

# Hepatitis C in hemodialysis: the contribution of injection drug use

## Authors

Bruno Galperim<sup>1,2</sup>  
Angelo A Mattos<sup>2</sup>  
Airton T Stein<sup>3</sup>  
Nuttiane C Schneider<sup>1</sup>  
André Buriol<sup>4</sup>  
André Fonseca<sup>4</sup>  
Vagner Lunge<sup>4</sup>  
Nilo Ikuta<sup>4</sup>

<sup>1</sup>Gastroenterology Service, Hospital Mãe de Deus and Hospital Nossa Senhora da Conceição, Porto Alegre, RS, Brazil.

<sup>2</sup>Graduate Program in Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSA), Porto Alegre, RS, Brazil.

<sup>3</sup>Teaching and Research Management, Grupo Hospitalar Conceição, Porto Alegre, RS, Brazil. Department of Collective Health, UFCSA and Universidade Luterana do Brasil (ULBRA), Canoas, RS, Brazil.

<sup>4</sup>Simbios Laboratório, ULBRA, Porto Alegre, RS, Brazil.

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## Correspondence to:

Bruno Galperim  
Rua Costa, 30/303  
Porto Alegre – RS – Brazil  
CEP: 90110-270  
Phone(Fax): +55-51-32302712  
E-mail: galperim@portoweb.com.br

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## ABSTRACT

**Background:** Hepatitis C virus (HCV) infection is the most common cause of acute or chronic hepatitis in patients on hemodialysis (HD). The purpose of this study was to describe the prevalence of positive HCV RNA and investigate injection drug use as an emerging risk factor in patients with chronic renal disease on HD. **Methods:** This was a multicenter cross-sectional study with 325 patients with chronic renal disease on HD in the period between August 1, 2005 to August 30, 2006, receiving care at four institutions in the city of Porto Alegre, Southern Brazil. Epidemiological data were collected by means of a structured questionnaire. The following laboratory tests were performed: alanine aminotransferase (ALT), anti-hepatitis C virus antibodies (anti-HCV), and qualitative polymerase chain reaction (PCR). **Results:** Of 325 patients, 68 had positive HCV RNA results. The comparison between patients with positive and negative PCR results revealed significant differences in duration of HD (mean = 71 *versus* 52.4 months;  $p = 0.02$ ); previous blood transfusion (92% *versus* 72%;  $p < 0.01$ ); injection drug use (13% *versus* 0.7%;  $p < 0.01$ ); anti-HCV positivity at start of HD therapy (60% *versus* 4%;  $p < 0.01$ ); and mean ALT value (39 *versus* 26.5;  $p < 0.01$ ). Logistic regression analysis showed a positive HCV RNA independently associated to being on HD for more than five years [OR: 2.1 (95% CI 1.2 - 3.8)]; previous blood transfusion [OR: 3.7 (95% CI 1.4 - 9.5)]; and injection drug use [OR: 22.6 (95% CI 4.2 - 119.6)]. **Conclusion:** Injection drug use was an independent risk factor for HCV infection among chronic renal disease patients on HD.

**Keywords:** hepatitis C virus, hemodialysis, injection drug use, risk factors.

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## INTRODUCTION

Hepatitis C virus (HCV) infection is the most common cause of acute or chronic hepatitis in patients on hemodialysis (HD). The worldwide prevalence of HCV viral markers among HD patients has been reported to range from 2.6% to 54%.<sup>1-5</sup> However, studies conducted in Brazil have revealed an increased prevalence of HCV viral markers among these patients, with rates ranging from 5.3% to 90.4%.<sup>6-17</sup>

Parenteral exposure is an effective means of HCV transmission in individuals who share needles and syringes, receive blood or blood product transfusions, or have catheters inserted for long-term vascular access, particularly in the hospital setting.<sup>3,18</sup>

Over decades, blood and blood product transfusion, volume transfused and dura-

tion of HD have been considered as the main risk factors for HCV infection in patients undergoing HD for longer than six months.<sup>3,19</sup> However, the risk from these sources seems to have lessened,<sup>20</sup> since blood and blood product transfusion have become safer due to improved donor screening and reduced need for transfusion. In this context, the association between injection drug use and HCV infection, which has already been established in the general population and among drug addicts, arises as a possible risk factor for HCV infection in HD patients.<sup>2,21-34</sup>

The objective of this study was to describe the prevalence of positive HCV RNA and investigate injection drug use as an emerging risk factor in chronic renal disease patients on hemodialysis.

## SUBJECTS AND METHODS

This was multicenter cross-sectional study with 325 patients with chronic renal disease on HD in the period between August 1, 2005 to August 30, 2006, receiving care at four institutions in the city of Porto Alegre, Southern Brazil. To be eligible, they had to be on hemodialysis for longer than six months, aged 18 years or more, agree to participate in the study, and have cognitive capacity to answer a questionnaire.

Using a structured questionnaire, previously trained interviewers, blind to laboratory results, the following information was collected from the patients: age, sex, duration of HD, previous blood and/or blood product transfusions, and injection drug use. Creatinine levels and anti-HCV results at the onset of HD therapy were obtained from the patient records.

All study participants signed an informed consent term. This study was approved by the Research Ethics Committees of all participating institutions.

### Laboratory tests

Blood samples were collected immediately before the HD session. The following tests were performed in all patients: alanine aminotransferase (ALT; dry-chemistry method; Johnson & Johnson); anti-HCV antibodies (anti-HCV, third-generation enhanced chemiluminescence immunoassay; Johnson & Johnson, Amersham, Bucks, UK); and detection of HCV RNA by polymerase chain reaction (PCR; in-house method with 200 IU/mL detection limit).

### Statistical analysis

Descriptive statistics were used for univariate analysis. Stratified analyses were performed, when necessary, to obtain odds ratios (OR) and 95% confidence intervals (95% CI) using the Mantel-Haenszel chi-square test. Variables significantly associated to HCV infection at the univariate analyses were included in the multiple logistic regression analysis. The level of statistical significance was set at  $p < 0.05$ .

## RESULTS

### Patient characteristics

The sample comprised 325 patients (58.2% males) with a mean age of  $54.4 \pm 15$  years (ranging from 22 to 90 years). Mean creatinine level was  $9.6 \pm 3.2$  mg/dL. High ALT levels were observed in 12 (3.7%) patients. There were 107 (32.9%) patients anti-HCV positive and one (0.3%) patient had an undetermined anti-HCV result (negative HCV RNA, with no history of intravenous drug use). HCV RNA was positive in 68 patients (21% of total sample; 63.5% of anti-HCV positive patients). Thirty-one percent of the patients had been on HD for longer than five years, 76% had previously undergone blood or blood product transfusions, and 11 (3.4%) reported using injection drugs.

### Comparison between PCR-positive and PCR-negative patients

Patients who reported use of injection drugs were significantly more likely to have positive HCV RNA results (OR = 19.4; 95%CI 3.7 – 135.9) (Table 1).

**Table 1. Comparison of HCV RNA-positive and negative chronic renal patients on hemodialysis**

Variable n (%)	Positive HCV RNA	Negative HCV RNA	OR (95% CI)	p-value	OR (95% CI) adjusted
No. of patients	68 (21)	257 (79)	-	-	-
Male sex	41 (62)	148 (57)	1.3 (0.7 to 2.4)	0.46	1.2 (0.6 to 2.1)
Age, mean $\pm$ SD	$53.2 \pm 14.2$	$54.6 \pm 14.8$	-	0.30	1 (0.9 to 1)
Time on hemodialysis* (months) mean $\pm$ SD	$71 \pm 65$	$52.4 \pm 54.6$	-	0.02	2.1 (1.2 to 3.8)
Blood transfusion	60 (92)	187 (72)	3.9 (1.5 to 10.5)	< 0.01	3.7 (1.4 to 9.5)
Injection drug use	9 (13)	2 (0.7)	19.4 (3.7 to 135.9)	< 0.01	22.6 (4.2 to 119.6)
Anti-HCV positive at start of hemodialysis	33/55 (60)	10/247 (4)	35.5 (14.5 to 89.6)	< 0.01	-
ALT (U/l), mean $\pm$ SD	$39.8 \pm 18.9$	$26.5 \pm 25.5$	-	< 0.01	-

ALT, alanine aminotransferase; CI, confidence interval; HCV, Hepatitis C virus; OR, odds ratio; PCR, polymerase chain reaction; SD, standard deviation.

\*For adjusted OR, time on hemodialysis > 5 years.

Multiple logistic regression showed that being on HD for more than five years (OR = 2.1; 95% CI 1.2 – 3.8), previous blood transfusion (OR = 3.7; 95% CI 1.4 – 9.5), and history of injection drug use (OR = 22.6; 95% CI 4.2 – 119.6) were independent risk factors for positive HCV RNA result (Table 1).

## DISCUSSION

The prevalence of anti-HCV antibodies varies greatly among patients on HD.<sup>1-15</sup> In this study, 32.9% of the patients were anti-HCV positive, which is close to that described by other authors in studies carried out in the same geographical region,<sup>12,14-17</sup> but higher than the mean prevalence of 15.4% reported in a Brazilian national census.<sup>6</sup> Mean anti-HCV prevalence is below 10% in developed countries,<sup>1,3,35</sup> and the increased prevalence rate observed in our study may reflect the poor-quality care provided to this population.

In the present study, 21% of all patients and 63.5% of the anti-HCV positive patients had positive HCV RNA results. These results are similar to those reported in European studies,<sup>36,37</sup> but lower than those found in the United States.<sup>31,38</sup> In comparison to other Brazilian studies, although our rates are consistent with findings from some studies,<sup>8,12</sup> our results were lower than those reported by several other studies (PCR positivity between 69% and 100% in anti-HCV positive patients).<sup>7,9,10,16,39,40</sup> This may be partially explained by the fact that the PCR technique employed in the present study had a detection limit of 200 IU/mL, which is less sensitive in HD patients, who often present low or variable viral loads.

Sex and age were not independently associated with HCV infection, which is consistent with the existing literature.<sup>39,41,42</sup>

Duration on HD has been described as the main independent risk factor for HCV infection,<sup>2,3,21,35,43-45</sup> and each additional year on HD represents an increase of 10% to 13% in the risk of infection.<sup>5,46</sup> In this study being on HD longer than five years was an independent risk factor for infection, which is in agreement with findings reported in other studies.<sup>8,10,14,37,47-50</sup>

The introduction of erythropoietin and iron supplementation in the management of anemia in patients with chronic renal disease has dramatically reduced the need for blood and blood product transfusions in this population. Similarly, the improvement in donor selection and the introduction of screening tests have reduced the risks of HCV infection associated with transfusion.<sup>2,19,21,51</sup> Therefore, the current risk rates for HCV infection in patients on HD may differ substantially from those reported 10 or 15 years ago.<sup>20</sup>

In this study, previous blood transfusion was an independent risk factor for HCV infection, according to the literature.<sup>48,49</sup> Although some studies found a signifi-

cant association between blood transfusion and HCV in univariate analyses, this association was not sustained in multivariate models.<sup>37,46,47</sup> Likewise, similar findings were reported in Brazilian studies.<sup>8,9,13,14,39,42,50</sup>

Some patients had HCV infection markers before they were started on hemodialysis therapy, which is a potentially undefined risk factor. In this study, 14.2% (76% with positive HCV RNA) of all patients were anti-HCV positive before starting HD therapy, as reported in previous studies.<sup>20,33</sup> Sandhu *et al.*<sup>34</sup> observed that HCV infection was eight times greater for patients with chronic renal disease and risk behavior.

Among the general population, injection drug use is the main risk factor for HCV infection and accounts for 68% of new cases.<sup>21</sup> Some authors have classified injection drug use as an additional risk factor for HCV infection in patients on HD.<sup>2,20,32-34,46,47</sup> In our study, this variable was an independent risk factor for HCV infection, with an adjusted OR of 22.6. This result is in agreement with findings reported by Sandhu *et al.*<sup>34</sup> and Bergman *et al.*<sup>20</sup> who found a non-adjusted OR of 55.3 and an adjusted OR of 6.6, respectively, and by other investigators.<sup>2,10,32,46,47</sup>

Jadoul<sup>35</sup> considers injection drug use as a risk factor, especially in American cohorts, which is supported by data from the Centers for Disease Control and Prevention (CDC).<sup>44</sup> This author also points out that drug use seems to be less important in European samples, as shown in studies conducted in Germany, France, and Belgium, where injection drug use was not a risk factor for HCV infection in patients on HD.<sup>37,49,52</sup> No similar reports analyzing this association in Latin American patients could be retrieved in our literature review.

In the general population,<sup>21</sup> as well as in groups of intranasal cocaine users<sup>53</sup> and alcohol abusers,<sup>54</sup> injection drug use has been shown to be an established risk factor for HCV infection. In our study, this association was clearly demonstrated in patients on HD. One possible limitation worth mentioning is that some patients in this study may not have admitted drug use, which could translate into underestimation.<sup>34</sup>

In summary, injection drug use was an important risk factor for HCV infection in this cohort of chronic renal failure patients on HD.

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