# A Call for Attention and Trials on Hepatitis B e Antigen–Negative, Alanine Aminotransferase–Normal Chronic Hepatitis B Virus Infection

## To the Editor:

We read with interest the article by Degertekin and Lok on the indications for therapy in hepatitis B.[1] We feel obliged to call for more attention and clinical trials on patients who are negative for hepatitis B e antigen (HBeAg) and have normal alanine aminotransferase (ALT) levels, who are not routinely considered as immediate candidates for antiviral therapy by current guidelines.

The question is, compared to which population is their prognosis considered "favorable"? As shown by a community-based prospective study conducted in Taiwan, the relative risk of hepatocellular carcinoma could still reach as high as 9.6 among HBeAg-negative men, compared with men who are negative for hepatitis B surface antigen (HBsAg).[2] It is accepted that HBeAg is indicative of active viral replication, and thus is a surrogate marker for hepatitis B virus (HBV) DNA. However, their correlation depends on how we interpret the statistics. If we look at the absolute proportion in another report by Chen et al.[3] and have the cutoff level lowered to $10^4$ copies/mL as indicated by Yuen et al.,[4] it was 34.9% among HBeAg-negative participants. Increasing evidence has shown that HBV DNA is predictive of long-term consequences of HBV infection, independent of HBeAg status and ALT level.[3-8] In this sense, the prognosis of HBeAg-negative, ALT-normal patients does not seem favorable, at least for those with high levels of HBV DNA, because the prime culprit that leads to morbidity and mortality, the virus, has always been there in abundance. Considering this population was in the majority among HBsAg carriers in the REVEAL-HBV Study[3] and the HBsAg carrier rate among the general population of China is 9.09%,[9] they should not be overlooked as long as they are still at high risk for disease progression.

It seems to be a paradox that largely due to a lack of studies, which is evident by our literature search, that directly provide evidence for or against antiviral therapy in this population, such patients do not routinely get treatment because no guidelines recommend so, which, in turn, results in even less possibility to gather sufficient evidence, whether positive or not. Quite a few practitioners may mistake "no evidence" as "evidence of no" by just telling their patients there is no need to initiate treatment while neglecting to inform them of the possible effect of available medications on prognosis improvement. Don't these patients, particularly those who are highly concerned about their own life and capable of affording treatment cost, deserve the right to have full access to complete information and the ability to decide for themselves whether to receive treatment after weighing possible benefits against the risks? Given the fact that current antivirals have been efficient in suppressing virus replication and their adverse effects are relatively minimal, treatment should never be excluded from consideration even if it is tentative. Chances exist that their response to treatment, i.e., HBV DNA reduction and HBsAg clearance, may be even better.

Therefore, we call for intensive attention and large-scale, randomized controlled trials with long-term follow-up in HBeAg-negative, ALT-normal patients, to investigate the impact of antivirals on surrogate serum biomarkers as well as the risk of advanced liver diseases, and to provide insight into the indications and endpoints of antiviral therapy.

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*Published online in Wiley InterScience (www.interscience.wiley.com).*
*DOI 10.1002/hep.23110*
*Potential conflict of interest: Nothing to report.*

## Reply:

We are in complete agreement with Drs. Zhao and Miao[1] that studies should be conducted to determine if patients with chronic hepatitis B virus (HBV) infection, who are negative for hepatitis B e antigen (HBeAg) and have normal alanine aminotransferase (ALT) will benefit from antiviral therapy. As we pointed out in our article,[2] some HBeAg-negative patients with normal ALT have significant liver disease on liver biopsy and some may develop cirrhosis or hepatocellular carcinoma. The risk is related to the duration and severity of liver injury prior to HBeAg seroconversion and the level of HBV replication after HBeAg seroconversion. Thus, in Figure 3 of our article, we qualified our recommendation to monitor for HBeAg-negative patients with normal ALT only if serum HBV DNA is less than 2000 IU/mL (less than 10,000 copies/mL). Furthermore, we recommended that these patients be monitored every 3 months for the first year so patients with fluctuating HBV DNA and/or ALT levels can be identified and treatment can be initiated if necessary.

Although current treatments for hepatitis B are largely safe, we would like to caution that the long-term safety of these treatments remains to be established. On April 20, 2009 Pharmasset Inc. announced the termination of worldwide phase III clinical trials of clevudine following reports of myopathy.[3] Clevudine was shown to be safe in previous studies, most of which involved short durations (4-24 weeks) of treatment, and had been approved for use in South Korea. Myopathy was not observed until after patients had been exposed to more than 8-12 months of clevudine.[4,5] Adverse events have also been

reported to be associated with other HBV treatments including renal tubular abnormalities and renal impairment in patients receiving adefovir or tenofovir and myopathy and neuropathy in those receiving telbivudine. Although these events are rare, careful balance of the benefits versus risks of treatment is warranted, particularly in patients who have quiescent disease.

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*Published online in Wiley InterScience (www.interscience.wiley.com).*
*DOI 10.1002/hep.23115*
*Potential conflict of interest: Dr. Lok is a consultant for and received grants from Bristol-Myers Squibb, Gilead, Pharmasset, Schering-Plough, and Roche. She also received grants from GlaxoSmithKline and Novartis.*

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# Portal Inflammation as Index of Steatohepatitis in Children with Nonalcoholic Fatty Liver Disease

To the Editor:

We read with great interest the article by Brunt et al.[1] In this study, the authors investigated the relationship between portal chronic inflammation and clinical features in the subjects with nonalcoholic fatty liver disease (NAFLD).

The study was conducted on biopsies and clinical parameters of 728 adults and 205 children who were enrolled in the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network. The major findings indicate that 83% of adult biopsies had mild or more than mild portal chronic inflammation, whereas in children this value reached up to 90%. Interestingly, in both groups, portal chronic inflammation (more than mild) correlates with advanced fibrosis.

In our cohort of pediatric patients, the predominant pattern of steatosis distribution is panacinar or azonal, and only in a few cases the steatosis was located in zone 1 or in zone 3. No Mallory bodies were seen, and the prevalent pattern of fibrosis was portal/periportal. Bridging fibrosis was present in only four cases and cirrhosis was absent.[2] Moreover, the analysis of histological features of about 200 of our pediatric patients, already described in a previous study,[3] demonstrated that a definite steatohepatitis (NASH) was more often associated with moderate and severe steatosis, mild/severe ballooning injury, and mild portal and lobular inflammation.

Brunt and coworkers demonstrated that in pediatric biopsies, "more than mild" compared with "none" was associated with steatosis location (zone 1 accentuation) and the pattern of portal/periportal fibrosis (or more advanced fibrosis). Interestingly, during a recent histopathology re-evaluation of our pediatric patients with NAFLD, we found no association between portal chronic inflammation and histologic severity of the disease. More than one possible explanation could explain this apparent discrepancy. First, our series of children differ on obesity degree, homeostasis model assessment of insulin resistance, and median values of alanine aminotransferase from the NASH Clinical Research Network ones. Second, because just two of our (consecutive) pediatric patients had "none" portal chronic inflammation, we could not trichotomize the outcome in those patients with "none", "mild", and "more than mild" as assessed by the NASH Clinical Research Network study. Third, the U.S. pediatric population is characterized by a quite different ethnic mix compared to our population, which included only Caucasian children. The same is true concerning genetic predisposition, lifestyle, and eating habits, which may be relevant in determining the framework of the complex clinical-histologic associations that characterize NAFLD in children.

In conclusion, although we believe that greater emphasis and importance should be given to the specific definition of grade/location and nature of inflammatory infiltrate, other studies are needed to confirm the importance of correlation between portal chronic inflammation and advanced NASH in specific pure pediatric populations.

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*Published online in Wiley InterScience (www.interscience.wiley.com).*
*DOI 10.1002/hep.23114*
*Potential conflict of interest: Nothing to report.*