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Short Communication

# Prevalence of hepatitis E virus RNA and antibodies in a cohort of kidney transplant recipients in Central Brazil

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ABSTRACT

*Objective:* To assess the prevalence of hepatitis E virus (HEV) RNA and antibodies among kidney transplant recipients (KTR) in Central Brazil. The presence of chronic HEV infection was also investigated.
*Methods:* A cohort study was conducted among 316 KTR treated at a referral center for kidney transplantation in Goiânia, Brazil. All serum samples were tested for the presence of HEV RNA (real-time PCR) and anti-HEV IgG/IgM (ELISA). Anti-HEV-positive samples were confirmed using an immunoblot test. HEV chronicity was investigated in a subgroup of patients with elevated alanine aminotransferase (ALT >40 IU/l) through HEV RNA detection in additional serum samples collected 3 and 6 months apart.
*Results:* A seroprevalence of 2.5% (95% confidence interval 1.2–5.1%) was found for anti-HEV IgG. There was no difference in characteristics between the anti-HEV IgG seropositive and seronegative KTR groups. Anti-HEV IgM was detected in only one patient (0.3%). All KTR were negative for HEV RNA.
*Conclusions:* These results show that HEV infection is infrequent in KTR in Central Brazil, with low seroprevalence rates of past and recent infection, and also an absence of active and chronic HEV infections.


## Introduction

Hepatitis E virus (HEV) is a cause of acute and chronic hepatitis and cirrhosis in transplant recipients (McPherson et al., 2018). In kidney transplant recipients (KTR), reported rates of past HEV infection (anti-HEV IgG: 3% to 43%) and active HEV infection (HEV RNA: 0% to 10%) have varied widely (Harrison et al., 2013; Naik et al., 2013; Hering et al., 2014; Moal et al., 2015; Scotto et al., 2015). In Brazil, only HEV genotype 3, which is associated with chronic infection, has been reported (Passos et al., 2013). HEV prevalence among KTR has been examined only retrospectively in São Paulo (Hering et al., 2014). Hepatitis E remains poorly understood in these patients because they are not routinely screened for this. The aim of this study was to assess the prevalence of HEV RNA and antibodies among KTR in Central Brazil. The presence of chronic HEV infection was investigated in patients with elevated alanine aminotransferase (ALT).

## Methods

A cohort study was conducted in the Santa Casa de Misericórdia hospital in the city of Goiânia (1.3 million inhabitants), a referral center for kidney transplantation in the state of Goiás, Central Brazil. Of a total of 370 KTR, 342 were on follow-up in 2014 and were invited to take part in the study. Of these, 316 agreed to participate. Informed consent was obtained from each patient before they answered a questionnaire to gather socio-demographic and behavioral characteristics. Clinical and laboratory data were obtained from the medical records. This study was approved by the Ethics Committee of the Santa Casa de Misericórdia (reference number 505.632).

All serum samples were tested for HEV RNA using a real-time PCR (limit of four copies of HEV RNA per reaction) (Jothikumar et al., 2006) and also for anti-HEV IgG and IgM using an ELISA

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(recomWell HEV IgG and recomWell HEV IgM; Mikrogen GmbH, Neuried, Germany). Anti-HEV-positive samples were confirmed using an immunoblot test (recomLine HEV IgG/IgM; Mikrogen GmbH). Additional serum samples from patients with ALT levels >40 IU/l were tested for HEV RNA 3 and 6 months apart.

The prevalence and 95% confidence intervals (95% CI) were calculated. Data were analyzed using IBM SPSS Statistics version 20 (IBM Corp.). Descriptive statistics were reported as the mean ± standard deviation for continuous variables and as the frequency and percentage for dichotomous variables. The Student *t*-test and Fisher's exact test were used to compare continuous variables and dichotomous variables, respectively. A *p*-value of <0.05 was considered statistically significant.

## Results

The characteristics of the KTR included in the study are shown in Table 1. Eight patients (2.5%; 95% CI 1.2–5.1%) were positive for anti-HEV IgG by ELISA and immunoblot. There was no statistically significant difference in characteristics between the anti-HEV IgG seropositive and seronegative KTR groups (Table 2). Anti-HEV IgM was detected in only one patient (0.3%), who was also anti-HEV IgG positive. All serum samples from KTR were negative for HEV RNA. ALT levels remained elevated for at least 3 months in 25 patients (four were infected with hepatitis C virus and another with hepatitis B virus).

## Discussion

The prevalence of anti-HEV IgG found in this study is similar to that shown among blood donors in the same region (4.0%; 95% CI 1.3–10.5%) (Silva et al., 2012), but lower than that observed in KTR in São Paulo, Brazil (14.6%; 95% CI 10.1–20.6%) (Hering et al., 2014). On the other hand, this prevalence is comparable to that obtained in another study among KTR in South America (Córdoba, Argentina: 5.7%; 95% CI 2.3–12.4%) (Pisano et al., 2017). Differences in regional endemicity, risk characteristics, and the performance of diagnostic assays for hepatitis E are the possible reasons for these differences in observed rates.

In this study, only one sample (0.3%) was anti-HEV IgM positive, but negative for HEV RNA. Similarly, a low rate of anti-HEV IgM (0.8%) has been reported elsewhere (Scotto et al., 2015). The absence of viremia can be explained by the short period of HEV RNA detection in serum samples in cases of self-limited infection (McPherson et al., 2018), which seems to be the profile of this study patient. On the other hand, HEV RNA testing is essential to exclude hepatitis E in the immunosuppressed population (McPherson et al., 2018). Furthermore, HEV RNA was detected in 3.1% and 10% of KTR in São Paulo (Hering et al., 2014; Passos et al., 2013). However, in line with other studies (Harrison et al., 2013; Naik et al., 2013), an absence of detectable HEV RNA was found in all serum samples tested in the present study, revealing no case of active or chronic infection in KTR during the study period. These data are also consistent with the finding of a reported lack of evidence of chronic hepatitis E despite the use of tacrolimus (Pisano et al., 2017), an immunosuppressive drug that may influence the course of HEV infection (McPherson et al., 2018).

In conclusion, besides the absence of active and chronic infections, these results revealed that HEV may be responsible for sporadic cases of recent or acute infection among KTR in Central Brazil. This study also showed a low prevalence of past HEV infection, comparable to those reported in other areas considered of low endemicity.

**Table 1**
Characteristics of the kidney transplant recipients included in the study (*N* = 316).

| Characteristic | |
|---|---|
| Age (years), mean ± SD | 46.4 ± 12.3 |
| Male, *n* (%) | 174 (55.1) |
| Previous residence in rural area, *n* (%) | 218 (69.4) |
| Consumption of bush meat, *n* (%) | 265 (77.1) |
| Previous blood transfusion, *n* (%) | 268 (84.8) |
| Hemodialysis before transplantation, *n* (%) | 310 (98.1) |
| Time after transplant (years), mean ± SD | 6.6 ± 4.8 |
| Live donor, *n* (%) | 159 (50.3) |
| Causes of renal failure, *n* (%) | |
| Hypertension | 76 (24.1) |
| Glomerulonephritis | 69 (21.8) |
| Polycystic kidney disease | 24 (7.6) |
| Diabetes | 18 (5.7) |
| Chronic pyelonephritis | 12 (3.8) |
| Others | 23 (7.3) |
| Undetermined | 94 (29.7) |
| Immunosuppression, *n* (%) | |
| Triple regimen (PDN, CI, and MF or AZA) | 278 (88.0) |
| Regimen including tacrolimus | 208 (65.8) |
| ALT >40 IU/l, *n* (%) | 25 (7.9) |

SD, standard deviation; PDN, prednisolone; CI, calcineurin inhibitor (tacrolimus or cyclosporin); MF, mycophenolate; AZA, azathioprine; ALT, alanine aminotransferase.

**Table 2**
Characteristics of kidney transplant recipients based on anti-HEV IgG status (*N* = 316).

| Characteristic | Anti-HEV-positive (*n* = 8) | Anti-HEV-negative (*n* = 308) | *p*-Value |
|---|---|---|---|
| Age (years), mean ± SD | 46.5 ± 11.3 | 46.4 ± 12.3 | 0.979 |
| Sex, *n* (%) | | | 0.734 |
| Male | 5 (62.5) | 169 (54.9) | |
| Female | 3 (37.5) | 139 (45.1) | |
| Previous residence in rural area, *n* (%) | 4 (50) | 214 (69.5) | 0.254 |
| Consumption of bush meat, *n* (%) | 7 (87.5) | 258 (83.8) | 0.777 |
| Previous blood transfusion, *n* (%) | 7 (87.5) | 261 (84.7) | 0.668 |
| Previous HD, *n* (%) | 8 (100) | 302 (98.1) | 0.690 |
| Time after transplant (years), mean ± SD | 8.5 ± 7.5 | 6.5 ± 4.7 | 0.254 |
| Creatinine, mean ± SD | 1.8 ± 0.7 | 1.4 ± 0.6 | 0.088 |
| ALT >40 IU/l, *n* (%) | 2 (25) | 23 (7.5) | 0.092 |
| Triple regimen of immunosuppression[a], *n* (%) | 7 (87.5) | 271 (90.3) | 0.967 |
| Regimen including tacrolimus | 5 (62.5) | 203 (65.9) | 0.441 |

HEV, hepatitis E virus; SD, standard deviation; HD, hemodialysis; ALT, alanine aminotransferase.
[a] Triple regimen of immunosuppression: prednisolone, calcineurin inhibitor (tacrolimus or cyclosporin), and mycophenolate or azathioprine.

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## Conflict of interest

No competing interest declared.

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