Case 3: A 63-year-old man with initial AST 68 IU/L and ALT 28 IU/L, alive on day 90.

Globally, aminotransferase levels were only slightly elevated, with mean initial ALT and AST levels of 49 ± 54 IU/L and 112 ± 105 IU/L; this is a point worth noting because previous authors have observed higher ALT levels in patients with HEV infection. Finally, HEV seroprevalence was 33%, with no significant association with demographic or clinical characteristics, including outcome, as shown in Table 1.

All in all, these data indicate that unsuspected acute HEV infection is not a common occurrence in American and European patients with acute or acute-on-chronic liver failure. However, HEV seroprevalence is high, indicating frequent infection, although asymptomatic in most cases. Fortuitous detection of HEV is therefore likely to occur during an episode of ALF or acute-on-chronic liver failure mainly due to another cause, especially in regions with a high seroprevalence such as southwestern France. HEV testing should be performed more systematically, especially in patients with high ALT levels; and further studies including larger numbers of HEV cases will have to be performed in order to determine the real impact of HEV on ALF patients' outcome.

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.28792

Potential conflict of interest: Dr. Paupard is on the speakers' bureau for Gilead, Takeda, and AbbVie and received grants from Pfizer.

REPLY:

The report of Renou et al. adds to our growing understanding of the complex epidemiology of hepatitis E virus (HEV) infection among individuals residing in industrialized countries. HEV is a single-stranded RNA virus that can be spread through contaminated drinking water, blood products, and as a zoonosis from infected animals. Acute HEV genotype 1 or 2 infection is a leading cause of acute hepatitis and jaundice worldwide as well as acute liver failure (ALF) in endemic countries, particularly in pregnant women. In addition, acute HEV has been

implicated in 20%-60% of hospitalized patients presenting with acute-on-chronic liver failure (ACLF) in some developing countries.[1] Sporadic acute HEV genotype 3 infection presumably transmitted from contaminated food or dairy products also accounts for some cases of icteric hepatitis in selected regions of Europe, such as Wales, Southwest France, and Denmark, but is exceedingly rare in most Western countries.[2] In support of this, only 3 of the 681 (0.4%) adult Americans with ALF from our multicenter, prospective study were HEV antibody (anti-HEV) immunoglobulin (Ig) M positive over a 13-year time span, and none of our cases were pregnant nor had detectable HEV RNA.[3] Other studies in the United States have also failed to implicate HEV as a significant cause of acute or chronic hepatitis in human immunodeficiency virus-positive or solid organ transplant patients. Last, the seroprevalence of detectable anti-HEV IgG is declining in the United States and other Western countries for unclear reasons.

Renou et al. now report that only 3 of 181 (1.6%) hospitalized patients with decompensated alcoholic liver disease enrolled in a multicenter French cohort study had a weakly positive anti-HEV IgM, and all of them were HEV RNA negative. In addition, anti-HEV IgG seropositivity (34%) was not associated with the severity of liver disease or clinical outcomes. The findings of Renou et al. are in keeping with a recent report from the HALT-C study group that also failed to implicate unsuspected acute HEV infection as a cause of decompensation in patients with advanced hepatitis C virus fibrosis.[4] Furthermore, investigators from Paris, France, recently reported that only 3 of their 84 (3.5%) hospitalized patients with severe alcoholic hepatitis had evidence of acute HEV infection, but 2 of the 3 anti-HEV IgM-positive patients had detectable HEV genotype 3 by polymerase chain reaction.[5] The difference in results across studies could, in part, relate to the variable sensitivity and specificity of the serological assays used. The Beijing Wantai test is believed to have the best performance characteristics among the available assays, but additional validation studies using a World Health Organization reference sample and carefully constructed test panels are needed.

We congratulate Renou et al. on their important work regarding the potential role of unsuspected HEV infection in hospitalized patients with decompensated alcoholic liver disease. However, additional studies from well-characterized cohorts of Western patients with ACLF are still needed to improve our understanding of the potential routes of transmission, pathogenesis, and clinical outcomes of previously unsuspected autochthonous HEV infection.

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DOI 10.1002/hep.28794

Potential conflict of interest: Dr. Fontana received grants from Bristol-Myers Squibb, Janssen, and Gilead. Dr. Lee consults for Novartis and Sanofi and received grants from Bristol-Myers Squibb, Gilead, Merck, Ocera, and Exalenz.