Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.023.

References

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Huey-Ling Chen[1,2,3]
Yen-Hsuan Ni[1,3]
Pei-Jer Chen[3,4,5]
Mei-Hwei Chang[1,3,*]
[1]*Department of Pediatrics, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan*
[2]*Department and Graduate Institute of Medical Education and Bioethics, College of Medicine, National Taiwan University, Taipei, Taiwan*
[3]*Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan*
[4]*Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan*
[5]*Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
*Corresponding author. Address: Department of Pediatrics, National Taiwan University Hospital, 17F, No. 8, Chung-Shan South Rd, Taipei 100, Taiwan.
E-mail address: changmh@ntu.edu.tw

Reply to: Correspondence relating to the manuscript "Early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B"

To the Editor:

We thank Chen *et al.* and Liu *et al.* for their interest in our article[1] and we also thank the *Journal of Hepatology* for the opportunity to reply to their comments.

First, all mothers of the infants in our study had positive serum HBsAg and HBeAg and a high-level of HBV DNA. These mothers and other family members were always worrying about whether their babies were infected with HBV. Therefore, these infants received relevant tests under their parents' requests, though they did not have apparent clinical symptoms. As professionals in the field of pediatric hepatology in HBV endemic areas, we believe that Dr. Chen and colleagues can profoundly understand the anxieties from these HBsAg-positive mothers.

Second, significant differences in the baseline characteristics existed between the infants in Group I in our study and the infants with non-fulminant hepatitis in the reference paper.[2] For example, among the infants in Group I in our study, HBV genotype C predominated and their mothers were all positive for HBeAg; while in the reference paper, HBV genotype B appeared to be prominent and 11/18 infants were born to HBeAg-negative mothers. According to the results in the reference paper that there was a statistical significance in maternal HBV status between the infants becoming chronic carriers (7/7 with HBeAg-positive mothers) and those recovering from infantile hepatitis B (11/13 with HBeAg-negative mothers), infants in our study seemed to be more likely to develop chronicity. Indeed, no infants in Group II developed spontaneous HBsAg loss before 1 year of age.

Additionally, Chen *et al.* mentioned the 2 HBeAg-negative infants at baseline. Both of them had persistence of HBsAg and a high-level of HBV DNA for more than 6 months.

Third, it is an important question whether infants or younger children with infantile-onset hepatitis B need to be treated. In my opinion, it is worthwhile to report the currently available data and to contemplate their merits. A recent investigation has shown that only 2 in 103 children with chronic hepatitis B (CHB) are eligible for treatment according to the current guidelines, which indicates low therapeutic coverage.[3] In our study, eventually, a total of 17 infants achieved HBsAg seroconversion and 1 developed HBeAg seroconversion in Group I. The seroconversion rate of HBsAg arrived at 94.44% (17/18). In contrast, the spontaneous HBsAg seroconversion rate in the reference paper[2] was 13/20 (65%). Should we choose to treat infantile-onset hepatitis B at an early stage, using safe and effective antivirals to significantly improve the HBsAg seroconversion rate, or choose to leave these infants in long-term follow-up waiting for the uncertain occurrence of spontaneous HBsAg seroconversion, while family members' experience severe anxiety regarding probable worse consequences? I believe every clinician has an answer.

Fourth, regarding the comments from Liu *et al.*, a problem raised by them still puzzles us. In their letter, they cited a paper by Yotsuyanagi *et al.* to indicate that the clearance of HBV in

adulthood can happen between 6 to 12 months from the onset of acute infection; meanwhile, they also stated that CHB was defined as the persistence of HBsAg or HBV DNA positivity for at least 6 months. In this case, whether patients involved in the cited paper were in acute or chronic state puzzles us. Now that the infected patients with persistent HBsAg positivity for more than 6 months from onset should be diagnosed as chronic HBV infection, in spite of HBsAg loss at any time after 6 months, the cases included in our study could be considered as patients with chronic infection because treatment also takes time (clearance of HBsAg takes time). Details can been seen in Table 1 in our manuscript, such as age of diagnosis (not age of onset), age of commencing treatment, and so on. Actually, it may be more complex. Moreover, HBV infection in infants displays unique characteristics. There is no comparability between results from the adult population and outcomes from infants and children. Regarding patient enrollment, it should be noted that infantile-onset hepatitis B is an unusual condition and such cases are not commonly encountered. In our study, patients attending the clinic who satisfied the inclusion criteria were enrolled.

Finally, as stated in our manuscript, further trials with larger cohorts are needed to support our results.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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Pan Zhao[1,2,*]

[1]*The Fifth Medical Center (formerly Beijing 302 Hospital), Chinese PLA General Hospital, Beijing 100039, China*

[2]*The First Affiliated Hospital of Xinxiang Medical University, Weihui, Henan 453100, China*

*Corresponding author. Addresses: The Fifth Medical Center (formerly Beijing 302 Hospital), Chinese PLA General Hospital, No.100 of West Fourth Ring Middle Road, Beijing 100039, China. The First Affiliated Hospital of Xinxiang Medical University, No.88 of Jiankang Road, Weihui, Henan 453100, China; Tel.: +86 10 66933464, fax: +86 10 66933020.

E-mail addresses: doczhaopan@126.com, zhaopan302@sina.com

Burden of hepatitis E infection and associated healthcare resource utilization among hematological malignancy-related hospitalizations: A national perspective in the United States, 2007–2014

To the Editor:

We read the paper recently published by von Felden *et al.* with great interest.[1] The authors have commendably presented multicenter data concerning the burden and impact of HEV infection among patients with hematological malignancies. The findings are important in that the occurrence of HEV infection can alter the course of hematological malignancy, even in patients with stable disease. In addition, the authors also reported that the presence of HEV significantly increases the risk of liver failure and related mortality among these patients. The findings hint towards possible worse prognosis in patients with hematologic malignancies, despite the prevailing notion of HEV infection being a merely benign and self-limiting condition (Table 1).

Keywords: Hepatitis E; Hematologic malignancy; Viral hepatitis; Hospitalizations; Inpatients; Hematologic neoplasms; Non-Hodgkin Lymphoma.

As the study only collected data from European nations and there is lack of reported epidemiologic data on the incidence of HEV infections among the United States (US) inpatient population, we provide additional evidence from the US inpatient cohort. In this retrospective nationwide analysis from January 2007 to December 2014, we queried the National Inpatient Sample (NIS) database which is representative of nationwide US hospitalizations.[2] The NIS comprehends a stratified sample of 20% non-federal US community hospitals and collected data infers findings generalizable to over 95% of the US population when weighted (~35 million annual hospital records). HEV-related hospitalizations were identified using the ICD-9 CM codes 070.43 (HEV infection with hepatic coma) and 070.53 (HEV infection without hepatic coma). Categorical variables and frequencies between the groups were assessed using the Pearson's Chi-square test. A 2-sided p value <0.05 was considered a threshold for statistical significance.