

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Researching the Role of Hepatitis E Virus in the Development of Drug-Induced Liver Injury

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**G&H** Could you summarize the current diagnostic approach to drug-induced liver injury?

**TD** Unfortunately, in general, we do not have useful diagnostic biomarkers for drug-induced liver injury (DILI) currently. Thus, the diagnosis, or so-called “causality assessment,” of DILI can be very challenging. In cases of suspected DILI, we consider a number of issues, including the timing of administration of the culprit drug relative to the onset liver injury, known as the latency, as well as the course of the liver injury once the drug is stopped, which is termed the dechallenge. One characteristic of DILI is that most cases will improve when the culprit drug is discontinued. The pattern of the injury, whether it is hepatocellular, cholestatic, or mixed, can also provide useful diagnostic information. Finally, we need to rule out the other causes of liver injury that can mimic DILI, including viral and autoimmune hepatitis, metabolic disease of the liver, alcohol-induced liver injury, hepatic ischemia, and biliary tract disease. In essence, DILI is a diagnosis of exclusion.

In rare cases, the patient may be rechallenged with the drug, sometimes unintentionally; if injury resolves after the drug is stopped and then recurs when the drug is reintroduced, this is considered the gold standard of DILI diagnosis. However, rechallenge can lead to severe liver injury and thus is rarely done intentionally.

**G&H** What is the currently estimated prevalence of DILI in the United States, in comparison to other causes of liver injury?

**TD** Data from the Acute Liver Failure Study Group (ALFSG) suggest that DILI is the most common cause of acute liver failure in the United States, despite the fact that it likely remains underreported. DILI is also the main reason that prescription drugs are restricted or removed from the market. DILI also has the potential to affect the entire population, as nearly all of us are exposed, in one form or another, to medications.

**G&H** What are the drugs that most commonly cause DILI?

**TD** In the United States, data from the multicenter, National Institutes of Health-supported Drug-Induced Liver Injury Network (DILIN) suggest that antibiotics are among the most common causes of DILI. Augmentin, in particular, which is very commonly prescribed for upper respiratory and other infections, seems to be the leading cause of drug-induced jaundice in the United States. Antimycobacterial drugs such as isoniazid (INH) and pyrazinamide (PZA) are also associated with DILI. A variety of other drugs, including anti-epileptic medications and even herbal products, although less commonly implicated, have been associated with DILI. In fact, liver injury has been documented in nearly every class of medication that is administered clinically.

**G&H** What is our current understanding of the incidence and prevalence of hepatitis E infection in the United States?

**TD** Hepatitis E virus (HEV) is a major cause of sporadic hepatitis in many developing countries with tropical or subtropical climates. It has historically been understood to be extremely rare in developed countries, including the United States, where most acute cases have been documented in travelers returning from endemic areas. Recent data from several countries, including Japan, the United Kingdom, and Germany, suggest that indigenous HEV in

industrialized countries is more common than previously recognized. Recent data from the United States suggest that 15–20% of blood donors have HEV immunoglobulin (Ig)G antibodies, suggesting prior infection or at least exposure to HEV.

The source of infection in developed countries is still not clear, but it is thought that at least some of these cases result from exposure to and infection from animals, particularly swine, as an HEV strain that infects swine is similar to one of the serotypes affecting humans. It is thought, based on epidemiologic studies, most recently from Germany, that consumption of undercooked pork and wild boar may be a risk factor, as well as some other exposures to animals. This may also be a source of indigenous HEV infection in the United States.

### **G&H** Can you describe the typical clinical course of HEV infection?

**TD** HEV manifestation has been compared to hepatitis A (HAV) because the clinical course is in many ways similar, although HEV tends to be more severe in certain populations such as pregnant women and immunocompromised patients. Like HAV, HEV infection does not lead to chronic disease, except possibly in immunocompromised patients such as those who have undergone solid organ transplant. Importantly, in terms of diagnosis, HEV RNA is only detectable relatively early following infection and can disappear by the time clinical symptoms appear.

### **G&H** How was the potential relationship of HEV to DILI established in your recently presented analysis of the DILIN cohort?

**TD** In the DILIN, after we prospectively identify and enroll suspected DILI cases, we collect detailed demographic and clinical data, serum, plasma, urine, genomic DNA, and liver tissue. All cases undergo a formal causality assessment by two different instruments: expert opinion and the Roussel Uclaf Causality Assessment Method (RUCAM). We also document clinical and laboratory follow-up of cases for at least 6 months.

In our analysis presented at the recent American Association for the Study of Liver Disease (AASLD) meeting, we hypothesized that some cases of apparent DILI that have been identified through the DILIN may actually represent occult hepatitis E. The specific aim of the study was to assess the frequency of HEV infection in a well-characterized cohort of prospectively identified patients with DILI in the United States. A total of 318 patients with suspected DILI were tested for IgG and IgM anti-HEV, and IgM-positive cases were tested for HEV

RNA, by ELISA and RT-PCR, respectively. An expert hepatopathologist, blinded to the diagnosis, analyzed liver tissue when liver biopsy was performed, and repeat causality assessment was performed after the HEV test results were available.

We found that 46 of the 318 cases, or 15%, were reactive to IgG HEV, which is very similar to the predicted background incidence of HEV based on IgG serologies in the US population. More importantly, 8 (2.5%) of the cases were reactive for IgM anti-HEV, suggesting acute HEV infection. Follow-up sera were available for 3 of these cases, and in all 3, there was seroconversion to anti-HEV IgG positivity at 6 months after enrollment, again suggesting that these cases may have represented acute HEV infection misdiagnosed as DILI.

However, the RT-PCR data revealed that none of the 8 anti-HEV-positive samples, which were collected 4–12 weeks after the onset of symptoms, were reactive to HEV RNA. As I mentioned, this was not surprising based on the kinetics of HEV RNA during infection. HEV RNA is detected in blood only early during infection and often disappears by the time clinical symptoms appear, whereas these cases were obviously identified and enrolled in the DILIN well after clinical symptoms appeared.

In terms of demographics, none of the 8 IgM anti-HEV cases had a recent travel history outside the United States and none were pregnant. Among these 8 cases, 2 patients developed liver failure and 1 died. The causality assessment prior to HEV testing revealed that 1 of the 8 cases was judged as probably related to DILI, whereas 3 of 8 were adjudicated as very likely, and 4 of the 8 cases were thought to be DILI. RUCAM scores on these cases were in the range of 7–10, which is characterized as very probable to definite for DILI.

After anti-HEV testing, 4 cases were still thought to be DILI and unlikely due to viral hepatitis based on their clinicopathologic features, whereas the remaining 4 cases were considered at least possibly due to HEV rather than DILI. These cases were characterized by severe hepatocellular injury, relatively minor increases in serum alkaline phosphatase, and jaundice. Based on these preliminary findings, the role of HEV testing in causality analysis for DILI certainly deserves further study.

### **G&H** Could these findings illustrate a causative relationship between exposure to HEV and later incidence of DILI, acute HEV mimicking DILI, or a combination of both scenarios?

**TD** My suspicion is that at least some of these cases represent HEV mimicking DILI. However, some of the 8 IgM-positive cases were still felt to be primarily related to DILI even after testing for HEV. In those cases, we must

consider the possibility that concomitant HEV combined with DILI resulted in clinical symptoms, as opposed to the subclinical injury that may have been observed with one or the other liver insult. Indeed, a recently published study from India, where HEV is endemic, suggests that HEV may in fact occur concurrently with hepatotoxicity from antituberculosis drugs like INH and PZA. The authors of that study hypothesized that there may be an interaction between the virus and the drugs in the genesis of severe liver injury.

### G&H How might your findings affect future clinical practice in cases of suspected DILI?

**TD** We regard these findings as preliminary data and without additional studies cannot make a strong recommendation for routine HEV testing for the diagnosis of apparent cases of DILI in the United States. However, in individual cases of suspected DILI with a hepatocellular pattern of liver injury or other features suggesting viral hepatitis, I believe that testing for HEV infection, even without a travel history or any other risk factors, may be appropriate. The results of our study have in fact influenced the protocol for the DILIN study, so that future patients enrolled prospectively in the United States will be routinely tested for HEV infection. Nonetheless, further study is needed before we can broadly recommend this practice in the clinic.

### G&H What are the next steps and long-term goals of the DILIN research group?

**TD** We will continue to prospectively collect data on and biosamples from suspected cases of DILI. In order to accomplish our long-term goal of better defining the clinical features, outcomes, and pathogenesis of DILI, we need the continued support of gastroenterologists, hepatologists, internists, and others who refer these cases of presumed DILI to our network. Information about the study and the locations of the 8 clinical sites can be found

on the DILIN web site (<https://dilin.dcri.duke.edu/>). An ongoing challenge for our group that is highlighted by our HEV study will be to identify and enroll patients with apparent DILI as quickly as possible and hopefully closer to the time of clinical presentation, which should allow us to better define the role of HEV infection in this cohort.

One of the main long-term goals of the DILIN is to develop accurate biomarkers for DILI. As part of that effort, our biosamples include genomic DNA from patients, which are now being used to identify DNA polymorphisms, or “signatures,” that are associated with and may ultimately predict risk for DILI. If successful, this work could one day be utilized for both diagnostic testing and as a screening tool for individuals before being treated with potentially hepatotoxic drugs. We are anticipating that by defining these polymorphisms, we will also gain major insights into the pathogenesis of DILI.

Other studies are also needed to better define the epidemiology of HEV in developed countries and clarify the source of infection. Interestingly, it seems that many cases of HEV that are indigenous to developed countries are very mild and have a subclinical course that is unrecognized, given the prevalence of IgG anti-HEV antibodies in the population.

### Suggested Reading

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