Diploma Thesis

Prevention strategies of occupational hepatitis C transmission in the health care setting

submitted by

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Affidavit

Herewith I, Angelika M. Rossmann, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties.
Furthermore, I confirm that no sources have been used in the preparation of the thesis other than those indicated in the thesis itself.

Graz, May 2009

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1 ABSTRACT

1.1 German

Das Hepatitis C Virus (HCV) repräsentiert eine beträchtliche Gefahr sowohl für Beschäftigte in Gesundheitsberufen als auch für PatientInnen. Bisher wurde von mehr als 200 Übertragungen von Beschäftigten in Gesundheitsberufen auf PatientInnen in wissenschaftlichen Publikationen berichtet. Daher erscheint es von großer Bedeutung, Personen mit einer HCV-Infektion, welche in Gesundheitsberufen arbeiten, zu identifizieren und Regulationen, wie mit ihnen umzugehen ist, einzuführen.

Derzeit gibt es keine übereinstimmenden Empfehlungen, Regulationen oder Richtlinien, betreffend der Verhinderung von Übertragung einer HCV-Infektion von Beschäftigten im Gesundheitswesen auf PatientInnen. In dieser Diplomarbeit wird versucht, Fragen, die in diesem Zusammenhang auftreten, zu beantworten: Sollten Beschäftigte im Gesundheitswesen auf HCV „gescreent“ oder individuell getestet werden und welche „Assay(s)“ sollen dazu verwendet werden? Wann und wie oft sollten Beschäftige in Gesundheitsberufen getestet werden? Was sollte mit Personen, welche im Gesundheitswesen arbeiten und mit HCV infiziert sind, geschehen?

Basierend auf einem Vergleich bestehender Empfehlungen, Regulationen und Richtlinien zu diesem Thema werden in dieser Diplomarbeit Empfehlungen entwickelt und nützliche Vorschläge gemacht. Diese Diplomarbeit, welche zum Forschungsfeld „Sustainable Health Research“ der Medizinischen Universität Graz gehört, ist in modifizierter Form im „Journal of Clinical Virology“ unter dem Titel „Health care worker-to-patient transmission of hepatitis C virus in the health care setting: many questions and few answers” im Druck.

1.2 English

Hepatitis C virus (HCV) infection represents a substantial risk to both, health care workers and patients. More than 200 cases of health care worker-to-patient transmission of HCV have been reported in scientific publications; it is thus of major importance to detect health care workers with HCV infection and to establish regulations how to deal with infected individuals working in specific health care settings. Currently, there are no consistent recommendations, regulations or guidelines concerning detection of HCV infected health care workers and efficient prevention of health care worker-to-patient transmission of HCV.

Questions arising include: Should health care workers be screened or tested individually on HCV infection and what kind of assay(s) should be used? When and how often should health care workers be tested? How should the health care worker with HCV infection be managed? Based on these questions, this diploma thesis reviews existing recommendations, regulations, and guidelines concerning this matter. Furthermore, recommendations how to better handle with this problem are developed and suggestions useful for establishing a future common regulatory framework are provided.

This work which is part of the research area "Sustainable Health Research" of the Medical University of Graz will be published in a modified version in the Journal of Clinical Virology (“Health care worker-to-patient transmission of hepatitis C virus in the health care setting: many questions and few answers”, 2009, in press).

2 THE HEPATITIS C VIRUS

2.1 Morphology

The hepatitis C Virus (HCV) was first identified in the USA in 1989. Infectious hepatic disease had been defined as “non A, non B hepatitis” prior to the identification of the causative agent. The characterization of the HCV led to the understanding of its primary role as post-transfusion hepatitis and its pathogenic tendency to induce persistent chronic liver infection leading to cirrhosis and liver cancer.

The HCV is a small, single-stranded, enveloped 9600-nucleotide RNA molecule of positive-polarity classified as a unique genus, designated Hepacivirus in the *Flaviviridae* family (Fig. 1, 2).

Fig. 1: Schematic design of HCV

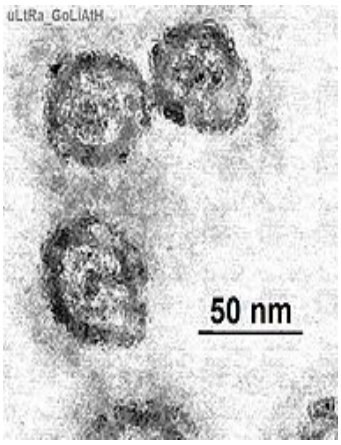


Fig. 2: Electron microscopy of hepatitis C virus

2.2 Genome, proteins and replication

The HCV genome consists of a single large open reading frame that encodes for a virus polyprotein of approximately 3000 amino acids. Towards the 5' end of the genome, the E2 and E1 region encoding two highly variable envelope antigens, the C region encoding the nucleocapsid protein, and the 5' noncoding (untranslated) region have been described (Fauci et al., 2008). Towards the 3' end of the genome, the NS2, NS3, NS4a, NS4b, NS5A, NS5B regions encoding the genes for 6 non-structural proteins and the 3' noncoding (untranslated) region have been described (Fauci et al., 2008). The non-structural regions encode replication proteins such as the helicase, the serin protease, and the RNA-dependent RNA polymerase (Fig. 3).

Fig. 3: Genome of HCV

There exist six viral genotypes which differ one from another in sequence homology by more than 30% and more than 50 subtypes. However, even HCV isolates show strong genetic divergence with a huge number of HCVs showing small genetic variation referred to as quasispecies in each infected patient. The diversity of HCV genomes results from mutations due to high error rates in RNA replication and interferes with effective humoral immunity. Neutralizing antibodies to HCV have been described but they do not play an efficient role in immunity against HCV infection. Furthermore, neither heterologous nor homologous immunity was reported after acute HCV infection (Fauci et al., 2008). The distribution of HCV genotypes/subtypes varies in different parts of the world. Several subtypes such as 1a, 1b, 2a, and 2b are ubiquitous, while others are confined to specific geographic areas. Worldwide, HCV genotype 1 is the most common. In a recent Austrian study, HCV genotype 1 was found to be responsible for HCV infection in up to 65% of patients investigated (Ferenci et al., 2008).

In Europe, subtype 1b appears to be the most common. Several studies performed showed consistency with the hypothesis that the relative risk of getting cirrhosis or hepatocellular carcinoma may be significantly higher in patients with subtype 1b (Bellentani et al., 1999; Roffi et al., 1998). HCV genotype 3 is significantly associated to intravenous drug abuse while almost all of the patients infected with HCV genotype 4 originate from Middle East countries. HCV genotypes 5 and 6 are largely confined to South Africa and Southeast Asia (Fauci et al., 2008; Ray at el., 2000).

Only a few facts are known about the HCV lifecycle (Fig. 4). The envelope glycoproteins are supposed to be the ligand for receptors on the hepatocytes. Several possible receptors for HCV have been identified such as CD81, the scavenger receptor class B type I, and the mannose binding lectins DC-SIGN and L-SIGN (Pawlotsky et al., 2004). After receptor mediated endocytosis and fusion of the virus envelope with the endosomal membrane, the viral nucleocapsid is thought to be uncoated and released into the cytoplasm. After IRES mediated translation of the viral RNA and processing in the endoplasmatic reticulum, the HCV RNA serves as a template for replication and coding of viral proteins is performed. After viral packaging and assembly the mature virion is finally released via exocytosis.

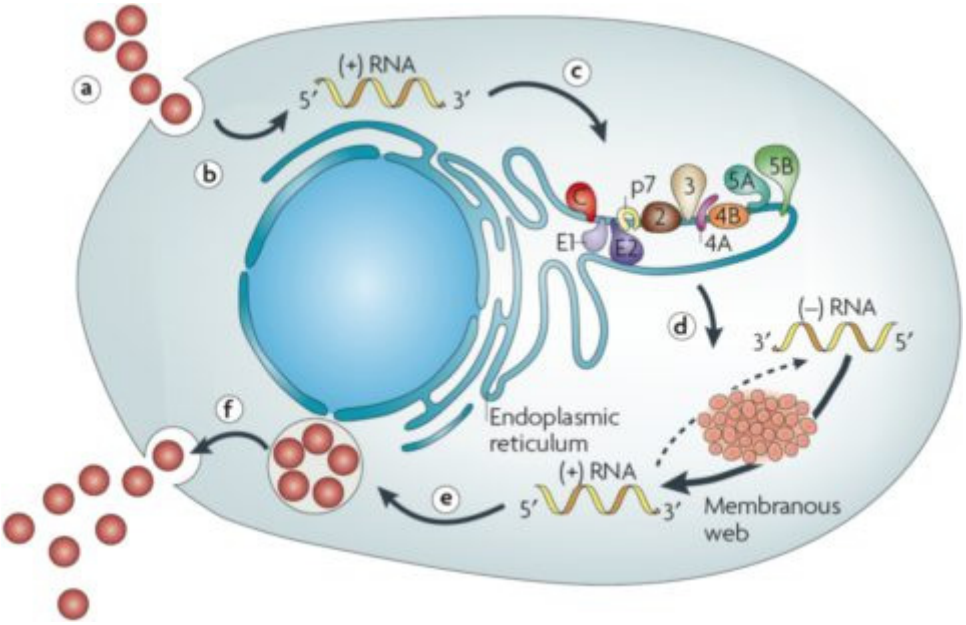


Fig. 4: Lifecycle of HCV

2.3 Prevalence of HCV Infection

The HCV infection is endemic in most parts of the world representing a major global health care problem (Fig. 5). With more than 170 million people infected with HCV worldwide corresponding up to 3% of the world's population, the World Health Organization (WHO) has declared HCV infection a major public health challenge with heterogeneous geographical and temporal relevance (World Health Organization, 1999). In Europe, the estimated prevalence of HCV infection ranges between 0.1% and 1.2% in Northern and Central Europe and between 2.5% and 3.5% in Southern Europe (Esteban et al., 2008). However, in certain areas, the HCV prevalence may be significantly higher with up to 26% of the general adult population in Southern Italy (Raffaele et al., 2001). In Eastern European countries, prevalence of HCV infection has been reported to be between 0.9% and 4.9% among blood donors, between 1% and 10% among health care workers, 13% to 48% among hemodialysis patients, and up to 92% in hemophilic patients (Naoumov et al., 1999). In the United States, national survey data suggest that the prevalence there is about 1.8% making it the country's most common chronic blood borne infection (Brown et al., 1999).

In contrast to countries with higher socioeconomic status, there is less data available about prevalence of HCV infection in countries with lower socioeconomic status. In the Eastern Mediterranean region, the HCV prevalence is estimated to be 4.6% with the highest seroprevalence rate reported for Egypt with 15% to 20% (http://who.int/inf/en; Frank et al., 2000). It is estimated that parenteral antischistosomal treatment played a major role in the spread of HCV throughout Egypt. In Pakistan, the HCV rate is estimated to be between 4.0% and 6.5% (Khattak et al., 2002; Luby et al., 1997). In the Western Pacific region and in parts of South America, prevalence rates are between 2.5% and 4.9% (http://who.int/inf/en). In India, HCV prevalence is estimated to be 0.9% according to a community based survey from Eastern India (Chowdhury et al., 2003). There is only few data available on HCV prevalence in Africa. In Central Africa, the seroprevalence was reported to be up to 6.5% in the general population (Ndong-Atom et al., 2008).

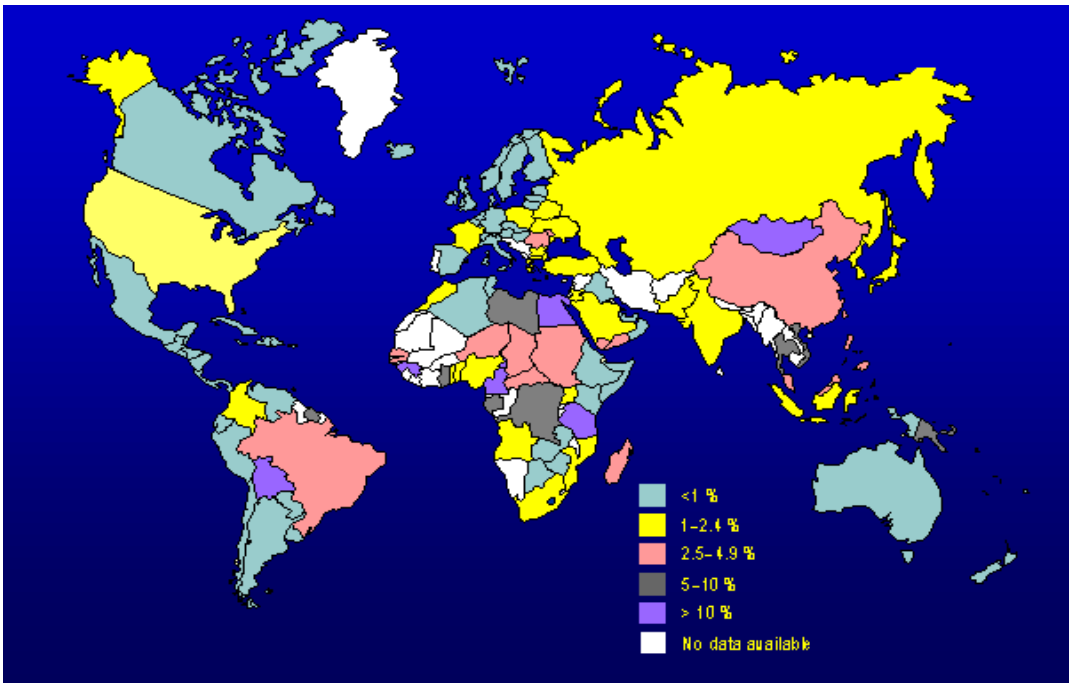


Fig. 5: HCV prevalence worldwide

The risk to health care workers acquiring HCV in the health care setting is well recognized (Table 1). In fact, aggregate serological data suggest that healthcare workers show a prevalence of HCV infection similar to that of the general population (Centers for Disease Control and Prevention, 1998).

	Study size (*n*)	Percentage with HCV antibodies (%)	Reference	Country
Healthcare workers	976	1.4	Geberding, 1994	USA
Healthcare workers	430	0.9	Germanaud et al., 1994	France
Healthcare workers	5813	2.0	Petrosillo et al., 1995	Italy
Healthcare workers	1949	0.2	Neal et al., 1997	UK
Liver transplantation personnel	57	5.3	Goetz et al., 1995	USA
Operating room personnel	104	4.4	Mujeeb et al.,1998	Pakistan

Table 1: Prevalence of HCV antibodies in healthcare professionals

According to the WHO model, the worldwide annual incidence of HCV infections among health care workers is estimated to reach 16,000 infections due to occupational exposure to percutaneous injuries (Esteban et al., 1996). In contrast to substantial progress in countries with higher socioeconomic status, protection of health care workers is still very incomplete in countries with lower socioeconomic status. It is estimated that three million health care workers experience the stressful event of a percutaneous injury with a contaminated sharp object each year. The average risk of HCV infection after a needle-stick injury with HCV-infected blood ranges between 2% and 3% (Table 2).

	Risk (%)
Hepatitis B infection after percutaneous injury (not vaccinated)	30
Bacterial infection after operation	1 - 15
HCV infection after percutaneous injury	2 - 3
HIV infection after needle-stick	0.3
Anesthesia-associated mortality	0.01
Mortality after penicillin-associated anaphylaxis	0.01 - 0.002

Table 2: Risk evaluation in the health care setting

2.4 Clinical course of HCV infection

During the acute phase of HCV infection, the vast majority of patients do not show any symptoms. Unspecific symptoms if any may include fatigue, nausea, vomiting, lethargy, abdominal pain, dark urine, and light (acholic) stool. In rare cases, more specific symptoms such as jaundice and hepatosplenomegaly may be present. The minority of newly infected patients is able to clear the infection. Because of the high mutability of the HCV genome and its ability to escape the immune system, the vast majority of infected patients develop a chronic HCV infection (Wong et al., 2006).

Chronic infection is defined as continuing disease for at least six months. It may be asymptomatic for several years until evidence of liver failure becomes clinically apparent. Some patients experience nausea, malaise, abdominal pain and/or pruritus. In the end stage of HCV infection, patients may develop spider angiomata, palmar erythema, and teleangiectasia. Chronic HCV infection causes chronic inflammation of the liver which leads to fibrosis and finally progresses to cirrhosis (Fig. 6). In case of advanced cirrhosis, splenomegaly, ascites, hepatic encephalopathy and/or esophageal varices may be observed. Cirrhosis develops in about 10% to 20% of patients with chronic infection and hepatocellular carcinoma develops in 1% to 5% of patients with chronic infection over a period of 20 to 30 years (Fig. 7).

Fig. 6: Liver showing macronodular cirrhosis

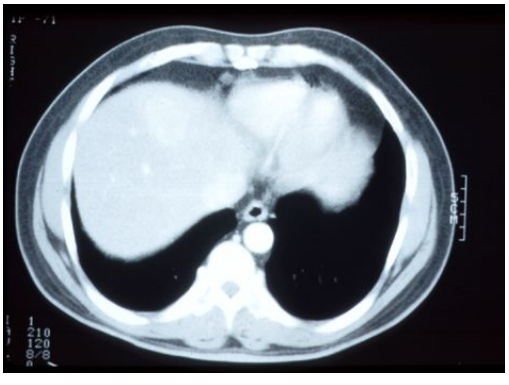


Fig. 7: Magnetic resonance image of the upper abdomen of a patient with hepatocellular carcinoma

2.5 *Diagnosis of HCV infection*

The clinical course of acute hepatitis C begins with an incubation period that ranges from 15 to 150 days. During the incubation period, usually 1 to 2 weeks following exposure, HCV RNA can be detected in serum, well before the appearance of HCV antibodies. HCV antibodies are usually detectable from 6 weeks after infection onwards (Fig. 8).

The majority of chronically infected patients are accidentally diagnosed, e.g. during admission to hospital when serum aminotransferase elevation becomes evident.

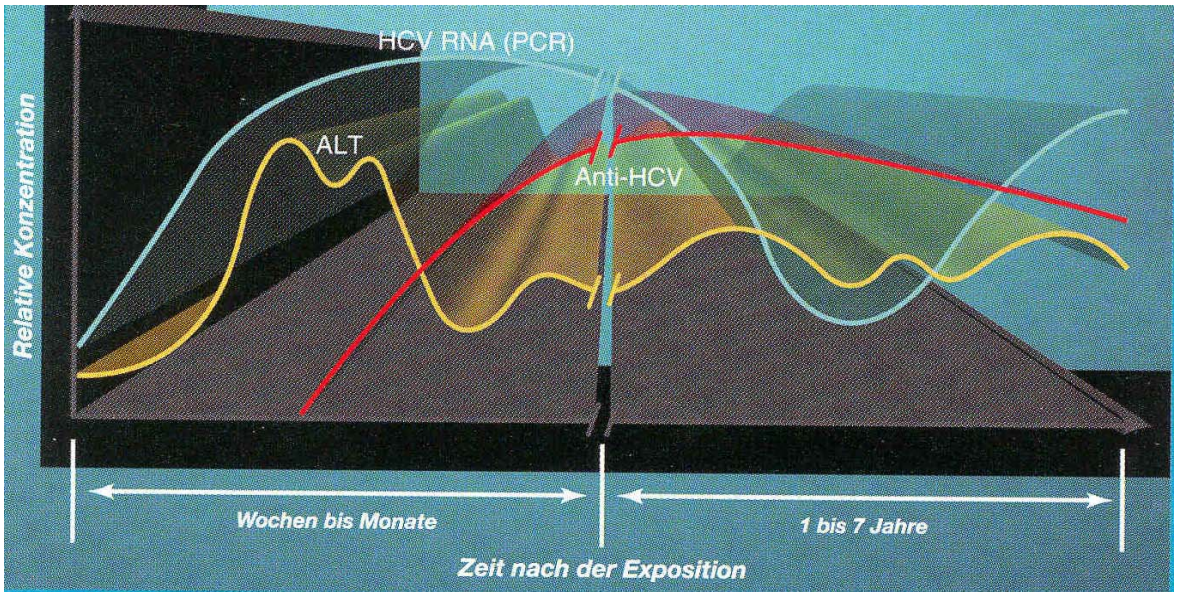


Fig.8: Laboratory parameters in acute and chronic HCV infection

2.6 Epidemiology and routes of transmission

HCV is primarily spread by direct contact with human blood. Transmission through transfusions that are not screened for HCV infection, through the reuse of inadequate sterilized needles, syringes or other medical equipment or through needle-sharing among drug users, is well documented (http://www.who.int/en/).

Sexual and perinatal transmission may also occur, although less frequently. Sex with an infected partner and with multiple partners has been identified as risk factors for HCV transmission but sexual transmission is far less efficient than that of other sexually transmitted pathogens. There exist no sufficient data showing whether specific sexually transmitted coinfections or particular sexual practices increase the likelihood of sexual transmission of HCV (Shepard et al., 2005). Acquisition of HCV infection through perinatal transmission is estimated to occur in 2.7% to 8.4% of infants born to HCV-infected mothers and is significantly higher with HIV coinfection and a high maternal viral load (Ferrero et al., 2003; Thomas et al., 1998).

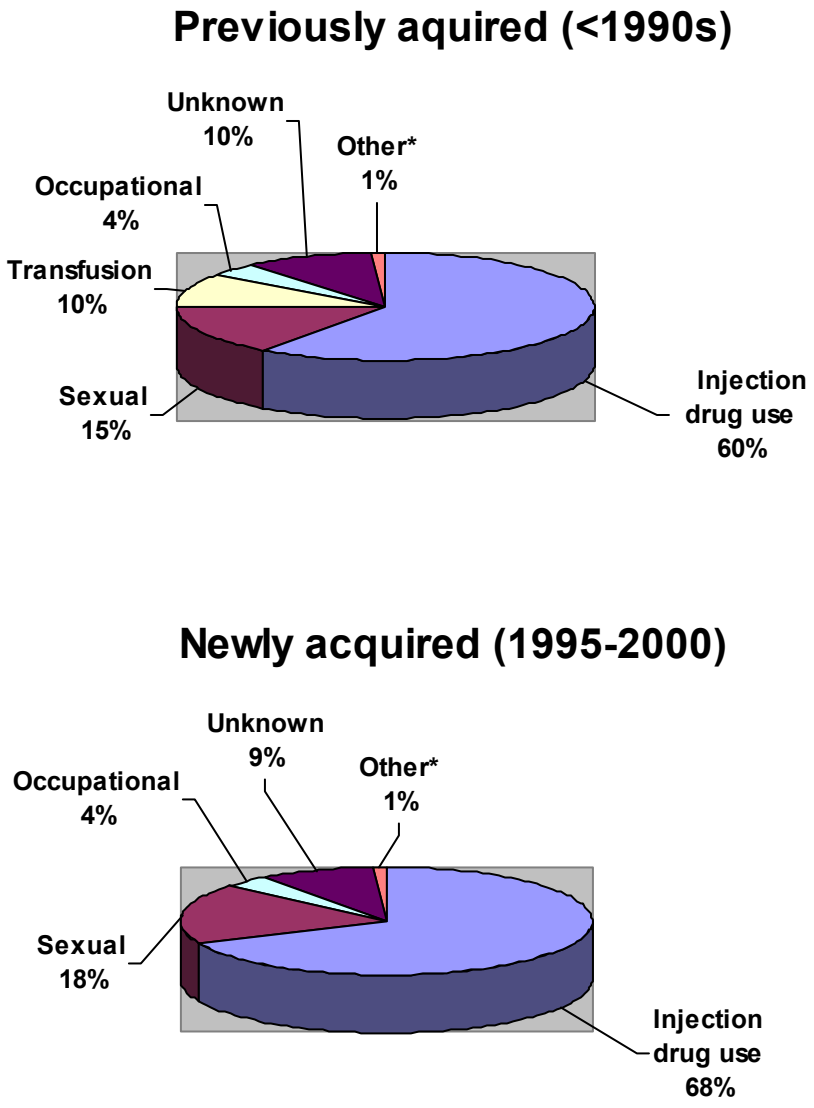
Other modes of transmission such as social, cultural and behavioural practices, percutaneous procedures such as piercing and tattooing, acupuncture, shaving in barbershops and other procedures in beauty shops may occur if inadequately sterilized equipment is used (Alter H. et al., 1997; Haley et al., 2001; Kao et al., 2000; Mele et al., 1995).
HCV is not spread by sneezing, hugging, coughing, food or water sharing eating utensils or casual contact.

In countries with lower socioeconomic status, the major ways of transmission are non-sterilized injection equipment and unscreened blood 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 (http://www.who.int/bloodsafety/global_database /en/SumRep_English.pdf).

A review of transfusion safety in Latin American countries revealed that blood products were screened for HCV in only 6 of 12 countries (Schmunis et al., 2001). In New Delhi, among 182 anti-HCV-negative hospitalized patients studied prospectively following a blood transfusion, HCV infection developed in 5.4% (Saxena et al., 1999). In India, HCV screening of blood products is mandated by law but usually not done due to financial constraints (Ray et al., 1999).

The epidemiology of HCV infection in the Western World has changed dramatically over the past few decades, primary as a result of the identification of HCV as the major cause of transfusion associated hepatitis and identification of the HCV genome (Henderson, 2003). Furthermore measures such as adoption of an all-volunteer donor system, screening of blood donations with surrogate laboratory tests for liver disease e.g. alanine aminotransferase, anti-HCV testing, and HCV nucleic acid testing have been introduced. Today, blood is so safe in many developed countries that classic methods to measure risk are no longer sensitive enough to provide meaningful estimates or document transfusion related transmission-events (Busch et al., 2003).

Prior to these precautions, transfusion and intravenous drug abuse were the most common routes of HCV transmission in countries with higher socioeconomic status. In the 1980s, the risk for HCV infection associated with transfusion was nearly 20% per unit transfused. Once the blood supply could be effectively screened for hepatitis C, the most important factor for transmission of HCV in developed countries became needle-sharing accounting for up to 60% of infections (Henderson, 2003). Intravenous drug abusers not only have the highest prevalence of HCV infection but also constitute a potential reservoir of HCV in the community (Fig. 9). The incidence varies between 31% to as high as 98% in different parts of the world (Memon et al., 2001). The prevalence of HCV infection increases proportionally with the duration of intravenous drug abuse.



*Other includes nosocomial, iatrogenic, perinatal

Fig. 9: Sources of HCV transmission

Because hepatitis C is a blood-borne infection and is transmitted efficiently by transfusion and needle-sharing, there is no doubt that an occupational risk for transmission of HCV in the health care setting exists, including transmission from patient-to-patient, from patient-to-health care worker, and from health care worker-to-patient.

2.6.1 Patient-to-patient transmission

Patient-to-patient transmission has been reported as the major way of transmission of HCV in the healthcare setting. In this context, the transmission of HCV in hemodialysis units requires special attention. The prevalence of HCV infected patients attending hemodialysis units, ranges between 3.9% and 71% in some countries (Wreghitt et al., 1999). The probability of acquiring HCV infection may be up to 12% per 100 treatment years (Forns et al., 2005). Environmental contamination, the dialysis apparatus, no separation of infected and non-infected patients, and lack of well-trained personnel have been recognized as possible reason for HCV transmission within hemodialysis units (Abacioglu et al., 2000; Alfurayh et al., 2000; Allander et al., 1995, Aucella et al., 2000; Bracho et al., 2005; Delarocque-Astagneau et al., 2002; Grethe et al., 2000; Katsoulidou et al., 1999; Kokubo et al., 2002; Kondili et al., 2006; Ross et al., 2009; Savey et al., 2005). Further possibilities for HCV transmission in the healthcare setting include unsafe injection practice, contamination of multidose vials, contaminated immunoglobulins, and organ transplantation (Chapel et al., 2001; Frank et al., 2000; Germain et al., 2005; Kahn et al 2000; Montella et al., 2003; Smith et al., 1999, Wreghitt et al., 1994). In general, the lack of sufficient hygienic standards has been described as major reason of HCV transmission in various healthcare settings such as hemodialysis units, plasmapheresis units, colonoscopy, endoscopy, anesthesia and gynecological procedures (Bronowicki et al., 1997; Datz et al., 1999; Izopet et al., 2005; Muscarella et al., 2001; Massari et al., 2001).

2.6.2 Patient-to-health care worker transmission

A number of case reports have documented occupational HCV transmission from anti-HCV positive patients to health care worker in a variety of settings (Marranconi et al., 1992; Mizuno et al., 1997; Nakano et al., 1995; Noguchi et al., 1997; Norder et al., 1998; Perez-Trallero et al., 1994; Ridzon et al., 1997; Schlipköter et al., 1990). In the majority of these events, direct percutaneous exposure to blood represented the route of transmission of HCV from the patient to the health care worker. The most common percutaneous injury resulting in occupational infection is the needle-stick with a hollow-bore, injection-style needle contaminated with HCV infected blood.

It is also documented that HCV has been transmitted after human bites and by a punch in the eye (Abel et al., 2000; Dusheiko et al., 1990).
Furthermore, there have been case reports of HCV transmission as a result of a blood splash to the conjunctiva (Hosoglu et al., 2003; Sartori et al., 1993).
Although HCV RNA has been detected in several body fluids from infected patients including saliva, urine, seminal fluid, menstrual blood, ascites and spinal fluid, no transmission has been documented yet. Substantially lower viral loads in these fluids in comparison with those in blood may be the reason (Laskus et al., 2002; Liou et al., 1992; Silverman et al., 1994).

2.6.3 Health care worker-to-patient transmission

The occupational risk to health care workers of acquiring hepatitis C virus in the health care setting is well recognized but during recent years patients as well as public health authorities became increasingly concerned about HCV transmission in the opposite direction, i.e. from the health care worker to the patient.

Transmission of HCV infection from health care workers to patients may be common, even in countries with high sanitary standard. More than 200 cases of health care worker-to-patient transmission of HCV have been reported in scientific publications and risk factors such as intravenous drug abuse or insufficient sanitary standard have been described (Bosch, 1998; Brown, 1999; Cody et al., 2002; Duckworth et al., 1999; Esteban et al., 1996; Mawdsley et al., 2005; Ross et al., 2002; Ross et al., 2002; Ross et al., 2000; Stark et al., 2006).

With regard to the incidence of health care worker-to-patient transmission just a few look-back investigations have been performed up to date.

In most cases, the surgeon is considered to be the source of infection through accidental exposure to his blood via abrasions or small cuts sustained by the surgeon during surgery (Table 3).

A retrospective study from 1992 to 1994 could prove that a Spanish cardiac surgeon with chronic hepatitis C transmitted HCV to five of his patients during open-heart surgery (Esteban et al., 1996). Their study could not clearly pinpoint the circumstances and mechanism of transmission but as injuries do regularly occur in the course of tying the wires during closure of the sternum, transmission is suggested to be associated with these percoutaneous wire injuries. According to the study the surgeon reported an overall incidence of about 20 percoutaneous injuries per 100 procedures and that he did not notice the glove perforation and the injury until after the procedure in many cases.

In 1999 three transmissions have been documented during gynecological procedures such as hysterectomy and cesarean section in the UK (Brown, 1999). In 2002 a study from Germany could prove HCV transmission during a cesarean section (Ross et al., 2002). According to a report by the Senate of Surgery of Great Britain and Ireland, which represents the surgeons' royal colleges and others, gynecology is one of the highest risk specialties for surgeon injury, with sharps injuries occurring in 10% of all procedures and up to 21% of vaginal hysterectomies (Brown, 1999).

The first HCV transmission by an orthopedic surgeon was documented in 2002. During a total hip arthroplasty, an additional trochanteric osteotomy was necessary and the trochanter had to be reattached by wire fixation. Although the operating team could not recall any circumstances that may have caused the transmission, an injury due to the wires could possibly have led to a percutaneous injury of the surgeon (Ross et al., 2002).

Reports of transmission from infected anesthetists or anesthetic assistants are rarer than reports of transmission involving infected surgeons (Table 4). A retrospective study performed in Germany provides evidence for the first time that a non-surgical staff member infected with HCV transmitted the virus to five patients, which has only been reported for hepatitis B virus so far (Ross et al., 2000). According to that study, the assistant was almost entirely responsible for the administration of the anesthesia including preparation of the narcotic drugs, venous and arterial puncture and intubation of the patients. A wound on the assistant’s right was reported to be the most plausible way of transmission, as he admitted usually not to wear gloves in the operating room because of diminution of his sense of touch. Cody et al. (2002) described transmission of HCV from an anesthetist to a patient in which the only anesthetic procedures performed were endotracheal intubation and peripheral intravenous puncture and no plausible way of transmission could be made out.

Comparable with these two incidents, another study from 2005 could prove the first case of HCV transmission during an anesthetic procedure in the UK. In contrast to the studies described above, the anesthetist was known to be hepatitis C positive and thus obliged to all existing infection measures, had washed his hands before the operation and had worn gloves throughout (Mawdsley et al., 2005).

Bosch et al. (1998) describes a Spanish anesthesiologist addicted to narcotics who injected himself with patient's narcotics before injecting them in the patient with the identical needle and syringe (Table 5). He was sentenced for more than 2000 years in prison for having infected more than 240 patients consciously (not yet published).

	Study size (*n*)	No. of patients infected	Transmission rate (%)	Reference
Surgeon (UK)	1900	3	0.2	Brown, 1999
Cardiac Surgeon (UK)	278	1	0.4	Duckworth et al., 1999
Anesthetist (USA)	348	1	0.3	Cody et al., 2002
Gynecologist (D)	2285	1	0.04	Ross et al., 2002
Orthopedic Surgeon (D)	207	1	0.5	Ross et al., 2002
Cardiac Surgeon (SP)	222	5	2.3	Esteban et al., 1996
Gynecologist (UK)	4500	8	0.2	Pugliese et al., 2000

Table 3: Evidence of HCV Infection among surgical patients

	No. of patients infected	Reference
Anesthesia assistant (D)	5	Ross et al.,2000
Anesthetist (USA)	1	Cody et al., 2002
Anesthetist (UK)	1	Mawdsley at al., 2005
Anesthetist (D)	3	Stark et al., 2006

Table 4: Evidence of HCV infection among surgical patients;
risk factor: lack of hygiene

	No. of patients infected	Reference
Anesthetist (SP)	240	Bosch, 1998
Operating room technician (USA)	40	Sehulster et al., 1997

Table 5: Evidence of HCV infection among surgical patients;
risk factor: intravenous drug abuse

3 STRATEGIES TO PREVENT HEALTH CARE WORKER-TO-PATIENT TRANSMISSION

3.1 Recommendations, regulations, and guidelines concerning prevention of health care worker-to-patient transmission of HCV

There are neither clear-cut nor uniform guidelines for the identification and management of HCV infected individuals employed in the health care setting. In Europe, most countries have no national policy for HCV infected health care workers; only in a few countries including Germany, Italy, and UK as well as in the USA (in alphabetical order) guidelines exist. In a few other countries, policies or instruments on the identification of infected health care workers and restrictions on their work have been implemented. However, all recommendations, regulations, and guidelines existing so far have been incoherent and incomprehensive with no general consensus on the question how to deal with HCV infected health care workers in a health care setting.

In this context, a clear definition of exposure-prone procedures is urgently needed. Most guidelines offer no, minimal or fairly unspecific guidance as to what constitute exposure-prone procedures.

The UK recommendations define all procedures with the risk that injury of the worker may result in the exposure of the patient's open tissues to the blood of the worker to be exposure-prone (http://www.doh.gov.uk/hepatitisc). Procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues inside a patient's open body cavity, wound or confined anatomical space with the hands or fingertips not completely visible at all times. Procedures, where the hands and fingertips of the worker are visible and outside the patient's body like the incision of external abscesses and internal examinations as well as simple endoscopic procedures or procedures that do not involve a certain risk of injury of the worker's gloved hands are considered not to be exposure-prone. It must be decided individually if a hepatitis C infected worker should continue to perform a procedure which itself is not exposure prone,

but complications arising could lead into the performance of an exposure-prone procedure.

In contrast, a recently published US article defines exposure-prone procedures as those during which a laboratory-confirmed clinical case of viral transmission from a health care worker to a patient has occurred (Reitsma et al., 2005). In that article all health care-related procedures were classified into three different classes of procedures (categories I-III).

Category I contains those where the risk of blood-blood contact between physician and patient is unlikely and thus only with minimal risk of viral transmission. The surgical field and the physician's hands are well visualized and the procedure is either superficial located or with minimal or no involvement of sharp instruments. In the absence of documented cases these procedures are considered to be safe until proven otherwise.

Category II entails those for which viral transmission is theoretically possible but unlikely. The operative field and the physician's hands are well visualized and there have never been any documented cases of transmission. Furthermore no deep spaces are reached other than with devices like scopes and catheters so that the physician's hands and sharps are never unseen.

Category III lists procedures for which there is definite risk of viral transmission. It consists of procedures that are proven to be exposure-prone as well as those that are highly likely to be exposure-prone but have not been documented to date. They are considered to be dangerous when performed by hepatitis C positive health care workers and are off-limits for infected physicians.

3.2 Should health care workers be screened or tested individually on HCV and what kind of assay(s) should be used

In the reviewed literature, the first part of this question has been answered controversially. In the majority of recommendations, systemic or periodic screening of health care workers on HCV infection has been declined, while few demand for screening tests. It must be stated that the group of people to be tested on HCV infection has not been clearly defined in the reviewed literature. Especially, the question how to deal with transient staff members such as students included in exchange programs and volunteers remains unanswered.

In Germany, screening for HCV antibodies is generally recommended for all employees working with body fluids, secretions and excretions, and tissues (Biostoffverordnung 2006). This also includes medical and dental students and self-employed people such as general practitioners and midwives.

In Italy, serological testing and evaluation of several infection markers have been recommended for each health care worker who directly performs invasive procedures (Mele et al., 2001). However, general screening of health care workers in order to identify individuals with HCV infection has been considered unnecessary as the number of positives is expected to be low and screening is costly and may be influenced by logistical problems.

In the UK, practitioners who are already involved in exposure-prone procedures are not legally obliged to undergo screening for HCV antibodies, except when they suffer an accidental needle stick. In contrast, each health care worker who plans to undertake professional training for a career that relies upon the performance of exposure-prone procedures must be screened for HCV antibodies (http://www.doh.gov.uk/hepatitisc). In this context, it is recommended that junior doctors entering any surgical specialty should be tested before performing exposure-prone procedures as well as future students should be tested before they enter the dental school.

The recommendations published by the United States Centers for Disease Control and Prevention (CDC) reject mandatory testing but encourage voluntary testing for health care workers who perform invasive procedures (Centers for Disease Control and Prevention, 1998). In a recently published article, the need for testing on HCV antibodies is strongly acknowledged (Reitsma et al., 2005).

In contrast, there exists consensus on the second part of the question as testing on HCV antibodies to be commonly regarded as the sufficient method.

3.3 When and how often should health care workers be screened

Several strategies have been proposed with regard to those issues. The majority of strategies are based on HCV antibody and/or alanine transaminase (ALT) testing. Primary determination of serum HCV RNA is not considered (Deuffic-Burban et al., 2009).

In Germany, testing on HCV antibodies should be done prior to the employment followed by regular testing (Biostoffverordnung, 2006). Intervals depend on the infection risk which has not been defined clearly varying 1 to 3 years.

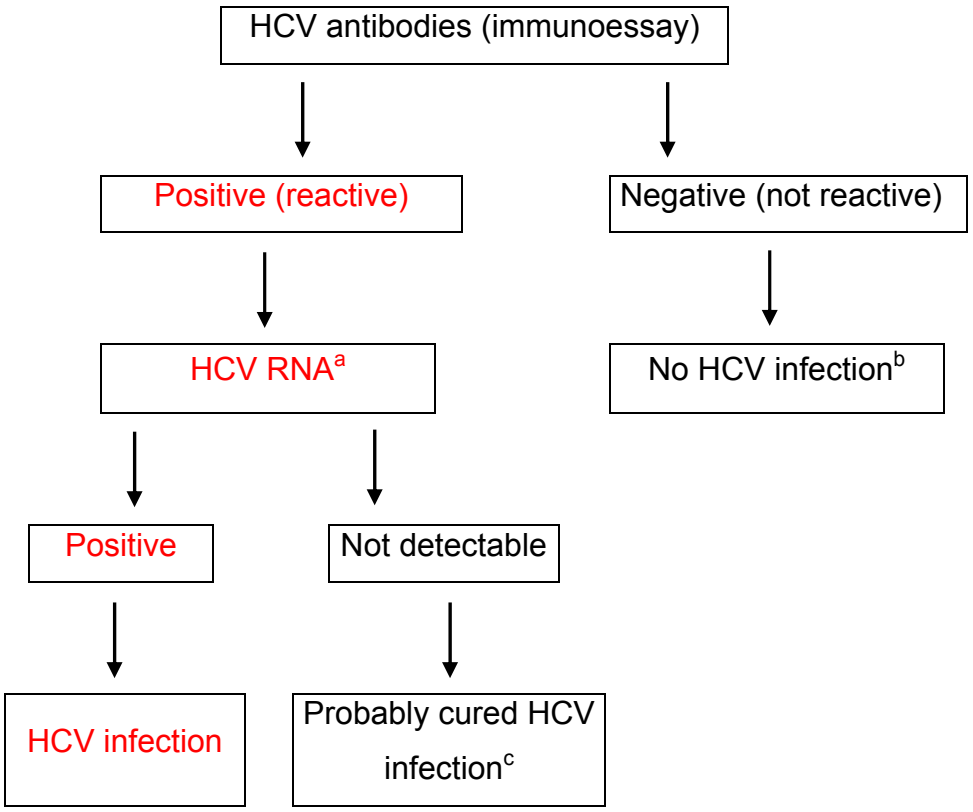
The Italian recommendations focus on testing health care workers who directly perform invasive procedures without indicating a particular time interval (Mele et al., 2001). Testing should be repeated only when health care workers report about having been exposed to blood or biological fluids.

In the UK, the first time for testing varies depending upon the particular career but in general, each medical student must be tested before being involved in exposure-prone procedures (Reitsma et al., 2005). Testing should be repeated after each accidental needle stick.

In the US, there is no requirement to undergo periodic testing, neither for medical students nor for health care workers involved in exposure-prone procedures (Centers for Disease Control and Prevention, 1998).

3.4 How should health care workers with HCV be managed

The general attitude throughout the literature demands limitations for health care workers with confirmed HCV infection; i.e., both HCV antibodies and HCV RNA are detectable. In contrast, there are usually no limitations recommended for those with detectable HCV antibodies but undetectable serum HCV RNA (Fig.10).



[a] Diagnostic method of choice in case of tentative HCV infection, immunosuppressed patients, and infants of HCV infected mothers during the first 18 months after birth.

[b] In case of asymptomatic and not immunosuppressed patients.

[c] The immunoblot assay may detect unspecified reactivity of the immunoassay. Repetition of detection of HCV RNA is recommended within 6 to 12 months.

Fig. 10: Algorithm of testing for HCV infection

Additionally, there is no consensus whether positive health care workers should be forced to disclose their HCV status to their patients. Some recommendations suggest infected physicians to inform patients of their infection status before undertaking an invasive procedure, whereas others leave disclosure of the HCV status up to the health care worker.

In Germany, guidelines do not demand any restrictions for health care workers with detectable HCV antibodies but undetectable serum HCV RNA or with serum HCV RNA concentration below $1x10^3$ IU/ml (Biostoffverordnung, 2006). If the serum HCV RNA concentration is found to be between $1x10^3$ and $1x10^5$ IU/ml, an expert committee decides whether restrictions are necessary. If the serum HCV RNA concentration exceeds $1x10^5$ IU/ml, the health care worker is considered to be at high risk of transmitting HCV and excluded to perform exposure-prone procedures. According to the German recommendations, there is no reason to exclude health care workers with HCV infection from their profession in general. In contrast, the forthcoming German recommendations refuse limits for HCV RNA and allow health care workers with positive HCV RNA to perform non-exposure-prone procedures. Health care workers should not be excluded from exposure-prone procedures in general, but exposure-prone procedures should be reduced to a minimum under strict consideration of safe practice. Furthermore, an expert committee should give advice in which area of the health care setting the health care worker may be employed (not yet published).

In Italy, health care workers with confirmed HCV infection must abstain from performing exposure prone procedures (Mele et al., 2001). If the serum HCV RNA remains undetectable when tested in a 3 months interval, no limitations are necessary. Furthermore, health care workers with sustained remission of infection, either as a response to treatment or occurring spontaneously should be re-evaluated and eventually reassigned their previous duties. Health care workers who do not directly perform invasive procedures do not constitute a risk of transmission of HCV, regardless of their infectious status; no limitation is thus necessary. These recommendations must also be applied to medical school and post-graduate students as well as institutions must help students and interns found

to be infected to choose a career best-suited to their individual potential. In Italy, health care workers are urged to inform their patients of their HCV status but this is left to the discretion of the health care worker whose privacy is protected by law. However, in situations in which the patient has been clearly exposed to blood or other body fluids of the health care worker the patient must be informed. Anyway, the institution must make every effort to ensure absolute privacy and confidentiality of each health care worker.

In the UK, health care workers with HCV infection should also be excluded from performing exposure-prone procedures (http://www.doh.gov.uk/hepatitisc). Health care workers with detectable HCV antibodies but undetectable serum HCV RNA as well as those who were treated successfully showing sustained virological response (undetectable serum HCV RNA for at least 6 months after cessation of treatment) and undetectable serum HCV RNA for another 6 months should be allowed to continue performing exposure-prone procedures. If health care workers with detectable serum HCV RNA intend to undertake professional training for a career that relies upon the performance of exposure-prone procedures, they should be excluded from such training unless they show a sustained virological response to treatment and undetectable serum HCV RNA for another 6 months. Furthermore, health care workers performing exposure-prone procedures are obliged to seek and follow confidential and professional advice on whether they should be tested when they think that they may have been at risk of acquiring hepatitis C. Health care workers who assume that they may have been infected and intend undertaking professional training relying upon the performance of exposure prone procedures but refuse testing should be excluded from such training. Similar to the Italian guidelines, it is emphasized that confidentiality and privacy of the infected health care worker has always to be ensured and disclosure of the HCV status is not necessary unless patients are or have been at risk.

In the United States, presently no working group recommends exclusion of infected health care workers from any aspect of patient care. As recommended for all health care-workers, those who are HCV positive should follow strict aseptic technique and standard precautions, including appropriate use of hand washing,

protective barriers, and care in the use and disposal of needles and other sharp instruments (American College of Surgeons, 1999; Beltrami et al., 2000; Centers for Disease Control and Prevention,1998).

The Society for Healthcare Epidemiologists of America has recently issued guidelines recommending all infected health care worker to use double gloving for exposure prone procedures and that infected providers should not be excluded from any aspect of patient care unless they are epidemiologically implicated in the transmission of infection despite adequate precautions (AIDS/TB Committee of the Society for Healthcare Epidemiology of America, 1997).

The American College of Surgeons has stated that surgeons infected with HCV have no reason to alter their practice but should seek expert advice and appropriate treatment to prevent chronic liver disease (American College of Surgeons, 1999). The CDC recommendation on prevention and control of HCV infection does not impose any restriction of professional activities of health care workers with HCV infection (Centers for Disease Control and Prevention, 1998).

Disclosure recommendations among individual federal states are controversial. The CDC proposes disclosure of the health care worker's HCV status to the patient, whereas a recently published article considers disclosure not necessarily effective and appropriate for health care workers (Centers for Disease Control and Prevention, 1998; Reitsma et al., 2005). It is argued that the significance of the potential for harm is not mitigated nor remedied by disclosure and that it would be an invasion of the health care worker's privacy if the law required disclosure of the health care worker's HCV status (Reitsma et al., 2005). Disclosure of the health care worker's HCV status may not improve the patient's safety but cause more harm because of patient's anxiety and health care worker's stigmatization (Closen et al., 1996). However, in case that an injury occurs and infection becomes a theoretical possibility, immediate notification is necessary for timely serological testing and prophylaxis (Reitsma et al., 2005). It has also been stated that the acknowledged social risks of disclosure could be avoided by refraining from performing procedures that expose patients to the risk of transmission (Fost, 2000). Evidence-based limits to the practice of health care workers with HCV infection may thus be appropriate and may be established according to the definition of exposure prone procedures (Reitsma et al., 2005).

In a recent article, a European Consensus group could not achieve any consensus as how to manage HCV infected health care workers who perform exposure-prone procedures (Gunson et al., 2003). On balance, it was not recommended exposure-prone procedures to be forbidden for any health care worker with HCV infection. However, it was recommended that all health care workers performing exposure-prone procedures know their HCV status as it may have implications for their future career. Those found to be infected should be referred to a hepatologist, as successful treatment minimizes the risk of transmission of HCV to patients. If there is a substantial blood letting into a patient's body cavity, then the status of the health care worker should be made known to the health care setting and the patient informed and treated if infection occurred.

4 SUGGESTIONS USEFUL FOR ESTABLISHING A COMMON REGULATORY FRAMEWORK

After reviewing the recent literature concerning recommendations, regulations, and guidelines on how to deal with health care worker-to-patient transmission of HCV, many questions remain unanswered and the need for establishing a national or, even better, an international regulatory framework to better handle this problem seems obvious. Future regulations and guidelines should be more clear and comprehensible for both the health care workers and those who are responsible for the appropriate execution of these specific regulations and guidelines. Furthermore, it seems to be meaningful to strengthen the health care worker's awareness by encouraging them to increase their self-competence. This may help to decrease the number of unreported cases of needle stick injuries or other incidents of exposure to blood or body fluids. To achieve this, individual institutional seminars on this specific issue should be held on a regular basis with obligatory attendance. This should be included in the quality assurance/quality control policies of any health care setting.

The question whether screening or individual testing on HCV infection should be introduced for health care workers and what kind of assay(s) should be used is of vital importance. It appears to be reasonable establishing the HCV status of any health care worker as early as possible, preferably before they decide about their career. It is thus of major significance demanding for HCV antibody screening for all individuals prior to start working in any health care setting including any transient members as e.g. students, PhDs, and volunteers, independently of exposure prone procedures performed. Health care workers already working in a health care setting should also undergo screening on HCV antibodies independently of exposure-prone procedures performed. The screening interval should be determined as once per year. The annual screening interval appears to be well-balanced regarding both the practical, logistical and financial demands and the compliance of all those to be tested. In case of detectable HCV antibodies, subsequent confirmation by serum HCV RNA testing using a highly sensitive real-time PCR assay must be done.

To evaluate the HCV status of health care workers after a needle stick injury, testing on HCV antibodies as soon as possible after the incident should be followed by the testing on serum HCV RNA after 2 weeks. In case of undetectable HCV RNA, repeat testing after another 4 weeks should be done. This strategy not only leads to an earlier detection of HCV transmission but also provides an earlier confirmation of the absence of HCV transmission. The period during which the health care worker's quality of life may deteriorate is thus shortened significantly. Although this strategy seems to be more expensive at first glance, it appears reasonably cost-effective when considering all consequences following such an incident.

Health care workers with HCV infection need to be managed by a hepatologist regarding further diagnostic procedures including determination of the HCV genotype, evaluation for antiviral therapy, and the time period of restriction from exposure-prone procedures. When affected health care workers are found to be suitable for receiving antiviral therapy, they should be advised to undergo therapy after determination of the HCV genotype. As soon as sustained virological response is documented, health care workers may be allowed to return working at their position without any restrictions on performing exposure-prone procedures. It is not advisable to manage health care workers with HCV infection based on their HCV viral load as the infective dose for HCV transmission being still unknown, different assays for detection of serum HCV RNA having divergent cut-off values and thus being not comparable. If viral clearance is not achieved for any reason, the health care worker must be excluded from performing exposure-prone procedures.

In conclusion, there exists an urgent need for improvement of guidelines concerning prevention of health care worker-to-patient transmission of HCV. Implementation of improved guidelines may have a significant impact on both avoiding health care worker-to-patient transmission of HCV and ensuring patient safety in the health care setting in general.

5 References

Abacioglu YH, Bacaksiz F, Bahar IH, Simmonds P. Molecular evidence of nosocomial transmission of hepatitis C virus in a haemodialysis unit. Eur J Clin Microbiol Infect Dis 2000;19:182-186

Abel S, Césaire R, Cales-Quist D, Béra O, Sobesky G, Cabié André. Occupational transmission of human immunodeficiency virus and hepatitis C virus after a punch. Clin Infect Dis 2000;31:1494-1495

AIDS/TB Committee of the Society for Healthcare Epidemiology of America. Management of healthcare workers infected with hepatitis B virus, hepatitis C virus, human immunodeficiency virus, or other bloodborne pathogens. Infect Control Hosp Epidemiol1997;18:349–363

Alfurayh O, Sabeel A, Al Ahdal MN, Almeshari K, Kessie G, Hamid M, Dela Cruz DM. Hand contamination with hepatitis C virus in staff looking after hepatitis C-positive hemodialysis patients. Am J Nephrol 2000; 20:103-106

Allander T, Gruber A, Naghavi M, Beyene A, Söderström T, Björkholm M, Grillner L, Persson MA. Frequent patient-to-patient transmission of hepatitis c virus in a haematology ward. Lancet 1995;345:603-607

Alter HJ, Conry-Cantilena C, Melpolder J, Tan D, Van Raden M, Herion D, Lau D, Hoofnagle JH. Hepatitis C in asymptomatic blood donors. Hepatology 1997;26:29S-33S

American College of Surgeons. Statement on the surgeon and hepatitis. Bull Am Coll Surg 1999;84:21-24

Aucella F, Vigilante M, Valente GL, Stallone C. Systematic monitor disinfection is effective in limiting HCV spread in hemodialysis. Blood Purif 2000;18:110-114

Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Crocè LS, Mazzoran L, Masutti F, Cristianini G, Tiribelli C. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. Gut 1999;44:874-880

Beltrami EM, Williams IT, Shapiro CN, Chamberland ME. Risk and management of blood-borne infections in health care workers. Clin Microbiol Rev 2000;13:385-407

Biostoffverordnung. Bundesgesetzblatt Teil I. 2006; 2407 and TRBA 250, May 2006 (www.nadelstichverletzung.de) [accessed 14.04.09]

Bosch X. Hepatitis C outbreak astounds Spain. Lancet 1998;351:1415

Bracho MA, Gosalbes MJ, Blasco D, Moya A, González-Candelas F. Molecular epidemiology of a hepatitis C virus outbreak in a hemodialysis unit. J Clin Microbiol 2005;43:2750-2755

Bronowicki JP, Vetter D, Uhl G, Hudziak H, Uhrlacher A, Vetter JM, Doffoel M. Lymphocyte reactivity to hepatitis C virus (HCV) antigend shows evidence for exposure to HCV in HCV-seronegative spouses of HCV-infected patients. J Infect Dis 1997;176:518-522

Brown P. Surgeon infects patient with hepatitis C. Br Med J 1999;319:1219

Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. JAMA 2003;289:959-963

Cariani E, Zonaro A, Primi D, Magni E, Incarbone C, Scalia P, Tanzi E, Zehender G, Zanetti AR. Detection of HCV RNA and antibodies to HCV after needlestick injury. Lancet 1991; 337:850

Centers for Disease Control and Prevention (CDC). Acute hepatitis C virus infections attributed to unsafe injection practices at an endoscopy clinic-Nevada, 2007. MMWR Morb Mortal Wkly Rep 2008; 57:513-517

Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Morb Mortal Wkly Rep 1998;47:1-39

Chapel HM, Christie JM, Peach V, Chapman RW. Five-year follow-up of patients with primary antibody deficiencies following an outbreak of acute hepatitis C. Clin Immunol 2001;99:320-324

Chowdhury A, Santra A, Chaudhury S et al. Hepatitis C virus infection in the general population: a community-based study in West Bengal, India. Hepatology 2003;37:802-809

Closen ML. HIV-AIDS, infected surgeons and dentists, and the medical profession's betrayal of its responsibility to patients. New York Law School Review 1996;41:57-139

Cody SH, Nainan OV, Garfein RS, Meyers H, Bell BP, Shapiro CN, Meeks EL, Pitt H, Mouzin E, Alter MJ, Margolis HS, Vugia DJ. Hepatitis C virus transmission from an anesthesiologist to a patient. Arch Intern med 2002;162:345-350

Datz C, Cramp M, Haas T, Dietze O, Nitschko H, Froesner G, Muss N, Sandhofer F, Vogel W. The natural course of hepatitis C virus infection 18 years after an epidemic outbreak of non-A, non-B hepatitis in a plasmapheresis centre. Gut 1999;44:563-567

Delarocque-Astagneau E, Baffoy N, Thiers V, Simon N, de Valk H, Laperche S, Couroucé AM, Astagneau P, Buisson C, Desenclos JC. Outbreak of hepatitis C virus infection in a hemidialysis unit-potential transmission by the hemodialysis machine? Infect Control Hosp Epidemiol 2002;23:328-334

Deuffic-Burban S, Abiteboul D, Lot F, Branger M, Bouvet E, Yazdanpanah Y. Costs and cost-effectiveness of different follow-up schedules for detection of occupational hepatitis C virus infection. Gut 2009;58:105-110

Duckworth GJ, Heptonstall J, Aitken C. Transmission of hepatitis C virus from a surgeon to a patient. The incident control team. Commun Dis Public Health 1999;2:188-192

Dusheiko GM, Smith M, Scheuer PJ. Hepatitis C transmitted by a human bite. Lancet 1990;336:503-504

Esteban JI, Gomez J, Martell M, Cabot B, Quer J, Camps J, González A, Otero T, Moya A, Esteban R et al. Transmission of hepatitis C virus by a cardiac surgeon. N Engl J Med 1996;334:555-560

Esteban JI, Sauleda S, Quer J. The changing epidemiology oh hepatitis C virus infection in Europe. J Hepatol 2008;48:148-162

Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J.Harrison's. Principles of Internal Medicine. 17th Edition

Ferenci P, Laferl H, Scherzer TM, Gschwantler M, Maieron A, Brunner H, Stauber R, Bischof M, Bauer B, Datz C, Löschenberger K, Formann E, Staufer K, Steindl-Munda P; Austrian Hepatitis Study Group. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. Gastroenterology 2008;135:451-458

Ferrero S, Lungaro P, Bruzzone BM, Gotta C, Bentivoglio G, Ragni N. Prospective study of mother-to-infant transmission of hepatitis C virus: a 10-year survey (1990-2000). Acta Obstet Gynecol Scand 2003;82:229-234

Forns X, Martínez-Bauer E, Feliu A, García-Retortillo M, Martín M, Gay E, Navasa M, Sánchez-Tapias JM, Bruguera M, Rodés J. Nosocomial transmission of HCV in the liver unit of a tertiary care center. Hepatology 2005;41:115-122

Fost N. Patient access to information on clinicians infected with blood-borne pathogens. JAMA 2000;284:1975-1976

Frank C, Mohamed MK, Strickland TG, Lavanchy D, Arthur RR, Magdar LS, El Khoby T, Abdel-Wahab Y, ALy Ohn El, Anwar W, Sallam I. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887-891

Geberding JL. Incidence and prevalence of human immunodeficiency virus, hepatitis B, hepatitis C virus, and cytomegalovirus among health care personnel at risk for blood exposure: final report from a longitudinal study. J Infect Dis 1994;170:1410-1417

Germain JM, Carbonne A, Thiers V, Gros H, Chastan S, Bouvet E, Astagneau P. Patient-to-patient transmission of hepatitis C virus through the use of multidose vials during general anesthesia. Infect Control Hosp Epidemiol 2005;26:789-792

Germanaud J, Barthez JP, Causse X. The occupational risk of hepatitis C infection among hospital employees. Am J Public Health 1994;84:122

Goetz AM Ndimbie OK, Wagener MM, Muder RR. Prevalence of hepatitis C infection in health care workers affiliated with a liver transplant center. Transplantation 1995; 59:990-994

Grethe S, Gemsa F, Monazahian M, Böhme I, Uy A, Thomssen R. Molecular epidemiology of an outbreak of HCV in a hemodialysis unit: direct sequencing of HCV-HVR1 as an appropriate tool for phylogenetic analysis. J Med Virol 2000;60:152-158

Gunson RN, Shouval D, Roggendorf M, Zaaijer H, Nicholas H, Holzmann H, de Schryver A, Reynders D, Connell J, Gerlich WH, Marinho RT, Tsantoulas D, Rigopoulou E, Rosenheim M, Valla D, Puro V, Struwe J, Tedder R, Aitken C, Alter M, Schalm SW, Carman WF; European Consensus Group. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in health care workers (HCWs): guidelines for prevention of transmission of HBV and HCV from HCW to patients. J Clin Virol 2003;27:213-230

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 (Baltimore) 2001;80:134-151

Henderson DK. Managing occupational Risks for heaptits C transmission in the health care setting. Clinical Microbiology Reviews 2003:16;546-568

Hofmann F, Kralj N, Beie M. Needle Stick injuries in Health care- Frequency, Causes and Preventive Strategie. Gesundheitswesen 2002;64:259-266

Hosoglu S, Celen MK, Akalin S, Geyik MF, Soyoral Y, Kara IH. Transmission of hepatitis C by blood splash into conjunctiva in a nurse. Am J Infect Control 2003;3:502-504

Izopet J, Sandres-Sauné K, Kamar N, Salama G, Dubois M, Pasquier C, Rostaing L. Incidence of HCV infection in French hemodialysis units: a prospective study. J Med Virol 2005;77:70-76

Kao JH, Chen DS. Transmission of hepatitis C virus in Asia: past and present perpectives. J Gastroenterol Hepatol 2000;15:E91-E96

Katsoulidou A, Paraskevis D, Kalapothaki V, Arvanitis D, Karayiannis P, Hadjiconstantiou V, Hatzakis A. Molecular epidemiology of a hepatitis C virus outbreak in a haemodialysis unit. Multicentre Haemodialysis Cohort Study on Viral Hepatitis. Nephrol Dial Transplant 1999;14:1188-1194

Katthak MF, Salamat N, Bhatti FA, Quereshi TZ. Seroprevalence of hepatitis B, C and HIV in blood donors in northern Pakistan. J Park Med Assoc 2002;52:398-402

Kokubo S, Horii T, Yonekawa O, Ozawa N, Mukaide M. A phylogenetic-tree analysis elucidating nosocomial transmission of hepatitis C virus in a haemodialysis unit. J Viral Hepat 2002;9:450-454

Kondili LA, Genovese D, Argentini C, Chionne P, Toscani P, Fabro R, Cocconi R, Rapicetta M. Nosocomial transmission in simultaneous outbreaks of hepatitis C and B virus infections in a hemodialysis center. Eur J Clin Microbiol Infect Dis 2006;25:527-531

Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M, Nikolopoulou GB, Vargas H, Rakela J.Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. J Virol 2002;76:10064-10068

Liou TC, Chang TT, Young KC, Lin XZ, Lin CY, Wu HL. Detection of HCV RNA in saliva, urine, seminal fluid, and ascites. J Med Virol 1992;37:197-202

Luby SP, Quamruddin K, Shah AA Omair A, Pahsa O, Khan AJ, McCormick JB, Hoodbhouy F, Fisher-Hoch S. The relationship between therapeutic infections and high prevalence of hepatitis C infection in Hafizabad, Pakistan. Epidemiol Infect 1997;119:349-356

Marranconi F, Mecenero V, Pellizzer GP, Bettini MC, Conforto M, Vaglia A, Stecca C, Cardone E, de Lalla F. HCV infection after accidental needlestick injury in health-care workers. Infection 1992;20:111

Massari M, Petrosillo N, Ippolito G, Solforosi L, Bonazzi L, Clementi M, Manzin A. Transmission of hepatitis C virus in a gynecological surgery setting. J Clin Microbiol 2001;39:2860-2863

Mawdsley J, Teo CG, Kyi M, Anderson M. Anaesthetist to patient transmission of hepatitis C virus associated with non exposure-prone procedures. J Med Virol 2005;75:399-401

Mele A, Corona R, Tosti ME, Palumbo F, Moiraghi A, Novaco F, Galanti C, Bernacchia R, Ferraro P. Beauty treatments and risk of parenterally transmitted hepatitis: results from the hepatits surveillance system in Italy. Scand J Infect Dis. 1995;27:441-444

Mele A, Ippolito G, Craxì A, Coppola RC, Petrosillo N, Piazza M, Puro V, Rizzetto M, Sagliocca L, Taliani G, Zanetti A, Barni M, Bianco E, Bollero E, Cargnel A, Cattaneo M, Chiaramonte M, Conti E, D'Amelio R, De Stefano DM, Di Giulio S, Franco E, Gallo G, Levrero M, Mannella E, Erli SM, Milazzo F, Moiraghi A, Polillo R, Prati D, Ragni P, Sagnelli E, Scognamiglio P, Sommella L, Stroffolini T, Terrana T, Tosolini G, Vitiello E, Zanesco L, Ziparo V, Maffei C, Moro ML, Satolli R, Traversa G. Risk management of HBsAg or anti-HCV postitive healthcare workers in hospital. Digest Liver Dis 2001;33:795-802

Memon MI, Memon MA. Hepatitis C: an epidemiological review. Journal of viral hepatitis 2002;9:84-100

Mizuno Y, Suzuki K, Mori M, Hayashi K, Owaki T, Hayashi H, Kumada K, Ohba K, Mizokami M. Study of needlestick accidents and hepatitis C virus infection in healthcare workers by molecular evolutionary analysis. J Hosp Infect 1997;35:149-154

Montella M, Crispo A, Serraino D, Rezza G, Franceschi S. Is the spread of HCV in Southern Italy attributable to iatrogenic transmission through unsterile injections? Eur J Cancer Prev 2003;12:85-86

Mujeeb SA, Khatri Y, Khanani R. Frequency of parenteral exposure and seroprevalence of HBV, HCV, and HIV among operating room personnel. J Hosp Infect 1998;38:133-137

Muscarella LF. Recommendations for preventing hepatitis C virus infection: analysis of a Brooklyn endoscopy clinic's outbreak. Infect Control Hosp Epidemiol 2001;22:669–669

Nakano Y, Kiyosawa K, Sodeyama T, Tanaka E, Matsumoto A, Ichijo T, Mizokami M, Furuta S. Acute hepatitis C transmitted by needlestick accident despite short duration interferon treatment.J Gastroenterol Hepatol 1995;10:609-611

Naoumov NV. Hepatits C virus infection in Eastern Europe. J Hepatol 1999;31,S1:84-87

Ndong-Atome GR, Makuwa M, Njouom R, Branger M, Brun-Vézinet F, Mahé A, Rousset D, Kazanji M.Hepatitis C virus prevalence and genetic diversity among pregnant women in Gabon, central Africa. BMC Infect Dis 2008;8:82

Neal KR, Dornan J, Irving WL. Prevalence of hepatitis C antibodies among health care workers of two teaching hospitals. Who is at risk? BMJ 1997;314:179-180

Noguchi S, Sata M, Suzuki H, Ohba K, Mizokami M, Tanikawa K. Early therapy with interferon for acute hepatitis C acquired through a needlestick. Clin Infect Dis 1997;24:992-994

Norder H, Bergström Å, Uhnoo I, Aldén J, Weiss L, Czajkowski J, Magnius L. Confirmation of nosocomial transmissiom of hepatits C virus by phylogenetic analysis of the NS5-B region. J Clin Microbiol 1998;36:3066-3069

Pawlotsky JM. Pathophysiology of hepatitis C virus infection and related liver disease. Trends Microbiol 2004;12:96-102

Perez-Trallero E, Cilla G, Saenz JR. Occupational transmission of HCV. Lancet 1994;20;344:548

Petrosillo N, Puro V, Ippolito G, Di Nardo V, Albertoni F, Chiaretti B, Rava' L, Sommella L, Ricci C, Zullo G, et al. Hepatitis B virus, hepatitis C virus and human immunodeficiency virus infection in health care workers: a multiple regression analysis of risk factors. J Hosp Infect 1995;30:273-281

Prüss-Üstün A, Rapiti E, Hutin Y. Estimation of the global burden of disease attributable to contaminated sharps injuries among health-care workers. Am J Ind med 2005;48:482-90.

Pugliese G, Favero MS. Multidose vial transmits HCV. Infect Control Hosp Epidemiol 2000;21:425.

Raffaele A, Valenti M, Iovenitti M, Matani A, Bruno ML, Altobelli E, D'Alessandro A, Barnabei R, Leonardis B, Taglieri G. High prevalence of HCV infection among the general population in a rural area of central Italy. Eur J Epidemiol 2001;17:41-46

Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL. Genetic epidemiology of hepatitis C virus throughout Egypt. J Infect Dis 2000;182:698–707

Ray VL, Chaudhary RK, Choudhury N. Transfusion safety in developing countries and the Indian scenario. Dev Biol (Basel) 1999;102:195-203

Reitsma AM, Closen ML, Cunningham M, Lombardo PA, Minich HNF, Moreno JD, Nichols RL, Pearson RD, Sawyer RG, Wispelwey B, Tereskerz PM.
Infected physicians and invasive procedures: Safe practice management. Clin Infect Dis 2005;40:1665-1672

Ridzon R, Gallagher K, Ciesielski C, Mast EE, Michael B, Ginsberg MB, Robertson BJ, Luo C, DeMaria A. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needlestick injury. N Engl J Med 1997; 336:919-922

Roffi L, Ricci A, Ogliari C, Scalori A, Minola E, Colloredo G, Donada C, Ceriani R, Rinaldi G, Paris B, Fornaciari G, Morales R, Del Poggio P, Sangiovanni A, Buonocore M, Bellia V, Riboli P, Nava MC, Panizzuti F, Piperno A, Pozzi M, Pioltelli P, Mancia G. HCV genotypes in Northern Italy: a survey of 1368 histologically proven chronic hepatitis C patients. J Hepatol 1998;29:701-706

Ross RS, Viazov S, Khudyakov YE, Xia GL, Lin Y, Holzmann H, Sebesta C, Roggendorg M, Janata O. Transmission of hepatitis C virus in an orthopaedic hospital ward. J Med Virol 2009;81:249-257

Ross RS, Viazov S, Roggendorf M. Phylogenetic analysis indicates transmission of hepatitis C virus from infected orthopaedic surgeon to a patient. J Med Virol 2002;66:461-467

Ross RS, Viazov S, Thormahlen M, Bartz L, Tamm J, Rautenberg P Roggendorf M, Deister A. Risk of hepatitis C virus transmission from an infected gynecologist to patients: results of a 7-year retrospective investigation. Arch Intern Med 2002;162:805-810

Ross SR, Viazov S, Gross T, Hofmann F, Seipp HM, Roggendorf M. Transmission of hepatitis C virus from a patient to an anaesthesiology assistant to five patients. N Engl J Med 2000;343:1851-1854

Sartori M, La Terra G, Aqlietta M, Manzin A, Navino C, VErzetti G. Transmission of hepatitis C via bloos splash into conjunctiva. Scand J Infect Dis 1993;25:270-271

Savey A, Simon F, Izopet J, Lepoutre A, Fabry J, Desenclos JC. A large nosocomial outbreak of hepatitis C virus infections at a hemodialysis center. Infect Control Hosp Epidemiol 2005;26:752-760

Saxena R, Thakur V, Sood B, Guptan RC, Gururaja S, Sarin SK. Transfusion-associated hepatitis in a tertiary referral hospital in India. A prospective study. Vox Sang 1999;77:6-10

Schlipköter U, Roggendorf M, Cholmakow K, Weise A, Deinhardt F. Transmission of hepatitis C virus (HCV) from a haemodialysis patient to a medical staff member. Scand I Infect Dis 1990;22:757-758

Schmunis GA, Zicker F, Cruz JR, Cuchi P. Safety of blood supply for infectious diseases in Latin American countries. Am J Trop Med Hyg 2001;65:924-930

Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558-567

Silverman AL, Puccio JE, Kulesza GW, McCray DG, Gordon SC. HCV RNA is present in the menstrual blood of women with chronic hepatitis C infection. Am J Gastroenterol 1994;89:1201-1202

Stark K, Hänel M, Berg T, Schreier E. Nosocomial transmission of hepatitis C Virus from an anesthesiologist to three patients - epidemiologic and molecular evidence. Arch Virol 2006;151:1025-1030

Tallis GF, Ryan GM, Lambert SB, Bowden DS, McCaw R, Birch CJ, Moloney M, Carnie JA, Locarnini SA, Rouch GJ, Catton MG. Evidence of patient-to-patient transmission of hepatits C virus through contaminated intravenous anaesthetic ampoules. J Viral Hepat 2003;10:234-239

Thomas DL, Villano SA, Riester KA, Hershow R, Mofenson LM, Landesman SH, Hollinger FB, Davenny K, Riley L, Diaz C, Tang HB, Quinn TC. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. J Infect Dis 1998;177:1480-1488

UK Department of Health. Health Service Circular 2002/010—Hepatitis C infected health care workers. Available at http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Healthservicecirculars/DH4004561 [accessed 14.04.09]

WHO. Global Database on blood safety summery report 1998-1999. http://www.who.int/bloodsafety/global_database/en/SumRep_English.pdf [accessed 14.04.09]

World Health Organization (WHO). Available from: http:/www.who.int/en/ [accessed 14.04.09]

World Health Organization. Hepatitis C-global prevalence (update). Weekly Epidemiological Record 1999;74:425

Wreghitt TG, Gray JJ, Allain JP, Poulain J, Garson JA, Deaville R, Maple C, Parameshwar J, Calne RY, Wallwork J, et al. Transmission of hepatitis C virus by organ transplantation in the United Kingdom.J Hepatol 1994;20(6):768-772.
Wreghitt TG. Blood-borne virus infections in dyialysis units-a review. Rev Med Virol 1999;9:101-109

6 List of figures

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