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Progression of HCV infection in patients with chronic kidney disease: Reply

To the Editor:

We thank Dr. Cholongitas and colleagues for their comments on our recent review in this Journal on HCV in patients with chronic kidney disease (CKD) and for highlighting findings from other groups who have performed liver biopsies in these patients. As they note we had suggested in a paper several years ago that hemodialysis or perhaps uremia may provide some protective effect against fibrosis development in patients with HCV infection [1]. As cited in our paper, an international group of hepatologists and nephrologists has developed guidelines, under the auspices of the National Kidney Foundation, to guide the management of patients with CKD and HCV infection [2]. Prospective studies with serial liver biopsies are clearly required in this patient population to further define the natural history of HCV infection at various stages of CKD including post renal transplantation particularly as treatment options for HCV expand.

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Hepatitis E virus as an emerging cause of chronic liver disease in organ transplant recipients

To the Editor:

We read with great interest the very complete and up-to-date review by R.H. Purcell and S.U. Emerson on hepatitis E virus (HEV) [1]. It highlights that this virus is the leading or the second leading cause of acute hepatitis in adults in many parts of the developing world, and that an increasing number of sporadic autochthonous acute hepatitis E cases have been recently reported in industrialized countries [1]. Unexpectedly, a new clinical feature has just been described in association with autochthonous hepatitis E virus (HEV) infections in developed countries [2–4]. Indeed, since February 2008, cases of HEV-related chronic hepatitis have been reported in organ transplant recipients by three different teams, including ours. This finding still adds significant interest to hepatitis E, and questions the extent and

clinical presentation and outcome of chronic HEV infections. We describe herein a new case of chronic hepatitis E in an organ transplant recipient, which was associated with very mild elevation of liver biological tests in contrast with previous reports.

A 45-year-old patient who had undergone kidney transplantation in 1991 and in 2004 presented in September 2006 with increased liver biological tests. Gamma-glutamyltransferases (GGT) level had risen from 42 to 170 IU/L between June 2006 and September 2006, concurrently with a fourfold increase in alanine amino transferases (ALT) level, from 6 to 35 IU/L (Fig. 1A). During the following months, GGT levels progressively decreased while ALT level plateaued at a significantly higher level than before September 2006 (Fig. 1A). Hepatitis C virus (HCV) serology and serum HCV RNA (Cobas TaqMan assay, Roche Diagnostics, Meylan, France) were negative. Hepatitis B virus (HBV) serology showed past immunization and HBV DNA (Cobas TaqMan assay) was undetectable in serum. No evidence for auto-immune hepatitis could be found. Ferritinemia and transferrin saturation were normal. Alcohol consumption was lower than 10 g/day. No modification of the patient's therapy could be noted. Diagnosis of hepatitis E virus (HEV) infection was established in March 2007 on the basis of IgG and IgM anti-HEV antibodies positivity (Optical Density Ratio, 5.4 and 4.3, respectively; Adaltis EIAGen kits, Adaltis Italia S.p.A., Casalecchio di Reno, Italy) and HEV RNA detection and sequencing in serum using in-house assays [5]. Retrospective HEV RNA and anti-HEV antibody testings that could be performed on five available sera collected between November 2002 and October 2005 were negative. Liver biopsy performed in August 2007 showed evidence for chronic hepatitis with periportal inflammation, piece-meal necrosis, and fibro-

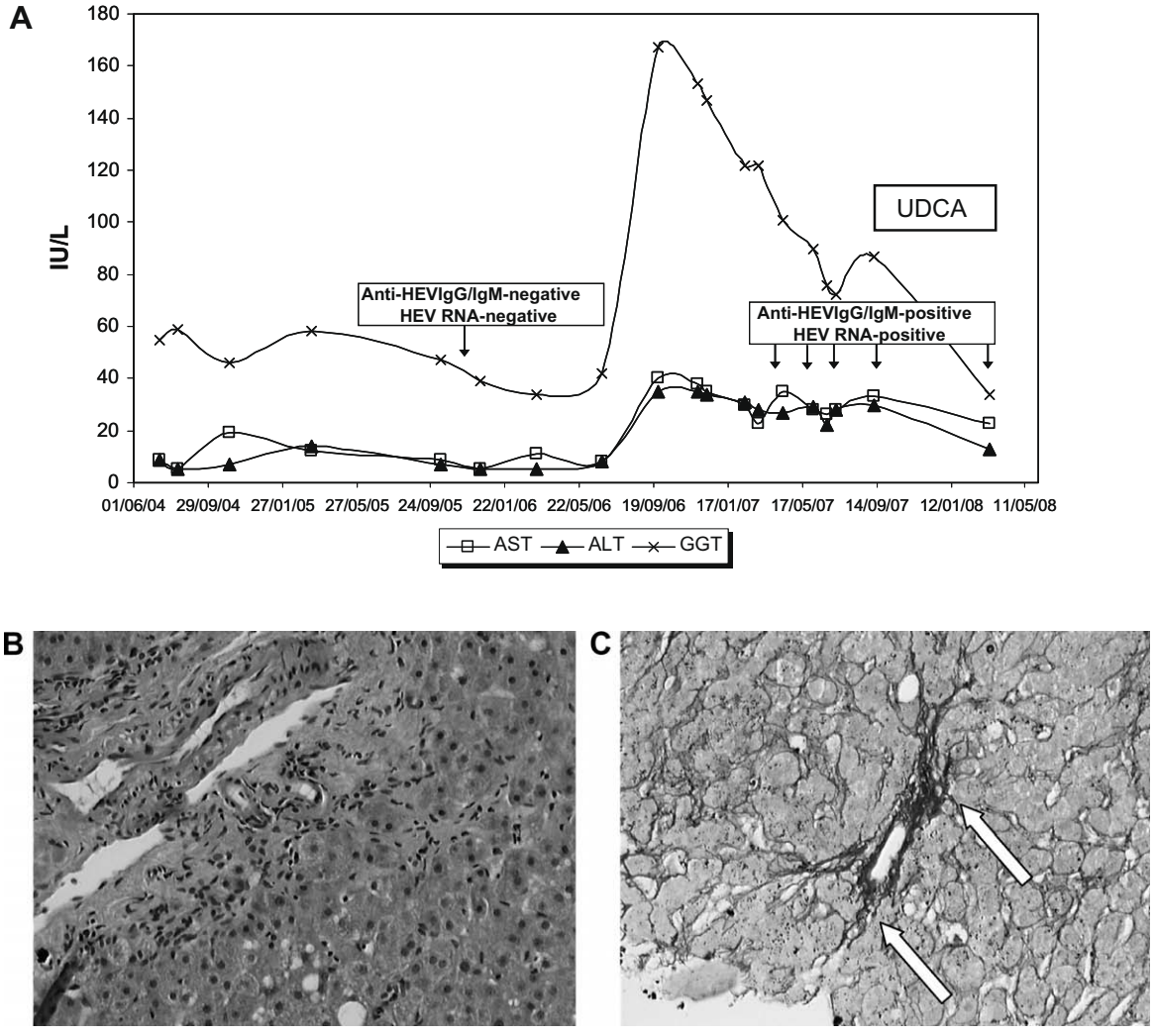

Fig. 1(A) Evolution of liver biological markers (ALT, AST, and GGT) and virological markers in serum. HEV RNA remained at stable titers from March 2007 to March 2008. (B and C). Liver biopsy was performed in August 2007 showing mild mononuclear inflammation with peace-meal necrosis and periportal fibrosis (arrows) ((B) haematoxylin and eosin; (C) Reticulin staining. Original magnification 200×). UDCA, ursodeoxychloic acid. [This figure appears in colour on the web.]

sis (Fig. 1B and C). Ursodeoxycholic acid (UDCA) was introduced in September 2007. Subsequently, liver biological tests slightly improved. However, HEV RNA remained detectable at stable titres in serum from March 2007 until March 2008. The patient did not report any recent travel abroad or contacts with travellers. HEV RNA ORF-2 sequence clustered into genotype 3f, which is found in autochthonous hepatitis E and in swine in Europe [1]. Thus, HEV sequences corresponding to the ten BLAST hits with the highest scores on sequence from the case reported here were from French and Spanish humans or Spanish swine (http://www.ncbi.nlm.nih.gov/BLAST/).

The present observation fulfils the criteria for chronic hepatitis, consisting in elevation of liver biological tests and HEV RNA detection lasting more than 6 months, in association with histological evidence for liver inflammation and fibrosis. Eleven cases of chronic HEV infection have been reported since the review by Purcell and Emerson on hepatitis E was published in a recent issue of the *Journal of Hepatology*. All cases occurred in solid-organ transplant recipients. Transplanted organs were liver, kidney, and kidney/ pancreas in 5, 4, and two cases, respectively. This clearly suggests that the atypical clinical and virological outcome for HEV infection in these cases could be related to the immunosuppressive treatment, which might have resulted in suboptimal anti-HEV specific immune responses and subsequent viral persistence. Such a hypothesis has been evocated by Kamar et al. who found significantly reduced CD2-, CD3-, and CD4-lymphocytes counts in patients in whom chronic disease developed, and it has been recently debated by Schildgen et al. [6] However, the present case distinguishes itself from previously reported chronic hepatitis E. Indeed, the patient did not present clinical signs for acute hepatitis and ALT level never exceeded 1.5-fold the upper normal limit (Fig. 1A). Noteworthy, ALT level returned to normal ranges following UDCA initiation despite stable HEV RNA titers in serum. In contrast, in previously reported chronic hepatitis E, ALT levels were nearly ten-fold the upper normal limit (mean highest ALT level = 276 IU/mL; range, 69–874 IU/mL) [2–4]. Furthermore, HEV-related cirrhosis could be found in five patients, including one in whom cirrhosis occurred as early as one year following infection, and two other cases that necessitated liver transplantation [3,4]. With regards to these severe clinical outcomes, it should be outlined that, in the present case, liver histology showed only mild hepatitis with very early fibrosis. Therefore, although a longer follow-up is mandatory to confirm this issue, the present observation suggests that chronic HEV infection may also result in mild chronic hepatitis with low activity and almost normal biological liver tests.

Altogether, these data deserve further studies to assess the actual incidence, prevalence and outcome of chronic HEV infection in organ transplant recipients and warrants for including HEV testing in diagnosis investigation in transplanted patients presenting with mild chronic elevation of liver biological tests.

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