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REVIEW ARTICLE

Transmission of hepatitis C virus by saliva?

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Saliva can contain a range of infectious agents and, despite several antimicrobial mechanisms, transmission of these can occur. Hepatitis C virus (HCV) is of increasing importance, and HCV is transmitted by unknown routes as well as by the percutaneous route and sexual contact. Contact with blood or other body fluids may be responsible, as may be receipt of unscreened blood or blood product transfusions. HCV-RNA can be detected by the polymerase chain reaction which also shows that HCV may be present in the saliva of HCV-infected patients. This might provide an argument for the possible transmission of HCV via contaminated saliva. Epidemiological studies however, suggest that the infective capacity of HCV viral particles in saliva is low, but it has not been possible to determine their infective potential. Moreover, HCV-specific receptors have not been defined on oral epithelial cells, nor has the role of host defence mechanisms been determined. New experimental animal models and the recently described infectious HCV pseudoparticles, capable of simulating HCV replication *in vitro*, could be useful in establishing any role of saliva in the transmission of HCV infection.
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Introduction

Hepatitis C virus (HCV) is spread mainly through sharing needles or 'works' when 'shooting' drugs, through needlesticks or sharps exposures, or from an infected mother to her baby during birth. Infected blood transfusions prior to the introduction of HCV screening and sexual intercourse are other known routes.

In the most rigorous epidemiological studies on HCV, the prevalence of patients in whom it is not possible to identify any risk factor for acquiring the infection ranges from 10% (Murphy *et al*, 2000) to 14% (Raguin *et al*, 1998). In these patients, the efficacy of the directed history is limited as it has been demonstrated that there is little benefit in routinely interviewing those HCV-infected people who have no history of injecting drugs or of having received a contaminated blood product transfusion (Roy *et al*, 2003). However, this situation suggests that unknown routes of transmission, different from the percutaneous route and from at-risk sexual contact, exist.

Some authors have suggested that living with HCV-infected patients could constitute a risk factor for acquiring the disease (Saltoglu *et al*, 1998; Alvarez-Muñoz *et al*, 2001). Indeed, in a systematic search of the MEDLINE database for all relevant articles published up to June 1997, on the subject of hepatitis C and household, intrafamiliar, sexual and intraspousal transmission of HCV, Ackerman *et al* (2000) found evidence that both sexual and non-sexual intrafamiliar transmission of HCV does occur; this, from an epidemiological point of view, suggests the possibility of infection by contact with body fluids other than blood. Investigation of body fluids by the polymerase chain reaction (PCR) demonstrates HCV-RNA in semen (Leruez-Ville *et al*, 2000; Pekler *et al*, 2003), urine (Liou *et al*, 1992; Numata *et al*, 1993) and sweat (Ortiz-Movilla *et al*, 2002) and saliva (Takamatsu *et al*, 1990).

The present study focused on describing the current evidence on the prevalence, origin and infectivity of HCV-RNA in saliva. Search strategy was developed on MEDLINE (to December 2003), as well as the following databases from 1990: OLDMEDLINE, EMBASE and Current Contents.

Prevalence and origin of HCV in saliva

There are numerous studies on the presence of HCV-RNA in saliva, but their results vary, reflecting the heterogeneity of the study populations and the diversity of detection techniques employed (Table 1). The collection and storage of saliva specimens for HCV detection can also affect the assay (Roy *et al*, 1999). Recently,

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Table 1 Studies on the presence of HCV-RNA in saliva

Author (year)	*HCV detection by*	*Number of patients tested*	*Type of patients tested*	*Number (percentage) with HCV in saliva*
Takamatsu *et al* (1990)	Nested PCR	5	Anti HCV+	5 (100)
Fried *et al* (1992)	Nested PCR	14	Anti HCV CLD	0 (0)
Wang *et al* (1992)	Nested PCR	14	Anti-HCV Post-transfusion hepatitis	7 (50)
Liou *et al* (1992)	Nested PCR	37	Anti HCV and serum HCV-RNA CLD	15 (48)
Numata *et al* (1993)	Single round Nested PCR	23	Anti-HCV	8 (34)
Couzigou *et al* (1993)	Nested PCR	37	Anti-HCV CLD	23 (62)
Mariette *et al* (1995)	Amplicor HCV	28	Serum HCV+ (13 HIV+)	17 (61)
Chen *et al* (1995)	Nested PCR	23	Serum HCV+ (11 HIV+)	4 (17)
Sugimura *et al* (1995)	Nested PCR	76	Anti-HCV+	27 (36)
Roy *et al* (1995)	Nested PCR	14	Serum HCV+ Blood donors	9 (64)
Tang *et al* (1996)	Single round PCR	16	Serum HCV+	5 (31)
Jorgensen *et al* (1996)	Single round PCR	16	Serum HCV+ Sicca syndrome	13 (83)
Caldwell *et al* (1996)	Single round PCR	33	Serum HCV+ (21 liver transplanted)	5 (15)
Roy *et al* (1996)	Nested PCR	21	Serum HCV+ Haemophiliacs (6 HIV+)	10 (48)
Kage *et al* (1997)	Nested PCR	11	Serum HCV+ Women postpartum	4 (36)
Ustundag *et al* (1997)	Nested PCR	10	Serum HCV+ Haemodialysed	3 (30)
Taliani *et al* (1997)	Nested PCR	20	Serum HCV + CAH or Cirrhosis	3 (15)
Roy *et al* (1998)	Nested PCR	33	Serum HCV+ IVDUs (19 HIV+)	19 (58)
Fabris *et al* (1999)	Nested PCR	39	Serum HCV+	22 (56)
Maticic *et al* (2001)	Cobas Amplicor2.0	48	Serum HCV+	17 (35)
Rey *et al* (2001)	Nested PCR	59	Anti-HCV/HIV+	22 (37)
Hermida *et al* (2002)	Nested PCR	61	Serum HCV-RNA	32 (52)

CLD, chronic liver disease; HCV, hepatitis C virus.

however, using a highly sensitive PCR method, it has been demonstrated that over 50% of HCV-infected patients have HCV-RNA detectable in their saliva (Hermida *et al*, 2002).

There is a direct relationship between the presence of the virus in the saliva and the viral load in blood (Wang *et al*, 1992; Mariette *et al*, 1995; Fabris *et al*, 1999; Hermida *et al*, 2002; Belec *et al*, 2003). This could suggest a transfer of viral particles from the circulation to the saliva via a concentration gradient, although some authors point out that viral RNA detection is not dependent upon the presence of occult blood in the samples and therefore is not necessarily a consequence or, at least, the sole consequence, of blood contamination secondary to mucosal lesions or periodontal disease (Liou *et al*, 1992; Fabris *et al*, 1999; Hermida *et al*, 2002). HCV could also enter the saliva via the gingival sulcus (Maticic *et al*, 2001), but this is clearly not the sole route since HCV-RNA has been found in saliva samples from edentate patients (Roy *et al*, 1998).

Centrifugation of saliva samples enables a fractionated analysis to be performed, and in some series, virus particles were only detected in the cellular fraction (Chen *et al*, 1995; Fabris *et al*, 1999; Belec *et al*, 2003). It is considered that HCV replication takes place mainly in the cytoplasm. There, the presence of negative-sense viral RNA and replicative double-stranded forms represent an evidence of virus multiplication (Negro *et al*, 1999). Some authors (Belec *et al*, 2003) found that viral shedding of HCV-RNA in saliva is restricted to the cell-associated, non-replicating (positive) strand. However, Carrozzo *et al* (2002) detected HCV-RNA negative strand in oral epithelial cells of 23% of anti-HCV-positive patients. Moreover, other authors have isolated HCV-RNA from the pellet, from the supernatant, or from both (Roy *et al*, 1996; Hermida *et al*, 2002), suggesting that HCV-RNA is not derived exclusively from the cellular component. The controversy generated by these discordant results is probably due to methodological differences, including specimen handling and storage, the presence of PCR inhibitors, correct design of primers, variability of biochemical reactions, contamination, and efficiency of postamplification systems (Pawlotsky, 1999).

Hepatitis C virus particles are also present in epithelial cells (Arrieta *et al*, 2000; Carrozzo *et al*, 2002), which partially explains their presence in the salivary cellular fraction. Peripheral blood mononuclear cells (PBMCs) are another vehicle for carrying HCV to saliva (Maticic *et al*, 2001). Poor oral hygiene, with gingivitis and oral mucosal lesions can cause the exudation of serum into the saliva and increase the shedding of potentially infected mononuclear cells into the salivary pool, but interestingly neither factor correlated with the presence of HCV-RNA in saliva (Roy *et al*, 1998). The presence of HCV-RNA in PBMCs and in saliva is not closely correlated, so it is unlikely that PBMCs represent a major vehicle for viral transfer to the saliva (Young *et al*, 1993).

An uneven distribution of quasi-species in blood and other tissues has been demonstrated in patients with chronic HCV infection, providing evidence for the presence of independent, compartmentalized extrahepatic replication (Laskus *et al*, 2000). Some HCV-RNA particles could appear in the saliva as a result of active HCV replication in the salivary glands (Arrieta *et al*, 2001). This could explain the HCV-RNA sequences

found in serum and oral tissues in some patients (Nagao *et al*, 2000a), the detection of different genotypes in serum and in saliva of a single patient (Roy *et al*, 1998), and the existence of patients who are serum-negative but saliva-positive for HCV (Harle *et al*, 1993; Mastromatteo *et al*, 2001).

The levels of HCV-RNA in the saliva are low in comparison with those found in the serum (Wang *et al*, 1992; Numata *et al*, 1993; Taliani *et al*, 1997). However, the results of even the most recent studies require careful interpretation as they have not employed quantification techniques specific for the saliva substrate (Rey *et al*, 2001).

HCV enters oral epithelial cells

The detection of HCV-RNA negative strands in samples of oral mucosa from patients with chronic hepatitis C indicates that this may be a point of entry for infection by HCV, which infects the epithelial cells and replicates within them (Arrieta *et al*, 2000; Nagao *et al*, 2000a; Carrozzo *et al*, 2002). The percentage of epithelial cells positive for HCV-RNA is lower than that reported in the liver (Arrieta *et al*, 2000; Carrozzo *et al*, 2002). Viral replication in the oral mucosa is probably a factor in the aetiopathogenesis of some intraoral extrahepatic manifestations associated with chronic hepatitis C such as lichen planus (Arrieta *et al*, 2000; Nagao *et al*, 2000a; Carrozzo *et al*, 2002; Pilli *et al*, 2002; Carrozzo and Gandolfo, 2003).

The mechanism by which the virus reaches the interior of the host cell is still not fully understood, although it has been suggested that infectivity depends on the co-expression of both E1 and E2 glycoproteins on the viral surface and is pH-dependent (Hsu *et al*, 2003). The presence of the CD81 tetraspanin receptor (Pileri *et al*, 1998) on the surface of the host cell is not sufficient alone to permit the entry of HCV – other receptors must also be expressed (Agnello *et al*, 1999; Scarselli *et al*, 2002; Bartosch *et al*, 2003a,b; Hsu *et al*, 2003). *In vitro* models of infection using infectious HCV pseudoparticles bearing unmodified HCV glycoproteins, show the principal targets of infection to include primary hepatocytes as well as hepatocarcinoma cells (Bartosch *et al*, 2003a,b; Hsu *et al*, 2003). However, several cell lines of non-hepatic origin which express all the cell entry surface molecules are not, or are poorly, permissive to HCV pseudoparticle infection, implying that additional liver-specific co-factor(s) are needed for HCV entry (Bartosch *et al*, 2003b).

To date, it has not been possible to demonstrate whether these receptors and co-factors are also present in oral epithelial cells.

Infectivity of HCV-RNA in saliva

Although there are authors who suggest the importance of HCV particles in human saliva in the intrafamilial propagation of the infection (Mastromatteo *et al*, 2001) it has not been possible to determine their infective potential. It may be that the specific and non-specific defence mechanisms present in saliva could attenuate or abolish the infective capacity of viral particles as is the case with HIV. Saliva of patients with chronic hepatitis C contains specific IgG and IgA neutralizing antibodies directed against the E1 and E2 surface glycoproteins which could block viral adhesion to the host cell (Belec *et al*, 2003).

Epidemiological studies suggest that the infective capacity of HCV viral particles in saliva is low (Wang *et al*, 1992; Fabris *et al*, 1999). There is no evidence that HCV is spread readily by kissing, sneezing, coughing, food, water or sharing eating or drinking utensils (Centers for Disease Control and Prevention, 1998). The prevalence of HCV infection among dental health care workers exposed to saliva is similar to that for the general population (Kuo *et al*, 1993; Thomas *et al*, 1996; Lodi *et al*, 1998; Cleveland *et al*, 1999; Ammon *et al*, 2000) but most of these studies have been conducted either at a time when the population prevalence of HCV infection was low, or on health care workers using universal precautions against infection. Nevertheless, in a recent follow-up study on over 25 000 unprotected orogenital contacts in a cohort of heterosexual couples there was not a single seroconversion to HCV (Marincovich *et al*, 2003) suggesting that orogenital transmission must be uncommon.

In the only reported study of this type, Abe and Inchauspe (1991) detected HCV-RNA in the serum from a chimpanzee recipient inoculated with HCV-infected saliva. The chimpanzee (*Pan troglodytes*) however, is the only animal apart from man with known susceptibility to HCV infection and, at the present time, is considered to be a species in danger of extinction, making it necessary to find other model systems for HCV research (Lanford and Bigger, 2002). In consequence, although some authors have made statements suggesting that, based on animal models, the non-percutaneous transmission of HCV is not an important mode of transmission (Suzuki *et al*, 1993), experiments performed on animals and published in the literature are, for ethical and economic reasons, actually rather scarce. Studies may now be forthcoming, since transgenic mice have been used to introduce xenotransplants of hepatocytes susceptible to hepatitis virus infection and others capable of expressing certain viral proteins are being developed (Lanford and Bigger, 2002).

The HCV infection can occasionally be transmitted by a human bite, because of the presence of infected blood or saliva in the mouth of the aggressor. In 1990, Dusheiko *et al* (1990) reported a case of chronic hepatitis in a 35-year-old male patient with a positive test to HCV antibody confirmed by anti-HCV ELISA assay. His clinical history included a recent episode of jaundice, nausea and pain in the right hypochondrium 1 month after having been bitten by a man in a bar-room fight, and this was therefore considered to be a case of HCV transmission by a human bite. The carrier status of the aggressor was not specified, nor were studies of genomic concordance available to confirm the origin of the infection. An important point therefore is

that there are no reports proving the direct transmission of HCV by saliva: the possibility of transmission of HCV by a human bite has not been confirmed by molecular studies (e.g. sequence analysis). However, this has been confirmed for other modalities as colonscopy (Bronowicki *et al*, 1997).

The observations of HCV infection in long-term hospitalized patients (Januszkiewicz-Lewandowska *et al*, 2003) and a reported case following the occupational exposure of a health care worker with unprotected chapped and abraded hands to a patient's vomit, faeces and urine (Beltrami *et al*, 2003), suggest that breaches of the skin or mucosae which permit direct contact of the virus with sub-epithelial cells may result in infection by HCV.

Conclusions

The fact that HCV-RNA can be present in the saliva of patients with chronic hepatitis C provides a biologic basis for the potential transmission of HCV via contaminated saliva. However, epidemiological studies show that infection by contact with contaminated saliva is rare. To date, it has not been possible to demonstrate any infective capacity of HCV particles detected in saliva. Moreover, it has not been confirmed whether these are complete virions or virus fragments or whether there is sufficient structural integrity to initiate the HCV life cycle. Furthermore, HCV-specific receptors have not been defined on oral epithelial cells, nor has the role of host defence mechanisms been determined.

The use of new experimental animal models and the recently described infectious HCV pseudoparticles, capable of simulating HCV replication *in vitro*, could be of great utility in establishing definitively the significance of HCV-RNA particles detected in the saliva in any transmission of HCV infection.

References

Abe K, Inchauspe G (1991). Transmission of hepatitis C by saliva (Letter). *Lancet* **337:** 248.

Ackerman Z, Ackerman E, Paltiel O (2000). Intrafamiliar transmission of hepatitis C virus: a systematic review. *J Viral Hepat* **7:** 93–103.

Agnello V, Abel G, Elfahal M *et al* (1999). Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. *Proc Natl Acad Sci USA* **96:** 12766–12771.

Alvarez-Muñoz MT, Vences-Aviles MA, Damacio L *et al* (2001). Hepatitis C virus RNA (HCV-RNA) in blood donors and family members seropositive for anti-HCV antibodies. *Arch Med Res* **32:** 442–445.

Ammon A, Reichart P, Pauli G *et al* (2000). Hepatitis B and C among Berlin dental personnel: incidence, risk factors, and effectiveness of barrier prevention measures. *Epidemiol Infect* **125:** 407–413.

Arrieta JJ, Rodriguez-Iñigo E, Casqueiro M *et al* (2000). Detection of hepatitis C virus replication by in situ hibridization in epithelial cells of anti-hepatitis C virus-positive patients with and without oral lichen planus. *Hepatology* **32:** 97–103.

Arrieta JJ, Rodríguez-Iñigo E, Ortiz-Movilla N *et al* (2001). In situ detection of hepatitis C virus RNA in salivary glands. *Am J Pathol* **158:** 259–264.

Bartosch B, Dubuisson J, Cosset FL (2003a). Infectious hepatitis C virus pseudo-particles containing functional E1-E2 envelope protein complexes. *J Exp Med* **197:** 633–642.

Bartosch B, Vitelli A, Granier C, Goujon C *et al* (2003b). Cell entry of hepatitis C virus requires a set of co-receptors that include the CD81 tetraspanin and the SR-B1 scavenger receptor. *J Biol Chem* **278:** 41624–41630.

Belec L, Legoff J, Si-Mohamed A *et al* (2003). Mucosal humoral immune response to hepatitis C virus E1/E2 surface glycoproteins and HCV shedding in saliva and cervicovaginal fluids from chronically-infected patients. *J Hepatol* **38:** 833–842.

Beltrami EM, Kozak A, Williams IT *et al* (2003). Transmission of HIV and hepatitis C virus from a nursing home patient to a health care worker. *Am J Infect Control* **31:** 168–175.

Bronowicki JP, Venard V, Botte C *et al* (1997). Patient-to-patient transmission of hepatitis C virus during colonoscopy. *N Engl J Med* **337:** 237–240.

Caldwell SH, Sue M, Bowden JH *et al* (1996). Hepatitis C virus in body fluids after liver transplantation. *Liver Transpl Surg* **2:** 124–129.

Carrozzo M, Gandolfo S (2003). Oral diseases possibly associated with hepatitis C virus. *Crit Rev Oral Biol Med* **14:** 115–127.

Carrozzo M, Quadri R, Latorre P *et al* (2002). Molecular evidence that the hepatitis C virus replicates in the oral mucosa. *J Hepatol* **37:** 364–369.

Centers for Disease Control and Prevention (1998). Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Morbid Mortal Wkly Rep* **47:** 1–33.

Chen M, Yun ZB, Salberg M *et al* (1995). Detection of hepatitis C virus RNA in the cell fraction of saliva before and after oral surgery. *J Med Virol* **45:** 223–226.

Cleveland JL, Gooch B, Shearer BG *et al* (1999). Risk and prevention of hepatitis C virus infection. Implications for dentistry. *JADA* **130:** 641–647.

Couzigou P, Richard L, Dumas F *et al* (1993). Detection of HCV-RNA in saliva of patients with chronic hepatitis C. *Gut* **34**(2 Suppl)**:** S59–S60.

Dusheiko GM, Smith M, Scheuer PJ (1990). Hepatitis C virus transmitted by human bite (Letter). *Lancet* **336:** 503–504.

Fabris P, Infantolino D, Biasin MR *et al* (1999). High prevalence of HCV-RNA in the saliva fraction of patients with chronic hepatitis C but no evidence of HCV transmission among sexual partners. *Infection* **27:** 86–91.

Fried WW, Shindo M, Fong Tl *et al* (1992). Absence of hepatitis C viral RNA from saliva and semen of patients with chronic hepatitis C. *Gastroenterology* **102:** 1306–1308.

Harle JR, Swiader L, Disdier P *et al* (1993). Identifying hepatitis C virus by the gene amplification technique in the saliva of patients for whom the search is simultaneously negative in their serum: 9 cases. *Rev Med Interne* **14:** 1005.

Hermida M, Ferreiro MC, Barral S *et al* (2002). Detection of HCV RNA in saliva of patients with hepatitis C virus infection by using a highly sensitive test. *J Virol Methods* **101:** 29–35.

Hsu M, Zhang J, Flint M *et al* (2003). Hepatitis C virus glycoproteins mediate pH-dependent cell entry psudotyped retroviral particles. *Proc Natl Acad Sci USA* **100:** 7271–7276.

Januszkiewicz-Lewandowska D, Wysoki J, Rembowska J *et al* (2003). Transmission of HCV infection among long-term hospitalized onco-haematological patients. *J Hosp Infect* **53:** 120–123.

Jorgensen C, Legouffe MC, Perney P *et al* (1996). Sicca syndrome associated with HCV virus infection. *Arthritis Rheum* **39:** 1166–1171.

Kage M, Ogasawara S, Kosai K *et al* (1997). Hepatitis C virus RNA present in saliva but absent in breast-milk of the hepatitis C carrier mother. *J Gastroenterol Hepatol* **12:** 518–521.

Kuo MY, Hahn LJ, Hong CY *et al* (1993). Low prevalence of hepatitis C virus infection among dentists in Taiwan. *J Med Virol* **40:** 10–13.

Lanford RE, Bigger C (2002). Advances in model systems for hepatitis C virus research. *Virology* **293**, 1–9.

Laskus T, Radkowski M, Wang LF *et al* (2000). Uneven distribution of hepatitis C virus quasispecies in tissues from subjects with end-stage liver disease: confounding effect of viral adsorption and mounting evidence for the presence of low-level extrahepatic replication. *J Virol* **74:** 1014–1017.

Leruez-Ville M, Kuntsmann JM, De Almeida M *et al* (2000). Detection of hepatitis C virus in the semen of infected men (Letter). *Lancet* **356:** 42–43.

Liou TC, Chanf TT, Young KC *et al* (1992). Detection of HCV RNA in saliva, urine, seminal fluid and ascites. *J Med Virol* **37:** 197–202.

Lodi G, Porter SR, Scully C (1998). Hepatitis C virus infection. Review and implications for the dentistry. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **86:** 8–22.

Mariette X, Loiseau P, Morinet F (1995). Hepatitis C virus in saliva (Letter). *Ann Intern Med* **122:** 556.

Marincovich B, Castilla J, del Romero J *et al* (2003). Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. *Sex Transm Infect* **79:** 160–162.

Mastromatteo AM, Rapaccini GL, Pompili M *et al* (2001). Hepatitis C virus infection: other biological fluids than blood may be responsible for intrafamiliar spread. *Hepatogastroenterology* **48:** 193–196.

Maticic M, Poljak M, Kramar B *et al* (2001). Detection of hepatitis C virus RNA from gingival crevicular fluid and its relation with virus presence in saliva. *J Peridontol* **72:** 11–16.

Murphy EL, Bryzman SM, Glynn SA *et al* (2000). Risk factors for hepatitis C virus infection in United States Blood donors. *Hepatology* **31:** 736–762.

Nagao Y, Sata M, Noguchi S *et al* (2000a). Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. *J Oral Pathol Med* **29:** 259–266.

Negro F, Krawczynski K, Quadri R *et al* (1999). Detection of genomic- and minus-strand of hepatitis C virus RNA in the liver of chronic hepatitis C patients by strand-specific semiquantitative reverse-transcriptase polymerase chain reaction. *Hepatology* **29:** 536–542.

Numata N, Ohori H, Hayakawa Y *et al* (1993). Demonstration of hepatitis C virus genome in saliva and urine of patients with type C hepatitis: usefulness of the single polymerase chain reaction method for detection of the HCV genome. *J Med Virol* **41:** 120–128.

Ortiz-Movilla N, Lazaro P, Rodriguez-Inigo E *et al* (2002). Hepatitis C virus replicates in sweat glands and is released into sweat in patients with chronic hepatitis C. *J Med Virol* **68:** 529–536.

Pawlotsky JM (1999). Diagnostic tests for hepatitis C. *J Hepatol* **31:** 71–79.

Pekler VA, Robbins WA, Nymathi A *et al* (2003). Use of Versant TMA and bDNA 3.0 assays to detect and quantify hepatitis C virus in semen. *J Clin Lab Anal* **17:** 260–270.

Pileri P, Uematsu Y, Campagnoli S *et al* (1998). Binding of hepatitis C virus to CD81. *Science* **282:** 938–941.

Pilli M, Penna A, Zerbini A *et al* (2002). Oral lichen planus pathogenesis: a role for the HCV-specific cellular immune response. *Hepatology* **36:** 1446–1452.

Raguin G, Rosenthal E, Cacoub P *et al* (1998). Hepatitis C in France: a national survey in the departments of internal medicine and infectious diseases. *Eur J Epidemiol* **14:** 545–548.

Rey D, Fritsch S, Schmitt C *et al* (2001). Quantitation of hepatitis C virus RNA in saliva and serum patients coinfected with HCV and human immunodeficiency virus. *J Med Virol* **63:** 117–119.

Roy KM., Bagg J, Bird GL *et al* (1995). Serological and salivary markers compared with biochemical markers for monitoring interferon treatment for hepatitis C virus infection. *J Med Virol* **47:** 429–434.

Roy KM, Bagg J, Follet EA *et al* (1996). Hepatitis C virus in saliva of haemophiliacs patients attending an oral surgery unit. *Br J Oral Maxillofac Surg* **34:** 162–165.

Roy KM, Bagg J, McCarron B *et al* (1998). Predominance of HCV type 2a in saliva from intravenous drug users. *J Med Virol* **54:** 271–275.

Roy KM, Bagg J, McCarron B (1999). The effect of saliva specimen collection, handling and storage protocols on hepatitis C virus (HCV) RNA detection by PCR. *Oral Dis* **5:** 123–127.

Roy KM, Goldberg D, Taylor A *et al* (2003). Investigating the source of hepatitis C virus infection among individuals whose route of infection is undefined: a study of ten cases. *Scand J Infect Dis* **35:** 326–328.

Saltoglu N, Tasova Y, Burgut R *et al* (1998). Sexual and non-sexual intrafamiliar spread of hepatitis C virus: intrafamiliar transmission of HCV. *Eur J Epidemiol* **14:** 225–228.

Scarselli E, Ansuini H, Cerino R *et al* (2002). The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. *EMBO J* **21:** 5017–5025.

Sugimura H, Yamamoto H, Watabiki H *et al* (1995). Correlation of detectability of hepatitis C virus genome in saliva of elderly Japanese symptomatic HCV carriers with their hepatic function. *Infection* **23:** 258–262.

Suzuki E, Kaneko S, Udono T *et al* (1993). Absence of nonpercutaneous transmission of hepatitis C virus in a colony of chimpanzees. *J Med Virol* **39:** 286–291.

Takamatsu K, Koyanagi Y, Okita K *et al* (1990). Hepatitis C virus in saliva (Letter). *Lancet* **336:** 1515.

Taliani G, Celestino D, Badolato MC *et al* (1997). Hepatitis C virus infection of salivary gland epithelial cells. *J Hepatol* **26:** 1200–1206.

Tang Z, Yang D, Hao L *et al* (1996). Detection and significance of HCV RNA in saliva, seminal fluid and vaginal discharge in patients with hepatitis C. *J Tongji Med Univ* **16:** 11–13.

Thomas DL, Gruninger SE, Siew C *et al* (1996). Occupational risk of hepatitis C infections among general dentists and oral surgeons in North America. *Am J Med* **100:** 41–45.

Ustundag Y, Hizel N, Boyacioglu S *et al* (1997). Detection of hepatitis GB virus-C and HCV genomes in the saliva of patients undergoing maintenance haemodialysis. *Nephrol Dial Transplant* **12:** 2087.

Wang JY, Wang TH, Sheu JC *et al* (1992). Hepatitis C virus RNA in saliva of patients with posttransfusion hepatitis and low efficiency of transmission among spouses. *J Med Virol* **36:** 28–31.

Young KC, Chang TT, Liou TC *et al* (1993). Detection of hepatitis C virus RNA in peripheral blood mononuclear cells and in saliva. *J Med Virol* **41:** 55–60.

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