Transmission routes of HCV infection in dialysis

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Abstract. Nosocomial transmission of hepatitis C virus (HCV) to haemodialysed patients, strongly suspected in epidemiological studies, has recently been unequivocally demonstrated by molecular virology reports. Potential transmission mechanisms include staff hands, dialysis monitors, and equipment items shared between patients. The respective involvement of each of these vectors in HCV transmission has not been determined. There is no conclusive data on the reality of HCV transmission by dialyser re-use. Prevention of HCV transmission relies on the use of erythropoietin, blood donor screening for anti-HCV antibodies and the application of 'Universal Precautions' (Atlanta CDC). In contrast, isolation of anti-HCV-positive dialysed patients does not appear to be warranted by prospective studies, as it might increase the risk of co-infection by different HCV strains, would entail additional costs and be at best partially effective. Recent data have shown that HCV transmission may be prevented by the observance of the 'Universal Precautions' without having to isolate HCV+ patients.

Risk factors of HCV seropositivity in dialysed patients

Analysing the risk factors of seropositivity for hepatitis C virus (HCV) revealed that several HCV transmission routes were to be suspected in dialysis, as soon as the first serological tests were made available.

The first and most obvious one was blood transfusion: many retrospective cross-sectional studies have reported increasing HCV antibody prevalence in proportion with the number of transfusions and/or a greater proportion of anti-HCV antibody carriers (HCV+) in dialysed patients who had been transfused at least once, relative to those who never had been transfused [1]. Nevertheless, several authors noted a high prevalence (up to 39%) of anti-HCV antibodies in haemodialysed patients who had never been transfused [2-4]. Also, in some studies the duration of haemodialysis appeared as a more potent risk factor than the number of transfusions [5]. These observations led to suspect nosocomial transmission, i.e. induced by hospital environment, of HCV through dialysis, especially because the prevalence of anti-HCV antibodies appeared to be greater in haemodialysed patients than in patients receiving peritoneal dialysis, and higher in institution-patients haemodialysed in collective units than in those haemodialysed at home [5].

Intravenous drug abuse also participates in HCV transmission, in the general population [6] and in dialysed patients alike [7,8]. This transmission route however is negligible or inexistent in dialysis units in Europe [9], contrary to the major cities of the US.

Nosocomial transmission?

The suspicion of nosocomial transmission was bolstered by several cases. In a longitudinal prospective study, we were able to demonstrate that three of the eight haemodialysed patients who exhibited confirmed seroconversion for HCV had not been transfused [9]. It was also striking, in that multicentre study conducted in 15 dialysis units including 13 that treated HCV+ patients, that the eight cases of seroconversion for HCV were observed in only three of those 13 units (3, 4 and 1 cases, respectively). In one of these three units, where the localization of patients in the dialysis rooms did not change throughout the study, we had also noted that patients immediately next to HCV+ patients were more at risk of seroconversion for HCV [9]. More recently, Simon et al. have reported four seroconversions in 2 months in four patients successively dialysed on the same haemodialysis monitor [10]. These arguments, always indirect, strongly bolster nonetheless the suspicion of nosocomial transmission.

Nosocomial transmission!

In the last 12 months, three studies have demonstrated the existence of nosocomial HCV transmission within haemodialysis units. Allander et al. [11] sequenced the hypervariable region E2 of the HCV strain genome of 14 patients, three of whom simultaneously exhibited HCV seroconversion. The region sequenced was the same in the three patients recently seroconverted, and almost identical (>98% homology) in two other patients, all patients being dialysed in the same room. This (near-) identity of sequence in five haemodialysed patients, while homology was far lower (<80%) with
HCV strains from other patients from the same country, either haemodialysed or not (control group), strongly suggests that these five patients had been contaminated by the same HCV strain.

Sampietro et al. [12] studied electrophoretic migration (SSCP) of fragments from the 5' non-coding region of HCV genotypes in 28 haemodialysed patients from the same unit and 25 non-dialysed controls from the same region. The electrophoretic profile of the dialysed patients' strains was rather homogeneous: there were six distinct profiles, including the three most frequent, in a total of 85% of patients, whereas none of the 16 profiles observed in controls interested more than 12% of them. The sequencing of strains from some patients in both groups confirmed that these differences in SSCP profile clearly reflect the sequence differences of HCV RNA. There again, the homogeneity of HCV genomic sequence in the haemodialysed group was clearly consistent with nosocomial transmission within that population.

Stuyver et al. [13] sequenced the Core genomic region of strains from 12 haemodialysed patients from a unit where a HCV seroconversion epidemic had taken place. Nine of these patients were infected by the same strain (genotype 1b, a subtype yet unknown characterized by two point mutations). This proves nosocomial transmission.

It is worth reminding that HCV nosocomial transmission is not specific to haemodialysis units. Allander et al. uncovered a 30-case epidemic in a haematology oncology unit [14].

Mechanisms of nosocomial transmission?

These are yet to be elucidated. Three main mechanisms are suspected: the first one is hand-borne transmission of HCV from a seropositive to a HCV-negative patient being dialysed at the same time in the same room, mainly by nursing personnel. This obviously implies that the so-called universal hygiene precautions were not rigorously observed.

A second mechanism that can be envisaged could involve contamination by the dialytic generator or monitor: e.g. from a patient dialysed in the afternoon on a monitor used that same morning on a HCV+ patient, without adequate sterilization of the equipment between the two sessions. If the monitor is incriminated, it means that the HCV can under certain circumstances pass through some types of haemodialysis membranes into the dialysate system and 'remain' there until the next session. In theory, the estimated HCV diameter (35 nm) precludes its passing through HD membranes, even the most permeable ones, whose pores are smaller than 7 nm [5]. It is however conceivable that damage to HD membrane may incidently allow passage to HCV. Data in that respect are conflicting: some but not all studies detected the HCV genome by PCR in the ultrafiltrate and/or the dialysate of a haemodialysed patient whose serum is HCV+ by PCR [15,16].

A third mechanism could involve the use of multidose vials or other items 'shared' by several patients. This mechanism has already been incriminated in hepatitis B transmission in dialysis and also appears to have contributed to nosocomial transmission of HCV in an Italian unit [17].

It is also theoretically conceivable that dialysate re-use contributes to HCV transmission. This hypothesis however has not been confirmed by currently available data [9]. The Atlanta Center of Disease Control (CDC) authorizes re-use in HCV+ patients [18].

What prevention for HCV nosocomial transmission?

Two already widely applied measures permit minimizing the risk of transfusional transmission: erythropoietin treatment which has reduced the transfusional requirements of chronic haemodialysed patients considerably, and HCV screening in blood donors.

The necessity to isolate HCV+ haemodialysed patients in a separate unit is much more controversial. It was recommended by several teams [2-4] in view of the success of that strategy in the prevention of virus B transmission in haemodialysis centres [19].

This recommendation to isolate HCV+ patients, applied in 1993 by 18% of European haemodialysis units [20] poses nonetheless several problems of implementation, effectiveness and security.

In all centres that are still treating virus B carriers, isolation of haemodialysed patients according to their HCV serology could require 4 dialysis rooms (B+C+, B+C-, B−C+, B−C−), incurring a significant over cost [21].

The effectiveness of isolation in preventing HCV transmission by dialysis can be put up to question. Indeed, if for the virus B, monthly screening for HBs antigen permits, after contamination, to rapidly isolate infected patients, the current HCV detection tests based on antibody screening only become positive after a few weeks to several months following infection [6]. This serologically silent window obviously reduces the effectiveness of isolation measures. This could be resolved by monthly detecting HCV RNA by PCR in all haemodialysed patients: this does not seem realistic today because of the cost and technical difficulty of the test.

Lastly, the security of HCV+ patients' isolation is perhaps less obvious than it seems. Effectively, conversely to the cross immunity between strains, which is the rule for virus B, acquired immunity against a HCV strain appears to offer little or no protection at all against infection by another strain. It is therefore conceivable that grouping HCV+ patients may expose them to an increased risk of infection by multiple HCV strains [20]. The clinical consequences of infection by several HCV strains remain to be assessed.

On the other hand, it has been demonstrated that the seroconversion rate for HCV can be kept very low without isolating HCV+ patients. In our study, the
séroconversion incidence during the first 18 months was 1.7% per year. During the following 18 months, that incidence was 0.56%/year [20]. Chauveau et al. [22] and Martin et al. [23] very recently have reported seroconversion incidences also below 1%/year over the last few years, in Paris and in the US, respectively.

What alternative to isolation?

In view of the probable mechanisms of HCV nosocomial transmission (see above), it would appear logical to reinforce the so-called universal hygiene precautions in haemodialysis units.

These precautions, recently reminded by the Atlanta CDC [18], include in particular the cleaning and disinfection of instruments, equipment and surrounding surfaces that may be contaminated, no sharing of items between patients, frequent hand washing and systematic use of regularly changed gloves by the caring personnel. These precautions contribute to preventing transmission of all blood-borne pathogens, including HCV. It is worth noting that such a reinforcement of these hygienic measures has made it possible to control epidemic nosocomial transmission of HCV in haemodialysis in Japan [24] and the US alike [25] without resorting to isolation. It is therefore possible that the effectiveness of isolation, asserted by several authors on the basis of reduced HCV seroconversion incidence after isolation, is in fact due to the concomitant reinforcement of hygienic measures and precautions [5].

Lastly, it appears logical that every haemodialysis unit should check the incidence of HCV seroconversion in its patients, annually for instance, and also regularly (e.g. monthly) measure transaminases for an early detection of a possible mini-epidemic of transaminase raise (e.g. monthly) and detection of HCV seroconversion incidence during the first 18 months. Preventing that transmission nosocomial because of enhanced security and fewer HCV transmission by dialysis is currently essentially universal hygienic precautions. [5].

In conclusion, it appears logical that every haemodialysis unit should check the incidence of HCV seroconversion in its patients, annually for instance, and also regularly (e.g. monthly) measure transaminases for an early detection of a possible mini-epidemic of transaminase raise (e.g. monthly) and detection of HCV seroconversion incidence during the first 18 months.

What alternative to isolation?

Preventing the transmission implies strict observance and regular verification of universal hygienic precautions.

References

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