exposures (Alary et al., 2005). Their study of 1085 men who have sex with men in Montreal found that despite a high percentage of them reporting a large number of sexual partners as well as unprotected anal intercourse only one study participant seroconverted during the time frame (Alary et al., 2005). This one seroconverter was an injection drug user that reported needle sharing within 6 months of first testing positive for HCV (Alary et. al., 2005).

An Amsterdam study of MSM's found an increased rate of HCV infection in those that were coinfected with HIV (van de Laar et al., 2007). During their study time frame of 1984 to 2003, they found that eight MSM's seroconverted for HCV and all eight were HIV positive as well (van de Laar et al., 2007). Van de Larr et al. (2007) followed 34 study participants that had an HCV diagnosis in hospital, all but one of which was HIV positive at time of seroconversion, and found that 59 % of these men also had one or two ulcerative (genital) coinfections within the

six months preceding seroconversion (i.e. lymphogranuloma venereum, syphilis, gonorrhea, etc.). The researchers hypothesize that the current outbreak of HCV among their participants could be triggered by the increase of riskier sexual activities observed in MSM's after the introduction of highly active antiretroviral therapy or HAART (van de Laar et.al., 2007).

A Canadian prevalence study (Myers et al., 2009) looked at a sample of homosexual and bisexual men and had participants complete a questionnaire and give saliva samples for HCV and HIV to assess the prevalence of both infections and any correlates between HCV and HIV. Their study found that those that were HIV positive were 5.5 times more likely to be HCV infected as compared to those that were HIV negative (Myers et al., 2009). The overall prevalence of HCV infection in their sample was slightly higher in this gay and bisexual community (1.9%) than in the general population of 1.7% (Myers et al., 2009). Myers et al., (2009) found that, as most studies, needle sharing was the major mode of transmission of HCV and that sexual transmission accounted for only a small portion of infections if any.

A study of HCV infection in Canada found that approximately 6% of newly acquired HCV infections might be related to sexual transmission (in contrary to the estimated 20% of acute hepatitis C cases in the United States). The study's authors (Wu et al., 2006) explain that the United States uses a surveillance system that is based on acute clinical cases only removing a bias towards injection drug users's who are tested regularly and diagnosed through HCV seroconversion.

McMahon et al. (2007) found that a history of injection drug use was consistently the strongest predictor of HCV across studies that they reviewed, as sharing syringes and other drug injection equipment (not merely the needles) is an efficient means of transmission for not only HCV but other bloodborne infections as well (i.e. HIV). The McMahon et al (2007) study used

various techniques to analyze data on risk exposure and HCV screening data from 265 drug using couples in New York City. Despite clustering of HCV among these couples, their results showed no evidence that sexual risk behaviours were associated with HCV infection at a couple's level. They hypothesized that the results were due to individual risk factors shared by both partners (McMahon, et al, 2007). Their study results however must be qualified with the reality that their sample consisted entirely of injection drug users and may not be applicable to the general population (McMahon, et al, 2007).

Terrault (2005) felt that:

> Since sexual transmission cannot be observed directly or experimentally manipulated, establishing sex as the mode of transmission requires the demonstration of new infection in susceptible partner following sexual contact, the confirmation of the same viral strains in the sexual partner and the exclusion of nonsexual modes of HCV acquisition. (p. 825)

Even the title of the earlier mentioned research paper (Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission) by van de Laar et al. (2007) stressed "most likely" meaning that they could not definitively make the determination of the mode of transmission.

D'Oliveira et al. (2005) make an important point about the studies with regards to the determination of sexual transmission of HCV and that these studies are limited by the possibility that some individuals might omit reporting the use of injection drugs and that undisclosed injecting drug use may be contributing factors in some HCV positive individuals.

Kao, Liu, Chen, et al (2000) studied 112 patients with chronic HCV and their anti-HCV seronegative spouses and found a seroconversion in only one spouse, concluding that the risk of interspousal transmission of HCV was 0.23% per year. A study in Thailand found similar results. Boonyard et al., (2003) studied 160 partners of HCV positive individuals and found a

prevalence of 2.5% of infected spouses. Of the 160 spouses, 4 were positive for anti-HCV antibody although only 3 were also HCV-RNA positive and all three of the positive spouses reported being exposed to other potential sources of infection (Boonyard et al., 2003). Kao et al. (2000) made a statement worth mentioning; that early on in a sexual relationship, the number of sexual contacts are generally more frequent and decrease over time, thus the increased rate of HCV infection in couples with longer marriage duration cannot be associated with sexual exposure alone.

Similar results were obtained earlier in a 1993 study (Hallam et al.) of the longstanding partners of 104 HCV positive haemophiliac patients at a haemophiliac centre in Oxford, England. Hallam et al. (2003) found that 2.9% or three of the 104 were HCV-RNA positive and that all of these three had other risk factors present (two had previous blood transfusions and the other was an injection drug user). Interestingly the researchers also commented that not only were the relationships in these couples longstanding but they predated advice on safer sexual practices (i.e. condoms) that was wide spread in the 1980's to avoid infection with HIV (Hallam, et.al. 1993).

Researchers in Italy followed a larger group, looking at 895 monogamous heterosexual partners of which one was anti-HCV antibody and HCV-RNA positive over a 10 year time frame. Partners were informed of possible routes of transmission and were instructed to refrain as much as possible from sharing personal hygiene items such as razors or toothbrushes (Vandelli et al., 2004). Participants were followed at yearly visits and completed questionnaires about their sexual behaviours. Vandelli et al. (2004) found that three of the spouses acquired HCV (or a rate of 0.37) but of those three; in couple one the female had a dental implant three months prior to seroconverting and her HCV genotype did not match the HCV genotype of her

husband; in couple two they did have concordant genotypes but the female was a nurse who had a needle-stick injury at work and became also HIV positive. Given these factors, Vanelli et al. (2004) found that the HCV infection rate of these 895 couples was 0.25 over the 10 years of their study and concluded that no general recommendations for condom use seem to be required for long-term monogamous relationships.

An earlier study in Italy (Guadagnino, 1998), examined 267 family contacts of 113 HCV positive patients over the course of just about two years. They found that 16, or 6% of the contacts were positive for HCV with the spouses having a significantly higher rate of infection than the nonsexual household contacts (Guadagnino, 1998). A unique note about this study is that they did not differentiate between HCV genotypes of the cases as nearly all chronic HCV patients from the studied area have the same genotype and differentiating would not have made any significance in determining if infection was acquired in the household setting or elsewhere.

Tahan et al. (2005) studied the spouses of 600 chronically infected patients in Turkey and found that over the study period of almost three years 12 of 600, or 2% of the spouses became anti-HCV antibody positive. The duration of marriage did not seem to have any relation to being HCV positive. Retrospectively, Tahan et al (2005) found that instead of length of relationship, the number of total sexual intercourse was the important factor in the sexual transmission.

A study from Southern India (Marx et.al., 2003) took a random sample from adults that live in what they termed "slum" communities. Those selected from the households (one adult per household) were sent to "health camps" where they underwent physical exams, laboratory testing and completed questionnaires. The total sample size was 1947 with those with a history of injection drug use being excluded to focus on the sex-related exposures. Results suggest that exposure to previous or current genital ulcer disease and in men, especially herpes simplex virus-

2 and male-male sexual exposure are associated with HCV transmission in this setting yet not associated with having multiple sex partners (Marx, et al, 2003). This result is conflicting with some other major health advisors that suggest that having multiple sexual partners increases the risk of contracting HCV. It did however reinforce the results of other studies that suggest that having a sexually transmitted infection or genital ulcer at time of sexual contact increases the risk of obtaining a HCV infection. Marx et al. (2003), state that blood containing HCV may be able to penetrate the genital epithelium more efficiently in areas where there are microlacerations and that these minute exposures may be sufficient for infection as it can equate to percutaneous exposure.

Researchers in Eygpt (Magder et al., 2005) did a cross sectional serological survey looking at two communities to estimate the risk of transmission between spouses. As mentioned earlier Egypt have the highest rates of HCV in the world reportedly due to a campaign to eradicate disease (schistosomiasis). The participants were interviewed to identify potential exposures, and serum samples were taken to determine if they were HCV positive. They used regression models to analyze the risks from community acquisition and spousal transmission (Magder, et al 2005). Magder at al (2005) determined that 6% of 694 married individuals with anti-HCV acquired HCV infection from their spouses.

A Spanish study found contradictory results from the Egyptian study in that not one of their participants became HCV positive (Marincovich et al., 2003). Marincovich et al's (2003) looked at a cohort of 171 people whose steady heterosexual partner was HIV infected and followed them over a period of time and obtained serum samples as well as obtained very explicit questionnaires about sexual interactions. Although one woman became infected with HIV, no participants became HCV positive during the study time frames (Marincovich et al.,

2003). Interesting about this study is that they closely examined the number of sexual exposures and the type rather than analyzing the number of years the partners were together as they found that the number of exposures can vary greatly between partners.

Conclusion:

Sexual transmission of HCV remains a controversial topic. Given that sexual behaviours are difficult to study and rely greatly on participants' honesty the results of this much needed research may at times not be as accurate as one would hope. Studies on the risk and probability of sexual transmission of HCV were not plentiful and many of the studies elicited from electronic database searches were more than 10 years old.

Of the studies summarized in the pamphlet tool, the percentage of seroconversion ranged from 0% to 6% and of those that converted a number had other risk factors that may have attributed to the results. Some studies show that there are certain conditions that increase the risk of sexual transmission above that of the general population.

This research indicates that, although very low, there is still a risk of sexual transmission of HCV. This information needs to be conveyed to those infected and their partners so that they can make informed decisions about their lives. It is also evident from reviewing this topic that health care providers need to remain updated on the latest research on HCV. It has been just under 20 years since scientists were first able to identify the virus in the laboratory; consequently there is much to be learned about HCV.

Appendix A

Hepatitis C Counseling Recommendations for health care providers

Sexual Transmission of Hepatitis C: Counselling Recommendations for Health care providers

This pamphlet is a compilation of information on the risk of sexual transmission of the hepatitis C virus (HCV) and includes a brief overview and counselling recommendations for health care providers. Sexual transmission of hepatitis C remains a controversial subject with conflicting and often limited research on the topic. This pamphlet will provide information to assist health care providers to counsel their patients about the risks involved.

Globally, the prevalence of HCV infection is estimated by the World Health Organization (2003) to be 3% or approximately 170 million people worldwide and is considered endemic throughout. Hepatitis C has a propensity to be asymptomatic in many infected individuals leading to a large number of undiagnosed cases.

HCV is expected to be a significant burden on health as well as economics in the upcoming 10-20 years as those infected begin to develop chronic symptoms and their disease progresses. HCV is transmitted through contact with blood infected with the virus.

A 2006 modeling study (Remis) in Ontario estimated that 53% of those infected had a history of injection drug use, 13% had infections attributable to blood transfusions, 0.38% were hemophilia patients, and the remaining 34% were attributed to "other modes of transmission". The "other modes of transmission" in this research are important to determine. Accurate information is necessary for counselling those infected with HCV (and those attempting not to become infected) so that educated choices can be made.

Current Recommendations for patient counselling:

Canadian recommendations (Public Health Agency of Canada):

- Sexual activity is generally considered "safe" unless it involves high-risk sexual activity or trauma
    - "High risk" is defined as:
        - Unprotected sex with an HCV+ partner
        - Unprotected sex with multiple partners

- Sexual activity where blood may be present (i.e. menstruation)

- All groups should be provided with information that will reduce their risk of sexual transmission

Center for Disease Control (CDC) recommendations:

- HCV positive people with one long-term steady partner do not need to change their sexual practices

Current Research Findings:

Research is limited on the topic as often the research is based on study participants being truthful about their risk factors. Although a sexual partner may become HCV positive this could be attributed to sharing the same risk factors such as injection drug use. Household transmission is also difficult to distinguish from sexual transmission as a spouse may become infected possibly due to the sharing of a toothbrush with blood on it or sharing a razor.

Researcher	Study title and year	Population studied and sample size	Percentage of seroconversion among sexual partners	Comments
Hallam et al.	Low Risk of Sexual Transmission of hepatitis C virus, 1993	104 HCV positive haemophiliac patients at a haemophiliac clinic	2.9% or three of the 104 were HCV-RNA positive	All 3 seroconverters also had other risk factors (2 had blood transfusions and one was an injection drug user)
Orlando & Lirussi	HCV infection: Sexual	Case report of one	After 24 years of a	Coincidently the wife

	or Non-sexual transmission between spouses? A case report and review of the literature (2007).	middle-aged couple of which the husband had chronic hepatitis C	monogamous relationship the wife presented with an acute HCV infection	also gave birth to three children during this relationship and all three are HCV negative.
Kao et al.	Low incidence of hepatitis C virus transmission between spouses: A prospective study (2000).	112 patients and their seronegative partners in Taiwan	Seroconversion occurred in one spouse making the annual risk of interspousal transmission in this case 0.23% per year.	The mean follow-up period was 45.9 months.
Alary et al.	Lack of evidence of sexual transmission of hepatitis C virus in a prospective cohort study of men who have sex with men (2005).	1085 MSM's* in Montreal between 1996-2001	Of the 1054 men who were negative at baseline, one seroconverted for an incidence rate of 0.38.	This one seroconverter reported needle sharing during the six months preceding the visit.
Marx et al.	Association of hepatitis C virus infection with sexual exposure in Southern India (2003).	1947 participants from 30 "slum" communities in India	A rate of seroconversion was not given. Study more analyzed whether other sexual risk factors increased risk of HCV and results showed that women with genital ulcers were 4 times more likely to	

			have HCV and men were three times more likely	
Vandelli et al.	Lack of Evidence of Sexual Transmission of Hepatitis C among Monogamous couples: results of a 10-year prospective follow-up study (2004).	895 heterosexual partners of HCV infected individuals followed over 10 years	3 spouses acquired HCV during the follow-up period for an incidence rate of 0.37.	One spouse reported having a dental implant 3 months prior to conversion and one other was a nurse who became HCV and HIV positive after a needle-stick injury (although HCV genotype concordant with her husband). The rate of infection adjusting for these factors is 0.25.
Tahan, et al	Sexual Transmission of HCV between spouses (2005).	600 spouses of chronically infected HCV patients during approximately 3 years	12 out of 600 became HCV positive or 2%	Claims to be the first study that emphasizes the significance of the total number of sexual intercourse activities
Magder et al.	Estimation of the risk of transmission of HCV between	1241 couples in two communities in Egypt; cross	6% of 694 married individuals acquired HCV infection from their	Used various regression models to

	spouses in Egypt based on seroprevalence data (2005).	sectional serological survey	spouses	obtain their results.
Myers et al.	The prevalence and correlates of hepatitis C virus (HCV) infection and HCV—HIV co-infection in a community sample of gay and bisexual men (2009).	5080 bisexual or gay men	Found a prevalence rate of 1.9% in this particular group with sexual transmission accounting for only "a small portion, if any"	This study found that those infected with HIV in this particular group were 5.5 times more likely to be infected with HCV
Marincovich et al.	Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples (2003).	171 heterosexual couples whose steady sexual partner is also HIV positive	No participants in the study became HCV positive during the study	One woman had HIV seroconversion following unprotected vaginal intercourse but did not become HCV positive
Guadagnino, et al	Hepatitis C virus infection in family setting (1998).	267 family contacts of 113 HCV positive patients during approximately 2 years	16, or 6% of the contacts were positive for HCV with the spouses having a significantly higher rate than the nonsexual household contacts	Study looked at household contacts; not only sexual contacts.

*MSM: men who have sex with men

This summary of relevant studies provides a starting point of which to base recommendations to your clients/patients. Of the studies summarized in the pamphlet tool the percentage of seroconversion as a result of sexual contact ranged from 0% to 6% and of those that converted a number of them had other risk factors that may have attributed to their results. Studies did show that there are certain conditions that increase the risk of sexual transmission above that of the general population.

The summarized studies above indicate that there is for the most part a risk of sexual transmission (although very low). Due to this lower risk; one could counsel clients that special precautions are not necessary unless engaging in high risk sexual behaviour.

Health care providers have an obligation to remain current on any latest research that will assist with counselling their patients.

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