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Health care-associated hepatitis C virus infection

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Abstract

Hepatitis C virus (HCV) is a blood-borne pathogen that has a worldwide distribution and infects millions of people. Care-associated HCV infections represented a huge part of hepatitis C burden in the past *via* contaminated blood and unsafe injections and continue to be a serious problem of public health. The present review proposes a panorama of health care-associated HCV infections *via* the three mode of contamination that have been identified: (1) infected patient to non-infected patient; (2) infected patient to non-infected health care

worker (HCW); and (3) infected HCW to non infected patient. For each condition, the circumstances of contamination are described together with the means to prevent them. As a whole, the more important risk is represented by unsafe practices regarding injections, notably with the improper use of multidose vials used for multiple patients. The questions of occupational exposures and infected HCWs are also discussed. In terms of prevention and surveillance, the main arm for combating care-associated HCV infections is the implementation of standard precautions in all the fields of cares, with training programs and audits to verify their good application. HCWs must be sensitized to the risk of blood-borne pathogens, notably by the use of safety devices for injections and good hygiene practices in the operating theatre and in all the invasive procedures. The providers performing exposed-prone procedures must monitor their HCV serology regularly in order to detect early any primary infection and to treat it without delay. With the need to stay vigilant because HCV infection is often a hidden risk, it can be hoped that the number of people infected by HCV *via* health care will decrease very significantly in the next years.

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Key words: Hepatitis C virus; Health care-associated infection; Health care worker; Standard precautions; Hemodialysis; Unsafe injections; Occupational exposure; Antiviral drugs

Core tip: Hepatitis C virus (HCV) is a blood-borne pathogen that has a worldwide distribution and infects millions of people. Care-associated HCV infections represented a huge part of hepatitis C burden in the past *via* contaminated blood and unsafe injections and continue to be a serious problem of public health. The present review proposes a panorama of health care-associated HCV infections *via* the three mode of contamination that have been identified: (1) infected patient to non-infected patient; (2) infected patient to non-infected health care worker; and (3) infected HCW

to non-infected patient.

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INTRODUCTION

With approximately 123 millions of people infected worldwide^[1], hepatitis C infection is a major public health threat. Since its discovery in 1989^[2], the hepatitis C virus (HCV) has been shown to be responsible for a chronic infection in up to 80% of infected people, with a possible evolution to major complications including cirrhosis and primary hepatocellular carcinoma. It has been evaluated that hepatitis C was involved in 27% of cirrhosis and 25% of hepatocellular carcinoma worldwide^[3]. According to the geographic area, 10% to 90% of liver transplants are due to complicated chronic hepatitis C^[4].

HCV is an RNA mono-stranded enveloped virus belonging to the *Flavivirus* family. Eleven genotypes are currently recognized with many subtypes within a same genotype. The infidelity of the HCV RNA-dependent RNA polymerase is mainly responsible for the huge variability of the viral genome, leading to the constitution of a quasi-species in chronically infected subjects.

This variability together with a poor understanding of the pathophysiology of chronic HCV infection explains the present inability at developing an effective prophylactic vaccine^[5]. However, different therapeutic strategies have been elaborated since 20 years for curing HCV infection with the hope of eradicating definitively the infection when the treatment is initiated before the installation of severe liver lesions. Actually, the more recent antiviral drugs have been shown to be able to cure HCV infection in almost all the patients, even in case of infection with strains of genotype 1, the more resistant ones to conventional interferon-ribavirin treatment (for a review, see^[6]). Besides a few side effects, the major difficulty with these new treatments remains their high cost, which prevents implementation to a large number of infected patients, notably in resource-limited areas.

From an epidemiological point of view, medical care exposing to HCV-infected blood may represent an opportunity for acquiring HCV infection. The aim of this review is to summarize the conditions that could lead to the transmission of HCV in various medical settings. After a few considerations on the place of care-associated hepatitis C in the global epidemiology of HCV, three situations will be considered: (1) transmission of HCV from infected patients to non-infected patients; (2) transmission of HCV from infected patients to health care workers (HCWs); and (3) transmission of HCV from infected HCWs to non-infected patients. Keeping in mind

the *primum non nocere* principle that must drive the medical practice, the last part of the review will discuss a few research directions that need to be explored in order to reduce the risk of HCV transmission in care settings.

PLACE OF CARE-ASSOCIATED HEPATITIS C IN THE GLOBAL EPIDEMIOLOGY OF HCV

The prevention of HCV infection is mediated for a large part by an excellent knowledge of HCV epidemiology. HCV is a model of blood-borne transmitted agent. Although present in various biological fluids, its transmission is mainly mediated by blood and by other fluids contaminated with blood. By opposition to hepatitis B virus (HBV) or human immunodeficiency virus (HIV), for which mucosal exposition plays a major role, HCV is usually transmitted *via* blood in which viral load may be very high. This observation explains the impressive historical epidemic of HCV infections that occurred *via* blood products in transfused patients when no specific screening test was available for identifying infected donors. It also makes understandable why intravenous drug users (IDU) are presently the main target population for HCV infection in many parts of the world. By contrast, sexual intercourse is not an efficient way for transmitting HCV, except in subjects with very high-risk sexual practices^[7,8]. In addition to drug injection or nasal sniffing, all the situations exposing to contaminated blood may lead to HCV infection, including tattooing^[9], piercing^[10], use of razors^[11] and manicure devices^[12].

Historically, medical cares have played an important role in the transmission of HCV infection. In addition to the transfusion of blood products, a number of situations involving medical cares, which are summarized in Figure 1, have been implicated in the dissemination of HCV. The medical cares may occur within hospitals or clinics (*i.e.*, hemodialysis units, surgery departments, transplantation wards...), in dispensaries or physician's office, or at patient's home (*i.e.*, *via* the use of contaminated syringes or needles). In addition to patients, HCWs may be involved either as victims (notably in case of accidental exposition to blood from infected patients) or, more rarely, as the source of infection when they are already infected by HCV (Figure 1). All these situations will be reviewed briefly in the next paragraphs.

Interestingly, the place of medical cares in the global epidemiology of hepatitis C varies greatly according to the geographical localization. Table 1, which was built mainly on the data recorded in two recent epidemiological review papers^[13,14], illustrates the different at-risk situations that were involved in the occurrence of hepatitis C in selected countries exhibiting a prevalence rate of HCV infection ranging from 14.9% (Egypt) to 0.4% (Germany) of the whole population. As previously reported^[16], three epidemiological patterns can be identified according to the age of infected patients: (1) highest peak of preva-

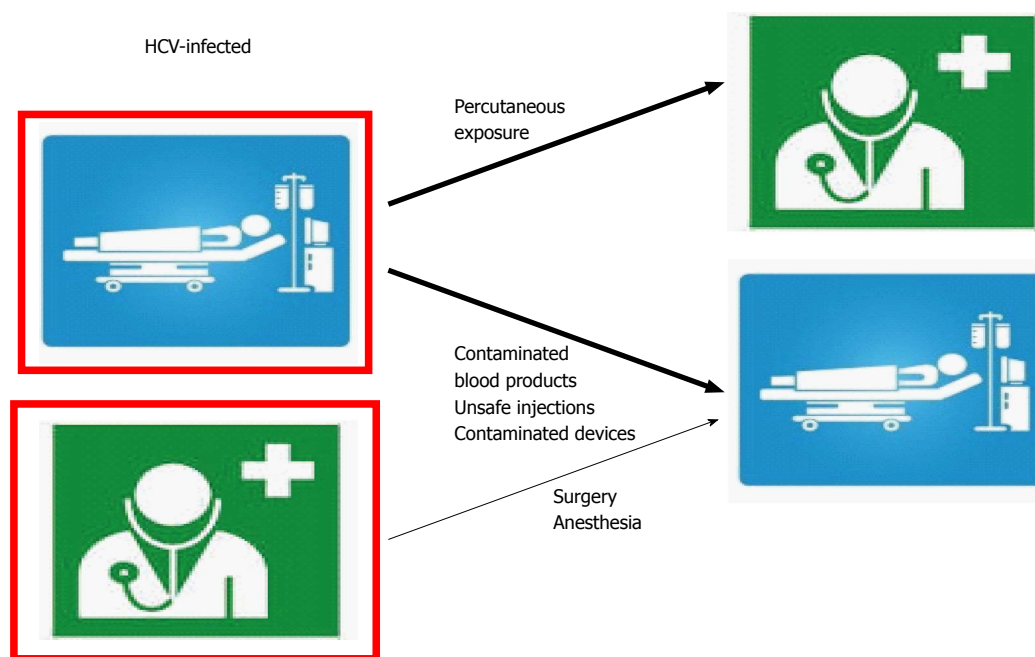


Figure 1 Schematic representation of the different modes of hepatitis C virus transmission in health care settings. The size of the arrows is proportional to the importance of the risk. A red border symbolizes hepatitis C virus (HCV) infection.

lence in middle-aged people (30-49 years) as observed in United States, Australia and several countries of Western Europe; (2) highest peak of prevalence in older adults as observed in Italy or Japan; and (3) high prevalence of infection in all age groups as observed in Egypt. Most of the care-associated HCV infections are linked to the two latter patterns whereas the first pattern is mostly related to IDU practices.

Two clinical features of HCV infection are responsible for the difficulty at establishing a precise relationship between hepatitis C and a definite mode of contamination. The first one is related to the fact that acute HCV infection is asymptomatic in a large majority of subjects. The second one is the long time - usually several decades - that separates the beginning of chronic infection (which represents 70% to 80% of HCV infections) from the occurrence of symptomatic hepatitis. These two clinical features explain why the discovery of HCV seropositive status occurs usually at the occasion of a systematic screening or at the stage of clinical complications, and why it may be very difficult to identify precisely the risk factor that was responsible for the initial contamination. Most of the risk factors identified in Table 1 have been assessed on large epidemiological studies comparing infected and non-infected subjects after multivariate analyses. When the identification of HCV seropositivity is not too old, notably in the case of care-associated outbreaks of small size, the use of molecular tools for demonstrating the genomic proximity between different HCV strains is very useful (reviewed in^[17]).

TRANSMISSION FROM INFECTED PATIENTS TO NON-INFECTED PATIENTS

Administration of blood products

As shown in Table 1, the administration of blood products, mainly labile but also stable ones, appears as a major risk factor for acquiring HCV infection in many parts of the world. In developed countries, this assessment is true for past infections contracted before the nineties when no specific test was available for screening the status of donors towards this agent. With the systematic implementation of HCV serology in blood donors in a great number of world areas together with the detection of HCV RNA by nucleic acid testing in several wealthy countries, the risk of acquiring HCV *via* blood products decreased dramatically. When both measures are associated, this risk becomes negligible, close to 0.1 per million of blood supplies^[18]. In resource-limited countries, the situation is more alarming: according to the WHO database on blood safety^[19], 39 countries performed no routine screening of HCV in blood products in 2012 and 47% of donations were tested in settings without quality insurance. These figures show clearly that the eradication of HCV transmission by blood supplies depends mainly on the quality of the screening of both donors and products, which is still out of range for several developing countries due to financial constraints.

Transmission of HCV in hemodialysis units

The prevalence of HCV infection is historically high in

Table 1 Distribution of main risk factors and hepatitis C virus genotypes in different countries worldwide (inspired from^[13-15])

Country	Prevalence rate of HCV infection	Risk factors (≥ 10%)		Most frequent (≥ 10%) genotype(s) (%)
		Three top (or less)	Level of confidence ¹	
Egypt	14.90%	Parenteral injections with multiuse syringe for schistosomiasis Blood transfusion Needle reuse	High	4 (93)
Italy	5.20%	Parenteral injections with multiuse syringe for popular therapies Blood transfusion IDU	Intermediate	1 (62) 2 (27)
Pakistan	4.70%	Syringe/needle reuse Surgery/dental work Blood transfusion	High	3 (68) 1 (12)
Taiwan	4.40%	Medical injection Blood transfusion Acupuncture	High	1 (48) 2 (40)
Romania	3.50%	Dental work Surgery Blood transfusion	Intermediate	1 (99)
Thailand	2.80%	IDU Tattooing Blood transfusion	Intermediate	3 (53) 1 (33)
Spain	2.64%	Surgery/dental work Syringe reuse IDU	Intermediate	1 (65) 3 (20)
Vietnam	2%-2.9%	Blood transfusion IDU Tattooing	Low	1 (47) 6 (47)
Russia	2%-2.5%	Blood transfusion IDU Acupuncture/tattooing	Intermediate	1 (56) 3 (35)
Israel	1.96%	Blood transfusion IDU	Intermediate	1 (70) 3 (20)
Poland	1.90%	Blood transfusion Healthcare-related occupational exposure IDU	Low	1 (58) 3 (31)
Czech Republic	1.5%-2%	IDU Blood transfusion Surgery	Intermediate	1 (79) 3 (20)
Switzerland	1.25%-1.75%	IDU Healthcare-related occupational exposure Blood transfusion	High	1 (51) 3 (30)
Portugal	1.50%	IDU Surgery Sexual contacts	Low	1 (52) 3 (34)
China	1%-1.9%	Syringe/needle reuse Blood transfusion Esophageal balloon	Low	1 (68) 2 (14) 6 (13)
Greece	1%-1.9%	IDU Blood transfusion	Intermediate	1 (47) 3 (27) 4 (15)
India	1%-1.9%	Blood transfusion Syringe/needle reuse Healthcare-related occupational exposure	Intermediate	3 (62) 1 (31)
Japan	1%-1.9%	Blood transfusion Syringe/needle reuse IDU	Intermediate	1 (63) 2 (25)
Saudi Arabia	1%-1.9%	Blood transfusion Parenteral injections with multiuse syringe for schistosomiasis Tattooing	Low	4 (74) 1 (14)
Syria	1%-1.9%	Blood transfusion Hemodialysis Tattooing	Intermediate	4 (59) 1 (29) 5 (10)
Brazil	1.40%	IDU and nasal drugs Syringe/needle reuse Healthcare-related occupational exposure	Not available	1 (65) 3 (30)

Australia	1.30%	IDU	High	3 (31) 1 (14)
South Korea	1.30%	<i>Blood transfusion</i> <i>History of endoscopy</i>	Intermediate	1 (50) 2 (45)
Canada	1.01%	Tattooing IDU <i>Blood transfusion</i>	Intermediate	1 (60) 3 (22) 2 (15)
Scotland	1.00%	IDU <i>Blood transfusion</i> Tattooing	High	1 (47) 3 (47)
Turkey	1.00%	<i>Blood transfusion</i> <i>Surgery</i> <i>Dental work</i>	Low	1 (97)
France	0.84%	IDU and nasal drugs	Intermediate	1 (57) 3 (21)
Norway	0.70%	IDU	High	1 (61) 3 (28) 2 (11)
England/ Wales	0.60%	IDU	High	1 (45) 3 (40)
Hungary	0.60%	<i>Surgery</i> <i>Blood transfusion</i> Tattooing	Low	1 (97)
Sweden	0.59%	IDU	High	1 (45) 3 (34) 2 (19)
Germany	0.40%	IDU <i>Blood transfusion</i>	High	1 (62) 3 (28)

¹The level of confidence of the different risks was appreciated by the size of the sampled population with regard to that of the whole population of the country. Risk factors related to health care are italicized. HCV: Hepatitis C virus; IDU: Intravenous drug users.

patients attending hemodialysis units. In developed countries, a significant decrease was observed in this population during the last decades: from 10.4% in 1995 to 7.8% in 2002 in the United States^[20]; from 13.5%, 42% and 20% in 1991 to 6.8%, 30% and 16% in 2000 in Belgium, France and Italy, respectively^[21]. A meta-analysis of HCV incidence rates in hemodialysis patients showed an overall estimation of 1.47 per 100 patient-years with extremes ranging from 0.00 to 8.05; the country's development level together with initial prevalence were able to explain 68% of the observed heterogeneity^[22].

Although blood transfusions may have contributed to propagate HCV in hemodialysis patients, the discontinuation of this practice did not interrupt the emergence of new cases. The role of nosocomial transmission of HCV has been assessed by molecular analyses that demonstrated the genomic identity of HCV strains within patients of the same unit^[23,24]. Environmental contamination by HCV-positive blood and insufficient adherence to hygienic measures were incriminated in such units where the exposure to blood is omnipresent^[25]. The role of blood is also illustrated by the higher incidence of HCV infections in patients attending hemodialysis units than in those under peritoneal dialysis or hemodialysed at home^[26]. By contrast, neither the use of hemodialysis machines dedicated to HCV infected patients nor isolation of these patients were shown as determinant for preventing new contaminations within the unit^[26].

It is important to note that HCV infection is an independent predictor of mortality in hemodialysis pa-

tients^[26]. This finding stresses the need to reinforce the hygienic measures and to monitor at least annually the markers of HCV infection in this population. For hemodialysis patients already contaminated by HCV, ribavirin is usually contraindicated; however a treatment based on continuous pegylated interferon could be recommended in order to reduce the risk of progression to cirrhosis and hepatocellular carcinoma and of HCV transmission to HCWs or other patients^[27,28].

Unsafe therapeutic injections and reuse of contaminated material

Unsafe therapeutic injections have been one of the most common ways to acquire HCV infection in the past and continue to be responsible for a large amount of nosocomial HCV contamination, both in developed and developing countries.

During the 20th century, unsafe injections using contaminated syringes or needles were responsible for large epidemics that explain the high prevalence of HCV infections in Egypt^[29] (spread of genotype 4 following injections with contaminated glass syringes used in nationwide campaigns for the treatment of schistosomiasis), some regions of India^[30] (injections with contaminated syringes used notably to treat kala-azar) or rural areas of central and southern Italy^[31-33] (parenteral injections of vitamins or nutrients with multi-use syringes) (Table 1). These practices were frequently related to traditional medicine. HCV contamination related to acupuncture^[34-36] proceeds of the same ignorance of the infectious risk attached to

Unsafe injection practices and disease transmission

Reuse of syringes combined with the use of single-dose vials for multiple patients undergoing anesthesia can transmit infectious diseases. The syringe does not have to be used on multiple patients for this to occur.

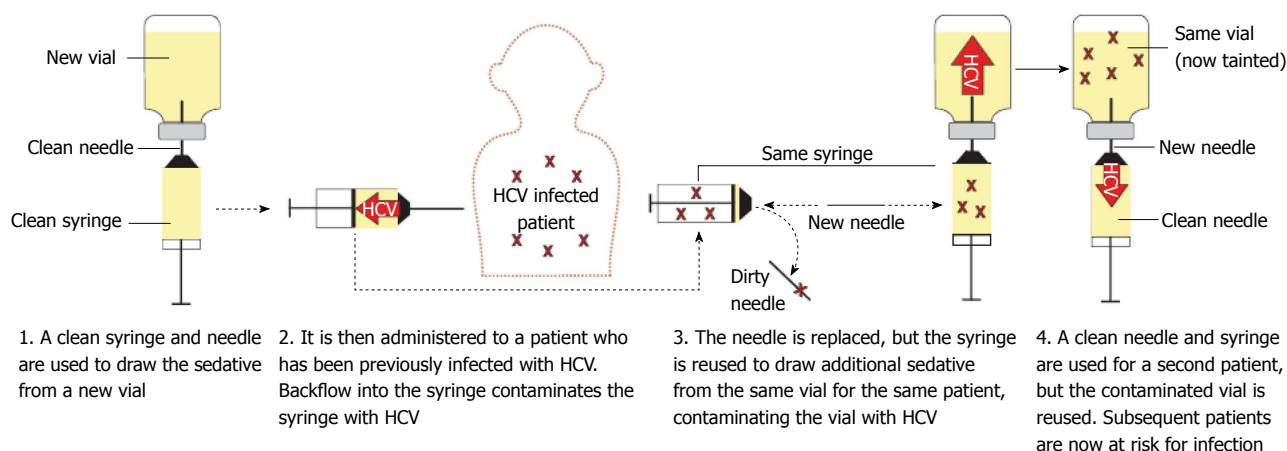


Figure 2 Example of mechanism of hepatitis C virus transmission *via* unsafe injection practices (borrowed from^[44]). HCV: Hepatitis C virus.

blood.

An atypical situation combining different mechanisms of transmission is that described in a very restricted rural area of the center of France where a cluster of more than 130 HCV infections of genotype 5 (a genotype presently limited to South Africa) was detected. Epidemiological and phylogenetic analyses demonstrated that there was a strong statistical link between infection by this rare genotype and living in this rural area^[37,38]. It was hypothesized that the outbreak spread first by the mean of injections, and maybe other treatments, performed before 1972 by a single physician (whose HCV status remains unknown), and then by transfusion to the other parts of the district in the 1970s and 1980s. This observation illustrates the complexity of the epidemiology of care-associated HCV infections.

More recently, similar unsafe practices were identified in nonhospital health care settings from developed countries. Following an outbreak of HCV infections in patients attending an endoscopy clinic in Nevada, United States, in 2007, 8 other clusters of HCV infections were identified retrospectively in different American settings (private physician office, pain remediation clinics, hematology and oncology clinic, nuclear imaging, chelation therapy, alternative medicine clinic, multiple endoscopy and ambulatory clinic, anesthesiologist office, hemodialysis centers)^[59]. Between 1998 and 2008, a total of 275 patients were found infected by unsafe injection practices involving reuse of syringes, medication vials (notably anesthetics) or saline bags^[40]. Similar outbreaks were reported in France^[41,42]. Another recent case report involving unsafe injection practices concerned a patient contaminated by HCV during myocardial perfusion imaging^[43]. One of the mechanisms by which HCV can be transmitted *via* single-dose vials used for multiple patients

is described in details in Figure 2. Due to the absence of symptoms in the vast majority of HCV infections, it can be assessed that these detected outbreaks must be the tip of a much larger problem, especially in areas exhibiting a high prevalence of HCV infection.

Other situations

Anecdotal reports of HCV infection were documented in patients having experienced contaminated devices including multi-use finger-sticks for self-monitoring of capillary blood glucose^[45,46], intravenous administration devices^[47] and transrectal prostate biopsy using an echography probe^[48]. Failure in hygienic measures was the probable cause of these transmissions. In other situations involving gynecological procedures^[49,50], pharmacologic studies^[51,52] and administration of oncologic treatments^[53-56], the mechanism of contamination remained unsolved. It was postulated that virus aerosolization might have been responsible for HCV transmission in some of these cases, although the use of contaminated multidose vials could not be ruled out.

Endoscopic practices were frequently suspected to transmit blood-borne pathogens and notably HCV, especially since the description of two HCV contaminations having occurred after retrograde cholangiography^[57] and colonoscopy associated to an intestinal biopsy^[58] in French settings. Other acute HCV infections were reported in American endoscopy clinics^[59,59]. However, except these few cases, the risk of transmitting HCV *via* digestive endoscopy is very low, estimated to less than 1 case per million of endoscopy acts, considering the very high number of endoscopic investigations performed annually worldwide^[60]. Moreover, when some cases were examined retrospectively, unsafe injections during the anesthetic process appeared as the more probable way of

virus transmission^[61].

Dental cares were also suspected to favor the transmission of HCV, notably *via* saliva that was shown to contain small amounts of HCV genome. However, to date, no HCV infection was reported in dentistry settings^[62,63].

Finally, transplantation of organ or tissue from an infected donor may result in an HCV infection in the recipient. Because systematic HCV serology testing is performed in donors, this event is very improbable. However, the situation occurred in 2000 in Oregon, United States: a donor who was seronegative for HCV was sampled during the “window period” of his HCV infection (the patient was tested retrospectively positive for HCV RNA), which led to the contamination of 8 recipients (3 organ and 5 tissue recipients)^[64]. To prevent this rare event, some regulatory authorities, notably in France, require a systematic HCV RNA testing in organ/tissue donors.

TRANSMISSION FROM INFECTED PATIENTS TO HEALTH CARE WORKERS

Due to the high prevalence of HCV persistent infection in hospitalized patients (much higher than in the general population), the probability of HCWs to be exposed to HCV-positive blood is elevated.

As a whole, the prevalence of HCV infection in HCWs is not significantly different from that of the general population; however, the prevalence criterion is not a good one since it does not take into account the frequency of exposition that varies greatly according to the type of care that are provided. Longitudinal studies of exposed HCWs are more prone to define the risk of being infected. In a meta-analysis from 26 longitudinal studies performed between 1991 and 2002, Henderson recorded a total of 2357 exposures for 44 HCV infections, which resulted in a percentage of contamination of 1.9^[10]. This author concludes: “a reasonable estimate... is that between 1% and 2% of those who are exposed develop markers of infection. This estimate places the occupational HCV risk directly between the risks for occupational HBV and HIV infections, approximately 10-fold less than the HBV risk, and approximately 10-fold higher than the HIV risk.” (Henderson). It was recently signified that some primary HCV infections acquired through percutaneous exposure are characterized by a shortened duration of incubation (9 d to 2 wk instead of 2 mo in average)^[65].

From an epidemiological point of view, the more at-risk situation is the exposition to a needle-stick injury containing blood from an infected patient, although mucosal exposure to a splash of blood resulted in HCV contamination in at least two instances^[66,67]. Anecdotal cases of contamination of HCWs by a punch^[68] or after human bite^[69,70] were also reported. Concerning needle-stick injuries, the following factors were associated to a higher risk of HCV infection (reviewed in^[71]): needle stick with a hollow-bore, deep puncture with injection

of a large volume of contaminated blood, elevated viral load in the source patient, surgery and obstetric acts, use of suture needles (especially when they are manipulated without visibility within the operating theatre), surgeries longer than 6 h, and surgical field crowded by many personnel. Among HCWs, nurses and physicians are the most exposed. Almost two-thirds of reported exposures occur with devices having no safety features; in a large proportion of incidents involving safety devices, the safety feature is not activated or the injury occurs before the safety component is activated^[71].

In sum, most if not all exposures to needle-stick injury could be preventable at the condition that safety procedures are correctly respected and adequate safety materials are used. The observance of Standard Precautions by HCWs is particularly important for preventing HCV infection because no preventive vaccine is available for this agent.

TRANSMISSION FROM INFECTED HEALTH CARE WORKERS TO NON-INFECTED PATIENTS

The first cases of transmission of HCV from infected HCWs to non-infected patients were recognized as soon as 1991. After the generalization of hepatitis B vaccination in HCWs^[72,73], HCV has become the more prevalent blood-borne viral agent at risk to be transmitted occupationally by HCWs. Between 1991 and 2005, 20 HCWs were signified to have transmitted HCV to approximately 400 patients (Table 2). The subject has been reviewed several times during the past 10 years^[10,96-99]. Schematically, two kinds of situations may be identified from the cases reported in Table 2. The first group of HCV transmission occurred from surgeons performing exposure-prone procedures (EPPs), with a majority of cardiothoracic specialists and gynecologist-obstetricians. The second group is represented by anesthesiologists or HCWs attending surgery wards who transmitted HCV following a poor respect of hygienic measures and notably of the non-use of gloves during invasive procedures; a number of these providers were shown to consume illicit drugs, leading to the use of patients' medications for their own use and to the direct contamination of a large number of patients *via* needle sharing (Table 2).

These situations, although relatively infrequent, are of great concern since they pose the question of the permissibility for HCV-infected HCWs to perform EPPs. A classification of the risks attached to invasive procedures has been proposed in 2005^[100]; this paper proposes a list of EPPs that could be subject to some limitations for HCWs chronically-infected by blood-borne pathogens. Despite the diversity of recommendations worldwide, there is a consensus for proposing a systematic testing of medical students at the beginning of their studies, of juniors when they opt for at-risk occupation carrier and of HCWs after each blood occupational exposure^[98].

Table 2 Cases of transmission of hepatitis C virus from health care workers to patients reported in the literature between 1991 and 2005

Year of identification of the index case	Country	Occupation of HCW	Infected patients (n)	Infected (in case of look-back study)	Risk factor(s) identified	Ref.
1991	United States	Technician of an ambulatory surgical center	Approximately 40	NA	IDU	[74]
1992-1994	Spain	Cardiothoracic surgeon	5	2.25%	EPPs (cardiac valve replacement)	[75]
1994	United Kingdom	Cardiothoracic surgeon	1	0.36%	EPPs	[76]
1996	United States	Anesthesiologist	1	0.28%	Probable IDU	[77]
1996	France	Not precised for confidentiality reasons	1	NA	Contaminated by another patient EPPs (coronary artery replacement surgery)	[78]
1998	Germany	Anesthesiologist assistant	5	NA	Contaminated by another patient <i>via</i> an unprotected wound on hand Failure to use standard precautions (notably lack of gloving)	[79]
1998	Spain	Anesthesiologist	217 to 275 over a 10-yr period	NA	IDU	[80,81]
1999	United Kingdom	Gynecologist-obstetrician	8 over a 20-yr period	0.18%	EPPs	[82-84]
1999	United Kingdom	General surgeon	4	0.29%	NA	[84]
1999	United Kingdom	General surgeon	2	0.27%	NA	[85]
2000	Germany	Orthopedic surgeon	1	0.48%	EPPs	[86]
2000	Germany	Gynecologist-obstetrician	1 over a 7-yr period	0.04%	EPPs	[87]
2000	United States	Cardiothoracic surgeon	14 over a 10-yr period	1.49%	Failure to use standard precautions EPPs	[88]
2001	United Kingdom	Gynecologist-obstetrician	1	NA	EPPs	[89]
2001	Germany	Anesthesiologist	3	NA	Failure to use standard precautions (notably lack of gloving)	[90]
2003	Israel	Anesthesiologist	33	NA	IDU	[91]
2004	United States	Nurse anesthetist	15	NA	IDU	[92]
2005	United Kingdom	Gynecologist-obstetrician	1	NA	EPPs	[93]
2005	United Kingdom	Gynecologist-obstetrician	1	NA	EPPs	[93,94]
Not specified	United Kingdom	Anesthesiologist	1	NA	None	[95]

NA: Not available; IDU: Intravenous drug user; EPPs: Exposure-prone procedures; HCW: Health care worker.

French recommendations were recently actualized in that sense^[101]. The use of serological testing is sufficient for achieving that goal^[98]. The management of HCWs exhibiting HCV chronic infection will be debated in the next section.

PREVENTION AND SURVEILLANCE OF CARE-ASSOCIATED HCV INFECTION AND FUTURE RESEARCH DIRECTIONS

Identification of patients with hepatitis C

Hepatitis C is a hidden disease. Most of acute HCV infections are asymptomatic and the chronic phase of hepatitis C is usually asymptomatic too, at least until the occurrence of complications linked to irreversible liver damages. It is important to keep in mind this observation in order to be very large with indications of HCV serology both in patients who can have been exposed to contaminating cares and in HCWs performing EPPs. The occurrence of a symptomatic acute hepatitis C is helpful for recognizing rapidly the contaminating episode and identifying retrospectively other patients exposed to the same risk but having developed an asymptomatic primary infection.

It is not recommended to screen systematically the patients that are submitted to at-risk cares with the aim of grouping all the HCV-infected patients at the end of the care episode; this strategy is not cost-effective and could contribute to reduce the vigilance of HCWs when non at-risk patients are cured. In addition, the HCV-negative patients can be at the phase of silent window during HCV primary infection or harbor other infectious agents. The strict respect of Standard Precautions is sufficient for preventing the transmission of blood-borne pathogens (see below).

By contrast, the systematic screening of HCWs involved in EPPs is highly encouraged. A serological testing performed annually seems reasonable in the absence of blood-exposure incident^[98].

Strict respect of Standard Precautions

Standard Precautions were first proposed in the 1980s by the Centers for Disease Control and Prevention under the name of universal precautions to combat infection by blood-borne viruses, and notably HIV, in HCWs^[102]. They include a series of measures aimed at preventing the contamination by potential pathogens of patients and HCWs when they are exposed to blood and other biological fluids. They consists in hand hygiene, use of

barrier precautions (gloves, masks, gowns...) and limited manipulation of sharp instruments that must be disposed in adapted containers. Another important aspect of Standard Precautions is the adoption of work practices that were shown to reduce the risk of exposure (“no touch” surgical techniques, limitation of the number of HCWs in the operating theatre and in the emergency wards when at-risk cares are performed, reduction of useless injection practices...)^[103].

The strict adherence to Standard Precautions is necessary and sufficient to avoid all the blood-borne infections, including hepatitis C, in patients and HCWs. Convincing HCWs of this evidence is a major goal of hygiene education: considerable efforts must be dedicated to the achievement of this objective in both initial and continuous training. Audits need to be conducted regularly for checking that all the providers correctly apply Standard Precautions.

Methods of disinfection and sterilization

Erasing HCV from hospital environment is essential for preventing its spread to patients^[25]. As an enveloped virus, HCV is fragile outside the human body and sensitive to most of the antiseptics and disinfectants, including hydro-alcoholic solutions used for hand disinfection. However, in plasma, it can survive drying and environmental exposure to room temperature for at least 16 h^[104]; it is why hypochlorite solution should be used as surface disinfectant for blood contaminated spills. Peracetic acid recommended for the disinfection of reusable not sterilisable medical devices such as endoscopes is highly active on HCV. The virus is inactivated by pasteurization (60 °C, 10 min) and steam sterilization.

Safe injection practices

The knowledge of safe injection practices is another essential aim of training programs. They include notably the use of sterile, single-use, disposable needles and syringes for each injection and the use of single-dose vials conditioned under adapted volume for a single patient (if multiple-dose vials are used, they must be used for a single patient) (see^[88] for a complete list of the current recommendations). The strict adherence to these recommendations would have been able to prevent most of the patient-to-patient transmission of HCV listed earlier in this review, both inside and outside the hospital, including in hemodialysis units and in endoscopy settings.

In order to protect HCWs performing injections or blood sampling from sharp injury, the use of engineered safety devices is also strongly recommended. Two kinds of devices are currently available: some of them need to be activated by the provider after use whereas others are activated automatically (self-retraction of the needle for instance)^[71,103].

Preventive measures specific to blood products, tissue and grafts

The quasi-abolishment of HCV transmission by blood

products has been achieved by the combination of different measures, in the places where they were implemented, including the clinical selection of donors and the systematic screening of donors' blood by specific serological and molecular testing. The same screening must be done for tissue and transplants; for the latter, there is an urgent need for developing individual rapid molecular tests that could be performed in emergency in parallel to serological tests.

Measures to prevent HCV infection in HCW after an exposure

Written protocols must be available in each care setting for the management of occupational exposure to blood and other body fluids. They must include an immediate disinfection of the wound with adequate products, the rapid screening of the source patient (when identified and with his/her authorization) for HIV, HBV and HCV, and a rapid counseling of the victim together with a reporting to the Occupational medicine department. In case of exposure to a patient infected by HCV, no urgent treatment is required but a biological follow-up including HCV-specific tests and alanine aminotransferase activity is indicated for identifying a possible primary infection. The frequency of testing may vary from a protocol to another but the usual recommendations includes day 0, month 1, month 3 and month 6. Because HCV RNA is elevated several weeks prior to HCV antibodies in the window period, molecular testing must be preferred to serology. A recent paper performed in HIV seropositive patients showed that the detection of HCV core antigen was almost as sensitive as and less expensive than RNA testing for the diagnosis of acute HCV infection^[105].

Therapeutic attitude in case of primary HCV infection in patients and HCWs

When a primary HCV infection is documented in a patient or a HCW either serologically or by molecular testing, it must be ascertained by a second testing on a different blood sample in order to prevent a false-positive result or a mistake in the specimen identification. Then, two attitudes may be proposed; either a specific treatment is initiated immediately, consisting usually in pegylated interferon for 12-24 wk, or the treatment is delayed for a few wk in the eventuality of a spontaneous clearance of HCV infection (which occurs in approximately one quarter of the patients). By now, it is difficult to define which the best strategy is: the first one is more prone to cure the infection definitively but the second one avoids a useless treatment and its side effects in a proportion of cases^[10,106]. A recent paper suggested that patients with acute infection without jaundice or belonging to the IL28B CT/TT genotype have less chance to control the infection; these patients would be good candidates to an immediate treatment^[107]. Globally, acute hepatitis C can be cured in more than 95%, whatever the genotype^[106,108,109].

The new antiviral drugs that act directly on HCV (directly active antivirals or DAAs), notably those directed

Table 3 Main preventive measures aimed at blocking the transmission of hepatitis C virus in health care settings according to the situations schematized in Figure 1

	Prevention of patient to patient HCV transmission	Prevention of patient to HCW HCV transmission	Prevention of HCW to patient HCV transmission
Standard Precautions	X	X	X
Work practice controls	X	X	X
Engineered safety devices for injections		X	X
Use of single-use devices for injections	X		
Biological screening of blood products, tissue and grafts	X		
Restriction of activity of infected providers			X
Antiviral treatment of infected providers			X

HCV: Hepatitis C virus; HCW: Health care worker.

against the viral polymerase, have not been investigated yet for the treatment of acute HCV infection^[106]. Their high cost is still prohibitive for competing pegylated interferon. In a near future, at least in developed countries, they will constitute a true alternative to interferon therapy, with better efficacy whatever the genotype, shortened administration and fewer side effects; biotherapies could be needed in order to circumvent the problem of viral resistance^[110].

Management of HCWs infected by HCV

It has been recalled previously that a screening of HCWs for HCV (together with other blood-borne viruses and immunization to HBV) must be done at the beginning of the initial formation. Similarly, those HCWs involved in EPPs must be checked regularly (at least once a year) for HCV status. When such a provider is detected positive (with an active HCV infection), there is no common recommendation in the international community (reviewed in^[99]): some countries as United Kingdom discard the HCW from at-risk procedures whereas others propose no formal attitude. The main difficulty is to combine two antagonistic exigencies: confidentiality for the HCW and protection of his/her patients. The attitude that has been recently adopted in France^[101] consists in referring the HCW to a specialized commission that should appreciate the risk according to the data available in the medical file and offer a tailored counseling to the HCW. If the risk of contaminating patients is judged significant, a suspension of the occupational functions is recommended together with the initiation of a specific antiviral treatment. If this treatment is found able to cure the HCV infection, the provider can reintegrate his/her previous activities. In the opposite case or if the HCW denies the treatment, a reorientation of the HCW's occupations is required. With the availability of new very potent antiviral treatments (DAAs)^[6,111], it is hoped that this dilemma will become easier to solve.

Hope for an HCV preventive vaccine?

More than 25 years after the discovery of HCV, searchers failed to set up an effective preventive vaccine against this agent despite huge efforts to reach this goal (for a recent review see^[5]). Despite the rapid development of DAAs

that are theoretically able to make possible the global eradication of HCV, their very high cost may constitute a strong restraint to the rapid completion of this objective, especially in resource-limited countries. Given this fact, there is still an urgent need for an HCV preventive vaccine, especially in intravenous drug users and HCWs that would be the two main targeted populations for HCV immunization.

However, the obstacles to the development of an HCV vaccine are numerous: (1) the variability of HCV is huge, with multiple types and subtypes together with the rapid emergence of a quasi-species in chronically-infected subjects; (2) the natural HCV infection is not fully protective against a re-exposure to the virus; (3) despite efforts to understand the respective role of neutralizing antibodies against envelop glycoproteins E1 and E2 and specific cytotoxic cellular immunity, there are no clear correlates of protective immunity against HCV; and (4) animal models able to experiment candidate vaccines are limited (Table 3).

Given the ability of HCV to generate a persisting infection, it was not possible to consider traditional approaches relying on attenuated or inactivated whole viruses. Consequently, two main pathways were undertaken with the goal of eliciting either neutralizing antibodies against surface proteins or specific T-cell immunity, by using recombinant vectors having incorporated envelop glycoproteins or non-structural proteins. Few candidate vaccines against HCV are currently in experimentation in phase I / II trials in humans.

Altogether, the development of an effective HCV vaccine is much more difficult than expected and the availability of a pan-genotypic protective vaccine is not expected before many years. The arrival of DAAs that are revolutionizing the current treatment of HCV infection may be an additional challenge to the research for an HCV vaccine, although the two approaches are more rather complementary than competitive.

CONCLUSION

The reservoir of HCV is mainly human and the new antiviral treatments are able to cure HCV chronic infection in 80%-100% of the cases. In this context and despite

the uncertainties related to the development of a HCV vaccine recalled above, it is reasonable to predict that HCV infection could be eradicated in the next decades. To reach this goal, it is important to stop the viral transmission, notably in the field of care-associated infections that are the object of the present review. In the past, many people have been contaminated *via* blood products and unsafe injections because the risk was unknown, the virus was unidentified and the hygienic practices were not well established. Before the era of HIV/AIDS, blood was considered as a safe matrix and blood-borne pathogens were not identified as serious health care problems. In the 1980s, the introduction of the concept of Standard Precautions initiated a new prevention paradigm. However, the way from mind to behavior changes is long and there is still a lot of work to be done for implementing good practices in all the fields of cares, as recently illustrated by the identification of clusters of care-associated HCV infections in one of the most advanced countries of the world in terms of quality of cares^[39,40]. In the light of these considerations, it is important to intensify the efforts of information and training towards the HCWs regarding the risks attached to blood and blood-borne infections. Technical problems are almost under control with the availability of single-use materials and engineered safety devices; virological tools are performing for the identification and follow-up of acute and chronic HCV infections and antiviral treatments are more and more potent for curing definitely and rapidly infected people. Despite the absence of a prophylactic vaccine, most of the conditions are met for controlling the HCV risk in health care settings. With the conviction that where there is will there is a way, this goal can and must be achieved in the next years.

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